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(54) **NON-FLAMMABLE INSECTICIDE
COMPOSITION AND USES THEREOF**

on Nov. 29, 2002. Provisional application No. 60/696,
878, filed on Jul. 6, 2005.

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(57) **ABSTRACT**

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Related U.S. Application Data

(63) Continuation-in-part of application No. 10/911,367, filed on Aug. 4, 2004.

Continuation-in-part of application No. 10/532,618, filed on Dec. 22, 2005, filed as 371 of international application No. PCT/IB03/05527, filed on Oct. 24, 2003.

(60) Provisional application No. 60/492,385, filed on Aug. 4, 2003. Provisional application No. 60/429,546, filed

The present invention provides a safe and effective insecticide composition suitable for treating a subject infested with a parasitic anthropode or to prevent infestation by an arthropod. The insecticide composition is a foamy composition, including a first insecticide; at least one organic carrier selected from a hydrophobic organic carrier, a polar solvent, an emollient and mixtures thereof, at a concentration of about 2% to about 5%, or about 5% to about 10%; or about 10% to about 20%; or about 20% to about 50% by weight; about 0.1% to about 5% by weight of a surface-active agent; about 0.01% to about 5% by weight of at least one polymeric agent selected from a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent; and (5) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition.

NON-FLAMMABLE INSECTICIDE COMPOSITION AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part application of co-pending U.S. patent application Ser. No. 10/532, 618 filed on Apr. 25, 2005 which is a 371 application of International Patent Application No. IB03/005527, designating the United States and filed on Oct. 24, 2003, which claims the benefit of priority under 35 U.S.C. §119(e) to U.S. Patent Application Ser. No. 60/429,546, filed on Nov. 29, 2002, both entitled "Cosmetic and Pharmaceutical Foam," and which claims the benefit of priority under 35 USC§119(a) to Israeli Patent Application No. 152486, filed Oct. 25, 2002, all of which are hereby incorporated in their entirety by reference.

[0002] This application is a continuation-in-part application of co-pending U.S. patent application Ser. No. 10/911, 367, filed on Aug. 4, 2004, which claims the benefit of priority under 35 U.S.C. §119(e) to U.S. Patent Application Ser. No. 60/492,385, filed on Aug. 4, 2003, both entitled "Foam Carrier Containing Amphiphilic Copolymer Gelling Agent" and both hereby incorporated in their entirety by reference.

[0003] This application claims the benefit of priority under 35 U.S.C. §119(e) to U.S. Patent Application Ser. No. 60/696,878, filed on Jul. 6, 2005, entitled "Non-Flammable Insecticide Composition and Uses Thereof," which is hereby incorporated in its entirety by reference.

BACKGROUND OF THE INVENTION

[0004] This invention relates to foamed insecticide compositions.

[0005] An insecticide is a compound used to kill or prevent the growth of parasite arthropods, such as insects and/or arachnids and/or crustacean; or a compound used to repel or prevent infestation by parasite arthropods, such as insects and/or arachnids and/or crustacean. Common infestations in humans include lice and scabies.

[0006] Infestation with lice is referred to as pediculosis. Lice are ectoparasites that live on the body. The 3 types of lice that parasitize humans are *Pediculus humanus capitis* (head louse), *Pediculus humanus corporis* (body louse), and *Phthirus pubis* (pubic louse).

[0007] Every year, between six and 12 million people in the United States, primarily children three to 10 years of age, are infested with head lice. Girls are at greater risk because they have more frequent head-to-head contact. Head lice affect people across the socioeconomic spectrum.

[0008] Scabies is an infestation of the skin with the microscopic mite *Sarcoptes scabiei*. Infestation is common, found worldwide, and affects people of all races and social classes. Scabies spreads rapidly under crowded conditions where there is frequent skin-to-skin contact between people, such as in hospitals, institutions, child-care facilities, and nursing homes.

[0009] Occasionally, a skin infection develops following a bite. Scratching as a result of insect bites can damage the skin and allow bacteria to get in. Infection causes redness

and tenderness around the bite, which may gradually spread, and sometimes can become serious.

[0010] Resistance of insects to pesticides is commonly known. For example, resistance of lice to 1 percent permethrin has been reported in the US and elsewhere. There are two broad mechanisms by which insect pests develop resistance to insecticides. They may produce large amounts of enzymes, such as esterases which either break down the insecticide molecule or bind to it so tightly that it cannot function (a process known as sequestration). The second mechanism involves mutation of the insecticide target site, such as the acetylcholinesterase enzyme in the nervous system. This effectively blocks the action of the insecticide. Both types of mechanism have been studied in various species of insect.

[0011] A common way to overcome resistance is to add a secondary active agent, which impedes that resistance mechanism. An example of such secondary active agent is piperonyl butoxide, which inhibits the ability of insects to degrade insecticides such as pyrethrum. Another approach is to add volatile solvents such as ethanol and propanol to the insecticide formulation.

[0012] U.S. Pat. No. 5,783,202 provides a pediculicidal mousse composition containing (a) from about 0.1 to about 10% w/w of a pediculicidal agent, preferably, pyrethrin, and, optionally from about 0.5 to about 15% w/w of a synergizer therefor, such as piperonyl butoxide, (b) about 70 to about 97% w/w of a foaming agent, which is preferably a quick breaking alcoholic foaming agent; and (c) from about 3 to about 20% w/w of an aerosol propellant.

[0013] A pediculicide mousse, which contains the active ingredients piperonyl butoxide (4%) and pyrethrum (0.33%) and the inactive ingredients cetearyl alcohol, isobutane, PEG-20 stearate, propane, propylene glycol, purified water, quaternium-52, SD Alcohol 3-C (26.5% w/w) is commercially available under the name "RID Lice Killing Mousse" (Bayer Corporation). However, this product possesses at least four disadvantages: (1) Irritability: due to the high alcohol content, the incidence of skin and eye irritation is high; (2) "Quick breaking" property: the foam is thermosensitive and breaks down rapidly at body temperature so that it cannot easily bespread manually throughout the scalp area; (3) Skin drying; and (4) Inflammability: 26.3% alcohol renders the foam inflammable. A test according to European Standard prEN 14851, titled "Aerosol containers—Aerosol foam flammability test" reveals that this product is inflammable.

[0014] Thus, the development of new formulations of permethrin, which will overcome these and other disadvantages, is warranted.

[0015] Furthermore, an easy to use product that addresses the frequent skin and eye irritation associated with pediculicide shampoo, cream rinses and lotions is highly desirable.

SUMMARY OF THE INVENTION

[0016] The present invention provides a safe and effective insecticide composition. In one aspect, the composition of the present invention is suitable for treating a subject infested with a parasite or preventing infestation by a parasite. In some embodiments, the parasite is an arthropod.

fen and triprene, juvenile hormones, moulting hormone agonists, such as chromafenozide, halofenozide, methoxyfenozide and tebufenozide, moulting hormones, such as α -ecdysone and ecdysterone, moulting inhibitors, such as diofenolan, precocenes, and dicyclanil.

[0041] In one or more embodiments, the insecticide is a nereistoxin analogue insecticide, such as bensultap, cartap, thiocyclam and thiosultap.

[0042] In one or more embodiments, the insecticide is a nicotinoid insecticide. Examples of nicotinide insecticides include flonicamid, nitroguanidine insecticides, such as clothianidin, dinotefuran, imidacloprid and thiamethoxam, nitromethylene insecticides, such as nitenpyram and nithiazine, and pyridylmethylamine insecticides, such as acetamiprid, imidacloprid, nitenpyram and thiacloprid.

[0043] In one or more embodiments, the insecticide is an organochlorine insecticide. Examples of organochlorine insecticides include bromo-DDT, campechlor, DDT, lindane, methoxychlor, pentachlorophenol, cyclodiene insecticides, such as aldrin, bromocyclen, chlordicyclen, chlordane, chlordcone, dieldrin, dilar, endosulfan, endrin, heptachlor, isobenzan, isodrin, kelevan and mirex.

[0044] In one or more embodiments, the insecticide is an organophosphorus insecticide. Examples of organophosphorus insecticides include organophosphate insecticides such as bromfenvinfos, chlorgenvinphos, crotoxyphos, dichlorvos, dicrotophos, dimethylvinphos, fospirate, heptenophos, methocrotophos, mevinphos, monocrotophos, naftalofos, phosphamidon, propaphos and tetrachlorvinphos, organothiophosphate insecticides, such as diocabenzofos, fosmethilan, phenthionate, acetion, amiton, cadusafos, chlorethoxyfos, chlormephos, demephion, demeton, disulfoton, ethion, ethoprophos, isothioate, malathion, methacifos, oxydemeton-methyl, oxydeprofos, oxydisulfoton, phorate, sulfotep, terbufos and thiometon, aliphatic amide organothiophosphate insecticides, such as amidithion, cyanthoate, dimethoate, ethoate-methyl, formothion, mecarbam, omethoate, prothoate, sophamide and vamidothion, oxime organothiophosphate insecticides, such as chlorphoxim, phoxim and phoxim-methyl, heterocyclic organothiophosphate insecticides, such as azamethiphos, coumaphos, coumitioate, dioxathion, endothion, menazon, morphothion, phosalone, pyraclofos, pyridaphenthion and quinothion, benzothiopyran organothiophosphate insecticides, such as dithicrofos and thicrofos, benzotriazine organothiophosphate insecticides, such as azinphos-ethyl and azinphos-methyl, isoindole organothiophosphate insecticides, such as dialfos and phosmet, isoxazole organothiophosphate insecticides, such as isoxathion and zolaprofos, pyrazolopyrimidine organothiophosphate insecticides, such as chlorprazophos and pyrazophos; pyridine organothiophosphate insecticides, such as chlorpyrifos and chlorpyrifos-methyl, pyrimidine organothiophosphate insecticides, such as butathifos, diazinon, etrimfos, lirimfos, pirimiphos-ethyl, pirimiphos-methyl, primidophos, pyrimitate and tebupirimfos, quinoxaline organothiophosphate insecticides, such as quinalphos and quinalphos-methyl, thiadiazole organothiophosphate insecticides, such as athidathion, lythidathion, methidathion and prothidathion, triazole organothiophosphate insecticides, such as isazofos and triazophos, phenyl organothiophosphate insecticides, such as azothoate, bromophos, bromophos-ethyl, carbophos-

nothion, chlorthiophos, cyanophos, cythioate, dicaphthon, dichlofenthion, etaphos, famphur, fenchlorphos, fenitrothion, fensulfothion, fenthion, fenthion-ethyl, heterophos, jodfenphos, mesulfenfos, parathion, parathion-methyl, phenkapton, phosnichlor, profenos, prothiophos, sulprofos, temephos, trichlormetaphos-3 and trifenos, phosphonate insecticides, such as butonate and trichlorfon, phosphonothioate insecticides such as mecarphon, phenyl ethylphosphonothioate insecticides, such as fonofos and trichloronat, phenyl phenylphosphonothioate insecticides, such as cyanofenphos, EPN and leptophos, phosphoramidate insecticides, such as crufomate, fenamiphos, fosthietan, mephosfolan, phosfolan and pirimetaphos, phosphoramidothioate insecticides, such as acephate, isocarbophos, isofenphos, methamidophos and propetamphos, and phosphorodiamide insecticides, such as dimefox, mazidox, mipafox and schradan.

[0045] In one or more embodiments, the insecticide is an oxadiazine insecticide, such as indoxacarb.

[0046] In one or more embodiments, the insecticide is a phthalimide insecticide, such as dialifos, phosmet and tetramethrin.

[0047] In one or more embodiments, the insecticide is a pyrazole insecticide, such as acetoprole, ethiprole, fipronil, pyrafluprole, pyriproxyfen, tebufenpyrad, tolfenpyrad and vaniliprole.

[0048] In one or more embodiments, the insecticide is a pyrethroid insecticide. Examples of pyrethroid insecticides include pyrethroid ester insecticides, such as acrinathrin, allethrin, bioallethrin, barthrin, bifenthrin, bioethanomethrin, cyclethrin, cycloprothrin, cyfluthrin, beta-cyfluthrin, cyhalothrin, cypermethrin, alpha-cypermethrin, beta-cypermethrin, theta-cypermethrin, zeta-cypermethrin, cyphenothrin, deltamethrin, dimefluthrin, dimethrin, empenthrin, fenfluthrin, fenpirithrin, fenpropothrin, fenvalerate, esfenvalerate, flucythrinate, flualinate, furethrin, imiprothrin, metofluthrin, permethrin, biopermethrin, transpermethrin, phenothrin, prallethrin, profluthrin, pyresmethrin, resmethrin, bioresmethrin, cismethrin, tefluthrin, teralethrin, tetramethrin, tralomethrin and transfluthrin, and pyrethroid ether insecticides, such as etofenprox, flufenprox, halfenprox, protrifenbutate and silafluofen.

[0049] In one or more embodiments, the insecticide is a pyrimidinamine insecticide, such as flufenprox and pyrimidifen.

[0050] In one or more embodiments, the insecticide is a pyrrole insecticide, such as chlorgafenapyr.

[0051] In one or more embodiments, the insecticide is a tetrone acid insecticide, such as spiromesifen and spirotetramat.

[0052] In one or more embodiments, the insecticide is a thiourea insecticide, such as diafenthuron.

[0053] In one or more embodiments, the insecticide is a urea insecticide, such as flucofurone and sulcofurone.

[0054] Yet, in additional embodiments, the insecticide is an unclassified insecticide, such as closantel, crotamiton, fenazaflor, fenoxacrim, flubendiamide, hydramethylnon, isoprothiolane, malonoben, metaflumizone, metoxadiazone, nifluridide, pyridaben, pyridalyl, rafoxanide, triarathene and triazamate.

[0055] The above listed insecticides, as well as others not listed, are suitable for use in the composition of the present invention. It is preferred to use insecticides that are approved by the FDA or other health authorities for the treatment of animals and humans.

[0056] Non-limiting examples of approved insecticides include hexachlorobenzene, carbamate, naturally occurring pyrethroids, permethrin, allethrin, bioallethrin, phenothrin, malathion and piperonyl butoxide. In a preferred embodiment of the present invention the insecticide is selected from the group consisting of hexachlorobenzene, carbamate, naturally occurring pyrethroids, permethrin, allethrin, bioallethrin, phenothrin, malathion and piperonyl butoxide.

[0057] In one or more embodiments, the insecticide is a naturally occurring insecticide compound. As used herein, the term "naturally-occurring insecticide" includes all insecticides that are obtained, derived or extracted from plant or vertebrate sources.

[0058] In the context of the present invention, an agent that kills or otherwise affects parasites, such as protozoa is also termed an insecticide (for the purpose of this application terminology only). Exemplary antiparasites are mebendazole, thiabendazole, metronidazole, and praziquantel.

[0059] Mixtures of these insecticides may also be employed according to the present invention.

[0060] The insecticide is included in the composition of the present invention in a concentration that provides a desirable ratio between the efficacy and safety. Typically, insecticides are included in the composition in a concentration between about 0.05% and about 12% by weight, depending on their potency against the parasitic arthropod to be eradicated. In some embodiments, the concentration is between about 0.5% and about 2% by weight; in other embodiment the concentration is between about 2% and about 5% by weight; and in other embodiments the concentration is between about 5% and about 12% by weight.

[0061] In one or more embodiments, the insecticide is encapsulated in particles, microparticles, nanoparticles, microcapsules, spheres, microspheres, nanocapsules, nanospheres, liposomes, niosomes, polymer matrix, nanocrystals or microsponges, and may be manufactured according to known methods.

Organic Carrier

[0062] The foamable composition of the present invention can be an emulsion, or microemulsion, including an aqueous phase and an organic carrier phase. The organic carrier is selected from a hydrophobic organic carrier (also termed herein "hydrophobic solvent"), an emollient, a solvent, and a mixture thereof.

[0063] A "hydrophobic organic carrier" as used herein refers to a material having solubility in distilled water at ambient temperature of less than about 1 gm per 100 mL, more preferable less than about 0.5 gm per 100 mL, and most preferably less than about 0.1 gm per 100 mL. It is liquid at ambient temperature. The identification of a hydrophobic organic carrier or "hydrophobic solvent", as used herein, is not intended to characterize the solubilization capabilities of the solvent for any specific active agent or any other component of the foamable composition. Rather, such

information is provided to aid in the identification of materials suitable for use as a hydrophobic carrier in the foamable compositions described herein.

[0064] In one or more embodiments, the hydrophobic organic carrier is an oil, such as mineral oil. According to one or more embodiments, the hydrophobic solvent is a liquid oil originating from vegetable, marine or animal sources. Suitable liquid oil includes saturated, unsaturated or polyunsaturated oils. Another class of hydrophobic solvents is the essential oils. Silicone oils also may be used and are desirable due to their known skin protective and occlusive properties.

[0065] A further class of organic carriers includes "emollients" that have a softening or soothing effect, especially when applied to body areas, such as the skin and mucosal surfaces. Emollients are not necessarily hydrophobic. Examples of suitable emollients include hexyleneglycol, propylene glycol, isostearic acid derivatives, isopropyl palmitate, isopropyl isostearate, diisopropyl adipate, diisopropyl dimerate, maleated soybean oil, octyl palmitate, cetyl lactate, cetyl ricinoleate, tocopheryl acetate, acetylated lanolin alcohol, cetyl acetate, phenyl trimethicone, glyceryl oleate, tocopheryl linoleate, wheat germ glycerides, arachidyl propionate, myristyl lactate, decyl oleate, propylene glycol ricinoleate, isopropyl lanolate, pentaerythrityl tetrastearate, neopentylglycol dicaprylate/dicaprate, isononyl isononanoate, isotridecyl isononanoate, myristyl myristate, triisocetyl citrate, octyl dodecanol, sucrose esters of fatty acids, octyl hydroxystearate and mixtures thereof.

[0066] In an embodiment of the present invention, the organic carrier is a polypropylene glycol alkyl ether (PPG alkyl ether). PPG alkyl ethers are liquid, water-insoluble propoxylated fatty alcohols, having the molecular formula of RO(CH₂CHOCH₃)_n, wherein "R" is a straight-chained or branched C₄ to C₂₂ alkyl group; and "n" is in the range between 4 and about 50. They are organic liquids that function as skin-conditioning agent in pharmaceutical and cosmetic formulations. Non-limiting exemplary PPG alkyl ethers include PPG stearyl ethers and PPG butyl ether. Preferred PPG alkyl ethers according to the present invention include PPG-15 stearyl ether, PPG-2 butyl ether, PPG-9-13 butyl ether and PPG-40 butyl ether.

[0067] According to a preferred embodiment, the organic carrier does not contain petrolatum, which is also referred to as "white petrolatum" anord Vaseline". Petrolatum often forms an impermeable occlusive barrier, so that metabolic products and excreta from damaged tissue are not easily removed or drained away. Furthermore, it is difficult for the active drug dissolved in the carrier to pass through the white petrolatum barrier layer into the treated tissue, so the efficacy of the drug is reduced. An additional disadvantage of petroleum jelly-based products relates to the greasy feeling left following their topical application onto the skin, mucosal membranes and wounds causing inconvenience to the user, thereby decreasing treatment compliance.

[0068] In one or more embodiments, the organic carrier contains a plant-derived oil, which possesses insecticide properties, i.e., a plant derived oil that has the ability to kill or prevent the growth of parasite arthropods or to repel or prevent infestation by parasite arthropods (herein referred to as a "second hydrophobic insecticide" or "plant derived insecticide").

[0069] Examples of plant-derived insecticides include but are not limited to the oils of anise, bergemont, canola, cassia, catnip, cedarwood, citronella, clove, eucalyptus, garlic, ginger, grapefruit, jojoba, lavender, lavandin, lemon, lime, orange, peppermint, rosemary, sage, spearmint, star anise, tea tree, tangerine, thyme and white clover.

[0070] In one or more embodiments, the “second insecticide” agent is an insect repellent. In one or more embodiment, the insect repellent is a chemical insect repellent, such as diethyl toluamide (DEET). In one or more embodiments, the insect repellent is a naturally-derived Insect repellent.

[0071] In one or more embodiments, the insect repellent is repellents that include terpenoid compounds, as described in U.S. Pat. No. 5,411,992, including:

[0072] (1) Terpenoid-alcohol or terpene-ols are terpenoids which have at least one hydroxyl group. Examples of terpene-ols include: $C_{10}H_{16}O$ compounds, perillyl alcohol, carveol, myrtenol, and cis-verbenol; $C_{10}H_{18}O$ compounds, myrtanol, iso-pinocampheol, dihydrocarveol, isopulegol, terpineol, terpinen-4-ol, nerol, geraniol, and linalool, and $C_{10}H_{20}O$ compounds, menthol, beta-citronellol, and dihydro-myrcenol.

[0073] (2) Terpenoid-esters are terpenoids, which have at least one ester group which is the product of the bonding of the hydroxyl group of a terpene-ol with an aliphatic carboxylic acid that can contain functional groups such as the hydroxyl or amine on the aliphatic chain. Examples of suitable aliphatic carboxylic acids include acetic acid, propionic acid, lactic acid, and various amino acids. Examples of terpenoid-esters include carvyl acetate, carvyl propionate, and menthyl lactate.

[0074] (3) Essential oils which contain terpenoids and perfumes which contain terpenoids. Non-limiting examples of essential oils which have high content of terpene-ols and esters include bergamot (62% terpenoids); sage (>50% terpenoids); styrax (>50% terpenoids); peppermint (>50% terpenoids); and pine Siberian (75% terpenoids).

[0075] Combining a first insecticide and a second insecticide having different mechanisms of action provides an enhanced and conceivably a synergistic effect against the parasitic arthropods.

Potent Solvent

[0076] In one or more embodiments, the organic carrier contains at least one solvent having a high solubilization capacity, termed herein a “potent solvent”. In the context of the present invention, a potent solvent is a solvent, other than a short chain alcohol or water, that solubilizes the first and/or second insecticide.

[0077] In one or more embodiments, the potent solvent is selected from the group consisting of a polyol, propylene glycol, hexylene glycol, butanediol, diethylene glycol, benzyl alcohol, terpenes, di-terpenes, tri-terpenes, limonene, terpene-ol, dioxolane, dimethylformamide, dimethyl sulfoxide (DMSO), methyl dodecyl sulfoxide, ethyl oleate, ethyl caprylate, diisopropyl adipate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, dimethylacetamide, azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, isosorbide derivatives, dimethyl isosorbide, glycofurool and ethoxydiglycol (transcutol) and mixtures thereof in any proportion.

[0078] Combining a first insecticide and a potent solvent increase penetration of the insecticide to its target site of action and dissolves the cuticle of the arthropod or the outer surface of the nits, thereby providing an enhanced and conceivably a synergistic effect against the parasitic arthropods.

[0079] In one or more embodiments, the organic carrier contains both a second insecticide and a potent solvent. The combination of a first insecticide, a second insecticide and a potent solvent in combination provides an exceptionally effective product for the treatment of parasitic arthropods, as demonstrated in the examples herein.

Polymeric Agent

[0080] The polymeric agent serves to stabilize the foam composition and to control drug residence in the target organ. Exemplary polymeric agents are classified below in a non-limiting manner. In certain cases, a given polymer can belong to more than one of the classes provided below.

[0081] In one or more embodiments, the polymeric agent includes at least one gelling agent. A gelling agent controls the residence of a therapeutic composition in the target site of treatment by increasing the viscosity of the composition, thereby limiting the rate of its clearance from the site. Many gelling agents are known in the art to possess mucoadhesive properties.

[0082] The gelling agent can be a natural gelling agent, a synthetic gelling agent and an inorganic gelling agent. Exemplary gelling agents that can be used in accordance with one or more embodiments of the present invention include, for example, naturally-occurring polymeric materials, such as locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenin gum, sodium alginate, xanthan gum, quince seed extract, tragacanth gum, guar gum, starch, chemically modified starches and the like, semi-synthetic polymeric materials such as cellulose ethers (e.g. hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethyl cellulose, methyldihydroxyethylcellulose, methyldihydroxypropylcellulose, hydroxypropylmethyl cellulose, hydroxyethylcarboxymethylcellulose, carboxymethylcellulose and carboxymethylhydroxyethylcellulose), guar gum, hydroxypropyl guar gum, soluble starch, cationic celluloses, cationic guarans, and the like, and synthetic polymeric materials, such as carboxyvinyl polymers, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid polymers, polymethacrylic acid polymers, polyvinyl acetate polymers, polyvinyl chloride polymers, polyvinylidene chloride polymers and the like. Mixtures of the above compounds are contemplated.

[0083] Further exemplary gelling agents include the acrylic acid/ethyl acrylate copolymers and the carboxyvinyl polymers, which consist essentially of a colloidal water-soluble polyalkenyl polyether crosslinked polymer of acrylic acid crosslinked with a crosslinking agent such as polyallyl sucrose or polyallyl pentaerythritol. Examples include Carbopol® 934, Carbopol® 940, Carbopol® 950, Carbopol® 980, Carbopol® 951 and Carbopol® 981.

[0084] The polymeric agent can be an inorganic gelling agent, such as silicone dioxide (fumed silica).

[0085] In an embodiment of the present invention, the polymeric agent includes at least one mucoadhesive or

bioadhesive agent. Mucoadhesive/bioadhesion has been defined as the attachment of synthetic or biological macromolecules to a biological tissue. Mucoadhesive agents are a class of polymeric biomaterials that exhibit the basic characteristic of a hydrogel, i.e. swell by absorbing water and interacting by means of adhesion with the mucous that covers epithelia. Compositions according to one or more embodiments of the present invention may contain a mucoadhesive macromolecule or polymer in an amount sufficient to confer bioadhesive properties. The bioadhesive macromolecule enhances the delivery of biologically active agents on or through the target surface. The mucoadhesive macromolecule may be selected from acidic synthetic polymers, preferably having at least one acidic group per four repeating or monomeric subunit moieties, such as poly(acrylic)- and/or poly(methacrylic) acid (e.g., Carbopol®, Carbomer®), poly(methylvinyl ether/maleic anhydride) copolymer, and their mixtures and copolymers; acidic synthetically modified natural polymers, such as carboxymethylcellulose (CMC); neutral synthetically modified natural polymers, such as (hydroxypropyl)methylcellulose; basic amine-bearing polymers such as chitosan; acidic polymers obtainable from natural sources, such as alginic acid, hyaluronic acid, pectin, gum tragacanth, and karaya gum; and neutral synthetic polymers, such as polyvinyl alcohol or their mixtures. An additional group of mucoadhesive polymers includes natural and chemically modified cyclodextrin, especially hydroxypropyl- β -cyclodextrin. Such polymers may be present as free acids, bases, or salts, usually in a final concentration of about 0.01% to about 0.5% by weight. Many mucoadhesive agents are known in the art to also possess gelling properties.

[0086] In one or more embodiments, the polymeric agent includes at least one film forming polymer. The film forming component may include at least one water-insoluble alkyl cellulose or hydroxyalkyl cellulose. Exemplary alkyl cellulose or hydroxyalkyl cellulose polymers include ethyl cellulose, propyl cellulose, butyl cellulose, cellulose acetate, hydroxypropyl cellulose, hydroxybutyl cellulose, and ethylhydroxyethyl cellulose, alone or in combination. In addition, a plasticizer or a cross linking agent may be used to modify the polymer's characteristics. For example, esters such as dibutyl or diethyl phthalate, amides such as diethylidiphenyl urea, vegetable oils, fatty acids and alcohols such as oleic and myristyl acid may be used in combination with the cellulose derivative.

[0087] In one or more embodiments, the polymeric agent includes at least one phase change polymer, which alters the composition behavior from fluid-like prior to administration to solid-like upon contact with the target mucosal surface. Such phase change results from external stimuli, such as changes in temperature or pH and exposure to specific ions (e.g., Ca²⁺). Non-limiting examples of phase change polymers include poly(N-isopropylamide) and Poloxamer 407®.

[0088] The polymeric agent is present in an amount in the range of about 0.01% to about 5.0% by weight of the foam composition. In one or more embodiments, it is typically less than about 1 wt % of the foamable composition.

Surface Active Agent

[0089] Surface-active agents (also termed "surfactants") include any agent linking oil and water in the composition, in the form of emulsion. A surfactant's hydrophilic/lipo-

philic balance (HLB) describes the emulsifier's affinity toward water or oil. The HLB scale ranges from 1 (totally lipophilic) to 20 (totally hydrophilic), with 10 representing an equal balance of both characteristics. Lipophilic emulsifiers form water-in-oil (w/o) emulsions; hydrophilic surfactants form oil-in-water (o/w) emulsions. The HLB of a blend of two emulsifiers equals the weight fraction of emulsifier A times its HLB value plus the weight fraction of emulsifier B times its HLB value (weighted average). The surface active agent according to the present invention has an HLB value, suitable for stabilizing an emulsion comprising the aqueous phase and the organic carrier of the composition.

[0090] According to one or more embodiments of the present invention, the surface-active agent has a hydrophilic lipophilic balance (HLB) between about 9 and about 14, which is the required HLB (the HLB required to stabilize an O/W emulsion of a given oil) of most oils and hydrophobic solvents. Thus, in one or more embodiments, the composition contains a single surface active agent having an HLB value between about 9 and 14, and in one or more embodiments, the composition contains more than one surface active agent and the weighted average of their HLB values is between about 9 and about 14. Yet, in other embodiments, when a water in oil emulsion is desirable, the composition contains one or more surface active agents, having an HLB value between about 2 and about 9.

[0091] The surface-active agent is selected from anionic, cationic, nonionic, zwitterionic, amphoteric and ampholytic surfactants, as well as mixtures of these surfactants. Such surfactants are well known to those skilled in the therapeutic and cosmetic formulation art. Nonlimiting examples of possible surfactants include polysorbates, such as polyoxyethylene (20) sorbitan monostearate (Tween 60) and poly(oxyethylene) (20) sorbitan monooleate (Tween 80); poly(oxyethylene) (POE) fatty acid esters, such as Myrj 45, Myrj 49, Myrj 52 and Myrj 59; poly(oxyethylene) alkyl ethers, such as poly(oxyethylene) cetyl ether, poly(oxyethylene) palmityl ether, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, brij 38, brij 52, brij 56 and brij W1; sucrose esters, partial esters of sorbitol and its anhydrides, such as sorbitan monolaurate and sorbitan monolaurate; mono or diglycerides, isoceteth-20, sodium methyl cocoyl taurate, sodium methyl oleoyl taurate, sodium lauryl sulfate, triethanolamine lauryl sulfate and betaines.

[0092] In one or more embodiments of the present invention, the surface-active agent includes at least one non-ionic surfactant. Ionic surfactants are known to be irritants. Therefore, non-ionic surfactants are preferred in applications including sensitive tissue such as found in most mucosal tissues, especially when they are infected or inflamed. We have surprisingly found that non-ionic surfactants alone provide foams of excellent quality, i.e. a score of "E" according to the grading scale discussed herein below.

[0093] In one or more embodiments, the surface active agent includes a mixture of at least one non-ionic surfactant and at least one ionic surfactant in a ratio in the range of about 100:1 to 6:1. In one or more embodiments, the non-ionic to ionic surfactant ratio is greater than about 6:1, or greater than about 8:1; or greater than about 14:1, or greater than about 16:1, or greater than about 20:1.

[0094] In one or more embodiments of the present invention, a combination of a non-ionic surfactant and an ionic

surfactant (such as sodium lauryl sulphate and cocamidopropylbetaine) is employed, at a ratio of between 1:1 and 20:1, or at a ratio of 4:1 to 10:1. The resultant foam has a low specific gravity, e.g., less than 0.1 g/ml.

[0095] The stability of the composition is especially pronounced when a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed. The ratio between the at least one non-ionic surfactant having HLB of less than 9 and the at least one non-ionic surfactant having HLB of equal or more than 9, is between 1:8 and 8:1, or at a ratio of 4:1 to 1:4. The resultant HLB of such a blend of at least two emulsifiers is between about 9 and about 14.

[0096] Thus, in an exemplary embodiment, a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed, at a ratio of between 1:8 and 8:1, or at a ratio of 4:1 to 1:4, wherein the HLB of the combination of emulsifiers is between about 9 and about 14.

[0097] In one or more embodiments of the present invention, the surface-active agent includes mono-, di- and triesters of sucrose with fatty acids (sucrose esters), prepared from sucrose and esters of fatty acids or by extraction from sucro-glycerides. Suitable sucrose esters include those having high monoester content, which have higher HLB values.

[0098] The total surface active agent is in the range of about 0.1 to about 5% of the composition, and is occasionally less than about 2% or less than about 1%.

Foam Adjuvant

[0099] Optionally, a therapeutically effective foam adjuvant is included in the foamable compositions of the present invention to increase the foaming capacity of surfactants and/or to stabilize the foam. In one or more embodiments of the present invention, the foam adjuvant agent includes fatty alcohols having 15 or more carbons in their carbon chain, such as cetyl alcohol and stearyl alcohol (or mixtures thereof). Other examples of fatty alcohols are arachidyl alcohol (C20), behenyl alcohol (C22), 1-triacontanol (C30), as well as alcohols with longer carbon chains (up to C50). Fatty alcohols, derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain, are especially well suited as foam adjuvant agents. The amount of the fatty alcohol required to support the foam system is inversely related to the length of its carbon chains. Foam adjuvants, as defined herein are also useful in facilitating improved spreadability and absorption of the composition.

[0100] In one or more embodiments of the present invention, the foam adjuvant agent includes fatty acids having 16 or more carbons in their carbon chain, such as hexadecanoic acid (C16) stearic acid (C18), arachidic acid (C20), behenic acid (C22), octacosanoic acid (C28), as well as fatty acids with longer carbon chains (up to C50), or mixtures thereof. As for fatty alcohols, the amount of fatty acids required to support the foam system is inversely related to the length of its carbon chain.

[0101] In one or more embodiments, a combination of a fatty acid and a fatty ester is employed.

[0102] Optionally, the carbon atom chain of the fatty alcohol or the fatty acid may be saturated or unsaturated, branched or unbranched, or hydroxylated or unhydroxylated. The fatty alcohol or the fatty acid may have at least one double bond. A further class of foam adjuvant agent includes a branched fatty alcohol or fatty acid. The carbon chain of the fatty acid or fatty alcohol also can be substituted with a hydroxyl group, such as 12-hydroxy stearic acid.

[0103] Fatty alcohols and fatty acids useful in one or more compositions of the present invention may possess therapeutic properties. Long chain saturated and mono unsaturated fatty alcohols, e.g., stearyl alcohol, erucyl alcohol, arachidyl alcohol and behenyl alcohol (docosanol) have been reported to possess antiviral, antiinfective, antiproliferative and antiinflammatory properties (see, U.S. Pat. No. 4,874,794). Longer chain fatty alcohols, e.g., tetracosanol, hexacosanol, heptacosanol, octacosanol, triacontanol, etc., are also known for their metabolism modifying properties and tissue energizing properties. Long chain fatty acids have also been reported to possess anti-infective characteristics.

Additional Therapeutic Agent

[0104] Several conditions involve a combination of etiological factors, some of which are related to the arthropod or another parasite infestation (that can be affected by an insecticide); and other etiological factors that require an additional therapeutic modality. For example, pediculosis may involve lice infection as well as secondary infection or inflammation, and therefore combined treatment with an insecticide and an anti-inflammatory agent or an antibiotic agent would be beneficial. Likewise, rosacea, which involves a parasite infection, inflammation and telangiectasia, can benefit from treatment with a combination of metronidazole and an additional therapeutic agent, selected from the group consisting of an anti-inflammatory agent, an immunomodulator, an anti-pruritic agent and a vasoconstrictor. Hence, in many cases, the inclusion of an additional therapeutic agent in the composition of the present invention, contributes to the clinical activity of the insecticide. Thus, in one or more embodiments, the composition further includes at least one additional therapeutic agent, in a therapeutically effective concentration.

[0105] In one or more embodiments, the at least one additional therapeutic agent is selected from the group consisting of a steroidal antiinflammatory agent, a nonsteroidal anti-inflammatory drug, an immunosuppressive agent, an immunomodulator, an immunoregulating agent, a hormonal agent, an antibiotic agent, an antifungal agent, an antiviral agent, an antiparasitic agent, a vasoactive agent, a vasoconstrictor, a vasodilator, vitamin A, a vitamin A derivative, vitamin B, a vitamin B derivative, vitamin C, a vitamin C derivative, vitamin D, a vitamin D derivative, vitamin E, a vitamin E derivative, vitamin F, a vitamin F derivative, vitamin K, a vitamin K derivative, a wound healing agent, a disinfectant, an anesthetic, an antiallergic agent, an alpha hydroxyl acid, lactic acid, glycolic acid, a beta-hydroxy acid, a protein, a peptide, a neuropeptide, a allergen, an immunogenic substance, a haptene, an oxidizing agent, an antioxidant, a dicarboxylic acid, azelaic acid, sebamic acid, adipic acid, fumaric acid, an insecticide, an antiproliferative agent, an anticancer agent, a photodynamic therapy agent, an anti-wrinkle agent, a radical scavenger, a metal oxide (e.g., titanium dioxide, zinc oxide, zirconium oxide, iron oxide),

silicone oxide, an anti wrinkle agent, a skin whitening agent, a skin protective agent, a masking agent, an anti-wart agent, a refatting agent, a lubricating agent and mixtures thereof.

[0106] The composition of the present invention may further optionally include a variety of formulation excipients, which are added in order to fine-tune the consistency of the formulation, protect the formulation components from degradation and oxidation and modify their consistency. Such excipients may be selected, for example, from stabilizing agents, antioxidants, humectants, preservatives, colorant and odorant agents and other formulation components, used in the art of formulation.

Propellant

[0107] Aerosol propellants are used to generate and administer the foamable composition as a foam. The total composition including propellant, foamable compositions and optional ingredients is referred to as the foamable carrier. The propellant makes up about 3% to about 25 wt % of the foamable carrier. Examples of suitable propellants include volatile hydrocarbons such as butane, propane, isobutane or mixtures thereof, chloro-fluoro carbons (CMCs) non-ozone-depleting and fluorocarbon propellants, such as 1,1,1,2 tetrafluoroethane and 1,1,1,2,3,3,3 heptafluoropropane.

Composition and Foam Physical Characteristics and Advantages

[0108] A pharmaceutical or cosmetic composition manufactured using the foam carrier according to one or more embodiments of the present invention is very easy to use. When applied onto the afflicted body surface of mammals, i.e., humans or animals, it is in a foam state, allowing free application without spillage. Upon further application of a mechanical force, e.g., by rubbing the composition onto the body surface, it freely spreads on the surface and is rapidly absorbed.

[0109] The foam composition of the present invention creates a stable emulsion having an acceptable shelf-life of at least one year, or at least two years at ambient temperature. Plant-derived oils, potent solvents and hydrocarbon propellants, which are a mixture of low molecular weight hydrocarbons, tend to impair the stability of emulsions. It has been observed, however, that emulsion compositions according to the present invention are surprisingly stable. Following accelerated stability studies, they demonstrate desirable texture; they form fine bubble structures that do not break immediately upon contact with a surface, spread easily on the treated area and absorb quickly.

[0110] The composition should also be free flowing, to allow it to flow through the aperture of the container, e.g., and aerosol container, and create an acceptable foam.

[0111] The foam of the present invention has several advantages, when compared with hydroalcoholic foam compositions, such as described in U.S. Pat. No. 5,783,202:

[0112] (1) Breakability. The foam of the present invention is thermally stable. Unlike hydroalcoholic foam compositions the foam of the present invention is not "quick breaking", i.e., it does not readily collapse upon exposure to body temperature environment. Sheer-force breakability of the foam is clearly advantageous

over thermally-induced breakability, since it allows comfortable application and well directed administration to the target area.

[0113] (2) Irritability. The insecticide composition of the present invention are non-irritant, as revealed in clinical trials, unlike the high incidence of skin and eye irritation caused by the hydroalcoholic foam.

[0114] (3) Skin drying. Alcohol is known to dry the skin and impair the integrity of the skin barrier. By contrast, the insecticide composition of the present invention is an emulsion, which provides skin refatting and skin barrier building effects.

[0115] (4) Inflammability. Alcohol renders the foam inflammable. A test according to European Standard prEN 14851, titled "Aerosol containers—Aerosol foam flammability test" revealed that compositions according to the present invention are non-inflammable, while the hydroalcoholic foam was inflammable.

[0116] In terms of usability, the foamable composition is most advantageous, as revealed by clinical trials:

[0117] (i) Ease of Application.

[0118] Due to the nature a foam product, Foamix Permethrin 1% Foam was found easier to use in comparison with other products available in the market.

[0119] When foam is released it expands in the hair and reaches every spot where lice can be found. This advantage is particularly meaningful in regards to such difficult to access areas as in the neck and behind the ears.

[0120] Using the product with applicator attached to foam container directly onto the scalp under the hair is very convenient.

[0121] (ii) The Foam is Drip-Free

[0122] The foam is not liquid and therefore is not leaking when applied.

[0123] This allows precise application, without the product being spread on clothes or other parts of the body.

[0124] Not a single case of contact with eyes was recorded throughout the study. (It should be noted that the issue of contact with eyes is a common problem when treating with shampoo, lotion and spray which usually cause eye irritation and burning.)

[0125] (iii) Patients' Response

[0126] Throughout the study it was evident that children enjoy being treated with foam and therefore do not resist the therapy.

[0127] Another property of the foam is specific gravity, as measured upon release from the aerosol can. Typically, foams have specific gravity of less than 0.12 g/mL or less than 0.05 g/mL.

Fields of Applications

[0128] The present invention provides safe and effective insecticide compositions, suitable to treat any surface or body, infested with an parasitic anthropode, or to prevent infestation by an arthropod. In one or more embodiments,

the insecticide composition can be used to kill or prevent the growth of parasite arthropods, such as insects and/or arachnids and/or crustacean. In one or more embodiments, the insecticide composition can be used to repel parasite arthropods or prevent infestation by parasite arthropods.

[0129] According to one or more embodiments of the present invention, the insecticide composition is intended for administration to an animal or a human subject. In one or more embodiments, the composition is intended to treat the skin, a body surface, a body cavity or a mucosal surface, e.g., the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum.

[0130] In other embodiments, the insecticide composition is intended for the treatment of plants, infested by arthropods.

[0131] Yet, in additional embodiments, the insecticide composition of bodies or surfaces other than animal, human or botanical subjects.

[0132] The insecticide compositions of the present invention are intended for the treatment of infestation by arthropods, including insects, arachnids and crustaceans. Exemplary arthropods to be treated by the insecticide compositions of the present invention are lice and blowfly larvae, bugs, fleas, gnats, ticks mites, chiggers, punkies, copepods, isopods and barnacles.

[0133] The insecticide compositions of the present invention are intended for the prevention of an insect-transmitted disease, such as typhus, Lyme disease, trench fever, leishmaniasis, malaria and relapsing fever.

[0134] The following examples exemplify the therapeutic compositions and pharmacological compositions and methods described herein. The examples are for the purposes of illustration only and are not intended to be limiting of the invention.

EXAMPLE 1

[0135] This example describes a foamable insecticide composition containing permethrin (1% or 5%), or malathion (0.5%). The following compositions were prepared by blending the listed ingredients.

	Foam A % w/w	Foam B % w/w	Foam C % w/w
Permethrin (first insecticide)	1.00	5.00	
Malathion (first insecticide)			0.50
Mineral oil	5.60	5.60	5.60
Isopropyl myristate	5.60	5.60	5.60
Glyceryl monostearate	0.45	0.45	0.45
Xanthan gum	0.25	0.25	0.25
Methocel K100M	0.25	0.25	0.25
Polysorbate 80	0.85	0.85	0.85
PEG-40 stearate	2.50	2.50	2.50
Sodium lauryl sulphate	0.40	0.40	0.40
Preservative		0.25	0.25
TEA		to pH 5.5	to pH 5.5
Propane/Butane	8.00	8.00	8.00
Purified water	to 100.00	to 100.00	to 100.00

EXAMPLE 2

[0136] This example describes a foamable insecticide composition containing permethrin (1%), malathion (0.5%)

or pyrethrum extract (0.33%)+piperonyl butoxide (4%), as “first insecticide” and diisopropyl adipate and dimethyl isosorbide as potent solvents.

	Foam D % w/w	Foam E % w/w	Foam F % w/w
Permethrin (first insecticide)	1.00		
Malathion (first insecticide)		0.50	
Pyrethrum extract (first insecticide)			0.33
Piperonyl butoxide (first insecticide)			4.00
Diisopropyl adipate (potent solvent)	3.00	3.00	3.00
Dimethyl isosorbide (potent solvent)	10.00	10.00	10.00
Isopropyl myristate	5.60	5.60	5.60
Glyceryl monostearate	0.45	0.45	0.45
Xanthan gum	0.25	0.25	0.25
Methocel K100M	0.25	0.25	0.25
Polysorbate 80	0.85	0.85	0.85
PEG-40 stearate	2.50	2.50	2.50
Sodium lauryl sulphate	0.40	0.40	0.40
Preservative		0.25	0.25
TEA		to pH 5.5	to pH 5.5
Propane/Butane	8.00	8.00	8.00
Purified water	to 100.00	to 100.00	to 100.00

Notes:

Depending on the severity of the insect infestation and the target site, the concentration of the permethrin can range between 0.1% and 10%.

Depending on the severity of the insect infestation and the target site, the concentration of malathion can range between 0.1% and 5%.

Depending on the severity of the insect infestation and the target site, the concentration of the pyrethroid extract can range between 0.1% and 10%.

EXAMPLE 3

[0137] This example describes a foamable insecticide composition, containing permethrin (1%), as “first insecticide” and star anise oil as “second insecticide.”

	Foam G % w/w
Permethrin (first insecticide)	1.00
Isopropyl myristate (potent solvent)	5.60
Star anise oil (second insecticide)	2.00
Glyceryl monostearate	0.45
Diisopropyl adipate	3.00
Xanthan gum	0.25
Methocel K100M	0.25
Polysorbate 80	0.85
PEG-40 stearate	2.50
Sodium lauryl sulphate	0.40
Preservative	0.25
TEA	to pH 5.5
Propane/Butane	8.00
Purified water	to 100.00

EXAMPLE 4

[0138] This example describes a foamable insecticide composition, concurrently containing permethrin (1%), malathion (0.5%) or pyrethrum extract (0.33%)+piperonyl butoxide (4%), as “first insecticide” and star anise oil as “second insecticide”, with or without a potent solvent.

-continued

	Foam H % w/w	Foam I % w/w	Foam J % w/w
Permethrin (first insecticide)	1.00		
Malathion (first insecticide)		0.50	
Pyrethrum extract (first insecticide)			0.33
Piperonyl butoxide (first insecticide)			4.00
Diisopropyl adipate (potent solvent)	3.00	3.00	3.00
Dimethyl isosorbide (potent solvent)	10.00	10.00	10.00
Star anise oil (second insecticide)	2.00	2.00	2.00
Isopropyl myristate	5.60	5.60	5.60
Glyceryl monostearate	0.45	0.45	0.45
Xanthan gum	0.25	0.25	0.25
Methocel K100M	0.25	0.25	0.25
Polysorbate 80	0.85	0.85	0.85
PEG-40 stearate	2.50	2.50	2.50
Sodium lauryl sulphate	0.40	0.40	0.40
Preservative	0.25	0.25	0.25
TEA	to pH 5.5	to pH 5.5	to pH 5.5
Propane/Butane	8.00	8.00	8.00
Purified water	to 100.00	to 100.00	to 100.00

EXAMPLE 5

[0139] This example describes an insecticide composition concurrently containing permethrin (1%), or malathion (0.5%), as “first insecticide”; star anise oil as “second insecticide”, with or without a potent solvent.

Ingredient	PER 079 % w/w	PER 091 % w/w
Glycerin	3.30	3.30
Total product:	100.00	100.00

Notes:
Propellant was added to the above compositions at a concentration of 8%. The total amount of hydrophobic carrier is in the range between 20% and 40%.

EXAMPLE 7

[0141] This example describes additional insecticide compositions containing permethrin 5%.

Ingredient Name	PER5-092 % w/w	PER5-093 % w/w	PER5-094 % w/w
Permethrin	5.05	5.05	5.05
PPG 15 stearyl ether	15.00	—	12.00
Isopropyl myristate	5.00	5.00	21.00
Benzyl alcohol	1.50	1.50	1.50
Glyceryl monostearate	0.50	0.50	1.00
Ceteareth-20	3.30	3.30	3.30

	Emulsion I % w/w	Emulsion II % w/w	Emulsion III % w/w	Emulsion IV % w/w
Permethrin (first insecticide)	1.00	1.00		
Malathion (first insecticide)			0.50	0.50
Mineral oil				5.60
Diisopropyl adipate (potent solvent)	3.00	3.00		
Dimethyl isosorbide (potent solvent)	10.00		10.00	
Star anise oil (second insecticide)	2.00	2.00	2.00	2.00
Isopropyl myristate	5.60	5.60	5.60	5.60
Glyceryl monostearate	0.45	0.45	0.45	0.45
Xanthan gum	0.25	0.25	0.25	0.25
Methocel K100M	0.25	0.25	0.25	0.25
Polysorbate 80	0.85	0.85	0.85	0.85
PEG-40 stearate	2.50	2.50	2.50	2.50
Preservative	0.25	0.25	0.25	0.25
TEA	to pH 5.5	to pH 5.5	to pH 5.5	to pH 5.5
Purified water	to 100.00	to 100.00	to 100.00	to 100.00

EXAMPLE 6

[0140] This example describes non-occlusive insecticide compositions containing permethrin 5%.

Ingredient	PER 079 % w/w	PER 091 % w/w
Permethrin	5.00	5.00
Mineral oil heavy	22.00	—
Isopropyl myristate	11.00	—
Benzyl alcohol	1.50	1.50
Glyceryl monostearate	0.50	0.50
Ceteareth-20	3.30	3.30
Stearyl alcohol	1.10	1.10
Purified water,	56.75	89.75
Carboxymethyl cellulose	0.55	0.55

-continued

Ingredient Name	PER5-092 % w/w	PER5-093 % w/w	PER5-094 % w/w
Stearyl alcohol	1.10	1.10	1.10
Water, purified	62.70	62.70	51.20
Carboxymethyl cellulose	0.55	0.55	0.55
Glycerin	—	—	3.30
Total product:	100.00	100.00	100.00

EXAMPLE 8

[0142] This example describes an open study to assess the efficacy, safety and usability of a 1% permethrin foam

containing a first insecticide, a second insecticide and a potent solvent, in the treatment of head lice (pediculosis capitis) in pediatric patients.

Study Objectives:

1. To assess the efficacy and safety of a 1% Permethrin Foam, in the treatment of head lice (pediculosis capitis) in pediatric patients
2. To detect any side effects of the Foamix 1% Permethrin Foam.
3. To assess the usability of the product.

Methodology:

[0143] The study was performed as a single center open study.

[0144] All patients' parents gave written informed consent to participate in the study.

[0145] The test article, Foamix 1% Permethrin Foam, was applied by the investigator, using an average quantity of 20 gram per patient, according to hair type (length, thickness, curliness etc), on wet or damp hair. The product penetrates under hair via applicator connected to foam container. The foam was spread onto hair through gentle rubbing in. The product remained in contact with hair for 10 minutes and then was washed off with water and a regular shampoo. The same procedure was repeated after 10 days.

[0146] 24 hours after the first treatment, patients were examined for lice visually and by 2-3 minutes combing. Lice and nits found were counted and recorded.

[0147] Dermal side effects (itching, pain, irritation, etc), along with any other adverse events were recorded throughout the study period.

Number of Patients: 56

Diagnosis and Main Criteria for Inclusion:

[0148] Healthy male and female pediatric patients, 3 and 15 years of age, diagnosed as having pediculosis capitis.

Test Article: Foam H of Example 4.

Dose: About 20 gr.

Mode of Administration:

[0149] The treatment was performed by the Investigator or by one of the staff member, under the Investigator's supervision an average quantity of 20 gr. per patient, according to hair type (length, thickness, curliness, etc), on wet or damp hair (after a 2-3 minutes wash).

[0150] The product penetrates under hair via applicator connected to foam container, as shown in the picture below.

[0151] The foam was spread onto hair through gentle rubbing in. The product remained in contact with hair for 10 minutes and then was washed off with water and a usual shampoo. Treatment was repeated in 10 days.

[0152] In order to measure the applied amount of product, the foam container was weighed before and after every use.

Results and Conclusions:

1. Efficacy:

[0153] The product is found effective in lice killing in 96.4% of the patients.

[0154] The product further eradicated viable nits in 60% of the patients.

2. Safety:

[0155] No drug-related adverse effects were recorded.

3. Usability:

A. Ease of Application:

[0156] Due to the nature a foam product, Foamix Permethrin 1% Foam was found easier to use in comparison with other products available in the market.

[0157] When foam is released it expands in the hair and reaches every spot where lice can be found. This advantage is particularly meaningful in regards to such difficult to access areas as in the neck and behind the ears.

[0158] Using the product with applicator attached to foam container directly onto the scalp under the hair is very convenient.

B. The Foam is Drip-Free

[0159] The foam is not liquid and therefore is not leaking when applied.

[0160] This allows precise application, without the product being spread on clothes or other parts of the body.

[0161] Not a single case of contact with eyes was recorded throughout the study. (It should be noted that the issue of contact with eyes is a common problem when treating with shampoo, lotion and spray which usually cause eye irritation and burning.)

C. Patients' Response

[0162] Throughout the study it was evident that children enjoy being treated with foam and therefore do not resist the therapy.

[0163] In conclusion, the present study provides evidence that Foam H of Example 4 is safe and effective in the treatment of head lice (pediculosis capitis) in pediatric patients.

EXAMPLE 9

[0164] This example describes a single-blind study of the transepidermal water loss effect of PER 079 and PER 091 vehicle formulations from Example 6 in subjects with normal skin in comparison with Petrolatum and No Treatment.

[0165] Transepidermal water loss (TEWL) is often used to assess the occlusive effect of a composition. A single-blind study was carried out to assess the effect of two principal vehicle formulations on TEWL, in comparison with petrolatum (positive control) and no treatment (negative control). Square areas of the same size, 4 cm² each were drawn in the forearms. The areas were randomly assigned to a single treatment with one of the preparations (PER 079, PER 091 or petrolatum) and one area remained untreated. 40 mg of each of the preparations were applied. The following table provides the TEWL values prior to treatment (baseline) and 30 minutes afterwards.





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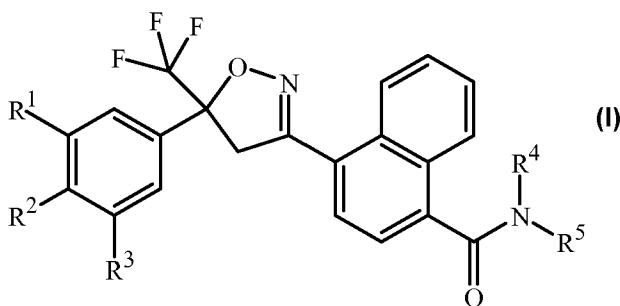
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(54) Title: NAPHTHALENE ISOXAZOLINE INVERTEBRATE PEST CONTROL AGENTS

environment with a biologically effective amount of a compound or a composition of the invention.

(57) Abstract: Disclosed are compounds of Formula (I), wherein R₁ is halogen, C₁-C₂ haloalkyl or C₁-C₂ haloalkoxy; R² is H, halogen or cyano; R³ is H, halogen or CF₃; R⁴ is H, C₂-C₇ alkylcarbonyl or C₂-C₇ alkoxy carbonyl; and R⁵ is C₁-C₆ alkyl or C₁-C₆ haloalkyl, each substituted with one substituent independently selected from hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonyl, C₂-C₇ alkylaminocarbonyl, C₃-C₉ dialkylaminocarbonyl, C₂-C₇ haloalkylaminocarbonyl and C₃-C₉ halodialkylaminocarbonyl. Also disclosed are compositions containing the compounds of Formula (I) and methods for controlling an invertebrate pest comprising contacting the invertebrate pest or its

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TITLE

NAPHTHALENE ISOXAZOLINE INVERTEBRATE PEST CONTROL AGENTS

FIELD OF THE INVENTION

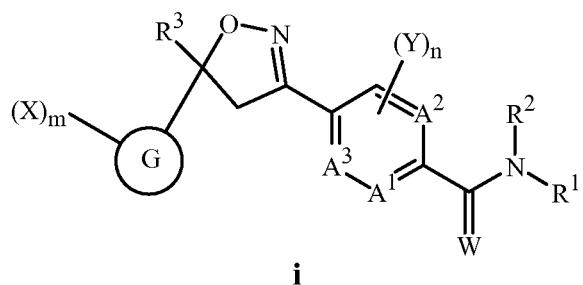
This invention relates to certain isoxazolines and their compositions suitable for agronomic, nonagricultural and animal health uses, methods of their use for controlling invertebrate pests such as arthropods in both agronomic and nonagricultural environments, and for treatment of parasite infections in animals or infestations in the general environment.

BACKGROUND OF THE INVENTION

The control of invertebrate pests is extremely important in achieving high crop efficiency. Damage by invertebrate pests to growing and stored agronomic crops can cause significant reduction in productivity and thereby result in increased costs to the consumer. The control of invertebrate pests in forestry, greenhouse crops, ornamentals, nursery crops, stored food and fiber products, livestock, household, turf, wood products, and public health is also important. Many products are commercially available for these purposes, but the need continues for new compounds that are more effective, less costly, less toxic, environmentally safer or have different sites of action.

The control of animal parasites in animal health is essential, especially in the areas of food production and companion animals. Existing methods of treatment and parasite control are being compromised due to growing resistance to many current commercial parasiticides. The discovery of more effective ways to control animal parasites is therefore imperative.

PCT Patent Publication WO 05/085216 discloses isoxazoline derivatives of Formula **i** as insecticides

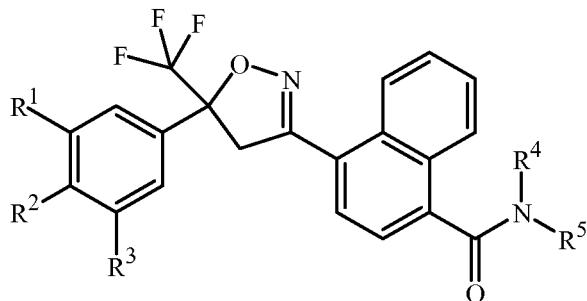


wherein, *inter alia*, each of A¹, A² and A³ are independently C or N; G is a benzene ring; 25 W is O or S; and X is halogen or C₁-C₆ haloalkyl.

The isoxazolines of the present invention are not disclosed in this publication.

SUMMARY OF THE INVENTION

This invention is directed to compounds of Formula **1** (including all stereoisomers) and compositions containing them and their use for controlling invertebrate pests:

**1**

wherein

R¹ is halogen, C₁–C₂ haloalkyl or C₁–C₂ haloalkoxy;R² is H, halogen or cyano;5 R³ is H, halogen or CF₃;R⁴ is H, C₂–C₇ alkylcarbonyl or C₂–C₇ alkoxy carbonyl; and10 R⁵ is C₁–C₆ alkyl or C₁–C₆ haloalkyl, each substituted with one substituentindependently selected from hydroxy, C₁–C₆ alkoxy, C₁–C₆ alkylthio, C₁–C₆alkylsulfinyl, C₁–C₆ alkylsulfonyl, C₂–C₇ alkylaminocarbonyl, C₃–C₉15 dialkylaminocarbonyl, C₂–C₇ haloalkylaminocarbonyl and C₃–C₉

halodialkylaminocarbonyl.

This invention is also directed to such compounds of Formula 1 (including all stereoisomers) and compositions containing them and their use for controlling invertebrate pests as described above, and further herein, provided that when R¹ and R³ are Cl, and R² and R⁴ are H, then R⁵ is other than CH₂C(O)NHCH₂CF₃, CH₂CH₂OH or CH₂CH₂OCH₃.

This invention also provides a composition comprising a compound of Formula 1 and at least one additional component selected from the group consisting of surfactants, solid diluents and liquid diluents. In one embodiment, this invention also provides a composition for controlling an invertebrate pest comprising a compound of Formula 1 (i.e. in a biologically effective amount) and at least one additional component selected from the group consisting of surfactants, solid diluents and liquid diluents, said composition optionally further comprising at least one additional biologically active compound or agent (i.e. in a biologically effective amount).

This invention further provides a spray composition for controlling an invertebrate pest comprising a compound of Formula 1 (i.e. in a biologically effective amount) or the composition described above, and a propellant. This invention also provides a bait composition for controlling an invertebrate pest comprising a compound of Formula 1 (i.e. in a biologically effective amount) or the compositions described in the embodiments above, one or more food materials, optionally an attractant, and optionally a humectant.

30 This invention further provides a trap device for controlling an invertebrate pest comprising said bait composition and a housing adapted to receive said bait composition,

wherein the housing has at least one opening sized to permit the invertebrate pest to pass through the opening so the invertebrate pest can gain access to said bait composition from a location outside the housing, and wherein the housing is further adapted to be placed in or near a locus of potential or known activity for the invertebrate pest.

5 This invention provides a method for controlling an invertebrate pest comprising contacting the invertebrate pest or its environment with a biologically effective amount of a compound of Formula 1 (e.g., as a composition described herein). This invention also relates to such method wherein the invertebrate pest or its environment is contacted with a composition comprising a biologically effective amount of a compound of Formula 1 and at 10 least one additional component selected from the group consisting of surfactants, solid diluents and liquid diluents, said composition optionally further comprising a biologically effective amount of at least one additional biologically active compound or agent.

15 This invention also provides a method for protecting a seed from an invertebrate pest comprising contacting the seed with a biologically effective amount of a compound of Formula 1 (e.g., as a composition described herein). This invention also relates to the treated seed.

20 This invention further provides a method for treating, preventing, inhibiting and/or killing ecto- and/or endoparasites comprising administering to and/or on the animal a parasitically effective amount of a compound of Formula 1 (e.g., as a composition described herein). This invention also relates to such method wherein a parasitically effective amount of a compound of Formula 1 (e.g., as a composition described herein) is administered to the environment (e.g., a stall or blanket) in which an animal resides.

DETAILS OF THE INVENTION

25 As used herein, the terms "comprises," "comprising," "includes," "including," "has," "having," "contains" or "containing," or any other variation thereof, are intended to cover a non-exclusive inclusion. For example, a composition, a mixture, process, method, article, or apparatus that comprises a list of elements is not necessarily limited to only those elements but may include other elements not expressly listed or inherent to such composition, mixture, process, method, article, or apparatus. Further, unless expressly stated to the contrary, "or" 30 refers to an inclusive or and not to an exclusive or. For example, a condition A or B is satisfied by any one of the following: A is true (or present) and B is false (or not present), A is false (or not present) and B is true (or present), and both A and B are true (or present).

35 Also, the indefinite articles "a" and "an" preceding an element or component of the invention are intended to be nonrestrictive regarding the number of instances (i.e. occurrences) of the element or component. Therefore "a" or "an" should be read to include one or at least one, and the singular word form of the element or component also includes the plural unless the number is obviously meant to be singular.

As referred to in this disclosure, the term "invertebrate pest" includes arthropods, gastropods and nematodes of economic importance as pests. The term "arthropod" includes

insects, mites, spiders, scorpions, centipedes, millipedes, pill bugs and symphylans. The term "gastropod" includes snails, slugs and other Stylommatophora. The term "nematode" includes all of the helminths, such as roundworms, heartworms, and phytophagous nematodes (Nematoda), flukes (Trematoda), Acanthocephala, and tapeworms (Cestoda).

5 In the context of this disclosure "invertebrate pest control" means inhibition of invertebrate pest development (including mortality, feeding reduction, and/or mating disruption), and related expressions are defined analogously.

The term "agronomic" refers to the production of field crops such as for food and fiber and includes the growth of corn, soybeans and other legumes, rice, cereal (e.g., wheat, oats, 10 barley, rye, rice, maize), leafy vegetables (e.g., lettuce, cabbage, and other cole crops), fruiting vegetables (e.g., tomatoes, pepper, eggplant, crucifers and cucurbits), potatoes, sweet potatoes, grapes, cotton, tree fruits (e.g., pome, stone and citrus), small fruit (berries, cherries) and other specialty crops (e.g., canola, sunflower, olives).

The term "nonagronomic" refers to other than field crops, such as horticultural crops 15 (e.g., greenhouse, nursery or ornamental plants not grown in a field), residential, agricultural, commercial and industrial structures, turf (e.g., sod farm, pasture, golf course, lawn, sports field, etc.), wood products, stored product, agro-forestry and vegetation management, public health (i.e. human) and animal health (e.g., domesticated animals such as pets, livestock and poultry, undomesticated animals such as wildlife) applications.

20 Nonagronomic applications include protecting an animal from an invertebrate parasitic pest by administering a parasitically effective (i.e. biologically effective) amount of a compound of the invention, typically in the form of a composition formulated for veterinary use, to the animal to be protected. As referred to in the present disclosure and claims, the terms "parasiticidal" and "parasitically" refers to observable effects on an invertebrate 25 parasite pest to provide protection of an animal from the pest. Parasiticidal effects typically relate to diminishing the occurrence or activity of the target invertebrate parasitic pest. Such effects on the pest include necrosis, death, retarded growth, diminished mobility or lessened ability to remain on or in the host animal, reduced feeding and inhibition of reproduction. These effects on invertebrate parasite pests provide control (including prevention, reduction 30 or elimination) of parasitic infestation or infection of the animal.

A parasite "infestation" refers to the presence of parasites in numbers that pose a risk to humans or animals. The infestation can be in the environment (e.g., in human or animal housing, bedding, and surrounding property or structures), on agricultural crops or other types of plants, or on the skin or fur of an animal. When the infestation is within an animal 35 (e.g., in the blood or other internal tissues), the term infestation is also intended to be synonymous with the term "infection" as that term is generally understood in the art, unless otherwise stated.

In the above recitations, the term “alkyl”, used either alone or in compound words such as “alkylthio” or “haloalkyl” includes straight-chain or branched alkyl, such as methyl, ethyl, *n*-propyl, *i*-propyl, or the different butyl, pentyl or hexyl isomers.

“Alkoxy” includes, for example, methoxy, ethoxy, *n*-propyloxy, isopropyloxy and the different butoxy, pentoxy and hexyloxy isomers. “Alkylthio” includes branched or straight-chain alkylthio moieties such as methylthio, ethylthio, and the different propylthio, butylthio, pentylthio and hexylthio isomers. “Alkylsulfinyl” includes both enantiomers of an alkylsulfinyl group. Examples of “alkylsulfinyl” include S(O)CH₃, S(O)CH₂CH₃, S(O)CH₂CH₂CH₃, S(O)CH(CH₃)₂ and the different butylsulfinyl, pentylsulfinyl and hexylsulfinyl isomers. Examples of “alkylsulfonyl” include S(O)₂CH₃, S(O)₂CH₂CH₃, S(O)₂CH₂CH₂CH₃, S(O)₂CH(CH₃)₂, and the different butylsulfonyl, pentylsulfonyl and hexylsulfonyl isomers. “Alkylamino” and “dialkylamino” are defined analogously to the above examples.

The term “halogen”, either alone or in compound words such as “haloalkyl”, or when used in descriptions such as “alkyl substituted with halogen” includes fluorine, chlorine, bromine or iodine. Further, when used in compound words such as “haloalkyl”, or when used in descriptions such as “alkyl substituted with halogen” said alkyl may be partially or fully substituted with halogen atoms which may be the same or different. Examples of “haloalkyl” or “alkyl substituted with halogen” include CF₃, CH₂Cl, CH₂CF₃ and CCl₂CF₃. The term “haloalkoxy” is defined analogously to the term “haloalkyl”. Examples of “haloalkoxy” include OCF₃, OCH₂CCl₃, OCH₂CH₂CHF₂ and OCH₂CF₃.

“Alkylcarbonyl” denotes a straight-chain or branched alkyl moiety bonded to a C(O) moiety. The chemical abbreviations C(O) and C(=O) as used herein represent a carbonyl moiety. Examples of “alkylcarbonyl” include C(O)CH₃, C(O)CH₂CH₂CH₃ and C(O)CH(CH₃)₂.

“Alkoxycarbonyl” denotes a straight-chain or branched alkyl moiety bonded to a CO₂ moiety. The chemical abbreviations CO₂ and C(=O)O as used herein represent an ester moiety. Examples of “aloxycarbonyl” include CO₂CH₃, CO₂CH₂CH₃, CO₂CH₂CH₂CH₃, CO₂CH(CH₃)₂ and the different butoxy- or pentoxy carbonyl isomers.

“Alkylaminocarbonyl” denotes a straight-chain or branched alkyl moiety bonded to a C(O)NH moiety. The chemical abbreviations C(O)NH, C(=O)NH, C(O)N and C(=O)N as used herein represent an amide moiety (i.e. an aminocarbonyl group). Examples of “alkylaminocarbonyl” include C(O)NHCH₃, C(O)NHCH₂CH₂CH₃ and C(O)NHCH(CH₃)₂. “Dialkylaminocarbonyl” denotes two independent straight-chain or branched alkyl moieties bonded to a C(O)N moiety. Examples of “dialkylaminocarbonyl” include C(O)N(CH₃)₂ and C(O)N(CH₃)(CH₂CH₃).

“Haloalkylaminocarbonyl” denotes a straight-chain or branched haloalkyl moiety bonded to a C(O)NH moiety, wherein “haloalkyl” is as defined above. Examples of “haloalkylaminocarbonyl” include C(O)NHCH₂CF₃ and C(O)NHCH₂CH₂CH₂Cl.

“Halodialkylaminocarbonyl” denotes one straight-chain or branched alkyl moiety and one straight-chain or branched haloalkyl moiety bonded to a C(O)N moiety, or two independent straight-chain or branched haloalkyl moieties bonded to a C(O)N moiety, wherein “haloalkyl” is as defined above. Examples of “halodialkylaminocarbonyl” include
5 C(O)N(CH₂CH₃)(CH₂CH₂Cl) and C(O)N(CF₂CF₃)₂. Examples of “C₂ alkyl substituted with C₁ alkylaminocarbonyl” include CH₂CH₂C(O)NHCH₃ and CH(CH₃)C(O)NHCH₃.

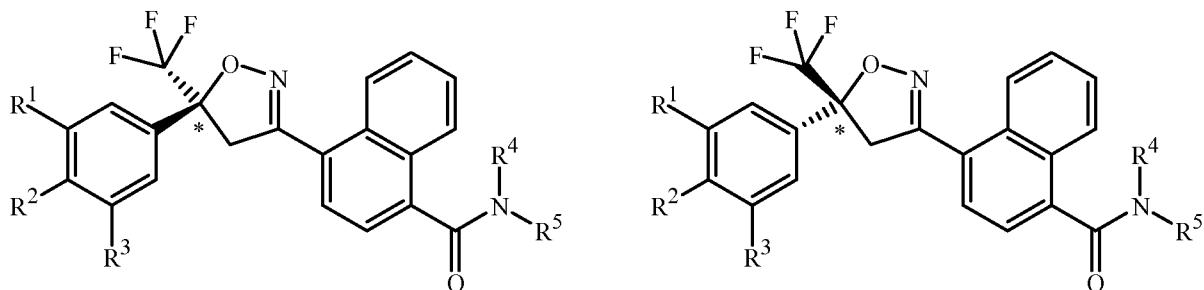
When R⁵ is C₁–C₆ alkyl or C₁–C₆ haloalkyl, each further substituted with one group as defined in the Summary of the Invention, the carbon atom through which said alkyl or haloalkyl group is bonded to the remainder of Formula 1 is assigned the 1-position. An
10 example of a C₂ alkyl group substituted with a C₃ haloalkylaminocarbonyl group attached at the 1-position of the C₂ alkyl group is *CH(CH₃)C(O)NHCH₂CF₃, wherein the asterisk denotes the 1-position.

The total number of carbon atoms in a substituent group is indicated by the “C_i–C_j” prefix where i and j are numbers from 1 to 9. For example, C₁–C₆ alkylsulfonyl designates
15 methylsulfonyl through hexylsulfonyl.

When a group contains a substituent which can be hydrogen, for example R⁴, then when this substituent is taken as hydrogen, it is recognized that this is equivalent to said group being unsubstituted.

A wide variety of synthetic methods are known in the art to enable preparation of
20 aromatic and nonaromatic heterocyclic rings and ring systems; for extensive reviews see the eight volume set of *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky and C. W. Rees editors-in-chief, Pergamon Press, Oxford, 1984 and the twelve volume set of *Comprehensive Heterocyclic Chemistry II*, A. R. Katritzky, C. W. Rees and E. F. V. Scriven editors-in-chief, Pergamon Press, Oxford, 1996.

25 Compounds of this invention can exist as one or more stereoisomers. The various stereoisomers include enantiomers, diastereomers and atropisomers. One skilled in the art will appreciate that one stereoisomer may be more active and/or may exhibit beneficial effects when enriched relative to the other stereoisomer(s) or when separated from the other stereoisomer(s). Additionally, the skilled artisan knows how to separate, enrich, and/or to
30 selectively prepare said stereoisomers. The compounds of the invention may be present as a mixture of stereoisomers, individual stereoisomers or as an optically active form. For example, two possible enantiomers of Formula 1 are depicted as Formula 1a and Formula 1b involving the isoxazoline chiral center identified with an asterisk (*). Analogously, other chiral centers are possible at, for example, R⁵.



Molecular depictions drawn herein follow standard conventions for depicting stereochemistry. To indicate stereoconfiguration, bonds rising from the plane of the drawing and towards the viewer are denoted by solid wedges wherein the broad end of the wedge is attached to the atom rising from the plane of the drawing towards the viewer. Bonds going below the plane of the drawing and away from the viewer are denoted by dashed wedges wherein the narrow end of the wedge is attached to the atom further away from the viewer. Constant width lines indicate bonds with a direction opposite or neutral relative to bonds shown with solid or dashed wedges; constant width lines also depict bonds in molecules or parts of molecules in which no particular stereoconfiguration is intended to be specified.

The more biologically active enantiomer is believed to be Formula **1a**. Formula **1a** has the (*S*) configuration at the chiral carbon and Formula **1b** has the (*R*) configuration at the chiral carbon.

This invention comprises racemic mixtures, for example, equal amounts of the enantiomers of Formulae **1a** and **1b**. In addition, this invention includes compounds that are enriched compared to the racemic mixture in an enantiomer of Formula **1**. Also included are the essentially pure enantiomers of compounds of Formula **1**, for example, Formula **1a** and Formula **1b**.

When enantiomerically enriched, one enantiomer is present in greater amounts than the other, and the extent of enrichment can be defined by an expression of enantiomeric excess (“ee”), which is defined as $(2x-1) \cdot 100\%$, where x is the mole fraction of the dominant enantiomer in the mixture (e.g., an ee of 20 % corresponds to a 60:40 ratio of enantiomers).

Preferably the compositions of this invention have at least a 50 % enantiomeric excess; more preferably at least a 75 % enantiomeric excess; still more preferably at least a 90 % enantiomeric excess; and the most preferably at least a 94 % enantiomeric excess of the more active isomer. Of particular note are enantiomerically pure embodiments of the more active isomer.

Compounds of Formula **1** can comprise additional chiral centers. For example, substituents and other molecular constituents such as R^5 may themselves contain chiral centers. The more biologically active enantiomers of compounds wherein R^5 contains the $\text{CH}(\text{CH}_3)\text{C}(\text{O})\text{N}$ moiety (e.g., compounds 94 and 106 of Index Table A) are believed to contain the (*R*) configuration at the chiral carbon. This invention comprises racemic

mixtures as well as enriched and essentially pure stereoconfigurations at these additional chiral centers.

Compounds of this invention can exist as one or more conformational isomers due to restricted rotation about the amide bond in Formula 1. This invention comprises mixtures of 5 conformational isomers. In addition, this invention includes compounds that are enriched in one conformer relative to others.

Compounds of this invention may exist as one or more crystalline polymorphs. This invention comprises both individual polymorphs and mixtures of polymorphs, including mixtures enriched in one polymorph relative to others.

10 Embodiments of the present invention as described in the Summary of the Invention include those described below. In the following Embodiments, reference to "a compound of Formula 1" includes the definitions of substituents specified in the Summary of the Invention unless further defined in the Embodiments.

Embodiment 1. A compound of Formula 1 wherein when R¹ and R³ are Cl, and R² and 15 R⁴ are H, then R⁵ is other than CH₂C(O)NHCH₂CF₃, CH₂CH₂OH or CH₂CH₂OCH₃.

Embodiment 2. A compound of Formula 1 wherein R¹ is Cl, Br or CF₃.

Embodiment 3. A compound of Embodiment 2 wherein R¹ is Cl.

Embodiment 4. A compound of Embodiment 2 wherein R¹ is Br.

