

NOVEL SULFONAMIDE TRPA1 RECEPTOR ANTAGONISTS

Field of the invention

The present invention concerns TRPA1 antagonists characterized by novel sulfonamide or cyclopropyl sulfonamide moieties and, when possible, pharmaceutically acceptable salts thereof along with the formulations containing them. The pharmaceutical compositions of the invention are useful in the treatment of pain, pulmonary diseases and other conditions ameliorated by the inhibition of the TRPA1 receptors.

Background of the invention

TRPA1 (ANKTM1, p120) is a *non*-selective cation channel that belongs to the Transient Receptor Potential (TRP) superfamily. TRPA1 was first identified as a transformation sensitive mRNA in cultured human lung fibroblasts (Jaquemar et al., *J. Bio. Chem.*, 1999, 274, 7325-7333). Subsequent studies indicated that TRPA1 is also highly expressed in sensory neurons of the dorsal root, trigeminal and nodose ganglia as well as in hair cells of the inner ear (Story et al., *Cell*, 2003, 112, 819-829; Corey et al., *Nature*, 2004, 432, 23730; Nagata et al., *J. Neurosci.*, 2005, 25, 4052-4061; Diogenes et al., *J. Dent. Res.*, 2007, 86, 550-555). In sensory neurons, TRPA1 expression is most abundant in small diameter neurons where it co-localizes with markers of peptidergic nociceptors such as TRPV1, CGRP and substance P (Story et al., *supra*; Bautista et al., *PNAS*, 2005, 102, 12248-12252; Nagata et al., *J. Neurosci.*, 2005, 25, 4052-4061; Diogenes et al., *J. Dent. Res.*, 2007, 86, 550-555).

The finding that TRPA1 is expressed in small diameter nociceptors has led to the suggestion that this channel may be involved in pain sensation. Indeed a number of additional observations support this suggestion. For example, TRPA1 expression is increased by inflammatory mediators such as NGF (Diogenes et al., *J. Dent. Res.*, 2007, 86, 550-555) and following nerve injury or inflammation (Obata et al., *J. Clin. Invest.*, 2005, 115, 2393-2401; Frederick et al., *Biochem. Biophys. Res. Commun.*, 2007, 358, 1058-1064). Bradykinin, a potent algogenic peptide released at sites of injury and

inflammation, activates TRPA1 *via* G-protein coupled BK2 receptors (Bandell et al., *Neuron*, 2004, 41, 849-857). In addition, TRPA1 is activated by a range of pungent or irritant compounds *per se* eliciting pain in animals and humans, such as mustard oil (AITC), cinnamaldehyde, acrolein, allicin, and formalin (Bandell et al., *supra*; Namer et al., *Neuroreport*, 2005, 16, 955-959; Bautista et al., *Cell*, 2006, 124, 1269-1282; Fujita et al., *Br. J. Pharmacol.*, 2007, 151, 153-160; McNamara et al., *PNAS*, 2007, 104, 13525-13530).

Finally, TRPA1 may also be activated by noxious cold (Bandell et al., *Neuron*, 2004, 41, 849-857; Jordt et al., *Nature*, 2004, 427, 260-265; Nagata et al., *J. Neurosci.*, 2005, 25, 4052-4061) and the intra-theal administration of TRPA1 anti-sense oligodeoxynucleotide suppresses inflammation as well as nerve injury, induced cold allodynia (Obata et al., *J. Clin. Invest.*, 2005, 115, 2393-2401). Likewise, mustard oil and bradykinin-induced acute pain and hyperalgesia is abolished in TRPA1^{-/-} mice (Bautista et al., *supra*; Kwan et al., *Neuron*, 2006, 50, 277-289).

TRPA1 receptors also play a role in airway disorders. Treatment with cigarette smoke extracts (CSE) increases Ca²⁺ influx in TRPA1-transfected cells, and promotes neuropeptide release from isolated guinea pig airway tissue. Furthermore, the effect of CSE on Ca²⁺ influx in dorsal root ganglion neurons is abolished in TRPA1-deficient mice. These data suggest a role for TRPA1 in the pathogenesis of CSE-induced diseases such as chronic obstructive pulmonary disease (COPD) (Andre et al., *J. Clin. Invest.*, 2008, 118, 2574-2582).

Recent data highlighted the TRPA1 channel role in inflammation and bronchial hyperactivity in a murine asthma model. Other studies provided evidence that inhalation of TRPA1 stimulants elicited cough reflex in guinea pigs and human volunteers. (Facchinetti et Patacchini, *The Open Drug Discovery J.* 2010, 2, 71-80). TRPA1 antagonists could emerge as novel drugs for treatment of COPD, asthma and chronic cough.

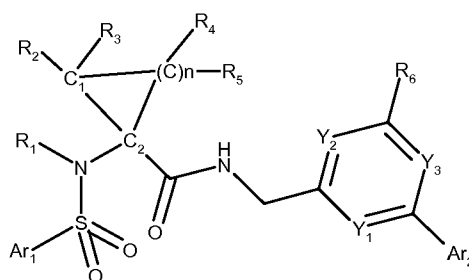
TRPA1 is found also in bladder and urethra urothelium, epithelium and nerve

fibers of the urothelium, sub-urothelial space, muscle layers and around blood vessels (Du et al., *Urology*, 2008, 72, 450-455; Andrade et al., *Biochem. Pharmacol.*, 2006, 72, 104-114; Gratzke et al., *Eur. Urology*, 2008, Apr 30 e-pub; Streng et al., *Eur. Urology*, 2008, 53, 391-400). TRPA1 expression is increased in bladder mucosa from patients with
 5 bladder outlet obstruction (Du et al., *Urology*, 2008, 72, 450-455). Activation of TRPA1 increases micturition frequency and reduces voiding volume (Streng et al., *supra*).

Activation of TRPA1 in the bladder by reactive metabolites of cyclophosphamide (e.g., acrolein) may be responsible for cystitis that sometimes accompanies the use of chemotherapeutic agents (Bautista et al., *supra*). TRPA1 is also expressed in colonic
 10 afferents, is upregulated following induction of experimental colitis, and TRPA1 antisense oligonucleotides suppresses colitis-induced hyperalgesia to colonic distension (Yang et al., *Neurosci Lett.*, 2008, 440, 237-241). These data suggest a role for TRPA1 in the pathogenesis of visceral pain and dysfunction, such as bladder instability, urinary incontinence, cystitis and colitis.

15 Description of the invention

The present invention relates to TRPA1 inhibitors of formula **(I)**



(I)

wherein:

20

Ar₁ is:

- i) phenyl substituted with 0, 1, 2 or 3 substituents R_a; or
- ii) a 5- or 6-membered monocyclic aromatic heterocycle ring optionally substituted with one or two substituents R_a; where each R_a is independently halo, -C₁-

₄alkyl, -OC₁₋₄alkyl, -CN, -CF₃, -OCF₃, -NO₂, -C(O)C₁₋₄alkyl or -CO₂H;

Ar₂ is:

i) phenyl substituted with 0, 1, 2 or 3 substituents R_b; where each R_b is independently halo, -C₁₋₄alkyl, -C(O)NR_cR_d, -OC₁₋₄alkyl, -OC₀₋₄alkylCF₃, -CN, -CF₃,
 5 -OCF₂H, -NO₂, -NR_cR_d, -S(O)₀₋₂C₁₋₄alkyl, -C(O)C₁₋₄alkyl, S(O)(O)NH₂, -(CH₂)₀₋₂-morpholinyl, piperidin-1-yl, piperazinyl, said piperazinyl being optionally substituted with a methyl, or two R_b substituents on adjacent carbon atoms taken together form -O(CH₂)₁₋₂O-;

ii) pyridyl substituted with 0, 1 or 2 substituents R_c; where each R_c is
 10 independently selected from halo, -C₁₋₄alkyl, -OC₁₋₄alkyl, -CF₃, -NR_cR_d or 4-morpholinyl;
 or

iii) a bicyclic 9-11-membered aromatic heterocycle optionally substituted with 1 substituent R_f; where R_f is -C₁₋₄alkyl;

R_c and R_d are each independently selected from H or -C₁₋₄alkyl;

15 R₁ is H, C₁₋₄alkyl-O-C₁₋₄alkyl, or C₁₋₄alkyl optionally substituted with halo;

R₂, R₃, R₄, and R₅ are each independently H, halo or -C₁₋₄alkyl;

n is 0 or 1 providing that when n is 1 the bond between C1 and C2 is single and when n is 0 the bond between C1 and C2 is double;

each Y₁, Y₂ and Y₃ is independently CH or N;

20 R₆ is

i) H, -C₁₋₄alkyl, -CF₃, -OR_z or -NR_hR_i;

where R_h is selected from

a) H, -C₀₋₄alkylCF₃, -C₁₋₄alkyl-N(CH₃)₂, saturated C₃₋₇cycloalkyl or -C₁₋₄alkyl-monocyclic heteroaryl ring;

25 b) -C₁₋₅alkyl optionally substituted with OH;

c) -C₁₋₄alkyl-heterocycloalkyl, said heterocycloalkyl being optionally substituted with -C₁₋₄alkyl; or

d) -C₀₋₄alkyl-phenyl, said phenyl being optionally substituted with one or two R_j

moieties; where each R_j is independently halo, $-\text{OC}_{1-4}\text{alkyl}$,

R_Z is $-\text{C}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkylCF}_3$ or $-\text{C}_{1-4}\text{alkyl-heterocycloalkyl}$;

ii) 1-pyrrolidinyl optionally substituted with a moiety selected from the group consisting of $-\text{NR}_k\text{R}_i$ and $-\text{C}_{1-4}\text{alkyl}$, said $-\text{C}_{1-4}\text{alkyl}$ being optionally substituted with $-\text{OH}$;

5 iii) 1-piperidinyl optionally substituted with $-\text{C}_{1-4}\text{alkyl}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$ or $-\text{C}_{0-4}\text{alkyl-phenyl}$;

iv) piperazinyl optionally substituted with $-\text{C}_{1-5}\text{alkyl}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{C}_{0-4}\text{alkylpyridyl}$, $-\text{C}_{0-4}\text{alkyl-1-methyl-piperidin-4-yl}$, $-\text{C}_{0-4}\text{alkylNR}_k\text{R}_i$ or $-\text{C}_{0-4}\text{alkyl-phenyl}$, said phenyl optionally substituted with one or two R_T substituents; where each R_T
10 substituent is selected from the group consisting of halo, $-\text{OCF}_3$, $-\text{C}_{1-4}\text{alkyl}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$, $-\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$ and $-\text{C}_{0-4}\text{alkylNR}_k\text{R}_i$, or two R_T substituents on adjacent carbon atoms taken together form $-\text{O}(\text{CH}_2)_{1-2}\text{O}-$;

v) phenyl optionally substituted with halo, $-\text{CF}_3$, $-\text{OCF}_3$;

vi) pyridyl;

15 vii) morpholin-yl;

R_k is H, $-\text{C}_{1-4}\text{alkyl}$ or $-\text{C}(\text{O})_{1-2}\text{C}_{1-4}\text{alkyl}$;

R_i is H or $\text{C}_{1-4}\text{alkyl}$.

When one asymmetrical carbon is present in a compound of the formula (I), such a compound may exist in optically active form or in the form of mixtures of optical
20 isomers, e. g. in the form of racemic mixtures. The present invention refers to all optical isomers and their mixtures, including the racemic mixtures.

In a further aspect of the present invention, compounds of formula I bearing a basic nitrogen may be prepared in the form of a pharmaceutically acceptable salt, especially an acid addition salt.

25 For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this

invention include addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, nitric acid, maleic acid, citric acid, tartaric acid, phosphoric acid, p-toluenesulfonic acid, benzenesulfonic acid.

- 5 Preferred pharmaceutically salts of the compounds of the present invention are those with the inorganic acids.

The salts may be formed by conventional means, such as by reacting the free base form of the suitable compounds of formula I with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble or in a solvent such
10 as water which is removed under vacuum.

The present invention also includes within its scope N-oxide of the compounds of formula I above. In general, such N-oxides may be formed on any available nitrogen atom. The N-oxides may be formed by conventional means, such as reacting the compound of formula I with peroxides in suitable solvents. The present invention
15 includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985. A prodrug may be a
20 pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation in vivo may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric
25 or sulfate ester, or reduction or oxidation of a susceptible functionality.

Examples of 5- or 6-membered monocyclic aromatic heterocycle rings are furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, thiadiazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazine.

Examples of a bicyclic 9-11-membered aromatic heterocycles are benzothiazole, benzoisothiazole, benzoxazole, benzoisoxazole, benzimidazole, benzotriazole, benzothiadiazaole, benzooxadiazole, quinoline, isoquinoline, naphthylidine, quinoxaline, phthalazine, cinnoline, indole, indazole, imidazopyridine, benzothiophene, benzofuran, dihydrobenzofuran, benzazepine, benzodiazepine.

Examples of -C₁₋₄alkyl-monocyclic heteroaryl rings are C₁₋₄alkylsubstituted furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, thiadiazole, pyridine, pyrazine, pyrimidine, pyridazine,

Examples of -C₁₋₄alkyl-heterocycloalkyls are C₁₋₄alkylsubstituted tetrahydrofuran, pyran.

In one embodiment each Y₁, Y₂ are CH and Y₃ is N.

In another embodiment each Y₁, Y₂ and Y₃ are CH.

In certain embodiments each Y₁, Y₂ and Y₃ are as above defined and

Ar₁ is:

i) phenyl substituted with one substituent R_a; where R_a is halo, preferably -Cl or -F, or -C₁₋₄alkyl, preferably methyl;

ii) a thienyl ring optionally substituted with one substituents R_a: where R_a is halo, preferably -Cl;

Ar₂ is:

i) phenyl substituted with 1 substituent R_b; where R_b is -OC₀₋₄alkylCF₃, preferably OCF₃, or R_b is -CF₃;

R₁ is H or C₁₋₄ alkyl optionally substituted with halo, preferably H, methyl or ethyl;

R₂, R₃, R₄, and R₅ are each independently H, or -C₁₋₄alkyl, preferably H or methyl;

R₆ is:

i) H;

ii) 1-pyrrolidinyl;

iii) phenyl optionally substituted with -CF₃ or -OCF₃;

iv) morpholin-yl.

Examples of compounds of Formula I are:

- 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 2-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 5 2-[(4-fluorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 10 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 2-(methyl(p-tolylsulfonyl)amino)-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]-methyl]prop-2-enamide;
- 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 15 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]-phenyl]-methyl]prop-2-enamide;
- 2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]-phenyl]methyl]prop-2-enamide;
- 20 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]-phenyl]methyl]prop-2-enamide;
- 2-[(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]-phenyl]methyl]prop-2-enamide;
- 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 25 2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-

- (trifluoromethyl)phenyl]-4-pyridyl)methyl]prop-2-enamide;
2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]prop-2-enamide;
2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]prop-2-enamide;
5 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]prop-2-enamide;
2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]prop-2-enamide;
10 N-[[2,6-bis[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]-2-[(4-chlorophenyl)-sulfonyl-ethyl-amino]prop-2-enamide;
N-[[2,6-bis[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]-2-[(4-chlorophenyl)-sulfonyl-methyl-amino]prop-2-enamide;
(Z)-2-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethoxy)-phenyl]-4-pyridyl)methyl]but-2-enamide;
15 (Z)-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]but-2-enamide;
(Z)-2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethyl)-phenyl]-phenyl)methyl]but-2-enamide;
20 (Z)-2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]-phenyl)methyl]but-2-enamide;
1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
25 1-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)-phenyl]-4-

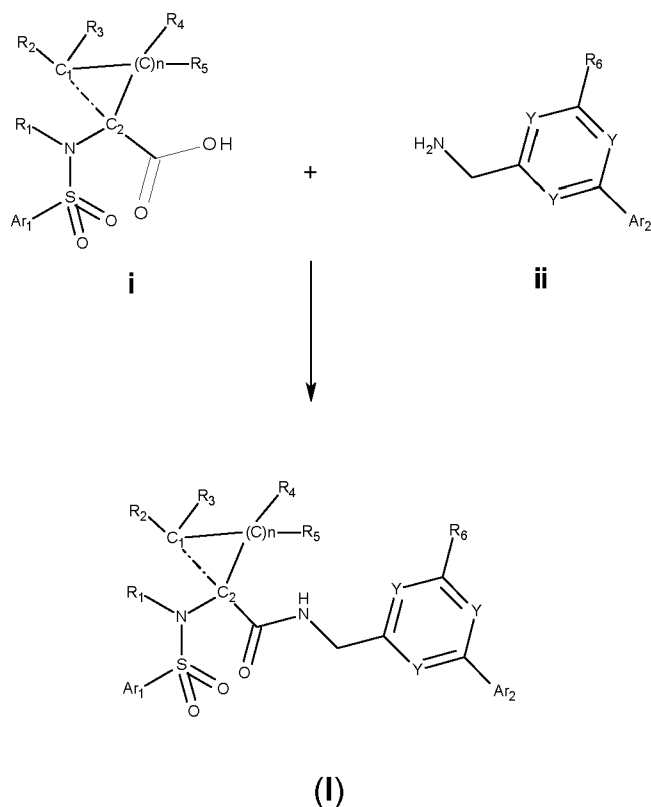
- pyridyl)methyl]cyclopropanecarboxamide;
1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]-
phenyl)methyl]cyclopropanecarboxamide;
1-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]-
5 phenyl)methyl]cyclopropanecarboxamide;
1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]-
phenyl)methyl]cyclopropanecarboxamide;
1-[(4-fluorophenyl)sulfonylamino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)-phenyl]-
4-pyridyl)methyl]cyclopropanecarboxamide;
10 1-[(4-fluorophenyl)sulfonylamino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-
4-pyridyl)methyl]cyclopropanecarboxamide;
1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-
(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
2-[(3,4-difluorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-
15 pyridyl)methyl]prop-2-enamide;
2-[(3-difluorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-
pyridyl)methyl]prop-2-enamide;
N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]-2-[ethyl-(4-
fluorophenyl)sulfonyl-amino]prop-2-enamide;
20 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-
(trifluoromethyl)phenyl]-4-pyridyl)methyl]prop-2-enamide;
2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-dimethylamino-6-[4-
(trifluoromethyl)phenyl]-4-pyridyl)methyl]prop-2-enamide;
2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-
25 4-pyridyl)methyl]prop-2-enamide;
N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]-2-(ethyl(2-
thienylsulfonyl)amino)prop-2-enamide;
2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-morpholino-6-[4-

- (trifluoromethyl)phenyl]-4-pyridyl)methyl]prop-2-enamide;
2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]prop-2-enamide;
2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-isopropoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]prop-2-enamide;
5 N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide;
1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
10 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl)methyl]cyclopropanecarboxamide;
1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-isopropoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
15 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
20 N-[[2-ethoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide;
1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-ethoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[1-oxido-2-[4-(trifluoromethyl)phenyl]pyridin-1-ium-4-yl)methyl]prop-2-enamide;
25 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl)methyl]prop-2-enamide;
2-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-

- pyridyl)methyl]prop-2-enamide;
- 1-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl)methyl]cyclopropanecarboxamide;
- 1-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl)methyl]cyclopropanecarboxamide;
- 5 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl)methyl]cyclopropanecarboxamide;
- 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl)methyl]cyclopropanecarboxamide;
- 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[4-[4-(trifluoromethyl)phenyl]-2-pyridyl)methyl]cyclopropanecarboxamide;
- 10 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
- 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
- N-[[2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]prop-2-enamide;
- 15 N-[[2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide;
- 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
- 20 N-[[2-(4-cyclohexylpiperazin-1-yl)-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide;
- 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-(4-cyclohexylpiperazin-1-yl)-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide.

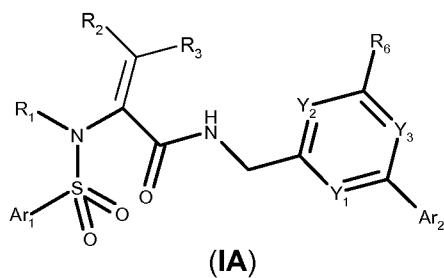
Compounds of Formula **(I)** are amides that can be prepared by standard procedures, by the reaction of a compound of general formula **i** with the corresponding amine **ii** in the presence of an acidic function activator, preferably diethyl cyanophosphonate DEPC as illustrated in the following Scheme 1.

