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(54) Titre : PYRAZOLYL BENZENESULFONAMIDES SUBSTITUES DESTINES A ETRE UTILISES DANS DES THERAPIES VETERINAIRES COMME AGENTS ANTI-INFLAMMATOIRES

(54) Title: SUBSTITUTED PYRAZOLYL BENZENESULFONAMIDES FOR USE IN VETERINARY THERAPIES AS ANTIINFLAMMATORY AGENTS

(57) Abrégé/Abstract:
A method of using pyrazolyl benzenesulfonamide compounds in treating inflammation and inflammation-related disorders in animals.

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(57) Abstract

A method of using pyrazolyl benzenesulfonamide compounds in treating inflammation and inflammation-related disorders in animals.

SUBSTITUTED PYRAZOLYL BENZENESULFONAMIDES FOR USE IN VETERINARY THERAPIES AS ANTIINFLAMMATORY AGENTS

FIELD OF THE INVENTION

This invention is in the field of methods for treating inflammation and inflammation-associated disorders, such as arthritis, in animals.

BACKGROUND OF THE INVENTION

There are few drugs that can be successfully used in veterinary medicine for the treatment of inflammation [Compendium of Veterinary Products, (K. Bennett 2d ed. 1993)]. See also The Merck Veterinary Manual, 1504-1509 (7th ed. 1991)

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG_2, PGH_2 and PGE_2, has been a common target of anti-inflammatory drug discovery. However, common non-steroidal anti-inflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential [C. MacAllister et al., ***JAVMA***, **202**, 71 (1993). An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved [R. McDonald and V. Langston, *Use of Corticosteroids and Non-steroidal Anti-inflammatory Agents*, in Textbook of Veterinary Internal Medicine, 284 (Ettinger and Feldman 4th ed. 1995)].

Carprofen has been described for the treatment of osteoarthritis in dogs [P. Vasseur et al., ***JAVMA***, **206**, 807 (1995)]. Piroxicam has been used in treatment of dogs with

carcinomas [D. Knapp et al., *J. of Vet. Int. Med.*, **8**, 273 (1994)].

Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX) [S. Rubin and M. Papich, *Nonsteroidal Anti-inflammatory Drugs*, in Current Veterinary Therapy, **X**, 47-54 (1989)]. The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase II (COX II)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.

Pyrazoles have been described for use in the treatment of inflammation. U.S. Patent No. 5,134,142 to Matsuo et al describes 1,5-diaryl pyrazoles, and specifically, 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-trifluoromethyl pyrazole, as having anti-inflammatory activity.

U.S. Patent No. 3,940,418 to R. Hamilton describes tricyclic 4,5-dihydrobenz[g]indazoles as antiinflammatory agents. In addition, R. Hamilton [*J. Heterocyclic Chem.*, **13**, 545 (1976)] describes tricyclic 4,5-dihydrobenz[g]indazoles as antiinflammatory agents. U.S. Patent No. 5,134,155 describes fused tricyclic pyrazoles having a saturated ring bridging the pyrazole and a phenyl radical as HMG-CoA reductase inhibitors. European publication EP 477,049, published Mar. 25, 1992, describes [4,5-dihydro-1-phenyl-1H-benz[g]indazol-3-yl]amides as having antipsychotic activity. European publication EP 347,773, published Dec. 27, 1989, describes [4,5-dihydro-1-phenyl-1H-benz[g]indazol-3-yl]propanamides as immunostimulants. M. Hashem et al [*J. Med. Chem.*, **19**, 229 (1976)] describes fused tricyclic pyrazoles, having a saturated ring bridging the pyrazole and a phenyl radical, as antibiotics.

Certain substituted pyrazolyl-benzenesulfonamides have been described in the literature as synthetic intermediates. Specifically, 4-[5-(4-chlorophenyl)-3-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide has been prepared from a pyrazoline compound as an intermediate for compounds having hypoglycemic activity [R. Soliman et al, *J. Pharm. Sci.*, **76**, 626 (1987)]. 4-[5-[2-(4-Bromophenyl)-2*H*-1,2,3-triazol-4-yl]-3-methyl-1*H*-pyrazol-1-yl]benzenesulfonamide has been prepared from a pyrazoline compound and described as potentially having hypoglycemic activity [H. Mokhtar, *Pak. J. Sci. Ind. Res.*, **31**, 762 (1988)]. Similarly, 4-[4-bromo-5-[2-(4-chlorophenyl)-2*H*-1,2,3-triazol-4-yl]-3-methyl-1*H*-pyrazol-1-yl]benzenesulfonamide has been prepared [H. Mokhtar et al, *Pak. J. Sci. Ind. Res.*, **34**, 9 (1991)].

The phytotoxicity of pyrazole derivatives is described [M. Cocco et al, *Il. Farmaco-Ed. Sci.*, **40**, 272 (1985)], specifically for 1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazole-3,4-dicarboxylic acid.

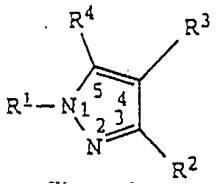
The use of styryl pyrazole esters for antidiabetes drugs is described [H. Mokhtar et al, *Pharmazie*, **33**, 649-651 (1978)]. The use of styryl pyrazole carboxylic acids for antidiabetes drugs is described [R. Soliman et al, *Pharmazie*, **33**, 184-5 (1978)]. The use of 4-[3,4,5-trisubstituted-pyrazol-1-yl]benzenesulfonamides as intermediates for sulfonylurea anti-diabetes agents is described, and specifically, 1-[4-(aminosulfonyl)phenyl]-3-methyl-5-phenyl-1*H*-pyrazole-4-carboxylic acid [R. Soliman et al, *J. Pharm. Sci.*, **72**, 1004 (1983)]. A series of 4-[3-substituted methyl-5-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamides has been prepared as intermediates for anti-diabetes agents, and more specifically, 4-[3-methyl-5-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide [H. Feid-Allah, *Pharmazie*, **36**, 754 (1981)]. In addition, 1-(4-[aminosulfonyl]phenyl)-5-phenylpyrazole-3-carboxylic acid has been prepared from the above described 4-[3-methyl-5-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide compound [R. Soliman et al, *J. Pharm. Sci.*, **70**, 602 (1981)].

However, pyrazolyl benzenesulfonamide compounds have not been previously described as veterinary agents.

WO 95/15316 describes the use of pyrazolyl benzenesulfonamides for the treatment of inflammation or inflammation disorders. WO 95/15318 describes the use of pyrazolyl compounds for the treatment of inflammation and inflammation disorders. EP-A 0 554 829 describes the use of 1,5-diarylpyrazlyl compounds for the treatment of inflammation and inflammation disorders.

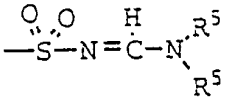
DESCRIPTION OF THE INVENTION

A class of compounds useful in treating veterinary inflammation-related disorders is defined by Formula I:



(I)

wherein R^1 is selected from aryl and heteroaryl, wherein R^1 is substituted at a substitutable position with one or more radicals selected from sulfamyl, halo, alkyl, alkoxy, hydroxyl, haloalkyl and



;

wherein R^2 is selected from hydrido, halo, alkyl, haloalkyl, cyano, nitro, formyl, carboxyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, cyanoalkyl, alkoxycarbonylcyanoalkenyl, aminocarbonylalkyl, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, cycloalkylaminocarbonyl, heterocyclicaminocarbonyl, carboxyalkylaminocarbonyl, aralkoxycarbonylalkylaminocarbonyl, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, haloaralkyl, carboxyhaloalkyl, alkoxycarbonylhaloalkyl, aminocarbonylhaloalkyl, alkylaminocarbonylhaloalkyl, N-alkylamino, N,N-dialkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, N-alkylaminoalkyl, N,N-dialkylaminoalkyl, N-arylaminoalkyl, N-

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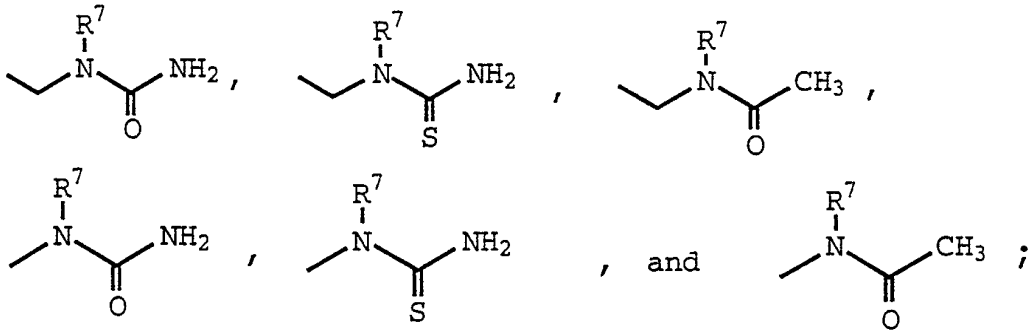
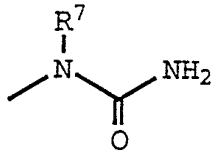
aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N,N-dialkylaminosulfonyl, N-alkyl-N-arylaminosulfonyl, heterocyclic,



wherein R^3 is selected from hydrido, alkyl, halo, haloalkyl, cyano, nitro, formyl, carboxyl, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, aminocarbonyl, alkoxy, N-alkylamino, N,N-dialkylamino, aminocarbonylalkyl, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N,N-dialkylaminosulfonyl, N-alkyl-N-arylaminosulfonyl, cycloalkyl, heterocyclic, heterocyclicalkyl and aralkyl;

wherein R^4 is selected from aralkenyl, aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkyl, alkenyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, aminocarbonyl, N-alkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, sulfamyl, N-alkylaminosulfonyl, amino, N-alkylamino,

N,N-dialkylamino, heterocyclic, cycloalkylalkyl, nitro, acylamino,



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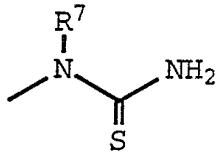
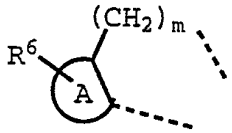


;

or wherein R^3 and R^4 together form



;

wherein m is 1 to 3, inclusive;

wherein A is selected from phenyl and five or six membered heteroaryl;

wherein R^5 is alkyl;

wherein R^6 is one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, aminocarbonyl, N-alkylaminocarbonyl, N-arylaminocarbonyl, alkyl, alkenyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, haloalkyl, hydrido, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, sulfamyl, N-alkylaminosulfonyl, amino, N-alkylamino, N,N-dialkylamino, heterocyclic, cycloalkylalkyl, nitro and acylamino; and

wherein R^7 is selected from hydrido, alkyl, aryl and aralkyl;

or a pharmaceutically-acceptable salt thereof.

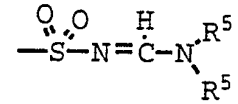
Compounds of Formula I would be useful for, but not limited to, the treatment of inflammation in an animal, and for treatment of other inflammation-associated disorders, such as, as an analgesic in the treatment of pain, or as an antipyretic for the treatment of fever. For example, compounds of Formula I would be useful to treat inflammation of the musculoskeletal system, including chronic inflammation of hard and soft tissue, joint disease and traumatic

injury. Compounds of Formula I would be useful to treat arthritis, including but not limited to rheumatoid arthritis, gouty arthritis, and osteoarthritis, myositis, and tendinitis. Such compounds of Formula I would be useful in the treatment of equine colic, mastitis, peritonitis, and skin related conditions such as burns and dermatitis. Compounds of Formula I also would be useful to treat gastrointestinal conditions such as gastritis, and ulcerative colitis, viral and bacterial infections of the GI tract, and for the prevention of cancers, including colorectal cancer. Compounds of Formula I would be useful in treating inflammation in such diseases as vascular diseases, gingivitis, hypersensitivity, conjunctivitis and other eye inflammation, swelling occurring after injury or surgery, myocardial ischemia, and the like. The compounds are useful as antiinflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects.

These compounds are useful for treatment of companion animals, exotic animals and farm animals, including mammals, rodents, avians, and the like. More preferred animals include horses, dogs, and cats.

The present invention preferably includes compounds which selectively inhibit cyclooxygenase II over cyclooxygenase I. Preferably, the compounds have a cyclooxygenase II IC_{50} of less than about 0.2 μM, and also have a selectivity ratio of cyclooxygenase II inhibition over cyclooxygenase I inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase I IC_{50} of greater than about 1 μM, and more preferably of greater than 10 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

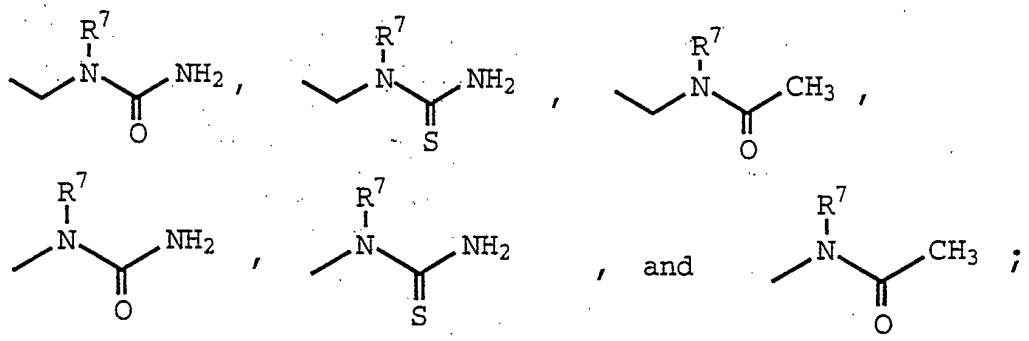
A preferred class of compounds consists of those compounds of Formula I wherein R^1 is selected from aryl selected from phenyl, naphthyl and biphenyl, and five- or six-membered heteroaryl, wherein R^1 is substituted at a substitutable position with one or more radicals selected from sulfamyl, halo, lower alkyl, lower alkoxy, hydroxyl, lower haloalkyl and



;

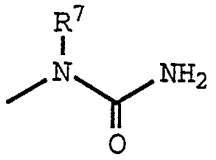
wherein R^2 is selected from hydrido, halo, lower alkyl, lower haloalkyl, cyano, nitro, formyl, carboxyl, lower alkoxycarbonyl, lower carboxyalkyl, lower alkoxycarbonylalkyl, amidino, cyanoamidino, lower cyanoalkyl, lower alkoxycarbonylcyanoalkenyl, aminocarbonyl, lower alkoxy, lower aryloxy, lower aralkoxy, lower aminocarbonylalkyl, lower N-alkylaminocarbonyl, N-arylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-arylaminocarbonyl, lower cycloalkylaminocarbonyl, lower heterocyclicaminocarbonyl, lower carboxyalkylaminocarbonyl, lower aralkoxycarbonylalkylaminocarbonyl, lower haloaralkyl, lower carboxyhaloalkyl, lower alkoxycarbonylhaloalkyl, lower aminocarbonylhaloalkyl, lower alkylaminocarbonylhaloalkyl, lower alkylcarbonyl, lower alkylcarbonylalkyl, lower alkylamino, lower N,N-dialkylamino, N-arylamino, lower N-aralkylamino, lower N-alkyl-N-aralkylamino, lower N-alkyl-N-arylamino, lower aminoalkyl, lower N-alkylaminoalkyl, lower N,N-dialkylaminoalkyl, lower N-arylaminoalkyl, lower N-aralkylaminoalkyl, lower N-alkyl-N-aralkylaminoalkyl, lower N-alkyl-N-arylaminoalkyl, arylthio, lower aralkylthio, lower hydroxyalkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower N-alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl,

lower N,N-dialkylaminosulfonyl, lower N-alkyl-N-arylaminosulfonyl, heterocyclic,



wherein R^3 is selected from hydrido, lower alkyl, halo, lower haloalkyl, cyano, nitro, formyl, carboxyl, lower alkoxycarbonyl, lower carboxyalkyl, lower alkoxycarbonylalkyl, amidino, cyanoamidino, aminocarbonyl, lower alkoxy, lower N-alkylamino, lower N,N-dialkylamino, lower aminocarbonylalkyl, lower N-alkylaminocarbonyl, lower N-arylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-arylaminocarbonyl, lower alkylcarbonyl, lower alkylcarbonylalkyl, lower hydroxyalkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower N-alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, lower N,N-dialkylaminosulfonyl, lower N-alkyl-N-arylaminosulfonyl, lower cycloalkyl, heterocyclic, lower heterocyclicalkyl and lower aralkyl; wherein R^4 is selected from lower aralkenyl, aryl, lower cycloalkyl, lower cycloalkenyl and five to ten membered heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkenyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower N-alkylaminocarbonyl, N-arylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-arylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy,

sulfamyl, lower N-alkylaminosulfonyl, amino, lower N-alkylamino, lower N,N-dialkylamino, five- or six-membered heterocyclic, lower cycloalkylalkyl, nitro, acylamino,



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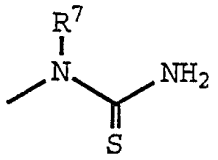
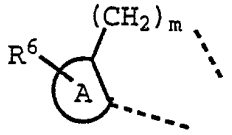


;

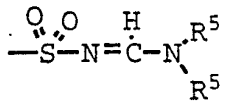
or wherein R^3 and R^4 together form



;

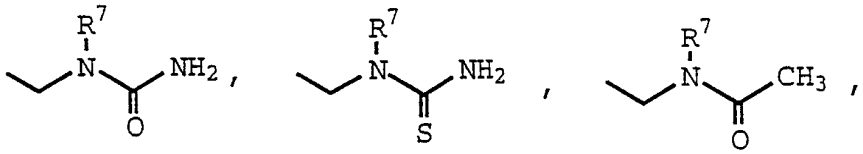
wherein m is 1 to 3, inclusive; wherein A is selected from phenyl and five or six membered heteroaryl; wherein R^5 is lower alkyl; wherein R^6 is one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower N-alkylaminocarbonyl, N-arylaminocarbonyl, lower alkyl, lower alkenyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-arylaminocarbonyl, lower haloalkyl, hydrido, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, sulfamyl, lower N-alkylaminosulfonyl, amino, lower N-alkylamino, lower N,N-dialkylamino, five- or six membered heterocyclic, lower cycloalkylalkyl, nitro and acylamino; and wherein R^7 is selected from hydrido, lower alkyl, aryl and lower aralkyl; or a pharmaceutically-acceptable salt thereof.

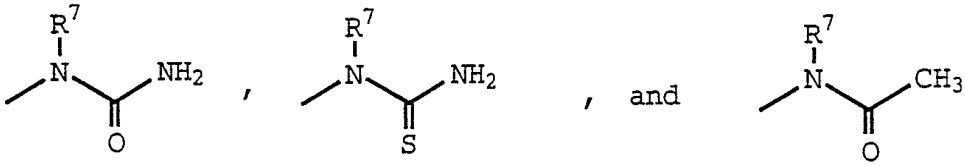
A more preferred class of compounds consists of those compounds of Formula I wherein R^1 is phenyl, wherein R^1 is substituted at a substitutable position with one or more radicals selected from sulfamyl, halo, lower alkyl, lower alkoxy, hydroxyl, lower haloalkyl and



;

wherein R^2 is selected from hydrido, lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, lower alkoxycarbonylcyanoalkenyl, lower haloaralkyl, lower carboxyhaloalkyl, lower alkoxycarbonylhaloalkyl, lower aminocarbonylhaloalkyl, lower alkylaminocarbonylhaloalkyl, lower N-alkylamino, lower N,N-dialkylamino, N-arylamino, lower N-aralkylamino, lower N-alkyl-N-aralkylamino, lower N-alkyl-N-arylamino, lower aminoalkyl, lower N-alkylaminoalkyl, lower N,N-dialkylaminoalkyl, lower N-arylaminoalkyl, lower N-aralkylaminoalkyl, lower N-alkyl-N-aralkylaminoalkyl, lower N-alkyl-N-arylaminoalkyl, aryloxy, lower aralkoxy, lower alkoxy, lower alkylthio, arylthio, lower aralkylthio, aminocarbonyl, lower aminocarbonylalkyl, lower N-alkylaminocarbonyl, N-arylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-arylaminocarbonyl, lower cycloalkylaminocarbonyl, lower carboxyalkylaminocarbonyl, lower aralkoxycarbonylalkylaminocarbonyl, lower hydroxyalkyl,

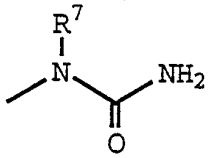
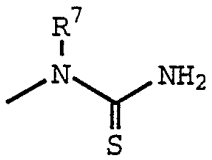
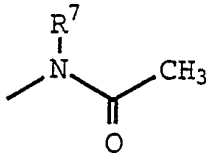




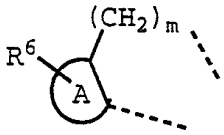
;

wherein R^3 is selected from hydrido, lower alkyl, halo, cyano, lower hydroxyalkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkoxy, lower N-alkylamino, lower N,N-dialkylamino, lower N-

alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, lower N,N-dialkylaminosulfonyl, lower N-alkyl-N-arylaminosulfonyl and lower cycloalkyl; wherein R^4 is selected from lower aralkenyl, aryl, lower cycloalkyl, lower cycloalkenyl and five to ten membered heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkenyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, sulfamyl, lower alkylaminosulfonyl, amino, lower N-alkylamino, lower N,N-dialkylamino, five or six membered heterocyclic, lower cycloalkylalkyl, nitro,

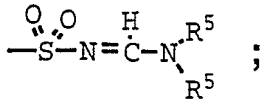




or wherein R^3 and R^4 together form



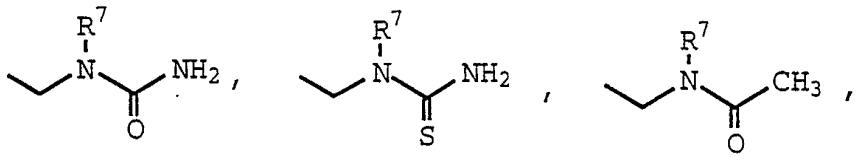
wherein m is 2; wherein A is selected from phenyl and five or six membered heteroaryl; wherein R^5 is lower alkyl; wherein R^6 is one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkenyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, sulfamyl, amino, lower N-alkylamino, lower N,N-dialkylamino, lower cycloalkylalkyl and nitro; and wherein R^7 is selected from hydrido, lower alkyl, aryl and lower aralkyl; or a pharmaceutically-acceptable salt thereof.

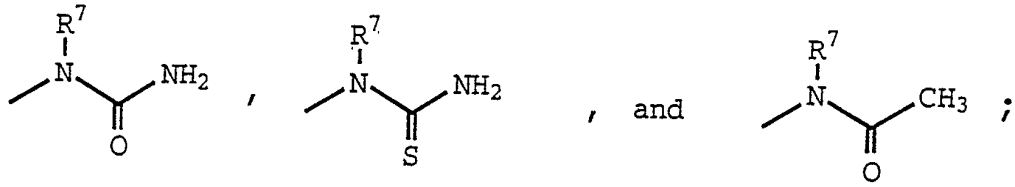
An even more preferred class of compounds consists of those compounds of Formula I wherein R^1 is phenyl, wherein R^1 is substituted at a substitutable position with one or more radicals selected from sulfamyl, halo, lower alkyl, lower alkoxy and



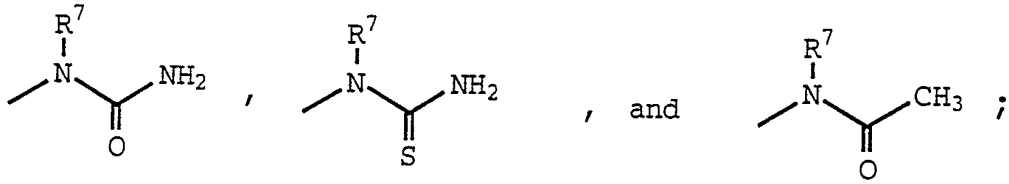
;

wherein R^2 is selected from hydrido, lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, lower alkoxycarbonylcyanoalkenyl, lower haloaralkyl, lower carboxyhaloalkyl, lower alkoxycarbonylhaloalkyl, lower aminocarbonylhaloalkyl, lower alkylaminocarbonylhaloalkyl, lower N-alkylamino, lower N,N-dialkylamino, N-arylamino, lower N-aralkylamino, lower N-alkyl-N-aralkylamino, lower N-alkyl-N-arylamino, lower aminoalkyl, lower N-alkylaminoalkyl, lower N,N-dialkylaminoalkyl, lower N-arylaminoalkyl, lower N-aralkylaminoalkyl, lower N-alkyl-N-aralkylaminoalkyl, lower N-alkyl-N-arylaminoalkyl, lower alkoxy, aryloxy, lower aralkoxy, lower alkylthio, arylthio, lower aralkylthio, aminocarbonyl, lower aminocarbonylalkyl, lower N-alkylaminocarbonyl, N-arylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-arylaminocarbonyl, lower cycloalkylaminocarbonyl, lower carboxyalkylaminocarbonyl, lower heterocyclicaminocarbonyl, lower aralkoxycarbonylalkylaminocarbonyl, lower hydroxyalkyl,

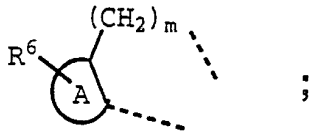




wherein R^3 is selected from hydrido, lower alkyl, halo, cyano, lower hydroxyalkyl, lower alkoxy, lower N-alkylamino, lower N,N-dialkylamino, lower alkylthio, lower alkylsulfonyl and lower cycloalkyl; wherein R^4 is selected from lower aralkenyl, aryl, lower cycloalkyl, lower cycloalkenyl and five to ten membered heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkenyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, sulfamyl, amino, lower N-alkylamino, lower N,N-dialkylamino, five or six membered heterocyclic, lower cycloalkylalkyl, nitro,



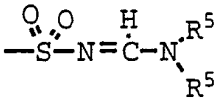
or wherein R^3 and R^4 together form



wherein m is 2; wherein A is selected from phenyl and five membered heteroaryl; wherein R^5 is lower alkyl; wherein R^6 is one or more radicals selected from halo, lower alkyl, lower alkylsulfonyl, lower haloalkyl, lower alkoxy, sulfamyl, amino and nitro; and wherein R^7 is

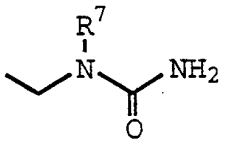
selected from hydrido, lower alkyl, aryl and lower aralkyl; or a pharmaceutically-acceptable salt thereof.

Within Formula I there is a subclass of compounds which consists of compounds wherein R^1 is phenyl substituted at a substitutable position with one or more radicals selected from halo, lower alkyl, sulfamyl and



;

wherein R^2 is selected from hydrido, lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, lower alkoxycarbonylcyanoalkenyl, lower haloaralkyl, lower carboxyhaloalkyl, lower alkoxycarbonylhaloalkyl, lower aminocarbonylhaloalkyl, lower alkylaminocarbonylhaloalkyl, lower N-alkylamino, lower N,N-dialkylamino, N-arylamino, lower N-aralkylamino, lower N-alkyl-N-aralkylamino, lower N-alkyl-N-arylamino, lower aminoalkyl, lower N-alkylaminoalkyl, lower N,N-dialkylaminoalkyl, lower N-arylaminoalkyl, lower N-aralkylaminoalkyl, lower N-alkyl-N-aralkylaminoalkyl, lower N-alkyl-N-arylaminoalkyl, lower alkoxy aryloxy, lower aralkoxy, lower alkylthio, arylthio, lower aralkylthio, aminocarbonyl, lower aminocarbonylalkyl, lower N-alkylaminocarbonyl, N-arylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-arylaminocarbonyl, lower cycloalkylaminocarbonyl, lower carboxyalkylaminocarbonyl, lower aralkoxycarbonylalkylaminocarbonyl, lower hydroxyalkyl,



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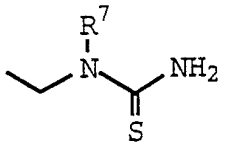

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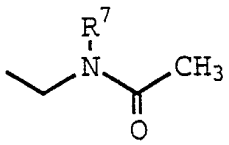

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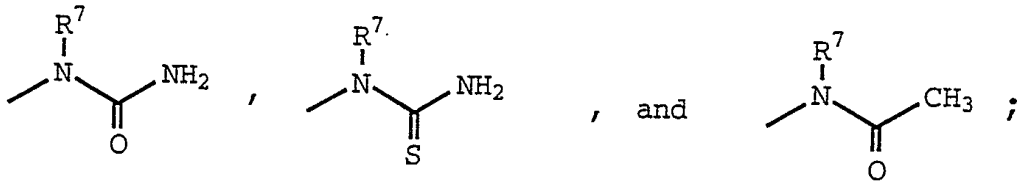
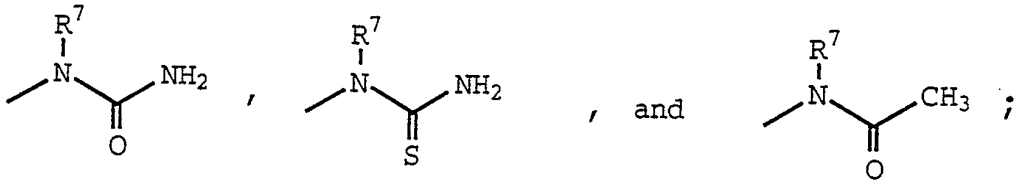
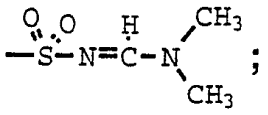


wherein R^3 is selected from hydrido, lower alkyl, halo, cyano, lower hydroxyalkyl, lower alkoxy, lower alkylthio, lower N-alkylamino, lower N,N-dialkylamino, lower alkylsulfonyl and lower cycloalkyl; wherein R^4 is selected from lower aralkenyl, aryl, lower cycloalkyl, lower cycloalkenyl and five to ten membered heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkenyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, sulfamyl, lower alkylaminocarbonyl, amino, lower N-alkylamino, lower N,N-dialkylamino, five or six membered heterocyclic, lower cycloalkylalkyl, nitro,



wherein R^5 is lower alkyl; and wherein R^7 is selected from hydrido, lower alkyl, aryl and lower aralkyl; or a pharmaceutically-acceptable salt thereof.

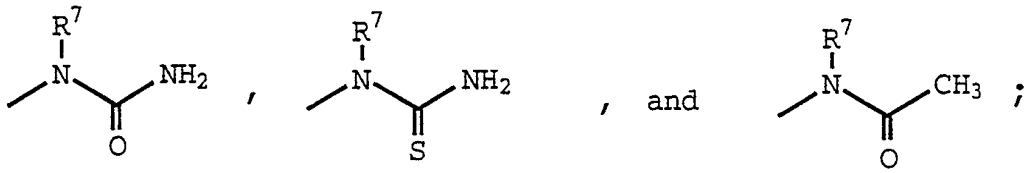
A class of compounds of particular interest consists of those compounds of Formula I wherein R^1 is phenyl, substituted at a substitutable position with one or more radicals selected from fluoro, chloro, methyl, sulfamyl and



wherein R^2 is selected from hydrido, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, trifluoroacetyl, cyanomethyl, ethoxycarbonylcyanoethenyl, 1,1-difluoro-1-phenylmethyl, 1,1-difluoro-1-phenylethyl, difluoroacetyl, methoxycarbonyldifluoromethyl, difluoroacetamidyl, N,N-dimethyldifluoroacetamidyl, N-phenyldifluoroacetamidyl, N-ethylamino, N-methylamino, N,N-dimethylamino, N,N-diethylamino, N-phenylamino, N-benzylamino, N-phenylethylamino, N-methyl-N-benzylamino, N-ethyl-N-phenylamino, N-methyl-N-phenylamino, aminomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, N-phenylaminomethyl, N-benzylaminomethyl, N-methyl-N-benzylaminomethyl, N-methyl-N-phenylaminomethyl, methoxy, ethoxy, phenoxy, benzyloxy, methylthio, phenylthio, benzylthio, N-methylurea, N-methylthiourea, N-methylacetamidyl, urea, ureamethyl, thiourea, thioureamethyl, acetamidyl, N-phenylthioureamethyl, N-benzylthioureamethyl, N-methylthioureamethyl, N-phenylureamethyl, N-benzylureamethyl, N-methylureamethyl, N-phenylacetamidylmethyl, N-benzylacetamidylmethyl, N-methylacetamidylmethyl, aminocarbonyl, aminocarbonylmethyl, N-methylaminocarbonyl, N-ethylaminocarbonyl, N-isopropylaminocarbonyl, N-propylaminocarbonyl, N-butylaminocarbonyl, N-isobutylaminocarbonyl, N-*tert*-butylaminocarbonyl, N-pentylaminocarbonyl, N-phenylaminocarbonyl, N,N-dimethylaminocarbonyl, N-

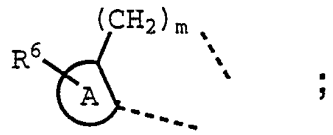
methyl-N-ethylaminocarbonyl, N-(3-fluorophenyl)aminocarbonyl, N-(4-methylphenyl)aminocarbonyl, N-(3-chlorophenyl)aminocarbonyl, N-methyl-N-(3-chlorophenyl)aminocarbonyl, N-(4-methoxyphenyl)aminocarbonyl, N-methyl-N-phenylaminocarbonyl, cyclopentylaminocarbonyl, cyclohexylaminocarbonyl, carboxymethylaminocarbonyl, benzyloxycarbonylmethylaminocarbonyl, hydroxypropyl, hydroxymethyl, and hydroxypropyl; wherein R^3 is selected from hydrido, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, hexyl, fluoro, chloro, bromo, cyano, methoxy, methylthio, methylsulfonyl, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino, cyclopropyl, cyclopentyl, hydroxypropyl, hydroxymethyl, and hydroxyethyl; and wherein R^4 is selected from phenylethenyl, phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, 1-cyclopentenyl, 4-cyclopentenyl, benzofuryl, 2,3-dihydrobenzofuryl, 1,2,3,4-tetrahydronaphthyl, benzothienyl, indenyl, indanyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl and pyrazinyl; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methylsulfinyl, methyl, ethyl, propyl, isopropyl, *tert*-butyl, isobutyl, hexyl, ethylenyl, propenyl, methylsulfonyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, aminocarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, bromodifluoromethyl, difluorochloromethyl,

dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, sulfamyl, methylaminosulfonyl, hydroxypropyl, hydroxyisopropyl, hydroxymethyl, hydroxyethyl, trifluoromethoxy, amino, N-methylamino, N-ethylamino, N-ethyl-N-methylamino, N,N-dimethylamino, N,N-diethylamino, formylamino, methylcarbonylamino, trifluoroacetamino, piperadinyl, piperazinyl, morpholino, cyclohexylmethyl, cyclopropylmethyl, cyclopentylmethyl, nitro,



and wherein R^7 is selected from hydrido, methyl, ethyl, phenyl and benzyl; or a pharmaceutically-acceptable salt thereof.

