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(54) **COMPOUNDS AND COMPOSITIONS FOR
THE TREATMENT OF CYSTIC FIBROSIS**

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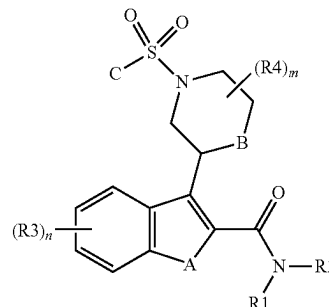
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(57) **ABSTRACT**

The present invention relates to compounds of Formula (Ia) or pharmaceutically acceptable salts, hydrates, solvates, clathrates, polymorphs, stereoisomers thereof. It further discloses a pharmaceutical composition comprising compounds of Formula (Ia) and the use of compounds of Formula (Ib), in particular to modulate CFTR protein or ABC protein activities.

(Ia)



9 Claims, No Drawings

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COMPOUNDS AND COMPOSITIONS FOR THE TREATMENT OF CYSTIC FIBROSIS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is filed pursuant to 35 U.S.C. 371 as a U.S. National Phase application of International Patent Application No. PCT/IB2020/050350, which was filed Jan. 16, 2020, claiming the benefit of Italian patent application no. 102019000000687 filed on Jan. 16, 2019. The entire text of the aforementioned applications is incorporated herein by reference in its entirety.

TECHNICAL FIELD

The present invention relates to novel compounds to modulate CFTR protein or ABC protein activities, in particular for the treatment of cystic fibrosis.

BACKGROUND ART

Cystic fibrosis is an autosomal recessive genetic disorder caused by mutations of the gene encoding for the cystic fibrosis transmembrane conductance regulator (CFTR). The incidence of the disease among the Caucasian population is 1/2000-3000 newborns, whereas it is much lower among native Africans and Asians. Despite progress in the treatment of cystic fibrosis, there is no cure.

The cystic fibrosis transmembrane conductance regulator (CFTR) gene encodes an epithelial ion channel responsible for aiding in the regulation of salt and water absorption and secretion in various tissues.

Specifically, CFTR is a 1480 amino acid plasma membrane protein that belongs to the superfamily of ATP-binding cassette (ABC) transporters. CFTR structure consists of a cytosolic N-terminus followed by six transmembrane helices, a nucleotide-binding domain (NBD1), a regulatory (R) domain, six additional transmembrane helices, a second nucleotide-binding domain (NBD2), and a cytosolic C-terminus (Riordan, *Annu Rev Biochem* 77:701-726, 2008; Liu, *Cell* 169:85-95, 2017). The transmembrane helices form a pore permeable to chloride, bicarbonate, iodide, and other anions. Opening of the pore requires the phosphorylation of the R domain by the CAMP-dependent protein kinase A as well as binding of two ATP molecules in two pockets formed by the assembly of NBD1 and NBD2.

CFTR is a CAMP/ATP-modulated anion channel that is expressed in a variety of cells types, and particularly in epithelial cells of various organs including lungs, pancreas, liver, and intestine (Mall and Hartl, *Eur Respir J* 44:1042-1054, 2014). Physiological signals that increase intracellular CAMP levels elicit CFTR activation. In most tissues, opening of CFTR pore leads to chloride and bicarbonate secretion. The sweat gland duct in which CFTR mediates chloride absorption and not secretion represents a notable exception.

In epithelial cells, normal functioning of CFTR is critical for the maintenance of electrolyte transport throughout the body, including respiratory and digestive tissues

The important role of CFTR is demonstrated by the severe pathological manifestations occurring in cystic fibrosis (CF), an inherited disease caused by mutations that lead to CFTR loss of function. In the lungs, lack of CFTR-dependent anion secretion impairs mucociliary clearance and innate antimicrobial mechanisms (Collawn and Matalon, *Am J Physiol* 307: L917-L923, 2014). Consequently, the airways become

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colonized by antibiotic-resistant bacteria that trigger a severe inflammatory response and a progressive loss of respiratory function.

The gene encoding CFTR has been identified and sequenced (see Gregory, R. J. et al. (1990) *Nature* 347:382-386; Rich, D. P. et al. (1990) *Nature* 347:358-362; Riordan, J. R. et al. (1989) *Science* 245:1066-1073). Defects in this gene cause mutations in CFTR protein resulting in cystic fibrosis, the most common fatal genetic disease in humans. Within the general United States population, up to 10 million people carry a single copy of the defective gene without apparent ill effects. In contrast, individuals with two copies of the cystic fibrosis associated gene suffer from the debilitating and fatal effects of cystic fibrosis, including chronic lung disease.

In addition to respiratory disease, cystic fibrosis patients typically suffer from gastrointestinal problems and pancreatic insufficiency. If left untreated, cystic fibrosis results in death. In addition, the majority of males with cystic fibrosis are infertile and fertility is decreased among females with cystic fibrosis. In contrast to the severe effects of two copies of the cystic fibrosis associated gene, individuals with a single copy of the cystic fibrosis associated gene may exhibit increased resistance to dehydration resulting from diarrhea. This heterozygote advantage could explain the relatively high frequency of the cystic fibrosis gene within the population.

Sequence analysis of the CFTR gene of cystic fibrosis patients has revealed a variety of disease causing mutations (Cutting, G. R. et al. (1990) *Nature* 346:366-369; Dean, M. et al. (1990) *Cell* 61:863-870; Kerem, B—S. et al. (1989) *Science* 245:1073-1080; Kerem, B—S. et al. (1990) *Proc. Natl. Acad. Sci. USA* 87:8447-8451). To date, more than 2000 CF-causing mutations in the cystic fibrosis gene have been identified, involving 6 classes of molecular defects of the protein (Class I: premature stop of CFTR protein synthesis; Class II: defective maturation and intracellular localization of the CFTR protein; Class III: impaired opening of CFTR pore; Class IV: reduced ability of CFTR pore to translocate anions; Class V: reduced CFTR protein synthesis due to altered RNA splicing; Class VI: reduced stability of CFTR at the plasma membrane leading to accelerated internalization and degradation).

A large majority of mutations have low or very low frequency (Bobadilla et al., *Hum Mutat* 19:575-606, 2002). However, a single mutation, F508del, is present in 50-90% of CF patients. F508del, i.e. loss of phenylalanine at position 508 within NBD1, causes multiple defects to CFTR protein (Okuyoneda et al., *Nat Chem Biol* 9:444-454, 2013). First of all, F508del-CFTR folding and stability are severely impaired. Such problems, which arise from the intrinsic instability of NBD1 and the altered interaction between NBD1 and the cytosolic loop 4, strongly reduce the trafficking of F508del-CFTR to the plasma membrane (trafficking defect). Indeed, mutant CFTR remains trapped in the endoplasmic reticulum (ER) where it is rapidly degraded by the ubiquitin-proteasome system (Lukacs and Verkman, *Trends Mol Med* 18:81-91, 2012). A second defect caused by F508del is the reduction of the open channel probability, i.e. the fraction of time spent by the channel in the open state (gating defect). Furthermore, if moved to the plasma membrane by rescue maneuvers, F508del-CFTR shows also a decreased half-time. Because of such defects, F508del mutation has combined class II, class III, and class VI characteristics.

The trafficking and gating defects can also be caused, often separately, by other CF mutations. For example, G85E,

L1077P, A455E, and N1303K, defined as class II mutations, impair CFTR trafficking (Van Goor et al., *J Cyst Fibros* 13:29-36, 2014). Instead, G551D, G1349D, G178R, and G970R, defined as class III mutations, do not affect trafficking but strongly reduce CFTR open time (Yu et al., *J Cyst Fibros* 11:237-245, 2012).

The most prevalent mutation, i.e. the F508del, is associated with a severe disease.

The reduced number of channels in the membrane and the defective gating lead to reduced anion transport across epithelia leading to defective ion and fluid transport.

As discussed above, it is believed that the deletion of residue 508 in CFTR prevents the nascent protein from folding correctly, resulting in the inability of this mutant protein to exit the ER, and traffic to the plasma membrane. As a result, insufficient amounts of the mature protein are present at the plasma membrane and chloride transport within epithelial tissues is significantly reduced. This cellular phenomenon of defective ER processing of ABC transporters by the ER machinery has been shown to be the underlying basis not only for cystic fibrosis disease, but for other diseases (Loo et al., *Journal of Bioenergetics and Biomembranes*, 2005, 37, 501-507).

At present, the treatment of lung disorders in cystic fibrosis requires the development of innovative drugs aimed at the concomitant aspects of the disease and, consequently, modulators of the defective CFTR protein, new antibacterials and new anti-inflammatory agents, which can be used in parallel to obtain a synergistic action. Trafficking and gating defects caused by mutations in the CFTR protein are amenable to pharmacological treatment (Veit et al., *Mol Biol Cell* 27:424-433, 2016). Mistrafficking can be targeted with small molecules called correctors. Gating can be improved with so-called potentiators. There have been several attempts to identify potentiators and correctors (Galiotta, *Pediatr Drugs* 15:393-402, 2013). The most advanced molecule is VX-770, also known as ivacaftor, developed by Vertex Pharmaceuticals (Van Goor et al., *Proc Natl Acad Sci USA* 106:18825-18830, 2009). Given its high efficacy in clinical trials (Ramsey et al., *N Engl J Med* 365:1663-1672, 2011), VX-770 has been approved for the treatment of patients with G551D and other eight mutations belonging to class III, who represent about 5% of all the cystic fibrosis patients. VX-770 has no significant therapeutic efficacy in patients who are homozygous for the F508del-CFTR mutation, confirming the need for customised treatments for sub-groups of patients suffering from cystic fibrosis depending on the specific CFTR protein molecular defect. For patients with the F508del-CFTR mutation, new molecules functioning as “correctors” of the mutated CFTR protein are under study. The VX-809 molecule, also known as lumacaftor, has been extensively characterized in cell models in vitro. In clinical trials on cystic fibrosis patients with F508del mutation, VX-809 did not show a clear therapeutic benefit (Clancy et al., *Thorax* 67:12-18, 2012). However, the combination of VX-809 and VX-770, commercially named Orkambi, elicited a significant although modest improvement in respiratory function (Wainwright et al., *N Engl J Med* 373:220-231, 2015). Recently, the combination of the corrector tezacaftor (also known as VX-661) with ivacaftor, commercially named Symdeko, has been approved for the treatment of cystic fibrosis patients homozygous for the CFTR F508del mutations and of patients having one copy of F508del-CFTR gene and one copy of a so-called “residual function” mutation CFTR gene. In clinical trials, Symdeko showed safety and efficacy in cystic fibrosis patients, but improvement in lung function is still modest (Taylor-Cousar

et al., *N Engl J Med* 377:2013-2023, 2017; Rowe et al., *N Engl J Med* 377:2024-2035, 2017). Briefly, the treatment of cystic fibrosis patients requires different modulators of the mutated CFTR protein, namely “correctors” and/or “potentiators”, depending on the mutations of the CFTR gene, which divide the patients into genetically distinct subgroups, and complementary medicaments with an antibacterial action and an anti-inflammatory action.

Accordingly, there is a need for novel compounds to be used for the treatment of CFTR mediated diseases, which involve CFTR modulator compounds.

DISCLOSURE OF INVENTION

The aim of the present invention is to provide novel compounds acting as CFTR modulators.

The aforementioned objective has been met according to compounds of claim 1, to a pharmaceutical composition of claim 7, to the uses of claims 8 and 9. Preferred embodiments are set out within the dependent claims.

The following paragraphs provide definitions of the various chemical moieties of the compounds according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a broader definition.

The term “alkyl”, as used herein, refers to saturated or partially unsaturated aliphatic hydrocarbon groups. Such term includes straight (unbranched) chains or branched chains.

Non-limiting examples of alkyl groups according to the invention are, for example, methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, iso-pentyl, n-hexyl, ethenyl, 1-propenyl, 2-propenyl, 1- or 2-butenyl, ethynyl, 1-propynyl, 2-propynyl, 1- or 2-butylnyl, and the like.

Alkyl groups according to the present invention may be unsubstituted or substituted by one or more substituents as defined below.

The term “cycloalkyl”, as used herein, refers to a saturated or partially unsaturated carbocyclic group having a single ring. It includes cycloalkenyl groups.

Non-limiting examples of cycloalkyl groups according to the invention are, for example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclopentene, cyclohexene, cyclohexadiene and the like.

Cycloalkyl groups according to the present invention may be unsubstituted or substituted by one or more substituents as defined below.

The term “heterocycloalkyl” group, (“non-aromatic heterocycle” group), refers to a cycloalkyl group (non aromatic group) wherein at least one of the carbon atoms has been replaced by a heteroatom selected from nitrogen, oxygen and sulfur. Heterocycloalkyl groups can be unsubstituted or substituted by one or more substituents as defined below.

Examples of heterocycloalkyls include, but are not limited to lactams, lactones, cyclic imides, cyclic thioimides, cyclic carbamates, 1-(1,2,5,6-tetrahydropyridyl), tetrahydrothiopyran, 4H-pyran, tetrahydropyran, piperidine (1-piperidinyl, 2-piperidinyl, 3-piperidinyl), 1,3-dioxin, 1,3-dioxane, 1,4-dioxin, 1,4-dioxane, piperazine, 1,3-oxathiane, 1,4-oxathian, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, morpholine (4-morpholinyl, 3-morpholinyl, 2-morpholinyl) trioxane, hexahydro-1,3,5-triazine, tetrahydrothiophene, tetrahydrofuran (tetrahydrofuran-2-yl, tetrahydrofuran-3-yl), pyrroline, pyrrolidine, pyrrolidone, pyrrolidindione, pyrazoline, pyrazolidine, imidazoline, imidazolidine, 1,3-dioxole, 1,3-dioxolane, 1,3-dithiole, 1,3-

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dithiolane, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, and 1,3-oxathiolane.

The term “halogen”, as used herein, refers to fluorine, chlorine, bromine and iodine.

The term “aryl”, as used herein, refers to a hydrocarbon consisting of an unsubstituted or substituted mono-, bi- or tricyclic ring system, wherein the rings are fused together and at least one of the carbocyclic ring is aromatic. The term “aryl” means for example a cyclic aromatic such as a 6-membered hydrocarbon ring, a two six-membered fused hydrocarbon rings. Non-limiting examples of aryl groups are, for example, phenyl, alpha- or beta-naphthyl, 9,10-dihydroanthracenyl, indanyl, fluorenyl and the like. Aryl groups according to the present invention may be unsubstituted or substituted by one or more substituents as defined below.

The term “heteroaryl”, as used herein, refers to an aryl as defined above wherein one to four carbon atoms are independently replaced by heteroatoms chosen from the group consisting of nitrogen, oxygen and sulphur. Non-limiting examples of heteroaryl groups are, for example, pyrrolyl, furyl, thiophenyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, indolyl, benzofuranyl, benzo-thiophenyl, benzimidazolyl, benzopyrazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, triazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxaliny. Heteroaryl groups according to the present invention may be unsubstituted or substituted by one or more substituents as defined below.

Unless otherwise indicated, the term “substituted”, as used herein, means that one or more hydrogen atoms of the above mentioned groups are replaced with another non-hydrogen atom or functional group referred to as substituent, provided that normal valencies are maintained and that the substitution results in a stable compound. Non-limiting example of substituents are, for example, OH, C_{1-6} alkyl, aryl, C_{1-6} alkylaryl, C_{3-6} cycloalkyl, $O-C_{1-6}$ alkyl, $O-C_{3-6}$ cycloalkyl, O-aryl, $O-C_{1-6}$ alkylaryl, heterocycloalkyl, O-heteroaryl, O-heterocycloalkyl, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, acyl, aroyl, heteroaryl, halogen, nitro, cyano, $COOR^z$, alkylthio, arylthio, alkylsulfanyl, arylsulfanyl, alkylsulfonyl, arylsulfonyl, $-O-C(=O)-NR^hR^k$, $-C(=O)-NR^hR^k$, and $-NR^pR^q$, wherein each of R^z , R^h , R^k , and R^k , independently represents hydrogen, C_{1-6} alkyl, C_{3-6} Cycloalkyl, aryl, C_{1-6} alkylaryl, heteroaryl, heterocycloalkyl, and R^p and R^q independently represents hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkylaryl, heteroaryl, heterocycloalkyl, $COOR^z$, $-C(=O)-NR^hR^k$, $-S(=O)_2-R^z$, and $-S(=O)_2-NR^hR^k$, and when R^h and R^k , or R^p and R^q are taken together with the nitrogen atom to which they are bound, the group $-NR^hR^k$ or the group NR^pR^q represent a heterocycloalkyl residue, and wherein the terms alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl are as above defined.

Preferred substituents are OH, C_{1-6} alkyl, $O-C_{1-6}$ alkyl, trifluoromethyl, difluoromethyl, halogen, C_{3-6} cycloalkyl, $O-C_{3-6}$ cycloalkyl, trifluoromethoxy, difluoromethoxy, cyano, $-NR^pR^q$ and $COOR^z$ wherein R^z is selected from the group consisting of H, methyl, ethyl, propyl, butyl, i-propyl, t-butyl, and R^p and R^q are independently selected from H, methyl, ethyl, butyl, i-propyl, phenyl, $COOR^z$, $COOR^z$, $-C(=O)-NR^hR^k$, and $-S(=O)_2-R^z$. More preferred substituents are selected from OH, methyl, methoxy, chlorine, fluorine, trifluoromethyl, trifluoromethoxy, cyano,

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$-NR^pR^q$ and $COOR^z$ wherein R^z is selected from the group consisting of H, methyl, ethyl and t-butyl, and R^p and R^q are independently selected from H, methyl, ethyl, butyl, i-propyl, phenyl, and acyl.

The term “pharmaceutically acceptable salts” refers to salts of the below identified compounds of Formula (Ia) and (Ib) that retain the desired biological activity and are accepted by regulatory authorities.

As used herein, the term “salt” refers to any salt of a compound according to the present invention prepared from an inorganic or organic acid or base and internally formed salts. Typically, such salts have a physiologically acceptable anion or cation.

Furthermore, the compounds of Formula (Ia) and (Ib) may form an acid addition salt or a salt with a base, depending on the kind of the substituents, and these salts are included in the present invention, as long as they are pharmaceutically acceptable salts.

Examples of such salts include, but are not restricted to acid addition salts formed with inorganic acids (e. g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, fumaric acid, maleic acid, ascorbic acid, benzoic acid, alginic acid, polyglutamic acid, methanesulfonic acid, p-toluene sulfonic acid, and naphthalene sulfonic acid.

The compounds of Formula (Ia) and (Ib) containing acidic protons may be converted into their therapeutically active, non-toxic base addition salt forms, e.g. metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e.g. lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Physiologically or pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compound.

Pharmaceutically acceptable salts may also be prepared from other salts including other pharmaceutically acceptable salts of the compounds of Formula (Ia) and (Ib) using conventional methods.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as “solvates”. For example, a complex with water is known as a “hydrate”. Solvates of the compounds of the invention are within the scope of the invention. The compounds of Formula (Ia) and (Ib) may readily be isolated in association with solvent molecules by crystallization or evaporation of an appropriate solvent to give the corresponding solvates.

The compounds of Formula (Ia) and (Ib) may be in crystalline form. In certain embodiments, the crystalline forms of the compounds of Formula (Ia) and (Ib) are polymorphs.

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in Formula (Ia) and (Ib) and following, but differ for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the compounds of the invention and pharmaceutically acceptable salts thereof include isotopes of

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hydrogen, carbon, nitrogen, oxygen, sulfur, fluorine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{35}S , ^{18}F , ^{36}Cl .

Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H , ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e. ^3H , and carbon-14, i.e. ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (Positron Emission Tomography). Furthermore, substitution with heavier isotopes such as deuterium, i.e. ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically-labelled compounds of Formula (Ia) and (Ib) and following of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by replacing a non-isotopically-labelled reagent with a readily available isotopically-labelled reagent.

Certain groups/substituents included in the present invention may be present as isomers or in one or more tautomeric forms. Accordingly, in certain embodiments, the compounds of Formula (Ia) and (Ib) may exist in the form of other tautomers or geometrical isomers in some cases, depending on the kinds of the substituents. In the present specification, the compounds may be described in only one form of such isomers, but the present invention includes all such isomers, isolated forms of the isomers, or a mixture thereof. Furthermore, the compounds of Formula (Ia) and (Ib) may have asymmetric carbon atoms or axial asymmetries in some cases and, correspondingly, they may exist in the form of optical isomers such as an (R)-form, an (S)-form, and the like. The present invention includes within the scope all such isomers, including racemates, enantiomers and mixtures thereof.

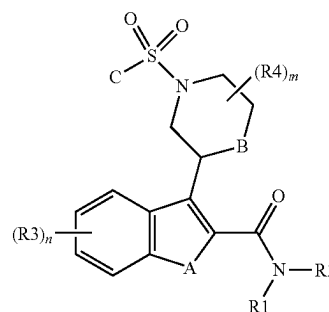
In particular, within the scope of the present invention are included all stereoisomeric forms, including enantiomers, diastereoisomers, and mixtures thereof, including racemates and the general reference to the compounds of Formula (Ia) and (Ib) includes all the stereoisomeric forms, unless otherwise indicated.

In general, the compounds or salts of the invention should be interpreted as excluding those compounds (if any) which are so chemically unstable, either per se or in water, that they are clearly unsuitable for pharmaceutical use through all administration routes, whether oral, parenteral, or otherwise. Such compounds are known to the skilled chemist.

BEST MODE FOR CARRYING OUT THE INVENTION

According to a first aspect of the invention, compounds of Formula (Ia):

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(Ia)

or pharmaceutically acceptable salts, hydrates, solvates, clathrates, polymorphs, stereoisomers thereof are provided.

In the compounds of Formula (Ia):

R1 and R2 are independently selected from the group consisting of hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, and C_{1-4} alkyl-O- C_{1-4} alkyl;

R3 is selected from the group consisting of C_{1-6} alkyl, halo C_{1-6} alkyl, OH, O- C_{1-6} alkyl, C_{1-6} alkyl-O- C_{1-6} alkyl, CN, NO_2 and halogen;

R4 is independently selected from the group consisting of C_{1-6} alkyl, halo C_{1-6} alkyl and halogen; A is selected from the group consisting of S, SO, and SO_2 ;

B is selected from the group consisting of $\text{CR}^{\text{iv}}\text{R}^{\text{v}}$, O, and NR^{ii} ;

C is selected from the group consisting of C_{1-6} alkyl, halo C_{1-6} alkyl, C_{3-6} cycloalkyl optionally substituted with one or more R5, C_{3-6} heterocycloalkyl optionally substituted with one or more R5, aryl optionally substituted with one or more R5, heteroaryl optionally substituted with one or more R5, C_{1-6} alkyl-O- C_{1-6} alkyl, C_{1-6} alkyl-O-aryl, C_{1-6} alkyl-O-heteroaryl, C_{1-6} alkyl-O- C_{3-6} heterocycloalkyl, aryl-O-aryl, and aryl-O-heteroaryl;

R5 is selected from the group consisting of C_{1-6} alkyl, halo C_{1-6} alkyl, O- C_{1-6} alkyl, C_{3-6} Cycloalkyl, C_{3-6} heterocycloalkyl, aryl, heteroaryl, O-aryl, O-aryl-O- C_{1-6} alkyl, O-heteroaryl, O- C_{3-6} heterocycloalkyl, O-halo C_{1-6} alkyl, OH, CN, NO_2 , SF_6 , halogen and COOR^{t} ;

n is an integer comprised from 0 to 2;

m is an integer comprised from 0 to 2;

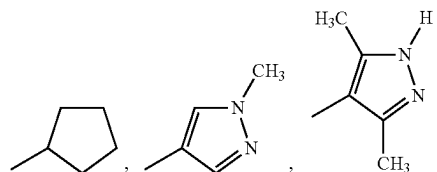
R^{i} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

R^{ii} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

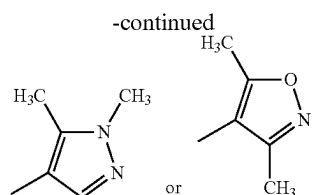
R^{iv} and R^{v} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl and hydroxy C_{1-6} alkyl;

provided that:

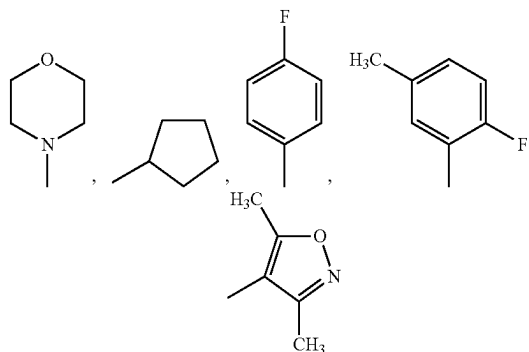
a) when A is S, B is O, R1 and R2 are both CH_3 , R3 and R4 are both H, C is not one of



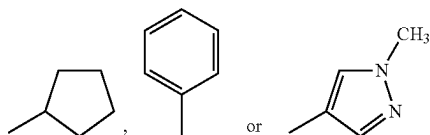
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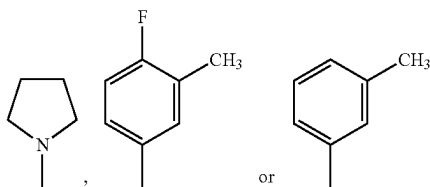
b) when A is S, B is O, R1 and R2 are respectively CH₃ and H, R3 and R4 are both H, C is not one of



c) when A is S, B is O, R1 and R2 are respectively isopropyl and H, R3 and R4 are both H, C is not one of



d) when A is S, B is O, R1 and R2 are both H, R3 and R4 are both H, C is not one of



e) when A is S, B is O, R1 and R2 are respectively H and CH₂CH₂OH, R3 and R4 are both H, C is not phenyl. According to a first embodiment, B is O.

According to a second embodiment, R1 and R2 are hydrogen, C₁₋₄alkyl and hydroxyC₁₋₄alkyl. In a further embodiment R1 and R2 are independently selected from the group consisting of hydrogen, methyl, ethyl, isopropyl and hydroxyethyl; preferably R1 and R2 are hydrogen.

According to a third embodiment, R3 and R4 are hydrogen.

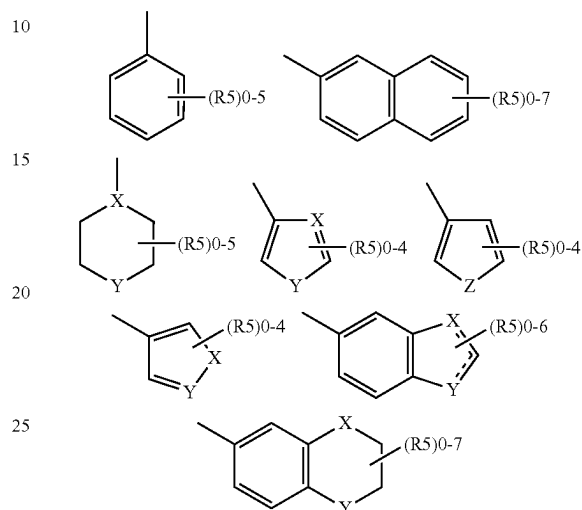
According to a fourth embodiment, A is selected from the group consisting of S and SO₂.

According to a fifth embodiment, C is selected from the group consisting of C₁₋₆alkyl, C₃₋₆cycloalkyl optionally substituted with one or more R5, C₃₋₆heterocycloalkyl optionally substituted with one or more R5, aryl optionally

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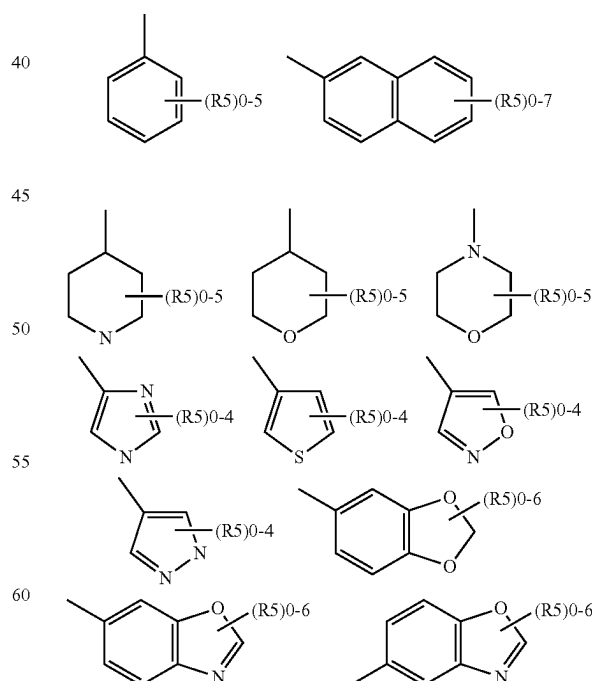
substituted with one or more R5, heteroaryl optionally substituted with one or more R5 and C₁₋₆alkyl-O-C₁₋₆alkyl.