Scheme 1



According to a first preferred embodiment, the invention relates to compounds of formula **(IA)**

5



wherein:

Ar₁ is:

- i) phenyl substituted with 0, 1, 2 or 3 substituents R_a; or
- ii) a 5-6-membered monocyclic aromatic heterocycle ring optionally substituted with one or two substituents R_a; where each R_a is independently halo, -C₁₋₄alkyl, -OC₁₋₄alkyl, -CN, -CF₃, -OCF₃, -NO₂, -C(O)C₁₋₄alkyl or -CO₂H;

Ar₂ is:

i) phenyl substituted with 0, 1, 2 or 3 substituents R_b ; where each R_b is independently halo, $-C_{1-4}alkyl$, $-C(O)NR_cR_d$, $-OC_{1-4}alkyl$, $-OC_{0-4}alkylCF_3$, $-CN$, $-CF_3$, $-CF_2H$, $-NO_2$, $-NR_cR_d$, $-S(O)_{0-2}C_{1-4}alkyl$, $-C(O)C_{1-4}alkyl$, $S(O)(O)NH_2$, $-(CH_2)_{0-2}$ -morpholinyl, piperidin-1-yl, piperazinyl, said piperazinyl optionally substituted with a methyl, or two R_b substituents on adjacent carbon atoms taken together form $-O(CH_2)_{1-2}O-$;

ii) pyridyl substituted with 0, 1 or 2 substituents R_e ; where each R_e is independently selected from halo, $-C_{1-4}alkyl$, $-OC_{1-4}alkyl$, $-CF_3$, $-NR_cR_d$ or 4-morpholinyl; or

10 iii) a bicyclic 9-11-membered aromatic heterocycle optionally substituted with 1 substituent R_f ; where R_f is $-C_{1-4}alkyl$;

R_c and R_d are each independently selected from H or $-C_{1-4}alkyl$;

R_1 is H, $C_{1-4}alkyl-O-C_{1-4}alkyl$, or $C_{1-4}alkyl$ optionally substituted with halo;

R_2 and R_3 are each independently H, halo or $-C_{1-4}alkyl$;

15 each Y_1 , Y_2 and Y_3 is independently CH or N;

R_6 is

i) H, $-C_{1-4}alkyl$, $-CF_3$, $-OR_z$ or $-NR_hR_i$;

where R_h is selected from

20 a) H, $-C_{0-4}alkylCF_3$, $-C_{1-4}alkyl-N(CH_3)_2$, saturated $C_{3-7}cycloalkyl$ or $-C_{1-4}alkyl$ -monocyclic heteroaryl ring;

b) $-C_{1-5}alkyl$ optionally substituted with OH;

c) $-C_{1-4}alkyl$ -heterocycloalkyl, said heterocycloalkyl being optionally substituted with $-C_{1-4}alkyl$; or

25 d) $-C_{0-4}alkyl$ -phenyl, said phenyl optionally substituted with one or two R_j moieties; where each R_j is independently halo, $-OC_{1-4}alkyl$,

R_z is $-C_{1-4}alkyl$, $-C_{1-4}alkylCF_3$ or $-C_{1-4}alkyl$ -heterocycloalkyl;

ii) 1-pyrrolidinyl optionally substituted with a moiety selected from the group consisting of $-NR_kR_i$ and $-C_{1-4}alkyl$, said $-C_{1-4}alkyl$ optionally substituted with $-OH$;

iii) 1-piperidinyl optionally substituted with $-C_{1-4}$ alkyl, $-C(O)NH_2$, $-CO_2C_{1-4}$ alkyl or $-C_{0-4}$ alkyl-phenyl;

iv) piperazinyl optionally substituted with $-C_{1-5}$ alkyl, $-OC_{1-4}$ alkyl, $-C_{0-4}$ alkylpyridyl, $-C_{0-4}$ alkyl-1-methyl-piperidin-4-yl, $-C_{0-4}$ alkylNR_kR_i or $-C_{0-4}$ alkyl-phenyl, said phenyl optionally substituted with one or two R_T substituents; where each R_T substituent is selected from the group consisting of halo, $-OCF_3$, $-C_{1-4}$ alkyl, $-OC_{1-4}$ alkyl, $-CO_2C_{1-4}$ alkyl, $-C(O)C_{1-4}$ alkyl and $-C_{0-4}$ alkylNR_kR_i, or two R_T substituents on adjacent carbon atoms taken together form $-O(CH_2)_{1-2}O-$;

v) phenyl optionally substituted with halo, $-CF_3$, $-OCF_3$;

vi) pyridyl;

vii) morpholin-yl;

R_k is H, $-C_{1-4}$ alkyl or $-C(O)_{1-2}C_{1-4}$ alkyl;

R_i is H or C_{1-4} alkyl.

In one embodiment, in the compounds of formula (IA) each Y₁, Y₂ are CH and Y₃ is N.

In another embodiment in the compounds of formula (IA) each Y₁, Y₂ and Y₃ are CH In certain embodiments in the compounds of formula (IA) each Y₁, Y₂ and Y₃ are as above defined and

Ar₁ is:

i) phenyl substituted with one substituent R_a; where R_a is halo, preferably -Cl or -F, or $-C_{1-4}$ alkyl, preferably methyl;

ii) a thienyl ring optionally substituted with one substituents R_a; where R_a is halo, preferably -Cl;

Ar₂ is:

i) phenyl substituted with 1 substituent R_b; where R_b is $-OC_{0-4}$ alkylCF₃, preferably OCF₃, or R_b is $-CF_3$;

R₁ is H or C_{1-4} alkyl optionally substituted with halo, preferably H, methyl or ethyl;

R₂, R₃, R₄, and R₅ are each independently H, or $-C_{1-4}$ alkyl, preferably H or methyl;

R₆ is:

- i) H;
- ii) 1-pyrrolidinyl;
- iii) phenyl optionally substituted with -CF₃ or -OCF₃;
- 5 iv) morpholin-yl.

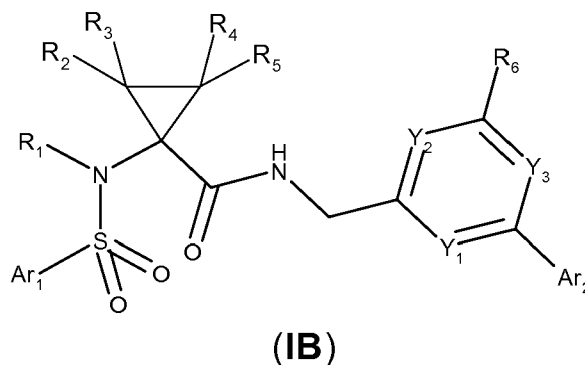
Examples of compounds of formula (IA) are:

- 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide
- 2-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 10 2-[(4-fluorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 15 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 2-(methyl(p-tolylsulfonyl)amino)-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]-methyl]prop-2-enamide;
- 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)-phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 20 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]-phenyl]-methyl]prop-2-enamide;
- 2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]-phenyl]methyl]prop-2-enamide;
- 25 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]-phenyl]methyl]prop-2-enamide;
- 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]-phenyl]methyl]prop-2-enamide

- 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide
- 2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 5 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide
- 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide
- 2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 10 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 15 N-[[2,6-bis[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-2-[(4-chlorophenyl)-sulfonyl-ethyl-amino]prop-2-enamide;
- N-[[2,6-bis[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]-2-[(4-chlorophenyl)-sulfonyl-methyl-amino]prop-2-enamide;
- (Z)-2-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethoxy)-phenyl]-4-pyridyl]methyl]but-2-enamide;
- 20 (Z)-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]but-2-enamide;
- (Z)-2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethyl)-phenyl]phenyl]methyl]but-2-enamide;
- 25 (Z)-2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]but-2-enamide;
- 2-[(3,4-difluorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;

- 2-[(3-difluorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]prop-2-enamide;
- 5 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 10 4-pyridyl]methyl]prop-2-enamide;
- N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-2-(ethyl(2-thienylsulfonyl)amino)prop-2-enamide;
- 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 15 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-isopropoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[1-oxido-2-[4-(trifluoromethyl)phenyl]pyridin-1-ium-4-yl]methyl]prop-2-enamide;
- 20 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl]methyl]prop-2-enamide;
- 2-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
- 25 N-[[2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]prop-2-enamide.

According to a second preferred embodiment, the invention relates to compounds of formula **(IB)**



wherein:

Ar₁ is:

- 5 i) phenyl substituted with 0, 1, 2 or 3 substituents R_a; or
- ii) a 5- or 6-membered monocyclic aromatic heterocycle ring optionally substituted with one or two substituents R_a; where each R_a is independently halo, -C₁₋₄alkyl, -OC₁₋₄alkyl, -CN, -CF₃, -OCF₃, -NO₂, -C(O)C₁₋₄alkyl or -CO₂H;

Ar₂ is:

- 10 i) phenyl substituted with 0, 1, 2 or 3 substituents R_b; where each R_b is independently halo, -C₁₋₄alkyl, -C(O)NR_cR_d, -OC₁₋₄alkyl, -OC₀₋₄alkylCF₃, -CN, -CF₃, -OCF₂H, -NO₂, -NR_cR_d, -S(O)₀₋₂C₁₋₄alkyl, -C(O)C₁₋₄alkyl, S(O)(O)NH₂, -(CH₂)₀₋₂-morpholinyl, piperidin-1-yl, piperazinyl, said piperazinyl optionally substituted with a methyl, or two R_b substituents on adjacent carbon atoms taken together form -O(CH₂)₁₋₂O-;
- 15 ii) pyridyl substituted with 0, 1 or 2 substituents R_e; where each R_e is independently selected from halo, -C₁₋₄alkyl, -OC₁₋₄alkyl, -CF₃, -NR_cR_d or 4-morpholinyl;

or

- iii) a bicyclic 9-11-membered aromatic heterocycle optionally substituted with 1
- 20 substituent R_f; where R_f is -C₁₋₄alkyl;

R_c and R_d are each independently selected from H or -C₁₋₄alkyl;

R₁ is H, C₁₋₄alkyl-O-C₁₋₄alkyl, or C₁₋₄alkyl optionally substituted with halo;

R₂, R₃, R₄, and R₅ are each independently H, halo or -C₁₋₄alkyl;

each Y₁, Y₂ and Y₃ is independently CH or N;

R₆ is

i) H, -C₁₋₄alkyl, -CF₃, -OR_z or -NR_hR_i;

where R_h is selected from

a) H, -C₀₋₄alkylCF₃, -C₁₋₄alkyl-N(CH₃)₂, saturated C₃₋₇cycloalkyl or -C₁₋₄alkyl-

5 monocyclic heteroaryl ring;

b) -C₁₋₅alkyl optionally substituted with OH;

c) -C₁₋₄alkyl-heterocycloalkyl, said heterocycloalkyl being optionally substituted with -C₁₋₄alkyl; or

d) -C₀₋₄alkyl-phenyl, said phenyl optionally substituted with one or two R_j moieties; where each R_j is independently halo, -OC₁₋₄alkyl,

R_z is -C₁₋₄alkyl, -C₁₋₄alkylCF₃ or -C₁₋₄alkyl-heterocycloalkyl;

ii) 1-pyrrolidinyl optionally substituted with a moiety selected from the group consisting of -NR_kR_i and -C₁₋₄alkyl, said -C₁₋₄alkyl optionally substituted with -OH;

iii) 1-piperidinyl optionally substituted with -C₁₋₄alkyl, -C(O)NH₂, -CO₂C₁₋₄alkyl or -C₀₋₄alkyl-phenyl;

iv) piperazinyl optionally substituted with -C₁₋₅alkyl, -OC₁₋₄alkyl, -C₀₋₄alkylpyridyl, -C₀₋₄alkyl-1-methyl-piperidin-4-yl, -C₀₋₄alkylNR_kR_i or -C₀₋₄alkyl-phenyl, said phenyl optionally substituted with one or two R_T substituents; where each R_T substituent is selected from the group consisting of halo, -OCF₃, -C₁₋₄alkyl, -OC₁₋₄alkyl, -CO₂C₁₋₄alkyl, -C(O) C₁₋₄alkyl and -C₀₋₄alkylNR_kR_i, or two R_T substituents on adjacent carbon atoms taken together form -O(CH₂)₁₋₂O-;

v) phenyl optionally substituted with halo, CF₃;

vi) pyridyl;

vii) morpholin-yl;

25 R_k is H, -C₁₋₄alkyl or -C(O)₁₋₂C₁₋₄alkyl;

R_i is H or C₁₋₄alkyl

In one embodiment, in the compounds of formula (IB) each Y₁, Y₂ are CH and Y₃ is N.

In another embodiment in the compounds of formula (IB) each Y₁, Y₂ and Y₃ are CH.

In another embodiments, in the compounds of formula (IB) each Y₁, Y₂ and Y₃ are as above defined and

5 Ar₁ is:

i) phenyl substituted with one substituent R_a; where R_a is halo, preferably -Cl or -F, or -C₁₋₄alkyl, preferably methyl;

ii) a thienyl ring optionally substituted with one substituents R_a: where R_a is halo, preferably -Cl;

10 Ar₂ is:

i) phenyl substituted with 1 substituent R_b; where R_b is -OC₀₋₄alkylCF₃, preferably OCF₃, or R_b is -CF₃;

R₁ is H or C₁₋₄ alkyl optionally substituted with halo, preferably H, methyl or ethyl;

R₂, R₃, R₄, and R₅ are each independently H, or -C₁₋₄alkyl, preferably H or methyl;

15 R₆ is:

i) H;

ii) 1-pyrrolidinyl;

iii) phenyl optionally substituted with -CF₃ or -OCF₃;

iv) morpholin-yl.

20 **Examples of compounds of formula (IB) are:**

1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;

1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;

25 1-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;

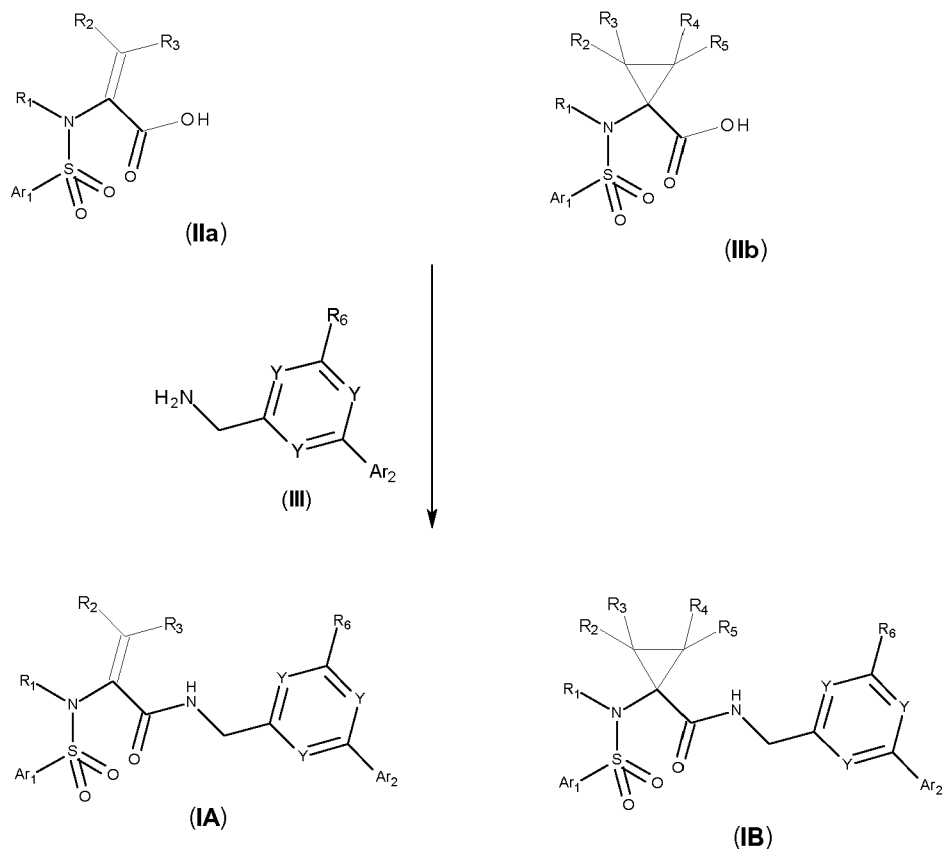
1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)-phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;

- 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]-phenyl]-methyl]cyclopropanecarboxamide;
- 1-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]-phenyl]methyl]cyclopropanecarboxamide;
- 5 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]-phenyl]methyl]cyclopropanecarboxamide;
- 1-[(4-fluorophenyl)sulfonylamino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)-phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
- 1-[(4-fluorophenyl)sulfonylamino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
- 10 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
- N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide;
- 15 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
- 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl]methyl]cyclopropanecarboxamide;
- 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
- 20 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-isopropoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
- 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
- 25 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
- N-[[2-ethoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide;

- 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-ethoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
- 1-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl]methyl]cyclopropanecarboxamide;
- 5 1-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]cyclopropanecarboxamide;
- 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]cyclopropanecarboxamide;
- 1-[(ethyl-(4-fluorophenyl)sulfonyl-amino)-N-[[4-[4-(trifluoromethyl)phenyl]-2-pyridyl]methyl]cyclopropanecarboxamide;
- 10 1-[(ethyl-(4-fluorophenyl)sulfonyl-amino)-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
- 1-[(ethyl-(4-fluorophenyl)sulfonyl-amino)-N-[[2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
- 15 N-[[2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-1-[(ethyl-(4-fluorophenyl)sulfonyl-amino)cyclopropanecarboxamide;
- 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
- N-[[2-(4-cyclohexylpiperazin-1-yl)-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-1-
- 20 [ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide;
- 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-(4-cyclohexylpiperazin-1-yl)-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide.

Compounds of formula **(IA)** and **(IB)** are amides that can be prepared by standard procedures, by the reaction of a compound of general formula **(IIa)** or **(IIb)** with the corresponding amine **(III)** in the presence of an acidic function activator such as, for example, DEPC, as illustrated in the following Scheme 2.

Scheme 2



Reagents: DEPC, THF

- 5 The compounds of formula (IIa) or (IIb) and the compounds of formula (III) are known compounds that can be prepared according to well established procedures, as it will be illustrated in the Examples and in Schemes 3-7 accompanying the Examples.

Compositions of the invention

- 10 The present invention also provides pharmaceutical compositions that comprise compounds of the present invention. The pharmaceutical compositions comprise compounds of the present invention that may be formulated together with one or more *non-toxic* pharmaceutically acceptable carriers.

- 15 The pharmaceutical compositions of this invention can be administered to humans and other mammals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments or drops), buccally or as an oral or nasal spray.

Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as, but not limited to, lactose, glucose and sucrose; starches such as, but not limited to, corn starch and potato starch; cellulose and its derivatives such as, but not limited to, sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as, but not limited to, cocoa butter and suppository waxes; oils such as, but not limited to, peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such a propylene glycol; esters such as, but not limited to, ethyl oleate and ethyl laurate; agar; buffering agents such as, but not limited to, magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as, but not limited to, sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or *non*-aqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and *non*-aqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), vegetable oils (such as olive oil), injectable organic esters (such as ethyl oleate) and suitable mixtures thereof. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal

agents, for example, paraben, chlorobutanol, phenol sorbic acid and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

- 5 In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which in turn, may depend upon crystal size and crystalline form.
- 10 Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

- Injectable depot forms are made by forming microencapsulated matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of
- 15 drug release can be controlled. Examples of other biodegradable polymers include poly (orthoesters) and poly (anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissues.

- The injectable formulations can be sterilized, for example, by filtration through a
- 20 bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

- Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound may be mixed with at least
- 25 one inert, pharmaceutically acceptable excipient or carrier, such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants such as glycerol; d)

disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard- filled gelatin capsules using such carriers as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragées, capsules, pills and granules can be prepared with coatings and shells such as enteric coatings and other coatings well-known in the pharmaceutical formulating art. They may optionally contain opacifying agents and may also be of a composition such that they release the active ingredient (s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned carriers.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof.

Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents
5 as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-
10 irritating carriers or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or
15 other lipid substances. Liposomes are formed by mono-or multi-lamellar hydrated liquid crystals, which are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients and the like. The preferred lipids are
20 natural and synthetic phospholipids and phosphatidyl cholines (lecithins) used separately or together.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N. Y. (1976), p. 33 et seq.

25 Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants that may be required. Ophthalmic formulations, eye

ointments, powders and solutions are also contemplated as being within the scope of this invention.

In the treatment of painful conditions such as those listed below, a suitable indicated dosage level is about 0.1mg to 2000mg/day, preferably from about 5mg to 1000mg per day. The compounds may be administered on a regimen of 1 to 4 times a day.

It will be appreciated that the amount of a compound of formula I required for use in any treatment will vary not only with the particular compounds or compositions selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient.

The agents of invention are useful TRPA1 receptor antagonists for the treatment of pain of various genesis or etiology and as anti-inflammatory agents for the treatment of inflammatory reactions, diseases or conditions. They are useful for the treatment of inflammatory pain, for the treatment of hyperalgesia, and in particular for the treatment of severe chronic pain. They are, for example, useful for the treatment of neuropathic pain conditions such as diabetic neuropathy, chemotherapy-induced neuropathy and post-herpetic neuralgia; "non-painful" neuropathies, complex regional pain syndromes, pain associated with carcinoma, often referred to as cancer pain, central nervous system pain, such as pain due to spinal cord or brain stem damage, low back pain, sciatica and ankylosing spondylitis, inflammation consequential to trauma, e.g. associated with burns or subsequent to surgical intervention, e.g. as post-operative analgesics, as well as for the treatment of inflammatory pain of diverse genesis, e.g. for the treatment of osteoarthritis and rheumatoid arthritis.

Other forms of pain associated with the activity of TRPA1 are headache, dental pain, pelvic pain, migraine, mastalgia and visceral pain.

The disorders in which TRPA1 is involved are not limited to pain. Such diseases include: nerve-related diseases, e.g. neuropathies, nerve injury and stroke; irritable bowel syndrome; gastrointestinal disorders, e.g. gastro-oesophageal reflux disease, Crohn's disease; respiratory diseases, e.g. asthma, chronic obstructive pulmonary disease, cough;

urinary incontinence; urinary bladder hypersensitiveness; skin diseases, e.g. psoriasis, dermatitis; cardiac diseases e.g. myocardial ischemia; hair growth related disorders e.g. hirsutism, alopecia; rhinitis; pancreatitis; vulvodynia; psychiatric disorders, e.g. anxiety or fear; obesity.

- 5 The compounds of the present invention have potent analgesic effect and potential anti-inflammatory activity and their pharmaceutically formulations are thought to alleviate or to treat in particular neuropathic pain conditions such as diabetic neuropathy and post-herpetic neuralgia, urinary incontinence, COPD and cough.

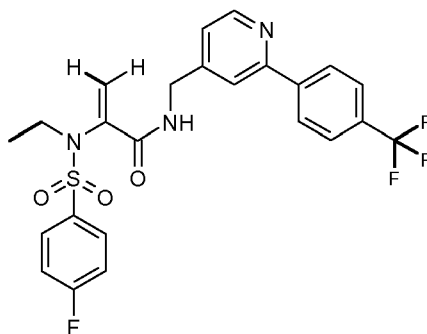
The invention will be now illustrated by means of the following examples.

10 **EXAMPLES**

All commercially available compounds were purchased from Vendors and were used without further purification. Reaction courses were monitored by thin-layer chromatography on silica gel (precoated F₂₅₄ Merck plates), the spots were examined with UV light and visualized with aqueous KMnO₄. Flash chromatography was performed using Merck silica gel (230-240 mesh). ¹H-NMR spectra were recorded on Varian 400 MHz spectrometer or Varian 200MHz using TMS as internal standard. Mass spectra were obtained with a Waters-Micromass ZMD spectrometer.