Within Formula I there is a second subclass of compounds of high interest wherein R^1 is phenyl substituted at a substitutable position with sulfamyl; wherein R^2 is selected from lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, lower carboxyalkyl, aminocarbonyl, lower N-alkylaminocarbonyl, N-arylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-arylaminocarbonyl, lower cycloalkylaminocarbonyl and lower hydroxyalkyl; wherein R^3 and R^4 together form



wherein m is 2; wherein A is selected from phenyl and five membered heteroaryl; and wherein R^6 is one or more radicals selected from halo, lower alkyl, lower alkylsulfonyl, lower haloalkyl, lower alkoxy, amino and nitro; or a pharmaceutically-acceptable salt thereof.

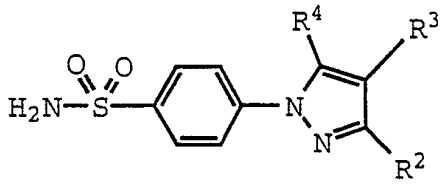
A class of compounds of particular interest consists of those compounds of Formula I wherein R^2 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, trifluoroacetyl, aminocarbonyl, N-methylaminocarbonyl, N-ethylaminocarbonyl, N-isopropylaminocarbonyl, N-propylaminocarbonyl, N-butylaminocarbonyl, N-isobutylaminocarbonyl, N-*tert*-butylaminocarbonyl, N-pentylaminocarbonyl, N-phenylaminocarbonyl, N,N-dimethylaminocarbonyl, N-methyl-N-ethylaminocarbonyl, N-(3-fluorophenyl)aminocarbonyl, N-(4-methylphenyl)aminocarbonyl, N-(3-chlorophenyl)aminocarbonyl, N-(4-methoxyphenyl)aminocarbonyl, N-methyl-N-phenylaminocarbonyl, cyclohexylaminocarbonyl, hydroxypropyl, hydroxymethyl and hydroxyethyl; wherein A is selected from phenyl, furyl and thienyl; and wherein R^6 is one or more radicals selected from fluoro, chloro, bromo, methylsulfonyl, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, amino, and nitro; or a pharmaceutically-acceptable salt thereof.

Within Formula I there is a third subclass of compounds of high interest wherein R^1 is selected from phenyl, naphthyl, biphenyl, and five- or six-membered heteroaryl, wherein R^1 is substituted at a substitutable position with one or more radicals selected from halo,

lower alkyl, lower alkoxy, hydroxyl and lower haloalkyl; wherein R^2 is selected from lower haloalkyl; wherein R^3 is hydrido; and wherein R^4 is aryl substituted at a substitutable position with sulfamyl; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula I wherein R^1 is selected from phenyl, naphthyl, benzofuryl, benzothienyl, indolyl, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl and pyrazinyl; wherein R^1 is substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichloropropyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, methyl, ethyl, propyl, hydroxyl, methoxy, ethoxy, propoxy and n-butoxy; wherein R^2 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, difluoroethyl, dichlorofluoromethyl, difluoropropyl, dichloroethyl and dichloropropyl; wherein R^3 is hydrido; and wherein R^4 is phenyl substituted at a substitutable position with sulfamyl; or a pharmaceutically-acceptable salt thereof.

Within Formula I there is a subclass of compounds of high interest represented by Formula II:



(II)

wherein R^2 is selected from hydrido, alkyl, haloalkyl, alkoxycarbonyl, cyano, cyanoalkyl, carboxyl, aminocarbonyl, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, carboxyalkylaminocarbonyl, carboxyalkyl, aralkoxycarbonylalkylaminocarbonyl, aminocarbonylalkyl,

alkoxycarbonylcyanoalkenyl and hydroxyalkyl; wherein R^3 is selected from hydrido, alkyl, cyano, hydroxyalkyl, cycloalkyl, alkylsulfonyl and halo; and wherein R^4 is selected from aralkenyl, aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfonyl, cyano, nitro, haloalkyl, alkyl, hydroxyl, alkenyl, hydroxyalkyl, carboxyl, cycloalkyl, alkylamino, dialkylamino, alkoxycarbonyl, aminocarbonyl, alkoxy, haloalkoxy, sulfamyl, heterocyclic and amino; provided R^2 and R^3 are not both hydrido; further provided that R^2 is not carboxyl or methyl when R^3 is hydrido and when R^4 is phenyl; further provided that R^4 is not triazolyl when R^2 is methyl; further provided that R^4 is not aralkenyl when R^2 is carboxyl, aminocarbonyl or ethoxycarbonyl; further provided that R^4 is not phenyl when R^2 is methyl and R^3 is carboxyl; and further provided that R^4 is not unsubstituted thienyl when R^2 is trifluoromethyl; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula II wherein R^2 is selected from hydrido, lower alkyl, lower haloalkyl, lower alkoxycarbonyl, cyano, lower cyanoalkyl, carboxyl, aminocarbonyl, lower alkylaminocarbonyl, lower cycloalkylaminocarbonyl, arylaminocarbonyl, lower carboxyalkylaminocarbonyl, lower aralkoxycarbonylalkylaminocarbonyl, lower aminocarbonylalkyl, lower carboxyalkyl, lower alkoxycarbonylcyanoalkenyl and lower hydroxyalkyl; wherein R^3 is selected from hydrido, lower alkyl, cyano, lower hydroxyalkyl, lower cycloalkyl, lower alkylsulfonyl and halo; and wherein R^4 is selected from aralkenyl, aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfonyl, cyano, nitro, lower haloalkyl, lower

alkyl, hydroxyl, lower alkenyl, lower hydroxyalkyl, carboxyl, lower cycloalkyl, lower alkylamino, lower dialkylamino, lower alkoxycarbonyl, aminocarbonyl, lower alkoxy, lower haloalkoxy, sulfamyl, five or six membered heterocyclic and amino; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as follows:

4-[5-(4-(N-ethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-(N-ethyl-N-methylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-fluoro-4-(N-methylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-chloro-4-(N-methylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-methyl-4-(N-methylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-(N,N-dimethylamino)-3-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-chloro-4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-(N,N-dimethylamino)-3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-(N-ethyl-N-methylamino)-3-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-chloro-4-(N-ethyl-N-methylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-(N-ethyl-N-methylamino)-3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-(N,N-diethylamino)-3-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-(3-chloro-4-(N,N-diethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-(N,N-diethylamino)-3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

N-[4-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-3-fluorophenyl]-N-methylacetamide;

N-[4-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-3-chlorophenyl]-N-methylacetamide;

N-[4-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-3-methylphenyl]-N-methylacetamide;

N-[4-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-3-fluorophenyl]-N-methylurea;

N-[4-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-3-chlorophenyl]-N-methylurea;

N-[4-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-3-methylphenyl]-N-methylurea;

N-[4-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-3-fluorophenyl]-N-methylthiourea;

N-[4-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-3-chlorophenyl]-N-methylthiourea;

N-[4-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-3-methylphenyl]-N-methylthiourea;

4-[5-(3-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-(N-ethyl-N-methylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chloro-3-(N-methylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methyl-3-(N-methylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

N-[3-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl]-N-methylacetamide;

N-[3-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-4-fluorophenyl]-N-methylacetamide;

N-[3-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-4-methylphenyl]-N-methylurea;

N-[3-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-4-fluorophenyl]-N-methylthiourea;

4-[5-(2-(N-ethyl-N-methylamino)-4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

N-[2-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-4-methylphenyl]-N-methylurea;

N-[2-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-4-fluorophenyl]-N-methylthiourea;

4-[5-(1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(7-fluoro-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-ethyl-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(7-methyl-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(7-chloro-1-methyl-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3-dihydro-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(7-fluoro-1-methyl-2,3-dihydro-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-aminomethyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(N-methylamino)methyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(N,N-dimethylamino)methyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-phenyl-3-(N-phenylamino)methyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(N-benzylamino)methyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(N-benzyl-N-methylamino)methyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(N-methyl-N-phenylamino)methyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

N-[[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]methyl]acetamide;

N-[[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]methyl]-N-methylacetamide;

N-[[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]methyl]-N-phenylacetamide;

N-[[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]methyl]-N-benzylacetamide;

N-[[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]methyl]urea;

N-[[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]methyl]-N-methylurea;

N-[[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]methyl]-N-phenylurea;

N-[[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]methyl]-N-benzylurea;

N-[[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]methyl]thiourea;

N-[[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]methyl]-N-methylthiourea;

N-[[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]methyl]-N-phenylthiourea;

N-[[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]methyl]-N-benzylthiourea;

4-[4-methoxy-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-methylthio-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-(N-methylamino)-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-(N,N-dimethylamino)-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-methoxy-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-ethoxy-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-phenoxy-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-benzyloxy-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-methylthio-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-benzylthio-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(N-methylamino)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(N,N-dimethylamino)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(N-benzyl-N-methylamino)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

N-[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]acetamide;

N-[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]-N-methylacetamide;

N-[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]-N-benzylacetamide;

N-[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]urea;

N-[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]-N-methylurea;

N-[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]-N-benzylurea;

N-[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]thiourea;

N-[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]-N-methylthiourea;

N-[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]-N-benzylthiourea;

4-[5-phenyl-3-(1,1-difluoro-1-phenylmethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-phenyl-3-(1,1-difluoro-2-phenylethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazole-3-difluoroacetic acid;

methyl 1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazole-3-difluoroacetate;

1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazole-3-difluoroacetamide;

N,N-dimethyl-1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazole-3-difluoroacetamide;

N-phenyl-1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazole-3-difluoroacetamide;

1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazole-3-acetic acid;

1-[4-(aminosulfonyl)phenyl]-4-chloro-5-phenyl-1H-pyrazole-3-difluoroacetic acid;

1-[4-(aminosulfonyl)phenyl]-4-bromo-5-phenyl-1H-pyrazole-3-difluoroacetic acid;

1-[4-(aminosulfonyl)phenyl]-4-chloro-5-(4-chlorophenyl)-1H-pyrazole-3-acetic acid;

1-[4-(aminosulfonyl)phenyl]-4-bromo-5-phenyl-1H-pyrazole-3-acetic acid;

(R)-2-[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]propanoic acid;

(S)-2-[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]propanoic acid;

(R)-2-[1-[4-(aminosulfonyl)phenyl]-4-chloro-5-phenyl-1H-pyrazol-3-yl]propanoic acid;

(S)-2-[1-[4-(aminosulfonyl)phenyl]-4-chloro-5-phenyl-1H-pyrazol-3-yl]propanoic acid;

(R)-2-[1-[4-(aminosulfonyl)phenyl]-4-bromo-5-phenyl-1H-pyrazol-3-yl]propanoic acid;

(S)-2-[1-[4-(aminosulfonyl)phenyl]-4-bromo-5-phenyl-1H-pyrazol-3-yl]propanoic acid;

2-[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]-2-methylpropanoic acid;

2-[1-[4-(aminosulfonyl)phenyl]-4-chloro-5-phenyl-1H-pyrazol-3-yl]-2-methylpropanoic acid;

2-[1-[4-(aminosulfonyl)phenyl]-4-bromo-5-phenyl-1H-pyrazol-3-yl]-2-methylpropanoic acid;

2-fluoro-4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

3-fluoro-4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

2-methyl-4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

3-methyl-4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

ethyl 1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxylate;

ethyl 1-[4-(aminosulfonyl)phenyl]-5-(4-methylphenyl)-1H-pyrazole-3-carboxylate;

isopropyl 1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxylate;

methyl-1-[4-(aminosulfonyl)phenyl]-5-(4-aminophenyl)-1H-pyrazole-3-carboxylate;

1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxylic acid;

tert-butyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxylate;

propyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxylate;

butyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxylate;

isobutyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxylate;

pentyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxylate;

methyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxylate;

methyl-1-[4-(aminosulfonyl)phenyl]-5-(4-methylphenyl)-1H-pyrazole-3-carboxylate;

methyl-1-[4-(aminosulfonyl)phenyl]-5-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate;

methyl-1-[4-(aminosulfonyl)phenyl]-5-(4-bromophenyl)-1H-pyrazole-3-carboxylate;

methyl-1-[4-(aminosulfonyl)phenyl]-5-(4-nitrophenyl)-1H-pyrazole-3-carboxylate;

methyl-1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole-3-carboxylate;

methyl-1-[4-(aminosulfonyl)phenyl]-5-(3,5-dichloro-4-methoxyphenyl)-1H-pyrazole-3-carboxylate;

methyl-1-[4-(aminosulfonyl)phenyl]-5-(3,5-difluoro-4-methoxyphenyl)-1H-pyrazole-3-carboxylate;

N-[4-methylphenyl]-1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole-3-carboxamide;

N-[3-chlorophenyl]-1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole-3-carboxamide;

N-[3-fluorophenyl]-1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole-3-carboxamide;

N-[3-fluorophenyl]-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

phenylmethyl N-[[1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazol-3-yl]carbonyl]glycinate;

1-[4-(aminosulfonyl)phenyl]-5-(4-bromophenyl)-1H-pyrazole-3-carboxamide;

1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N-phenyl-1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole-3-carboxamide;

N-(4-methoxyphenyl)-1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole-3-carboxamide;

N-(4-methylphenyl)-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N,N-dimethyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N-methyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N-methyl-N-ethyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N-phenyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N-methyl-N-phenyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N-ethyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N-isopropyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N-propyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N-butyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N-isobutyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N-*tert*-butyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N-pentyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N-cyclohexyl-1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole-3-carboxamide;

N-cyclopentyl-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

4-[5-(4-chlorophenyl)-3-(pyrrolidinocarboxamide)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(piperidinocarboxamide)-1H-pyrazol-1-yl]benzenesulfonamide;

N-(3-chlorophenyl)-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N-(2-pyridyl)-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

N-methyl-N-(3-chlorophenyl)-1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxamide;

1-[4-(aminosulfonyl)phenyl]-5-(4-nitrophenyl)-1H-pyrazole-3-carboxamide;

1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole-3-carboxamide;

1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazole-3-carboxamide;

1-[4-(aminosulfonyl)phenyl]-5-(3-chloro-4-methoxyphenyl)-1H-pyrazole-3-carboxamide;

1-[4-(aminosulfonyl)phenyl]-5-(4-methylthiophenyl)-1H-pyrazole-3-carboxamide;

1-[4-(aminosulfonyl)phenyl]-5-(4-methoxyphenyl)-1H-pyrazole-3-carboxamide;

1-[4-(aminosulfonyl)phenyl]-5-(4-methylphenyl)-1H-pyrazole-3-carboxamide;

N-methyl 1-[4-(aminosulfonyl)phenyl]-5-(4-methoxyphenyl)-1H-pyrazole-3-carboxamide;

N-[[1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazol-3-yl]carbonyl]glycine;

1-[4-(aminosulfonyl)phenyl]-5-(3-bromo-4-methoxyphenyl)-1H-pyrazole-3-carboxamide;

1-[4-(aminosulfonyl)phenyl]-5-(3,5-dichloro-4-methoxyphenyl)-1H-pyrazole-3-carboxamide;

4-[5-(4-bromophenyl)-3-cyano-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-cyano-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-cyano-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-cyano-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-cyano-5-(4-methylthiophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-chloro-4-methoxyphenyl)-3-cyano-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,5-dichloro-4-methoxyphenyl)-3-cyano-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-bromo-4-methoxyphenyl)-3-cyano-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-cyano-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-nitrophenyl)-3-(cyano)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-(4-chlorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-bromo-5-(4-chlorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-(3,5-dichloro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-bromo-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-(3-chloro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-bromo-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-cyano-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-(3,5-difluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-methyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-fluoro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-4-methylsulfonyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-ethyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-methyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methoxyphenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-4-ethyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-ethyl-5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-ethyl-5-(4-methoxy-3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-ethyl-5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-cyclopropyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-ethyl-5-(3-fluoro-4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-hydroxymethyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-methyl-5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-fluoro-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-bromo-5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-(3,5-dichloro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-bromo-3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-3-cyano-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-(4-chlorophenyl)-3-cyano-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-bromo-3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-bromo-3-cyano-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

ethyl [1-(4-aminosulfonylphenyl)-4-bromo-5-(4-chlorophenyl)-1H-pyrazol-3-yl]carboxylate;

methyl [1-(4-aminosulfonylphenyl)-4-chloro-5-phenyl-1H-pyrazol-3-yl]carboxylate;

methyl [1-(4-aminosulfonylphenyl)-4-chloro-5-(4-chlorophenyl)-1H-pyrazol-3-yl]carboxylate;

ethyl [1-(4-aminosulfonylphenyl)-4-chloro-5-(4-chlorophenyl)-1H-pyrazol-3-yl]carboxylate;

methyl [1-(4-aminosulfonylphenyl)-4-chloro-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxylate;

methyl [1-(4-aminosulfonylphenyl)-4-bromo-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxylate;

methyl [1-(4-aminosulfonylphenyl)-4-chloro-5-(3-chloro-4-methoxyphenyl)-1H-pyrazol-3-yl]carboxylate;

methyl [1-(4-aminosulfonylphenyl)-4-chloro-5-(3,5-dichloro-4-methoxyphenyl)-1H-pyrazol-3-yl]carboxylate;

methyl [1-(4-aminosulfonylphenyl)-5-(3-bromo-4-methoxyphenyl)-4-chloro-1H-pyrazol-3-yl]carboxylate;

[1-(4-aminosulfonylphenyl)-4-chloro-5-phenyl-1H-pyrazol-3-yl]carboxamide;

[1-(4-aminosulfonylphenyl)-4-chloro-5-(4-chlorophenyl)-1H-pyrazol-3-yl]carboxamide;

[1-(4-aminosulfonylphenyl)-4-chloro-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxamide;

[1-(4-aminosulfonylphenyl)-4-bromo-5-(4-chlorophenyl)-1H-pyrazol-3-yl]carboxamide;

[1-(4-aminosulfonylphenyl)-4-bromo-5-phenyl-1H-pyrazol-3-yl]carboxamide;

[1-(4-aminosulfonylphenyl)-4-chloro-5-(4-chlorophenyl)-1H-pyrazol-3-yl]carboxylic acid;

[1-(4-aminosulfonylphenyl)-4-chloro-5-phenyl-1H-pyrazol-3-yl]carboxylic acid;

[1-(4-aminosulfonylphenyl)-4-chloro-5-(3,5-dichloro-4-methoxyphenyl)-1H-pyrazol-3-yl]carboxylic acid;

4-[4-chloro-3-isopropyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-3-methyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-3-hydroxymethyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-(4-chlorophenyl)-3-hydroxymethyl-1H-pyrazol-1-yl]benzenesulfonamide;

[1-(4-aminosulfonylphenyl)-4-chloro-5-(4-chlorophenyl)-1H-pyrazol-3-yl]propanoic acid;

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-cyanophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,4-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,6-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-trifluoromethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-trifluoromethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-aminophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluoro-2-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-ethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,5-dimethyl-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chloro-3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-ethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,4-dimethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methoxy-3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-bromo-4-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-hydroxy-3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-chloro-4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dimethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-chloro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-chloro-4-methoxy-5-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-ethyl-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluoro-2-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-hydroxymethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methoxy-3-(1-propenyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,5-dichloro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,4-dimethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-chloro-4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methoxy-3-propylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,5-difluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-fluoro-4-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-cyclopropylmethyl-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzoic acid;

4-[5-(3-methyl-4-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-chloro-4-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methyl-3-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-(N-methylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-amino-4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

methyl-4-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzoate;

4-[1-[4-(aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzamide;

4-[5-(3,5-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,4,6-trifluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,6-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,4,6-trichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dimethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-chloro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chloro-2-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-methylsulfinylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-methylsulfinylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylsulfinylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-fluoro-4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluoro-3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-chloro-4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chloro-2-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-hydroxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dihydroxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-isopropylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

N-[4-[1-[4-(aminosulfonyl)phenyl]-3-trifluoromethyl-1H-pyrazol-5-yl]phenyl]acetamide;

N-[4-[1-[4-(aminosulfonyl)phenyl]-3-trifluoromethyl-1H-pyrazol-5-yl]phenyl]formamide;

N-[4-[1-[4-(aminosulfonyl)phenyl]-3-trifluoromethyl-1H-pyrazol-5-yl]phenyl]trifluoroacetamide;

4-[5-(4-[N-methylaminosulfonyl]phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,5-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-n-butoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-[aminosulfonyl]phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,5-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3,4-trifluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4,5-trifluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,4,5-trifluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,5,6-trifluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3,4,5-tetrafluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3,4,6-tetrafluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3,5,6-tetrafluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(pentafluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3,4-trichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4,5-trichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,4,5-trichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,5,6-trichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3,4,5-tetrachlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3,4,6-tetrachlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3,5,6-tetrachlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3,4,5,6-pentachlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-*tert*-butylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-isobutylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-trifluoromethylphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylthiophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-(1-morpholino)phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-phenyl-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dimethylphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[1-[4-(aminosulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazol-5-yl]benzoic acid;

methyl 4-[1-[4-(aminosulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazol-5-yl]benzoate;

4-[1-(4-aminosulfonylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzamide;

4-[5-(2-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-cyanophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-chloro-4-methylphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-chloro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chloro-3-methylphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dimethoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,5-dichloro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,5-difluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-bromo-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylsulfonylphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-bromo-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-chloro-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-cyclohexenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(biphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1,4-benzodioxan-6-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-(4-methylcyclohexyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(methyl-1-cyclohexenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-methyl-1-cyclopentenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(benzofuran-2-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1,3-benzodioxol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-pyrazinyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-(morpholino)phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,5-dimethyl-3-furyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-methyl-2-furyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-chloro-1-methyl-4-cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dibromo-4-methylcyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-methoxycyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,4-dimethyl-3-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,5-dichloro-3-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(benzofuran-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-bromo-2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-chloro-2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-indanyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-methyl-2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3-dihydrobenzofuran-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-cyclohexenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-benzothienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dihydro-2H-1-benzopyran-6-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dihydro-2H-1-benzothiopyran-6-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-phenylethenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methyl-1,3-benzodioxol-6-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methyl-1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-pyrazinyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(biphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1,2,3,4-tetrahydronaphth-6-yl])-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-naphthyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-thiazolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-oxazolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(cyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(cyclopentyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(cycloheptyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-cyclopentenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(6-methyl-3-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-cyclohexenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-cyclohexenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylcyclohex-4-ene-1-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-chloro-2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-bromo-2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(6-methoxy-2-naphthyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(heptafluoropropyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(chlorodifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(pentafluoroethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-chloro-4-methoxyphenyl)-3-(chloromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(chlorodifluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(phenyl)-3-(fluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(dichloromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(bromodifluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(fluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(chloromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(dichloromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(dichlorofluoromethyl)-1H-pyrazol-1-yl]benzene sulfonamide;

4-[5-(4-fluorophenyl)-3-(trichloromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(1,1-difluoroethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(1,1-difluoropropyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(1,1-dichloroethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(1,1-dichloropropyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-nitro-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(amidino)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(methylsulfonyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(N-methyl-aminosulfonyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-3-(imidazolyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-3-(2-pyridyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(N-cyanoamidino)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(tetrazolyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(phenylsulfonyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(N-phenylaminosulfonyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(N,N-dimethylaminosulfonyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(N-methyl-N-phenylaminosulfonyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(N-ethylaminosulfonyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(N-isopropylaminosulfonyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(N-methyl-N-ethylaminosulfonyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(N-methyl-N-(3-chlorophenyl) aminosulfonyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(N-methyl-N-(2-pyridyl) aminosulfonyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-methyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-isobutyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(3-hydroxypropyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-3-(3-hydroxypropyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,5-dichloro-4-methoxyphenyl)-3-(3-hydroxypropyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylphenyl)-3-(2-hydroxyisopropyl)-1H-pyrazol-1-yl]benzenesulfonamide;

1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole-3-propanoic acid;

1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-propanoic acid;

1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-propanamide;

methyl 1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole-3-propanoate;

4-[3-(3-hydroxymethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(3-hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(3-hydroxymethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,5-dichloro-4-methoxyphenyl)-3-(3-hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-chloro-4-methoxyphenyl)-3-(3-hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

ethyl 3-[1-(4-aminosulfonylphenyl)-5-(phenyl)-1H-pyrazol-3-yl]-2-cyano-2-propenoate;

4-[5-(4-chlorophenyl)-3-(chloro)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(bromo)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(fluoro)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-4,5-dihydro-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-4,5-dihydro-7-methyl-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[4,5-dihydro-7-methoxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[4,5-dihydro-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[4,5-dihydro-7-methyl-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[4,5-dihydro-6,8-dimethyl-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[4,5-dihydro-6,8-dimethoxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

methyl[1-(4-aminosulfonylphenyl)-4,5-dihydro-7-methoxy-1H-benz[g]indazol-3-yl]carboxylate;

4-[4,5-dihydro-3-trifluoromethyl-1H-thieno[3,2,g]indazol-1-yl]benzenesulfonamide;

4-[1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1-(4-fluorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1-(4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide; and

4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide.

A family of specific compounds of particular interest within Formula II consists of compounds and pharmaceutically-acceptable salts thereof as follows:

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide; and

4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylsulfonyl", it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, iso-amyl, hexyl and the like. The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of such radicals include ethenyl, n-propenyl, butenyl, and the like. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl,

dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxyalkyl radicals are "lower alkoxyalkyl" radicals having one to six carbon atoms and one or two alkoxy radicals. Examples of such radicals include methoxymethyl, methoxyethyl, ethoxyethyl, methoxybutyl and methoxypropyl. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. The term "heterocyclic" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms[e.g. pyrrolidinyl, imidazolidinyl,

piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include unsaturated 5 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the

like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclic group" may have 1 to 3 substituents such as lower alkyl, hydroxy, oxo, amino and lower alkylamino. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. More preferred examples of heteroaryl radicals include benzofuryl, 2,3-dihydrobenzofuryl, benzothienyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, and pyrazinyl. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$.

"Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The term "arylsulfonyl" embraces aryl radicals as defined above, attached to a sulfonyl radical. Examples of such radicals include phenylsulfonyl. The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl," whether alone or used with terms such as "N-alkylaminosulfonyl", "N-arylaminosulfonyl", "N,N-dialkylaminosulfonyl" and "N-alkyl-N-arylaminosulfonyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2NH_2$). The terms "N-alkylaminosulfonyl" and "N,N-dialkylaminosulfonyl" denote sulfamyl radicals substituted, respectively, with one alkyl radical, or two alkyl radicals. More preferred alkylaminosulfonyl radicals are "lower alkylaminosulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylaminosulfonyl radicals include N-methylaminosulfonyl, N-ethylaminosulfonyl and N-methyl-N-ethylaminosulfonyl. The terms "N-arylaminosulfonyl" and "N-alkyl-N-arylaminosulfonyl" denote sulfamyl radicals substituted, respectively, with one aryl radical, or one

alkyl and one aryl radical. More preferred N-alkyl-N-arylaminosulfonyl radicals are "lower N-alkyl-N-arylsulfonyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower N-alkyl-N-aryl aminosulfonyl radicals include N-methyl-phenylaminosulfonyl and N-ethyl-phenylaminosulfonyl The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$. The terms "alkanoyl" or "carboxyalkyl" embrace radicals having a carboxy radical as defined above, attached to an alkyl radical. The alkanoyl radicals may be substituted or unsubstituted, such as formyl, acetyl, propionyl (propanoyl), butanoyl (butyryl), isobutanoyl (isobutyryl), valeryl (pentanoyl), isovaleryl, pivaloyl, hexanoyl or the like. The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes -(C=O)-. The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. More preferred alkylcarbonyl radicals are "lower alkylcarbonyl" radicals having one to six carbon atoms. Examples of such radicals include methylcarbonyl and ethylcarbonyl. The term "alkylcarbonylalkyl", denotes an alkyl radical substituted with an "alkylcarbonyl" radical. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Preferably, "lower alkoxycarbonyl" embraces alkoxy radicals having one to six carbon atoms. Examples of such "lower alkoxycarbonyl" ester radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. More preferred alkoxycarbonylalkyl radicals are "lower alkoxycarbonylalkyl" having lower alkoxycarbonyl radicals as defined above attached to one to six carbon atoms. Examples of such lower alkoxycarbonylalkyl radicals include methoxycarbonylmethyl, *tert*-butoxycarbonylethyl, and methoxycarbonylethyl. The term "aminocarbonyl" when used by itself or with other terms such

as "aminocarbonylalkyl", "N-alkylaminocarbonyl", "N-arylaminocarbonyl", "N,N-dialkylaminocarbonyl", "N-alkyl-N-arylaminocarbonyl", "N-alkyl-N-hydroxyaminocarbonyl" and "N-alkyl-N-hydroxyaminocarbonylalkyl", denotes an amide group of the formula $-C(=O)NH_2$. The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals which have been substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to an aminocarbonyl radical. The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical. The term "aminocarbonylalkyl" embraces alkyl radicals substituted with aminocarbonyl radicals. The term "N-cycloalkylaminocarbonyl" denoted aminocarbonyl radicals which have been substituted with at least one cycloalkyl radical. More preferred are "lower cycloalkylaminocarbonyl" having lower cycloalkyl radicals of three to seven carbon atoms, attached to an aminocarbonyl radical. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl radical. The term "amidino" denotes an $-C(=NH)-NH_2$ radical. The term "cyanoamidino" denotes an $-C(=N-CN)-NH_2$ radical. The term "heterocyclicalkyl" embraces heterocyclic-substituted alkyl radicals. More preferred heterocyclicalkyl radicals are "lower heterocyclicalkyl" radicals having one to six carbon atoms and a heterocyclic radical. Examples include such radicals as pyrrolidinylmethyl, pyridylmethyl and thienylmethyl. The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The terms benzyl and phenylmethyl

are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "cycloalkenyl" embraces unsaturated cyclic radicals having three to ten carbon atoms, such as cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio, (CH_3-S-). The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- atom. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" having one to six carbon atoms. Examples include aminomethyl, aminoethyl and aminobutyl. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with at least one alkyl radical. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" having one to six carbon atoms attached to a lower aminoalkyl radical as described above. The terms "N-alkylamino" and "N,N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Suitable "alkylamino" may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aralkylamino" denotes amino groups which have been substituted with one or two aralkyl radicals, such as N-benzylamino. The "aralkylamino" radicals may be further substituted on the aryl ring portion

of the radical. The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups which have been substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical, respectively, to an amino group. The terms "N-arylaminoalkyl" and "N-aralkylaminoalkyl" denote amino groups which have been substituted with one aryl radical or one aralkyl radical, respectively, and having the amino group attached to an alkyl radical. More preferred arylaminoalkyl radicals are "lower arylaminoalkyl" having the arylamino radical attached to one to six carbon atoms. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl. The terms "N-alkyl-N-arylaminoalkyl" and "N-aralkyl-N-alkylaminoalkyl" denote N-alkyl-N-arylamino and N-alkyl-N-aralkylamino groups, respectively, and having the amino group attached to alkyl radicals. The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid. The term "acylamino" embraces an amino radical substituted with an acyl group. An examples of an "acylamino" radical is acetylamino or acetamido ($CH_3C(=O)$-NH-) where the amine may be further substituted with alkyl, aryl or aralkyl. The term "arylthio" embraces aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio. The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. An example of "aralkylthio" is benzylthio. The term "aryloxy" embraces aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy. The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having phenyl radicals attached to lower alkoxy radical as described above. The term "haloaralkyl" embraces aryl radicals as defined above attached to haloalkyl radicals. The term "carboxyhaloalkyl" embraces carboxyalkyl radicals as defined above having halo radicals attached to the alkyl portion. The term "alkoxycarbonylhaloalkyl"

embraces alkoxycarbonyl radicals as defined above substituted on a haloalkyl radical. The term "aminocarbonylhaloalkyl" embraces aminocarbonyl radicals as defined above substituted on a haloalkyl radical. The term "alkylaminocarbonylhaloalkyl" embraces alkylaminocarbonyl radicals as defined above substituted on a haloalkyl radical. The term "alkoxycarbonylcyanoalkenyl" embraces alkoxycarbonyl radicals as defined above, and a cyano radical, both substituted on an alkenyl radical. The term "carboxyalkylaminocarbonyl" embraces aminocarbonyl radicals substituted with carboxyalkyl radicals, as defined above. The term "aralkoxycarbonylalkylaminocarbonyl" embraces aminocarbonyl radicals substituted with aryl-substituted alkoxycarbonyl radicals, as defined above. The term "cycloalkylalkyl" embraces cycloalkyl radicals having three to ten carbon atoms attached to an alkyl radical, as defined above. More preferred cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to lower alkyl radicals as defined above. Examples include radicals such as cyclopropylmethyl, cyclobutylmethyl, and cyclohexylethyl. The term "aralkenyl" embraces aryl radicals attached to alkenyl radicals having two to ten carbon atoms, such as phenylbutenyl, and phenylethenyl or styryl.