20 Embodiment 5. A compound of Embodiment 2 wherein R¹ is CF₃.

Embodiment 6. A compound of Formula 1 wherein R² is H, F or Cl.

Embodiment 7. A compound of Embodiment 6 wherein R² is H.

Embodiment 8. A compound of Embodiment 6 wherein R² is F.

Embodiment 9. A compound of Embodiment 6 wherein R² is Cl.

25 Embodiment 10. A compound of Formula 1 wherein R³ is H, Cl, Br or CF₃.

Embodiment 11. A compound of Embodiment 10 wherein R³ is H.

Embodiment 12. A compound of Embodiment 10 wherein R³ is Cl.

Embodiment 13. A compound of Embodiment 10 wherein R³ is Br.

Embodiment 14. A compound of Embodiment 10 wherein R³ is CF₃.

30 Embodiment 15. A compound of Formula 1 wherein R⁴ is H.

Embodiment 16. A compound of Formula 1 wherein R⁵ is C₁-C₆ alkyl or C₁-C₆ haloalkyl, each substituted with one hydroxy or C₁-C₆ alkoxy.

Embodiment 17. A compound of Formula 1 wherein R⁵ is C₁-C₆ alkyl or C₁-C₆ haloalkyl, each substituted with one C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl or C₁-C₆ alkylsulfonyl.

Embodiment 18. A compound of Formula 1 wherein R⁵ is C₁-C₆ alkyl or C₁-C₆ haloalkyl, each substituted with one C₂-C₇ alkylaminocarbonyl, C₃-C₉ dialkylaminocarbonyl, C₂-C₇ haloalkylaminocarbonyl or C₃-C₉ halodialkylaminocarbonyl.

- Embodiment 19. A compound of Embodiment 18 wherein R⁵ is C₁–C₆ alkyl substituted with C₂–C₇ haloalkylaminocarbonyl.
- Embodiment 20. A compound of Formula 1 or Embodiment 1 wherein R¹ is F, Br, I, C₁–C₂ haloalkyl or C₁–C₂ haloalkoxy.
- 5 Embodiment 21. A compound of Formula 1 or Embodiment 1 wherein R¹ is halogen.
- Embodiment 22. A compound of Formula 1 or Embodiment 1 wherein R¹ is C₁–C₂ haloalkyl.
- Embodiment 23. A compound of Formula 1 or Embodiment 1 wherein R¹ is C₁–C₂ haloalkoxy.
- 10 Embodiment 24. A compound of Embodiment 23 wherein R¹ is OCF₃.
- Embodiment 25. A compound of Formula 1 or Embodiment 1 wherein R² is halogen.
- Embodiment 26. A compound of Formula 1 or Embodiment 1 wherein R² is cyano.
- Embodiment 27. A compound of Formula 1 or Embodiment 1 wherein R² is H or F.
- Embodiment 28. A compound of Formula 1 or Embodiment 1 wherein R³ is halogen.
- 15 Embodiment 29. A compound of Formula 1 or Embodiment 1 wherein R³ is H, F, Cl, Br or CF₃.
- Embodiment 30. A compound of Formula 1 or Embodiment 1 wherein R³ is Cl, Br or CF₃.
- Embodiment 31. A compound of Embodiment 28 wherein R³ is F.
- 20 Embodiment 32. A compound of Formula 1 or Embodiment 1 wherein R⁴ is C₂–C₇ alkylcarbonyl.
- Embodiment 33. A compound of Formula 1 or Embodiment 1 wherein R⁴ is C₂–C₇ alkoxy carbonyl.
- Embodiment 34. A compound of Embodiment 32 wherein R⁴ is C(O)Me.
- 25 Embodiment 35. A compound of Embodiment 33 wherein R⁴ is CO₂Me.
- Embodiment 36. A compound of Embodiment 33 wherein R⁴ is CO₂(t-Bu).
- Embodiment 37. A compound of Formula 1 or Embodiment 1 wherein R⁵ is C₁–C₆ alkyl substituted with one substituent independently selected from C₁–C₆ alkylthio, C₁–C₆ alkylsulfinyl, C₁–C₆ alkylsulfonyl, C₂–C₇ alkylaminocarbonyl and C₂–C₇ haloalkylaminocarbonyl.
- 30 Embodiment 38. A compound of Embodiment 37 wherein R⁵ is C₁–C₄ alkyl substituted with one C₁–C₄ alkylthio, C₁–C₄ alkylsulfinyl or C₁–C₄ alkylsulfonyl.
- Embodiment 39. A compound of Embodiment 38 wherein R⁵ is C₂–C₃ alkyl substituted with one C₁–C₂ alkylthio, C₁–C₂ alkylsulfinyl or C₁–C₂ alkylsulfonyl.
- 35 Embodiment 40. A compound of Embodiment 39 wherein R⁵ is CH₂CH₂SCH₃, CH₂CH₂S(O)CH₃ or CH₂CH₂SO₂CH₃.

Embodiment 41. A compound of Embodiment 37 wherein R⁵ is C₁–C₆ alkyl substituted with one C₂–C₇ alkylaminocarbonyl or C₃–C₇ haloalkylaminocarbonyl.

Embodiment 42. A compound of Embodiment 41 wherein the one C₂–C₇ alkylaminocarbonyl or C₃–C₇ haloalkylaminocarbonyl substituent is attached to the C₁–C₆ alkyl group at the 1-position.

Embodiment 43. A compound of Embodiment 42 wherein R⁵ is C₁–C₄ alkyl substituted with C₂–C₄ alkylaminocarbonyl.

Embodiment 44. A compound of Embodiment 42 wherein R⁵ is C₁–C₄ alkyl substituted with C₃–C₄ haloalkylaminocarbonyl.

Embodiment 45. A compound of Embodiment 44 wherein R⁵ is C₁–C₂ alkyl substituted with C(O)NHCH₂CF₃.

Embodiments of this invention, including Embodiments 1–45 above as well as any other embodiments described herein, can be combined in any manner, and the descriptions of variables in the embodiments pertain not only to the compounds of Formula 1 but also to the starting compounds and intermediate compounds useful for preparing the compounds of Formula 1. In addition, embodiments of this invention, including Embodiments 1–45 above as well as any other embodiments described herein, and any combination thereof, pertain to the compositions and methods of the present invention.

Combinations of Embodiments 1–45 are illustrated by:

Embodiment A. A compound of Formula 1 wherein

R⁴ is H; and

R⁵ is C₁–C₆ alkyl substituted with one C₃–C₇ haloalkylaminocarbonyl;

provided that when R¹ and R³ are Cl, and R² and R⁴ are H, then R⁵ is other than

CH₂C(O)NHCH₂CF₃, CH₂CH₂OH or CH₂CH₂OCH₃.

Embodiment B. A compound of Embodiment A wherein

R¹ is Cl, Br or CF₃;

R² is H, F or Cl; and

R³ is H, Cl, Br or CF₃.

Embodiment C. A compound of Embodiment B wherein

R² is H.

Embodiment D. A compound of Embodiment C wherein

R¹ and R³ are Cl.

Embodiment E. A compound of Embodiment C wherein

R¹ and R³ are Br.

Embodiment F. A compound of Embodiment B wherein

R¹ and R³ are Cl; and

R² is F.

Embodiment G. A compound of Embodiment B wherein

R¹, R² and R³ are Cl.

Embodiment H. A compound of Embodiment C wherein

R¹ is CF₃; and

R³ is H.

5 Embodiment I. A compound of Embodiment C wherein

R¹ and R³ are CF₃.

Embodiment K. A compound of Formula 1 or Embodiment 1 wherein

R⁴ is H; and

R⁵ is C₁–C₆ alkyl substituted with one substituent independently selected from C₁–C₆ alkylthio, C₁–C₆ alkylsulfinyl, C₁–C₆ alkylsulfonyl, C₂–C₇ alkylaminocarbonyl and C₂–C₇ haloalkylaminocarbonyl.

Embodiment L. A compound Embodiment K wherein

R¹ is Cl, Br or CF₃;

R² is H; and

15 R³ is H, F, Cl, Br or CF₃.

Embodiment M. A compound Embodiment L wherein

R¹ is CF₃.

Embodiment N. A compound Embodiment M wherein

R³ is Cl, Br or CF₃.

20 Embodiment O. A compound Embodiment N wherein

R⁵ is C₁–C₆ alkyl substituted with one C₂–C₇ alkylaminocarbonyl or C₃–C₇ haloalkylaminocarbonyl.

Specific embodiments include compounds of Formula 1 selected from the group consisting of:

4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-(2-hydroxyethyl)-1-naphthalenecarboxamide,

4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-(2-methoxyethyl)-1-naphthalenecarboxamide,

4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,

4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[1,1-dimethyl-2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,

4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,

4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-[(2-methylpropyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,

4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-(ethylmethylamino)-2-oxoethyl]-1-naphthalenecarboxamide,

4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-

(ethylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
N-[2-[(2-chloroethyl)amino]-2-oxoethyl]-4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-1-naphthalenecarboxamide,
4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-[(2-fluoroethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-oxo-2-[(2,2,3,3,3-pentafluoropropyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[4,5-dihydro-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(methylthio)ethyl]-1-naphthalenecarboxamide,
4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(methylthio)ethyl]-1-naphthalenecarboxamide,
4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(methylsulfinyl)ethyl]-1-naphthalenecarboxamide,
4-[4,5-dihydro-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(methylsulfonyl)ethyl]-1-naphthalenecarboxamide,
4-[5-(3,5-dibromophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(methylthio)ethyl]-1-naphthalenecarboxamide,
4-[5-(3,5-dibromophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[(1*R*)-1-methyl-2-(methylthio)ethyl]-1-naphthalenecarboxamide,
4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[1-methyl-3-(methylthio)propyl]-1-naphthalenecarboxamide,
4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[3-(methylthio)propyl]-1-naphthalenecarboxamide,
4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-[(1,1-dimethylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-[(1-ethylpropyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[1,1-dimethyl-2-(methylthio)ethyl]-1-naphthalenecarboxamide,
4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[(1*R*)-1-methyl-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[4,5-dihydro-5-(trifluoromethyl)-5-[3-(trifluoromethyl)phenyl]-3-isoxazolyl]-*N*-[2-(methylthio)ethyl]-1-naphthalenecarboxamide,

4-[4,5-dihydro-5-(trifluoromethyl)-5-[3-(trifluoromethyl)phenyl]-3-isoxazolyl]-*N*-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[4,5-dihydro-5-(trifluoromethyl)-5-[3-(trifluoromethyl)phenyl]-3-isoxazolyl]-*N*-2-(hydroxypropyl)-1-naphthalenecarboxamide,
4-[(5*S*)-5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*[(1*R*)-1-methyl-2-(methylthio)ethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[4,5-dihydro-5-(trifluoromethyl)-5-[3-(trifluoromethyl)phenyl]-3-isoxazolyl]-*N*-[2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,
4-[4,5-dihydro-5-(trifluoromethyl)-5-[3-(trifluoromethyl)phenyl]-3-isoxazolyl]-*N*-[2-(methylsulfonyl)ethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,
4-[4,5-dihydro-5-(trifluoromethyl)-5-[3-(trifluoromethyl)phenyl]-3-isoxazolyl]-*N*-(3-hydroxypropyl)-1-naphthalenecarboxamide, and
4-[(5*S*)-5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide.

Further specific embodiments include compounds of Formula 1 selected from the group consisting of:

4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(methylsulfonyl)ethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(methylsulfonyl)ethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(methylsulfonyl)ethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(methylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(ethylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(methylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(ethylamino)-2-oxoethyl]-1-naphthalenecarboxamide,

4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(methylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(ethylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[1-methyl-2-(methylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(ethylamino)-1-methyl-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[1-methyl-2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[1-methyl-2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[1-methyl-2-(methylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(ethylamino)-1-methyl-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[1-methyl-2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[1-methyl-2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[1-methyl-2-(methylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(ethylamino)-1-methyl-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[1-methyl-2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide, and

4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[1-methyl-2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide.

Of note is that compounds of this invention are characterized by favorable metabolic and/or soil residual patterns and exhibit activity controlling a spectrum of agronomic and nonagronomic invertebrate pests.

Of particular note, for reasons of invertebrate pest control spectrum and economic importance, protection of agronomic crops from damage or injury caused by invertebrate pests by controlling invertebrate pests are embodiments of the invention. Compounds of this invention, because of their favorable translocation properties or systemicity in plants, also protect foliar or other plant parts which are not directly contacted with a compound of Formula 1 or a composition comprising the compound.

Also noteworthy as embodiments of the present invention are compositions comprising a compound of any of the preceding Embodiments, as well as any other embodiments described herein, and any combinations thereof, and at least one additional component selected from the group consisting of a surfactant, a solid diluent and a liquid diluent, said compositions optionally further comprising at least one additional biologically active compound or agent.

Further noteworthy as embodiments of the present invention are compositions for controlling an invertebrate pest comprising a compound of any of the preceding Embodiments (i.e. in a biologically effective amount), as well as any other embodiments described herein, and any combinations thereof, and at least one additional component selected from the group consisting of a surfactant, a solid diluent and a liquid diluent, said compositions optionally further comprising at least one additional biologically active compound or agent.

Further Embodiments of the present invention include:

Embodiment A1. A composition for protecting an animal from an invertebrate

parasitic pest comprising a compound of Formula 1 and at least one veterinarianly acceptable carrier, said composition optionally further comprising at least one additional parasitically active compound.

Embodiment A2. The composition of Embodiment A1 wherein at least one additional parasitically active compound is an anthelmintic.

Embodiment A3. The composition of Embodiment A1 wherein at least one additional parasitically active compound is selected from the group consisting of macrocyclic lactones, benzimidazoles, salicylamides, substituted phenols, pyrimidines, cyclic depsipeptides, piperazine salts, nitroscanate, praziquantel and imidazothiazoles.

Embodiment A4. The composition of Embodiment A3 wherein at least one additional parasitically active compound is selected from the group consisting of avermectins, milbemycins and spinosyns.

Embodiment A5. The composition of Embodiment A1 wherein at least one additional 5 parasitically active compound is selected from the group consisting of abamectin, doramectin, emamectin, eprinomectin, ivermectin, selamectin, milbemycin, moxidectin and pyrantel.

Embodiment A6. The composition of Embodiment A1 in a form for oral administration.

10 Embodiment A7. The composition of Embodiment A1 in a form for topical administration.

Embodiment A8. The composition of Embodiment A1 in a form for parenteral administration.

15 Embodiments of the invention further include methods for controlling an invertebrate pest comprising contacting the invertebrate pest or its environment with a biologically effective amount of a compound of any of the preceding Embodiments (e.g., as a composition described herein). Of particular note is a method for protecting an animal comprising administering to the animal a parasitically effective amount of a compound of any of the preceding Embodiments (e.g., as a composition described herein).

20 Further Embodiments of the present invention include:

Embodiment B1. The method for protecting an animal from an invertebrate parasitic pest comprising administering to the animal a parasitically effective amount of a compound of Formula 1 as described in the Summary of the Invention.

25 Embodiment B2. The method of Embodiment B1 provided that when the animal is a mouse, the invertebrate parasitic pest is a flea, and the parasitically effective amount of the compound of Formula 1 is administered orally, then the compound of Formula 1 is other than 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide.

30 Embodiment B3. The method of Embodiment B1 wherein the parasitically effective amount of the compound of Formula 1 is administered orally.

Embodiment B4. The method of Embodiment B1 wherein the parasitically effective amount of the compound of Formula 1 is administered parenterally.

35 Embodiment B5. The method of Embodiment B1 wherein the parasitically effective amount of the compound of Formula 1 is administered by injection.

Embodiment B6. The method of Embodiment B1 wherein the parasitically effective amount of the compound of Formula 1 is administered topically.

Embodiment B7. The method of Embodiment B1 wherein the animal to be protected is a vertebrate.

Embodiment B8. The method of Embodiment B7 wherein the animal to be protected is a mammal, avian or fish.

Embodiment B9. The method of Embodiment B8 wherein the animal to be protected is a human.

5 Embodiment B10. The method of Embodiment B8 wherein the animal to be protected is livestock.

Embodiment B11. The method of Embodiment B8 wherein the animal to be protected is a canine.

10 Embodiment B11a. The method of Embodiment B8 wherein the animal to be protected is a dog.

Embodiment B12. The method of Embodiment B8 wherein the animal to be protected is a feline.

Embodiment B12a. The method of Embodiment B8 wherein the animal to be protected is a cat.

15 Embodiment B13. The method of Embodiment B1 wherein the invertebrate parasitic pest is an ectoparasite.

Embodiment B14. The method of Embodiment B1 wherein the invertebrate parasitic pest is an endoparasite or helminth.

20 Embodiment B15. The method of Embodiment B1 wherein the invertebrate parasitic pest is an arthropod.

Embodiment B16. The method of Embodiment B1 wherein the invertebrate parasitic pest is a fly, mosquito, mite, tick, louse, flea, maggot, bed bug or kissing bug.

Embodiment B17. The method of Embodiment B16 wherein the invertebrate parasitic pest is a mosquito.

25 Embodiment B18. The method of Embodiment B16 wherein the invertebrate parasitic pest is a tick or mite.

Embodiment B19. The method of Embodiment B16 wherein the invertebrate parasitic pest is a louse.

30 Embodiment B20. The method of Embodiment B16 wherein the invertebrate parasitic pest is a flea.

Embodiment B21. The method of Embodiment B16 wherein the invertebrate parasitic pest is a bed bug or kissing bug.

Embodiment B22. The method of Embodiment B16 wherein the animal is a cat or dog and the invertebrate parasitic pest is a flea, tick or mite.

35 Embodiment B23. The method of Embodiment B1 wherein the parasitically effective amount of a compound of Formula 1 is administered monthly or at a longer interval.

Embodiment B24. The method of Embodiment B23 wherein the parasitically effective amount of a compound of Formula 1 is administered once a month.

Embodiment B25. The method of Embodiment B23 wherein the parasitically effective amount of a compound of Formula 1 is administered once every six months.

The compounds of Formula 1 or any of Embodiments 1–45 or Embodiments A–O can
5 be used for the protection of an animal from an invertebrate parasitic pest by oral, topical or parenteral administration of the compound.

Therefore, the invention is understood to include the compounds of Formula 1 or any of Embodiments 1–45 or Embodiments A–O (and compositions containing them) for use as an animal medicament, or more particularly a parasiticidal animal medicament. The animals
10 to be protected are as defined in any of Embodiments B7–B12a. The invertebrate parasitic pests are as defined in any of Embodiments B13–B21. The medicament may be in oral, topical or parenteral dosage forms.

The invention is also understood to include the use of compounds of Formula 1 or any of Embodiments 1–45 or Embodiments A–O in the manufacture of medicaments for the
15 protection of an animal from a an invertebrate parasitic pest. The animals to be protected are as defined in any of Embodiments B7–B12a. The invertebrate parasitic pests are as defined in any of Embodiments B13–B21. The medicament may be in oral, topical or parenteral dosage forms.

The invention is also understood to include compounds of Formula 1 or any of Embodiments 1–45 or Embodiments A–O for use in the manufacture of medicaments for the
20 protection of an animal from an invertebrate parasitic pest. The animals to be protected are as defined in any of Embodiments B7–B12a. The invertebrate parasitic pests are as defined in any of Embodiments B13–B21. The medicament may be in oral, topical or parenteral dosage forms.

The invention is also understood to include compounds of Formula 1 or any of Embodiments 1–45 or Embodiments A–O packaged and presented for the protection of an animal from an invertebrate parasitic pest. The animals to be protected are as defined in any of Embodiments B7–B12a. The invertebrate parasitic pests are as defined in any of Embodiments B13–B21. The compounds of the invention may be packaged and presented
30 as oral, topical or parenteral dosage forms.

The invention is also understood to include a process for manufacturing a composition for protecting an animal from an invertebrate parasitic pest characterized in that a compound of Claim 1 is admixed with at least one pharmaceutically or veterinarilly acceptable carrier. The animals to be protected are as defined in any of Embodiments B7–B12a. The invertebrate parasitic pests are as defined in any of Embodiments B13–B21. The compositions of the invention may be packaged and presented as oral, topical or parenteral dosage forms.
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Embodiments of the invention also include a method for protecting a seed from an invertebrate pest comprising contacting the seed with a biologically effective amount of a compound of any of the preceding Embodiments (e.g., as a composition described herein).

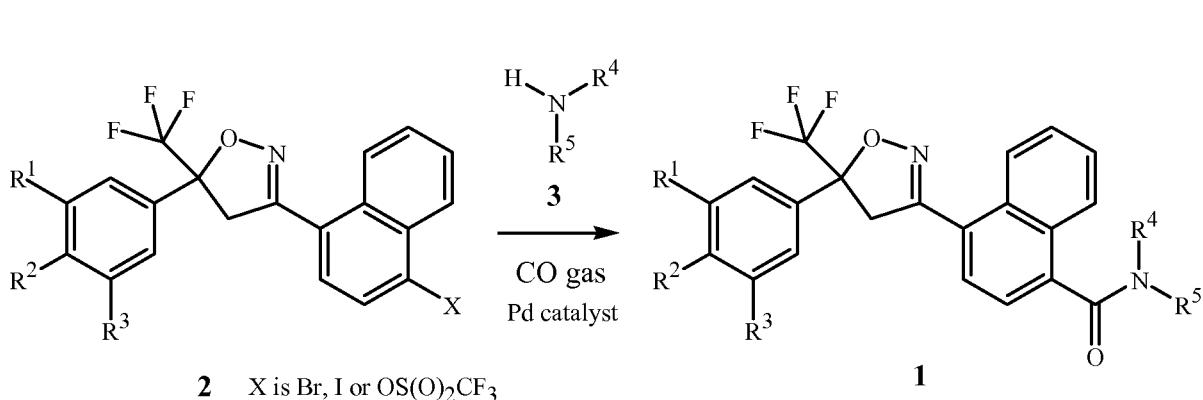
Embodiments of the invention also include a composition comprising a compound of any of the preceding Embodiments, in the form of a soil drench liquid formulation. Embodiments of the invention further include methods for controlling an invertebrate pest comprising contacting the soil with a liquid composition as a soil drench comprising a biologically effective amount of a compound of any of the preceding Embodiments.

Embodiments of the invention also include a spray composition for controlling an invertebrate pest comprising a compound of any of the preceding Embodiments (i.e. in a biologically effective amount) and a propellant. Embodiments of the invention further include a bait composition for controlling an invertebrate pest comprising a compound of any of the preceding Embodiments (i.e. in a biologically effective amount), one or more food materials, optionally an attractant, and optionally a humectant. Embodiments of the invention also include a device for controlling an invertebrate pest comprising said bait composition and a housing adapted to receive said bait composition, wherein the housing has at least one opening sized to permit the invertebrate pest to pass through the opening so the invertebrate pest can gain access to said bait composition from a location outside the housing, and wherein the housing is further adapted to be placed in or near a locus of potential or known activity for the invertebrate pest.

One or more of the following methods and variations as described in Schemes 1–10 can be used to prepare the compounds of Formula 1. The definitions of R¹, R², R³, R⁴ and R⁵ in the compounds of Formulae 1–15 below are as defined above in the Summary of the Invention unless otherwise noted.

Compounds of Formula 1 can be prepared by aminocarbonylation of aryl bromides, iodides or triflates of Formula 2 wherein X is Br, I or OS(O)₂CF₃, with appropriately substituted amino compounds of Formula 3 as shown in Scheme 1.

Scheme 1



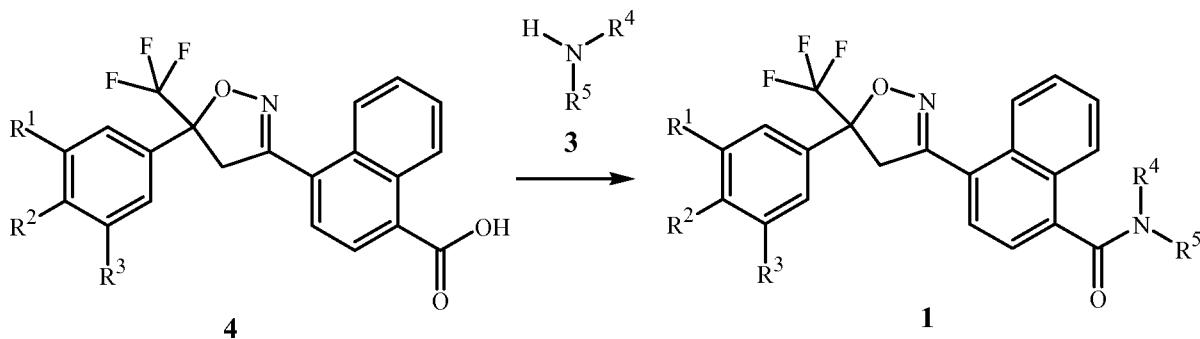
This reaction is typically carried out with an aryl bromide of Formula **2** wherein X is Br in the presence of a palladium catalyst under a CO atmosphere. The palladium catalysts used for the present method typically comprises palladium in a formal oxidation state of either 0 (i.e. Pd(0)) or 2 (i.e. Pd(II)). A wide variety of such palladium-containing compounds and complexes are useful as catalysts for the present method. Examples of palladium-containing compounds and complexes useful as catalysts in the method of Scheme 1 include $\text{PdCl}_2(\text{PPh}_3)_2$ (bis(triphenylphosphine)palladium(II) dichloride), $\text{Pd}(\text{PPh}_3)_4$ (tetrakis(triphenylphosphine)palladium(0)), $\text{Pd}(\text{C}_5\text{H}_7\text{O}_2)_2$ (palladium(II) acetyl-acetonate), $\text{Pd}_2(\text{dba})_3$ (tris(dibenzylideneacetone)dipalladium(0)), and $\text{PdCl}_2(\text{dpdpf})$ [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II). The method of Scheme 1 is generally conducted in a liquid phase, and therefore to be most effective the palladium catalyst preferably has good solubility in the liquid phase. Useful solvents include, for example, ethers such as 1,2-dimethoxyethane, amides such as *N,N*-dimethylacetamide, and non-halogenated aromatic hydrocarbons such as toluene.

The method of Scheme 1 can be conducted over a wide range of temperatures, ranging from about 25 to about 150 °C. Of note are temperatures from about 60 to about 110 °C, which typically provide fast reaction rates and high product yields. The general methods and procedures for aminocarbonylation with an aryl bromide and an amine are well known in the literature; see, for example, H. Horino et al., *Synthesis* **1989**, 715; and J. J. Li, G. W. Gribble, editors, *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*, **2000**.

Compounds of Formula **1** can also be prepared by coupling carboxylic acids of Formula **4** with appropriately substituted amino compounds of Formula **3** as shown in Scheme 2.

Scheme 2

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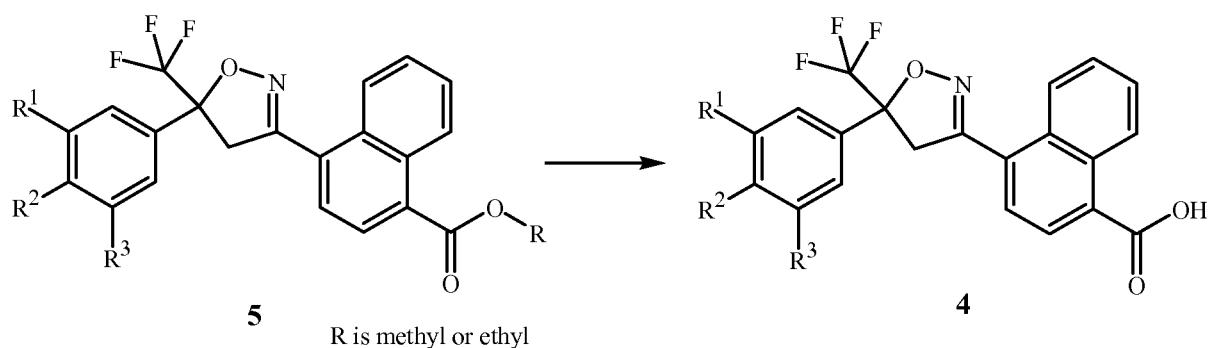


This reaction is generally carried out in the presence of a dehydrating coupling reagent such as dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, 1-propanephosphonic acid cyclic anhydride or carbonyl diimidazole in the presence of a base such as triethylamine, pyridine, 4-(dimethylamino)pyridine or *N,N*-diisopropylethylamine in an anhydrous aprotic solvent such as dichloromethane or tetrahydrofuran at a temperature typically between 25 and 70 °C.

Compounds of Formula **1** wherein R⁵ is C₁–C₆ alkyl or C₁–C₆ haloalkyl substituted with C₂–C₇ alkylaminocarbonyl, C₃–C₉ dialkylaminocarbonyl, C₂–C₇ haloalkylaminocarbonyl or C₃–C₉ halodialkylaminocarbonyl can also be prepared in a stepwise manner by the following method. Coupling of the compounds of Formula **2** or the carboxylic acids of Formula **4** with amino esters by the general methods described for Schemes 1 and 2 yields ester intermediates. These ester intermediates are hydrolyzed to the corresponding carboxylic acids, which are then coupled with the appropriate amines to form the abovementioned compounds of Formula **1**. For example, see Synthesis Example 4 (Steps C, D and E), Synthesis Example 5 (Steps B, C and D) and Synthesis Example 6.

Compounds of Formula **4** can be prepared by hydrolysis of esters of Formula **5**, wherein R is methyl or ethyl, as shown in Scheme 3.

Scheme 3

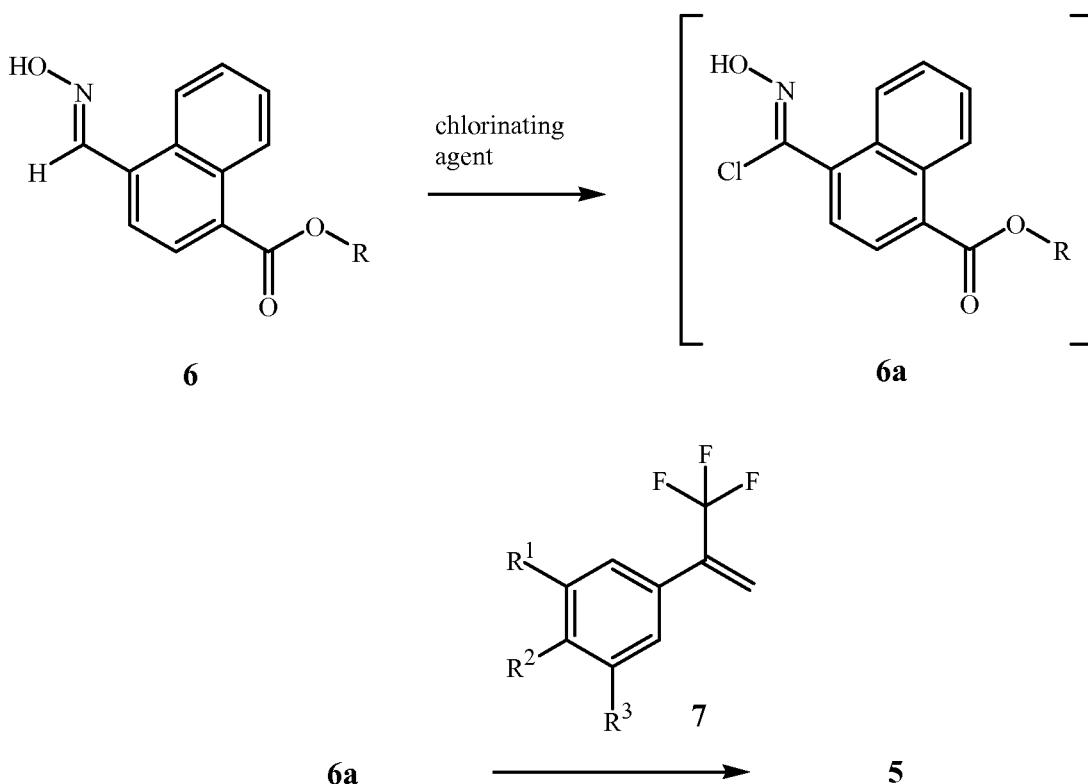


15

20

In the method of Scheme 3, the ester of Formula **5** is converted to the corresponding carboxylic acid of Formula **4** by general procedures well known in the art. For example, treatment of a methyl or ethyl ester of Formula **5** with aqueous lithium hydroxide in tetrahydrofuran, followed by acidification yields the corresponding carboxylic acid of Formula **4**.

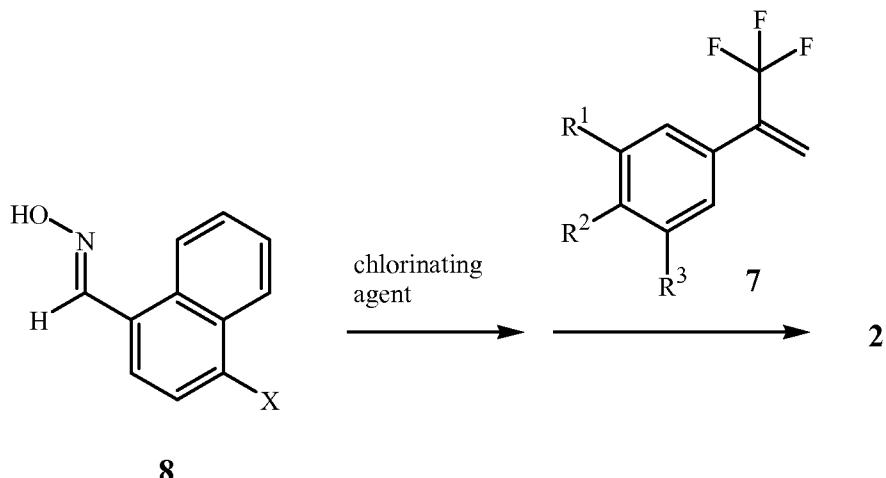
Esters of Formula **5** can be prepared from compounds of Formula **2** by a method analogous to the method of Scheme 1 wherein an alcohol such as methanol or ethanol is substituted for the amine. Alternatively, compounds of Formula **5** can be prepared by the reaction of styrenes of Formula **7** with oximes of Formula **6** as shown in Scheme 4.

Scheme 4

The method of Scheme 4 typically involves the chlorination of oximes of Formula **6** to form the hydroximoyl chlorides of Formula **6a**. The intermediates of Formula **6a** are dehydrochlorinated under basic conditions to form nitrile oxides, which then undergo 1,3-dipolar cycloaddition with styrenes of Formula **7** to afford compounds of Formula **5**. In a typical procedure, a chlorinating reagent such as sodium hypochlorite, *N*-chlorosuccinimide, or chloramine-T is combined with the oxime in the presence of the styrene. Depending on the reaction conditions, amine bases such as pyridine or triethylamine may be necessary to facilitate the dehydrochlorination reaction. The reaction can be run in a wide variety of solvents including tetrahydrofuran, diethyl ether, methylene chloride, dioxane, and toluene with temperatures ranging from room temperature to the reflux temperature of the solvent. General procedures for cycloaddition of nitrile oxides with olefins are well documented in the chemical literature; for example, see Lee, *Synthesis*, **1982**, *6*, 508-509; Kanemasa et al., *Tetrahedron*, **2000**, *56*, 1057-1064; EP 1,538,138-A1, as well as references cited within.

Compounds of Formula **2** can be prepared by the 1,3-dipolar cycloaddition of styrenes of Formula **7** with nitrile oxides derived from oximes of Formula **8** as shown in Scheme 5.

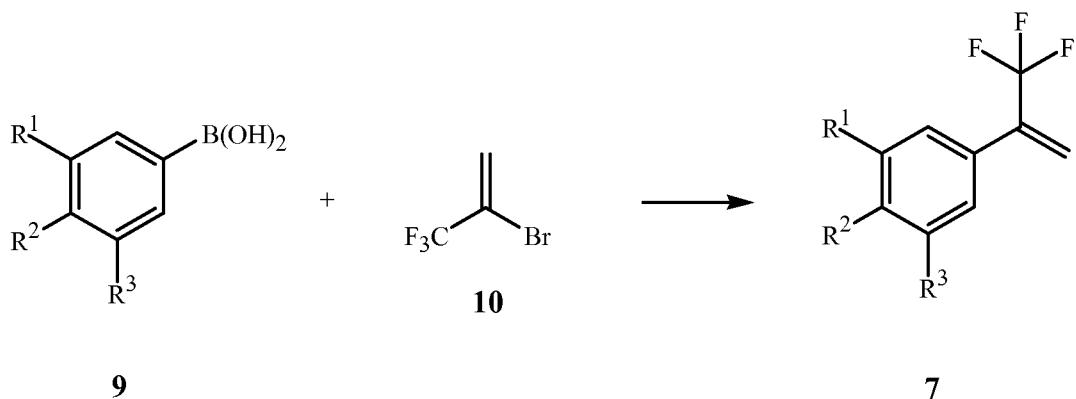
Scheme 5



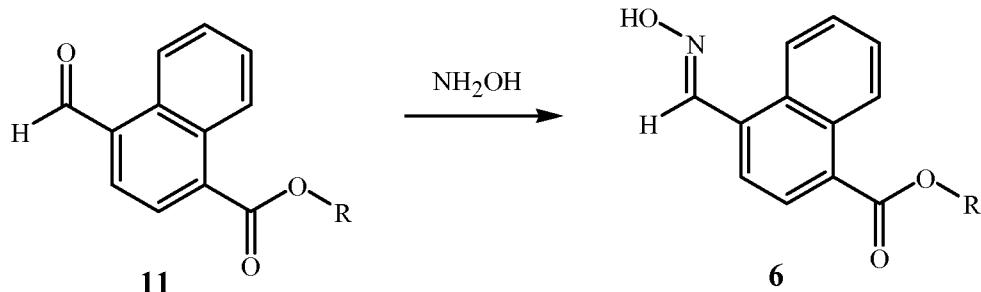
In the method of Scheme 5, the compounds of Formula 2, wherein X is as defined previously, are generated by contacting the compound of Formula 8 with a chlorinating reagent followed by the addition of a styrene of Formula 7. The method of Scheme 5 is conducted analogously to the method of Scheme 4 previously described.

The styrenes of Formula 7 can be prepared by the palladium-catalyzed coupling of aryl boronic acids of Formula 9 with the commercially available 2-bromo-3,3,3-trifluoropropene (Formula 10). General procedures for this method as shown in Scheme 6 are documented in the chemical literature; see Pan et al., *J. Fluorine Chemistry*, **1999**, *95*, 167-170. Other methods for preparing styrenes of Formula 7 are well known in the art.

Scheme 6

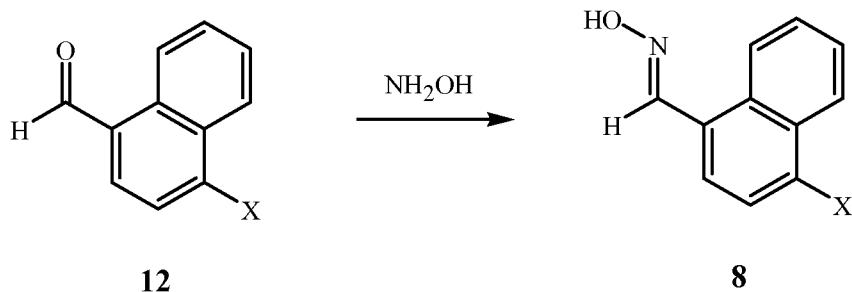


15 The oximes of Formula 6 can be prepared by the reaction of aldehydes of Formula 11, wherein R is as defined previously, with hydroxylamine as shown in Scheme 7. For example, see, H. K. Jung et al. *Bioorg. Med. Chem.* **2004**, *12*, 3965. The aldehydes of Formula 11 can be prepared by a wide variety of methods known in the art; some of the aldehydes are known compounds.

Scheme 7

As shown in Scheme 8, the oximes of Formula **8**, wherein X is as defined previously,

5 can be prepared from the corresponding aldehydes of Formula **12** analogous to the method of Scheme 7.

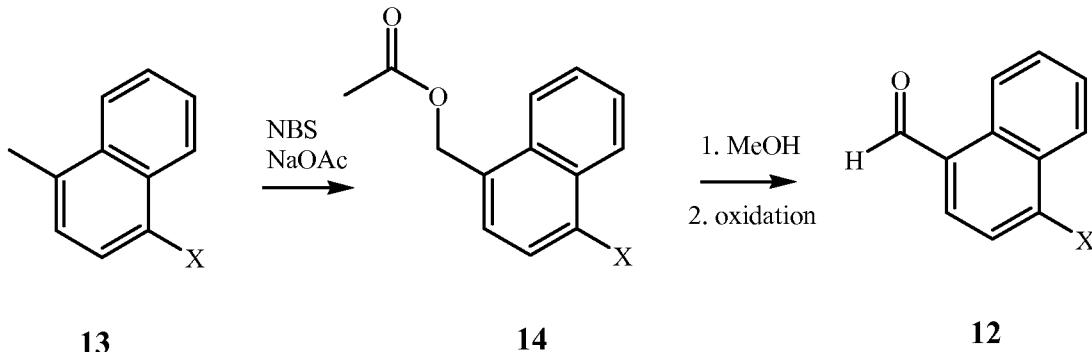
Scheme 8

10

12**8**

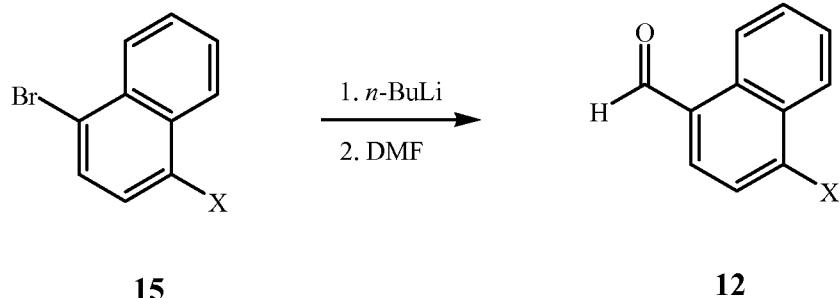
Compounds of Formula **12** are commercially available or known compounds, or they can be prepared by a wide variety of methods known in the art. For example, compounds of Formula **12** can be prepared by direct formylation of the corresponding aryl halides; see G. E. Boswell et al. *J. Org. Chem.* **1995**, *65*, 6592; or by reduction of the corresponding aryl esters, see references P. R. Bernstein et al. *Bioorg. Med. Chem. Lett.* **2001**, 2769 and L. W. 15 Deady et al. *Aust. J. Chem.* **1989**, *42*, 1029.

Scheme 9 illustrates the preparation of intermediate acetates of Formula **14** from the corresponding methyl-substituted compounds of Formula **13** (wherein X is as defined previously) by reaction with *N*-bromosuccinimide (NBS) in the presence of 2,2'-azobis(2-methylpropionitrile) (AIBN) and sodium acetate. The intermediate acetates of Formula **14** are then converted to the aldehydes of Formula **12** by ester hydrolysis and oxidation.

Scheme 9

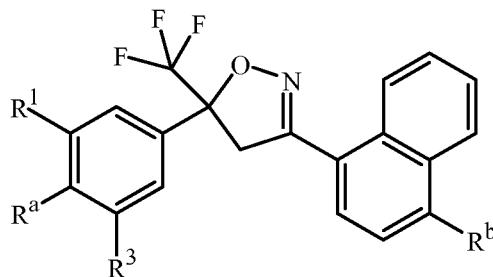
The compounds of Formula **13** are commercially available or known compounds, or
5 they can be prepared by a wide variety of methods known in the art.

An alternative method for preparing aldehydes of Formula **12** (wherein X is as defined previously) is shown in Scheme 10. The formyl group of Formula **12** can be introduced onto the naphthalene ring system by metallation of the bromide of Formula **15** followed by reaction of the lithium intermediate with *N,N*-dimethylformamide (DMF). For references to
10 this general method, see *Synthesis*, **2006**, 293 and *Bioorg. Med. Chem.* **2004**, *12*, 715.

Scheme 10

15 Examples of intermediates useful in the preparation of compounds of this invention are shown in Tables I-1 through I-6. The following abbreviations are used in the Tables which follow: Me means methyl, Et means ethyl, *t*-Bu means $-\text{C}(\text{CH}_3)_3$, S(O) means sulfinyl, S(O)₂ means sulfonyl, Ph means phenyl, C(O) means carbonyl and CHO means formyl.

TABLE I-1

R¹ is Cl, R^a is H, R³ is Cl

<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>
CO ₂ H	CO ₂ Me	CO ₂ Et	CO ₂ t-Bu	CO ₂ CH ₂ Ph	Br	I	
OH	OMe	OS(O) ₂ CF ₃	nitro	NH ₂	cyano		Me
CH ₂ Cl	CH ₂ Br	CH ₂ OH	CH ₂ OC(O)Me	CHO	C(O)CH ₃		

5

R¹ is Cl, R^a is F and R³ is Cl

<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>
CO ₂ H	CO ₂ Me	CO ₂ Et	CO ₂ t-Bu	CO ₂ CH ₂ Ph	Br	I	
OH	OMe	OS(O) ₂ CF ₃	nitro	NH ₂	cyano		Me
CH ₂ Cl	CH ₂ Br	CH ₂ OH	CH ₂ OC(O)Me	CHO	C(O)CH ₃		

R¹ is Cl, R^a is Cl and R³ is Cl

<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>
CO ₂ H	CO ₂ Me	CO ₂ Et	CO ₂ t-Bu	CO ₂ CH ₂ Ph	Br	I	
OH	OMe	OS(O) ₂ CF ₃	nitro	NH ₂	cyano		Me
CH ₂ Cl	CH ₂ Br	CH ₂ OH	CH ₂ OC(O)Me	CHO	C(O)CH ₃		

10

R¹ is Br, R^a is H and R³ is Br

<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>
CO ₂ H	CO ₂ Me	CO ₂ Et	CO ₂ t-Bu	CO ₂ CH ₂ Ph	Br	I	
OH	OMe	OS(O) ₂ CF ₃	nitro	NH ₂	cyano		Me
CH ₂ Cl	CH ₂ Br	CH ₂ OH	CH ₂ OC(O)Me	CHO	C(O)CH ₃		

R¹ is CF₃, R^a is H and R³ is F

<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>
CO ₂ H	CO ₂ Me	CO ₂ Et	CO ₂ t-Bu	CO ₂ CH ₂ Ph	Br	I	
OH	OMe	OS(O) ₂ CF ₃	nitro	NH ₂	cyano		Me
CH ₂ Cl	CH ₂ Br	CH ₂ OH	CH ₂ OC(O)Me	CHO	C(O)CH ₃		

R¹ is CF₃, R^a is H and R³ is Cl

<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>
CO ₂ H	CO ₂ Me	CO ₂ Et	CO ₂ <i>t</i> -Bu	CO ₂ CH ₂ Ph	Br		I
OH	OMe	OS(O) ₂ CF ₃	nitro	NH ₂	cyano		Me
CH ₂ Cl	CH ₂ Br	CH ₂ OH	CH ₂ OC(O)Me	CHO	C(O)CH ₃		

R¹ is CF₃, R^a is H and R³ is Br

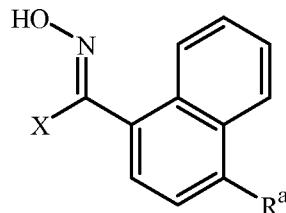
<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>
CO ₂ H	CO ₂ Me	CO ₂ Et	CO ₂ <i>t</i> -Bu	CO ₂ CH ₂ Ph	Br		I
OH	OMe	OS(O) ₂ CF ₃	nitro	NH ₂	cyano		Me
CH ₂ Cl	CH ₂ Br	CH ₂ OH	CH ₂ OC(O)Me	CHO	C(O)CH ₃		

5

R¹ is CF₃, R^a is H and R³ is CF₃

<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>	<u>R^b</u>
CO ₂ H	CO ₂ Me	CO ₂ Et	CO ₂ <i>t</i> -Bu	CO ₂ CH ₂ Ph	Br		I
OH	OMe	OS(O) ₂ CF ₃	nitro	NH ₂	cyano		Me
CH ₂ Cl	CH ₂ Br	CH ₂ OH	CH ₂ OC(O)Me	CHO	C(O)CH ₃		

TABLE I-2

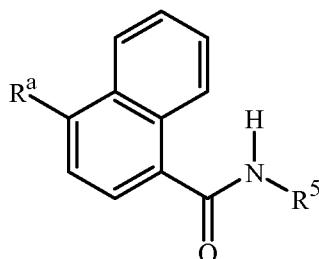


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<u>X</u>	<u>R^a</u>	<u>X</u>	<u>R^a</u>	<u>X</u>	<u>R^a</u>
H	CO ₂ Me	Cl	CO ₂ Me	Br	CO ₂ Me
H	CO ₂ Et	Cl	CO ₂ Et	Br	CO ₂ Et
H	CO ₂ <i>t</i> -Bu	Cl	CO ₂ <i>t</i> -Bu	Br	CO ₂ <i>t</i> -Bu
H	CO ₂ CH ₂ Ph	Cl	CO ₂ CH ₂ Ph	Br	CO ₂ CH ₂ Ph
H	CH ₂ OC(O)Me	Cl	CH ₂ OC(O)Me	Br	CH ₂ OC(O)Me
H	Br	Cl	Br	Br	Br
H	I	Cl	I	Br	I
H	OH	Cl	OH	Br	OH
H	OMe	Cl	OMe	Br	OMe
H	OS(O) ₂ CF ₃	Cl	OS(O) ₂ CF ₃	Br	OS(O) ₂ CF ₃
H	nitro	Cl	nitro	Br	nitro

<u>X</u>	<u>R^a</u>	<u>X</u>	<u>R^a</u>	<u>X</u>	<u>R^a</u>
H	NH ₂	Cl	NH ₂	Br	NH ₂
H	cyano	Cl	cyano	Br	cyano
H	Me	Cl	Me	Br	Me
H	CH ₂ Cl	Cl	CH ₂ Cl	Br	CH ₂ Cl
H	CH ₂ Br	Cl	CH ₂ Br	Br	CH ₂ Br
H	CH ₂ OH	Cl	CH ₂ OH	Br	CH ₂ OH
H	OCH ₂ Ph	Cl	OCH ₂ Ph	Br	OCH ₂ Ph
H	C(O)Me	Cl	C(O)Me	Br	C(O)Me
H	C(O)Et	Cl	C(O)Et	Br	C(O)Et

TABLE I-3

R^a is CHO

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃

CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R^a is CH=NOH

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl

CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R^a is C(Cl)=NOH

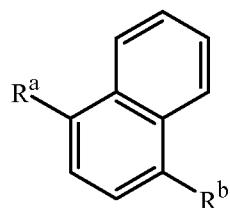
<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃

CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R^a is C(Br)=NOH

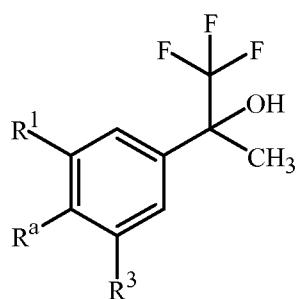
<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl

$\text{CH}(\text{Me})\text{CH}_2\text{CH}_2\text{SMe}$	$\text{CH}_2\text{C}(\text{O})\text{NH}(\text{Et})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NHCH}_2\text{CHF}_2$
$\text{CH}_2\text{CH}(\text{Me})\text{CH}_2\text{SMe}$	$\text{CH}_2\text{C}(\text{O})\text{NH}(n\text{-Pr})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NHCH}_2\text{CF}_3$
$\text{CH}_2\text{C}(\text{Me})_2\text{CH}_2\text{SMe}$	$\text{CH}_2\text{C}(\text{O})\text{NH}(i\text{-Pr})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NHCH}_2\text{CH}_2\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{Me}$	$\text{CH}_2\text{C}(\text{O})\text{NH}(i\text{-Bu})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NHCH}(\text{Me})\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{Et}$	$\text{CH}_2\text{C}(\text{O})\text{NH}(s\text{-Bu})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NHCH}_2\text{CH}(\text{Me})\text{CF}_3$

TABLE I-4

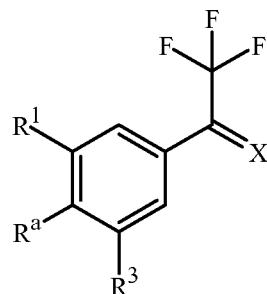
5

<u>R^a</u>	<u>R^b</u>	<u>R^a</u>	<u>R^b</u>	<u>R^a</u>	<u>R^b</u>	<u>R^a</u>	<u>R^b</u>
Me	H	CH_2Cl	CO_2H	CO_2H	CO_2H	CH_2OH	CO_2Me
Me	$\text{C}(\text{O})\text{Me}$	CH_2Cl	CO_2Me	CO_2H	CO_2Me	CH_2OH	CO_2Et
Me	$\text{C}(\text{O})\text{Et}$	CH_2Cl	CO_2Et	CO_2H	CO_2Et	CHO	CO_2Me
Me	CO_2H	CH_2Br	CO_2H	$\text{C}(\text{O})\text{Cl}$	CO_2Me	CHO	CO_2Et
Me	CO_2Me	CH_2Br	CO_2Me	$\text{C}(\text{O})\text{Cl}$	CO_2Et		
Me	CO_2Et	CH_2Br	CO_2Et				

TABLE I-5

10

<u>R¹</u>	<u>R^a</u>	<u>R³</u>	<u>R¹</u>	<u>R^a</u>	<u>R³</u>	<u>R¹</u>	<u>R^a</u>	<u>R³</u>
Cl	H	Cl	CF ₃	H	Br	Br	N(CH ₂ Ph) ₂	Br
Cl	Cl	Cl	CF ₃	H	CF ₃	CF ₃	N(CH ₂ Ph) ₂	Cl
Cl	F	Cl	Cl	NH ₂	Cl	CF ₃	N(CH ₂ Ph) ₂	Br
Br	H	Br	Br	NH ₂	Br	Cl	NHC(O)Me	Cl
CF ₃	H	H	CF ₃	NH ₂	Cl	Br	NHC(O)Me	Br
CF ₃	H	F	CF ₃	NH ₂	Br	CF ₃	NHC(O)Me	Cl
CF ₃	H	Cl	Cl	N(CH ₂ Ph) ₂	Cl	CF ₃	NHC(O)Me	Br

TABLE I-6

5

			<u>X is CH₂</u>						<u>X is O</u>		
<u>R¹</u>	<u>R^a</u>	<u>R³</u>	<u>R¹</u>	<u>R^a</u>	<u>R³</u>	<u>R¹</u>	<u>R^a</u>	<u>R³</u>	<u>R¹</u>	<u>R^a</u>	<u>R³</u>
Cl	H	Cl	Cl	N(CH ₂ Ph) ₂	Cl	Cl	H	Cl	Cl	N(CH ₂ Ph) ₂	Cl
Br	H	Br	Br	N(CH ₂ Ph) ₂	Br	Br	H	Br	Br	N(CH ₂ Ph) ₂	Br
CF ₃	H	H	CF ₃	N(CH ₂ Ph) ₂	H	CF ₃	H	H	CF ₃	N(CH ₂ Ph) ₂	H
CF ₃	H	F	CF ₃	N(CH ₂ Ph) ₂	F	CF ₃	H	F	CF ₃	N(CH ₂ Ph) ₂	F
CF ₃	H	Cl	CF ₃	N(CH ₂ Ph) ₂	Cl	CF ₃	H	Cl	CF ₃	N(CH ₂ Ph) ₂	Cl
CF ₃	H	Br	CF ₃	N(CH ₂ Ph) ₂	Br	CF ₃	H	Br	CF ₃	N(CH ₂ Ph) ₂	Br
CF ₃	H	CF ₃	CF ₃	N(CH ₂ Ph) ₂	CF ₃	CF ₃	H	CF ₃	CF ₃	N(CH ₂ Ph) ₂	CF ₃
Cl	NH ₂	Cl	Cl	NHC(O)Me	Cl	Cl	NH ₂	Cl	Cl	NHC(O)Me	Cl
Br	NH ₂	Br	Br	NHC(O)Me	Br	Br	NH ₂	Br	Br	NHC(O)Me	Br
CF ₃	NH ₂	H	CF ₃	NHC(O)Me	H	CF ₃	NH ₂	H	CF ₃	NHC(O)Me	H
CF ₃	NH ₂	F	CF ₃	NHC(O)Me	F	CF ₃	NH ₂	F	CF ₃	NHC(O)Me	F
CF ₃	NH ₂	Cl	CF ₃	NHC(O)Me	Cl	CF ₃	NH ₂	Cl	CF ₃	NHC(O)Me	Cl
CF ₃	NH ₂	Br	CF ₃	NHC(O)Me	Br	CF ₃	NH ₂	Br	CF ₃	NHC(O)Me	Br
CF ₃	NH ₂	CF ₃	CF ₃	NHC(O)Me	CF ₃	CF ₃	NH ₂	CF ₃	CF ₃	NHC(O)Me	CF ₃
Cl	Cl	Cl	Cl	F	Cl	Cl	Cl	Cl	Cl	F	Cl

It is recognized that some reagents and reaction conditions described above for preparing compounds of Formula 1 may not be compatible with certain functionalities present in the intermediates. In these instances, the incorporation of protection/deprotection sequences or functional group interconversions into the synthesis will aid in obtaining the desired products. The use and choice of the protecting groups will be apparent to one skilled in chemical synthesis (see, for example, Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991). One skilled in the art will recognize that, in some cases, after the introduction of a given reagent as it is depicted in any individual scheme, it may be necessary to perform additional routine synthetic steps not described in detail to complete the synthesis of compounds of Formula 1. One skilled in the art will also recognize that it may be necessary to perform a combination of the steps illustrated in the above schemes in an order other than that implied by the particular sequence presented to prepare the compounds of Formula 1.

One skilled in the art will also recognize that compounds of Formula 1 and the intermediates described herein can be subjected to various electrophilic, nucleophilic, radical, organometallic, oxidation, and reduction reactions to add substituents or modify existing substituents.

Without further elaboration, it is believed that one skilled in the art using the preceding description can utilize the present invention to its fullest extent. The following Synthesis Examples are, therefore, to be construed as merely illustrative, and not limiting of the disclosure in any way whatsoever. Steps in the following Synthesis Examples illustrate a procedure for each step in an overall synthetic transformation, and the starting material for each step may not have necessarily been prepared by a particular preparative run whose procedure is described in other Examples or Steps. Percentages are by weight except for chromatographic solvent mixtures or where otherwise indicated. Parts and percentages for chromatographic solvent mixtures are by volume unless otherwise indicated. ¹H NMR spectra are reported in ppm downfield from tetramethylsilane; "s" means singlet, "d" means doublet, "t" means triplet, "q" means quartet, "m" means multiplet, "dd" means doublet of doublets, "dt" means doublet of triplets, "br s" means broad singlet, and "br t" means broad triplet.

SYNTHESIS EXAMPLE 1

Preparation of 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-(methylthio)ethyl]-1-naphthalenecarboxamide

35 Step A: Preparation of methyl 4-[(hydroxyimino)methyl]-1-naphthalenecarboxylate

A solution of hydroxylamine (1.33 mL, 50% in water) was added to a stirred solution of methyl 4-formyl-1-naphthalenecarboxylate (2.2 g, prepared as described in *Journal of Medicinal Chemistry* **2002**, 45(26), 5755-5775) in methanol (50 mL). After stirring at

room temperature for 2 h, the reaction mixture was concentrated under reduced pressure to provide the title compound as a pale yellow solid (2.55 g). ^1H NMR (CDCl_3): δ 8.93 (d, 1H), 8.86 (s, 1H), 8.41 (d, 1H), 8.14 (d, 1H), 7.82 (d, 1H), 7.63 (m, 2H), 4.02 (s, 3H).

5 Step B: Preparation of methyl 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-1-naphthalenecarboxylate

N-Chlorosuccinimide (1.16 g, 8.72 mmol) was added to a stirred solution of methyl 4-[(hydroxyimino)methyl]-1-naphthalenecarboxylate (i.e. the product of Step A, 1.0 g, 4.36 mmol) in *N,N*-dimethylformamide (5.0 mL). This mixture was stirred for 1.5 h at room temperature, and then a solution of 1,3-dichloro-5-[1-(trifluoromethyl)ethenyl]benzene (3.20 g, 13.1 mmol, prepared from commercially available 2-bromo-3,3,3-trifluoropropene by the method described in *J. Fluorine Chem.* **1999**, 95, 167-170) and triethylamine (6.1 mL, 43.6 mmol) in *N,N*-dimethylformamide (4.0 mL) was added. After stirring for an additional 2 h at room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluted with ethyl acetate/hexanes to afford the title compound as a pale yellow oil (700 mg). ^1H NMR (CDCl_3): δ 8.88 (d, 1H), 8.80 (d, 1H), 8.10 (d, 1H), 7.68 (m, 2H), 7.55 (m, 3H), 7.46 (dd, 1H), 4.27 (d, 1H), 4.03 (s, 3H), 3.91 (d, 1H).

20 Step C: Preparation of 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-1-naphthalenecarboxylic acid

A solution of lithium hydroxide monohydrate (350 mg, 8.34 mmol) in water (10 mL) was added to a stirred solution of methyl 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-1-naphthalenecarboxylate (i.e. the product of Step B, 650 mg, 1.39 mmol) in tetrahydrofuran (10 mL), followed by the addition of methanol (10 mL). The resulting mixture was stirred overnight at room temperature and then partitioned between water and diethyl ether. The aqueous layer was acidified with 6 *N* aqueous hydrochloric acid to pH 2 and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure to provide the title compound as a white solid (450 mg). ^1H NMR (CDCl_3): δ 9.08 (d, 1H), 8.80 (d, 1H), 8.31 (d, 1H), 7.71 (m, 2H), 7.57 (m, 3H), 7.46 (dd, 1H), 4.28 (d, 1H), 3.91 (d, 1H).

35 Step D: Preparation of 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(methylthio)ethyl]-1-naphthalenecarboxamide

Oxalyl chloride (0.24 mL) was added to a stirred suspension of 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-1-naphthalenecarboxylic acid

(i.e. the product of Step C, 620 mg) in dichloromethane (20 mL), followed by the addition of two drops of *N,N*-dimethylformamide. The reaction mixture was stirred at room temperature for 1.5 h and then concentrated under vacuum. The residue was dissolved in dichloromethane (10 mL) and added to a stirred solution of 2-(methylthio)ethylamine (0.13 5 mL) and triethylamine (0.38 mL) in dichloromethane (10 mL). The resulting reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with water and extracted with dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with ethyl acetate/hexanes to 10 provide the title compound (510 mg), a compound of this invention, as a white solid. ¹H NMR (CDCl₃): δ 8.78 (d, 1H), 8.27 (d, 1H), 7.56–7.64 (m, 4H), 7.49 (d, 1H), 7.46 (dd, 1H), 7.40 (d, 1H), 6.57 (br t, 1H), 4.23 (d, 1H), 3.88 (d, 1H), 3.71 (q, 2H), 2.79 (t, 2H), 2.15 (s, 3H).

SYNTHESIS EXAMPLE 2

15 Preparation of 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-(methylsulfinyl)ethyl]-1-naphthalenecarboxamide

m-Chloroperoxybenzoic acid (47 mg, 70% purity) was added at -78 °C to a stirred solution of 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-(methylthio)ethyl]-1-naphthalenecarboxamide (i.e. the product of Example 1, Step D, 20 100 mg) in dichloromethane (10 mL). The reaction mixture was stirred at -78 to -70 °C for 2.5 h, then quenched with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic extract was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure to provide the title compound (102 mg), a compound of 25 this invention, as a white solid. ¹H NMR (CDCl₃): δ 8.78 (d, 1H), 8.29 (d, 1H), 7.42–7.64 (m, 7H), 7.37 (br t, 1H), 4.23 (d, 1H), 4.00 (q, 2H), 3.88 (d, 1H), 3.18 (dt, 1H), 2.89 (dt, 1H), 2.62 (s, 3H).

SYNTHESIS EXAMPLE 3

Preparation of 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-(methylsulfonyl)ethyl]-1-naphthalenecarboxamide

30 H₂O₂ (0.056 mL, 30% in H₂O) was added to a stirred solution of 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-(methylsulfinyl)ethyl]-1-naphthalenecarboxamide (i.e. the product of Example 2, 100 mg) in acetic acid (1.0 mL). The reaction mixture was stirred at 60 °C for 4 h, then cooled to room temperature, diluted with water, adjusted to pH 4 with 1.0 M aqueous NaOH solution, and extracted with chloroform. The organic extract was washed with brine, dried over sodium sulfate, and 35 concentrated under reduced pressure to provide the title compound (100 mg), a compound of this invention, as a white solid. ¹H NMR (CDCl₃): δ 8.80 (d, 1H), 8.29 (d, 1H), 7.43–7.66 (m, 7H), 6.94 (br t, 1H), 4.24 (d, 1H), 4.04 (q, 2H), 3.40 (t, 2H), 3.01 (s, 3H).

SYNTHESIS EXAMPLE 4

Preparation of 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide

5 Step A: Preparation of 4-bromo-1-naphthalenecarboxaldehyde oxime

An aqueous solution of hydroxylamine (1.25 mL, 50% in water) was added to a stirred solution of 4-bromo-1-naphthalenecarboxaldehyde (3.7 g, 15.7 mmol, prepared from commercially available 1,4-dibromonaphthalene by the method described in *European Journal of Organic Chemistry* **2006**, *10*, 2329-2335) in ethanol (30 mL). After stirring at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure to provide the title compound as a pale yellow solid (3.8 g). ¹H NMR ($\text{Me}_2\text{S}(\text{O})\text{-d}_6$): δ 11.60 (s, 1H), 8.81 (s, 1H), 8.71 (d, 1H), 8.24 (d, 1H), 7.95 (d, 1H), 7.74 (m, 3H).

10 Step B: Preparation of 3-(4-bromo-1-naphthalenyl)-5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)isoxazole

15 *N*-Chlorosuccinimide (1.70 g, 12.7 mmol) was added to a solution of 4-bromo-1-naphthalenecarboxaldehyde oxime (i.e. the product of Step A, 2.33 g, 9.3 mmol) in *N,N*-dimethylformamide (6.0 mL). The reaction mixture was stirred for 1 h at room temperature, and then a solution of 1,3-dichloro-5-[1-(trifluoromethyl)ethenyl]benzene (2.70 g, 11.2 mmol, prepared from commercially available 2-bromo-3,3,3-trifluoropropene by the method described in *J. Fluorine Chem.* **1999**, *95*, 167-170) and triethylamine (4.5 mL, 32.0 mmol) in *N,N*-dimethylformamide (9.0 mL) was added. After stirring for an additional 2 h at room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluted with ethyl acetate/hexanes to afford the title compound as a white solid (2.9 g). ¹H NMR (CDCl_3): δ 8.87 (m, 1H), 8.32 (m, 1H), 7.77 (d, 1H), 7.66 (m, 2H), 7.55 (s, 2H), 7.46 (dd, 1H), 7.32 (d, 1H), 4.24 (d, 1H), 3.88 (d, 3H).

20 Step C: Preparation of *N*-[[4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-1-naphthalenyl]carbonyl]glycine methyl ester

25 A mixture of 3-(4-bromo-1-naphthalenyl)-5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)isoxazole (i.e. the product of Step B, 500 mg), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (82 mg), glycine methyl ester hydrochloride (514 mg) and triethylamine (2.8 mL) in toluene (10 mL) was purged with carbon monoxide for 15 minutes. The reaction mixture was stirred at 70 °C under a carbon monoxide atmosphere overnight. The mixture was then cooled to room temperature, filtered through a short pad of Celite® diatomaceous filter aid, and rinsed with a small amount of ethyl acetate. The filtrate

was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel eluted with ethyl acetate/hexanes to provide the title compound as a white solid (310 mg). ^1H NMR (CDCl_3): δ 8.75 (d, 1H), 8.28 (d, 1H), 7.45–7.60 (m, 6H), 7.36 (d, 1H), 6.78 (br t, 1H), 4.26 (d, 2H), 4.21 (d, 1H), 3.87 (d, 1H), 3.80 (s, 3H).

5

Step D: Preparation of *N*-[[4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-1-naphthalenyl]carbonyl]glycine

An aqueous solution of LiOH (300 mg, in 5 mL of H_2O) was added to a stirred solution of *N*-[[4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-1-naphthalenyl]carbonyl]glycine methyl ester (i.e. the product of Step C, 620 mg) in tetrahydrofuran (5 mL). After stirring at room temperature for 1 h, the reaction mixture was diluted with water and extracted with hexane. The aqueous layer was acidified with 6.0 *N* HCl to pH 2, and a white precipitate formed. The aqueous mixture was extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure to provide the title compound (600 mg) as a white solid. ^1H NMR ($\text{Me}_2\text{S}(\text{O})-\text{d}_6$): δ 9.02 (t, 1H), 8.81 (d, 1H), 8.37 (d, 1H), 7.92 (d, 1H), 7.83 (t, 1H), 7.65–7.74 (m, 5H), 4.58 (d, 1H), 4.54 (d, 1H), 4.02 (d, 2H).

Step E: Preparation of 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide

PS-Carbodiimide (0.53 g, 123 mmol/g, Argonaut Technologies, Inc.) was added to a stirred mixture of *N*-[[4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-1-naphthalenyl]carbonyl]glycine (i.e. the product of Step D, 510 mg) and 2,2,2-trifluoroethylamine (0.072 mL) in dichloromethane (3 mL) at room temperature. The mixture was stirred at room temperature for 5 h, then filtered and concentrated under reduced pressure. The residue was purified by column chromatography to provide the title compound (99 mg), a compound of this invention, as a white solid. ^1H NMR (CDCl_3): δ 8.82 (d, 1H), 8.26 (d, 1H), 7.46–7.67 (m, 7H), 7.09 (m, 2H), 4.28 (d, 2H), 4.25 (d, 1H), 3.96 (m, 2H), 3.88 (d, 1H).

SYNTHESIS EXAMPLE 5

Preparation of 4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide

35 Step A: Preparation of 5-[3,5-bis(trifluoromethyl)phenyl]-3-(4-bromo-1-naphthalenyl)-4,5-dihydro-5-(trifluoromethyl)isoxazole

N-Chlorosuccinimide (2.05 g, 15.5 mmol) was added to a solution of 4-bromo-1-naphthalenecarboxaldehyde oxime (i.e. the product of Example 4, Step A, 3.20 g, 12.8

mmol) in *N,N*-dimethylformamide (20.0 mL). The reaction mixture was stirred for 1 h at room temperature, and then a solution of 1,3-bis(trifluoromethyl)-5-[1-(trifluoromethyl)ethenyl]benzene (5.13 g, 16.6 mmol, prepared according to the method described in *J. Org. Chem.* **1959**, *24*, 238-239) and triethylamine (5.4 mL, 38.4 mmol) in 5 *N,N*-dimethylformamide (10.0 mL) was added. After stirring for an additional 2 h at room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluted with ethyl acetate/hexanes to afford the title compound as a white solid (3.2 g). ¹H NMR 10 (CDCl₃): δ 8.89 (m, 1H), 8.35 (m, 1H), 8.13 (s, 2H), 7.99 (s, 1H), 7.81 (d, 1H), 7.69 (m, 2H), 7.37 (d, 1H), 4.38 (d, 1H), 3.94 (d, 3H).

Step B: Preparation of *N*-[[4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-1-naphthalenyl]carbonyl]glycine methyl ester

15 A mixture of 5-[3,5-bis(trifluoromethyl)phenyl]-3-(4-bromo-1-naphthalenyl)-4,5-dihydro-5-(trifluoromethyl)isoxazole (i.e. the product of Step A, 1.2 g), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (88 mg), glycine methyl ester hydrochloride (1.1 g) and triethylamine (6.0 mL) in toluene (20 mL) was purged with carbon monoxide for 15 minutes. The reaction mixture was stirred at 70 °C under a carbon monoxide atmosphere 20 overnight. The mixture was then cooled to room temperature, filtered through a short pad of Celite® diatomaceous filter aid, and rinsed with a small amount of ethyl acetate. The filtrate was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel eluted with ethyl acetate/hexanes to provide the title compound as a white solid (0.9 g). ¹H NMR (CDCl₃): δ 8.79 (d, 1H), 8.32 (d, 1H), 8.15 (s, 2H), 8.00 (s, 1H), 7.60 (m, 2H), 7.55 (d, 1H), 7.43 (d, 1H), 6.66 (br t, 1H), 4.36 (d, 1H), 4.29 (d, 2H), 3.94 (d, 1H), 3.82 (s, 3H).

Step C: Preparation of *N*-[[4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-1-naphthalenyl]carbonyl]glycine

30 An aqueous solution of LiOH (300 mg, in 10 mL of H₂O) was added to a stirred solution of *N*-[[4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-1-naphthalenyl]carbonyl]glycine methyl ester (i.e. the product of Step B, 850 mg) in tetrahydrofuran (10 mL). After stirring at room temperature for 1 h, the reaction mixture was diluted with water and extracted with hexane. The aqueous layer was acidified 35 with 6.0 N HCl to pH 2, and a white precipitate formed. The aqueous mixture was extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure to provide the title compound (800 mg) as a white solid. ¹H NMR (CDCl₃): δ 8.63 (d, 1H), 8.12 (d, 1H), 8.10 (s, 2H), 7.99 (s, 1H), 7.23–7.48 (m, 4H), 7.09 (br t, 1H), 4.20 (d, 1H), 4.19 (s, 2H), 3.83 (d, 1H).

Step D: Preparation of 4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide

5 PS-Carbodiimide (400 mg, 123 mmol/g, Argonaut Technologies, Inc.) was added to a stirred mixture of *N*-[[4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-1-naphthalenyl]carbonyl]glycine (i.e. the product of Step C, 140 mg) and 2,2,2-trifluoroethylamine (0.038 mL) in dichloromethane (3 mL) at room temperature. The mixture was stirred at room temperature overnight, then filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with ethyl acetate/hexanes to provide the title compound (115 mg), a compound of this invention, as a white solid. ¹H NMR (CDCl₃): δ 8.77 (d, 1H), 8.16 (d, 1H), 8.13 (s, 2H), 8.01 (s, 1H), 7.51–7.60 (m, 3H), 7.46 (t, 1H), 7.42 (d, 1H), 7.33 (d, 1H), 4.31 (d, 1H), 4.23 (d, 2H), 3.83–3.92 (m, 3H).

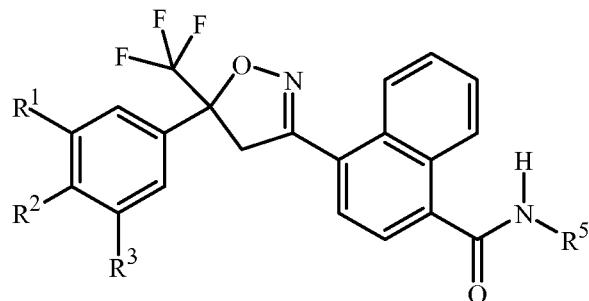
15 SYNTHESES EXAMPLE 6

Preparation of 4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide

Trimethylacetyl chloride (0.078 mL) was added to a stirred mixture of *N*-[[4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-1-naphthalenyl]carbonyl]glycine (i.e. the product of Example 5, Step C, 307 mg) and pyridine (0.052 mL) in dichloromethane (6 mL) at room temperature. The mixture was stirred at room temperature for 2 h, and then isopropylamine (0.29 mL) and triethylamine (1.8 mL) were added. After stirring at room temperature for an additional 1 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with ethyl acetate/hexanes to provide the title compound (235 mg), a compound of this invention, as a white solid. ¹H NMR (CD₃C(O)CD₃): δ 8.92 (d, 1H), 8.49 (d, 1H), 8.38 (s, 2H), 8.26 (s, 1H), 7.88 (d, 1H), 7.84 (br t, 1H), 7.75 (d, 1H), 7.64–7.72 (m, 2H), 7.15 (br s, 1H), 4.74 (d, 1H), 4.65 (d, 1H), 4.09 (d, 2H), 1.15 (d, 6H).

30 By the procedures described herein together with methods known in the art, the following compounds of Tables 1 to 5 can be prepared. The following abbreviations are used in the Tables which follow: Me means methyl, Et means ethyl, *i*-Pr means CH(CH₃)₂, *i*-Bu means CH₂CH(CH₃)₂, *s*-Bu means CH(CH₃)CH₂CH₃, *t*-Bu means C(CH₃)₃, CN means cyano, S(O) means sulfinyl, S(O)₂ means sulfonyl, and C(O) means carbonyl (e.g., C(O)Me means methylcarbonyl). Amides represented as RC(O)NHR' or RC(O)NR'R'' are as defined previously in the Summary of the Invention.