In a sixth embodiment, C is selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkyl-O-C₁₋₆alkyl, C₃₋₆cycloalkyl optionally substituted with one or more R5,



wherein X and Y are selected from the group consisting of C, O and N, and Z is selected from the group consisting of N, O and S.

In a seventh embodiment, C is selected from the group consisting of:



According to an eighth embodiment, the compounds of Formula (Ia) are selected from the group consisting of:

-
- 002 rac-3-[4-(1,2-dimethylimidazol-4-yl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 003 rac-3-[4-(benzenesulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
 - 004 rac-3-[4-(1H-imidazol-4-ylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
 - 005 rac-3-[4-(3-thienylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
 - 006 rac-3-[4-(4-phenoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 007 rac-methyl 3-[2-(2-carbamoylbenzothiophen-3-yl)morpholin-4-yl] sulfonylbenzoate
 - 008 rac-3-[4-(3,5-dimethylisoxazol-4-yl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 009 rac-3-[4-(3-bromophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 010 rac-3-[4-(4-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 011 rac-3-[4-[4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 012 rac-3-[4-(m-tolylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
 - 015 rac-3-[4-[4-(2-oxopyrrolidin-1-yl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 016 rac-3-[4-cyclohexylsulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 017 rac-3-[4-(1,3-benzodioxol-5-ylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
 - 018 rac-3-[(4-(2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
 - 019 rac-3-[4-[4-(4-methoxyphenoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 020 rac-3-[4-(3-fluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 021 rac-3-[4-(3,4-difluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 022 rac-3-[4-(4-fluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 023 rac-3-[4-(4-methoxy-3-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 024 rac-3-[4-[4-(4-pyridyloxy)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 025 rac-3-[4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]-N,N-dimethylbenzothiophene-2-carboxamide
 - 026 rac-3-[4-(3-fluoro-4-methyl-phenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 027 rac-3-[4-(5-fluoro-2-methyl-phenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 028 rac-3-[4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]-N-methylbenzothiophene-2-carboxamide
 - 029 rac-3-[4-(4-fluoro-3-methyl-phenyl)sulfonyl morpholin-2-yl]-N-(2-hydroxyethyl)benzothiophene-2-carboxamide
 - 030 rac-N-ethyl-3-[4-(4-fluoro-3-methyl-phenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 031 rac-3-[4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]-N-isopropylbenzothiophene-2-carboxamide
 - 032 rac-3-[4-(2,4,6-trimethylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 033 rac-3-[4-(p-tolylsulfonyl)morpholin-2-yl] benzothiophene-2-carboxamide
 - 034 rac-3-[4-[(2-methyl-1,3-benzoxazol-6-yl) sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
 - 035 rac-3-[4-[3-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 036 rac-3-[4-(4-tert-butylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 037 rac-3-[4-(4-cyanophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 038 rac-3-[4-[4-fluoro-3-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 039 rac-3-[4-[4-(trifluoromethoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 040 rac-3-[4-(4-chlorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 041 rac-3-[4-[3-fluoro-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 042 3-[(R) or (S)-4-[4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide

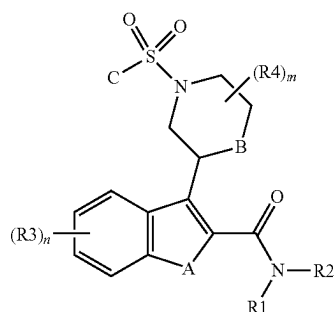
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- 043 3-[(S) or (R)-4-[4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 044 rac-3-[4-[3-methyl-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 045 rac-3-[4-[3-methoxy-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 046 rac-3-[4-[4-methoxy-3-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 047 rac-3-[4-(4-methoxy-3-nitro-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 048 rac-3-[4-(3-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 049 rac-3-[4-[3-(trifluoromethoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 050 rac-3-[4-(2-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 051 rac-3-[4-(4-phenylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 052 rac-3-[4-(2-naphthylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
 - 053 rac-3-[4-(3-fluoro-4-methoxy-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 054 rac-3-[4-(3,4-dimethoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 055 3-[(S) or (R)-4-[3-fluoro-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 056 3-[(R) or (S)-4-[3-fluoro-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 057 rac-3-[4-[4-methyl-2,3-dihydro-1,4-benzoxazin-7-yl)sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
 - 058 rac-3-[4-tetrahydropyran-4-ylsulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 059 rac-3-[4-(2-methoxyethylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
 - 060 rac-3-[4-[4-(pentafluoro-lambda6-sulfanyl) phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 061 rac-3-[4-butylsulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 062 rac-3-[4-(3-cyanophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 063 rac-methyl 4-[2-(2-carbamoylbenzothiophen-3-yl)morpholin-4-yl]sulfonylbenzoate
 - 064 rac-tert-butyl 4-[2-(2-carbamoylbenzothiophen-3-yl)morpholin-4-yl]sulfonylpiperidine-1-carboxylate
 - 065 rac-3-[4-(4-nitrophenyl)sulfonylmorpholin-2-yl] benzothiophene-2-carboxamide
 - 066 rac-3-[4-[2-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 067 rac-3-[4-[2-(trifluoromethoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 068 rac-3-[4-(4-hydroxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 069 rac-3-[4-(4-isopropoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 070 3-[(S) or (R)-4-[(2-methyl-1,3-benzoxazol-6-yl) sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
 - 071 3-[(R) or (S)-4-[(2-methyl-1,3-benzoxazol-6-yl) sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
 - 072 3-[(S) or (R)-4-(3-fluoro-4-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
 - 073 3-[(R) or (S)-4-(3-fluoro-4-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
and
 - 074 rac-1,1-dioxo-3-[4-[3-fluoro-4-(trifluoromethyl) phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide.
-

A second aspect of the present invention relates to a pharmaceutical composition comprising a compound of Formula (Ia) or pharmaceutically acceptable salts, hydrates, solvates, clathrates, polymorphs, stereoisomers thereof and

a pharmaceutically acceptable carrier, stabilizer, diluent or excipient thereof. A person skilled in the art is aware of a whole variety of such carrier, diluent or excipient compounds suitable to formulate a pharmaceutical composition.

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Compounds (Ib) have the following Formula:



or pharmaceutically acceptable salts, hydrates, solvates, clathrates, polymorphs, stereoisomers thereof wherein:

R1 and R2 are independently selected from the group consisting of hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, and C₁₋₄alkyl-O-C₁₋₄alkyl;

R3 is selected from the group consisting of C₁₋₆alkyl, haloC₁₋₆alkyl, OH, O-C₁₋₆alkyl, C₁₋₆alkyl-O-C₁₋₆alkyl, CN, NO₂ and halogen;

R4 is independently selected from the group consisting of C₁₋₆alkyl, haloC₁₋₆alkyl and halogen;

A is selected from the group consisting of S, SO, and SO₂; B is selected from the group consisting of CR^{iv}R^v, O, and NRⁱⁱ;

C is selected from the group consisting of C₁₋₆alkyl, haloC₁₋₆alkyl, C₃₋₆cycloalkyl optionally substituted with one or more R5, C₃₋₆heterocycloalkyl optionally substituted with one or more R5, aryl optionally substituted with one or more R5, heteroaryl optionally substituted with one or more R5, C₁₋₆alkyl-O-C₁₋₆alkyl, C₁₋₆alkyl-O-aryl, C₁₋₆alkyl-O-heteroaryl, C₁₋₆alkyl-O-C₃₋₆heterocycloalkyl, aryl-O-aryl, and aryl-O-heteroaryl;

R5 is selected from the group consisting of C₁₋₆alkyl, haloC₁₋₆alkyl, O-C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocycloalkyl, aryl, heteroaryl, O-aryl, O-aryl-O-C₁₋₆alkyl, O-heteroaryl, O-C₃₋₆heterocycloalkyl, O-haloC₁₋₆alkyl, OH, CN, NO₂, SF₆, halogen and COORⁱ;

n is an integer comprised from 0 to 2;

m is an integer comprised from 0 to 2;

Rⁱ is independently selected from the group consisting of hydrogen and C₁₋₆alkyl;

Rⁱⁱ is independently selected from the group consisting of hydrogen and C₁₋₆alkyl;

R^{iv} and R^v are independently selected from the group consisting of hydrogen, C₁₋₆alkyl and hydroxyC₁₋₆alkyl.

According to a further embodiment, B is O.

According to a further embodiment, R1 and R2 are hydrogen, C₁₋₄alkyl and hydroxyC₁₋₄alkyl. In a further embodiment R1 and R2 are independently selected from the group consisting of hydrogen, methyl, ethyl, isopropyl and hydroxyethyl; preferably R1 and R2 are hydrogen.

According to a further embodiment, R3 and R4 are hydrogen.

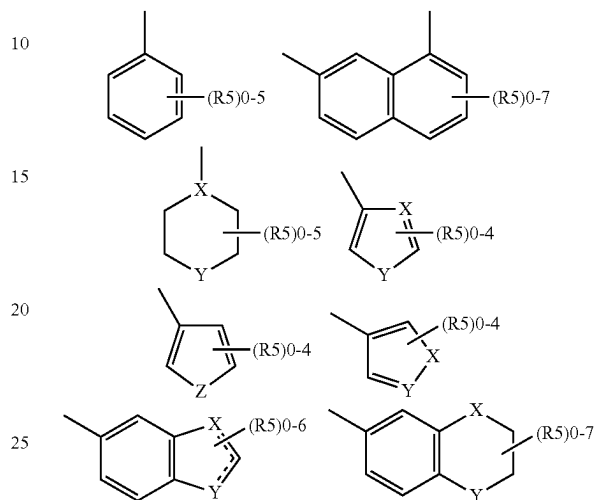
According to a further embodiment, A is selected from the group consisting of S and SO₂.

According to a further embodiment, C is selected from the group consisting of C₁₋₆alkyl, C₃₋₆cycloalkyl optionally substituted with one or more R5, C₃₋₆heterocycloalkyl optionally substituted with one or more R5, aryl optionally

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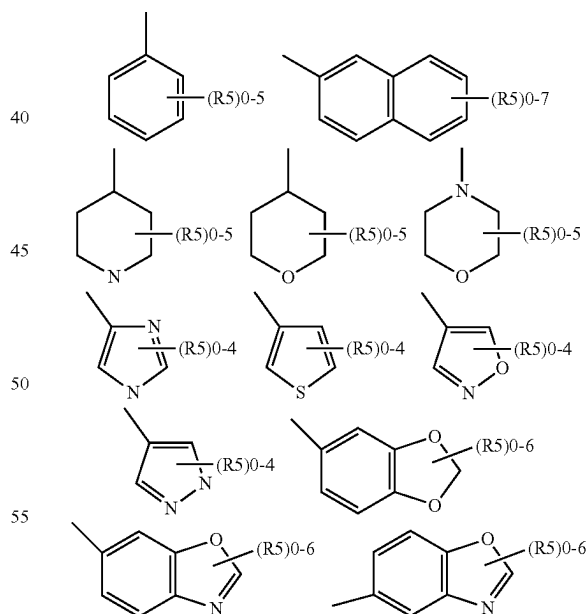
substituted with one or more R5, heteroaryl optionally substituted with one or more R5 and C₁₋₆alkyl-O-C₁₋₆alkyl.

In a further embodiment, C is selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkyl-O-C₁₋₆alkyl, C₃₋₆Cycloalkyl optionally substituted with one or more R5,



wherein X and Y are selected from the group consisting of C, O and N and Z is selected from the group consisting of N, O and S.

In a further embodiment, C is selected from the group consisting of:



Compounds of Formula (Ia), together with a conventionally employed adjuvant, carrier, diluent or excipient may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, or in the form of sterile

injectable solutions for parenteral administration (including subcutaneous and intravenous use). Such pharmaceutical compositions and unit dosage thereof may comprise ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

Pharmaceutical compositions containing a compound of this invention can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, the compounds of this invention are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

The pharmaceutical compositions of the present invention can be administered by a variety of routes including oral, rectal, subcutaneous, intravenous, intramuscular, intranasal and pulmonary routes. The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include pre-filled, pre-measured ampoules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions.

Liquid forms suitable for oral administration may include a suitable aqueous or non-aqueous vehicle with buffers, suspending and dispensing agents, colorants, flavours and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth, acacia, corn starch or gelatine; an excipient such as starch, dicalcium phosphate or lactose, a disintegrating agent such as alginic acid, Primogel or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose, lactose or saccharin; or a flavouring agent such as peppermint, methyl salicylate, or orange flavouring.

Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art.

The pharmaceutical compositions may be in the form of tablets, pills, capsules, solutions, suspensions, emulsion, powders, suppository and as sustained release formulations.

If desired, tablets may be coated by standard aqueous or non-aqueous techniques. In certain embodiments, such compositions and preparations can contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 1 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that therapeutically active dosage will be obtained.

When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to modify the physical form of the dosage unit.

For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring agent such as cherry or orange flavor. To prevent breakdown during transit through the upper portion of the gastrointestinal tract, the composition be an enteric coated formulation.

The active compounds can also be administered intranasally as, for example, liquid drops or spray.

Compositions for pulmonary administration include, but are not limited to, dry powder compositions consisting of the powder of a compound of Formula (Ia) or a salt thereof, and the powder of a suitable carrier and/or lubricant. The compositions for pulmonary administration can be inhaled from any suitable dry powder inhaler device known to a person skilled in the art.

Administration of the compositions is performed under a protocol and at a dosage sufficient to reduce the inflammation and pain in the subject. In some embodiments, in the pharmaceutical compositions of the present invention the active principle or active principles are generally formulated in dosage units. The dosage unit may contain from 0.1 to 1000 mg of a compound of Formula (Ia) per dosage unit for daily administration.

In some embodiments, the amounts effective for a specific formulation will depend on the severity of the disease, disorder or condition, previous therapy, the individual's health status and response to the drug. In some embodiments, the dose is in the range from 0.001% by weight to about 60% by weight of the formulation.

When used in combination with one or more other active ingredients, the compound of the present invention and the other active ingredient may be used in lower doses than when each is used singly.

Concerning formulations with respect to any variety of routes of administration, methods and formulations for the administration of drugs are disclosed in Remington's Pharmaceutical Sciences, 17th Edition, Gennaro et al. Eds., Mack Publishing Co., 1985, and Remington's Pharmaceutical Sciences, Gennaro A R ed. 20th Edition, 2000, Williams & Wilkins PA, USA, and Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Williams & Wilkins Eds., 2005; and in Loyd V. Allen and Howard C. Ansel, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 10th Edition, Lippincott Williams & Wilkins Eds., 2014.

The above described components for orally administered or injectable compositions are merely representative.

The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems.

A third aspect of the present invention relates to compounds of Formula (Ib) as disclosed above or the pharmaceutical composition thereof, for the use as a medicament.

A fourth aspect of the present invention relates to compounds of Formula (Ib) or pharmaceutically acceptable solvates, salts, hydrates, clathrates, polymorphs, stereoisomers thereof, for the use to modulate, in particular to correct, CFTR protein or ABC protein activities.

Compounds of Formula (Ia) and (Ib) as disclosed above may also be effective for the treatment of patients with other protein misfolding diseases. In this respect, other, structurally different CFTR correctors were found to rescue proteins (AVPR2, HCNH2, and ABCC8) with mutations causing trafficking defects (Sampson et al., *Orphanet J Rare Dis* 8:11, 2013). The compounds of Formula (Ia) and (Ib) may be indicated in particular for ABC proteins that share with CFTR a similar structure, particularly at the level of nucleotide-binding domains (Rudashevskaya et al., *Drug Discov*

Today Technol 12: e87-94, 2014). A list of ABC proteins with trafficking defects and associated diseases that could benefit from modulators CFTR includes ABCA1 (Tangier disease), ABCA3 (fatal surfactant deficiency), ABCA 4 (Stargardt disease), ABCB 4 (progressive familial intrahepatic cholestasis type 3), ABCB11 (progressive familial intrahepatic cholestasis type 2), ABCC2 (Dubin-Johnson syndrome), ABCC8 (hyperinsulinemic hypoglycemia of infancy) and ABCG2 (gout).

According to an aspect of the present invention, compounds of Formula (Ia) and (Ib) as disclosed above or the pharmaceutical composition thereof can be used in the treatment of a disease selected from the group consisting of cystic fibrosis, chronic obstructive pulmonary disease, chronic constipation, and dry eye syndrome, preferably cystic fibrosis.

In particular, the following compounds can be used:

001	rac-3-[4-(4-Fluoro-3-methyl-benzenesulfonyl)-morpholin-2-yl]-benzo[b]thiophene-2-carboxylic acid amide
002	rac-3-[4-(1,2-dimethylimidazol-4-yl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
003	rac-3-[4-(benzenesulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
004	rac-3-[4-(1H-imidazol-4-ylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
005	rac-3-[4-(3-thienylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
006	rac-3-[4-(4-phenoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
007	rac-methyl 3-[2-(2-carbamoylbenzothiophen-3-yl)morpholin-4-yl] sulfonylbenzoate
008	rac-3-[4-(3,5-dimethylisoxazol-4-yl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
009	rac-3-[4-(3-Bromophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
010	rac-3-[4-(4-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
011	rac-3-[4-[4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
012	rac-3-[4-(m-tolylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
013	3-[(R) or (S)-4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
014	3-[(S) or (R)-4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
015	rac-3-[4-[4-(2-oxopyrrolidin-1-yl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
016	rac-3-[4-cyclohexylsulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
017	rac-3-[4-(1,3-benzodioxol-5-ylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
018	rac-3-[4-(2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
019	rac-3-[4-[4-(4-methoxyphenoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
020	rac-3-[4-(3-fluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
021	rac-3-[4-(3,4-difluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
022	rac-3-[4-(4-fluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
023	rac-3-[4-(4-methoxy-3-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
024	rac-3-[4-[4-(4-pyridyloxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
025	rac-3-[4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]-N,N-dimethylbenzothiophene-2-carboxamide
026	rac-3-[4-(3-fluoro-4-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
027	rac-3-[4-(5-fluoro-2-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
028	rac-3-[4-(4-fluoro-3-methyl-phenyl)sulfonylmorpholin-2-yl]-N-methylbenzothiophene-2-carboxamide
029	rac-3-[4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]-N-(2-hydroxyethyl) benzothiophene-2-carboxamide
030	rac-N-ethyl-3-[4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
031	rac-3-[4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]-N-isopropylbenzothiophene-2-carboxamide
032	rac-3-[4-(2,4,6-trimethylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
033	rac-3-[4-(p-tolylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
034	rac-3-[4-[(2-methyl-1,3-benzoxazol-6-yl) sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
035	rac-3-[4-[3-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
036	rac-3-[4-(4-tert-butylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
037	rac-3-[4-(4-cyanophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide

038	rac-3-[4-[4-fluoro-3-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
039	rac-3-[4-[4-(trifluoromethoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
040	rac-3-[4-(4-chlorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
041	rac-3-[4-[3-fluoro-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
042	3-[(R) or (S)-4-[4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
043	3-[(S) or (R)-4-[4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
044	rac-3-[4-[3-methyl-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
045	rac-3-[4-[3-methoxy-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
046	rac-3-[4-[4-methoxy-3-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
047	rac-3-[4-(4-methoxy-3-nitro-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
048	rac-3-[4-(3-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
049	rac-3-[4-[3-(trifluoromethoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
050	rac-3-[4-(2-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
051	rac-3-[4-(4-phenylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
052	rac-3-[4-(2-naphthylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
053	rac-3-[4-(3-fluoro-4-methoxy-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
054	rac-3-[4-(3,4-dimethoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
055	3-[(S) or (R)-4-[3-fluoro-4-(trifluoromethyl) phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
056	3-[(R) or (S)-4-[3-fluoro-4-(trifluoromethyl) phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
057	rac-3-[4-[(4-methyl-2,3-dihydro-1,4-benzoxazin-7-yl)sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
058	rac-3-[4-tetrahydropyran-4-ylsulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
059	rac-3-[4-(2-methoxyethylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
060	rac-3-[4-[4-(pentafluoro-lambda6-sulfanyl) phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
061	rac-3-[4-butylsulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
062	rac-3-[4-(3-cyanophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
063	rac-methyl 4-[2-(2-carbamoylbenzothiophen-3-yl)morpholin-4-yl]sulfonylbenzoate
064	rac-tert-butyl 4-[2-(2-carbamoylbenzothiophen-3-yl)morpholin-4-yl]sulfonylpiperidine-1-carboxylate
065	rac-3-[4-(4-nitrophenyl)sulfonylmorpholin-2-yl] benzothiophene-2-carboxamide
066	rac-3-[4-[2-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
067	rac-3-[4-[2-(trifluoromethoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
068	rac-3-[4-(4-hydroxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
069	rac-3-[4-(4-isopropoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
070	3-[(S) or (R)-4-[(2-methyl-1,3-benzoxazol-6-yl) sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
071	3-[(R) or (S)-4-[(2-methyl-1,3-benzoxazol-6-yl) sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
072	3-[(S) or (R)-4-(3-fluoro-4-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
073	3-[(R) or (S)-4-(3-fluoro-4-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
074	rac-1,1-dioxo-3-[4-[3-fluoro-4-(trifluoromethyl) phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
075	3-[4-(3,5-dimethyl-isoxazole-4-sulfonyl)-morpholin-2-yl]-benzo[b]thiophene-2-carboxylic acid methylamide
076	3-[4-(1-methyl-1H-pyrazole-4-sulfonyl)-morpholin-2-yl]-benzo[b]thiophene-2-carboxylic acid isopropylamide
077	3-[4-(cyclopentylsulfonyl)-2-morpholinyl]-N-isopropyl-1-benzothiophene-2-carboxamide

078	3-[4-(cyclopentylsulfonyl)-2-morpholinyl]-N,N-dimethyl-1-benzothiophene-2-carboxamide
079	3-{4-[(1,5-dimethyl-1H-pyrazol-4-yl)sulfonyl]-2-morpholinyl}-N,N-dimethyl-1-benzothiophene-2-carboxamide
080	N-(2-hydroxyethyl)-3-[4-(phenylsulfonyl)-2-morpholinyl]-1-benzothiophene-2-carboxamide
081	3-(4-cyclopentanesulfonylmorpholin-2-yl)-benzo[b]thiophene-2-carboxylic acid methylamide
082	3-{4-[(2-fluoro-5-methylphenyl)sulfonyl]-2-morpholinyl}-N-methyl-1-benzothiophene-2-carboxamide
083	3-{4-[(3,5-dimethyl-1H-pyrazol-4-yl)sulfonyl]-2-morpholinyl}-N,N-dimethyl-1-benzothiophene-2-carboxamide
084	3-(4-cyclopentylsulfonylmorpholin-2-yl)benzothiophene-2-carboxamide
085	N-methyl-3-(4-morpholinylsulfonylmorpholin-2-yl)benzothiophene-2-carboxamide
087	3-[4-(benzenesulfonyl)morpholin-2-yl]-N-isopropyl-benzothiophene-2-carboxamide
088	3-[4-(4-fluorophenyl)sulfonylmorpholin-2-yl]-N-methyl-benzothiophene-2-carboxamide
089	N,N-dimethyl-3-[4-(1-methylpyrazol-4-yl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide and
090	3-[4-(3,5-dimethylisoxazol-4-yl)sulfonylmorpholin-2-yl]-N,N-dimethyl-benzothiophene-2-carboxamide.

In the following, the present invention shall be illustrated by means of some examples, which are not construed to be viewed as limiting the scope of the invention.

The following abbreviations are hereinafter used in the accompanying examples: acetic acid (AcOH), aryl (Ar), apparent triplet (app-t), apparent doublet of triplet (app-dt), apparent doublet (app-d), apparent singlet (app-s), aqueous (aq.), atmospheres (atm), benzyl (Bn), broad signal (bs), tert-butyl (tBu), tert-butylmethyl ether (TBME); normal-butyl lithium (nBuLi), calculated (calcd), carbon nuclear magnetic resonance spectroscopy (¹³C NMR), m-chloro perbenzoic acid (m-CPBA), cyclohexane (CyH or Cy), Deuterium (D), doublet (d), dichloromethane (DCM), doublet of doublet (dd), doublet of doublet of triplets (ddt), diisopropyl azodicarboxylate (DIAD), ethyldiisopropylamine (DIPEA), doublet of quartet (dq), N, N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexadeuteriodimethyl sulfoxide (DMSO-d₆), doublet of triplet (dt), N-(3-dimethylamino propyl)-N'-ethylcarbodiimide (EDC), half maximal effective concentration (EC₅₀), equivalents (equiv. or eq.), enantiomeric excess (e.e.), electrospray ionization (ESI), ethyl (Et), diethyl ether (Et₂O), ethyl acetate (EtOAc), hour (h), proton nuclear magnetic resonance spectroscopy (¹H NMR), 1-[bis(dimethylamino)methylene]-1H-1, 2, 3-triazolo[4,5-b] pyridinium 3-oxid hexafluorophosphate (HATU), 1-hydroxybenzotriazole hydrate (HOBt), high performance liquid chromatography (HPLC), hertz (Hz), infrared spectroscopy (IR), half maximal inhibitory concentration (IC₅₀), coupling constant (J), potassium carbonate (K₂CO₃), liter (L), lithium hydroxide (LiOH), molarity (M), multiplet (m), methyl (Me), (MeOH), milligram (mg), acetonitrile (MeCN), methanol megahertz (MHz), minutes (min), milliliter (mL), millimole (mmol), Mass Spectrometry (MS), molecular weight (MW), sodium hydride (NaH), sodium bicarbonate (NaHCO₃), sodium carbonate (Na₂CO₃), sodium sulphate (Na₂SO₄), ammonium chloride (NH₄Cl), not determined (nd), nanomolar (nM), Nuclear Magnetic Resonance (NMR), protecting group (Pg), parts per million (ppm), triphenylphosphine (PPh₃), isopropyl (i-Pr), quartet (q), substituent (R), racemic (rac-), room temperature (rt), singlet(s), temperature (T), triplet or time (t), retention time (tr), triethylamine (TEA or Et₃N), trifluoroacetic acid (TFA), tetrahydrofuran (THF), thin-layer chro-

matography (TLC), ultraviolet (UV), Ultra-Performance Liquid Chromatography-Mass Spectroscopy (UPLC-MS), anionic ligand, halide, substituent, or number (X), chemical shift (δ), microliter (μL), micromolar (μM), Watt (W). Chemicals, Materials and Methods

Solvents and reagents were obtained from commercial suppliers and were used without further purification.

Automated column chromatography purifications were performed on Teledyne ISCO apparatus (CombiFlash® Rf) with pre-packed silica gel columns of different sizes (Re-disep). Hydrogenation reactions were performed on H-Cube® continuous hydrogenation equipment (SS-reaction line version), employing disposable catalyst cartridges (CatCart®) preloaded with the required heterogeneous catalyst. NMR experiments were run on a Bruker Avance III 400 system (400.13 MHz for ¹H, and 100.62 MHz for ¹³C), equipped with a BBI probe and Z-gradients and Bruker FT NMR Avance III 600 MHz spectrometer equipped with a 5 mm CryoProbe™ QCI ¹H/¹⁹F-¹³C/¹⁵N-D quadruple resonance, a shielded z-gradient coil and the automatic sample changer SampleJet™ NMR system (600 MHz for ¹H, 151 MHz for ¹³C and 565 MHz for ¹⁹F). Chemical shifts for ¹H and ¹³C spectra were recorded in parts per million using the residual non-deuterated solvent as the internal standard (for CDCl₃: 7.26 ppm, ¹H and 77.16 ppm, ¹³C; for DMSO-d₆: 2.50 ppm, ¹H; 39.52 ppm, ¹³C, for D₂O: TSP as internal standard 0.00 ppm).

The analyses by UPLC/MS were run on a Waters ACQUITY UPLC/MS system consisting of a SQD (Single Quadrupole Detector) Mass Spectrometer equipped with an Electrospray Ionization interface and a Photodiode Array Detector. The PDA range was 210-400 nm. The analyses were performed on either an ACQUITY UPLC HSS T3 C₁₈ column (50×2.1 mmID, particle size 1.8 μm) with a VanGuard HSS T3 C₁₈ pre-column (5×2.1 mmID, particle size 1.8 μm) (LogD<1) or an ACQUITY UPLC BEH C₁₈ column (50×2.1 mmID, particle size 1.7 μm) with a VanGuard BEH C₁₈ pre-column (5×2.1 mmID, particle size 1.7 μm) (LogD>1).

The mobile phase was 10 mM NH₄OAc in H₂O at pH 5 adjusted with AcOH (A) and 10 mM NH₄OAc in MeCN—H₂O (95:5) at pH 5 (B).

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Electrospray ionization in positive and negative mode was applied in the mass scan range 100-650 Da or 150-750 Da.