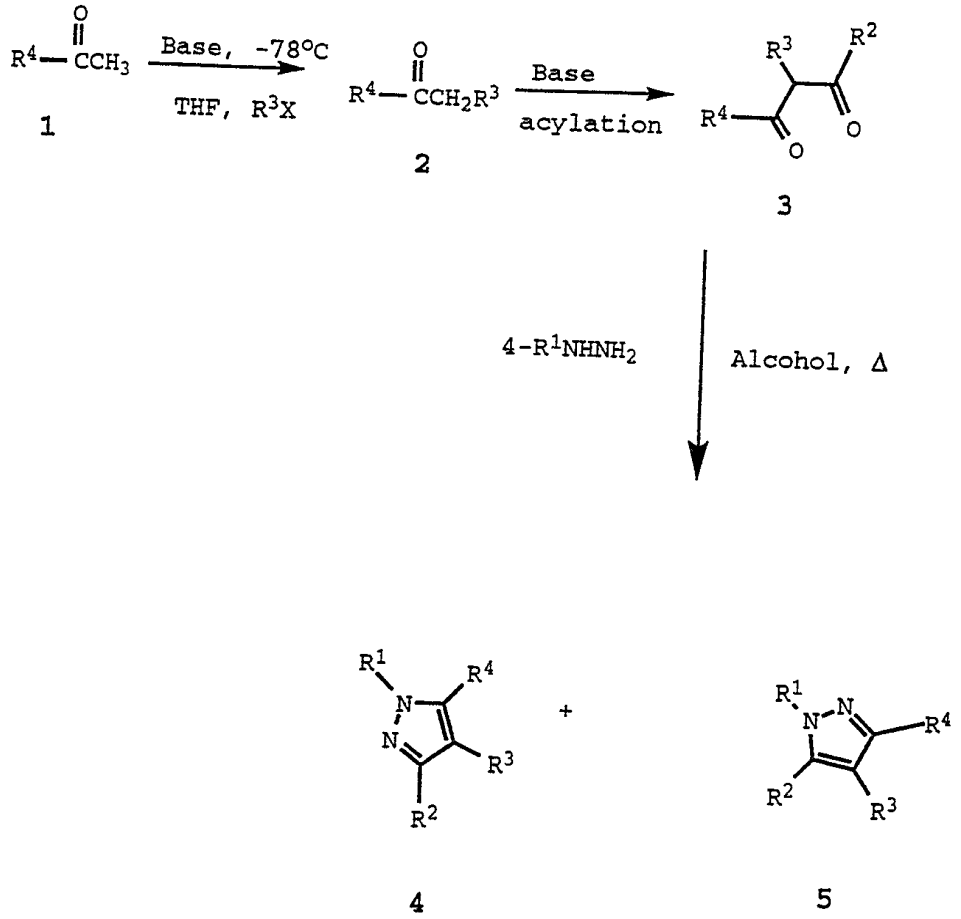
Also included in the family of compounds of Formula I are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are

formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicyclic, salicyclic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, β-hydroxybutyric, salicyclic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the following procedures of Schemes I-VIII, wherein the R^1-R^7 substituents are as defined for Formula I, above, except where further noted.

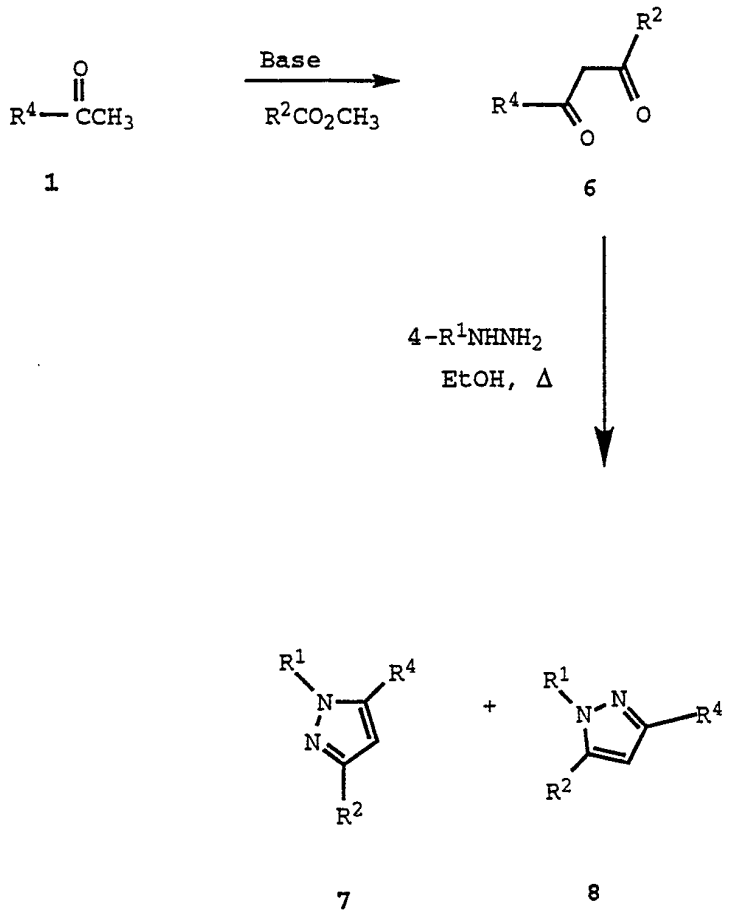
SCHEME I



Synthetic Scheme I shows the preparation of tetrasubstituted pyrazoles from starting material 1. In step 1 of synthetic Scheme I, the phenyl-methyl ketone (1) is treated with a base and an alkylating reagent (R^3X, where X represents a leaving group such as tosyl) to give the substituted ketone (2). In step 2, the substituted ketone (2) is treated with base, such as sodium methoxide, and an acylating reagent such as an ester ($R^2CO_2CH_3$), or ester equivalent (R^2CO-imidazole, to give the intermediate diketone (3) in a procedure similar to that developed by Reid and Calvin, *J. Amer. Chem. Soc.*, **72**, 2948-2952 (1950). In step 3, the diketone (3) is reacted with a substituted hydrazine in acetic acid or an alcoholic solvent to give a mixture of pyrazoles (4) and (5).

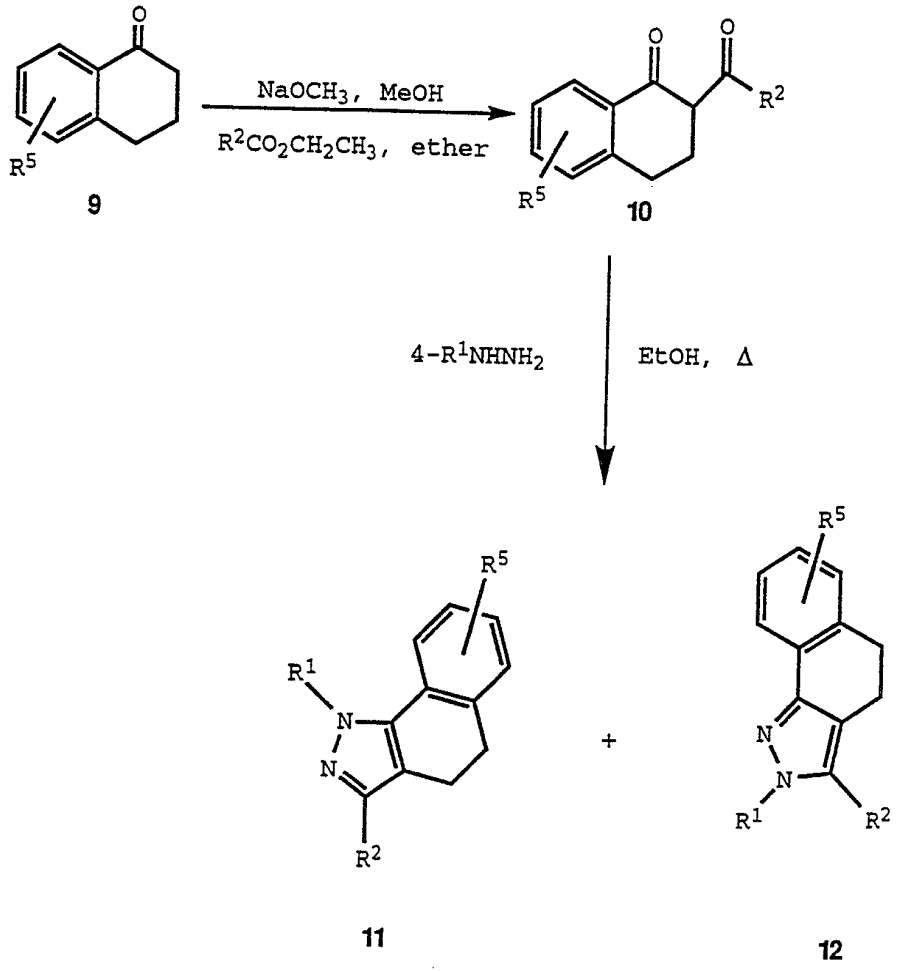
Separation of the desired pyrazole (4) can be achieved by chromatography or recrystallization.

SCHEME II



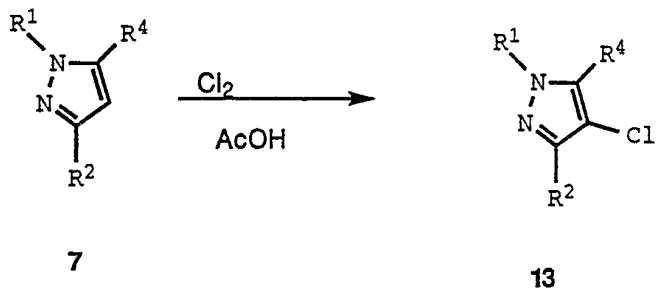
Synthetic Scheme II shows the preparation of compounds embraced by Formula I, where R^3 is a hydrogen atom. In step 1, ketone (1) is treated with a base, preferably NaOMe or NaH, and an ester, or ester equivalent, to form the intermediate diketone (6) which is used without further purification. In step 2, diketone (6) in an anhydrous protic solvent, such as absolute ethanol or acetic acid, is treated with the hydrochloride salt or the free base of a substituted hydrazine at reflux for 10 to 24 hours to afford a mixture of pyrazoles (7) and (8). Recrystallization from diethyl ether/hexane or chromatography affords (7), usually as a light yellow or tan solid.

Scheme III



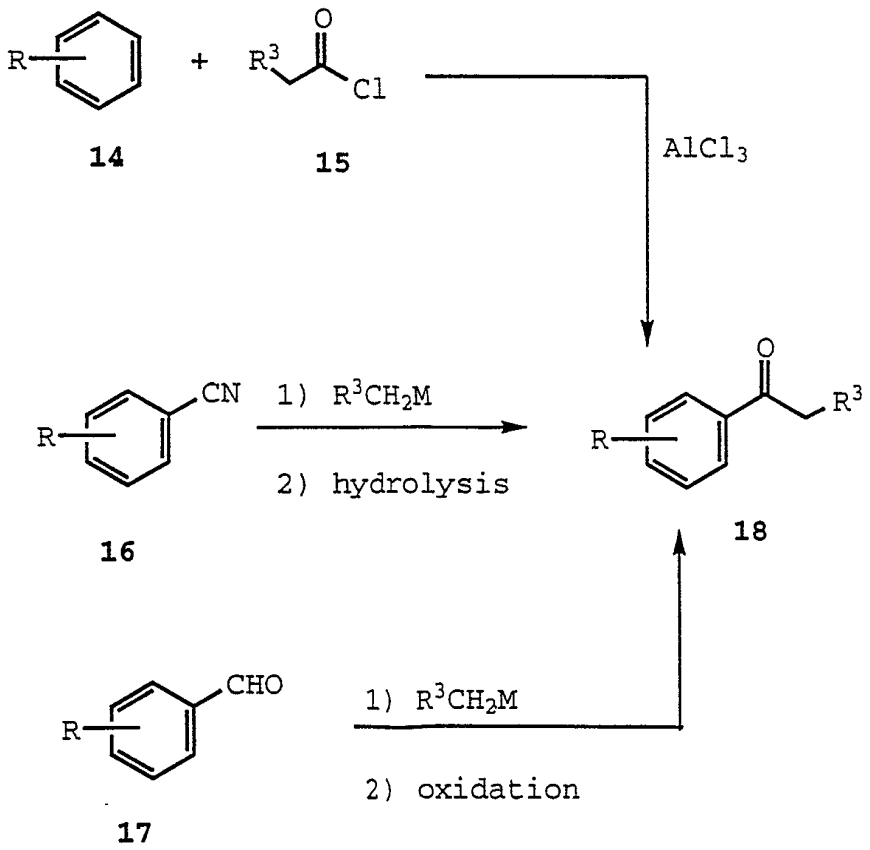
Synthetic Scheme III shows the procedure for preparation of 4,5-dihydrobenz[g]indazole compounds embraced by Formula I. In step 1, ethyl trifluoroacetate is reacted with base, such as 25% sodium methoxide in a protic solvent, such as methanol, and a 1-tetralone derivative (9) to give the intermediate diketone (10). In step 2, the diketone (10) in an anhydrous protic solvent, such as absolute ethanol or acetic acid, is treated with the free base or hydrochloride salt of a substituted hydrazine at reflux for 24 hours to afford a mixture of pyrazoles (11) and (12). Recrystallization gives the 4,5-dihydro benz[g]indazolyl-benzenesulfonamide (11).

Scheme IV



Synthetic Scheme IV shows the preparation of pyrazole compounds (**13**), where R^3 is chlorine, from the available pyrazole compounds (**7**), where R^3 is hydrogen. Chlorination results from passing a stream of chlorine gas at room temperature through a solution containing (**7**).

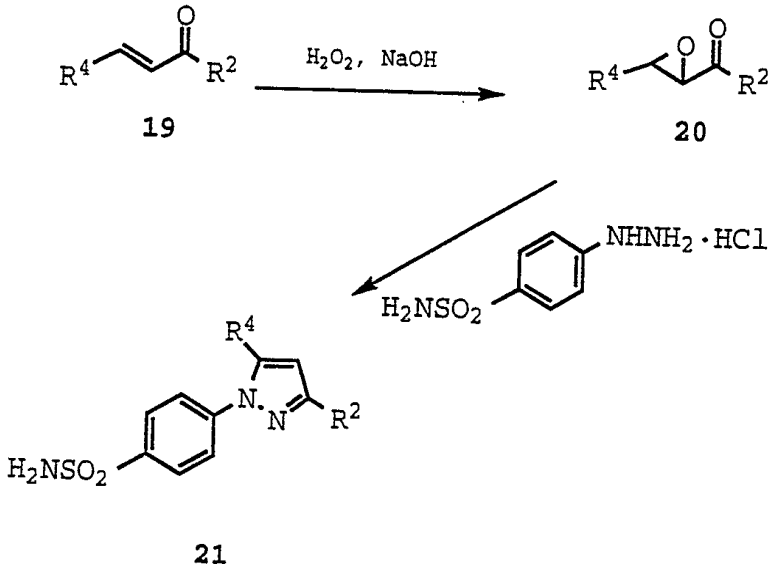
Scheme V



Synthetic Scheme V shows the preparation of substituted ketones **18** which are not commercially available as used in Scheme I. The ketones can be prepared

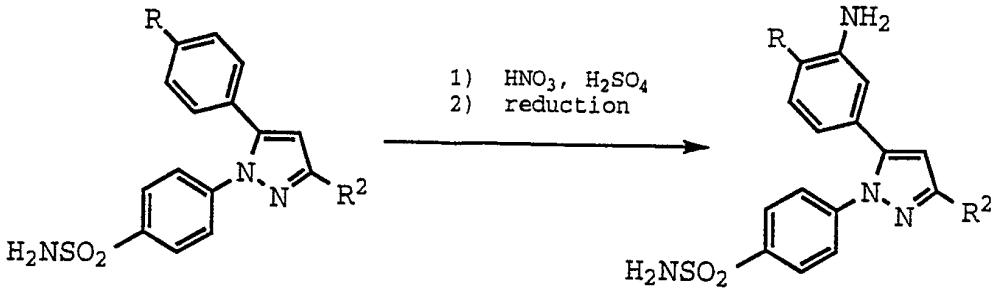
by standard Friedel-Craft acylation of the starting substituted benzenes **14** with acid chlorides or anhydrides **15**. Alternatively, the ketones can be prepared from phenylcarbonitriles **16** by standard organometallic techniques where M represents metals such as lithium, magnesium, and the like. An alternative organometallic route is shown from the aldehydes **17** where M represents metals such as lithium, magnesium, and the like. Oxidation with a suitable oxidizing agent, such as CrO_3, follows to produce the ketones.

Scheme VI



Synthetic Scheme VI shows an alternative regioselective method of constructing the pyrazole **21**. Commercially available enones **19** can be epoxidized to give epoxyketones **20**, which are treated with 4-sulfonamidophenylhydrazine hydrochloride to provide the pyrazole **21**.

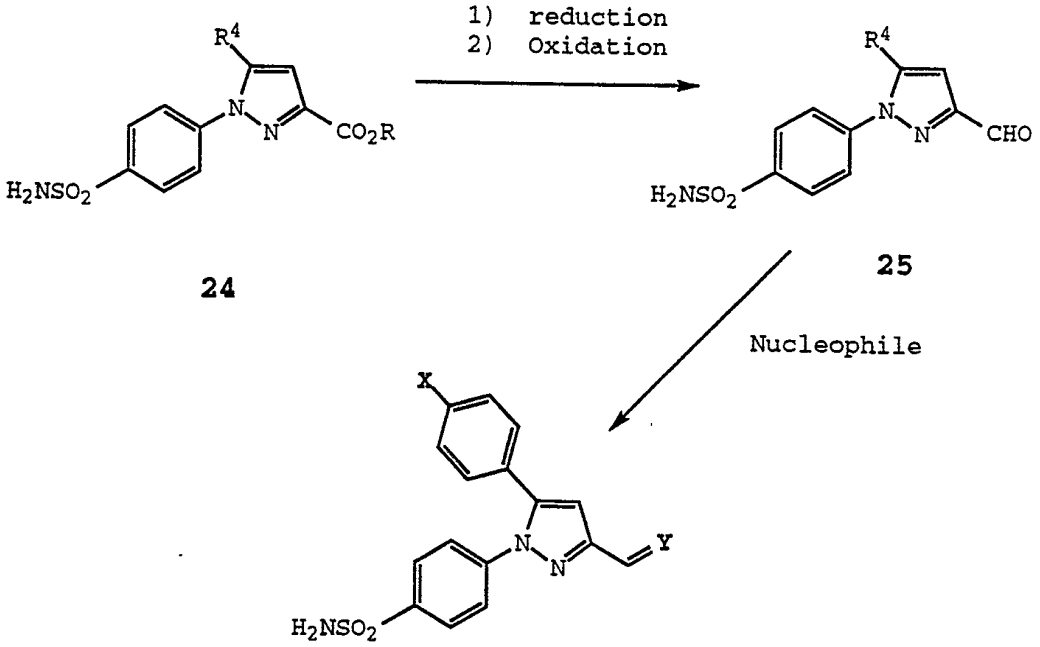
Scheme VII



22 23

Synthetic Scheme VII shows the preparation of pyrazoles **23** (where R^4 is 3-amino-4-substituted phenyl) from starting material **22**. Appropriate 5-(4-substituted aryl)pyrazoles can be nitrated next to the R-group under standard nitration conditions and the nitro group reduced to the amino group, preferably with hydrazine and Pd/C. The amino compounds can be further manipulated by alkylation of the amino group.

Scheme VIII



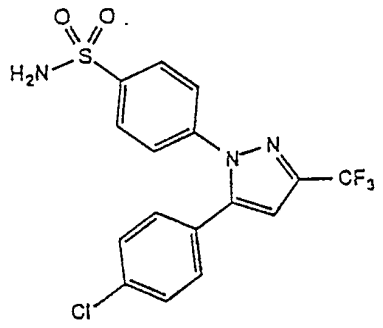
24 25 26

Synthetic Scheme VIII shows the preparation of pyrazoles 26 from esters 24. Reduction of the ester 24 to the alcohol, preferably with lithium aluminum hydride (LAH) followed by oxidation, preferably with MnO_2, gives the aldehyde 25. Various nucleophiles (such as hydroxamates and 1,3-dicarbonyl compounds) can be condensed with the aldehyde to give the desired oximes or olefins 26.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formulas I-II. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention.

All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated. HRMS is an abbreviation for High resolution mass spectrometry. In the following tables, "ND" represents "not determined".

Example 1



4-[5-(4-Chlorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

AMENDED SHEET
IPEA/EP

Step 1: Preparation of 4,4,4-trifluoro-1-[4-(chloro)phenyl]-butane-1,3-dione.

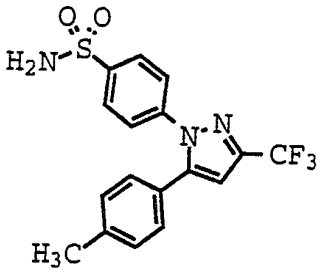
Ethyl trifluoroacetate (23.52 g, 166 mmol) was placed in a 500 mL three-necked round bottom flask, and dissolved in methyl *tert*-butyl ether (75 mL). To the stirred solution was added 25% sodium methoxide (40 mL, 177 mmol) via an addition funnel over a 2 minute period. Next 4'-chloroacetophenone (23.21 g, 150 mmol) was dissolved in methyl *tert*-butyl ether (20 mL), and added to the reaction dropwise over 5 minutes. After stirring overnight (15.75 hours), 3N HCl (70 mL) was added. The organic layer was collected, washed with brine (75 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a 35.09 g of yellow-orange solid. The solid was recrystallized from iso-octane to give 31.96 g (85%) of the dione: mp 66-67°C.

Step 2: Preparation of 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide.

4-Sulphonamidophenylhydrazine hydrochloride (982 mg, 4.4 mmol 1.1 equivalent) was added to a stirred solution of 4,4,4-trifluoro-1-[4-(chloro)phenyl]-butane-1,3-dione from Step 1 (1.00 g, 4.0 mmol) in ethanol (50 mL). The reaction was heated to reflux and stirred for 20 hours. (HPLC area percent showed a 96:3 ratio of 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide to its regioisomer (4-[3-(4-chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide). After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water and with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a light brown solid which was recrystallized from ethyl acetate and iso-octane to give the pyrazole (1.28 g, 80%, mp 143-145°C). HPLC showed that

the purified material was a 99.5:0.5 mixture of 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide to its regioisomer. ^{1}H NMR ($CDCl_3/CD_3OD$ 10/1) d 5.2 (s, 2H), 6.8 (s, 1H), 7.16 (d, j = 8.5 Hz, 2H), 7.35 (d, j = 8.5 Hz, 2H), 7.44 (d, j = 8.66, 2H), 7.91 (d, j = 8.66, 2H); ^{13}C NMR ($CDCl_3/CD_3OD$ 10/1) d 106.42 (d, j = 0.03 Hz), 121.0 (q, j = 276 Hz), 125.5, 126.9, 127.3, 129.2, 130.1, 135.7, 141.5, 143.0, 143.9 (q, j = 37 Hz), 144.0; ^{19}F NMR ($CDCl_3/CD_3OD$ 10/1) d -62.9. EI GC-MS M+ = 401.

Example 2



4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

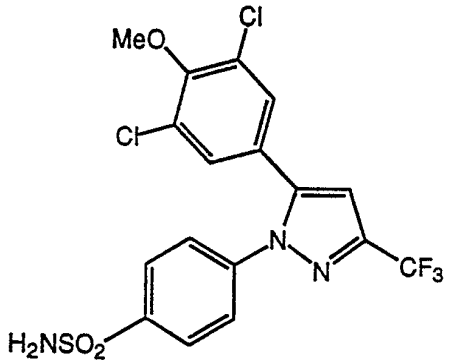
Step 1: Preparation of 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione

4'-Methylacetophenone (5.26 g, 39.2 mmol) was dissolved in 25 mL of methanol under argon and 12 mL (52.5 mmol) sodium methoxide in methanol (25%) was added. The mixture was stirred for 5 minutes and 5.5 mL (46.2 mmol) ethyl trifluoroacetate was added. After refluxing for 24 hours, the mixture was cooled to room temperature and concentrated. 100 mL 10% HCl was added and the mixture extracted with 4 X 75 mL ethyl acetate. The extracts were dried over $MgSO_4$, filtered and concentrated to afford 8.47 g (94%) of a brown oil which was carried on without further purification.

Step 2: Preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

To the dione from Step 1 (4.14 g, 18.0 mmol) in 75 mL absolute ethanol was added 4.26 g (19.0 mmol) 4-sulphonamidophenylhydrazine hydrochloride. The reaction was refluxed under argon for 24 hours. After cooling to room temperature and filtering, the reaction mixture was concentrated to afford 6.13 g of an orange solid. The solid was recrystallized from methylene chloride/hexane to give 3.11 g (8.2 mmol, 46%) of the product as a pale yellow solid: mp 157-159°C; Anal. calc'd for $C_{17}H_{14}N_3O_2SF_3$: C, 53.54; H, 3.70; N, 11.02. Found: C, 53.17; H, 3.81; N, 10.90.

Example 3



4-[5-(3,5-Dichloro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

Step 1: Preparation of 3,5-dichloro-4-methoxyacetophenone

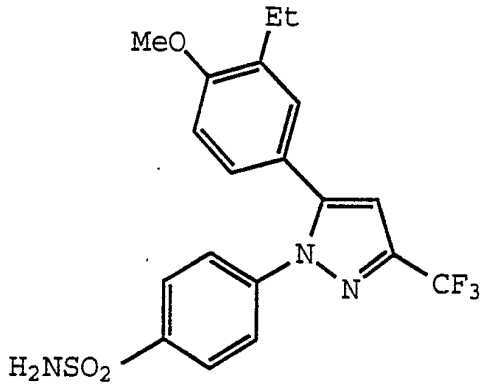
To a cooled solution (0°C) of 7.44 g (55.8 mmol) $AlCl_3$ in 25 mL of CH_2Cl_2 under argon was added 2.5 mL of acetic anhydride dropwise. After stirring for 0.5 hours,

4.18 g (23.6 mmol) of 2,6-dichloroanisole was added dropwise. The reaction was stirred at 0°C for 1 hour, warmed to room temperature and stirred for 12 hours. The reaction was poured into 6 mL conc. hydrochloric acid/80 mL ice water. The aqueous phase was extracted with ethyl acetate (3 X 75 mL). The combined organic washes were dried over $MgSO_4$, filtered, and stripped to afford the crude product as a yellow oil. NMR analysis showed that acylation only occured para to the methoxy. The crude oil was used without any further purification.

Steps 2 and 3: Preparation of 4-[5-(3,5-dichloro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The title compound was prepared in the same manner as Example 2, Steps 1 and 2 and was purified on a prep plate eluting with 10:1 hexane/ethyl acetate to afford a yellow solid: Anal. calc'd for $C_{17}H_{12}N_3O_3SF_3Cl_2 \cdot H_2O$: C, 42.16; H, 2.91; N, 8.68. Found: C, 42.03; H, 2.54; N, 8.45.

Example 4



4-[5-(3-Ethyl-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

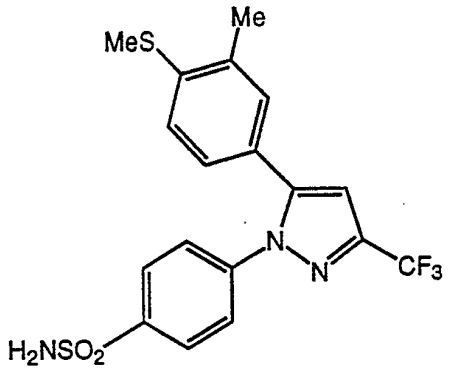
Step 1: Preparation of 3-ethyl-4-methoxyacetophenone

$AlCl_3$ (4.9 g, 36.8 mmol) was added to a solution of 2-ethylanisole (2.5 g, 18.4 mmol) in methylene chloride (50 mL). Acetyl chloride (1.3 mL, 18.4 mmol) was added dropwise to the reaction mixture, which was then stirred at reflux for 0.5 hours. After cooling to room temperature, the reaction was poured over crushed ice and followed up with a methylene chloride/water extraction. The organic layer was dried over magnesium sulfate, filtered and concentrated. The crude product was chromatographed on a 4000 micron chromatotron plate with 10% ethyl acetate/90% hexane as eluant to afford 2.3 g of desired material.

Steps 2 and 3: Preparation of 4-[5-(3-ethyl-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The title compound was prepared using the procedure described in Example 2, Steps 1 and 2: Anal. calcd for $C_{19}H_{18}N_3O_3SF_3$: C, 53.64; H, 4.26; N, 9.88. Found: C, 53.69; H, 4.36; N, 9.88.

Example 5



4-[5-(3-Methyl-4-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

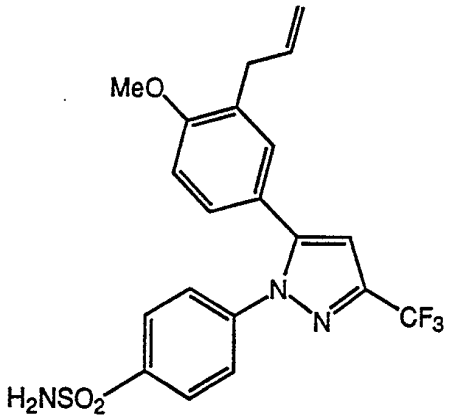
Step 1: Preparation of 2-methylthioanisole

Methyl iodide (0.5 mL, 8.1 mmol) and potassium carbonate (1.1 g, 8.1 mmol) were added to a solution of o-thiocresol (1.0 g, 8.1 mmol) in 10 mL of DMF. The reaction was stirred at 50°C for 4 hours and poured into hexane and water. The organic layer was separated, dried over magnesium sulfate and concentrated to afford 1.1 g of desired material.

Steps 2, 3 and 4: Preparation of 4-[5-(3-methyl-4-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The title compound was prepared using the procedures found in Example 4, Steps 1, 2 and 3: Anal. calcd. for $C_{18}H_{16}N_3O_2S_2F_3$: C, 50.58; H, 3.77; N, 9.83. Found: C, 50.84; H, 3.62; N, 9.62.

Example 6



4-[5-(3-(3-Propenyl)-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

Step 1: Preparation of 3-allyl-4-methoxyacetophenone

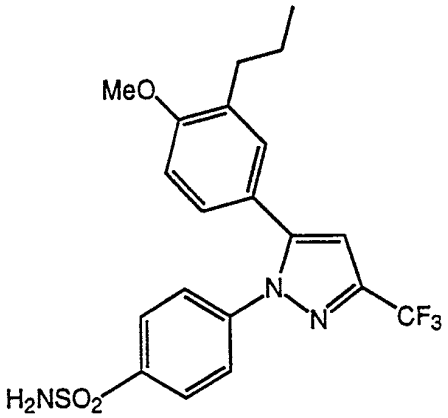
Potassium hydroxide (3.2 g, 56.8 mmol) was added to a solution of 3-allyl-4-hydroxyacetophenone (10 g, 56.8) in 125 mL THF. Dimethyl sulfate (excess) was added and the

reaction was stirred at 50°C for 16 hours. The reaction was cooled, concentrated and poured into EtOAc and water. The organic layer was separated and washed with dilute sodium hydroxide to get rid of unreacted starting material. The ethyl acetate layer was dried and concentrated to afford 9.2 g of 3-allyl-4-methoxy acetophenone.