Abbrev.: TEA (triethylamine), DMF (dimethylformamide), DEPC (diethylcyanophosphonate), TetrakisPd (tetrakis(triphenylphosphine Palladium(0))), DME (Dimethoxyethane), XPhos (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl).

Example 1: 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide



Synthesis of methyl (2S)-2-[(4-fluorophenyl)sulfonylamino]-3-hydroxypropanoate 2A

A suspension of L-serine-methyl ester hydrochloride **1** (5 g, 32.13 mmol) in CH₂Cl₂ (100 mL) was added with TEA (1.1 mol eq, 4.9 mL) and the mixture stirred at r.t. for 10 minutes. Then 4-fluorobenzensulfonyl chloride (1 mol eq, 6.26 g) and additional TEA (1.1 mol eq) were added and the resulting solution heated at 50°C for 6h. The solvent was removed under reduced pressure, water was added to the residue (100 mL) and the aqueous phase finally extracted with EtOAc (3x40 mL). The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure. The residue was recrystallized from ethyl ether to afford **2A** as white solid (7.10 g, 80% yield). ¹HNMR (DMSO, 200 MHz) δ 3.48 (s, 3H), 3.53 (m, 2H), 3.86 (t, 1H), 5.07 (t, 1H), 7.41 (m, 2H), 7.83 (m, 2H), 8.33 (bs, 1H).

Synthesis of methyl (2S)-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-3-hydroxypropanoate 3B

A solution of **2A** (1 g, 3.6 mmol) in DMF (15 mL) was added with an. K₂CO₃ (1.4 mol eq, 0.7 g) and, after few minutes, 2-iodoethane (1.2 mol eq, 0.45 ml) was added and the mixture heated at 50°C for 5h. The solvent was removed under reduced pressure, water was added to the residue (80 mL) and the aqueous phase extracted with EtOAc (3x30 mL). The combined organic phases were dried using Na₂SO₄ and evaporated under reduced pressure to obtain **3B** as a pale yellow oil (1.1 g, quantitative yield). ¹HNMR (DMSO, 200 MHz) δ 1.13 (t, 3H, J=8), 3.29 (q, 2H), 3.41 (s, 3H), 3.79 (m, 2H), 4.53 (t, 1H), 5.14 (t, 1H), 7.41 (t, 2H, J=10), 7.86 (m, 2H).

Synthesis of 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]prop-2-enoic acid 4B

A solution of **3B** (1.1 g, 3.6 mmol) in dioxane (25 mL) was added with 20% NaOH aq. solution (20 mL) and the mixture heated at 80°C for 4 h. The organic solvent was removed under reduced pressure and the aqueous phase acidified with 10% HCl and extracted with CH₂Cl₂ (3x30 mL). The combined organic phases were dried using Na₂SO₄, evaporated under reduced pressure and then the resulting residue purified by

flash chromatography (100% EtOAc) to obtain **4B** as white solid (0.7 g, 66% yield).
¹HNMR (DMSO, 200 MHz) δ 1.12 (t, 3H), 3.29 (q, 2H), 5.69 (s, 1H), 6.32 (s, 1H), 7.39 (m, 2H), 7.89 (m, 2H), 12.9 (bs, 1H).

Synthesis of 2-[4-(trifluoromethyl)phenyl]pyridine-4-carbonitrile **20A**

5 2-Chloropyridine-4-carbonitrile **19** (2.96 g, 21,35 mmol) was dissolved in 100 ml of dimethoxyethane. The solution was added with 70 ml of water, sodium bicarbonate (3 equiv., 5.38 g), [4-(trifluoromethyl)phenyl]boronic acid (1.2 equiv., 4.87 g) and the mixture was then stirred at rt for 5'. The mixture was degassed and placed under argon. A catalytic amount of tetrakispladium was added and the mixture heated at 100°C
10 overnight. The solvents were evaporated off and the resulting residue dissolved with ethyl acetate and then washed with water and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The crude was crystallized from ethyl acetate and petroleum ether to give a beige solid. (2.5 g, 47% yield).

Synthesis of [2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **21A**

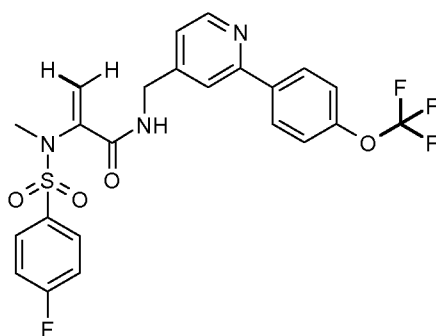
15 The nitrile **20A** (3 g, 12 mmol) dissolved in 50 ml of diethyl ether was added dropwise to a mixture of LiAlH₄ (912 mg, 2 equiv.) in diethyl ether (80 mL) and stirred at 0°C. Then, the mixture was stirred at room temperature overnight. The excess of LiAlH₄ was destroyed by water addition at 0°C, the solid formed was filtered, washed with Et₂O and the filtrate was dried over Na₂SO₄ and evaporated to dryness to obtain 2.5g of the
20 amine as a yellow oil. The amine was used for the following step without purification.

Preparation of 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 1

Acid **4B** (273.28 mg, 1 mmol) was dissolved in 10 ml of THF and at rt DEPC (1.1 equiv, 0.15 ml) and [2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **21A** (1.1
25 equiv., 277.5 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30 ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (EtOAc 1/petroleum

ether 1) afforded 100 mg of a white solid. Yield = 19% ^1H NMR (DMSO, 400 MHz) δ 1.09 (3H, t, J = 7.2Hz), 3.39 (2H, q, J = 6.8Hz), 4.48 (2H, d, J = 6Hz), 5.15 (1H, s), 6.14 (1H, s), 7.36 (1H, dd, J = 4.8 Hz, J' = 1.2 Hz), 7.47 (2H, t, J = 8.8 Hz), 7.84 (4H, m), 8.01 (1H, s), 8.30 (2H, d, J = 8Hz), 8.64 (1H, dd, J = 5.2Hz, J' = 0.8Hz), 8.89 (1H, bt) [M^{+1}]
 5 508.7 ($\text{C}_{24}\text{H}_{21}\text{F}_4\text{N}_3\text{O}_3\text{S}$ requires 507.50).

Example 2: 2-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide



10 **Synthesis of methyl (2S)-2-[(4-fluorophenyl)sulfonyl-methyl-amino]-3-hydroxy-propanoate 3A**

A solution of **2A** (2 g, 7.2 mmol) in DMF (20 mL) was added with an. K_2CO_3 (1.5 mol eq, 1.49 g) and, after few minutes, iodomethane (1.2 mol eq, 0.8 ml) was added and the mixture heated at 50°C for 12h. The solvent was removed under reduced pressure,
 15 water was added to the residue (100 mL) and the aqueous phase extracted with EtOAc (3x40 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure to obtain **3A** as a pale yellow oil (2.3 g, quantitative yield). ^1H NMR (DMSO, 200 MHz) δ 2.82 (s, 3H), 3.50 (s, 3H), 3.69 (m, 3H), 4.60 (t, 1H, J =6), 5.12 (t, 1H, J =6.1), 7.44 (m, 2H), 7.83 (m, 2H).

20 **Synthesis of 2-[(4-fluorophenyl)sulfonyl-methyl-amino]prop-2-enoic acid 4A**

A solution of **3A** (2.3 g, 7.2 mmol) in dioxane (35 mL) was added with 20% NaOH aq. solution (20 mL) and the mixture was heated at 50°C for 2 h. The organic solvent was removed under reduced pressure and the aqueous phase acidified with 10% HCl. The solid formed was collected by filtration, washed with water (2x20 mL) and dried to obtain

4A as white solid (1.05 g, 51% yield). ¹HNMR (DMSO, 200 MHz) δ 2.92 (s, 3H), 5.57 (s, 1H), 6.09 (s, 1H), 7.50 (m, 2H), 7.85 (m, 2H), 13.01 (bs, 1H).

Synthesis of 2-[4-(trifluoromethoxy)phenyl]pyridine-4-carbonitrile **20B**

A solution of **19** (2.5 g, 18 mmol) in DME (90 mL) was added 4-trifluoromethoxy phenyl boronic acid (1.1 mol eq, 4.46 g) and NaHCO₃ (3 mol eq, 4.66 g) suspended in water (50 mL). The mixture was degassed under vacuum, then Tetrakis(palladium) was added (catalytic amount) and the reaction stirred at 100°C under inert atmosphere for 12h. The solvent was removed under reduced pressure and water was added to the residue (100 mL). The aqueous phase was extracted with EtOAc (3x50 mL) and the combined organic layer was washed with brine (100 mL) and dried over Na₂SO₄. The solvent was evaporated under vacuum to obtain **20B** as a pale yellow crystals (96% Yield, 4.6 g, 17.4 mmol). ¹HNMR (DMSO, 200 MHz) δ 7.5 (dd, 2H, J= 2), 7.84 (dd, 1H, J= 1.8), 8.31 (d, 2H, J= 9.8), 8.54 (d, 1H, J=2), 8.93 (dd, 1H, J= 1.9).

Synthesis of [2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **21B**

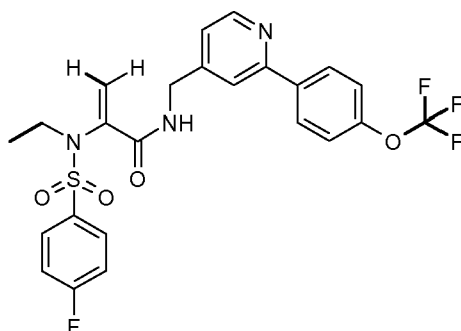
A solution of nitrile **20B** (3 g, 11.3 mmol) in diethyl ether (30 mL) was added in small amounts to a mixture of LiAlH₄ (0.9 g, 2 mol eq) in diethyl ether (35 mL) and stirred at 0°C. After the addition was completed, the mixture was stirred at room temperature overnight. The excess of LiAlH₄ was destroyed at 0°C by addition of small amount of water (30 mL), the solid formed was filtered off and the organic filtrate separated, washed with brine (50 mL) and dried over Na₂SO₄. The organic phase was evaporated under reduced pressure to obtain **21B** as a yellow oil (3.1 g, quantitative yield). ¹HNMR (DMSO, 200 MHz) δ 3.08 (s, 2H), 3.8 (bs, 2H), 7.33 (dd, 1H, J=1.8), 7.47 (dd, 2H, J= 2), 7.96 (s, 1H), 8.20 (dd, 2H, J= 1.8), 8.57 (dd, 1H, J= 1.2).

Preparation of 2-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide **Example 2**

A solution of acid **4A** (0.26 g, 1 mmol) in THF (25 mL) was added with DEPC (0.18 mL, 1.3 mol eq) and the mixture was stirred at room temperature for about 5 minutes. Then [2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **21B** (0.27 g, 1.1

mol eq) and a catalytic amount of TEA were added. The reaction mixture was then stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (30 mL) and washed with water (50 mL) and brine. The separated organic phase, after drying over Na₂SO₄, was evaporated under reduced pressure and the residue was purified by flash chromatography (8:2 EtOAc:Petroleum ether) to afford a pale yellow solid (0.1 g) after crystallization from a mixture of diethyl ether/petroleum ether. Yield = 23%, ¹HNMR (DMSO, 200 MHz) δ 2.95 (3H, s), 4.49 (d, 2H, J=6 Hz), 5.10 (s, 1H), 5.88 (s, 1H), 7.35 (dd, 1H), 7.47 (m, 4H), 7.48 (m, 2H), 7.96 (s, 1H), 8.21 (dd, 2H), 8.61 (d, 1H, J= 4 Hz), 8.94 (t, 1H); [M⁺] 509.47 (C₂₃H₁₉F₄N₃O₄S requires 509.10).

Example 3: 2-[(4-fluorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide



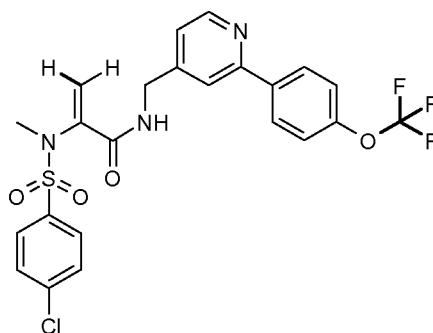
Preparation of 2-[(4-fluorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 3

A solution of acid **4B** (0.25 g, 1 mmol) in THF (20 mL) was added with DEPC (0.17 mL, 1.3 mol eq) and the mixture was stirred at room temperature for about 5 minutes. Then [2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **21B** (0.27 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (30 mL) and washed with water (50 mL) and brine. The separated organic phase, after drying over Na₂SO₄, was evaporated under reduced pressure and the residue purified by flash chromatography (7:3 EtOAc:Petroleum ether)

to afford a pale orange solid (0.12 g) after crystallization from a mixture of diethyl ether/petroleum ether.

Pale yellow solid. Yield = 30%, ^1H NMR (DMSO, 200 MHz) δ 1.08 (t, 3H, J = 6.8 Hz), 3.40 (q, 2H), 4.48 (d, 2H, J = 6), 5.15 (s, 1H), 6.14 (s, 1H), 7.29 (d, 1H), 7.43 (m, 4H), 7.86-7.88 (m, 3H), 8.21 (d, 2H), 8.58 (d, 1H), 8.85 (t, 1H); $[\text{M}^+]$ 523.50 ($\text{C}_{24}\text{H}_{21}\text{F}_4\text{N}_3\text{O}_4\text{S}$ requires 523.14).

Example 4: 2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide



Synthesis of methyl (2S)-2-[(4-chlorophenyl)sulfonylamino]-3-hydroxypropanoate **2C**

A suspension of L-serine-methyl ester hydrochloride (5 g, 32.13 mmol) in CH_2Cl_2 (100 mL) was added with TEA (1.1 mol eq, 4.9 mL) and the mixture was stirred at r.t. for 10 minutes. Then 4-chlorobenzensulfonyl chloride (1 mol eq, 6.81 g) and additional TEA (1.1 mol eq) were added and the solution heated at 50°C for 5h. The solvent was removed under reduced pressure, water was added to the residue (100 mL) and the aqueous phase extracted with EtOAc (3x40 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to reduced pressure. The residue was recrystallized from ethyl ether to afford **2C** as white solid (8.6 g, 91% yield). ^1H NMR (DMSO, 200 MHz) δ 3.51 (s, 3H), 3.60 (m, 2H), 3.91 (t, 1H), 5.17 (t, 1H), 7.50 (d, 2H, J =8), 7.89 (d, 2H, J =7.8), 8.35 (bs, 1H).

Synthesis of methyl (2S)-2-[(4-chlorophenyl)sulfonyl-methyl-amino]-3-hydroxypropanoate **3C**

A solution of **2C** (8.5g, 28 mmol) in DMF (30 mL) was added with an. K_2CO_3 (1.5 mol eq, 5.99 g) and, after few minutes, iodomethane (1.2 mol eq, 3.21 mL) was added and the mixture heated at 50°C for 12h. The solvent was removed under reduced pressure, water was added to the residue (150 mL) and the aqueous phase extracted with EtOAc (3x60 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure to afford **3C** as a pale yellow oil (8.6 g, 97% yield). 1H NMR (DMSO, 200 MHz) δ 2.88 (s, 3H), 3.52 (s, 3H), 3.66 (m, 2H), 4.02 (q, 1H, J=6), 4.602 (t, 1H, J=6.1), 5.11 (t, 1H), 7.64 (d, 2H), 7.76 (d, 2H).

Synthesis of 2-[(4-chlorophenyl)sulfonyl-methyl-amino]prop-2-enoic acid **4C**

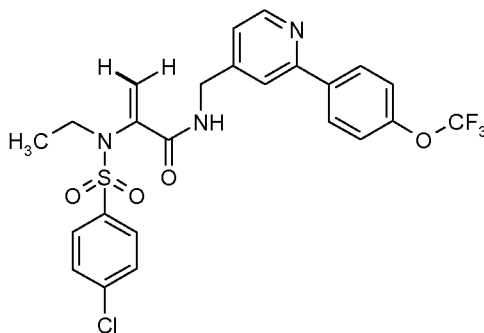
A solution of **3C** (8.5 g, 27.6 mmol) in dioxane (20 mL) was added with 20% NaOH aq. solution (30 mL) and the mixture heated at 80°C for 5 h. The organic solvent was removed under reduced pressure and the aqueous phase acidified with 10% HCl and extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure to afford **4C** as a pale yellow deliquescent solid (4.3 g, 62% yield). 1H NMR (DMSO, 200 MHz) δ 2.91 (s, 3H), 5.58 (s, 1H), 6.09 (s, 1H), 7.72-7.60 (m, 4H), 13.05 (bs, 1H).

Preparation of 2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 4

A solution of acid **4C** (0.50 g, 1.8 mmol) in THF (30 mL) was added with DEPC (0.35 mL, 1.3 mol eq) and the mixture stirred at room temperature several minutes. Then [2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **21B** (0.53 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc and washed with water and brine. The separated organic phase was dried over an. Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash chromatography (7:3 EtOAc:Petroleum ether) to afford a pale yellow viscous oil (0.17 g). Yield = 18%, 1H NMR (DMSO, 200 MHz) δ 2.98 (s, 3H), 4.22 (d, 2H), 5.08 (s, 1H), 5.85 (s, 1H), 7.4 (m, 3H), 7.65 (dd, 4H, J=8), 7.95 (s, 1H), 8.2 (d, 2H), 8.58 (d, 1H),

8.95 (t, 1H); $[M^{+}]$ 525.93 ($C_{23}H_{19}ClF_3N_3O_4S$ requires 525.07).

Example 5: 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide



5

Synthesis of ethyl (2S)-2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-3-hydroxy-propanoate 3D

Compound **2C** (1.65 g, 5.6 mmol) dissolved in DMF (15 ml) was added with K_2CO_3 (1.1 equiv., 854 mg) and ethyl iodide (1.1 equiv., 0.63 ml) and the reaction was stirred at rt overnight. The reaction was diluted with ethyl acetate and washed several times with water and finally with Brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude residue by crystallization from ethyl ether and petroleum ether afforded 1.6 g of a semisolid. Yield = 88%. 1H NMR (DMSO, 200 MHz) δ 1.00 (3H, d, J = 6.2 Hz), 3.32 (3H, s), 3.34 (2H, m), 3.75 (2H, m), 4.42 (1H, t), 5.08 (1H, bs), 7.62 (2H, m), 7.76 (2H, m)

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Synthesis of 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]prop-2-enoic acid 4D

Compound **3D** (1.4 g, 4.45 mmol) dissolved in THF (20 ml) and water (5 ml) was added with $LiOH \cdot H_2O$ (3 equiv., 560 mg) and the reaction was stirred at rt 3 hours. The reaction was concentrated under vacuum. Water was added and 10% HCl till precipitation of the acid. The acid was extracted with ethyl acetate and the organic phase was washed with Brine, dried over sodium sulfate and concentrated under vacuum to give 1.3g of a white solid. Yield = 95%. 1H NMR (DMSO, 200 MHz) δ 1.17 (3H, t, J = 7.8 Hz), 3.32 (2H, m), 3.76 (2H, m), 4.42 (1H, t), 5.08 (1H, bs), 7.61 (2H, m), 7.82 (2H, m), 12.85 (1H, bs). The intermediate acid (1.23 g, 4 mmol) dissolved in pyridine (10 ml) was added

20

dropwise with acetyl chloride (1.4 equiv., 0.45 ml) at 0°C and the reaction was then stirred at rt for 5 hours. The reaction was quenched by addition of 10% HCl and then extracted with ethyl acetate. The organic phase was washed 2 times with water, with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was

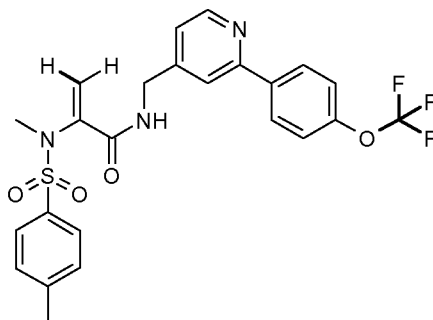
5 crystallized from diethyl ether and petroleum ether to give 500 mg of a beige solid. Yield = 43%. ¹HNMR (DMSO, 200 MHz) δ 1.00 (3H, t, J = 7.2 Hz), 3.40 (2H, m), 5.72 (1H, s), 6.33 (1H, s), 7.72 (4H, m), 13.00 (1H, bs)

Preparation of 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 5

10 Acid **4D** (221.45 mg, 1 mmol) was dissolved in 10 ml of THF and at rt DEPC (1.1 equiv, 0.15 ml) and [2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **21B** (1.1 equiv., 295 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in EtOAc (30ml) and washed with water (1 X 20ml) and brine. The organic phase was dried over sodium sulfate and concentrated under

15 vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:petroleum ether) afforded 100 mg of a white solid. Yield = 18.5% ¹HNMR (DMSO, 400 MHz) δ 1.08 (3H, t), 3.40 (2H, q), 4.42 (2H, d), 5.20 (1H, s), 6.08 (1H, s), 7.23 (1H, d), 7.45 (2H, d), 7.72 (4H, dd), 7.85 (1H, s), 8.20 (2H, d), 8.60 (1H, d), 8.74 (1H, bt) [M⁺] 540.1 (C₂₄H₂₁ClF₃N₃O₄S requires 539.95).

20 **Example 6:** 2-(methyl(p-tolylsulfonyl)amino)-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide



Synthesis of methyl (2S)-3-hydroxy-2-(p-tolylsulfonylamino)propanoate 2E

A suspension of L-serine-methyl ester hydrochloride **1** (5 g, 32.13 mmol) in CH₂Cl₂ (150 mL) was added with TEA (1.1 mol eq, 4.92 mL) and the mixture was stirred at r.t. for 10 minutes. Then p-tolylbenzenesulfonyl chloride (1 mol eq, 6.14 g) and additional TEA (1.1 mol eq) were added and the solution was heated at 50°C for 5h. The solvent was removed under reduced pressure, water was added to the residue (150 mL) and the aqueous phase extracted with EtOAc (3x50 mL). The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure to afford **2E** as white solid (8.10 g, 90% yield).