TABLE 1



R¹ is Cl, R² is H and R³ is Cl

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NH(Me)
CH ₂ CH ₂ OMe	CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NH(Et)
CH ₂ CH ₂ OEt	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ CH ₂ SO ₂ (<i>i</i> -Pr)	CH ₂ C(O)NH(<i>i</i> -Pr)
CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>t</i> -Bu)	CH ₂ C(O)NH(<i>n</i> -Bu)
CH ₂ CH(CF ₃)OH	CH ₂ CH ₂ SO ₂ (<i>t</i> -Bu)	CH ₂ C(O)NH(<i>i</i> -Bu)
CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NH(<i>s</i> -Bu)
CH ₂ C(CF ₃)(Me)OH	CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NH(<i>t</i> -Bu)
CH(Me)CH ₂ OH	CH ₂ C(Me) ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ (<i>t</i> -Bu)
C(Me) ₂ CH ₂ OH	CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NMe ₂
CH(Et)CH ₂ OH	C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NMe(Et)
CH(<i>i</i> -Pr)CH ₂ OH	CH(Et)CH ₂ SO ₂ Me	CH ₂ C(O)NEt ₂
CH(<i>t</i> -Bu)CH ₂ OH	CH(<i>i</i> -Pr)CH ₂ SO ₂ Me	CH ₂ C(O)NMe(<i>n</i> -Pr)
CH(Me)CH(CF ₃)OH	CH(<i>t</i> -Bu)CH ₂ SO ₂ Me	CH ₂ C(O)NMe(<i>i</i> -Pr)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NMe(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ CH ₂ OEt	CH ₂ CH ₂ CH ₂ SO ₂ (<i>i</i> -Bu)	CH(Me)C(O)NH(Et)
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH ₂ CH ₂ SO ₂ (<i>t</i> -Bu)	CH(Me)C(O)NH(<i>n</i> -Pr)
CH(Me)CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)NH(<i>i</i> -Pr)
C(Me) ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Bu)
CH(<i>i</i> -Pr)CH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH(Me)CH ₂ OH	CH(Et)CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>t</i> -Bu)
CH ₂ CH ₂ CH(Me)OH	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH(Me)(O)NHCH ₂ (<i>t</i> -Bu)
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ C(O)NHCH ₂ CH ₂ F	C(Me) ₂ C(O)NH(Me)
CH ₂ CH ₂ SMe	CH ₂ C(O)NHCH ₂ CH ₂ Cl	C(Me) ₂ C(O)NH(Et)
CH ₂ CH ₂ SEt	CH ₂ C(O)NHCH ₂ CHF ₂	C(Me) ₂ C(O)NH(<i>n</i> -Pr)
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃	C(Me) ₂ C(O)NH(<i>i</i> -Pr)

CH ₂ CH ₂ S(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH(Me)F	C(Me) ₂ C(O)NH(<i>n</i> -Bu)
CH ₂ CH ₂ S(<i>i</i> -Bu)	CH ₂ C(O)NHCH ₂ C(Me) ₂ F	C(Me) ₂ C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ S(<i>t</i> -Bu)	CH ₂ C(O)NH(CH ₂) ₂ CH ₂ F	C(Me) ₂ C(O)NH(<i>s</i> -Bu)
CH ₂ CH(Me)SMe	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃	C(Me) ₂ C(O)NH(<i>t</i> -Bu)
CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NHCH ₂ CHFCF ₃	C(Me) ₂ C(O)NHCH ₂ (<i>t</i> -Bu)
CH ₂ C(Me) ₂ SMe	CH ₂ C(O)NHCH ₂ CF ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ F
CH(Me)CH ₂ SMe	CH ₂ C(O)NHCH(Me)CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NHCH(CF ₃) ₂	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH(Et)CH ₂ SMe	CH ₂ C(O)NHC(Me) ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(<i>i</i> -Pr)CH ₂ SMe	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ CH ₂ F
CH(<i>i</i> -Bu)CH ₂ SMe	CH ₂ C(O)NH(CH ₂) ₂ CF ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NHCH ₂ (CF ₂) ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CF ₂ CF ₃
CH ₂ CH ₂ CH ₂ SET	CH ₂ C(O)NHCH(<i>i</i> -Pr)CF ₃	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ CH ₂ S(<i>i</i> -Bu)	CH(Me)C(O)NHCH ₂ CH ₂ F	CH ₂ C(O)N(Me)CH(CF ₃) ₂
CH ₂ CH ₂ CH ₂ S(<i>t</i> -Bu)	CH(Me)C(O)NHCH ₂ CH ₂ Cl	CH ₂ C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH(Me)C(O)NHCH ₂ CHF ₂	CH(Me)C(O)N(Me)CH ₂ CH ₂ F
CH ₂ CH ₂ CH(CF ₃)SMe	CH(Me)C(O)NHCH ₂ CF ₃	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ CH(Me)F	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH(Et)CH ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ C(Me) ₂ F	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ SMe	CH(Me)C(O)NH(CH ₂) ₂ CH ₂ F	CH(Me)C(O)N(Me)(CH ₂) ₂ CH ₂ F
CH ₂ C(Me) ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NHCH ₂ CHFCF ₃	CH(Me)C(O)N(Me)CH ₂ CF ₂ CF ₃
CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NHCH ₂ CF ₂ CF ₃	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃	CH(Me)C(O)N(Me)CH(CF ₃) ₂
CH ₂ CH ₂ S(O)(<i>i</i> -Pr)	CH(Me)C(O)NHCH(CF ₃) ₂	CH(Me)C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ S(O)(<i>t</i> -Bu)	CH(Me)C(O)NHC(Me) ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ F
CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NHCH ₂ (CF ₂) ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NHCH(CF ₃) ₂	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ F	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
C(Me) ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ Cl	C(Me) ₂ C(O)N(Me)CH ₂ CF ₂ CF ₃
CH(Et)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CHF ₂	C(Me) ₂ C(O)N(Me)CH(Me)CF ₃
CH(<i>i</i> -Pr)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH(CF ₃) ₂
CH(<i>i</i> -Bu)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH(Me)F	C(Me) ₂ C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ C(Me) ₂ F	C(Me) ₂ C(O)NHCH(CF ₃) ₂
CH ₂ CH ₂ CH ₂ S(O)Et	C(Me) ₂ C(O)NH(CH ₂) ₂ CH ₂ F	C(Me) ₂ C(O)NHCH(CF ₃) ₂
CH ₂ CH ₂ CH ₂ S(O)(<i>i</i> -Bu)	C(Me) ₂ C(O)NHCH ₂ CH ₂ CF ₃	C(Me) ₂ C(O)NHC(Me) ₂ CF ₃

<chem>CH2CH2CH2S(O)(i-Bu)</chem>	<chem>C(Me)2C(O)NHCH2CHFCF3</chem>	<chem>C(Me)2C(O)NHCH2CH(Me)CF3</chem>
<chem>CH2CH2CH(Me)S(O)Me</chem>	<chem>C(Me)2C(O)NHCH2CF2CF3</chem>	<chem>C(Me)2C(O)NH(CH2)2CF2CF3</chem>
<chem>CH2CH2CH(CF3)S(O)Me</chem>	<chem>CH2CH(Me)CH2S(O)Me</chem>	<chem>C(Me)2C(O)NHCH2(CF2)2CF3</chem>
<chem>CH(Me)CH2CH2S(O)Me</chem>	<chem>CH2C(Me)2CH2S(O)Me</chem>	<chem>C(Me)2C(O)NHCH(i-Pr)CF3</chem>
<chem>CH(Et)CH2CH2S(O)Me</chem>		

R¹ is Cl, R² is F and R³ is Cl

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
<chem>CH2CH2OH</chem>	<chem>CH2CH2SO2Me</chem>	<chem>CH2C(O)NH(Me)</chem>
<chem>CH2CH2OMe</chem>	<chem>CH2CH2SO2Et</chem>	<chem>CH2C(O)NH(Et)</chem>
<chem>CH2CH2OEt</chem>	<chem>CH2CH2SO2(n-Pr)</chem>	<chem>CH2C(O)NH(n-Pr)</chem>
<chem>CH2CH2O(i-Pr)</chem>	<chem>CH2CH2SO2(i-Pr)</chem>	<chem>CH2C(O)NH(i-Pr)</chem>
<chem>CH2CH(Me)OH</chem>	<chem>CH2CH2SO2(i-Bu)</chem>	<chem>CH2C(O)NH(n-Bu)</chem>
<chem>CH2CH(CF3)OH</chem>	<chem>CH2CH2SO2(t-Bu)</chem>	<chem>CH2C(O)NH(i-Bu)</chem>
<chem>CH2C(Me)2OH</chem>	<chem>CH2CH(Me)SO2Me</chem>	<chem>CH2C(O)NH(s-Bu)</chem>
<chem>CH2C(CF3)(Me)OH</chem>	<chem>CH2CH(CF3)SO2Me</chem>	<chem>CH2C(O)NH(t-Bu)</chem>
<chem>CH(Me)CH2OH</chem>	<chem>CH2C(Me)2SO2Me</chem>	<chem>CH2C(O)NHCH2(t-Bu)</chem>
<chem>C(Me)2CH2OH</chem>	<chem>CH(Me)CH2SO2Me</chem>	<chem>CH2C(O)NMe2</chem>
<chem>CH(Et)CH2OH</chem>	<chem>C(Me)2CH2SO2Me</chem>	<chem>CH2C(O)NMe(Et)</chem>
<chem>CH(i-Pr)CH2OH</chem>	<chem>CH(Et)CH2SO2Me</chem>	<chem>CH2C(O)NEt2</chem>
<chem>CH(i-Bu)CH2OH</chem>	<chem>CH(i-Pr)CH2SO2Me</chem>	<chem>CH2C(O)NMe(n-Pr)</chem>
<chem>CH(Me)CH(CF3)OH</chem>	<chem>CH(i-Bu)CH2SO2Me</chem>	<chem>CH2C(O)NMe(i-Pr)</chem>
<chem>CH2CH2CH2OH</chem>	<chem>CH2CH2CH2SO2Me</chem>	<chem>CH2C(O)NMe(s-Bu)</chem>
<chem>CH2CH2CH2OMe</chem>	<chem>CH2CH2CH2SO2Et</chem>	<chem>CH(Me)C(O)NH(Me)</chem>
<chem>CH2CH2CH2OEt</chem>	<chem>CH2CH2CH2SO2(i-Bu)</chem>	<chem>CH(Me)C(O)NH(Et)</chem>
<chem>CH2CH2CH(CF3)OH</chem>	<chem>CH2CH2CH2SO2(t-Bu)</chem>	<chem>CH(Me)C(O)NH(n-Pr)</chem>
<chem>CH(Me)CH2CH2OH</chem>	<chem>CH2CH2CH(Me)SO2Me</chem>	<chem>CH(Me)C(O)NH(i-Pr)</chem>
<chem>C(Me)2CH2CH2OH</chem>	<chem>CH2CH2CH(CF3)SO2Me</chem>	<chem>CH(Me)C(O)NH(n-Bu)</chem>
<chem>CH(i-Pr)CH2CH2OH</chem>	<chem>CH(Me)CH2CH2SO2Me</chem>	<chem>CH(Me)C(O)NH(i-Bu)</chem>
<chem>CH2CH(Me)CH2OH</chem>	<chem>CH(Et)CH2CH2SO2Me</chem>	<chem>CH(Me)C(O)NH(s-Bu)</chem>
<chem>CH2C(Me)2CH2OH</chem>	<chem>CH2CH(Me)CH2SO2Me</chem>	<chem>CH(Me)C(O)NH(t-Bu)</chem>
<chem>CH2CH2CH(Me)OH</chem>	<chem>CH2C(Me)2CH2SO2Me</chem>	<chem>CH(Me)(O)NHCH2(t-Bu)</chem>
<chem>CH2CH2C(Me)2OH</chem>	<chem>CH2C(O)NHCH2CH2F</chem>	<chem>C(Me)2C(O)NH(Me)</chem>
<chem>CH2CH2SMe</chem>	<chem>CH2C(O)NHCH2CH2Cl</chem>	<chem>C(Me)2C(O)NH(Et)</chem>
<chem>CH2CH2SEt</chem>	<chem>CH2C(O)NHCH2CHF2</chem>	<chem>C(Me)2C(O)NH(n-Pr)</chem>
<chem>CH2CH2S(n-Pr)</chem>	<chem>CH2C(O)NHCH2CF3</chem>	<chem>C(Me)2C(O)NH(i-Pr)</chem>
<chem>CH2CH2S(i-Pr)</chem>	<chem>CH2C(O)NHCH2CH(Me)F</chem>	<chem>C(Me)2C(O)NH(n-Bu)</chem>
<chem>CH2CH2S(i-Bu)</chem>	<chem>CH2C(O)NHCH2C(Me)2F</chem>	<chem>C(Me)2C(O)NH(i-Bu)</chem>

CH ₂ CH ₂ S(<i>t</i> -Bu)	CH ₂ C(O)NH(CH ₂) ₂ CH ₂ F	C(Me) ₂ C(O)NH(<i>s</i> -Bu)
CH ₂ CH(Me)SMe	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃	C(Me) ₂ C(O)NH(<i>t</i> -Bu)
CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NHCH ₂ CHFCF ₃	C(Me) ₂ C(O)NHCH ₂ (<i>t</i> -Bu)
CH ₂ C(Me) ₂ SMe	CH ₂ C(O)NHCH ₂ CF ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ F
CH(Me)CH ₂ SMe	CH ₂ C(O)NHCH(Me)CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NHCH(CF ₃) ₂	CH ₂ C(O)N(Me)CH ₂ CH ₂ HF ₂
CH(Et)CH ₂ SMe	CH ₂ C(O)NHC(Me) ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(<i>i</i> -Pr)CH ₂ SMe	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ CH ₂ F
CH(<i>i</i> -Bu)CH ₂ SMe	CH ₂ C(O)NH(CH ₂) ₂ CF ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NHCH ₂ (CF ₂) ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CF ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NHCH(<i>i</i> -Pr)CF ₃	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ CH ₂ S(<i>i</i> -Bu)	CH(Me)C(O)NHCH ₂ CH ₂ F	CH ₂ C(O)N(Me)CH(CF ₃) ₂
CH ₂ CH ₂ CH ₂ S(<i>t</i> -Bu)	CH(Me)C(O)NHCH ₂ CH ₂ Cl	CH ₂ C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH(Me)C(O)NHCH ₂ CH ₂ HF ₂	CH(Me)C(O)N(Me)CH ₂ CH ₂ F
CH ₂ CH ₂ CH(CF ₃)SMe	CH(Me)C(O)NHCH ₂ CF ₃	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ CH(Me)F	CH(Me)C(O)N(Me)CH ₂ CH ₂ HF ₂
CH(Et)CH ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ C(Me) ₂ F	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ SMe	CH(Me)C(O)NH(CH ₂) ₂ CH ₂ F	CH(Me)C(O)N(Me)(CH ₂) ₂ CH ₂ F
CH ₂ C(Me) ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NHCH ₂ CHFCF ₃	CH(Me)C(O)N(Me)CH ₂ CF ₂ CF ₃
CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NHCH ₂ CF ₂ CF ₃	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃	CH(Me)C(O)N(Me)CH(CF ₃) ₂
CH ₂ CH ₂ S(O)(<i>i</i> -Pr)	CH(Me)C(O)NHCH(CF ₃) ₂	CH(Me)C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ S(O)(<i>i</i> -Bu)	CH(Me)C(O)NHC(Me) ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ F
CH ₂ CH ₂ S(O)(<i>t</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(CH ₂) ₂ CF ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ HF ₂
CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NHCH ₂ (CF ₂) ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NHCH(<i>i</i> -Pr)CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ CH ₂ F
CH(Me)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ F	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
C(Me) ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ Cl	C(Me) ₂ C(O)N(Me)CH ₂ CF ₂ CF ₃
CH(Et)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ HF ₂	C(Me) ₂ C(O)N(Me)CH(Me)CF ₃
CH(<i>i</i> -Pr)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH(CF ₃) ₂
CH(<i>i</i> -Bu)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH(Me)F	C(Me) ₂ C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ C(Me) ₂ F	C(Me) ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	C(Me) ₂ C(O)NH(CH ₂) ₂ CH ₂ F	C(Me) ₂ C(O)NHCH(CF ₃) ₂
CH ₂ CH ₂ CH ₂ S(O)(<i>i</i> -Bu)	C(Me) ₂ C(O)NHCH ₂ CH ₂ CF ₃	C(Me) ₂ C(O)NHC(Me) ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)(<i>t</i> -Bu)	C(Me) ₂ C(O)NHCH ₂ CHFCF ₃	C(Me) ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CF ₂ CF ₃	C(Me) ₂ C(O)NH(CH ₂) ₂ CF ₂ CF ₃

<chem>CH2CH2CH(CF3)S(O)Me</chem>	<chem>CH2CH(Me)CH2S(O)Me</chem>	<chem>C(Me)2C(O)NHCH2(CF2)2CF3</chem>
<chem>CH(Me)CH2CH2S(O)Me</chem>	<chem>CH2C(Me)2CH2S(O)Me</chem>	<chem>C(Me)2C(O)NHCH(i-Pr)CF3</chem>
<chem>CH(Et)CH2CH2S(O)Me</chem>		

R¹ is Br, R² is H and R³ is Br

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
<chem>CH2CH2OH</chem>	<chem>CH2CH2SO2Me</chem>	<chem>CH2C(O)NH(Me)</chem>
<chem>CH2CH2OMe</chem>	<chem>CH2CH2SO2Et</chem>	<chem>CH2C(O)NH(Et)</chem>
<chem>CH2CH2OEt</chem>	<chem>CH2CH2SO2(n-Pr)</chem>	<chem>CH2C(O)NH(n-Pr)</chem>
<chem>CH2CH2O(i-Pr)</chem>	<chem>CH2CH2SO2(i-Pr)</chem>	<chem>CH2C(O)NH(i-Pr)</chem>
<chem>CH2CH(Me)OH</chem>	<chem>CH2CH2SO2(i-Bu)</chem>	<chem>CH2C(O)NH(n-Bu)</chem>
<chem>CH2CH(CF3)OH</chem>	<chem>CH2CH2SO2(t-Bu)</chem>	<chem>CH2C(O)NH(i-Bu)</chem>
<chem>CH2C(Me)2OH</chem>	<chem>CH2CH(Me)SO2Me</chem>	<chem>CH2C(O)NH(s-Bu)</chem>
<chem>CH2C(CF3)(Me)OH</chem>	<chem>CH2CH(CF3)SO2Me</chem>	<chem>CH2C(O)NH(t-Bu)</chem>
<chem>CH(Me)CH2OH</chem>	<chem>CH2C(Me)2SO2Me</chem>	<chem>CH2C(O)NHCH2(t-Bu)</chem>
<chem>C(Me)2CH2OH</chem>	<chem>CH(Me)CH2SO2Me</chem>	<chem>CH2C(O)NMe2</chem>
<chem>CH(Et)CH2OH</chem>	<chem>C(Me)2CH2SO2Me</chem>	<chem>CH2C(O)NMe(Et)</chem>
<chem>CH(i-Pr)CH2OH</chem>	<chem>CH(Et)CH2SO2Me</chem>	<chem>CH2C(O)NEt2</chem>
<chem>CH(i-Bu)CH2OH</chem>	<chem>CH(i-Pr)CH2SO2Me</chem>	<chem>CH2C(O)NMe(n-Pr)</chem>
<chem>CH(Me)CH(CF3)OH</chem>	<chem>CH(i-Bu)CH2SO2Me</chem>	<chem>CH2C(O)NMe(i-Pr)</chem>
<chem>CH2CH2CH2OH</chem>	<chem>CH2CH2CH2SO2Me</chem>	<chem>CH2C(O)NMe(s-Bu)</chem>
<chem>CH2CH2CH2OMe</chem>	<chem>CH2CH2CH2SO2Et</chem>	<chem>CH(Me)C(O)NH(Me)</chem>
<chem>CH2CH2CH2OEt</chem>	<chem>CH2CH2CH2SO2(i-Bu)</chem>	<chem>CH(Me)C(O)NH(Et)</chem>
<chem>CH2CH2CH(CF3)OH</chem>	<chem>CH2CH2CH2SO2(t-Bu)</chem>	<chem>CH(Me)C(O)NH(n-Pr)</chem>
<chem>CH(Me)CH2CH2OH</chem>	<chem>CH2CH2CH(Me)SO2Me</chem>	<chem>CH(Me)C(O)NH(i-Pr)</chem>
<chem>C(Me)2CH2CH2OH</chem>	<chem>CH2CH2CH(CF3)SO2Me</chem>	<chem>CH(Me)C(O)NH(n-Bu)</chem>
<chem>CH(i-Pr)CH2CH2OH</chem>	<chem>CH(Me)CH2CH2SO2Me</chem>	<chem>CH(Me)C(O)NH(i-Bu)</chem>
<chem>CH2CH(Me)CH2OH</chem>	<chem>CH(Et)CH2CH2SO2Me</chem>	<chem>CH(Me)C(O)NH(s-Bu)</chem>
<chem>CH2C(Me)2CH2OH</chem>	<chem>CH2CH(Me)CH2SO2Me</chem>	<chem>CH(Me)C(O)NH(t-Bu)</chem>
<chem>CH2CH2CH(Me)OH</chem>	<chem>CH2C(Me)2CH2SO2Me</chem>	<chem>CH(Me)(O)NHCH2(t-Bu)</chem>
<chem>CH2CH2C(Me)2OH</chem>	<chem>CH2C(O)NHCH2CH2F</chem>	<chem>C(Me)2C(O)NH(Me)</chem>
<chem>CH2CH2SMe</chem>	<chem>CH2C(O)NHCH2CH2Cl</chem>	<chem>C(Me)2C(O)NH(Et)</chem>
<chem>CH2CH2SEt</chem>	<chem>CH2C(O)NHCH2CHF2</chem>	<chem>C(Me)2C(O)NH(n-Pr)</chem>
<chem>CH2CH2S(n-Pr)</chem>	<chem>CH2C(O)NHCH2CF3</chem>	<chem>C(Me)2C(O)NH(i-Pr)</chem>
<chem>CH2CH2S(i-Pr)</chem>	<chem>CH2C(O)NHCH2CH(Me)F</chem>	<chem>C(Me)2C(O)NH(n-Bu)</chem>
<chem>CH2CH2S(i-Bu)</chem>	<chem>CH2C(O)NHCH2C(Me)2F</chem>	<chem>C(Me)2C(O)NH(i-Bu)</chem>
<chem>CH2CH2S(t-Bu)</chem>	<chem>CH2C(O)NH(CH2)2CH2F</chem>	<chem>C(Me)2C(O)NH(s-Bu)</chem>

CH ₂ CH(Me)SMe	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃	C(Me) ₂ C(O)NH(<i>t</i> -Bu)
CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NHCH ₂ CHFCF ₃	C(Me) ₂ C(O)NHCH ₂ (<i>t</i> -Bu)
CH ₂ C(Me) ₂ SMe	CH ₂ C(O)NHCH ₂ CF ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ F
CH(Me)CH ₂ SMe	CH ₂ C(O)NHCH(Me)CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NHCH(CF ₃) ₂	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH(Et)CH ₂ SMe	CH ₂ C(O)NHC(Me) ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(<i>i</i> -Pr)CH ₂ SMe	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ CH ₂ F
CH(<i>i</i> -Bu)CH ₂ SMe	CH ₂ C(O)NH(CH ₂) ₂ CF ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NHCH ₂ (CF ₂) ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CF ₂ CF ₃
CH ₂ CH ₂ CH ₂ SET	CH ₂ C(O)NHCH(<i>i</i> -Pr)CF ₃	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ CH ₂ S(<i>i</i> -Bu)	CH(Me)C(O)NHCH ₂ CH ₂ F	CH ₂ C(O)N(Me)CH(CF ₃) ₂
CH ₂ CH ₂ CH ₂ S(<i>t</i> -Bu)	CH(Me)C(O)NHCH ₂ CH ₂ Cl	CH ₂ C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH(Me)C(O)NHCH ₂ CH ₂ HF	CH(Me)C(O)N(Me)CH ₂ CH ₂ F
CH ₂ CH ₂ CH(CF ₃)SMe	CH(Me)C(O)NHCH ₂ CF ₃	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ CH(Me)F	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH(Et)CH ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ C(Me) ₂ F	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ SMe	CH(Me)C(O)NH(CH ₂) ₂ CH ₂ F	CH(Me)C(O)N(Me)(CH ₂) ₂ CH ₂ F
CH ₂ C(Me) ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NHCH ₂ CHFCF ₃	CH(Me)C(O)N(Me)CH ₂ CF ₂ CF ₃
CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NHCH ₂ CF ₂ CF ₃	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃	CH(Me)C(O)N(Me)CH(CF ₃) ₂
CH ₂ CH ₂ S(O)(<i>i</i> -Pr)	CH(Me)C(O)NHCH(CF ₃) ₂	CH(Me)C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ S(O)(<i>i</i> -Bu)	CH(Me)C(O)NHC(Me) ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ F
CH ₂ CH ₂ S(O)(<i>t</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(CH ₂) ₂ CF ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NHCH ₂ (CF ₂) ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NHCH(CF ₃) ₂	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ CH ₂ F
CH(Me)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ F	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
C(Me) ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ Cl	C(Me) ₂ C(O)N(Me)CH ₂ CF ₂ CF ₃
CH(Et)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ HF	C(Me) ₂ C(O)N(Me)CH(Me)CF ₃
CH(<i>i</i> -Pr)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH(CF ₃) ₂
CH(<i>i</i> -Bu)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH(Me)F	C(Me) ₂ C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ C(Me) ₂ F	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	C(Me) ₂ C(O)NH(CH ₂) ₂ CH ₂ F	C(Me) ₂ C(O)NHCH(CF ₃) ₂
CH ₂ CH ₂ CH ₂ S(O)(<i>i</i> -Bu)	C(Me) ₂ C(O)NHCH ₂ CH ₂ CF ₃	C(Me) ₂ C(O)NHC(Me) ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)(<i>t</i> -Bu)	C(Me) ₂ C(O)NHCH ₂ CHFCF ₃	C(Me) ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CF ₂ CF ₃	C(Me) ₂ C(O)NH(CH ₂) ₂ CF ₂ CF ₃
CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ CH(Me)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ (CF ₂) ₂ CF ₃

$\text{CH}(\text{Me})\text{CH}_2\text{CH}_2\text{S(O)Me}$	$\text{CH}_2\text{C}(\text{Me})_2\text{CH}_2\text{S(O)Me}$	$\text{C}(\text{Me})_2\text{C(O)NHCH}(i\text{-Pr})\text{CF}_3$
$\text{CH}(\text{Et})\text{CH}_2\text{CH}_2\text{S(O)Me}$		

R¹ is CF₃, R² is H and R³ is F

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
$\text{CH}_2\text{CH}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NH(Me)}$
$\text{CH}_2\text{CH}_2\text{OMe}$	$\text{CH}_2\text{CH}_2\text{SO}_2\text{Et}$	$\text{CH}_2\text{C(O)NH(Et)}$
$\text{CH}_2\text{CH}_2\text{OEt}$	$\text{CH}_2\text{CH}_2\text{SO}_2(n\text{-Pr})$	$\text{CH}_2\text{C(O)NH}(n\text{-Pr})$
$\text{CH}_2\text{CH}_2\text{O}(i\text{-Pr})$	$\text{CH}_2\text{CH}_2\text{SO}_2(i\text{-Pr})$	$\text{CH}_2\text{C(O)NH}(i\text{-Pr})$
$\text{CH}_2\text{CH}(\text{Me})\text{OH}$	$\text{CH}_2\text{CH}_2\text{SO}_2(i\text{-Bu})$	$\text{CH}_2\text{C(O)NH}(n\text{-Bu})$
$\text{CH}_2\text{CH}(\text{CF}_3)\text{OH}$	$\text{CH}_2\text{CH}_2\text{SO}_2(t\text{-Bu})$	$\text{CH}_2\text{C(O)NH}(i\text{-Bu})$
$\text{CH}_2\text{C}(\text{Me})_2\text{OH}$	$\text{CH}_2\text{CH}(\text{Me})\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NH}(s\text{-Bu})$
$\text{CH}_2\text{C}(\text{CF}_3)(\text{Me})\text{OH}$	$\text{CH}_2\text{CH}(\text{CF}_3)\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NH}(t\text{-Bu})$
$\text{CH}(\text{Me})\text{CH}_2\text{OH}$	$\text{CH}_2\text{C}(\text{Me})_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NHCH}_2(t\text{-Bu})$
$\text{C}(\text{Me})_2\text{CH}_2\text{OH}$	$\text{CH}(\text{Me})\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NMe}_2$
$\text{CH}(\text{Et})\text{CH}_2\text{OH}$	$\text{C}(\text{Me})_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NMe(Et)}$
$\text{CH}(i\text{-Pr})\text{CH}_2\text{OH}$	$\text{CH}(\text{Et})\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NEt}_2$
$\text{CH}(i\text{-Bu})\text{CH}_2\text{OH}$	$\text{CH}(i\text{-Pr})\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NMe}(n\text{-Pr})$
$\text{CH}(\text{Me})\text{CH}(\text{CF}_3)\text{OH}$	$\text{CH}(i\text{-Bu})\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NMe}(i\text{-Pr})$
$\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NMe}(s\text{-Bu})$
$\text{CH}_2\text{CH}_2\text{CH}_2\text{OMe}$	$\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{Et}$	$\text{CH}(\text{Me})\text{C(O)NH(Me)}$
$\text{CH}_2\text{CH}_2\text{CH}_2\text{OEt}$	$\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_2(i\text{-Bu})$	$\text{CH}(\text{Me})\text{C(O)NH(Et)}$
$\text{CH}_2\text{CH}_2\text{CH}(\text{CF}_3)\text{OH}$	$\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_2(t\text{-Bu})$	$\text{CH}(\text{Me})\text{C(O)NH}(n\text{-Pr})$
$\text{CH}(\text{Me})\text{CH}_2\text{CH}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{CH}(\text{Me})\text{SO}_2\text{Me}$	$\text{CH}(\text{Me})\text{C(O)NH}(i\text{-Pr})$
$\text{C}(\text{Me})_2\text{CH}_2\text{CH}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{CH}(\text{CF}_3)\text{SO}_2\text{Me}$	$\text{CH}(\text{Me})\text{C(O)NH}(n\text{-Bu})$
$\text{CH}(i\text{-Pr})\text{CH}_2\text{CH}_2\text{OH}$	$\text{CH}(\text{Me})\text{CH}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}(\text{Me})\text{C(O)NH}(i\text{-Bu})$
$\text{CH}_2\text{CH}(\text{Me})\text{CH}_2\text{OH}$	$\text{CH}(\text{Et})\text{CH}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}(\text{Me})\text{C(O)NH}(s\text{-Bu})$
$\text{CH}_2\text{C}(\text{Me})_2\text{CH}_2\text{OH}$	$\text{CH}_2\text{CH}(\text{Me})\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}(\text{Me})\text{C(O)NH}(t\text{-Bu})$
$\text{CH}_2\text{CH}_2\text{CH}(\text{Me})\text{OH}$	$\text{CH}_2\text{C}(\text{Me})_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}(\text{Me})(\text{O})\text{NHCH}_2(t\text{-Bu})$
$\text{CH}_2\text{CH}_2\text{C}(\text{Me})_2\text{OH}$	$\text{CH}_2\text{C(O)NHCH}_2\text{CH}_2\text{F}$	$\text{C}(\text{Me})_2\text{C(O)NH(Me)}$
$\text{CH}_2\text{CH}_2\text{SMe}$	$\text{CH}_2\text{C(O)NHCH}_2\text{CH}_2\text{Cl}$	$\text{C}(\text{Me})_2\text{C(O)NH(Et)}$
$\text{CH}_2\text{CH}_2\text{SEt}$	$\text{CH}_2\text{C(O)NHCH}_2\text{CHF}_2$	$\text{C}(\text{Me})_2\text{C(O)NH}(n\text{-Pr})$
$\text{CH}_2\text{CH}_2\text{S}(n\text{-Pr})$	$\text{CH}_2\text{C(O)NHCH}_2\text{CF}_3$	$\text{C}(\text{Me})_2\text{C(O)NH}(i\text{-Pr})$
$\text{CH}_2\text{CH}_2\text{S}(i\text{-Pr})$	$\text{CH}_2\text{C(O)NHCH}_2\text{CH}(\text{Me})\text{F}$	$\text{C}(\text{Me})_2\text{C(O)NH}(n\text{-Bu})$
$\text{CH}_2\text{CH}_2\text{S}(i\text{-Bu})$	$\text{CH}_2\text{C(O)NHCH}_2\text{C}(\text{Me})_2\text{F}$	$\text{C}(\text{Me})_2\text{C(O)NH}(i\text{-Bu})$
$\text{CH}_2\text{CH}_2\text{S}(t\text{-Bu})$	$\text{CH}_2\text{C(O)NH}(\text{CH}_2)_2\text{CH}_2\text{F}$	$\text{C}(\text{Me})_2\text{C(O)NH}(s\text{-Bu})$
$\text{CH}_2\text{CH}(\text{Me})\text{SMe}$	$\text{CH}_2\text{C(O)NHCH}_2\text{CH}_2\text{CF}_3$	$\text{C}(\text{Me})_2\text{C(O)NH}(t\text{-Bu})$
$\text{CH}_2\text{CH}(\text{CF}_3)\text{SMe}$	$\text{CH}_2\text{C(O)NHCH}_2\text{CHFCF}_3$	$\text{C}(\text{Me})_2\text{C(O)NHCH}_2(t\text{-Bu})$

CH ₂ C(Me) ₂ SMe	CH ₂ C(O)NHCH ₂ CF ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ F
CH(Me)CH ₂ SMe	CH ₂ C(O)NHCH(Me)CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NHCH(CF ₃) ₂	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH(Et)CH ₂ SMe	CH ₂ C(O)NHC(Me) ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(<i>i</i> -Pr)CH ₂ SMe	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ CH ₂ F
CH(<i>i</i> -Bu)CH ₂ SMe	CH ₂ C(O)NH(CH ₂) ₂ CF ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NHCH ₂ (CF ₂) ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CF ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NHCH(<i>i</i> -Pr)CF ₃	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ CH ₂ S(<i>i</i> -Bu)	CH(Me)C(O)NHCH ₂ CH ₂ F	CH ₂ C(O)N(Me)CH(CF ₃) ₂
CH ₂ CH ₂ CH ₂ S(<i>t</i> -Bu)	CH(Me)C(O)NHCH ₂ CH ₂ Cl	CH ₂ C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH(Me)C(O)NHCH ₂ CH ₂ HF ₂	CH(Me)C(O)N(Me)CH ₂ CH ₂ F
CH ₂ CH ₂ CH(CF ₃)SMe	CH(Me)C(O)NHCH ₂ CF ₃	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ CH(Me)F	CH(Me)C(O)N(Me)CH ₂ CH ₂ F
CH(Et)CH ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ C(Me) ₂ F	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ SMe	CH(Me)C(O)NH(CH ₂) ₂ CH ₂ F	CH(Me)C(O)N(Me)(CH ₂) ₂ CH ₂ F
CH ₂ C(Me) ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NHCH ₂ CHFCF ₃	CH(Me)C(O)N(Me)CH ₂ CF ₂ CF ₃
CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NHCH ₂ CF ₂ CF ₃	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃	CH(Me)C(O)N(Me)CH(CF ₃) ₂
CH ₂ CH ₂ S(O)(<i>i</i> -Pr)	CH(Me)C(O)NHCH(CF ₃) ₂	CH(Me)C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ S(O)(<i>i</i> -Bu)	CH(Me)C(O)NHC(Me) ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ F
CH ₂ CH ₂ S(O)(<i>t</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(CH ₂) ₂ CF ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ HF ₂
CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NHCH ₂ (CF ₂) ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CF ₂ CF ₃
CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NHCH(<i>i</i> -Pr)CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ CH ₂ F
CH(Me)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ F	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
C(Me) ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ Cl	C(Me) ₂ C(O)N(Me)CH ₂ CF ₂ CF ₃
CH(Et)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ HF ₂	C(Me) ₂ C(O)N(Me)CH(Me)CF ₃
CH(<i>i</i> -Pr)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH(CF ₃) ₂
CH(<i>i</i> -Bu)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH(Me)F	C(Me) ₂ C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ C(Me) ₂ F	C(Me) ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	C(Me) ₂ C(O)NH(CH ₂) ₂ CH ₂ F	C(Me) ₂ C(O)NHCH(CF ₃) ₂
CH ₂ CH ₂ CH ₂ S(O)(<i>i</i> -Bu)	C(Me) ₂ C(O)NHCH ₂ CH ₂ CF ₃	C(Me) ₂ C(O)NHC(Me) ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)(<i>t</i> -Bu)	C(Me) ₂ C(O)NHCH ₂ CHFCF ₃	C(Me) ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(Me)S(O)Me	C(Me) ₂ C(O)NHCH ₂ CF ₂ CF ₃	C(Me) ₂ C(O)NH(CH ₂) ₂ CF ₂ CF ₃
CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ CH(Me)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ (CF ₂) ₂ CF ₃
CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(Me) ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH(<i>i</i> -Pr)CF ₃
CH(Et)CH ₂ CH ₂ S(O)Me		

R¹ is CF₃, R² is H and R³ is Cl

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NH(Me)
CH ₂ CH ₂ OMe	CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NH(Et)
CH ₂ CH ₂ OEt	CH ₂ CH ₂ SO ₂ (n-Pr)	CH ₂ C(O)NH(n-Pr)
CH ₂ CH ₂ O(i-Pr)	CH ₂ CH ₂ SO ₂ (i-Pr)	CH ₂ C(O)NH(i-Pr)
CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (t-Bu)	CH ₂ C(O)NH(n-Bu)
CH ₂ CH(CF ₃)OH	CH ₂ CH ₂ SO ₂ (i-Bu)	CH ₂ C(O)NH(i-Bu)
CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NH(s-Bu)
CH ₂ C(CF ₃)(Me)OH	CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NH(t-Bu)
CH(Me)CH ₂ OH	CH ₂ C(Me) ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ (t-Bu)
C(Me) ₂ CH ₂ OH	CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NMe ₂
CH(Et)CH ₂ OH	C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NMe(Et)
CH(i-Pr)CH ₂ OH	CH(Et)CH ₂ SO ₂ Me	CH ₂ C(O)NEt ₂
CH(i-Bu)CH ₂ OH	CH(i-Pr)CH ₂ SO ₂ Me	CH ₂ C(O)NMe(n-Pr)
CH(Me)CH(CF ₃)OH	CH(i-Bu)CH ₂ SO ₂ Me	CH ₂ C(O)NMe(i-Pr)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NMe(s-Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ CH ₂ OEt	CH ₂ CH ₂ CH ₂ SO ₂ (i-Bu)	CH(Me)C(O)NH(Et)
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH ₂ CH ₂ SO ₂ (t-Bu)	CH(Me)C(O)NH(n-Pr)
CH(Me)CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)NH(i-Pr)
C(Me) ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)NH(n-Bu)
CH(i-Pr)CH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(i-Bu)
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(s-Bu)
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH(Me)C(O)NH(t-Bu)
CH ₂ CH ₂ CH(Me)OH	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH(Me)(O)NHCH ₂ (t-Bu)
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ C(O)NHCH ₂ CH ₂ F	C(Me) ₂ C(O)NH(Me)
CH ₂ CH ₂ SMe	CH ₂ C(O)NHCH ₂ CH ₂ Cl	C(Me) ₂ C(O)NH(Et)
CH ₂ CH ₂ SEt	CH ₂ C(O)NHCH ₂ CHF ₂	C(Me) ₂ C(O)NH(n-Pr)
CH ₂ CH ₂ S(n-Pr)	CH ₂ C(O)NHCH ₂ CF ₃	C(Me) ₂ C(O)NH(i-Pr)
CH ₂ CH ₂ S(i-Pr)	CH ₂ C(O)NHCH ₂ CH(Me)F	C(Me) ₂ C(O)NH(n-Bu)
CH ₂ CH ₂ S(i-Bu)	CH ₂ C(O)NHCH ₂ C(Me) ₂ F	C(Me) ₂ C(O)NH(i-Bu)
CH ₂ CH ₂ S(t-Bu)	CH ₂ C(O)NH(CH ₂) ₂ CH ₂ F	C(Me) ₂ C(O)NH(s-Bu)
CH ₂ CH(Me)SMe	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃	C(Me) ₂ C(O)NH(t-Bu)
CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NHCH ₂ CHFCF ₃	C(Me) ₂ C(O)NHCH ₂ (t-Bu)
CH ₂ C(Me) ₂ SMe	CH ₂ C(O)NHCH ₂ CF ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ F
CH(Me)CH ₂ SMe	CH ₂ C(O)NHCH(Me)CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NHCH(CF ₃) ₂	CH ₂ C(O)N(Me)CH ₂ CHF ₂

CH(Et)CH ₂ SMe	CH ₂ C(O)NHC(Me) ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(<i>i</i> -Pr)CH ₂ SMe	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ CH ₂ F
CH(<i>i</i> -Bu)CH ₂ SMe	CH ₂ C(O)NH(CH ₂) ₂ CF ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NHCH ₂ (CF ₂) ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CF ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NHCH(<i>i</i> -Pr)CF ₃	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ CH ₂ S(<i>i</i> -Bu)	CH(Me)C(O)NHCH ₂ CH ₂ F	CH ₂ C(O)N(Me)CH(CF ₃) ₂
CH ₂ CH ₂ CH ₂ S(<i>t</i> -Bu)	CH(Me)C(O)NHCH ₂ CH ₂ Cl	CH ₂ C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH(Me)C(O)NHCH ₂ CHF ₂	CH(Me)C(O)N(Me)CH ₂ CH ₂ F
CH ₂ CH ₂ CH(CF ₃)SMe	CH(Me)C(O)NHCH ₂ CF ₃	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ CH(Me)F	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH(Et)CH ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ C(Me) ₂ F	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ SMe	CH(Me)C(O)NH(CH ₂) ₂ CH ₂ F	CH(Me)C(O)N(Me)(CH ₂) ₂ CH ₂ F
CH ₂ C(Me) ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NHCH ₂ CHFCF ₃	CH(Me)C(O)N(Me)CH ₂ CF ₂ CF ₃
CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NHCH ₂ CF ₂ CF ₃	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃	CH(Me)C(O)N(Me)CH(CF ₃) ₂
CH ₂ CH ₂ S(O)(<i>i</i> -Pr)	CH(Me)C(O)NHCH(CF ₃) ₂	CH(Me)C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ S(O)(<i>i</i> -Bu)	CH(Me)C(O)NHC(Me) ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ F
CH ₂ CH ₂ S(O)(<i>t</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(CH ₂) ₂ CF ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NHCH ₂ (CF ₂) ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NHCH(<i>i</i> -Pr)CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ CH ₂ F
CH(Me)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ F	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
C(Me) ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ Cl	C(Me) ₂ C(O)N(Me)CH ₂ CF ₂ CF ₃
CH(Et)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CHF ₂	C(Me) ₂ C(O)N(Me)CH(Me)CF ₃
CH(<i>i</i> -Pr)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH(CF ₃) ₂
CH(<i>i</i> -Bu)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH(Me)F	C(Me) ₂ C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ C(Me) ₂ F	C(Me) ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	C(Me) ₂ C(O)NH(CH ₂) ₂ CH ₂ F	C(Me) ₂ C(O)NHCH(CF ₃) ₂
CH ₂ CH ₂ CH ₂ S(O)(<i>i</i> -Bu)	C(Me) ₂ C(O)NHCH ₂ CH ₂ CF ₃	C(Me) ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH ₂ S(O)(<i>t</i> -Bu)	C(Me) ₂ C(O)NHCH ₂ CHFCF ₃	C(Me) ₂ C(O)NH(CH ₂) ₂ CF ₂ CF ₃
CH ₂ CH ₂ CH(Me)S(O)Me	C(Me) ₂ C(O)NHCH ₂ CF ₂ CF ₃	C(Me) ₂ C(O)NHCH ₂ CF ₂ CF ₃
CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ CH(Me)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ (CF ₂) ₂ CF ₃
CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(Me) ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH(<i>i</i> -Pr)CF ₃
CH(Et)CH ₂ CH ₂ S(O)Me		

R¹ is CF₃, R² is H and R³ is Br

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NH(Me)
CH ₂ CH ₂ OMe	CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NH(Et)
CH ₂ CH ₂ OEt	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ CH ₂ SO ₂ (<i>i</i> -Pr)	CH ₂ C(O)NH(<i>i</i> -Pr)
CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>t</i> -Bu)	CH ₂ C(O)NH(<i>n</i> -Bu)
CH ₂ CH(CF ₃)OH	CH ₂ CH ₂ SO ₂ (<i>t</i> -Bu)	CH ₂ C(O)NH(<i>i</i> -Bu)
CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NH(<i>s</i> -Bu)
CH ₂ C(CF ₃)(Me)OH	CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NH(<i>t</i> -Bu)
CH(Me)CH ₂ OH	CH ₂ C(Me) ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ (<i>t</i> -Bu)
C(Me) ₂ CH ₂ OH	CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NMe ₂
CH(Et)CH ₂ OH	C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NMe(Et)
CH(<i>i</i> -Pr)CH ₂ OH	CH(Et)CH ₂ SO ₂ Me	CH ₂ C(O)NET ₂
CH(<i>i</i> -Bu)CH ₂ OH	CH(<i>i</i> -Pr)CH ₂ SO ₂ Me	CH ₂ C(O)NMe(<i>n</i> -Pr)
CH(Me)CH(CF ₃)OH	CH(<i>i</i> -Bu)CH ₂ SO ₂ Me	CH ₂ C(O)NMe(<i>i</i> -Pr)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NMe(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ CH ₂ OEt	CH ₂ CH ₂ CH ₂ SO ₂ (<i>i</i> -Bu)	CH(Me)C(O)NH(Et)
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH ₂ CH ₂ SO ₂ (<i>t</i> -Bu)	CH(Me)C(O)NH(<i>n</i> -Pr)
CH(Me)CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)NH(<i>i</i> -Pr)
C(Me) ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Bu)
CH(<i>i</i> -Pr)CH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>t</i> -Bu)
CH ₂ CH ₂ CH(Me)OH	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH(Me)(O)NHCH ₂ (<i>t</i> -Bu)
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ C(O)NHCH ₂ CH ₂ F	C(Me) ₂ C(O)NH(Me)
CH ₂ CH ₂ SMe	CH ₂ C(O)NHCH ₂ CH ₂ Cl	C(Me) ₂ C(O)NH(Et)
CH ₂ CH ₂ SEt	CH ₂ C(O)NHCH ₂ CHF ₂	C(Me) ₂ C(O)NH(<i>n</i> -Pr)
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃	C(Me) ₂ C(O)NH(<i>i</i> -Pr)
CH ₂ CH ₂ S(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH(Me)F	C(Me) ₂ C(O)NH(<i>n</i> -Bu)
CH ₂ CH ₂ S(<i>i</i> -Bu)	CH ₂ C(O)NHCH ₂ C(Me) ₂ F	C(Me) ₂ C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ S(<i>t</i> -Bu)	CH ₂ C(O)NH(CH ₂) ₂ CH ₂ F	C(Me) ₂ C(O)NH(<i>s</i> -Bu)
CH ₂ CH(Me)SMe	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃	C(Me) ₂ C(O)NH(<i>t</i> -Bu)
CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NHCH ₂ CHFCF ₃	C(Me) ₂ C(O)NHCH ₂ (<i>t</i> -Bu)
CH ₂ C(Me) ₂ SMe	CH ₂ C(O)NHCH ₂ CF ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ F
CH(Me)CH ₂ SMe	CH ₂ C(O)NHCH(Me)CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NHCH(CF ₃) ₂	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH(Et)CH ₂ SMe	CH ₂ C(O)NHC(Me) ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CF ₃

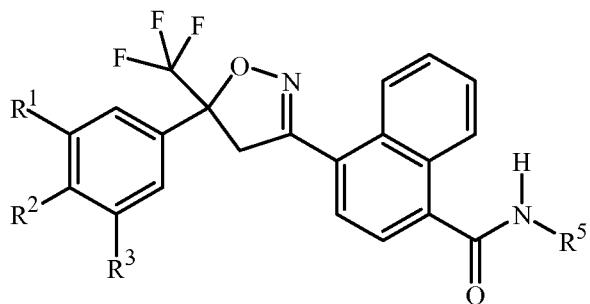
CH(<i>i</i> -Pr)CH ₂ SMe	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ CH ₂ F
CH(<i>i</i> -Bu)CH ₂ SMe	CH ₂ C(O)NH(CH ₂) ₂ CF ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NHCH ₂ (CF ₂) ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CF ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NHCH(<i>i</i> -Pr)CF ₃	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ CH ₂ S(<i>i</i> -Bu)	CH(Me)C(O)NHCH ₂ CH ₂ F	CH ₂ C(O)N(Me)CH(CF ₃) ₂
CH ₂ CH ₂ CH ₂ S(<i>t</i> -Bu)	CH(Me)C(O)NHCH ₂ CH ₂ Cl	CH ₂ C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH(Me)C(O)NHCH ₂ CHF ₂	CH(Me)C(O)N(Me)CH ₂ CH ₂ F
CH ₂ CH ₂ CH(CF ₃)SMe	CH(Me)C(O)NHCH ₂ CF ₃	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ CH(Me)F	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH(Et)CH ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ C(Me) ₂ F	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ SMe	CH(Me)C(O)NH(CH ₂) ₂ CH ₂ F	CH(Me)C(O)N(Me)(CH ₂) ₂ CH ₂ F
CH ₂ C(Me) ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NHCH ₂ CHFCF ₃	CH(Me)C(O)N(Me)CH ₂ CF ₂ CF ₃
CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NHCH ₂ CF ₂ CF ₃	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃	CH(Me)C(O)N(Me)CH(CF ₃) ₂
CH ₂ CH ₂ S(O)(<i>i</i> -Pr)	CH(Me)C(O)NHCH(CF ₃) ₂	CH(Me)C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ S(O)(<i>t</i> -Bu)	CH(Me)C(O)NHC(Me) ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ F
CH ₂ CH ₂ S(O)(<i>t</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(CH ₂) ₂ CF ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NHCH ₂ (CF ₂) ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NHCH(<i>i</i> -Pr)CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ CH ₂ F
CH(Me)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ F	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
C(Me) ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ Cl	C(Me) ₂ C(O)N(Me)CH ₂ CF ₂ CF ₃
CH(Et)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CHF ₂	C(Me) ₂ C(O)N(Me)CH(Me)CF ₃
CH(<i>i</i> -Pr)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH(CF ₃) ₂
CH(<i>i</i> -Bu)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH(Me)F	C(Me) ₂ C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ C(Me) ₂ F	C(Me) ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	C(Me) ₂ C(O)NH(CH ₂) ₂ CH ₂ F	C(Me) ₂ C(O)NHCH(CF ₃) ₂
CH ₂ CH ₂ CH ₂ S(O)(<i>i</i> -Bu)	C(Me) ₂ C(O)NHCH ₂ CH ₂ CF ₃	C(Me) ₂ C(O)NHC(Me) ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)(<i>t</i> -Bu)	C(Me) ₂ C(O)NHCH ₂ CHFCF ₃	C(Me) ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(Me)S(O)Me	C(Me) ₂ C(O)NHCH ₂ CF ₂ CF ₃	C(Me) ₂ C(O)NH(CH ₂) ₂ CF ₂ CF ₃
CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ CH(Me)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ (CF ₂) ₂ CF ₃
CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(Me) ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH(<i>i</i> -Pr)CF ₃
CH(Et)CH ₂ CH ₂ S(O)Me		

R¹ is CF₃, R² is H and R³ is CF₃

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NH(Me)
CH ₂ CH ₂ OMe	CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NH(Et)
CH ₂ CH ₂ OEt	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ CH ₂ SO ₂ (<i>i</i> -Pr)	CH ₂ C(O)NH(<i>i</i> -Pr)
CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>t</i> -Bu)	CH ₂ C(O)NH(<i>n</i> -Bu)
CH ₂ CH(CF ₃)OH	CH ₂ CH ₂ SO ₂ (<i>t</i> -Bu)	CH ₂ C(O)NH(<i>i</i> -Bu)
CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NH(<i>s</i> -Bu)
CH ₂ C(CF ₃)(Me)OH	CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NH(<i>t</i> -Bu)
CH(Me)CH ₂ OH	CH ₂ C(Me) ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ (<i>t</i> -Bu)
C(Me) ₂ CH ₂ OH	CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NMe ₂
CH(Et)CH ₂ OH	C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NMe(Et)
CH(<i>i</i> -Pr)CH ₂ OH	CH(Et)CH ₂ SO ₂ Me	CH ₂ C(O)NET ₂
CH(<i>i</i> -Bu)CH ₂ OH	CH(<i>i</i> -Pr)CH ₂ SO ₂ Me	CH ₂ C(O)NMe(<i>n</i> -Pr)
CH(Me)CH(CF ₃)OH	CH(<i>i</i> -Bu)CH ₂ SO ₂ Me	CH ₂ C(O)NMe(<i>i</i> -Pr)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NMe(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ CH ₂ OEt	CH ₂ CH ₂ CH ₂ SO ₂ (<i>i</i> -Bu)	CH(Me)C(O)NH(Et)
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH ₂ CH ₂ SO ₂ (<i>t</i> -Bu)	CH(Me)C(O)NH(<i>n</i> -Pr)
CH(Me)CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)NH(<i>i</i> -Pr)
C(Me) ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Bu)
CH(<i>i</i> -Pr)CH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>t</i> -Bu)
CH ₂ CH ₂ CH(Me)OH	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH(Me)(O)NHCH ₂ (<i>t</i> -Bu)
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ C(O)NHCH ₂ CH ₂ F	C(Me) ₂ C(O)NH(Me)
CH ₂ CH ₂ SMe	CH ₂ C(O)NHCH ₂ CH ₂ Cl	C(Me) ₂ C(O)NH(Et)
CH ₂ CH ₂ SEt	CH ₂ C(O)NHCH ₂ CHF ₂	C(Me) ₂ C(O)NH(<i>n</i> -Pr)
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃	C(Me) ₂ C(O)NH(<i>i</i> -Pr)
CH ₂ CH ₂ S(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH(Me)F	C(Me) ₂ C(O)NH(<i>n</i> -Bu)
CH ₂ CH ₂ S(<i>i</i> -Bu)	CH ₂ C(O)NHCH ₂ C(Me) ₂ F	C(Me) ₂ C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ S(<i>t</i> -Bu)	CH ₂ C(O)NH(CH ₂) ₂ CH ₂ F	C(Me) ₂ C(O)NH(<i>s</i> -Bu)
CH ₂ CH(Me)SMe	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃	C(Me) ₂ C(O)NH(<i>t</i> -Bu)
CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NHCH ₂ CHFCF ₃	C(Me) ₂ C(O)NHCH ₂ (<i>t</i> -Bu)
CH ₂ C(Me) ₂ SMe	CH ₂ C(O)NHCH ₂ CF ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ F
CH(Me)CH ₂ SMe	CH ₂ C(O)NHCH(Me)CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NHCH(CF ₃) ₂	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH(Et)CH ₂ SMe	CH ₂ C(O)NHC(Me) ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CF ₃

CH(<i>i</i> -Pr)CH ₂ SMe	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ CH ₂ F
CH(<i>i</i> -Bu)CH ₂ SMe	CH ₂ C(O)NH(CH ₂) ₂ CF ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NHCH ₂ (CF ₂) ₂ CF ₃	CH ₂ C(O)N(Me)CH ₂ CF ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NHCH(<i>i</i> -Pr)CF ₃	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ CH ₂ S(<i>i</i> -Bu)	CH(Me)C(O)NHCH ₂ CH ₂ F	CH ₂ C(O)N(Me)CH(CF ₃) ₂
CH ₂ CH ₂ CH ₂ S(<i>t</i> -Bu)	CH(Me)C(O)NHCH ₂ CH ₂ Cl	CH ₂ C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH(Me)C(O)NHCH ₂ CHF ₂	CH(Me)C(O)N(Me)CH ₂ CH ₂ F
CH ₂ CH ₂ CH(CF ₃)SMe	CH(Me)C(O)NHCH ₂ CF ₃	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ CH(Me)F	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH(Et)CH ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ C(Me) ₂ F	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ SMe	CH(Me)C(O)NH(CH ₂) ₂ CH ₂ F	CH(Me)C(O)N(Me)(CH ₂) ₂ CH ₂ F
CH ₂ C(Me) ₂ CH ₂ SMe	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NHCH ₂ CHFCF ₃	CH(Me)C(O)N(Me)CH ₂ CF ₂ CF ₃
CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NHCH ₂ CF ₂ CF ₃	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃	CH(Me)C(O)N(Me)CH(CF ₃) ₂
CH ₂ CH ₂ S(O)(<i>i</i> -Pr)	CH(Me)C(O)NHCH(CF ₃) ₂	CH(Me)C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ S(O)(<i>t</i> -Bu)	CH(Me)C(O)NHC(Me) ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ F
CH ₂ CH ₂ S(O)(<i>t</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(CH ₂) ₂ CF ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NHCH ₂ (CF ₂) ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NHCH(<i>i</i> -Pr)CF ₃	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ CH ₂ F
CH(Me)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ F	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
C(Me) ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH ₂ Cl	C(Me) ₂ C(O)N(Me)CH ₂ CF ₂ CF ₃
CH(Et)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CHF ₂	C(Me) ₂ C(O)N(Me)CH(Me)CF ₃
CH(<i>i</i> -Pr)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CF ₃	C(Me) ₂ C(O)N(Me)CH(CF ₃) ₂
CH(<i>i</i> -Bu)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ CH(Me)F	C(Me) ₂ C(O)N(Me)C(Me) ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ C(Me) ₂ F	C(Me) ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	C(Me) ₂ C(O)NH(CH ₂) ₂ CH ₂ F	C(Me) ₂ C(O)NHCH(CF ₃) ₂
CH ₂ CH ₂ CH ₂ S(O)(<i>i</i> -Bu)	C(Me) ₂ C(O)NHCH ₂ CH ₂ CF ₃	C(Me) ₂ C(O)NHC(Me) ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)(<i>t</i> -Bu)	C(Me) ₂ C(O)NHCH ₂ CHFCF ₃	C(Me) ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(Me)S(O)Me	C(Me) ₂ C(O)NHCH ₂ CF ₂ CF ₃	C(Me) ₂ C(O)NH(CH ₂) ₂ CF ₂ CF ₃
CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ CH(Me)CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH ₂ (CF ₂) ₂ CF ₃
CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(Me) ₂ CH ₂ S(O)Me	C(Me) ₂ C(O)NHCH(<i>i</i> -Pr)CF ₃
CH(Et)CH ₂ CH ₂ S(O)Me		

TABLE 2



5 R¹ is Cl, R² and R³ are H

<u>R</u> ⁵	<u>R</u> ⁵	<u>R</u> ⁵
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃

CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ is Cl, R² is H and R³ is F

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃

$\text{CH}_2\text{C}(\text{Me})_2\text{CH}_2\text{SMe}$	$\text{CH}_2\text{C}(\text{O})\text{NH}(i\text{-Pr})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NHCH}_2\text{CH}_2\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{Me}$	$\text{CH}_2\text{C}(\text{O})\text{NH}(i\text{-Bu})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NHCH}(\text{Me})\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{Et}$	$\text{CH}_2\text{C}(\text{O})\text{NH}(s\text{-Bu})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NHCH}_2\text{CH}(\text{Me})\text{CF}_3$

R¹ and R² are Cl, R³ is H

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(i-Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(n-Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(i-Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(i-Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(s-Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (n-Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SM _e	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(n-Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(n-Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(i-Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(i-Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(s-Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹, R² and R³ are Cl

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(i-Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(n-Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(i-Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(i-Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(s-Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (n-Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(n-Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(n-Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(i-Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(i-Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(s-Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ and R³ are Cl, R² is cyano

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe ₂

CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ is Br, R² and R³ are H

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)

CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ is Br, R² is H and R³ is F

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)

CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ is Br, R² is H and R³ is Cl

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂

CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (n-Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(n-Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(n-Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(i-Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(i-Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(s-Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ and R³ are Br, R² is F

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(i-Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(n-Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(i-Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(i-Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(s-Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃

CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ is Br, R² and R³ are Cl

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃

CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ and R³ are Br, R² is Cl

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH ₂ (Me)CH ₂ S(O)Me	CH ₂ (Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH ₂ (Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH ₂ (Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH ₂ (Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH ₂ (Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ (Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl

CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ is CF₃, R² and R³ are H

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂

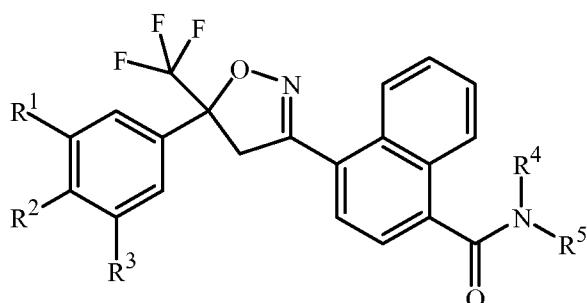
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ is OCF₃, R² is H and R³ is Br

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃

CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

TABLE 3

5 R¹ is Cl, R² is H, R³ is Cl, R⁴ is C(O)Me

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)NH(<i>i</i> -Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)	

R¹ is Cl, R² is H, R³ is Cl, R⁴ is CO₂Me

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂

CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SM _e	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)NH(<i>i</i> -Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)	

R¹ is Cl, R² is H, R³ is Cl, R⁴ is CO₂(*t*-Bu)

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SM _e	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SM _e	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)NH(<i>i</i> -Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)	

R¹ is Cl, R² is F, R³ is Cl, R⁴ is C(O)Me

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SM _e	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SM _e	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃

CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)NH(<i>i</i> -Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)	

R¹ is Cl, R² is F, R³ is Cl, R⁴ is CO₂Me

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)NH(<i>i</i> -Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)	

R¹ is Cl, R² is F, R³ is Cl, R⁴ is CO₂(*t*-Bu)

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃

$\text{CH}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NH}(n\text{-Pr})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NHCH}(\text{Me})\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{SO}_2\text{Et}$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NH}(i\text{-Pr})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NHCH}_2\text{CH}(\text{Me})\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{SO}_2(n\text{-Pr})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NH}(i\text{-Bu})$	$\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{Et}$
$\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NH}(s\text{-Bu})$	

R¹ is Br, R² is H, R³ is Br, R⁴ is C(O)Me

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)NH(<i>i</i> -Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)	

R¹ is Br, R² is H, R³ is Br, R⁴ is CO₂Me

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)NH(<i>i</i> -Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)	

R¹ is Br, R² is H, R³ is Br, R⁴ is CO₂(t-Bu)

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(n-Pr)	CH ₂ C(O)NH(n-Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NH(i-Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(i-Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(s-Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(n-Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(i-Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (n-Pr)	CH(Me)C(O)NH(i-Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(s-Bu)	

R¹ is CF₃, R² is H, R³ is F, R⁴ is C(O)Me

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(n-Pr)	CH ₂ C(O)NH(n-Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NH(i-Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(i-Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(s-Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(n-Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(i-Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (n-Pr)	CH(Me)C(O)NH(i-Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(s-Bu)	

R¹ is CF₃, R² is H, R³ is F, R⁴ is CO₂Me

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂

CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SM _e	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)NH(<i>i</i> -Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)	

R¹ is CF₃, R² is H, R³ is F, R⁴ is CO₂(*t*-Bu)

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SM _e	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SM _e	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)NH(<i>i</i> -Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)	

R¹ is CF₃, R² is H, R³ is Cl, R⁴ is C(O)Me

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SM _e	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SM _e	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃

CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)NH(<i>i</i> -Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)	

R¹ is CF₃, R² is H, R³ is Cl, R⁴ is CO₂Me

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)NH(<i>i</i> -Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)	

R¹ is CF₃, R² is H, R³ is Cl, R⁴ is CO₂(*t*-Bu)

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃

$\text{CH}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NH}(n\text{-Pr})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NHCH}(\text{Me})\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{SO}_2\text{Et}$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NH}(i\text{-Pr})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NHCH}_2\text{CH}(\text{Me})\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{SO}_2(n\text{-Pr})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NH}(i\text{-Bu})$	$\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{Et}$
$\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NH}(s\text{-Bu})$	

R¹ is CF₃, R² is H, R³ is Br, R⁴ is C(O)Me

<u>R</u> ⁵	<u>R</u> ⁵	<u>R</u> ⁵
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)NH(<i>i</i> -Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)	

R¹ is CF₃, R² is H, R³ is Br, R⁴ is CO₂Me

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)NH(<i>i</i> -Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)	

R¹ is CF₃, R² is H, R³ is Br, R⁴ is CO₂(t-Bu)

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(n-Pr)	CH ₂ C(O)NH(n-Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NH(i-Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(i-Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(s-Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(n-Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(i-Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (n-Pr)	CH(Me)C(O)NH(i-Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(s-Bu)	

R¹ is CF₃, R² is H, R³ is CF₃, R⁴ is C(O)Me

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(n-Pr)	CH ₂ C(O)NH(n-Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NH(i-Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(i-Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(s-Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(n-Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(i-Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (n-Pr)	CH(Me)C(O)NH(i-Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(s-Bu)	

R¹ is CF₃, R² is H, R³ is CF₃, R⁴ is CO₂Me

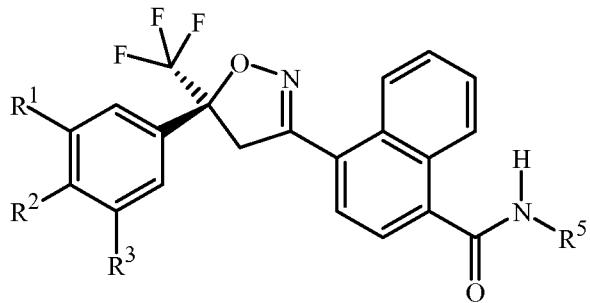
<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂

CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)NH(<i>i</i> -Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)	

R¹ is CF₃, R² is H, R³ is CF₃, R⁴ is CO₂(*t*-Bu)

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Me)	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ SEt	CH ₂ C(O)NH(Et)	CH ₂ C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH ₂ C(O)NH(<i>n</i> -Pr)	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ C(O)NH(<i>i</i> -Bu)	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>s</i> -Bu)	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NMe ₂	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)NH(<i>i</i> -Bu)	CH ₂ CH ₂ CH ₂ SO ₂ Et
CH ₂ CH ₂ CH ₂ SO ₂ Me	CH(Me)C(O)NH(<i>s</i> -Bu)	

TABLE 4



5 R¹ is Cl, R² is H and R³ is Cl

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(i-Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(n-Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(i-Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(i-Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(s-Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (n-Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(n-Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃

CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ is Cl, R² is F and R³ is Cl

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃

$\text{CH}_2\text{C}(\text{Me})_2\text{CH}_2\text{SMe}$	$\text{CH}_2\text{C}(\text{O})\text{NH}(i\text{-Pr})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NHCH}_2\text{CH}_2\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{Me}$	$\text{CH}_2\text{C}(\text{O})\text{NH}(i\text{-Bu})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NHCH}(\text{Me})\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{Et}$	$\text{CH}_2\text{C}(\text{O})\text{NH}(s\text{-Bu})$	$\text{CH}(\text{Me})\text{C}(\text{O})\text{NHCH}_2\text{CH}(\text{Me})\text{CF}_3$

R¹ is Br, R² is H and R³ is Br

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(i-Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(n-Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(i-Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(i-Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(s-Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (n-Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(n-Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(n-Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(i-Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(i-Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(s-Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ is CF₃, R² is H and R³ is F

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(i-Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(n-Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(i-Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(i-Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(s-Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (n-Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(n-Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(n-Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(i-Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(i-Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(s-Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ is CF₃, R² is H and R³ is Cl

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(i-Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(n-Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(i-Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(i-Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(s-Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (n-Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(n-Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(n-Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(i-Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(i-Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(s-Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ is CF₃, R² is H and R³ is Br

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)

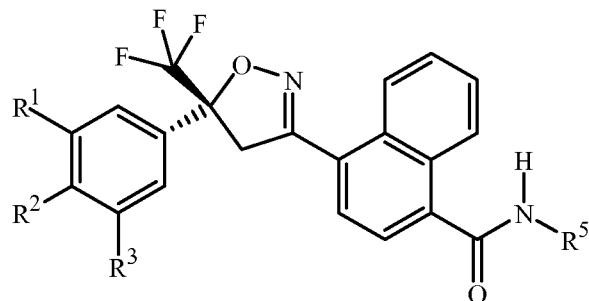
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ is CF₃, R² is H and R³ is CF₃

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)

CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

TABLE 5



R¹ is Cl, R² is H and R³ is Cl

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(i-Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(n-Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(i-Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(i-Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(s-Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (n-Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(n-Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂

$\text{CH}_2\text{CH}(\text{Me})\text{CH}_2\text{SMe}$	$\text{CH}_2\text{C(O)NH}(n\text{-Pr})$	$\text{CH}(\text{Me})\text{C(O)NHCH}_2\text{CF}_3$
$\text{CH}_2\text{C(Me)}_2\text{CH}_2\text{SMe}$	$\text{CH}_2\text{C(O)NH}(i\text{-Pr})$	$\text{CH}(\text{Me})\text{C(O)NHCH}_2\text{CH}_2\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{S(O)Me}$	$\text{CH}_2\text{C(O)NH}(i\text{-Bu})$	$\text{CH}(\text{Me})\text{C(O)NHCH(Me)CF}_3$
$\text{CH}_2\text{CH}_2\text{S(O)Et}$	$\text{CH}_2\text{C(O)NH}(s\text{-Bu})$	$\text{CH}(\text{Me})\text{C(O)NHCH}_2\text{CH}(\text{Me})\text{CF}_3$

R¹ is Cl, R² is F and R³ is Cl

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
$\text{CH}_2\text{CH}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{S(O)}(n\text{-Pr})$	$\text{CH}_2\text{C(O)NMe}_2$
$\text{CH}_2\text{CH}_2\text{OMe}$	$\text{CH}_2\text{CH}(\text{Me})\text{S(O)Me}$	$\text{CH}_2\text{C(O)NMe(Et)}$
$\text{CH}_2\text{CH}_2\text{OEt}$	$\text{CH}_2\text{CH}(\text{CF}_3)\text{S(O)Me}$	$\text{CH}(\text{Me})\text{C(O)NH(Me)}$
$\text{CH}_2\text{CH}_2\text{O}(i\text{-Pr})$	$\text{CH}_2\text{C(Me)}_2\text{S(O)Me}$	$\text{CH}(\text{Me})\text{C(O)NH(Et)}$
$\text{CH}_2\text{CH}(\text{Me})\text{OH}$	$\text{CH}(\text{Me})\text{CH}_2\text{S(O)Me}$	$\text{CH}(\text{Me})\text{C(O)NH}(n\text{-Pr})$
$\text{CH}_2\text{C(Me)}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{CH}_2\text{S(O)Me}$	$\text{CH}(\text{Me})\text{C(O)NH}(i\text{-Pr})$
$\text{CH}(\text{Me})\text{CH}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{CH}_2\text{S(O)Et}$	$\text{CH}(\text{Me})\text{C(O)NH}(i\text{-Bu})$
$\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{CH}(\text{Me})\text{S(O)Me}$	$\text{CH}(\text{Me})\text{C(O)NH}(s\text{-Bu})$
$\text{CH}_2\text{CH}_2\text{CH}_2\text{OMe}$	$\text{CH}_2\text{CH}_2\text{CH}(\text{CF}_3)\text{S(O)Me}$	$\text{CH}_2\text{C(O)N(Me)CH}_2\text{CH}_2\text{Cl}$
$\text{CH}_2\text{CH}_2\text{CH}_2\text{OEt}$	$\text{CH}(\text{Me})\text{CH}_2\text{CH}_2\text{S(O)Me}$	$\text{CH}_2\text{C(O)N(Me)CH}_2\text{CHF}_2$
$\text{CH}_2\text{CH}_2\text{CH}(\text{CF}_3)\text{OH}$	$\text{CH}_2\text{CH}(\text{Me})\text{CH}_2\text{S(O)Me}$	$\text{CH}_2\text{C(O)N(Me)CH}_2\text{CF}_3$
$\text{CH}(\text{Me})\text{CH}_2\text{CH}_2\text{OH}$	$\text{CH}_2\text{C(Me)}_2\text{CH}_2\text{S(O)Me}$	$\text{CH}_2\text{C(O)N(Me)CH}_2\text{CH}_2\text{CF}_3$
$\text{CH}_2\text{CH}(\text{Me})\text{CH}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)N(Me)CH(Me)CF}_3$
$\text{CH}_2\text{C(Me)}_2\text{CH}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{SO}_2\text{Et}$	$\text{CH}(\text{Me})\text{C(O)N(Me)CH}_2\text{CH}_2\text{Cl}$
$\text{CH}_2\text{CH}_2\text{CH}(\text{Me})\text{OH}$	$\text{CH}_2\text{CH}_2\text{SO}_2(n\text{-Pr})$	$\text{CH}(\text{Me})\text{C(O)N(Me)CH}_2\text{CHF}_2$
$\text{CH}_2\text{CH}_2\text{C(Me)}_2\text{OH}$	$\text{CH}_2\text{CH}(\text{Me})\text{SO}_2\text{Me}$	$\text{CH}(\text{Me})\text{C(O)N(Me)CH}_2\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{SMe}$	$\text{CH}_2\text{CH}(\text{CF}_3)\text{SO}_2\text{Me}$	$\text{CH}(\text{Me})\text{C(O)N(Me)CH}_2\text{CH}_2\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{SEt}$	$\text{CH}_2\text{C(Me)}_2\text{SO}_2\text{Me}$	$\text{CH}(\text{Me})\text{C(O)N(Me)CH(Me)CF}_3$
$\text{CH}_2\text{CH}_2\text{S}(n\text{-Pr})$	$\text{CH}(\text{Me})\text{CH}_2\text{SO}_2\text{Me}$	$\text{C(Me)}_2\text{C(O)N(Me)CH}_2\text{CH}_2\text{Cl}$
$\text{CH}_2\text{CH}(\text{Me})\text{SMe}$	$\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{C(Me)}_2\text{C(O)N(Me)CH}_2\text{CF}_3$
$\text{CH}_2\text{CH}(\text{CF}_3)\text{SMe}$	$\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{Et}$	$\text{CH}_2\text{C(O)NHCH}_2\text{CH}_2\text{Cl}$
$\text{CH}_2\text{C(Me)}_2\text{SMe}$	$\text{CH}_2\text{CH}_2\text{CH}(\text{Me})\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NHCH}_2\text{CHF}_2$
$\text{CH}(\text{Me})\text{CH}_2\text{SMe}$	$\text{CH}_2\text{CH}_2\text{CH}(\text{CF}_3)\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NHCH}_2\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{CH}_2\text{SMe}$	$\text{CH}(\text{Me})\text{CH}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NHCH}_2\text{CH}_2\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{CH}_2\text{SEt}$	$\text{CH}_2\text{CH}(\text{Me})\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NHCH(Me)CF}_3$
$\text{CH}_2\text{CH}_2\text{CH}(\text{Me})\text{SMe}$	$\text{CH}_2\text{C(Me)}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NHCH}_2\text{CH}(\text{Me})\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{CH}(\text{CF}_3)\text{SMe}$	$\text{CH}_2\text{C(O)NH(Me)}$	$\text{CH}(\text{Me})\text{C(O)NHCH}_2\text{CH}_2\text{Cl}$
$\text{CH}(\text{Me})\text{CH}_2\text{CH}_2\text{SMe}$	$\text{CH}_2\text{C(O)NH(Et)}$	$\text{CH}(\text{Me})\text{C(O)NHCH}_2\text{CHF}_2$
$\text{CH}_2\text{CH}(\text{Me})\text{CH}_2\text{SMe}$	$\text{CH}_2\text{C(O)NH}(n\text{-Pr})$	$\text{CH}(\text{Me})\text{C(O)NHCH}_2\text{CF}_3$
$\text{CH}_2\text{C(Me)}_2\text{CH}_2\text{SMe}$	$\text{CH}_2\text{C(O)NH}(i\text{-Pr})$	$\text{CH}(\text{Me})\text{C(O)NHCH}_2\text{CH}_2\text{CF}_3$

$\text{CH}_2\text{CH}_2\text{S(O)Me}$	$\text{CH}_2\text{C(O)NH}(i\text{-Bu})$	$\text{CH}(\text{Me})\text{C(O)NHCH(Me)CF}_3$
$\text{CH}_2\text{CH}_2\text{S(O)Et}$	$\text{CH}_2\text{C(O)NH}(s\text{-Bu})$	$\text{CH}(\text{Me})\text{C(O)NHCH}_2\text{CH(Me)CF}_3$