Steps 2 and 3: Preparation of 4-[5-(3-(3-propenyl)-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The title compound was prepared using the procedures described in Example 2, Steps 1 and 2: Anal. calc'd for $C_{20}H_{18}N_3F_3O_3S$: C, 54.92; H, 4.15; N, 9.61. Found: C, 54.70; H, 4.12; N, 9.43.

Example 7



4-[5-(3-Propyl-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

Step 1: Preparation of 3-n-propyl-4-methoxyacetophenone

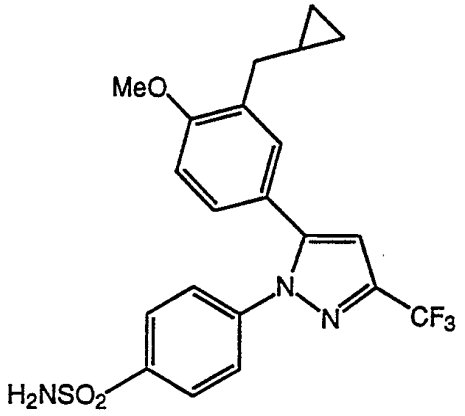
To a solution of the product in Example 6, Step 1 (3 g, 17.0 mmol) in 50 mL of ethanol was added a catalytic amount of 4% Pd/C. The reaction mixture was stirred in a Parr shaker at room temperature at 5 psi hydrogen for 0.5 hours. The reaction was filtered and

concentrated to afford 4 g of pure 3-propyl-4-methoxy acetophenone.

Steps 2 and 3: Preparation of 4-[5-(3-n-propyl-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The title compound was prepared using the procedures described in Example 2, Steps 1 and 2: Anal. calcd. for $C_{20}H_{20}N_3F_3O_3S$: C, 54.66; H, 4.59; N, 9.56. Found: C, 54.84; H, 4.65; N, 9.52.

Example 8



4-[5-(3-Cyclopropylmethyl-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

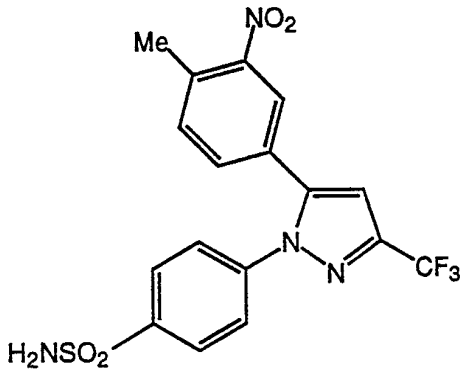
Step 1: Preparation of 3-cyclopropylmethyl-4-methoxyacetophenone

To a solution of the product in Example 6, Step 1 (3 g, 17.0 mmol) and catalytic $Pd(OAc)_2$ in 20 mL Et_2O was added ethereal diazomethane until starting material was consumed. The reaction was filtered, concentrated and chromatographed on a 4000 micron chromatotron plate (20% EA/80% hexane as eluant) to afford 2.5 g of desired ketone.

Steps 2 and 3: Preparation of 4-[5-(3-cyclopropylmethyl-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The title compound was prepared using the procedures described in Example 2, Steps 1 and 2: Anal. calc'd. for $C_{21}H_{20}N_3F_3SO_3$: C, 55.87; H, 4.47; N, 9.31. Found: C, 55.85; H, 4.27; N, 9.30.

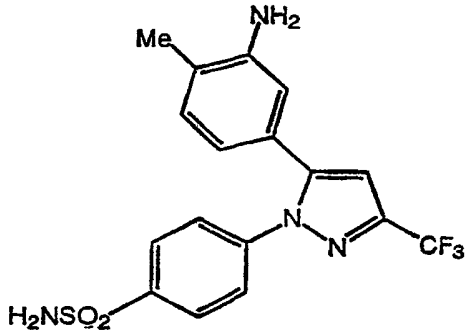
Example 9



4-[4-Methyl-3-nitrophenyl)-3-(trifluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide

To a solution of the product of Example 2 (500 mg, 1.31 mmol) in 5mL of sulfuric acid was added nitric acid (0.6 mL, 1.31 mmol) and the reaction was stirred at room temperature for 0.5 hours. The mixture was poured over ice, the solid precipitate was filtered and chromatographed on a 4000 micron plate (20% EtOAc/80% hexane as eluant) to afford 410 mg of desired material: Anal. calc'd for $C_{17}H_{13}N_4O_4SF_3$: C, 47.89; H, 3.07; N, 13.14. Found: C, 47.86; H, 2.81; N, 13.15.

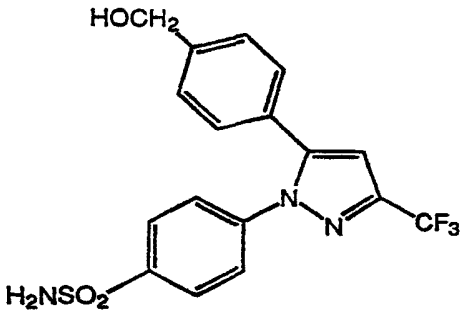
Example 10



4-[5-(3-Amino-4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

A catalytic amount of 10% Pd/C was added to a solution of hydrazine hydrate (0.022 mL, 0.7 mmol) in 10 mL of ethanol. The reaction mixture was refluxed for 15 minutes before the addition of the compound from Example 9 (100 mg, 0.23 mmol), and the resulting reaction mixture was refluxed for another 2 hours. The reaction was cooled, filtered through Celite™ and concentrated to afford 100 mg of title compound: Anal. calc'd for $C_{17}H_{15}N_4O_2SF_3 \cdot 0.5\ CO_2$: C, 50.24; H, 3.61; N, 13.39. Found: C, 50.49; H, 3.44; N, 13.37.

Example 11



4-[5-(4-Hydroxymethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

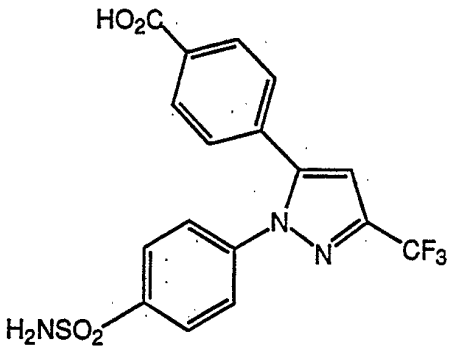
Step 1: Preparation of 4-[5-(4-bromomethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The product from Example 2 (1.13 g, 3.0 mmol) and N-bromosuccinimide (NBS, 0.64 g, 3.6 mmol) were dissolved in 40 mL of benzene and irradiated with a UV lamp for 3 hours. The reaction was cooled to room temperature and poured into 50 mL of H_2O. The organic phase was separated, washed with brine and dried over $MgSO_4$. The crude pyrazole was obtained as an amber oil. The oil was purified via radical band chromatography eluting with 30% ethyl acetate/70% hexane to afford the 4-bromomethyl compound as a yellow oil which crystallized upon standing.

Step 2: Preparation of 4-[5-(4-hydroxymethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The bromo methyl compound from Step 1 was dissolved in 30 mL of acetone/4 mL of H_2O and refluxed for 120 hours. The reaction was concentrated and the residue dissolved in 50 mL of ethyl acetate and dried over $MgSO_4$. The crude product was obtained as an amber oil. The oil was purified via radial band chromatography eluting with 30% ethyl acetate/70% hexane to afford the title compound as a yellow solid: Anal. calc'd for $C_{17}H_{14}N_3O_3SF_3$: C, 51.38; H, 3.55; N, 10.57. Found: C, 51.28; H, 3.59; N, 10.31.

Example 12

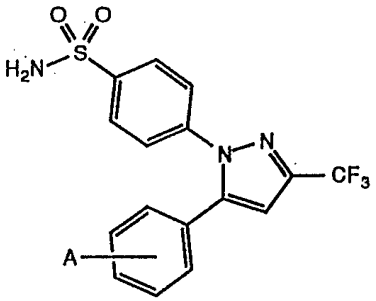


4-[1-(4-(Aminosulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzoic acid

To the product from Example 11 in 2 mL of acetone was added 1.33 M Jones reagent until an orange color persisted. The reaction was poured into 20 mL of ethyl acetate and 20 mL of H_2O and the organic layer separated, washed with saturated sodium bisulfite and dried over $MgSO_4$. The crude product was filtered through silica gel/Celite to afford the title compound as a yellow solid: HRMS m/z 411.0507 (calc'd for $C_{17}H_{12}N_3O_4SF_3$, 411.0500).

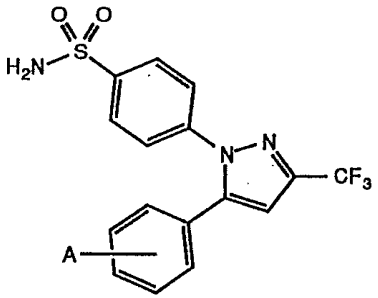
The following compounds in Table I were prepared according to procedures similar to that exemplified in Examples 1-12, with the substitution of the appropriate acetophenone.

TABLE I



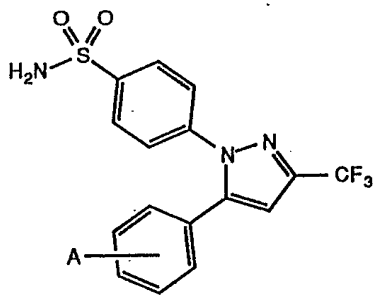
Ex.	A	M.P. (°C)	Analytical
13	4-Br	137-139	Calc. C, 43.07; H, 2.48; N, 9.42; Br, 17.91
			Obs. C, 43.01; H, 2.32; N, 9.39; Br, 17.62
14	3-Cl	154-155	Calc. C, 47.83; H, 2.76;N, 10.46; Cl, 8.82
			Obs. C, 47.61; H, 2.85; N, 10.31; Cl, 8.43
15	2-Cl	159-160	Calc. C, 47.83; H, 2.76; N, 10.46
			Obs. C, 47.47; H, 2.65; N, 10.31
16	4-CF_3	144-145	Calc. C, 46.90; H, 2.55; N, 9.65
			Found: C, 46.98; H, 2.57; N, 9.61
17	4-F	168-169	Calc. C, 49.87; H, 2.88; N, 10.90
			Found: C, 49.83; H, 2.89; N, 10.86

TABLE I (cont.)



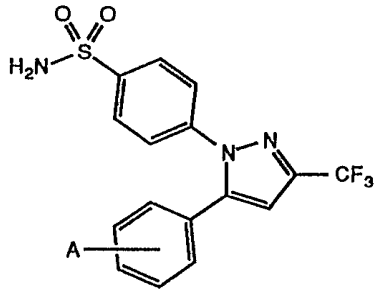
Ex.	A	M.P. (°C)	Analytical
18	H	164-165	Calc. C, 52.31; H, 3.29; N, 11.43 Found: C, 52.14; H, 3.07; N, 11.34
19	4-OCH_3	153-154	Calc. C, 51.38; H, 3.55; N, 10.57 Found: C, 51.00; H, 3.48; N, 10.24
20	4-OCF_3	101-103	Calc. C, 45.24; H, 2.46; N, 9.31 Found: C, 45.22; H, 2.37; N, 9.29
21	2-CH_3	126-128	Calc. C, 53.54; H, 3.70; N, 11.02 Found: C, 53.52; H, 3.55; N, 11.06
22	2,4-di-F	127-130	M+H 404
23	2,6-di-F	178-180	M+H 404
24	4-CN	196-197.5	

TABLE I (cont.)



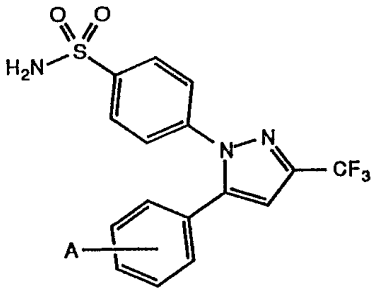
Ex.	A	M.P. (°C)	Analytical
25	3,4-di-Cl	145-147	Calc. C, 44.05; H, 2.31; N, 9.63; Cl, 16.25 Found: C, 44.00; H, 2.20; N, 9.63; Cl, 16.46
26	2,4-di-Cl	153-155	Calc.C, 43.87; H, 2.35; N, 9.59 Found: C, 43.78; H, 2.13; N, 9.56
27	4-NO_2	169-172 (dec)	Calc. C, 46.61; H, 2.69; N, 13.59; S, 7.78 Obs.: C, 46.52; H, 2.67; N, 13.51; S, 7.84
28	2-F	165-166	Calc. C, 49.87; H, 2.88; N, 10.90 Found: C, 49.49; H, 2.62; N, 10.79
29	4-NH_2	124-127 (dec)	HRMS: 382.0671
30	4-F, 2-CH_3	170-171	Calc. C, 51.13; H, 3.28; N, 10.52 Found: C, 50.83, H, 2.98; N, 10.55

TABLE I (cont.)



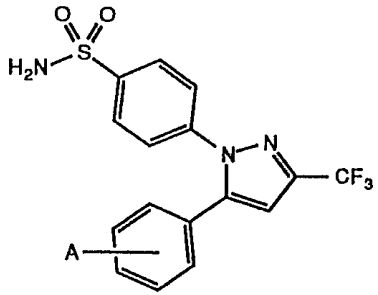
Ex.	A	M.P. (°C)	Analytical
31	3-CH_3	135-137	Calc. C, 53.54; H, 3.70; N, 11.02 Found: C, 53.15; H, 3.58; N, 10.96
32	4-OCH_2CH_3	141-142	Calc. C, 51.43; H, 4.08; N, 9.99 Found: C, 51.49; H, 3.80; N, 10.08
33	4-OCH_3, 3,5-di-CH_3	143-144	Calc. C, 53.64; H, 4.26; N, 9.87 Found: C, 53.49; H, 4.39; N, 9.64
34	3-F	143-144	Calc. C, 49.87; H, 2.88; N, 10.90 Found: C, 49.80; H, 2.80; N, 10.84
35	4-OCH_3, 3-F	155-156	Calc. C, 49.16; H, 3.15; N, 10.11 Found: C, 48.77; H, 2.93; N, 9.96
36	4-SCH_3	165-166	Calc. C, 49.39; H, 3.41; N, 10.16 Found: C, 49.48; H, 3.46; N, 10.26

TABLE I (cont.)



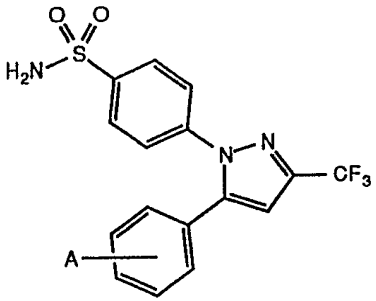
Ex.	A	M.P. (°C)	Analytical
37	4-Cl, 3-CH_3	ND	Calc. C, 49.10; H, 3.15; N, 10.11 Found: C, 49.00; H, 3.00; N, 10.10
38	4-CH_2CH_3	ND	Calc. C, 54.68; H, 4.08; N, 10.63 Found: C, 54.54; H, 3.73; N, 10.67
39	2,4-di-CH_3	ND	Calc. C, 54.68; H, 4.08; N, 10.63 Found: C, 54.31; H, 4.32; N, 10.39
40	2-OCH_3	167-168	Calc. C, 51.38; H, 3.55; N, 10.57 Found: C, 51.29; H, 3.34; N, 10.52
41	4-OCH_3, 3-CH_3	146-147	
42	4-SCH_3, 3-Br	141-144	HRMS: 490.9595
43	4-CH_3, 3-Cl	186-190	Calc. C, 49.10; H, 3.15; N, 10.11 Found: C, 49.21;H, 3.17; N, 10.10

TABLE I (cont.)



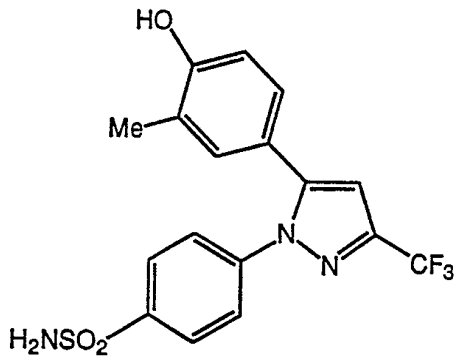
Ex.	A	M.P. (°C)	Analytical
44	3,4-di-OCH_3	192-193	Calc. C, 50.58; H, 3.77; N, 9.83 Found: C, 50.58; H, 3.83; N, 9.72
45	4-OCH_3, 3-Cl	166-168	Calc. C, 47.29; H, 3.03; N, 9.73 Found: C, 47.21; H, 2.91; N, 9.55
46	4-OCH_3, 3-Cl, 5-CH_3	ND	Calc. C, 48.49; H, 3.39; N, 9.42 Found: C, 48.27; H, 3.42; N, 9.22
47	2-OCH_3, 4-F	163-164	Calc. C, 49.16; H, 3.15; N, 10.12 Found: C, 49.32; H, 3.27; N, 10.18
48	2,4-di-OCH_3	ND	Calc. C, 50.58; H, 3.77; N, 9.83 Found: C, 50.40; H, 3.78; N, 9.83
49	4-F, 3-Cl	ND	Calc. C, 45.78; H, 2.40; N, 10.01 Found: C, 45.75; H, 2.34; N, 10.15

TABLE I (cont.)



Ex.	A	M.P. (°C)	Analytical
50	4-OCH_3, 3,5-di-F	ND	Calc. C, 47.12; H, 2.79; N, 9.70 Found: C, 46.72; H, 2.75; N, 9.54
51	4-SCH_3, 3-F	ND	Calc. C, 47.33; H, 3.04; N, 9.74 Found: C, 47.25; H, 3.39; N, 9.45
52	4-SCH_3, 3-Cl	ND	Calc. C, 45.59; H, 2.93; N, 9.38 Found: C, 45.56; H, 2.76; N, 9.52
53	4-$N(CH_3)_2$	ND	HRMS: 410.1016
54	4-$N(CH_2CH_3)_2$	ND	HRMS: 438.1353

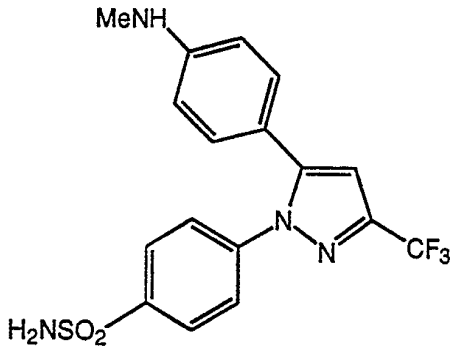
Example 55



4-[5-(4-Hydroxy-3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

To a solution of the product of Example 41 (240 mg, 0.58 mmol) in DMF (3 mL) was added NaSMe (205 mg, 2.9 mmol) and the mixture heated to reflux for 2 hours. The mixture was cooled, poured into 0.1N HCl and extracted with EtOAc (3x). The combined extracts were dried over $MgSO_4$ and concentrated. Flash chromatography using 1:1 hexane/ethyl acetate provided 31 mg of the title compound: Anal. calc'd for $C_{17}H_{14}N_3O_3SF_3 \cdot 0.25\ H_2O$: C, 50.80; H, 3.64; N, 10.45. Found: C, 50.71; H, 3.47; N, 10.39.

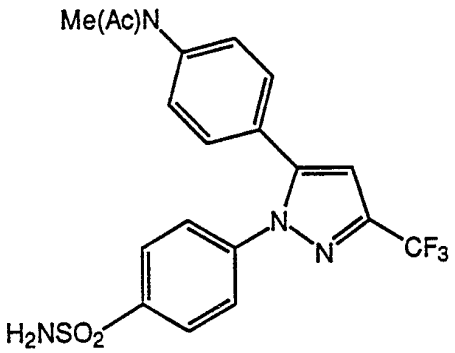
Example 56



4-[5-(4-(N-Methylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

To a solution of the product from Example 53 (431 mg, 1.0 mmol) in 10 ml methanol was added 36 mg (0.17 mmol) ruthenium (III) chloride hydrate, followed by 1.5 mL 30% hydrogen peroxide (14.7 mmol) over 2 hours. The reaction was quenched with 25 mL of 1M KOH in methanol and concentrated to give 1.24 g of a brown solid. The solid was purified on a prep plate eluting with 2/97/1 methanol/methylene chloride/ammonium chloride to give 52 mg (0.14 mmol, 12%) of the product as a yellow solid.

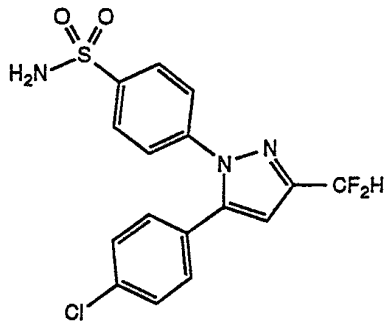
Example 57



N-[4-[1-[4-(Aminosulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl]-N-methylacetamide

19 mg (0.051 mmol) of the product from Example 56 was treated with 0.03 mL acetic anhydride (0.32 mmol) and 0.03 mL triethylamine (0.22 mmol) in 3 mL methylene chloride at room temperrature for 12 hours. The reaction mixtured was concentrated and the residue dissolved in 10 mL ethyl acetate. After washing with brine (2 x 10 mL), the solution was dried over $MgSO_4$, filtered and concentrated to afford the title compound (18.4 mg, 74%) as a yellow solid: HRMS m/e 438.0976 (calc'd for $C_{19}H_{17}N_4O_3SF_3$, 438.0974).

Example 58



4-[5-(4-Chlorophenyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

Step 1: Preparation of 4,4-difluoro-1-[4-(chloro)phenyl]-butane-1,3-dione.

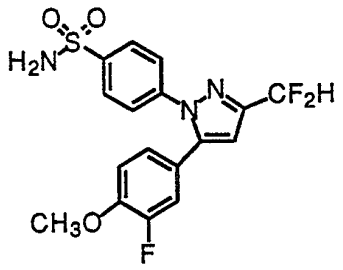
Ethyl difluoroacetate (24.82 g, 200 mmol) was placed in a 500 mL three-necked round bottom flask, and dissolved in diethyl ether (200 mL). To the stirred solution was added 25% sodium methoxide in methanol (48 mL, 210 mmol) via an addition funnel over a 2 minute period. Next, 4'-chloroacetophenone (25.94 g, 200 mmol) was dissolved in diethyl ether (50 mL), and added to the reaction dropwise over 5 minutes. After stirring overnight (18 hours), 1N HCl (250 mL) and ether (250 mL) were added. The organic layer was collected, washed with brine (250 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 46.3 g of a yellow solid. The solid was recrystallized from methylene chloride and iso-octane to give 31.96 g (69%) of the dione: mp 65-66.5°C.

Step 2: Preparation of 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

4-Sulphonamidophenylhydrazine hydrochloride (1.45 g, 6.5 mmol 1.3 equivalent) and 4,4-difluoro-1-[4-

(chloro)phenyl]butane-1,3-dione from Step 1 (1.16 g, 5 mmol) were dissolved in ethanol (10 mL). The reaction was heated to reflux and stirred for 20 hours. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate (100 mL), washed with water (100 mL) and with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 1.97 g of a light brown solid which was recrystallized from ethanol and water to give 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1.6 g, 83%): mp 185-186°C.

Example 59



4-[5-(3-Fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide

<u>Step 1: Preparation of 3'-fluoro-4'-methoxy-acetophenone.</u>

Aluminum chloride (80.0 g, 0.6 mol) and chloroform (750 mL) were placed in a 2 L three-necked round bottom flask fitted with a mechanical stirrer and cooled by means of an ice bath. To the stirred solution acetyl chloride (51.0 g, 0.65 mol) was added dropwise, maintaining the temperature between 5-10°C. The mixture was stirred for 10 minutes at 5°C before the dropwise addition at 5-10°C of 2-fluoroanisole (62.6 g, 0.5 mol). The mixture was stirred at 0-10°C for 1 hour and poured into ice (1 L). The resultant layers were separated and the aqueous layer was extracted with dichloromethane (2x250 mL). The combined

organic layers were washed with water (2x150 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to a volume of 300 mL. Hexanes were added and a white solid formed which was isolated by filtration and air dried. This material was recrystallized from a mixture of dichloromethane and hexanes to afford (77.2 g, 92%) of material suitable for use in the next step: mp 92-94°C; ^1H NMR (DMSO-d_6) 7.8 (m, 2H), 7.3 (t, 1H), 3.9 (s, 3H), 2.5 (s, 3H).

Step 2: Preparation of 4,4-difluoro-1-(3-fluoro-4-methoxyphenyl)-butane-1,3-dione.

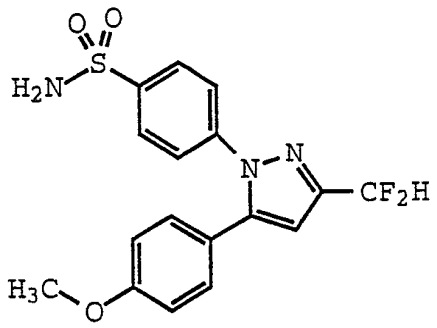
Ethyl difluoroacetate (4.06 g, 32.7 mmol) was placed in a 250 mL Erlenmeyer flask, and dissolved in methyl *tert*-butyl ether (50 mL). To the stirred solution was added 25% sodium methoxide (7.07 g, 32.7 mmol) followed by 3'-fluoro-4'-methoxyacetophenone from Step 1 (5.0 g, 29.7 mmol). After stirring for 16 hours, 1N HCl (50 mL) was added. The organic layer was collected, washed with water (2x50 mL), dried over anhydrous $MgSO_4$, filtered, and added to hexanes to precipitate a tan solid (7.0 g, 96%): mp 70-72°C; ^1H NMR (DMSO-d_6) 8.0 (m, 3H), 7.3 (t, 1H), 6.9 (s, 1H), 6.5 (t, 1H), 3.9 (s, 3H).

Step 3: Preparation of 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

4,4-Difluoro-1-(3-fluoro-4-methoxyphenyl)-butane-1,3-dione from Step 2 (7.0 g, 28.4 mmol) was dissolved in ethanol (150 mL). To the stirred mixture was added 4-sulphonamidophenylhydrazine hydrochloride (7.4 g, 33 mmol) and stirred at reflux overnight (16 hours). The mixture was cooled and water was added until crystals slowly appeared. The product was isolated by filtration and air dried to provide the desired product as a light tan solid (9.8 g, 87%): mp 159-161°C; ^1H NMR (DMSO-d_6) 7.85

(d, 2H), 7.5 (m, 6H), 7.3-6.9 (m, 5H), 3.8 (s 3H). Anal. Calc'd for $C_{17}H_{14}N_3SO_3F_3$: C, 51.38; H, 3.55; N, 10.57. Found: C, 51.46; H, 3.52; N, 10.63.

Example 60



4-[3-Difluoromethyl-5-(4-methoxyphenyl)-1-H-pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 4,4,4-trifluoromethyl-1-(4-methoxyphenyl)butane-1,3-dione.

To a stirred solution of 4-methoxyacetophenone (11.43 g, 76.11 mmol) and ethyl difluoroacetate (8.4 mL, 10.4 g, 83.72 mmol) in diethyl ether (300 mL) in a 500 mL round bottomed flask was added sodium methoxide in methanol (18.2 mL of a 25% solution, 79.91 mmol). The solution became a dark lavender color within thirty minutes, and then a gray suspension within 1.5 hours. The reaction was stirred for 60 hours. Diethyl ether (300 mL) was added and the mixture was acidified (pH 2) with 1N HCl. The mixture was transferred to a separatory funnel, mixed and separated. The ethereal phase was washed with water, dried over magnesium sulfate, and filtered. Hexane was added causing precipitation of an orange solid 5.25 g of 4,4,4-trifluoromethyl-1-(4-methoxyphenyl)butane-1,3-dione. An additional 3.43 g of product was obtained by recrystallization of the concentrated mother liquor from hexane: ^1H NMR ($CDCl_3$) 400 mHz 15.58 (br s, 1 H), 7.94 (d,

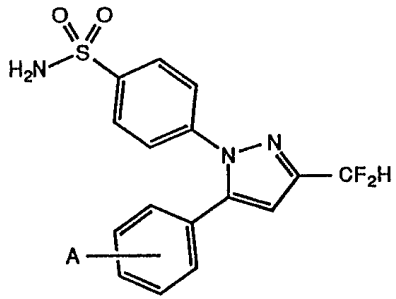
J = 8.87 Hz, 2H), 6.98 (d, J = 8.87 Hz, 2H), 6.49 (s, 1H), 6.00 (t, J = 54.55 Hz, 1 H), 3.89 (s, 3H).

Step 2. Preparation of 4-[5-(4-methoxyphenyl)-3-difluoromethyl-1-H-pyrazol-1-yl]benzenesulfonamide.

A mixture of 4,4,4-trifluoromethyl-1-(4-methoxyphenyl)butane-1,3-dione from Step 1 (2.006 g, 8.79 mmol) and 4-sulfonamidophenylhydrazine hydrochloride salt (2.065 g, 9.23 mmol) dissolved in ethanol (25 mL) was heated to reflux for 16 hours. The reaction was cooled to room temperature, was concentrated and recrystallized from methanol yielding 4-[5-(4-methoxyphenyl)-3-difluoromethyl-1-H-pyrazol-1-yl]benzenesulfonamide as fluffy tan crystals (1.49 g, 45%): mp 133-135°C; ^{1}H NMR ($CDCl_3$) 300 mHz 7.90 (d, J = 8.863 Hz, 2H), 7.45 (d, J = 8.863 Hz, 2H), 7.14 (d, J = 8.863 Hz, 2H), 6.88 (d, J = 8.863 Hz, 2H), 6.77 (t, J = 56.47 Hz, 1H), 6.68 (s, 1 H), 4.96(br s, 2 H), 3.83(s, 3 H); ^{19}NMR ($CDCl_3$) 300 mHz -112.70 (d, J = 57.9 Hz). High resolution mass spectrum Calc'd for $C_{17}H_{15}F_2N_3O_3S$: 379.0802. Found: 379.0839. Elemental analysis calc'd for $C_{17}H_{15}F_2N_3O_3S$: C, 53.82; H, 3.99; N, 11.08. Found: C, 53.75; H, 3.99; N, 11.04.

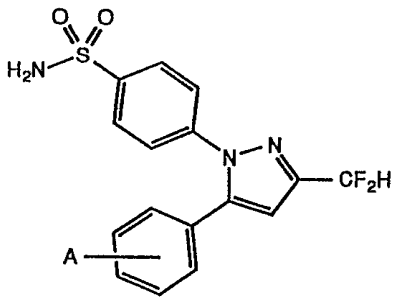
The following compounds in Table II were obtained according to procedures similar to that exemplified in Examples 58-60, with the substitution of the appropriate acetophenone.

TABLE II



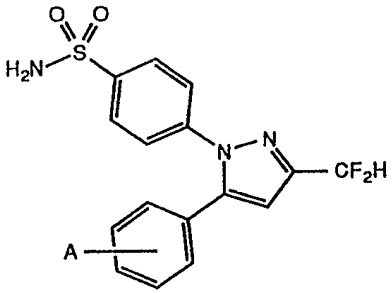
Ex.	A	M.P. (°C)	Anal.
61	4-CF_3	202-205	M+H 418
62	4-SCH_3	157-158	
63	4-(1-morpholino)	167-171	M+ 434
64	4-CH_3	158-159	Calc. C, 56.19; H, 4.16; N, 11.56
			Obs. C, 56.25; H, 4.17; N, 11.61
65	3,4-di-CH_3	168-171	Calc. C, 57.28; H, 4.54;N, 11.13
			Obs. C, 57.34; H, 4.59; N, 11.16
66	4-CO_2CH_3	157-158	Calc. C, 53.56; H, 3.09; N, 15.61
			Obs. C, 53.45; H, 3.11; N, 15.62
67	4-$CONH_2$	235-236	HRMS: 393.0833
68	4-CO_2H	258-260 (dec)	HRMS: 394.0662
69	2-F,4-OCH_3	138-140	Calc. C, 51.38; H, 3.55; N, 10.57
			Obs. C, 51.14; H, 3.48; N, 10.40

TABLE II (cont.)



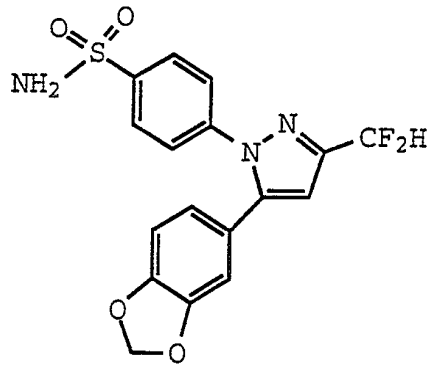
Ex.	A	M.P.(°C)	Anal.
70	4-CN	222-224	Calc. C, 54.54; H, 3.23; N, 14.97
			Obs.: C, 54.58; H, 3.21; N, 15.06
71	3-Cl, 4-CH_3	156-158	Calc. C, 51.32; H, 3.55; N, 10.56
			Obs: C, 51.46; H, 3.53; N, 10.53
72	3-Cl, 4-OCH_3	160	Calc. C,49.34; H,3.41; N,10.15; Cl,8.57; S,7.75
			Obs.: C,49.41; H,3.37; N,10.17; Cl,8.62; S,7.67
73	4-Cl, 3-CH_3	163-165	Calc. C, 51.32; H, 3.55; N, 10.56
			Obs.: C, 51.42; H, 3.57; N, 10.53
74	3,4-di-OCH_3	181-185	Calc. C, 52.81; H, 4.19; N, 10.26
			Obs.: C, 52.86; H, 4.19; N, 10.20
75	3,5-di-Cl, 4-OCH_3	170-173	Calc. C, 45.55; H, 2.92; N, 9.37
			Obs.: C, 45.83; H, 3.05; N, 9.31

TABLE II (cont.)