¹HNMR (DMSO, 200 MHz) δ 2.37 (s, 3H), 3.44 (s, 3H), 3.50 (m, 2H), 3.81 (t, 1H), 5.04 (t, 1H, J=5.8), 7.38 (d, 2H, J=8), 7.66 (d, 2H, J=7.9), 8.15 (bd, 1H).

Synthesis of methyl (2S)-3-hydroxy-2-(methyl(p-tolylsulfonyl)amino)propanoate 3E

A solution of **2E** (2 g, 7.35 mmol) in DMF (15 mL) was added with an.K₂CO₃ (1.5 mol eq, 1.52 g) and, after few minutes, iodomethane (1.2 mol eq, 0.81 ml) was added and the mixture was heated at 50°C overnight. The solvent was removed under reduced pressure, water was added to the residue (120 mL) and the aqueous phase was extracted with EtOAc (3x50 mL). The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure to afford **3E** as a pale yellow oil (2.1 g, quantitative yield). ¹HNMR (DMSO, 200 MHz) δ 2.38 (s, 3H), 2.87 (s, 3H), 3.64 (s, 3H), 3.70 (t, 2H), 4.58 (t, 1H), 5.11 (t, 1H), 7.40 (d, 2H, J=8), 7.61 (d, 2H, J=8).

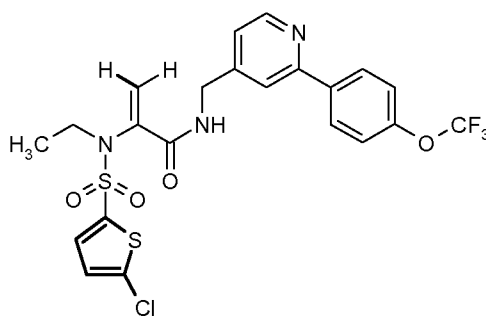
Synthesis of 2-(methyl(p-tolylsulfonyl)amino)prop-2-enoic acid 4E

A solution of **3E** (1.4 g, 4.87 mmol) in dioxane (30 mL) was added with 20% NaOH aq. solution (30 mL) and the mixture was heated at 60°C overnight. The organic solvent was removed under reduced pressure and the aqueous phase was acidified with 10% HCl and extracted with CH₂Cl₂ (3x50 mL). The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure to afford **4E** as a pale yellow solid (0.8 g, 65% yield). ¹HNMR (DMSO, 200 MHz) δ 2.81 (s, 3H), 2.88 (s, 3H), 5.46 (s, 1H), 6.02 (s, 2H), 7.41 (d, 2H, J=7.8), 7.66 (d, 2H, H=8), 13.01 (bs, 1H).

Preparation of 2-(methyl(p-tolylsulfonyl)amino)-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 6

A solution of acid **4E** (0.57 g, 2.2 mmol) in THF (30 mL) was added with DEPC (0.43 mL, 1.3 mol eq) and the mixture was stirred at room temperature for about 5 minutes. Then [2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **21B** (0.66 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc and washed with water and brine. The separated organic phase was evaporated under reduced pressure and the residue was purified by flash chromatography (7:3 EtOAc:Petroleum ether) to afford a pale yellow solid (0.27 g) after crystallization from a mixture of diethyl ether/petroleum ether. Yield = 25%, ¹HNMR (DMSO, 200 MHz) δ 2.48 (s, 3H), 2.86 (s, 3H), 4.49 (d, 2H, J= 6), 5.00 (s, 1H), 5.85 (s, 1H), 7.35 (d, 1H), 7.42 (m, 4H), 7.71 (d, 2H, J= 8.2), 7.97 (s, 1H), 8.21 (dd, 2H, J= 2.2), 8.61 (d, 1H, J= 4), 8.90 (t, 1H); [M⁺] 505.51 (C₂₄H₂₂F₃N₃O₄S requires 505.12).

Example 7: 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide



Synthesis of methyl (2S)-2-[(5-chloro-2-thienyl)sulfonylamino]-3-hydroxypropanoate **5**

L-Serine methyl ester hydrochloride (5 g, 32.13 mmol) dissolved in methylene chloride (200 ml) was added with TEA (2 equiv., 8.95 ml) and in one portion 5-chlorothiophene-2-sulfonyl chloride (1.0 equiv., 6.97 g). The reaction was refluxed for 4 hours. The solvent was evaporated and the crude was dissolved in AcOEt (100 ml) and washed with water (1 X 80 ml) and brine. The organic phase was dried over sodium

sulfate and concentrated under vacuum. The purification of the crude residue by crystallization from diethyl ether and petroleum ether afforded 10 g of the white product. Yield = 93% ¹HNMR (DMSO, 200 MHz) δ 2.81 (2H, q, J = 7.2 Hz), 3.52 (3H, s), 3.92 (1H, t), 5.06 (1H, bs), 7.24 (1H, dd, J = 4.2 Hz), 7.45 (1H, dd, J = 4Hz), 8.92 (1H, bs)

5 Synthesis of methyl (2S)-2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-3-hydroxy-propanoate 6

Compound **5** (10 g, 30 mmol) dissolved in DMF (100 ml) was added with K₂CO₃ (1.1 equiv., 4.56 g) and ethyl iodide (1.1 equiv., 3.16 ml) and the reaction was stirred at rt overnight. The reaction was diluted with ethyl acetate and washed several times with
10 water and finally with Brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude residue by crystallization from ethyl ether and petroleum ether afforded 10 g of a semisolid. Yield = 93%. ¹HNMR (DMSO, 200 MHz) δ 1.17 (3H, t, J = 7Hz), 3.40 (2H, q), 3.54 (3H, s), 3.80 (2H, t, J = 5.8 Hz), 4.50 (1H, t), 5.00 (1H, bt), 7.28 (1H, dd, J = 4 Hz, J' = 1Hz), 7.57 (1H, dd, J =
15 4.2Hz, J' = 1Hz).

Synthesis of 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]prop-2-enoic acid 7

Compound **6** (10 g, 28 mmol) dissolved in THF (100 ml) and water (50 ml) was added with LiOH·H₂O (3 equiv., 3.52 g) and the reaction was stirred at rt 3 hours. The reaction was concentrated under vacuum. Water was added and 10% HCl till precipitation
20 of the acid. The acid was extracted with ethyl acetate and the organic phase was washed with Brine, dried over sodium sulfate and concentrated under vacuum to give 8g of a white solid. Yield = 81.5%. ¹HNMR (DMSO, 200 MHz) δ 1.17 (3H, t, J = 5.6Hz), 3.35 (2H, q), 4.04 (2H, q, J = 7 Hz), 4.39 (1H, t), 5.96 (1H, bs), 7.26 (1H, dd, J = 4 Hz, J' = 0.6Hz), 7.55 (1H, dd, J = 3.8Hz, J' = 0.4Hz), 12.98 (1H, bs). The intermediate acid (2.45
25 g, 7 mmol) dissolved in pyridine (10 ml) was added dropwise with acetyl chloride (1.4 equiv., 0.8 ml) at 0°C and the reaction was then stirred at rt for 5 hours The reaction was quenched by addition of 10% HCl and then extracted with ethyl acetate. The organic phase was washed 2 times with water, with brine, dried over sodium sulfate and

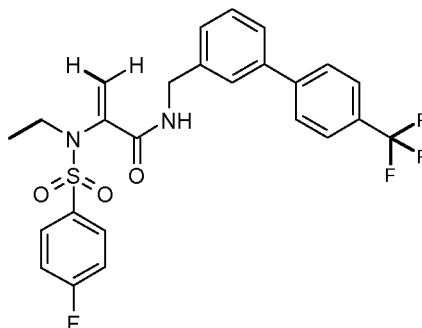
concentrated under vacuum. The crude product was crystallized from diethyl ether and petroleum ether to give 1g of a beige solid. Yield = 43%. ¹HNMR (DMSO, 200 MHz) δ 1.04 (3H, t, J = 7.4Hz), 3.44 (2H, q), 5.82 (1H, s), 6.39 (1H, s), 7.31 (1H, d, J = 4.2 Hz), 7.55 (1H, d, J = 4Hz), 13.05 (1H, bs)

5 Preparation of 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 7

Acid **7** (665 mg, 2 mmol) was dissolved in 10 ml of THF and at rt DEPC (1.1 equiv, 0.3 ml) and [2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **21B** (1.1 equiv., 590 mg) were added to the solution. The mixture was stirred at rt overnight then
 10 evaporated. The residue was dissolved in AcOEt (30 ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:petroleum ether) afforded 200 mg of a pale yellow solid. Yield = 18.3% ¹HNMR (DMSO, 200 MHz) δ 1.12 (3H, t, J = 7Hz), 3.47 (2H, q, J = 7.2Hz), 4.48 (2H, d, J = 6Hz), 5.41 (1H, s),
 15 6.25 (1H, s), 7.28 (2H, m), 7.48 (2H, d, J = 7.8Hz), 7.60 (1H, d, J = 4.2Hz), 7.90 (1H, bs), 8.19 (2H, dd, J = 6.8 Hz), 8.61 (1H, d, J = 5 Hz), 8.89 (1H, bt) [M⁺] 546.1 (C₂₂H₁₉ClF₃N₃O₄S₂ requires 545.98).

Example 8: 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]prop-2-enamide

20



Synthesis of [3-[4-(trifluoromethyl)phenyl]phenyl]methanamine 23A

A suspension of 3-bromobenzylamine hydrochloride **22** (1 g, 4.49 mmol) in DME (50 mL) was added with 4-trifluoromethyl phenyl boronic acid (1.2 mol eq, 1.0 g) and

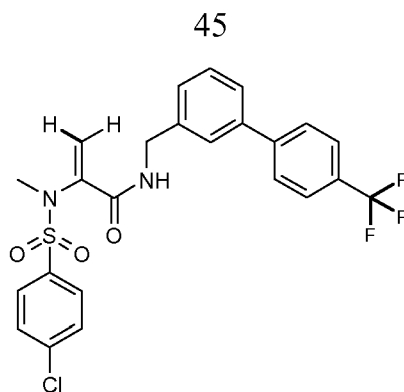
NaHCO₃ (3 mol eq, 1.13 g) suspended in water (30 mL). The mixture was degassed under vacuum, then Tetrakis(palladium) was added (catalytic amount) and the reaction was stirred at 100°C under inert atmosphere for 12h. The solvent was removed under reduced pressure and water was added to the residue (80 mL). The aqueous phase was extracted with EtOAc (3x40 mL) and the combined organic layer was washed with brine (50 mL) and dried over Na₂SO₄. The solvent was evaporated under vacuum to afford **23A** as a pale brown oil (1.5 g, quantitative yield).

¹HNMR (DMSO, 400 MHz) δ 1.86 (bs, 2H), 3.79 (s, 2H), 7.39 (d, 1H), 7.44 (t, 1H), 7.56 (d, 1H), 7.71 (s, 1H), 7.82 (d, 2H), 7.90 (d, 2H).

10 **Preparation of 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]prop-2-enamide Example 8**

A solution of acid **4B** (0.30 g, 1.1 mmol) in THF (20 mL) was added with DEPC (0.22 mL, 1.3 mol eq) and the mixture stirred at room temperature for 10 minutes. Then [3-[4-(trifluoromethoxy)phenyl]phenyl]methanamine **23A** (0.303 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (45 mL) and washed with water (50 mL) and brine. The separated organic phase was dried over an. Na₂SO₄ and evaporated under reduced pressure. The residue was purified by flash chromatography (3:7 EtOAc:Petroleum ether) to afford a white solid (0.11 g). Yield = 22%, ¹HNMR (DMSO, 200 MHz) δ. 1.089 (t, 3H), 3.38 (m, 2H), 4.46 (d, 2H, J=4.2), 5.16 (s, 1H), 6.09 (s, 1H), 7.35 (d, 1H), 7.43 (m, 3H), 7.60 (d, 1H), 7.69 (s, 1H), 7.78 (d, 2H), 7.88 (m, 4H), 8.79 (bs, 1H). [M⁺] 506.51 (C₂₅H₂₂F₄N₂O₃S requires 506.12).

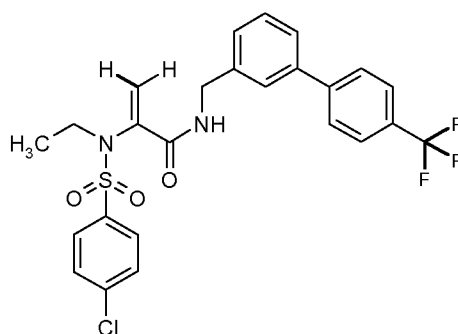
25 **Example 9: 2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]prop-2-enamide**



Preparation of 2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]prop-2-enamide Example 9

Acid **4C** (827 mg, 3 mmol) was dissolved in 10 ml of THF and at rt DEPC (1.1 equiv, 0.5 ml) and [3-[4-(trifluoromethyl)phenyl]phenyl]methanamine **23A** (1.1 equiv., 835 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30 ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:petroleum ether) afforded 200 mg of a beige solid. Yield = 13% ¹HNMR (DMSO, 200 MHz) δ 2.93 (3H, s), 4.44 (2H, d, J = 5.8Hz), 5.13 (1H, s), 5.85 (1H, s), 7.76 (12H, m), 8.82 (1H, bt) [M⁺] 509.1 (C₂₄H₂₀ClF₃N₂O₃S requires 508.94).

Example 10: 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]prop-2-enamide

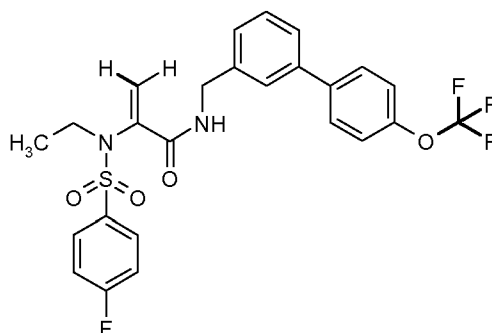


Preparation of 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]prop-2-enamide Example 10

Acid **4D** (869 mg, 3 mmol) was dissolved in 10 ml of THF and at rt DEPC (1.1

equiv, 0.5ml) and [3-[4-(trifluoromethyl)phenyl]phenyl]methanamine **23A** (1.1 equiv., 835 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30 ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:petroleum ether) afforded 200 mg of a beige solid. Yield = 13% ¹HNMR (DMSO, 200 MHz) δ 1.06 (3H, t, J = 7Hz), 3.39 (2H, q, J = 7Hz), 4.44 (2H, d, J = 6Hz), 5.20 (1H, s), 6.10 (1H, s), 7.40 (1H, d), 7.46 (1H, t, J = 7.6Hz), 7.76 (10H, m), 8.79 (1H, bt) [M⁺] 523.1 (C₂₅H₂₂ClF₃N₂O₃S requires 522.97).

Example 11: 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl]methyl]prop-2-enamide



Synthesis of [3-[4-(trifluoromethyl)phenyl]phenyl]methanamine **23B**

A suspension of 3-bromobenzylamine hydrochloride **22** (1 g, 4.49 mmol) in DME (50 mL) was added with 4-trifluoromethoxy phenyl boronic acid (1.2 mol eq, 1.11 g) and NaHCO₃ (3 mol eq, 1.13 g) suspended in water (30 mL). The mixture was degassed under vacuum, then Tetrakis(palladium) was added (catalytic amount) and the reaction was stirred at 100°C under inert atmosphere for 12h. The solvent was removed under reduced pressure and water was added to the residue (80 mL). The aqueous phase was extracted with EtOAc (3x40 mL) and the combined organic layer was washed with brine (50 mL) and dried over Na₂SO₄. The solvent was evaporated under vacuum to afford **23B** as a pale brown oil (1.5g, quantitative yield).

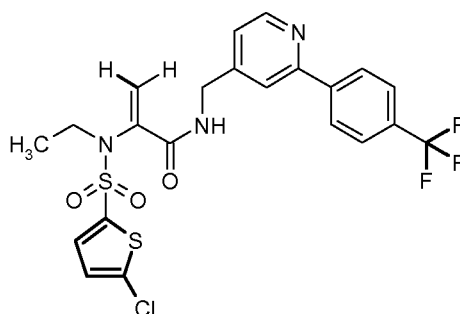
¹HNMR (DMSO, 200 MHz) δ 3.80 (bs, 2H), 3.77 (s, 2H), 7.42 (m, 2H), 7.52 (d,

1H), 7.68 (s, 1H), 7.79 (d, 2H), 7.89 (d, 2H)

Preparation of 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl]methyl]prop-2-enamide Example 11

A solution of acid **4B** (0.35 g, 1.28 mmol) in THF (25 mL) was added with DEPC (0.25 mL, 1.3 mol eq) and the mixture was stirred at room temperature for 10'. Then [3-[4-(trifluoromethoxy)phenyl]phenyl]methanamine **23B** (0.376 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water (40 mL) was added to the residue that is extracted with EtOAc (3x 25 mL) and washed with brine (1x40 mL). The separated organic phase was anydrified over Na₂SO₄, evaporated to dryness and the residue was purified by flash chromatography (1:1 EtOAc:Petroleum ether) to afford a white solid (0.15 g) after recrystallization from ethyl ether. Yield = 24%, ¹HNMR (DMSO, 200 MHz) δ 1.08 (t, 3H, J=8), 3.37 (q, 2H, J=7.5), 4.44 (d, 2H, J06.1), 5.16 (s, 1H), 6.09 (s, 1H), 7.32 (d, 1H), 7.46 (m, 5H), 7.53(d, 1H), 7.62 (s, 1H), 7.76 (dd, 2H), 7.86 (m, 2H), 8.78 (t, 1H); [M⁺] 522.51 (C₂₅H₂₂F₄N₂O₄S requires 522.12).

Example 12: 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide

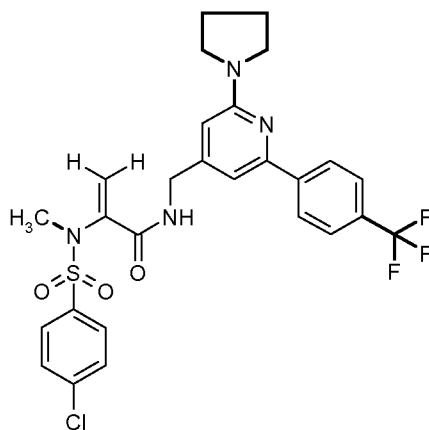


Preparation of 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 12

Acid **7** (295.76 mg, 1 mmol) was dissolved in 10 ml of THF and at rt DEPC (1.1 equiv, 0.15 ml) and [2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **21A** (1.1 equiv., 277.5 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30 ml) and washed with water (1 X 20

ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (1:1 EtOAc:petroleum ether) afforded 100 mg of a beige solid. Yield = 18.8% ^1H NMR (DMSO, 200 MHz) δ 1.12 (3H, t, J = 7Hz), 3.47 (2H, q), 4.48 (2H, d, J = 6.4Hz), 5.41 (1H, s), 6.25 (1H, s), 7.34 (2H, m), 7.59 (1H, d, J = 4Hz), 7.84 (2H, d, J = 8Hz), 7.98 (1H, bs), 8.28 (2H, d, J = 8 Hz), 8.63 (1H, d, J = 5 Hz), 8.91 (1H, bt) [M^{+1}] 530.1 ($\text{C}_{22}\text{H}_{19}\text{ClF}_3\text{N}_3\text{O}_3\text{S}_2$ requires 529.98).

Example 13: 2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide



Synthesis of 2-chloro-6-pyrrolidin-1-yl-pyridine-4-carbonitrile **25A**

A solution of 2,6-dichloropyridine-4-carbonitrile **24** (4 g, 23.5 mmol) in abs. EtOH (10 mL) was added with pyrrolidine (1.15 mL, 1 mol eq) and the mixture was heated at 70°C for 6 h. The solvent was removed under reduced pressure, water was added to the residue and the aqueous phase was extracted with EtOAc (3x40 mL). The combined organic phase was washed with brine (1x60 mL), dried over Na_2SO_4 and evaporated to afford **25A** as a pale yellow deliquescent solid (4.2g, 20 mmol, 87% Yield). ^1H NMR (DMSO, 400 MHz) δ 2.00 (m, 4H), 3.42 (m, 4H), 6.39 (s, 1H), 6.61 (s, 1H).

Synthesis of 2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]pyridine-4-carbonitrile **26A** (Bertelot et al., PCT, WO2010/141805 A1)

The nitrile **25A** (2.1 g, 10.3 mmol), 4-trifluoromethylphenylboronic acid (2.15 g, 1.1 mol eq), palladium acetate (45 mg, 0.02 mol eq), cesium carbonate (6.5 g, 2 mol eq),

and XPhos (190 mg, 0.04 mol eq) were mixed, placed under a nitrogen atmosphere and dioxane (10 mL) was added. The mixture was heated at 100°C overnight. After cooling, the mixture was filtered through a celite pad, washed with dioxane (2 x 20 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography (9.5:0.5 petroleum ether:EtOAc) to afford **26A** as a pale yellow semi-solid (2.8 g, 85% Yield). ¹HNMR (DMSO, 200 MHz) δ 1.93 (m, 4H), 3.45 (m, 4H), 6.91 (s, 1H), 7.55 (s, 1H), 7.82 (d, 2H, J=8), 8.26 (d, 2H, J=8.1).