R¹ is Br, R² is H and R³ is Br

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
$\text{CH}_2\text{CH}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{S(O)}(n\text{-Pr})$	$\text{CH}_2\text{C(O)NMe}_2$
$\text{CH}_2\text{CH}_2\text{OMe}$	$\text{CH}_2\text{CH(Me)S(O)Me}$	$\text{CH}_2\text{C(O)NMe(Et)}$
$\text{CH}_2\text{CH}_2\text{OEt}$	$\text{CH}_2\text{CH(CF}_3\text{)S(O)Me}$	$\text{CH}(\text{Me})\text{C(O)NH(Me)}$
$\text{CH}_2\text{CH}_2\text{O}(i\text{-Pr})$	$\text{CH}_2\text{C(Me)}_2\text{S(O)Me}$	$\text{CH}(\text{Me})\text{C(O)NH(Et)}$
$\text{CH}_2\text{CH}(\text{Me})\text{OH}$	$\text{CH}(\text{Me})\text{CH}_2\text{S(O)Me}$	$\text{CH}(\text{Me})\text{C(O)NH}(n\text{-Pr})$
$\text{CH}_2\text{C(Me)}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{CH}_2\text{S(O)Me}$	$\text{CH}(\text{Me})\text{C(O)NH}(i\text{-Pr})$
$\text{CH}(\text{Me})\text{CH}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{CH}_2\text{S(O)Et}$	$\text{CH}(\text{Me})\text{C(O)NH}(i\text{-Bu})$
$\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{CH(Me)S(O)Me}$	$\text{CH}(\text{Me})\text{C(O)NH}(s\text{-Bu})$
$\text{CH}_2\text{CH}_2\text{CH}_2\text{OMe}$	$\text{CH}_2\text{CH}_2\text{CH(CF}_3\text{)S(O)Me}$	$\text{CH}_2\text{C(O)N(Me)CH}_2\text{CH}_2\text{Cl}$
$\text{CH}_2\text{CH}_2\text{CH}_2\text{OEt}$	$\text{CH}(\text{Me})\text{CH}_2\text{CH}_2\text{S(O)Me}$	$\text{CH}_2\text{C(O)N(Me)CH}_2\text{CHF}_2$
$\text{CH}_2\text{CH}_2\text{CH(CF}_3\text{)OH}$	$\text{CH}_2\text{CH}(\text{Me})\text{CH}_2\text{S(O)Me}$	$\text{CH}_2\text{C(O)N(Me)CH}_2\text{CF}_3$
$\text{CH}(\text{Me})\text{CH}_2\text{CH}_2\text{OH}$	$\text{CH}_2\text{C(Me)}_2\text{CH}_2\text{S(O)Me}$	$\text{CH}_2\text{C(O)N(Me)CH}_2\text{CH}_2\text{CF}_3$
$\text{CH}_2\text{CH}(\text{Me})\text{CH}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)N(Me)CH(Me)CF}_3$
$\text{CH}_2\text{C(Me)}_2\text{CH}_2\text{OH}$	$\text{CH}_2\text{CH}_2\text{SO}_2\text{Et}$	$\text{CH}(\text{Me})\text{C(O)N(Me)CH}_2\text{CH}_2\text{Cl}$
$\text{CH}_2\text{CH}_2\text{CH}(\text{Me})\text{OH}$	$\text{CH}_2\text{CH}_2\text{SO}_2(n\text{-Pr})$	$\text{CH}(\text{Me})\text{C(O)N(Me)CH}_2\text{CHF}_2$
$\text{CH}_2\text{CH}_2\text{C(Me)}_2\text{OH}$	$\text{CH}_2\text{CH}(\text{Me})\text{SO}_2\text{Me}$	$\text{CH}(\text{Me})\text{C(O)N(Me)CH}_2\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{SMe}$	$\text{CH}_2\text{CH(CF}_3\text{)SO}_2\text{Me}$	$\text{CH}(\text{Me})\text{C(O)N(Me)CH}_2\text{CH}_2\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{SEt}$	$\text{CH}_2\text{C(Me)}_2\text{SO}_2\text{Me}$	$\text{CH}(\text{Me})\text{C(O)N(Me)CH(Me)CF}_3$
$\text{CH}_2\text{CH}_2\text{S}(n\text{-Pr})$	$\text{CH}(\text{Me})\text{CH}_2\text{SO}_2\text{Me}$	$\text{C(Me)}_2\text{C(O)N(Me)CH}_2\text{CH}_2\text{Cl}$
$\text{CH}_2\text{CH}(\text{Me})\text{SMe}$	$\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{C(Me)}_2\text{C(O)N(Me)CH}_2\text{CF}_3$
$\text{CH}_2\text{CH(CF}_3\text{)SMe}$	$\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{Et}$	$\text{CH}_2\text{C(O)NHCH}_2\text{CH}_2\text{Cl}$
$\text{CH}_2\text{C(Me)}_2\text{SMe}$	$\text{CH}_2\text{CH}_2\text{CH}(\text{Me})\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NHCH}_2\text{CHF}_2$
$\text{CH}(\text{Me})\text{CH}_2\text{SMe}$	$\text{CH}_2\text{CH}_2\text{CH(CF}_3\text{)SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NHCH}_2\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{CH}_2\text{SMe}$	$\text{CH}(\text{Me})\text{CH}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NHCH}_2\text{CH}_2\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{CH}_2\text{SEt}$	$\text{CH}_2\text{CH}(\text{Me})\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NHCH(Me)CF}_3$
$\text{CH}_2\text{CH}_2\text{CH}(\text{Me})\text{SMe}$	$\text{CH}_2\text{C(Me)}_2\text{CH}_2\text{SO}_2\text{Me}$	$\text{CH}_2\text{C(O)NHCH}_2\text{CH(Me)CF}_3$
$\text{CH}_2\text{CH}_2\text{CH(CF}_3\text{)SMe}$	$\text{CH}_2\text{C(O)NH(Me)}$	$\text{CH}(\text{Me})\text{C(O)NHCH}_2\text{CH}_2\text{Cl}$
$\text{CH}(\text{Me})\text{CH}_2\text{CH}_2\text{SMe}$	$\text{CH}_2\text{C(O)NH(Et)}$	$\text{CH}(\text{Me})\text{C(O)NHCH}_2\text{CHF}_2$
$\text{CH}_2\text{CH}(\text{Me})\text{CH}_2\text{SMe}$	$\text{CH}_2\text{C(O)NH}(n\text{-Pr})$	$\text{CH}(\text{Me})\text{C(O)NHCH}_2\text{CF}_3$
$\text{CH}_2\text{C(Me)}_2\text{CH}_2\text{SMe}$	$\text{CH}_2\text{C(O)NH}(i\text{-Pr})$	$\text{CH}(\text{Me})\text{C(O)NHCH}_2\text{CH}_2\text{CF}_3$
$\text{CH}_2\text{CH}_2\text{S(O)Me}$	$\text{CH}_2\text{C(O)NH}(i\text{-Bu})$	$\text{CH}(\text{Me})\text{C(O)NHCH(Me)CF}_3$
$\text{CH}_2\text{CH}_2\text{S(O)Et}$	$\text{CH}_2\text{C(O)NH}(s\text{-Bu})$	$\text{CH}(\text{Me})\text{C(O)NHCH}_2\text{CH(Me)CF}_3$

R¹ is CF₃, R² is H and R³ is F

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(i-Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(n-Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(i-Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(i-Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(s-Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (n-Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(n-Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(n-Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(i-Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(i-Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(s-Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ is CF₃, R² is H and R³ is Cl

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(n-Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)

CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ is CF₃, R² is H and R³ is Br

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)

CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)
CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH(Me)CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

R¹ is CF₃, R² is H and R³ is CF₃

<u>R⁵</u>	<u>R⁵</u>	<u>R⁵</u>
CH ₂ CH ₂ OH	CH ₂ CH ₂ S(O)(<i>n</i> -Pr)	CH ₂ C(O)NMe ₂
CH ₂ CH ₂ OMe	CH ₂ CH(Me)S(O)Me	CH ₂ C(O)NMe(Et)
CH ₂ CH ₂ OEt	CH ₂ CH(CF ₃)S(O)Me	CH(Me)C(O)NH(Me)
CH ₂ CH ₂ O(<i>i</i> -Pr)	CH ₂ C(Me) ₂ S(O)Me	CH(Me)C(O)NH(Et)
CH ₂ CH(Me)OH	CH(Me)CH ₂ S(O)Me	CH(Me)C(O)NH(<i>n</i> -Pr)
CH ₂ C(Me) ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Me	CH(Me)C(O)NH(<i>i</i> -Pr)
CH(Me)CH ₂ OH	CH ₂ CH ₂ CH ₂ S(O)Et	CH(Me)C(O)NH(<i>i</i> -Bu)
CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH(Me)S(O)Me	CH(Me)C(O)NH(<i>s</i> -Bu)

CH ₂ CH ₂ CH ₂ OMe	CH ₂ CH ₂ CH(CF ₃)S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH ₂ OEt	CH(Me)CH ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ CH(CF ₃)OH	CH ₂ CH(Me)CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CF ₃
CH(Me)CH ₂ CH ₂ OH	CH ₂ C(Me) ₂ CH ₂ S(O)Me	CH ₂ C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH(Me)CH ₂ OH	CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)N(Me)CH(Me)CF ₃
CH ₂ C(Me) ₂ CH ₂ OH	CH ₂ CH ₂ SO ₂ Et	CH(Me)C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH ₂ CH(Me)OH	CH ₂ CH ₂ SO ₂ (<i>n</i> -Pr)	CH(Me)C(O)N(Me)CH ₂ CHF ₂
CH ₂ CH ₂ C(Me) ₂ OH	CH ₂ CH(Me)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CF ₃
CH ₂ CH ₂ SMe	CH ₂ CH(CF ₃)SO ₂ Me	CH(Me)C(O)N(Me)CH ₂ CH ₂ CF ₃
CH ₂ CH ₂ SEt	CH ₂ C(Me) ₂ SO ₂ Me	CH(Me)C(O)N(Me)CH(Me)CF ₃
CH ₂ CH ₂ S(<i>n</i> -Pr)	CH(Me)CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CH ₂ Cl
CH ₂ CH(Me)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	C(Me) ₂ C(O)N(Me)CH ₂ CF ₃
CH ₂ CH(CF ₃)SMe	CH ₂ CH ₂ CH ₂ SO ₂ Et	CH ₂ C(O)NHCH ₂ CH ₂ Cl
CH ₂ C(Me) ₂ SMe	CH ₂ CH ₂ CH(Me)SO ₂ Me	CH ₂ C(O)NHCH ₂ CHF ₂
CH(Me)CH ₂ SMe	CH ₂ CH ₂ CH(CF ₃)SO ₂ Me	CH ₂ C(O)NHCH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SMe	CH ₂ CH ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ CH ₂ SEt	CH ₂ CH(Me)CH ₂ SO ₂ Me	CH ₂ C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ CH(Me)SMe	CH ₂ C(Me) ₂ CH ₂ SO ₂ Me	CH ₂ C(O)NHCH ₂ CH(Me)CF ₃
CH ₂ CH ₂ CH(CF ₃)SMe	CH ₂ C(O)NH(Me)	CH(Me)C(O)NHCH ₂ CH ₂ Cl
CH(Me)CH ₂ CH ₂ SMe	CH ₂ C(O)NH(Et)	CH(Me)C(O)NHCH ₂ CHF ₂
CH ₂ CH(Me)CH ₂ SMe	CH ₂ C(O)NH(<i>n</i> -Pr)	CH(Me)C(O)NHCH ₂ CF ₃
CH ₂ C(Me) ₂ CH ₂ SMe	CH ₂ C(O)NH(<i>i</i> -Pr)	CH(Me)C(O)NHCH ₂ CH ₂ CF ₃
CH ₂ CH ₂ S(O)Me	CH ₂ C(O)NH(<i>i</i> -Bu)	CH(Me)C(O)NHCH(Me)CF ₃
CH ₂ CH ₂ S(O)Et	CH ₂ C(O)NH(<i>s</i> -Bu)	CH(Me)C(O)NHCH ₂ CH(Me)CF ₃

A compound of this invention will generally be used as an invertebrate pest control active ingredient in a composition, i.e. formulation, with at least one additional component selected from the group consisting of surfactants, solid diluents and liquid diluents, which serves as a carrier. The formulation or composition ingredients are selected to be consistent with the physical properties of the active ingredient, mode of application and environmental factors such as soil type, moisture and temperature.

Useful formulations include both liquid and solid compositions. Liquid compositions include solutions (including emulsifiable concentrates), suspensions, emulsions (including microemulsions and/or suspoemulsions) and the like, which optionally can be thickened into gels. The general types of aqueous liquid compositions are soluble concentrate, suspension concentrate, capsule suspension, concentrated emulsion, microemulsion and suspoemulsion. The general types of nonaqueous liquid compositions are emulsifiable concentrate, microemulsifiable concentrate, dispersible concentrate and oil dispersion.

The general types of solid compositions are dusts, powders, granules, pellets, prills, pastilles, tablets, filled films (including seed coatings) and the like, which can be water-dispersible (“wettable”) or water-soluble. Films and coatings formed from film-forming solutions or flowable suspensions are particularly useful for seed treatment. Active 5 ingredient can be (micro)encapsulated and further formed into a suspension or solid formulation; alternatively the entire formulation of active ingredient can be encapsulated (or “overcoated”). Encapsulation can control or delay release of the active ingredient. An emulsifiable granule combines the advantages of both an emulsifiable concentrate formulation and a dry granular formulation. High-strength compositions are primarily used 10 as intermediates for further formulation.

Sprayable formulations are typically extended in a suitable medium before spraying. Such liquid and solid formulations are formulated to be readily diluted in the spray medium, usually water. Spray volumes can range from about one to several thousand liters per hectare, but more typically are in the range from about ten to several hundred liters per 15 hectare. Sprayable formulations can be tank mixed with water or another suitable medium for foliar treatment by aerial or ground application, or for application to the growing medium of the plant. Liquid and dry formulations can be metered directly into drip irrigation systems or metered into the furrow during planting. Liquid and solid formulations can be applied onto seeds of crops and other desirable vegetation as seed treatments before planting to 20 protect developing roots and other subterranean plant parts and/or foliage through systemic uptake.

The formulations will typically contain effective amounts of active ingredient, diluent and surfactant within the following approximate ranges which add up to 100 percent by weight.

	Weight Percent		
	<u>Active Ingredient</u>	<u>Diluent</u>	<u>Surfactant</u>
Water-Dispersible and Water-soluble Granules, Tablets and Powders	0.001–90	0–99.999	0–15
Oil Dispersions, Suspensions, Emulsions, Solutions (including Emulsifiable Concentrates)	1–50	40–99	0–50
Dusts	1–25	70–99	0–5
Granules and Pellets	0.001–99	5–99.999	0–15
High Strength Compositions	90–99	0–10	0–2

25 Solid diluents include, for example, clays such as bentonite, montmorillonite, attapulgite and kaolin, gypsum, cellulose, titanium dioxide, zinc oxide, starch, dextrin,

sugars (e.g., lactose, sucrose), silica, talc, mica, diatomaceous earth, urea, calcium carbonate, sodium carbonate and bicarbonate, and sodium sulfate. Typical solid diluents are described in Watkins et al., *Handbook of Insecticide Dust Diluents and Carriers*, 2nd Ed., Dorland Books, Caldwell, New Jersey.

5 Liquid diluents include, for example, water, *N,N*-dimethylalkanamides (e.g., *N,N*-dimethylformamide), limonene, dimethyl sulfoxide, *N*-alkylpyrrolidones (e.g., *N*-methylpyrrolidinone), ethylene glycol, triethylene glycol, propylene glycol, dipropylene glycol, polypropylene glycol, propylene carbonate, butylene carbonate, paraffins (e.g., white mineral oils, normal paraffins, isoparaffins), alkylbenzenes, alkynaphthalenes, glycerine, 10 glycerol triacetate, sorbitol, triacetin, aromatic hydrocarbons, dearomatized aliphatics, alkylbenzenes, alkynaphthalenes, ketones such as cyclohexanone, 2-heptanone, isophorone and 4-hydroxy-4-methyl-2-pentanone, acetates such as isoamyl acetate, hexyl acetate, heptyl acetate, octyl acetate, nonyl acetate, tridecyl acetate and isobornyl acetate, other esters such as alkylated lactate esters, dibasic esters and γ -butyrolactone, and alcohols, which can be 15 linear, branched, saturated or unsaturated, such as methanol, ethanol, *n*-propanol, isopropyl alcohol, *n*-butanol, isobutyl alcohol, *n*-hexanol, 2-ethylhexanol, *n*-octanol, decanol, isodecyl alcohol, isoctadecanol, cetyl alcohol, lauryl alcohol, tridecyl alcohol, oleyl alcohol, cyclohexanol, tetrahydrofurfuryl alcohol, diacetone alcohol and benzyl alcohol. Liquid diluents also include glycerol esters of saturated and unsaturated fatty acids (typically 20 C_6-C_{22}), such as plant seed and fruit oils (e.g., oils of olive, castor, linseed, sesame, corn (maize), peanut, sunflower, grapeseed, safflower, cottonseed, soybean, rapeseed, coconut and palm kernel), animal-sourced fats (e.g., beef tallow, pork tallow, lard, cod liver oil, fish oil), and mixtures thereof. Liquid diluents also include alkylated fatty acids (e.g., methylated, ethylated, butylated) wherein the fatty acids may be obtained by hydrolysis of 25 glycerol esters from plant and animal sources, and can be purified by distillation. Typical liquid diluents are described in Marsden, *Solvents Guide*, 2nd Ed., Interscience, New York, 1950.

The solid and liquid compositions of the present invention often include one or more surfactants. When added to a liquid, surfactants (also known as "surface-active agents") 30 generally modify, most often reduce, the surface tension of the liquid. Depending on the nature of the hydrophilic and lipophilic groups in a surfactant molecule, surfactants can be useful as wetting agents, dispersants, emulsifiers or defoaming agents.

Surfactants can be classified as nonionic, anionic or cationic. Nonionic surfactants useful for the present compositions include, but are not limited to: alcohol alkoxylates such 35 as alcohol alkoxylates based on natural and synthetic alcohols (which may be branched or linear) and prepared from the alcohols and ethylene oxide, propylene oxide, butylene oxide or mixtures thereof; amine ethoxylates, alkanolamides and ethoxylated alkanolamides; alkoxylated triglycerides such as ethoxylated soybean, castor and rapeseed oils; alkylphenol alkoxylates such as octylphenol ethoxylates, nonylphenol ethoxylates, dinonyl phenol

ethoxylates and dodecyl phenol ethoxylates (prepared from the phenols and ethylene oxide, propylene oxide, butylene oxide or mixtures thereof); block polymers prepared from ethylene oxide or propylene oxide and reverse block polymers where the terminal blocks are prepared from propylene oxide; ethoxylated fatty acids; ethoxylated fatty esters and oils; 5 ethoxylated methyl esters; ethoxylated tristyrylphenol (including those prepared from ethylene oxide, propylene oxide, butylene oxide or mixtures thereof); fatty acid esters, glycerol esters, lanolin-based derivatives, polyethoxylate esters such as polyethoxylated sorbitan fatty acid esters, polyethoxylated sorbitol fatty acid esters and polyethoxylated glycerol fatty acid esters; other sorbitan derivatives such as sorbitan esters; polymeric 10 surfactants such as random copolymers, block copolymers, alkyd peg (polyethylene glycol) resins, graft or comb polymers and star polymers; polyethylene glycols (pegs); polyethylene glycol fatty acid esters; silicone-based surfactants; and sugar-derivatives such as sucrose esters, alkyl polyglycosides and alkyl polysaccharides.

Useful anionic surfactants include, but are not limited to: alkylaryl sulfonic acids and 15 their salts; carboxylated alcohol or alkylphenol ethoxylates; diphenyl sulfonate derivatives; lignin and lignin derivatives such as lignosulfonates; maleic or succinic acids or their anhydrides; olefin sulfonates; phosphate esters such as phosphate esters of alcohol alkoxylates, phosphate esters of alkylphenol alkoxylates and phosphate esters of styryl phenol ethoxylates; protein-based surfactants; sarcosine derivatives; styryl phenol ether 20 sulfate; sulfates and sulfonates of oils and fatty acids; sulfates and sulfonates of ethoxylated alkylphenols; sulfates of alcohols; sulfates of ethoxylated alcohols; sulfonates of amines and amides such as *N,N*-alkyltaurates; sulfonates of benzene, cumene, toluene, xylene, and dodecyl and tridecylbenzenes; sulfonates of condensed naphthalenes; sulfonates of naphthalene and alkyl naphthalene; sulfonates of fractionated petroleum; sulfosuccinamates; 25 and sulfosuccinates and their derivatives such as dialkyl sulfosuccinate salts.

Useful cationic surfactants include, but are not limited to: amides and ethoxylated amides; amines such as *N*-alkyl propanediamines, tripropylenetriamines and dipropylenetetramines, and ethoxylated amines, ethoxylated diamines and propoxylated amines (prepared from the amines and ethylene oxide, propylene oxide, butylene oxide or 30 mixtures thereof); amine salts such as amine acetates and diamine salts; quaternary ammonium salts such as quaternary salts, ethoxylated quaternary salts and diquaternary salts; and amine oxides such as alkyldimethylamine oxides and bis-(2-hydroxyethyl)-alkylamine oxides.

Also useful for the present compositions are mixtures of nonionic and anionic 35 surfactants or mixtures of nonionic and cationic surfactants. Nonionic, anionic and cationic surfactants and their recommended uses are disclosed in a variety of published references including *McCutcheon's Emulsifiers and Detergents*, annual American and International Editions published by McCutcheon's Division, The Manufacturing Confectioner Publishing Co.; Sisley and Wood, *Encyclopedia of Surface Active Agents*, Chemical Publ. Co., Inc.,

New York, 1964; and A. S. Davidson and B. Milwidsky, *Synthetic Detergents*, Seventh Edition, John Wiley and Sons, New York, 1987.

Compositions of this invention may also contain formulation auxiliaries and additives, known to those skilled in the art as formulation aids (some of which may be considered to 5 also function as solid diluents, liquid diluents or surfactants). Such formulation auxiliaries and additives may control: pH (buffers), foaming during processing (antifoams such polyorganosiloxanes), sedimentation of active ingredients (suspending agents), viscosity (thixotropic thickeners), in-container microbial growth (antimicrobials), product freezing (antifreezes), color (dyes/pigment dispersions), wash-off (film formers or stickers), 10 evaporation (evaporation retardants), and other formulation attributes. Film formers include, for example, polyvinyl acetates, polyvinyl acetate copolymers, polyvinylpyrrolidone-vinyl acetate copolymer, polyvinyl alcohols, polyvinyl alcohol copolymers and waxes. Examples of formulation auxiliaries and additives include those listed in *McCutcheon's Volume 2: Functional Materials*, annual International and North American editions published by 15 McCutcheon's Division, The Manufacturing Confectioner Publishing Co.; and PCT Publication WO 03/024222.

The compound of Formula 1 and any other active ingredients are typically incorporated into the present compositions by dissolving the active ingredient in a solvent or by grinding in a liquid or dry diluent. Solutions, including emulsifiable concentrates, can be 20 prepared by simply mixing the ingredients. If the solvent of a liquid composition intended for use as an emulsifiable concentrate is water-immiscible, an emulsifier is typically added to emulsify the active-containing solvent upon dilution with water. Active ingredient slurries, with particle diameters of up to 2,000 µm can be wet milled using media mills to obtain particles with average diameters below 3 µm. Aqueous slurries can be made into finished 25 suspension concentrates (see, for example, U.S. 3,060,084) or further processed by spray drying to form water-dispersible granules. Dry formulations usually require dry milling processes, which produce average particle diameters in the 2 to 10 µm range. Dusts and powders can be prepared by blending and usually grinding (such as with a hammer mill or fluid-energy mill). Granules and pellets can be prepared by spraying the active material upon 30 preformed granular carriers or by agglomeration techniques. See Browning, "Agglomeration", *Chemical Engineering*, December 4, 1967, pp 147-48, *Perry's Chemical Engineer's Handbook*, 4th Ed., McGraw-Hill, New York, 1963, pages 8-57 and following, and WO 91/13546. Pellets can be prepared as described in U.S. 4,172,714. Water-dispersible and water-soluble granules can be prepared as taught in U.S. 4,144,050, 35 U.S. 3,920,442 and DE 3,246,493. Tablets can be prepared as taught in U.S. 5,180,587, U.S. 5,232,701 and U.S. 5,208,030. Films can be prepared as taught in GB 2,095,558 and U.S. 3,299,566.

For further information regarding the art of formulation, see T. S. Woods, "The Formulator's Toolbox – Product Forms for Modern Agriculture" in *Pesticide Chemistry and*

Bioscience, The Food–Environment Challenge, T. Brooks and T. R. Roberts, Eds., Proceedings of the 9th International Congress on Pesticide Chemistry, The Royal Society of Chemistry, Cambridge, 1999, pp. 120–133. See also U.S. 3,235,361, Col. 6, line 16 through Col. 7, line 19 and Examples 10–41; U.S. 3,309,192, Col. 5, line 43 through Col. 7, line 62 and Examples 8, 12, 15, 39, 41, 52, 53, 58, 132, 138–140, 162–164, 166, 167 and 169–182; U.S. 2,891,855, Col. 3, line 66 through Col. 5, line 17 and Examples 1–4; Klingman, *Weed Control as a Science*, John Wiley and Sons, Inc., New York, 1961, pp 81–96; Hance et al., *Weed Control Handbook*, 8th Ed., Blackwell Scientific Publications, Oxford, 1989; and *Developments in formulation technology*, PJB Publications, Richmond, UK, 2000.

In the following Examples, all percentages are by weight and all formulations are prepared in conventional ways. Compound numbers refer to compounds in Index Table A. Without further elaboration, it is believed that one skilled in the art using the preceding description can utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative, and not limiting of the disclosure in any way whatsoever. Percentages are by weight except where otherwise indicated.

Example A

High Strength Concentrate

Compound 1	98.5%
silica aerogel	0.5%
synthetic amorphous fine silica	1.0%

Example B

Wettable Powder

Compound 3	65.0%
dodecylphenol polyethylene glycol ether	2.0%
sodium ligninsulfonate	4.0%
sodium silicoaluminate	6.0%
montmorillonite (calcined)	23.0%

Example C

Granule

Compound 11	10.0%
attapulgite granules (low volatile matter, 0.71/0.30 mm; U.S.S. No. 25–50 sieves)	90.0%

Example D

Extruded Pellet

Compound 17	25.0%
anhydrous sodium sulfate	10.0%
crude calcium ligninsulfonate	5.0%
sodium alkynaphthalenesulfonate	1.0%
calcium/magnesium bentonite	59.0%

Example EEmulsifiable Concentrate

Compound 18	10.0%
polyoxyethylene sorbitol hexoleate	20.0%
C ₆ -C ₁₀ fatty acid methyl ester	70.0%

Example FMicroemulsion

Compound 19	5.0%
polyvinylpyrrolidone-vinyl acetate copolymer	30.0%
alkylpolyglycoside	30.0%
glyceryl monooleate	15.0%
water	20.0%

Example GSeed Treatment

Compound 26	20.00%
polyvinylpyrrolidone-vinyl acetate copolymer	5.00%
montan acid wax	5.00%
calcium ligninsulfonate	1.00%
polyoxyethylene/polyoxypropylene block copolymers	1.00%
stearyl alcohol (POE 20)	2.00%
polyorganosilane	0.20%
colorant red dye	0.05%
water	65.75%

Example HFertilizer Stick

Compound 28	2.5%
pyrrolidone-styrene copolymer	4.8%
tristyrylphenyl 16-ethoxylate	2.3%
talc	0.8%
corn starch	5.0%
Nitrophoska® Permanent 15-9-15 slow-release fertilizer (BASF)	36.0%
kaolin	38.0%
water	10.6%

Example IHigh Strength Concentrate

Compound 37	98.5%
silica aerogel	0.5%
synthetic amorphous fine silica	1.0%

Example JWettable Powder

Compound 40	65.0%
dodecylphenol polyethylene glycol ether	2.0%
sodium ligninsulfonate	4.0%
sodium silicoaluminate	6.0%
montmorillonite (calcined)	23.0%

Example KGranule

Compound 49	10.0%
attapulgite granules (low volatile matter, 0.71/0.30 mm; U.S.S. No. 25–50 sieves)	90.0%

Example LExtruded Pellet

Compound 52	25.0%
anhydrous sodium sulfate	10.0%
crude calcium ligninsulfonate	5.0%
sodium alkylnaphthalenesulfonate	1.0%
calcium/magnesium bentonite	59.0%

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Example MEmulsifiable Concentrate

Compound 62	10.0%
polyoxyethylene sorbitol hexoleate	20.0%
C ₆ –C ₁₀ fatty acid methyl ester	70.0%

Example NMicroemulsion

Compound 66	5.0%
polyvinylpyrrolidone-vinyl acetate copolymer	30.0%
alkylpolyglycoside	30.0%
glyceryl monooleate	15.0%
water	20.0%

Example OSeed Treatment

Compound 94	20.00%
polyvinylpyrrolidone-vinyl acetate copolymer	5.00%
montan acid wax	5.00%
calcium ligninsulfonate	1.00%
polyoxyethylene/polyoxypropylene block copolymers	1.00%
stearyl alcohol (POE 20)	2.00%
polyorganosilane	0.20%
colorant red dye	0.05%
water	65.75%

Example PFertilizer Stick

Compound 95	2.5%
pyrrolidone-styrene copolymer	4.8%
tristyrylphenyl 16-ethoxylate	2.3%
talc	0.8%
corn starch	5.0%
Nitrophoska® Permanent 15-9-15 slow-release fertilizer (BASF)	36.0%
kaolin	38.0%
water	10.6%

Compounds of this invention exhibit activity against a wide spectrum of invertebrate pests. These pests include invertebrates inhabiting a variety of environments such as, for example, plant foliage, roots, soil, harvested crops or other foodstuffs, building structures or animal integuments. These pests include, for example, invertebrates feeding on foliage (including leaves, stems, flowers and fruits), seeds, wood, textile fibers or animal blood or tissues, and thereby causing injury or damage to, for example, growing or stored agronomic crops, forests, greenhouse crops, ornamentals, nursery crops, stored foodstuffs or fiber products, or houses or other structures or their contents, or being harmful to animal health or public health. Those skilled in the art will appreciate that not all compounds are equally effective against all growth stages of all pests.

These present compounds and compositions are thus useful agronomically for protecting field crops from phytophagous invertebrate pests, and also nonagronomically for protecting other horticultural crops and plants from phytophagous invertebrate pests. This utility includes protecting crops and other plants (i.e. both agronomic and nonagronomic) that contain genetic material introduced by genetic engineering (i.e. transgenic) or modified by mutagenesis to provide advantageous traits. Examples of such traits include tolerance to

herbicides, resistance to phytophagous pests (e.g., insects, mites, aphids, spiders, nematodes, snails, plant-pathogenic fungi, bacteria and viruses), improved plant growth, increased tolerance of adverse growing conditions such as high or low temperatures, low or high soil moisture, and high salinity, increased flowering or fruiting, greater harvest yields, more rapid 5 maturation, higher quality and/or nutritional value of the harvested product, or improved storage or process properties of the harvested products. Transgenic plants can be modified to express multiple traits. Examples of plants containing traits provided by genetic engineering or mutagenesis include varieties of corn, cotton, soybean and potato expressing an insecticidal *Bacillus thuringiensis* toxin such as YIELD GARD®, KNOCKOUT®, 10 STARLINK®, BOLLGARD®, NuCOTN® and NEWLEAF®, and herbicide-tolerant varieties of corn, cotton, soybean and rapeseed such as ROUNDUP READY®, LIBERTY LINK®, IMI®, STS® and CLEARFIELD®, as well as crops expressing N-acetyltransferase (GAT) to provide resistance to glyphosate herbicide, or crops containing the HRA gene providing 15 resistance to herbicides inhibiting acetolactate synthase (ALS). The present compounds and compositions may interact synergistically with traits introduced by genetic engineering or modified by mutagenesis, thus enhancing phenotypic expression or effectiveness of the traits or increasing the invertebrate pest control effectiveness of the present compounds and 20 compositions. In particular, the present compounds and compositions may interact synergistically with the phenotypic expression of proteins or other natural products toxic to invertebrate pests to provide greater-than-additive control of these pests.

Compositions of this invention can also optionally comprise plant nutrients, e.g., a fertilizer composition comprising at least one plant nutrient selected from nitrogen, phosphorus, potassium, sulfur, calcium, magnesium, iron, copper, boron, manganese, zinc, and molybdenum. Of note are compositions comprising at least one fertilizer composition 25 comprising at least one plant nutrient selected from nitrogen, phosphorus, potassium, sulfur, calcium and magnesium. Compositions of the present invention which further comprise at least one plant nutrient can be in the form of liquids or solids. Of note are solid formulations 30 in the form of granules, small sticks or tablets. Solid formulations comprising a fertilizer composition can be prepared by mixing the compound or composition of the present invention with the fertilizer composition together with formulating ingredients and then preparing the formulation by methods such as granulation or extrusion. Alternatively solid formulations can be prepared by spraying a solution or suspension of a compound or 35 composition of the present invention in a volatile solvent onto a previous prepared fertilizer composition in the form of dimensionally stable mixtures, e.g., granules, small sticks or tablets, and then evaporating the solvent.

Examples of agronomic or nonagronomic invertebrate pests include eggs, larvae and adults of the order Lepidoptera, such as armyworms, cutworms, loopers, and heliothines in the family Noctuidae (e.g., pink stem borer (*Sesamia inferens* Walker), corn stalk borer (*Sesamia nonagrioides* Lefebvre), southern armyworm (*Spodoptera eridania* Cramer), fall

armyworm (*Spodoptera fugiperda* J. E. Smith), beet armyworm (*Spodoptera exigua* Hübner), cotton leafworm (*Spodoptera littoralis* Boisduval), yellowstriped armyworm (*Spodoptera ornithogalli* Guenée), black cutworm (*Agrotis ipsilon* Hufnagel), velvetbean caterpillar (*Anticarsia gemmatalis* Hübner), green fruitworm (*Lithophane antennata* Walker), cabbage armyworm (*Barathra brassicae* Linnaeus), soybean looper (*Pseudoplusia includens* Walker), cabbage looper (*Trichoplusia ni* Hübner), tobacco budworm (*Heliothis virescens* Fabricius)); borers, casebearers, webworms, coneworms, cabbageworms and skeletonizers from the family Pyralidae (e.g., European corn borer (*Ostrinia nubilalis* Hübner), navel orangeworm (*Amyelois transitella* Walker), corn root webworm (*Crambus caliginosellus* Clemens), sod webworms (Pyralidae: *Crambinae*) such as sod worm (*Herpetogramma licarsialis* Walker), sugarcane stem borer (*Chilo infuscatellus* Snellen), tomato small borer (*Neoleucinodes elegantalis* Guenée), green leafroller (*Cnaphalocerus medinalis*), grape leaffolder (*Desmia funeralis* Hübner), melon worm (*Diaphania nitidalis* Stoll), cabbage center grub (*Hellula hydralis* Guenée), yellow stem borer (*Scirpophaga incertulas* Walker), early shoot borer (*Scirpophaga infuscatellus* Snellen), white stem borer (*Scirpophaga innotata* Walker), top shoot borer (*Scirpophaga nivella* Fabricius), dark-headed rice borer (*Chilo polychrysus* Meyrick), cabbage cluster caterpillar (*Crocidiolomia binotalis* English)); leafrollers, budworms, seed worms, and fruit worms in the family Tortricidae (e.g., codling moth (*Cydia pomonella* Linnaeus), grape berry moth (*Endopiza viteana* Clemens), oriental fruit moth (*Grapholita molesta* Busck), citrus false codling moth (*Cryptophlebia leucotreta* Meyrick), citrus borer (*Ecdytolopha aurantiana* Lima), redbanded leafroller (*Argyrotaenia velutinana* Walker), obliquebanded leafroller (*Choristoneura rosaceana* Harris), light brown apple moth (*Epiphyas postvittana* Walker), European grape berry moth (*Eupoecilia ambiguella* Hübner), apple bud moth (*Pandemis pyrusana* Kearfott), omnivorous leafroller (*Platynota stultana* Walsingham), barred fruit-tree tortrix (*Pandemis cerasana* Hübner), apple brown tortrix (*Pandemis heparana* Denis & Schiffermüller)); and many other economically important lepidoptera (e.g., diamondback moth (*Plutella xylostella* Linnaeus), pink bollworm (*Pectinophora gossypiella* Saunders), gypsy moth (*Lymantria dispar* Linnaeus), peach fruit borer (*Carposina nipponensis* Walsingham), peach twig borer (*Anarsia lineatella* Zeller), potato tuberworm (*Phthorimaea operculella* Zeller), spotted teniform leafminer (*Lithocolletis blancardella* Fabricius), Asiatic apple leafminer (*Lithocolletis ringoniella* Matsumura), rice leaffolder (*Lerodea eufala* Edwards), apple leafminer (*Leucoptera scitella* Zeller)); eggs, nymphs and adults of the order Blattodea including cockroaches from the families Blattellidae and Blattidae (e.g., oriental cockroach (*Blatta orientalis* Linnaeus), Asian cockroach (*Blatella asahinai* Mizukubo), German cockroach (*Blattella germanica* Linnaeus), brownbanded cockroach (*Supella longipalpa* Fabricius), American cockroach (*Periplaneta americana* Linnaeus), brown cockroach (*Periplaneta brunnea* Burmeister), Madeira cockroach (*Leucophaea maderae* Fabricius)), smoky brown cockroach (*Periplaneta fuliginosa* Service), Australian Cockroach

(*Periplaneta australasiae* Fabr.), lobster cockroach (*Nauphoeta cinerea* Olivier) and smooth cockroach (*Symploce pallens* Stephens)); eggs, foliar feeding, fruit feeding, root feeding, seed feeding and vesicular tissue feeding larvae and adults of the order Coleoptera including weevils from the families Anthribidae, Bruchidae, and Curculionidae (e.g., boll weevil (5 *Anthonomus grandis* Boheman), rice water weevil (*Lissorhoptrus oryzophilus* Kuschel), granary weevil (*Sitophilus granarius* Linnaeus), rice weevil (*Sitophilus oryzae* Linnaeus)), annual bluegrass weevil (*Listronotus maculicollis* Dietz), bluegrass billbug (*Sphenophorus parvulus* Gyllenhal), hunting billbug (*Sphenophorus venatus vestitus*), Denver billbug (10 *Sphenophorus cicatrifriatus* Fahraeus)); flea beetles, cucumber beetles, rootworms, leaf beetles, potato beetles, and leafminers in the family Chrysomelidae (e.g., Colorado potato beetle (*Leptinotarsa decemlineata* Say), western corn rootworm (*Diabrotica virgifera virgifera* LeConte)); chafers and other beetles from the family Scarabaeidae (e.g., Japanese beetle (*Popillia japonica* Newman), oriental beetle (*Anomala orientalis* Waterhouse, *Exomala orientalis* (Waterhouse) Barraud), northern masked chafer (*Cyclocephala borealis* Arrow), southern masked chafer (*Cyclocephala immaculata* Olivier or *C. lurida* Bland), dung beetle and white grub (*Aphodius* spp.), black turfgrass ataenius (*Ataenius spretulus* Haldeman), green June beetle (*Cotinis nitida* Linnaeus), Asiatic garden beetle (*Maladera castanea* Arrow), May/June beetles (*Phyllophaga* spp.) and European chafer (20 *Rhizotrogus majalis* Razoumowsky)); carpet beetles from the family Dermestidae; wireworms from the family Elateridae; bark beetles from the family Scolytidae and flour beetles from the family Tenebrionidae. In addition, agronomic and nonagronomic pests include: eggs, adults and larvae of the order Dermaptera including earwigs from the family Forficulidae (e.g., European earwig (*Forficula auricularia* Linnaeus), black earwig (*Chelisoches morio* Fabricius)); eggs, immatures, adults and nymphs of the orders Hemiptera and Homoptera such as, plant bugs from the family Miridae, cicadas from the family Cicadidae, leafhoppers (25 (e.g. *Empoasca* spp.) from the family Cicadellidae, bed bugs (e.g., *Cimex lectularius* Linnaeus) from the family Cimicidae, planthoppers from the families Fulgoroidae and Delphacidae, treehoppers from the family Membracidae, psyllids from the family Psyllidae, whiteflies from the family Aleyrodidae, aphids from the family Aphididae, phylloxera from the family Phylloxeridae, mealybugs from the family Pseudococcidae, scales from the families Coccidae, Diaspididae and Margarodidae, lace bugs from the family Tingidae, stink bugs from the family Pentatomidae, chinch bugs (e.g., hairy chinch bug (*Blissus leucopterus hirtus* Montandon) and southern chinch bug (*Blissus insularis* Barber)) and other seed bugs from the family Lygaeidae, spittlebugs from the family Cercopidae squash bugs from the family Coreidae, and red bugs and cotton stainers from the family Pyrrhocoridae. Also included are eggs, larvae, nymphs and adults of the order Acari (mites) such as spider mites and red mites in the family Tetranychidae (e.g., European red mite (*Panonychus ulmi* Koch), two spotted spider mite (*Tetranychus urticae* Koch), McDaniel mite (*Tetranychus mcdanieli* McGregor)); flat mites in the family Tenuipalpidae (e.g., citrus flat mite (*Brevipalpus lewisi* 30 McGregor))

McGregor)); rust and bud mites in the family Eriophyidae and other foliar feeding mites and mites important in human and animal health, i.e. dust mites in the family Epidermoptidae, follicle mites in the family Demodicidae, grain mites in the family Glycyphagidae; ticks in the family Ixodidae, commonly known as hard ticks (e.g., deer tick (*Ixodes scapularis* Say),
5 Australian paralysis tick (*Ixodes holocyclus* Neumann), American dog tick (*Dermacentor variabilis* Say), lone star tick (*Amblyomma americanum* Linnaeus), brown dog tick (*Rhipicephalus sanguineus*) and cattle ticks (e.g., *Rhipicephalus annulatus* and *Rhipicephalus microplus*)) and ticks in the family Argasidae, commonly known as soft ticks (e.g., relapsing fever tick (*Ornithodoros turicata*), common fowl tick (*Argas radiatus*)); scab
10 and itch mites in the families Psoroptidae, Pyemotidae, and Sarcoptidae; eggs, adults and immatures of the order Orthoptera including grasshoppers, locusts and crickets (e.g., migratory grasshoppers (e.g., *Melanoplus sanguinipes* Fabricius, *M. differentialis* Thomas), American grasshoppers (e.g., *Schistocerca americana* Drury), desert locust (*Schistocerca gregaria* Forskal), migratory locust (*Locusta migratoria* Linnaeus), bush locust (*Zonocerus spp.*), house cricket (*Acheta domesticus* Linnaeus), mole crickets (e.g., tawny mole cricket (*Scapteriscus vicinus* Scudder) and southern mole cricket (*Scapteriscus borellii* Giglio-Tos)); eggs, adults and immatures of the order Diptera including leafminers (e.g., *Liriomyza spp.* such as serpentine vegetable leafminer (*Liriomyza sativae* Blanchard)), midges, fruit flies (Tephritidae), frit flies (e.g., *Oscinella frit* Linnaeus), soil maggots, house flies (e.g.,
20 *Musca domestica* Linnaeus), lesser house flies (e.g., *Fannia canicularis* Linnaeus, *F. femoralis* Stein), stable flies (e.g., *Stomoxys calcitrans* Linnaeus), face flies, horn flies, blow flies (e.g., *Chrysomya spp.*, *Phormia spp.*), and other muscoid fly pests, horse flies (e.g., *Tabanus spp.*), bot flies (e.g., *Gastrophilus spp.*, *Oestrus spp.*), cattle grubs (e.g., *Hypoderma spp.*), deer flies (e.g., *Chrysops spp.*), keds (e.g., *Melophagus ovinus* Linnaeus) and other
25 Brachycera, mosquitoes (e.g., *Aedes spp.*, *Anopheles spp.*, *Culex spp.*), black flies (e.g., *Prosimulium spp.*, *Simulium spp.*), biting midges, sand flies, sciarids, and other Nematocera; eggs, adults and immatures of the order Thysanoptera including onion thrips (*Thrips tabaci* Lindeman), flower thrips (*Frankliniella spp.*), and other foliar feeding thrips; insect pests of the order Hymenoptera including ants of the Family Formicidae including the Florida
30 carpenter ant (*Camponotus floridanus* Buckley), red carpenter ant (*Camponotus ferrugineus* Fabricius), black carpenter ant (*Camponotus pennsylvanicus* De Geer), white-footed ant (*Technomyrmex albipes* fr. Smith), big headed ants (*Pheidole sp.*), ghost ant (*Tapinoma melanocephalum* Fabricius); Pharaoh ant (*Monomorium pharaonis* Linnaeus), little fire ant (*Wasmannia auropunctata* Roger), fire ant (*Solenopsis geminata* Fabricius), red imported fire ant (*Solenopsis invicta* Buren), Argentine ant (*Iridomyrmex humilis* Mayr), crazy ant (*Paratrechina longicornis* Latreille), pavement ant (*Tetramorium caespitum* Linnaeus), cornfield ant (*Lasius alienus* Förster) and odorous house ant (*Tapinoma sessile* Say). Other Hymenoptera including bees (including carpenter bees), hornets, yellow jackets, wasps, and sawflies (*Neodiprion spp.*; *Cephus spp.*); insect pests of the order Isoptera including termites

in the Termitidae (e.g., *Macrotermes* sp., *Odontotermes obesus* Rambur), Kalotermitidae (e.g., *Cryptotermes* sp.), and Rhinotermitidae (e.g., *Reticulitermes* sp., *Coptotermes* sp., *Heterotermes tenuis* Hagen) families, the eastern subterranean termite (*Reticulitermes flavipes* Kollar), western subterranean termite (*Reticulitermes hesperus* Banks), Formosan 5 subterranean termite (*Coptotermes formosanus* Shiraki), West Indian drywood termite (*Incisitermes immigrans* Snyder), powder post termite (*Cryptotermes brevis* Walker), drywood termite (*Incisitermes snyderi* Light), southeastern subterranean termite (*Reticulitermes virginicus* Banks), western drywood termite (*Incisitermes minor* Hagen), arboreal termites such as *Nasutitermes* sp. and other termites of economic importance; insect 10 pests of the order Thysanura such as silverfish (*Lepisma saccharina* Linnaeus) and firebrat (*Thermobia domestica* Packard); insect pests of the order Mallophaga and including the head louse (*Pediculus humanus capitis* De Geer), body louse (*Pediculus humanus* Linnaeus), chicken body louse (*Menacanthus stramineus* Nitszsch), dog biting louse (*Trichodectes canis* De Geer), fluff louse (*Goniocotes gallinae* De Geer), sheep body louse (*Bovicola ovis* Schrank), short-nosed cattle louse (*Haematopinus eurysternus* Nitzsch), long-nosed cattle 15 louse (*Linognathus vituli* Linnaeus) and other sucking and chewing parasitic lice that attack man and animals; insect pests of the order Siphonoptera including the oriental rat flea (*Xenopsylla cheopis* Rothschild), cat flea (*Ctenocephalides felis* Bouche), dog flea (*Ctenocephalides canis* Curtis), hen flea (*Ceratophyllus gallinae* Schrank), sticktight flea (*Echidnophaga gallinacea* Westwood), human flea (*Pulex irritans* Linnaeus) and other fleas 20 afflicting mammals and birds. Additional arthropod pests covered include: spiders in the order Araneae such as the brown recluse spider (*Loxosceles reclusa* Gertsch & Mulaik) and the black widow spider (*Latrodectus mactans* Fabricius), and centipedes in the order Scutigeromorpha such as the house centipede (*Scutigera coleoptrata* Linnaeus). Compounds 25 of the present invention also have activity on members of the Classes Nematoda, Cestoda, Trematoda, and Acanthocephala including economically important members of the orders Strongylida, Ascaridida, Oxyurida, Rhabditida, Spirurida, and Enoplida such as but not limited to economically important agricultural pests (i.e. root knot nematodes in the genus *Meloidogyne*, lesion nematodes in the genus *Pratylenchus*, stubby root nematodes in the 30 genus *Trichodorus*, etc.) and animal and human health pests (i.e. all economically important flukes, tapeworms, and roundworms, such as *Strongylus vulgaris* in horses, *Toxocara canis* in dogs, *Haemonchus contortus* in sheep, *Dirofilaria immitis* Leidy in dogs, *Anoplocephala perfoliata* in horses, *Fasciola hepatica* Linnaeus in ruminants, etc.).

Compounds of the invention show particularly high activity against pests in the order 35 Lepidoptera (e.g., *Alabama argillacea* Hübner (cotton leaf worm), *Archips argyrospila* Walker (fruit tree leaf roller), *A. rosana* Linnaeus (European leaf roller) and other *Archips* species, *Chilo suppressalis* Walker (rice stem borer), *Cnaphalocrosis medinalis* Guenée (rice leaf roller), *Crambus caliginosellus* Clemens (corn root webworm), *Crambus teterrellus* Zincken (bluegrass webworm), *Cydia pomonella* Linnaeus (codling moth), *Earias insulana*

Boisduval (spiny bollworm), *Earias vittella* Fabricius (spotted bollworm), *Helicoverpa armigera* Hübner (American bollworm), *Helicoverpa zea* Boddie (corn earworm), *Heliothis virescens* Fabricius (tobacco budworm), *Herpetogramma licarsialis* Walker (sod webworm), *Lobesia botrana* Denis & Schiffermüller (grape berry moth), *Pectinophora gossypiella* Saunders (pink bollworm), *Phyllocnistis citrella* Stainton (citrus leafminer), *Pieris brassicae* Linnaeus (large white butterfly), *Pieris rapae* Linnaeus (small white butterfly), *Plutella xylostella* Linnaeus (diamondback moth), *Spodoptera exigua* Hübner (beet armyworm), *Spodoptera litura* Fabricius (tobacco cutworm, cluster caterpillar), *Spodoptera frugiperda* J. E. Smith (fall armyworm), *Trichoplusia ni* Hübner (cabbage looper) and *Tuta absoluta* Meyrick (tomato leafminer)).

Compounds of the invention also have significant activity on members from the order Homoptera including: *Acyrthosiphon pisum* Harris (pea aphid), *Aphis craccivora* Koch (cowpea aphid), *Aphis fabae* Scopoli (black bean aphid), *Aphis gossypii* Glover (cotton aphid, melon aphid), *Aphis pomi* De Geer (apple aphid), *Aphis spiraecola* Patch (spirea aphid), *Aulacorthum solani* Kaltenbach (foxglove aphid), *Chaetosiphon fragaefolii* Cockerell (strawberry aphid), *Diuraphis noxia* Kurdjumov/Mordvilko (Russian wheat aphid), *Dysaphis plantaginea* Paaserini (rosy apple aphid), *Eriosoma lanigerum* Hausmann (woolly apple aphid), *Hyalopterus pruni* Geoffroy (mealy plum aphid), *Lipaphis erysimi* Kaltenbach (turnip aphid), *Metopolophium dirrhodium* Walker (cereal aphid), *Macrosiphum euphorbiae* Thomas (potato aphid), *Myzus persicae* Sulzer (peach-potato aphid, green peach aphid), *Nasonovia ribisnigri* Mosley (lettuce aphid), *Pemphigus* spp. (root aphids and gall aphids), *Rhopalosiphum maidis* Fitch (corn leaf aphid), *Rhopalosiphum padi* Linnaeus (bird cherry-oat aphid), *Schizaphis graminum* Rondani (greenbug), *Sitobion avenae* Fabricius (English grain aphid), *Theroaphis maculata* Buckton (spotted alfalfa aphid), *Toxoptera aurantii* Boyer de Fonscolombe (black citrus aphid), and *Toxoptera citricida* Kirkaldy (brown citrus aphid); *Adelges* spp. (adelgids); *Phylloxera devastatrix* Pergande (pecan phylloxera); *Bemisia tabaci* Gennadius (tobacco whitefly, sweetpotato whitefly), *Bemisia argentifolii* Bellows & Perring (silverleaf whitefly), *Dialeurodes citri* Ashmead (citrus whitefly) and *Trialeurodes vaporariorum* Westwood (greenhouse whitefly); *Empoasca fabae* Harris (potato leafhopper), *Laodelphax striatellus* Fallen (smaller brown planthopper), *Macrolestes quadrilineatus* Forbes (aster leafhopper), *Nephrotettix cinticeps* Uhler (green leafhopper), *Nephrotettix nigropictus* Stål (rice leafhopper), *Nilaparvata lugens* Stål (brown planthopper), *Peregrinus maidis* Ashmead (corn planthopper), *Sogatella furcifera* Horvath (white-backed planthopper), *Sogatodes oryzicola* Muir (rice delphacid), *Typhlocyba pomaria* McAtee white apple leafhopper, *Erythroneura* spp. (grape leafhoppers); *Magicicada septendecim* Linnaeus (periodical cicada); *Icerya purchasi* Maskell (cottony cushion scale), *Quadraspidiotus perniciosus* Comstock (San Jose scale); *Planococcus citri* Risso (citrus mealybug); *Pseudococcus* spp. (other mealybug complex); *Cacopsylla pyricola* Foerster (pear psylla), *Trioza diospyri* Ashmead (persimmon psylla).

Compounds of this invention may also have activity on members from the order Hemiptera including: *Acrosternum hilare* Say (green stink bug), *Anasa tristis* De Geer (squash bug), *Blissus leucopterus leucopterus* Say (chinch bug), *Cimex lectularius* Linnaeus (bed bug) *Corythucha gossypii* Fabricius (cotton lace bug), *Cyrtopeltis modesta* Distant (tomato bug), *Dysdercus suturellus* Herrich-Schäffer (cotton stainer), *Euchistus servus* Say (brown stink bug), *Euchistus variolarius* Palisot de Beauvois (one-spotted stink bug), *Graptosthetus* spp. (complex of seed bugs), *Leptoglossus corculus* Say (leaf-footed pine seed bug), *Lygus lineolaris* Palisot de Beauvois (tarnished plant bug), *Nezara viridula* Linnaeus (southern green stink bug), *Oebalus pugnax* Fabricius (rice stink bug), *Oncopeltus fasciatus* Dallas (large milkweed bug), *Pseudatomoscelis seriatus* Reuter (cotton fleahopper). Other insect orders controlled by compounds of the invention include Thysanoptera (e.g., *Frankliniella occidentalis* Pergande (western flower thrips), *Scirtothrips citri* Moulton (citrus thrips), *Sericothrips variabilis* Beach (soybean thrips), and *Thrips tabaci* Lindeman (onion thrips); and the order Coleoptera (e.g., *Leptinotarsa decemlineata* Say (Colorado potato beetle), *Epilachna varivestis* Mulsant (Mexican bean beetle) and wireworms of the genera *Agriotes*, *Athous* or *Limonius*).

Note that some contemporary classification systems place Homoptera as a suborder within the order Hemiptera.

Of note is use of compounds of this invention for controlling silverleaf whitefly (*Bemisia argentifolii*). Of note is use of compounds of this invention for controlling western flower thrip (*Frankliniella occidentalis*). Of note is use of compounds of this invention for controlling potato leafhopper (*Empoasca fabae*). Of note is use of compounds of this invention for controlling corn planthopper (*Peregrinus maidis*). Of note is use of compounds of this invention for controlling cotton melon aphid (*Aphis gossypii*). Of note is use of compounds of this invention for controlling green peach aphid (*Myzus persicae*). Of note is use of compounds of this invention for controlling diamondback moth (*Plutella xylostella*). Of note is use of compounds of this invention for controlling fall armyworm (*Spodoptera frugiperda*).

Compounds of this invention can also be mixed with one or more other biologically active compounds or agents including insecticides, fungicides, nematocides, bactericides, acaricides, herbicides, herbicide safeners, growth regulators such as insect molting inhibitors and rooting stimulants, chemosterilants, semiochemicals, repellents, attractants, pheromones, feeding stimulants, other biologically active compounds or entomopathogenic bacteria, virus or fungi to form a multi-component pesticide giving an even broader spectrum of agronomic and nonagronomic utility. Thus the present invention also pertains to a composition comprising a compound of Formula 1 (i.e. in a biologically effective amount), at least one additional component selected from the group consisting of surfactants, solid diluents and liquid diluents, and at least one additional biologically active compound or agent. For mixtures of the present invention, the other biologically active compounds or agents can be

formulated together with the present compounds, including the compounds of Formula 1, to form a premix, or the other biologically active compounds or agents can be formulated separately from the present compounds, including the compounds of Formula 1, and the two formulations combined together before application (e.g., in a spray tank) or, alternatively, 5 applied in succession.

Examples of such biologically active compounds or agents with which compounds of this invention can be formulated are insecticides such as abamectin, acephate, acequinocyl, acetamiprid, acrinathrin, amidoflumet, amitraz, avermectin, azadirachtin, azinphos-methyl, bifenthrin, bifenazate, bistrifluron, borate, 3-bromo-1-(3-chloro-2-pyridinyl)-N-[4-cyano-2- 10 methyl-6-[(methylamino)carbonyl]phenyl]-1H-pyrazole-5-carboxamide, buprofezin, cadusafos, carbaryl, carbofuran, cartap, carzol, chlorantraniliprole, chlorfenapyr, chlorfluazuron, chlorpyrifos, chlorpyrifos-methyl, chromafenozone, clofentezin, clothianidin, cyflumetofen, cyfluthrin, beta-cyfluthrin, cyhalothrin, gamma-cyhalothrin, lambda-cyhalothrin, 15 cypermethrin, alpha-cypermethrin, zeta-cypermethrin, cyromazine, deltamethrin, diafenthuron, diazinon, dieldrin, diflubenzuron, dimefluthrin, dimehypo, dimethoate, dinotefuran, diofenolan, emamectin, endosulfan, esfenvalerate, ethiprole, etofenprox, etoxazole, fenbutatin oxide, fenothiocarb, fenoxy carb, fenpropothrin, fenvalerate, fipronil, flonicamid, flubendiamide, flucythrinate, flufenirim, flufenoxuron, fluvalinate, tau-fluvalinate, fonophos, formetanate, fosthiazate, halofenozone, hexaflumuron, 20 hexythiazox, hydramethylnon, imidacloprid, indoxacarb, insecticidal soaps, isofenphos, lufenuron, malathion, metaflumizone, metaldehyde, methamidophos, methidathion, methiodicarb, methomyl, methoprene, methoxychlor, metofluthrin, monocrotophos, methoxyfenozone, nitenpyram, nithiazine, novaluron, noviflumuron, oxamyl, parathion, 25 parathion-methyl, permethrin, phorate, phosalone, phosmet, phosphamidon, pirimicarb, profenofos, profluthrin, propargite, protrifenbute, pymetrozine, pyrafluprole, pyrethrin, pyridaben, pyridalyl, pyrifluquinazon, pyriproxyfen, rotenone, ryanodine, spinetoram, spinosad, spirodiclofen, spiromesifen, spirotetramat, sulprofos, tebufenozone, 30 tebufenpyrad, teflubenzuron, tefluthrin, terbufos, tetrachlorvinphos, tetramethrin, thiacloprid, thiamethoxam, thiodicarb, thiosultap-sodium, tolfenpyrad, tralomethrin, triazamate, trichlorfon, triflumuron, *Bacillus thuringiensis* delta-endotoxins, entomopathogenic bacteria, entomopathogenic viruses and entomopathogenic fungi.

Of note are insecticides such as abamectin, acetamiprid, acrinathrin, amitraz, avermectin, azadirachtin, bifenthrin, 3-bromo-1-(3-chloro-2-pyridinyl)-N-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1H-pyrazole-5-carboxamide, buprofezin, 35 cadusafos, carbaryl, cartap, chlorantraniliprole, chlorfenapyr, chlorpyrifos, clothianidin, cyfluthrin, beta-cyfluthrin, cyhalothrin, gamma-cyhalothrin, lambda-cyhalothrin, cypermethrin, alpha-cypermethrin, zeta-cypermethrin, cyromazine, deltamethrin, dieldrin, dinotefuran, diofenolan, emamectin, endosulfan, esfenvalerate, ethiprole, etofenprox, etoxazole, fenothiocarb, fenoxy carb, fenvalerate, fipronil, flonicamid, flubendiamide,

flufenoxuron, fluvalinate, formetanate, fosthiazate, hexaflumuron, hydramethylnon, imidacloprid, indoxacarb, lufenuron, metaflumizone, methiodicarb, methomyl, methoprene, methoxyfenozide, nitenpyram, nithiazine, novaluron, oxamyl, pymetrozine, pyrethrin, pyridaben, pyridalyl, pyriproxyfen, ryanodine, spinetoram, spinosad, spirodiclofen, 5 spromesifen, spirotetramat, tebufenozide, tetramethrin, thiacloprid, thiamethoxam, thiodicarb, thiosultap-sodium, tralomethrin, triazamate, triflumuron, *Bacillus thuringiensis* delta-endotoxins, all strains of *Bacillus thuringiensis* and all strains of *Nucleo polyhydrosis* viruses.

One embodiment of biological agents for mixing with compounds of this invention 10 include entomopathogenic bacteria such as *Bacillus thuringiensis*, and the encapsulated delta-endotoxins of *Bacillus thuringiensis* (e.g., Cellcap, MPV, MPVII); entomopathogenic fungi such as green muscardine fungus; and entomopathogenic (both naturally occurring and genetically modified) viruses including baculovirus, nucleopolyhedro virus (NPV) such as *Helicoverpa zea* nucleopolyhedrovirus (HzNPV), *Anagrypha falcifera* nucleopolyhedrovirus 15 (AfNPV); and granulosis virus (GV) such as *Cydia pomonella* granulosis virus (CpGV).

Of particular note is such a combination where the other invertebrate pest control active ingredient belongs to a different chemical class or has a different site of action than the compound of Formula 1. In certain instances, a combination with at least one other invertebrate pest control active ingredient having a similar spectrum of control but a 20 different site of action will be particularly advantageous for resistance management. Thus, a composition of the present invention can further comprise at least one additional invertebrate pest control active ingredient having a similar spectrum of control but belonging to a different chemical class or having a different site of action. These additional biologically active compounds or agents include, but are not limited to, sodium channel modulators such 25 as bifenthrin, cypermethrin, cyhalothrin, lambda-cyhalothrin, cyfluthrin, beta-cyfluthrin, deltamethrin, dimefluthrin, esfenvalerate, fenvalerate, indoxacarb, metofluthrin, profluthrin, pyrethrin and tralomethrin; cholinesterase inhibitors such as chlorpyrifos, methomyl, oxamyl, thiodicarb and triazamate; neonicotinoids such as acetamiprid, clothianidin, dinotefuran, imidacloprid, nitenpyram, nithiazine, thiacloprid and thiamethoxam; insecticidal 30 macrocyclic lactones such as spinetoram, spinosad, abamectin, avermectin and emamectin; GABA (γ -aminobutyric acid)-gated chloride channel antagonists such as avermectin or blockers such as ethiprole and fipronil; chitin synthesis inhibitors such as buprofezin, cyromazine, flufenoxuron, hexaflumuron, lufenuron, novaluron, noviflumuron and triflumuron; juvenile hormone mimics such as diofenolan, fenoxy carb, methoprene and 35 pyriproxyfen; octopamine receptor ligands such as amitraz; molting inhibitors and ecdysone agonists such as azadirachtin, methoxyfenozide and tebufenozide; ryanodine receptor ligands such as ryanodine, anthranilic diamides such as chlorantraniliprole (see U.S. Patent 6,747,047, PCT Publications WO 2003/015518 and WO 2004/067528) and flubendiamide (see U.S. Patent 6,603,044); nereistoxin analogs such as cartap; mitochondrial electron

transport inhibitors such as chlорfenapyr, hydramethylnon and pyridaben; lipid biosynthesis inhibitors such as spirodiclofen and spiromesifen; cyclodiene insecticides such as dieldrin or endosulfan; pyrethroids; carbamates; insecticidal ureas; and biological agents including nucleopolyhedro viruses (NPV), members of *Bacillus thuringiensis*, encapsulated delta-5 endotoxins of *Bacillus thuringiensis*, and other naturally occurring or genetically modified insecticidal viruses.

Further examples of biologically active compounds or agents with which compounds of this invention can be formulated are: fungicides such as acibenzolar, aldimorph, amisulbrom, azaconazole, azoxystrobin, benalaxyl, benomyl, benthiavalicarb, benthiavalicarb-isopropyl, binomial, biphenyl, bitertanol, blasticidin-S, Bordeaux mixture (Tribasic copper sulfate), boscalid/nicobifen, bromuconazole, bupirimate, buthiobate, carboxin, carpropamid, captafol, captan, carbendazim, chloroneb, chlorothalonil, chlozolinate, clotrimazole, copper oxychloride, copper salts such as copper sulfate and copper hydroxide, cyazofamid, cyflunamid, cymoxanil, cyproconazole, cyprodinil, dichlofluanid, diclocymet, diclomezine, dicloran, diethofencarb, difenoconazole, dimethomorph, dimoxystrobin, diniconazole, diniconazole-M, dinocap, discostrobin, dithianon, dodemorph, dodine, econazole, etaconazole, edifenphos, epoxiconazole, ethaboxam, ethirimol, ethridiazole, famoxadone, fenamidone, fenarimol, fenbuconazole, fencaramid, fenfuram, fenhexamide, fenoxanil, fenpiclonil, fenpropidin, fenpropimorph, fentin acetate, fentin hydroxide, ferbam, ferfurazoate, ferimzone, fluazinam, fludioxonil, flumetover, fluopicolide, fluoxastrobin, fluquinconazole, fluquinconazole, flusilazole, flusulfamide, flutolanil, flutriafol, folpet, fosetyl-aluminum, fuberidazole, furalaxyl, furametapyr, hexaconazole, hymexazole, guazatine, imazalil, imibenconazole, iminoctadine, iodicarb, ipconazole, iprobenfos, iprodione, iprovalicarb, isoconazole, isoprothiolane, kasugamycin, kresoxim-methyl, mancozeb, mandipropamid, maneb, mapanipyrim, mefenoxam, mepronil, metalaxyl, metconazole, methasulfocarb, metiram, metominostrobin/fenominostrobin, mepanipyrim, metrafenone, miconazole, myclobutanil, neo-asozin (ferric methanearsonate), nuarimol, octhilinone, ofurace, orysastrobin, oxadixyl, oxolinic acid, oxpoconazole, oxycarboxin, paclobutrazol, penconazole, pencycuron, penthiopyrad, perfurazoate, phosphonic acid, phthalide, picobenzamid, picoxystrobin, polyoxin, probenazole, prochloraz, procymidone, propamocarb, propamocarb-hydrochloride, propiconazole, propineb, proquinazid, prothioconazole, pyraclostrobin, pryzophos, pyrifenoxy, pyrimethanil, pyrifenoxy, pyrolnitrine, pyroquilon, quinconazole, quinoxifen, quintozene, silthiofam, simeconazole, spiroxamine, streptomycin, sulfur, tebuconazole, techrazene, tecloftalam, tecnazene, tетraconazole, thiabendazole, thifluzamide, thiophanate, thiophanate-methyl, thiram, tiadinil, tolclofos-methyl, tolyfluanid, triadimefon, triadimenol, triarimol, triazoxide, tridemorph, trimoprhamide tricyclazole, trifloxystrobin, triforine, triticonazole, uniconazole, validamycin, vinclozolin, zineb, ziram, and zoxamide; nematocides such as aldicarb, imicyafos, oxamyl and fenamiphos; bactericides such as

streptomycin; acaricides such as amitraz, chinomethionat, chlorobenzilate, cyhexatin, dicofol, dienochlor, etoxazole, fenazaquin, fenbutatin oxide, fenpropothrin, fenpyroximate, hexythiazox, propargite, pyridaben and tebufenpyrad.

In certain instances, combinations of a compound of this invention with other biologically active (particularly invertebrate pest control) compounds or agents (i.e. active ingredients) can result in a greater-than-additive (i.e. synergistic) effect. Reducing the quantity of active ingredients released in the environment while ensuring effective pest control is always desirable. When synergism of invertebrate pest control active ingredients occurs at application rates giving agronomically satisfactory levels of invertebrate pest control, such combinations can be advantageous for reducing crop production cost and decreasing environmental load.

Compounds of this invention and compositions thereof can be applied to plants genetically transformed to express proteins toxic to invertebrate pests (such as *Bacillus thuringiensis* delta-endotoxins). Such an application may provide a broader spectrum of plant protection and be advantageous for resistance management. The effect of the exogenously applied invertebrate pest control compounds of this invention may be synergistic with the expressed toxin proteins.

General references for these agricultural protectants (i.e. insecticides, fungicides, nematocides, acaricides, herbicides and biological agents) include *The Pesticide Manual, 13th Edition*, C. D. S. Tomlin, Ed., British Crop Protection Council, Farnham, Surrey, U.K., 2003 and *The BioPesticide Manual, 2nd Edition*, L. G. Copping, Ed., British Crop Protection Council, Farnham, Surrey, U.K., 2001.

For embodiments where one or more of these various mixing partners are used, the weight ratio of these various mixing partners (in total) to the compound of Formula 1 is typically between about 1:3000 and about 3000:1. Of note are weight ratios between about 1:300 and about 300:1 (for example ratios between about 1:30 and about 30:1). One skilled in the art can easily determine through simple experimentation the biologically effective amounts of active ingredients necessary for the desired spectrum of biological activity. It will be evident that including these additional components can expand the spectrum of invertebrate pests controlled beyond the spectrum controlled by the compound of Formula 1 alone.

Table A lists specific combinations of a compound of Formula 1 with other invertebrate pest control agents illustrative of the mixtures, compositions and methods of the present invention. The first column of Table A lists the specific invertebrate pest control agents (e.g., "Abamectin" in the first line). The second column of Table A lists the mode of action (if known) or chemical class of the invertebrate pest control agents. The third column of Table A lists embodiment(s) of ranges of weight ratios for rates at which the invertebrate pest control agent can be applied relative to a compound of Formula 1 (e.g., "50:1 to 1:50" of abamectin relative to a compound of Formula 1 by weight). Thus, for example, the first

line of Table A specifically discloses the combination of a compound of Formula 1 with abamectin can be applied in a weight ratio between 50:1 to 1:50. The remaining lines of Table A are to be construed similarly. Of further note Table A lists specific combinations of a compound of Formula 1 with other invertebrate pest control agents illustrative of the mixtures, compositions and methods of the present invention and includes additional embodiments of weight ratio ranges for application rates.

Table A

Invertebrate Pest Control Agent	Mode of Action or Chemical Class	Typical Weight Ratio
Abamectin	macrocyclic lactones	50:1 to 1:50
Acetamiprid	neonicotinoids	150:1 to 1:200
Amitraz	octopamine receptor ligands	200:1 to 1:100
Avermectin	macrocyclic lactones	50:1 to 1:50
Azadirachtin	ecdysone agonists	100:1 to 1:120
Beta-cyfluthrin	sodium channel modulators	150:1 to 1:200
Bifenthrin	sodium channel modulators	100:1 to 1:10
Buprofezin	chitin synthesis inhibitors	500:1 to 1:50
Cartap	nereistoxin analogs	100:1 to 1:200
Chlorantraniliprole	ryanodine receptor ligands	100:1 to 1:120
Chlорfenапyr	mitochondrial electron transport inhibitors	300:1 to 1:200
Chlorpyrifos	cholinesterase inhibitors	500:1 to 1:200
Clothianidin	neonicotinoids	100:1 to 1:400
Cyfluthrin	sodium channel modulators	150:1 to 1:200
Cyhalothrin	sodium channel modulators	150:1 to 1:200
Cypermethrin	sodium channel modulators	150:1 to 1:200
Cyromazine	chitin synthesis inhibitors	400:1 to 1:50
Deltamethrin	sodium channel modulators	50:1 to 1:400
Dieldrin	cyclodiene insecticides	200:1 to 1:100
Dinotefuran	neonicotinoids	150:1 to 1:200
Diofenolan	molting inhibitor	150:1 to 1:200
Emamectin	macrocyclic lactones	50:1 to 1:10
Endosulfan	cyclodiene insecticides	200:1 to 1:100
Esfenvalerate	sodium channel modulators	100:1 to 1:400
Ethiprole	GABA-regulated chloride channel blockers	200:1 to 1:100
Fenothiocarb		150:1 to 1:200
Fenoxy carb	juvenile hormone mimics	500:1 to 1:100

Invertebrate Pest Control Agent	Mode of Action or Chemical Class	Typical Weight Ratio
Fenvalerate	sodium channel modulators	150:1 to 1:200
Fipronil	GABA-regulated chloride channel blockers	150:1 to 1:100
Flonicamid		200:1 to 1:100
Flubendiamide	ryanodine receptor ligands	100:1 to 1:120
Flufenoxuron	chitin synthesis inhibitors	200:1 to 1:100
Hexaflumuron	chitin synthesis inhibitors	300:1 to 1:50
Hydramethylnon	mitochondrial electron transport inhibitors	150:1 to 1:250
Imidacloprid	neonicotinoids	1000:1 to 1:1000
Indoxacarb	sodium channel modulators	200:1 to 1:50
Lambda-cyhalothrin	sodium channel modulators	50:1 to 1:250
Lufenuron	chitin synthesis inhibitors	500:1 to 1:250
Metaflumizone		200:1 to 1:200
Methomyl	cholinesterase inhibitors	500:1 to 1:100
Methoprene	juvenile hormone mimics	500:1 to 1:100
Methoxyfenozide	ecdysone agonists	50:1 to 1:50
Nitenpyram	neonicotinoids	150:1 to 1:200
Nithiazine	neonicotinoids	150:1 to 1:200
Novaluron	chitin synthesis inhibitors	500:1 to 1:150
Oxamyl	cholinesterase inhibitors	200:1 to 1:200
Pymetrozine		200:1 to 1:100
Pyrethrin	sodium channel modulators	100:1 to 1:10
Pyridaben	mitochondrial electron transport inhibitors	200:1 to 1:100
Pyridalyl		200:1 to 1:100
Pyriproxyfen	juvenile hormone mimics	500:1 to 1:100
Ryanodine	ryanodine receptor ligands	100:1 to 1:120
Spinetoram	macrocyclic lactones	150:1 to 1:100
Spinosad	macrocyclic lactones	500:1 to 1:10
Spirodiclofen	lipid biosynthesis inhibitors	200:1 to 1:200
Spiromesifen	lipid biosynthesis inhibitors	200:1 to 1:200
Tebufenozide	ecdysone agonists	500:1 to 1:250
Thiacloprid	neonicotinoids	100:1 to 1:200
Thiamethoxam	neonicotinoids	1250:1 to 1:1000
Thiodicarb	cholinesterase inhibitors	500:1 to 1:400
Thiosultap-sodium		150:1 to 1:100
Tralomethrin	sodium channel modulators	150:1 to 1:200

Invertebrate Pest Control Agent	Mode of Action or Chemical Class	Typical Weight Ratio
Triazamate	cholinesterase inhibitors	250:1 to 1:100
Triflumuron	chitin synthesis inhibitors	200:1 to 1:100
<i>Bacillus thuringiensis</i>	biological agents	50:1 to 1:10
<i>Bacillus thuringiensis</i> delta-endotoxin	biological agents	50:1 to 1:10
NPV (e.g., Gemstar)	biological agents	50:1 to 1:10
(a)	ryanodine receptor ligands	100:1 to 1:120

(a) 3-bromo-1-(3-chloro-2-pyridinyl)-N-[4-cyano-2-methyl-6-[(methylamino)carbonyl]-phenyl]-1*H*-pyrazole-5-carboxamide

Of note is the composition of the present invention wherein the at least one additional biologically active compound or agent is selected from the Invertebrate Pest Control Agents listed in Table A above.

The weight ratios of a compound, including a compound of Formula 1, to the additional invertebrate pest control agent typically are between 1000:1 and 1:1000, with one embodiment being between 500:1 and 1:500, another embodiment being between 250:1 and 1:200 and another embodiment being between 100:1 and 1:50.

Listed below in Table B are embodiments of specific compositions comprising a compound of Formula 1 (compound numbers refer to compounds in Index Table A) and an additional invertebrate pest control agent.