Ex.	A	M.P.(°C)	Anal.
76	3,5-di-F, 4-OCH_3	149-150	Calc. C, 49.16; H, 3.15; N, 10.12 Obs.: C, 49.24; H, 3.16; N, 10.13
77	2-OCH_3	129-132	Calc. C, 53.82; H, 3.99; N, 11.08 Obs.: C, 53.82; H, 3.97; N, 11.15
78	3-Br, 4-OCH_3	164	HRMS : 456.9883
79	4-SO_2CH_3	209-210	
80	4-C_6H_5	167-170	M+ 425
81	H	171-172	HRMS: 349.0737

Example 82



4-[5-(1,3-Benzodioxol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 1-(1,3-benzodioxol-5-yl)-4,4-difluorobutane-1,3-dione.

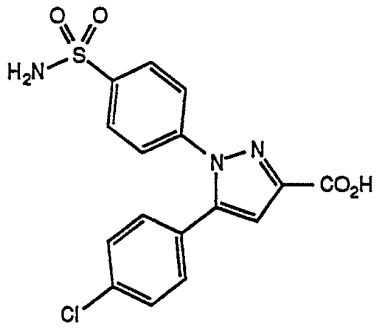
Ethyl difluoroacetate (1.72 g, 11 mmol) was dissolved in ether (25 mL). To the stirred solution was added 25% sodium methoxide (2.38 g, 11 mmol) followed by 3',4'-(methylenedioxy)acetophenone (1.64 g, 10 mmol). After stirring 16 hours, 1N HCl (25 mL) was added. The organic layer was collected and washed with water (2x25 mL), dried over magnesium sulfate, filtered, and concentrated. The resulting crude dione was used in the next step without further purification or characterization.

Step 2. Preparation of 5-(1,3-benzodioxol-5-yl)-4-[3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

1-(1,3-Benzodioxol-5-yl)-4,4-difluorobutane-1,3-dione from Step 1 (2.4 g, 10 mmol) was dissolved in ethanol (100 mL). To the stirred mixture was added 4-sulfonamidophenylhydrazine hydrochloride (2.46 g, 11 mmol) and heated to reflux for 16 hours. The mixture was cooled and water was added until crystals slowly appeared. Filtration yielded a light tan solid (3.3 g, 84 %): mp

214-218°C; ^{1}H NMR (D_6-DMSO): 7.86 (d, J=8.7Hz, 2H), 7.51 (d, J=8.7Hz, 2H), 7.49 (brs, 2H), 7.3-6.7 (m, 5H), 6.06(s, 2H). Anal. Calc'd for $C_{17}H_{13}N_3SO_4F_2$: C, 51.91; H, 3.33; N, 10.68. Found: C, 51.90; H, 3.25; N, 10.65.

Example 83



4-[4-(Aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylic acid

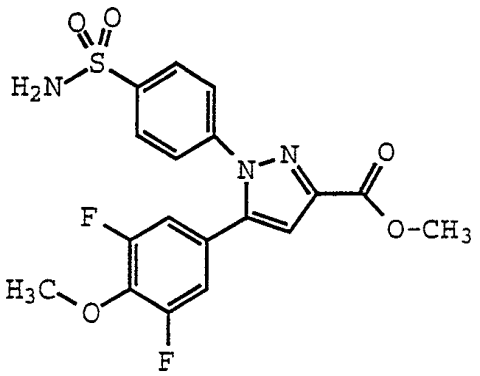
Step 1: Preparation of methyl-4-[4-(chloro)phenyl]-2,4-dioxobutanoate .

Dimethyl oxalate (23.6 g, 200 mmol) was placed in a 500 mL three-necked round bottom flask, and dissolved in diethyl ether (200 mL). To the stirred solution was added 25% sodium methoxide in methanol (48 mL, 210 mmol) via an addition funnel over a 2 minute period. Next, 4'-chloroacetophenone (25.94 g, 200 mmol) was dissolved in diethyl ether (50 mL), and added to the reaction dropwise over 3 minutes. After stirring overnight (18 hours), 1N HCl (400 mL) and ethyl acetate (750 mL) were added. The organic layer was collected, washed with brine (350 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 45.7 g of a yellow solid. The solid was recrystallized from ethyl acetate and iso-octane to give 23 g (48%) of the dione: mp 108.5-110.5°C.

Step 2: Preparation of 4-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylic acid

4-Sulphonamidophenylhydrazine hydrochloride (1.45 g, 6.5 mmol, 1.3 equivalent) and methyl-4-[4-(chloro)phenyl]-2,4-dioxobutanoate (1.2 g, 5 mmol) were dissolved in ethanol (50 mL). The reaction was heated to reflux and stirred for 20 hours. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate (200 mL) and washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 1.7 g of a light brown solid which was recrystallized from methanol and water to yield 1.6 g (85%) of a white solid. This material was dissolved in methanol (150 mL) and 3N NaOH (75 mL) and stirred at reflux for 3 hours. The methanol was removed *in vacuo* and the aqueous solution acidified with concentrated HCl. The product was extracted into ethyl acetate (200 mL), which was washed with brine (100 mL), dried over $MgSO_4$ filtered and concentrated to give 4-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylic acid, 1.4 g (74%): mp 135°C (dec).

Example 84



Methyl 1-(4-aminosulfonylphenyl)-5-(3,5-difluoro-4-methoxyphenyl)-1-H-pyrazole-3-carboxylate

Step 1. Preparation of 3,5-difluoro-4-methoxy-acetophenone.

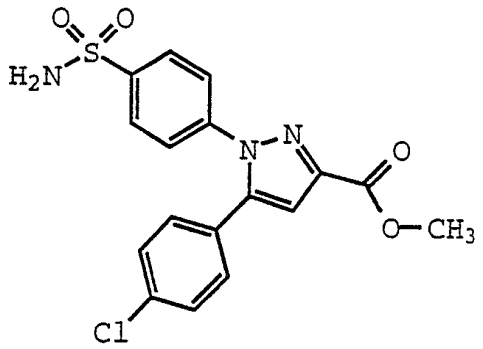
To a stirred suspension of $AlCl_3$ (24.05 g, 180.40 mmol) in chloroform (300 mL, dried by passage through alumina) at 4°C (ice bath) under nitrogen was added acetyl chloride (11.0 mL, 152.65 mmol) over 20 minutes. This chilled suspension was stirred at 0°C for 30 minutes and 2,6-difluoro anisole was added dropwise over 30 minutes. The resulting suspension was warmed to room temperature and stirred overnight. The reaction was quenched by slowly pouring it into a rapidly stirred ice/water mixture. The water layer was extracted with methylene chloride (2x50 mL) and the organic phases were combined and concentrated *in vacuo* yielding a clear mobile oil. In a 50 mL round bottomed flask was added the above clear oil, DMF (25 mL), K_2CO_3 (15 g). Methyl iodide (6 mL) was added and the suspension stirred at 45°C under nitrogen overnight. Water (1 mL) was added and the mixture was heated for an additional 14 hours. The crude reaction mixture was cooled to room temperature, diluted with water (250 mL) and extracted with diethyl ether (3x100 mL). The ether phase was washed with sodium bicarbonate saturated solution, potassium bisulfate (0.1 N solution), dried over $MgSO_4$, filtered and concentrated *in vacuo* yielding a clear mobile liquid. This liquid was distilled (30°C, 1 mm) yielding 12.5 g of a clear liquid which was a mixture of 3,5-difluoro-4-methoxyacetophenone and 3,5-difluoro-4-acetoxyacetophenone in an 85:15 ratio. The yield based upon this ratio was 41%. This ketone was used as is.

Step 2. Preparation of methyl 1-(4-aminosulfonylphenyl)-5-(3,5-difluoro-4-methoxyphenyl)-1-H-pyrazole-3-carboxylate

To a stirred solution of 3,5-difluoro-4-methoxyacetophenone from Step 1 (6.46 g, 34.70 mmol) and

dimethyl oxalate (6.15 g, 52.05 mmol) in methanol (80 mL), was added sodium methoxide solution (13.4 mL of 25% solution, 58.99 mmol) in one portion and the reaction stirred overnight. The crude reaction was diluted with methylene chloride, washed with potassium bisulfate (0.1N solution), brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* yielding methyl 4-(3,5-difluoro-4-methoxyphenyl)-2,4-dioxo-butanoate as an off white crystalline solid which was used as is. A mixture of 4-(3,5-difluoro-4-methoxyphenyl)-2,4-dioxo-butanoate and 4-sulfonamidophenylhydrazine hydrochloride salt (7.76 g, 34.70 mmol) dissolved in methanol was warmed to reflux for 9 hours. Upon allowing the clear reaction to cool to room temperature, a crystalline precipitate formed which was collected by vacuum filtration yielding 5.45 g, (37% based upon the 3,5-difluoro-4-methoxyacetophenone) of methyl 1-(4-aminosulfonylphenyl)-5-(3,5-difluoro-4-methoxyphenyl)-1-H-pyrazole-3-carboxylate as an off-white solid: mp 185-190°C; ^1H NMR ($CDCl_3$/300 mHz) 7.95 (d, J = 8.86, 2H), 7.49 (d, J = 8.86, 2H), 7.02 (s, 1H), 6.77 (m, 2H), 4.99 (s, 2H), 4.04 (s, 3 H), 3.98 (s, 3H); ^{19}F NMR ($CDCl_3$/300 mHz) -126.66. Anal. Calc'd for $C_{17}H_{13}F_2N_3O_3S$: C, 51.06; H, 3.57; N, 9.92. Found: C, 51.06; H, 3.54, N, 9.99.

Example 85



Methyl [1-(4-aminosulfonylphenyl)-5-(4-chlorophenyl)-1H-pyrazole-3-yl]carboxylate

Step 1. Preparation of methyl 4-[4-(chloro)phenyl]-2,4-dioxobutanoate

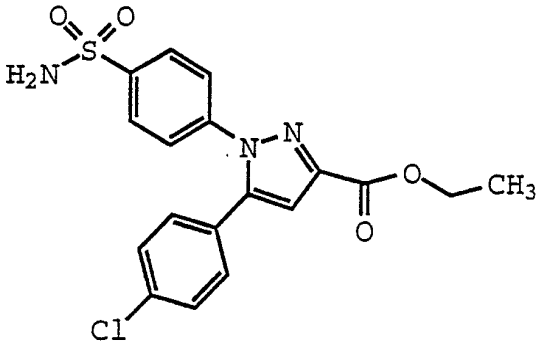
Dimethyl oxalate (15.27 g, 0.129 mol) and 4'-chloroacetophenone (20.0 g, 0.129 mol) were charged to a 500 mL round-bottom flask, with provisions made for magnetic stirring, and diluted with methanol (300 mL). Sodium methoxide (25% in methanol, 70 mL) was added in one portion. The reaction was stirred at room temperature for 16 hours. The reaction became an insoluble mass during this time. The solid was mechanically broken up, then concentrated hydrochloric acid (70 mL) was added, and the white suspension was stirred vigorously at room temperature for sixty minutes. The suspension was cooled to 0°C and held for 30 minutes. The soild was filtered, and the filter cake was washed with cold water (100 mL). Upon drying, methyl 4-[4-(chloro)phenyl]-2,4-dioxobutanoate was obtained (16.94 g, 54.4%) as the enol: ^{1}H NMR ($CDCl_3$/300MHz) 7.94 (d, J=8.66 Hz, 2H), 7.48 (d, J=8.66 Hz, 2H), 7.04 (s, 1H), 3.95 (s, 3H), 3.48 (s, 1H).

Step 2. Preparation of methyl [1-(4-aminosulfonylphenyl)-5-(4-chlorophenyl)-1H-pyrazole-3-yl]carboxylate.

A 100 mL round-bottomed flask equipped with magnetic stirrer and nitrogen inlet was charged with methyl 4-[4-(chloro)phenyl]-2,4-dioxobutanoate from Step 1 (5.0 g, 20.78 mmol), 4-sulfonamidylphenylhydrazine hydrochloride (5.11 g, 22.86 mmol) and methanol (50 mL). The reaction vessel was heated to reflux and held for 16 hours. A precipitate formed overnight. The suspension was cooled to 0°C, held for 0.5 hour, filtered and washed with cold water to provide, after air-drying, 7.91 g (91%) of crude product. Recrystallized 3.50 g from boiling ethanol to yield 3.14 g (97%) of pure methyl [1-(4-aminosulfonylphenyl)-5-(4-chlorophenyl)-1H-pyrazole-3-

yl]carboxylate: mp 227°C; ^{1}H NMR ($CDCl_3$/300MHz) 7.91 (d, J=8.86 Hz, 2H), 7.44 (d, J=8.86 Hz, 2H), 7.33 (d, J=8.66 Hz, 2H), 7.14 (d, J=8.66 Hz, 2H), 7.03 (s, 1H), 3.96 (s, 3H). Mass Spectrum, MH+ = 392. Anal. Calc'd for $C_{17}H_{14}N_3O_4ClS$: C, 52.11; H, 3.60; N, 10.72; Cl, 9.05; S, 8.18. Found: C, 52.07; H, 3.57; N, 10.76; Cl, 9.11; S, 8.27.

Example 86

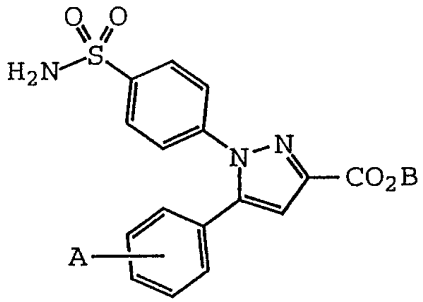


Ethyl [1-(4-aminosulfonylphenyl)-5-(4-chlorophenyl)-1H-pyrazole-3-yl]carboxylate

Methyl [1-(4-aminosulfonylphenyl)-5-(4-chlorophenyl)-1H-pyrazole-3-yl]carboxylate (Example 85) (0.10 g) was dissolved in absolute ethanol (10 mL) and a catalytic amount of 21% NaOEt/EtOH was added. The reaction was stirred without temperature control for 72 hours, then water (10 mL) was added. The product crystallized, the suspension was cooled to 0°C and held for 30 minutes. The product was filtered, washed with water (5 mL) and dried to yield 0.071 g (70%) of a white solid: Mass Spectrum: MH+ = 406. Anal. Calc'd for $C_{18}H_{16}N_3O_4ClS$: C, 53.27; H, 3.97; N, 10.35; Cl, 8.74; S, 7.90. Found: C, 53.04; H, 4.00; N, 10.27; Cl, 8.69; S, 7.97.

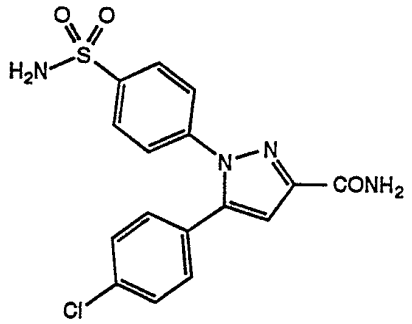
The following compounds in Table III were prepared according to procedures similar to that exemplified in Examples 83-86, with the substitution of the appropriate reagents.

TABLE III



Ex.	A	B	M.P.(°C)	Analytical.
87	4-NO_2	-CH_3	216-220	MH+ = 403
88	4-F	-CH_3	ND	Calc. C,54.40; H,3.76; N,11.19; S,8.54
				Obs. C,54.49; H,3.70; N, 11.25; S, 8.50
89	4-NH_2	-CH_3	267-269(dec)	MH+ = 373
90	4-Br	-CH_3	221-224	MH+ = 438
91	4-OCH_3	-CH_3	169-171	HRMS : 387.0930
92	4-CH_3	-CH_3	213-215	HRMS : 371.0965
93	4-CH_3	-CH_2CH_3	219-220	Calc. C, 59.21; H, 4.97; N, 10.90
				Obs. C, 58.73; H, 4.96; N, 10.78
94	4-Cl	-$CH_2CH_2CH_3$	ND	Calc. C, 54.35; H, 4.32; N, 10.01; Cl, 8.44; S, 7.64
				Obs. C, 54.11; H, 4.28; N, 10.14; Cl, 8.54; S, 7.64
95	3,5-di-Cl, 4-OCH_3	-CH_3	225-229	

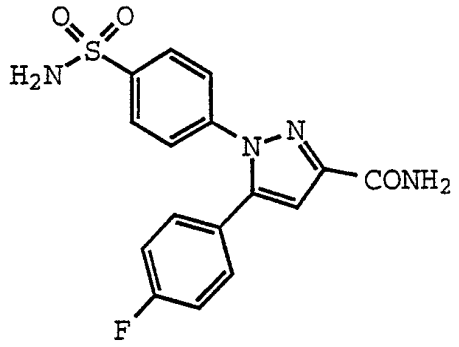
Example 96



4-[4-(Aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1*H*-pyrazole-3-carboxamide

4-[4-(Aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylic acid (Example 83) (1.08 g, 2.86 mmol), HOBt (0.66 g, 4.3 mmol) and EDC (0.66 g, 3.4 mmol) were dissolved in dimethylformamide (DMF) (20 mL) and stirred at ambient temperature for 5 minutes. To this solution was added NH_4OH (30%, 2.9 mL) and the reaction stirred for an additional 18 hours. This solution was then poured into ethyl acetate (200 mL) and 1N HCl (200 mL), shaken and separated. The organic layer was washed with saturated $NaHCO_3$ (150 mL) and brine (150 mL), dried over $MgSO_4$, filtered and concentrated to yield 0.9 g of a white solid which was recrystallized from ethyl acetate and iso-octane to yield 4-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1*H*-pyrazole-3-carboxamide (0.85 g, 79%): mp 108-110°C.

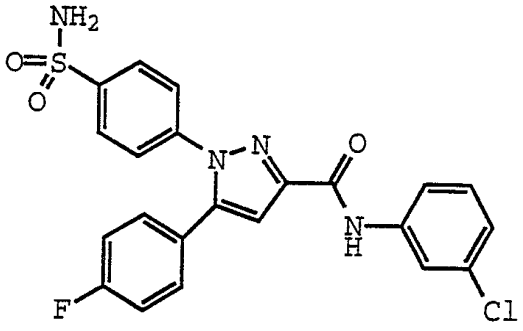
Example 97



[1-(Aminosulfonylphenyl)-5-(4-fluorophenyl-1H-pyrazol-3-yl]carboxamide

A 250 mL three-neck round-bottom flask, equipped with a thermometer, gas sparging tube, reflux condenser and provisions for magnetic stirring, was charged with methyl[1-(4-aminosulfonylphenyl)-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxylate (Example 88) (3.0 g, 7.99 mmol), methanol (100 mL), and a catalytic amount of sodium cyanide. Anhydrous ammonia gas was sparged through the reaction vessel for 16 hours without temperature control. The suspension turned a deep red during this time. The reaction was sparged with anhydrous nitrogen at room temperature for 20 minutes, cooled to 0°C and held for 30 minutes. The solid was filtered and washed with cold water (50 mL) to yield, upon drying, 1.87 g (65%) of [1-(4-aminosulfonylphenyl)-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxamide as a white solid: mp 214-216°C; ^{1}H NMR ($CDCl_3/CD_3OD$/300MHz) 7.64 (d, J=8.66 Hz, 2H), 7.14 (d, J=8.66 Hz, 2H), 6.95 (m, 2H), 6.82 - 6.67 (m,6H), 6.39(s, 1H); ^{19}F NMR ($CDCl_3$/ CD_3OD/282.2MHz) -112.00(m). Mass spectrum, MH+ = 361. Anal. Calc'd for $C_{16}H_{13}N_4O_3FS$: C, 53.33; H, 3.64; N, 15.55; S, 8.90. Found: C, 53.41; H, 3.69; N, 15.52; S, 8.96.

Example 98



N-(3-Chlorophenyl)-[1-(4-aminosulfonylphenyl)-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxamide

Step 1. Preparation of methyl 4-[4-fluorophenyl]-2,4-dioxobutanoate.

Dimethyl oxalate (18.80 g, 0.159 mol) and 4'-fluoroacetophenone (20.0 g, 0.145 mol) were charged to a 1000 mL round-bottom flask and diluted with methanol (400 mL). The reaction flask was placed in a sonication bath (Bransonic 1200), and sodium methoxide (25% in methanol, 70 mL) was added over 25 minutes. The reaction was sonicated at 45°C for 16 hours. The reaction became an insoluble mass during this time. The solid was mechanically broken up, then poured into a hydrochloric acid solution (1N, 500 mL). A magnetic stirrer was added, and the white suspension was stirred vigorously at room temperature for 60 minutes. The suspension was cooled to 0°C and held for 30 minutes. The solid was filtered, and the filter cake was then washed with cold water (100 mL). Upon drying, methyl 4-[4-fluorophenyl]-2,4-diketobutanoate was obtained (22.91 g, 70.6%) as the enol: ^{1}H NMR ($CDCl_3$/300MHz) 8.03 (ddd, J = 8.86 Hz, J=8.66 Hz, J=5.03Hz, 2H), 7.19 (dd, J=8.86 Hz, J=8.66 Hz, 2H), 7.04 (s, 1H), 3.95(s, 3H). ^{19}F NMR ($CDCl_3$/282.2 MHz) - 103.9(m).

Step 2. Preparation of methyl 4-[1-(4-aminosulfonylphenyl)-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxylate.

A 500 mL one-neck round-bottom flask equipped for magnetic stirring was charged with methyl 4-[4-fluorophenyl]-2,4-diketobutanoate from Step 1 (1.00 mg, 44.61 mmol), 4-sulfonamidylphenylhyrazine hydrochloride (10.98 g, 49.07 mmol) and methanol (200 mL). The suspension was heated and held at reflux for three hours, then cooled to room temperature. The suspension was cooled to 0°C, held for 30 minutes, filtered, washed with water (100 mL), and dried to yield 14.4 g (86%) of methyl 4-[1-(4-aminosulfonylphenyl)-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxylate as a white solid: ^{1}H NMR ($CDCl_3$/300MHz) 7.85 (d, J=8.66 Hz, 2H), 7.36 (d, J=8.66 Hz, 2H), 7.18 (ddd, J = 8.66 Hz, J=8.46 Hz, J=4.85 Hz, 2H), 7.00 (dd, J=8.66 Hz, J=8.46 Hz, 2H), 6.28 (s, 1H), 3.90(s, 3H). ^{19}F NMR ($CDCl_3$/282.2MHz): -111.4(m). Mass spectrum, MH+ = 376. Anal. Calc'd for $C_{17}H_{14}N_3O_4FS$: C, 54.40; H, 3.76; N, 11.19; S, 8.54. Found: C, 54.49; H, 3.70; N, 11.25; S, 8.50.

Step 3. Preparation of [1-(4-aminosulfonylphenyl)-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxylic acid.

A 500 mL one-neck round-bottom flask, equipped with provisions for magnetic stirring, was charged with methyl 4-[1-(4-aminosulfonylphenyl)-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxylate from Step 2 (10.0 g, 26.64 mmol) and tetrahydrofuran (200 mL). Aqueous sodium hydroxide (2.5N, 27 mL) and water (25 mL) were added, and the suspension was heated to reflux and held for 16 hours. The solids all dissolved during this time. The reaction was cooled to room temperature, and hydrochloric acid solution (1N, 110 mL) was added. The aqueous suspension was extracted with methylene chloride (2x200 mL). The combined

organic soultion was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to an oil. Trituration with 300 mL of methylene chloride yielded, upon filtration and drying, 9.0 g, (94%) of [1-(4-aminosulfonylphenyl)-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxylic acid as a white solid: mp 138-142°C (dec); ^{1}H NMR (CD_3OD/300MHz) 7.93 (d, J=8.66 Hz, 2H), 7.51 (d, J=8.66 Hz, 2H), 7.31 (ddd, J = 8.86 Hz, J=8.66 Hz, J=4.83 Hz, 2H), 7.11 (dd, J=8.86 Hz, J=8.66 Hz, 2H), 7.06 (s, 1H). ^{19}F NMR (CD_3OD/282.2MHz): -114.01(m).

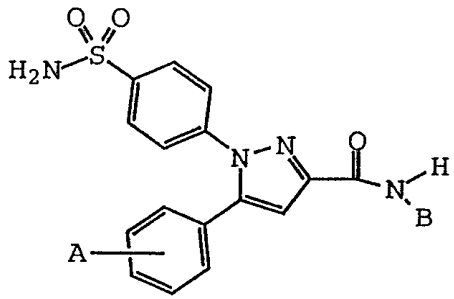
Step 4. Preparation of N-(3-chlorophenyl)-[1-(4-aminosulfonylphenyl)-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxamide

A 100 mL one-neck round-bottom flask, equipped with provisions for magnetic stirring, was charged with [1-(4-aminosulfonylphenyl)-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxylic acid from Step 3 (0.500 g, 1.38 mmol), 1-hydroxybenzotriazole hydrate (0.206 g, 1.522 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.318 g, 1.66 mmol) and N,N-dimethylformamide (30 mL). The solution was stirred at room temperature for forty minutes, then 3-chloroaniline (0.154 mL, 1.453 mmol) was added. The reaction was held at room temperature for sixteen hours, then poured into an aqueous solution of citric acid (5%, 100 mL). The aqueous solution was extracted with ethyl acetate (2x60 mL), and the combined organic solutions were washed with aqueous citric acid (60 mL), saturated sodium bicarbonate solution (2x60 mL) and 50% saturated sodium chloride solution (2x60 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to an oil. Trituration with 20 mL of dichloromethane yielded, upon filtration and drying, 0.439 g (67%) of N-(3-chlorophenyl)-[1-(4-aminosulfonylphenyl)-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxamide as a white solid: mp 207-212°C; ^{1}H NMR ($CDCl_3$/CD_3OD/300MHz) 8.90 (s, 1H), 7.86 (d, J=8.66 Hz, 2H),

7.79 (t, J=2.01 Hz, 1H), 7.46 (dd, J = 7.05 Hz, J=2.01 Hz, 1H), 7.33 (d, J=8.86 Hz, 2H), 7.21-7.11 (m, 3H), 7.02 - 6.94 (m, 4H). ^{19}F NMR ($CDCl_3/CD_3OD$/282.2MHz): -111.38(m). Mass spectrum, MH+ = 470. Anal. Calc'd for $C_{22}H_{16}N_4O_3ClFS$: C, 56.11; H, 3.42; N, 11.90; Cl, 6.81; S, 7.53. Found: C, 55.95; H, 3.50; N, 11.85; Cl, 6.82; S, 7.50.

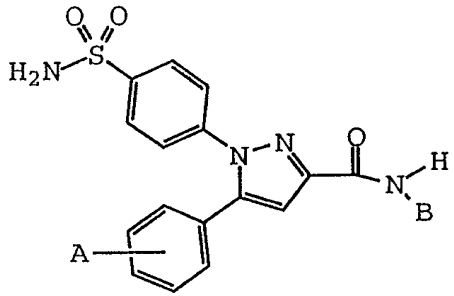
The following compounds in Table IV were prepared according to procedures similar to that exemplified in Examples 96-98, with the substitution of the appropriate starting material.

TABLE IV



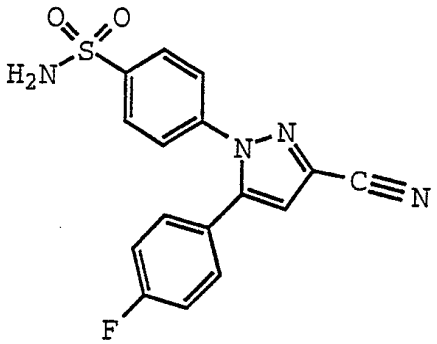
Ex.	A	B	M.P. °C	Analytical
99	4-Br	H	143-145	MH+ = 421
100	4-F	phenyl-	233-236	MH+ = 436
101	4-NO_2	H	278-281	MH+ = 387
102	4-F	4-CH_3O-phenyl-	209-211	MH+ = 466
103	4-F	4-CH_3-phenyl-	222-225	MH+ = 451
104	4-F	cyclohexyl-	224-227	MH+ = 442
105	4-F	3-F-phenyl-	227	MH+ = 454
106	4-Cl	3-F-phenyl-	174-176 (dec)	MH+ = 471
107	H	H	ND	MH+ = 343
108	4-OCH_3, 3-Cl	H	ND	MH+ = 408
109	4-SCH_3	H	115 (dec)	HRMS : 389.0743

TABLE IV (cont.)



Ex.	A	B	M.P. °C	Analytical
110	4-OCH_3	H	115-140	Calc. C,54.83; H,4.33; N, 15.04
				Obs. C, 54.76; H,4.34; N, 14.98
111	4-CH_3	H	139-140	HRMS·H2O: 356.0939
112	4-OCH_3	-CH_3	209	MH+ = 387
113	4-Cl	glycine benzyl ester	136	MH+ = 525
114	4-Cl	glycine	124-130	MH+ = 435
115	4-OCH_3, 3-Br	H	ND	M+Li = 457/459
116	4-OCH_3, 3,5-di-Cl	H	185 (dec)	HRMS: 440.0113

Example 117



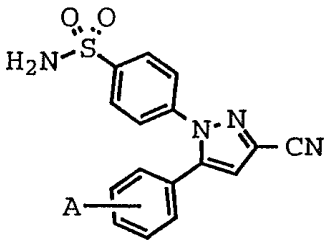
4-[3-Cyano-5-(4-fluorophenyl-1H-pyrazol-1-yl]benzenesulfonamide

A dry 100 ml three-neck flask, equipped with a reflux condenser, thermometer, pressure-equalizing addition funnel and provisions for magnetic stirring was charged with anhydrous DMF (20 mL) and cooled to 0°C. Oxalyl chloride (0.530 mL, 6.105 mmol) was added over twenty seconds, causing a 5°C exotherm. The white precipitate formed dissolved as the reaction cooled to 0°C. The reaction was held at 0°C for ten minutes, then a solution of [1-(4-aminosulfonylphenyl)-5-(4-fluorophenyl)-1H-pyrazol-3-yl]carboxamide (Example 97) in anhydrous DMF was added to the vigorously stirring solution over approximately two minutes. After fifteen minutes, pyridine (1.0 mL, 12.21 mmol) was added to quench the reaction. The mixture was poured into dilute hydrochloric acid (1N, 100 mL) and extracted with ethyl acetate (2x75 mL). The combined organic solution was washed with 1N HCl (2x100 mL) and with 50% saturated NaCl (3x100 mL). The organic solution was dried over magnesium sulfate, filtered and concentrated *in vacuo* to a crude oil. The oil was applied to a column of silica gel and eluted with ethyl acetate and hexane (40% ethyl acetate) to obtain, upon concentration of the appropriate fractions, 0.66 g (69%) of 4-[3-cyano-5-(4-fluorophenyl-1H-pyrazol-1-yl]benzenesulfonamide as a white solid: mp 184-185°C; ^{1}H NMR ($CDCl_3$/300MHz) 7.94 (d, J=8.86

Hz, 2H), 7.44 (d, J=8.86 Hz, 2H), 7.23-7.07 (m, 4H), 6.87 (s, 1H), 4.88 (brs, 2H); ^{19}F NMR ($CDCl_3$/282.2MHz) -109.90(m). Mass spectrum, MH+ = 343. Anal. Calc'd for $C_{16}H_{11}N_4O_2FS$: C, 56.14; H, 3.24; N, 16.37; S, 9.36. Found: C, 56.19; H, 3.16; N, 16.39; S, 9.41.

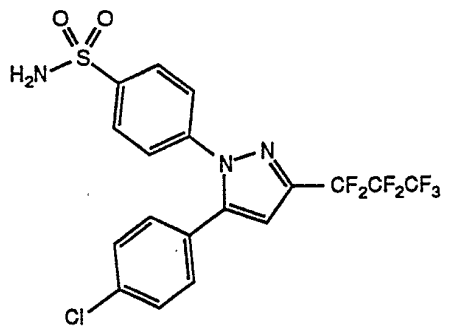
The following compounds in Table V were prepared according to procedures similar to that exemplified in Example 117, with the substitution of the appropriate starting material.