Analyses were performed either with "Polar method", "Generic method" and "Apolar Method" herein reported:

Polar Method:

Column: Waters ACQUITY UPLC HSS T3 C₁₈/1.8 μm, 50×2.1 mmID

Pre-column: VanGuard HSS T3 C₁₈, 1.8 μm, 5×2.1 mmID

Linear gradient: 0-0.2 min: 0% B, 0.2-2.7 min: 0-50% B, 2.7-2.8 min: 50-100% B, 2.8-3.0 min: 100% B

Flow rate: 0.5 mL/min

Generic Method:

Column: Waters ACQUITY UPLC BEH C₁₈, 1.7 μm, 50×2.1 mmID

Pre-column: VanGuard BEH C₁₈, 1.7 μm, 5×2.1 mmID

Linear gradient: 0-0.2 min: 5% B, 0.2-2.7 min: 5-95% B, 2.7-2.8 min: 95-100% B, 2.8-3.0 min: 100% B

Flow rate: 0.5 mL/min

Apolar Method:

Column: Waters ACQUITY UPLC BEH C₁₈, 1.7 μm, 50×2.1 mmID

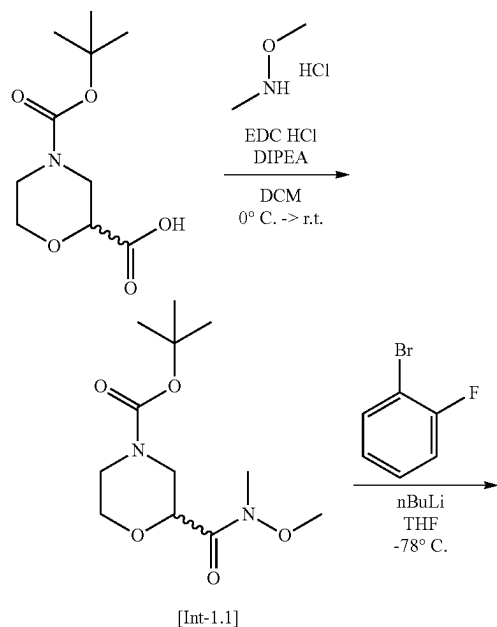
Pre-column: VanGuard BEH C₁₈, 1.7 μm, 5×2.1 mmID

Gradient: 0-0.2 min: 50% B, 0.2-2.7 min: 50-100% B, 2.7-3.0 min: 100% B

Flow rate: 0.5 mL/min

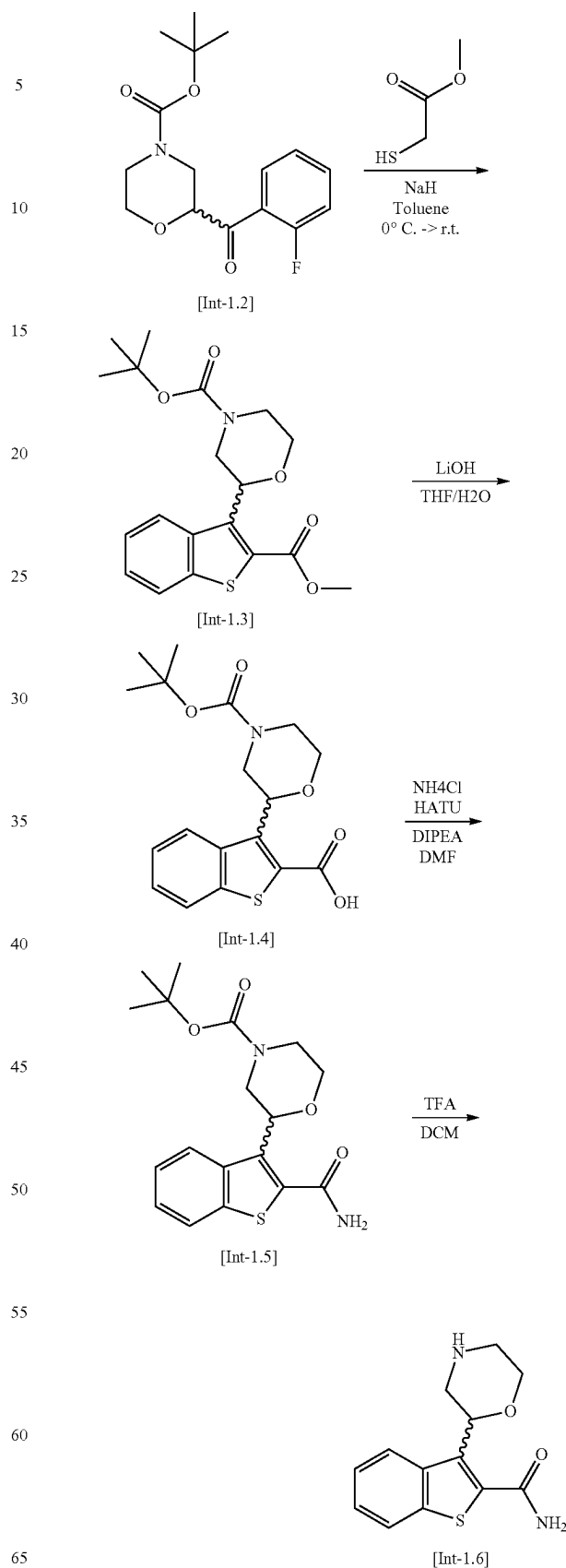
The chiral separations by HPLC were run on a Waters Alliance HPLC instrument consisting of an e2695 Separation Module and a 2998 Photodiode Array Detector. The PDA range was 210-400 nm. The analyses were performed in isocratic mode on a Daicel ChiralCel OD-H column (250×4.6 mmID, particle size 5 μm) at 25° C.

Synthesis of
3-morpholin-2-ylbenzothiophene-2-carboxamide
(Int-1.6)



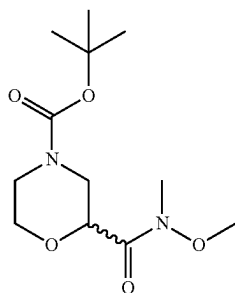
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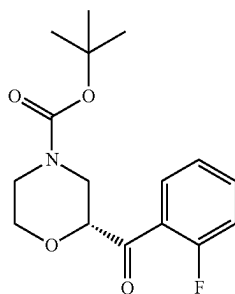


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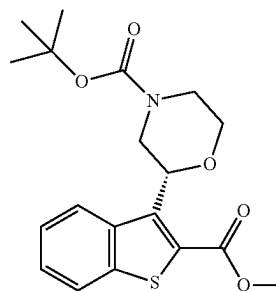
[Int-1.1] tert-Butyl 2-[methoxy(methyl) carbamoyl] morpholine-4-carboxylate: To a solution of 4-tert-butoxycarbonylmorpholine-2-carboxylic acid (2.0 g, 8.65 mmol) in dry DCM (40 mL) at 0° C., HOBt (0.257 g, 1.90 mmol) and DIPEA (3.32 mL, 19.03 mmol) were added. After 20 minutes N, O-dimethylhydroxylamine hydrochloride (0.928 g, 9.51 mmol) and EDC hydrochloride (1.824 g, 9.51 mmol) were added and the mixture was stirred at room temperature for 72 h. The reaction was diluted with DCM (40 mL) and then organic phase was washed with water (30 mL), sat. aq. NH₄Cl (30 mL) and brine (30 mL). Organic layer was dried with Na₂SO₄, filtered and solvent evaporated. Crude compound was purified by silica gel flash-column chromatography, eluting with gradient from 0% to 80% of TBME in Cyclohexane. The title compound was isolated as a viscous oil (1.95 g, 7.14 mmol, 82%): ¹H NMR (400 MHz, DMSO-d₆) δ 4.26 (d, J=9.5 Hz, 1H), 3.95-3.78 (m, 2H), 3.70 (s, 3H), 3.64 (s, 1H), 3.48 (td, J=11.2, 3.0 Hz, 1H), 3.12 (s, 3H), 2.98 (t, J=11.2 Hz, 2H), 1.41 (s, 9H). UPLC-MS: t_R=1.68 min (Generic method); MS (ESI) m/z calcd for C₁₂H₂₁N₂O₅ (M+H)⁺: 275.1, found: 275.



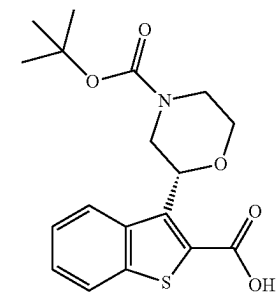
[Int-1.2] tert-Butyl 2-(2-fluorobenzoyl) morpholine-4-carboxylate: In a flame dried flask, 1-bromo-2-fluorobenzene (0.641 mL, 5.83 mmol) was dissolved in dry THF (40 mL) and the mixture was cooled to -78° C. n-BuLi 1.6M in THF (4.734 mL, 7.58 mmol) was added dropwise. Mixture was stirred for 1 h and a solution of Int-1.1 (1.6 g, 5.83 mmol), dissolved in dry THF (5.0 mL), was added dropwise, maintaining temperature at -78° C. After 2 h the mixture was quenched with sat. aq. NH₄Cl and EtOAc was added (20 mL). Layers were separated, and aqueous layer was extracted with EtOAc (2x20 mL). Organics were washed with brine, dried with Na₂SO₄, filtered and the solvent evaporated. The crude product was purified by silica gel flash-column chromatography, eluting with gradient from 0% to 40% of EtOAc in cyclohexane. Fractions containing products were collected, and the solvent evaporated. The

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afforded oil was stripped with Et₂O and dried under vacuum. The title compound was isolated as an oil (1.2 g, 66%): ¹H NMR (400 MHz, DMSO-d₆) δ 7.81-7.71 (m, 1H), 7.73-7.62 (m, 1H), 7.38-7.31 (m, 1H), 7.25-7.14 (m, 1H), 4.67 (d, J=9.1 Hz, 1H), 4.02-3.75 (m, 2H), 3.68-3.45 (m, 2H), 3.05 (ddd, J=14.7, 9.1, 2.9 Hz, 1H), 2.29 (s, 1H), 1.38 (s, 9H). UPLC-MS: t_R=2.28 min (Generic method); MS (ESI) m/z calcd for C₁₆H₂₁FNO₄ (M+H)⁺: 309, found: 310.



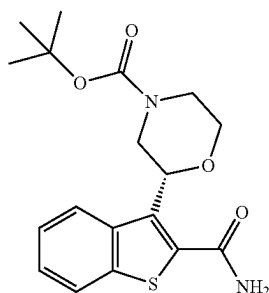
[Int-1.3] tert-Butyl 2-(2-methoxycarbonylbenzothiophen-3-yl) morpholine-4-carboxylate: In a flame dried flask, methyl thioglycolate (0.45 mL, 5.04 mmol) was dissolved in dry toluene at 0° C. under N₂ atmosphere, and NaH (0.464 g, 11.6 mmol) was added portion wise. The reaction mixture was stirred at room temperature for 30 min, then cooled to 0° C. Int-1.2 (1.2 g, 3.88 mmol) was added and the mixture stirred at 40° C. for 3 hours, then left stirring at room temperature overnight. Upon full conversion of the starting material, the reaction was quenched with aq. 1M HCl until pH=7 then extracted with EtOAc. The organic layer was washed with brine, dried, filtered and concentrated. The crude product was purified by silica gel flash-column chromatography, eluting with EtOAc in cyclohexane from 0% to 30%. The title compound was isolated as a pale yellow oil (0.82 g, 56%): ¹H NMR (400 MHz, DMSO-d₆) δ 8.52 (d, J=8.3 Hz, 1H), 8.05 (d, J=8.1 Hz, 1H), 7.55 (td, J=8.2, 1.2 Hz, 1H), 7.46 (td, J=8.2, 1.2 Hz, 1H), 5.62 (d, J=10.8 Hz, 1H), 4.03 (dd, J=8.2, 1.2 Hz, 2H), 3.90 (s, 3H), 3.57 (t, J=11.8 Hz, 1H), 1.44 (s, 9H). UPLC-MS: t_R=2.79 min (Generic method); MS (ESI) m/z calcd for C₁₉H₂₄NO₅S (M+H)⁺: 378.1, found: 378.



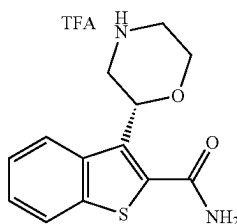
[Int-1.4] 3-(4-tert-butoxycarbonylmorpholin-2-yl) benzothiophene-2-carboxylic acid: To a solution of Int-1.3 (0.330 g, 0.86 mmol) in THF (10 mL), aqueous solution of LiOH (1N, 3.0 mL) was added dropwise and the reaction was stirred at room temperature overnight. The reaction was quenched upon addition of aq. 2M HCl until pH=4/5.

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Aqueous layer was extracted with DCM (3×10 mL). The combined organic layers were washed with brine, dried, filtered and solvent evaporated. The crude compound was purified by silica gel flash-column chromatography, eluting with DCM/MeOH 95:5 with 5% AcOH. The title compound was isolated as a white powder (0.311 g, quantitative): ¹H NMR (400 MHz, DMSO-d₆) δ 8.48 (d, J=8.2 Hz, 1H), 8.00 (d, J=8.0 Hz, 1H), 7.50 (ddd, J=8.2, 7.0, 1.2 Hz, 1H), 7.42 (ddd, J=8.2, 7.0, 1.2 Hz, 1H), 5.66 (dd, J=10.9, 2.9 Hz, 1H), 4.04 (dd, J=11.5, 3.1 Hz, 1H), 3.97-3.81 (m, 2H), 3.63-3.50 (m, 2H), 1.82-1.67 (m, 2H). UPLC-MS: t_R=1.79 min (Generic method); MS (ESI) m/z calcd for C₁₈H₂₀NO₅S (M-H)⁻: 362.1, found: 362.



[Int-1.5] tert-Butyl 2-(2-carbamoylbenzothiophen-3-yl)morpholine-4-carboxylate: To a solution of Int-1.4 (0.300 g, 0.85 mmol) in dry DMF (5.0 mL) at 0° C., HATU (0.470 g, 1.24 mmol) and DIPEA (0.316 mL, 3.30 mmol) were added. After 10 minutes NH₄Cl (0.088 g, 1.65 mmol) was added to the solution and the mixture left stirring overnight at room temperature. The reaction was treated with sat. aq. NH₄Cl and the mixture was extracted with EtOAc (3×15 mL). The organic layers were washed with brine, dried with Na₂SO₄ filtered and evaporated. The crude product was purified by silica gel flash-column chromatography, eluting with a gradient from 0% to 40% of EtOAc in DCM to afford the title product (0.313 g, 96%): ¹H NMR (400 MHz, DMSO-d₆) δ 8.52 (dt, J=8.1, 1.0 Hz, 1H), 8.06 (dt, J=8.1, 1.0 Hz, 1H), 7.56 (ddd, J=8.3, 7.0, 1.2 Hz, 1H), 7.47 (ddd, J=8.3, 7.1, 1.2 Hz, 1H), 5.63 (dd, J=10.8, 2.9 Hz, 1H), 4.07 (dd, J=11.7, 3.2 Hz, 1H), 4.01-3.94 (m, 2H), 3.91 (s, 3H), 3.58 (td, J=11.8, 2.7 Hz, 1H), 3.20 (bs, 2H), 1.45 (s, 9H). UPLC-MS: t_R=2.27 min (Generic method); MS (ESI) m/z calcd for C₁₈H₂₃N₂O₄S (M-H)⁻: 363.1, found: 363.

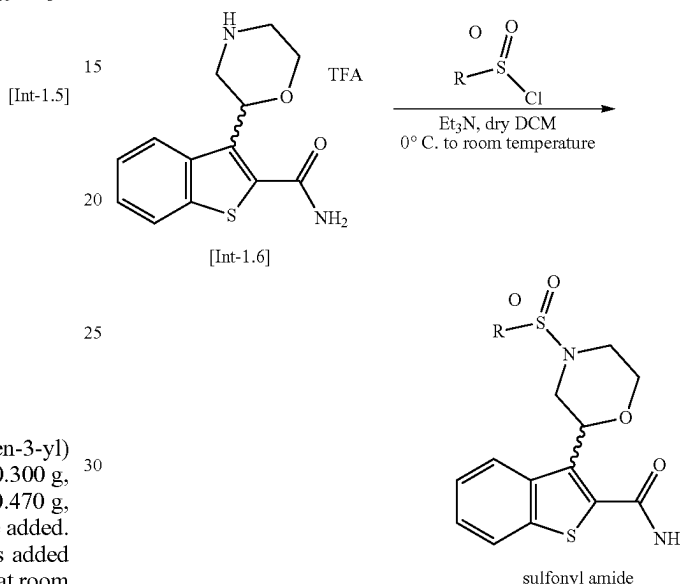


[Int-1.6] 3-Morpholin-2-ylbenzothiophene-2-carboxamide trifluoroacetate: To a solution of Int-1.5 (0.313 g, 0.86 mmol) in dry DCM at 0° C., TFA (0.282 mL, 4.32 mmol) was slowly added. The reaction was allowed to stir overnight at room temperature. The reaction mixture was evaporated under reduced pressure. The crude compound was

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purified with preparative LC/MS to obtain the title compound as a white powder (0.2 g, 89%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.32 (dd, J=8.2, 1.1 Hz, 1H), 8.16-8.03 (m, 1H), 7.97 (dd, J=8.2, 1.1 Hz, 1H), 7.82-7.67 (m, 1H), 7.48-7.39 (m, 1H), 5.32 (dd, J=10.5, 2.8 Hz, 1H), 3.96 (dd, J=11.1, 3.0 Hz, 1H), 3.61-3.60 (m, 1H), 3.03 (dd, J=12.4, 10.5 Hz, 1H), 2.88 (dq, J=24.2, 12.1, 11.5, 2.6 Hz, 2H). UPLC-MS: t_R=1.25 min (Generic method); MS (ESI) m/z calcd for C₁₃H₁₅N₂O₂S (M+H)⁺: 263.1, found: 263.

General Protocol for Sulfonyl Amide Synthesis (GP1).



In a round-bottomed flask, under nitrogen, Int-1.6 (1.1 eq) was dissolved in dry DCM (0.25M) and Et₃N (1.2 eq) was added. The sulfonyl chloride (1.0 eq) was added and the mixture was stirred until UPLC-MS analysis showed completion of the reaction (from 10 min to 1h). The reaction mixture was quenched with water, layers were separated and the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. Desired compounds were afforded in moderate to good yields after purification by silica gel flash-column chromatography.

3-[4-(4-Fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl] benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.06 g, 0.16 mmol) and (4-fluoro-3-methyl-phenyl) sulfonyl chloride (0.03 g, 0.14 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.05 g, 74%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.14 (d, J=8.2, 1.1 Hz, 1H), 8.09-7.93 (m, 2H), 7.87-7.72 (m, 2H), 7.69-7.60 (m, 1H), 7.49-7.32 (m, 3H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.11 (d, J=11.6, 2.9 Hz, 1H), 3.85-3.56 (m, 3H), 2.67 (td, J=10.9, 3.7 Hz, 2H), 2.32 (s, 3H). UPLC-MS: t_R=2.33 min (Generic method); MS (ESI) m/z calcd for C₂₀H₂₀FN₂O₄S₂ (M+H)⁺: 435.1, found: 435.

3-[4-(1,2-Dimethylimidazol-4-yl) sulfonylmorpholin-2-yl] benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.1 mmol) and (1,2-dimethylimidazol-4-yl) sulfonyl chloride (0.02 g, 0.09 mmol). The product was obtained, after purification by silica gel flash-column chromatography with Cyclohexane/EtOAc as the eluent, as a white solid (0.03 g, 79%). ¹H NMR

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(400 MHz, DMSO- d_6) δ 8.19 (d, $J=8.1$ Hz, 1H), 8.10-7.95 (m, 2H), 7.77 (bs, 1H), 7.75 (s, 1H), 7.47 (ddd, $J=8.2$, 7.0, 1.3 Hz, 1H), 7.41 (ddd, $J=8.2$, 7.0, 1.3 Hz, 1H), 5.49 (dd, $J=10.7$, 2.8 Hz, 1H), 4.13 (dd, $J=11.5$, 2.9 Hz, 1H), 3.73 (td, $J=11.7$, 2.5 Hz, 1H), 3.68-3.51 (m, 5H), 2.91 (t, $J=11.2$ Hz, 1H), 2.83 (td, $J=11.9$, 3.3 Hz, 1H), 2.30 (s, 3H). UPLC-MS: $t_R=1.68$ min (Generic method); MS (ESI) m/z calcd for $C_{18}H_{21}N_4O_4S_2$ (M+H) $^+$: 421.1, found: 421.

3-[4-(Benzenesulfonyl) morpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.09 mmol) and benzenesulfonyl chloride (10.8 μ L, 0.08 mmol). The product was obtained, after purification by silica gel flash-column chromatography with Cyclohexane/EtOAc as the eluent, as a white solid (0.03 g, 99%). 1H NMR (400 MHz, DMSO- d_6) δ 8.09 (d, $J=8.2$ Hz, 1H), 8.01-7.96 (m, 2H), 7.81-7.71 (m, 4H), 7.65 (t, $J=7.6$ Hz, 2H), 7.43 (ddd, $J=8.2$, 7.0, 1.2 Hz, 1H), 7.33 (ddd, $J=8.2$, 7.1, 1.2 Hz, 1H), 5.52 (dd, $J=10.5$, 2.8 Hz, 1H), 4.11 (dd, $J=11.5$, 2.9 Hz, 1H), 3.85-3.58 (m, 3H), 2.60 (dd, $J=12.2$, 9.7 Hz, 2H). UPLC-MS: $t_R=2.13$ min (Generic method); MS (ESI) m/z calcd for $C_{19}H_{19}N_2O_4S_2$ (M+H) $^+$: 403.1, found: 403.

3-[4-(1H-Imidazol-4-ylsulfonyl) morpholin-2-yl] benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.10 mmol) and 1H-imidazol-4-yl-sulfonyl chloride (0.02 g, 0.09 mmol). The product was obtained, after purification by silica gel flash-column chromatography with cyclohexane/EtOAc as the eluent, as a white solid (0.02 g, 46%). 1H NMR (400 MHz, DMSO- d_6) δ 12.92 (s, 1H), 8.14 (d, $J=8.1$ Hz, 1H), 8.02-7.96 (m, 2H), 7.90 (s, 1H), 7.82 (s, 1H), 7.77 (bs, 1H), 7.46 (ddd, $J=8.2$, 7.1, 1.3 Hz, 1H), 7.39 (ddd, $J=8.2$, 7.1, 1.2 Hz, 1H), 5.50 (dd, $J=10.7$, 2.8 Hz, 1H), 4.13 (dd, $J=11.7$, 2.9 Hz, 1H), 3.85-3.50 (m, 3H), 2.90-2.72 (m, 2H). UPLC-MS: $t_R=1.57$ min (Generic method); MS (ESI) m/z calcd for $C_{16}H_{17}N_4O_4S_2$ (M+H) $^+$: 393.1, found: 393.

3-[4-(3-Thienylsulfonyl) morpholin-2-yl] benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.10 mmol) and 3-thienylsulfonyl chloride (0.02 g, 0.09 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/MeOH as the eluent, as a white solid (0.02 g, 64%). 1H NMR (400 MHz, DMSO- d_6) δ 8.13 (d, $J=8.1$ Hz, 1H), 8.10-8.00 (m, 3H), 7.89-7.80 (bs, 1H), 7.69 (dd, $J=3.7$, 1.3 Hz, 1H), 7.45 (ddd, $J=8.2$, 7.0, 1.2 Hz, 1H), 7.37 (ddd, $J=8.3$, 7.1, 1.2 Hz, 1H), 7.29 (dd, $J=5.0$, 3.8 Hz, 1H), 5.55 (dd, $J=10.5$, 2.8 Hz, 1H), 4.16 (dd, $J=10.5$, 2.8 Hz, 1H), 3.76 (dt, $J=11.5$, 2.9 Hz, 2H), 3.64 (d, $J=11.8$ Hz, 1H), 2.75-2.61 (m, 2H). UPLC-MS: $t_R=2.10$ min (Generic method); MS (ESI) m/z calcd for $C_{17}H_{17}N_2O_4S_3$ (M+H) $^+$: 409.0, found: 409.

3-[4-(4-Phenoxyphenyl) sulfonylmorpholin-2-yl] benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.08 mmol) and (4-phenoxyphenyl) sulfonyl chloride (0.02 g, 0.07 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/MeOH as the eluent, as a white solid (0.03 g, 96%). 1H NMR (400 MHz, DMSO- d_6) δ 8.13 (d, $J=8.1$, 1.0 Hz, 1H), 8.08-7.99 (m, 2H), 7.89-7.72 (m, 3H), 7.55-7.42 (m, 3H), 7.37 (ddd, $J=8.2$, 7.1, 1.2 Hz, 1H), 7.29 (ddd, $J=8.2$, 7.1, 1.2 Hz, 1H), 7.21-7.10 (m, 4H), 5.52 (dd, $J=10.5$, 2.8 Hz, 1H), 4.11 (d, $J=11.7$ Hz, 1H), 3.83-3.67 (m, 2H), 3.62 (d, $J=11.7$ Hz, 1H), 2.73-2.56 (m, 2H). UPLC-MS: $t_R=2.55$ min (Generic method); MS (ESI) m/z calcd for $C_{25}H_{23}N_2O_5S_2$ (M+H) $^+$: 495.1, found: 495.

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Methyl 3-[2-(2-carbamoylbenzothiophen-3-yl) morpholin-4-yl]sulfonylbenzoate: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.08 mmol) and methyl 3-chlorosulfonylbenzoate (0.02 g, 0.07 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/MeOH as the eluent, as a white solid (0.03 g, 83%). 1H NMR (400 MHz, DMSO- d_6) δ 8.29 (dt, $J=7.9$, 1.3 Hz, 1H), 8.22 (t, $J=1.8$ Hz, 1H), 8.11 (dd, $J=8.3$, 1.1 Hz, 1H), 8.09-7.97 (m, 3H), 7.81 (t, $J=7.9$ Hz, 1H), 7.78 (bs, 1H), 7.43 (ddd, $J=8.2$, 7.1, 1.2 Hz, 1H), 7.33 (ddd, $J=8.2$, 7.1, 1.1 Hz, 1H), 5.51 (dd, $J=10.5$, 2.8 Hz, 1H), 4.12 (d, $J=11.2$ Hz, 1H), 3.90 (s, 3H), 3.80 (d, $J=11.2$ Hz, 1H), 3.76-3.63 (m, 2H), 2.80-2.59 (m, 2H). UPLC-MS: $t_R=2.16$ min (Generic method); MS (ESI) m/z calcd for $C_{21}H_{21}N_2O_6S_2$ (M+H) $^+$: 461.1, found: 461.

3-[4-(3,5-Dimethylisoxazol-4-yl) sulfonylmorpholin-2-yl] benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.10 mmol) and (3,5-dimethylisoxazol-4-yl) sulfonyl chloride (0.02 g, 0.08 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/MeOH as the eluent, as a white solid (0.04 g, 97%). 1H NMR (400 MHz, DMSO- d_6) δ 8.29 (d, $J=8.0$, 1.0 Hz, 1H), 8.08-7.95 (m, 2H), 7.80 (bs, 1H), 7.47 (ddd, $J=8.2$, 7.1, 1.3 Hz, 1H), 7.41 (ddd, $J=8.2$, 7.1, 1.3 Hz, 1H), 5.49 (dd, $J=10.5$, 2.8 Hz, 1H), 4.14 (d, $J=11.7$ Hz, 1H), 3.81-3.67 (m, 2H), 3.63 (d, $J=11.7$ Hz, 1H), 3.14-2.95 (m, 2H), 2.60 (s, 3H), 2.32 (s, 3H). UPLC-MS: $t_R=2.07$ min (Generic method); MS (ESI) m/z calcd for $C_{18}H_{20}N_3O_5S_2$ (M+H) $^+$: 422.1, found: 422.

3-[4-(3-Bromophenyl) sulfonylmorpholin-2-yl] benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.08 mmol) and (3-bromophenyl) sulfonyl chloride (0.02 g, 0.07 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/MeOH as the eluent, as a white solid (0.03 g, 81%). 1H NMR (400 MHz, DMSO- d_6) δ 8.15 (dd, $J=8.2$, 1.1 Hz, 1H), 8.08-8.00 (m, 2H), 7.99-7.88 (m, 1H), 7.87-7.70 (m, 3H), 7.60 (t, $J=7.9$ Hz, 1H), 7.45 (ddd, $J=8.2$, 7.0, 1.2 Hz, 1H), 7.36 (ddd, $J=8.3$, 7.1, 1.2 Hz, 1H), 5.51 (dd, $J=10.6$, 2.8 Hz, 1H), 4.11 (d, $J=11.2$ Hz, 1H), 3.81 (d, $J=11.2$ Hz, 1H), 3.77-3.53 (m, 2H), 2.71 (td, $J=11.6$, 11.1, 3.2 Hz, 2H). UPLC-MS: $t_R=2.34$ min (Generic method); MS (ESI) m/z calcd for $C_{19}H_{18}BrN_2O_4S_2$ (M+H) $^+$: 481.0, found: 481.