Table B

Mixture No.	Comp. and Invertebrate Pest Control Agent		Mixture No.	Comp. and Invertebrate Pest Control Agent
A-1	1 and Abamectin		B-1	11 and Abamectin
A-2	1 and Acetamiprid		B-2	11 and Acetamiprid
A-3	1 and Amitraz		B-3	11 and Amitraz
A-4	1 and Avermectin		B-4	11 and Avermectin
A-5	1 and Azadirachtin		B-5	11 and Azadirachtin
A-6	1 and Beta-cyfluthrin		B-6	11 and Beta-cyfluthrin
A-7	1 and Bifenthrin		B-7	11 and Bifenthrin
A-8	1 and Buprofezin		B-8	11 and Buprofezin
A-9	1 and Cartap		B-9	11 and Cartap
A-10	1 and Chlorantraniliprole		B-10	11 and Chlorantraniliprole
A-11	1 and Chlорfenapyr		B-11	11 and Chlорfenapyr
A-12	1 and Chlorpyrifos		B-12	11 and Chlorpyrifos
A-13	1 and Clothianidin		B-13	11 and Clothianidin
A-14	1 and Cyfluthrin		B-14	11 and Cyfluthrin

Mixture No.	Comp. No.	and	Invertebrate Pest Control Agent		Mixture No.	Comp. No.	and	Invertebrate Pest Control Agent
A-15	1	and	Cyhalothrin		B-15	11	and	Cyhalothrin
A-16	1	and	Cypermethrin		B-16	11	and	Cypermethrin
A-17	1	and	Cyromazine		B-17	11	and	Cyromazine
A-18	1	and	Deltamethrin		B-18	11	and	Deltamethrin
A-19	1	and	Dieldrin		B-19	11	and	Dieldrin
A-20	1	and	Dinotefuran		B-20	11	and	Dinotefuran
A-21	1	and	Diofenolan		B-21	11	and	Diofenolan
A-22	1	and	Emamectin		B-22	11	and	Emamectin
A-23	1	and	Endosulfan		B-23	11	and	Endosulfan
A-24	1	and	Esfenvalerate		B-24	11	and	Esfenvalerate
A-25	1	and	Ethiprole		B-25	11	and	Ethiprole
A-26	1	and	Fenothiocarb		B-26	11	and	Fenothiocarb
A-27	1	and	Fenoxy carb		B-27	11	and	Fenoxy carb
A-28	1	and	Fenvale rate		B-28	11	and	Fenvale rate
A-29	1	and	Fipronil		B-29	11	and	Fipronil
A-30	1	and	Flonicamid		B-30	11	and	Flonicamid
A-31	1	and	Flubendiamide		B-31	11	and	Flubendiamide
A-32	1	and	Flufenoxuron		B-32	11	and	Flufenoxuron
A-33	1	and	Hexaflumuron		B-33	11	and	Hexaflumuron
A-34	1	and	Hydramethyl non		B-34	11	and	Hydramethyl non
A-35	1	and	Imidacloprid		B-35	11	and	Imidacloprid
A-36	1	and	Indoxacarb		B-36	11	and	Indoxacarb
A-37	1	and	Lambda-cyhalothrin		B-37	11	and	Lambda-cyhalothrin
A-38	1	and	Lufenuron		B-38	11	and	Lufenuron
A-39	1	and	Metaflumizone		B-39	11	and	Metaflumizone
A-40	1	and	Methomyl		B-40	11	and	Methomyl
A-41	1	and	Methoprene		B-41	11	and	Methoprene
A-42	1	and	Methoxyfenozide		B-42	11	and	Methoxyfenozide
A-43	1	and	Nitenpyram		B-43	11	and	Nitenpyram
A-44	1	and	Nithiazine		B-44	11	and	Nithiazine
A-45	1	and	Novaluron		B-45	11	and	Novaluron
A-46	1	and	Oxamyl		B-46	11	and	Oxamyl
A-47	1	and	Pymetrozine		B-47	11	and	Pymetrozine
A-48	1	and	Pyrethrin		B-48	11	and	Pyrethrin
A-49	1	and	Pyridaben		B-49	11	and	Pyridaben
A-50	1	and	Pyridalyl		B-50	11	and	Pyridalyl
A-51	1	and	Pyriproxyfen		B-51	11	and	Pyriproxyfen

Mixture No.	Comp. No.	and	Invertebrate Pest Control Agent	Mixture No.	Comp. No.	and	Invertebrate Pest Control Agent
A-52	1	and	Ryanodine	B-52	11	and	Ryanodine
A-53	1	and	Spinetoram	B-53	11	and	Spinetoram
A-54	1	and	Spinosad	B-54	11	and	Spinosad
A-55	1	and	Spirodiclofen	B-55	11	and	Spirodiclofen
A-56	1	and	Spiromesifen	B-56	11	and	Spiromesifen
A-57	1	and	Tebufenozide	B-57	11	and	Tebufenozide
A-58	1	and	Thiacloprid	B-58	11	and	Thiacloprid
A-59	1	and	Thiamethoxam	B-59	11	and	Thiamethoxam
A-60	1	and	Thiodicarb	B-60	11	and	Thiodicarb
A-61	1	and	Thiosultap-sodium	B-61	11	and	Thiosultap-sodium
A-62	1	and	Tralomethrin	B-62	11	and	Tralomethrin
A-63	1	and	Triazamate	B-63	11	and	Triazamate
A-64	1	and	Triflumuron	B-64	11	and	Triflumuron
A-65	1	and	<i>Bacillus thuringiensis</i>	B-65	11	and	<i>Bacillus thuringiensis</i>
A-66	1	and	<i>Bacillus thuringiensis</i>	B-66	11	and	<i>Bacillus thuringiensis</i>
			delta-endotoxin				delta-endotoxin
A-67	1	and	NPV (e.g., Gemstar)	B-67	11	and	NPV (e.g., Gemstar)
C-1	17	and	Abamectin	D-1	20	and	Abamectin
C-2	17	and	Acetamiprid	D-2	20	and	Acetamiprid
C-3	17	and	Amitraz	D-3	20	and	Amitraz
C-4	17	and	Avermectin	D-4	20	and	Avermectin
C-5	17	and	Azadirachtin	D-5	20	and	Azadirachtin
C-6	17	and	Beta-cyfluthrin	D-6	20	and	Beta-cyfluthrin
C-7	17	and	Bifenthrin	D-7	20	and	Bifenthrin
C-8	17	and	Buprofezin	D-8	20	and	Buprofezin
C-9	17	and	Cartap	D-9	20	and	Cartap
C-10	17	and	Chlorantraniliprole	D-10	20	and	Chlorantraniliprole
C-11	17	and	Chlorfenapyr	D-11	20	and	Chlorfenapyr
C-12	17	and	Chlorpyrifos	D-12	20	and	Chlorpyrifos
C-13	17	and	Clothianidin	D-13	20	and	Clothianidin
C-14	17	and	Cyfluthrin	D-14	20	and	Cyfluthrin
C-15	17	and	Cyhalothrin	D-15	20	and	Cyhalothrin
C-16	17	and	Cypermethrin	D-16	20	and	Cypermethrin
C-17	17	and	Cyromazine	D-17	20	and	Cyromazine
C-18	17	and	Deltamethrin	D-18	20	and	Deltamethrin
C-19	17	and	Dieldrin	D-19	20	and	Dieldrin
C-20	17	and	Dinotefuran	D-20	20	and	Dinotefuran

Mixture No.	Comp. No.	and	Invertebrate Pest Control Agent	Mixture No.	Comp. No.	and	Invertebrate Pest Control Agent
C-21	17	and	Diofenolan	D-21	20	and	Diofenolan
C-22	17	and	Emamectin	D-22	20	and	Emamectin
C-23	17	and	Endosulfan	D-23	20	and	Endosulfan
C-24	17	and	Esfenvalerate	D-24	20	and	Esfenvalerate
C-25	17	and	Ethiprole	D-25	20	and	Ethiprole
C-26	17	and	Fenothiocarb	D-26	20	and	Fenothiocarb
C-27	17	and	Fenoxy carb	D-27	20	and	Fenoxy carb
C-28	17	and	Fenvale rate	D-28	20	and	Fenvale rate
C-29	17	and	Fipronil	D-29	20	and	Fipronil
C-30	17	and	Flonicamid	D-30	20	and	Flonicamid
C-31	17	and	Flubendiamide	D-31	20	and	Flubendiamide
C-32	17	and	Flufenoxuron	D-32	20	and	Flufenoxuron
C-33	17	and	Hexaflumuron	D-33	20	and	Hexaflumuron
C-34	17	and	Hydramethylnon	D-34	20	and	Hydramethylnon
C-35	17	and	Imidacloprid	D-35	20	and	Imidacloprid
C-36	17	and	Indoxacarb	D-36	20	and	Indoxacarb
C-37	17	and	Lambda-cyhalothrin	D-37	20	and	Lambda-cyhalothrin
C-38	17	and	Lufenuron	D-38	20	and	Lufenuron
C-39	17	and	Metaflumizone	D-39	20	and	Metaflumizone
C-40	17	and	Methomyl	D-40	20	and	Methomyl
C-41	17	and	Methoprene	D-41	20	and	Methoprene
C-42	17	and	Methoxyfenozide	D-42	20	and	Methoxyfenozide
C-43	17	and	Nitenpyram	D-43	20	and	Nitenpyram
C-44	17	and	Nithiazine	D-44	20	and	Nithiazine
C-45	17	and	Novaluron	D-45	20	and	Novaluron
C-46	17	and	Oxamyl	D-46	20	and	Oxamyl
C-47	17	and	Pymetrozine	D-47	20	and	Pymetrozine
C-48	17	and	Pyrethrin	D-48	20	and	Pyrethrin
C-49	17	and	Pyridaben	D-49	20	and	Pyridaben
C-50	17	and	Pyridalyl	D-50	20	and	Pyridalyl
C-51	17	and	Pyriproxyfen	D-51	20	and	Pyriproxyfen
C-52	17	and	Ryanodine	D-52	20	and	Ryanodine
C-53	17	and	Spinetoram	D-53	20	and	Spinetoram
C-54	17	and	Spinosad	D-54	20	and	Spinosad
C-55	17	and	Spirodiclofen	D-55	20	and	Spirodiclofen
C-56	17	and	Spiromesifen	D-56	20	and	Spiromesifen
C-57	17	and	Tebufeno zide	D-57	20	and	Tebufeno zide

Mixture No.	Comp. No.	and	Invertebrate Pest Control Agent		Mixture No.	Comp. No.	and	Invertebrate Pest Control Agent
C-58	17	and	Thiacloprid		D-58	20	and	Thiacloprid
C-59	17	and	Thiamethoxam		D-59	20	and	Thiamethoxam
C-60	17	and	Thiodicarb		D-60	20	and	Thiodicarb
C-61	17	and	Thiosultap-sodium		D-61	20	and	Thiosultap-sodium
C-62	17	and	Tralomethrin		D-62	20	and	Tralomethrin
C-63	17	and	Triazamate		D-63	20	and	Triazamate
C-64	17	and	Triflumuron		D-64	20	and	Triflumuron
C-65	17	and	<i>Bacillus thuringiensis</i>		D-65	20	and	<i>Bacillus thuringiensis</i>
C-66	17	and	<i>Bacillus thuringiensis</i> delta-endotoxin		D-66	20	and	<i>Bacillus thuringiensis</i> delta-endotoxin
C-67	17	and	NPV (e.g., Gemstar)		D-67	20	and	NPV (e.g., Gemstar)
E-1	37	and	Abamectin		F-1	52	and	Abamectin
E-2	37	and	Acetamiprid		F-2	52	and	Acetamiprid
E-3	37	and	Amitraz		F-3	52	and	Amitraz
E-4	37	and	Avermectin		F-4	52	and	Avermectin
E-5	37	and	Azadirachtin		F-5	52	and	Azadirachtin
E-6	37	and	Beta-cyfluthrin		F-6	52	and	Beta-cyfluthrin
E-7	37	and	Bifenthrin		F-7	52	and	Bifenthrin
E-8	37	and	Buprofezin		F-8	52	and	Buprofezin
E-9	37	and	Cartap		F-9	52	and	Cartap
E-10	37	and	Chlorantraniliprole		F-10	52	and	Chlorantraniliprole
E-11	37	and	Chlorfenapyr		F-11	52	and	Chlorfenapyr
E-12	37	and	Chlorpyrifos		F-12	52	and	Chlorpyrifos
E-13	37	and	Clothianidin		F-13	52	and	Clothianidin
E-14	37	and	Cyfluthrin		F-14	52	and	Cyfluthrin
E-15	37	and	Cyhalothrin		F-15	52	and	Cyhalothrin
E-16	37	and	Cypermethrin		F-16	52	and	Cypermethrin
E-17	37	and	Cyromazine		F-17	52	and	Cyromazine
E-18	37	and	Deltamethrin		F-18	52	and	Deltamethrin
E-19	37	and	Dieldrin		F-19	52	and	Dieldrin
E-20	37	and	Dinotefuran		F-20	52	and	Dinotefuran
E-21	37	and	Diofenolan		F-21	52	and	Diofenolan
E-22	37	and	Emamectin		F-22	52	and	Emamectin
E-23	37	and	Endosulfan		F-23	52	and	Endosulfan
E-24	37	and	Esfenvalerate		F-24	52	and	Esfenvalerate
E-25	37	and	Ethiprole		F-25	52	and	Ethiprole
E-26	37	and	Fenothiocarb		F-26	52	and	Fenothiocarb

Mixture No.	Comp. No.	and	Invertebrate Pest Control Agent		Mixture No.	Comp. No.	and	Invertebrate Pest Control Agent
E-27	37	and	Fenoxy carb		F-27	52	and	Fenoxy carb
E-28	37	and	Fenvale rate		F-28	52	and	Fenvale rate
E-29	37	and	Fipronil		F-29	52	and	Fipronil
E-30	37	and	Flonicamid		F-30	52	and	Flonicamid
E-31	37	and	Flubendiamide		F-31	52	and	Flubendiamide
E-32	37	and	Flufenoxuron		F-32	52	and	Flufenoxuron
E-33	37	and	Hexaflumuron		F-33	52	and	Hexaflumuron
E-34	37	and	Hydramethylnon		F-34	52	and	Hydramethylnon
E-35	37	and	Imidacloprid		F-35	52	and	Imidacloprid
E-36	37	and	Indoxacarb		F-36	52	and	Indoxacarb
E-37	37	and	Lambda-cyhalothrin		F-37	52	and	Lambda-cyhalothrin
E-38	37	and	Lufenuron		F-38	52	and	Lufenuron
E-39	37	and	Metaflumizone		F-39	52	and	Metaflumizone
E-40	37	and	Methomyl		F-40	52	and	Methomyl
E-41	37	and	Methoprene		F-41	52	and	Methoprene
E-42	37	and	Methoxyfenozide		F-42	52	and	Methoxyfenozide
E-43	37	and	Nitenpyram		F-43	52	and	Nitenpyram
E-44	37	and	Nithiazine		F-44	52	and	Nithiazine
E-45	37	and	Novaluron		F-45	52	and	Novaluron
E-46	37	and	Oxamyl		F-46	52	and	Oxamyl
E-47	37	and	Pymetrozine		F-47	52	and	Pymetrozine
E-48	37	and	Pyrethrin		F-48	52	and	Pyrethrin
E-49	37	and	Pyridaben		F-49	52	and	Pyridaben
E-50	37	and	Pyridalyl		F-50	52	and	Pyridalyl
E-51	37	and	Pyriproxyfen		F-51	52	and	Pyriproxyfen
E-52	37	and	Ryanodine		F-52	52	and	Ryanodine
E-53	37	and	Spinetoram		F-53	52	and	Spinetoram
E-54	37	and	Spinosad		F-54	52	and	Spinosad
E-55	37	and	Spirodiclofen		F-55	52	and	Spirodiclofen
E-56	37	and	Spiromesifen		F-56	52	and	Spiromesifen
E-57	37	and	Tebufenozide		F-57	52	and	Tebufenozide
E-58	37	and	Thiacloprid		F-58	52	and	Thiacloprid
E-59	37	and	Thiamethoxam		F-59	52	and	Thiamethoxam
E-60	37	and	Thiodicarb		F-60	52	and	Thiodicarb
E-61	37	and	Thiosultap-sodium		F-61	52	and	Thiosultap-sodium
E-62	37	and	Tralomethrin		F-62	52	and	Tralomethrin
E-63	37	and	Triazamate		F-63	52	and	Triazamate

Mixture No.	Comp. No.	and	Invertebrate Pest Control Agent		Mixture No.	Comp. No.	and	Invertebrate Pest Control Agent
E-64	37	and	Triflumuron		F-64	52	and	Triflumuron
E-65	37	and	<i>Bacillus thuringiensis</i>		F-65	52	and	<i>Bacillus thuringiensis</i>
E-66	37	and	<i>Bacillus thuringiensis</i>	delta-endotoxin	F-66	52	and	<i>Bacillus thuringiensis</i>
E-67	37	and	NPV (e.g., Gemstar)		F-67	52	and	NPV (e.g., Gemstar)
E-68	37	and	(a)		F-68	52	and	(a)
G-1	62	and	Abamectin		H-1	94	and	Abamectin
G-2	62	and	Acetamiprid		H-2	94	and	Acetamiprid
G-3	62	and	Amitraz		H-3	94	and	Amitraz
G-4	62	and	Avermectin		H-4	94	and	Avermectin
G-5	62	and	Azadirachtin		H-5	94	and	Azadirachtin
G-6	62	and	Beta-cyfluthrin		H-6	94	and	Beta-cyfluthrin
G-7	62	and	Bifenthrin		H-7	94	and	Bifenthrin
G-8	62	and	Buprofezin		H-8	94	and	Buprofezin
G-9	62	and	Cartap		H-9	94	and	Cartap
G-10	62	and	Chlorantraniliprole		H-10	94	and	Chlorantraniliprole
G-11	62	and	Chlorfenapyr		H-11	94	and	Chlorfenapyr
G-12	62	and	Chlorpyrifos		H-12	94	and	Chlorpyrifos
G-13	62	and	Clothianidin		H-13	94	and	Clothianidin
G-14	62	and	Cyfluthrin		H-14	94	and	Cyfluthrin
G-15	62	and	Cyhalothrin		H-15	94	and	Cyhalothrin
G-16	62	and	Cypermethrin		H-16	94	and	Cypermethrin
G-17	62	and	Cyromazine		H-17	94	and	Cyromazine
G-18	62	and	Deltamethrin		H-18	94	and	Deltamethrin
G-19	62	and	Dieldrin		H-19	94	and	Dieldrin
G-20	62	and	Dinotefuran		H-20	94	and	Dinotefuran
G-21	62	and	Diofenolan		H-21	94	and	Diofenolan
G-22	62	and	Emamectin		H-22	94	and	Emamectin
G-23	62	and	Endosulfan		H-23	94	and	Endosulfan
G-24	62	and	Esfenvalerate		H-24	94	and	Esfenvalerate
G-25	62	and	Ethiprole		H-25	94	and	Ethiprole
G-26	62	and	Fenothiocarb		H-26	94	and	Fenothiocarb
G-27	62	and	Fenoxy carb		H-27	94	and	Fenoxy carb
G-28	62	and	Fenvalerate		H-28	94	and	Fenvalerate
G-29	62	and	Fipronil		H-29	94	and	Fipronil
G-30	62	and	Flonicamid		H-30	94	and	Flonicamid
G-31	62	and	Flubendiamide		H-31	94	and	Flubendiamide

Mixture No.	Comp. No.	and	Invertebrate Pest Control Agent		Mixture No.	Comp. No.	and	Invertebrate Pest Control Agent	
G-32	62	and	Flufenoxuron		H-32	94	and	Flufenoxuron	
G-33	62	and	Hexaflumuron		H-33	94	and	Hexaflumuron	
G-34	62	and	Hydramethylnon		H-34	94	and	Hydramethylnon	
G-35	62	and	Imidacloprid		H-35	94	and	Imidacloprid	
G-36	62	and	Indoxacarb		H-36	94	and	Indoxacarb	
G-37	62	and	Lambda-cyhalothrin		H-37	94	and	Lambda-cyhalothrin	
G-38	62	and	Lufenuron		H-38	94	and	Lufenuron	
G-39	62	and	Metaflumizone		H-39	94	and	Metaflumizone	
G-40	62	and	Methomyl		H-40	94	and	Methomyl	
G-41	62	and	Methoprene		H-41	94	and	Methoprene	
G-42	62	and	Methoxyfenozide		H-42	94	and	Methoxyfenozide	
G-43	62	and	Nitenpyram		H-43	94	and	Nitenpyram	
G-44	62	and	Nithiazine		H-44	94	and	Nithiazine	
G-45	62	and	Novaluron		H-45	94	and	Novaluron	
G-46	62	and	Oxamyl		H-46	94	and	Oxamyl	
G-47	62	and	Pymetrozine		H-47	94	and	Pymetrozine	
G-48	62	and	Pyrethrin		H-48	94	and	Pyrethrin	
G-49	62	and	Pyridaben		H-49	94	and	Pyridaben	
G-50	62	and	Pyridalyl		H-50	94	and	Pyridalyl	
G-51	62	and	Pyriproxyfen		H-51	94	and	Pyriproxyfen	
G-52	62	and	Ryanodine		H-52	94	and	Ryanodine	
G-53	62	and	Spinetoram		H-53	94	and	Spinetoram	
G-54	62	and	Spinosad		H-54	94	and	Spinosad	
G-55	62	and	Spirodiclofen		H-55	94	and	Spirodiclofen	
G-56	62	and	Spiromesifen		H-56	94	and	Spiromesifen	
G-57	62	and	Tebufenozyde		H-57	94	and	Tebufenozyde	
G-58	62	and	Thiacloprid		H-58	94	and	Thiacloprid	
G-59	62	and	Thiamethoxam		H-59	94	and	Thiamethoxam	
G-60	62	and	Thiodicarb		H-60	94	and	Thiodicarb	
G-61	62	and	Thiosultap-sodium		H-61	94	and	Thiosultap-sodium	
G-62	62	and	Tralomethrin		H-62	94	and	Tralomethrin	
G-63	62	and	Triazamate		H-63	94	and	Triazamate	
G-64	62	and	Triflumuron		H-64	94	and	Triflumuron	
G-65	62	and	<i>Bacillus thuringiensis</i>		H-65	94	and	<i>Bacillus thuringiensis</i>	
G-66	62	and	<i>Bacillus thuringiensis</i>	delta-endotoxin	H-66	94	and	<i>Bacillus thuringiensis</i>	delta-endotoxin
G-67	62	and	NPV (e.g., Gemstar)		H-67	94	and	NPV (e.g., Gemstar)	

Mixture No.	Comp. and Invertebrate Pest Control Agent		Mixture No.	Comp. and Invertebrate Pest Control Agent
G-68	62 and (a)		H-68	94 and (a)

(a) 3-bromo-1-(3-chloro-2-pyridinyl)-N-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide

The specific mixtures listed in Table B typically combine a compound of Formula 1 with the other invertebrate pest agent in the ratios specified in Table A.

5 Invertebrate pests are controlled in agronomic and nonagronomic applications by applying one or more compounds of this invention, typically in the form of a composition, in a biologically effective amount, to the environment of the pests, including the agronomic and/or nonagronomic locus of infestation, to the area to be protected, or directly on the pests to be controlled.

10 Thus the present invention comprises a method for controlling an invertebrate pest in agronomic and/or nonagronomic applications, comprising contacting the invertebrate pest or its environment with a biologically effective amount of one or more of the compounds of the invention, or with a composition comprising at least one such compound or a composition comprising at least one such compound and a biologically effective amount of at least one additional biologically active compound or agent. Examples of suitable compositions comprising a compound of the invention and at least one additional biologically active compound or agent include granular compositions wherein the additional active compound is present on the same granule as the compound of the invention or on granules separate from those of the compound of the invention.

15 To achieve contact with a compound or composition of the invention to protect a field crop from invertebrate pests, the compound or composition is typically applied to the seed of the crop before planting, to the foliage (e.g., leaves, stems, flowers, fruits) of crop plants, or to the soil or other growth medium before or after the crop is planted.

20 One embodiment of a method of contact is by spraying. Alternatively, a granular composition comprising a compound of the invention can be applied to the plant foliage or the soil. Compounds of this invention can also be effectively delivered through plant uptake by contacting the plant with a composition comprising a compound of this invention applied as a soil drench of a liquid formulation, a granular formulation to the soil, a nursery box treatment or a dip of transplants. Of note is a composition of the present invention in the form of a soil drench liquid formulation. Also of note is a method for controlling an invertebrate pest comprising contacting the invertebrate pest or its environment with a biologically effective amount of a compound of the present invention or with a composition comprising a biologically effective amount of a compound of the present invention. Of further note is this method wherein the environment is soil and the composition is applied to the soil as a soil drench formulation. Of further note is that compounds of this invention are also effective by localized application to the locus of infestation. Other methods of contact

include application of a compound or a composition of the invention by direct and residual sprays, aerial sprays, gels, seed coatings, microencapsulations, systemic uptake, baits, ear tags, boluses, foggers, fumigants, aerosols, dusts and many others. One embodiment of a method of contact is a dimensionally stable fertilizer granule, stick or tablet comprising a compound or composition of the invention. The compounds of this invention can also be impregnated into materials for fabricating invertebrate control devices (e.g., insect netting).

Compounds of this invention are also useful in seed treatments for protecting seeds from invertebrate pests. In the context of the present disclosure and claims, treating a seed means contacting the seed with a biologically effective amount of a compound of this invention, which is typically formulated as a composition of the invention. This seed treatment protects the seed from invertebrate soil pests and generally can also protect roots and other plant parts in contact with the soil of the seedling developing from the germinating seed. The seed treatment may also provide protection of foliage by translocation of the compound of this invention or a second active ingredient within the developing plant. Seed treatments can be applied to all types of seeds, including those from which plants genetically transformed to express specialized traits will germinate. Representative examples include those expressing proteins toxic to invertebrate pests, such as *Bacillus thuringiensis* toxin or those expressing herbicide resistance such as glyphosate acetyltransferase, which provides resistance to glyphosate.

One method of seed treatment is by spraying or dusting the seed with a compound of the invention (i.e. as a formulated composition) before sowing the seeds. Compositions formulated for seed treatment generally comprise a film former or adhesive agent. Therefore typically a seed coating composition of the present invention comprises a compound of Formula 1, and a film former or adhesive agent. Seed can be coated by spraying a flowable suspension concentrate directly into a tumbling bed of seeds and then drying the seeds. Alternatively, other formulation types such as wetted powders, solutions, suspensions, emulsifiable concentrates and emulsions in water can be sprayed on the seed. This process is particularly useful for applying film coatings on seeds. Various coating machines and processes are available to one skilled in the art. Suitable processes include those listed in P. Kosters et al., *Seed Treatment: Progress and Prospects*, 1994 BCPC Monograph No. 57, and references listed therein.

The treated seed typically comprises a compound of the present invention in an amount from about 0.1 g to 1 kg per 100 kg of seed (i.e. from about 0.0001 to 1% by weight of the seed before treatment). A flowable suspension formulated for seed treatment typically comprises from about 0.5 to about 70% of the active ingredient, from about 0.5 to about 30% of a film-forming adhesive, from about 0.5 to about 20% of a dispersing agent, from 0 to about 5% of a thickener, from 0 to about 5% of a pigment and/or dye, from 0 to about 2% of an antifoaming agent, from 0 to about 1% of a preservative, and from 0 to about 75% of a volatile liquid diluent.

The compounds of this invention can be incorporated into a bait composition that is consumed by an invertebrate pest or used within a device such as a trap, bait station, and the like. Such a bait composition can be in the form of granules which comprise (a) active ingredients, namely a compound of Formula 1; (b) one or more food materials; optionally (c) 5 an attractant, and optionally (d) one or more humectants. Of note are granules or bait compositions which comprise between about 0.001-5% active ingredients, about 40-99% food material and/or attractant; and optionally about 0.05-10% humectants, which are effective in controlling soil invertebrate pests at very low application rates, particularly at doses of active ingredient that are lethal by ingestion rather than by direct contact. Some 10 food materials can function both as a food source and an attractant. Food materials include carbohydrates, proteins and lipids. Examples of food materials are vegetable flour, sugar, starches, animal fat, vegetable oil, yeast extracts and milk solids. Examples of attractants are odorants and flavorants, such as fruit or plant extracts, perfume, or other animal or plant component, pheromones or other agents known to attract a target invertebrate pest. 15 Examples of humectants, i.e. moisture retaining agents, are glycols and other polyols, glycerine and sorbitol. Of note is a bait composition (and a method utilizing such a bait composition) used to control at least one invertebrate pest selected from the group consisting of ants, termites and cockroaches. A device for controlling an invertebrate pest can comprise the present bait composition and a housing adapted to receive the bait composition, wherein 20 the housing has at least one opening sized to permit the invertebrate pest to pass through the opening so the invertebrate pest can gain access to the bait composition from a location outside the housing, and wherein the housing is further adapted to be placed in or near a locus of potential or known activity for the invertebrate pest.

The compounds of this invention can be applied without other adjuvants, but most 25 often application will be of a formulation comprising one or more active ingredients with suitable carriers, diluents, and surfactants and possibly in combination with a food depending on the contemplated end use. One method of application involves spraying a water dispersion or refined oil solution of a compound of the present invention. Combinations with spray oils, spray oil concentrations, spreader stickers, adjuvants, other solvents, and 30 synergists such as piperonyl butoxide often enhance compound efficacy. For nonagronomic uses such sprays can be applied from spray containers such as a can, a bottle or other container, either by means of a pump or by releasing it from a pressurized container, e.g., a pressurized aerosol spray can. Such spray compositions can take various forms, for example, sprays, mists, foams, fumes or fog. Such spray compositions thus can further 35 comprise propellants, foaming agents, etc. as the case may be. Of note is a spray composition comprising a compound or a composition of the present invention and a carrier. One embodiment of such a spray composition comprises a compound or a composition of the present invention and a propellant. Representative propellants include, but are not limited to, methane, ethane, propane, butane, isobutane, butene, pentane, isopentane,

neopentane, pentene, hydrofluorocarbons, chlorofluorocarbons, dimethyl ether, and mixtures of the foregoing. Of note is a spray composition (and a method utilizing such a spray composition dispensed from a spray container) used to control at least one invertebrate pest selected from the group consisting of mosquitoes, black flies, stable flies, deer flies, horse flies, wasps, yellow jackets, hornets, ticks, spiders, ants, gnats, and the like, including individually or in combinations.

Nonagronomic uses refer to invertebrate pest control in the areas other than fields of crop plants. Nonagronomic uses of the present compounds and compositions include control of invertebrate pests in stored grains, beans and other foodstuffs, and in textiles such as clothing and carpets. Nonagronomic uses of the present compounds and compositions also include invertebrate pest control in ornamental plants, forests, in yards, along roadsides and railroad rights of way, and on turf such as lawns, golf courses and pastures. Nonagronomic uses of the present compounds and compositions also include invertebrate pest control in houses and other buildings which may be occupied by humans and/or companion, farm, ranch, zoo or other animals. Nonagronomic uses of the present compounds and compositions also include the control of pests such as termites that can damage wood or other structural materials used in buildings.

Nonagronomic uses of the present compounds and compositions also include protecting human and animal health by controlling invertebrate pests that are parasitic or transmit infectious diseases. The controlling of animal parasites includes controlling external parasites that are parasitic to the surface of the body of the host animal (e.g., shoulders, armpits, abdomen, inner part of the thighs) and internal parasites that are parasitic to the inside of the body of the host animal (e.g., stomach, intestine, lung, veins, under the skin, lymphatic tissue). External parasitic or disease-transmitting pests include, for example, chiggers, ticks, lice, mosquitoes, flies, mites and fleas. Internal parasites include heartworms, hookworms and helminths. Compounds and compositions of the present invention are particularly suitable for combating external parasitic or disease-transmitting pests. Compounds and compositions of the present invention are suitable for systemic and/or non-systemic control of infestation or infection by parasites on animals.

Compounds and compositions of the present invention are suitable for combating parasites that infest animal subjects including those in the wild, livestock and agricultural working animals. Livestock is the term used to refer (singularly or plurally) to a domesticated animal intentionally reared in an agricultural setting to make produce such as food or fiber, or for its labor; examples of livestock include cattle, sheep, goats, horses, pigs, donkeys, camels, buffalo, rabbits, hens, turkeys, ducks and geese (e.g., raised for meat, milk, butter, eggs, fur, leather, feathers and/or wool). By combating parasites, fatalities and performance reduction (in terms of meat, milk, wool, skins, eggs, etc.) are reduced, so that applying a composition comprising a compound of the present invention allows more economic and simple husbandry of animals.

Compounds and compositions of the present invention are especially suitable for combating parasites that infest companion animals and pets (e.g., dogs, cats, pet birds and aquarium fish), research and experimental animals (e.g., hamsters, guinea pigs, rats and mice), as well as animals raised for/in zoos, wild habitats and/or circuses.

5 In an embodiment of this invention, the animal is preferably a vertebrate, and more preferably a mammal, avian or fish. In a particular embodiment, the animal subject is a mammal (including great apes, such as humans). Other mammalian subjects include primates (e.g., monkeys), bovine (e.g., cattle or dairy cows), porcine (e.g., hogs or pigs), ovine (e.g., goats or sheep), equine (e.g., horses), canine (e.g., dogs), feline (e.g., house cats),
10 camels, deer, donkeys, buffalos, antelopes, rabbits, and rodents (e.g., guinea pigs, squirrels, rats, mice, gerbils, and hamsters). Avians include Anatidae (swans, ducks and geese), Columbidae (e.g., doves and pigeons), Phasianidae (e.g., partridges, grouse and turkeys), Thesienidae (e.g., domestic chickens), Psittacines (e.g., parakeets, macaws, and parrots), game birds, and ratites (e.g., ostriches).

15 Of particular note is the embodiment wherein the animals to be protected are domesticated dogs (i.e. *Canis lupus familiaris*) and domestic house cats (i.e. *Felis catus*).

Birds treated or protected by the inventive compounds can be associated with either commercial or noncommercial aviculture. These include Anatidae, such as swans, geese, and ducks, Columbidae, such as doves and domestic pigeons, Phasianidae, such as partridge, 20 grouse and turkeys, Thesienidae, such as domestic chickens, and Psittacines, such as parakeets, macaws, and parrots raised for the pet or collector market, among others.

For purposes of the present invention, the term "fish" shall be understood to include without limitation, the Teleosti grouping of fish, i.e., teleosts. Both the Salmoniformes order (which includes the Salmonidae family) and the Perciformes order (which includes the 25 Centrarchidae family) are contained within the Teleosti grouping. Examples of potential fish recipients include the Salmonidae, Serranidae, Sparidae, Cichlidae, and Centrarchidae, among others.

Other animals are also contemplated to benefit from the inventive methods, including marsupials (such as kangaroos), reptiles (such as farmed turtles), and other economically 30 important domestic animals for which the inventive methods are safe and effective in treating or preventing parasite infection or infestation.

Examples of invertebrate parasitic pests controlled by administering a parasitically effective amount of a compound of this invention to an animal to be protected include ectoparasites (arthropods, acarines, etc) and endoparasites (helminths, e.g., nematodes, 35 trematodes, cestodes, acanthocephalans, etc.).

The disease or group of diseases described generally as helminthiasis is due to infection of an animal host with parasitic worms known as helminths. The term 'helminths' is meant to include nematodes, trematodes, cestodes and acanthocephalans. Helminthiasis is

a prevalent and serious economic problem with domesticated animals such as swine, sheep, horses, cattle, goats, dogs, cats and poultry.

Among the helminths, the group of worms described as nematodes causes widespread and at times serious infection in various species of animals. Nematodes that are contemplated to be treated by the compounds of this invention and by the inventive methods include, without limitation, the following genera: *Acanthocheilonema*, *Aelurostrongylus*, *Ancylostoma*, *Angiostrongylus*, *Ascaridia*, *Ascaris*, *Brugia*, *Bunostomum*, *Capillaria*, *Chabertia*, *Cooperia*, *Crenosoma*, *Dictyocaulus*, *Dioctophyme*, *Dipetalonema*, *Diphyllobothrium*, *Dirofilaria*, *Dracunculus*, *Enterobius*, *Filaroides*, *Haemonchus*, *Heterakis*, *Lagochilascaris*, *Loa*, *Mansonella*, *Muellerius*, *Necator*, *Nematodirus*, *Oesophagostomum*, *Ostertagia*, *Oxyuris*, *Parafilaria*, *Parascaris*, *Physaloptera*, *Protostrongylus*, *Setaria*, *Spirocerca*, *Stephanofilaria*, *Strongyloides*, *Strongylus*, *Thelazia*, *Toxascaris*, *Toxocara*, *Trichinella*, *Trichonema*, *Trichostrongylus*, *Trichuris*, *Uncinaria* and *Wuchereria*.

Of the above, the most common genera of nematodes infecting the animals referred to above are *Haemonchus*, *Trichostrongylus*, *Ostertagia*, *Nematodirus*, *Cooperia*, *Ascaris*, *Bunostomum*, *Oesophagostomum*, *Chabertia*, *Trichuris*, *Strongylus*, *Trichonema*, *Dictyocaulus*, *Capillaria*, *Heterakis*, *Toxocara*, *Ascaridia*, *Oxyuris*, *Ancylostoma*, *Uncinaria*, *Toxascaris* and *Parascaris*. Certain of these, such as *Nematodirus*, *Cooperia* and *Oesophagostomum* attack primarily the intestinal tract while others, such as *Haemonchus* and *Ostertagia*, are more prevalent in the stomach while others such as *Dictyocaulus* are found in the lungs. Still other parasites may be located in other tissues such as the heart and blood vessels, subcutaneous and lymphatic tissue and the like.

Trematodes that are contemplated to be treated by the compounds of this invention and by the inventive methods include, without limitation, the following genera: *Alaria*, *Fasciola*, *Nanophyetus*, *Opisthorchis*, *Paragonimus* and *Schistosoma*.

Cestodes that are contemplated to be treated by the compounds of this invention and by the inventive methods include, without limitation, the following genera: *Diphyllobothrium*, *Diplydium*, *Spirometra* and *Taenia*.

The most common genera of parasites of the gastrointestinal tract of humans are *Ancylostoma*, *Necator*, *Ascaris*, *Strongyloides*, *Trichinella*, *Capillaria*, *Trichuris* and *Enterobius*. Other medically important genera of parasites which are found in the blood or other tissues and organs outside the gastrointestinal tract are the filarial worms such as *Wuchereria*, *Brugia*, *Onchocerca* and *Loa*, as well as *Dracunculus* and extra intestinal stages of the intestinal worms *Strongyloides* and *Trichinella*.

Numerous other helminth genera and species are known to the art, and are also contemplated to be treated by the compounds of the invention. These are enumerated in great detail in *Textbook of Veterinary Clinical Parasitology, Volume 1, Helminths*, E. J. L. Soulsby, F. A. Davis Co., Philadelphia, Pa.; *Helminths, Arthropods and Protozoa*, (6th

Edition of Monnig's Veterinary Helminthology and Entomology), E. J. L. Soulsby, The Williams and Wilkins Co., Baltimore, Md.

The compounds of Formula 1 are effective against a number of animal ectoparasites (e.g., arthropod ectoparasites of mammals and birds).

5 Insect and acarine pests include, e.g., biting insects such as flies and mosquitoes, mites, ticks, lice, fleas, true bugs, parasitic maggots, and the like.

Adult flies include, e.g., the horn fly or *Haematobia irritans*, the horse fly or *Tabanus* spp., the stable fly or *Stomoxys calcitrans*, the black fly or *Simulium* spp., the deer fly or *Chrysops* spp., the louse fly or *Melophagus ovinus*, and the tsetse fly or *Glossina* spp.

10 Parasitic fly maggots include, e.g., the bot fly (*Oestrus ovis* and *Cuterebra* spp.), the blow fly or *Phaenicia* spp., the screwworm or *Cochliomyia hominivorax*, the cattle grub or *Hypoderma* spp., the fleeceworm and the *Gastrophilus* of horses. Mosquitoes include, for example, *Culex* spp., *Anopheles* spp. and *Aedes* spp.

Mites include *Mesostigmata* spp. e.g., mesostigmatids such as the chicken mite, 15 *Dermanyssus gallinae*; itch or scab mites such as Sarcoptidae spp. for example, *Sarcoptes scabiei*; mange mites such as Psoroptidae spp. including *Chorioptes bovis* and *Psoroptes ovis*; chiggers e.g., Trombiculidae spp. for example the North American chigger, *Trombicula alfreddugesi*.

Ticks include, e.g., soft-bodied ticks including Argasidae spp. for example *Argas* spp. 20 and *Ornithodoros* spp.; hard-bodied ticks including Ixodidae spp., for example *Rhipicephalus sanguineus*, *Dermacentor variabilis*, *Dermacentor andersoni*, *Amblyomma americanum*, *Ixodes scapularis* and other *Rhipicephalus* spp. (including the former *Boophilus* genera).

Lice include, e.g., sucking lice, e.g., *Menopon* spp. and *Bovicola* spp.; biting lice, e.g., 25 *Haematopinus* spp., *Linognathus* spp. and *Solenopotes* spp.

Fleas include, e.g., *Ctenocephalides* spp., such as dog flea (*Ctenocephalides canis*) and cat flea (*Ctenocephalides felis*); *Xenopsylla* spp. such as oriental rat flea (*Xenopsylla cheopis*); and *Pulex* spp. such as human flea (*Pulex irritans*).

True bugs include, e.g., Cimicidae or e.g., the common bed bug (*Cimex lectularius*); 30 Triatominae spp. including triatomid bugs also known as kissing bugs; for example *Rhodnius prolixus* and *Triatoma* spp.

Generally, flies, fleas, lice, mosquitoes, gnats, mites, ticks and helminths cause tremendous losses to the livestock and companion animal sectors. Arthropod parasites also are a nuisance to humans and can vector disease-causing organisms in humans and animals.

35 Numerous other arthropod pests and ectoparasites are known to the art, and are also contemplated to be treated by the compounds of the invention. These are enumerated in great detail in *Medical and Veterinary Entomology*, D. S. Kettle, John Wiley & Sons, New York and Toronto; *Control of Arthropod Pests of Livestock: A Review of Technology*, R. O. Drummond, J. E. George, and S. E. Kunz, CRC Press, Boca Raton, Fla.

It is also contemplated that the compounds and compositions of this invention may be effective against a number of protozoa endoparasites of animals, including those summarized by Table 1, as follows.

<u>Table 1</u>			
<u>Exemplary Parasitic Protozoa and Associated Human Diseases</u>			
<u>Phylum</u>	<u>Subphylum</u>	<u>Representative Genera</u>	<u>Human Disease or Disorder</u>
Sarcomastigophora (with flagella, pseudopodia, or both)	Mastigophora (Flagella)	<i>Leishmania</i>	Visceral, cutaneous and mucocutaneous Infection
		<i>Trypanosoma</i>	Sleeping sickness
			Chagas' disease
		<i>Giardia</i>	Diarrhea
		<i>Trichomonas</i>	Vaginitis
	Sarcodina (pseudopodia)	<i>Entamoeba</i>	Dysentery, liver Abscess
		<i>Dientamoeba</i>	Colitis
		<i>Naegleria</i> and <i>Acanthamoeba</i>	Central nervous system and corneal ulcers
		<i>Babesia</i>	Babesiosis
Apicomplexa (apical complex)		<i>Plasmodium</i>	Malaria
		<i>Isospora</i>	Diarrhea
		<i>Sarcocystis</i>	Diarrhea
		<i>Cryptosporidium</i>	Diarrhea
		<i>Toxoplasma</i>	Toxoplasmosis
		<i>Eimeria</i>	Chicken coccidiosis
Microspora		<i>Enterocytozoon</i>	Diarrhea
Ciliaphora (with cilia)		<i>Balantidium</i>	Dysentery
Unclassified		<i>Pneumocystis</i>	Pneumonia

In particular, the compounds of this invention are effective against ectoparasites including: flies such as *Haematobia (Lyperosia) irritans* (horn fly), *Stomoxys calcitrans* (stable fly), *Simulium* spp. (blackfly), *Glossina* spp. (tsetse flies), *Hydrotaea irritans* (head

fly), *Musca autumnalis* (face fly), *Musca domestica* (house fly), *Morellia simplex* (sweat fly), *Tabanus* spp. (horse fly), *Hypoderma bovis*, *Hypoderma lineatum*, *Lucilia sericata*, *Lucilia cuprina* (green blowfly), *Calliphora* spp. (blowfly), *Protophormia* spp., *Oestrus ovis* (nasal botfly), *Culicoides* spp. (midges), *Hippobosca equine*, *Gastrophilus intestinalis*,
5 *Gastrophilus haemorrhoidalis* and *Gastrophilus nasalis*; lice such as *Bovicola (Damalinia) bovis*, *Bovicola equi*, *Haematopinus asini*, *Felicola subrostratus*, *Heterodoxus spiniger*, *Lignonathus setosus* and *Trichodectes canis*; keds such as *Melophagus ovinus*; mites such as *Psoroptes* spp., *Sarcoptes scabei*, *Chorioptes bovis*, *Demodex equi*, *Cheyletiella* spp.,
10 *Notoedres cati*, *Trombicula* spp. and *Otodectes cyanotis* (ear mites); ticks such as *Ixodes* spp., *Boophilus* spp., *Rhipicephalus* spp., *Amblyomma* spp., *Dermacentor* spp., *Hyalomma* spp. and *Haemaphysalis* spp.; and fleas such as *Ctenocephalides felis* (cat flea) and *Ctenocephalides canis* (dog flea).

Biologically active compounds or agents useful in the compositions of the present invention include the organophosphate pesticides. This class of pesticides has very broad activity as insecticides and, in certain instances, anthelmintic activity. Organophosphate pesticides include, e.g., dicrotophos, terbufos, dimethoate, diazinon, disulfoton, trichlorfon, azinphos-methyl, chlorpyrifos, malathion, oxydemeton-methyl, methamidophos, acephate, ethyl parathion, methyl parathion, mevinphos, phorate, carbofenthion and phosalone. It is also contemplated to include combinations of the inventive methods and compounds with carbamate-type pesticides, including, e.g., carbaryl, carbofuran, aldicarb, molinate, methomyl, carbofuran, etc., as well as combinations with the organochlorine-type pesticides. It is further contemplated to include combinations with biological pesticides, including repellents, the pyrethrins (as well as synthetic variations thereof, e.g., allethrin, resmethrin, permethrin, tralomethrin), and nicotine, that is often employed as an acaricide. Other contemplated combinations are with miscellaneous pesticides including: *Bacillus thuringiensis*, chlorobenzilate, formamidines (e.g., amitraz), copper compounds (e.g., copper hydroxide and cupric oxychloride sulfate), cyfluthrin, cypermethrin, dicofol, endosulfan, esfenvalerate, fenvalerate, lambda-cyhalothrin, methoxychlor and sulfur.

Of note are additional biologically active compounds or agents selected from art-known anthelmintics, such as, for example, macrocyclic lactones (e.g., ivermectin, moxidectin, milbemycin), benzimidazoles (e.g., albendazole, triclabendazole), salicylanilides (e.g., closantel, oxyclozanide), substituted phenols (e.g., nitroxynil), pyrimidines (e.g., pyrantel), imidazothiazoles (e.g., levamisole), cyclic depsipeptides (e.g., emodepside), piperazine salts, nitroscanate and praziquantel.

Other biologically active compounds or agents useful in the compositions of the present invention can be selected from Insect Growth Regulators (IGRs) and Juvenile Hormone Analogues (JHAs) such as diflubenzuron, triflumuron, fluazuron, cyromazine, methoprene, etc., thereby providing both initial and sustained control of parasites (at all

stages of insect development, including eggs) on the animal subject, as well as within the environment of the animal subject.

Of note are biologically active compounds or agents useful in the compositions of the present invention selected from the avermectin class of antiparasitic compounds. As stated 5 above, the avermectin family of compounds includes very potent antiparasitic agents known to be useful against a broad spectrum of endoparasites and ectoparasites in mammals.

A preferred compound for use within the scope of the present invention is ivermectin. Ivermectin is a semi-synthetic derivative of avermectin and is generally produced as a mixture of at least 80% 22,23-dihydroavermectin B_{1a} and less than 20% 22,23-10 dihydroavermectin B_{1b}. Ivermectin is disclosed in U.S. Patent No. 4,199,569.

Abamectin is an avermectin that is disclosed as avermectin B_{1a}/B_{1b} in U.S. Patent No. 4,310,519. Abamectin contains at least 80% of avermectin B_{1a} and not more than 20% of avermectin B_{1b}.

Another preferred avermectin is doramectin, also known as 25-cyclohexyl-avermectin 15 B₁. The structure and preparation of doramectin is disclosed in U.S. Patent No. 5,089,480.

Another preferred avermectin is moxidectin. Moxidectin, also known as LL-F28249 alpha, is known from U.S. Patent No. 4,916,154.

Another preferred avermectin is selamectin. Selamectin is 25-cyclohexyl-25-de(1-methylpropyl)-5-deoxy-22,23-dihydro-5-(hydroxyimino)-avermectin B₁ monosaccharide.

Milbemycin, or B41, is a substance which is isolated from the fermentation broth of a milbemycin-producing strain of Streptomyces. The microorganism, the fermentation conditions and the isolation procedures are described in U.S. Patent Nos. 3,950,360 and 3,984,564.

Emamectin (4"-deoxy-4"-epi-methylaminoavermectin B₁), which can be prepared as 25 described in U.S. Patent Nos. 5,288,710 and 5,399,717, is a mixture of two homologues, 4"-deoxy-4"-epi-methylaminoavermectin B_{1a} and 4"-deoxy-4"-epi-methylaminoavermectin B_{1b}. Preferably, a salt of emamectin is used. Non-limiting examples of salts of emamectin which may be used in the present invention include the salts described in U.S. Patent No. 5,288,710, e.g., salts derived from benzoic acid, substituted benzoic acid, benzenesulfonic 30 acid, citric acid, phosphoric acid, tartaric acid, maleic acid, and the like. Most preferably, the emamectin salt used in the present invention is emamectin benzoate.

Eprinomectin is chemically known as 4"-epi-acetylamino-4"-deoxy-avermectin B₁. Eprinomectin was specifically developed to be used in all cattle classes and age groups. It was the first avermectin to show broad-spectrum activity against both endo- and ecto-35 parasites while also leaving minimal residues in meat and milk. It has the additional advantage of being highly potent when delivered topically.

The composition of the present invention optionally comprises combinations of one or more of the following antiparasite compounds: imidazo[1,2-b]pyridazine compounds as described by U.S. Patent Application Publication No. 2005/0182059 A1; 1-(4-mono and di-

halomethylsulphonylphenyl)-2-acylamino-3-fluoropropanol compounds, as described by U.S. Patent No. 7,361,689; trifluoromethanesulfonanilide oxime ether derivatives, as described by U.S. Patent No. 7,312,248; and *n*-[(phenyloxy)phenyl]-1,1,1-trifluoromethanesulfonamide and *n*-[(phenylsulfanyl)phenyl]-1,1,1-trifluoromethanesulfonamide derivatives, as described by PCT Patent Application Publication WO 2006/135648.

The compositions of the present invention may also further comprise a flukicide. Suitable flukicides include, for example, triclabendazole, fenbendazole, albendazole, clorsulon and oxicabendazole. It will be appreciated that the above combinations may further include combinations of antibiotic, antiparasitic and anti-fluke active compounds.

In addition to the above combinations, it is also contemplated to provide combinations of the inventive methods and compounds, as described herein, with other animal health remedies such as trace elements, anti-inflammatories, anti-infectives, hormones, dermatological preparations, including antiseptics and disinfectants, and immunobiologicals such as vaccines and antisera for the prevention of disease.

For example, such antifungals include one or more antibiotics that are optionally co-administered during treatment using the inventive compounds or methods, e.g., in a combined composition and/or in separate dosage forms. Art-known antibiotics suitable for this purpose include, for example, those listed herein below.

One useful antibiotic is florfenicol, also known as D-(*threo*)-1-(4-methylsulfonylphenyl)-2-dichloroacetamido-3-fluoro-1-propanol. Another preferred antibiotic compound is D-(*threo*)-1-(4-methylsulfonylphenyl)-2-difluoroacetamido-3-fluoro-1-propanol. Another useful antibiotic is thiampenicol. Processes for the manufacture of these antibiotic compounds, and intermediates useful in such processes, are described in U.S. Patent Nos. 4,31,857; 4,582,918; 4,973,750; 4,876,352; 5,227,494; 4,743,700; 5,567,844; 5,105,009; 5,382,673; 5,352,832; and 5,663,361. Other florfenicol analogs and/or prodrugs have been disclosed and such analogs also can be used in the compositions and methods of the present invention (see e.g., U.S. Patent Nos. 7,041,670 and 7,153,842).

Another useful antibiotic compound is tilmicosin. Tilmicosin is a macrolide antibiotic that is chemically defined as 20-dihydro-20-deoxy-20-(*cis*-3,5-dimethylpiperidin-1-yl)-desmycosin and is disclosed in U.S. Patent No. 4,820,695.

Another useful antibiotic for use in the present invention is tulathromycin. Tulathromycin may be prepared in accordance with the procedures set forth in U.S. Patent No. 6,825,327.

Further antibiotics for use in the present invention include the cephalosporins such as, for example, ceftiofur, cefquinome, etc. The concentration of the cephalosporin in the formulation of the present invention optionally varies between about 1 mg/mL to 500 mg/mL.

Another useful antibiotic includes the fluoroquinolones, such as, for example, enrofloxacin, danofloxacin, difloxacin, orbifloxacin and marbofloxacin. In the case of enrofloxacin, it may be administered in a concentration of about 100 mg/mL. Danofloxacin may be present in a concentration of about 180 mg/mL.

5 Other useful macrolide antibiotics include compounds from the class of ketolides, or, more specifically, the azalides. Such compounds are described in, for example, U.S. Patent Nos. 6,514,945; 6,472,371; 6,270,768; 6,437,151; 6,271,255; 6,239,12; 5,958,888; 6,339,063; and 6,054,434.

10 Other useful antibiotics include the tetracyclines, particularly chlortetracycline and oxytetracycline. Other antibiotics may include β -lactams such as penicillins, e.g., penicillin, ampicillin, amoxicillin, or a combination of amoxicillin with clavulanic acid or other beta lactamase inhibitors.

15 Nonagronomic applications in the veterinary sector are by conventional means such as by enteral administration in the form of, for example, tablets, capsules, drinks, drenching preparations, granulates, pastes, boli, feed-through procedures, or suppositories; or by parenteral administration, such as by injection (including intramuscular, subcutaneous, intravenous, intraperitoneal) or implants; by nasal administration; by topical administration, for example, in the form of immersion or dipping, spraying, washing, coating with powder, or application to a small area of the animal, and through articles such as neck collars, ear 20 tags, tail bands, limb bands or halters which comprise compounds or compositions of the present invention.

25 Any of the compounds of the present invention, or a suitable combination of such compounds, may be administered directly to the animal subject and/or indirectly by applying it to the local environment in which the animal dwells (such as bedding, enclosures, or the like). Direct administration includes contacting the skin, fur or feathers of a subject animal with the compounds, or by feeding or injecting the compounds into the animal.

30 The compounds of the present invention may be administered in a controlled release form, e.g., in a subcutaneous slow release formulation, or in the form of a controlled release device affixed to an animal such as a flea collar. Collars for the controlled release of an insecticide agent for long term protection against flea infestation in a companion animal are art-known, and are described, for example, by U.S. Patent Nos. 3,852,416; 4,224,901; 5,555,848; and 5,184,573.

35 Typically a parasiticidal composition according to the present invention comprises a mixture of a compound of Formula 1 with one or more pharmaceutically or veterinarily acceptable carriers comprising excipients and auxiliaries selected with regard to the intended route of administration (e.g., oral, topical or parenteral administration such as injection) and in accordance with standard practice. In addition, a suitable carrier is selected on the basis of compatibility with the one or more active ingredients in the composition, including such considerations as stability relative to pH and moisture content. Therefore of note is a

composition for protecting an animal from an invertebrate parasitic pest comprising a compound of the invention (i.e. in a parasitically effective amount) and at least one veterinarianally acceptable carrier.

For parenteral administration including intravenous, intramuscular and subcutaneous injection, a compound of the present invention can be formulated in suspension, solution or emulsion in oily or aqueous vehicles, and may contain adjuncts such as suspending, stabilizing and/or dispersing agents. The compounds of the present invention may also be formulated for bolus injection or continuous infusion. Pharmaceutical compositions for injection include aqueous solutions preferably in physiologically compatible buffers containing other excipients or auxiliaries as are known in the art of pharmaceutical formulation. Additionally, suspensions of the active compounds may be prepared in a lipophilic vehicle. Suitable lipophilic vehicles include fatty oils such as sesame oil, synthetic fatty acid esters such as ethyl oleate and triglycerides, or materials such as liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

In addition to the formulations described supra, the compounds of the present invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular or subcutaneous injection. The compounds of the present invention may be formulated for this route of administration with suitable polymeric or hydrophobic materials (e.g., in an emulsion with a pharmacologically acceptable oil).

For administration by inhalation, the compounds of the present invention can be delivered in the form of an aerosol spray using a pressurized pack or a nebulizer and a suitable propellant, e.g., without limitation, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane or carbon dioxide. In the case of a pressurized aerosol, the dosage unit may be controlled by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Compounds of the present invention have been discovered to have favorable pharmacokinetic and pharmacodynamic properties providing systemic availability from oral administration and ingestion. Therefore after ingestion by the animal to be protected, parasitically effective concentrations of compounds of the invention in the bloodstream protect the treated animal from blood-sucking pests such as fleas, ticks and lice. Therefore of note is a composition for protecting an animal from an invertebrate parasite pest in a form for oral administration (i.e. comprising, in addition to a parasitically effective amount of a

compound of the invention, one or more carriers selected from binders and fillers suitable for oral administration and feed concentrate carriers).

For oral administration in the form of solutions (the most readily available form for absorption), emulsions, suspensions, pastes, gels, capsules, tablets, boluses, powders, granules, rumen-retention and feed/water/lick blocks, a compound of the present invention can be formulated with binders/fillers known in the art to be suitable for oral administration compositions, such as sugars and sugar derivatives (e.g., lactose, sucrose, mannitol, sorbitol), starch (e.g., maize starch, wheat starch, rice starch, potato starch), cellulose and derivatives (e.g., methylcellulose, carboxymethylcellulose, ethylhydroxycellulose), protein derivatives (e.g., zein, gelatin), and synthetic polymers (e.g., polyvinyl alcohol, polyvinylpyrrolidone). If desired, lubricants (e.g., magnesium stearate), disintegrating agents (e.g., cross-linked polyvinylpyrrolidinone, agar, alginic acid) and dyes or pigments can be added. Pastes and gels often also contain adhesives (e.g., acacia, alginic acid, bentonite, cellulose, xanthan gum, colloidal magnesium aluminum silicate) to aid in keeping the composition in contact with the oral cavity and not being easily ejected.

A preferred embodiment is a composition formulated into a chewable and/or edible product (e.g., a chewable treat or edible tablet). Such a product would ideally have a taste, texture and/or aroma favored by the animal to be protected so as to facilitate oral administration of the compound of Formula 1.

If the parasiticidal compositions are in the form of feed concentrates, the carrier is typically selected from high-performance feed, feed cereals or protein concentrates. Such feed concentrate-containing compositions can, in addition to the parasiticidal active ingredients, comprise additives promoting animal health or growth, improving quality of meat from animals for slaughter or otherwise useful to animal husbandry. These additives can include, for example, vitamins, antibiotics, chemotherapeutics, bacteriostats, fungistats, coccidiostats and hormones.

The compounds of Formula 1 may also be formulated in rectal compositions such as suppositories or retention enemas, using, e.g., conventional suppository bases such as cocoa butter or other glycerides.

Formulations for topical administration are typically in the form of a powder, cream, suspension, spray, emulsion, foam, paste, aerosol, ointment, salve or gel. More typically a topical formulation is a water-soluble solution, which can be in the form of a concentrate that is diluted before use. Parasiticidal compositions suitable for topical administration typically comprise a compound of the present invention and one or more topically suitable carriers. In applications of a parasiticidal composition topically to the exterior of an animal as a line or spot (i.e. "spot-on" treatment), the active ingredient migrates over the surface of the animal to cover most or all of its external surface area. As a result, the treated animal is particularly protected from invertebrate pests that feed off the epidermis of the animal such as ticks, fleas and lice. Therefore formulations for topical localized administration often comprise at least

one organic solvent to facilitate transport of the active ingredient over the skin and/or penetration into the epidermis of the animal. Carriers in such formulations include propylene glycol, paraffins, aromatics, esters such as isopropyl myristate, glycol ethers, alcohols such as ethanol, *n*-propanol, 2-octyl dodecanol or oleyl alcohol; solutions in esters 5 of monocarboxylic acids, such as isopropyl myristate, isopropyl palmitate, lauric acid oxalic ester, oleic acid oleyl ester, oleic acid decyl ester, hexyl laurate, oleyl oleate, decyl oleate, caproic acid esters of saturated fatty alcohols of C₁₂-C₁₈ chain length; solutions of esters of dicarboxylic acids, such as dibutyl phthalate, diisopropyl isophthalate, adipic acid diisopropyl ester, di-*n*-butyl adipate or solutions of esters of aliphatic acids, e.g., glycols. It 10 may be advantageous for a crystallization inhibitor or a dispersant known from the pharmaceutical or cosmetic industry also to be present.

A pour-on formulation may also be prepared for control of parasites in an animal of agricultural value. The pour-on formulations of this invention can be in the form of a liquid, powder, emulsion, foam, paste, aerosol, ointment, salve or gel. Typically, the pour-on 15 formulation is liquid. These pour-on formulations can be effectively applied to sheep, cattle, goats, other ruminants, camelids, pigs and horses. The pour-on formulation is typically applied by pouring in one or several lines or in a spot-on the dorsal midline (back) or shoulder of an animal. More typically, the formulation is applied by pouring it along the back of the animal, following the spine. The formulation can also be applied to the animal by 20 other conventional methods, including wiping an impregnated material over at least a small area of the animal, or applying it using a commercially available applicator, by means of a syringe, by spraying or by using a spray race. The pour-on formulations include a carrier and can also include one or more additional ingredients. Examples of suitable additional 25 ingredients are stabilizers such as antioxidants, spreading agents, preservatives, adhesion promoters, active solubilisers such as oleic acid, viscosity modifiers, UV blockers or absorbers, and colourants. Surface active agents, including anionic, cationic, non-ionic and ampholytic surface active agents, can also be included in these formulations.

The formulations of this invention typically include an antioxidant, such as BHT (butylated hydroxytoluene). The antioxidant is generally present in amounts of at 0.1-5% 30 (wt/vol). Some of the formulations require a solubilizer, such as oleic acid, to dissolve the active agent, particularly if spinosad is used. Common spreading agents used in these pour-on formulations include isopropyl myristate, isopropyl palmitate, caprylic/capric acid esters of saturated C₁₂-C₁₈ fatty alcohols, oleic acid, oleyl ester, ethyl oleate, triglycerides, silicone 35 oils and dipropylene glycol methyl ether. The pour-on formulations of this invention are prepared according to known techniques. When the pour-on formulation is a solution, the parasiticide/insecticide is mixed with the carrier or vehicle, using heat and stirring if required. Auxiliary or additional ingredients can be added to the mixture of active agent and carrier, or they can be mixed with the active agent prior to the addition of the carrier. If the

pour-on formulation is an emulsion or suspension, the formulations can be similarly prepared using known techniques.

Other delivery systems for relatively hydrophobic pharmaceutical compounds can be employed. Liposomes and emulsions are well-known examples of delivery vehicles or carriers for hydrophobic drugs. In addition, organic solvents such as dimethylsulfoxide can be used, if needed.

For agronomic applications, the rate of application required for effective control (i.e. "biologically effective amount") will depend on such factors as the species of invertebrate to be controlled, the pest's life cycle, life stage, its size, location, time of year, host crop or animal, feeding behavior, mating behavior, ambient moisture, temperature, and the like. Under normal circumstances, application rates of about 0.01 to 2 kg of active ingredients per hectare are sufficient to control pests in agronomic ecosystems, but as little as 0.0001 kg/hectare may be sufficient or as much as 8 kg/hectare may be required. For nonagronomic applications, effective use rates will range from about 1.0 to 50 mg/square meter but as little as 0.1 mg/square meter may be sufficient or as much as 150 mg/square meter may be required. One skilled in the art can easily determine the biologically effective amount necessary for the desired level of invertebrate pest control.

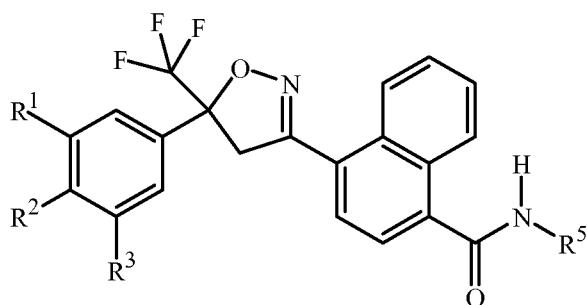
In general for veterinary use, a compound of Formula 1 is administered in a parasitically effective amount to an animal to be protected from invertebrate parasite pests. A parasitically effective amount is the amount of active ingredient needed to achieve an observable effect diminishing the occurrence or activity of the target invertebrate parasite pest. One skilled in the art will appreciate that the parasitically effective dose can vary for the various compounds and compositions of the present invention, the desired parasitical effect and duration, the target invertebrate pest species, the animal to be protected, the mode of application and the like, and the amount needed to achieve a particular result can be determined through simple experimentation.

For oral, subcutaneous or spot-on administration to homeothermic animals, a dose of a compound of the present invention administered at suitable intervals typically ranges from about 0.01 mg/kg to about 100 mg/kg, and preferably from about 0.01 mg/kg to about 30 mg/kg of animal body weight. For other topical (e.g., dermal) administration, including dips and sprays, a dose typically contains from about 0.01 ppm to about 150,000 ppm, more typically from about 0.01 ppm to about 100,000 ppm, preferably from about 0.01 ppm to about 5,000 ppm, and most preferably from about 0.01 ppm to about 3,000 ppm, of a compound of the present invention.

Suitable intervals for the administration of compounds of the present invention to homeothermic animals range from about daily to about yearly. Of note are administration intervals ranging from about weekly to about once every 6 months. Of particular note are monthly administration intervals (i.e. administering the compound to the animal once every month).

The following Tests demonstrate the control efficacy of compounds of this invention on specific pests. “Control efficacy” represents inhibition of invertebrate pest development (including mortality) that causes significantly reduced feeding. The pest control protection afforded by the compounds is not limited, however, to these species. See Index Tables A–D 5 for compound descriptions. The following abbreviations are used in the Index Tables which follow: Pr is $\text{CH}_2\text{CH}_2\text{CH}_3$, *i*-Pr is $\text{CH}(\text{CH}_3)_2$ and *i*-Bu is $\text{CH}_2\text{CH}(\text{CH}_3)_2$. (*R*) or (*S*) denotes the absolute chirality of the asymmetric carbon center. The abbreviation “Ex.” stands for “Example” and is followed by a number indicating in which synthesis example the compound is prepared.

10

INDEX TABLE A

<u>Compound</u>	<u>R¹</u>	<u>R²</u>	<u>R³</u>	<u>R⁵</u>	<u>m.p. (°C)</u>
1 (Ex. 4)	Cl	H	Cl	$\text{CH}_2\text{C(O)NHCH}_2\text{CF}_3$	**
2	Cl	H	Cl	(<i>S</i>)- $\text{CH}(\text{i-Pr})\text{C(O)NHCH}_2\text{CF}_3$	*
3	Cl	H	Cl	(<i>S</i>)- $\text{CH}(\text{CH}_3)\text{C(O)NHCH}_2\text{CF}_3$	*
4	Cl	H	Cl	$\text{C(CH}_3)_2\text{C(O)NHCH}_2\text{CF}_3$	*
5	Cl	H	Cl	$\text{CH}_2\text{C(O)NHCH(CH}_3)_2$	*
6	Cl	H	Cl	$\text{CH}_2\text{C(O)NHCH}_2\text{CH(CH}_3)_2$	*
7	Cl	H	Cl	$\text{CH}_2\text{C(O)N(CH}_3)\text{CH}_2\text{CH}_3$	*
8	Cl	H	Cl	$\text{CH}_2\text{C(O)NHCH}_2\text{CH}_3$	*
9	Cl	H	Cl	$\text{CH}_2\text{CH}_2\text{C(O)NHCH}_2\text{CF}_3$	*
10	Cl	H	Cl	$\text{CH}_2\text{C(O)NHCH}_2\text{CH}_2\text{Cl}$	*
11	Cl	H	Cl	$\text{CH}_2\text{CH}_2\text{OH}$	*
12	Cl	H	Cl	$\text{CH}_2\text{C(O)NHCH}_2\text{CH}_2\text{F}$	*
13	Cl	H	Cl	$\text{CH}_2\text{C(O)NHCH}_2\text{CF}_2\text{CF}_2\text{CF}_3$	*
14	Cl	H	Cl	$\text{CH}_2\text{C(O)NHCH}_2\text{CF}_2\text{CF}_3$	*
15	Cl	Cl	Cl	$\text{CH}_2\text{CH}_2\text{SCH}_3$	*
16	Cl	H	Cl	(<i>R</i>)- $\text{CH}(\text{CH}_3)\text{C(O)NHCH}_2\text{CF}_3$	*
17 (Ex. 1)	Cl	H	Cl	$\text{CH}_2\text{CH}_2\text{SCH}_3$	**
18 (Ex. 2)	Cl	H	Cl	$\text{CH}_2\text{CH}_2\text{S(O)CH}_3$	**

<u>Compound</u>	<u>R¹</u>	<u>R²</u>	<u>R³</u>	<u>R⁵</u>	<u>m.p. (°C)</u>
19	Cl	Cl	Cl	CH ₂ C(O)NHCH ₂ CF ₃	*
20 (Ex. 3)	Cl	H	Cl	CH ₂ CH ₂ S(O) ₂ CH ₃	**
21	Br	H	Br	CH ₂ CH ₂ SCH ₃	*
22	Cl	H	Cl	CH ₂ CH ₂ CH ₂ SCH ₃	*
23	Br	H	Br	CH ₂ C(O)NHCH ₂ CF ₃	*
24	Cl	H	Cl	CH ₂ C(O)NHC(CH ₃) ₃	*
25	Cl	H	Cl	CH ₂ C(O)NHCH(CH ₂ CH ₃) ₂	*
26	Cl	H	Cl	CH(CH ₃)CH ₂ CH ₂ SCH ₃	*
27	Cl	H	Cl	C(CH ₃) ₂ CH ₂ SCH ₃	*
28	Cl	H	Cl	CH ₂ CH ₂ OCH ₃	*
29	Cl	H	Cl	(R)-CH(CH ₃)CH ₂ SCH ₃	*
30	Cl	H	Cl	CH(CH ₃)CH ₂ SCH ₃	*
31	Cl	H	Cl	(R)-CH(CH ₃)CH ₂ OH	*
32	Cl	H	Cl	C(CH ₃) ₂ CH ₂ OH	*
33	Cl	H	Cl	(R)-CH(CH ₃)C(O)NH(i-Pr)	*
34	CF ₃	H	H	CH ₂ CH ₂ SCH ₃	*
35	CF ₃	H	H	CH ₂ C(O)NHCH ₂ CF ₃	*
36	CF ₃	H	H	CH ₂ CH(OH)CH ₃	*
37 (Ex. 5)	CF ₃	H	CF ₃	CH ₂ C(O)NHCH ₂ CF ₃	**
38	CF ₃	H	H	CH ₂ C(O)NHCH(CH ₃) ₂	*
39	CF ₃	H	H	CH ₂ CH ₂ S(O) ₂ CH ₃	*
40 (Ex. 6)	CF ₃	H	CF ₃	CH ₂ C(O)NHCH(CH ₃) ₂	**
41	CF ₃	H	H	CH(CH ₃)CH ₂ OH	*
42	CF ₃	H	H	CH ₂ CH ₂ CH ₂ OH	*
43	CF ₃	H	H	CH ₂ C(CH ₃) ₂ OH	*
44	CF ₃	H	H	CH ₂ CH ₂ CH(OH)CH ₃	*
45	CF ₃	H	H	CH ₂ C(OH)(CF ₃)CH ₃	*
46	CF ₃	H	H	CH(CH ₂ CH ₃)CH ₂ OH	*
47	CF ₃	H	H	CH(CH ₃)CH ₂ OCH ₃	*
48	CF ₃	H	H	CH ₂ CH ₂ CH ₂ SCH ₂ CH ₃	*
49	CF ₃	H	CF ₃	CH ₂ CH ₂ S(O) ₂ CH ₃	*
50	CF ₃	H	Br	CH ₂ CH ₂ SCH ₃	*
51	CF ₃	H	H	CH ₂ CH ₂ SCH ₂ CH ₃	*
52	CF ₃	H	Br	CH ₂ C(O)NHCH ₂ CF ₃	*
53	CF ₃	H	Br	CH ₂ C(O)NHCH(CH ₃) ₂	*
54	CF ₃	H	Br	CH ₂ CH ₂ S(O) ₂ CH ₃	*
55	CF ₃	H	H	CH ₂ CH ₂ SCH(CH ₃) ₂	*

<u>Compound</u>	<u>R¹</u>	<u>R²</u>	<u>R³</u>	<u>R⁵</u>	<u>m.p. (°C)</u>
56	CF ₃	H	H	CH ₂ CH ₂ CH ₂ SCH(CH ₃) ₂	*
57	CF ₃	H	H	CH ₂ CH ₂ SC(CH ₃) ₃	*
58	CF ₃	H	CF ₃	CH ₂ CH ₂ SCH ₃	*
59	CF ₃	H	CF ₃	CH(CH ₃)CH ₂ SCH ₃	*
60	CF ₃	H	CF ₃	(R)-CH(CH ₃)CH ₂ SCH ₃	*
61	CF ₃	H	H	CH ₂ C(CH ₃) ₂ CH ₂ OH	*
62	CF ₃	H	Cl	CH ₂ C(O)NHCH ₂ CF ₃	106-108
63	CF ₃	H	Cl	CH ₂ C(O)NHCH(CH ₃) ₂	*
64	CF ₃	H	H	CH ₂ CH(OH)CH ₂ CH ₃	*
65	CF ₃	H	Cl	CH ₂ CH ₂ SCH ₃	*
66	CF ₃	H	Cl	CH ₂ CH ₂ S(O) ₂ CH ₃	*
67	CF ₃	H	CF ₃	CH ₂ CH(OH)CH ₃	*
68	CF ₃	H	CF ₃	CH(CH ₃)CH ₂ OH	*
69	CF ₃	H	CF ₃	CH ₂ CH ₂ OH	*
70	Br	H	H	CH ₂ C(O)NHCH ₂ CF ₃	*
71	OCF ₃	H	H	CH ₂ CH ₂ SCH ₃	*
72	OCF ₃	H	H	CH ₂ C(O)NHCH ₂ CF ₃	*
73	F	H	F	CH ₂ C(O)NHCH ₂ CF ₃	*
74	F	H	H	CH ₂ C(O)NHCH ₂ CF ₃	*
75	F	H	F	CH ₂ C(O)NHCH(CH ₃) ₂	*
76	F	H	H	CH ₂ C(O)NHCH(CH ₃) ₂	*
77	F	H	F	CH ₂ CH ₂ SCH ₃	156-160
78	F	H	H	CH ₂ CH ₂ SCH ₃	146-150
79	CF ₃	H	CF ₃	CH ₂ CH ₂ S(O)CH ₃	*
80	F	H	F	CH ₂ CH ₂ S(O) ₂ CH ₃	171-175
81	F	H	H	CH ₂ CH ₂ S(O) ₂ CH ₃	152-156
82	Cl	H	Cl	CH ₂ OH	*
83	CF ₃	H	CF ₃	(R)-CH(CH ₃)C(O)NH(i-Pr)	*
84	CF ₃	H	CF ₃	(R)-CH(CH ₃)C(O)NHP <i>r</i>	*
85	CF ₃	H	CF ₃	CH(CH ₃)C(O)NHCH ₂ CF ₃	95-96
86	CF ₃	H	CF ₃	CH(CH ₃)C(O)NHCH ₃	145-146
87	CF ₃	H	CF ₃	CH(CH ₃)C(O)NH(i-Pr)	162-163
88	CF ₃	H	CF ₃	CH(CH ₃)C(O)NHCH ₂ CH ₃	168-170
89	CF ₃	H	CF ₃	CH(CH ₃)C(O)NHP <i>r</i>	135-136
90	CF ₃	H	CF ₃	CH(CH ₃)C(O)NH(i-Bu)	83-84
91	CF ₃	H	CF ₃	CH ₂ C(O)NHCH(CF ₃)CH ₃	101-102
92	CF ₃	H	CF ₃	CH ₂ CH ₂ SCH ₂ CH ₃	*

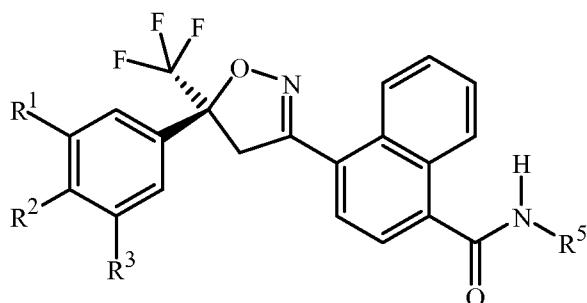
<u>Compound</u>	<u>R¹</u>	<u>R²</u>	<u>R³</u>	<u>R⁵</u>	<u>m.p. (°C)</u>
93	CF ₃	H	CF ₃	(<i>R</i>)-CH(CH ₃)C(O)NH(<i>i</i> -Bu)	*
94	CF ₃	H	CF ₃	(<i>R</i>)-CH(CH ₃)C(O)NHCH ₂ CF ₃	*
95	CF ₃	H	CF ₃	(<i>R</i>)-CH(CH ₃)C(O)NHCH ₃	*
96	CF ₃	H	CF ₃	(<i>R</i>)-CH(CH ₃)C(O)NHCH ₂ CH ₃	*
97	CF ₃	H	CF ₃	(<i>R</i>)-CH(CH ₃)C(O)NHCH ₂ C(CH ₃) ₃	*
98	CF ₃	H	CF ₃	CH ₂ CH ₂ S(O)CH ₂ CH ₃	*
99	CF ₃	H	CF ₃	CH ₂ CH ₂ S(O) ₂ CH ₂ CH ₃	*
100	CF ₃	H	CF ₃	CH ₂ C(O)NHCH ₂ CH ₃	92-97
101	CF ₃	H	CF ₃	CH ₂ C(O)NHCH ₂ CH ₂ CH ₃	*
102	CF ₃	H	CF ₃	CH ₂ C(O)NH(<i>i</i> -Bu)	94-99
103	CF ₃	H	CF ₃	CH ₂ C(O)NHCH ₂ C(CH ₃) ₃	102-105
104	CF ₃	H	CF ₃	(<i>S</i>)-CH ₂ C(O)NHCH(CF ₃)CH ₃	100-105
105	CF ₃	H	CF ₃	CH ₂ C(O)NHCH ₃	*
106	CF ₃	H	Cl	(<i>R</i>)-CH(CH ₃)C(O)NHCH ₂ CF ₃	*
107	CF ₃	H	Cl	(<i>R</i>)-CH(CH ₃)C(O)NH(<i>i</i> -Pr)	*
108	CF ₃	H	Cl	(<i>R</i>)-CH(CH ₃)C(O)NHP <i>r</i>	*
109	CF ₃	H	Cl	(<i>R</i>)-CH(CH ₃)C(O)NHCH ₃	*
110	CF ₃	H	Cl	(<i>R</i>)-CH(CH ₃)C(O)NHCH ₂ CH ₃	*
111	CF ₃	H	Cl	(<i>R</i>)-CH(CH ₃)C(O)NH(<i>i</i> -Bu)	*
112	CF ₃	H	Cl	(<i>R</i>)-CH(CH ₃)C(O)NHCH ₂ C(CH ₃) ₃	*
113	CF ₃	H	Cl	CH ₂ C(O)NHCH(CF ₃)CH ₃	101-102
114	CF ₃	H	Cl	CH ₂ CH ₂ S(O)CH ₃	78-79
115	CF ₃	H	Cl	CH(CH ₃)C(O)NHCH(CF ₃)CH ₃	96-97
116	CF ₃	H	Cl	CH ₂ C(O)NHCH ₃	95-96
117	CF ₃	H	Cl	CH ₂ C(O)NHP <i>r</i>	101-102
118	CF ₃	H	Cl	CH ₂ C(O)NH(<i>i</i> -Bu)	99-100
119	CF ₃	H	Cl	CH ₂ C(O)NHCH ₂ CH ₃	182-183
120	CF ₃	H	Cl	CH ₂ C(O)NHCH ₂ C(CH ₃) ₃	101-102
121	CF ₃	H	CF ₃	CH(CH ₃)C(O)NHCH(CF ₃)CH ₃	93-94
122	Cl	H	Cl	CH ₂ C(O)NHCH(CF ₃)CH ₃	99-100
123	Cl	H	Cl	CH(CH ₃)C(O)NHCH(CF ₃)CH ₃	118-119
124	CF ₃	H	CF ₃	CH(CH ₃)C(O)NHCH ₂ C(CH ₃) ₃	96-98
125	CF ₃	H	Cl	CH(CH ₃)C(O)NHCH ₃	104-105
126	CF ₃	H	Cl	CH(CH ₃)C(O)NHCH ₂ CH ₃	85-86
127	CF ₃	H	Cl	CH(CH ₃)C(O)NHCH ₂ CF ₃	90-92
128	CF ₃	H	Cl	CH(CH ₃)C(O)NH(<i>i</i> -Pr)	93-94
129	CF ₃	H	Cl	CH(CH ₃)C(O)NHP <i>r</i>	84-85

<u>Compound</u>	<u>R¹</u>	<u>R²</u>	<u>R³</u>	<u>R⁵</u>	<u>m.p. (°C)</u>
130	CF ₃	H	Cl	CH(CH ₃)C(O)NH(<i>i</i> -Bu)	143-144
131	CF ₃	H	Cl	CH(CH ₃)C(O)NHCH ₂ C(CH ₃) ₃	91-92
132	CF ₃	H	F	CH ₂ CH ₂ SCH ₃	*
133	CF ₃	H	F	CH ₂ CH ₂ S(O)CH ₃	*
134	CF ₃	H	F	CH ₂ CH ₂ S(O) ₂ CH ₃	*
135	CF ₃	H	F	CH ₂ C(O)NHCH ₂ CF ₃	*
136	OCF ₃	H	Cl	CH ₂ C(O)NHCH ₂ CF ₃	*
137	CF ₃	H	F	(<i>R</i>)-CH(CH ₃)C(O)NHCH ₂ CH ₃	*
138	CF ₃	H	F	(<i>R</i>)-CH(CH ₃)C(O)NHCH ₃	*
139	CF ₃	H	F	(<i>R</i>)-CH(CH ₃)C(O)NHCH ₂ CF ₃	*
140	CF ₃	H	Br	(<i>R</i>)-CH(CH ₃)C(O)NHCH ₂ CF ₃	*
141	CF ₃	H	Br	(<i>R</i>)-CH(CH ₃)C(O)NHCH ₃	*
142	CF ₃	H	Br	(<i>R</i>)-CH(CH ₃)C(O)NHCH ₂ CH ₃	*
143	CF ₃	H	Br	CH ₂ C(O)NHCH ₃	*
144	CF ₃	H	Br	CH ₂ C(O)NHCH ₂ CH ₃	*
145	CF ₃	H	CF ₃	CH ₂ C(O)NHCH ₂ CH ₂ Cl	*

* See Index Table D for ¹H NMR data.