Synthesis of [2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine 27A

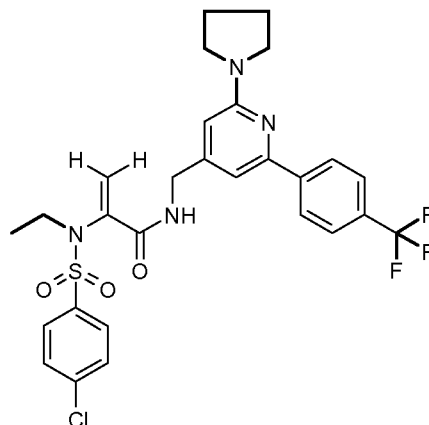
A solution of nitrile **26A** (2.8 g, 8.8 mmol) in diethyl ether (30 mL) was added in small amounts to a mixture of LiAlH₄ (0.67 g, 2 mol eq) in diethyl ether (30 mL) stirred at 0°C. After the addition was completed, the mixture was stirred at room temperature overnight. The excess of LiAlH₄ was destroyed at 0°C by addition of small amount of water (30 mL), the solid formed was filtered off and the organic filtrate was separated, washed with brine (50 mL) and dried over Na₂SO₄. The organic phase was evaporated under reduced pressure to afford **27A** as a pale yellow oil (2.8 g, 87% yield). ¹HNMR (DMSO, 200 MHz) δ 1.91 (m, 4H), 2.20 (bs, 2H), 3.37 (m, 4H), 3.70 (s, 2H), 6.48 (s, 1H), 7.20 (s, 1H), 7.78 (d, 2H, J=8), 8.23 (d, 2H, J=8).

Preparation of 2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 13

A solution of acid **4C** (0.40 g, 1.45 mmol) in THF (20 mL) was added with DEPC (0.28 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes. Then [2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27A** (0.51 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water was added to the residue that is extracted with EtOAc (3x 25 mL) and washed with brine (1x40 mL). The separated organic phase was dried over Na₂SO₄, evaporated to dryness and the residue was purified by flash chromatography (1:1 EtOAc:Petroleum

ether) to afford a white solid (0.18 g) after crystallization from ethyl ether. Yield = 22%, ^1H NMR (DMSO, 200 MHz) δ 1.95 (m, 4H), 2.95 (s, 3H), 3.46 (m, 4H), 4.36 (d, 2H), 5.12 (s, 1H), 5.86 (s, 1H), 6.52 (s, 1H), 7.22 (s, 1H), 7.73 (d, 2H, J=7.9), 7.82-7.79 (m, 5H), 8.26 (d, 2H, J=7.8), 8.85 (t, 1H); $[\text{M}^{+1}]$ 579.03 ($\text{C}_{27}\text{H}_{26}\text{ClF}_3\text{N}_4\text{O}_3\text{S}$ requires 578.13).

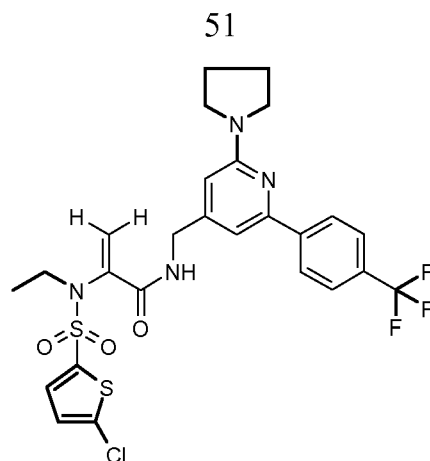
Example 14: 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide



Preparation of 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 14

Acid **4D** (289.74 mg, 1 mmol) was dissolved in 10 ml of THF and at rt DEPC (1.1 equiv, 0.15ml) and [2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27A** (1.1 equiv., 353.47 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:petroleum ether) afforded 140 mg of a pale yellow solid. Yield = 23.6% ^1H NMR (DMSO, 200 MHz) δ 1.09 (3H, t), 1.91 (4H, m), 3.38 (6H, m), 4.40 (2H, d), 5.17 (1H, s), 6.11 (1H, d), 6.34 (1H, s), 7.19 (1H, s), 7.78 (6H, m), 8.28 (2H, d), 8.80 (1H, bt) $[\text{M}^{+1}]$ 593.9 ($\text{C}_{28}\text{H}_{28}\text{ClF}_3\text{N}_4\text{O}_3\text{S}$ requires 593.06).

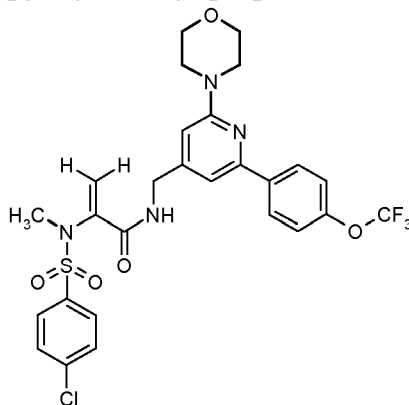
Example 15: 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide



Preparation of 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 15

Acid 7 (295.76 mg, 1 mmol) was dissolved in 10 ml of THF and at rt DEPC (1.1 equiv, 0.15 ml) and [2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27A** (1.1 equiv., 353.47 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30 ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:petroleum ether) afforded 150 mg of a pale yellow solid. Yield = 25% ¹HNMR (DMSO, 200 MHz) δ 1.07 (3H, t), 1.94 (4H, m), 3.41 (6H, m), 4.37 (2H, d), 5.39 (1H, s), 6.21 (1H, s), 6.31 (1H, s), 7.20 (1H, s), 7.34 (1H, d, J = 4.2Hz), 7.57 (1H, d, J = 4Hz), 7.91 (2H, d), 8.48 (2H, d), 8.75 (1H, bt) [M^{+1}] 599.9 ($C_{26}H_{26}ClF_3N_4O_3S_2$ requires 599.09).

Example 16: 2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide



Synthesis of 2-chloro-6-morpholino-pyridine-4-carbonitrile 25B

2,6-dichloropyridine-4-carbonitrile **24** (4gr, 23,13 mmol) was dissolved in 100 ml of ethanol. To the solution were added TEA (1 equiv., 3.22 ml), morpholine (1equiv., 2 ml) and the mixture was stirred at 70°C for 4 hours. (TLC AcOEt 3 / petroleum ether 7).

5 The solvent was evaporated and the residue was dissolved with ethyl acetate, washed with water and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The crude was crystallized from ethyl acetate and petroleum ether to give a beige solid. (4.6 g, 89% yield) ¹HNMR (DMSO, 400 MHz) δ 3.58 (4H, m), 3.64 (4H, m), 7.10 (1H, s), 7.32 (1H, s)

10 **Synthesis of 2-morpholino-6-[4-(trifluoromethoxy)phenyl]pyridine-4-carbonitrile 26D**

The carbonitrile **25B** (2.3 g, 10.28 mmol) was dissolved in 80 ml of dimethoxyethane. To the solution were added 40 ml of water, sodium bicarbonate (3 equiv., 2.6 g), [4-(trifluoromethoxy)phenyl]boronic acid (1.2 equiv., 2.54 g) and the
15 mixture was stirred at rt for 5'. The mixture was degassed and put under argon. A catalytic amount of tetrakispladium was added and the mixture was heated at 100°C overnight. The solvents were evaporated off and the residue was dissolved with ethyl acetate, washed with water and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The crude was crystallized from ethyl acetate and
20 petroleum ether to give a beige solid. (2.0 g, 55.5% yield) ¹HNMR (DMSO, 400 MHz) δ 3.61 (4H, m), 3.72 (4H, m), 7.20 (1H, s), 7.79 (1H, s), 7.82(2H, d, J = 8Hz), 8.35 (2H, d, J = 8Hz)

Synthesis of [2-morpholino-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine 27D

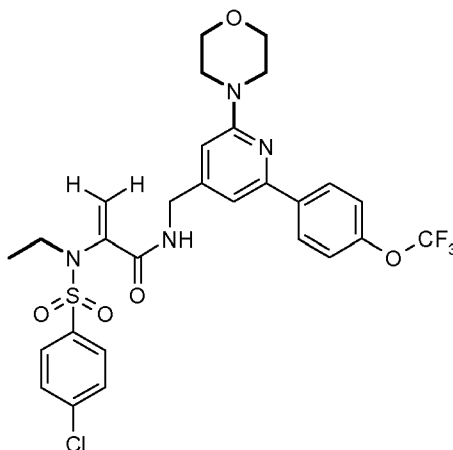
25 The nitrile **26D** (2 g, 5.7 mmol) dissolved in 50 ml of diethyl ether was added dropwise to a mixture of LiAlH₄ (434 mg, 2 equiv.) in diethyl ether (60 mL) stirred at 0°C. Then the mixture was stirred at room temperature overnight. The excess of LiAlH₄ was destroyed by water addition at 0°C, the solid formed was filtered, washed with Et₂O

and the filtrate was dried over Na₂SO₄ and evaporated to dryness to obtain 1.3 g of the amine **27D** as a yellow oil. Yield = 65% ¹HNMR (DMSO, 400 MHz) δ 3.30 (2H, bs), 3.51 (4H, m), 3.76 (6H, m), 6.80 (1H, s), 7.29 (1H, s), 7.42(2H, d, J = 8Hz), 8.18 (2H, dd)

Preparation of 2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 16

A solution of acid **4C** (0.40 g, 1.45 mmol) in THF (25 mL) was added with DEPC (0.28 mL, 1.3 mol eq) and the mixture was stirred at room temperature for about 5 minutes. Then [2-morpholino-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **27D** (0.56 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc and washed with water and brine. After drying over Na₂SO₄, the separated organic phase was evaporated under reduced pressure and the residue was purified by flash chromatography (7:3 EtOAc:Petroleum ether) to afford a pale yellow solid (0.24 g) after crystallization from a mixture of diethyl ether/petroleum ether. Yield = 36%, ¹HNMR (DMSO, 200 MHz) δ 2.95 (s, 3H), 3.55 (m, 4H), 3.70 (m, 4H), 4.40 (d, 2H, J= 6), 5.12 (s, 1H), 5.87 (s, 1H), 6.82 (s, 1H), 7.29 (s, 1H), 7.43 (d, 2H, J= 8.2), 7.83-7.74 (m, 4H), 8.17 (d, 2H, J=8), 8.86 (t, 1H); [M⁺] 611.03 (C₂₇H₂₆ClF₃N₄O₅S requires 610.13).

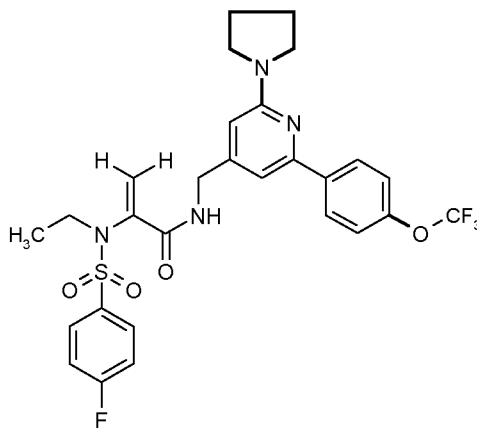
Example 17: 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide



Preparation of 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 17

Acid **4D** (289.74 mg, 1 mmol) was dissolved in 10 ml of THF and at rt DEPC (1.1 equiv, 0.15 ml) and [2-morpholino-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **27D** (1.1 equiv., 388 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30 ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:petroleum ether) afforded 140 mg of a pale yellow solid. Yield = 22% ¹HNMR (DMSO, 400 MHz) δ 1.15 (3H, t), 3.38 (2H, q), 3.50 (4H, m), 3.70 (4H, m), 4.40 (2H, d), 5.20 (1H, s), 6.18 (1H, s), 6.80 (1H, s), 7.20 (1H, s), 7.42 (2H, d), 7.76 (2H, d), 7.82 (2H, d), 8.18 (2H, d), 8.89 (1H, bt) [M⁺] 626.9 (C₂₈H₂₈ClF₃N₄O₅S requires 625.06).

Example 18: 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide



Synthesis of 2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]pyridine-4-carbonitrile 26C

A solution of nitrile **25A** (2.58 g, 12.5 mmol) in DME (90 mL) was added with 4-trifluoromethoxy phenyl boronic acid (2.64 g, 1.0 mol eq.) and NaHCO₃ (3.15 g, 3 mol eq.) suspended in water (45 mL). The mixture was degassed under vacuum, then Palladium Tetrakis was added (catalytic amount) and the reaction was stirred at 100°C

under inert atmosphere for 12h. The solvent was removed under reduced pressure and water was added to the residue (80 mL). The aqueous phase was extracted with EtOAc (3x60 mL) and the combined organic layer was washed with brine (80 mL) and dried over Na₂SO₄. The solvent was evaporated under vacuum to afford **26C** as deliquescent yellow solid (3.2 g, 9.6 mmol, 77% Yield). ¹HNMR (DMSO, 400 MHz) δ 1.85 (m, 4H), 3.42 (m, 4H), 6.38 (s, 1H), 7.08(s, 1H), 7.38 (d, 2H, J=8), 8.05 (d, 2H, J=8).

Synthesis of [2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine 27C

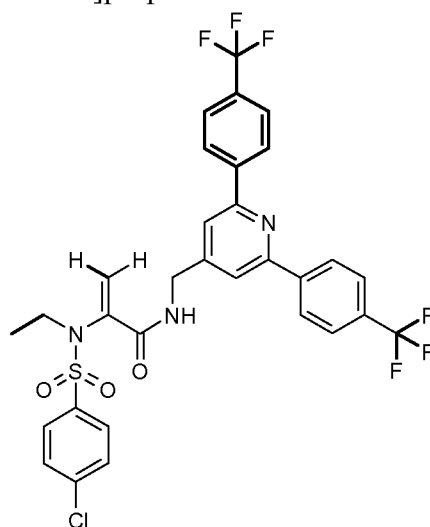
A solution of nitrile **26C** (1.1g, 3.3 mmol) in diethyl ether (30 mL) was added in small amounts to a mixture of LiAlH₄ (0.25 g, 2 mol eq) in diethyl ether (30 mL) stirred at 0°C. After the addition was completed, the mixture was stirred at room temperature overnight. The excess of LiAlH₄ was destroyed at 0°C by addition of small amount of water (30 mL), the solid formed was filtered off and the organic filtrate was separated, washed with brine (50 mL) and dried over Na₂SO₄. The organic phase was evaporated under reduced pressure and the residue was purified by flash chromatography (7:3 EtOAc:MeOH) to afford **27C** as a pale yellow oil (0.87 g, 77% yield). ¹HNMR (DMSO, 400 MHz) δ 1.97 (m, 4H), 3.48 (m, 4H), 3.68 (s, 2H), 4.15 (bs, 2H), 6.44 (s, 1H), 7.15 (s, 1H), 7.43 (d, 2H, J=8), 8.17 (d, 2H, J=8).

Preparation of 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 18

A solution of acid **4B** (0.21 g, 0.76 mmol) in THF (20 mL) was added with DEPC (0.15 mL, 1.3 mol eq) and the mixture was stirred at room temperature for about 5 minutes. Then [2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **27C** (0.29 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (30 mL) and washed with water (50 mL) and brine. The separated organic phase, after drying over Na₂SO₄, was evaporated under reduced pressure and the residue was purified by flash chromatography

(7:3 Petroleum ether: EtOAc:) to afford a white solid after recrystallization from diethyl ether (0.10 g, 22% Yield). ^1H NMR (DMSO, 200 MHz) δ 1.08 (t, 3H, J = 6.8 Hz), 1.94 (m, 4H), 3.39 (m, 2H), 3.44 (m, 4H), 4.37 (d, 2H, J = 6), 5.13 (s, 1H), 6.11 (s, 1H), 6.42 (s, 1H), 7.11 (s, 1H), 7.46-7.38 (m, 4H), 7.87 (m, 2H), 8.17 (d, 2H, J = 9.6), 8.77 (t, 1H); $[M^{+1}]$ 592.60 ($\text{C}_{28}\text{H}_{28}\text{F}_4\text{N}_4\text{O}_4\text{S}$ requires 592.17).

Example 19: N-[[2,6-bis[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-2-[(4-chlorophenyl)sulfonyl-ethyl-amino]prop-2-enamide



Synthesis of 2,6-bis[4-(trifluoromethyl)phenyl]pyridine-4-carbonitrile **28A**

2-6-dichloropyridine-4-carbonitrile **24** (3.7 g, 21.35 mmol) was dissolved in 100 ml of dimethoxyethane. To the solution were added 70 ml of water, sodium bicarbonate (3 equiv., 5.38 g), [4-(trifluoromethyl)phenyl]boronic acid (2.4 equiv., 9.74 g) and the mixture was stirred at rt for 5'. The mixture was degassed and put under argon. A catalytic amount of tetrakis(palladium) was added and the mixture was heated at 100°C overnight. The solvents were evaporated off and the residue was dissolved with ethyl acetate, washed with water and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The crude was crystallized from ethyl acetate and petroleum ether to give **28A** as a beige solid. (2.5 g, 30% yield)

Synthesis of [2,6-bis[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **29A**

The nitrile **28A** (4.7 g, 12 mmol) dissolved in 50 ml of diethyl ether was added dropwise to a mixture of LiAlH_4 (912 mg, 2 equiv.) in diethyl ether (80 mL) stirred at

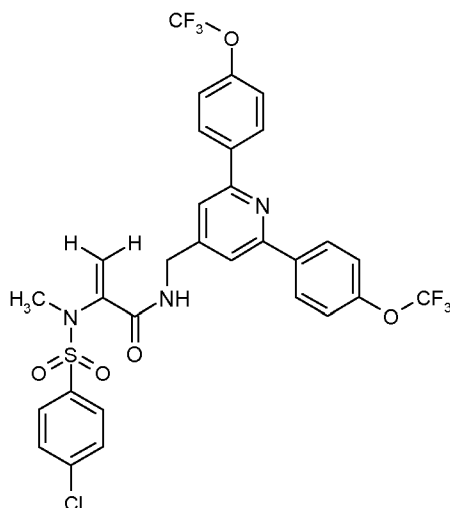
0°C. Then the mixture was stirred at room temperature overnight. The excess of LiAlH₄ was destroyed by water addition at 0°C, the solid formed was filtered, washed with Et₂O and the filtrate was dried over Na₂SO₄ and evaporated to dryness to obtain 2.5 g of the amine **29A** as yellow solid. Yield = 52% ¹HNMR (DMSO, 400 MHz) δ 2.25 (2H, bs),
 5 3.90 (2H, s), 7.90 (4H, d, J = 8Hz), 8.11 (2H, s), 8.40 (4H, d, J = 8Hz)

Preparation of N-[[2,6-bis[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-2-[(4-chlorophenyl)sulfonyl-ethyl-amino]prop-2-enamide Example 19

Acid **4D** (289.74 mg, 1 mmol) was dissolved in 10 ml of THF and at rt DEPC (1.1 equiv, 0.15 ml) and [2,6-bis[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **29A** (1.1
 10 equiv., 400 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30 ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:petroleum ether) afforded 140 mg of a white solid. Yield = 21% ¹HNMR (DMSO, 400 MHz) δ 1.25
 15 (3H, t), 3.40 (2H, q), 4.60 (2H, d), 5.18 (1H, s), 6.18 (1H, s), 7.70 (2H, d), 7.82 (2H, d), 7.86 (4H, d), 8.02 (2H, s), 8.40 (4H, d), 8.89 (1H, bt) [M⁺] 668.9 (C₃₁H₂₄ClF₆N₃O₃S requires 668.05).

Example 20: N-[[2,6-bis[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]-2-[(4-chlorophenyl)sulfonyl-methyl-amino]prop-2-enamide

20



Synthesis of 2,6-bis[4-(trifluoromethoxy)phenyl]pyridine-4-carbonitrile 28B

A solution of **24** (4.0 g, 19.4 mmol) in DME (120 mL) was added with 4-trifluoromethoxy phenyl boronic acid (1.1 mol eq, 4.2 g) and NaHCO₃ (3 mol eq, 4.9 g) suspended in water (90 mL). The mixture was degassed under vacuum, then a catalytic
5 amount of Tetrakis(palladium) was added and the reaction was stirred at 100°C under inert atmosphere for 12h. The solvent was removed under reduced pressure and water was added to the residue (100 mL). The aqueous phase was extracted with EtOAc (3x60 mL) and the combined organic layer was washed with brine (80 mL) and dried over Na₂SO₄. The solvent was evaporated under vacuum to afford **28B** as deep yellow solid after
10 recrystallization from diethyl ether/petroleum ether (68% Yield, 5.4 g, 13.8 mmol).
¹HNMR (DMSO, 400 MHz) δ 7.53 (d, 4H, J=7.8), 8.38 (d, 4H, J= 7.9), 8.48 (s, 2H).

Synthesis of [2,6-bis[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine 29B

A solution of nitrile **28B** (2.0 g, 5.1 mmol) in diethyl ether (40 mL) was added in small amounts to a mixture of LiAlH₄ (0.39 g, 2 mol eq) in diethyl ether (50 mL) stirred
15 at 0°C. After the addition was completed, the mixture was stirred at room temperature overnight. The excess of LiAlH₄ was destroyed at 0°C by addition of small amount of water (40 mL), the solid formed was filtered off and the organic filtrate was separated, washed with brine (50 mL) and dried over Na₂SO₄. The organic phase was evaporated under reduced pressure to afford **29B** as a pale orange oil (83% yield, 1.67 g, 4.2 mmol.).
20 ¹HNMR (DMSO, 400 MHz) δ 3.321 (bs, 2H), 4.01 (s, 2H), 7.50 (d, 4H, J=7.9), 7.98 (s, 2H), 8.31 (d, 4H, J=8).

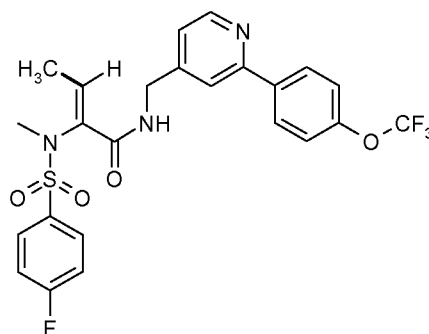
Preparation of N-[[2,6-bis[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]-2-[(4-chlorophenyl)sulfonyl-methyl-amino]prop-2-enamide Example 20

A solution of acid **4C** (0.50 g, 1.8 mmol) in THF (30 mL) was added with DEPC
25 (0.35 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes. Then [2,6-bis[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **29B** (0.66 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water was

added to the residue that is extracted with EtOAc (3x 30 mL) and washed with brine (1x50 mL). The separated organic phase was dried over Na₂SO₄, evaporated to dryness and the residue was purified by flash chromatography (6:4 EtOAc:Petroleum ether) to afford a white solid (0.22 g) after crystallization from diethyl ether. Yield = 18%, ¹HNMR (DMSO, 400 MHz) δ 2.96 (s, 3H), 4.55 (d, 2H, J=4), 5.13 (s, 1H), 5.90 (s, 1H), 7.49 (d, 4H), 7.25 (d, 2H), 7.79 (d, 2H), 7.96 (s, 2H), 8.31 (d, 4H, J= 6.8), 9.00 (t, 1H); [M⁺]

686.02 (C₃₀H₂₂ClF₆N₃O₅S requires 685.08).