3-[4-(4-Methoxyphenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.10 mmol) and (4-methoxyphenyl) sulfonyl chloride (0.02 g, 0.09 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/MeOH as the eluent, as a white solid (0.03 g, 89%). 1H NMR (400 MHz, DMSO- d_6) δ 8.11 (dt, $J=8.2$, 1.0 Hz, 1H), 8.08-7.95 (m, 2H), 7.78 (bs, 1H), 7.70 (dt, $J=8.2$, 1.2 Hz, 2H), 7.44 (ddd, $J=8.2$, 7.0, 1.2 Hz, 1H), 7.35 (ddd, $J=8.2$, 7.1, 1.2 Hz, 1H), 7.14 (dt, $J=8.2$, 1.2 Hz, 2H), 5.51 (dd, $J=10.5$, 2.8 Hz, 1H), 4.11 (d, $J=11.8$, 2.8 Hz, 1H), 3.86 (s, 3H), 3.80-3.67 (m, 2H), 3.61 (d, $J=11.9$ Hz, 1H), 2.58 (t, $J=10.8$ Hz, 3H). UPLC-MS: $t_R=2.15$ min (Generic method); MS (ESI) m/z calcd for $C_{20}H_{21}N_2O_5$ (M+H) $^+$: 433.1, found: 433.

3-[4-[4-(Trifluoromethyl)phenyl]sulfonylmorpholin-2-yl] benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.04 g, 0.12 mmol) and (4-trifluoromethylphenyl) sulfonyl chloride (0.04 g, 0.11 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.05 g, 95%). 1H NMR (400 MHz, DMSO- d_6) δ 8.15 (dd, $J=8.2$, 1.0 Hz, 1H), 8.01 (s,

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4H), 8.01-7.99 (m, 2H), 7.79 (bs, 1H), 7.44 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.34 (ddd, J=8.2, 7.1, 1.1 Hz, 1H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.11 (d, J=10.9 Hz, 1H), 3.70 (t, J=12.1 Hz, 2H), 3.84 (d, J=11.4 Hz, 1H), 2.83-2.62 (m, 2H). UPLC-MS: t_R =2.40 min (Generic method); MS (ESI) m/z calcd for $C_{20}H_{18}F_3N_2O_4S_2$ (M+H)⁺: 471.1, found: 471.

3-[4-(m-Tolylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.10 mmol) and (3-methylphenyl) sulfonyl chloride (0.02 g, 0.09 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/MeOH as the eluent, as a white solid (0.04 g, 99%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.10 (d, J=8.1 Hz, 1H), 8.06-7.97 (m, 2H), 7.88-7.65 (m, 1H), 7.60 (bs, 1H), 7.59-7.48 (m, 3H), 7.44 (ddd, J=8.1, 7.1, 1.2 Hz, 1H), 7.34 (ddd, J=8.2, 7.0, 1.2 Hz, 1H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.10 (d, J=11.3, 2.9 Hz, 1H), 3.86-3.60 (m, 3H), 2.72-2.56 (m, 2H), 2.41 (s, 3H). UPLC-MS: t_R =2.25 min (Generic method); MS (ESI) m/z calcd for $C_{20}H_{21}N_2O_4S_2$ (M+H)⁺: 417.1, found: 417.

3-[4-[4-(2-Oxopyrrolidin-1-yl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.08 mmol) and [4-(2-oxopyrrolidin-1-yl)phenyl]sulfonyl chloride (0.02 g, 0.07 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/MeOH as the eluent, as a white solid (0.01 g, 20%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.11 (d, J=8.2 Hz, 1H), 8.07-7.97 (m, 2H), 7.95-7.90 (m, 2H), 7.86-7.71 (m, 3H), 7.44 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.34 (ddd, J=8.3, 7.1, 1.2 Hz, 1H), 5.52 (dd, J=10.5, 2.7 Hz, 1H), 4.11 (d, J=10.3 Hz, 1H), 3.88 (t, J=7.0 Hz, 2H), 3.82-3.60 (m, 3H), 2.65-2.54 (m, 4H), 2.10 (q, J=7.5 Hz, 2H). UPLC-MS: t_R =1.98 min (Generic method); MS (ESI) m/z calcd for $C_{23}H_{24}N_3O_5S_2$ (M+H)⁺: 486.1, found: 486.

3-(4-Cyclohexylsulfonylmorpholin-2-yl)benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.09 mmol) and cyclohexylsulfonyl chloride (0.02 g, 0.08 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/MeOH as the eluent, as a white solid (0.02 g, 71%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.37 (d, J=7.5 Hz, 1H), 8.11-7.93 (m, 2H), 7.78 (bs, 1H), 7.47 (td, J=7.2, 1.5 Hz, 2H), 5.42 (dd, J=10.5, 2.9 Hz, 1H), 4.11 (d, J=10.6 Hz, 1H), 3.70-3.55 (m, 3H), 2.04 (dd, J=19.9, 11.3 Hz, 2H), 1.85-1.72 (m, 2H), 1.63 (d, J=12.6 Hz, 1H), 1.46-1.07 (m, 9H). UPLC-MS: t_R =2.22 min (Generic method); MS (ESI) m/z calcd for $C_{19}H_{25}N_2O_4S_2$ (M+H)⁺: 409.1, found: 409.

3-[4-(1,3-Benzodioxol-5-ylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.07 mmol) and 1,3-benzodioxol-5-ylsulfonyl chloride (0.01 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.02 g, 63%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.15 (d, J=8.2, 1.1 Hz, 1H), 8.07-7.95 (m, 2H), 7.78 (bs, 1H), 7.44 (ddd, J=8.2, 7.0, 1.2 Hz, 1H), 7.36 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.33-7.26 (m, 2H), 7.11 (d, J=8.1 Hz, 1H), 6.19 (dd, J=4.6, 1.1 Hz, 2H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.11 (dd, J=11.7, 2.7 Hz, 1H), 3.81-3.66 (m, 2H), 3.61 (d, J=11.9 Hz, 1H), 2.64 (td, J=11.4, 11.0, 3.0 Hz, 2H). UPLC-MS: t_R =2.09 min (Generic method); MS (ESI) m/z calcd for $C_{20}H_{19}N_2O_6S_2$ (M+H)⁺: 447.1, found: 447.

3-[4-(2,3-Dihydro-1,4-benzodioxin-6-ylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g,

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0.07 mmol) and 1,3-benzodioxol-5-ylsulfonyl chloride (0.01 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 44%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.13 (dt, J=8.2, 1.1 Hz, 1H), 8.04-7.97 (m, 2H), 7.77 (bs, 1H), 7.44 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.35 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.21 (dd, J=8.1, 1.2 Hz, 2H), 7.06 (dd, J=8.0, 0.8 Hz, 1H), 5.50 (dd, J=10.6, 2.8 Hz, 1H), 4.42-4.20 (m, 4H), 4.16-4.06 (m, 1H), 3.70 (td, J=11.7, 2.6 Hz, 2H), 3.60 (d, J=11.9 Hz, 1H), 2.67-2.55 (m, 2H). UPLC-MS: t_R =2.10 min (Generic method); MS (ESI) m/z calcd for $C_{21}H_{21}N_2O_6S_2$ (M+H)⁺: 461.1, found: 461.

3-[4-[4-(4-Methoxyphenoxy)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.07 mmol) and [4-(4-methoxyphenoxy)phenyl]sulfonyl chloride (0.02 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.02 g, 62%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.13 (d, J=8.2 Hz, 1H), 8.08-7.95 (m, 2H), 7.78 (bs, 1H), 7.76-7.68 (m, 2H), 7.45 (ddd, J=8.2, 7.0, 1.2 Hz, 1H), 7.37 (ddd, J=8.3, 7.1, 1.2 Hz, 1H), 7.14-7.06 (m, 3H), 7.06-7.00 (m, 3H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.11 (d, J=9.5 Hz, 1H), 3.78 (s, 3H), 3.76-3.65 (m, 2H), 3.61 (d, J=11.8 Hz, 1H), 2.68-2.54 (m, 2H). UPLC-MS: t_R =2.48 min (Generic method); MS (ESI) m/z calcd for $C_{26}H_{25}N_2O_6S_2$ (M+H)⁺: 525.1, found: 525.

3-[4-(3-Fluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.07 mmol) and (3-fluorophenyl) sulfonyl chloride (0.01 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 30%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.13 (dd, J=8.2, 1.0 Hz, 1H), 8.03-7.97 (m, 2H), 7.77 (bs, 1H), 7.73-7.66 (m, 1H), 7.67-7.58 (m, 3H), 7.43 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.34 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.11 (d, 1H), 3.79 (d, J=11.4, 2.3 Hz, 1H), 3.75-3.62 (m, 2H), 2.76-2.59 (m, 2H). UPLC-MS: t_R =2.17 min (Generic method); MS (ESI) m/z calcd for $C_{19}H_{18}FN_2O_4S_2$ (M+H)⁺: 421.1, found: 421.

3-[4-(3,4-Difluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.07 mmol) and (3,4-difluorophenyl) sulfonyl chloride (0.01 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 31%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.16 (d, J=8.2 Hz, 1H), 8.06-7.97 (m, 2H), 7.93 (ddd, J=8.5, 6.8, 1.6 Hz, 1H), 7.77 (bs, 1H), 7.74-7.61 (m, 2H), 7.44 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.35 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.10 (dd, J=10.5, 2.8 Hz, 1H), 3.78 (dd, J=10.5, 2.8 Hz, 1H), 3.75-3.59 (m, 2H), 2.80-2.68 (m, 2H). UPLC-MS: t_R =2.24 min (Generic method); MS (ESI) m/z calcd for $C_{19}H_{17}F_2N_2O_4S_2$ (M+H)⁺: 439.1, found: 439.

3-[4-(4-Fluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.07 mmol) and (4-fluorophenyl) sulfonyl chloride (0.01 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.02 g, 59%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.13 (d, J=8.3 Hz, 1H), 8.05-7.98 (m, 2H), 7.90-7.84 (m, 2H), 7.81 (bs, 1H), 7.57-7.41 (m, 3H), 7.35 (ddd, J=8.2, 7.0, 1.2 Hz, 1H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.11 (dd, J=11.7, 2.8 Hz, 1H), 3.82-3.59 (m, 3H), 2.64 (dd, J=12.3, 9.6 Hz,

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2H). UPLC-MS: t_R =2.18 min (Generic method); MS (ESI) m/z calcd for $C_{19}H_{18}FN_2O_4S_2$ (M+H)⁺: 421.1, found: 421.

3-[4-(4-Methoxy-3-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.10 mmol) and (4-methoxy-3-methylphenyl) sulfonyl chloride (0.02 g, 0.09 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 34%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.10 (dt, J=8.2, 1.1 Hz, 1H), 8.05-7.95 (m, 2H), 7.76 (bs, 1H), 7.61-7.50 (m, 2H), 7.43 (ddd, J=8.2, 7.1, 1.3 Hz, 1H), 7.33 (ddd, J=8.3, 7.1, 1.2 Hz, 1H), 7.12 (d, J=8.6 Hz, 1H), 5.49 (dd, J=10.5, 2.8 Hz, 1H), 4.08 (d, J=11.9 Hz, 1H), 3.87 (s, 3H), 3.79-3.63 (m, 2H), 3.59 (d, J=11.8 Hz, 1H), 2.57 (td, J=11.4, 4.2 Hz, 2H), 2.19 (s, 3H). UPLC-MS: t_R =2.28 min (Generic method); MS (ESI) m/z calcd for $C_{21}H_{23}N_2O_5S_2$ (M+H)⁺: 447.1, found: 447.

3-[4-[4-(4-Pyridyloxy)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.10 mmol) and [3-(4-pyridyloxy)phenyl]sulfonyl chloride (0.03 g, 0.09 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.02 g, 54%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.54 (dt, J=8.2, 1.1 Hz, 2H), 8.13 (d, J=8.2 Hz, 1H), 8.05-7.96 (m, 2H), 7.84 (dt, J=8.2, 1.1 Hz, 2H), 7.76 (bs, 1H), 7.44 (ddd, J=8.2, 7.0, 1.2 Hz, 1H), 7.41-7.30 (m, 3H), 7.07 (dt, J=8.2, 1.1 Hz, 2H), 5.50 (dd, J=10.5, 2.8 Hz, 1H), 4.18-4.04 (m, 1H), 3.81-3.59 (m, 3H), 2.76-2.57 (m, 2H). UPLC-MS: t_R =2.05 min (Generic method); MS (ESI) m/z calcd for $C_{24}H_{22}N_3O_5S_2$ (M+H)⁺: 496.1, found: 496.

3-[4-(3-Fluoro-4-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.04 g, 0.10 mmol) and (3-fluoro-4-methyl-phenyl) sulfonyl chloride (0.03 g, 0.09 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.03 g, 70%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.13 (d, J=8.1 Hz, 1H), 8.02-7.96 (m, 2H), 7.76 (bs, 1H), 7.59-7.49 (m, 3H), 7.43 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.34 (ddd, J=8.2, 7.0, 1.1 Hz, 1H), 5.50 (dd, J=10.5, 2.8 Hz, 1H), 4.09 (dd, J=11.3, 3.0 Hz, 1H), 3.81-3.59 (m, 3H), 2.74-2.57 (m, 2H), 2.32 (s, 3H). UPLC-MS: t_R =2.28 min (Generic method); MS (ESI) m/z calcd for $C_{20}H_{20}FN_2O_4S_2$ (M+H)⁺: 435.1, found: 435. Yield: 70%.

3-[4-(5-Fluoro-2-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.04 g, 0.10 mmol) and (2-methyl-5-fluoro-phenyl) sulfonyl chloride (0.02 g, 0.09 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.02 g, 45%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.24 (dd, J=8.0, 1.1 Hz, 1H), 8.00 (dd, J=7.9, 1.0 Hz, 1H), 7.99 (bs, 1H), 7.75 (bs, 1H), 7.61 (dd, J=8.8, 2.7 Hz, 1H), 7.56-7.35 (m, 4H), 5.45 (dd, J=10.6, 2.8 Hz, 1H), 4.10 (dd, J=11.4, 2.9 Hz, 1H), 3.77-3.52 (m, 3H), 3.14-2.94 (m, 2H), 2.56 (s, 3H). UPLC-MS: t_R =2.26 min (Generic method); MS (ESI) m/z calcd for $C_{20}H_{20}FN_2O_4S_2$ (M+H)⁺: 435.1, found: 435. Yield: 45%.

3-[4-(2,4,6-Trimethylphenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.07 mmol) and (2,4,6-trimethylphenyl) sulfonyl chloride (0.01 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 42%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.28 (d, J=1.5 Hz, 1H), 8.01 (d, J=1.5 Hz, 1H),

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7.97 (bs, 1H), 7.73 (bs, 1H), 7.51-7.36 (m, 2H), 7.09 (s, 2H), 5.42 (dd, J=10.6, 2.8 Hz, 1H), 4.08 (dd, J=11.6, 2.7 Hz, 1H), 3.65-3.50 (m, 2H), 3.31-3.25 (m, 1H), 3.18-3.05 (m, 2H), 2.57 (s, 6H), 2.28 (s, 3H). UPLC-MS: t_R =2.53 min (Generic method); MS (ESI) m/z calcd for $C_{22}H_{25}N_2O_4S_2$ (M+H)⁺: 445.1, found: 445.

3-[4-(p-Tolylsulfonyl) morpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.07 mmol) and (4-methylphenyl) sulfonyl chloride (0.01 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 50%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.08 (dt, J=8.4, 1.1 Hz, 1H), 8.04-7.96 (m, 2H), 7.76 (bs, 1H), 7.62 (d, J=8.4 Hz, 2H), 7.47-7.37 (m, 3H), 7.32 (dd, J=8.3, 7.1, 1.2 Hz, 1H), 5.49 (dd, J=10.5, 2.8 Hz, 1H), 4.08 (dd, J=11.6, 2.9 Hz, 1H), 3.80-3.53 (m, 3H), 2.65-2.51 (m, 2H), 2.39 (s, 3H). UPLC-MS: t_R =2.30 min (Generic method); MS (ESI) m/z calcd for $C_{20}H_{21}N_2O_4S_2$ (M+H)⁺: 417.1, found: 417.

3-[4-[(2-Methyl-1,3-benzoxazol-6-yl) sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.07 mmol) and (2-methyl-1,3-benzoxazol-6-yl) sulfonyl chloride (0.01 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 40%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.13 (dd, J=1.7, 0.5 Hz, 1H), 8.07 (dt, J=8.3, 1.0 Hz, 1H), 8.03-7.94 (m, 2H), 7.86 (d, J=8.4 Hz, 1H), 7.82-7.66 (m, 2H), 7.40 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.28 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.50 (dd, J=10.5, 2.8 Hz, 1H), 4.08 (d, J=11.3 Hz, 1H), 3.79 (d, J=11.2 Hz, 1H), 3.68 (t, J=12.0 Hz, 2H), 2.66 (s, 3H), 2.64-2.56 (m, 2H). UPLC-MS: t_R =2.05 min (Generic method); MS (ESI) m/z calcd for $C_{21}H_{20}N_3O_5S_2$ (M+H)⁺: 458.1, found: 458.

3-[4-[3-(Trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.07 mmol) and [3-(trifluoromethyl)phenyl]sulfonyl chloride (0.01 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 50%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.16-8.06 (m, 3H), 8.05-7.94 (m, 3H), 7.88 (t, J=8.2 Hz, 1H), 7.75 (bs, 1H), 7.42 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.31 (ddd, J=8.2, 7.0, 1.2 Hz, 1H), 5.49 (dd, J=10.5, 2.8 Hz, 1H), 4.09 (dd, J=11.1, 3.0 Hz, 1H), 3.82 (dd, J=11.1, 3.1 Hz, 1H), 3.68 (t, J=10.4 Hz, 2H), 2.79-2.63 (m, 2H). UPLC-MS: t_R =2.40 min (Generic method); MS (ESI) m/z calcd for $C_{20}H_{18}F_3N_2O_4S_2$ (M+H)⁺: 471.1, found: 471.

3-[4-(4-tert-Butylphenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.07 mmol) and (4-tert-butylphenyl) sulfonyl chloride (0.01 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 47%). ¹H NMR (400 MHz, DMSO- d_6) δ 8.06 (dt, J=8.2, 1.0 Hz, 1H), 8.02-7.96 (m, 2H), 7.73 (bs, 1H), 7.69-7.59 (m, 4H), 7.41 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.29 (ddd, J=8.2, 7.1, 1.1 Hz, 1H), 5.49 (dd, J=10.5, 2.8 Hz, 1H), 4.09 (dd, J=10.5, 2.8 Hz, 1H), 3.80-3.54 (m, 3H), 2.71-2.54 (m, 2H), 1.29 (s, 9H). UPLC-MS: t_R =2.65 min (Generic method); MS (ESI) m/z calcd for $C_{23}H_{27}N_2O_4S_2$ (M+H)⁺: 459.1, found: 459.

3-[4-(4-Cyanophenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.07 mmol) and (4-cyanophenyl) sulfonyl chloride (0.01 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-

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column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 34%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.12 (dt, J=8.2, 1.0 Hz, 1H), 8.09 (d, J=8.3 Hz, 2H), 8.01-7.96 (m, 2H), 7.94 (d, J=8.3 Hz, 2H), 7.75 (bs, 1H), 7.42 (ddd, J=8.2, 7.0, 1.2 Hz, 1H), 7.33 (ddd, J=8.3, 7.1, 1.2 Hz, 1H), 5.46 (dd, J=10.5, 2.8 Hz, 1H), 4.08 (dd, J=11.2, 3.0 Hz, 1H), 3.79 (d, J=11.3 Hz, 1H), 3.67 (t, J=10.3 Hz, 2H), 2.72 (td, J=11.7, 11.2, 3.4 Hz, 2H). UPLC-MS: t_R=2.14 min (Generic method); MS (ESI) m/z calcd for C₂₀H₁₈N₃O₄S₂ (M+H)⁺: 428.1, found: 428.

3-[4-[4-Fluoro-3-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.07 mmol) and [4-fluoro-3-(trifluoromethyl)phenyl]sulfonyl chloride (0.02 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 47%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.22-8.13 (m, 2H), 8.04 (dd, J=6.7, 2.3 Hz, 1H), 8.01-7.95 (m, 2H), 7.82-7.66 (m, 3H), 7.42 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.33 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.48 (dd, J=10.5, 2.8 Hz, 1H), 4.15-4.02 (m, 1H), 3.85-3.74 (m, 1H), 3.74-3.62 (m, 2H), 2.78 (td, J=11.8, 11.2, 3.4 Hz, 2H). UPLC-MS: t_R=2.46 min (Generic method); MS (ESI) m/z calcd for C₂₀H₁₇F₄N₂O₄S₂ (M+H)⁺: 489.1, found: 489.

3-[4-[4-(Trifluoromethoxy)phenyl]sulfonylmorpholin-2-yl] benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.07 mmol) and [4-(trifluoromethoxy)phenyl]sulfonyl chloride (0.02 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 46%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.10 (dt, J=8.4, 1.0 Hz, 1H), 8.02-7.98 (m, 2H), 7.90 (dt, J=8.4, 1.0 Hz, 2H), 7.78 (bs, 1H), 7.60 (dt, J=8.9, 1.0 Hz, 2H), 7.42 (ddd, J=8.2, 7.0, 1.2 Hz, 1H), 7.31 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.49 (dd, J=10.5, 2.8 Hz, 1H), 4.09 (dd, J=11.3, 2.9 Hz, 1H), 3.77 (d, J=11.3 Hz, 1H), 3.73-3.58 (m, 2H), 2.73-2.60 (m, 2H). UPLC-MS: t_R=2.48 min (Generic method); MS (ESI) m/z calcd for C₂₀H₁₈F₃N₂O₄S₂ (M+H)⁺: 487.1, found: 487.

3-[4-(4-Chlorophenyl) sulfonylmorpholin-2-yl] benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.07 mmol) and (4-chlorophenyl) sulfonyl chloride (0.01 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 46%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.10 (dt, J=8.2, 1.0 Hz, 1H), 8.03-7.95 (m, 2H), 7.80-7.73 (m, 3H), 7.71-7.64 (m, 2H), 7.41 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.32 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.47 (dd, J=10.5, 2.8 Hz, 1H), 4.07 (dd, J=11.7, 2.9 Hz, 1H), 3.78-3.57 (m, 3H), 2.70-2.57 (m, 2H). UPLC-MS: t_R=2.37 min (Generic method); MS (ESI) m/z calcd for C₁₉H₁₈ClN₂O₄S₂ (M+H)⁺: 437.0, found: 437.

3-[4-[3-Fluoro-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.03 g, 0.07 mmol) and [3-fluoro-4-(trifluoromethyl)phenyl]sulfonyl chloride (0.02 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 27%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.19 (d, J=8.2 Hz, 1H), 8.09-7.95 (m, 4H), 7.81 (d, J=8.3 Hz, 1H), 7.76 (bs, 1H), 7.44 (ddd, J=8.2, 7.0, 1.2 Hz, 1H), 7.34 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.50 (dd, J=10.6, 2.8 Hz, 1H), 4.10 (dd, J=11.4, 3.0 Hz, 1H), 3.84 (d, J=11.3 Hz, 1H), 3.77-3.61 (m, 2H),

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2.95-2.77 (m, 2H). UPLC-MS: t_R=2.50 min (Generic method); MS (ESI) m/z calcd for C₂₀H₁₇F₄N₂O₄S₂ (M+H)⁺: 489.1, found: 489.

3-[4-[3-Methyl-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.01 g, 0.05 mmol) and [3-methyl-4-(trifluoromethyl)phenyl]sulfonyl chloride (0.02 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 44%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.15 (dt, J=8.3, 1.0 Hz, 1H), 8.08-7.93 (m, 2H), 7.89 (td, J=8.3, 1.0 Hz, 2H), 7.86-7.67 (m, 2H), 7.42 (ddd, J=8.1, 7.1, 1.3 Hz, 1H), 7.33 (ddd, J=8.3, 7.1, 1.2 Hz, 1H), 5.48 (dd, J=10.5, 2.8 Hz, 1H), 4.09 (dd, J=10.5, 2.8 Hz, 1H), 3.82 (dd, J=11.4, 2.3 Hz, 1H), 3.75-3.60 (m, 2H), 2.83-2.63 (m, 2H), 2.52 (s, 3H). UPLC-MS: t_R=2.48 min (Generic method); MS (ESI) m/z calcd for C₂₁H₂₀F₃N₂O₄S₂ (M+H)⁺: 485.1, found: 485.

3-[4-[3-Methoxy-4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.01 g, 0.05 mmol) and [3-methoxy-4-(trifluoromethyl)phenyl]sulfonyl chloride (0.02 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 32%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.14 (d, J=8.1, 1.0 Hz, 1H), 8.04-7.93 (m, 2H), 7.84 (d, J=8.6 Hz, 1H), 7.73 (bs, 1H), 7.45 (d, J=6.5 Hz, 2H), 7.40 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.31 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.47 (dd, J=10.5, 2.8 Hz, 1H), 4.07 (dd, J=11.3, 2.9 Hz, 1H), 3.95 (s, 3H), 3.82 (dd, J=11.3, 2.9 Hz, 1H), 3.73-3.60 (m, 2H), 2.90-2.72 (m, 2H). UPLC-MS: t_R=2.42 min (Generic method); MS (ESI) m/z calcd for C₂₁H₂₀F₃N₂O₅S₂ (M+H)⁺: 501.1, found: 501.

3-[4-[4-Methoxy-3-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.01 g, 0.05 mmol) and [4-methoxy-3-(trifluoromethyl)phenyl]sulfonyl chloride (0.02 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 24%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.12 (dt, J=8.1, 0.9 Hz, 1H), 8.02 (dd, J=8.9, 2.4 Hz, 1H), 8.00-7.94 (m, 2H), 7.83 (d, J=2.4 Hz, 1H), 7.73 (bs, 1H), 7.50-7.36 (m, 2H), 7.31 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.47 (dd, J=10.5, 2.8 Hz, 1H), 4.08 (dd, J=11.3, 2.9 Hz, 1H), 3.97 (s, 3H), 3.77 (dd, J=11.1, 2.4 Hz, 1H), 3.74-3.56 (m, 2H), 2.65 (td, J=11.2, 3.7 Hz, 2H). UPLC-MS: t_R=2.33 min (Generic method); MS (ESI) m/z calcd for C₂₁H₂₀F₃N₂O₅S₂ (M+H)⁺: 501.1, found: 501.

3-[4-(4-Methoxy-3-nitro-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.06 mmol) and (4-methoxy-3-nitro-phenyl)sulfonyl chloride (0.01 g, 0.06 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 31%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.22 (d, J=2.4 Hz, 1H), 8.13 (d, J=8.2, 1.1 Hz, 1H), 8.08-7.91 (m, 3H), 7.72 (bs, 1H), 7.52 (d, J=9.0 Hz, 1H), 7.41 (ddd, J=8.1, 7.0, 1.2 Hz, 1H), 7.32 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.47 (dd, J=10.5, 2.8 Hz, 1H), 4.08 (dd, J=11.5, 2.9 Hz, 1H), 3.99 (s, 3H), 3.80-3.57 (m, 3H), 2.78-2.60 (m, 2H). UPLC-MS: t_R=2.12 min (Generic method); MS (ESI) m/z calcd for C₂₀H₂₀N₃O₇S₂ (M+H)⁺: 478.1, found: 478.

3-[4-(3-Methoxyphenyl) sulfonylmorpholin-2-yl] benzothiophene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.04 mmol) and

(3-methoxyphenyl) sulfonyl chloride (0.01 g, 0.04 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 31%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.10 (dt, J=8.3, 1.0 Hz, 1H), 8.03-7.96 (m, 2H), 7.78 (bs, 1H), 7.54 (t, J=8.0 Hz, 1H), 7.43 (ddd, J=8.1, 7.0, 1.2 Hz, 1H), 7.38-7.25 (m, 3H), 7.21 (dd, J=2.6, 1.6 Hz, 1H), 5.50 (dd, J=10.5, 2.8 Hz, 1H), 4.09 (dd, J=11.1, 3.0 Hz, 1H), 3.79-3.60 (m, 3H), 2.72-2.58 (m, 2H). UPLC-MS: t_R=2.14 min (Generic method); MS (ESI) m/z calcd for C₂₀H₂₁N₂O₅S₂ (M+H)⁺: 433.1, found: 433.