TABLE V



Ex.	A	M.P.(°C)	Anal.
118	4-Br	156-157	HRMS: 401.9833
119	4-Cl	142-143	
120	4-OCH_3	ND	HRMS : 354.0774
121	4-CH_3	90-95	HRMS: 338.0849
122	4-SCH_3	192-193	
123	4-OCH_3, 3-Cl	179	MH+ = 389
124	4-OCH_3, 3,5-di-Cl	121-125	HRMS : 422.0051
125	4-OCH_3, 3-Br	213	MH+ = 433
126	4-NO_2	230-232	MH+ = 370
127	H	ND	MH+ = 325

Example 128



4-[5-(4-Chlorophenyl)-3-(heptafluoropropyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

Step 1: Preparation of 4,4,5,5,6,6,6-heptafluoro-1-[4-(chloro)phenyl]hexane-1,3-dione.

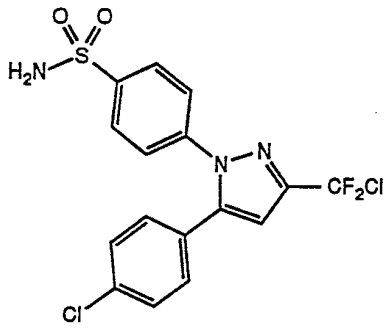
Ethyl heptafluorobutyrate (5.23 g, 21.6 mmol) was placed in a 100 mL round bottom flask, and dissolved in ether (20 mL). To the stirred solution was added 25% sodium methoxide (4.85 g, 22.4 mmol) followed by 4-chloroacetophenone (3.04 g, 19.7 mmol). The reaction was stirred at room temperature overnight (15.9 hours) and treated with 3N HCl (17 mL). The organic layer was collected, washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and recrystallized from iso-octane to give the diketone as a white solid (4.27 g, 62%): mp 27-30°C; ^1H NMR ($CDCl_3$) 300 MHz 15.20 (br s, 1H), 7.89 (d, J=8.7 Hz, 2H), 7.51 (d, J=8.7 Hz, 2H), 6.58 (S, 1H); ^{19}F NMR ($CDCl_3$) 300 MHz: -80.94 (t), -121.01 (t), -127.17 (s); M+H 351.

Step 2: Preparation of 4-[5-(4-chlorophenyl)-3-(heptafluoropropyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

The 4-sulfonamidophenylhydrazine hydrochloride (290 mg, 1.30 mmol) was added to a stirred solution of the diketone from Step 1 (400 mg, 1.14 mmol) in ethanol

(5 mL). The reaction was heated to reflux and stirred overnight (23.8 hours). The ethanol was removed *in vacuo*, and the residue was dissolved in ethyl acetate, washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a white solid which was passed through a column of silica gel with ethyl acetate/hexane (40%) and recrystallized from ethyl acetate/isooctane to give the pyrazole as a white solid (0.24 g, 42%): mp 168-71°C; ^1H NMR ($CDCl_3$) 300 MHz 7.90 (d, J=8.7 Hz, 2H), 7.45 (d, J=8.7 Hz, 2H), 7.34 (d, J=8.5 Hz, 2H), 7.19 (d, J=8.5 Hz, 2H), 6.79 (s, 1 H), 5.20 (br s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz: -80.48 (t), -111.54 (t), -127.07 (s).

Example 129



4-[5-(4-Chlorophenyl)-3-(chloro-difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

Step 1: Preparation of 4-chloro-4,4-difluoro-1-[4-(chloro)phenyl]-butane-1,3-dione.

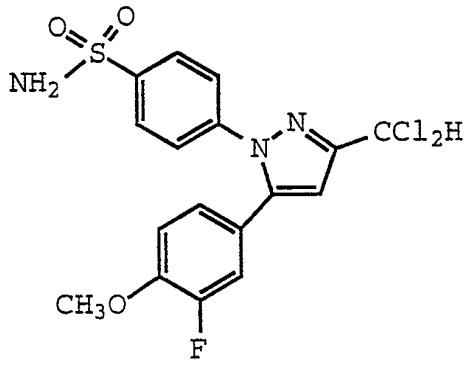
Methyl 2-chloro-2,2-difluoroacetate (4.20 g, 29 mmol) was placed in a 100 mL round bottom flask, and dissolved in ether (10 mL). To the stirred solution was added 25% sodium methoxide (6.37 g, 29 mmol) followed by 4'-chloroacetophenone (4.10 g, 26.5 mmol). The reaction was stirred at room temperature overnight (20.4 hours), then poured into a separatory funnel and washed with 3N HCl (15 mL), brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* and recrystallized from iso-octane

to give the diketone as a yellow solid (3.78 g, 53%): mp 53-55°C; ^1H NMR ($CDCl_3$) 300 MHz 14.80 (br s, 1H), 7.87 (d, J=8.7 Hz, 2H), 7.50 (d, J=8.7 Hz, 2H), 6.49 (S, 1H); ^{19}F NMR ($CDCl_3$) 300 MHz: -66.03 (s); M+ 267.

Step 2: Preparation of 4-[5-(4-chlorophenyl)-3-(chloro-difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

4-Sulfonamidophenylhydrazine hydrochloride (1.39 g, 6.2 mmol) was added to a stirred solution of the diketone from Step 1 (1.43 g, 5.7 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred overnight (15.75 hours). The ethanol was removed *in vacuo*, and the residue was dissolved in ethyl acetate, washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a white solid which was recrystallized from ethyl acetate/isooctane to give the pyrazole as a white solid (0.32 g, 41%): mp 130-33°C; ^1H NMR ($CDCl_3$) 300 MHz 7.90 (d, J=8.9 Hz, 2H), 7.47 (d, J=8.7 Hz, 2H), 7.35 (d, J=8.5 Hz, 2H), 7.19 (d, J=8.7 Hz, 2H), 6.76 (s, 1 H), 5.13 (br s, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz: -48.44 (s); M+ 417/419.

Example 130



4-[3-(Dichloromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 3'-fluoro-4'-methoxy-acetophenone.

Aluminum chloride (80.0 g, 0.6 mol) and chloroform (750 mL) were placed in a 2 L three-necked round bottom flask fitted with a mechanical stirrer and cooled by means of an ice bath. To the stirred solution was added acetyl chloride (51.0 g, 0.65 mol) dropwise, maintaining the temperature between 5-10°C. The mixture was allowed to stir for 10 minutes. at 5°C before the dropwise addition at 5-10°C of 2-fluoroanisole (63.06 g, 0.5 mol).The mixture was stirred at 0-10°C for 1 hour and poured into ice (1 L). The resultant layers were separated and the aqueous layer was extracted with methylene chloride (2x250 mL). The combined organic layers were washed with water (2x150 mL), dried over magnesium sulfate, and concentrated to 300 mL. Hexanes were added and a white solid (77.2 g, 92%) was crystallized from the mixture: mp 92-94°C; ^{1}H NMR (d_6-DMSO) 7.8 (m, 2H), 7.3 (t, J=8.7Hz, 1H), 3.9 (s, 3H), 2.5 (s, 3H).

Step 2. Preparation of 4,4-dichloro-1-(3-fluoro-4-methoxyphenyl)-butane-1,3-dione.

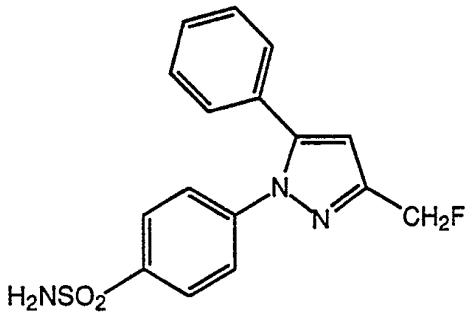
Methyl dichloroacetate (1.57 g, 11 mmol) was dissolved ether (25 mL). To the stirred solution was added 25% sodium methoxide (2.38 g, 11 mmol) followed by 3'-fluoro-4'-methoxyacetophenone from Step 1 (1.68 g, 10 mmol). After stirring 16 hours 1N HCl (25 mL) was added. The organic layer was collected and washed with water (2x25 mL), dried over magnesium sulfate, filtered, and concentrated. The resulting crude dione was used in the next step without further purification or characterization.

Step 3. Preparation of 4-[3-(dichloromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-

yllbenzenesulfonamide.

4,4-Dichloro-1-(3-fluoro-4-methoxyphenyl)-butane-1,3-dione from Step 2 (2.8 g, 10 mmol) was dissolved in ethanol (100 mL). To the stirred mixture was added 4-sulfonamidophenylhydrazine hydrochloride (2.46 g, 11 mmol) and heated to reflux for 16 hours. The mixture was cooled and water was added until crystals slowly appeared. Filtration yielded a light tan solid (2.7 g, 63 %): mp 190-193°C; ^1H NMR (DMSO-d_6) 7.84 (d, J=8.4Hz, 2H), 7.53 (s, 1H), 7.48 (d, J=8.4Hz, 2H), 7.47 (brs, 2H), 7.3-7.0 (m, 3H), 6.95 (s, 1H), 3.85 (s, 3H). Anal. Calc'd for $C_{17}H_{14}N_3SO_3FCl_2$: C, 47.45; H, 3.28; N, 9.76. Found: C, 47.68; H, 3.42; N, 10.04.

Example 131



4-[3-Fluoromethyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide

Step 1: Preparation methyl 4-phenyl-2,4-dioxobutanoate

To a solution of dimethyl oxalate (11.81 g, 100 mmol) in ether (200 mL) is added 24 mL of 25% sodium methoxide in methanol, followed by a solution of acetophenone (12.02 g, 100 mmol) in ether (20 mL) and the mixture stirred overnight at room temperature. The mixture was partitioned between 1N HCl and EtOAc and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated to give 18.4 g of crude butanoate.

Step 2: Preparation of methyl 1-[(4-(aminosulfonyl) phenyl]-5-phenyl-1H-pyrazole 3-carboxylate

The ester was prepared from the butanoate in Step 1 using the procedure described in Example 2, Step 2.

Step 3: Preparation 4-[3-hydroxymethyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide

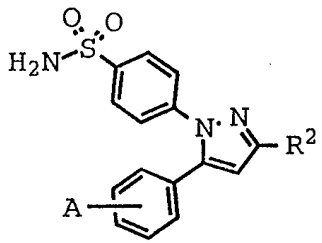
To a solution of ester in Step 2 (4.0 g, 10.4 mmol) in 50 mL THF was added $LiAlH_4$ (0.592 g, 15.6 mmol) in portions and the mixture refluxed overnight. The reaction was cooled and quenched with 1N $NaHSO_4$ and extracted with ether (3X). The combined extracts were dried over $MgSO_4$ and concentrated to give 3.5 g crude alcohol. Flash chromatography using 1:1 hexane/EtOAc provided the title compound.

Step 4: Preparation 4-[3-fluoromethyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide

To a mixture of the alcohol from Step 3 (212 mg, 0.64 mmol) in dichloromethane (4 mL) was added diethylaminosulfur trifluoride (0.13 mL, 1.0 mmol). The reaction mixture was stirred at room temperature for 3 hours and partitioned between water and dichloromethane. The aqueous solution was extracted with dichloromethane. The organic solution was washed with brine and concentrated. The residue was chromatographed on silica (1:1 hexane:ethyl acetate) to give the desired product (72 mg, 34%): mp 162-163°C; Anal. calc'd for $C_{16}H_{14}N_3O_2SF$: C, 58.00; H, 4.26; N, 12.68. Found: C, 57.95; H, 4.03; N, 12.58.

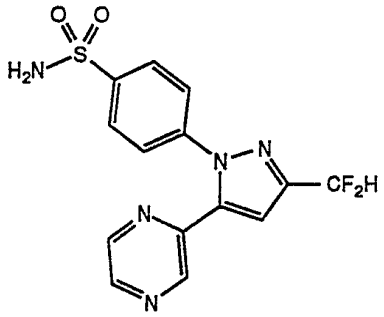
The following compounds in Table VI were prepared according to procedures similar to that exemplified in Examples 128-131, with the substitution of the appropriate substituted acetyl and acetate starting materials.

TABLE VI



Ex.	A	R^2	M.P. (°C)	Anal.
132	4-Cl	$-CF_2CF_3$	145.5-150	
133	4-Cl	$-CH_2Cl$	198-201	Calc. C, 50.27; H, 3.43; N, 10.99
				Found C, 50.34; H, 3.43; N, 10.96
134	3-F,4-OCH_3	$-CF_2Cl$	120-124	Calc. C, 47.29; H, 3.04; N, 9.74
				Found C, 47.28; H, 3.37; N, 9.88
135	3-F,4-OCH_3	$-CBrF_2$	120-122	Calc. C, 42.87; H, 2.75; N, 8.82
				Found C, 42.99; H, 3.81; N, 9.92
136	3-Cl,4-OCH_3	$-CH_2Cl$	ND	Calc. C, 49.53; H, 2.84; N, 8.66
				Found C, 50.03; H, 3.81; N, 9.92

Example 137



4-[5-(2-Pyrazinyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

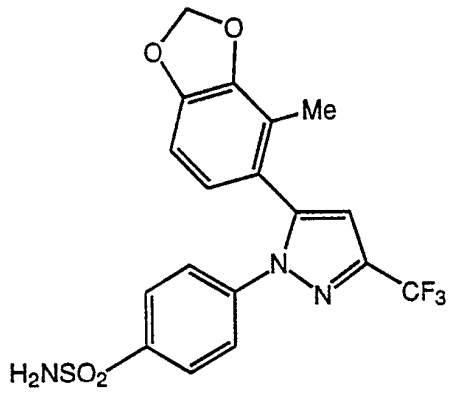
Step 1: Preparation of 4,4-difluoro-1-(2-pyrazinyl)-butane-1,3-dione.

Ethyl difluoroacetate (2.23 g, 18 mmol) was placed in a 100 mL round bottom flask and dissolved in ether (10 mL). To the stirred solution was added 25% sodium methoxide (4.68 g, 22 mmol) followed by acetylpyrazine (2.00 g,16 mmol). After two hours stirring at room temperature, a precipitate formed and THF (10 mL) was added to the reaction. The reaction was stirred an additional 25.9 hours, then treated with 3N HCl (10 mL). The organic layer was collected, washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* and recrystallized from methylene chloride/iso-octane to give the diketone as a brown solid (2.23 g, 68%); mp 103-110°C; ^1H NMR ($CDCl_3$) 300 MHz 14.00 (br s, 1H), 9.31 (d, J=1.4 Hz, 1H), 8.76 (d, J=2.4 Hz, 1H), 8.68 (dd, J=1.4 Hz 2.4 Hz, 1H), 7.20 (s, 1H), 6.03 (t, J=54.0 Hz, 1H); ^{19}F NMR ($CDCl_3$) 300 MHz: -127.16 (d); M+ 200.

Step 2: Preparation of 4-[5-(2-pyrazinyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

4-Sulfonamidophenylhydrazine hydrochloride (0.37 g, 1.65 mmol) was added to a stirred suspension of the diketone from Step 1 (0.30 g, 1.50 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred for 5.3 hours. The ethanol was removed *in vacuo*, and the residue was dissolved in ethyl acetate, washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a brown solid (0.36 g) which was recrystallized from ethyl acetate/ethanol/isooctane to give the pyrazole as a brown solid (0.20 g, 38%): mp 191-94°C; ^1H NMR (acetone d_6) 300 MHz 8.94(d, J=1.4 Hz, 1H), 8.62 (d, J=2.4 Hz, 1H), 8.52 (dd, J=1.4 Hz 2.4 Hz, 1H), 7.95 (d, J=8.7 Hz, 2H), 7.61 (d, J=8.7 Hz, 2H), 7.30 (s, 1H), 7.02 (t, J=54.6 Hz, 1H), 6.73 (br s, 2 H); ^{19}F NMR (acetone d_6) 300 MHz: -113.67 (d); M+ 351.

Example 138



4-[5-(4-methyl-1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

Step 1: Preparation of 4-methyl-1,3-benzodioxole

11.6 g Adogen 464 and 7 mL of dibromomethane were refluxed in 50 mL of H_2O for 0.5 hours under argon. 3-Methylcatechol (8.89 g, 71.6 mmol) was added over 2 hours and the mixture refluxed for an additional 1 hour.

Distillation of the product from the reaction mixture afforded the title compound as a yellow oil: HRMS m/e 136.0524 (calc'd for $C_8H_8O_2$, 136.0524).

Step 2: Preparation of 5-acetyl-4-methyl-1,3-benzodioxole (A) and 6-acetyl-4-methyl-1,3-benzodioxole (B)

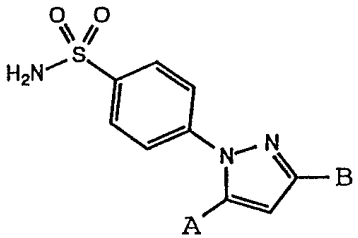
13.8 g of polyphosphoric acid and 5 mL of acetic anhydride were heated to 45°C under a drying tube of $CaSO_4$ until liquified. The product from Step 1 was added and the reaction was stirred at 45°C for 4.5 hours. The reaction was cooled to room temperature and quenched with 150 mL of ice water. The aqueous phase was washed with ethyl acetate (4x 50 mL). The combined organic extracts were dried over $MgSO_4$ and filtered to give the crude product as a red oil. The oil was chromatographed on silica gel eluting with 10% ethyl acetate/90% hexane to afford two products: A: Anal. calcd for $C_{10}H_{10}O_3$: C, 67.07; H, 5.66. Found: C, 67.41; H, 5.75, and B: MS, M^+ 178.

Steps 3 and 4: 4-[5-(4-methyl-1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The title compound was prepared from product A using the procedures described in Example 2, Steps 1 and 2: White solid: Anal. calcd for $C_{18}H_{14}N_3O_4SF_3$: C, 50.82; H, 3.22; N, 9.88. Found: C, 50.71; H, 3.34; N, 9.55.

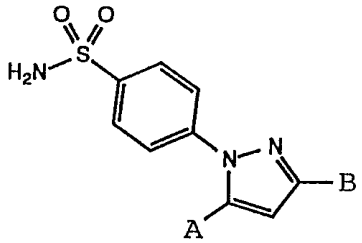
The following compounds in Table VII were prepared according to procedures similar to that exemplified in Examples 137-138, with the substitution of the appropriate starting material.

TABLE VII



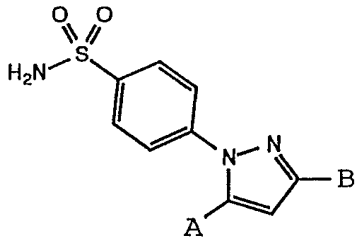
Ex.	A	B	M.P.(°C)	Anal.
139	5-bromo-2-thienyl	CF_2H	168-169	M+Li 440/442
140	2-thienyl	CF_2H	190-191	M+Li 367
141	5-chloro-2-thienyl	CF_2H	168-170	M+ 389/391
142	1-cyclohexenyl	CF_2H	160-161	M+ 353.
143	1,4-benzodioxan	CF_2H	115-119	Calc. C,53.06; H,3.71; N, 10.32
				Obs. C,52.40; H,3.98; N,9.96
144	4-methylcyclohex-3-ene-1-yl	CF_2H	164-168	HRMS: 367.1194
145	2-methylcyclopenten-1-yl	CF_2H	165-166	HRMS: 353.1033
146	2,5-dimethyl-3-thienyl	CF_2H	125-127	Calc. C,50.12; H,3.94; N, 10.96
				Obs. C,50.21; H,3.92; N,11.00
147	2,5-dimethyl-3-furyl	CF_2H	139-142	Calc. C,52.31; H,4.12; N, 11.44
				Obs. C,52.07; H,4.16; N,11.37
148	5-methyl-2-furyl	CF_2H	177-179	Calc C,50.99; H,3.71; N, 11.89
				Obs. C,51.08; H,3.68; N, 11.95

TABLE VII (cont.)



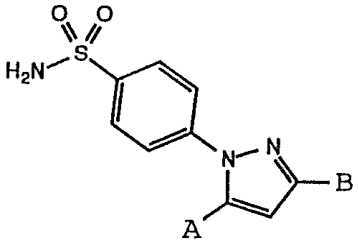
Ex.	A	B	M.P.(°C)	Anal.
149	4-bromo-4-methylcyclohex-1-yl	CF_2H	175-178(dec)	HRMS: 448.0520
150	4-methylcyclohex-1-yl	CF_2H	190-192	HRMS: 369.1341
151	4-chloro-4-methylcyclohex-1-yl	CF_2H	197-199	HRMS: 403.0958
152	3,4-dibromo-4-methylcyclohex-1-yl	CF_2H	172-173	
153	2-methoxycyclohex-1-yl	CF_2H	177-179	HRMS: 386.1357
154	2-benzofuryl	CF_2H	215-217	Calc C,55.52; H,3.37; N,10.79 Obs. C,55.52; H,3.32; N,10.85
155	2,5-dichloro-3-thien-yl	CF_2H	154-156	Calc. C,39.63; H, 2.14; N, 9.90 Obs. C,39.63; H,2.13; N, 9.89
156	2-benzofuryl	CF_3	227-228	Calc. C, 53.07; H, 2.97; N, 10.31 Obs. C, 53.02; H, 2.96; N, 10.39
157	5-chloro-2-thienyl	CF_3	161-165	HRMS: 406.9784

TABLE VII (cont.)



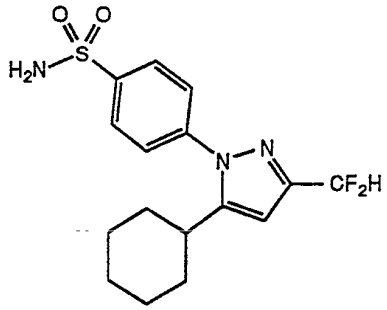
Ex.	A	B	M.P.(°C)	Anal.
158	5-bromo-2-thienyl	CF_3	ND	Calc: C,37.18; H,2.01; N,9.29; Br, 17.67 Found: C, 37.25; H, 1.93; N, 9.45; Br, 17.40
159	5-indanyl	CF_3	118-120	Calc: C, 56.01; H, 3.96; N, 10.31 Found: C, 56.02; H, 4.06; N, 10.22
160	5-methylthien-2-yl	CF_3	188-190	Calc. C, 46.51; H, 3.12; N, 10.85 Found: C, 46.17; H, 3.10; N, 10.75
161	2,3-dihydrobenzofuryl	CF_3	152-153	Calc. C, 52.81; H, 3.45; N, 10.26 Found: C, 52.67; H, 3.78; N, 10.13
162	1-cyclohexenyl	CF_3	135-138	HRMS: 371.0918
163	6-tetrahydronaphthyl	CF_3	143-145	Calc. C, 57.00; H, 4.31; N, 9.97 Found: C, 56.72; H, 4.27; N, 9.90

TABLE VII (cont.)



Ex.	A	B	M.P.(°C)	Anal.
164	3-benzothienyl	CF_3	164-165	Calc. C, 51.06; H, 2.86; N, 9.92 Obs. C, 50.96; H, 2.73; N, 9.78
165	3,4-dihydrobenzopyranyl	CF_3	ND	HRMS : 423.0855
166	styryl	CF_3	166-167	Calc. C, 54.96; H, 3.59; N, 10.68 Obs. C, 54.77; H, 3.59; N, 10.47
167	4-methyl-1,3-benzodioxol-6-yl	CF_3	ND	Calc. C, 50.82; H, 3.22; N, 9.88 Obs. C, 50.64; H, 3.35; N, 9.72
168	3-pyridyl	CF_3	202-204	Calc. C, 48.91; H, 3.01; N, 15.21 Obs. C, 48.97; H, 3.16; N, 14.96
169	3,4-dihydrobenzothiopyranyl	CF3	ND	Calc. C,51.95; H, 3.67; N, 9.56 Obs. C, 51.98; H, 3.78; N, 9.48

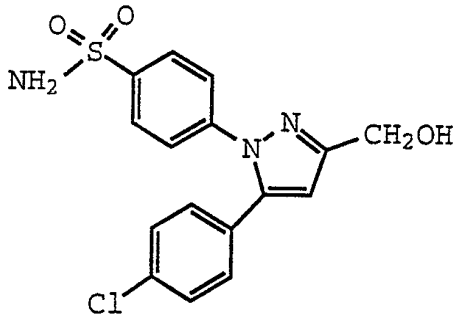
Example 170



4-[5-(1-Cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

4-[5-(1-Cyclohexenyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (Example 142) (0.31 g, 0.88 mmol) was dissolved in ethanol (15 mL), 10% palladium on charcoal was added, and the suspension was stirred at room temperature under hydrogen (36 psi) for 18.25 hours. The reaction was filtered through celite, and the ethanol removed *in vacuo* to give a white solid, which was recrystallized from methylene chloride/isooctane (0.31 g, 99%): mp 199-203°C; ^{1}H NMR (acetone-d_6) 300 MHz 8.05 (d, J=8.7 Hz, 2H), 7.60 (d, J=8.5 Hz, 2H), 6.69 (t, J=55.0 Hz 1 H), 6.47 (s, 1H), 5.02 (br s, 2H), 2.67 (m, 1H), 1.71-1.88(m, 5H), 1.24-1.43 (m, 5H); ^{19}F NMR (acetone-d_6) 300 MHz: -112.86 (d).

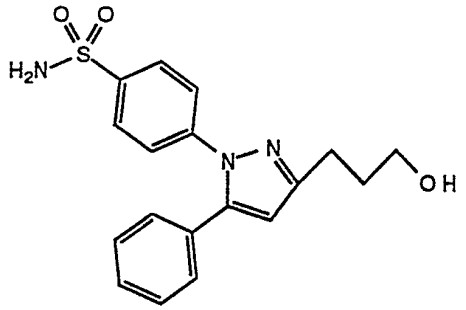
Example 171



4-[5-(4-Chlorophenyl)-3-hydroxymethyl-1H-pyrazol-1-yl]benzenesulfonamide

4-[4-(Aminosulfonyl)phenyl-5-(4-chlorophenyl)-1H-pyrazole-3-carboxylic acid (Example 83) (3.8 g, 10 mmol) and tetrahydrofuran (100 mL) were stirred at room temperature during the dropwise addition of 1.0M borane-tetrahydrofuran complex (30 mL, 30 mmol). The mixture was heated to reflux for 16 hours. The solution was cooled and methanol was added dropwise until gas evolution ceased. Ethyl acetate (100 mL) was added and the mixture was washed successively with 1N hydrochloric acid, brine, sat. aq. sodium bicarbonate solution, and water, dried over magnesium sulfate, filtered and concentrated. The resultant product was recrystallized from ethanol:water to yield 2.6 g (71%) of a white solid: mp 192-194°C; ^{1}H NMR (d_6-DMSO/300 MHz) 7.81 (d, J=8.7Hz, 2H), 7.46 (d, J=8.4Hz, 2H), 7.42 (brs, 2H), 7.40 (d, J=8.7Hz, 2H), 7.26 (d, J=8.4Hz, 2H), 6.63 (s, 1H), 5.35 (t, J=8.0Hz, 1H), 4.50 (d, J=8.0Hz, 2H). Anal. Calc'd for $C_{16}H_{14}N_6SO_2Cl$: C, 52.82; H, 3.88; N, 11.55. Found: C, 52.91; H, 3.88; N, 11.50.

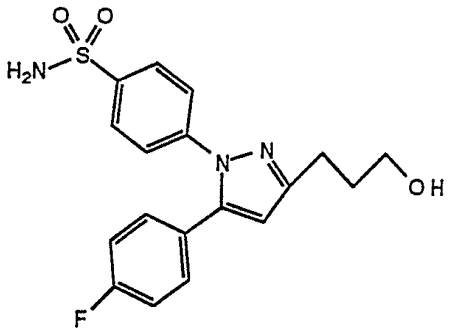
Example 172



4-[5-Phenyl-3-(3-hydroxypropyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

A 60% dispersion of sodium hydride in mineral oil (4.0 g, 100 mmol) was twice washed with hexane (100 mL each) and dried under a stream of nitrogen. Ether (300 mL) was added followed by dropwise addition of ethanol (0.25 mL) and γ-butyrolactone (4.0 mL, 52 mmol). The mixture was cooled to 10°C and acetophenone (5.8 mL, 50 mmol) in ether (40 mL) was added dropwise over 1 hour. The mixture was warmed to 25°C and stirred overnight. The mixture was cooled to 0°C and quenched with ethanol (5 mL) followed by 10% aqueous ammonium sulfate (100 mL). The organic solution was separated, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel with 1:1 hexane/ethyl acetate to give the desired diketone (3.4 g) as an oil. Pyridine (0.34 mL, 4.2 mmol) and the diketone (700 mg, 3.4 mmol) in methanol (3 mL) were added to a slurry of 4-sulfonamidophenylhydrazine-HCl (750 mg, 3.4 mmol) in methanol (8 mL). The mixture was stirred at 25°C overnight and concentrated *in vacuo*. The residue was dissolved in methylene chloride and the solution washed with 1N HCl. The organic solution was separated, dried and concentrated. The residue was chromatographed on silica gel using ethyl acetate to give the desired pyrazole (435 mg) as a solid: Anal. calc'd for $C_{18}H_{19}N_3O_3S$: C, 60.49; H, 5.36; N, 11.75. Found: C, 60.22; H, 5.63; N, 11.54.

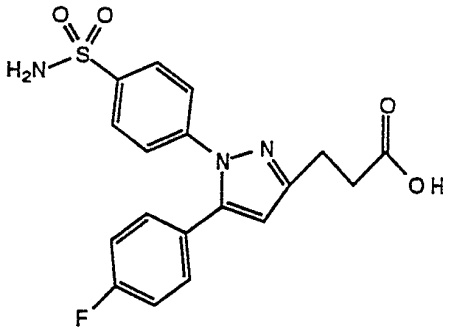
Example 173



4-[5-(4-Fluorophenyl)-3-(3-hydroxypropyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

Following the procedure of Example 172, but substituting 4-fluoroacetophenone for acetophenone afforded 4-[5-(4-fluorophenyl)-3-(3-hydroxypropyl)-1*H*-pyrazol-1-yl]benzenesulfonamide. Anal. calc'd for $C_{18}H_{18}N_3O_3SF \cdot 0.25\ H_2O$: C, 56.90; H, 4.91; N, 11.05. Found: C, 56.80; H, 4.67; N, 11.02.

Example 174

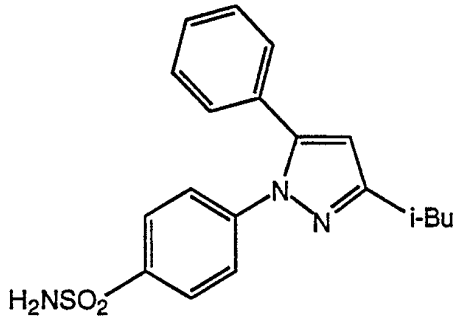


4-[4-(Aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1*H*-pyrazole]-3-propanoic acid

Jones reagent (0.64 mL of a 2.67 M solution) was added dropwise to a solution of 4-[5-(4-fluorophenyl)-3-(3-hydroxypropyl)-1*H*-pyrazol-1-yl]benzenesulfonamide from Example 173 (295 mg, 0.78 mmol) in acetone (8 mL). The

mixture was stirred at 25°C for 2 hours. The solution was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with water (3x). The organic solution was dried over $MgSO_4$ and concentrated. The residual oil was crystallized from ether/hexane to give the desired acid (149 mg): mp 180-182°C; Anal. calc'd for $C_{18}H_{16}N_3O_4SF$: C, 55.52; H, 4.14; N, 10.79. Found: C, 55.47; H, 4.22; N, 10.50.

Example 175



4-(3-Isobutyl-5-phenyl-1H-pyrazol-1-yl)benzenesulfonamide

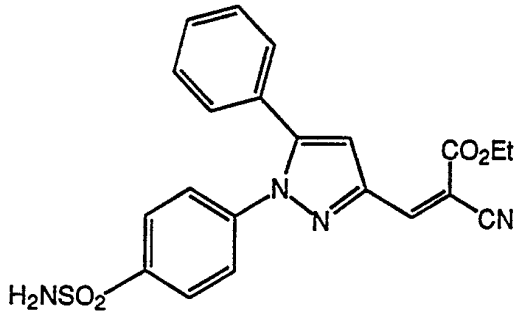
Step 1: Preparation of 2,3-epoxy-5-methyl-1-phenyl-3-hexanone

To a solution of 5-methyl-1-phenyl-1-hexen-3-one (2.0 g, 10.6 mmol) in 15 mL EtOH and 5 mL acetone was added a mixture of 30% hydrogen peroxide (2 mL) and 4 N NaOH (1.5 mL) dropwise and the mixture stirred at 25°C for 1-3 hours. Water (50 mL) was added and the precipitate filtered and dried at 40°C *in vacuo* to provide 1.9 g of the epoxide as a white solid: Anal. calc'd for $C_{13}H_{16}O_2 \cdot 0.1\ H_2O$: C, 75.77; H, 7.92. Found: C, 75.47; H, 7.56.

Step 2: Preparation of 4-(3-isobutyl-5-phenyl-1H-pyrazol-1-yl)benzenesulfonamide

The epoxide prepared above in Step 1 (1.26 g, 6.11 mmol) and 4-sulfonamidophenylhydrazine hydrochloride (1.38 g, 6.17 mmol) were stirred in 20 mL EtOH with AcOH (0.5 mL) and the mixture refluxed for 3 hours, cooled and quenched with 50 mL H_2O. The aqueous layer was extracted with ethyl acetate (3x50 mL), the combined extracts were dried over $MgSO_4$ and concentrated. Flash chromatography using 70:30 hexane/ethyl acetate provided the title compound (0.41 g, 19%) as a white solid: Calc'd for $C_{19}H_{21}N_3O_2S$: C, 64.20; H, 5.96; N, 11.82. Found: C, 64.31; H, 6.29; N, 11.73.