Example 21: (Z)-2-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]but-2-enamide



Synthesis of methyl (2S)-2-[(4-fluorophenyl)sulfonylamino]-3-hydroxybutanoate **9A**

To L-threonine methyl ester hydrochloride **8** (4.8 g, 28.33 mmol) dissolved in methylene chloride (200ml) was added with TEA (2 equiv., 7.89 ml) and in one portion 4-fluorobenzenesulfonyl chloride (1.0 equiv., 28.79 mmol, 5.6 g). The reaction was refluxed for 4 hours. The solvent was evaporated and the crude was dissolved in AcOEt (100 ml) and washed with water (1 X 80 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude residue by crystallization from diethyl ether and petroleum ether afforded 7.45 g of the white product **9A**. Yield = 90% ¹HNMR (DMSO, 200 MHz) δ 1.01 (3H, d, J = 6.2 Hz), 3.39 (3H, s), 3.78 (1H, bs), 3.96 (1H, m), 4.93 (1H, d, J = 5.6 Hz), 7.39 (2H, m), 7.83 (2H, m), 8.12 (1H, bs)

Synthesis of methyl (2S)-2-[methyl-(4-fluorophenyl)sulfonyl-amino]-3-hydroxy-butanoate 10A

Compound **9A** (5.5 g, 19 mmol) dissolved in DMF (15 ml) was added with K_2CO_3 (1.1 equiv., 2.75 g) and methyl iodide (1.1 equiv., 1.94 ml) and the reaction was stirred at
5 rt overnight. The reaction was diluted with ethyl acetate and washed several times with water and finally with Brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude residue by crystallization from ethyl ether and petroleum ether afforded 5 g of **10A** as a semisolid. Yield = 86%. 1H NMR (DMSO, 200 MHz) δ 1.10 (3H, d, J = 6.2 Hz), 2.94 (3H, s), 3.46 (3H, s), 4.22 (1H, q, J =
10 6.4 Hz), 4.39 (1H, d, J = 5.2 Hz), 5.16 (1H, d, J = 3.2 Hz), 7.40 (2H, m), 7.82 (2H, m)

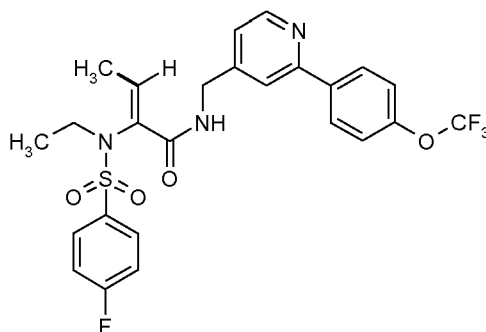
Synthesis of (Z)-2-[methyl-(4-fluorophenyl)sulfonyl-amino]but-2-enoic acid 11A

Compound **10A** (4.576 g, 15 mmol) dissolved in THF (30 ml) and water (10 ml) was added with $LiOH \cdot H_2O$ (3 equiv., 1.88 g) and the reaction was stirred at rt for 3 hours.
15 The reaction was concentrated under vacuum. Water was added and then 10% HCl till precipitation of the acid. The acid was extracted with ethyl acetate and the organic phase was washed with Brine, dried over sodium sulfate and concentrated under vacuum to give 4 g of a white solid. Yield = 93%. 1H NMR (DMSO, 200 MHz) δ 1.08 (3H, t, J = 7 Hz), 2.95 (3H, s), 4.02 (1H, q), 4.26 (1H, bs), 5.08 (1H, bs), 7.43 (2H, m), 7.85 (2H, m), 12.84
20 (1H, bs). The intermediate acid (2 g, 9.7 mmol) dissolved in pyridine (10 ml) was added dropwise with acetyl chloride (1.4 equiv., 1.1 ml) at 0°C and the reaction was then stirred at rt for 5 hours. The reaction was quenched by addition of 10% HCl and then extracted with ethyl acetate. The organic phase was washed 2 times with water, with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was crystallized
25 from diethyl ether and petroleum ether to give 1g of a beige solid. Yield = 50%. 1H NMR (DMSO, 200 MHz) δ 1.76 (3H, d, J = 7 Hz), 2.95 (3H, s), 7.04 (1H, q, J = 7 Hz), 7.45 (2H, m), 7.83 (2H, m), 12.74 (1H, bs)

Preparation of (Z)-2-[methyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]but-2-enamide Example 21

Acid **11A** (515 mg, 2.5 mmol) was dissolved in 10 ml of THF and at rt DEPC (1.1 equiv, 0.38ml) and [2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **21B** (1.1 equiv., 737 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30 ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (1:1 EtOAc:petroleum ether) afforded 200 mg of a pale yellow solid. Yield = 15% ¹HNMR (DMSO, 200 MHz) δ 1.74 (3H, d J = 7.4 Hz), 3.06 (3H, s), 4.40 (2H, d, J = 6 Hz), 6.83 (1H, q, J = 7 Hz), 7.44 (5H, m), 7.83 (3H, m), 8.18 (2H, d, J = 8.2 Hz), 8.59 (1H, d, J = 5.2 Hz), 8.70 (1H, bt) [M⁺] 524.3 (C₂₄H₂₁F₄N₃O₄S requires 523.50).

Example 22: (Z)-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]but-2-enamide



Synthesis of methyl (2S)-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-3-hydroxybutanoate **10B**

Compound **9A** (1 g, 3.0 mmol) dissolved in DMF (10 ml) was added with K₂CO₃ (1.1 equiv., 456 mg) and ethyl iodide (1.1 equiv., 0.316 ml) and the reaction was stirred at rt overnight. The reaction was diluted with ethyl acetate and washed several times with water and finally with Brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude residue by crystallization from ethyl ether and petroleum ether afforded 895 mg of a semisolid. Yield = 93%. ¹HNMR

(DMSO, 200 MHz) δ 1.13 (3H, d, J = 6.2 Hz), 1.26 (3H, t, J = 7 Hz), 3.32 (3H, s), 3.41 (2H, q, J = 7.8 Hz), 4.02 (1H, bs), 4.23 (1H, m), 5.13 (1H, d, J = 4.6 Hz), 7.42 (2H, m), 7.84 (2H, m)

Synthesis of (Z)-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]but-2-enoic acid 11B

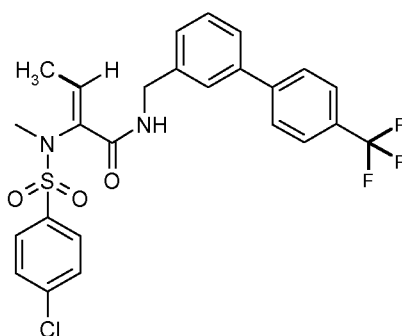
5 Compound **10B** (895 mg, 2.8 mmol) dissolved in THF (10 ml) and water (5 ml) was added with LiOH·H₂O (3 equiv., 352 mg) and the reaction was stirred at rt 3 hours. The reaction was concentrated under vacuum. Water was added and 10% HCl till precipitation of the acid. The acid was extracted with ethyl acetate and the organic phase was washed with Brine, dried over sodium sulfate and concentrated under vacuum to give
10 770 mg of a white solid. Yield = 96%. ¹HNMR (DMSO, 200 MHz) δ 1.00 (3H, t, J = 7.2 Hz), 1.17 (3H, t, J = 7 Hz), 3.34 (2H, q, J = 7.8 Hz), 4.02 (1H, m), 4.21 (1H, bs), 5.13 (1H, bs), 7.43 (2H, m), 7.85 (2H, m), 12.84 (1H, bs). The intermediate acid (1.6 g, 7 mmol) dissolved in pyridine (10 ml) was added dropwise with acetyl chloride (1.4 equiv., 0.8 ml) at 0°C and the reaction was then stirred at rt for 5 hours. The reaction was
15 quenched by addition of 10% HCl and then extracted with ethyl acetate. The organic phase was washed 2 times with water, with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was crystallized from diethyl ether and petroleum ether to give 650 mg of **11B** as a beige solid. Yield = 32%. ¹HNMR (DMSO, 200 MHz) δ 1.00 (3H, t, J = 7.4 Hz), 1.80 (3H, d J = 7.2 Hz), 3.47 (2H, m), 7.18 (1H, q, J = 6.6 Hz), 7.43 (2H, m), 7.83 (2H, m), 12.64 (1H, bs)
20

Preparation of (Z)-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]but-2-enamide Example 22

Acid **11B** (574 mg, 2 mmol) was dissolved in 10 ml of THF and at rt DEPC (1.1 equiv, 0.3 ml) and [2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **21B** (1.1
25 equiv., 590 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (1:1 EtOAc:petroleum

ether) afforded 195 mg of a white solid. Yield = 18% ^1H NMR (DMSO, 200 MHz) δ 1.00 (3H, t, J = 7.2 Hz), 1.46 (3H, d J = 7.4 Hz), 3.43 (2H, q, J = 7 Hz), 4.40 (2H, d, J = 6 Hz), 6.83 (1H, q, J = 7 Hz), 7.25 (1H, dd, J = 6.4 Hz), 7.42 (4H, m), 7.85 (3H, m), 8.18 (2H, d, J = 8.2 Hz), 8.60 (1H, d, J = 5 Hz), 8.74 (1H, bt) $[\text{M}^{+1}]$ 538.1 ($\text{C}_{25}\text{H}_{23}\text{F}_4\text{N}_3\text{O}_4\text{S}$ requires 537.53).

Example 23: (Z)-2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]but-2-enamide



10 **Synthesis of methyl (2S)-2-[(4-chlorophenyl)sulfonylamino]-3-hydroxy-butanoate 9C**

L-Threonine methyl ester hydrochloride **8** (4.8 g, 28.33 mmol) dissolved in methylene chloride (200 ml) was added with TEA (2equiv., 7.89 ml) and in one portion 4-chlorobenzenesulfonyl chloride (1.0 equiv., 5.97 g). The reaction was refluxed for 4 hours. The solvent was evaporated and the crude was dissolved in AcOEt (100 ml) and washed with water (1 X 80 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude residue by crystallization from diethyl ether and petroleum ether afforded 9.6 g of the white product. Yield = 98% ^1H NMR (DMSO, 200 MHz) δ 1.00 (3H, d, J = 6.4 Hz), 3.40 (3H, s), 3.78 (1H, d, J = 4 Hz), 3.95 (1H, m), 4.96 (1H, d, J = 5.6 Hz), 7.64 (2H, m), 7.77 (2H, m), 8.12 (1H, bs)

Synthesis of methyl (2S)-2-[methyl-(4-chlorophenyl)sulfonyl-amino]-3-hydroxy-butanoate 10C

Compound **9C** (3, 8.7 mmol) dissolved in DMF (10 ml) was added with K_2CO_3

(1.1 equiv., 1.3) and methyl iodide (1.1 equiv., 0.88 ml) and the reaction was stirred at rt overnight. The reaction was diluted with ethyl acetate and washed several times with water and finally with Brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude residue by crystallization from ethyl ether and petroleum ether afforded 2.85 g of **10C** as a semisolid. Yield = 93.7%.
5 ¹HNMR (DMSO, 200 MHz) δ 1.08 (3H, d, J = 6.4 Hz), 2.94 (3H, s), 3.46 (3H, s), 4.22 (1H, q), 4.41 (1H, d), 5.20 (1H, d), 7.65 (2H, m), 7.74 (2H, m)

**Synthesis of (Z)-2-[methyl-(4-chlorophenyl)sulfonyl-amino]but-2-enoic acid
11C**

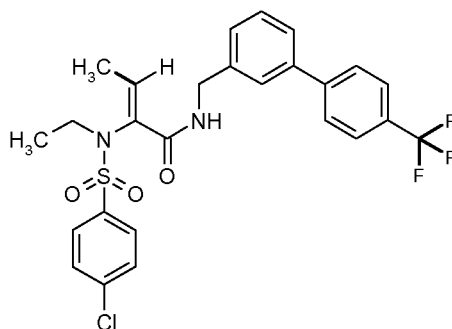
10 Compound **10C** (2.85 g, 8.15 mmol) dissolved in THF (30 ml) and water (10 ml) was added with LiOH·H₂O (3 equiv., 1.03 g) and the reaction was stirred at rt for 3 hours. The reaction was concentrated under vacuum. Water was added and then 10% HCl till precipitation of the acid. The acid was extracted with ethyl acetate and the organic phase was washed with Brine, dried over sodium sulfate and concentrated under vacuum to give
15 2.5 g of a white solid. Yield = 91%. ¹HNMR (DMSO, 200 MHz) δ 1.08 (3H, t, J = 7 Hz), 2.73 (3H, s), 4.02 (1H, q), 4.26 (1H, bs), 5.02 (1H, bs), 7.63 (2H, m), 7.79 (2H, m), 12.09 (1H, bs) The intermediate acid (2.5 g, 7.45 mmol) dissolved in pyridine (10 ml) was added dropwise with acetyl chloride (1.4 equiv., 0.83 ml) at 0°C and the reaction was then stirred at 50°C for 5 hours. The reaction was quenched by addition of 10% HCl and then
20 extracted with ethyl acetate. The organic phase was washed 2 times with water, with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was crystallized from diethyl ether and petroleum ether to give 870mg of **11C** as a beige solid. Yield = 40%. ¹HNMR (DMSO, 200 MHz) δ 1.77 (3H, d, J = 7.2 Hz), 3.32 (3H, s), 7.04 (1H, q, J = 6.8 Hz), 7.64 (2H, m), 7.77 (2H, m), 12.74 (1H, bs)

25 **Preparation of (Z)-2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]but-2-enamide Example 23**

Acid **11C** (868 mg, 3 mmol) was dissolved in 10 ml of THF and at rt DEPC (1.1 equiv, 0.5ml) and [3-[4-(trifluoromethyl)phenyl]phenyl]methanamine **23A** (1.1 equiv.,

837 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30 ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:petroleum ether) afforded 200 mg of a pale yellow solid. Yield = 13% ¹HNMR (DMSO, 200 MHz) δ 1.47 (3H, d, J = 7 Hz), 3.01 (3H, s), 4.27 (2H, d, J = 6.2 Hz), 6.68 (1H, q), 7.60 (12H, m), 8.64 (1H, bt) [M^{+1}] 523.2 (C₂₅H₂₂ClF₃N₂O₃S requires 522.97).

Example 24: (Z)-2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]but-2-enamide



Synthesis of methyl (2S)-2-[ethyl-(4-chlorophenyl)sulfonyl-amino]-3-hydroxybutanoate **10D**

Compound **9C** (3 g, 8.94 mmol) dissolved in DMF (15 ml) was added with K₂CO₃ (1.1 equiv., 1.36 g) and ethyl iodide (1.1 equiv., 1 ml) and the reaction was stirred at rt overnight. The reaction was diluted with ethyl acetate and washed several times with water and finally with Brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude residue by crystallization from ethyl ether and petroleum ether afforded 2.8 g of a semisolid. Yield = 97%. ¹HNMR (DMSO, 200 MHz) δ 1.00 (3H, d, J = 6.2 Hz), 1.26 (3H, t, J = 7 Hz), 3.32 (3H, s), 3.34 (2H, m), 4.02 (1H, bs), 4.23 (1H, m), 5.14 (1H, d, J = 4.4 Hz), 7.62 (2H, m), 7.76 (2H, m)

Synthesis of (Z)-2-[ethyl-(4-chlorophenyl)sulfonyl-amino]but-2-enoic acid **11D**

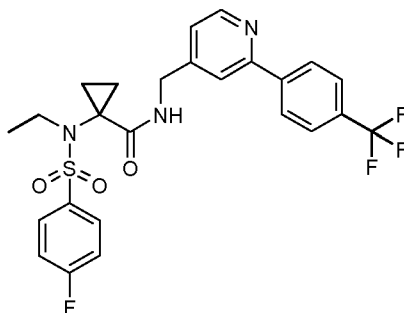
Compound **10D** (2.08 g, 6.2 mmol) dissolved in THF (20 ml) and water (5 ml) was added with LiOH·H₂O (3 equiv., 783 mg) and the reaction was stirred at rt 3 hours. The

reaction was concentrated under vacuum. Water was added and 10% HCl till precipitation of the acid. The acid was extracted with ethyl acetate and the organic phase was washed with Brine, dried over sodium sulfate and concentrated under vacuum to give 1.75 g of a white solid. Yield = 88%. ¹HNMR (DMSO, 200 MHz) δ 1.02 (3H, t, J = 6.4 Hz), 1.17 (3H, t, J = 7 Hz), 3.31 (2H, m), 4.02 (1H, m), 4.21 (1H, bs), 5.13 (1H, bs), 7.63 (2H, m), 7.78 (2H, m), 12.88 (1H, bs). The intermediate acid (1.75 g, 5.44 mmol) dissolved in pyridine (10 ml) was added dropwise with acetyl chloride (1.4 equiv., 0.6 ml) at 0°C and the reaction was then stirred at rt for 5 hours. The reaction was quenched by addition of 10% HCl and then extracted with ethyl acetate. The organic phase was washed 2 times with water, with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was crystallized from diethyl ether and petroleum ether to give 600 mg of **11D** as a beige solid. Yield = 36%. ¹HNMR (DMSO, 200 MHz) δ 1.00 (3H, t, J = 7.2 Hz), 1.80 (3H, d, J = 7 Hz), 3.45 (2H, m), 7.20 (1H, q), 7.63 (2H, d, J = 8.6 Hz), 7.76 (2H, d, J = 8.6 Hz), 12.64 (1H, bs)

Preparation of (Z)-2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]but-2-enamide Example 24

Acid **11D** (600 mg, 1.97 mmol) was dissolved in 10 ml of THF and at rt DEPC (1.1 equiv, 0.3ml) and [3-[4-(trifluoromethyl)phenyl]phenyl]methanamine **23A** (1.1 equiv., 550 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:petroleum ether) afforded 150 mg of a white solid. Yield = 14% ¹HNMR (DMSO, 200 MHz) δ 0.98 (3H, t, J = 7.2 Hz), 1.53 (3H, d J = 7.4 Hz), 3.36 (2H, q, J = 7 Hz), 4.28 (2H, d, J = 6 Hz), 6.80 (1H, q, J = 7 Hz), 7.8 (12H, m), 8.60 (1H, bt) [M⁺] 537.1 (C₂₆H₂₄ClF₃N₂O₃S requires 536.99).

Example 25: 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide



Synthesis of methyl 1-[(4-fluorophenyl)sulfonylamino]cyclopropanecarboxylate 13A

A suspension of methyl-1-aminocyclopropane carboxylate hydrochloride **12** (0.6 g, 3.96 mmol) in CH₂Cl₂ (60 mL) was added with TEA (1.1 mol eq, 0.6 mL) and the mixture was stirred at r.t. for 10 minutes. Then 4-fluorobenzensulfonyl chloride (1 mol eq, 0.77 g) and additional TEA (1.1 mol eq) were added and the solution was heated at 60°C overnight. The solvent was removed under reduced pressure, water was added to the residue (100 mL) and the aqueous phase was extracted with EtOAc (3x40 mL). The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure to afford **13A** as transparent oil (1.07 g, 99% yield). ¹HNMR (DMSO, 200 MHz) δ 1.17 (m, 2H), 1.27 (m, 2H), 3.32 (s, 3H), 7.46 (t, 2H, J=9), 7.80 (m, 2H), 8.78 (bs, 1H).

Synthesis of methyl 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxylate 14A

A solution of **13A** (1g, 3.67 mmol) in DMF (15 mL) was added with an. K₂CO₃ (1.5 mol eq, 0.76 g) and, after few minutes, 2-iodoethane (1.2 mol eq, 0.45 ml) was added and the mixture was heated at 50°C for 12h. The solvent was removed under reduced pressure, water was added to the residue (60 mL) and the aqueous phase was extracted with EtOAc (3x30 mL). The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure to afford **14A** as a pale yellow oil (1.1 g, 98% yield). ¹HNMR (DMSO, 200 MHz) δ 1.095 (t, 3H, J=8), 4.43 (bs, 4H), 2.88 (s, 3H), 3.32 (m, 2H), 7.42 (t, 2H, J=8.2), 7.87 (m, 2H).

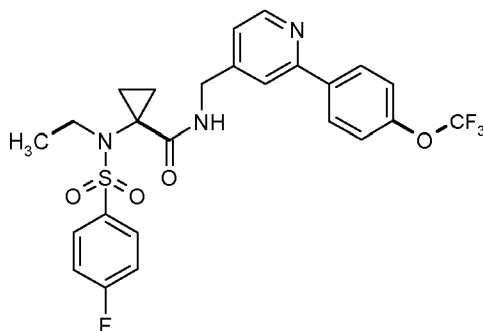
Synthesis of 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxylic acid **15A**

A solution of **14A** (1.3 g, 4.33 mmol) in dioxane (40 mL) was added with 10% NaOH aq. solution (20 mL) and the mixture was heated at 50°C overnight. The organic solvent was removed under reduced pressure and the aqueous phase was acidified with 10% HCl. The solid formed was collected by filtration, washed with water (2x20 mL) and dried to afford **15A** as white solid (1.0 g, 81% yield). ¹HNMR (DMSO, 200 MHz) δ 1.10 (t, 3H, J=7.2), 1.65 (bs, 4H), 7.39 (m, 2H), 7.84 (m, 2H), 12.90 (bs, 1H).