3-[4-[3-(Trifluoromethoxy)phenyl]sulfonylmorpholin-2-yl]benzothioephene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.04 mmol) and [3-(trifluoromethoxy)phenyl]sulfonyl chloride (0.01 g, 0.04 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 32%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.10 (dt, J=8.3, 1.0 Hz, 1H), 8.07-7.94 (m, 2H), 7.83 (ddd, J=5.9, 4.6, 3.3 Hz, 1H), 7.80-7.75 (m, 3H), 7.74 (dt, J=2.3, 1.0 Hz, 1H), 7.43 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.32 (ddd, J=8.2, 7.1, 1.1 Hz, 1H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.10 (dd, J=11.1, 2.9 Hz, 1H), 3.80 (dt, J=11.4, 2.3 Hz, 1H), 3.69 (ddd, J=14.2, 11.1, 3.7 Hz, 2H), 2.74-2.58 (m, 2H). UPLC-MS: t_R=2.38 min (Generic method); MS (ESI) m/z calcd for C₂₀H₁₈F₃N₂O₅S₂ (M+H)⁺: 487.1, found: 487.

3-[4-(2-Methoxyphenyl) sulfonylmorpholin-2-yl] benzothioephene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.04 mmol) and (2-methoxyphenyl) sulfonyl chloride (0.01 g, 0.04 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.005 g, 23%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.19 (dt, J=7.9, 1.1 Hz, 1H), 8.03-7.97 (m, 2H), 7.78 (bs, 1H), 7.74 (dd, J=7.8, 1.7 Hz, 1H), 7.64 (ddd, J=8.3, 7.3, 1.7 Hz, 1H), 7.44 (ddd, J=8.1, 7.1, 1.3 Hz, 1H), 7.38 (ddd, J=8.2, 7.0, 1.3 Hz, 1H), 7.27 (dd, J=8.4, 1.0 Hz, 1H), 7.08 (td, J=7.6, 1.0 Hz, 1H), 5.43 (dd, J=10.7, 2.9 Hz, 1H), 4.09 (dd, J=11.4, 2.8 Hz, 1H), 3.72-3.56 (m, 2H), 3.08-2.88 (m, 3H). UPLC-MS: t_R=2.04 min (Generic method); MS (ESI) m/z calcd for C₂₀H₂₁N₂O₅S₂ (M+H)⁺: 433.1, found: 433.

3-[4-(4-Phenylphenyl) sulfonylmorpholin-2-yl] benzothioephene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.04 mmol) and (4-phenylphenyl) sulfonyl chloride (0.01 g, 0.04 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.005 g, 28%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.11 (dt, J=8.3, 1.0 Hz, 1H), 8.03 (bs, 1H), 8.00-7.96 (m, 1H), 7.92 (d, J=8.5 Hz, 2H), 7.82 (d, J=8.5 Hz, 2H), 7.75 (bs, 1H), 7.77-7.70 (m, 2H), 7.55-7.47 (m, 2H), 7.47-7.37 (m, 2H), 7.30 (ddd, J=8.2, 7.0, 1.1 Hz, 1H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.11 (dd, J=10.5, 2.8 Hz, 1H), 3.80 (d, J=10.9 Hz, 1H), 3.77-3.60 (m, 2H), 2.76-2.56 (m, 2H). UPLC-MS: t_R=2.50 min (Generic method); MS (ESI) m/z calcd for C₂₅H₂₃N₂O₅S₂ (M+H)⁺: 479.1, found: 479.

3-[4-(2-Naphthylsulfonyl)morpholin-2-yl]benzothioephene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.04 mmol) and 2-naphthylsulfonyl chloride (0.01 g, 0.04 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.005 g, 27%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.47 (d, J=1.8 Hz, 1H), 8.19 (d, J=1.8 Hz, 1H), 8.14 (d, J=8.8 Hz, 1H), 8.10-7.99 (m, 4H), 7.97 (dt, J=8.2, 0.9 Hz, 1H),

7.81-7.64 (m, 3H), 7.38 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.24 (ddd, J=8.3, 7.1, 1.2 Hz, 1H), 5.52 (dd, J=10.5, 2.8 Hz, 1H), 4.09 (dd, v1H), 3.85 (d, J=11.3 Hz, 1H), 3.76-3.62 (m, 2H), 2.74-2.59 (m, 2H). UPLC-MS: t_R=2.35 min (Generic method); MS (ESI) m/z calcd for C₂₃H₂₁N₂O₅S₂(M+H)⁺: 453.1, found: 453.

3-[4-(3-Fluoro-4-methoxy-phenyl)sulfonylmorpholin-2-yl]benzothioephene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.04 mmol) and (3-fluoro-4-methoxy-phenyl)sulfonyl chloride(0.01 g, 0.04 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.005 g, 28%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.13 (d, J=8.1 Hz, 1H), 8.05-7.94 (m, 2H), 7.78 (bs, 1H), 7.64 (dd, J=10.7, 2.2 Hz, 1H), 7.62-7.55 (m, 1H), 7.43 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.40-7.31 (m, 2H), 5.50 (dd, J=10.5, 2.8 Hz, 1H), 4.10 (dd, J=10.5, 2.8 Hz, 1H), 3.93 (s, 3H), 3.80-3.54 (m, 3H), 2.67-2.56 (m, 2H). UPLC-MS: t_R=2.16 min (Generic method); MS (ESI) m/z calcd for C₂₀H₂₀FN₂O₅S₂ (M+H)⁺: 451.1, found: 451.

3-[4-(3,4-Dimethoxyphenyl)sulfonylmorpholin-2-yl]benzothioephene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.04 mmol) and (3,4-dimethoxyphenyl)sulfonyl chloride (0.01 g, 0.04 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.005 g, 26%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.11 (dd, J=8.3, 1.1 Hz, 1H), 8.03-7.98 (m, 2H), 7.78 (bs, 1H), 7.43 (ddd, J=8.1, 7.0, 1.2 Hz, 1H), 7.34 (ddd, J=9.7, 8.4, 1.7 Hz, 2H), 7.18 (d, J=2.1 Hz, 1H), 7.14 (d, J=8.5 Hz, 1H), 5.50 (dd, J=10.5, 2.8 Hz, 1H), 4.09 (dd, J=10.5, 2.8 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.77-3.59 (m, 3H), 2.66-2.58 (m, 2H). UPLC-MS: t_R=2.05 min (Generic method); MS (ESI) m/z calcd for C₂₁H₂₃N₂O₆S₂ (M+H)⁺: 463.1, found: 463.

3-[4-[(4-Methyl-2,3-dihydro-1,4-benzoxazin-7-yl) sulfonyl]morpholin-2-yl]benzothioephene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.04 mmol) and (4-methyl-2,3-dihydro-1,4-benzoxazin-7-yl)sulfonyl chloride(0.01 g, 0.04 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.007 g, 30%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.13 (dd, J=8.1, 1.1 Hz, 1H), 8.04-7.99 (m, 2H), 7.78 (bs, 1H), 7.45 (ddd, J=8.1, 7.0, 1.2 Hz, 1H), 7.36 (ddd, J=8.3, 7.1, 1.2 Hz, 1H), 6.94 (dd, J=8.3, 2.1 Hz, 1H), 6.89 (d, J=2.1 Hz, 1H), 6.84 (d, J=8.3 Hz, 1H), 5.50 (dd, J=10.5, 2.8 Hz, 1H), 4.31 (dd, J=10.5, 2.8 Hz, 2H), 4.10 (d, J=11.6, 2.8 Hz, 1H), 3.71 (d, J=11.5 Hz, 2H), 3.60 (d, J=11.8 Hz, 1H), 3.32-3.28 (m, 2H), 2.84 (s, 3H), 2.74-2.56 (m, 2H). UPLC-MS: t_R=2.14 min (Generic method); MS (ESI) m/z calcd for C₂₂H₂₄N₃O₅S₂(M+H)⁺: 474.1, found: 474.

3-(4-Tetrahydropyran-4-yl)sulfonylmorpholin-2-yl benzothioephene-2-carboxamide: The title compound was prepared following GP1, from Int-1.6 (0.02 g, 0.05 mmol) and 4-tetrahydropyran-4-yl-sulfonylchloride(0.01 g, 0.05 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.008 g, 41%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.37 (dd, J=8.1, 1.1 Hz, 1H), 8.06-8.00 (m, 2H), 7.76 (bs, 1H), 7.53-7.41 (m, 2H), 5.43 (dd, J=10.5, 2.9 Hz, 1H), 4.12 (dd, J=11.4, 2.8 Hz, 1H), 3.99-3.87 (m, 2H), 3.72-3.63 (m, 2H), 3.60 (d, J=12.5 Hz, 1H), 3.53 (tt, J=11.9, 3.7 Hz, 1H), 1.91 (d, J=12.9 Hz, 2H), 1.67 (dq, J=11.9, 3.7 Hz, 2H). UPLC-MS: t_R=1.79 min (Generic method); MS (ESI) m/z calcd for C₁₈H₂₃N₂O₅S₂ (M+H)⁺: 411.1, found: 411.

3-[4-(2-Methoxyethylsulfonyl)morpholin-2-yl]benzothio-
 phenene-2-carboxamide: The title compound was prepared
 following GP1, from Int-1.6 (0.02 g, 0.06 mmol) and
 2-methoxyethylsulfonyl chloride (0.01 g, 0.05 mmol). The
 product was obtained, after purification by silica gel flash-
 column chromatography with DCM/EtOAc as the eluent, as
 a white solid (0.007 g, 37%). ¹H NMR (400 MHz, DMSO-
 d₆) δ 8.34 (dd, J=8.1, 1.1 Hz, 1H), 8.08-7.99 (m, 2H), 7.80
 (bs, 1H), 7.53-7.40 (m, 2H), 5.46 (dd, J=10.6, 2.9 Hz, 1H),
 4.14 (dd, J=11.6, 2.8 Hz, 1H), 3.74-3.68 (m, 1H), 3.66 (td,
 J=5.5, 4.2 Hz, 2H), 3.56 (dd, J=21.8, 11.9 Hz, 2H), 3.42 (t,
 J=5.8 Hz, 2H), 3.27 (s, 3H), 3.21 (dd, J=12.1, 3.2 Hz, 2H).
 UPLC-MS: t_R=1.79 min (Generic method); MS (ESI) m/z
 calcd for C₁₆H₂₁N₂O₅S₂(M+H)⁺: 385.1, found: 385.

3-[4-[4-(Pentafluoro-lambda6-sulfanyl)phenyl]sulfo-
 nylmorpholin-2-yl]benzothio-phenene-2-carboxamide: The
 title compound was prepared following GP1, from Int-1.6
 (0.02 g, 0.05 mmol) and [4-(pentafluoro-lambda6-sulfanyl)
 phenyl]sulfonylchloride (0.02 g, 0.05 mmol). The product
 was obtained, after purification by silica gel flash-column
 chromatography with DCM/EtOAc as the eluent, as a white
 solid (0.01 g, 31%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.17
 (dd, J=8.9, 1.9 Hz, 2H), 8.04-7.97 (m, 3H), 7.79 (bs, 1H),
 7.44 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.34 (ddd, J=8.2, 7.1, 1.2
 Hz, 1H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.11 (d, J=11.5 Hz,
 1H), 3.84 (d, J=11.2 Hz, 1H), 3.78-3.56 (m, 2H), 2.88-2.72
 (m, 2H). UPLC-MS: t_R=2.43 min (Generic method); MS
 (ESI) m/z calcd for C₁₉H₁₈FN₂O₄S₃(M+H)⁺: 529.1, found:
 529.

3-(4-Butylsulfonylmorpholin-2-yl)benzothio-phenene-2-car-
 boxamide: The title compound was prepared following GP1,
 from Int-1.6 (0.02 g, 0.05 mmol) and 4-butylsulfonylchlor-
 ide (0.01 g, 0.05 mmol). The product was obtained, after
 purification by silica gel flash-column chromatography with
 DCM/EtOAc as the eluent, as a white solid (0.005 g, 27%).
¹H NMR (400 MHz, DMSO-d₆) δ 8.37 (dd, J=8.9, 1.9 Hz,
 1H), 8.06-7.99 (m, 2H), 7.76 (bs, 1H), 7.47 (qd, J=8.9, 1.9
 Hz, 2H), 5.47 (dd, J=10.5, 2.8 Hz, 1H), 4.14 (dd, J=11.5, 2.8
 Hz, 1H), 3.69 (td, J=11.7, 2.6 Hz, 1H), 3.65-3.51 (m, 2H),
 3.28-3.17 (m, 2H), 3.17-3.08 (m, 2H), 1.75-1.59 (m, 2H),
 1.41 (h, J=7.4 Hz, 2H), 0.91 (t, J=7.4 Hz, 3H). UPLC-MS:
 t_R=2.08 min (Generic method); MS (ESI) m/z calcd for
 C₁₇H₂₃N₂O₄S₂(M+H)⁺: 383.1, found: 383.

3-[4-(3-Cyanophenyl)sulfonylmorpholin-2-yl]benzothi-
 ophenene-2-carboxamide: The title compound was prepared
 following GP1, from Int-1.6 (0.02 g, 0.05 mmol) and
 (3-cyanophenyl)sulfonylchloride (0.01 g, 0.05 mmol). The
 product was obtained, after purification by silica gel flash-
 column chromatography with DCM/EtOAc as the eluent, as
 a white solid (0.01 g, 56%). ¹H NMR (400 MHz, DMSO-d₆)
 δ 8.28 (t, J=1.6 Hz, 1H), 8.21 (dt, J=7.8, 1.3 Hz, 1H), 8.15
 (dd, J=8.2, 1.1 Hz, 1H), 8.09 (dt, J=7.9, 1.9, 1.1 Hz, 1H),
 8.06-7.94 (m, 2H), 7.83 (t, J=1.6 Hz, 1H), 7.76 (bs, 1H),
 7.44 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.34 (ddd, J=8.3, 7.1, 1.2
 Hz, 1H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.10 (dd, J=11.1, 3.0
 Hz, 1H), 3.82 (d, J=11.4 Hz, 1H), 3.70 (t, J=10.6 Hz, 2H),
 2.80-2.63 (m, 2H). UPLC-MS: t_R=2.04 min (Generic
 method); MS (ESI) m/z calcd for C₂₀H₁₀N₃O₄S₂(M+H)⁺:
 328.1, found: 428.

Methyl 4-[2-(2-carbamoylbenzothio-phen-3-yl)morpho-
 lin-4-yl]sulfonylbenzoate: The title compound was prepared
 following GP1, from Int-1.6 (0.07 g, 0.19 mmol) and methyl
 4-chlorosulfonylbenzoate chloride (0.04 g, 0.17 mmol). The
 product was obtained, after purification by silica gel flash-
 column chromatography with DCM/EtOAc as the eluent, as
 a white solid (0.03 g, 33%). ¹H NMR (400 MHz, DMSO-d₆)
 δ 8.20-8.15 (m, 2H), 8.13 (dt, J=8.2, 1.0 Hz, 1H), 8.04-7.98

(m, 2H), 7.96-7.90 (m, 1H), 7.80 (bs, 1H), 7.44 (ddd, J=8.2,
 7.1, 1.2 Hz, 1H), 7.33 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.51 (dd,
 J=10.5, 2.8 Hz, 1H), 4.11 (dd, 1H), 3.92 (s, 3H), 3.82 (d,
 J=11.1 Hz, 1H), 3.70 (t, J=12.2 Hz, 2H), 2.69 (t, J=11.1 Hz,
 2H). UPLC-MS: t_R=2.12 min (Generic method); MS (ESI)
 m/z calcd for C₂₁H₂₁N₂O₆S₂(M+H)⁺: 461.1, found: 461.

tert-Butyl 4-[2-(2-carbamoylbenzothio-phen-3-yl) mor-
 pholin-4-yl]sulfonylpiperidine-1-carboxylate: The title
 compound was prepared following GP1, from Int-1.6 (0.07
 g, 0.19 mmol) and tert-butyl 4-chlorosulfonylpiperidine-1-
 carboxylate (0.05 g, 0.17 mmol). The product was obtained,
 after purification by silica gel flash-column chromatography
 with DCM/EtOAc as the eluent, as a white solid (0.05 g,
 64%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.38 (dd, J=8.9, 1.9
 Hz, 1H), 8.06-8.02 (m, 2H), 7.77 (bs, 1H), 7.47 (qd, J=8.9,
 1.9 Hz, 2H), 5.44 (dd, J=10.6, 2.8 Hz, 1H), 4.12 (d, J=8.9
 Hz, 1H), 4.10-3.96 (m, 2H), 3.74-3.56 (m, 3H), 3.53-3.42
 (m, 1H), 3.42-3.35 (m, 1H), 2.78 (s, 2H), 2.01 (dd, J=23.1,
 12.7 Hz, 2H), 1.48 (tt, J=12.2, 6.1 Hz, 3H), 1.41 (s, 9H).
 UPLC-MS: t_R=2.21 min (Generic method); MS (ESI) m/z
 calcd for C₂₃H₃₂N₃O₆S₂(M+H)⁺: 510.2, found: 510.

3-[4-(4-Nitrophenyl)sulfonylmorpholin-2-yl]benzothi-
 ophenene-2-carboxamide: The title compound was prepared
 following GP1, from Int-1.6 (0.07 g, 0.19 mmol) and
 (4-nitrophenyl)sulfonyl chloride (0.04 g, 0.17 mmol). The
 product was obtained, after purification by silica gel flash-
 column chromatography with DCM/EtOAc as the eluent, as
 a white solid (0.05 g, 68%). ¹H NMR (400 MHz, DMSO-d₆)
 δ 8.42 (d, J=8.9 Hz, 2H), 8.16 (dt, J=8.9, 1.9 Hz, 1H), 8.07
 (d, J=8.9 Hz, 2H), 8.05-7.98 (m, 2H), 7.79 (bs, 1H), 7.44
 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.34 (ddd, J=8.3, 7.1, 1.2 Hz,
 1H), 5.51 (dd, J=10.5, 2.7 Hz, 1H), 4.12 (dd, J=11.4, 3.0 Hz,
 1H), 3.88 (dd, 1H), 3.76-3.64 (m, 2H), 2.88-2.74 (m, 2H).
 UPLC-MS: t_R=2.13 min (Generic method); MS (ESI) m/z
 calcd for C₁₉H₁₈N₃O₆S₂(M+H)⁺: 448.1, found: 448.

3-[4-[2-(Trifluoromethyl)phenyl]sulfonylmorpholin-2-
 yl]benzothio-phenene-2-carboxamide: The title compound was
 prepared following GP1, from Int-1.6 (0.02 g, 0.05 mmol)
 and [2-(trifluoromethyl)phenyl]sulfonyl chloride (0.01 g,
 0.05 mmol). The product was obtained, after purification by
 silica gel flash-column chromatography with DCM/EtOAc
 as the eluent, as a white solid (0.005 g, 20%). ¹H NMR (400
 MHz, DMSO-d₆) δ 8.26 (dt, J=8.0, 1.1 Hz, 1H), 8.16-8.12
 (m, 1H), 8.08-8.04 (m, 2H), 8.02 (dt, J=8.1, 1.0 Hz, 1H),
 7.95-7.89 (m, 2H), 7.76 (bs, 1H), 7.46 (ddd, J=8.2, 7.0, 1.3
 Hz, 1H), 7.40 (ddd, J=8.2, 7.1, 1.3 Hz, 1H), 5.49 (dd, J=10.6,
 2.9 Hz, 1H), 4.14 (dd, J=11.0, 2.8 Hz, 1H), 3.80 (dd, J=11.8,
 2.6 Hz, 1H), 3.76-3.65 (m, 2H), 3.10 (td, J=12.1, 11.5, 3.5
 Hz, 2H). UPLC-MS: t_R=2.21 min (Generic method); MS
 (ESI) m/z calcd for C₂₀H₁₈F₃N₂O₄S₂(M+H)⁺: 471.1, found:
 471.

3-[4-[2-(Trifluoromethoxy)phenyl]sulfonylmorpholin-2-
 yl]benzothio-phenene-2-carboxamide: The title compound was
 prepared following GP1, from Int-1.6 (0.02 g, 0.05 mmol)
 and [2-(trifluoromethoxy)phenyl]sulfonyl chloride (0.01 g,
 0.05 mmol). The product was obtained, after purification by
 silica gel flash-column chromatography with DCM/EtOAc
 as the eluent, as a white solid (0.006 g, 26%). ¹H NMR (400
 MHz, DMSO-d₆) δ 8.20 (dt, J=7.9, 1.7 Hz, 1H), 8.04-8.00
 (m, 2H), 7.96 (dd, J=7.9, 1.7 Hz, 1H), 7.86 (ddd, J=8.2, 7.4,
 1.7 Hz, 1H), 7.76 (bs, 1H), 7.65 (d, J=8.3, 1.5 Hz, 1H), 7.60
 (ddd, J=7.7, 1.1 Hz, 1H), 7.45 (ddd, J=8.1, 7.1, 1.2 Hz, 1H),
 7.38 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.48 (dd, J=10.6, 2.8 Hz,
 1H), 4.15 (dd, J=11.1, 3.0 Hz, 1H), 3.81-3.61 (m, 3H),
 3.06-2.88 (m, 2H). UPLC-MS: t_R=2.27 min (Generic
 method); MS (ESI) m/z calcd for C₂₀H₁₈F₃N₂O₅S₂(M+H)⁺:
 487.1, found: 487.

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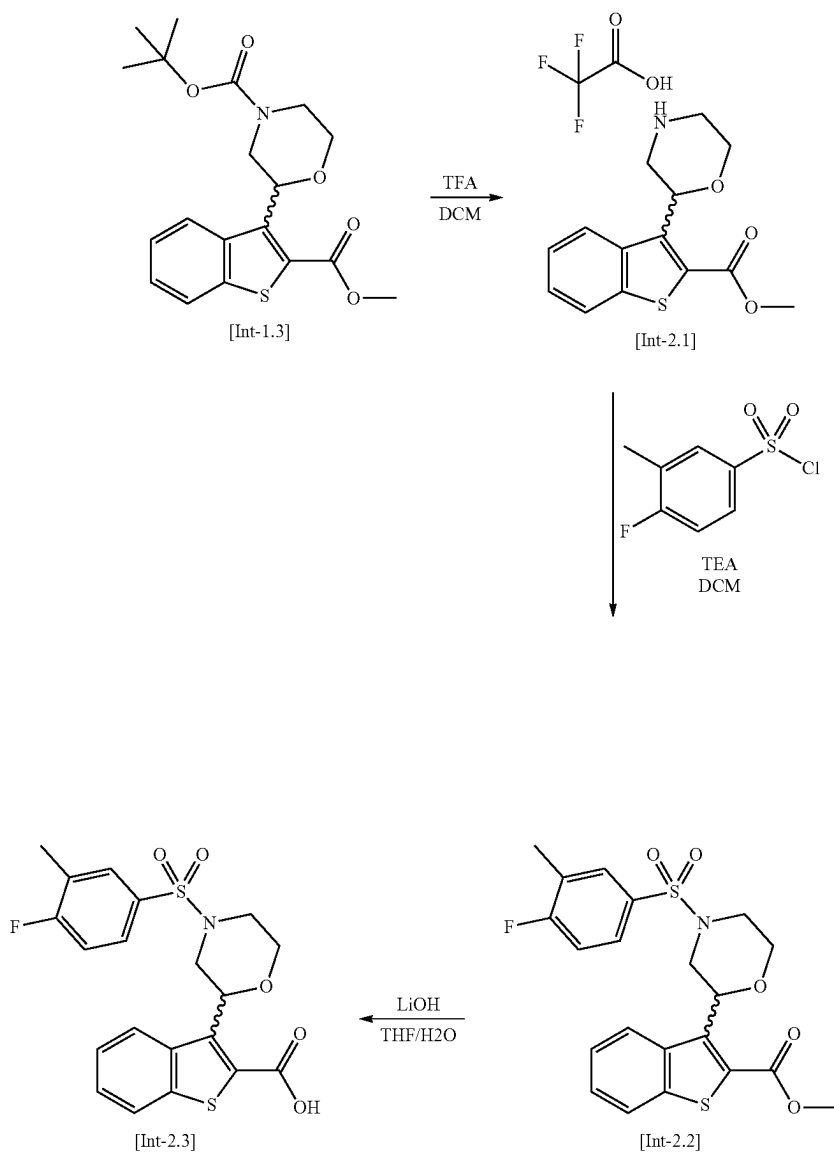
3-[4-(4-Hydroxyphenyl)sulfonylmorpholin-2-yl]benzothio-
 thiophene-2-carboxamide: The title compound was prepared
 following GP1, from Int-1.6 (0.07 g, 0.19 mmol) and
 (4-hydroxyphenyl)sulfonyl chloride (0.04 g, 0.17 mmol).
 The product was obtained, after purification by silica gel
 flash-column chromatography with DCM/EtOAc as the elu-
 ent, as a white solid (0.05 g, 53%). ¹H NMR (400 MHz,
 DMSO-d₆) δ 10.52 (bs, 1H), 8.08 (d, J=8.2, 1H), 8.04-7.90
 (m, 2H), 7.79 (bs, 1H), 7.60-7.53 (m, 2H), 7.45-7.39 (m,
 1H), 7.37-7.30 (m, 1H), 6.95-6.89 (m, 2H), 5.49 (dd, J=10.5,
 2.8 Hz, 1H), 4.09 (dd, J=11.5, 3.0 Hz, 1H), 3.76-3.64 (m,
 2H), 3.56 (d, J=11.7 Hz, 1H), 2.61-2.51 (m, 2H). UPLC-MS:
 t_R=1.85 min (Generic method); MS (ESI) m/z calcd for
 C₁₉H₁₉N₂O₅S₂(M+H)⁺: 419.1, found: 419.

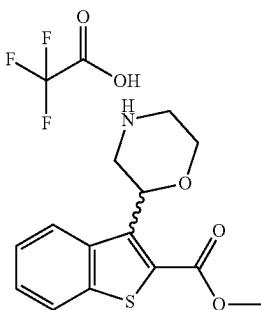
3-[4-(4-Isopropoxyphenyl)sulfonylmorpholin-2-yl]ben-
 zothiophene-2-carboxamide: To a solution of compound 068
 (0.040 g, 0.10 mmol) in THF (1.0 mL), PPh₃ (0.052 g, 0.20
 mmol) and DIAD (0.040 g, 0.20 mmol) were added. After 30
 minutes of stirring at room temperature, IPA (0.012 g, 0.20

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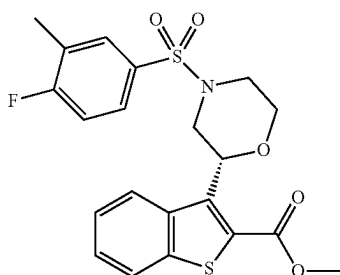
mmol) was added and the resulting solution was allowed to
 react overnight. The reaction was quenched by adding water
 and the aqueous phase was extracted with EtOAc (3×10
 mL). The combined organic layers were dried over Na₂SO₄
 and concentrated under vacuum. Subsequent flash chroma-
 tography (DCM/EtOAc 0% to 80%) afforded the title com-
 pound as white solid (0.008 g, 18%) ¹H NMR (400 MHz,
 DMSO-d₆) δ 8.11-8.07 (m, 1H), 8.03-7.91 (m, 2H), 7.79 (bs,
 J=20.4 Hz, 1H), 7.68-7.60 (m, 2H), 7.46-7.39 (m, 1H),
 7.35-7.29 (m, 1H), 7.13-7.05 (m, 2H), 5.49 (dd, J=10.6, 2.8
 Hz, 1H), 4.72 (m, 1H), 4.09 (dd, J=11.4, 3.0 Hz, 1H),
 3.75-3.65 (m, 2H), 3.59 (d, J=11.8 Hz, 1H), 2.61-2.52 (m,
 2H), 1.31-1.26 (m, 6H). UPLC-MS: t_R=2.31 min (Generic
 method); MS (ESI) m/z calcd for C₂₂H₂₅N₂O₅S₂ (M+H)⁺:
 461.1, found: 461.

Synthesis of 3-benzothiophene-2-carboxylic acid
 intermediate (Int-2.3)

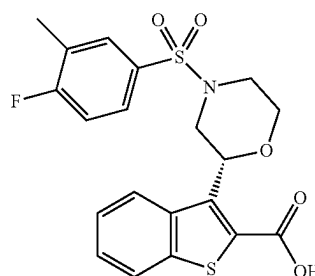




[Int-2.1] Methyl 3-morpholin-4-ylbenzothiophene-2-carboxylate;2,2,2-trifluoroacetate: To a solution of Int-1.3 (0.4 g, 1.06 mmol) in dry DCM at 0° C., TFA was slowly added (0.347 mL, 5.30 mmol). The reaction was allowed to stir at room temperature for 7 hours. The solvent was evaporated under reduced pressure. The title compound (0.294 g, quantitative) was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 8.48 (d, J=7.8 Hz, 1H), 8.05 (d, J=7.6 Hz, 1H), 7.50 (dt, J=33.7, 7.1 Hz, 2H), 5.99 (d, J=7.0 Hz, 1H), 4.19 (d, J=12.0 Hz, 2H), 3.89 (s, 3H), 3.52-3.38 (m, 4H). UPLC-MS: t_R=1.62 min (Generic method); MS (ESI) m/z calcd for C₁₄H₁₆NO₃S (M+H)⁺: 278.1, found:278.