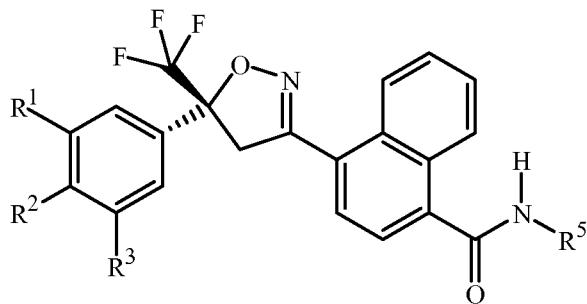
** See synthesis example for ¹H NMR data.

INDEX TABLE B



<u>Compound</u>	<u>R¹</u>	<u>R²</u>	<u>R³</u>	<u>R⁵</u>	<u>m.p. (°C)</u>
173	Cl	H	Cl	(<i>R</i>)-CH(CH ₃)CH ₂ SCH ₃	84-86
174	Cl	H	Cl	CH ₂ C(O)NHCH ₂ CF ₃	*

* See Index Table D for ¹H NMR data.

INDEX TABLE C

<u>Compound</u>	<u>R¹</u>	<u>R²</u>	<u>R³</u>	<u>R⁵</u>	<u>m.p.</u> (°C)
176	Cl	H	Cl	(R)-CH(CH ₃)CH ₂ SCH ₃	*
177	Cl	H	Cl	CH ₂ C(O)NHCH ₂ CF ₃	*

* See Index Table D for ¹H NMR data.

INDEX TABLE D

<u>Compound</u>	<u>¹H NMR Data (CDCl₃ solution unless indicated otherwise)^a</u>
2	δ 8.82 (d, 1H), 8.22 (d, 1H), 7.44–7.67 (m, 7H), 6.96 (br t, 1H), 6.82 (d, 1H), 4.67 (t, 1H), 4.23 (d, 1H), 4.07 (m, 1H), 3.83 (m, 2H), 2.26 (m, 1H), 1.09 (d, 3H), 1.08 (d, 3H).
3	δ 8.81 (d, 1H), 8.22 (d, 1H), 7.41–7.66 (m, 7H), 7.21 (br t, 1H), 6.82 (m, 1H), 4.88 (m, 1H), 4.23 (d, 1H), 3.94 (m, 2H), 3.87 (d, 1H), 1.56 (d, 3H).
4	δ 8.77 (d, 1H), 8.17 (d, 1H), 7.39–7.67 (m, 7H), 6.63 (br s, 1H), 4.24 (d, 1H), 3.98 (m, 2H), 3.88 (d, 1H), 1.74 (s, 6H).
5	δ 8.83 (d, 1H), 8.30 (d, 1H), 7.46–7.67 (m, 7H), 7.1 (br s, 1H), 6.20 (br s, 1H), 4.25 (d, 1H), 4.17 (d, 2H), 4.10 (m, 1H), 3.89 (d, 1H), 1.19 (d, 6H).
6	δ 8.83 (d, 1H), 8.31 (d, 1H), 7.46–7.67 (m, 7H), 7.08 (br s, 1H), 6.35 (br s, 1H), 4.26 (d, 1H), 4.22 (d, 2H), 3.89 (d, 1H), 3.14 (t, 2H), 0.93 (d, 3H).
7	δ 8.85 (d, 1H), 8.38 (d, 1H), 7.46–7.70 (m, 7H), 7.20 (m, 1H), 4.37 & 4.33 (d, 2H), 4.27 (d, 1H), 3.91 (d, 1H), 3.49 & 3.39 (q, 2H), 3.04 & 3.00 (s, 3H), 1.27 & 1.16 (t, 3H).
8	δ 8.83 (d, 1H), 8.30 (d, 1H), 7.45–7.67 (m, 7H), 7.06 (br s, 1H), 6.26 (br s, 1H), 4.25 (d, 1H), 4.19 (d, 2H), 3.88 (d, 1H), 3.34 (m, 2H), 1.17 (t, 3H).
9	δ 8.75 (d, 1H), 8.14 (d, 1H), 7.46–7.59 (m, 5H), 7.37 (d, 1H), 7.32 (d, 1H), 7.02 (br t, 1H), 6.97 (br t, 1H), 4.21 (d, 1H), 3.71–3.88 (m, 5H), 2.64 (t, 2H).
10	δ 8.83 (d, 1H), 8.32 (d, 1H), 7.46–7.68 (m, 7H), 6.97 (br s, 1H), 6.72 (br s, 1H), 4.26 (d, 1H), 4.24 (d, 2H), 3.89 (d, 1H), 3.65 (m, 4H).
11	δ 8.65 (d, 1H), 8.08 (d, 1H), 7.55 (s, 2H), 7.44–7.52 (m, 7H), 7.27 (d, 1H), 7.19 (d, 1H), 6.93 (br t, 1H), 4.16 (d, 1H), 3.81 (d, 1H), 3.73 (s, br, 2H), 3.53 (m, 2H), 3.27 (br s 1H).

- 12 δ 8.82 (d, 1H), 8.30 (d, 1H), 7.46–7.67 (m, 7H), 6.98 (br s, 1H), 6.65 (br s, 1H), 4.58 (t, 1H), 4.46 (t, 1H), 4.25 (d, 1H), 4.24 (d, 2H), 3.88 (d, 1H), 3.67 (q, 2H), 3.60 (q, 2H).
- 13 δ 8.82 (d, 1H), 8.24 (d, 1H), 7.44–7.67 (m, 7H), 7.15 (m, 2H), 4.29 (d, 2H), 4.23 (d, 1H), 4.04 (dt, 2H), 3.87 (d, 1H).
- 14 δ 8.80 (d, 1H), 8.22 (d, 1H), 7.41–7.65 (m, 7H), 7.30 (t, 1H), 7.23 (t, 1H), 4.27 (d, 2H), 4.23 (d, 1H), 3.98 (dt, 2H), 3.87 (d, 1H).
- 15 δ 8.76 (d, 1H), 8.26 (d, 1H), 7.70 (s, 2H), 7.59 (m, 2H), 7.47 (d, 1H), 7.39 (d, 1H), 6.60 (br t, 1H), 4.23 (d, 1H), 3.87 (d, 1H), 3.71 (q, 2H), 2.78 (t, 2H), 2.15 (s, 3H).
- 16 δ 8.80 (d, 1H), 8.19 (d, 1H), 7.39–7.66 (m, 7H), 7.31 (t, 1H), 6.92 (m, 1H), 4.90 (m, 1H), 4.23 (d, 1H), 3.93 (m, 2H), 3.87 (d, 1H), 1.56 (d, 3H).
- 19 δ 8.80 (d, 1H), 8.25 (d, 1H), 7.69 (s, 2H), 7.63 (m, 2H), 7.54 (d, 1H), 7.44 (d, 1H), 7.19 (br t, 1H), 7.14 (br t, 1H), 4.28 (d, 2H), 4.24 (d, 1H), 3.94 (m, 2H), 3.87 (d, 1H).
- 21 δ 8.74 (d, 1H), 8.22 (d, 1H), 7.76 (s, 2H), 7.56 (m, 3H), 7.42 (d, 1H), 7.33 (d, 1H), 6.69 (br t, 1H), 4.21 (d, 1H), 3.87 (d, 1H), 3.67 (q, 2H), 2.76 (t, 2H), 2.14 (s, 3H).
- 22 δ 8.81 (d, 1H), 8.26 (d, 1H), 7.46–7.67 (m, 7H), 6.32 (br t, 1H), 4.25 (d, 1H), 3.90 (d, 1H), 3.65 (q, 2H), 2.64 (t, 2H), 2.13 (s, 3H), 1.99 (m, 2H).
- 23 δ 8.78 (d, 1H), 8.20 (d, 1H), 7.34–7.76 (m, 9H), 4.25 (d, 2H), 4.21 (d, 1H), 3.89 (m, 2H), 3.85 (d, 1H).
- 24 δ 8.84 (d, 1H), 8.31 (d, 1H), 7.46–7.66 (m, 7H), 7.05 (t, 1H), 6.08 (d, 1H), 4.25 (d, 1H), 4.14 (d, 2H), 3.89 (d, 1H), 1.38 (s, 9H).
- 25 δ 8.83 (d, 1H), 8.30 (d, 1H), 7.46–7.66 (m, 7H), 7.18 (t, 1H), 6.17 (d, 1H), 4.25 (d, 1H), 4.22 (d, 2H), 3.88 (d, 1H), 3.80 (m, 1H), 1.57 (m, 2H), 1.40 (m, 2H), 0.90 (t, 6H).
- 26 δ 8.80 (d, 1H), 8.25 (d, 1H), 7.46–7.67 (m, 7H), 6.04 (d, 1H), 4.43 (m, 1H), 4.24 (d, 1H), 3.88 (d, 1H), 2.64 (dt, 2H), 2.14 (s, 3H), 1.91 (q, 2H), 1.34 (d, 3H).
- 27 δ 8.81 (d, 1H), 8.34 (d, 1H), 7.46–7.66 (m, 7H), 6.02 (br s 1H), 4.24 (d, 1H), 3.88 (d, 1H), 3.14 (s, 2H), 2.21 (s, 3H), 1.58 (s, 6H).
- 28 δ 8.65 (d, 1H), 8.08 (d, 1H), 7.55 (s, 2H), 7.445–7.52 (m, 7H), 7.27 (d, 1H), 7.19 (d, 1H), 6.93 (br t 1H), 4.16 (d, 1H), 3.81 (d, 1H), 3.73 (s, br, 2H), 3.53 (m, 2H), 3.27 (br s 1H).
- 29 δ 8.79 (d, 1H), 8.30 (d, 1H), 7.44–7.66 (m, 7H), 6.18 (d, 1H), 4.52 (m, 1H), 4.25 (d, 1H), 3.88 (d, 1H), 2.79 (m, 2H), 2.21 (s, 3H), 1.40 (d, 3H).
- 30 δ 8.81 (d, 1H), 8.32 (d, 1H), 7.46–7.67 (m, 7H), 6.13 (d, 1H), 4.52 (m, 1H), 4.25 (d, 1H), 3.88 (d, 1H), 2.79 (m, 2H), 2.21 (s, 3H), 1.40 (d, 3H).
- 31 δ 8.78 (d, 1H), 8.24 (d, 1H), 7.40–7.64 (m, 7H), 6.31 (d, 1H), 4.37 (m, 1H), 4.23 (d, 1H), 3.86 (d, 1H), 3.83 (m, 1H), 3.66 (m, 1H), 2.65 (br t 1H), 1.32 (d, 3H).
- 32 δ 8.81 (d, 1H), 8.23 (d, 1H), 7.46–7.68 (m, 7H), 6.09 (s, 1H), 4.31 (t, 1H), 4.24 (d, 1H), 3.88 (d, 1H), 3.78 (d, 2H), 1.47 (s, 6H).
- 33 δ 8.82 (d, 1H), 8.26 (d, 1H), 7.43–7.66 (m, 7H), 7.00 (br t, 1H), 6.33 (br d, 1H), 4.77 (m, 1H), 4.24 (d, 1H), 4.07 (m, 1H), 3.88 (d, 1H), 1.54 (d, 3H), 1.18 (d, 6H).

- 34 δ 8.91 (d, 1H), 8.3 (m, 1H), 7.9 (m, 1H), 7.85 (m, 1H), 7.7–7.6 (m, 5H), 7.54 (d, 1H), 6.39 (br s, 1H), 4.32 (d, 1H), 3.95 (d, 1H), 3.78 (m, 2H), 2.83 (m, 2H), 2.17 (s, 3H).
- 35 δ 8.82 (d, 1H), 8.25 (d, 1H), 7.93 (s, 1H), 7.87 (d, 1H), 7.74 (d, 1H), 7.59–7.66 (m, 3H), 7.56 (d, 1H), 7.47 (d, 1H), 7.13 (br t, 1H), 7.09 (br t, 1H), 4.30 (d, 1H), 4.28 (d, 2H), 3.95 (m, 2H), 3.93 (d, 1H).
- 36 δ 8.90 (d, 1H), 8.28 (d, 1H), 7.92 (s, 1H), 7.88 (m, 1H), 7.72 (m, 1H), 7.65–7.5 (m, 4H), 7.48 (m, 1H), 7.45 (m, 1H), 6.46 (br s, 1H), 4.32 (d, 1H), 4.1 (m, 1H), 3.94 (d, 1H), 3.77 (m, 1H), 3.4 (m, 1H), 1.3 (t, 3H).
- 38 δ 8.84 (d, 1H), 8.32 (d, 1H), 7.93 (s, 1H), 7.87 (d, 1H), 7.73 (d, 1H), 7.63 (m, 4H), 7.50 (d, 1H), 7.01 (br t, 1H), 6.05 (br d, 1H), 4.32 (d, 1H), 4.17 (d, 1H), 3.94 (d, 1H), 1.19 (d, 1H).
- 39 δ (CD₃C(O)CD₃) 8.90 (d, 1H), 8.40 (d, 1H), 8.1–8.0 (m, 3H), 7.9–7.8 (m, 3H), 7.7–7.6 (m, 3H), 4.65 (d, 1H), 4.45 (d, 1H), 3.97 (m, 2H), 3.53 (m, 2H), 3.07 (s, 3H).
- 41 δ (CD₃C(O)CD₃) 8.85 (d, 1H), 8.3 (d, 1H), 8.06 (s, 1H), 8.01 (d, 1H), 7.85 (m, 1H), 7.8 (m, 1H), 7.75 (m, 1H), 7.7–7.5 (m, 3H), 4.59 (d, 1H), 4.40 (d, 1H), 4.25 (m, 1H), 4.1 (br s, 1H), 3.82 (m, 2H), 1.25 (d, 2H).
- 42 δ (CD₃C(O)CD₃) 8.9 (d, 1H), 8.38 (d, 1H), 8.1–8.0 (m, 2H), 7.9–7.78 (m, 4H), 7.7–7.6 (m, 3H), 4.63 (d, 1H), 4.49 (d, 1H), 3.8 (m, 1H), 3.7 (m, 2H), 3.6 (m, 2H), 1.9–1.8 (m, 2H).
- 43 δ (CD₃S(O)CD₃) 8.9 (d, 1H), 8.5 (m, 1H), 8.22 (d, 1H), 8.0–7.9 (m, 4H), 7.8 (m, 1H), 7.7–7.6 (m, 3H), 4.6 (d, 1H), 4.38–4.32 (m, 2H), 3.4–3.3 (m, 2H, partially obscured by H₂O band), 1.19 (s, 6H).
- 44 δ (CD₃C(O)CD₃) 8.92 (d, 1H), 8.38 (d, 1H), 8.1–8.0 (m, 2H), 7.9–7.78 (m, 4H), 7.7–7.6 (m, 3H), 4.63 (d, 1H), 4.46 (d, 1H), 3.95 (m, 1H), 3.70 (m, 1H), 3.52 (m, 1H), 2.8 (br s, 1H), 1.8 (m, 1H), 1.66 (m, 1H), 1.20 (d, 3H).
- 45 δ 8.78 (d, 1H), 8.2 (d, 1H), 7.92 (s, 1H), 7.86 (m, 1H), 7.72 (m, 1H), 7.68–7.52 (m, 3H), 7.5 (m, 1H), 7.4 (m, 1H), 6.68 (br s, 1H), 4.4 (br s, 1H), 4.28 (d, 1H), 3.9 (d, 1H), 3.75–3.85 (m, 2H), 1.44 (s, 3H).
- 46 δ (CD₃C(O)CD₃) 8.9 (d, 1H), 8.38 (d, 1H), 8.05 (m, 2H), 7.88 (m, 1H), 7.82–7.78 (m, 2H), 7.7–7.6 (m, 3H), 7.47 (br d, 1H), 4.61 (d, 1H), 4.43 (d, 1H), 4.16 (m, 1H), 4.0 (m, 1H), 3.7 (m, 2H), 1.78 (m, 1H), 1.59 (m, 1H), 1.03 (t, 3H).
- 47 δ (CD₃C(O)CD₃) 8.9 (d, 1H), 8.38 (d, 1H), 8.05 (m, 2H), 7.9–7.8 (m, 3H), 7.7–7.6 (m, 3H), 7.5 (br d, 1H), 4.62 (d, 1H), 4.5 (d, 1H), 4.42 (m, 1H), 3.58 (m, 1H), 3.46 (m, 1H), 3.37 (s, 3H), 1.22 (d, 3H).
- 48 δ (CD₃C(O)CD₃) 8.91 (m, 1H), 8.35 (m, 1H), 8.04–8.08 (m, 2H), 7.78–7.90 (m, 4H), 7.62–7.71 (m, 3H), 4.64 (d, 1H), 4.48 (d, 1H), 3.60 (m, 2H), 2.68 (m, 2H), 2.57 (m, 2H), 1.97 (m, 2H), 1.23 (t, 3H).
- 49 δ 8.81 (d, 1H), 8.30 (d, 1H), 8.14 (s, 2H), 8.00 (s, 1H), 7.63 (m, 2H), 7.58 (d, 1H), 7.46 (d, 1H), 6.93 (br t, 1H), 4.36 (d, 1H), 4.05 (q, 2H), 3.94 (d, 1H), 3.41 (t, 2H), 3.01 (s, 3H).

50 δ 8.73 (d, 1H), 8.20 (d, 1H), 8.03 (s, 1H), 7.87 (s, 2H), 7.55 (m, 2H), 7.39 (d, 1H), 7.32 (d, 1H),
6.75 (br t, 1H), 4.26 (d, 1H), 3.89 (d, 1H), 3.66 (q, 2H), 2.75 (t, 2H), 2.13 (s, 3H).
51 δ (CD₃C(O)CD₃) 8.92 (m, 1H), 8.41 (m, 1H), 8.05–8.07 (m, 2H), 7.63–7.90 (m, 7H), 4.64 (d,
1H), 4.48 (d, 1H), 3.68 (m, 2H), 2.86 (m, 2H), 2.64 (q, 2H), 1.27 (t, 3H).
52 δ 8.78 (d, 1H), 8.19 (d, 1H), 8.02 (s, 1H), 7.87 (m, 2H), 7.35–7.63 (m, 6H), 4.28 (d, 1H), 4.25 (d,
2H), 3.89 (m, 3H).
53 δ (CD₃C(O)CD₃) 8.91 (d, 1H), 8.48 (d, 1H), 8.22 (s, 1H), 8.07 (s, 2H), 7.89 (br t, 1H), 7.86 (d,
1H), 7.73 (d, 1H), 7.66 (m, 2H), 7.17 (br d, 1H), 4.66 (d, 1H), 4.56 (d, 1H), 4.09 (d, 2H), 4.03 (m,
1H), 1.14 (d, 6H).
54 δ 8.77 (d, 1H), 8.25 (d, 1H), 8.02 (s, 1H), 7.87 (s, 2H), 7.58 (m, 2H), 7.51 (d, 1H), 7.39 (d, 1H),
7.07 (br t, 1H), 4.27 (d, 1H), 3.99 (q, 2H), 3.37 (t, 2H), 2.99 (s, 3H).
55 δ (CD₃C(O)CD₃) 8.91 (m, 1H), 8.40 (m, 1H), 8.04–8.08 (m, 2H), 7.62–7.90 (m, 7H), 4.64 (d,
1H), 4.47 (d, 1H), 3.65 (m, 2H), 3.07 (m, 1H), 2.86 (m, 2H), 1.26 (d, 6H).
56 δ (CD₃C(O)CD₃) 8.91 (m, 1H), 8.35 (m, 1H), 8.04–8.07 (m, 2H), 7.61–7.91 (m, 7H), 4.63 (d,
1H), 4.47 (d, 1H), 3.59 (m, 2H), 2.97 (m, 1H), 2.69 (m, 2H), 1.95 (m, 2H), 1.24 (d, 6H).
57 δ (CD₃C(O)CD₃) 8.92 (m, 1H), 8.41 (m, 1H), 8.04–8.08 (m, 2H), 7.62–7.90 (m, 7H), 4.64 (d,
1H), 4.48 (d, 1H), 3.64 (m, 2H), 2.90 (m, 2H), 1.36 (s, 9H).
58 δ 8.82 (d, 1H), 8.31 (d, 1H), 8.14 (s, 2H), 8.00 (s, 1H), 7.64 (m, 2H), 7.56 (d, 1H), 7.49 (d, 1H),
6.47 (br t, 1H), 4.37 (d, 1H), 3.95 (d, 1H), 3.75 (q, 2H), 2.81 (t, 2H), 2.16 (s, 3H).
59 δ 8.82 (d, 1H), 8.33 (d, 1H), 8.14 (s, 2H), 8.00 (s, 1H), 7.65 (m, 2H), 7.58 (d, 1H), 7.50 (d, 1H),
6.11 (br d, 1H), 4.53 (m, 1H), 4.37 (d, 1H), 3.94 (d, 1H), 2.79 (m, 2H), 2.21 (s, 3H), 1.41 (d, 3H).
60 δ 8.81 (d, 1H), 8.32 (d, 1H), 8.14 (s, 2H), 8.00 (s, 1H), 7.64 (m, 2H), 7.56 (d, 1H), 7.48 (d, 1H),
6.15 (br d, 1H), 4.52 (m, 1H), 4.37 (d, 1H), 3.94 (d, 1H), 2.79 (m, 2H), 2.21 (s, 3H), 1.40 (d, 3H).
61 δ (CD₃C(O)CD₃) 8.91 (m, 1H), 8.35 (m, 1H), 8.0–8.08 (m, 3H), 7.80–7.91 (m, 3H), 7.65–7.75
(m, 3H), 4.65 (d, 1H), 4.50 (d, 1H), 4.23 (t, 1H), 3.40 (m, 2H), 3.34 (m, 2H), 0.97 (s, 6H).
63 δ (CD₃C(O)CD₃) 8.92 (d, 1H), 8.50 (d, 1H), 8.08 (s, 1H), 8.03 (s, 1H), 7.95 (s, 1H), 7.88 (d, 1H),
7.85 (br t, 1H), 7.75 (d, 1H), 7.67 (m, 2H), 7.15 (br s, 1H), 4.67 (d, 1H), 4.57 (d, 1H), 4.09 (d,
2H), 4.05 (m, 1H), 1.15 (d, 6H).
64 δ (CD₃C(O)CD₃) 8.91 (m, 1H), 8.38 (m, 1H), 8.04–8.08 (m, 2H), 7.62–7.90 (m, 7H), 4.64 (d,
1H), 4.48 (d, 1H), 4.04 (m, 1H), 3.76 (m, 1H), 3.62 (m, 1H), 3.42 (m, 1H), 1.60 (m, 1H), 1.51 (m,
1H), 1.01 (t, 3H).
65 δ 8.80 (d, 1H), 8.29 (d, 1H), 7.87 (s, 1H), 7.82 (s, 1H), 7.72 (s, 1H), 7.62 (m, 2H), 7.53 (d, 1H),
7.45 (d, 1H), 6.51 (br t, 1H), 4.30 (d, 1H), 3.91 (d, 1H), 3.74 (q, 2H), 2.80 (t, 2H), 2.16 (s, 3H).
66 δ 8.80 (d, 1H), 8.29 (d, 1H), 7.87 (s, 1H), 7.81 (s, 1H), 7.72 (s, 1H), 7.55–7.66 (m, 3H), 7.45 (d,
1H), 6.98 (br t, 1H), 4.29 (d, 1H), 4.04 (m, 2H), 3.91 (d, 1H), 3.41 (dd, 2H), 3.01 (s, 3H).
67 δ 8.70 (m, 1H), 8.12–8.19 (m, 3H), 8.01 (s, 1H), 7.23–7.57 (m, 4H), 6.87 (br m, 1H), 4.27 (d, 1H),
4.05 (m, 1H), 3.88 (d, 1H), 3.67 (m, 1H), 3.5 (br m, 1H), 3.32 (m, 1H), 1.25 (d, 3H).

- 68 δ 8.62 (m, 1H), 8.14 (s, 2H), 8.05 (m, 1H), 8.02 (s, 1H), 7.09–7.49 (m, 4H), 6.85 (br m, 1H), 4.24 (d, 1H), 4.18 (br m, 1H), 3.86 (d, 1H), 3.67 (m, 1H), 3.42–3.62 (br m, 2H), 1.24 (d, 3H).
- 69 δ 8.84 (m, 1H), 8.32 (m, 1H), 8.14 (s, 2H), 8.00 (s, 1H), 7.50–7.70 (m, 4H), 6.47 (br m, 1H), 4.38 (d, 1H), 3.95 (d, 1H), 3.92 (m, 2H), 3.74 (m, 2H).
- 70 δ 8.78 (d, 1H), 8.24–8.12 (m, 1H), 8.18 (s, 1H), 7.82 (s, 1H), 7.66–7.30 (m, 9H), 4.29–4.18 (m, 3H), 3.95–3.84 (m, 3H).
- 71 δ 8.84–8.74 (m, 1H), 8.34–8.17 (m, 1H), 7.64–7.29 (m, 8H), 6.61 (s, 1H), 4.34–3.81 (m, 2H), 3.71 (q, 2H), 2.79 (t, 2H), 2.15 (s, 3H).
- 72 δ 8.80 (d, 1H), 8.30–8.17 (m, 1H), 7.67–7.49 (m, 7H), 7.44 (d, 1H), 7.32–7.19 (m, 2H), 4.35–4.15 (m, 3H), 4.01–3.82 (m, 3H).
- 79 δ 8.82 (m, 1H), 8.33 (m, 1H), 8.14 (s, 2H), 8.00 (s, 1H), 7.46–7.68 (m, 4H), 7.29 (br m, 1H), 4.36 (d, 1H), 4.05 (m, 2H), 3.94 (d, 1H), 3.21 (m, 1H), 2.93 (m, 1H), 2.65 (s, 3H).
- 82 δ 8.80 (m, 1H), 8.27 (m, 1H), 7.64–7.52 (m, 5H), 7.45–7.40 (m, 2H), 7.13 (m, 1H), 5.01 (m, 2H), 4.20 (m, 1H), 3.88 (m, 2H).
- 83 δ 8.83 (m, 1H), 8.26 (m, 1H), 8.14 (s, 2H), 8.00 (s, 1H), 7.43–7.66 (m, 4H), 7.04 (t, 1H), 6.34 (br d, 1H), 4.77 (m, 1H), 4.35 (d, 1H), 4.06 (m, 1H), 3.92 (d, 1H), 1.54 (d, 3H), 1.18 (d, 6H).
- 84 δ 8.82 (d, 1H), 8.24 (d, 1H), 8.14 (s, 2H), 8.00 (s, 1H), 7.40–7.65 (m, 4H), 7.09 (br t, 1H), 6.61 (br s, 1H), 4.82 (m, 1H), 4.34 (d, 1H), 3.92 (d, 1H), 3.25 (m, 2H), 1.55 (m, 5H), 0.92 (t, 3H).
- 92 δ 8.77 (m, 1H), 8.25 (m, 1H), 8.15 (s, 2H), 8.00 (s, 1H), 7.36–7.62 (m, 4H), 6.67 (br m, 1H), 4.34 (d, 1H), 3.93 (d, 1H), 3.68 (m, 2H), 2.81 (m, 2H), 2.58 (m, 2H), 1.29 (t, 3H).
- 93 δ 8.81 (m, 1H), 8.24 (m, 1H), 8.13 (s, 2H), 8.01 (s, 1H), 7.39–7.65 (m, 4H), 7.10 (m, 1H), 6.67 (m, 1H), 4.84 (m, 1H), 4.34 (d, 1H), 3.92 (d, 1H), 3.12 (m, 2H), 1.78 (m, 1H), 1.56 (d, 3H), 0.91 (d, 6H).
- 94 δ 8.80 (m, 1H), 8.19 (m, 1H), 8.13 (s, 2H), 8.01 (s, 1H), 7.30–7.65 (m, 5H), 6.95 (m, 1H), 4.90 (m, 1H), 4.33 (d, 1H), 3.91 (m, 3H), 1.57 (d, 3H).
- 95 δ 8.82 (d, 1H), 8.25 (d, 1H), 8.14 (s, 2H), 8.00 (s, 1H), 7.42–7.65 (m, 4H), 7.01 (br s, 1H), 6.51 (br s, 1H), 4.79 (m, 1H), 4.35 (d, 1H), 3.92 (d, 1H), 2.87 & 2.86 (s, 3H), 1.55 (d, 3H).
- 96 δ 8.82 (d, 1H), 8.26 (d, 1H), 8.14 (s, 2H), 8.00 (s, 1H), 7.43–7.66 (m, 4H), 7.00 (br s, 1H), 6.44 (br s, 1H), 4.78 (m, 1H), 4.36 (d, 1H), 3.93 (d, 1H), 3.33 (m, 2H), 1.55 (d, 3H), 1.17 (t, 3H).
- 97 δ 8.82 (d, 1H), 8.26 (d, 1H), 8.14 (s, 2H), 8.00 (s, 1H), 7.41–7.66 (m, 4H), 7.05 (br t, 1H), 6.61 (br t, 1H), 4.87 (m, 1H), 4.35 (m, 1H), 3.92 (d, 1H), 3.16 (m, 1H), 3.04 (m, 1H), 1.57 (d, 3H), 0.92 (s, 9H).
- 98 δ (CD₃C(O)CD₃) 8.89 (m, 1H), 8.40 (s, 2H), 8.29–8.36 (m, 2H), 8.26 (s, 1H), 7.80 (m, 1H), 7.58–7.67 (m, 3H), 4.72 (d, 1H), 4.62 (d, 1H), 3.85 (m, 2H), 3.13 (m, 1H), 2.91 (m, 1H), 2.81 (m, 1H), 2.67 (m, 1H), 1.21 (t, 3H).
- 99 δ (CD₃C(O)CD₃) 8.92 (m, 1H), 8.42 (m, 1H), 8.37 (s, 2H), 8.26 (s, 1H), 7.97 (br s, 1H), 7.88 (d, 1H), 7.75 (d, 1H), 7.63–7.73 (m, 2H), 4.74 (d, 1H), 4.64 (d, 1H), 3.96 (m, 2H), 3.49 (m, 2H), 3.19 (m, 2H), 1.36 (t, 3H).

- 106 δ 8.78 (m, 1H), 8.18 (m, 1H), 7.87 (s, 1H), 7.82 (s, 1H), 7.72 (s, 1H), 7.33–7.65 (m, 5H), 6.97 (m, 1H), 4.91 (m, 1H), 4.28 (d, 1H), 3.86–3.99 (m, 3H), 1.56 (d, 3H).
- 107 δ 8.82 (d, 1H), 8.27 (d, 1H), 7.87 (s, 1H), 7.82 (s, 1H), 7.72 (s, 1H), 7.45–7.65 (m, 4H), 6.96 (m, 1H), 6.24 (m, 1H), 4.75 (m, 1H), 4.30 (d, 1H), 4.10 (m, 1H), 3.91 (d, 1H), 1.54 (d, 3H), 1.20 (d, 6H).
- 108 δ 8.82 (d, 1H), 8.26 (d, 1H), 7.87 (s, 1H), 7.82 (s, 1H), 7.72 (s, 1H), 7.42–7.66 (m, 4H), 7.02 (br s, 1H), 6.52 (br s, 1H), 4.81 (m, 1H), 4.29 (d, 1H), 3.90 (d, 1H), 3.25 (m, 2H), 1.56 (m, 5H), 0.92 (t, 3H).
- 109 δ 8.83 (d, 1H), 8.27 (d, 1H), 7.87 (s, 1H), 7.81 (s, 1H), 7.72 (s, 1H), 7.45–7.67 (m, 4H), 6.88 (br s, 1H), 6.34 (br s, 1H), 4.78 (m, 1H), 4.30 (d, 1H), 3.91 (d, 1H), 2.89 & 2.87 (s, 3H), 1.55 (d, 3H).
- 110 δ 8.82 (d, 1H), 8.26 (d, 1H), 7.87 (s, 1H), 7.82 (s, 1H), 7.72 (s, 1H), 7.43–7.66 (m, 4H), 6.98 (br s, 1H), 6.44 (br s, 1H), 4.79 (m, 1H), 4.29 (d, 1H), 3.90 (d, 1H), 3.33 (m, 2H), 1.55 (d, 3H), 1.17 (t, 3H).
- 111 δ 8.82 (d, 1H), 8.24 (d, 1H), 7.87 (s, 1H), 7.81 (s, 1H), 7.72 (s, 1H), 7.41–7.65 (m, 4H), 7.08 (br t, 1H), 6.65 (br t, 1H), 4.84 (m, 1H), 4.29 (d, 1H), 3.89 (d, 1H), 3.12 (m, 2H), 1.55 (d, 3H), 0.91 (d, 6H).
- 112 δ 8.82 (m, 1H), 8.24 (m, 1H), 7.87 (s, 1H), 7.82 (s, 1H), 7.72 (s, 1H), 7.40–7.65 (m, 4H), 7.10 (br t, 1H), 6.68 (br t, 1H), 4.88 (m, 1H), 4.28 (d, 1H), 3.89 (d, 1H), 3.17 (dd, 1H), 3.03 (dd, 1H), 1.57 (d, 3H), 0.91 (s, 9H).
- 132 δ (CD₃C(O)CD₃) 8.90 (m, 1H), 8.41 (m, 1H), 7.62–7.93 (m, 8H), 4.65 (d, 1H), 4.52 (d, 1H), 3.69 (m, 2H), 2.81 (m, 2H), 2.17 (s, 3H).
- 133 δ (CD₃C(O)CD₃) 8.88 (m, 1H), 8.36 (m, 1H), 8.26 (s, 1H), 7.58–7.88 (m, 7H), 4.63 (d, 1H), 4.51 (d, 1H), 3.86 (m, 2H), 3.16 (m, 1H), 2.94 (m, 1H), 2.58 (s, 3H).
- 134 δ (CD₃C(O)CD₃) 8.91 (m, 1H), 8.42 (m, 1H), 7.63–8.0 (m, 8H), 4.66 (d, 1H), 4.53 (d, 1H), 3.98 (m, 2H), 3.52 (m, 2H), 3.08 (s, 3H).
- 135 δ (CD₃C(O)CD₃) 8.91 (m, 1H), 8.50 (m, 1H), 8.04 (br m, 1H), 7.64–8.0 (m, 8H), 4.67 (d, 1H), 4.54 (d, 1H), 4.25 (m, 2H), 4.02–4.11 (m, 2H).
- 136 δ 8.81 (d, 1H), 8.25 (d, 1H), 7.71–7.53 (m, 4H), 7.45 (d, 2H), 7.35 (s, 1H), 7.20–7.08 (m, 2H), 4.32–4.22 (m, 3H), 4.00–3.82 (m, 3H).
- 137 δ 8.78 (m, 1H), 8.20 (m, 1H), 7.77 (s, 1H), 7.32–7.65 (m, 7H), 6.94 (br m, 1H), 4.80 (m, 1H), 4.27 (d, 1H), 3.88 (d, 1H), 3.28 (m, 2H), 1.50 (t, 3H), 1.12 (m, 3H).
- 138 δ 8.76 (m, 1H), 8.18 (m, 1H), 7.72 (s, 1H), 7.31–7.64 (m, 7H), 7.04 (br m, 1H), 4.81 (m, 1H), 4.26 (d, 1H), 3.88 (d, 1H), 2.79 (m, 3H), 1.49 (m, 3H).
- 139 δ 8.75 (m, 1H), 8.13 (m, 1H), 7.71 (s, 1H), 7.30–7.64 (m, 7H), 7.11 (br m, 1H), 4.88 (m, 1H), 4.26 (d, 1H), 3.83–3.96 (m, 3H), 1.52 (d, 3H).
- 140 δ 8.79 (m, 1H), 8.18 (m, 1H), 8.02 (s, 1H), 7.87 (m, 2H), 7.36–7.64 (m, 5H), 7.02 (m, 1H), 4.90 (m, 1H), 4.27 (d, 1H), 3.85–3.98 (m, 3H), 1.54 (d, 3H).

141 δ 8.81 (d, 1H), 8.23 (d, 1H), 8.02 (s, 1H), 7.87 (s, 2H), 7.37–7.63 (m, 4H), 7.12 (br t, 1H), 6.69 (br s, 1H), 4.81 (m, 1H), 4.28 (d, 1H), 3.88 (d, 1H), 2.84 (s, 3H), 1.54 (d, 3H).
142 δ 8.78 (d, 1H), 8.19 (d, 1H), 8.02 (s, 1H), 7.87 (s, 2H), 7.32–7.62 (m, 5H), 6.96 (br s, 1H), 4.82 (m, 1H), 4.26 (d, 1H), 3.89 (d, 1H), 3.26 (m, 2H), 1.52 (d, 3H), 1.11 (t, 3H).
143 δ (CD₃C(O)CD₃) 8.90 (m, 1H), 8.47 (m, 1H), 8.23 (s, 1H), 8.08 (s, 2H), 7.59–7.84 (m, 4H), 7.42 (br m, 1H), 6.87 (br m, 1H), 4.65 (d, 1H), 4.55 (d, 1H), 4.12 (m, 2H), 2.75 (d, 3H).
144 δ (CD₃C(O)CD₃) 8.92 (m, 1H), 8.51 (m, 1H), 8.22 (s, 1H), 8.06–8.10 (m, 2H), 7.85–7.93 (m, 2H), 7.63–7.80 (m, 3H), 7.31 (br m, 1H), 4.68 (d, 1H), 4.57 (d, 1H), 4.11 (m, 2H), 3.29 (m, 2H), 1.12 (t, 3H).
145 δ (CD₃C(O)CD₃) 8.89 (m, 1H), 8.46 (m, 1H), 8.40 (s, 2H), 8.25 (s, 1H), 8.07 (m, 1H), 7.59–7.83 (m, 5H), 4.71 (d, 1H), 4.62 (d, 1H), 4.17 (m, 2H), 3.65 (m, 2H), 3.58 (m, 2H).
173 δ 8.77 (d, 1H), 8.27 (d, 1H), 7.56–7.63 (m, 4H), 7.51 (d, 1H), 7.46 (dd, 1H), 7.41 (d, 1H), 6.24 (d, 1H), 4.50 (m, 1H), 4.23 (d, 1H), 3.87 (d, 1H), 2.77 (m, 2H), 2.20 (s, 3H), 1.39 (d, 3H).
174 δ 8.82 (d, 1H), 8.26 (d, 1H), 7.56–7.68 (m, 5H), 7.46 (m, 2H), 7.04 (br s, 2H), 4.28 (d, 2H), 4.24 (d, 1H), 3.96 (m, 2H), 3.88 (d, 1H).
176 δ 8.82 (d, 1H), 8.35 (d, 1H), 7.62–7.69 (m, 2H), 7.60 (d, 1H), 7.56 (d, 2H), 7.51 (d, 1H), 7.46 (dd, 1H), 6.06 (d, 1H), 4.54 (m, 1H), 4.26 (d, 1H), 3.89 (d, 1H), 2.80 (m, 2H), 2.21 (s, 3H), 1.41 (d, 3H).
177 δ 8.81 (d, 1H), 8.24 (d, 1H), 7.54–7.67 (m, 5H), 7.46 (m, 2H), 7.19 (br t, 1H), 7.13 (br t, 1H), 4.28 (d, 2H), 4.24 (d, 1H), 3.95 (m, 2H), 3.88 (d, 1H).

a ¹H NMR data are in ppm downfield from tetramethylsilane. Couplings are designated by (s)-singlet, (d)-doublet, (t)-triplet, (q)-quartet, (dd)-doublet of doublets, (dt)-doublet of triplets, (br)-broad peaks, (m)-multiplet.

5

BIOLOGICAL EXAMPLES OF THE INVENTION TEST A

For evaluating control of diamondback moth (*Plutella xylostella*) the test unit consisted of a small open container with a 12–14-day-old radish plant inside. This was pre-infested with about 50 neonate larvae that were dispensed into the test unit via corncob grits using a
10 bazooka inoculator. The larvae moved onto the test plant after being dispensed into the test unit.

Test compounds were formulated using a solution containing 10% acetone, 90% water and 300 ppm X-77™ Spreader Lo-Foam Formula non-ionic surfactant containing alkylarylpolyoxyethylene, free fatty acids, glycols and isopropanol (Loveland Industries, Inc.
15 Greeley, Colorado, USA). The formulated compounds were applied in 1 mL of liquid through a SUJ2 atomizer nozzle with 1/8 JJ custom body (Spraying Systems Co. Wheaton, Illinois, USA) positioned 1.27 cm (0.5 inches) above the top of each test unit. All experimental compounds in these tests were sprayed at 50 ppm, and the test was replicated

three times. After spraying of the formulated test compound, each test unit was allowed to dry for 1 h and then a black, screened cap was placed on top. The test units were held for 6 days in a growth chamber at 25 °C and 70% relative humidity. Plant feeding damage was then visually assessed based on foliage consumed, and a pest mortality rating was also 5 counted and calculated for each test unit.

Of the compounds of Formula 1 tested the following provided very good to excellent levels of control efficacy (20% or less feeding damage or 80% or more mortality): 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 10 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143 and 144.

15 TEST B

For evaluating control of fall armyworm (*Spodoptera frugiperda*) the test unit consisted of a small open container with a 4–5-day-old corn (maize) plant inside. This was pre-infested (using a core sampler) with 10–15 1-day-old larvae on a piece of insect diet. Test compounds were formulated and sprayed at 50 ppm as described for Test A and 20 replicated three times. After spraying, the test units were maintained in a growth chamber and then the control efficacy was rated for each test unit as described for Test A.

Of the compounds of Formula 1 tested the following provided very good to excellent levels of control efficacy (20% or less feeding damage or 80% or more mortality): 1, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 33, 25 34, 35, 36, 37, 38, 39, 40, 41, 43, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 58, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143 and 144.

30 TEST C

For evaluating control of potato leafhopper (*Empoasca fabae*) through contact and/or systemic means, the test unit consisted of a small open container with a 5–6-day-old Soleil bean plant (primary leaves emerged) inside. White sand was added to the top of the soil, and one of the primary leaves was excised prior to application. Test compounds were formulated 35 and sprayed as described for Test A. All experimental compounds in these tests were sprayed at 250 or 50 ppm as noted, and the test was replicated three times. After spraying, the test units were allowed to dry for 1 h before they were post-infested with 5 potato leafhoppers (18- to 21-day-old adults). A black, screened cap was placed on the top of the cylinder. The test units were held for 6 days in a growth chamber at 19–21 °C and 50–70%

relative humidity. The control efficacy of each test compound was then visually assessed by insect mortality.

Of the compounds of Formula 1 tested at 250 ppm, the following provided very good to excellent levels of control efficacy (80% or more mortality): 3, 4, 5, 7, 8, 10, 12, 13, 14, 5 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 27, 29, 30, 33, 34, 35, 37, 38, 39, 40, 45, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 63, 65, 66, 67, 68, 71, 72, 79, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134 and 135.

10 Of the compounds of Formula 1 tested at 50 ppm, the following provided very good to excellent levels of control efficacy (80% or more mortality): 3, 4, 5, 7, 8, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 26, 27, 29, 30, 33, 34, 35, 37, 38, 39, 40, 45, 47, 48, 49, 50, 51, 52, 53, 54, 55, 57, 58, 59, 60, 62, 63, 65, 66, 71, 72, 79, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 15 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 125, 126, 127, 128, 129, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143 and 144.

TEST D

For evaluating control of corn planthopper (*Peregrinus maidis*) through contact and/or systemic means, the test unit consisted of a small open container with a 3–4-day-old maize plant (spike) inside. White sand was added to the top of the soil prior to application. Test compounds were formulated and sprayed at 250 ppm and replicated three times as described for Test A. After spraying, the test units were allowed to dry for 1 h before they were post-infested with 10–20 corn planthoppers (18- to 20-day-old nymphs) by sprinkling them onto the sand with a salt shaker. A black, screened cap was placed on the top of the cylinder. 25 The test units were held for 6 days in a growth chamber at 19–21 °C and 50–70% relative humidity. Each test unit was then visually assessed for insect mortality.

Of the compounds tested, the following resulted in at least 80% mortality: 4, 16, 21, 33, 50, 63, 65, 67, 68, 88, 95, 96, 100, 105, 106, 107, 108, 109, 110, 119, 125, 126, 129, 132, 137, 138, 139, 140, 141 and 142.

30

TEST E

For evaluating control of the western flower thrips (*Frankliniella occidentalis*) through contact and/or systemic means, the test unit consisted of a small open container with a 5–7-day-old Soleil Bean plant inside. Test compounds were formulated and sprayed as described for Test A. All experimental compounds in these tests were sprayed at 250 or 50 ppm as noted, and the test was replicated three times. After spraying, the test units were allowed to dry for 1 h, 22–27 adult thrips were added to each unit and then a black, screened cap was placed on top. The test units were held for 6 days at 25 °C and 45–55% relative humidity. A mortality rating was assessed along with a plant damage rating for each test unit.

Of the compounds of Formula 1 tested at 250 ppm, the following provided very good to excellent levels of control efficacy (20% or less feeding damage or 80% or more mortality): 1, 3, 4, 5, 6, 7, 8, 11, 12, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 47, 48, 49, 50, 51, 52, 53, 54, 58, 59, 5, 60, 62, 63, 65, 66, 67, 73, 77, 79, 80, 83, 84, 85, 86, 87, 88, 92, 94, 95, 96, 106, 107, 108, 109, 110, 111, 112, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134 and 135.

Of the compounds of Formula 1 tested at 50 ppm, the following provided very good to excellent levels of control efficacy (20% or less feeding damage or 80% or more mortality):

10 1, 3, 4, 5, 6, 7, 8, 11, 12, 15, 16, 17, 18, 19, 20, 21, 22, 23, 26, 27, 28, 29, 30, 31, 32, 33, 34, 37, 38, 39, 40, 41, 42, 44, 47, 49, 50, 51, 52, 53, 54, 58, 59, 60, 62, 63, 65, 66, 67, 79, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 117, 118, 119, 120, 122, 123, 125, 126, 127, 128, 129, 130, 132, 133, 134, 136, 137, 138, 139, 140, 141, 142, 143 and 144.

15 TEST F

For evaluating control of green peach aphid (*Myzus persicae*) through contact and/or systemic means, the test unit consisted of a small open container with a 12–15-day-old radish plant inside. This was pre-infested by placing on a leaf of the test plant 30–40 aphids on a piece of leaf excised from a culture plant (cut-leaf method). The larvae moved onto the 20 test plant as the leaf piece desiccated. After pre-infestation, the soil of the test unit was covered with a layer of sand.

Test compounds were formulated and sprayed as described for Test A. All experimental compounds in these tests were sprayed at 250 ppm, and the test was replicated three times. After spraying of the formulated test compound, each test unit was allowed to 25 dry for 1 h and then a black, screened cap was placed on top. The test units were held for 6 days in a growth chamber at 19–21 °C and 50–70% relative humidity. Each test unit was then visually assessed for insect mortality.

Of the compounds tested, the following resulted in at least 80% mortality: 1, 4, 5, 6, 7, 8, 10, 12, 15, 16, 19, 21, 22, 23, 27, 30, 33, 34, 35, 37, 38, 40, 47, 50, 52, 53, 54, 58, 60, 62, 30 63, 65, 66, 67, 68, 79, 83, 86, 88, 89, 91, 92, 94, 95, 96, 98, 100, 101, 102, 104, 105, 106, 107, 108, 109, 110, 111, 113, 114, 116, 117, 118, 119, 122, 125, 126, 127, 128, 129, 130, 132, 133, 135, 136, 137, 138, 139, 140, 141, 142, 143 and 144.

TEST G

For evaluating control of cotton melon aphid (*Aphis gossypii*) through contact and/or systemic means, the test unit consisted of a small open container with a 6–7-day-old cotton plant inside. This was pre-infested with 30–40 insects on a piece of leaf according to the cut-leaf method described for Test F, and the soil of the test unit was covered with a layer of sand.

Test compounds were formulated and sprayed at 250 ppm and the test was replicated three times. After spraying, the test units were maintained in a growth chamber and then visually rated assessed for insect mortality

Of the compounds tested, the following resulted in at least 80% mortality: 1, 8, 10, 19, 5 21, 23, 30, 33, 34, 38, 40, 47, 50, 52, 53, 55, 58, 60, 63, 65, 67, 68, 69, 79, 84, 88, 95, 96, 100, 101, 106, 107, 108, 109, 110, 117, 119, 125, 126, 132, 133, 135, 137, 138, 139, 141, 142, 143 and 144.

TEST H

For evaluating control of silverleaf whitefly (*Bemisia tabaci*), the test unit consisted of 10 a 14–21-day-old cotton plant grown in Redi-earth® media (Scotts Co.) with at least two true leaves infested with 2nd and 3rd instar nymphs on the underside of the leaves.

Test compounds were formulated in no more than 2 mL of acetone and then diluted with water to 25–30 mL. The formulated compounds were applied using a flat fan air-assisted nozzle (Spraying Systems 122440) at 10 psi (69 kPa). Plants were sprayed to run-off on a turntable sprayer (patent publication EP-110617-A1). All experimental compounds 15 in this screen were sprayed at 250 ppm and replicated three times. After spraying of the test compound, the test units were held for 6 days in a growth chamber at 50–60% relative humidity and 28 °C daytime and 24 °C nighttime temperature. Then the leaves were removed and then dead and live nymphs were counted to calculate percent mortality.

20 Of the compounds tested, the following resulted in at least 80% mortality: 1, 7, 8, 16, 33, 35, 40, 47, 52, 53, 62, 63, 65, 67, 68, 70, 84, 85, 86, 88, 89, 94, 95, 96, 100, 101, 106, 107, 108, 109, 110, 117, 119, 122, 125, 126, 127, 129, 135, 136, 137, 139, 140, 141 and 142.

TEST I

For evaluating control of the cat flea (*Ctenocephalides felis*), a CD-1® mouse (about 30 25 g, male, obtained from Charles River Laboratories, Wilmington, MA) was orally dosed with a test compound in an amount of 10 mg/kg solubilized in propylene glycol/glycerol formal (60:40). Two hours after oral administration of the test compound, approximately 8 to 16 adult fleas were applied to each mouse. The fleas were then evaluated for mortality 48 hours after flea application to the mouse.

30 Of the compounds tested, the following resulted in at least 50% mortality: 1, 4, 5, 7, 8, 10, 11, 12, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 27, 29, 30, 34, 35, 36, 37, 38, 39, 40, 41, 42, 44, 49, 50, 52, 53, 54, 58, 59, 60, 62, 63, 64, 65, 66, 67, 69, 70, 71, 72, 75, 79, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 94, 95, 96, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 110, 111, 113, 114, 115, 116, 117, 118, 125, 126, 127, 128, 129, 132, 133, 135, 136, 137, 35 138, 139, 140, 141, 142, 165, 168, 170, 172, 173, 174 and 177.

TEST J

For evaluating control of the cat flea (*Ctenocephalides felis*), a CD-1® mouse (about 30 g, male, obtained from Charles River Laboratories, Wilmington, MA) was orally dosed with a test compound in an amount of 10 mg/kg solubilized in propylene glycol/glycerol formal

(60:40). Twenty-four hours after oral administration of the test compound, approximately 8 to 16 adult fleas were applied to each mouse. The fleas were then evaluated for mortality 48 hours after flea application to the mouse.

Of the compounds tested, the following resulted in at least 50% mortality: 1, 4, 5, 11, 5 12, 15, 16, 17, 18, 19, 20, 21, 23, 27, 29, 30, 34, 35, 37, 40, 49, 50, 52, 53, 54, 58, 60, 62, 63, 65, 66, 68, 70, 79, 83, 84, 85, 86, 87, 88, 89, 91, 92, 95, 96, 98, 99, 100, 101, 102, 104, 105, 106, 107, 108, 110, 111, 112, 113, 114, 116, 125, 126, 127, 128, 132, 133, 135, 136, 137, 138, 140, 141, 142, 173, 174 and 177

TEST K

10 For evaluating control of the cat flea (*Ctenocephalides felis*), a CD-1® mouse (about 30 g, male, obtained from Charles River Laboratories, Wilmington, MA) was subcutaneously dosed with a test compound in an amount of 10 mg/kg solubilized in propylene glycol/glycerol formal (60:40). Two hours after administration of the test compound, approximately 8 to 16 adult fleas were applied to each mouse. The fleas were then evaluated 15 for mortality 48 hours after flea application to the mouse.

Of the compounds tested, the following resulted in at least 50% mortality: 1, 4 and 11.

TEST L

20 For evaluating control of the cat flea (*Ctenocephalides felis*), a test compound was solubilized in acetone/water (75:25) to a final test concentration of 500 ppm. Then 20 µL of the 500 ppm solution was applied to filter paper in the bottom of a tube. The tube was allowed to dry for 3 h, after which time approximately 10 adult fleas were added to the tube and the tube was capped. The fleas were evaluated for mortality 48 hours later.

Of the compounds tested, the following resulted in at least 50% mortality: 1, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 28, 34, 35, 37, 40, 52, 58, 62 and 66.

TEST M

25 For evaluating control of the relapsing fever tick (*Ornithodoros turicata*), a test compound was solubilized in propylene glycol/glycerol formal (60:40) and then diluted in bovine blood to a final test concentration of 30 ppm. The treated blood was placed in a tube, and the top of the tube was covered with a membrane. Approximately 5 *Ornithodoros turicata* nymphs were placed on the membrane and allowed to feed on the treated blood until 30 fully engorged. The ticks were then evaluated for mortality 48 hours later.

Of the compounds tested, the following resulted in at least 50% mortality: 1, 5, 15, 16 and 20.

TEST N

35 For evaluating control of the cat flea (*Ctenocephalides felis*), a six-month-old or older beagle was infested with 100 adult fleas. One day later, the beagle was orally dosed with a test compound in an amount of 2.5 mg/kg solubilized in propylene glycol/glycerol formal (60:40). The dog was infested again with 100 adult fleas 6, 13, 20 and 27 days after the oral administration of the test compound. The dog was combed one day after the oral

administration of the test compound, and again one day after each of the subsequent infestations (i.e. 7, 14, 21 and 28 days after oral administration of the test compound) to remove the fleas. The collected fleas were counted and evaluated for mortality.

Of the compounds tested, the following resulted in at least 90% mortality through 29
5 days: 1, 37, 40, 49, 52, 58, 62, 66 and 94.

TEST O

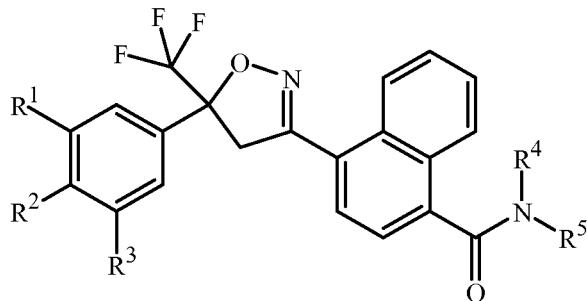
For evaluating control of the American dog tick (*Dermacentor variabilis*), a six-month-old or older beagle was orally dosed with a test compound in an amount of 2.5 mg/kg solubilized in propylene glycol/glycerol formal (60:40). The dog was then infested with 50
10 adult American dog ticks 2, 9, 16, 23 and 30 days after the oral administration of the test compound. The dog was combed 2 days after each infestation (i.e. 4, 11, 18, 25 and 32 days after oral administration of the test compound) to remove the ticks. The collected ticks were counted and evaluated for mortality.

Of the compounds tested, the following resulted in at least 90% mortality through 32
15 days: 1, 37 and 62.

CLAIMS

What is claimed is:

1. A compound of Formula 1,



1

wherein

R¹ is halogen, C₁–C₂ haloalkyl or C₁–C₂ haloalkoxy;

R² is H, halogen or cyano;

R³ is H, halogen or CF₃;

10 R⁴ is H, C₂–C₇ alkylcarbonyl or C₂–C₇ alkoxy carbonyl; and

R⁵ is C₁–C₆ alkyl or C₁–C₆ haloalkyl, each substituted with one substituent

independently selected from hydroxy, C₁–C₆ alkoxy, C₁–C₆ alkylthio, C₁–C₆ alkylsulfinyl, C₁–C₆ alkylsulfonyl, C₂–C₇ alkylaminocarbonyl, C₃–C₉ dialkylaminocarbonyl, C₂–C₇ haloalkylaminocarbonyl and C₃–C₉

15 halodialkylaminocarbonyl;

provided that when R¹ and R³ are Cl, and R² and R⁴ are H, then R⁵ is other than CH₂C(O)NHCH₂CF₃, CH₂CH₂OH or CH₂CH₂OCH₃.

2. A compound of Claim 1 wherein

R⁴ is H; and

20 R⁵ is C₁–C₆ alkyl substituted with one substituent independently selected from C₁–C₆ alkylthio, C₁–C₆ alkylsulfinyl, C₁–C₆ alkylsulfonyl, C₂–C₇ alkylaminocarbonyl and C₂–C₇ haloalkylaminocarbonyl.

3. A compound of Claim 2 wherein

R¹ is Cl, Br or CF₃;

25 R² is H; and

R³ is H, F, Cl, Br or CF₃.

4. A compound of Claim 3 wherein
R¹ is CF₃.
5. A compound of Claim 4 wherein
R³ is Cl, Br or CF₃.
- 5 6. A compound of Claim 5 wherein
R⁵ is C₁–C₆ alkyl substituted with one C₂–C₇ alkylaminocarbonyl or C₃–C₇ haloalkylaminocarbonyl.
7. A compound of Claim 1 that is selected from the group consisting of

4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-(methylsulfonyl)ethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-(methylsulfonyl)ethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-(methylsulfonyl)ethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-(methylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-(ethylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-(methylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-(ethylamino)-2-oxoethyl]-1-naphthalenecarboxamide,

4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(methylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(ethylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[1-methyl-2-(methylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(ethylamino)-1-methyl-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[1-methyl-2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-chloro-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[1-methyl-2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[1-methyl-2-(methylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[2-(ethylamino)-1-methyl-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-[1-methyl-2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide,

2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3-bromo-5-(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[1-methyl-2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[1-methyl-2-(methylamino)-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-(ethylamino)-1-methyl-2-oxoethyl]-1-naphthalenecarboxamide,
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[1-methyl-2-[(1-methylethyl)amino]-2-oxoethyl]-1-naphthalenecarboxamide, and
4-[5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[1-methyl-2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide.

8. A composition for controlling an invertebrate pest comprising a compound of Claim 1 and at least one additional component selected from the group consisting of surfactants, solid diluents and liquid diluents, said composition optionally further comprising at least one additional biologically active compound or agent.

5 9. The composition of Claim 8 wherein the at least one additional biologically active compound or agent is selected from the group consisting of abamectin, acephate, acequinocyl, acetamiprid, acrinathrin, amidoflumet, amitraz, avermectin, azadirachtin, azinphos-methyl, bifenthrin, bifenazate, bistrifluron, borate, 3-bromo-1-(3-chloro-2-pyridinyl)-N-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide, buprofezin, cadusafos, carbaryl, carbofuran, cartap, carzol, chlorantraniliprole, chlорfenapyr, chlorfluazuron, chlorpyrifos, chlorpyrifos-methyl, chromafenozide, clofentezin, clothianidin, cyflumetofen, cyfluthrin, beta-cyfluthrin, cyhalothrin, gamma-cyhalothrin, lambda-cyhalothrin, cypermethrin, alpha-cypermethrin, zeta-cypermethrin, cyromazine, deltamethrin, diafenthuron, diazinon, dieldrin, diflubenzuron, dimefluthrin, 10 dimehypo, dimethoate, dinotefuran, diofenolan, emamectin, endosulfan, esfenvalerate, ethiprole, etofenprox, etoxazole, fenbutatin oxide, fenothiocarb, fenoxy carb, fenpropathrin, fenvalerate, fipronil, flonicamid, flubendiamide, flucythrinate, flufennerim, flufenoxuron, fluvalinate, tau-fluvalinate, fonophos, formetanate, fosthiazate, halofenozide, hexaflumuron, hexythiazox, hydramethylnon, imidacloprid, indoxacarb, insecticidal soaps, isofenphos,

lufenuron, malathion, metaflumizone, metaldehyde, methamidophos, methidathion, methiodicarb, methomyl, methoprene, methoxychlor, metofluthrin, monocrotophos, methoxyfenozide, nitenpyram, nithiazine, novaluron, noviflumuron, oxamyl, parathion, parathion-methyl, permethrin, phorate, phosalone, phosmet, phosphamidon, pirimicarb, 5 profenofos, profluthrin, propargite, protrifenbute, pymetrozine, pyrafluprole, pyrethrin, pyridaben, pyridalyl, pyrifluquinazon, pyriproxyfen, rotenone, ryanodine, spinetoram, spinosad, spirodiclofen, spiromesifen, spirotetramat, sulprofos, tebufenozide, tebufenpyrad, teflubenzuron, tefluthrin, terbufos, tetrachlorvinphos, tetramethrin, thiacloprid, thiamethoxam, thiodicarb, thiosultap-sodium, tolfenpyrad, tralomethrin, triazamate, 10 trichlorfon, triflumuron, *Bacillus thuringiensis* delta-endotoxins, entomopathogenic bacteria, entomopathogenic viruses and entomopathogenic fungi.

10. The composition of Claim 9 wherein the at least one additional biologically active compound or agent is selected from the group consisting of abamectin, acetamiprid, acrinathrin, amitraz, avermectin, azadirachtin, bifenthrin, 3-bromo-1-(3-chloro-2-pyridinyl)- 15 *N*-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide, buprofezin, cadusafos, carbaryl, cartap, chlorantraniliprole, chlорfenapyr, chlorpyrifos, clothianidin, cyfluthrin, beta-cyfluthrin, cyhalothrin, gamma-cyhalothrin, lambda-cyhalothrin, cypermethrin, alpha-cypermethrin, zeta-cypermethrin, cyromazine, deltamethrin, dieldrin, dinotefuran, diofenolan, emamectin, endosulfan, esfenvalerate, 20 ethiprole, etofenprox, etoxazole, fenothiocarb, fenoxy carb, fenvalerate, fipronil, flonicamid, flubendiamide, flufenoxuron, fluvalinate, formetanate, fosthiazate, hexaflumuron, hydramethylnon, imidacloprid, indoxacarb, lufenuron, metaflumizone, methiodicarb, methomyl, methoprene, methoxyfenozide, nitenpyram, nithiazine, novaluron, oxamyl, pymetrozine, pyrethrin, pyridaben, pyridalyl, pyriproxyfen, ryanodine, spinetoram, spinosad, 25 spirodiclofen, spiromesifen, spirotetramat, tebufenozide, tetramethrin, thiacloprid, thiamethoxam, thiodicarb, thiosultap-sodium, tralomethrin, triazamate, triflumuron, *Bacillus thuringiensis* delta-endotoxins, all strains of *Bacillus thuringiensis* and all strains of *Nucleopolyhedrosis* viruses.

11. A composition comprising a compound of Claim 1 and at least one veterinarianally acceptable carrier, said composition optionally further comprising at least one additional parasitically active compound.

12. The composition of Claim 11 wherein the at least one additional parasitically active compound is an anthelmintic.

13. The composition of Claim 11 wherein the at least one additional parasitically active compound is selected from the group consisting of abamectin, doramectin, emamectin, eprinomectin, ivermectin, selamectin, milbemycin, moxidectin and pyrantel.
14. The composition of Claim 11 in a form for oral administration.
- 5 15. The composition of Claim 11 in a form for topical administration.
16. The composition of Claim 11 in a form for parenteral administration.
17. A method for controlling an invertebrate pest comprising contacting the invertebrate pest or its environment with a biologically effective amount of a compound of Claim 1.
- 10 18. A method for protecting an animal from an invertebrate parasitic pest comprising administering to the animal a parasitically effective amount of a compound of Formula 1,
- The chemical structure of Compound 1 is shown. It features a naphthalene ring substituted at position 1 with a carboxamide group ($\text{C}(=\text{O})\text{NR}^4\text{R}^5$). At position 2, there is a methylene group bearing a trifluoroethylamino group ($\text{CF}_3\text{CH}_2\text{NH}_2$). The structure continues with a 4,5-dihydroisoxazole ring fused to the naphthalene ring at positions 1 and 5. This is further substituted with a trifluoromethyl group (CF_3) and a chlorine atom. The isoxazole ring is also substituted with a methylene group that connects to a phenyl ring. The phenyl ring is substituted with a chlorine atom (Cl), a bromine atom (Br), or a trifluoromethyl group (CF_3).
- 1
- wherein
- 15 R^1 is halogen, $\text{C}_1\text{--}\text{C}_2$ haloalkyl or $\text{C}_1\text{--}\text{C}_2$ haloalkoxy;
- R^2 is H, halogen or cyano;
- R^3 is H, halogen or CF_3 ;
- R^4 is H, $\text{C}_2\text{--}\text{C}_7$ alkylcarbonyl or $\text{C}_2\text{--}\text{C}_7$ alkoxy carbonyl; and
- 20 R^5 is $\text{C}_1\text{--}\text{C}_6$ alkyl or $\text{C}_1\text{--}\text{C}_6$ haloalkyl, each substituted with one substituent independently selected from hydroxy, $\text{C}_1\text{--}\text{C}_6$ alkoxy, $\text{C}_1\text{--}\text{C}_6$ alkylthio, $\text{C}_1\text{--}\text{C}_6$ alkylsulfinyl, $\text{C}_1\text{--}\text{C}_6$ alkylsulfonyl, $\text{C}_2\text{--}\text{C}_7$ alkylaminocarbonyl, $\text{C}_3\text{--}\text{C}_9$ dialkylaminocarbonyl, $\text{C}_2\text{--}\text{C}_7$ haloalkylaminocarbonyl and $\text{C}_3\text{--}\text{C}_9$ halodialkylaminocarbonyl;
- provided that when the animal is a mouse, the invertebrate parasitic pest is a flea, and the parasitically effective amount of the compound of Formula 1 is administered orally, then the compound of Formula 1 is other than 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-1-naphthalenecarboxamide.

19. The method of Claim 18 wherein the parasitically effective amount of a compound of Formula 1 is administered orally.

20. The method of Claim 18 wherein the parasitically effective amount of a compound of Formula 1 is administered parenterally.

5 21. The method of Claim 20 wherein the parasitically effective amount of a compound of Formula 1 is administered by injection.

22. The method of Claim 18 wherein the parasitically effective amount of a compound of Formula 1 is administered topically.

10 23. The method of Claim 18 wherein the animal to be protected is a mammal, avian or fish.

24. The method of Claim 23 wherein the animal to be protected is livestock.

25. The method of Claim 23 wherein the animal to be protected is a canine.

26. The method of Claim 23 wherein the animal to be protected is a feline.

15 27. The method of Claim 18 wherein the invertebrate parasitic pest is an ectoparasite.

28. The method of Claim 18 wherein the invertebrate parasitic pest is an arthropod.

29. The method of Claim 18 wherein the invertebrate parasitic pest is a fly, mosquito, mite, tick, louse, flea, maggot, bed bug or kissing bug.

20 30. The method of Claim 29 wherein the animal is a cat or dog and the invertebrate parasitic pest is a flea, tick or mite.

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Veröffentlicht:

- mit internationalem Recherchenbericht
- vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

WO 2004/098290 A1

(54) Title: AGENTS FOR CONTROLLING PARASITES ON ANIMALS

(54) Bezeichnung: MITTEL ZUM BEKÄMPFEN VON PARASITEN AN TIERN

(57) Abstract: The invention relates to novel, skin-compatible, dermally administerable liquid formulations containing a pyrethrin or pyrethroid, MGK 264 in a ratio of at least 1: 20, and an additional insecticide preferably selected from the group of neonicotinoids for controlling parasitic arthropods on animals.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft neue, hautverträgliche, dermal applizierbare flüssige Formulierungen enthaltend ein Pyrethrin oder Pyrethroid, MGK 264 im Verhältnis von mindestens 1:20 sowie ein weiteres Insektizid bevorzugt aus der Gruppe der Neonicotinoide zur Bekämpfung von parasitierenden Arthropoden an Tieren.

Mittel zum Bekämpfen von Parasiten an Tieren

Die Erfindung betrifft neue Mittel zur Bekämpfung von Parasiten an Tieren, enthaltend ein Pyrethrin oder Pyrethroid sowie MGK 264; die Mittel enthalten gegebenenfalls einen weiteren insektiziden und/oder acariziden Wirkstoff.

- 5 Zur Anwendung zum Teil schwer wasserlöslicher Wirkstoffe in Form von dermal applizierbaren Flüssigformulierungen ist es notwendig, homogene Lösungen oder Emulsionen auf Basis von organischen Lösungsmitteln und insektiziden Wirkstoffen herzustellen. Dazu werden die Wirkstoffe zumeist in organischen Lösungsmitteln wie Isopropanol, 2-Butoxy-ethylacetat, Ethylen-glykoldiacetat gelöst und gegebenenfalls mit weiteren Zusatzstoffen vermischt. Die Herstellung
10 solcher Formulierungen ist in US 4 874 753, EP-A 137 627 und GB 2 135 886 beschrieben. Die Nachteile der besagten Systeme liegen z.B. bei Verwendung von Wirkstoffen aus der Klasse der Pyrethrine sowie Pyrethroide, insbesondere α -Cyanopyrethroide darin, dass sie zu schweren Haut-irritationen führen und ferner eine geringe Langzeitwirkung aufweisen. Es ist wünschenswert, diese Formulierungen durch solche zu ersetzen, die hautverträglich sowie toxikologisch unbedenklich sind und sich durch eine Langzeitwirkung von mehreren Wochen auszeichnen.
15

Um den besagten Nachteil beispielsweise der bekannten Pyrethroide und Pyrethrine zu beheben, wird in AU-627 847 und EP-A 413 610 vorgeschlagen, diese Wirkstoffe in hochsiedenden Lösungsmitteln wie Monopropylenglykol zu lösen, die zusätzlich noch natürliche, hautverträgliche Öle wie Pinienöl, Sonnenblumenöl oder Sojaöl enthalten. Der WO 91/13545 kann entnommen
20 werden, dass gut wirksame, hautverträgliche Flüssigformulierungen hergestellt werden können, indem man die besagten Wirkstoffe in Mengen von >50% in aliphatischen Lösungsmitteln wie 2-(2-Butoxyethoxy)ethanol oder 2-(2-Methoxy-ethoxy)ethanol löst. Der Nachteil dieser Formulierungen liegt darin, dass sie den Einsatz größerer Wirkstoff-Mengen benötigen und zudem bei sensiblen Tierrassen zu Hautirritationen führen. Um durch Einsatz geringer Wirkstoffmengen
25 eine akzeptable biologische Wirkung zu erreichen, wird in der Patentschrift US 5 466 458 die Verwendung von Emulsionen auf Basis der besagten Wirkstoffe mit den langkettigen, aliphatischen Aminen oder Alkoholen wie Hexadecan-1-ol, 1-Octadecylamine vorgeschlagen. Die Verwendung der langkettigen Amine hat den Nachteil, dass sie die besagten Wirkstoffe im Laufe der Zeit abbauen. Die Formulierungen auf Basis langkettiger Alkohole weisen in den meisten Fällen keine
30 ausreichende Langzeitwirkung auf.