Preparation of 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide **Example 25**

Acid **15A** (303 mg, 1 mmol) was dissolved in 5 ml of THF and at rt DEPC (1.1 equiv, 0.17 ml) and [2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **21A** (1.1 equiv., 277.5 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (1:1 EtOAc:Petroleum ether) afforded 140 mg of a white solid. Yield = 26.8% ¹HNMR (DMSO, 400 MHz) δ 1.09 (2H, bs), 1.23 (3H, t, J = 7.2 Hz), 1.40 (2H, bs), 3.40 (2H, q, J = 6.8 Hz), 4.41 (2H, bs), 7.26 (1H, dd), 7.42 (2H, t, J = 8.8 Hz), 7.87 (4H, m), 7.98 (1H, bs), 8.30 (3H, bd), 8.64 (1H, dd, J = 4.8 Hz) [M⁺] 521.9 (C₂₅H₂₃F₄N₃O₃S requires 521.53).

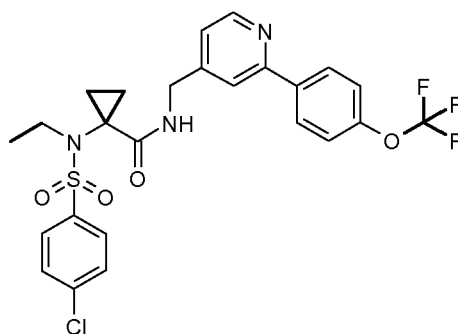
Example 26: 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide



Preparation of 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide Example 26

A solution of acid **15A** (0.5 g, 1.7 mmol) in THF (30 mL) was added with DEPC (0.34 mL, 1.3 mol eq) and the mixture was stirred at room temperature for about 5 minutes. Then [2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **21B** (0.51 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (40 mL) and washed with water (50 mL) and brine. The separated organic phase was dried over Na₂SO₄ and evaporated under reduced pressure and the residue was purified by flash chromatography (7:3 EtOAc:Petroleum ether) to afford a white solid (0.18 g) after crystallization from diethyl ether. Yield = 30%, ¹HNMR (DMSO, 200 MHz) δ 1.09 (bs, 2H), 1.22 (t, 3H, J= 8), 1.26 (bs, 2H), 3.41 (bs, 2H), 4.43 (d, 2H, J= 6); 7.27 (d, 1H, J= 4), 7.46-7.42 (m, 4H), 7.90 (m, 3H), 8.23 (m, 3H), 8.61 (d, 1H, J= 5.2). [M⁺] 537.53 (C₂₅H₂₃F₄N₃O₄S requires 537.13).

Example 27: 1-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide



Synthesis of methyl 1-[(4-chlorophenyl)sulfonylamino]cyclopropanecarboxylate 13B

To methyl 1-aminocyclopropanecarboxylate hydrochloride **12** (500 mg, 3.298 mmol) dissolved in methylene chloride (20ml) was added with TEA (2 equiv., 1 ml) and in one portion 4-chlorobenzenesulfonyl chloride (1.0 equiv., 765 mg). The reaction was refluxed for 4 hours. The solvent was evaporated and the crude was dissolved in EtOAc

(50 ml) and washed with water (1 X 30 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude residue by crystallization from diethyl ether and petroleum ether afforded 800 mg of the white product **13B**. Yield = 84% ¹HNMR (DMSO, 200 MHz) δ 1.16 (2H, m), 1.30 (2H, m), 3.32 (3H, s), 7.70 (4H, m), 8.87 (1H, bs)

Synthesis of methyl 1-[(4-chlorophenyl)sulfonyl-ethyl-amino]cyclopropanecarboxylate 14B

Compound **13B** (800 mg, 2.76 mmol) dissolved in DMF (10 ml) was added with K₂CO₃ (1.1 equiv., 420 mg) and ethyl iodide (1.1 equiv., 0.3 ml) and the reaction was stirred at rt overnight. The reaction was diluted with ethyl acetate and washed several times with water and finally with Brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude residue by crystallization from ethyl ether and petroleum ether afforded 750 mg of **14B** as a semisolid. Yield = 85.5%. ¹HNMR (DMSO, 200 MHz) δ 1.096 (3H, t, J = 7.2 Hz), 1.17 (2H, m), 1.43 (2H, bs), 3.34 (2H, m), 3.43 (3H, s), 7.68 (2H, m), 7.79 (2H, m)

Synthesis of 1-[(4-chlorophenyl)sulfonyl-ethyl-amino]cyclopropanecarboxylic acid 15B

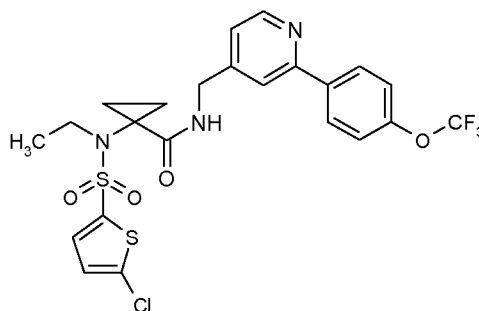
Compound **14B** (750 mg, 2.36 mmol) dissolved in THF (10 ml) and water (5 ml) was added with LiOH·H₂O (3 equiv., 297 mg) and the reaction was stirred at rt 3 hours. The reaction was concentrated under vacuum. Water was added and 10% HCl till precipitation of the acid. The acid was extracted with ethyl acetate and the organic phase was washed with Brine, dried over sodium sulfate and concentrated under vacuum to give 650 mg of **15B** as a white solid. Yield = 90%. ¹HNMR (DMSO, 200 MHz) δ 1.06 (3H, t, J = 7.2 Hz), 1.38 (2H, m), 1.35 (2H, bs), 3.33 (2H, bm), 7.43 (2H, m), 7.77 (2H, m), 12.46 (1H, bs)

Preparation of 1-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide Example 27

Acid **15B** (303 mg, 1 mmol) was dissolved in 5 ml of THF and at rt DEPC (1.1

equiv, 0.17 ml) and [2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **21B** (1.1 equiv., 295 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30 ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:Petroleum ether) afforded 100mg of a white solid. Yield = 18% ¹HNMR (DMSO, 200 MHz) δ 1.12 (2H, bs), 1.22 (3H, t, J = 7.2 Hz), 1.40 (2H, bs), 3.40 (2H, q, J = 4.8 Hz), 4.41 (2H, d, J = 5.4 Hz), 7.26 (1H, dd, J = 3.8 Hz), 7.49 (2H, d, J = 8 Hz), 7.65 (2H, dd, J = 8.6 Hz), 7.84 (2H, dd, J = 6.8 Hz, J' = 1.6 Hz), 7.90 (1H, bs), 8.20 (2H, dd, J = 6.8 Hz, J' = 1.8 Hz), 8.28 (1H, t), 8.59 (1H, d, J = 5.2 Hz) [M^{+1}] 553.9 (C₂₅H₂₃ClF₃N₃O₄S requires 553.98).

Example 28: 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide



Synthesis of methyl 1-[(5-chloro-2-thienyl)sulfonylamino]cyclopropanecarboxylate 16

A suspension of methyl-1-aminocyclopropanecarboxylate hydrochloride **12** (1 g, 1.43 mmol) in CH₂Cl₂ (100 mL) was added with TEA (1.1 mol eq, 1.01 mL) and the mixture was stirred at r.t. for 10 minutes. Then 5-chloro-thiophene-2-sulfonyl chloride (1 mol eq, 1.43 g) and additional TEA (1.1 mol eq) were added and the solution was heated at 50°C overnight. The solvent was removed under reduced pressure, water was added to the residue (100 mL) and the aqueous phase was extracted with EtOAc (3x50 mL). The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure to afford **16** as a pale orange oil (quantitative yield). ¹HNMR (DMSO, 200 MHz) δ 1.23 (m, 2H), 1.35 (m, 2H), 1.98 (s, 3H), 7.23 (d, 1H, J = 4), 7.73 (d, 1H, J = 3.9), 9.12 (bs, 1H).

Synthesis of methyl 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]cyclopropanecarboxylate **17**

A solution of **16** (2 g, 6.7 mmol) in DMF (20 mL) was added with an. K₂CO₃ (1.5 mol eq, 1.4 g) and, after few minutes, 2-iodoethane (1.2 mol eq, 0.84 ml) was added and the mixture was heated at 50°C for 4h. The solvent was removed under reduced pressure, water was added to the residue (100 mL) and the aqueous phase was extracted with EtOAc (3x50 mL). The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure to afford **17** as a pale yellow oil (2.1 g, 95% yield). ¹HNMR (DMSO, 200 MHz) δ 1.18 (m, 2H), 1.25 (t, 3H), 1.37 (m, 2H), 1.98 (s, 3H), 3.45 (m, 2H), 7.28 (d, 1H, J= 4), 7.78 (d, 1H, J=3.9)

Synthesis of 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]cyclopropanecarboxylic acid **18**

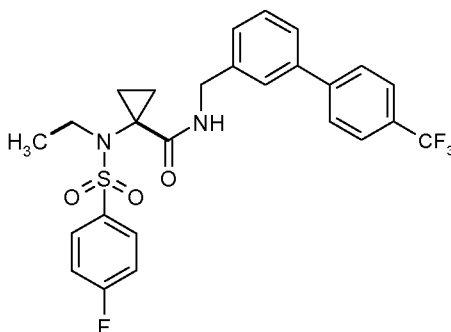
A solution of **17** (2.1 g, 6.5 mmol) in dioxane (20 mL) was added with 10% NaOH aq. solution (20 mL) and the mixture was heated at 50°C overnight. The organic solvent was removed under reduced pressure and the aqueous phase was acidified with 10% HCl. The solid formed was collected by filtration, washed with water (2x20 mL) and dried to afford **18** as a pale yellow solid (1.6 g, 85% yield). ¹HNMR (DMSO, 200 MHz) δ 1.13 (t, 3H, J=7.4), 1.39 (bs, 4H), 3.36 (m, 2H), 7.25 (d, 2H, J=4.1), 7.52 (d, 2H, H=4)), 12.90 (bs, 1H).

Preparation of 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide Example **28**

A solution of acid **18** (0.50 g, 1.62 mmol) in THF (25 mL) was added with DEPC (0.32 mL, 1.3 mol eq) and the mixture was stirred at room temperature for 10'. Then [2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **21B** (0.47 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water (40 mL) was added to the residue that was extracted with EtOAc (3x 25 mL) and washed with brine (1x40 mL). The separated organic phase was dried over Na₂SO₄, evaporated to

dryness and the residue was purified by flash chromatography (1:1 EtOAc:Petroleum ether) to afford a pale yellow oil (0.31 g). Yield = 35%, ^1H NMR (DMSO, 200 MHz) δ 1.22 (t, 3H), 1.40 (bs, 2H), 1.61 (bs, 2H), 4.16 (q, 2H), 4.42 (d, 2H, $J=6.1$), 7.26 (m, 2H), 7.46 (d, 2H, $J=8$), 7.6 (dd, 1H), 7.87 (s, 1H), 8.21 (d, 2H, $J=7.9$), 8.25 (t, 1H), 8.60 (d, 1H, $J=4$); $[\text{M}^{+1}]$ 560.01 ($\text{C}_{23}\text{H}_{21}\text{ClF}_3\text{N}_3\text{O}_4\text{S}_2$ requires 559.06).

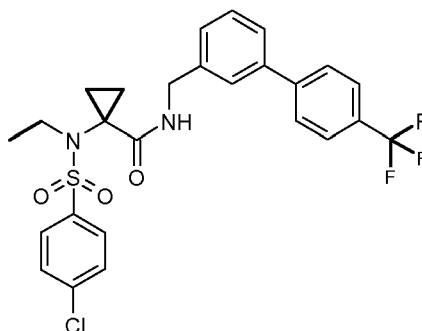
Example 29: 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]cyclopropanecarboxamide



Preparation of 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]cyclopropanecarboxamide Example 29

A solution of acid **15A** (0.30 g, 1.45 mmol) in THF (20 mL) was added with DEPC (0.21 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes. Then 3-[4-(trifluoromethyl)phenyl]phenylmethanamine **23A** (0.29 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water was added to the residue that is extracted with EtOAc (3x 25 mL) and washed with brine (1x40 mL). The separated organic phase was dried over Na_2SO_4 , evaporated to dryness and the residue was purified by flash chromatography (7:3 EtOAc:Petroleum ether) to afford a white solid (0.13 g) after crystallization from ethyl ether. Yield = 25%, ^1H NMR (DMSO, 200 MHz) δ 1.055 (t, 2H), 1.17 (t, 3H, $J=7$), 1.28 (bs, 2H), 3.43 (q, 2H), 4.29 (d, 2H, $J=6$), 7.25 (d, 2H), 7.40 (m, 3H), 7.47 (m, 3H), 7.87-7.83 (m, 4H), 8.15 (t, 1H); $[\text{M}^{+1}]$ 520.54 ($\text{C}_{26}\text{H}_{24}\text{F}_4\text{N}_2\text{O}_3\text{S}$ requires 520.14).

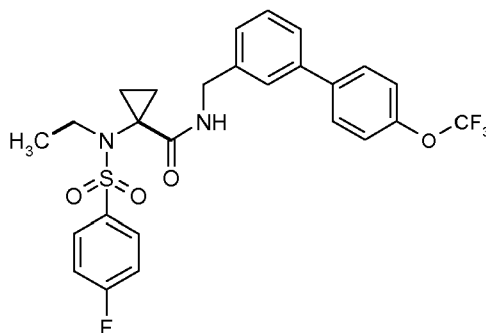
Example 30: 1-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]cyclopropanecarboxamide



Preparation of 1-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]cyclopropanecarboxamide Example 30

Acid **15B** (303 mg, 1 mmol) was dissolved in 5 ml of THF and at rt DEPC (1.1 equiv, 0.17ml) and [3-[4-(trifluoromethyl)phenyl]phenyl]methanamine **23A** (1.1 equiv., 276 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30 ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:Petroleum ether) afforded 90 mg of a white solid. Yield = 17% ¹HNMR (DMSO, 200 MHz) δ 1.11 (2H, bm), 1.18 (3H, t, J = 7 Hz), 1.38 (2H, bs), 3.40 (2H, bm), 4.38 (2H, d, J = 5.8 Hz), 7.30 (1H, dd), 7.46 (1H, t, J = 7.6 Hz), 7.64 (4H, m), 7.85 (6H, m), 7.90 (1H, bs), 8.10 (1H, t) [M⁺] 537.3 (C₂₆H₂₄ClF₃N₂O₃S requires 536.99).

Example 31: 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl]methyl]cyclopropanecarboxamide

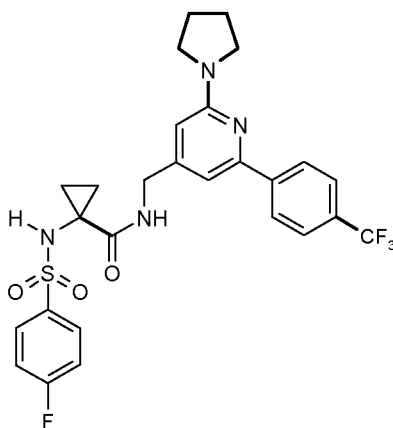


Preparation of 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl]methyl]cyclopropanecarboxamide Example 31

A solution of acid **15A** (0.30 g, 1.8 mmol) in THF (20 mL) was added with DEPC (0.21 mL, 1.3 mol eq) and the mixture was stirred at room temperature for 10 minutes.

- 5 Then [3-[4-(trifluoromethoxy)phenyl]phenyl]methanamine **23B** (0.308 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (45 mL) and washed with water (50 mL) and brine. The separated organic phase was dried over an. Na₂SO₄ and evaporated under reduced pressure. The residue was purified by flash chromatography (1:1 EtOAc:Petroleum ether) to afford a white solid (0.15 g). Yield = 28%, ¹HNMR (DMSO, 200 MHz) δ 1.08 (m, 2H), 1.20 (t, 3H, J=8), 1.38 (bs, 2H), 3.42 (q, 2H), 4.38 (d, 2H, J=5.6), 7.27 (d, 1H, J=4), 7.46-7.39 (m, 6H), 7.55 (d, 1H), 7.59 (s, 1H), 7.78 (m, 2H), 7.87 (m, 2H), 8.08 (t, 1H). [M⁺] 536.54 (C₂₆H₂₄F₄N₂O₄S requires 536.14).

- 15 **Example 32:** 1-[(4-fluorophenyl)sulfonylamino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide



Synthesis of 1-[(4-fluorophenyl)sulfonylamino]cyclopropanecarboxylic acid 15C

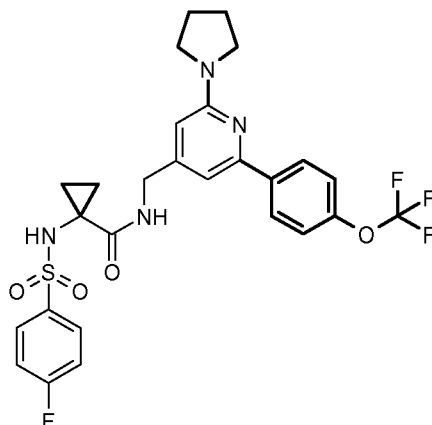
- 20 Compound **13A** (645 mg, 2.36 mmol) dissolved in THF (10 ml) and water (5 ml) was added with LiOH·H₂O (3 equiv., 297 mg) and the reaction was stirred at rt 3 hours. The reaction was concentrated under vacuum. Water was added and 10% HCl till

precipitation of the acid. The acid was extracted with ethyl acetate and the organic phase was washed with Brine, dried over sodium sulfate and concentrated under vacuum to give 600 mg of **15C** as a white solid. Yield = 98%. ¹HNMR (DMSO, 200 MHz) δ 1.38 (2H, m), 1.35 (2H, bs), 7.42 (2H, m), 7.80 (2H, m), 8.80 (1H, bs), 12.46 (1H, bs)

Preparation of 1-[(4-fluorophenyl)sulfonylamino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide Example 32

A solution of acid **15C** (0.50 g, 1.75 mmol) in THF (25 mL) was added with DEPC (0.34 mL, 1.3 mol eq) and the mixture was stirred at room temperature for 5'. Then [2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27A** (0.61 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water (40 mL) was added to the residue that is extracted with EtOAc (3x 25 mL) and washed with brine (1x40 mL). The separated organic phase was dried over Na₂SO₄, evaporated to dryness and the residue was purified by flash chromatography (1:1 EtOAc:Petroleum ether) to afford a pale orange solid (0.21 g) after crystallization from a mixture of ethyl ether/petroleum ether. Yield = 22%, ¹HNMR (DMSO, 200 MHz) δ 0.71 (m, 2H), 1.09 (m, 2H), 1.96 (m, 4H), 3.38 (m, 4H), 4.18 (d, 2H, J= 6.1), 6.33 (s, 1H), 6.46 (s, 1H), 7.47-7.38 (m, 4H), 7.88-7.80 (m, 4H), 8.37 (t, 1H), 8.71 (bs, 1H); [M⁺] 562.58 (C₂₇H₂₆F₄N₄O₃S requires 562.16).

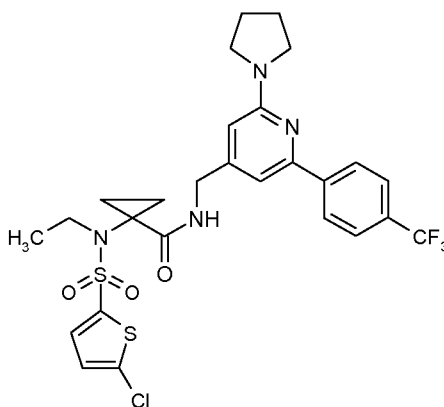
Example 33: 1-[(4-fluorophenyl)sulfonylamino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide



Preparation of 1-[(4-fluorophenyl)sulfonylamino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide Example 33

Acid **15C** (260 mg, 1 mmol) was dissolved in 5 ml of THF and at rt DEPC (1.1 equiv, 0.17 ml) and [2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **27C** (1.1 equiv., 371 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in EtOAc (30 ml) and washed with water (1 X 20 ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:Petroleum ether) afforded 130 mg of a white solid. Yield = 22%
¹HNMR (DMSO, 200 MHz) δ 0.71 (2H, bm), 1.08 (2H, bm), 1.92 (4H, m), 3.47 (4H, m), 4.29 (2H, d, J = 5.6 Hz), 6.41 (1H, s), 7.09 (1H, s), 7.45 (4H, m), 7.82 (2H, m), 8.17 (2H, d, J = 9Hz), 8.38 (1H, t), 8.71 (1H, bs) [M⁺] 579.4 (C₂₇H₂₆F₄N₄O₄S requires 578.58).

Example 34: 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide



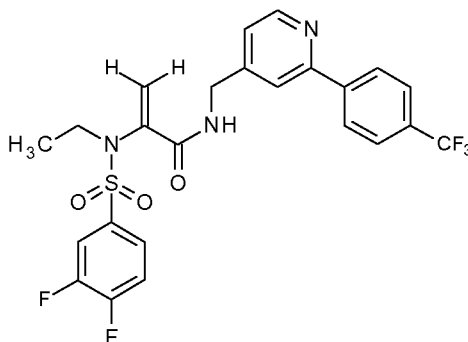
Preparation of 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide

Example 34

A solution of acid **18** (0.24 g, 0.76 mmol) in THF (20 mL) was added with DEPC (0.15 mL, 1.3 mol eq) and the mixture was stirred at room temperature for several minutes. Then [2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27A** (0.27g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction

mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc and washed with water (1x50 mL) and brine. After drying over Na₂SO₄, the separated organic phase was evaporated under reduced pressure and the residue was purified by flash chromatography (1:1 EtOAc:Petroleum ether) to afford a pale yellow solid (0.18 g) after crystallization from a mixture of ethyl ether/petroleum ether. Yield = 38%, ¹HNMR (DMSO, 200 MHz) δ 0.86 (t, 3H), 1.21 (m, 4H), 1.91 (m, 4H), 3.42 (m, 6H), 4.21 (d, 2H, J=6.2), 6.26 (s, 1H), 6.45 (s, 1H), 7.27 (d, 1H, J=4), 7.58 (d, 1H, J=3.8), 7.82 (d, 2H, J=7.8), 8.21 (d, 2H, J=8.1), 8.41 (t, 1H); [M⁺] 613.11 (C₂₇H₂₈ClF₃N₄O₃S₂ requires 612.12).