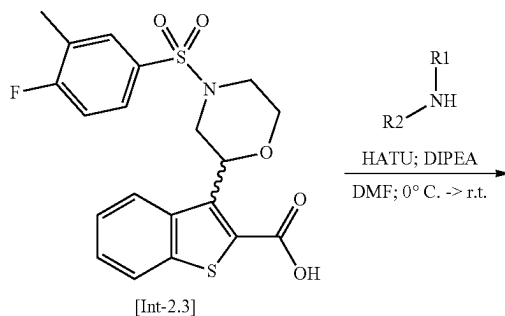


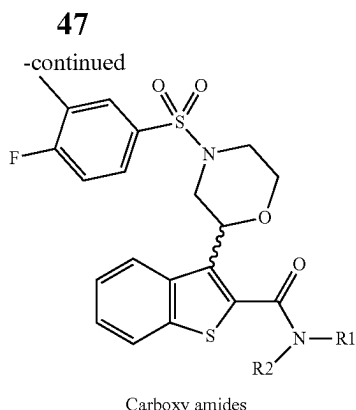
[Int-2.2] Methyl 3-[4-(4-fluoro-3-methyl-phenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxylate: In a 20 mL round-bottomed flask, under nitrogen, Int-2.1 (0.294 g, 1.06 mmol) and Et₃N (0.161 mL, 1.16 mmol) were added in dry DCM, followed by 4-fluoro-3-methylbenzenesulfonyl chloride (0.201 g, 0.96 mmol). After 1 hour at room temperature, the mixture was quenched with water, and the organic layer was separated and washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified with CombiFlash (DCM/EtOAc) to yield the title compound (0.433 g, quantitative). ¹H NMR (400 MHz, DMSO-d₆) δ 8.29 (dt, J=8.4, 1.0 Hz, 1H), 8.02 (dt, J=8.1, 0.9 Hz, 1H), 7.76 (dd, J=8.2, 1.2 Hz, 1H), 7.70-7.59 (m, 1H), 7.50 (ddd, J=8.2, 7.0, 1.2 Hz, 1H), 7.42-7.32 (m, 2H), 5.76 (dd, J=10.4, 2.7 Hz, 1H), 4.13 (dd, J=11.6, 2.9 Hz, 1H), 3.92 (s, 3H), 3.82-3.58 (m, 3H), 2.69 (td, J=11.7, 3.3 Hz, 1H), 2.60 (t, J=11.7 Hz, 1H). UPLC-MS: t_R=2.79 min (Generic method); MS (ESI) m/z calcd for C₂₁H₂₁FNO₅S₂ (M+H)⁺: 450.1, found:450.



[Int-2.3] 3-[4-(4-fluoro-3-methyl-phenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxylic acid: To a solution of Int-2.2 (0.433 g, 0.99 mmol) in THF (15 mL), aqueous LiOH 1N (5 mL) was added dropwise and the reaction was stirred overnight at room temperature. The reaction was quenched upon addition of HCl 2N, until pH=4/5, and the resulting aqueous phase was extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine, dried, filtered and concentrated to give a crude product, which was purified with CombiFlash (DCM/MeOH 95:5+5% AcOH), to obtain the desired compound as a white powder (0.384 g, 89%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.24 (d, J=8.3 Hz, 1H), 7.98 (d, J=8.1 Hz, 1H), 7.74 (dd, J=7.1, 2.4 Hz, 1H), 7.63 (ddd, J=8.0, 4.8, 2.4 Hz, 1H), 7.46 (ddd, J=8.2, 7.0, 1.2 Hz, 1H), 7.40-7.26 (m, 2H), 5.81 (dd, J=10.4, 2.7 Hz, 1H), 4.11 (dd, J=11.6, 3.0 Hz, 1H), 3.78-3.57 (m, 3H), 2.65 (td, J=11.8, 3.3 Hz, 1H), 2.55 (t, J=11.0 Hz, 1H), 2.27 (s, 3H). UPLC-MS: t_R=1.91 min (Generic method); MS (ESI) m/z calcd for C₂₀H₁₉FNO₅S₂ (M+H)⁺: 436.1, found: 436.

General Protocol for Carboxy Amide Derivatives Synthesis (GP2).





To a solution of Int-2.3 (1.0 eq) in dry DMF (0.1 M) cooled to 0° C., HATU (1.5 eq) and DIPEA (4.0 eq) were sequentially added. After 10 minutes, the desired amine (2.0 eq) was added and the mixture stirred for 30 min at room temperature. Sat. aq. NH₄Cl was added to quench the reaction and the mixture was extracted with EtOAc (3×). Collected organic layers were washed with brine, dried (Na₂SO₄), filtered and evaporated to give a crude product, which was purified with CombiFlash (DCM/EtOAc) to obtain the desired compounds in good yields.

3-[4-(4-Fluoro-3-methyl-phenyl)sulfonylmorpholin-2-yl]-N,N-dimethyl-benzothiophene-2-carboxamide: The title compound was prepared following GP2, from Int-2.3 (0.05 g, 0.11 mmol) and dimethyl amine (2.0 M THF solution, 11.0 μL, 0.22 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.03 g, 63%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.03-7.99 (m, 1H), 7.98-7.94 (m, 1H), 7.74 (dd, J=7.8, 2.7 Hz, 1H), 7.63 (ddd, J=7.8, 4.8, 2.7 Hz, 1H), 7.46-7.37 (m, 3H), 4.91 (dd, J=10.6, 2.7 Hz, 1H), 4.04 (dd, J=10.6, 2.7 Hz, 1H), 3.76 (td, J=11.6, 2.5 Hz, 1H), 3.63 (t, J=12.9 Hz, 2H), 2.94 (d, 6H), 2.72-2.56 (m, 2H), 2.31 (s, 3H). UPLC-MS: t_R=2.45 min (Generic method); MS (ESI) m/z calcd for C₂₂H₂₄FN₂O₄S₂ (M+H)⁺: 463.1, found: 463.

3-[4-(4-Fluoro-3-methyl-phenyl)sulfonylmorpholin-2-yl]-N-methyl-benzothiophene-2-carboxamide: The title compound was prepared following GP2, from Int-2.3 (0.05 g, 0.11 mmol) and methyl amine (2.0 M THF solution, 11.0 μL, 0.22 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.02 g, 47%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.46 (d, J=4.7 Hz, 1H), 8.11 (dt, J=8.2, 1.1 Hz, 1H), 7.99 (dt, J=8.2, 1.0 Hz, 1H), 7.79-7.72 (m, 1H), 7.63 (ddd, J=7.6, 4.6, 2.5 Hz, 1H), 7.42 (ddd, J=8.1, 7.0, 1.2 Hz, 1H), 7.40-7.35 (m, 1H), 7.33 (ddd, J=8.2, 6.5, 1.3 Hz, 1H), 5.42 (dd, J=10.5, 2.8 Hz, 1H), 4.07 (dd, J=10.9, 3.0 Hz, 1H), 3.77 (d, J=11.2 Hz, 1H), 3.71-3.54 (m, 2H), 2.77 (d, J=4.5 Hz, 3H), 2.70-2.56 (m, 2H), 2.30 (d, J=2.2 Hz, 3H). UPLC-MS: t_R=2.38 min (Generic method); MS (ESI) m/z calcd for C₂₁H₂₂FN₂O₄S₂ (M+H)⁺: 449.1, found: 449.

3-[4-(4-Fluoro-3-methyl-phenyl)sulfonylmorpholin-2-yl]-N-(2-hydroxyethyl) benzothiophene-2-carboxamide: The title compound was prepared following GP2, from Int-2.3 (0.04 g, 0.08 mmol) and ethanolamine (10.0 μL, 0.16 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.02 g, 38%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.53 (t, J=5.6 Hz, 1H), 8.10 (dd, J=8.2, 1.1 Hz, 1H), 7.99 (dd, J=8.2, 1.1 Hz, 1H), 7.74 (dt, J=8.2, 1.1 Hz, 1H), 7.68-7.58 (m, 1H), 7.48-7.29 (m, 3H), 5.40 (dd, J=10.6,

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2.8 Hz, 1H), 4.75 (t, J=5.5 Hz, 1H), 4.08 (dd, J=11.5, 2.8 Hz, 1H), 3.84-3.66 (m, 2H), 3.61 (dd, J=12.0 Hz, 1H), 3.54-3.40 (m, 2H), 3.29-3.20 (m, 1H), 2.74-2.58 (m, 2H), 2.29 (s, 3H). UPLC-MS: t_R=2.21 min (Generic method); MS (ESI) m/z calcd for C₂₂H₂₄FN₂O₅S₂ (M+H)⁺: 479.1, found: 479.

N-Ethyl-3-[4-(4-fluoro-3-methyl-phenyl)sulfonyl morpholin-2-yl]benzothiophene-2-carboxamide: The title compound was prepared following GP2, from Int-2.3 (0.05 g, 0.11 mmol) and ethyl amine (2.0 M THF solution, 11.0 μL, 0.22 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.01 g, 18%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.54 (t, J=5.6 Hz, 1H), 8.11 (d, J=8.1 Hz, 1H), 7.98 (d, J=8.1 Hz, 1H), 7.75 (dd, J=8.2, 1.1 Hz, 1H), 7.69-7.57 (m, 1H), 7.49-7.27 (m, 3H), 6.97 (bs, 1H), 5.39 (dd, J=10.5, 2.8 Hz, 1H), 4.09 (dd, J=11.8, 3.0 Hz, 1H), 3.80-3.53 (m, 3H), 3.30-3.18 (m, 2H), 2.63 (t, J=11.0 Hz, 2H), 2.29 (s, 3H). UPLC-MS: t_R=2.46 min (Generic method); MS (ESI) m/z calcd for C₂₂H₂₄FN₂O₄S₂ (M+H)⁺: 463.1, found: 463.

3-[4-(4-Fluoro-3-methyl-phenyl)sulfonylmorpholin-2-yl]-N-isopropyl-benzothiophene-2-carboxamide: The title compound was prepared following GP2, from Int-2.3 (0.05 g, 0.11 mmol) and isopropyl amine (17.8 μL, 0.22 mmol). The product was obtained, after purification by silica gel flash-column chromatography with DCM/EtOAc as the eluent, as a white solid (0.04 g, 73%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.40 (d, J=7.7 Hz, 1H), 8.09 (dt, J=8.0, 1.0 Hz, 1H), 7.98 (dt, J=8.0, 1.0 Hz, 1H), 7.74 (dd, J=7.7, 2.4 Hz, 1H), 7.63 (ddd, J=7.7, 4.9, 2.4 Hz, 1H), 7.46-7.30 (m, 3H), 5.33 (dd, J=10.5, 2.8 Hz, 1H), 4.10 (dd, J=11.6, 2.9 Hz, 1H), 4.01 (q, J=6.7 Hz, 1H), 3.78-3.68 (m, 1H), 3.63 (d, J=11.9 Hz, 1H), 2.71-2.53 (m, 2H), 2.29 (s, 3H), 1.13 (d, J=6.6 Hz, 3H), 1.06 (d, J=6.6 Hz, 3H). UPLC-MS: t_R=2.57 min (Generic method); MS (ESI) m/z calcd for C₂₃H₂₆FN₂O₄S₂ (M+H)⁺: 477.1, found: 477.

Pure enantiomers were obtained from the corresponding racemates, after separation by chiral column chromatography.

3-[(R)-4-(4-Fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was obtained from racemic 001, using a Daicel ChiralCel OD-H column (250×4.6mmID, particle size 5 μm) at 25° C. Mobile phase: Heptane-EtOH (90:10). Flow Rate: 1 mL/min; UV: 278 nm. ¹H NMR (400 MHz, DMSO-d₆) δ 8.14 (d, J=8.2, 1.1 Hz, 1H), 8.09-7.93 (m, 2H), 7.87-7.72 (m, 2H), 7.69-7.60 (m, 1H), 7.49-7.32 (m, 3H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.11 (d, J=11.6, 2.9 Hz, 1H), 3.85-3.56 (m, 3H), 2.67 (td, J=10.9, 3.7 Hz, 2H), 2.32 (s, 3H). UPLC-MS: t_R=2.33 min (Generic method); MS (ESI) m/z calcd for C₂₀H₂₀FN₂O₄S₂ (M+H)⁺: 435.1, found: 435. Chiral HPLC: t_R=29.995 min, >99.5% ee.

3-[(S)-4-(4-Fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was obtained from racemic 001, using a Daicel ChiralCel OD-H column (250×4.6mmID, particle size 5 μm) at 25° C. Mobile phase: Heptane-EtOH (90:10). Flow Rate: 1 mL/min; UV: 278 nm. ¹H NMR (400 MHz, DMSO-d₆) δ 8.14 (d, J=8.2, 1.1 Hz, 1H), 8.09-7.93 (m, 2H), 7.87-7.72 (m, 2H), 7.69-7.60 (m, 1H), 7.49-7.32 (m, 3H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.11 (d, J=11.6, 2.9 Hz, 1H), 3.85-3.56 (m, 3H), 2.67 (td, J=10.9, 3.7 Hz, 2H), 2.32 (s, 3H). UPLC-MS: t_R=2.33 min (Generic method); MS (ESI) m/z calcd for C₂₀H₂₀FN₂O₄S₂ (M+H)⁺: 435.1, found: 435. Chiral HPLC: t_R=36.540 min, >99.5% ee.

3-[(R)-4-[4-(Trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound

was obtained from racemic 011, using a Daicel ChiralCel OD-H column (250×4.6mmID, particle size 5 μm) at 25° C. Mobile phase: Heptane-EtOH (90:10). Flow Rate: 1 mL/min; UV: 278 nm. ¹H NMR (400 MHz, DMSO-d₆) δ 8.15 (dd, J=8.2, 1.0 Hz, 1H), 8.01 (s, 4H), 8.01-7.99 (m, 2H), 7.79 (bs, 1H), 7.44 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.34 (ddd, J=8.2, 7.1, 1.1 Hz, 1H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.11 (d, J=10.9 Hz, 1H), 3.70 (t, J=12.1 Hz, 2H), 3.84 (d, J=11.4 Hz, 1H), 2.83-2.62 (m, 2H). UPLC-MS: t_R=2.40 min (Generic method); MS (ESI) m/z calcd for C₂₀H₁₈F₃N₂O₄S₂ (M+H)⁺: 471.1, found: 471. Chiral HPLC: t_R=39.324 min, >99.5% ee.

3-[(S)-4-[4-(Trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was obtained from racemic 011, using a Daicel ChiralCel OD-H column (250×4.6mmID, particle size 5 μm) at 25° C. Mobile phase: Heptane-EtOH (90:10). Flow Rate: 1 mL/min; UV: 278 nm. ¹H NMR (400 MHz, DMSO-d₆) δ 8.15 (dd, J=8.2, 1.0 Hz, 1H), 8.01 (s, 4H), 8.01-7.99 (m, 2H), 7.79 (bs, 1H), 7.44 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.34 (ddd, J=8.2, 7.1, 1.1 Hz, 1H), 5.51 (dd, J=10.5, 2.8 Hz, 1H), 4.11 (d, J=10.9 Hz, 1H), 3.70 (t, J=12.1 Hz, 2H), 3.84 (d, J=11.4 Hz, 1H), 2.83-2.62 (m, 2H). UPLC-MS: t_R=2.40 min (Generic method); MS (ESI) m/z calcd for C₂₀H₁₈F₃N₂O₄S₂ (M+H)⁺: 471.1, found: 471. Chiral HPLC: t_R=30.875 min, >99.5% ee.

3-[(S)-4-[3-Fluoro-4-(trifluoromethyl) phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was obtained from racemic 041, using a Daicel ChiralCel OD-H column (250×4.6mmID, particle size 5 μm) at 25° C. Mobile phase: Heptane-EtOH (90:10). Flow Rate: 1 mL/min; UV: 278 nm. ¹H NMR (400 MHz, DMSO-d₆) δ 8.19 (d, J=8.2 Hz, 1H), 8.09-7.95 (m, 4H), 7.81 (d, J=8.3 Hz, 1H), 7.76 (bs, 1H), 7.44 (ddd, J=8.2, 7.0, 1.2 Hz, 1H), 7.34 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.50 (dd, J=10.6, 2.8 Hz, 1H), 4.10 (dd, J=11.4, 3.0 Hz, 1H), 3.84 (d, J=11.3 Hz, 1H), 3.77-3.61 (m, 2H), 2.95-2.77 (m, 2H). UPLC-MS: t_R=2.50 min (Generic method); MS (ESI) m/z calcd for C₂₀H₁₇F₄N₂O₄S₂ (M+H)⁺: 489.1, found: 489. Chiral HPLC: t_R=36.123 min, >99.5% ee.

3-[(R)-4-[3-Fluoro-4-(trifluoromethyl) phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was obtained from racemic 041, using a Daicel ChiralCel OD-H column (250×4.6mmID, particle size 5 μm) at 25° C. Mobile phase: Heptane-EtOH (90:10). Flow Rate: 1 mL/min; UV: 278 nm. ¹H NMR (400 MHz, DMSO-d₆) δ 8.19 (d, J=8.2 Hz, 1H), 8.09-7.95 (m, 4H), 7.81 (d, J=8.3 Hz, 1H), 7.76 (bs, 1H), 7.44 (ddd, J=8.2, 7.0, 1.2 Hz, 1H), 7.34 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.50 (dd, J=10.6, 2.8 Hz, 1H), 4.10 (dd, J=11.4, 3.0 Hz, 1H), 3.84 (d, J=11.3 Hz, 1H), 3.77-3.61 (m, 2H), 2.95-2.77 (m, 2H). UPLC-MS: t_R=2.50 min (Generic method); MS (ESI) m/z calcd for C₂₀H₁₇F₄N₂O₄S₂ (M+H)⁺: 489.1, found: 489. Chiral HPLC: t_R=27.703 min, >99.5% ee.

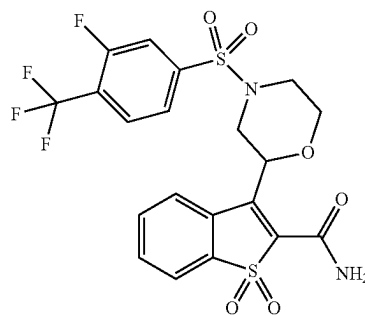
3-[(S)-4-[(2-Methyl-1,3-benzoxazol-6-yl) sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide: The title compound was obtained from racemic 034, using a Daicel ChiralCel OD-H column (250×4.6mmID, particle size 5 μm) at 25° C. Mobile phase: Heptane-EtOH (50:50). Flow Rate: 1 mL/min; UV: 278 nm. ¹H NMR (400 MHz, DMSO-d₆) δ 8.13 (dd, J=1.7, 0.5 Hz, 1H), 8.07 (dt, J=8.3, 1.0 Hz, 1H), 8.03-7.94 (m, 2H), 7.86 (d, J=8.4 Hz, 1H), 7.82-7.66 (m, 2H), 7.40 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.28 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.50 (dd, J=10.5, 2.8 Hz, 1H), 4.08 (d, J=11.3 Hz, 1H), 3.79 (d, J=11.2 Hz, 1H), 3.68 (t, J=12.0 Hz, 2H), 2.66 (s, 3H), 2.64-2.56 (m, 2H). UPLC-MS: t_R=2.05

min (Generic method); MS (ESI) m/z calcd for C₂₁H₂₀N₃O₅S₂ (M+H)⁺: 458.1, found: 458. Chiral HPLC: t_R=11.8 min, >98.5% ee.

3-[(R)-4-[(2-Methyl-1,3-benzoxazol-6-yl) sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide: The title compound was obtained from racemic 034, using a Daicel ChiralCel OD-H column (250×4.6mmID, particle size 5 μm) at 25° C. Mobile phase: Heptane-EtOH (50:50). Flow Rate: 1 mL/min; UV: 278 nm. ¹H NMR (400 MHz, DMSO-d₆) δ 8.13 (dd, J=1.7, 0.5 Hz, 1H), 8.07 (dt, J=8.3, 1.0 Hz, 1H), 8.03-7.94 (m, 2H), 7.86 (d, J=8.4 Hz, 1H), 7.82-7.66 (m, 2H), 7.40 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.28 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.50 (dd, J=10.5, 2.8 Hz, 1H), 4.08 (d, J=11.3 Hz, 1H), 3.79 (d, J=11.2 Hz, 1H), 3.68 (t, J=12.0 Hz, 2H), 2.66 (s, 3H), 2.64-2.56 (m, 2H). UPLC-MS: t_R=2.05 min (Generic method); MS (ESI) m/z calcd for C₂₁H₂₀N₃O₅S₂ (M+H)⁺: 458.1, found: 458. Chiral HPLC: t_R=8.3 min, >99.5% ee.

3-[(S)-4-(3-Fluoro-4-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was obtained from racemic 026, using a Daicel ChiralCel OD-H column (250×4.6mmID, particle size 5 μm) at 25° C. Mobile phase: Heptane-EtOH (90:10). Flow Rate: 1 mL/min; UV: 278 nm. ¹H NMR (400 MHz, DMSO-d₆) δ 8.22-8.13 (m, 2H), 8.04 (dd, J=6.7, 2.3 Hz, 1H), 8.01-7.95 (m, 2H), 7.82-7.66 (m, 3H), 7.42 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.33 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.48 (dd, J=10.5, 2.8 Hz, 1H), 4.15-4.02 (m, 1H), 3.85-3.74 (m, 1H), 3.74-3.62 (m, 2H), 2.78 (td, J=11.8, 11.2, 3.4 Hz, 2H). UPLC-MS: t_R=2.46 min (Generic method); MS (ESI) m/z calcd for C₂₀H₁₇F₄N₂O₄S₂ (M+H)⁺: 489.1, found: 489. Chiral HPLC: t_R=15.2 min, >97.8% ee.

3-[(R)-4-(3-Fluoro-4-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide: The title compound was obtained from racemic 041, using a Daicel ChiralCel OD-H column (250×4.6mmID, particle size 5 μm) at 25° C. Mobile phase: Heptane-EtOH (90:10). Flow Rate: 1 mL/min; UV: 278 nm. ¹H NMR (400 MHz, DMSO-d₆) δ 8.22-8.13 (m, 2H), 8.04 (dd, J=6.7, 2.3 Hz, 1H), 8.01-7.95 (m, 2H), 7.82-7.66 (m, 3H), 7.42 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.33 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 5.48 (dd, J=10.5, 2.8 Hz, 1H), 4.15-4.02 (m, 1H), 3.85-3.74 (m, 1H), 3.74-3.62 (m, 2H), 2.78 (td, J=11.8, 11.2, 3.4 Hz, 2H). UPLC-MS: t_R=2.46 min (Generic method); MS (ESI) m/z calcd for C₂₀H₁₇F₄N₂O₄S₂ (M+H)⁺: 489.1, found: 489. Chiral HPLC: t_R=10.7 min, >97.8% ee.



3-[4-[3-Fluoro-4-(trifluoromethyl)phenyl]sulfonyl morpholin-2-yl]-1,1-dioxo-benzothiophene-2-carboxamide: To a solution of compound 041 (0.074 g, 0.15 mmol) in DCM (2.1 mL) m-CPBA (0.1 g, 0.45 mmol) was added at 0° C. The solution was stirred overnight at room temperature, washed with sat. sol. NaHCO₃ and dried over Na₂SO₄. The crude

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product was passed through a pad of silica gel using cyclohexane/AcOEt 0% to 40% as eluent. The title compound was obtained by recrystallization in CH₃CN/H₂O (0.016 g, 20%), as white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.16 (bs, 1H), 8.09-8.04 (m, 1H), 8.02 (dd, J=5.7, 3.0 Hz, 1H), 7.98 (d, J=10.3 Hz, 1H), 7.96-7.92 (m, 1H), 7.82 (d, J=8.2 Hz, 1H), 7.73-7.67 (m, 2H), 7.56 (bs, 1H), 5.12 (dd, J=10.6, 2.6 Hz, 1H), 4.06 (dd, J=11.1, 2.8 Hz, 1H), 3.90 (d, J=11.6 Hz, 1H), 3.69 (t, J=10.7 Hz, 2H), 2.94-2.76 (m, 2H). UPLC-MS: t_R=2.02 min (Generic method); MS (ESI) m/z calcd for C₂₀H₁₇F₄N₂O₆S₂ (M+H)⁺: 521.0, found: 521.

Methods

Fluorescence Assay for CFTR Activity

Mutant CFTR activity was determined with the functional assay based on the halide-sensitive yellow fluorescent protein, HS—YFP (Galletta et al., FEBS Lett 499:220-224, 2001). CFBE41o- and FRT cells with stable expression of mutant CFTR and HS—YFP were plated on clear-bottom 96-well black microplates (Code 3603, Corning Life Sciences) at a density of 50,000 cells/well and kept at 37° C. in 5% CO₂ for 24 hours.

For the corrector assay, cells were treated for further 24 hours with test compounds, vehicle (DMSO), or the positive control VX-809. After treatment, the culture medium was removed and cells in each well were stimulated for 30 min at 37° C. with 60 μL PBS (containing 137 mM NaCl, 2.7 mM KCl, 8.1 mM Na₂HPO₄, 1.5 mM KH₂PO₄, 1 mM CaCl₂, and 0.5 mM MgCl₂) plus forskolin (20 μM) and genistein (50 μM).

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For determination of potentiator activity on F508del-CFTR, cells were incubated for 24 hours at 27° C. to allow trafficking of the mutant protein to plasma membrane. Cells were then stimulated with for 30 min with PBS containing forskolin (20 μM) plus the compound to be tested at the desired concentration. For determination of potentiator activity on G551D-CFTR or G1349D-CFTR, cells were directly stimulated with forskolin plus test compound without previous incubation at low temperature. At the time of assay, microplates carrying CFBE41o- or FRT cells were transferred to microplate readers (BMG Labtech) equipped with high-quality excitation (HQ500/20x: 500±10 nm) and emission (HQ535/30M: 535±15 nm) filters for YFP (Chroma Technology). The assay consisted of a continuous 14 s fluorescence reading with 2 s before and 12 s after injection of an iodide-containing solution (165 μL of a modified PBS containing I⁻ instead of Cl⁻; final I⁻ concentration in the well: 100 mM). Data were normalized to the initial background-subtracted fluorescence. Enhanced CFTR activity, induced by correctors and/or potentiators, results in accelerated I⁻ influx that in turn causes faster HS—YFP quenching (Pedemonte et al., *Mol Pharmacol* 68:1736-1746, 2005; Pedemonte et al., *J Clin Invest* 115:2564-2571, 2015). To determine fluorescence quenching rate associated with I⁻ influx, the final 10 s of data for each well were fitted with an exponential function to extrapolate initial slope (dF/dt).

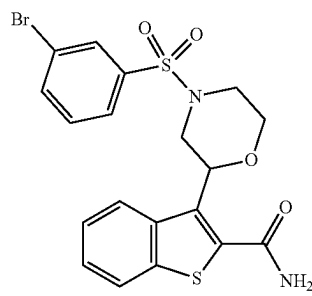
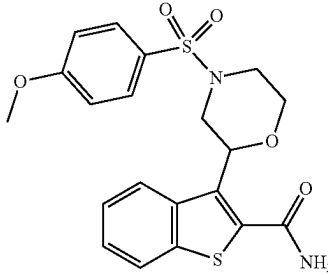
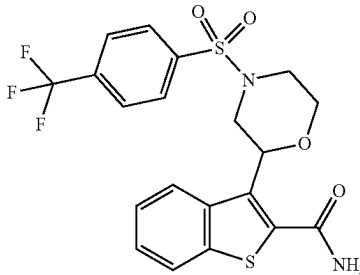
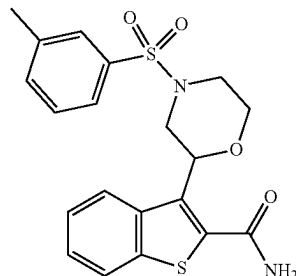
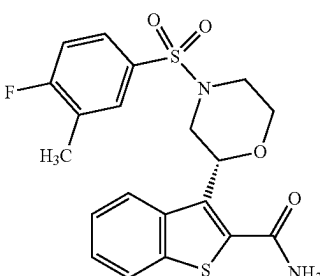
EC₅₀ obtained are illustrated in Table 1 wherein+: EC₅₀>2 μM; ++: 1.0 μM <EC₅₀<2 μM; +++: EC₅₀<1 μM.