Ferner wird in der WO 01/35739 vorgeschlagen, die bezüglich Hautirritation kritischen Pyrethroide, insbesondere α -Cyanopyrethroide, mit Polysiloxanen, die zusätzlich quarternäre Ammoniumgruppen enthalten, zu kombinieren. Diese elegante Zubereitungsform hat jedoch den

Nachteil, dass sie den Einsatz größerer Pyrethroid-Mengen erfordert. Diese Tatsache kann in vielen Fällen zur Zieltier- oder Umwelt-Unverträglichkeit führen.

Der Literatur kann entnommen werden, dass man synthetische oder natürliche Pyrethroide mit organischen Synergisten wie Piperonylbutoxid (PBO), (2-(2-Ethylhexyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindol-1,3(2H)-dion (MGK 264), S,S,S-Tributylphosphorotriothioat (DEF) oder Synepirin kombinieren kann [s. beispielsweise JOURNAL OF ECONOMIC ENTOMOLOGY, (1994 Aug) 87 (4) 879-84, 1994; JOURNAL OF ECONOMIC ENTOMOLOGY, (1987 Aug) 80 (4) 728-32 oder India Chemosphere, (Nov., 1997) Vol. 35, No. 10, pp. 2365-2374. ISSN: 0045-6535, Japanese Journal of Sanitary Zoology, (1995) Vol. 46, No. 1, pp. 25-30. ISSN: 0424-7086. 5 1995 sowie J ECON ENTOMOL, (1987) 80 (6), 1117-1121. CODEN: JEENAI. ISSN: 0022-0493. 10 1987)]. Ferner kann der o.a. Literatur entnommen werden, dass die Wirksamkeit der Pyrethroid-haltigen Zubereitungen gegen adulte Flöhe verbessert werden kann, wenn man Pyrethroide mit den besagten Synergisten in Mengen 1:5 bis zu max. 1:20 kombiniert. Der Literatur [siehe beispielsweise DEP. ENTOMOL., UNIV. GEORGIA, COASTAL PLAIN EXP. STN., TIFTON, GA. 15 31793 oder India Chemosphere, (1998) 36/15 (3055-3060) 1998] kann entnommen werden, dass eine maximale Wirksamkeitserhöhung bei einem Mengenverhältnis Wirkstoff zu Synergist von 1:5 erreicht wird (z.B. bei Permethrin/MGK-264 oder Fenvalerate/PBO).

Es ist weiterhin bekannt, dass Shampoos enthaltend Dipropylpyridin-2,5-dicarboxylat, MGK 264, 20 Piperonylbutoxid, und Pyrethrine zur Bekämpfung von Flöhen bei Kleintieren verwendet werden können [siehe beispielsweise Wang I.-H.; Moorman R.; Burleson J.I.-H. Wang, Journal of Liquid Chromatography and Related Technologies, (1996) 19/20 (3293-3304)].

Des weiteren ist bekannt, dass Carbamate wie Propoxur in Kombination mit PPO und MGK 264 in Mengenverhältnissen 1,00 : 0,04: 0,1 sich zur Umgebungsbehandlung eignen (s. beispielsweise Firmenprospekt der Fa. Sano Bruns Enterprises Ltd. Israel, 1990 AO1N-047/44).
25 In 1999 US 0 124 306 werden Kombinationen mit Imidacloprid und/oder Fipronil und/oder Pyrethroiden zur Schädlingsbekämpfung im Agrobereich, beschrieben. Ferner werden in EP-A-981 956 (US-6 080 796) Schäume auf Basis der o.a. Wirkstoffe sowie in der Patentanmeldung EP-A-981 955 (US-6 033 731) Polymerlegierungen, welche aus Suspensionen oder Emulsionen der Wirkstoffe Imidacloprid und Permethrin hergestellt werden, zur Parasitenbekämpfung beschrieben.

Alle genannten Zubereitungsformen haben den Nachteil, dass sie, bei einer akzeptablen Applikationsform, zur Bekämpfung von Ektoparasiten wie Flöhen, Zecken und Mücken für eine Dauer von mindestens drei, vorzugsweise jedoch von vier Wochen nicht geeignet sind und zudem den Einsatz von größeren Wirkstoff-Mengen erfordern.
30

Der vorliegenden Erfindung liegt die Aufgabe zur Grunde, Mittel enthaltend Pyrethroide oder Pyrethrine bereitzustellen, die sich zur Bekämpfung von Parasiten, vorzugsweise Ektoparasiten, an Tieren eignen. Solche Zubereitungen sollten sich durch hohe parasitizide Wirksamkeit und gute Verträglichkeit beim behandelten Tier auszeichnen. Darüberhinaus sind auch gute Anwender- und
5 Umweltverträglichkeit von Bedeutung. Es sollten sich flüssige Zubereitungen realisieren lassen, welche die elegante Spot on Applikation ermöglichen.

Überraschenderweise wird diese Aufgabe dadurch gelöst, dass man Pyrethroide und/oder Pyrethrine insbesondere α -Cyanopyrethroide, in Kombination mit dem Synergisten MGK 264 entgegen der bisher bekannten Lehre in Mengen von mindestens 1:20 einsetzt.

10 Bei den erfindungsgemäßen Mengenverhältnissen von mindestens 1:20 erreicht man erstaunlicherweise eine wesentlich verbesserte Zieltier- und Anwender-Verträglichkeit und einen enormen wirkungssteigernden, synergistischen Effekt.

Die Erfindung betrifft daher Mittel, enthaltend

- 15 a) mindestens einen Wirkstoff der Verbindungsklasse der Pyrethroide und/oder der Verbindungsklasse der Pyrethrine,
b) MGK 264

in einem Gewichtsverhältnis der Komponenten a : b von mindestens 1:20

sowie

- 20 c) gegebenenfalls weitere Wirkstoffe und
d) gegebenenfalls weitere Hilfs- und Trägerstoffe.

Die Pyrethrine werden in der Regel in Kombination mit einem Pyrethroid eingesetzt.

Die erfindungsgemäßen Mittel sind vorzugsweise fluid oder flüssig und eignen sich insbesondere hervorragend zur Herstellung von Spot-on- und Pour-on-Formulierungen für den Einsatz bei der Parasitenbekämpfung am Tier.

25 Als geeignete Wirkstoffe (Komponente a) hervorgehoben seien die Pyrethrine sowie die Pyrethroide wie zum Beispiel: Fenvalerate [α -(p-Cl-phenyl)-isovaleriansäure- α -cyano-3-phenoxybenzylester], Flumethrin [3-[2-(4-Chlorphenyl)-2-chlorvinyl]-2,2-dimethyl-cyclo-propancarbon-säure-(α -cyano-4-fluor-3-phenoxy)-benzylester] und seine Enantiomere sowie Stereoisomere, Cyfluthrin [2,2-Dimethyl-3-(2,2-dichlorvinyl)-cyclopropancarbonsäure-(α -cyano-4-fluor-3-phen-

oxy)-benzylester], Permethrin [3-Phenoxybenzyl-cis,trans-3-(2,2-dichlorvinyl)-2,2-dimethylcyclopropancarboxylat], Cypermethrin [2,2-Dimethyl-3-(2,2-dichlorvinyl)-cyclopropancarbonsäure- α -cyano-3-phenoxy-benzylester], Deltamethrin [α -Cyano-3-phenoxybenzyl-cis,trans-3-(2,2-dibromvinyl)-2,2-dimethylcyclopropancarboxylat], Fluvalinate [2-Cyano-3-phenoxybenzyl-2-(2-chlor- α,α,α -trifluor-p-toluido)-3-methylbutyrat]. Bevorzugt eingesetzt werden Pyrethroide mit akarazider Wirkung. Besonders bevorzugt sind die α -Cyanopyrethroide, insbesondere die Ester der α -Cyano-3-phenylbenzylalkohole und der 4-Fluoro- α -cyano-3-phenoxybenzylalkohole. Von diesen insbesondere bevorzugt sind Flumethrin, Cyfluthrin und β -Cyfluthrin.

In den erfindungsgemäßen Mitteln liegen die Pyrethrine und/oder Pyrethroide üblicherweise in Mengen von 0,01-20 Gew.-%, bevorzugt 0,05-5,0 Gew.-%, besonders bevorzugt 0,075-0,75 Gew.-%, ganz besonders bevorzugt 0,10-0,50 Gew.-%, jeweils bezogen auf das Gewicht des fertigen Mittels vor. Im Falle von Sprayapplikationen sind die Konzentrationen üblicherweise geringer, und zwar liegen sie bevorzugt im Bereich 0,02 bis 0,1 Gew.-%, besonders bevorzugt 0,03 bis 0,1 Gew.-%, ganz besonders bevorzugt 0,03 bis 0,075 Gew.-%.

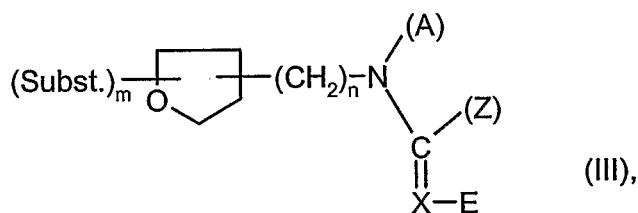
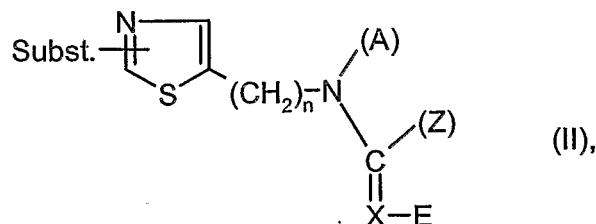
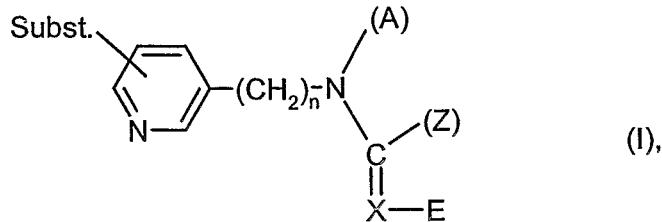
Das Gewichtsverhältnis der Menge an Pyrethrin und/oder Pyrethroid zur Menge an MGK 264 liegt bei mindestens 1:20 („mindestens“ bedeutet hier, dass der Anteil an MGK 264 im Verhältnis zu Pyrethrin/Pyrethroid auch höher sein kann), bevorzugt 1:30, besonders bevorzugt 1:40. Üblicherweise stellt man das Verhältnis nicht größer als 1:100, bevorzugt 1:80, besonders bevorzugt 1:60 ein.

Selbstverständlich können in den erfindungsgemäßen Mitteln weitere Wirkstoffe als Kombinationspartner eingesetzt werden.

Als Kombinationswirkstoffe seien bevorzugt genannt die im Bereich zur Bekämpfung von ekto-parasitierenden Arthropoden eingesetzten Insektizide wie Neonicotinoid-Insektizide, Spinosyne, N-Phenylpyrazole, Carbamate, Phosphor- und Phosphonsäureester, Wachstumshemmer sowie Mischungen dieser Wirkstoffe untereinander. Auch können weitere Synergisten zugesetzt werden. Als Synergisten im Sinne dieser Anmeldung werden Verbindungen verstanden, die selbst nicht die gewünschte Wirksamkeit aufweisen, als Mischpartner jedoch zu einer Steigerung der Wirksamkeit der aktiven Wirkstoffe führen.

Als Neonicotinoid-Insektizide seien genannt Verbindungen der Formeln (I), (II) und (III):

- 5 -



5

in welchen

n für 1 oder 2 steht,

m für 0, 1 oder 2 steht,

Subst. für einen der oben aufgeführten Substituenten, bevorzugt für Halogen, besonders
10 bevorzugt für Chlor, steht,

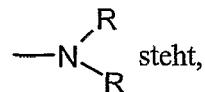
A für eine monofunktionelle Gruppe aus der Reihe Wasserstoff, Acyl, Alkyl, Aryl steht oder
für eine bifunktionelle Gruppe steht, die mit dem Rest Z verknüpft ist;

E für einen elektronenziehenden Rest steht;

X für die Reste -CH= oder =N- steht, wobei der Rest -CH= anstelle eines H-Atoms mit dem
15 Rest Z verknüpft sein kann;

Z für eine monofunktionelle Gruppe aus der Reihe Alkyl, -O-R, -S-R,

- 6 -



oder für eine bifunktionelle Gruppe steht, die mit dem Rest A oder dem Rest X verknüpft ist.

Bevorzugt sind Verbindungen der Formeln (I), (II) und (III), worin die Reste folgende Bedeutung
5 haben:

A steht besonders bevorzugt für Wasserstoff sowie für gegebenenfalls substituierte Reste aus der Reihe C₁-C₈-Acyl, C₁-C₁₀-Alkyl, C₆-C₁₀-Aryl. A steht ferner für eine bifunktionelle Gruppe. Genannt sei gegebenenfalls substituiertes Alkylen mit 1-4, insbesondere 1-2 C-Atomen, wobei als Substituenten die weiter oben aufgezählten Substituenten genannt seien und wobei die Alkylengruppen durch 1 oder 2 gleiche oder verschiedenen Heteroatome aus der Reihe N, O, S unterbrochen sein können.
10

A und Z können gemeinsam mit den Atomen, an welche sie gebunden sind, einen gesättigten oder ungesättigten heterocyclischen Ring bilden. Der heterocyclische Ring kann weitere 1 oder 2 gleiche oder verschiedene Heteroatome und/oder Heterogruppen enthalten. Als Heteroatome stehen vorzugsweise Sauerstoff, Schwefel oder Stickstoff und als Heterogruppen N-Alkyl, wobei Alkyl der N-Alkyl-Gruppe vorzugsweise 1 bis 4, insbesondere 1 oder 2 Kohlenstoffatome enthält. Als Alkyl seien Methyl, Ethyl, n- und i-Propyl und n-, i- und t-Butyl genannt. Der heterocyclische Ring enthält 5 bis 7, vorzugsweise 5 oder 6 Ringglieder.
15

20 Als Beispiele für den heterocyclischen Ring seien Pyrrolidin, Piperidin, Piperazin, Hexamethylenimin, Hexahydro-1,3,5-triazin, Morphin genannt, die gegebenenfalls bevorzugt durch Methyl substituiert sein können.

E steht für einen elektronenentziehenden Rest, wobei insbesondere NO₂, CN, Halogenalkylcarbonyl, insbesondere mit 1-4 Kohlenstoffatomen und 1 bis 5 Halogenatomen, wie z.B. COCF₃, genannt seien.
25

X steht für -CH= oder -N=.

Z steht für gegebenenfalls substituierte Reste C₁-C₁₀-Alkyl, -OR, -SR, -NRR, wobei die Substituenten bevorzugt die bei R angegebene Bedeutung haben.

Z kann außer dem obengenannten Ring gemeinsam mit dem Atom, an welches es gebunden



an der Stelle von X einen gesättigten oder ungesättigten heterocyclischen Ring bilden. Der heterocyclische Ring kann weitere 1 oder 2 gleiche oder verschiedene Heteroatome und/oder Heterogruppen enthalten. Als Heteroatome stehen vorzugsweise Sauerstoff, 5 Schwefel oder Stickstoff und als Heterogruppen N-Alkyl, wobei die Alkyl oder N-Alkyl-Gruppe vorzugsweise 1 bis 4, insbesondere 1 oder 2 Kohlenstoffatome enthält. Als Alkyl seien Methyl, Ethyl, n- und i-Propyl und n-, i- und t-Butyl genannt. Der heterocyclische Ring enthält 5 bis 7, vorzugsweise 5 oder 6 Ringglieder.

10 Als Beispiele für den heterocyclischen Ring seien Pyrrolidin, Piperidin, Piperazin, Hexamethylenimin, Morpholin und N-Methylpiperazin genannt.

R steht für Wasserstoff sowie für gegebenenfalls substituierte Reste aus der Reihe Acyl, Alkyl, Aryl, Aralkyl, Heteroaryl, Heteroarylalkyl.

15 Als Acylreste seien genannt Formyl, Alkylcarbonyl, Arylcarbonyl, Alkylsulfonyl, Arylsulfonyl, (Alkyl)-(Aryl)-phosphoryl, die ihrerseits substituiert sein können.

Als Alkyl seien genannt C₁₋₁₀-Alkyl, insbesondere C₁₋₄-Alkyl, im einzelnen Methyl, Ethyl, i-Propyl, sec.- oder t.-Butyl, die ihrerseits substituiert sein können.

Als Aryl seien genannt Phenyl, Naphthyl, insbesondere Phenyl.

Als Aralkyl seien genannt Phenylmethyl, Phenethyl.

20 Als Heteroaryl seien genannt Heteroaryl mit bis zu 10 Ringatomen und N, O, S insbesondere N als Heteroatomen. Im einzelnen seien genannt Thienyl, Furyl, Thiazolyl, Imidazolyl, Pyridyl, Benzthiazolyl.

Als Heteroarylalkyl seien genannt Heteroarylmethyl, Heteroarylethyl mit bis zu 6 Ringatomen und N, O, S, insbesondere N als Heteroatomen.

25 Als Substituenten seien beispielhaft und vorzugsweise aufgeführt:

Alkyl mit vorzugsweise 1 bis 4, insbesondere 1 oder 2 Kohlenstoffatomen, wie Methyl, Ethyl, n- und i-Propyl und n-, i- und t-Butyl; Alkoxy mit vorzugsweise 1 bis 4, insbesondere 1 oder 2 Kohlenstoffatomen, wie Methoxy, Ethoxy, n- und i-Propyloxy und n-, i-

und t-Butyloxy; Alkylthio mit vorzugsweise 1 bis 4, insbesondere 1 oder 2 Kohlenstoffatomen, wie Methylthio, Ethylthio, n- und i-Propylthio und n-, i- und t-Butylthio; Halogenalkyl mit vorzugsweise 1 bis 4, insbesondere 1 oder 2 Kohlenstoffatomen und vorzugsweise 1 bis 5, insbesondere 1 bis 3 Halogenatomen, wobei die Halogenatome gleich oder verschieden sind und als Halogenatome, vorzugsweise Fluor, Chlor oder Brom, insbesondere Fluor stehen, wie Trifluormethyl; Hydroxy; Halogen, vorzugsweise Fluor, Chlor, Brom und Jod, insbesondere Fluor, Chlor und Brom; Cyano; Nitro; Amino; Monoalkyl und Dialkylamino mit vorzugsweise 1 bis 4, insbesondere 1 oder 2 Kohlenstoffatomen je Alkylgruppe, wie Methylamino, Methyl-ethyl-amino, n- und i-Propylamino und Methyl-n-butylamino; Carboxyl; Carbalkoxy mit vorzugsweise 2 bis 4, insbesondere 2 oder 3 Kohlenstoffatomen, wie Carbomethoxy und Carboethoxy; Sulfo (-SO₃H); Alkylsulfonyl mit vorzugsweise 1 bis 4, insbesondere 1 oder 2 Kohlenstoffatomen, wie Methylsulfonyl und Ethylsulfonyl; Arylsulfonyl mit vorzugsweise 6 oder 10 Arylkohlenstoffatomen, wie Phenylsulfonyl sowie Heteroarylarnino und Heteroarylalkylarnino wie Chlorpyridylarnino und Chlorpyridylmethylanino.

Ganz besonders bevorzugt sind Verbindungen der Formeln (I), (II) und (III), worin

N für 1 steht,

m für 0 steht,

Subst. für Chlor steht,

20 A für Wasserstoff oder C₁₋₃-Alkyl steht,

Z für C₁₋₃-Alkyl, -NH₂, -NH(C₁₋₃-Alkyl) oder -N(C₁₋₃-Alkyl)₂ steht,

oder

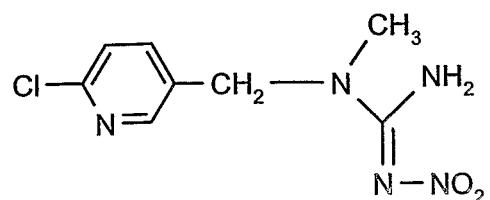
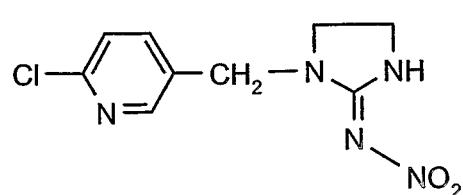
A und Z gemeinsam mit den Atomen, an welche sie gebunden sind, einen gesättigten 5- oder 6-gliedrigen heterocyclischen Ring bilden, der 1 oder 2 gleiche oder verschiedene Heteroatome oder Heterogruppen enthält, ausgewählt aus O, S, -NH-, -N(C₁₋₃-Alkyl),

X für -CH= oder =N- steht,

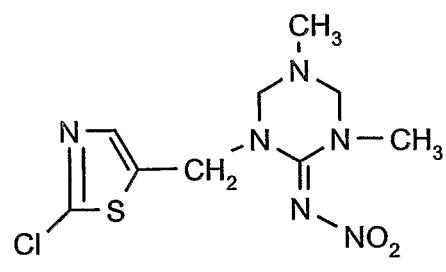
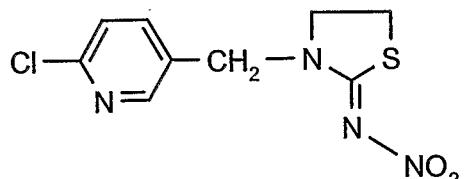
E für -NO₂ oder CN steht.

Im einzelnen seien folgende Verbindungen genannt:

- 9 -

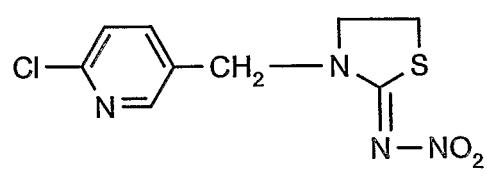
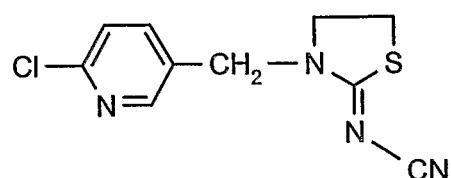
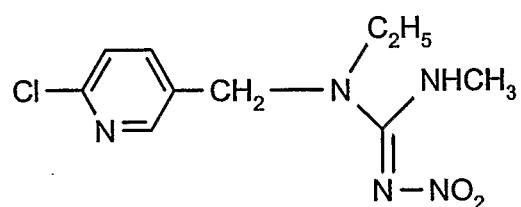
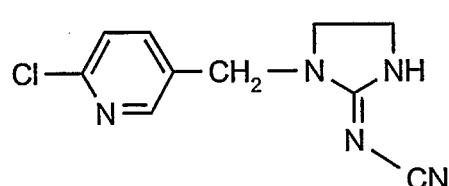
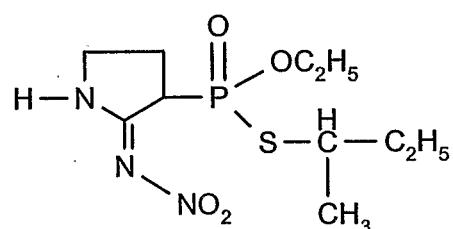
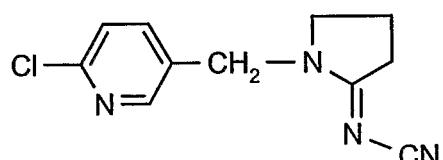


Imidacloprid



AKD 1022

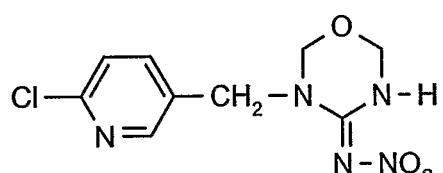
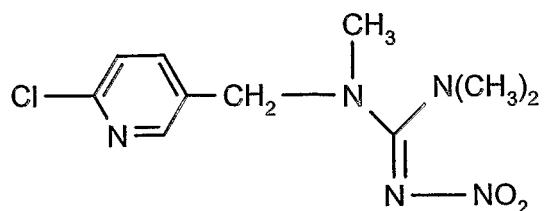
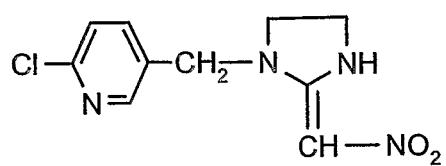
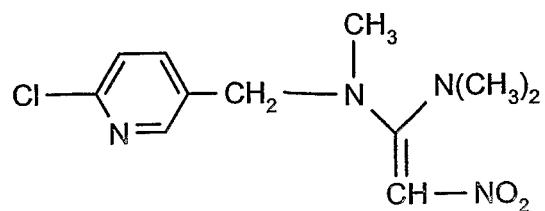
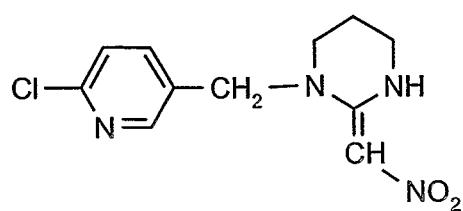
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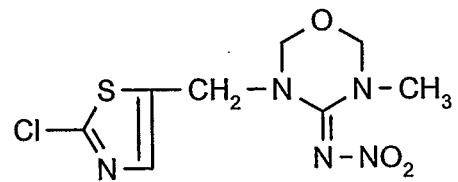
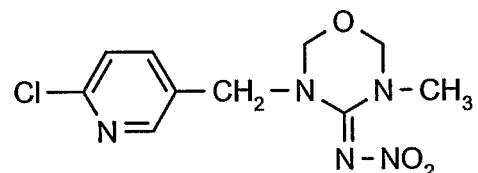
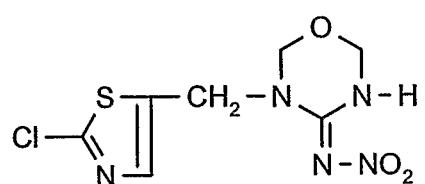
10

Thiacloprid

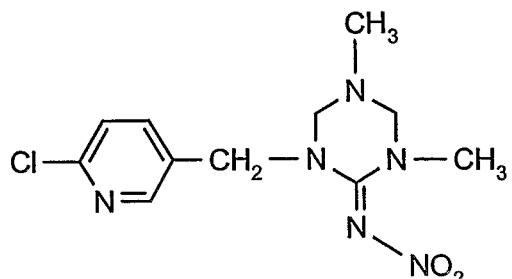
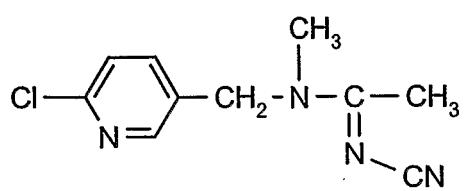
- 10 -



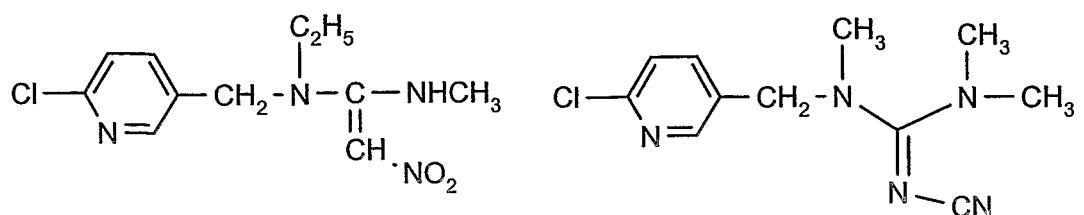
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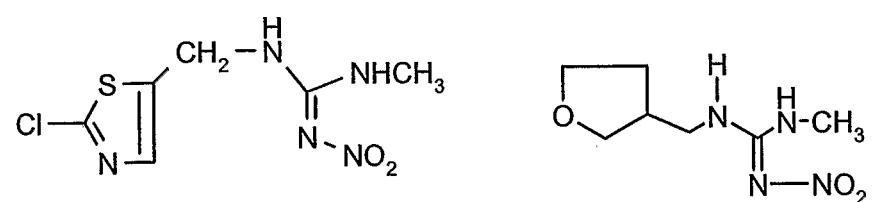
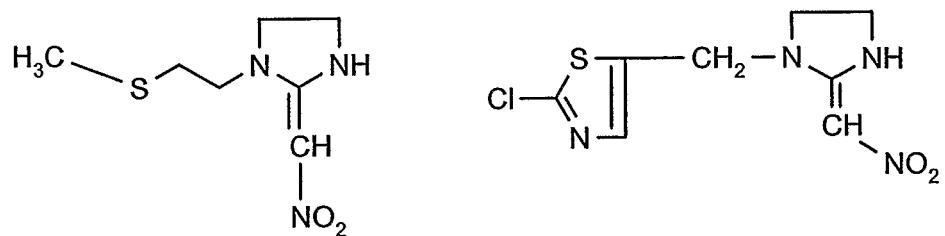
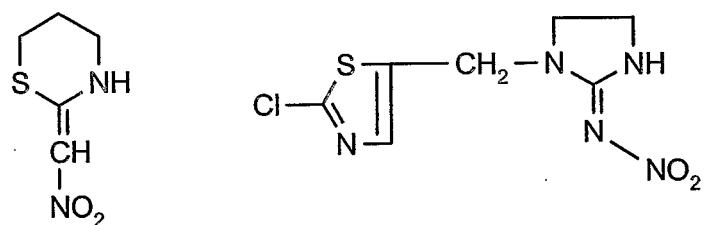
Thiamethoxam



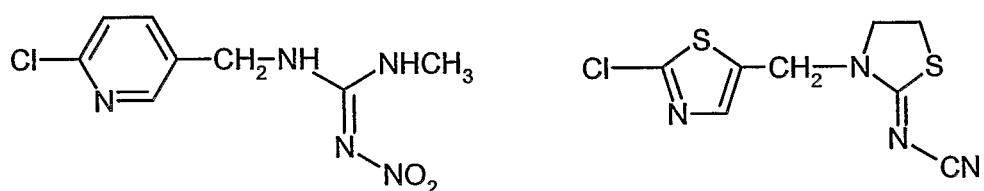
- 11 -



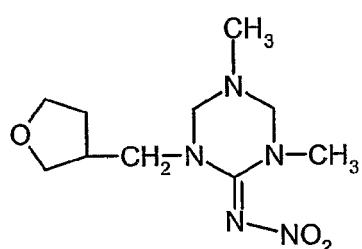
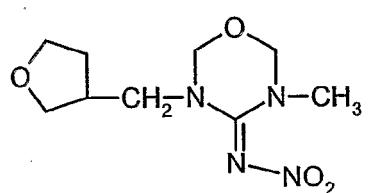
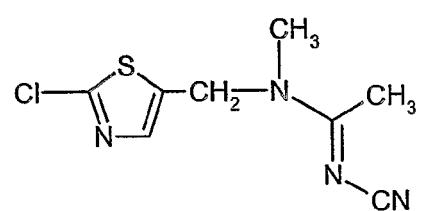
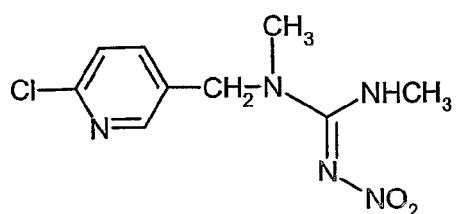
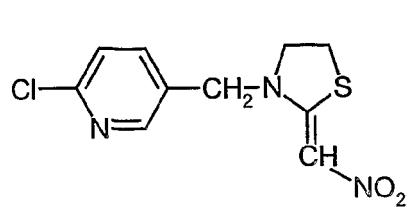
Nitenpyram



Chlothianidine

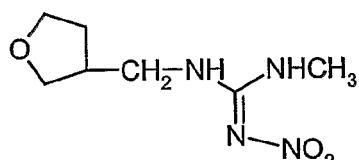
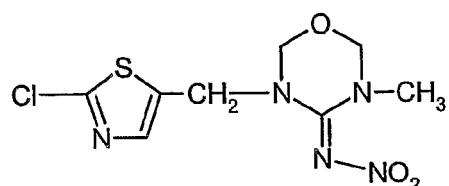
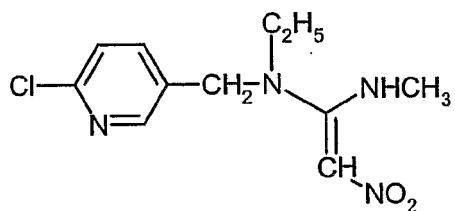
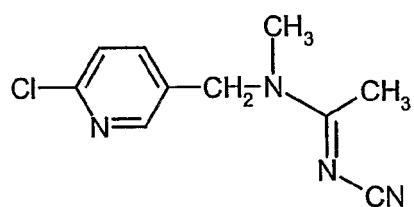


- 12 -



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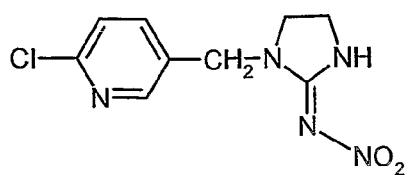
Besonders hervorgehoben seien die Verbindungen



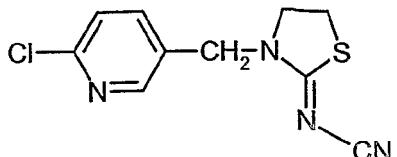
10

Weiterhin besonders hervorgehoben seien die Verbindungen

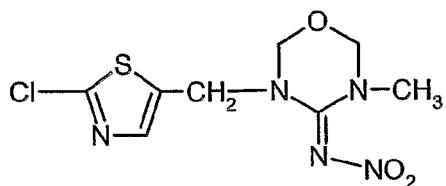
- 13 -



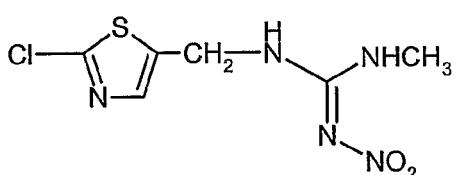
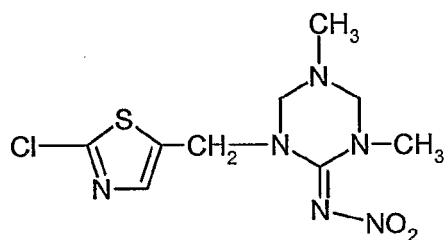
Imidacloprid



Thiacloprid

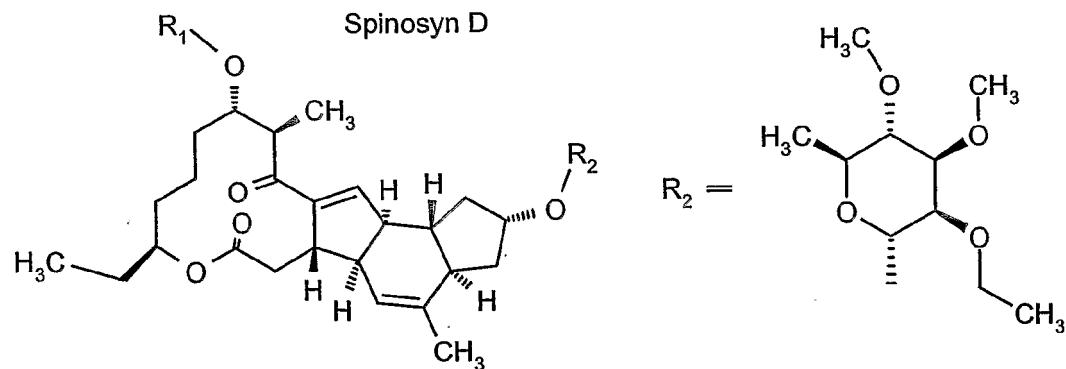
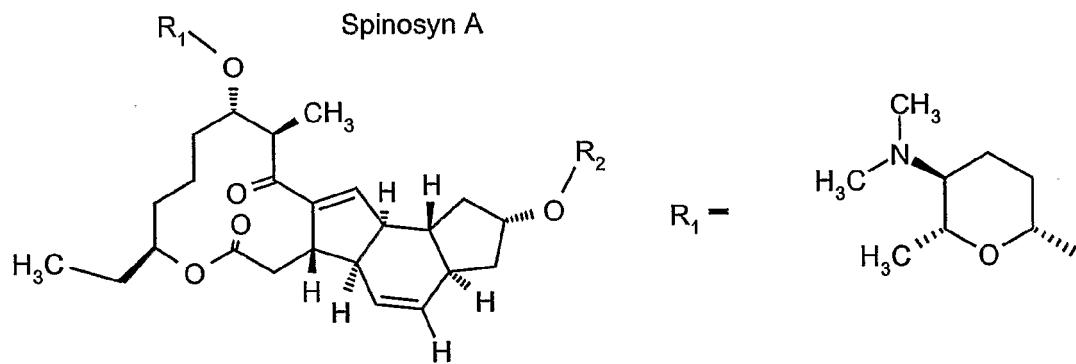


Thiamethoxam



5

Als Spinosyne seien hier insbesondere genannt Spinosyn A und D

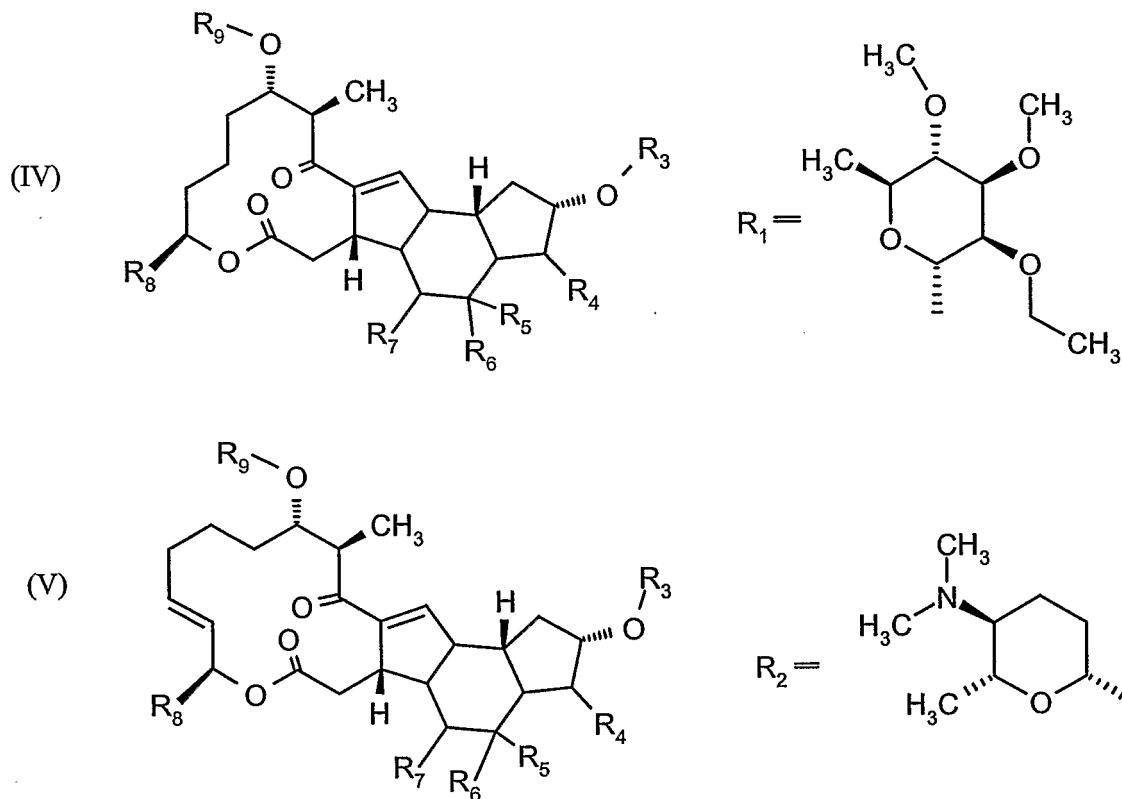


wie beschrieben in Boeck et al. in EP- 375 316 A1 and Deamicis et al. in WO 97/00265 A1.

Ebenfalls als Spinosyne werden hier verstanden synthetische und semi-synthetische Derivate der natürlichen Spinosyne bzw. Derivate die aus gentechnisch modifizierten Stämmen von z.B. Saccharopolyspora Spezies gewonnen werden, wie zum Beispiel beschrieben in WO 02/77004 und

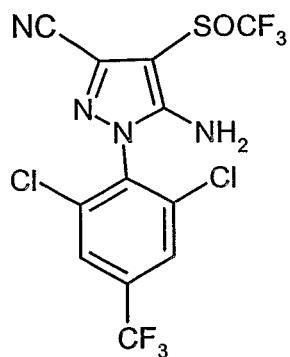
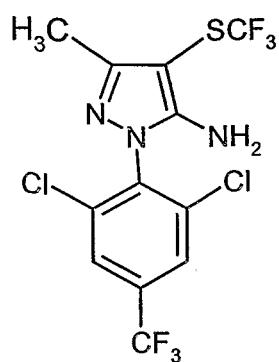
5 WO 02/77005.

Beispielhaft genannt seien Verbindungen der Formeln (IV) und (V) wobei R₃ ein Glykosid (R₃ = R₁) ist, R₄ ist H, OH oder Alkoxy; R₅ ist H, Methyl, R₆ und R₇ sind H oder zur Doppelbindung oder zu einer Epoxygruppe kombiniert, R₈ in Formel (IV) ist trans-1-Butenyl, 1,3-Butadienyl, Butyl, 3-Hydroxy-butenyl, Propyl, 1-Propenyl, 1,2-Epoxy-1-butyl, 3-Oxo-1-but enyl, 10 CH₃CH(OCH₃)CH=CH-, CH₃CH=CHCH(CH₂CO₂CH₃)-, oder CH₃CH=CHCH[CH₂CON(CH₃)]-; R₉ ist H oder Glykosid (R₉ = R₂).

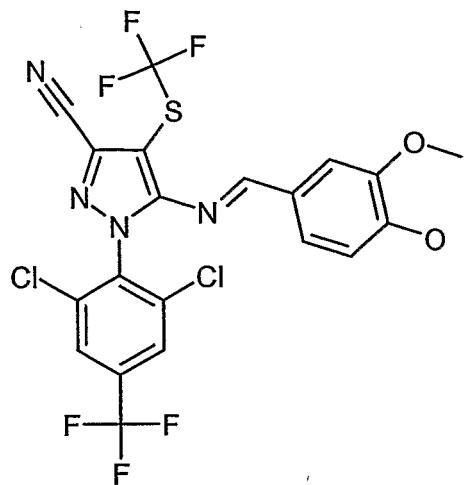


Als Phenylpyrazole seien zum Beispiel die folgenden Verbindungen genannt:

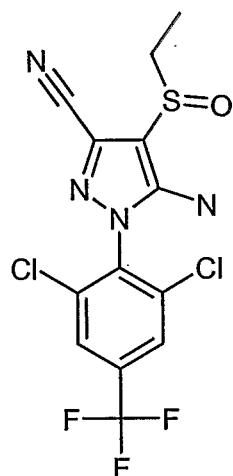
- 15 -



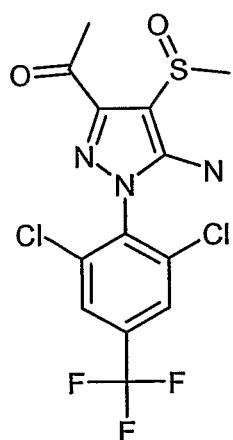
Fipronil



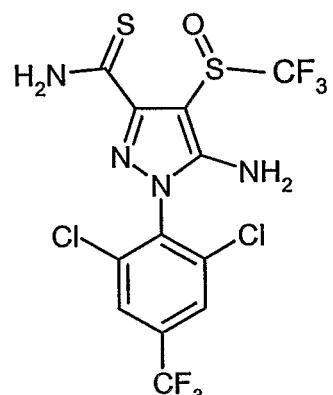
Vanilliprole,

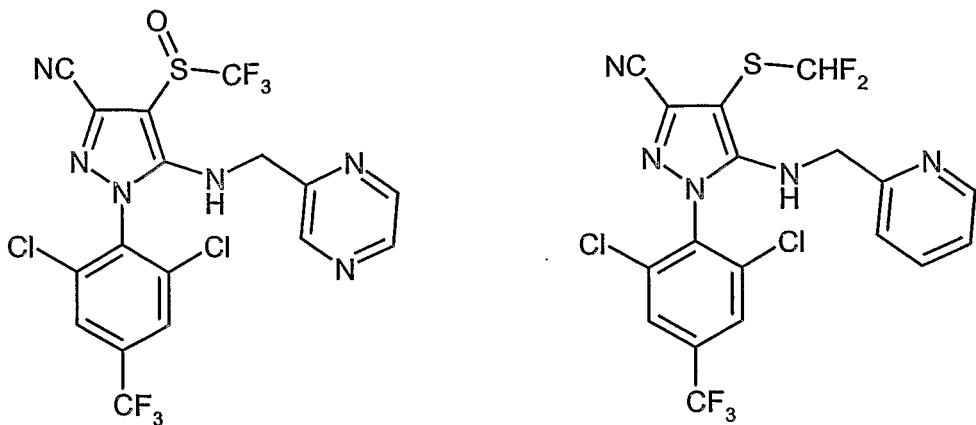


Ethiprole,



Acetoprole,



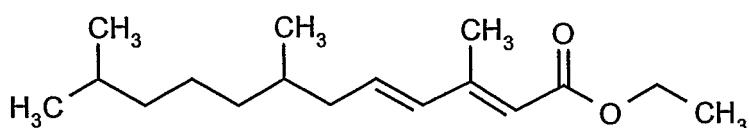
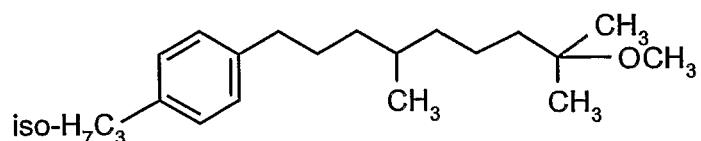
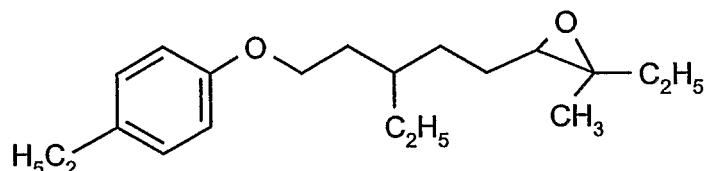


Als Carbamate seien genannt substituierte Phenyl- und Naphthylcarbamate, bevorzugte Beispiele sind:

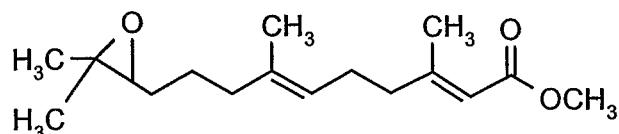
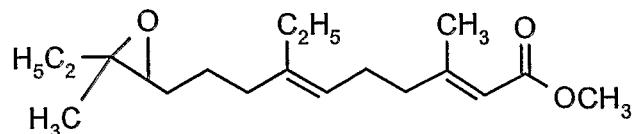
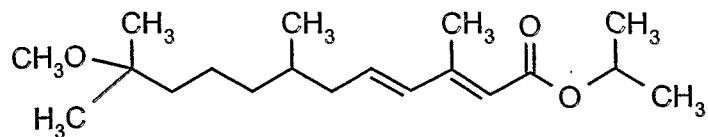
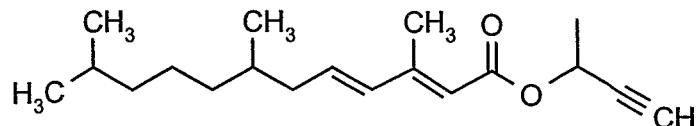
- 2-Oxobutylphenyl-N-methylcarbamat,
- 5 - 4-Dimethylamino-3-methyl-phenyl-N-methylcarbamat,
- 2-isopropoxy-phenyl-N-methylcarbamat,
- 1-Naphthyl-N-methylcarbamat,
- m-Tolyl-N-methylcarbamat,
- 3,4-Xylyl-N-methylcarbamat,
- 10 - 3,5-Xylyl-N-methylcarbamat,
- 2-[1,3-Dioxolan-2-yl]-phenyl-N-methylcarbamat.

Als Phosphorsäureester seien bevorzugt genannt die Verbindungen mit den Common Names Phoxim, Fenitrothion, Dichlorvos, Trichlorfon und Malathion.

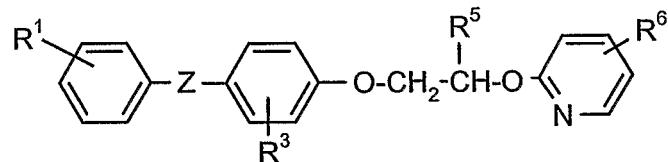
- 15 Juvenilhormone und juvenilhormonartige Verbindungen sind z.B. die folgenden:



- 17 -



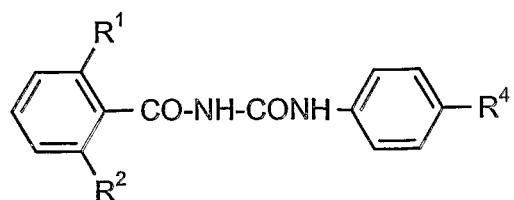
5 Substituierte Diarylether sind zum Beispiel die folgenden Verbindungen:



R ¹	R ³	R ⁵	R ⁶	Z
H	H	CH ₃	2-Cl	O
5-F	H	CH ₃	H	O
H	H	CF ₃	H	O
H	H	C ₂ H ₅	H	O
H	H	H	H	O
H	H	CH ₃	H	CH ₂
H	H	CH ₃	H	C(CH ₃) ₂

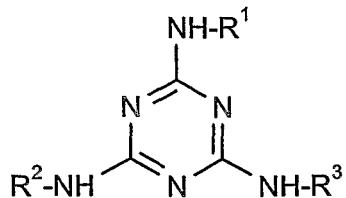
- 18 -

Benzoylharnstoffe sind z.B. die folgenden Verbindungen:



R¹	R²	R⁴
H	Cl	CF ₃
Cl	Cl	CF ₃
F	F	CF ₃
H	F	CF ₃
H	Cl	SCF ₃
F	F	SCF ₃
H	F	SCF ₃
H	Cl	OCF ₃
F	F	OCF ₃
H	F	OCF ₃
F	F	O-
F	F	O-
F	F	O-

Triazine sind z.B. die folgenden Verbindungen:



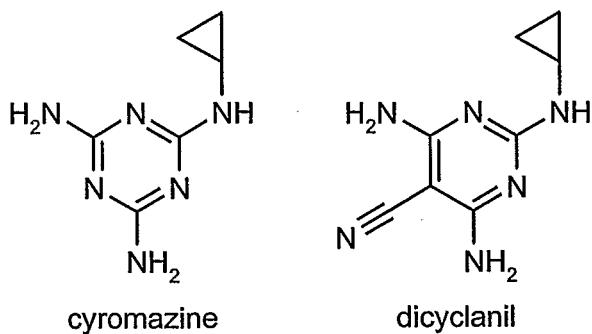
R ¹	R ²	R ³
Cyclopropyl	H	H
Cyclopropyl	H	CH ₃
Cyclopropyl	H	C ₂ H ₅
Cyclopropyl	H	C ₃ H _{7-n}
Cyclopropyl	H	C ₄ H _{9-n}
Cyclopropyl	H	C ₅ H _{11-n}
Cyclopropyl	H	C ₆ H _{13-n}
Cyclopropyl	H	C ₇ H _{15-n}
Cyclopropyl	H	C ₈ H _{17-n}
Cyclopropyl	H	C ₁₂ -H _{25-n}
Cyclopropyl	H	CH ₂ -C ₄ H _{9-n}
Cyclopropyl	H	CH ₂ CH(CH ₃)C ₂ H ₅
Cyclopropyl	H	CH ₂ CH=CH ₂
Cyclopropyl	Cl	C ₂ H ₅
Cyclopropyl	Cl	C ₆ H _{13-n}
Cyclopropyl	Cl	C ₈ H _{17-n}

- 20 -

R ¹	R ²	R ³
Cyclopropyl	Cl	C ₁₂ H _{25-n}
Cyclopropyl	H	Cyclopropyl
Cyclopropyl	H	COCH ₃
Cyclopropyl	H	COCH ₃ HCl
Cyclopropyl	H	COC ₂ H ₅ HCl
Cyclopropyl	H	COC ₂ H ₅
Cyclopropyl	H	COC ₃ H _{7-n}
Cyclopropyl	H	COC ₃ H _{7-i}
Cyclopropyl	H	COC ₄ H _{9-t} HCl
Cyclopropyl	H	COC ₄ H _{9-n}
Cyclopropyl	H	COC ₆ H _{13-n}
Cyclopropyl	H	COC _{11-H23-n}
Cyclopropyl	COCH ₃	COC ₂ H ₅
Cyclopropyl	COC ₃ H _{7-n}	COC ₆ H _{13-n}
Cyclopropyl	COCH ₃	COC ₃ H _{7-n}
Cyclopropyl	COC ₂ H ₅	COC ₃ H _{7-n}
Cyclopropyl	H	COCCyclopropyl
Cyclopropyl	COCCyclopropyl	COCCyclopropyl
Cyclopropyl	COCH ₃	COCH ₃
Isopropyl	H	H

R ¹	R ²	R ³
Isopropyl	H	COCH ₃
Isopropyl	H	COC ₃ H _{7-n}
Cyclopropyl	H	CONHCH ₃
Cyclopropyl	H	CONHC ₃ H _{7-i}
Cyclopropyl	CONHCH ₃	CONHCH ₃
Cyclopropyl	H	SCNHCH ₃
Cyclopropyl	H	CONHCH ₂ CH=CH ₂
Cyclopropyl	CONHCH ₂ CH=CH ₂	CONHCH ₂ CH=CH ₂
Cyclopropyl	CSNHCH ₃	CSNHCH ₃

Insbesondere seien hier genannt Cyromazin und Dicylanil.



Die Mengen der Kombinationswirkstoffe, die gegebenenfalls zusätzlich zu den Pyrethrinen/Pyrethroiden eingesetzt werden, können von 0,05 bis 25 % breit variiert werden, wobei die Mengen im Bereich 0,1 bis 15,0 % besonders und die Mengen im Bereich 0,5 bis 10,0 % ganz besonders zu bevorzugen sind. Prozentangaben sind hier als Gewichtsprozente bezogen auf die fertige Zubereitung zu verstehen.

Besonders bevorzugt sind Kombinationen der Pyrethroide und Pyrethrine, insbesondere α -Cyano-10 pyrethroide, vorzugsweise Flumethrin, Cyfluthrin sowie β -Cyfluthrin, mit Neonicotinoiden, insbe-

sondere Imidacloprid, Thiamethoxam, Clothianidin, Nitenpyram, Acetamiprid und Thiacloprid, oder mit Spinosynen, insbesondere Spinosad.

Selbstverständlich können den erfindungsgemäßen Zubereitungen weitere Synergisten wie Piperonylbutoxid, Tributylphosphit und Sesamöl zugefügt werden. Diese Synergisten sind bei-
5 spielsweise in EP-A 413 610 beschrieben.

Als Stabilisatoren und Antioxidantien seien genannt Sulfite oder Metabisulfite wie Kalium-
metabisulfit; organische Säuren wie Citronensäure, Ascorbinsäure; Phenole, Butylhydroxytoluol,
Butylhydroxyanisol, Tocopherol. Wobei die organischen Säuren Citronensäure und Äpfelsäure zu
bevorzugen sind. Ganz besonders bevorzugte Stabilisatoren sind Citronensäure und Butylhydroxy-
10 toluol. Ihr Anteil kann im Bereich 0,05 bis 2,5 Gew.-% breit variiert werden. Wobei die Mengen
im Bereich 0,075 bis 0,15 Gew.-% besonders bevorzugt werden. In Sprayformulierungen liegt die
Untergrenze der üblichen Konzentrationen niedriger, in der Regel bei 0,01 Gew.-%, bevorzugt
liegen in Sprayformulierungen die Konzentrationen bei 0,03 bis 0,1 Gew.-%.

Zur Herstellung der erfindungsmäßigen Zubereitungen können aromatische Alkohole wie Benzyl-
15 alkohol, cyclische Carbonate wie Propylen- und Ethylenkarbonat, Pyrrolidone wie Pyrrolidon-2,
N-Methylpyrrolidon, N-Oktyl-, N-Butyl-pyrrolidon, niedrigsiedende Alkohole wie Isopropanol,
Ethanol, höhere Alkohole wie n-Octylalkohol, Lanolinalkohol und n-Butanol, cyklische und
acyklische Ketone wie Aceton, Methylmethyleketon und Cyclohexanon, Glykole wie Ethylen- und
Propylenglykol, aliphatische cyclische oder acyclische Ether wie Tetrahydrofurfurylalkohol,
20 Diethylenglykolmonoethylether, Dipropylenglykolmonopropylether und Glycofurool, aliphatische
oder aromatische Fettsäureester wie Isopropylmyristat, Isopropylpalmitat und Benzylbenzoat,
Triglyceride auf Basis Ölsäure, Palmitinsäure, Linolsäure, Stearinsäure, Caprylsäure und
Caprinsäure, Laktone wie Butyrolacton bzw. deren Mischungen untereinander eingesetzt werden.
Besonders bevorzugt werden Carbonate, Alkohole und Pyrrolidone eingesetzt.

25 Der Lösungsmittelanteil der erfindungsgemäßen Mittel hängt selbstverständlich von der Art und
Menge der weiteren Inhaltsstoffe ab und kann daher stark variieren. Üblicherweise beträgt der
Lösungsmittelgehalt mindestens 10 Gew.-%, bevorzugt mindestens 50 Gew.-%, besonders bevor-
zugt mindestens 60 Gew.-%.

Weiterhin können die erfindungsgemäßen Formulierungen polymere und/oder oligomere ober-
30 flächenaktive neutrale, kationische bzw. anionische Hilfsmitteln wie Polyvinylpyrrolidon, Poly-
vinylalkohol, Polyoxyethylen-, -oxypropyle-Sorbitansäureester, Polyoxyethylen-Stearate bzw.
Umsetzungsprodukte der Phenoxyphenole und/oder Methoxysilanen mit Ethylenoxid und
Propylenoxid, Alkali- und Erdalkalisalze der Carbon- und Sulfonsäuren, quarternäre Ammonium-

salze wie Benzylammoniumchlorid - gegebenenfalls auch in Kombination miteinander - in Mengen von 0,1 bis 5 Gew.-%, vorzugsweise 0,2 bis 2,0 Gew.% enthalten, um das Fließverhalten, die Viskosität sowie Haar- und Fellaffinität zu verbessern.

Geruchsmaskierungsmittel sind z.B. Mischungen organischer Fettsäureester. Sie sind bevorzugt zu

5 0,1 bis 2 Gew.-% in den erfindungsgemäßen Formulierungen enthalten.

Falls die erfindungsgemäßen Mittel in Form eines Aerosolsprays eingesetzt werden, wird eine Vorlösung zusammen mit einem Treibmittel in übliche Spraydosen o.ä. abgefüllt. Übliche Treibmittel oder Treibgase sind z. B. gasförmige Kohlenwasserstoffe wie Propan, Butan (bevorzugt ist eine Propan-Butan-Mischung, insbesondere im Verhältnis 80:20), Fluorkohlenwasserstoffe, Fluor-10 chlorkohlenwasserstoffe, N₂O, CO₂, Stickstoff.

Überraschenderweise zeichnen sich die erfindungsgemäßen Flüssigformulierungen durch eine hervorragende Lagerungsstabilität von mehreren Jahren in allen Klimazonen sowie durch ausgezeichnete Haut-, Anwender- und Umweltverträglichkeit aus. Sie eignen sich erstaunlicherweise auch hervorragend zum Abfüllen und Ausbieten in lagerungskritischen „Single dose Kunststofftuben“, die üblicherweise aus Polypropylen bestehen, eine Wandstärke von 300-500 µm und ein Abfüllvolumen von 1,0 bis 4,0 ml aufweisen.

Solche mit den erfindungsgemäßen Mitteln gefüllte Single-Dose-Kunststofftuben sind daher ebenfalls Gegenstand der vorliegenden Erfindung.

Die erfindungsgemäßen Flüssigformulierungen zeigen zudem einen nicht zu erwartenden 20 synergistischen, d.h. wirkungssteigernden Effekt bei Verwendung von Pyrethroiden/Pyrethrinen als Wirkstoff.

Die erfindungsgemäßen Mittel sind umweltverträglich und aufgrund der sehr geringen Toxizität anwenderfreundlich.

Die erfindungsgemäßen Mittel eignen sich bei günstiger Warmblütotoxicität zur Bekämpfung von 25 parasitierenden Insekten, insbesondere Flöhen und Zecken, die bei Tieren, insbesondere bei Warmblütern, besonders bevorzugt bei Säugetieren vorkommen. Dies können Haus- und Nutztiere sowie Zoo-, Labor-, Versuchs- und Hobbytiere sein. Die erfindungsgemäßen Mittel sind dabei gegen alle oder einzelne Entwicklungsstadien der Schädlinge sowie gegen resistente und normal sensible Arten der Schädlinge wirksam.

30 Zu den Schädlingen gehören:

Aus der Ordnung der Anoplura z.B. Haematopinus spp., Linognathus spp., Solenopotes spp., Pediculus spp., Pthirus spp.;

aus der Ordnung der Mallophaga z.B. Trimenopon spp., Menopon spp., Eomenacanthus spp., Menacanthus spp., Trichodectes spp., Felicola spp., Damalinea spp., Bovicola spp.;

- 5 aus der Ordnung der Diptera in der Unterordnung Brachycera z.B. Chrysops spp., Tabanus spp., Musca spp., Hydrotaea spp., Muscina spp., Haematobosca spp., Haematobia spp., Stomoxys spp., Fannia spp., Glossina spp., Lucilia spp., Calliphora spp., Auchmeromyia spp., Cordylobia spp., Cochliomyia spp., Chrysomyia spp., Sarcophaga spp., Wohlfartia spp., Gasterophilus spp., Oesteromyia spp., Oedemagena spp., Hypoderma spp., Oestrus spp., Rhinoestrus spp., Melophagus 10 spp., Hippobosca spp. .

aus der Ordnung der Diptera in der Unterordnung Nematocera z.B. Culex spp., Aedes spp., Anopheles spp., Culicoides spp., Phlebotomus spp., Simulium spp..

aus der Ordnung der Siphonaptera z.B. Ctenocephalides spp., Echidnophaga spp., Ceratophyllus spp., Pulex spp..

- 15 aus der Ordnung der Metastigmata z.B. Hyalomma spp., Rhipicephalus spp., Boophilus spp., Amblyomma spp., Haemaphysalis spp., Dermacentor spp., Ixodes spp., Argas spp., Ornithodoros spp., Otobius spp.;

aus der Ordnung der Mesostigmata z.B. Dermanyssus spp., Ornithonyssus spp., Pneumonyssus spp..

- 20 aus der Ordnung der Prostigmata z.B. Cheyletiella spp., Psorergates spp., Myobia spp., Demodex spp., Neotrombicula spp.;

aus der Ordnung der Astigmata z.B. Acarus spp., Myocoptes spp., Psoroptes spp., Chorioptes spp., Otodectes spp., Sarcoptes spp., Notoedres spp., Knemidocoptes spp., Neoknemidocoptes spp., Cytodites spp., Laminosioptes spp..

- 25 Besonders hervorgehoben sei die Wirkung gegen Siphonaptera, insbesondere gegen Flöhe und Zecken.

Zu den Nutz- und Zuchttieren gehören Säugetiere wie z.B. Rinder, Pferde, Schafe, Schweine, Ziegen, Kamele, Wasserbüffel, Esel, Kaninchen, Damwild, Rentiere, Pelztiere wie z.B. Nerze, Chinchilla, Waschbär, Vögel wie z.B. Hühner, Gänse, Puten, Enten.

Zu Labor- und Versuchstieren gehören Mäuse, Ratten, Meerschweinchen, Goldhamster, Hunde und Katzen.

Zu den Hobbytieren gehören Hunde und Katzen.

Insbesondere hervorgehoben sei die Anwendung bei Katze und Hund.

5 Die Anwendung kann sowohl prophylaktisch als auch therapeutisch erfolgen.

Die erfindungsgemäß neuen Flüssigformulierungen sind grundsätzlich zur Spot on, Pour on, und Pump- sowie Aerosolspray-Applikationen geeignet. Die bevorzugten Applikationsformen sind Pour on, Pump Spray. Die Spot on Applikation ist ganz besonders bevorzugt.

10 Zur Herstellung der erfindungsgemäßen, flüssigen Formulierung werden die gewünschten Bestandteile in entsprechenden Mengen miteinander vermischt, z.B. durch den Einsatz konventioneller Rührkessel oder anderer geeigneter Geräte.

Falls die Inhaltsstoffe es erfordern, kann auch unter Schutzatmosphäre oder anderen Methoden des Sauerstoffausschlusses gearbeitet werden.

Die nachfolgenden Beispiele sollen die Erfindung erläutern:

Beispiele**Beispiel 1a**

Eine homogene Spot on Formulierung (100 ml) bestehend aus

1,00 g	Flumethrin
5 10,00g	Imidacloprid
40,00 g	MGK 264
48,00 g	N-Methylpyrrolidon//THFA (Tetrahydrofurfurylalkohol) (70:30)
0,10 g	Citronensäure
0,10 g	BHT (Butylhydroxytoluol)

10

Beispiel 1b

Eine homogene Spot on Formulierung (100 ml) bestehend aus

0,50 g	Flumethrin
10,00g	Imidacloprid
15 40,00 g	MGK 264
48,50 g	N-Methylpyrrolidon//THFA (Tetrahydrofurfurylalkohol) (70:30)
0,10 g	Citronensäure
0,10 g	BHT (Butylhydroxytoluol)

Beispiel 2a

20 Eine homogene Spot on Formulierung (100 ml) bestehend aus

0,50 g	Flumethrin
10,00g	Imidacloprid
10,00 g	MGK 264
59,40g	N-Methylpyrrolidon//THFA (Tetrahydrofurfurylalkohol) (70:30)
25 25,00g	Miglyol 812
0,10 g	Citronensäure
0,10 g	BHT (Butylhydroxytoluol)

Beispiel 2b

Eine homogene Spot on Formulierung (100 ml) bestehend aus

0,35 g	Flumethrin
10,00g	Imidacloprid
5 10,00 g	MGK 264
59,55 g	N-Methylpyrrolidon//THFA (Tetrahydrofurfurylalkohol) (70:30)
25,00g	Miglyol 812
0,10 g	Citronensäure
0,10 g	BHT (Butylhydroxytoluol)

10 Beispiel 2c

Eine homogene Spot on Formulierung (100 ml) bestehend aus

0,20 g	Flumethrin
10,00g	Imidacloprid
10,00g	MGK 264
15 59,70g	N-Methylpyrrolidon//THFA (Tetrahydrofurfurylalkohol) (70:30)
25,00g	Miglyol 812
0,10 g	Citronensäure
0,10 g	BHT (Butylhydroxytoluol)

Beispiel 3

20 Eine homogene Spot on Formulierung (100 ml) bestehend aus

0,50 g	Flumethrin
10,00g	Imidacloprid
20,00 g	MGK 264
50,00 g	N-Methylpyrrolidon//Propylencarbonat (70:30)
25 13,75 g	Miglyol 812
0,1 g	Citronensäure
0,1 g	BHT (Butylhydroxytoluol)

Beispiel 4

Eine homogene Spot on Formulierung (100 ml) bestehend aus

0,50 g	Flumethrin
10,00g	Imidacloprid
5 10,00 g	MGK 264
72,85 g	Benzylalcohol
14,48g	Propylencarbonat
0,1 g	Citronensäure
0,1 g	BHT (Butylhydroxytoluol)

10 Beispiel 5

Eine homogene Spot on Formulierung (100 ml) bestehend aus

0,35 g	Flumethrin
10,00 g	Imidacloprid
10,00 g	MGK 264
15 72,70 g	Benzylalcohol
14,33 g	Propylencarbonat
0,1 g	Citronensäure
0,1 g	BHT (Butylhydroxytoluol)

Beispiel 6

20 Eine homogene Spot on Formulierung (100 ml) bestehend aus

0;35 g	Flumethrin
10,00 g	Imidacloprid
15,00 g	MGK 264
65,46 g	Benzylalcohol
25 12,94 g	Propylencarbonat
0,1 g	Citronensäure
0,1 g	BHT (Butylhydroxytoluol)
5,00 g	Wasser

Beispiel 7

Eine homogene Spot on Formulierung (100 ml) bestehend aus

0,35 g	Flumethrin
10,00 g	Imidacloprid
5 15,00 g	MGK 264
44,98 g	N-Methylpyrrolidon
32,08 g	THFA
0,1 g	Citronensäure
0,1 g	BHT (Butylhydroxytoluol)

- 10 Neben der besonders bevorzugten Spot-on Applikation ist bevorzugt auch eine Verteilung der genannten Wirkstoffkombinationen durch Sprühen mittels Pumpspray oder Aerosolspray möglich. Hierzu sind andere Formulierungen erforderlich, die in den nachfolgenden Herstellbeispielen beschrieben werden.

Beispiel 8

- 15 Eine Pumpsprayformulierung (250 ml) bestehend aus

2.50 g	Imidacloprid
0.125 g	Flumethrin
5.00 g	MGK 264
0.125 g	BHT
20 0.125 g	Citronensäure
20.80 g	Benzylalkohol
4.125 g	Propylencarbonat
25.00 g	Wasser
154.63 g	Isopropanol

25

Zur Applikation der Formulierung für die Wirksamkeitsstudien an Hunden und Katzen wurde ein konventioneller Pumpspray-Sprühkopf mit D(v0,5) von ca. 65 µm eingesetzt.

Beispiel 9

Eine Pumpsprayformulierung (250 ml) bestehend aus

- 2.50 g Imidacloprid
0.125 g Flumethrin
5 5.00 g MGK 264
0.125 g BHT
0.125 g Citronensäure
20.80 g Benzylalkohol
4.125 g Propylencarbonat
10 25.00 g Wasser
154.63g Isopropanol

Zur Applikation der Formulierung für die Wirksamkeitsstudien an Hunden und Katzen wurde ein konventioneller Pumpspray-Sprühkopf mit D(v0,5) von ca. 65 µm eingesetzt.

Beispiel 10a

- 15 Eine Pumpsprayformulierung (250 ml) bestehend aus

- 2.50 g Thiamethoxam
0.125 g Flumethrin
5.00 g MGK 264
0.125 g BHT
20 0.125 g Citronensäure
20.80 g Benzylalkohol
4.125 g Propylencarbonat
25.00 g Wasser
154.63 g Isopropanol

- 25 Zur Applikation der Formulierung für die Wirksamkeitsstudien an Hunden und Katzen wurde ein konventioneller Pumpspray-Sprühkopf mit D(v0,5) von ca. 65 µm eingesetzt.

Beispiel 10b

Eine Pumpsprayformulierung (250 ml) bestehend aus

- 2.50 g Thiacoiprid
30 0.125 g Flumethrin

	5.00 g	MGK 264
	0.125 g	BHT
	0.125 g	Citronensäure
	20.80 g	Benzylalkohol
5	4.125 g	Propylenkarbonat
	25.00 g	Wasser
	154.63 g	Isopropanol

Zur Applikation der Formulierung für die Wirksamkeitsstudien an Hunden und Katzen wurde ein konventioneller Pumpspray-Sprühkopf mit D(v0,5) von ca. 65µm eingesetzt.

10 Beispiel 11

Eine 250 ml Vorlösung zur Herstellung von üblichen Aerosol-Sprays bestehend aus

	2.00 g	Thiamethoxam
	0.15 g	Flumethrin
	5.00 g	MGK 264
15	0.125 g	BHT
	0.025 g	Citronensäure
	36.475 g	Benzylalkohol
	7.225 g	Propylenkarbonat
	25.00 g	Wasser
20	141.25 g	Isopropanol

Eine konventionelle Weissblech-Aerosoldose wurde mit 140 g der Vorlösung gemäß Beispiel 11 und mit 60 g einer Treibgasmischung Propan/Butan (Propan:Butan = 80:20) abgefüllt, mit einem üblichen Aerosol-Sprühkopf der Fa. Kosmos versehen und dann zur Durchführung von Wirksamkeitsstudien an Hunden und Katzen eingesetzt.

25 Beispiel 12

Eine 250 ml Vorlösung zur Herstellung von üblichen Aerosol-Sprays bestehend aus

	2.00 g	Imidacloprid
	0.15 g	Flumethrin
	5.00 g	MGK 264
30	0.125 g	BHT
	0.025 g	Citronensäure

36.475 g	Benzylalkohol
7.225 g	Propylencarbonat
25.00 g	Wasser
141.25 g	Isopropanol

- 5 Eine konventionelle Weissblech-Aerosoldose wurde mit 140 g der Vorlösung gemäß Beispiel 12 und mit 60 g einer Treibgasmischung Propan/Butan (Propan:Butan = 80:20) abgefüllt, mit einer herkömmlichen Aerosol-Sprühkopf der Fa. Kosmos versehen und dann zur Durchführung von Wirksamkeitsstudien an Hunden und Katzen eingesetzt.

Beispiel 13

- 10 Eine 250 ml Vorlösung zur Herstellung von üblichen Aerosol-Sprays bestehend aus

2.00 g	Thiacloprid
0.15 g	Flumethrin
5.00 g	MGK 264
0.125 g	BHT
15 0.025 g	Citronensäure
36.475 g	Benzylalkohol
7.225 g	Propylencarbonat
25.00 g	Wasser
141.25 g	Isopropanol

- 20 Eine konventionelle Weissblech-Aerosoldose wurde mit 140 g der Vorlösung gemäß Beispiel 13 und mit 60 g einer Treibgasmischung Propan/Butan (Propan:Butan = 80:20) abgefüllt, mit einem üblichen Aerosol-Sprühkopf der Fa. Kosmos versehen und dann zur Durchführung von Wirksamkeitsstudien an Hunden und Katzen eingesetzt.

Der in den Beispielen 11- 13 eingesetzte Aerosol-Sprühkopf der Fa. Kosmos findet bei der Herstellung von handelsüblichen insektizidhaltigen Aerosol-Sprays (z.B. Bolfo Flohschutz Spray, Bolfo Plus Spray der Fa. Bayer HealthCare AG D-51368 Leverkusen) Anwendung.

- Aus den weiteren Laborprüfungen zur Zecken-Wirksamkeit gemäß Beispielen 1, 2, 5 und 9 geht hervor, dass die o.a. erfindungsgemäßen Formulierung eine sehr gute Wirkung gegen Zecken aufweisen, sich durch ihre Zieltier und Anwenderverträglichkeit auszeichnen und zum Bekämpfen
30 von Flöhen Zecken an Kleintieren hervorragend geeignet sind.

A. Wirksamkeit gegen Flöhe am Hund

Ctenocephalides felis

An den Tagen -4 und -1 werden Hunde mit ca. 100 adulten, nüchternen Ctenocephalides felis pro Hund infestiert. Dabei werden die Flöhe auf den Nacken des Tieres ausgebracht.

- 5 Am Tag 0 wird der Infestationserfolg am Hund überprüft, indem am wachen Tier nach Flöhen gesucht wird. Die Zahl der lebenden Flöhe wird protokolliert.

Nach der Zählung der Flöhe werden die Tiere behandelt. Die Hunde der Kontrollgruppe werden nicht behandelt. Die zu prüfenden Arzneimittel werden den Tieren dermal als Spot-on bei einer Applikationsmenge von 0,1 ml/kg Körpergewicht oder als Spray mit einer Applikationsmenge von
10 1-1,5 ml/kg Körpergewicht verabreicht. Die Applikation erfolgt einmalig am Tag 0. Es werden nur klinisch gesunde Tiere verwendet.