Example 176



Ethyl 3-[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]-2-cyano-2-propenoate

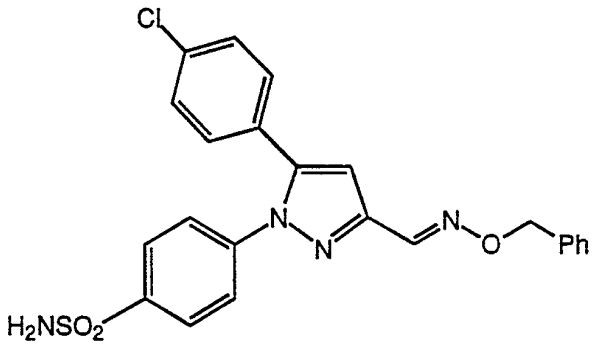
<u>Step 1: Preparation of 4-[3-formyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide</u>

To a solution of the alcohol prepared in Example 131, Step 3 (1.1 g, 3.3 mmol) in ethyl acetate (20 mL) was added MnO_2 (5 g, 60 mmol) and the mixture stirred at room temperature overnight. The mixture was filtered through Celite and the solution was concentrated to provide the crude aldehyde.

Step 2: Preparation of ethyl 3-[1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazol-3-yl]-2-cyano-2-propenoate

To a solution of the aldehyde from Step 1 (1.2 g, 3.6 mmol) in benzene (18 mL) was added ethyl cyanoacetate (0.38 mL, 3.6 mmol), ammonium acetate (50 mg, 0.7 mmol) and glacial acetic acid (0.17 mL, 2.8 mmol). The solution was heated at reflux for 18 hours, cooled, and partitioned between water and ethyl acetate. The organic solution was washed with a saturated aqueous sodium bicarbonate solution, water and brine. The organic solution was dried and concentrated. The residue was chromatographed on silica (40% hexane in ethyl acetate) to give the desired product (1.0 g, 66%): Anal. calc'd for $C_{21}H_{18}N_4O_4S$: C, 59.82; H, 4.30; N, 13.22. Found: C, 59.70; H, 4.29; N, 13.26.

Example 177



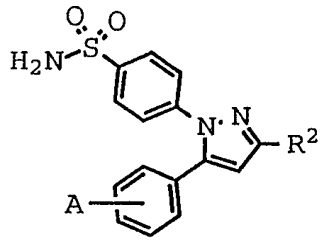
4-[5-(4-Chlorophenyl)-3-[[(phenylmethoxy)imino]methyl]-1H-pyrazol-1-yl]benzenesulfonamide

To a suspension of 220 mg (0.58 mmol) 4-[5-(4-chlorophenyl)-3-formyl-1H-pyrazol-1-yl]benzenesulfonamide (prepared as described in Example 176, Step 1) in dichloromethane (3 mL) was added pyridine (0.12 mL, 1.3 mmol) and O-benzylhyroxylamine hydrochloride (110 mg, 0.68

mmol) and the reaction stirred at room temperature for 18 hours. The mixture was partitioned between pH 7 buffer and dichloromethane and the organic layer was washed with water, dried and concentrated. Flash chromatography on silica gel (2:1 hexane/EtOAc) provided the title compound (151 mg, 56%): mp 158-159°C; Anal. calc'd for $C_{23}H_{19}N_4O_3SCl \cdot 0.25\ H_2O$: C, 58.59; H, 4.17; N, 11.88. Found: C, 58.43; H, 4.03; N, 11.85.

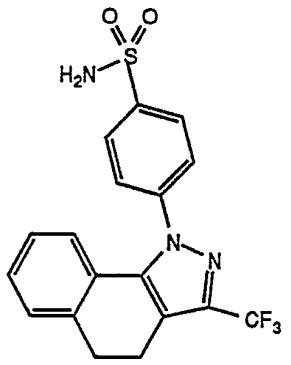
The following compounds in Table VIII were prepared according to procedures similar to that exemplified in Examples 171-177, with the substitution of the appropriate starting material.

TABLE VIII



Ex.	A	R^2	M.P.(°C)	Anal.
178	H	$-CH_2OH$	183-184	HRMS: 329.0845
179	4-OCH_3	$-CH_2OH$	140-142	Calc. C, 56.81; H, 4.77; N, 11.69 Found: C, 56.92; H, 4.76; N, 11.64
180	3,5-di-Cl, 4-OCH_3	$-CH_2OH$	191-193	HRMS 427.0199
181	3-Cl, 4-OCH_3	$-CH_2OH$	ND	Calc. C, 51.84; H, 4.09; N, 10.67 Cl, 9.00; S, 8.14 Found: C, 51.77; H, 4.02; N, 10.73; Cl, 9.11; S, 8.03
182	4-CH_3	$-C(CH_3)_2OH$	178-179	
183	4-Cl	$-(CH_2)_2CO_2H$	156-159	
184	4-Cl	$-CH_2CONH_2$	198-200	
185	H	$-CH_3$	ND	Calc. C, 60.46; H, 5.07; N, 13.21 Found: C, 60.48; H, 4.95; N, 13.19
186	4-Cl	$-CH_2CN$	212-214	Calc. C, 54.77; H, 3.51 N, 15.03 Found: C, 54.94; H, 3.61; N, 14.88

Example 187



4-[4,5-Dihydro-3-(trifluoromethyl)-1*H*-benz[g]indazol-1-yl]benzenesulfonamide

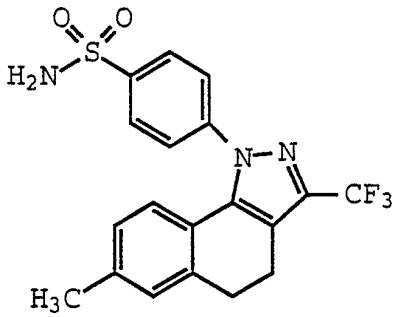
Step 1: Preparation of 2-trifluoroacetyl-1-tetralone.

A 250 mL one necked round bottomed flask equipped with a reflux condenser, nitrogen inlet and provisions for magnetic stirring was charged with ethyl trifluoroacetate (28.4 g, 0.2 mol) and 75 mL of ether. To this solution was added 48 mL of 25% sodium methoxide in methanol (0.21 mol). A solution of 1-tetralone (29.2 g, 0.2 mol) in 50 mL of ether was added over about 5 minutes. The reaction mixture was stirred at room temperature for 14 hours and was diluted wih 100 mL of 3N HCl. The phases were separated and the organic layer was washed with 3N HCl, and with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was taken up in 70 mL of boiling ethanol/water and cooled to room temperature, whereupon crystals of 2-trifluoroacetyl-1-tetralone formed which were isolated by filtration and air dried to give pure compound (32 g, 81%): mp 48-49°C; ^1H NMR $CDCl_3$ δ 2.8 (m, 2H), 2.9 (m, 2H), 7.2 (d, j = 3.0 Hz, 1H), 7.36 (m, 1H), 7.50 (m, 1H), 7.98 (m, 1H); ^{19}F NMR $CDCl_3$ δ -72.0. EI GC-MS M+ = 242.

Step 2: Preparation of 4-[4,5-dihydro-3-(trifluoromethyl)-1*H*-benz[*g*]indazol-1-yl]benzenesulfonamide.

A 100 mL one necked round bottomed flask equipped with reflux condenser, nitrogen inlet and provisions for magnetic stirring was charged with 2-trifluoroacetyl-1-tetralone from Step 1 (1.21 g, 5.0 mmol), 4-sulfonamidophenylhydrazine hydrochloride (1.12 g, 5.0 mmol) and 25 mL of absolute ethanol. The solution was warmed to reflux for 15 hours and concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water, and with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was recrystallized from a mixture of ethyl acetate and isooctane to give 1.40 g, 71% of pure product: mp 257-258°C; ^1H NMR ($CDCl_3/CD_3OD$, 4:1) δ 2.7 (m, 2H), 2.9 (m, 2H), 6.6 (m, 1H), 6.9 (m, 1H), 7.1 (m, 1H), 7.16 (m, 1H), 7.53 (m, 2H), 7.92 (m, 2H); ^{19}F NMR ($CDCl_3$) δ -62.5. FAB-MS M+H = 394.

Example 188



4-[4,5-Dihydro-7-methyl-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide

Step 1. Preparation of 6-methyl-2-(trifluoroacetyl)tetralone.

Ethyl trifluoroacetate (5.33 g, 37.5 mmol) was dissolved in ether (50 mL) and treated with a sodium

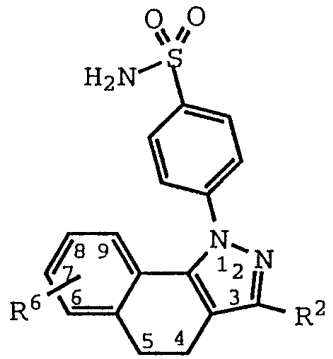
methoxide solution (25% in methanol, 9.92 g, 45.9 mmol) followed by 6-methyltetralone (5.94 g, 37.1 mmol). The reaction was stirred at room temperature for 6.1 hours then treated with 3N HCl (20 mL). The organic layer was collected, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a brown oil (8.09 g) that was used in the next step without further purification.

Step 2. Preparation of 4-[4,5-dihydro-7-methyl-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (1.80 g, 8.0 mmol) was added to a stirred solution of the diketone from Step 1 (1.86 g, 7.3 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred for 14.8 hours. The reaction mixture was cooled and filtered. The filtrate was concentrated *in vacuo*, dissolved in ethyl acetate, washed with water and with brine, dried over $MgSO_4$ and reconcentrated *in vacuo* to give the pyrazole as a brown solid (1.90 g, 64%):
mp 215-218°C. ^1H NMR (acetone-d_6) 300 MHz 8.10 (d, 2H), 7.80 (d, 2H), 7.24(s, 1H), 6.92 (d, 1H), 6.79 (br s, 2H), 6.88 (d,1H), 3.02 (m, 2H), 2.85 (m, 2H), 2.30 (s, 3H). ^{19}F NMR (acetone-d_6) 282 MHz -62.46 (s). High resolution mass spectrum Calc'd. for $C_{19}H_{17}F_3N_3O_2S$: 408.0994. Found: 408.0989.

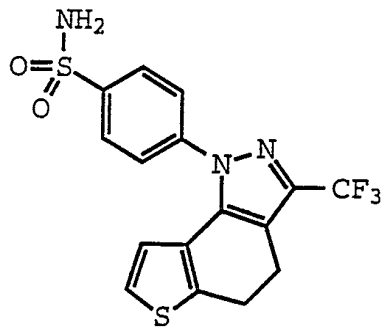
The following compounds in Table IX were prepared according to procedures similar to that exemplified in Examples 187-188, with the substitution of the appropriate ester.

TABLE IX



Ex.	R^2	R^6	M.P.(°C)	Anal.
189	$-CHF_2$	$6-OCH_3$	275-277	HRMS: 405.0961
190	$-CHF_2$	$7-CH_3$	240-241	HRMS: 390.1122
191	$-CF_3$	$6,8-CH_3$	284-288	HRMS: 422.1089
192	$-CF_3$	$7-OCH_3$	277-278	HRMS: 423.0838
193	$-CF_3$	$7,8-OCH_3$	269-275	HRMS: 453.1011
194	$-CHF_2$	$7-OCH_3$	256-257	
195	$-CO_2CH_3$	$7-OCH_3$	274-276	HRMS: 414.1117

Example 196



4-[4,5-Dihydro-3-(trifluoromethyl)-1H thieno[3,2-g]indazol-1-yl]benzenesulfonamide

Step 1. Preparation of 4-keto-4,5,6,7-tetrahydrothianaphthene.

4-(2-Thienyl)butyric acid (28.42 g, 167 mmol) was placed in a round bottom flask with acetic anhydride (30 mL) and phosphoric acid (0.6 mL), and heated to reflux for 3.2 hours. The reaction mixture was poured into 100 mL of water, extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a brown oil (22.60 g) which was vacuum distilled (1mm Hg, 107-115°C) to give a white solid (13.08 g, 51%): mp 34-40°C); ^1H NMR ($CDCl_3$) 300 MHz 7.29 (d, J=5.2 Hz, 1H), 6.99 (d, J=5.2 Hz, 1H), 2.95 (t, J=6.0 Hz, 2H), 2.47(m, 2H), 2.13(m, 2H). M+H = 153.

Step 2. Preparation of 4-keto-4,5,6,7-tetrahydro-5-(trifluoroacetyl)thianaphthene.

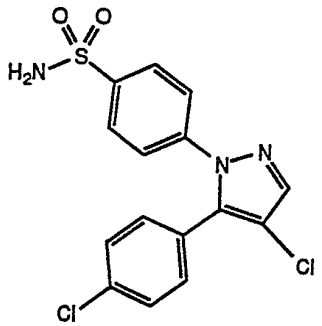
Ethyl trifluoroacetate (11.81 g, 83.1 mmol) was dissolved in ether (50 mL) and treated with a sodium methoxide solution (25% in methanol, 18.35 g, 84.9 mmol) followed by 4-keto-4,5,6,7-tetrahydrothianaphthene from Step 1 (12.57 g, 82.6 mmol) dissolved in ether (25 mL). The reaction was stirred for 69.4 hours at room

temperature, then treated with 3N HCl (40 mL). The organic layer was collected, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a brown solid which was recrystallized from ether/hexane to give the diketone (10.77 g, 52%) as brown needles; mp 54-64°C; ^1H NMR ($CDCl_3$) 300 MHz 15.80 (s, 1H), 7.41 (d, J=5.2 Hz, 1H), 7.17 (d, J=5.2 Hz, 1H), 3.04 (m, 2H), 2.91 (m, 2H); ^{19}F NMR ($CDCl_3$) 282 MHz -70.37 (s). M+H=249.

Step 3. Preparation of 4-[4,5-dihydro-3-(trifluoromethyl)-1H thieno[3,2-g]indazol-1-yl]benzenesulfonamide.

4-Sulfonamidophenylhydrazine hydrochloride (2.36 g, 10.6 mmol) was added to a stirred solution of the diketone from Step 2 (2.24 g, 9.0 mmol) in ethanol (20 mL). The reaction was heated to reflux and stirred 14.7 hours. The reaction mixture was filtered and washed with ethanol and with water to give the desired pyrazole as a white solid (2.69 g, 75%): mp 288-290°C; ^1H NMR (acetone-d_6) 300 MHz 8.12 (d, J=8.7 Hz, 2H), 7.83 (d, J=8.7 Hz, 2H), 7.27 (d, J=5.2 Hz, 1H), 6.81 (br s, 2H), 6.59 (s, J=5.4 Hz,1H), 3.18 (m, 2H), 3.01 (m, 2H); ^{19}F NMR (acetone-d_6) 282 MHz -62.46 (s). High resolution mass spectrum Calc'd. for $C_{16}H_{12}F_3N_3O_2S_2$: 399.0323. Found: 399.0280.

Example 197



4-[5-(4-Chlorophenyl)-4-chloro-1*H*-pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 3-[4-(chloro)phenyl]-propane-1,3-dione.

Ethyl formate (8.15 g, 0.11 mol) and 4'-chloroacetophenone (15.4 g, 0.1 mol) were stirred in ether (150 mL) at room temperature. Sodium methoxide (25%) (23.77 g, 0.11 mol) was added dropwise. The mixture was stirred at room temperature for 16 hours and was then treated with 150 mL of 1N hydrochloric acid. The phases were separated and the ethereal solution washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford 18.3 g of a yellow oil. The resulting crude mixture was used directly in the next step without purification.

Step 2. Preparation of 4-[5-(4-chlorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide.

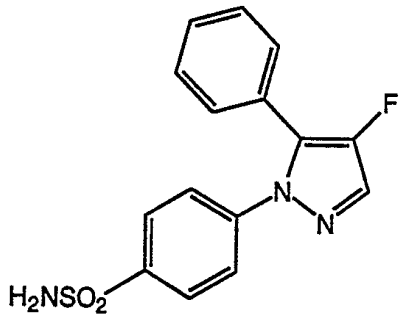
3-[4-(Chloro)phenyl]-propane-1,3-dione from Step 1 (18.3 g, 0.1 mol) and 4-sulfonamidophenylhydrazine hydrochloride (22.4 g, 0.1 mol) were dissolved in 150 mL of absolute ethanol and heated to reflux for 16 hours. The solution was cooled to room temperature, diluted with 100 mL of water and let stand, whereupon crystals of pyrazole

formed that were isolated by filtration to provide 8.4 g (25%) of a white solid: mp 185-187°C; ^{1}H NMR ($CDCl_3$/300 MHz) 7.89 (d, J=8.7Hz, 2H), 7.76 (d, J=1.8Hz, 1H), 7.43 (d,J=8.7Hz, 2H), 7.34 (d, J=8.7Hz, 2H), 7.17 (d, J=8.7Hz, 2H), 6.53 (d, J=1.8Hz, 1H), 4.93 (brs, 2H). Anal. Calc'd for $C_{15}H_{12}N_3SO_2Cl$: C, 53.97; H, 3.62; N, 12.59. Found: C, 54.08; H, 3.57; N, 12.64.

Step 3. Preparation of 4-[5-(4-chlorophenyl)-4-chloro-1H-pyrazol-1-yl]benzenesulfonamide.

4-[5-(4-Chlorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide from Step 2 (3.0 g, 9 mmol) was dissolved in 50 mL of acetic acid, and 9 mL of 1M chlorine in acetic acid was added dropwise. The mixture was stirred for 16 hours when sat. aq. sodium bicarbonate solution was slowly added until the mixture was neutral to pH paper. The mixture was extracted with ethyl acetate (3 X 50 mL), combined and washed with sat. aq. sodium bicarbonate and with brine, dried over magnesium sulfate, filtered, and concentrated. The resultant product was recrystallized from isopropanol to yield 2.6 g (78%) of a white solid: mp 168-171°C (dec); ^{1}H NMR (DMSO-D_6/300 MHz) 8.08 (s, 1H), 7.83 (d, J=8.7Hz, 2H), 7.55 (d, J=8.7Hz, 2H), 7.46 (brs, 2H), 7.44 (d, J=8.7Hz, 2H), 7.35 (d, J=8.7Hz, 2H). Anal. Calc'd for $C_{15}H_{11}N_3SO_2Cl_2$: C, 48.93; H, 3.01; N, 11.41. Found: C, 49.01; H, 2.97; N, 11.41.

Example 198



4-(4-Fluoro-5-phenyl-1H-pyrazol-1-yl)benzenesulfonamide

Step 1: Preparation of 2-fluoroacetophenone

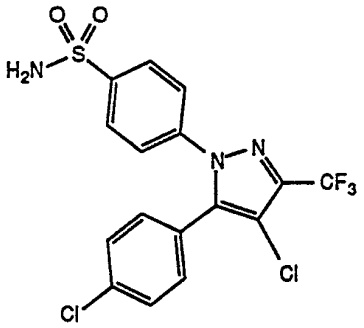
To a solution of 2-hydroxyacetophenone (2.5 g, 18.4 mmol) in 100 mL CH_2Cl_2 at -78°C, was added triflic anhydride (10 g, 35.4 mmol) followed by 2,6-lutidine (4.1 mL, 35.4 mmol) and the mixture stirred at -78°C for 50 minutes. The mixture was poured into CH_2Cl_2 and water and the CH_2Cl_2 layer separated, washed with brine, dried over Na_2SO_4 and concentrated to a peach solid. To a solution of the crude triflate in 100 mL THF was added 35 mL of 1N tetrabutylammonium fluoride in THF. The mixture was refluxed for 15 minutes, cooled and poured into ether and water. The ether layer was separated, washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel using 20:1 hexane/EtOAc furnished the α-fluoroketone (0.852 g, 33.5%).

Step 2: Preparation of 4-(4-fluoro-5-phenyl-1H-pyrazol-1-yl)benzenesulfonamide

A solution of 2-fluoroacetophenone (200 mg, 1.45 mmol) in 2 mL dimethylformamide-dimethylacetal was refluxed for 18 hours. The mixture was cooled and concentrated to give the crude enaminoketone. Without further

purification, the enaminoketone was treated with 4-sulfonamidophenyl hydrazine hydrochloride (0.34 g, 1.52 mmol) in 10 mL EtOH at reflux for 17 hours. The mixture was cooled, filtered and the filtrate concentrated to a yellow gum. Flash chromatography using a gradient of 5:1 to 2:1 hexane/EtOAc provided 0.11 g of a yellow solid: Recrystallization from ether/hexane gave the product as a pale yellow solid, mp 194-194.5°C; Anal. calc'd for $C_{15}H_{12}N_3O_2SF \cdot 0.2\ H_2O$: C, 56.14; H, 3.89; N, 13.09. Found: C, 55.99; H, 3.65; N, 12.92.

Example 199

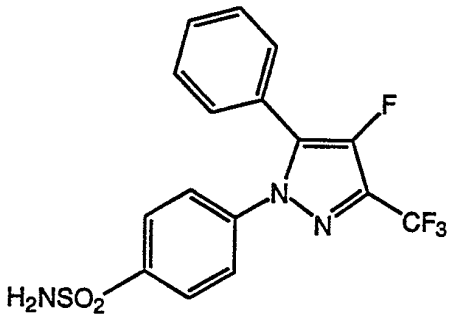


4-[5-(4-Chlorophenyl)-3-(trifluoromethyl)-4-chloro-1*H*-pyrazol-1-yl]benzenesulfonamide

A 100 mL three-necked round-bottomed flask equipped with reflux condenser, gas dispersion tube and provisions for magnetic stirring was charged with 4-[5-(4-chlorophenyl)-3-trifluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide (Example 1)(500 mg, 1.2 mmol) and 50 mL of glacial acetic acid. The solution was stirred at room temperature and treated with a stream of chlorine gas for a period of 15 minutes. The solution was then stirred at room temperature for 1.25 hours and then diluted with 100 mL of water. The solution was then extracted three times with ether and the combined ethereal phase washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a white solid that was recrystallized from ether/petroleum ether to provide 390 mg (75%) of 4-[5-(4-

chlorophenyl)-4-chloro-3-trifluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide: mp 180-182°C; ^{1}H NMR ($CDCl_3$/300MHz) 7.97 (d, J=6.6Hz, 2H), 7.49 (d, J=6.3Hz, 2H), 7.45 (d, J=6.3Hz, 2H), 7.25 (d, J=6.6Hz, 2H), 5.78 (brs, 2H).

Example 200



4-[4-Fluoro-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

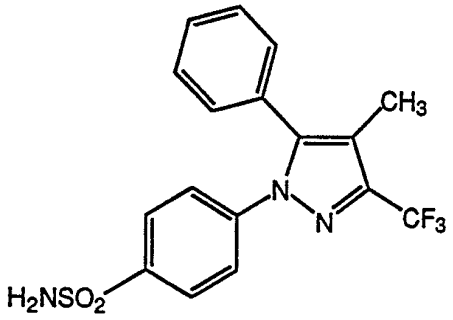
Step 1: Preparation of 4,4,4-trifluoro-1-phenyl-butane-1,3-dione

To a solution of 2-fluoroacetophenone from Step 1 of Example 198 (0.48 g, 3.4 mmol) in 25 mL THF at -78°C, was added 1N lithium bis(trimethylsilyl)amide (4 mL) and the mixture stirred at -78°C for 45 minutes. 1-(Trifluoroacetyl)imidazole (0.65 mL, 5.7 mmol) was added and the mixture stirred at -78°C for 30 minutes and at 0°C for 30 minutes. The mixture was quenched with 0.5 N HCl, poured into ether and water, and the ether layer separated, washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel using a gradient of 10:1 to 4:1 hexane/EtOAc furnished the 1,3-diketone (0.34 g, 43%).

Step 2: Preparation of 4-[4-fluoro-5-phenyl-3-trifluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide

The diketone from Step 1 (0.34 g, 1.45 mmol) was treated with 4-sulfonamidophenyl hydrazine hydrochloride (0.35 g, 1.56 mmol) in 15 mL EtOH at reflux for 15 hours. The mixture was cooled, filtered and the filtrate concentrated to a yellow gum. Flash chromatography using 3:1 hexane/EtOAc provided 0.28 g of a yellow solid. Recrystallization from CH_2Cl_2/hexane gave the product as a pale yellow solid: Anal. calc'd for $C_{16}H_{11}N_3O_2SF_4$: C, 49.87; H, 2.88; N, 10.90. Found: C, 49.79; H, 2.88; N, 10.81.

Example 201



4-[4-Methyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

<u>Step 1: Preparation of 2-methyl-1-phenyl-4,4,4-trifluorobutane-1,3-dione</u>

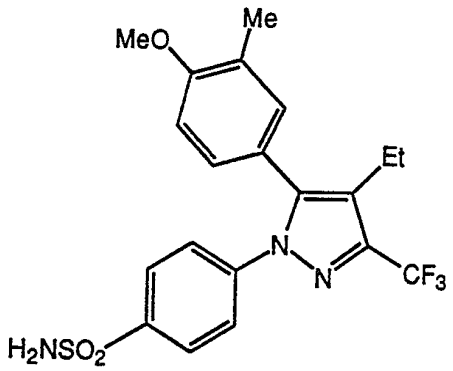
To a solution of propiophenone (965 mg, 7.2 mmol) in THF (20 mL) at -78°C was added sodium bis(trimethylsilyl)amide (7.9 mL of a 1M solution in THF). The solution was kept at -78°C for 0.5 hour and then warmed to -20°C over 1 hour. The solution was cooled to -78°C and 1-(trifluoroacetyl)imidazole (1.5 g, 9.1 mmol) in THF (4 mL) was added via cannula. The solution was warmed to room temperature and stirred overnight. The mixture was partitioned between 1N HCl and ether. The organic solution

was dried (Na_2SO_4) and concentrated to give the crude diketone (1.9 g).

Step 2: Preparation of 4-[4-methyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide

The diketone from Step 1 was dissolved in absolute ethanol (25 mL) and 4-sulfonamidophenylhydrazine hydrochloride (2.0 g, 9.0 mmol) was added. The mixture was heated at reflux for 19 hours. Volatiles were removed *in vacuo* and the residue dissolved in ethyl acetate. The organic solution was washed with water and brine, dried and concentrated. The residue was chromatographed on silica (2:1 hexane/ethyl acetate) to give the title pyrazole (1.52 g, 49%): mp 145-146°C; Calc'd for $C_{17}H_{14}N_3O_2SF_3$: C, 53.54; H, 3.70; N, 11.01. Found: C, 53.41; H, 3.66; N, 10.92.

Example 202



4-[4-Ethyl-5-(3-methyl-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

Step 1: Preparation of 4-methoxy-3-methylbutyrophenone:

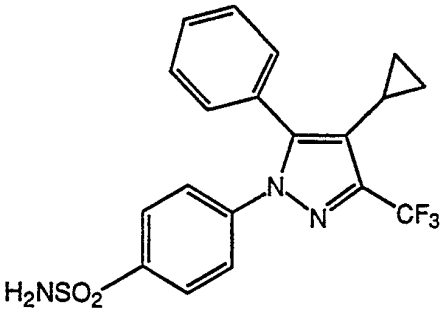
To a suspension of aluminum chloride (10.3 g, 77.2 mmol) in dichloromethane (40 mL) at 0 °C was added

dropwise a solution of 2-methylanisole (5.0 mL, 35.3 mmol) and butyric anhydride (5.8 mL, 35.3 mmol). The reaction solution was kept at 0°C for 2 hours and then warmed to room temperature and stirred overnight. The reaction solution was poured into conc. HCl (9 mL) and ice water (80 mL). The reaction was extracted with dichloromethane and the organic layer was washed with 2N NaOH and brine, dried and concentrated. The residue was chromatographed on silica (9:1 hexane:ethyl acetate) to give the desired product (5.2 g, 77 %).

Steps 2 and 3: Preparation of 4-[4-ethyl-5-(3-methyl-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide:

The title compound was prepared from the butyrophenone in Step 1 using the procedure described in Example 201, Steps 1 and 2: mp 135-136°C; Calc'd for $C_{20}H_{20}N_3O_3SF_3$: C, 54.66; H, 4.59; N, 9.56. Found: C, 54.11; H, 4.38; N, 9.43.

Example 203



4-[4-Cyclopropyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

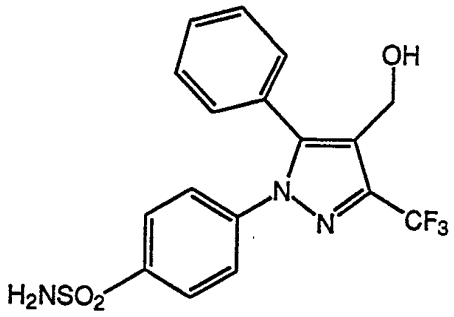
Step 1: Preparation of 2-cyclopropylacetophenone:

To a suspension of sodium cyanide (1.8 g, 37.0 mmol) in dimethyl sulfoxide (20 mL) at 60°C was added dropwise (bromomethyl)cyclopropane (5.0 g, 37.0 mmol). The addition was done at such a rate to keep the temperature of the reaction at 60°C. After the addition was completed, the reaction mixture was heated at 80°C for 15 minutes. The mixture was cooled and partitioned between ether and water. The organic solution was washed with 1N HCl and water, dried and concentrated. The residue was dissolved in ether (5 mL) and added to a solution of phenyl magnesium bromide (25 mL of a 3M solution in ether) in ether (20 mL) and benzene (25 mL). The reaction mixture was stirred at room temperature for 20 hours, then poured into a 1N HCl solution and stirred for 1.5 hours. The organic solution was separated and the aqueous solution extracted with dichloromethane. The organic solution was dried and concentrated. The residue was chromatographed on silica (9:1 hexane:ethyl acetate) to give the desired product (2.0 g, 34%).

Steps 2 and 3: Preparation of 4-[4-cyclopropyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide:

The title compound was prepared from the acetophenone in Step 1 using the procedure described in Example 201), Steps 1 and 2: mp 173-174°C; Calc'd for $C_{19}H_{16}N_3O_2SF_3$: C, 56.01; H, 3.96; N, 10.31. Found: C, 55.85; H, 3.78; N, 10.19.

Example 204



4-[4-hydroxymethyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

Step 1: Preparation of 4-[4-bromomethyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide:

To a solution of 4-[4-methyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide prepared in Example 201 (500 mg, 1.3 mmol) in carbon tetrachloride (9 mL) and benzene (4 mL) was added N-bromosuccinimide (285 mg, 1.6 mmol). The mixture was irradiated with a sunlamp for 3.5 hours. The reaction mixture was partitioned between dichloromethane and water and the organic solution was dried and concentrated to give the desired product, 412 mg (69%).

Step 2: Preparation of 4-[4-formyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide:

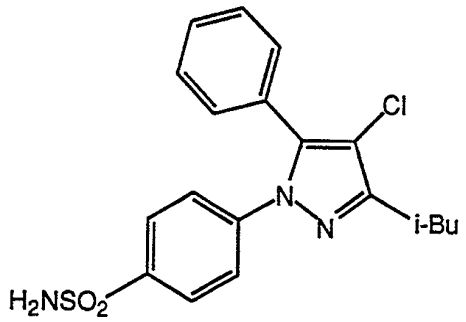
To a solution of the compound prepared in Step 1 (362 mg, 0.79 mmol) in dimethyl sulfoxide (7 mL) was added collidine (0.14 mL, 1.0 mmol). The solution was heated at 120°C for 3 hours and then kept at overnight at room temperature. The reaction solution was partitioned between ethyl acetate and water and the organic solution was washed

with water, dried and concentrated. The residue was chromatographed (1:1 hexane:ethyl acetate) to give the desired product (205 mg, 66%).

Step 3: Preparation of 4-[4-hydroxymethyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide:

To a solution of the aldehyde prepared in Step 2 (165 mg, 0.41 mmol) in methanol (3.5 mL) at 0°C was added sodium borohydride (16 mg, 0.41 mmol). The reaction solution was kept at 0°C for 2.5 hours. The reaction was quenched with the addition of an aqueous 1M $KHSO_4$ solution (3 mL). The mixture was extracted with dichloromethane and the organic solution dried and concentrated. The residue was chromatographed on silica (1:1 hexane:ethyl acetate) to give the desired product (36 mg, 46 %): m.p. 179-180°C; ^1H NMR d 7.91 (m, 2H), 7.53-7.40 (m, 5H), 6.75 (s, 2H), 4.53 (d, 2h, J = 5.0 Hz), 4.30 (t, 1H, J = 5.0 Hz).