#	Structure	Substance Name	Molecular Formula	Activity
001		rac-3-[4-(4-fluoro-3-methyl-benzenesulfonyl)-morpholin-2-yl]-benzo[b]thiophene-2-carboxylic acid amide	C20 H19 F N2 O4 S2	+
002		rac-3-[4-(1,2-dimethylimidazol-4-yl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C18 H20 N4 O4 S2	+
003		rac-3-[4-(benzenesulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide	C19 H18 N2 O4 S2	+

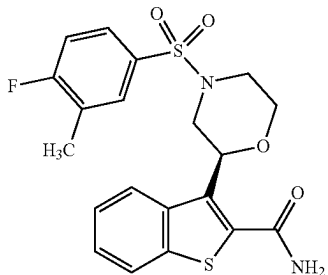
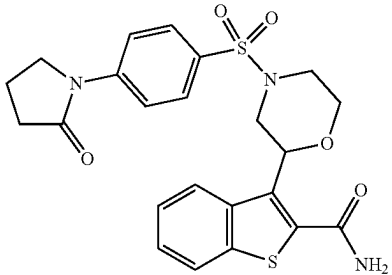
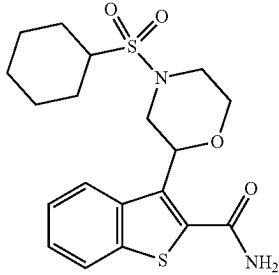
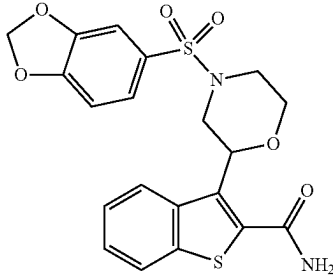
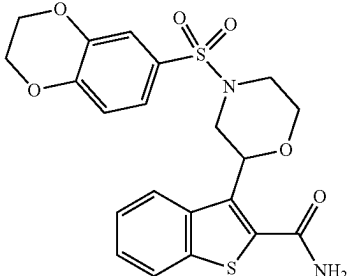
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#	Structure	Substance Name	Molecular Formula	Activity
004		rac-3-[4-(1H-imidazol-4-ylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide	C16 H16 N4 O4 S2	+
005		rac-3-[4-(3-thienylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide	C17 H16 N2 O4 S3	+
006		rac-3-[4-(4-phenoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C25 H22 N2 O5 S2	+++
007		rac-methyl 3-[2-(2-carbamoylbenzothiophen-3-yl)morpholin-4-yl]sulfonylbenzoate	C21 H20 N2 O6 S2	+
008		rac-3-[4-(3,5-dimethylisoxazol-4-yl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C18 H19 N3 O5 S2	+

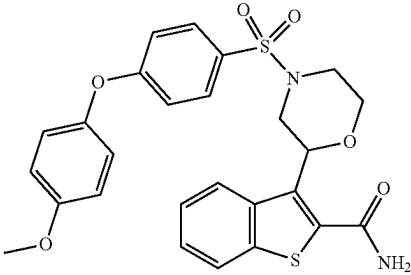
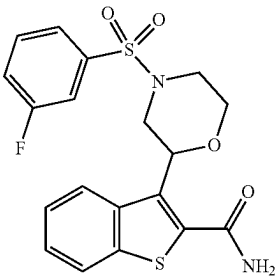
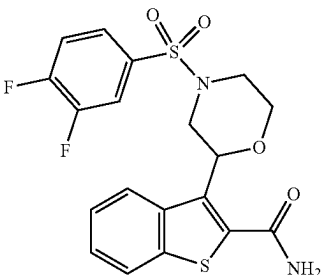
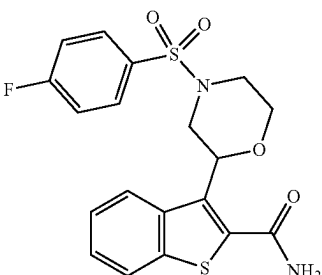
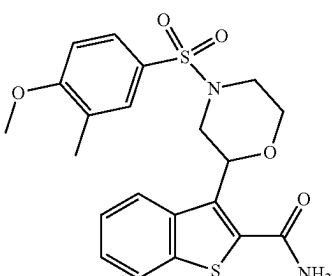
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#	Structure	Substance Name	Molecular Formula	Activity
009		rac-3-[4-(3-bromophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C ₁₉ H ₁₇ Br N ₂ O ₄ S ₂	+
010		rac-3-[4-(4-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C ₂₀ H ₂₀ N ₂ O ₅ S ₂	++
011		rac-3-[4-(4-(trifluoromethyl)phenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C ₂₀ H ₁₇ F ₃ N ₂ O ₄ S ₂	++
012		rac-3-[4-(m-tolylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide	C ₂₀ H ₂₀ N ₂ O ₄ S ₂	++
013		3-[(R)-4-(4-fluoro-3-methylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C ₂₀ H ₁₉ F N ₂ O ₄ S ₂	+

-continued

#	Structure	Substance Name	Molecular Formula	Activity
014		3-[(S)-4-(4-fluoro-3-methylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H19 F N2 O4 S2	+
015		rac-3-[4-(2-oxopyrrolidin-1-yl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C23 H23 N3 O5 S2	+
016		rac-3-[4-(cyclohexyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C19 H24 N2 O4 S2	+
017		rac-3-[4-(1,3-benzodioxol-5-yl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H18 N2 O6 S2	++
018		rac-3-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C21 H20 N2 O6 S2	+++

-continued

#	Structure	Substance Name	Molecular Formula	Activity
019		rac-3-[4-[4-(4-methoxyphenoxy)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C ₂₆ H ₂₄ N ₂ O ₆ S ₂	+
020		rac-3-[4-(3-fluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C ₁₉ H ₁₇ F N ₂ O ₄ S ₂	++
021		rac-3-[4-(3,4-difluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C ₁₉ H ₁₆ F ₂ N ₂ O ₄ S ₂	+
022		rac-3-[4-(4-fluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C ₁₉ H ₁₇ F N ₂ O ₄ S ₂	+
023		rac-3-[4-(4-methoxy-3-methylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C ₂₁ H ₂₂ N ₂ O ₅ S ₂	+

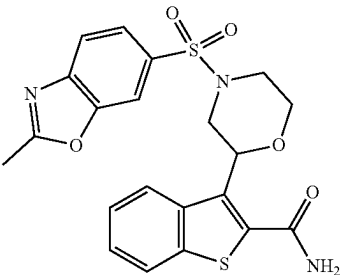
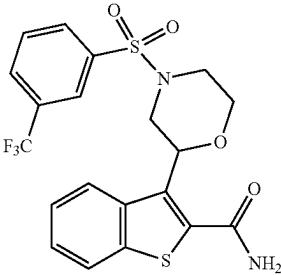
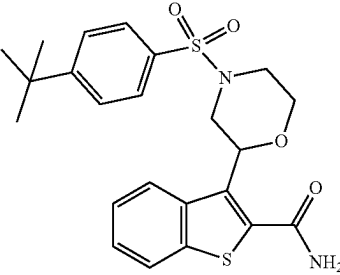
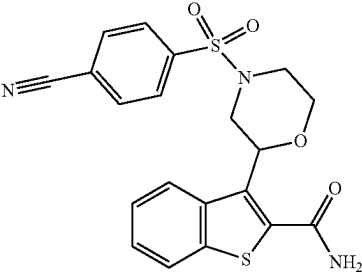
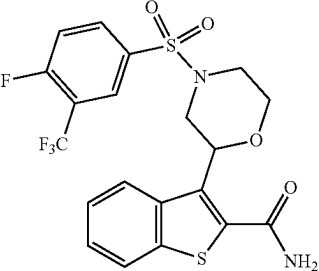
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#	Structure	Substance Name	Molecular Formula	Activity
024		rac-3-[4-[4-(4-pyridyloxy)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C24 H21 N3 O5 S2	+
025		rac-3-[4-(4-fluoro-3-methylphenyl)sulfonylmorpholin-2-yl]-N,N-dimethyl-benzothiophene-2-carboxamide	C22 H23 F N2 O4 S2	+
026		rac-3-[4-(3-fluoro-4-methylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H19 F N2 O4 S2	+++
027		rac-3-[4-(5-fluoro-2-methylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H19 F N2 O4 S2	+
028		rac-3-[4-(4-fluoro-3-methylphenyl)sulfonylmorpholin-2-yl]-N-methylbenzothiophene-2-carboxamide	C21 H21 F N2 O4 S2	+

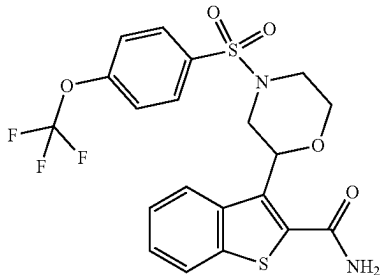
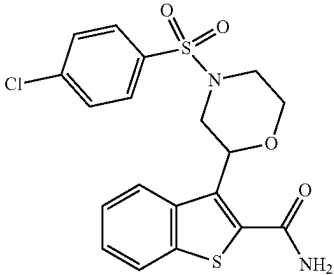
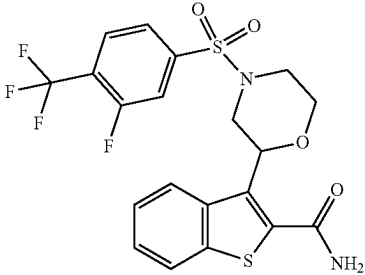
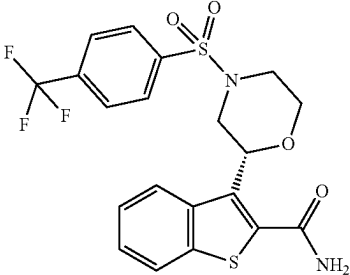
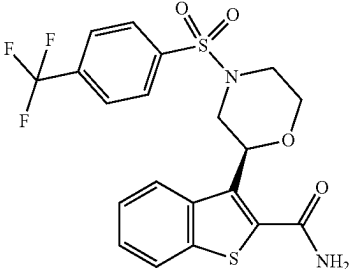
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#	Structure	Substance Name	Molecular Formula	Activity
029		rac-3-[4-(4-fluoro-3-methylphenyl)sulfonylmorpholin-2-yl]-N-(2-hydroxyethyl)benzothiophene-2-carboxamide	C22 H23 F N2 O5 S2	+
030		rac-N-ethyl-3-[4-(4-fluoro-3-methylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C22 H23 F N2 O4 S2	+
031		rac-3-[4-(4-fluoro-3-methylphenyl)sulfonylmorpholin-2-yl]-N-isopropylbenzothiophene-2-carboxamide	C23 H25 F N2 O4 S2	+
032		rac-3-[4-(2,4,6-trimethylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C22 H24 N2 O4 S2	+
033		rac-3-[4-(p-tolylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide	C20 H20 N2 O4 S2	+++

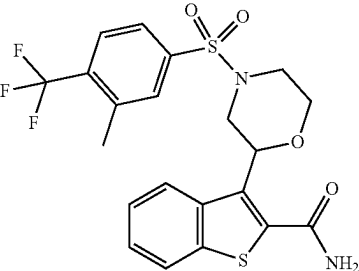
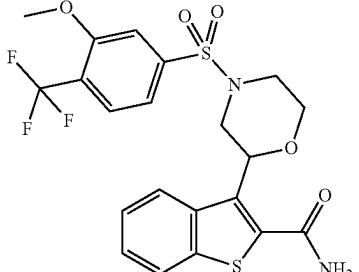
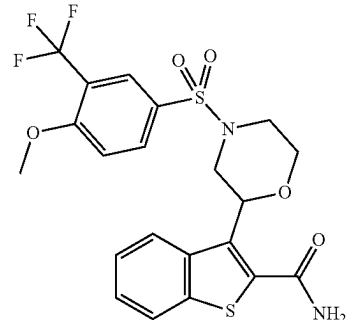
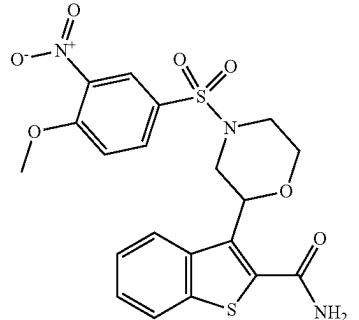
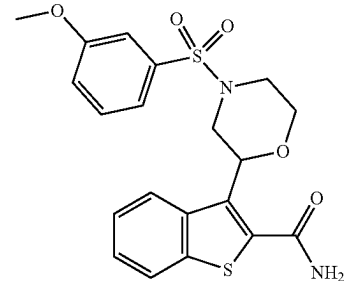
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#	Structure	Substance Name	Molecular Formula	Activity
034		rac-3-[4-[(2-methyl-1,3-benzoxazol-6-yl)sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide	C21 H19 N3 O5 S2	+++
035		rac-3-[4-[3-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H17 F3 N2 O4 S2	+++
036		rac-3-[4-(4-tert-butylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C23 H26 N2 O4 S2	+++
037		rac-3-[4-(4-cyanophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H17 N3 O4 S2	+
038		rac-3-[4-[4-fluoro-3-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H16 F4 N2 O4 S2	+

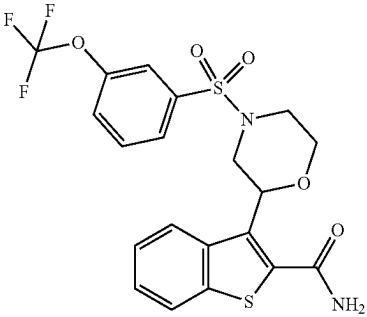
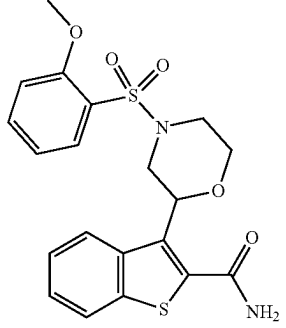
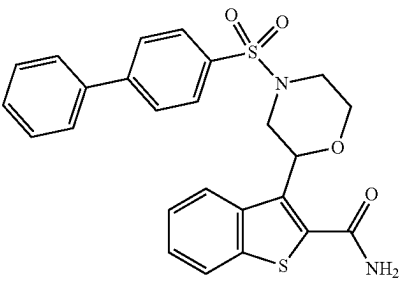
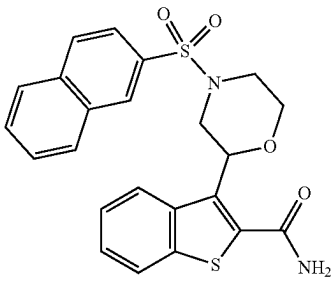
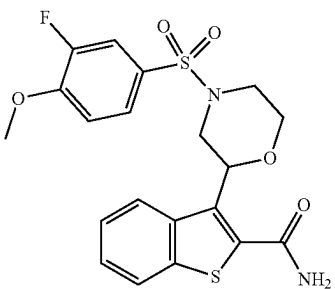
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#	Structure	Substance Name	Molecular Formula	Activity
039		rac-3-[4-[4-(trifluoromethoxy)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H17 F3 N2 O5 S2	+++
040		rac-3-[4-(4-chlorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C19 H17 Cl N2 O4 S2	++
041		rac-3-[4-[3-fluoro-4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H16 F4 N2 O4 S2	+++
042		3-[(R)-4-[4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H17 F3 N2 O4 S2	+
043		3-[(S)-4-[4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H17 F3 N2 O4 S2	+++

-continued

#	Structure	Substance Name	Molecular Formula	Activity
044		rac-3-[4-[3-methyl-4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C21 H19 F3 N2 O4 S2	++
045		rac-3-[4-[3-methoxy-4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C21 H19 F3 N2 O5 S2	++
046		rac-3-[4-[4-methoxy-3-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C21 H19 F3 N2 O5 S2	+++
047		rac-3-[4-(4-methoxy-3-nitrophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H19 N3 O7 S2	+
048		rac-3-[4-(3-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H20 N2 O5 S2	+

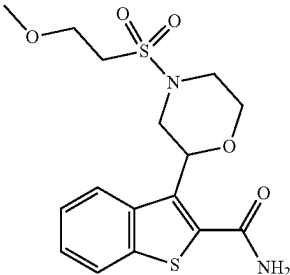
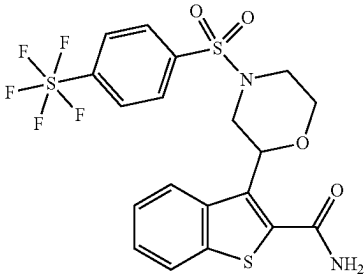
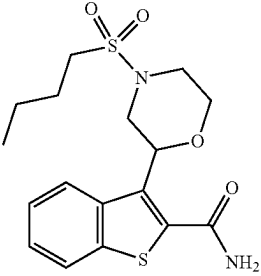
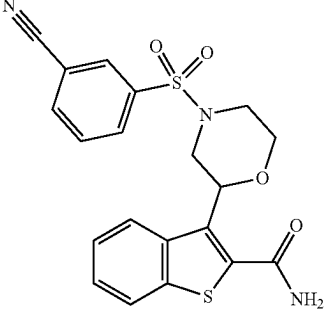
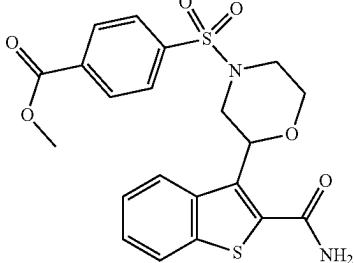
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#	Structure	Substance Name	Molecular Formula	Activity
049		rac-3-[4-(3-(trifluoromethoxy)phenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H17 F3 N2 O5 S2	+
050		rac-3-[4-(2-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H20 N2 O5 S2	+
051		rac-3-[4-(4-phenylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C25 H22 N2 O4 S2	+++
052		rac-3-[4-(2-naphthylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide	C23 H20 N2 O4 S2	+
053		rac-3-[4-(3-fluoro-4-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H19 F N2 O5 S2	+

-continued

#	Structure	Substance Name	Molecular Formula	Activity
054		rac-3-[4-(3,4-dimethoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C21 H22 N2 O6 S2	+
055		3-[(S)-4-[3-fluoro-4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H16 F4 N2 O4 S2	+
056		3-[(R)-4-[3-fluoro-4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H16 F4 N2 O4 S2	+++
057		rac-3-[4-[(4-methyl-2,3-dihydro-1,4-benzoxazin-7-yl)sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide	C22 H23 N3 O5 S2	+++
058		rac-3-[4-tetrahydropyran-4-ylsulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C18 H22 N2 O5 S2	+

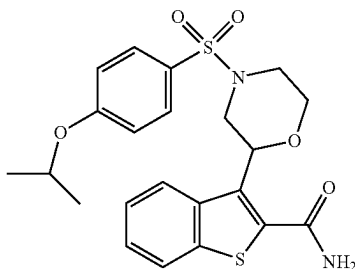
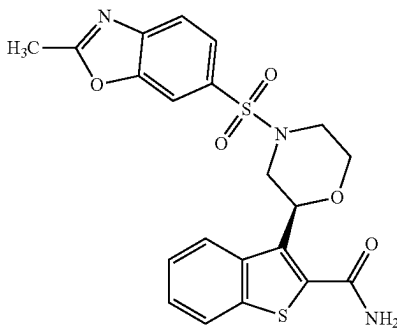
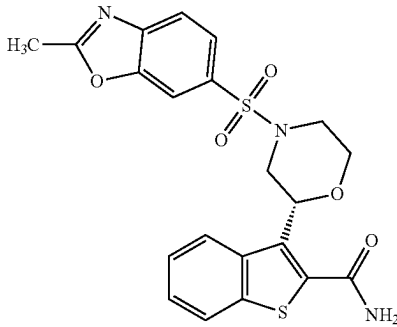
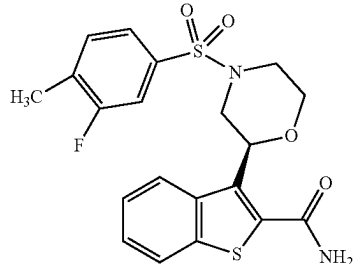
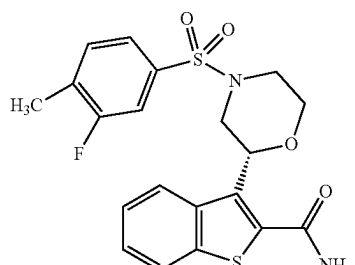
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#	Structure	Substance Name	Molecular Formula	Activity
059		rac-3-[4-(2-methoxyethylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide	C ₁₆ H ₂₀ N ₂ O ₅ S ₂	+
060		rac-3-[4-[4-(pentafluoro-lambda6-sulfonyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C ₁₉ H ₁₇ F ₅ N ₂ O ₄ S ₃	++
061		rac-3-[4-butylsulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C ₁₇ H ₂₂ N ₂ O ₄ S ₂	+
062		rac-3-[4-(3-cyanophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C ₂₀ H ₁₇ N ₃ O ₄ S ₂	+
063		rac-methyl 4-[2-(2-carbamoylbenzothiophen-3-yl)morpholin-4-yl]sulfonylbenzoate	C ₂₁ H ₂₀ N ₂ O ₆ S ₂	+

-continued

#	Structure	Substance Name	Molecular Formula	Activity
064		rac-tert-butyl 4-[2-(2-carbamoylbenzothiophen-3-yl)morpholin-4-yl]sulfonylpiperidine-1-carboxylate	C23 H31 N3 O6 S2	+
065		rac-3-[4-(4-nitrophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C19 H17 N3 O6 S2	+
066		rac-3-[4-[2-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H17 F3 N2 O4 S2	+
067		rac-3-[4-[2-(trifluoromethoxy)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H17 F3 N2 O5 S2	+
068		rac-3-[4-(4-hydroxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C19 H18 N2 O5 S2	+

-continued

#	Structure	Substance Name	Molecular Formula	Activity
069		rac-3-[4-(4-isopropoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C22 H24 N2 O5 S2	+++
070		3-[(S)-4-[(2-methyl-1,3-benzoxazol-6-yl)sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide	C21 H19 N3 O5 S2	+
071		3-[(R)-4-[(2-methyl-1,3-benzoxazol-6-yl)sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide	C21 H19 N3 O5 S2	+++
072		3-[(S)-4-(3-fluoro-4-methylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H19 F N2 O4 S2	+
073		3-[(R)-4-(3-fluoro-4-methylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H19 F N2 O4 S2	+++

-continued

#	Structure	Substance Name	Molecular Formula	Activity
074		rac-1,1-dioxo-3-[4-[3-fluoro-4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	C20 H16 F4 N2 O6 S2	+++
075		3-[4-(3,5-dimethyl-isoxazole-4-sulfonyl)-morpholin-2-yl]-benzo[b]thiophene-2-carboxylic acid methylamide	C19 H21 N3 O5 S2	+
076		3-[4-(1-methyl-1H-pyrazole-4-sulfonyl)-morpholin-2-yl]-benzo[b]thiophene-2-carboxylic acid isopropylamide	C20 H24 N4 O4 S2	+
078		3-[4-(cyclopentylsulfonyl)-2-morpholinyl]-N,N-dimethyl-1-benzothiophene-2-carboxamide	C20 H26 N2 O4 S2	+
079		3-[4-[(1,5-dimethyl-1H-pyrazol-4-yl)sulfonyl]-2-morpholinyl]-N,N-dimethyl-1-benzothiophene-2-carboxamide	C20 H24 N4 O4 S2	+

-continued

#	Structure	Substance Name	Molecular Formula	Activity
080		N-(2-hydroxyethyl)-3-[4-(phenylsulfonyl)-2-morpholinyl]-1-benzothiophene-2-carboxamide	C21 H22 N2 O5 S2	+
081		3-(4-cyclopentanesulfonyl-morpholin-2-yl)-benzo[b]thiophene-2-carboxylic acid methylamide	C19 H24 N2 O4 S2	+
082		3-{4-[(2-fluoro-5-methylphenyl)sulfonyl]-2-morpholinyl}-N-methyl-1-benzothiophene-2-carboxamide	C21 H21 F N2 O4 S2	
083		3-{4-[(3,5-dimethyl-1H-pyrazol-4-yl)sulfonyl]-2-morpholinyl}-N,N-dimethyl-1-benzothiophene-2-carboxamide	C20 H24 N4 O4 S2	+

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Transepithelial Electrical Conductance (TEEC)

FRT cells expressing F508del-CFTR were plated on HTS Transwell-24 well permeable supports (Code 3379, Corning Life Sciences) at a density of 200,000 cells/well. After six days, cells were incubated for 24 hrs with test correctors, vehicle, or VX-809. Compounds were dissolved in both basolateral (800 μ L) and apical (300 μ L) culture medium. After treatment, the culture medium was removed and replaced on both sides with a saline solution containing (in mM): 130 NaCl, 2.7 KCl, 1.5 KH_2PO_4 , 1 CaCl_2 , 0.5 MgCl_2 , 10 glucose, 10 Na-Hepes (pH 7.4). The basolateral and apical side received 800 μ L and 100 μ L, respectively. The 24-well tray with cells was placed on a block heater (SBH 130D, Stuart) to keep the temperature at 37° C. during the entire experiment. After 10 min, the basal transepithelial electrical resistance (TEER) across each layer of FRT cells was measured with a STX100C electrode pair connected to

an EVOM2 voltohmmeter (World Precision Instruments). To stimulate F508del-CFTR, each well received (apical side) 50 μ L of saline solution containing 60 μ M forskolin and 150 μ M genistein (final concentrations: 20 μ M forskolin, 50 μ M genistein). Forskolin was also pipetted in the basolateral medium to obtain the 20 μ M concentration. After 10 min TEER was measured again in each well. To block F508del-CFTR function, the inhibitor PPQ-102 was used at the final concentration of 30 μ M. To achieve the desired concentration, 75 μ L of the apical solution in each well was replaced with an equal volume of saline solution containing 20 μ M forskolin, 50 μ M genistein, and 60 μ M PPQ-102. After further 10 min, the transepithelial electrical resistance was measured. All values of TEER were converted to transepithelial electrical conductance (TEEC) using the formula $\text{TEEC}=1/\text{TEER}$. The parameter to indicate activity of F508del-CFTR in each well (ATEEC) was calculated from

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the difference in TEEC measured after maximal stimulation of F508del-CFTR with forskolin and genistein and after block with PPQ-102.

Corrector activities obtained on selected compounds tested at 5.0 μM (expressed as ΔTEEC values) are illustrated in Table 2, wherein+: $\Delta\text{TEEC}<2000\ \mu\text{S}$; ++: $2000\ \mu\text{S}<\Delta\text{TEEC}<3000\ \mu\text{S}$; +++: $\Delta\text{TEEC}>3000\ \mu\text{S}$.

TABLE 2

#	Substance Name	activity
001	rac-3-[4-(4-fluoro-3-methyl-benzenesulfonyl)-morpholin-2-yl]-benzo[b]thiophene-2-carboxylic acid amide	++
011	rac-3-[4-[4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	++
034	rac-3-[4-[(2-methyl-1,3-benzoxazol-6-yl)sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide	++
039	rac-3-[4-[4-(trifluoromethoxy)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	++
041	rac-3-[4-[3-fluoro-4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	+++
042	3-[(R) or (S)-4-[4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	+
043	3-[(S) or (R)-4-[4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	+++

Short-Circuit Current Recordings on Human Bronchial Epithelial Cells

Human bronchial epithelial (HBE) cells obtained from CF patients (F508del/F508del genotype) were plated on Snapwell inserts (Code 3801, Corning Life Sciences) at a density of 500,000 cells per insert. Cells were cultured for two weeks in a differentiating medium whose compositions has been previously described (Scudieri et al., J Physiol 590: 6141-6155, 2012). For the first week, the medium was kept on both apical and basolateral sides of inserts (submerged condition). For the second week, the apical medium was removed (air-liquid condition, ALC). To test the activity of correctors, cells were treated for 24 hrs with compounds dissolved in the basolateral medium. After treatment, Snapwell inserts carrying differentiated bronchial epithelia were mounted in a vertical chamber resembling an Ussing system with internal fluid circulation. Both apical and basolateral hemichambers were filled with 5 mL of a Krebs bicarbonate solution containing (in mM): 126 NaCl, 0.38 KH_2PO_4 , 2.13 K_2HPO_4 , 1 MgSO_4 , 1 CaCl_2 , 24 NaHCO_3 , and 10 glucose. Both sides were continuously bubbled with a gas mixture containing 5% CO_2 -95% air and the temperature of the solution was kept at 37° C. The transepithelial voltage was short-circuited with a voltage-clamp (DVC-1000, World Precision Instruments) connected to the apical and basolateral chambers via Ag/AgCl electrodes and agar bridges (1 M KCl in 1% agar). The offset between voltage electrodes and the fluid resistance were canceled before experiments. The short-circuit current was recorded with a PowerLab 4/25 (ADInstruments) analogical to digital converter connected to a Macintosh computer. During recordings, cells were sequentially treated with: amiloride (10 μM , apical side) to block Na^+ absorption through ENaC channel; CPT-cAMP (100 μM , apical and basolateral side) plus VX-770 (1 μM , apical side) to stimulate F508del-CFTR activity; CFTRinh-172 (10 μM , apical side) to fully inhibit F508del-CFTR. The

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difference between the current measured with CPT-cAMP plus potentiator and the current remaining after CFTRinh-172 treatment ($\Delta\text{I}_{\text{CFTR}}$) was taken as the parameter reflecting F508del-CFTR expression in the apical membrane.