Am Tag 1 und 2 werden alle Hunde auf lebende Flöhe überprüft. Die Ergebnisse werden in den Rohdaten festgehalten.

Am Tag 7, 14, 21 und 28 werden alle Hunde mit ca. 100 adulten, nüchternen Ctenocephalides felis pro Hund reinfestiert. Jeweils einen Tag nach Reinfestation werden alle Hunde auf lebende Flöhe kontrolliert. Die Ergebnisse werden in den Rohdaten protokolliert.

Eine Formulierung wird als hochwirksam erachtet, wenn am Tag 1 und jeweils am zweiten Tag nach Reinfestation eine Wirksamkeit >95% festgestellt wird und diese Wirkung über mindestens 3-4 Wochen anhält.

- 20 Für die Berechnung der Wirksamkeit wird eine modifizierte Formel nach Abbott benutzt:

$$\text{Wirksamkeit \%} = \frac{\bar{\Omega} \text{ Anzahl Flöhe KG} - \bar{\Omega} \text{ Anzahl Flöhe BG}}{\bar{\Omega} \text{ Anzahl Flöhe KG}} \times 100$$

KG: Kontrollgruppe

BG: Behandlungsgruppe

Die Arzneimittel gemäß den Formulierungsbeispielen 1 bis 5 in einer Dosierung von 0,1 ml/kg als
25 Spot on appliziert, erwiesen sich gegen Ctenocephalides felis als hochwirksam.

Die Arzneimittel gemäß den Formulierungsbeispielen 8 bis 10 in einer Dosierung von 1-1.5ml/kg als Spray appliziert, erwiesen sich gegen Ctenocephalides felis als hochwirksam.

B. Wirksamkeit gegen Zecken (*Rhipicephalus sanguineus*, *Haemaphysalis leachi*) am Hund

Jeweils an den Tagen -4 und -1 werden Hunde mit 2% Rompun® (Bayer AG, Wirkstoff:

5 Xylazinhydrochlorid) (0,1ml/kg Körpergewicht) sediert. Nachdem alle Hunde sediert sind (nach ca. 10-15 Minuten) werden sie in Transportboxen überführt und 50 *Rhipicephalus sanguineus* oder *Haemaphysalis leachi* (25♀, 25♂) pro Hund auf den Nacken des Tieres ausgebracht. Die Tiere werden nach ca. 1 ½ Stunden wieder aus der Transportkiste in den Käfig gesetzt.

Am Tag 0 wird der Infestationserfolg am Hund überprüft, indem am wachen Tier nach Zecken

10 gesucht wird. Intensiv wird dabei gesucht im Kopf- und Ohrenbereich inkl. Ohrenfalte, im Bereich des Nackens, am Unterbauch, an der Unterbrust, an der seitlichen Flanke sowie zwischen den Zehen und an den Gliedmaßen. Die Zahl der angesogenen lebenden Zecken wird protokolliert. Tote Zecken werden entfernt.

Nach der Zählung der Zecken werden die Tiere behandelt. Die Hunde der Kontrollgruppe werden

15 nicht behandelt. Die zu prüfenden Arzneimittel werden den Tieren dermal als Spot-on mit 0,1 ml/kg Körpergewicht oder als Spray mit 1-1.5 ml/kg Körpergewicht verabreicht. Die Applikation erfolgt einmalig am Tag 0. Es werden nur klinisch gesunde Tiere verwendet.

Am Tag 1 und Tag 2 werden alle Hunde auf lebende und tote angesogene Zecken überprüft. Die

Ergebnisse werden in den Rohdaten festgehalten. Am Tag 2 werden alle lebenden und toten
20 Zecken vom Hund entfernt.

Am Tag 7, 14, 21 und 28 werden alle Hunde mit jeweils 50 *Rhipicephalus sanguineus* oder

Haemaphysalis leachi (25♀, 25♂) pro Hund reinfestiert. Jeweils zwei Tage nach Reinfestation werden alle Hunde auf lebende und tote angesogene Zecken kontrolliert. Die Ergebnisse werden in den Rohdaten protokolliert. Am zweiten Tag nach Reinfestation werden alle lebenden und toten
25 Zecken vom Hund entfernt.

Eine Formulierung wird als hochwirksam erachtet, wenn am Tag 2 und jeweils am zweiten Tag nach Reinfestation eine Wirksamkeit >90 % festgestellt wird und diese Wirkung über mindestens 3 Wochen anhält.

- 35 -

Für die Berechnung der Wirksamkeit wird eine modifizierte Formel nach Abbott benutzt:

$$\text{Wirksamkeit \%} = \frac{\varnothing \text{ Anzahl Zecken KG} - \varnothing \text{ Anzahl Zecken BG}}{\varnothing \text{ Anzahl Zecken KG}} \times 100$$

KG: Kontrollgruppe

BG: Behandlungsgruppe

- 5 Die Arzneimittel in einer Dosierung gemäß den Formulierungsbeispielen 1 bis 5 von 0,1ml/kg als Spot on appliziert, erwiesen sich gegen Rhipicephalus sanguineus als hochwirksam.

Die Arzneimittel gemäß den Formulierungsbeispielen 8 bis 10 in einer Dosierung von 1-1.5 ml/kg als Spray appliziert, erwiesen sich gegen Rhipicephalus sanguineus und Haemaphysalis leachi als hochwirksam.

10 C. Wirksamkeit gegen Flöhe (Ctenocephalides felis) an der Katze

An Tag -1 werden Katzen mit ca. 100 adulten, nüchternen Ctenocephalides felis pro Katze infestiert. Dabei werden die Flöhe auf den Nacken des Tieres ausgebracht.

Am Tag 0 wird der Infestationserfolg an der Katze überprüft, indem am wachen Tier nach Flöhen gesucht wird. Die Zahl der lebenden Flöhe wird protokolliert.

- 15 Nach der Zählung der Flöhe werden die Tiere behandelt. Die Katzen der Kontrollgruppe werden nicht behandelt. Die zu prüfenden Arzneimittel gemäß der Beispiele 1 bis 4 werden den Tieren dermal als Spot-on bei einer Applikationsmenge von 0,1 ml/kg Körpergewicht verabreicht. Die Applikation erfolgt einmalig am Tag 0. Es werden nur klinisch gesunde Tiere verwendet.

- 20 An Tag 2 werden alle Katzen auf lebende Flöhe überprüft. Die Ergebnisse werden in den Rohdaten festgehalten.

Am Tag 6, 13, 20 und 27 werden alle Katzen mit ca. 100 adulten, nüchternen Ctenocephalides felis pro Katze reinfestiert. Jeweils zwei Tage nach Reinfestation werden alle Katzen auf lebende Flöhe kontrolliert. Die Ergebnisse werden in den Rohdaten protokolliert.

Eine Formulierung wird als hochwirksam erachtet, wenn am Tag 2 und jeweils am zweiten Tag nach Reinfestation eine Wirksamkeit >95% festgestellt wird und diese Wirkung über mindestens 3-4 Wochen anhält.

Für die Berechnung der Wirksamkeit wird eine modifizierte Formel nach Abbott benutzt:

$$\text{Wirksamkeit \%} = \frac{\bar{\Omega} \text{ Anzahl Flöhe KG} - \bar{\Omega} \text{ Anzahl Flöhe BG}}{\bar{\Omega} \text{ Anzahl Flöhe KG}} \times 100$$

5

KG: Kontrollgruppe

BG: Behandlungsgruppe

Die Arzneimittel gemäß den Formulierungsbeispielen 1 bis 5 in einer Dosierung von 0,1 ml/kg als Spot on appliziert, erwiesen sich gegen Ctenocephalides felis als hochwirksam.

10 D. Wirksamkeit gegen Zecken (*Haemaphysalis leachi*) an der Katze

Jeweils am Tag -2 werden Katzen mit einem milden Sedativum (Acepromazin maleat) sediert. Nachdem alle Katzen sediert sind (nach ca. 10-15 Minuten) werden 30 *Haemaphysalis leachi* (15♀, 15♂) pro Katze auf den Nacken des Tieres ausgebracht.

15 Am Tag -1 wird der Infestationserfolg an den Katzen überprüft, indem am wachen Tier nach Zecken gesucht wird. Intensiv wird dabei gesucht im Kopf- und Ohrenbereich, im Bereich des Nackens, am Unterbauch, an der Unterbrust, an der seitlichen Flanke sowie an den Gliedmaßen. Die Zahl der angesogenen lebenden Zecken wird protokolliert. Tote Zecken werden entfernt.

Nach der Zählung der Zecken werden die Tiere gruppiert. Die Behandlung erfolgt an Tag 0. Die 20 Katzen der Kontrollgruppe werden nicht behandelt. Die zu prüfenden Arzneimittel werden den Tieren derartig appliziert, dass sie eine Dosis von 0,1 ml/kg Körpergewicht erhalten. Die Applikation erfolgt einmalig am Tag 0. Es werden nur klinisch gesunde Tiere verwendet.

An Tag 2 werden alle Katzen auf lebende und tote angesogene Zecken überprüft. Die Ergebnisse werden in den Rohdaten festgehalten. Alle lebenden und toten Zecken werden von der Katze entfernt.

25 Am Tag 6, 13, 20 und 27 werden alle Katzen mit jeweils 30 *Haemaphysalis leachi* (15♀, 15♂) pro Katze reinfestiert. Jeweils zwei Tage nach Reinfestation werden alle Katzen auf lebende und tote

angesogene Zecken kontrolliert. Die Ergebnisse werden in den Rohdaten protokolliert. Am zweiten Tag nach Reinfestation werden alle lebenden und toten Zecken von der Katze entfernt.

Eine Formulierung wird als hochwirksam erachtet, wenn am Tag 2 und jeweils am zweiten Tag nach Reinfestation eine Wirksamkeit >90 % festgestellt wird und diese Wirkung über mindestens
5 3 Wochen anhält.

Für die Berechnung der Wirksamkeit wird eine modifizierte Formel nach Abbott benutzt:

$$\text{Wirksamkeit \%} = \frac{\bar{\Omega} \text{ Anzahl Zecken KG} - \bar{\Omega} \text{ Anzahl Zecken BG}}{\bar{\Omega} \text{ Anzahl Zecken KG}} \times 100$$

KG: Kontrollgruppe

BG: Behandlungsgruppe

- 10 Die Arzneimittel in einer Dosierung gemäß den Formulierungsbeispielen 1 bis 4 von 0,1ml/kg als Spot on appliziert, erwiesen sich gegen Haemaphysalis leachi als hochwirksam.

E. Floh- und Zeckenwirksamkeit über 4 bis 5 Wochen

Die Floh- und Zeckenwirksamkeit der erfundungsgemäßen Mittel wurde über vier bis fünf Wochen getestet. Die Versuchsdurchführung folgte der Beschreibung unter den Punkten A bis D.

Tabelle 1 Floh- und Zeckenwirksamkeit des Mittels gemäß Beispiel 1a und 1b am Hund

d 0		Appl. Vol.		Woche 0		Woche 1		Woche 2		Woche 3		Woche 4		Woche 5																			
Beispiel 1a		0,10		100		81		100		94		100		96		100																	
Beispiel 1b		0,10		100		100		100		100		100		99		100																	
1. Infestation: Tag -4																																	
2. Infestation: Tag -1																																	
3. Infestation: Tag 7																																	
4. Infestation: Tag 14																																	
5. Infestation: Tag 21																																	
6. Infestation: Tag 28																																	
7. Infestation: Tag 35																																	
Behandlung		Wirkung ml/kg		Wirkung																													
		CF %		RS %		CF %		RS %		CF %		RS %		CF %		RS %																	
Beispiel 1a		0,10		100		81		100		94		100		96		100																	
Beispiel 1b		0,10		100		100		100		100		99		100		98																	
		d1		d2		d9		d16		d23		d30		d37																			

Appl. Vol. = Aufgetragenes Volumen in ml/kg Körpergewicht

CF % = Wirksamkeit gegen Ctenocephalides felis Flöhe in %, berechnet über geometrische Mittelwertbestimmung gegenüber einer unbehandelten Kontrollgruppe

RS % = Wirksamkeit gegen Rhipicephalus sanguineus Zecken in %, berechnet über geometrische Mittelwertbestimmung gegenüber einer unbehandelten Kontrollgruppe

d = Tag

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Tabelle 2 Floh- und Zeckenwirksamkeit des Mittels gemäß Beispiel 2a, 2b und 2c am Hund

		1. Infestation: Tag -4				2. Infestation: Tag -1				3. Infestation: Tag 7				4. Infestation: Tag 14				5. Infestation: Tag 21				6. Infestation: Tag 28				7. Infestation: Tag 35					
		Appl. Vol.		Woche 0		Woche 1		Woche 2		Woche 3		Woche 4		Woche 5																	
Behandlung	ml/kg	d1	d2	d8	6p	Wirkung	Wirkung	d16	d23	Wirkung	Wirkung	CF %	RS %	CF %	RS %	Wirkung	Wirkung	CF %	RS %	Wirkung	Wirkung	CF %	RS %	Wirkung	Wirkung	CF %	RS %				
Beispiel 2a	0.10	100	100	90	94	RS %	CF %	72	100	100	99	RS %	CF %	100	99	100	100	RS %	CF %	97	94	99	99	RS %	CF %	94	75	100	100	RS %	CF %
Beispiel 2b	0.10	60	61	93	96	RS %	CF %	98	99	100	100	RS %	CF %	100	99	100	100	RS %	CF %	97	94	99	99	RS %	CF %	84	56	79	90	RS %	CF %
Beispiel 2c	0.10	60	61	96	98	RS %	CF %	82	77	90	99	RS %	CF %	58	13	83	89	RS %	CF %	54	33	89	93	RS %	CF %	58	13	83	89	RS %	CF %

Appl. Vol. = Aufgetragenes Volumen in ml / kg Körpergewicht

CF % = Wirksamkeit gegen Ctenocephalides felis Flöhe in %, berechnet über geometrische Mittelwertbestimmung gegenüber einer unbehandelten Kontrollgruppe

RS % = Wirksamkeit gegen Rhipicephalus sanguineus Zecken in %, berechnet über geometrische Mittelwertbestimmung gegenüber einer unbehandelten Kontrollgruppe

d = Tag

- 40 -

Tabelle 3 Floh- und Zeckenwirksamkeit des Mittels gemäß Beispiel 2b und 5 an der Katze

Behandlung		1. Infestation: Tag -2			2. Infestation: Tag 7			3. Infestation: Tag 14			4. Infestation: Tag 21			5. Infestation: Tag 28																						
Beispiel 2b	Beispiel 5	Wirkung ml/kg	CF %	HL %	100	93	91	100	97	91	100	99	80	91	84	97	71	HL %	Wirkung	CF %	HL %															
0.10	0.10	24	100	35	100	93	67	100	97	91	100	99	80	91	84	97	71	HL %	Wirkung	CF %	HL %															

Appl. Vol. = Aufgetragenes Volumen in ml / kg Körpergewicht

CF % = Wirksamkeit gegen Ctenocephalides felis Flöhe in %, berechnet über geometrische Mittelwertbestimmung gegenüber einer unbehandelten Kontrollgruppe

HL % = Wirksamkeit gegen Haemaphysalis leachi Zecken in %, berechnet über geometrische Mittelwertbestimmung gegenüber einer unbehandelten Kontrollgruppe

d = Tag

Tabelle 4 Floh- und Zeckenwirksamkeit des Mittels gemäß Beispiel 9 am Hund

1. Infestation: Tag -4		2. Infestation: Tag -1		3. Infestation: Tag 7		4. Infestation: Tag 14		5. Infestation: Tag 21		6. Infestation: Tag 28		7. Infestation: Tag 35		Woche 0		Woche 1		Woche 2		Woche 3		Woche 4		Woche 5					
Behandlung	ml/kg	Parasite		Wirkung		Wirkung		Wirkung		Wirkung		Wirkung		d0		Appl. Vol.		Woch 0		Woch 1		Woch 2		Woch 3		Woch 4		Woch 5	
		d2	Wirkung	d8	Wirkung	d14	Wirkung	d21	Wirkung	d28	Wirkung	d35	Wirkung	Wirkung	Wirkung	Wirkung	Wirkung	Wirkung	Wirkung	Wirkung	Wirkung	Wirkung	Wirkung	Wirkung	Wirkung	Wirkung	Wirkung		
Beispiel 9	1.30	CF	100	CF	100	CF	100	CF	100	CF	100	CF	100	CF	100	CF	100	CF	100	CF	100	CF	100	CF	100	CF	100		
		HL	89	RS	87	RS	87	RS	87	RS	87	RS	87	RS	87	RS	87	RS	87	RS	87	RS	87	RS	87	RS	87		

Appl. Vol. = Aufgetragenes Volumen in ml / kg Körpergewicht

CF % = Wirksamkeit gegen Ctenocephalides felis Flöhe in %, berechnet über geometrische Mittelwertbestimmung gegenüber einer unbehandelten Kontrollgruppe

HL % = Wirksamkeit gegen Haemaphysalis leachi Zecken in %, berechnet über geometrische Mittelwertbestimmung gegenüber einer unbehandelten Kontrollgruppe

RS % = Wirksamkeit gegen Rhipicephalus sanguineus Zecken in %, berechnet über geometrische Mittelwertbestimmung gegenüber einer unbehandelten Kontrollgruppe

d = Tag

Patentansprüche

1. Mittel enthaltend

a) mindestens einen Wirkstoff der Verbindungsklasse der Pyrethroide und/oder der Verbindungsklasse der Pyrethrine

5 b) MGK 264

in einem Gewichtsverhältnis der Komponenten a : b von mindestens 1:20,

sowie

c) gegebenenfalls weitere Wirkstoffe und

d) gegebenenfalls weitere Hilfs- und Trägerstoffe.

10 2. Mittel gemäß Anspruch 1, enthaltend ein α -Cyanopyrethroid.

3. Mittel gemäß Anspruch 1, enthaltend ein α -Cyanopyrethroid ausgewählt aus Flumethrin, Cyfluthrin und β -Cyfluthrin.

4. Mittel gemäß Anspruch 1, enthaltend ein Neonicotinoid-Insektizid als weiteren Wirkstoff.

5. Mittel gemäß Anspruch 1, enthaltend Imidacloprid.

15 6. Verwendung von Pyrethrinen und/oder Pyrethroiden in Kombination mit MGK 264 zur Herstellung von Mitteln gemäß Anspruch 1 zur Bekämpfung von Parasiten.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/004359

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A01N53/00
//(A01N53/00, 51:00, 47:40, 37:32)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	WO 86/03374 A (ADAMS VETERINARY RES LAB) 19 June 1986 (1986-06-19) page 7, line 29 – page 8, line 9 page 9, line 24 – page 10, line 11 page 10, line 26 – line 28 page 11, line 12 – line 22 page 14, line 1 – line 29 page 16; table 16 page 22; example II page 58, line 26 – page 59, line 28 claims 1,11,31,45	1-3,6
Y	----- -/-	4,5

Further documents are listed in the continuation of box C

Patent family members are listed in annex

° Special categories of cited documents

- *A* document defining the general state of the art which is not considered to be of particular relevance
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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

& document member of the same patent family

Date of the actual completion of the international search

6 October 2004

Date of mailing of the international search report

27/10/2004

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/004359

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1995, ONO YOSHIHIRO ET AL: "Synergistic effect of synthetic synergists on pyrethroids against adults of the cat flea, <i>Ctenocephalides felis</i> (Bouche)" XP002299303 Database accession no. PREV199698561306 cited in the application abstract</p> <p>& JAPANESE JOURNAL OF SANITARY ZOOLOGY, vol. 46, no. 1, 1995, pages 25-30, ISSN: 0424-7086 cited in the application</p> <p>-----</p> <p>EP 0 596 317 A (SUMITOMO CHEMICAL CO) 11 May 1994 (1994-05-11) page 1, line 13 - line 22 page 1, line 36 - line 38</p> <p>-----</p> <p>DATABASE WPI Section Ch, Week 199539 Derwent Publications Ltd., London, GB; Class C03, AN 1995-299442 XP002299306 & JP 07 196420 A (SUMITOMO CHEM CO LTD) 1 August 1995 (1995-08-01) abstract -& DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002299304 retrieved from STN-INTERNATIONAL Database accession no. 123:249228 abstract</p> <p>-----</p> <p>R.H.ROBERTS ET AL.: "Effects of Additives on the Toxicity of Pyrethrins to Stable Flies and Horn Flies" JOURNAL OF ECONOMIC ENTOMOLOGY., vol. 56, no. 5, October 1963 (1963-10), pages 699-702, XP002299302 USENTOMOLOGICAL SOCIETY OF AMERICA. COLLEGE PARK, MARYLAND. page 700; table 2</p> <p>-----</p> <p>WO 02/087338 A (DORN HUBERT ; GILGES MARTIN (DE); HANSEN OLAF (DE); BAYER AG (DE); SIR) 7 November 2002 (2002-11-07) the whole document</p> <p>-----</p> <p>-/-</p>	1-3,6
Y		1-6
X		1,6
X		1,2
X		1,6
Y		1-6

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/004359

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002299305 retrieved from STN-INTERNATIONAL Database accession no. 109:124423 abstract & JP 63 126805 A (NIHON TOKUSHU NOYAKU SEIZO) 30 May 1988 (1988-05-30) ----- AU 666 399 B (VIRBAC AUSTRALIA PTY LIMITED) 8 February 1996 (1996-02-08) page 1, line 3 - page 3, line 15 -----	5
A		1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No PCT/EP2004/004359	
---	--

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 8603374	A 19-06-1986	US 4668666 A		26-05-1987
		GB 2181648 A ,B		29-04-1987
		JP 62500935 T		16-04-1987
		WO 8603374 A1		19-06-1986
EP 0596317	A 11-05-1994	JP 6192020 A		12-07-1994
		AU 662080 B2		17-08-1995
		AU 4884793 A		19-05-1994
		BR 9304420 A		07-06-1994
		CN 1102539 A ,B		17-05-1995
		DE 69307830 D1		13-03-1997
		DE 69307830 T2		15-05-1997
		EG 20266 A		31-05-1998
		EP 0596317 A1		11-05-1994
		ES 2096835 T3		16-03-1997
		KR 249918 B1		01-04-2000
		MX 9306840 A1		31-01-1995
		RU 2129787 C1		10-05-1999
		TR 27910 A		11-10-1995
		ZA 9308002 A		09-06-1994
JP 7196420	A 01-08-1995	NONE		
WO 02087338	A 07-11-2002	DE 10117676 A1		10-10-2002
		BR 0208733 A		20-07-2004
		CA 2443159 A1		07-11-2002
		CZ 20032724 A3		14-01-2004
		EE 200300490 A		15-12-2003
		WO 02087338 A1		07-11-2002
		EP 1379138 A1		14-01-2004
		HU 0303840 A2		29-03-2004
		JP 2004525188 T		19-08-2004
		NO 20034512 A		01-12-2003
		SK 12352003 A3		03-02-2004
		US 2004161441 A1		19-08-2004
JP 63126805	A 30-05-1988	JP 2050660 C		10-05-1996
		JP 7084365 B		13-09-1995
AU 666399	B 08-02-1996	AU 666399 B2		08-02-1996
		AU 4740493 A		31-03-1994
		NZ 248678 A		22-12-1994

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP2004/004359

A. KLASIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 7 A01N53/00

//(A01N53/00, 51:00, 47:40, 37:32)

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B RECHERCHIERTE GEBIETE

Recherchierte Mindestprufstoff (Klassifikationssystem und Klassifikationssymbole)

IPK 7 A01N

Recherchierte aber nicht zum Mindestprufstoff gehorende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl verwendete Suchbegriffe)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr Anspruch Nr
X	WO 86/03374 A (ADAMS VETERINARY RES LAB) 19. Juni 1986 (1986-06-19) Seite 7, Zeile 29 – Seite 8, Zeile 9 Seite 9, Zeile 24 – Seite 10, Zeile 11 Seite 10, Zeile 26 – Zeile 28 Seite 11, Zeile 12 – Zeile 22 Seite 14, Zeile 1 – Zeile 29 Seite 16; Tabelle 16 Seite 22; Beispiel II Seite 58, Zeile 26 – Seite 59, Zeile 28 Ansprüche 1,11,31,45	1-3,6
Y	----- -/-	4,5

Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

Siehe Anhang Patentfamilie

- * Besondere Kategorien von angegebenen Veröffentlichungen
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- *&* Veröffentlichung, die Mitglied derselben Patentfamilie ist

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Absendedatum des internationalen Recherchenberichts

6. Oktober 2004

27/10/2004

Name und Postanschrift der Internationalen Recherchenbehörde
Europäisches Patentamt, P B 5818 Patentlaan 2
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Fax (+31-70) 340-3016

Bevollmächtigter Bediensteter

Lamers, W

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP2004/004359

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN		
Kategorie ^a	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr Anspruch Nr
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1995, ONO YOSHIHIRO ET AL: "Synergistic effect of synthetic synergists on pyrethroids against adults of the cat flea, <i>Ctenocephalides felis</i> (Bouche)" XP002299303 Database accession no. PREV199698561306 in der Anmeldung erwähnt Zusammenfassung	1-3,6
Y	& JAPANESE JOURNAL OF SANITARY ZOOLOGY, Bd. 46, Nr. 1, 1995, Seiten 25-30, ISSN: 0424-7086 in der Anmeldung erwähnt -----	1-6
X	EP 0 596 317 A (SUMITOMO CHEMICAL CO) 11. Mai 1994 (1994-05-11) Seite 1, Zeile 13 - Zeile 22 Seite 1, Zeile 36 - Zeile 38 -----	1,6
X	DATABASE WPI Section Ch, Week 199539 Derwent Publications Ltd., London, GB; Class C03, AN 1995-299442 XP002299306 & JP 07 196420 A (SUMITOMO CHEM CO LTD) 1. August 1995 (1995-08-01) Zusammenfassung -& DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002299304 gefunden im STN-INTERNATIONAL Database accession no. 123:249228 Zusammenfassung -----	1,2
X	R.H.ROBERTS ET AL.: "Effects of Additives on the Toxicity of Pyrethrins to Stable Flies and Horn Flies" JOURNAL OF ECONOMIC ENTOMOLOGY., Bd. 56, Nr. 5, Oktober 1963 (1963-10), Seiten 699-702, XP002299302 USENTOMOLOGICAL SOCIETY OF AMERICA. COLLEGE PARK, MARYLAND. Seite 700; Tabelle 2 -----	1,6
Y	WO 02/087338 A (DORN HUBERT ; GILGES MARTIN (DE); HANSEN OLAF (DE); BAYER AG (DE); SIR) 7. November 2002 (2002-11-07) das ganze Dokument -----	1-6
		-/-

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP2004/004359

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002299305 gefunden im STN-INTERNATIONAL Database accession no. 109:124423 Zusammenfassung & JP 63 126805 A (NIHON TOKUSHU NOYAKU SEIZO) 30. Mai 1988 (1988-05-30) -----	5
A	AU 666 399 B (VIRBAC AUSTRALIA PTY LIMITED) 8. Februar 1996 (1996-02-08) Seite 1, Zeile 3 – Seite 3, Zeile 15 -----	1-6

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen
PCT/EP2004/004359

Im Recherchenbericht angeführtes Patentdokument		Datum der Veröffentlichung		Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
WO 8603374	A	19-06-1986	US GB JP WO	4668666 A 2181648 A ,B 62500935 T 8603374 A1		26-05-1987 29-04-1987 16-04-1987 19-06-1986
EP 0596317	A	11-05-1994	JP AU AU BR CN DE DE EG EP ES KR MX RU TR ZA	6192020 A 662080 B2 4884793 A 9304420 A 1102539 A ,B 69307830 D1 69307830 T2 20266 A 0596317 A1 2096835 T3 249918 B1 9306840 A1 2129787 C1 27910 A 9308002 A		12-07-1994 17-08-1995 19-05-1994 07-06-1994 17-05-1995 13-03-1997 15-05-1997 31-05-1998 11-05-1994 16-03-1997 01-04-2000 31-01-1995 10-05-1999 11-10-1995 09-06-1994
JP 7196420	A	01-08-1995		KEINE		
WO 02087338	A	07-11-2002	DE BR CA CZ EE WO EP HU JP NO SK US	10117676 A1 0208733 A 2443159 A1 20032724 A3 200300490 A 02087338 A1 1379138 A1 0303840 A2 2004525188 T 20034512 A 12352003 A3 2004161441 A1		10-10-2002 20-07-2004 07-11-2002 14-01-2004 15-12-2003 07-11-2002 14-01-2004 29-03-2004 19-08-2004 01-12-2003 03-02-2004 19-08-2004
JP 63126805	A	30-05-1988	JP JP	2050660 C 7084365 B		10-05-1996 13-09-1995
AU 666399	B	08-02-1996	AU AU NZ	666399 B2 4740493 A 248678 A		08-02-1996 31-03-1994 22-12-1994

EFICÁCIA DE CARRAPATICIDAS EM REBANHOS DE BOVINOS LEITEIROS DE MUNICÍPIOS DA REGIÃO CENTRO SUL DO PARANÁ

*EFFICACY OF ACARICIDES IN DAIRY CATTLE HERDS IN SOUTHERN REGION
OF PARANÁ STATE, BRAZIL.*

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RESUMO

Com objetivo de avaliar a eficácia dos principais carrapaticidas de uso externo, utilizados para o controlo do *Boophilus microplus*, foram realizados testes “in vitro” com teleóginas provenientes de bovinos com aptidão leiteira, naturalmente infestados, de 17 propriedades rurais do estado do Paraná. Utilizaram-se acaricidas a base de clorfenvinfós/diclorofenil (0,05%/0,015%), cipermetrina (0,015%), amitraz (0,025%), deltameetrina (0,0025%), alfametrina (0,05%), cipermetrina/clorfenvinfós (0,0625%/0,0345%) e triclorfon/coumafós/cyfluthrin (0,388%/0,005%/0,005%). A eficácia dos carrapaticidas variou de 0,23% a 100%. Todos apresentaram em ao menos uma propriedade eficácia inferior a 95%. A resistência do *B. microplus* a mais de um princípio ativo, foi constatado em seis propriedades. Somente em cinco propriedades os carrapatos apresentaram-se sensíveis a todas as formulações testadas.

PALAVRAS-CHAVE: *Boophilus microplus*, resistência, carrapaticidas, bovinos

SUMMARY

The aim of this study was to evaluate the efficacy of the main acaricides of external use, against *B. microplus*. The test was performed “in vitro” with engorged females from dairy herds, naturally infected, in 17 farms from Paraná State, Brazil. The acaricides utilized were clorfenvinfós/diclorofenil (0,05%/0,015%), cipermetrina (0,015%), amitraz (0,025%), deltameetrina (0,0025%), alfametrina (0,05%), cipermetrina/clorfenvinfós (0,0625%/0,0345%) and triclorfon/coumafós/cyfluthrin (0,388%/0,005%/0,005%). The efficiency of acaricides varied from 0,23% to 100%.

All of them presented a property efficiency less than 95% in one of the farmers. The resistance of *B. microplus* to more than one drug was observed in six farms and only in five, all ticks showed sensibility of the tested formulations.

KEY WORDS: *Boophilus microplus*, resistance, acaricides, cattle

INTRODUÇÃO

A resistência do *B. microplus* a carrapaticidas ocorre em quase todas as regiões onde ele está presente, devido principalmente aos freqüentes tratamentos com produtos químicos e manejo inadequado.

Wharton (1967) afirmou que cepas resistentes a acaricidas, aparecem por seleção e recombinações de genes resistentes em populações de carrapatos expostas a pressões de seleção por inseticidas. Segundo Nolan (1985), basicamente insetos e carrapatos resistentes conseguem escapar da eficiência de um produto de três maneiras: redução na taxa de penetração do carrapaticida no carrapato; mudanças no metabolismo, armazenamento e excreção do produto pelo carrapato; mudanças no local de ação, o que possibilita ao carrapato menor sensibilidade aos efeitos do produto.

No Brasil, o primeiro relato de resistência do *B. microplus* aos arsenicais, ocorreu no Rio Grande do Sul (FREIRE, 1953). Nesse mesmo Estado, estirpes de carrapatos resistentes aos organofosforados foram relatadas por Laranja et al. (1974) e aos piretróides por Alves Branco et al. (1993) e Martins et al. (1995). Alves Branco e Pinheiro (1989) observaram um alto potencial de resistência do *B. microplus* às bases químicas piretróides e organofosforados. Na Zona da Mata em Pernambuco, Faustino et al. (1995) concluíram que o *B. microplus* apresenta resistência aos carrapaticidas

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a base de amitraz e aos piretróides cipermetrina e deltametrina. No Rio de Janeiro, Leite (1988) relatou o primeiro caso de resistência a piretróide, posteriormente, Flausino et al. (1995) observaram resistência ao amitraz e aos piretróides alfametrina, deltametrina e lambda cyhalotrin. Na região Norte do Paraná, Merlini e Yamamura (1998) relataram a resistência ao amitraz, deltametrina e a associação triclorfon/coumaphos. Em São Paulo Mendes e Veríssimo (1999) ratificaram a existência de resistência do carapato *B. microplus* ao piretróide cipermetrina. Em Minas Gerais, Furlong (1999) constatou resistência aos fosforados, imidinas e piretróides. No Planalto Catarinense, Souza et al. (1984) observaram inibição de postura inferior a 74% para todos os carapaticidas fosforados testados, sugerindo a existência de resistência do *B. microplus* em duas das três propriedades estudadas. Souza et al. (1999) verificaram que o amitraz apresentou eficácia superior a 95% em todas as propriedades. Eficácia inferior a 95% foi verificado em 60%, 46,67%, 13,34% e 20% das propriedades, para os carapaticidas coumafós, deltametrina, cipermetrina/clorfenvinfós e alfametrina, respectivamente, o que indica o desenvolvimento de resistência do *B. microplus* a estes produtos. Em Goiás, Silva et al. (2000) relataram resistência a cialotrina e Fernandes (2001) a deltametrina e cipermetrina.

O comportamento das estirpes frente aos diferentes produtos, pode ser aferido usando-se os testes "in vivo" através do banho do animal parasitado, ou "in vitro" tratando-se os ínstares em condições de laboratório.

A inexistência de registro sobre a atuação de carapaticidas e possíveis focos de resistência do *B. microplus* na região Centro Sul do estado do Paraná motivaram a realização do presente trabalho.

MATERIAL E MÉTODOS

Local de coleta:

Os carapatos foram coletados de bovinos com aptidão leiteira, em 17 propriedades localizadas na região Centro Sul do estado do Paraná, municípios de Iraí, Prudentópolis, Imbituva, Rebouças, Mallet, Ivaí e Guamiranga, no período de novembro de 1999 a abril de 2000.

Carapatos:

Em cada propriedade foram coletadas amostras aleatórias, de 120 a 200 teleóginas, acondicionando-as em frascos livres de resíduos de carapaticidas e com

tampa que permitia aeração, mantidas a temperatura ambiente e transportadas ao laboratório de Parasitologia e Doenças Parasitárias do Centro de Ciências Agroveterinárias- CAV/UDESC, onde num período inferior a 24 horas, foram submetidas ao teste "in vitro" de avaliação de eficácia de carapaticidas. O critério adotado para considerar o carapaticida eficaz foi o valor mínimo de 95%, conforme legislação para comercialização de carapaticidas no País (BRASIL, 1990).

Carapaticidas:

Foram utilizados carapaticidas à base de clorfenvinfós/diclorofenil (0,05%/0,015%), cipermetrina (0,015%), amitraz (0,025%), deltametrina (0,0025%), alfametrina (0,05%), cipermetrina/clorfenvinfós (0,0625%/0,0345%) e triclorfon/coumafós/cyfluthrin (0,388%/0,005%/0,005%).

Avaliação da eficácia:

As teleóginas coletadas de cada propriedade foram examinadas e selecionadas as de melhor vitalidade, sendo formados oito grupos de 10 teleóginas de tamanho uniforme. Cada grupo foi pesado e acondicionado em placa de Petri devidamente identificado, imerso durante cinco minutos em um dos carapaticidas. Um dos grupos de teleóginas foi imerso em água e considerado controle.

Após imersão, as teleóginas foram secadas em papel absorvente e colocadas em câmara climatizada do tipo BOD, regulada a temperatura de 27 °C, umidade relativa superior a 80% e escotofase para realização das posturas. Depois de 18 dias mensurou-se a massa dos ovos de cada grupo, em balança de precisão de 0,001g e acondicionada em tubo de ensaio, retornando à câmara climatizada nas condições anteriormente descritas, para se avaliar os índices de ecldibilidade e a eficácia dos produtos.

Foi calculado o Índice de Reprodução (IR) pela fórmula:

$$\text{IR} = \frac{\text{Peso da massa de ovos X \% de eclosão}}{\text{Peso das teleóginas}} \times 20.000$$

A percentagem de eficácia pela seguinte fórmula:

$$\% \text{ de eficácia} = \frac{(\text{IR controle} - \text{IR tratado})}{\text{IR controle}} \times 100$$

RESULTADOS E DISCUSSÃO

Os resultados da avaliação de eficácia de diferentes carrapaticidas em 17 propriedades rurais da região Centro Sul do Paraná estão expressos nas Tabelas 1 e 2.

Na Tabela 1, observa-se a eficácia de 61,17% para o amitraz em apenas uma propriedade, nas demais variou de 97,49% a 100%, o que sugere a ocorrência de resistência naquela propriedade. A resistência do *B. microplus* a este carrapaticida também foi registrado por Glória et al. (1993) e Flausino et al. (1995) no Rio de Janeiro, Merlini e Yamamura (1998) no Paraná e Furlong (1999) em Minas Gerais, o que não foi verificado por Souza et al. (1999) em Santa Catarina.

A análise dos resultados da eficácia do

carrapaticida fosforado, clorfenvinfós/diclorofenil e associações fosforados com piretróides (cipermetrina/clorfenvinfós e triclorfon/coumafós/cyfluthrin), sugere a ocorrência de resistência do carapato em propriedades da região Centro Sul do Paraná. Fato também observado por Laranja et al. (1974, 1989), Arregui et al. (1974), Arteche et al. (1975), no Rio Grande do Sul; Souza et al. (1984, 1999) em Santa Catarina; Borges e Loss (1993) em Goiás; Merlini e Yamamura (1998) no Paraná; Furlong (1999) em Minas Gerais.

Com os piretróides (cipermetrina, deltametrina e alfametrina) foi verificado maior número de propriedades com resistência (53,3%, 18,75% e 18,75%, respectivamente). Resistência a piretróides também foi observado por Alves-Branco et al. (1992, 1993) e Martins et al. (1995) no Rio Grande do Sul; Faustino et

TABELA 1. Percentagem de eficácia de diferentes carrapaticidas por propriedade rural da região Centro Sul do Paraná.

Propriedades	Clorfenvinfós/					Cipermetrina/	Clorfenvinfós/	Triclorfon/
	Diclorofenil	Cipermetrina	Amitraz	Deltametrina	Alfametrina			
1	100,00	39,90	100,00	97,76	100,00	97,74	-	-
2	100,00	70,80	98,72	22,80	50,21	80,32	-	-
3	99,06	0,23	97,49	100,00	21,21	97,39	-	-
4	97,89	57,34	100,00	99,44	100,00	99,65	-	-
5	100,00	100,00	100,00	100,00	100,00	100,00	-	-
6	100,00	59,73	100,00	65,70	100,00	73,15	100,00	-
7	69,06	96,80	61,17	100,00	100,00	100,00	42,09	-
8	100,00	100,00	100,00	100,00	100,00	84,03	100,00	-
9	100,00	99,31	100,00	100,00	100,00	100,00	100,00	-
10	100,00	96,68	100,00	100,00	100,00	100,00	100,00	-
11	100,00	89,99	100,00	100,00	100,00	100,00	100,00	-
12	100,00	97,00	99,90	96,00	98,00	100,00	100,00	-
13	100,00	99,04	100,00	99,27	100,00	100,00	99,91	-
14	100,00	6,25	100,00	96,34	86,41	-	100,00	-
15	100,00	89,56	100,00	-	-	-	-	-
16	100,00	-	100,00	100,00	100,00	100,00	85,11	-
17	-	-	100,00	44,21	100,00	100,00	92,59	-

TABELA 2. Percentagem de eficácia de diferentes carrapaticidas em 17 propriedades rurais da região Centro Sul do Paraná.

% de eficácia	Clorfenvinfós/					Cipermetrina/					Triclorfon/					
	Diclorofenil	Cipermetrina	Amitraz	Deltametrina	Alfametrina	Clorfenvinfós	Coumafós/	Cyfluthrin	Nº	%	Nº	%	Nº	%	Nº	%
95 - 100	15	93,75	7	46,67	16	94,12	13	81,25	13	81,25	12	80,00	8	72,73		
85 - 95	0	-	2	13,33	0	-	0	-	1	6,25	0	-	2	18,18		
75 - 85	0	-	0	-	0	-	0	-	0	-	2	13,33	0	-		
65 - 75	1	6,25	1	6,67	0	-	1	6,25	0	-	1	6,67	0	-		
55 - 65	0	-	2	13,33	1	5,88	0	-	0	-	0	-	0	-		
< 55	0	-	3	20,00	0	-	2	12,50	2	12,50	0	-	1	9,09		
TOTAL	16	100,00	15	100,00	17	100,00	16	100,00	16	100,00	15	100,00	11	100,00		

al. (1995) em Pernambuco; Leite (1988) e Flausino et al. (1995) no Rio de Janeiro; Souza et al. (1999) em Santa Catarina; Furlong (1999) em Minas Gerais; Silva et al. (2000) e Fernandes (2001) em Goiás.

As diferenças de percentuais de propriedades com carapatos resistentes aos carrapaticidas estão provavelmente relacionadas ao uso anterior destes produtos, ao manejo utilizado nas propriedades e aos índices de favorabilidade para o desenvolvimento do *B. microplus* nas diversas regiões.

As eficácia dos carrapaticidas inferiores a 95%, foram interpretadas como resistência e ocorreram em todos os produtos analisados. Esta afirmação tem como suporte o fato dos carrapaticidas na maioria das vezes, dependendo da propriedade, apresentaram eficácia de 100%.

O maior número de casos de resistência foi observado com os piretróides, destacando-se a cipermetrina em 53,33% das propriedades. Estirpes de *B. microplus* com resistência a mais de um carrapaticida foi verificado em seis (35,29%) das propriedades.

Verificou-se que das 17 propriedades apenas em cinco a eficácia dos carrapaticidas testados foi superior a 95% (Tabela 1).

CONCLUSÕES

Na região do Centro Sul do estado do Paraná a resistência do *B. microplus* frente pelo menos um dos carrapaticidas: clorfenvinfós/diclorfenil, cipermetrina, deltametrina, alfametrina, cipermetrina/clorfenvinfós, triclorfon/coumafós/cyflutrin e coumafós, está presente em 70,59% das 17 propriedades analisadas.

Com os piretróides: cipermetrina, deltametrina e alfametrina, foi verificado o maior número de propriedades com *B. microplus* resistente (53,3%, 18,75% e 18,75%, respectivamente).

A eficácia do amitraz variou de 97,49% a 100%, exceto em uma propriedade na qual o *B. microplus* apresentou resistência. Resistência múltipla do *B. microplus*, entre grupos químicos diferentes, ocorreu em 29,41% das propriedades.

REFERÊNCIAS BIBLIOGRÁFICAS

- ALVES-BRANCO, F.P.J., PINHEIRO, A.C. Controle do *Boophilus microplus* com esquema de banhos estratégicos em bovinos Hereford. Bagé: EMBRAPA/CNPq, 1989. (Circular Técnica, 04)
- ALVES-BRANCO, F.P.J., SAPPER, M.F.M., PINHEIRO, A.C. Diagnóstico de resistência de *Boophilus microplus* a piretróides. In: CONGRESSO ESTADUAL DE MEDICINA VETERINÁRIA, 11., 1992, Gramado. Anais..., Gramado: SOVERGS, 1992. p. 44.
- ALVES-BRANCO, F.P.J., SAPPER, M.F.M., PINHEIRO, A.C. Estirpes de *Boophilus microplus* resistentes a piretróides. In: SEMINÁRIO BRASILEIRO DE PARASITOLOGIA VETERINÁRIA, 8., 1993, Londrina. Anais..., Londrina: CBPV, 1993. p. A4.
- ARREGUI, L.A., LARANJA, R.J., ARTECHE, C.C.P. Comparação "in vitro" de duas estirpes de *Boophilus microplus* (Canestrini, 1887), sensível e resistente, quanto ao seu comportamento frente ao Coumaphos 16, dado e concentração que inibe a postura viável de teleóginas em 50%, C.I.P.V. 50. **Boletim do Instituto de Pesquisa Veterinária Desidério Finamor**, Guaíba, v. 2, p. 9-25, 1974.
- ARTECHE, C.C.P., ARREGUI, L.A., LARANJA, R.J. Alguns aspectos da resistência do *Boophilus microplus* (Canestrini, 1887) aos carrapaticidas organofosforados no Rio Grande do Sul (Brasil). **Boletim do Instituto de Pesquisa Veterinária Desidério Finamor**. Guaíba, v. 3, p. 91-101, 1975.
- BORGES, L.M.F., LOSS, A.C.S. Estudos "in vitro" da eficácia de carrapaticidas em amostras de *Boophilus microplus* (Canestrini, 1887) provenientes de microrregiões de Goiânia-GO. In: SEMINÁRIO BRASILEIRO DE PARASITOLOGIA VETERINÁRIA, 7., 1993, Londrina. Anais..., Londrina: CBPV, 1993. p. A5.
- BRASIL. Ministério da Agricultura. Portaria n.90. Normas para produção, controle e utilização de produtos antiparasitários. **Diário Oficial**, 22 jan. 1990, sec.1, col. 2.
- FAUSTINO, M. A. G., PENA, E. J. M., GURGEL, A. E. B. Eficácia "in vitro" de produtos carrapaticidas em fêmeas ingurgitadas de cepas de *Boophilus microplus* da sub-região da Zona da Mata de Pernambuco. **Revista Brasileira de Parasitologia Veterinária**, Campo Grande, v. 4, n. 2, p.58, 1995. Suplemento 1.
- FERNANDES, F.F. Toxicological effects and resistance to pyrethroids in *Boophilus microplus* from Goiás, Brazil. **Arquivo Brasileiro de Medicina Veterinária e Zootecnia**, Belo Horizonte, v.53, n.5, p.538-543, 2001.

- FLAUSINO, J. R. N., GOMES, C. C. G.; GRISI, L. Avaliação da resistência do carapato *Boophilus microplus* ao amitraz e a piretróides, no Município de Seropédica, Rio de Janeiro. **Revista Brasileira de Parasitologia Veterinária**, Campo Grande, v. 4, n.2, p. 45, 1995. Suplemento 1.
- FREIRE, J. J. Arseno e cloro resistência e emprego de tiofosfato de dietilparanitrofenila (Parathion) na luta anticarrapato *Boophilus microplus* (Canestrini, 1887). **Boletim da Diretoria de Produção Animal**, Guaiba, v. 9, n. 17, p. 3-31, 1953.
- FURLONG, J. Diagnóstico de la susceptibilidad de la garrafa del ganado *Boophilus microplus*, a los acaricidas en el estado de Minas gerais, Brazil. In: SEMINARIO INTERNACIONAL DE PARASITOLOGIA ANIMAL, 4., 1999 Anais... Jalisco, CONASAG, INIFAP, INFRAVET, IICA, AMPAVE, FILASA, 1999, p. 41-46
- GLÓRIA, M. A., FLAUSTINO, J. R. N., GRISI, L. Resistência do *Boophilus microplus* (Canestrini, 1887) ao amitraz no estado do Rio de Janeiro com base em testes de imersão de fêmeas ingurgitadas. In: SEMINÁRIO BRASILEIRO DE PARASITOLOGIA VETERINÁRIA, 8., 1993, Londrina. Anais..., Londrina: CBPV, 1993, p. A7.
- LARANJA, R. J., ARTECHE, C. C. P., ARREGUI, L. A. Concentração que inibe a postura viável em 50% de três carrapaticidas organofosforados "in vitro" frente a teleóginas de uma estirpe sensível. **Boletim do Instituto de Pesquisa Veterinária Desidério Finamor**. Guaiba, v. 2, p. 9-14, 1974.
- LARANJA, R. J., MARTINS, J. R., CERESÉR, V. H., CORREA, B. L., FERRAZ, C. Identificação de uma estirpe de *Boophilus microplus* resistentes a carrapaticidas piretróides, no estado do Rio Grande do Sul. In: SEMINÁRIO BRASILEIRO DE PARASITOLOGIA VETERINÁRIA, 6., 1989, Bagé. Anais... Bagé: CBPV, 1989. p. 83.
- LEITE, R. C. *Boophilus microplus* (Canestrini, 1887): Susceptibilidade, uso atual e retrospectivo de carrapaticidas em propriedades das regiões fisiográficas da baixada do Grande Rio e Rio de Janeiro: Uma abordagem epidemiológica. 1988. 122p. Tese (Doutorado em Parasitologia Veterinária), Universidade Federal Rural do Rio de Janeiro. Itaguaí. 1988.
- MARTINS, J.R., CERESÉR, V. H., CORREIA, B.L., ARTECHE, C.C.P., QUEIROLO, M. T. Resistência a carrapaticidas piretróides: Diagnóstico da situação no Rio Grande do Sul. **Revista Brasileira de Parasitologia Veterinária**, Campo Grande, v. 4, n. 2, p. 47, 1995. Suplemento 1.
- MENDES, M.C., VERÍSSIMO, C.J. Carapato *Boophilus microplus* resistente ao piretróide cypermethrin. In: SEMINÁRIO BRASILEIRO DE PARASITOLOGIA VETERINÁRIA, 11., SEMINÁRIO BRASILEIRO DE PARASITOLOGIA VETERINÁRIA DOS PAÍSES DO MERCOSUL, 2., SIMPÓSIO DE CONTROLE INTEGRADO DE PARASITOS DE BOVINOS, 1., 1999, Salvador. Anais... Ilhéus: Universidade Estadual de Santa Cruz, 1999. p.73.
- MERLINI, L.S., YAMAMURA, M.H. Estudo *in vitro* da resistência de *Boophilus microplus* a carrapaticidas na pecuária leiteira do Norte do estado do Paraná. **Semina: Ciências Agrárias**, Santa Maria, v.19, n.1, p.38-44, 1998
- NOLAN, J. Resistance mechanisms to chemical products in arthropods parasites of veterinarian importance. **Veterinary Parasitology**, Amsterdam, v.18, n. 2, p.155-166, 1985.
- SILVA, M.C.L., NEVES SOBRINHO, R.N., LINHARES, G.F.C. Avaliação *in vitro* do clorfenvinifós e da cialotrina sobre o *Boophilus microplus*, colhidos em bovinos da Bacia Leiteira da Microregião de Goiânia-Goiás. **Ciência Animal Brasileira**, Fortaleza, v.1, n.2, p.143-148, 2000.
- SOUZA, A.P. de, PALOSCHI, C.G., BELLATO, V., et al. **Susceptibilidade do carapato a carrapaticidas em diferentes propriedades no Planalto Catarinense**. Florianópolis: EMPASC, 1984. 9p. (EMPASC. Comunicado Técnico, 72).
- SOUZA, A.P. de, BELLATO, V., C.G., SARTOR, et al. Avaliação "in vitro" da eficácia de carrapaticidas no Estado de Santa Catarina. In: SEMINÁRIO BRASILEIRO DE PARASITOLOGIA VETERINÁRIA, 11., SEMINÁRIO BRASILEIRO DE PARASITOLOGIA VETERINÁRIA DOS PAÍSES DO MERCOSUL, 2., SIMPÓSIO DE CONTROLE INTEGRADO DE PARASITOS DE BOVINOS, 1., 1999, Salvador. Anais... Ilhéus: Universidade Estadual de Santa Cruz, 1999. p.81
- WHARTON, R.H. Acaricide resistance and cattle tick control. **Australian Veterinary Journal**, Brunswink, v. 43, p. 394-399, 1967.



Avaliação comparativa da eficácia de fitoterápicos e produtos químicos carrapaticidas no controle do *Boophilus microplus* (Canestrini, 1887) por meio do biocarrapaticidograma

[Comparative evaluation of the efficacy of phytotherapeutics and chemical products against tick in the control of the *Boophilus microplus* (Canestrini, 1887) through engorged female bioassay]

"Artigo Científico/Scientific Article"

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Resumo

Neste estudo objetivou-se avaliar a eficácia de fitoterápicos e produtos químicos carrapaticidas no controle do *Boophilus microplus*. Foram avaliados, *in vitro*, três produtos comerciais para o controle de *Boophilus microplus*, sendo dois à base de cipermetrina + DDVP, um à base de triclorfon + coumafós + cifulutrin e quatro extratos de produtos vegetais, *Cymbopogon citratus* (capim santo), *Lippia alba* (erva cidreira), *Ipomoea asarifolia* (salsa) e o *Azadirachta indica* (óleo de nim a 1%), em três diferentes concentrações. Os resultados revelaram eficácia inferior a 95% para os produtos químicos testados. Os fitoterápicos apresentaram indícios de atividade biológica na mortalidade de fêmeas ingurgitadas e inibição de eclosão, porém, o *Azadirachta indica* alcançou índices de eficácia superiores a 95% em todas as concentrações testadas, sendo a melhor opção dentre os princípios ativos testados neste experimento.

Palavras-chave: *Boophilus microplus*, controle, bovino.

Abstract

The aim of this research was to evaluate the efficacy of plant extracts and chemical products for the control of *Boophilus microplus*. Three commercial products for the control of *Boophilus microplus* were *in vitro* evaluated, chemical compounds of cypermethrin + DDVP and organophosphate as recommended by the manufacturer, and also four plant extracts, *Azadirachta indica* (1%), *Cymbopogon densiflorus*, *Lippia alba* and *Ipomoea asarifolia* at different concentrations. The results showed that the chemical compounds tested had efficacy lower than 95% against the *Boophilus microplus* samples in the experiment. The extracts of all plants have shown some biological activity in the mortality of ingurgitated females and inhibition of egg hatch, however the extract of *Azadirachta indica* presented efficacy higher than 95% in all tested concentrations, being the best sample tested in this experiment.

Key-words: *Boophilus microplus*, control, bovine.

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Introdução

Vários são os métodos desenvolvidos visando o controle de carapato, destacando-se o uso de substâncias químicas acaricidas, cuja desvantagem inclui a diminuição da periodicidade dos tratamentos em virtude da resistência ao princípio ativo, bem como a possibilidade da presença de resíduos nos produtos de origem animal e dos danos ao meio ambiente e à saúde humana (GARCIA e OZAKI, 1993; FRISCH, 1999).

A utilização de produtos naturais e o controle biológico no combate aos carapatos apresentam maior segurança, baixo custo, boa eficácia, nenhum dano ao ecossistema e à saúde humana (FURLONG, 1993). O efeito acaricida do nim indiano (*Azadirachta indica*) sobre o *Boophilus microplus* tem despertado o interesse dos pesquisadores. Webb e David (2002) realizaram teste a campo para avaliar o uso de extratos da semente de nim para controle de espécies de ixodídeos comuns em bovinos e concluíram que é um composto de grande utilidade para este propósito.

Partindo deste pressuposto, objetivou-se, com este trabalho, avaliar a eficácia de fitoterápicos e produtos químicos carrapaticidas no controle do *B. microplus*.

Material e Métodos

Foram colhidas 400 teleóginas de *B. microplus* manualmente, de bovinos naturalmente infestados, pertencentes a duas propriedades, sendo uma no Município de Paudalho, localizado na Zona da Mata Norte e outra em Gravatá, situado Agreste do Estado de Pernambuco. As amostras de carapatos colhidas foram acondicionadas em recipientes plásticos que permitiam aeração adequada para o transporte.

Os testes de eficácia foram realizados no Laboratório de Doenças Parasitárias dos Animais Domésticos do Departamento de Medicina Veterinária - Universidade Federal Rural de Pernambuco, por meio da técnica do biocarrapaticidograma, segundo Drummond et al. (1973).

As teleóginas colhidas foram lavadas em água corrente, submetidas à secagem com

papel absorvente e distribuídos em 10 grupos, fazendo-se uma seleção baseada na aparência, motilidade, integridade física e ingurgitamento (LEITE et al., 1995), procedendo-se a separação por ordem decrescente de tamanho, a fim de se obterem pesos mais homogêneos entre os grupos (ARANTES et al., 1995). Em seguida, os grupos de teleóginas foram pesados em balança analítica e transferidos para as Placas de Petri, identificadas com o peso total das teleóginas, local da colheita e data do teste.

Foram utilizados três produtos químicos comercialmente disponíveis para o controle do *B. microplus*, sendo dois à base de cipermetrina + DDVP (ciper. + DDVP) e um à base de triclorfon + coumafós + ciflutrin (tricl. + coum. + cif) e extratos das plantas capim santo (*Cymbopogon citratus*), salsa (*Ipomoea asarifolia*), erva cidreira (*Lippia alba*) e o nim indiano (*Azadirachta indica*). Dos acaricidas químicos, foram preparadas as soluções segundo a dosagem recomendada pelo fabricante. Para a preparação dos extratos das plantas, foram utilizadas 400g de folhas frescas, sendo submetidas à Trituração em triturador manual doméstico e os homogeneizados foram filtrados em gaze, obtendo-se o extrato bruto. Para o nim indiano, utilizou-se uma formulação comercial do produto óleo de nim emulsionado, na concentração de 1%. Dos extratos brutos das plantas e da formulação comercial do óleo de nim, prepararam-se diluições de 50% em água destilada e 50% em álcool hidratado a 92%, de forma que foram testadas três concentrações de cada planta e do óleo de nim.

Cada grupo de dez teleóginas foi submetido ao banho de imersão, utilizando-se copo descartável de 50 mL, contendo 20 mL das soluções a serem testadas, mantendo-se o líquido em constante agitação durante cinco minutos. Os grupos controles foram imersos em água destilada e álcool. Foram utilizadas duas repetições para cada produto testado e para os grupos controles. Após o banho de imersão, o excesso de acaricida das teleóginas foi retirado usando-se papel absorvente. Em

seguida cada grupo de teleóginas foi recolocado nas placas de Petri de origem, já previamente identificado com a data do início do teste, peso total do grupo, nome do princípio ativo testado, bem como a respectiva concentração, permanecendo à temperatura ambiente, no referido laboratório.

A umidade relativa (acima de 70%) e a temperatura diária no laboratório (25 a 30 °C) foram aferidas através de um termômetro instalado no local. Após o período de oviposição, as posturas foram removidas de cada placa, pesadas em balança analítica e transferidas para seringas descartáveis de 20 mL, devidamente adaptadas, vedadas com tampa de algodão hidrófilo e mantidas nas mesmas condições. Após o período de incubação, foi feita a leitura da eclodibilidade das larvas, adotando-se como parâmetro a verificação visual. Para a avaliação da eficácia dos produtos foram empregadas as fórmulas matemáticas de acordo com Drummond et al. (1971/1973).

$$ER = \frac{\text{Peso da massa dos ovos} \times \% \text{ Eclosão}}{\text{Peso das Fêmeas}} \times 20.000^*$$

ER = Eficiência Reprodutiva
* = Número de larvas por 1 grama de ovos.

$$EP = \frac{ER \text{ Controle} - ER \text{ Produto}}{ER \text{ Controle}} \times 100\%$$

EP = Eficiência do Produto

A eficácia de cada produto foi calculada com base na E.R. do grupo controle-água e do grupo controle-álcool. Para a interpretação dos resultados, considerou-se como eficácia dos princípios ativos o valor mínimo de 95%, conforme legislação pertinente para a comercialização de carrapaticidas no país (Brasil, 1990).

Resultados e Discussão

Os resultados relativos aos produtos químicos testados nas propriedades de Paudalho e Gravatá estão na Tabela 1. Em ambas, nenhum dos produtos químicos testados alcançou o índice necessário para ser considerado eficaz. Na amostra de Paudalho, a cipermetrina + DDVP demonstraram uma

atividade, muito reduzida, na inibição da eclosão (10%) e na mortalidade de teleóginas (15%), enquanto o produto à base de Triclorfon + Coumafós + Ciflutrín não apresentou nenhuma atividade na mortalidade das teleóginas, porém inibiu a eclosão em 70%, alcançando uma efetividade abaixo do permitido.

Na amostra de Gravatá observou-se, com a cipermetrina + DDVP, uma atividade de inibição da eclosão de 50% e uma mortalidade de 20%, enquanto que os produtos à base de Triclorfon + Coumafós + Ciflutrín, demonstraram uma atividade de inibição da eclosão de 15%, e um índice de 40% de mortalidade das teleóginas.

Estes resultados diferem dos registrados por Faustino et al. (1995), em testes *in vitro* com teleóginas, utilizando-se a cipermetrina high cis + DDVP em amostras da cidade do Recife, com valores de 95,58% e 100% em dois testes realizados. Estes mesmos autores testaram compostos desta base, ainda em amostras de *Boophilus microplus* dos Municípios de Limoeiro e Palmares, obtendo, respectivamente, 99,97% e 100% de eficácia. Índices superiores aos observados também foram registrados por Santana (2000) em amostras dos Municípios de Paudalho (95,20%) e Cabo de Santo Agostinho (99,30%), na Zona da Mata de Pernambuco e de Sanharó (100%), na Região Agreste.

Os mesmos produtos formulados pela associação de organofosforados não têm sido amplamente pesquisados na região Nordeste quanto à sua eficácia. No entanto, Santana (2000) avaliou um produto cuja base compunha-se da associação triclorfon + coumafós contra amostra do Município do Cabo de Santo Agostinho, verificando-se 100% de eficácia.

Pode-se observar que o tratamento com álcool, apesar de reduzir a eclodibilidade, propiciou uma eficiência reprodutiva maior do que os carrapaticidas e, consequentemente, uma eficácia menor, em relação às duas formulações comerciais de cipermetrina + DDVP na propriedade Paudalho e a todos os produtos químicos na propriedade de Gravatá.

Tabela 1 - Eficiência de carrapaticidas comerciais em testes *in vitro* com teleóginas de *Boophilus microplus* procedentes de bovinos naturalmente infestados criados nos Municípios de Paudalho e Gravatá-PE.

Grupo/Cidade	Mortalidade (%)	Eclosão (%)	Eficiência reprodutiva	Eficiência do produto (%)	
				Água*	Álcool**
Paudalho					
Controle/água	0,00	100,00	1340217,13	-	-
Controle/álcool	0,00	25,00	290026,10	78,36	-
Ciper. + DDVP (1)	0,00	10,00	98785,02	92,63	65,94
Ciper. + DDVP (2)	15,00	10,00	98803,79	93,00	67,65
Tricl. + Coum. + Cif.	0,00	70,00	656633,54	51,00	0,00
Gravatá					
Controle/água	0,00	100,00	1585867,40	-	-
Controle/álcool	0,00	45,00	652779,90	58,84	-
Ciper. + DDVP (1)	15,00	50,00	231923,75	85,37	64,47
Ciper. + DDVP (2)	20,00	10,00	573507,45	63,84	12,14
Tricl. + Coum. + Cif.	40,00	15,00	147397,55	90,71	77,42

* Cálculo baseado no controle-água;

** Cálculo baseado no controle-álcool;

Ciper = Cipermetrina; (1) = Produto Comercial nº 1; (2) = Produto Comercial nº 2; Tricl.+ Coum.+ Cif. = Triclorfon+ Coumafós+ Ciflutrín.

Os resultados relativos aos fitoterápicos testados nas propriedades de Paudalho e Gravatá estão nas Tabelas 2 a 5. A Tabela 2 refere-se aos resultados obtidos com o *Cymbopogon citratus*, cuja efetividade não foi expressiva ao ser comparada com produtos químicos. Observou-se 10% de mortalidade das teleóginas contra índices que variaram de 15 a 20% para cipermetrina + DDVP e 40% alcançados pelo triclorfon + coumafós + ciflutrín. Observou-se inibição da eclosão, embora os valores sejam inferiores aos comparados com compostos químicos.

Os resultados obtidos são inferiores aos registrados por Carneiro et al. (2000), cuja eficiência do produto foi de 68,78%, em amostra de teleóginas de *Boophilus microplus* da Universidade Federal de Alfenas - MG. Esta diferença se deve provavelmente ao fato de que os referidos autores usaram o óleo essencial da planta, possibilitando uma melhor atividade do princípio ativo, enquanto que no presente estudo foi utilizado o extrato bruto em solução aquosa e alcoólica e testada logo

após o preparo.

Verificou-se que as soluções alcoólicas e aquosas, apesar da pequena diferença, apresentaram maior eficácia que o extrato bruto em ambas as amostras de *Boophilus microplus*, indicando um possível efeito potencializador, haja vista que o álcool puro apresentou certo grau de efetividade. No entanto, pode significar também, uma ação sobre a liberação do princípio ativo.

Na Tabela 3 constam os dados da *Ipomoea asarifolia*, cujos resultados continuam inferiores aos dos produtos químicos analisados. A solução alcoólica da salsa, na propriedade de Paudalho alcançou 69,52% de eficiência, indicando uma possibilidade a ser pesquisada para o controle de *Boophilus microplus*. Não sendo verificado ação letal sobre as teleóginas e no que se refere à inibição da eclosão, ocorreu o mesmo observado com o *Cymbopogon citratus*. O efeito do álcool foi evidentemente demonstrado nas formulações alcoólicas desta planta.

Tabela 2 - Eficiência carrapaticida de extratos aquosos e alcoólicos de *Cymbopogon citratus* em testes *in vitro* com teleóginas de *Boophilus microplus* procedentes de bovinos naturalmente infestados criados nos Municípios de Paudalho e Gravatá-PE.

Grupo/Cidade	Mortalidade (%)	Eclosão (%)	Eficiência reprodutiva	Eficiência do produto (%)	
				Água*	Álcool**
Paudalho					
Controle/água	0,00	100,00	1340217,30	-	-
Controle/álcool	0,00	25,00	290026,10	78,36	-
Extrato bruto	10,00	75,00	1041935,90	22,25	0,00
Sol. aquosa a 50%	10,00	70,00	962698,57	32,95	0,00
Sol. alcoólica a 50%	0,00	50,00	695516,60	48,10	0,00
Gravatá					
Controle/água	0,00	100,00	1585867,40	-	-
Controle/álcool	0,00	45,00	652779,90	58,84	-
Extrato bruto	10,00	85,00	1257373,30	20,71	0,00
Sol. aquosa a 50%	10,00	65,00	1019571,30	35,70	0,00
Sol. alcoólica a 50%	0,00	55,00	835902,36	47,29	0,00

* Cálculo baseado no controle-água;

** Cálculo baseado no controle-álcool.

Tabela 3 - Eficiência carrapaticida de extratos aquosos e alcoólicos de *Ipomoea asarifolia* em testes *in vitro* com teleóginas de *Boophilus microplus* procedentes de bovinos naturalmente infestados criados nos Municípios de Paudalho e Gravatá-PE.

Grupo/Cidade	Mortalidade (%)	Eclosão (%)	Eficiência reprodutiva	Eficiência do produto (%)	
				Água*	Álcool**
Paudalho					
Controle/água	0,00	100,00	1340217,30	-	-
Controle/álcool	0,00	25,00	290026,10	78,36	-
Extrato bruto	0,00	75,00	1022063,50	23,73	0,00
Sol. aquosa a 50%	0,00	65,00	748141,97	44,17	0,00
Sol. alcoólica a 50%	0,00	35,00	408459,81	69,52	0,00
Gravatá					
Controle/água	0,00	100,00	158586,40	-	-
Controle/álcool	0,00	45,00	652779,90	58,84	-
Extrato bruto	0,00	75,00	1182154,30	25,45	0,00
Sol. aquosa a 50%	0,00	65,00	997838,24	37,07	0,00
Sol. alcoólica a 50%	0,00	55,00	834090,30	47,40	0,00

* Cálculo baseado no controle-água;

** Cálculo baseado no controle-álcool.

Os resultados obtidos em relação a *Lippia alba* demonstraram pouca influência nos parâmetros analisados (Tabela 4) para se denotar atividade carrapaticida expressiva, com índices de eficácia que não chegaram a atingir os 30%. Embora tenha sido observada certa atividade na inibição da eclosão, os

valores de ER foram extremamente altos, se comparados com os controles.

Avaliando-se a atual situação do controle químico do *Boophilus microplus* e levando-se em consideração as vantagens do produto natural, os resultados observados em relação ao *Cymbopogon citratus* e *Ipomoea*

asarifolia, esta última apresentou eficácia de 69,52%, podendo significar uma atividade considerável. Uma grande possibilidade de existência de princípios ativos com atividades carrapaticidas podem ser encontradas nestas

plantas. No entanto, devem ser complementadas pesquisas mais aprofundadas para fracionamento dos extratos, identificação, purificação e caracterização estrutural das substâncias.

Tabela 4 - Eficiência carrapaticida de extratos aquosos e alcoólicos de *Lippia alba* em testes *in vitro* com teleóginas de *Boophilus microplus* procedentes de bovinos naturalmente infestados criados nos Municípios de Paudalho e Gravatá-PE.

Grupo/Cidade	Mortalidade (%)	Eclosão (%)	Eficiência reprodutiva	Eficiência do produto (%)	
				Água*	Álcool**
Paudalho					
Controle/água	0,00	100,00	1340210,30	-	-
Controle/álcool	0,00	25,00	290026,10	58,84	-
Extrato bruto	0,00	85,00	1059156,90	15,17	0,00
Sol. aquosa a 50%	0,00	85,00	890985,17	24,75	0,00
Sol. alcoólica a 50%	0,00	75,00	1043029,70	29,02	0,00
Gravatá					
Controle/água	0,00	100,00	1585867,40	-	-
Controle/álcool	0,00	45,00	652779,90	58,84	-
Extrato bruto	0,00	85,00	134525,20	15,17	0,00
Sol. aquosa a 50%	0,00	75,00	1352426,70	24,75	0,00
Sol. alcoólica a 50%	0,00	75,00	1125608,60	29,02	0,00

* Cálculo baseado no controle-água;

** Cálculo baseado no controle-álcool.

O resultado dos testes com *Azadirachta indica* (Tabela 5) demonstraram atividade na mortalidade de teleóginas e inibição da eclosão, chegando a atingir 100%, quando se utilizou a formulação comercial pura e índice de 95% com as soluções aquosa e alcoólica em ambas as amostras de carrapato analisadas. Estes resultados são superiores àqueles publicados por Silva et al. (2002), comparando duas formulações de óleo de nim, observando percentuais de ecldobilidade de 50 e 10%, respectivamente, para as formulações 1 e 2 na concentração de 50%.

Os índices de eficácia obtidos revelaram excelente efetividade no controle do *Boophilus microplus* para a formulação utilizada, observando-se níveis acima de 95%, tanto para a solução aquosa quanto para a alcoólica e eficácia de 100% para o óleo emulsionado puro em ambas as amostras. Estes dados confirmam os reportados por Silva et al.

(2002), em uma das formulações testadas, cujo índice de eficácia foi de 96,33%. No entanto, a outra formulação analisada por estes autores, apresentou eficácia de 68,35%, inferior ao resultado obtido.

Mansingh e Williams (1998) apud Silva et al. (2002), em teste *in vitro* com a *Azadirachta indica* contra *B. microplus*, demonstraram seus efeitos sobre a produção de ovos e ecldobilidade. A efetividade desta planta também já foi avaliada em teste de campo sobre diferentes espécies de ixodídeos, obtendo-se menores contagens de teleóginas nos animais tratados com extratos da semente da planta que naqueles banhados com água (WEBB e DAVID, 2002). Estes autores concluíram que extratos de nim podem ter um papel significante na redução do uso indiscriminado de químicos sintéticos potencialmente prejudiciais ao homem animais e ao ecossistema.

Tabela 5 - Eficiência carrapaticida de extratos aquosos e alcoólicos de *Azadirachta indica* em testes *in vitro* com teleóginas de *Boophilus microplus* procedentes de bovinos naturalmente infestados criados nos municípios de Paudalho e Gravatá-PE.

Grupo/Cidade	Mortalidade (%)	Eclosão (%)	Eficiência reprodutiva	Eficiência do produto (%)	
				Água*	Álcool**
Paudalho					
Controle/água	0,00	100,00	1340217,30	-	-
Controle/álcool	0,00	25,00	290026,10	78,36	-
Extrato bruto	40,00	0,00	0,00	100,00	100,00
Sol. aquosa a 50%	0,00	5,00	595175,06	95,55	79,47
Sol. alcoólica a 50%	15,00	5,00	482758,62	96,39	83,35
Gravatá					
Controle/água	0,00	100,00	1585867,40	-	-
Controle/álcool	0,00	45,00	652779,90	58,84	-
Extrato bruto	0,00	0,00	0,00	100,00	100,00
Sol. aquosa a 50%	0,00	5,00	63946,60	95,96	90,20
Sol. alcoólica a 50%	20,00	5,00	152000,00	97,41	92,96

* Cálculo baseado no controle-água;

** Cálculo baseado no controle-álcool.

Nas condições em que este trabalho foi realizado, os resultados obtidos permitem concluir que a solução comercial de óleo de nim a 1 % (*Azadirachta indica*) apresenta maior eficácia quando comparada aos outros princípios ativos testados.

Referências

ARANTES, G. et al. O carapato do bovino, *Boophilus microplus*, no município de Uberlândia, MG. Análise da sua resistência contra carrapaticidas comerciais. **Revista Brasileira de Parasitologia Veterinária**, v.4, n.2, p.89-93, 1995.

BRASIL. Ministério da Agricultura. Portaria n.90, de 04 de dezembro de 1989. Normas para produção, controle e utilização de produtos antiparasitários. Diário Oficial, 22 jan. 1990, séc. 1, col. 2.

CARNEIRO, M.C.B. et al. Susceptibilidade *in vitro* de fêmeas ingurgitadas de *B. microplus* a alguns óleos vegetais. In: SIMPÓSIO DE PLANTAS MEDICINAIS DO BRASIL, XVI, 2000, Recife, **Anais...**, Recife, 2000. p.264.

DRUMMOND, R.O. et al. Laboratory testing of insecticides for control of the winter tick. **Journal of Economic Entomology**, v.64, p. 686-688, 1971.

DRUMMOND, R.O. et al. *Boophilus annulatus* and *Boophilus microplus*: Laboratory tests of insecticides. **Journal of Economic Entomology**, v.66, p.130, 1973.

FAUSTINO, M.A.G. et al. Eficácia *in vitro* de produtos carrapaticidas em fêmeas ingurgitadas de cepas de *Boophilus microplus* da sub-região da Zona da Mata de Pernambuco. In: SEMINÁRIO DE MEDICINA VETERINÁRIA, 8. 1995, Campo Grande, **Anais...** Campo Grande, 1995, p.58.

FRISCH, J. E. Towards a permanent solution for controlling cattle ticks. Int. **Journal of Parasitology**, v.29, p. 57-71, 1999.

FURLONG, J. Controle do carapato dos bovinos na região Sudeste do Brasil. **Caderno Técnico da Escola de Veterinária**, UFMG, n.8, p.46-61, 1993.

GARCIA, J.F.; OZAKI, L. S. Perspectivas de controle imunológico de carapatos de rebanhos bovinos. **A Hora Veterinária**, v.7, p.9-12, 1993.

LEITE, R.C. et al. *In vitro* susceptibility of engorged females from different populations of *Boophilus microplus* to commercial acaricide. **Revista Brasileira de Parasitologia Veterinária**, v.4, n.2, p.283-294, 1995.

SANTANA, V.L. A. Situação do controle químico do *Boophilus microplus* (Canestrini, 1887) das sub-regiões da Zona da Mata e Agreste do Estado de Pernambuco com base em testes *in vitro* de eficácia de carrapaticidas em fêmeas ingurgitadas. Recife, 2000, 79 f. Dissertação (Mestrado em Ciência Veterinária) –

Programa de Pós-Graduação em Ciência Veterinária, Universidade Federal Rural de Pernambuco.

SILVA, W.J. et al. Avaliação de duas formulações comerciais de *Azadirachta indica* (Meliaceae) sobre fêmeas de *Boophilus microplus* (Acari: Ixodidae). In: CONGRESSO BRASILEIRO DE PARASITOLOGIA VETERINÁRIA, 12. 2002. Rio de Janeiro. **Anais...** Rio de Janeiro: Colégio Brasileiro de Parasitologia Veterinária, 2002. CD-ROM.

WEBB, E. C.; DAVID, M. The efficacy of neem seeds extract (*Azadirachta indica*) to control tick in Tswana, Simmental and Brahman cattle. **South African Journal of Animal Science**, v.32, n.1, p.1-6, 2002.