Example 205



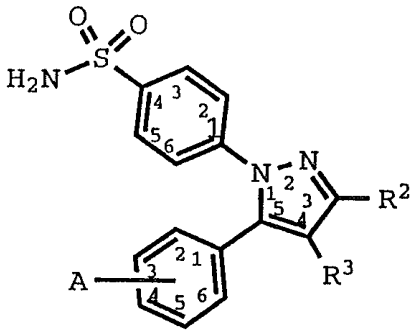
4-(4-Chloro-3-isobutyl-5-phenyl-1H-pyrazol-1-yl)benzenesulfonamide

To a solution of the pyrazole prepared in Example 175 (0.15 g, 0.42 mmol) in CH_2Cl_2 (10 mL) was added an excess of sulfuryl chloride slowly at room temperature. The mixture was stirred at room temperature for 2 hours,

quenched with water and the aqueous layer extracted three time with methylene chloride. The combined organic layers were dried over $MgSO_4$ and concentrated to give an oil which was purified by flash chromatography on silica gel using 70:30 hexane/ethyl acetate as eluent to give the desired compound: HRMS m/z 389.0970 (calc'd for $C_{19}H_{20}ClN_3SO_2$, 389.0965).

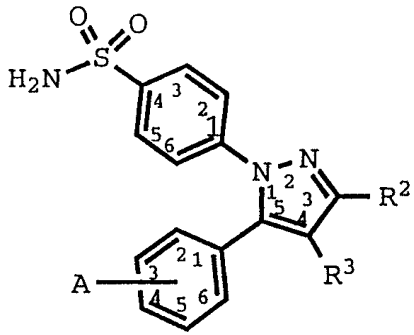
The following compounds in Table X were prepared according to procedures similar to that examplified in Examples 197-205, with the substitution of the appropriate starting material.

TABLE X



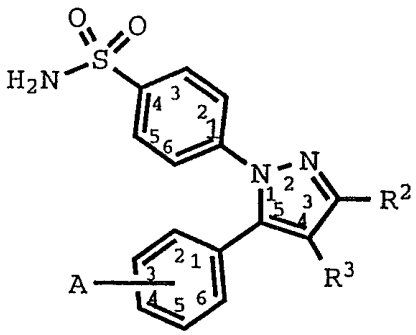
Ex.	R^3	R^2	A	MP(°C)	Analytical
206	Cl	H	4-F	175-178	Calc C,51.22; H,3.15; N,11.94 Obs. C,51.43; H,3.10; N,11.82
207	Br	H	4-Cl	209-210	Calc. C,43.66; H,2.69; N,10.18 Obs. C,43.74; H,2.70; N,10.23
208	Cl	H	H	172-174	Calc. C,53.98; H,3.62; N,12.59 Cl, 10.62; S, 9.60 Obs. C,54.17; H,3.64, N,12.45 Cl, 10.46; S, 9.42
209	Cl	H	3,5-di-Cl, 4-OCH_3	211-212	Calc. C,44.41; H,2.80; N, 9.71 Obs. C, 44.72; H,3.04, N, 9.72
210	Br	H	4-CH_3	ND	HRMS : 391.0003

TABLE X (cont.)



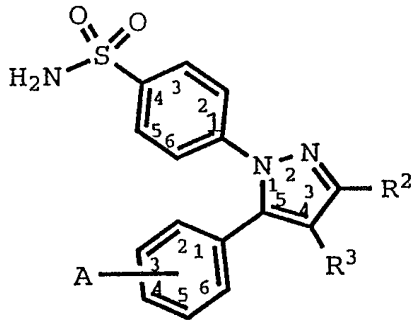
Ex.	R^3	R^2	A	MP(°C)	Analytical
211	Cl	H	4-CH_3	160-163	Calc. C,55.25; H,4.06; N,12.08 Obs. C,55.06; H,4.03, N, 12.02
212	Cl	H	3-Cl, 4-OCH_3	ND	Calc. C,48.25; H,3.29; N,10.55 Cl, 17.80; S, 8.05 Obs. C,48.10; H,3.31, N,10.52 Cl, 17.70; S, 7.98
213	Cl	H	4-OCH_3	155-156	Calc. C,52.82; H,3.88; N,11.55 Obs. C,52.18; H,3.93, N,11.41
214	Br	H	4-OCH_3	130-132	
215	CN	H	4-OCH_3	216-219	HRMS: 355.0860

TABLE X (cont.)



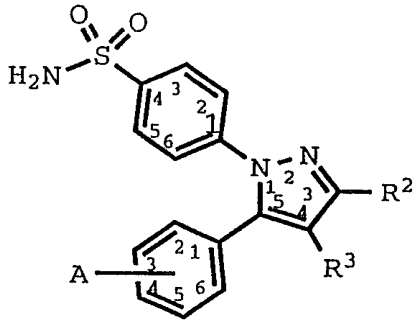
Ex.	R^3	R^2	A	MP(°C)	Analytical
216	Cl	H	3,5-di-F, 4-OCH_3	198-199	Calc. C,48.07; H, 3.03; N,10.51 Obs. C,48.45; H, 3.55, N, 10.10
217	SO_2CH_3	H	Cl	182-185	Calc. C,46.66; H,3.43; N,10.20 Obs. C,46.57; H, 3.49, N,10.39
218	C_2H_5	CF_3	H	177-178	Calc. C, 54.68; H, 4.08; N, 10.62 Obs. C, 54.61; H, 4.10; N, 10.54
219	CH_3	CF_3	4-OCH_3	158-159	Calc. C, 52.55; H, 3.92; N, 10.21 Obs. C, 52.27; H, 4.00; N, 10.16
220	CH_3	CF_3	4-Cl	154-155	Calc. C, 49.10; H, 3.15; N, 10.10 Obs. C, 49.05; H, 3.02; N, 9.96
221	CH_3	CF_3	4-F	103-104	Calc. C, 51.13; H, 3.28; N, 10.52 Obs. C, 51.09; H, 3.26; N, 10.34

TABLE X (cont.)



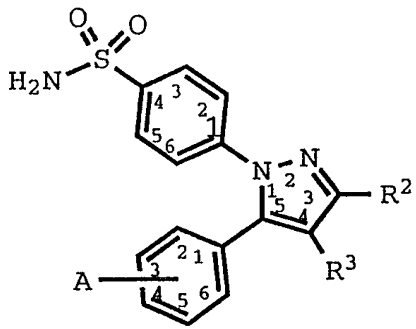
Ex.	R^3	R^2	A	MP(°C)	Analytical
222	C_2H_5	CF_3	4-Cl	ND	Calc. C, 50.30; H, 3.52; N, 9.77 Obs. C, 50.40; H, 3.51; N, 9.72
223	CH_3	CF_3	4-CH_3	144-145	Calc. C, 54.68; H, 4.08; N, 10.62 Obs. C, 54.38; H, 3.87; N, 10.31
224	C_2H_5	CF_3	4-CH_3	142-143	Calc. C, 55.74; H, 4.43; N, 10.26 Obs. C, 55.60; H, 4.37; N, 10.17
225	C_2H_5	CF_3	4-OCH_3	160-161	Calc. C, 53.64; H, 4.26; N, 9.87 Obs. C, 53.55; H, 4.23; N, 9.65
226	C_2H_5	CF_3	3-F, 4-OCH_3	156-157	Calc. C, 51.46; H, 3.86; N, 9.47 Obs. C, 51.27; H, 3.75; N, 9.33
227	Br	CHF_2	4-Cl	224-226	Calc. C, 41.53; H, 2.40; N,9.08 Obs. C, 41.50; H, 2.38; N, 9.00

TABLE X (cont.)



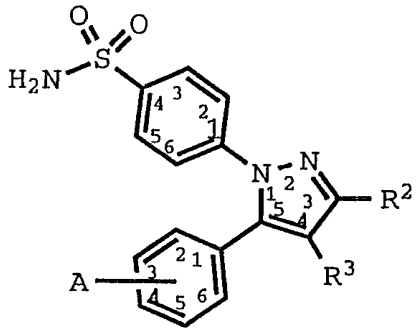
Ex.	R^3	R^2	A	MP(°C)	Analytical
228	Cl	CHF_2	3,5-di-Cl, 4-OCH_3	92-102(dec)	Calc C, 42.30; H, 2.51; N, 8.70 Obs. C, 42.50; H, 2.67, N, 8.56
229	Cl	CHF_2	H	174-176	Calc. C,50.07; H, 3.15; N, 10.95 Obs. C, 50.07; H,3.18, N, 10.98
230	Br	CHF_2	H	184-186	Calc C, 44.87; H, 2.82; N, 9.81 Obs. C, 44.98; H, 2.81, N, 9.64
231	Cl	CHF_2	4-OCH_3	171-172	HRMS: 413.0351
232	Cl	CN	H	174-177(sub)	Calc. C,53.56; H, 3.09; N,15.61; Cl, 9.98; S, 8.94 Obs. C, 53.81; H, 3.18; N,15.43; Cl, 9.78; S, 8.91

TABLE X (cont.)



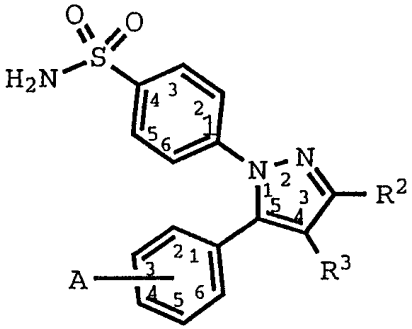
Ex.	R^3	R^2	A	MP(°C)	Analytical
233	Cl	CN	4-Cl	ND	Calc. C, 48.87; H,2.56; N,14.25; Cl, 18.03; S, 8.15 Obs. C, 48.99; H, 2.55; N,14.30; Cl, 17.96; S, 8.08
234	Cl	CN	4-F	ND	Calc. C,51.00; H, 2.68; N,14.87; Cl, 9.41; S, 8.51 Obs. C, 51.19; H, 2.73; N,14.98; Cl, 9.22; S, 8.56
235	Br	CN	4-F	ND	Calc. C,45.62; H, 2.39; N,13.30; Br, 18.97; S, 7.61 Obs. C, 45.51; H,2.36; N,13.21; Br, 19.09; S, 7.51

TABLE X (cont.)



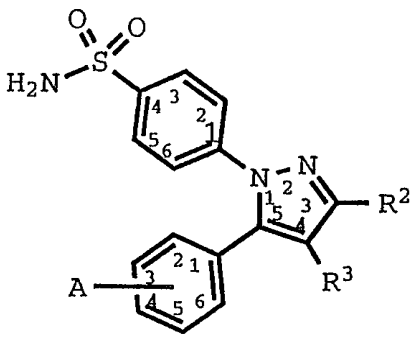
Ex.	R^3	R^2	A	MP(°C)	Analytical
236	Br	CN	H	ND	Calc. C,47.66; H, 2.75; N,13.89; Br, 19.81; S, 7.95 Obs. C, 47.62; H, 2.77; N,13.77; Br, 19.74; S, 8.04
237	Br	$CO_2C_2H_5$	4-Cl	ND	HRMS: 482.9707
238	Cl	CO_2CH_3	H	ND	HRMS: 342.0495
239	Cl	CO_2CH_3	4-Cl	ND	HRMS: 426.0128
240	Cl	$CO_2C_2H_5$	4-Cl	ND	HRMS: 440.0207
241	Cl	CO_2CH_3	4-F	ND	HRMS: 410.0391
242	Br	CO_2CH_3	4-F	ND	HRMS: 453.9880

TABLE X (cont.)



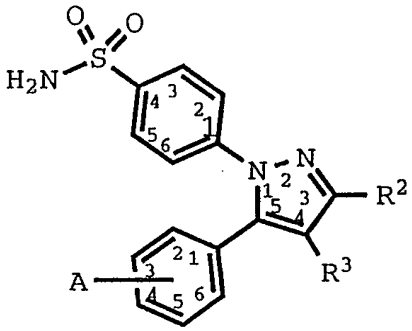
Ex.	R^3	R^2	A	MP(°C)	Analytical
243	Cl	CO_2CH_3	4-OCH_3, 3-Cl	ND	Calc. C, 47.38; H, 3.31; N, 9.21; Cl, 15.54; S, 7.03 Obs. C, 47.10; H, 3.26; N, 9.01; Cl, 15.74; S, 6.92
244	Cl	CO_2CH_3	4-OCH_3, 3,5-di-Cl	198-199	Calc. C, 44.06; H,2.88; N, 8.56. Obs. C, 43.59; H,2.77; N, 8.44
245	Cl	CO_2CH_3	4-OCH_3, 3-Br	ND	Calc. C, 43.18, H, 3.02; N, 8.39; S, 6.40 Obs. C, 43.25; H, 2.97; N, 8.40; S, 6.59
246	Cl	$CONH_2$	H ND	HRMS: 377.0539	
247	Cl	$CONH_2$	4-Cl ND	HRMS: 411.0115	

TABLE X (cont.)



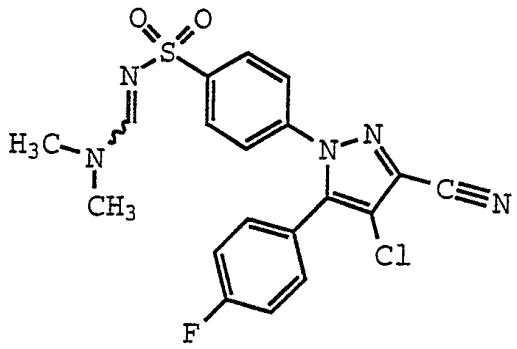
Ex.	R^3	R^2	A	MP(°C)	Analytical
248	Cl	$CONH_2$	4-F	ND	HRMS: 395.0397
249	Br	$CONH_2$	4-F	ND	Calc. C, 43.75, H, 2.75; N, 12.75; Br, 18.19; S, 7.30 Obs. C, 43.65; H, 2.78; N, 12.66; Br, 18.13; S, 7.21
250	Br	$CONH_2$	H	ND	HRMS: 419.9920
251	Cl	CO_2H	H	ND	HRMS 377.0249
252	Cl	CO_2H	4-Cl	ND	Calc. C, 46.62, H, 2.69; N, 10.19; Cl, 17.20; S, 7.78 Obs. C, 46.59, H, 2.68; N, 10.21; Cl, 17.25; S, 7.73

TABLE X (cont.)



Ex.	R^3	R^2	A	MP(°C)	Analytical
253	Cl	CO_2H	4-OCH_3, 3,5-di-Cl	220(dec)	Calc. C, 42.83; H, 2.54; N,8.81
					Obs. C, 43.65; H, 2.52; N, 8.78
254	Cl	CH_3	H	ND	Calc. C,55.25; H, 4.06; N,12.08
					Obs. C,55.24; H,4.26; N, 12.17
255	Cl	CH_2OH	H	195-197	HRMS: 363.0431
256	Cl	CH_2OH	4-Cl	203-204	Calc. C,48.25; H,3.29; N,10.55
					Obs. C, 48.36; H,3.27; N, 10.50
257	Cl	$(CH_2)_2CO_2H$	4-Cl	212-214	Calc. C, 49.10; H, 3.43; N,9.54
					Obs. C, 49.23; H, 3.45; N, 9.49
258	OCH_3	CF_3	H	137-138	Calc. C,51.38; H, 3.55; N,10.57
					Obs. C,51.40; H, 3.47; N, 10.47

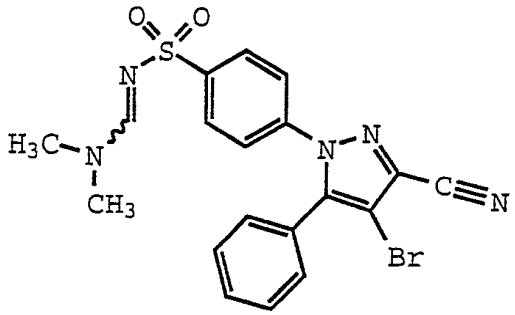
Example 259



4-[4-Chloro-3-cyano-5-[4-(fluoro)phenyl])-1H-pyrazol-1-yl]-N-[(dimethylamino)methylene] benzenesulfonamide

Increasing the polarity of the eluant used in the purification in Example 234 to 60% ethyl acetate, upon concentration of the appropriate fractions, yielded 4-[4-chloro-3-cyano-5-[4-(fluoro)phenyl])-1H-pyrazol-1-yl]-N-[(dimethylamino)methylene]benzenesulfonamide (0.485 g, 15%): High Resolution Mass Spectrum (MLi+) calc'd: 438.0779. Found: 438.0714. Elemental analysis calc'd for $C_{19}H_{15}N_5O_2FClS$: C, 52.84: H, 3.50: N, 16.22; Cl, 8.21; S, 7.42. Found: C, 52.76; H, 3.52; N, 16.12; Cl, 8.11; S, 7.35.

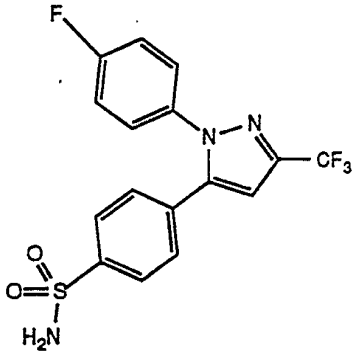
Example 260



4-[4-Bromo-3-cyano-5-phenyl-1H-pyrazol-1-yl]-N-[(dimethylamino)methylene]benzenesulfonamide

Similarly, 4-[4-bromo-3-cyano-5-phenyl-1H-pyrazol-1-yl]-N-[(dimethylamino)methylene] benzenesulfonamide was isolated from the purification of Example 235 (0.153 g, 28%): High Resolution Mass Spectrum (M+) calc'd: 457.0208. Found: 457.0157. Elemental analysis calc'd for $C_{19}H_{16}N_5O_2BrS$: C, 49.79: H, 3.52: N, 15.28; Br, 17.43; S, 6.99. Found: C, 49.85; H, 3.56; N, 15.10; Br, 17.52; S, 6.87.

Example 261



4-[1-(4-Fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]benzenesulfonamide

Step 1: Preparation of N,N-bis(4-methoxybenzyl)-4-(aminosulfonyl)acetophenone.

To a solution of 4-(aminosulfonyl)acetophenone (2.0g, 9.0 mmol) in dimethylsulfoxide (25 mL) was added sodium hydride (450 mg, 19.0 mmol). The reaction mixture was stirred for 45 minutes and then 4-methoxybenzyl bromide (3.5 g, 19.0 mmol) in dimethylsulfoxide (5 mL) was added via cannula. The mixture was stirred at room temperature for 24 hours and partitioned between ethyl acetate and pH 7 buffer. The aqueous solution was extracted with ethyl acetate. The organic solution was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica (2:1 hexane:ethyl acetate) to give the desired product (815 mg, 21%).

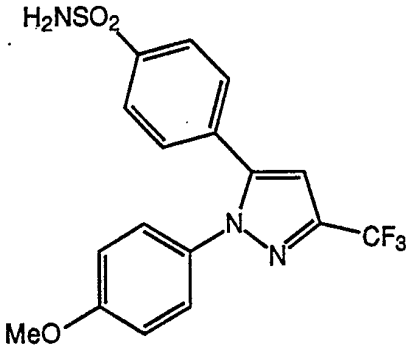
Step 2: Preparation of N,N-bis(4-methoxybenzyl)-4-[1-(4-fluorophenyl)-3-trifluoromethyl-1H-pyrazol-5-yl]benzenesulfonamide

To a 25% sodium methoxide solution in methanol (0.2 mL) was added ethyl trifluoroacetate (75 mg, 0.53 mmol) and the protected acetophenone from Step 1 (235 mg, 0.53 mmol). THF (0.5 mL) was added and the reaction mixture was heated at reflux for 2 hours and then stirred at room temperature overnight. The mixture was partitioned between ether and 1N HCl solution. The organic solution was dried and concentrated to give the crude diketone (279 mg), which was diluted with absolute ethanol (2.5 mL). To this slurry was added pyridine (49 mg, 0.62 mmol) and 4-fluorophenylhydrazine hydrochloride (80 mg, 0.50 mmol). The mixture was stirred at room temperature for 24 hours and concentrated *in vacuo*. The residue was dissolved in methylene chloride and washed with 1N HCl. The organic solution was dried and concentrated. The residue was chromatographed on silica (3:1 hexane:ethyl acetate) to give the protected pyrazole (159 mg, 51%).

Step 3: Preparation of 4-[1-(4-fluorophenyl)-3-trifluoromethyl-1H-pyrazol-5-yl]benzenesulfonamide.

To a solution of the protected pyrazole (50 mg, 0.08 mmol) in acetonitrile (1 mL) and water (0.3 mL) was added ceric ammonium nitrate (360 mg, 0.65 mmol). The reaction solution was kept at room temperature for 16 hours. The solution was poured into water (15 mL) and extracted with ethyl acetate (2 x 25 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica (2:1 hexane:ethyl acetate) to give the desired product (13 mg, 42%): ^1H NMR (CD_3OD) 7.88 (d,2H), 7.46 (d, 2H), 7.39 (dd, 2H), 7.21 (t, 2H), 7.06 (s, 1H).

Example 262



4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide

The title compound was prepared using the procedure described in Example 261: HRMS m/z 397.0702 (calc'd for $C_{17}H_{14}N_3O_3SF_3$, 397.0708).

BIOLOGICAL EVALUATION

Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test was performed with materials, reagents and procedures essentially as described by Winter, et al., (*Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962)). Male Sprague-Dawley rats were selected in each group so that the average body weight was as consistant as possible. Rats were fasted with free access to water for over sixteen hours prior to the test. The rats were dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One to two hours later a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline was administered and the volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a group of drug-treated animals was compared

with that of a group of placebo-treated animals and the percentage inhibition of edema was determined (Otterness and Bliven, *Laboratory Models for Testing NSAIDs*, in **Non-steroidal Anti-Inflammatory Drugs**, (J. Lombardino, ed. 1985)). The % inhibition shows the % decrease from control paw volume determined in this procedure and the data for selected compounds in this invention are summarized in Table I.

Rat Carrageenan-induced Analgesia Test

The analgesia test using rat carrageenan was performed with materials, reagents and procedures essentially as described by Hargreaves, et al., (*Pain*, **32**, 77 (1988)). Male Sprague-Dawley rats were treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats were placed in a special plexiglass container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty minute period, thermal stimulation was begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell turned off the lamp and timer when light was interrupted by paw withdrawal. The time until the rat withdraws its foot was then measured. The withdrawal latency in seconds was determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal determined. Results are shown in Table XI.

TABLE XI.

	RAT PAW EDEMA % Inhibition @ 10mg/kg body weight	ANALGESIA % Inhibition @ 30mg/kg body weight
Examples		
1	44	94
2	35	38
58	36	65
59	25	41
60	49	39
82	22*	
86	42*	
98	2*	
117	32	
129	47*	
170	18*	
171	14	37
188	32*	
197	45*	27
199	35	

.* Assay performed at 30 mg/kg body weight

Evaluation of COX I and COX II activity *in vitro*

The compounds of this invention exhibited inhibition *in vitro* of COX II. The COX II inhibition activity of the compounds of this invention illustrated in the Examples was determined by the following methods.

a. Preparation of recombinant COX baculoviruses

A 2.0 kb fragment containing the coding region of either human or murine COX-I or human or murine COX-II was cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-I and COX-II in a manner

similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses were isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells (2x10e8) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses were purified by three rounds of plaque purification and high titer (10E7 - 10E8 pfu/ml) stocks of virus were prepared. For large scale production, SF9 insect cells were infected in 10 liter fermentors (0.5 x 10^6/ml) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio] -1-propanesulfonate (CHAPS). The homogenate was centrifuged at 10,000xG for 30 minutes, and the resultant supernatant was stored at -80°C before being assayed for COX activity.

b. Assay for COX I and COX II activity:

COX activity was assayed as PGE_2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme were incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 µM). Compounds were pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after ten minutes at 37°C/room temperature by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE_2 formed was measured by standard

ELISA technology (Cayman Chemical). Results are shown in Table XII.

TABLE XII.

Example	Human COX II ID_{50} µM	Human COX I ID_{50} µM
1	<.1	18
2	<.1	15.0
3	<.1	>100
4	.6	37.5
5	<.1	6.3
6	.2	78.7
7	14	>100
8	37.7	>100
9	.1	55.2
10	2.7	>100
12	20	>100
55	22	77.9
56	<.1	11.7
57	47.9	>100
58	<.1	5.7
59	<.1	26.8
60	<.1	.8
82	<.1	1.1
84	<.1	65.5
85	73.6	>100
86	.5	>100
96	6.5	>100
97	96	>100
98	<.1	1.7
117	.3	>100
128	1.1	>100
129	<.1	13.5
130	3.6	12.5
131	.2	>100
138	.6	<.1
170	.1	>100

TABLE XII (cont.)

Example	Human COX II ID_{50} µM	Human COX I ID_{50} µM
171	.8	>100
172	4.2	>100
173	4.7	>100
174	3.5	100
175	66.9	>100
176	.3	>100
187	1.1	13.6
188	.2	19.8
196	.6	4.1
197	<.1	3.4
198	4.2	56.5
199	<.1	<.1
200	<.1	.5
201	<.1	2.2
202	<.1	91
203	27	>100
204	6.7	>100
205	<.1	2.1
259	1.1	>100
260	1.1	>100
261	<.1	<.1
262	<.1	<.1

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of this combination therapy in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The

active compounds and composition may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.5 and about 20 mg/kg body weight and most preferably between about 0.1 to 10 mg/kg body weight, may be appropriate.

The therapeutically active compounds can be administered on an as needed basis. Alternatively, the therapeutically active compounds can be administered at a once a week, once a month, or other suitable frequency, based on the formulation, compound half life, administration substantially simultaneous with feeding, age of animal, and other related properties. A daily dose can be administered in one to four doses per day.

In the case of skin conditions, it may be preferable to apply a topical preparation of compounds

of this invention to the affected area two to four times a day.

For inflammations of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butanel-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60™, Span 80™, cetostearyl

alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

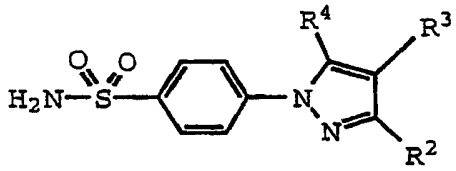
Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The antiinflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl

alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

The embodiment of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. Use of a compound of Formula II



(II)

wherein R^2 is selected from hydrido, C_1-C_{20}-alkyl, C_1-C_{20}-haloalkyl, C_1-C_{10}-alkoxycarbonyl, cyano, C_1-C_{20}-cyanoalkyl, carboxyl, aminocarbonyl, C_1-C_{20}-alkylaminocarbonyl, C_3-C_{10}-cycloalkylaminocarbonyl, arylaminocarbonyl, carboxy-C_1-C_{20}-alkylaminocarbonyl, carboxyl-C_1-C_{20}-alkyl, aryl-C_1-C_{10}-alkoxycarbonyl-C_1-C_{20}-alkylaminocarbonyl, aminocarbonyl-C_1-C_{20}-alkyl, C_1-C_{10}-alkoxycarbonylcyano-C_2-C_{20}-alkenyl, C_1-C_{10}-hydroxyalkyl and alkanoyl;

wherein R^3 is selected from hydrido, C_1-C_{20}-alkyl, cyano, C_1-C_6-hydroxyalkyl, C_3-C_{10}-cycloalkyl, C_1-C_{20}-alkylsulfonyl and halo; and

wherein R^4 is selected from aryl-C_2-C_{20}-alkenyl, aryl, C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkenyl and heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, C_1-C_{10}-alkylthio, C_1-C_{20}-alkylsulfonyl, cyano, nitro, C_1-C_{20}-haloalkyl, C_1-C_{20}-alkyl, hydroxyl, C_2-C_{20}-alkenyl, C_1-C_{10}-hydroxyalkyl, carboxyl, C_3-C_{10}-cycloalkyl, C_1-C_{20}-alkylamino, C_1-C_{20}-dialkylamino, C_1-C_{10}-alkoxycarbonyl, aminocarbonyl, C_1-C_{10}-alkoxy, C_1-C_{10}-haloalkoxy, sulfamyl, heterocyclic and amino;

or a pharmaceutically-acceptable salt thereof for preparing a medicament for treating inflammation or an inflammation-associated disorder selected from pain; fever; inflammation of the musculoskeletal system, including

chronic inflammation of hard and soft tissue, joint disease and traumatic injury; arthritis, selected from rheumatoid arthritis, gouty arthritis, and osteoarthritis; myositis, and tendinitis; equine colic; mastitis; peritonitis; skin related conditions selected from burns and dermatitis; gastrointestinal conditions selected from gastritis, and ulcerative colitis, viral and bacterial infections of the GI tract, cancer; inflammation as a result of vascular diseases, gingivitis, hypersensitivity, conjunctivitis and other eye inflammation, swelling occurring after injury or surgery, and myocardial ischemia, in an animal selected from dogs, cats and horses.

2. The use according to claim 1 wherein R^2 is selected from hydrido, C_1-C_{10}-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxycarbonyl, cyano, C_1-C_{10}-cyanoalkyl, carboxyl, aminocarbonyl, C_1-C_{10}-alkylaminocarbonyl, C_3-C_7-cycloalkylaminocarbonyl, arylaminocarbonyl, carboxy-C_1-C_{10}-alkylaminocarbonyl, aryl-C_1-C_6-alkoxycarbonyl-C_1-C_{10}-alkylaminocarbonyl, aminocarbonyl-C_1-C_{10}-alkyl, C_1-C_{10}-carboxyalkyl, C_1-C_6-alkoxycarbonyloyano-C_2-C_6-alkenyl, C_1-C_6-hydroxyalkyl and alkanoyl; wherein R^3 is selected from hydrido, C_1-C_{10}-alkyl, cyano, C_1-C_6hydroxyalkyl, C_3-C_7-cycloalkyl, C_1-C_6-alkylsulfonyl and halo; and wherein R^4 is selected from aryl-C_2-C_{20}-alkenyl, aryl, C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkenyl and heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, C_1-C_{10}-alkylthio, C_1-C_6-alkylsulfonyl, cyano, nitro, C_1-C_6-haloalkyl, C_1-C_{10}-alkyl, hydroxyl, C_2-C_6- alkenyl, C_1-C_6-hydroxyalkyl, carboxyl, C_3-C_7-cycloalkyl, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1-C_6-alkoxycarbonyl, aminocarbonyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, sulfamyl, five or six membered heterocyclic and amino; or a pharmaceutically-acceptable salt thereof.

3. The use according to claim 2 wherein the compound is selected from compounds and their pharmaceutically-acceptable salts, of the group consisting of

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide; and

4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

4. The use according to claim 1 in treatment of an inflammation.

5. The use according to claim 1 in treatment of an inflammation-associated disorder, selected from pain and fever.

6. The use according to claim 2 wherein R^2 is selected from hydrido,methyl, ethyl, isopropyl, tert-butyl, isobutyl,hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, trifluoroacetyl, cyanomethyl, ethoxycarbonylcyanoethenyl, aminocarbonyl, aminocarbonylmethyl, N-methylaminocarbonyl, N-ethylaminocarbonyl, N-isopropylaminocarbonyl, N-propylaminocarbonyl, N-butylaminocarbonyl, N-isobutylaminocarbonyl, N-tert-butylaminocarbonyl, N-pentylaminocarbonyl, N-phenylaminocarbonyl, N,N-dimethylaminocarbonyl, N-methyl-N-ethylaminocarbonyl, N-(3-fluorophenyl)aminocarbonyl, N-(4-methylphenyl)aminocarbonyl, N-(3-chlorophenyl)aminocarbonyl, N-methyl-N-(3-chlorophenyl)aminocarbonyl, N-(4-methoxyphenyl)aminocarbonyl, N-methyl-N-phenylaminocarbonyl, cyclopentylaminocarbonyl, cyclohexylaminocarbonyl,

carboxymethylaminocarbonyl, benzyloxycarbonylmethylaminocarbonyl, hydroxypropyl, hydroxymethyl, and hydroxypropyl; wherein R^3 is selected from hydrido, methyl, ethyl, isopropyl, tert-butyl, isobutyl, hexyl, fluoro, chloro, bromo, cyano, methylsulfonyl, cyclopropyl, cyclopentyl, hydroxypropyl, hydroxymethyl, and hydroxyethyl; and wherein R^4 is selected from phenylethenyl, phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycoheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, 1-cyclopentenyl, 4-cyclopentenyl, benzofuryl, 2,3-dihydrobenzofuryl, 1,2,3,4-tetrahydronaphthyl, benzothienyl, indenyl, indanyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, and pyrazinyl; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methyl, ethyl, propyl, isopropyl, tert-butyl, isobutyl, hexyl, ethylenyl, propenyl, methylsulfonyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, aminocarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, bromodifluoromethyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, sulfamyl, hydroxypropyl, hydroxyisopropyl, hydroxymethyl, hydroxyethyl, trifluoromethoxy, N-methylamino, N-ethylamino, N-ethyl-N-methylamino, N,N-dimethylamino, N,N-diethylamino, amino, piperadinyl, piperazinyl, morpholino, and nitro; or a pharmaceutically-acceptable salt thereof.

7. The use according to claim 3 wherein the compound is 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

8. The use according to any one of claims 1, 2, 3, 6 or 7, wherein the cancer is colorectal cancer.