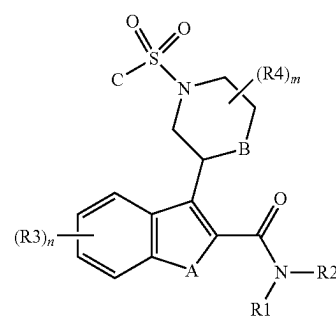
Activities of selected compounds on HBE cells (expressed as $\Delta\text{I}_{\text{CFTR}}$) are illustrated in Table 3 wherein+: $\Delta\text{I}_{\text{CFTR}}<2.0\ \mu\text{A}$; ++: $2.0\ \mu\text{A}<\Delta\text{I}_{\text{CFTR}}<3.0\ \mu\text{A}$; +++: $\Delta\text{I}_{\text{CFTR}}>3.0\ \mu\text{A}$.

TABLE 3

#	Substance Name	activity
001	rac-3-[4-(4-fluoro-3-methyl-benzenesulfonyl)-morpholin-2-yl]-benzo[b]thiophene-2-carboxylic acid amide	+
011	rac-3-[4-[4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	+++
013	3-[(R) or (S)-4-(4-fluoro-3-methyl-phenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	++
018	rac-3-[(4-(2,3-dihydro-1,4-benzodioxin-6-yl)sulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide	++
034	rac-3-[4-[(2-methyl-1,3-benzoxazol-6-yl)sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide	+++
041	rac-3-[4-[3-fluoro-4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	++
044	rac-3-[4-[3-methyl-4-(trifluoromethyl)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	++
071	3-[(R) or (S)-4-[(2-methyl-1,3-benzoxazol-6-yl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide	+++

The invention claimed is:

1. A compound of Formula (Ia):



(Ia)

or pharmaceutically acceptable salts, hydrates, solvates, clathrates, polymorphs, stereoisomers thereof wherein: R1 and R2 are independently selected from the group consisting of hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, and C_{1-4} alkyl-O- C_{1-4} alkyl; R3 is selected from the group consisting of hydrogen, C_{1-6} alkyl, halo C_{1-6} alkyl, OH, O- C_{1-6} alkyl, C_{1-6} alkyl-O- C_{1-6} alkyl, CN, NO_2 and halogen; R4 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halo C_{1-6} alkyl and halogen; A is selected from the group consisting of S, SO, and SO_2 ; B is selected from the group consisting of $\text{CR}^{\text{iv}}\text{R}^{\text{v}}$, O, and NR^{ii} ; C is selected from the group consisting of C_{1-6} alkyl, halo C_{1-6} alkyl, C_{3-6} cycloalkyl optionally substituted with one or more R5, C_{3-6} heterocycloalkyl optionally

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substituted with one or more R⁵, aryl optionally substituted with one or more R⁵, heteroaryl optionally substituted with one or more R⁵, C₁₋₆alkyl-O-C₁₋₆alkyl, C₁₋₆alkyl-O-aryl, C₁₋₆alkyl-O-heteroaryl, C₁₋₆alkyl-O-C₃₋₆heterocycloalkyl, aryl-O-aryl, and aryl-O-heteroaryl;

R⁵ is selected from the group consisting of C₁₋₆alkyl, haloC₁₋₆alkyl, O-C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocycloalkyl, aryl, heteroaryl, O-aryl, O-aryl-O-C₁₋₆alkyl, O-heteroaryl, O-C₃₋₆heterocycloalkyl, O-haloC₁₋₆alkyl, OH, CN, NO₂, SF₆, halogen and COORⁱ;

n is an integer comprised from 0 to 2;

m is an integer comprised from 0 to 2;

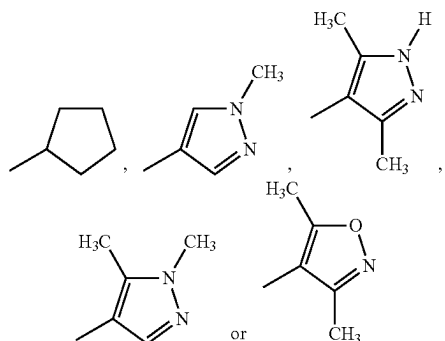
Rⁱ is independently selected from the group consisting of hydrogen and C₁₋₆alkyl;

Rⁱⁱ is independently selected from the group consisting of hydrogen and C₁₋₆alkyl;

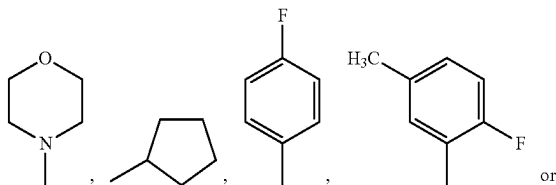
R^{iv} and R^v are independently selected from the group consisting of hydrogen, C₁₋₆alkyl and hydroxyC₁₋₆alkyl;

provided that:

a) when A is S, B is O, R¹ and R² are both CH₃, R³ and R⁴ are both hydrogen, C is not one of

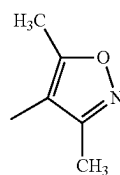


b) when A is S, B is O, R¹ and R² are respectively CH₃ and hydrogen, R³ and R⁴ are both hydrogen, C is not one of

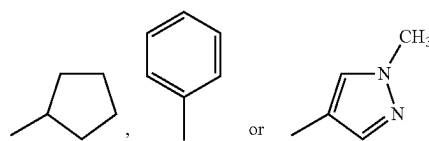


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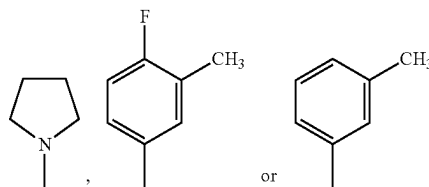
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c) when A is S, B is O, R¹ and R² are respectively isopropyl and hydrogen, R³ and R⁴ are both hydrogen, C is not one of



d) when A is S, B is O, R¹ and R² are both H, R³ and R⁴ are both hydrogen, C is not one of



e) when A is S, B is O, R¹ and R² are respectively hydrogen and CH₂CH₂OH, R³ and R⁴ are both hydrogen, C is not phenyl.

2. The compound according to claim 1, wherein B is O.

3. The compound according to claim 1, wherein R¹ and R² are hydrogen.

4. The compound according to claim 1, wherein R³ and R⁴ are hydrogen.

5. The compound according to claim 1, wherein A is selected from the group consisting of S and SO₂.

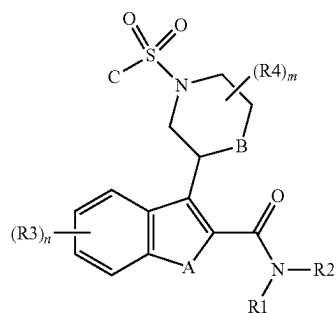
6. The compound according to claim 1, wherein the compound is selected from the group consisting of:

- | | |
|-----|--|
| 002 | rac-3-[4-(1,2-dimethylimidazol-4-yl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide |
| 003 | rac-3-[4-(benzenesulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide |
| 004 | rac-3-[4-(1H-imidazol-4-ylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide |
| 005 | rac-3-[4-(3-thienylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide |
| 006 | rac-3-[4-(4-phenoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide |
| 007 | rac-methyl 3-[2-(2-carbamoylbenzothiophen-3-yl)morpholin-4-yl] sulfonylbenzoate |
| 008 | rac-3-[4-(3,5-dimethylisoxazol-4-yl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide |
| 009 | rac-3-[4-(3-bromophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide |
| 010 | rac-3-[4-(4-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide |

011	rac-3-[4-[4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
012	rac-3-[4-(m-tolylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
015	rac-3-[4-[4-(2-oxopyrrolidin-1-yl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
016	rac-3-[4-cyclohexylsulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
017	rac-3-[4-(1,3-benzodioxol-5-ylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
018	rac-3-[(4-(2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
019	rac-3-[4-[4-(4-methoxyphenoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
020	rac-3-[4-(3-fluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
021	rac-3-[4-(3,4-difluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
022	rac-3-[4-(4-fluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
023	rac-3-[4-(4-methoxy-3-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
024	rac-3-[4-[4-(4-pyridyloxy)phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
025	rac-3-[4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]-N,N-dimethylbenzothiophene-2-carboxamide
026	rac-3-[4-(3-fluoro-4-methyl-phenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
027	rac-3-[4-(5-fluoro-2-methyl-phenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
028	rac-3-[4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]-N-methylbenzothiophene-2-carboxamide
029	rac-3-[4-(4-fluoro-3-methyl-phenyl)sulfonyl morpholin-2-yl]-N-(2-hydroxyethyl)benzothiophene-2-carboxamide
030	rac-N-ethyl-3-[4-(4-fluoro-3-methyl-phenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
031	rac-3-[4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]-N-isopropylbenzothiophene-2-carboxamide
032	rac-3-[4-(2,4,6-trimethylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
033	rac-3-[4-(p-tolylsulfonyl)morpholin-2-yl] benzothiophene-2-carboxamide
034	rac-3-[4-[(2-methyl-1,3-benzoxazol-6-yl) sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
035	rac-3-[4-[3-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
036	rac-3-[4-(4-tert-butylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
037	rac-3-[4-(4-cyanophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
038	rac-3-[4-[4-fluoro-3-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
039	rac-3-[4-[4-(trifluoromethoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
040	rac-3-[4-(4-chlorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
041	rac-3-[4-[3-fluoro-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
042	3-[(R)-4-[4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
043	3-[(S)-4-[4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
044	rac-3-[4-[3-methyl-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
045	rac-3-[4-[3-methoxy-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
046	rac-3-[4-[4-methoxy-3-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
047	rac-3-[4-(4-methoxy-3-nitro-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
048	rac-3-[4-(3-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
049	rac-3-[4-[3-(trifluoromethoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
050	rac-3-[4-(2-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
051	rac-3-[4-(4-phenylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
052	rac-3-[4-(2-naphthylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
053	rac-3-[4-(3-fluoro-4-methoxy-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide

054	rac-3-[4-(3,4-dimethoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
055	3-[(S)-4-[3-fluoro-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
056	3-[(R)-4-[3-fluoro-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
057	rac-3-[4-[(4-methyl-2,3-dihydro-1,4-benzoxazin-7-yl)sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
058	rac-3-[4-tetrahydropyran-4-ylsulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
059	rac-3-[4-(2-methoxyethylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
060	rac-3-[4-[4-(pentafluoro-lambda6-sulfanyl) phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
061	rac-3-[4-butylsulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
062	rac-3-[4-(3-cyanophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
063	rac-methyl 4-[2-(2-carbamoylbenzothiophen-3-yl)morpholin-4-yl]sulfonylbenzoate
064	rac-tert-butyl 4-[2-(2-carbamoylbenzothiophen-3-yl)morpholin-4-yl]sulfonylpiperidine-1-carboxylate
065	rac-3-[4-(4-nitrophenyl)sulfonylmorpholin-2-yl] benzothiophene-2-carboxamide
066	rac-3-[4-[2-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
067	rac-3-[4-[2-(trifluoromethoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
068	rac-3-[4-(4-hydroxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
069	rac-3-[4-(4-isopropoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
070	3-[(S)-4-[(2-methyl-1,3-benzoxazol-6-yl) sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
071	3-[(R)-4-[(2-methyl-1,3-benzoxazol-6-yl) sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
072	3-[(S)-4-(3-fluoro-4-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
073	3-[(R)-4-(3-fluoro-4-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
074	rac-1,1-dioxo-3-[4-[3-fluoro-4-(trifluoromethyl) phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide.

7. A pharmaceutical composition comprising a compound of formula (Ia):



or pharmaceutically acceptable salts, hydrates, solvates, clathrates, polymorphs, stereoisomers thereof wherein:

R1 and R2 are independently selected from the group consisting of hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, and C₁₋₄alkyl-O-C₁₋₄alkyl;

R3 is selected from the group consisting of hydrogen, C₁₋₆alkyl, haloC₁₋₆alkyl, OH, O-C₁₋₆alkyl, C₁₋₆alkyl-O-C₁₋₆alkyl, CN, NO₂ and halogen;

R4 is independently selected from the group consisting of hydrogen, C₁₋₆alkyl, haloC₁₋₆alkyl and halogen;

A is selected from the group consisting of S, SO, and SO₂;

B is selected from the group consisting of CR^{iv}R^v, O, and NRⁱⁱ;

C is selected from the group consisting of C₁₋₆alkyl, haloC₁₋₆alkyl, C₃₋₆cycloalkyl optionally substituted with one or more R5, C₃₋₆heterocycloalkyl optionally substituted with one or more R5, aryl optionally substituted with one or more R5, heteroaryl optionally substituted with one or more R5, C₁₋₆alkyl-O-C₁₋₆alkyl, C₁₋₆alkyl-O-aryl, C₁₋₆alkyl-O-heteroaryl, C₁₋₆alkyl-O-C₃₋₆heterocycloalkyl, aryl-O-aryl, and aryl-O-heteroaryl;

R5 is selected from the group consisting of C₁₋₆alkyl, haloC₁₋₆alkyl, O-C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocycloalkyl, aryl, heteroaryl, O-aryl, O-aryl-O-C₁₋₆alkyl, O-heteroaryl, O-C₃₋₆heterocycloalkyl, O-haloC₁₋₆alkyl, OH, CN, NO₂, SF₆, halogen and COORⁱ;

n is an integer comprised from 0 to 2;

m is an integer comprised from 0 to 2;

Rⁱ is independently selected from the group consisting of hydrogen and C₁₋₆alkyl;

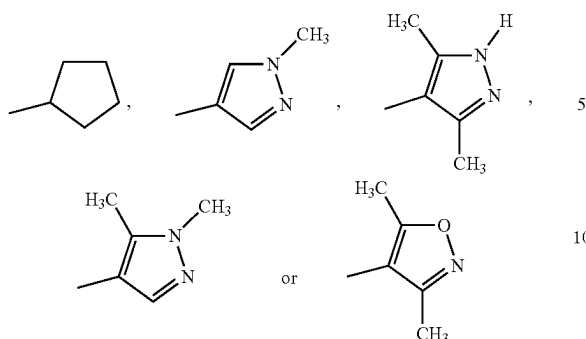
Rⁱⁱ is independently selected from the group consisting of hydrogen and C₁₋₆alkyl;

R^{iv} and R^v are independently selected from the group consisting of hydrogen, C₁₋₆alkyl and hydroxyC₁₋₆alkyl;

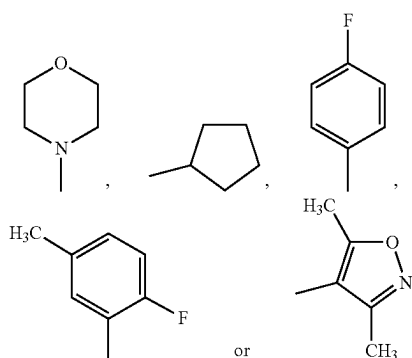
provided that:

a) when A is S, B is O, R1 and R2 are both CH₃, R3 and R4 are both hydrogen, C is not one of

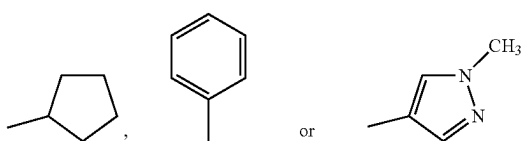
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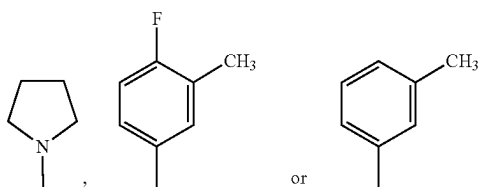
b) when A is S, B is O, R1 and R2 are respectively CH₃ and hydrogen, R3 and R4 are both hydrogen, C is not one of



c) when A is S, B is O, R1 and R2 are respectively isopropyl and hydrogen, R3 and R4 are both hydrogen, C is not one of



d) when A is S, B is O, R1 and R2 are both hydrogen, R3 and R4 are both hydrogen, C is not one of

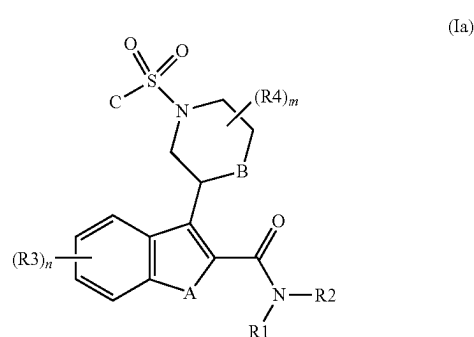


e) when A is S, B is O, R1 and R2 are respectively hydrogen and CH₂CH₂OH, R3 and R4 are both hydrogen, C is not phenyl;

and at least a pharmaceutically acceptable excipient.

8. A method for treating cystic fibrosis or modulating CFTR protein activities, the method comprising administering to a subject in need thereof a compound of formula (Ia)

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or pharmaceutically acceptable salts, hydrates, solvates, clathrates, polymorphs, stereoisomers thereof wherein:

R1 and R2 are independently selected from the group consisting of hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, and C₁₋₄alkyl-O-C₁₋₄alkyl;

R3 is selected from the group consisting of hydrogen, C₁₋₆alkyl, haloC₁₋₆alkyl, OH, O-C₁₋₆alkyl, C₁₋₆alkyl-O-C₁₋₆alkyl, CN, NO₂ and halogen;

R4 is independently selected from the group consisting of hydrogen, C₁₋₆alkyl, haloC₁₋₆alkyl and halogen;

A is selected from the group consisting of S, SO, and SO₂;

B is selected from the group consisting of CR^{iv}R^v, O, and NRⁱⁱ;

C is selected from the group consisting of C₁₋₆alkyl, haloC₁₋₆alkyl, C₃₋₆cycloalkyl optionally substituted with one or more R5, C₃₋₆heterocycloalkyl optionally substituted with one or more R5, aryl optionally substituted with one or more R5, heteroaryl optionally substituted with one or more R5, C₁₋₆alkyl-O-C₁₋₆alkyl, C₁₋₆alkyl-O-aryl, C₁₋₆alkyl-O-heteroaryl, C₁₋₆alkyl-O-C₃₋₆heterocycloalkyl, aryl-O-aryl, and aryl-O-heteroaryl;

R5 is selected from the group consisting of C₁₋₆alkyl, haloC₁₋₆alkyl, O-C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocycloalkyl, aryl, heteroaryl, O-aryl, O-aryl-O-C₁₋₆alkyl, O-heteroaryl, O-C₃₋₆heterocycloalkyl, O-haloC₁₋₆alkyl, OH, CN, NO₂, SF₆, halogen and COORⁱ;

n is an integer comprised from 0 to 2;

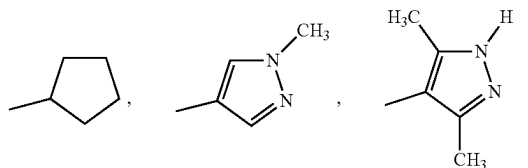
m is an integer comprised from 0 to 2;

Rⁱ is independently selected from the group consisting of hydrogen and C₁₋₆alkyl;

Rⁱⁱ is independently selected from the group consisting of hydrogen and C₁₋₆alkyl;

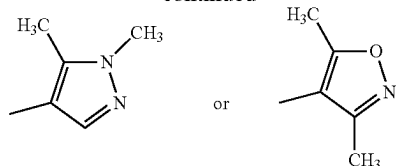
R^{iv} and R^v are independently selected from the group consisting of hydrogen, C₁₋₆alkyl and hydroxyC₁₋₆alkyl; provided that:

a) when A is S, B is O, R1 and R2 are both CH₃, R3 and R4 are both hydrogen, C is not one of

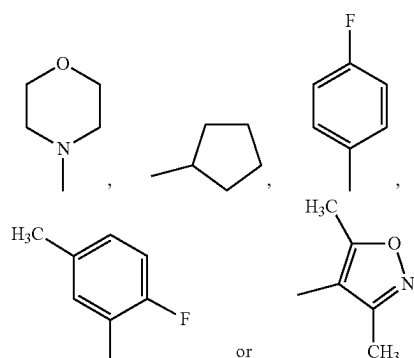


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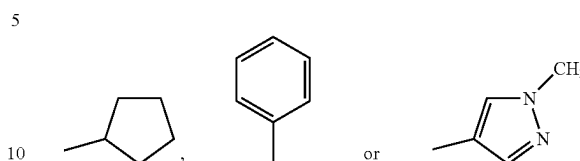


b) when A is S, B is O, R1 and R2 are respectively CH₃ and hydrogen, R3 and R4 are both hydrogen, C is not one of

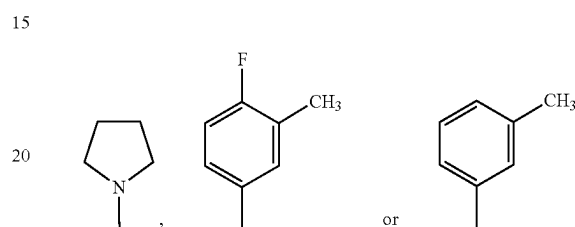


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c) when A is S, B is O, R1 and R2 are respectively isopropyl and hydrogen, R3 and R4 are both hydrogen, C is not one of



d) when A is S, B is O, R1 and R2 are both hydrogen, R3 and R4 are both hydrogen, C is not one of



e) when A is S, B is O, R1 and R2 are respectively hydrogen and CH₂CH₂OH, R3 and R4 are both hydrogen, C is not phenyl.

9. The method according to claim 8, wherein the compound is selected from the group consisting of:

- 001 rac-3-[4-(4-Fluoro-3-methyl-benzenesulfonyl)-morpholin-2-yl]-benzo[b]thiophene-2-carboxylic acid amide
- 002 rac-3-[4-(1,2-dimethylimidazol-4-yl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
- 003 rac-3-[4-(benzenesulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
- 004 rac-3-[4-(1H-imidazol-4-ylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
- 005 rac-3-[4-(3-thienylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
- 006 rac-3-[4-(4-phenoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
- 007 rac-methyl 3-[2-(2-carbamoylbenzothiophen-3-yl)morpholin-4-yl] sulfonylbenzoate
- 008 rac-3-[4-(3,5-dimethylisoxazol-4-yl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
- 009 rac-3-[4-(3-Bromophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
- 010 rac-3-[4-(4-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
- 011 rac-3-[4-[4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
- 012 rac-3-[4-(m-tolylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
- 013 3-[(R) or (S)-4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
- 014 3-[(S)-4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
- 015 rac-3-[4-[4-(2-oxopyrrolidin-1-yl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
- 016 rac-3-[4-cyclohexylsulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
- 017 rac-3-[4-(1,3-benzodioxol-5-ylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
- 018 rac-3-[(4-(2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
- 019 rac-3-[4-[4-(4-methoxyphenoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
- 020 rac-3-[4-(3-fluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
- 021 rac-3-[4-(3,4-difluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
- 022 rac-3-[4-(4-fluorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
- 023 rac-3-[4-(4-methoxy-3-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
- 024 rac-3-[4-[4-(4-pyridyloxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide

025	rac-3-[4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]-N,N-dimethyl-benzothiophene-2-carboxamide
026	rac-3-[4-(3-fluoro-4-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
027	rac-3-[4-(5-fluoro-2-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
028	rac-3-[4-(4-fluoro-3-methyl-phenyl)sulfonylmorpholin -2-yl]-N-methyl-benzothiophene-2-carboxamide
029	rac-3-[4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]-N-(2-hydroxyethyl) benzothiophene-2-carboxamide
030	rac-N-ethyl-3-[4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
031	rac-3-[4-(4-fluoro-3-methyl-phenyl) sulfonylmorpholin-2-yl]-N-isopropyl-benzothiophene-2-carboxamide
032	rac-3-[4-(2,4,6-trimethylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
033	rac-3-[4-(p-tolylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
034	rac-3-[4-[(2-methyl-1,3-benzoxazol-6-yl) sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
035	rac-3-[4-[3-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
036	rac-3-[4-(4-tert-butylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
037	rac-3-[4-(4-cyanophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
038	rac-3-[4-[4-fluoro-3-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
039	rac-3-[4-[4-(trifluoromethoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
040	rac-3-[4-(4-chlorophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
041	rac-3-[4-[3-fluoro-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
042	3-[(R)-4-[4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
043	3-[(S)-4-[4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
044	rac-3-[4-[3-methyl-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
045	rac-3-[4-[3-methoxy-4-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
046	rac-3-[4-[4-methoxy-3-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
047	rac-3-[4-(4-methoxy-3-nitro-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
048	rac-3-[4-(3-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
049	rac-3-[4-[3-(trifluoromethoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
050	rac-3-[4-(2-methoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
051	rac-3-[4-(4-phenylphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
052	rac-3-[4-(2-naphthylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
053	rac-3-[4-(3-fluoro-4-methoxy-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
054	rac-3-[4-(3,4-dimethoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
055	3-[(S)-4-[3-fluoro-4-(trifluoromethyl) phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
056	3-[(R)-4-[3-fluoro-4-(trifluoromethyl) phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
057	rac-3-[4-[(4-methyl-2,3-dihydro-1,4-benzoxazin-7-yl)sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
058	rac-3-[4-tetrahydropyran-4-ylsulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
059	rac-3-[4-(2-methoxyethylsulfonyl)morpholin-2-yl]benzothiophene-2-carboxamide
060	rac-3-[4-[4-(pentafluoro-lambda6-sulfanyl) phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
061	rac-3-[4-butylsulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
062	rac-3-[4-(3-cyanophenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
063	rac-methyl 4-[2-(2-carbamoylbenzothiophen-3-yl)morpholin-4-yl]sulfonylbenzoate
064	rac-tert-butyl 4-[2-(2-carbamoylbenzothiophen-3-yl)morpholin-4-yl]sulfonylpiperidine-1-carboxylate
065	rac-3-[4-(4-nitrophenyl)sulfonylmorpholin-2-yl] benzothiophene-2-carboxamide

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066	rac-3-[4-[2-(trifluoromethyl)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
067	rac-3-[4-[2-(trifluoromethoxy)phenyl] sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
068	rac-3-[4-(4-hydroxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
069	rac-3-[4-(4-isopropoxyphenyl)sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
070	3-[(S)-4-[(2-methyl-1,3-benzoxazol-6-yl) sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
071	3-[(R)-4-[(2-methyl-1,3-benzoxazol-6-yl) sulfonyl]morpholin-2-yl]benzothiophene-2-carboxamide
072	3-[(S)-4-(3-fluoro-4-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
073	3-[(R)-4-(3-fluoro-4-methyl-phenyl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
074	rac-1,1-dioxo-3-[4-[3-fluoro-4-(trifluoromethyl) phenyl]sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
075	3-[4-(3,5-dimethyl-isoxazole-4-sulfonyl)-morpholin-2-yl]-benzo[b]thiophene-2-carboxylic acid methylamide
076	3-[4-(1-methyl-1H-pyrazole-4-sulfonyl)-morpholin-2-yl]-benzo[b]thiophene-2-carboxylic acid isopropylamide
077	3-[4-(cyclopentylsulfonyl)-2-morpholinyl]-N-isopropyl-1-benzothiophene-2-carboxamide
078	3-[4-(cyclopentylsulfonyl)-2-morpholinyl]-N,N-dimethyl-1-benzothiophene-2-carboxamide
079	3-{4-[(1,5-dimethyl-1H-pyrazol-4-yl)sulfonyl]-2-morpholinyl}-N,N-dimethyl-1-benzothiophene-2-carboxamide
080	N-(2-hydroxyethyl)-3-[4-(phenylsulfonyl)-2-morpholinyl]-1-benzothiophene-2-carboxamide
081	3-(4-cyclopentanesulfonyl-morpholin-2-yl)-benzo[b]thiophene-2-carboxylic acid methylamide
082	3-{4-[(2-fluoro-5-methylphenyl)sulfonyl]-2-morpholinyl}-N-methyl-1-benzothiophene-2-carboxamide
083	3-{4-[(3,5-dimethyl-1H-pyrazol-4-yl)sulfonyl]-2-morpholinyl}-N,N-dimethyl-1-benzothiophene-2-carboxamide
084	3-(4-cyclopentylsulfonylmorpholin-2-yl)benzothiophene-2-carboxamide
085	N-methyl-3-(4-morpholinosulfonylmorpholin-2-yl)benzothiophene-2-carboxamide
087	3-[4-(benzenesulfonyl)morpholin-2-yl]-N-isopropyl-benzothiophene-2-carboxamide
088	3-[4-(4-fluorophenyl)sulfonylmorpholin-2-yl]-N-methyl-benzothiophene-2-carboxamide
089	N,N-dimethyl-3-[4-(1-methylpyrazol-4-yl) sulfonylmorpholin-2-yl]benzothiophene-2-carboxamide
	and
090	3-[4-(3,5-dimethylisoxazol-4-yl)sulfonylmorpholin-2-yl]-N,N-dimethyl-benzothiophene-2-carboxamide.

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