Example 35: 2-[(3,4-difluorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide



Synthesis of methyl (2S)-2-[(3,4-difluorophenyl)sulfonylamino]-3-hydroxypropanoate **2G**

A suspension of L-serine-methyl ester hydrochloride (1.5 g, 9.5 mmol) in CH₂Cl₂ (70 mL) was added with TEA (1.1 mol eq, 1.45 mL) and the mixture was stirred at r.t. for 10 minutes. Then 3,4-difluorobenzensulfonyl chloride (1 mol eq, 2.0 g) and additional TEA (1.1 mol eq) were added and the solution heated at 60°C overnight. The solvent was removed under reduced pressure, water was added to the residue (100 mL) and the aqueous phase extracted with EtOAc (3x40 mL). The recombined organic phases were dried over Na₂SO₄ and evaporated to reduced pressure. The residue was recrystallized from ethyl ether to afford **2G** as a pale orange solid (2.85 g, 94% yield). ¹HNMR

(DMSO, 200 MHz) δ 3.45 (s, 3H), 3.54 (m, 2H), 3.95 (m, 1H), 5.01 (t, 1H), 7.66 (m, 2H), 7.88 (m, 1H), 8.46 (d, 1H, J=8).

Synthesis of methyl (2S)-2-[(3,4-difluorophenyl)sulfonyl-ethyl-amino]-3-hydroxy-propanoate 3G

5 A solution of **2G** (2.85g, 8.8 mmol) in DMF (20 mL) was added with an. K_2CO_3 (1.5 mol eq, 1.83 g) and, after few minutes, 2-iodoethane (1.2 mol eq, 1.09 mL) was added and the mixture heated at 50°C for 12h. The solvent was removed under reduced pressure, water was added to the residue (150 mL) and the aqueous phase extracted with EtOAc (3x60 mL). The recombined organic phases were dried over Na_2SO_4 and
10 evaporated under reduced pressure to afford **3G** as a pale yellow oil (2.8 g, 90% yield). 1H NMR (DMSO, 200 MHz) δ 1.15 (m, 3H), 1.98 (s, 3H), 3.08 (m, 2H), 4.04 (q, 2H, J=8), 4.58 (t, 1H), 5.15 (bm, 1H), 7.71 (m, 2H), 7.94 (m, 1H).

Synthesis of 2-[ethyl-(3,4-difluorophenyl)sulfonyl-amino]prop-2-enoic acid 4G

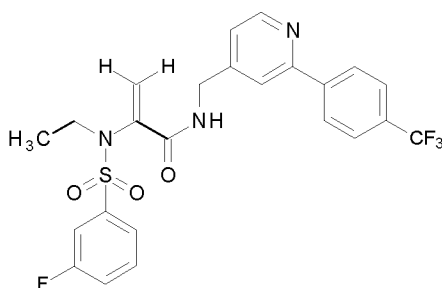
15 A solution of **3G** (2.8 g, 7.9 mmol) in dioxane (30 mL) was added with 20% NaOH aq. solution (20 mL) and the mixture heated at 80°C for 5 h. The organic solvent was removed under reduced pressure and the aqueous phase acidified with 10% HCl and extracted with CH_2Cl_2 (3x30 mL). The recombined organic phases were anhydriified using Na_2SO_4 , evaporated under reduced pressure and then the resulting residue purified
20 by flash chromatography (100% EtOAc) to obtain **4G** as white solid (1g, 44% yield). 1H NMR (DMSO, 200 MHz) δ 1.07 (t, 3H), 3.42 (q, 2H), 5.78 (s, 1H), 6.36 (s, 1H), 7.67 (m, 2H), 7.87 (m, 1H), 13.02 (bs, 1H).

Preparation of 2-[ethyl-(3,4-difluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 35

25 Acid **4G** (500 mg, 1.7 mmol) was dissolved in 20 ml of THF and at rt DEPC (1.3 equiv, 0.34ml) and [2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **21A** (1.1 equiv., 476 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30 mL) and washed with water (1 X

20mL) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (EtOAc 1 /petroleum ether 1) afforded 120 mg of a white solid. Yield = 24% ¹HNMR (DMSO, 200 MHz) δ 1.09 (3H, t, J = 7.2 Hz), 3.45 (2H, q, J = 6.8Hz), 4.51 (2H, d, J = 6Hz), 5.31 (1H, s), 6.17 (1H, s), 7.38 (1H, dd, J = 4.8 Hz, J' = 1.2 Hz), 7.68 (2H, t, J = 8.8 Hz), 7.83 (d, 3H), 8.02 (s, 1H), 8.32 (d, 2H, J=7.8), 8.67 (d, 1H, J=5.8), 8.93 (t, 1H). [M⁺] 525.11 (C₂₄H₂₀F₅N₃O₃S requires 524.98).

Example 36: 2-[(3-difluorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide



Synthesis of methyl (2S)-2-[(3-fluorophenyl)sulfonylamino]-3-hydroxypropanoate **2F**

A suspension of L-serine-methyl ester hydrochloride (1.6 g, 10.3 mmol) in CH₂Cl₂ (70 mL) was added with TEA (1.1 mol eq, 1.6 mL) and the mixture was stirred at r.t. for 10 minutes. Then 3-fluorobenzensulfonyl chloride (1 mol eq, 2.0 g) and additional TEA (1.1 mol eq) were added and the solution heated at 60°C overnight. The solvent was removed under reduced pressure, water was added to the residue (100 mL) and the aqueous phase extracted with EtOAc (3x40 mL). The recombined organic phases were dried over Na₂SO₄ and evaporated to reduced pressure. The residue was recrystallized from ethyl ether to afford **2F** as a pale yellow solid (2.80 g, 95% yield). ¹HNMR (DMSO, 200 MHz) δ 3.41 (s, 3H), 3.48 (m, 2H), 4.01 (m, 1H), 5.20 (t, 1H), 7.58 (m, 2H), 7.81(m, 2H), 8.52 (d, 1H, J=8).

Synthesis of methyl (2S)-2-[(3-fluorophenyl)sulfonyl-ethyl-amino]-3-hydroxy-propanoate 3F

A solution of **2F** (3.0 g, 10.8 mmol) in DMF (15 mL) was added with an. K₂CO₃ (1.5 mol eq, 2.24 g) and, after few minutes, 2-iodoethane (1.2 mol eq, 1.33 mL) was added and the mixture heated at 50°C for 12h. The solvent was removed under reduced pressure, water was added to the residue (150 mL) and the aqueous phase extracted with EtOAc (4x50 mL). The recombined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure to afford **3F** as a pale orange viscous oil (3.2 g, 95% yield). ¹HNMR (DMSO, 200 MHz) δ 1.15 (m, 3H), 2.00 (s, 3H), 3.79 (q, 2H, J=8), 4.06 (t, 1H), 4.59 (t, 1H), 5.18 (m, 2H), 7.94 (m, 4H).

Synthesis of 2-[ethyl-(3-fluorophenyl)sulfonyl-amino]prop-2-enoic acid 4F

A solution of **3F** (3.0 g, 9.8 mmol) in dioxane (30 mL) was added with 20% NaOH aq. solution (20 mL) and the mixture heated at 80°C for 5 h. The organic solvent was removed under reduced pressure and the aqueous phase acidified with 10% HCl. The solid formed was filtered under vacuum, washed with cold water (1x50 mL) and dried to afford **4F** as white solid (650 mg, 25% yield). ¹HNMR (DMSO, 200 MHz) δ 1.11 (t, 3H, J=7.7), 3.43 (q, 2H), 5.78 (s, 1H), 6.36 (s, 1H), 7.69 (m, 2H), 7.84 (m, 2H), 12.98 (bs, 1H).

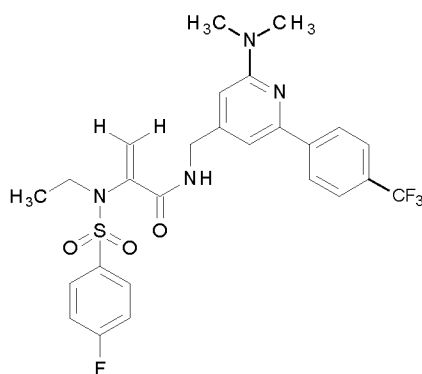
Preparation of 2-[ethyl-(3-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 36

Acid **4F** (330 mg, 1.2 mmol) was dissolved in 15 mL of THF and at rt DEPC (1.3 equiv, 0.23 mL) and [2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **21A** (1.1 mol equiv., 335 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30 mL) and washed with water (1 X 20 mL) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (EtOAc 1 /petroleum ether 1) afforded 100 mg of a white solid. Yield = 20% ¹HNMR (DMSO, 200 MHz) δ 1.09 (3H, t, J = 7.2 Hz), 3.44 (2H, q, J = 6.8 Hz), 4.50 (2H, d, J = 6 Hz), 5.21 (1H, s), 6.14 (1H, s), 7.34 (1H, dd, J = 4.8), 7.65 (m, 4H), 7.81 (d, 2H, J=7.9), 8.01 (s, 1H), 8.31 (d,

2H, J=7.8), 8.65 (d, 1H, J=5.8), 8.92 (t, 1H). $[M^{+}]$ 507.62 ($C_{24}H_{21}F_4N_3O_3S$ requires 507.50).

Example 37: N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]pyridin-4-yl]methyl]-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]prop-2-enamide

5



Synthesis of 2-chloro-6-(*N,N'*-dimethylamino)-pyridine-4-carbonitrile **25C**

Compound **24** (1.5 g, 8.7 mmol) was added with hexamethylphosphoramide (1.56 mL, 1 mol eq) and the mixture was heated at 120°C for 12 h. The reaction was cooled and then water was added (300 mL). The solid formed was collected by filtration and washed three times with water (3x30 mL) then dried to afford **25C** as a pale yellow solid (1.28 g, 82% Yield). ^1H NMR (DMSO, 200 MHz) δ 3.04 (s, 6H), 7.10 (s, 1H), 8.23 (s, 1H).

Synthesis of 2-(*N,N'*-dimethylamino)-6-[4-(trifluoromethyl)phenyl]pyridine-4-carbonitrile **26E**

The nitrile **25C** (2.0 g, 11.1 mmol), 4-trifluoromethylphenylboronic acid (2.32 g, 1.1 mol eq), palladium acetate (50 mg, 0.02 mol eq), cesium carbonate (7.23 g, 2 mol eq), and XPhos (210 mg, 0.04 mol eq) were mixed, placed under a nitrogen atmosphere and dioxane (10 mL) was added. The mixture was heated at 100°C for 3 h. After cooling, the mixture was filtered through a celite pad, washed with dioxane (2 x 20 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography (9.5/0.5 petroleum ether/EtOAc) to afford **26E** as a pale yellow solid (2.2 g, 68% Yield). ^1H NMR (DMSO, 200 MHz) δ 3.13 (s, 6H), 7.12 (s, 1H), 7.58 (s, 1H), 7.82 (d, 2H, J=7.7), 8.30 (d, 2H, J=7.8).

Synthesis of [2-(*N,N'*-dimethylamino)-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27E**

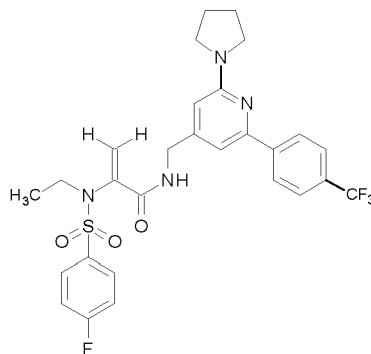
A solution of nitrile **26E** (2.2 g, 7.6 mmol) in diethyl ether (50 mL) was added in small amounts to a mixture of LiAlH₄ (0.58 g, 2 mol eq) in diethyl ether (50 mL) stirred at 0°C. After the addition was completed, the mixture was stirred at room temperature overnight. The excess of LiAlH₄ was destroyed at 0°C by addition of small amount of water (30 mL), the solid formed was filtered off and the organic filtrate was separated, washed with brine (50 mL) and dried over Na₂SO₄. The organic phase was evaporated under reduced pressure to afford **27E** as a pale yellow oil (2.13 g, 95% yield). ¹HNMR (DMSO, 200 MHz) δ 3.08 (s, 6H), 3.97 (s, 2H), 6.66 (s, 1H), 7.24 (s, 1H), 7.77 (d, 2H, J=7.5), 8.24 (d, 2H, J=8).

Preparation of N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]prop-2-enamide Example 37

Acid **4B** (830 mg, 3.0 mmol) was dissolved in 25 ml of THF and at rt, then DEPC (1.3 mol equiv, 0.59 mL) and [2-(*N,N'*-dimethylamino)-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27E** (1.1 mol equiv., 970 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. Water was added to the residue (100 mL) and extracted with EtOAc (3x30 mL). The organic phases were dried over sodium sulfate and evaporated to dryness. The residue was purified by chromatographic column (8/2 EtOAc/petroleum ether) to afford 260 mg of a white solid. Yield = 16% ¹HNMR (DMSO, 400 MHz) δ 1.06 (t, 3H, J=7.7), 3.07 (s, 6H), 3.38 (q, 2H, J=7.6), 4.38 (d, 2H, J= 8), 5.10 (s, 1H), 6.10 (s, 1H), 6.59 (s, 1H), 7.21 (s, 1H), 7.47 (m, 2H), 7.78 (d, 2H, J=7.6), 7.84 (m, 2H), 8.23 (d, 2H, J=8), 8.79 (t, 1H). [M⁺] 550.57 (C₂₆H₂₆F₄N₄O₃S requires 550.81).

Example 38: 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide

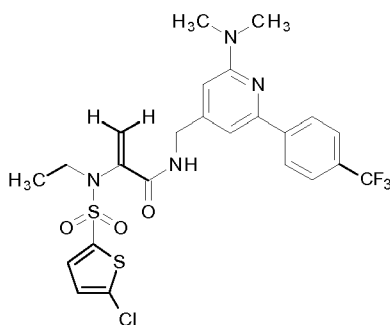
84



Preparation of 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 38

A solution of acid **4B** (0.15 g, 0.53 mmol) in THF (10 mL) was added with DEPC (0.10 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes. Then [2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27A** (0.17 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water was added to the residue that is extracted with EtOAc (3x 25 mL) and washed with brine (1x40 mL). The separated organic phase was dried over Na₂SO₄, evaporated to dryness and the residue was purified by flash chromatography (1/1 EtOAc/Petroleum ether) to afford a white solid (90 mg) after crystallization from ethyl ether. Yield = 32%. ¹HNMR (DMSO, 200 MHz) δ 1.092 (t, 3H, J=5.6), 1.95 (m, 4H), 3.4-3.46 (m, 6H), 4.39 (d, 2H, J=6), 5.13 (s, 1H), 6.12 (s, 1H), 6.47 (s, 1H), 7.20 (s, 1H), 7.51 (t, 2H, J=7.9), 7.80-7.90 (m, 4H), 8.27 (d, 2H, J=8.1), 8.78 (bt, 1H). [M⁺] 576.28 (C₂₈H₂₈F₄N₄O₃S requires 576.60).

Example 39: 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide

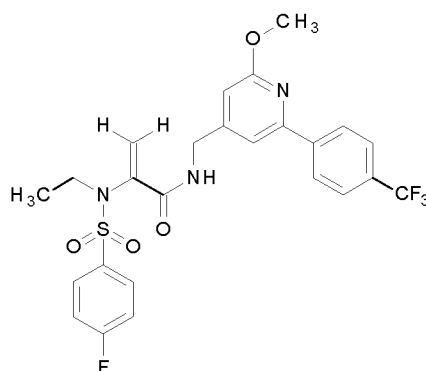


Preparation of 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide

Example 39

A solution of acid **7I** (0.16 g, 0.54 mmol) in THF (12 mL) was added was added
 5 DEPC (0.10 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes. Then [2-(*N,N'*-dimethylamino)-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27E** (0.175 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water was added to the residue that is extracted
 10 with EtOAc (3x 20mL) and washed with brine (1x30mL). The separated organic phase was dried over Na₂SO₄, evaporated to dryness and the residue was purified by flash chromatography (1/1 EtOAc/Petroleum ether) to afford a white solid (60 mg) after crystallization from ethyl ether. Yield = 19%. ¹HNMR (DMSO, 200 MHz) δ 1.12 (t, 3H, J=7.2), 3.09 (s, 6H), 3.46 (m, 2H), 4.39 (d, 2H, J=6.5), 5.39 (s, 1H), 6.23 (s, 1H), 6.64 (s, 1H), 7.20 (s, 1H), 7.36 (d, 1H, J=4), 7.62 (d, 1H, J=3.9), 7.81 (d, 2H, J= 7.8), 8.26 (d, 2H, J=7.9), 8.81 (bt, 1H). [M⁺] 572.85 (C₂₄H₂₄ClF₃N₄O₃S₂ requires 573.05).

Example 40: 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide



20 Synthesis of 2-chloro-6-methoxy-pyridine-4-carbonitrile 25F

A solution of compound **24** (2.0 g, 11.6 mmol) in methanol (20 mL) was added with sodium methoxyde (628 mg, 1 mol eq) and the mixture was heated at 60°C for 6h. The reaction was cooled, evaporated to dryness and then water was added (300 mL). The

aqueous phase was extracted with EtOAc (3x25 mL) and the recombined organic phases were dried over sodium sulfate and evaporated under reduced pressure to afford **25F** as transparent viscous oil (1.95g, quantitative yield). ¹HNMR (DMSO, 200 MHz) δ 3.80 (s, 3H), 7.17 (s, 1H), 7.90 (s, 1H).

5 **Synthesis of 2-methoxy-6-[4-(trifluoromethyl)phenyl]pyridine-4-carbonitrile 26I**

The nitrile **25F** (2.3 g, 13.8 mmol), 4-trifluoromethylphenylboronic acid (2.61 g, 1.1 mol eq), palladium acetate (62 mg, 0.02 mol eq), cesium carbonate (8.97 g, 2 mol eq), and XPhos (260 mg, 0.04 mol eq) were mixed, placed under a nitrogen atmosphere and
10 dioxane (10 mL) was added. The mixture was heated at 100°C for 4 h. After cooling, the mixture was filtered through a celite pad, washed with dioxane (2 x 30 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography (9:1 petroleum ether:EtOAc) to afford **26I** as a pale yellow solid (840mg, 25% Yield).
¹HNMR (DMSO, 200 MHz) δ 4.03 (s, 3H), 7.46 (s, 1H), 7.90 (d, 2H, J=7.8), 8.17 (s, 1H),
15 8.40 (d, 2H, J=8).

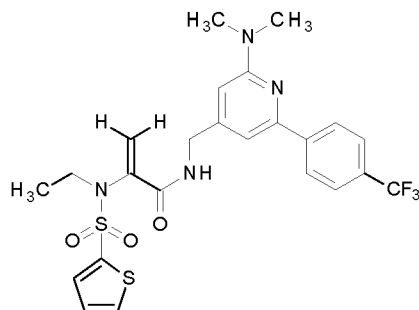
Synthesis of [2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine 27I

A solution of nitrile **26I** (420 mg, 1.5 mmol) in diethyl ether (30 mL) was added in small amounts to a mixture of LiAlH₄ (115 mg, 2 mol eq) in diethyl ether (20 mL)
20 stirred at 0°C. After the addition was completed, the mixture was stirred at room temperature overnight. The excess of LiAlH₄ was destroyed at 0°C by addition of small amount of water (30 mL), the solid formed was filtered off and the organic filtrate was separated, washed with brine (50 mL) and dried over Na₂SO₄. The organic phase was evaporated under reduced pressure to afford **27I** as a pale yellow oil (370 mg, 88% yield).
25 ¹HNMR (DMSO, 200 MHz) δ 4.13 (s, 3H), 4.22 (s, 2H), 7.56 (s, 1H), 7.88 (d, 2H, J=7.8), 8.26 (s, 1H), 8.51 (d, 2H, J=8).

Preparation of 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide Example40

A solution of acid **4B** (0.31g, 1.1 mmol) in THF (20 mL) was added with DEPC (0.22 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes. Then [2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27I** (0.36 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water was added to the residue that is extracted with EtOAc (3x 30 mL) and washed with brine (1x40 mL). The separated organic phase was dried over Na₂SO₄, evaporated to dryness and the residue was purified by flash chromatography (1/1 EtOAc/Petroleum ether) to afford a white solid (180 mg) after crystallization from ethyl ether. Yield = 30%. ¹HNMR (DMSO, 200 MHz) δ 1.08 (t, 3H, J=6), 3.39 (m, 2H), 3.95 (s, 3H), 4.45 (d, 2H, J=6.2), 5.14 (s, 1H), 6.13 (s, 1H), 6.79 (s, 1H), 7.47 (t, 2H, J=8.2), 7.64 (s, 1H), 7.85 (m, 4H), 8.31 (d, 2H, J=7.8), 8.84 (bt, 1H). [M⁺] 537.05 (C₂₅H₂₃F₄N₃O₄S requires 537.53).

Example 41: N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-2-(ethyl(2-thienylsulfonyl)amino)prop-2-enamide



Synthesis of methyl (2S)-3-hydroxy-2-(2-thienylsulfonylamino)propanoate **5H**

A suspension of L-serine-methyl ester hydrochloride (3.0 g, 19.3 mmol) in CH₂Cl₂ (80 mL) was added with TEA (1.1 mol eq, 2.9 mL) and the mixture was stirred at r.t. for 10 minutes. Then 2-thiophen-sulphonyl chloride (1 mol eq, 3.52 g) and additional TEA (1.1 mol eq) were added and the solution heated at 60°C overnight. The solvent was removed under reduced pressure, water was added to the residue (100 mL) and the aqueous phase extracted with EtOAc (3x40 mL). The recombined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure to afford **5H** as white solid (4.9 g, 95% yield). ¹HNMR (DMSO, 200 MHz) δ 3.61 (s, 2H), 3.82 (t, 2H, J=6.3), 4.14 (m,

1H), 4.62 (t, 1H), 5.25 (t, 1H), 7.21 (m, 1H), 7.75 (dd, 1H, J=2.1), 7.96 (dd, 1H, J=1.9), 8.23 (d, 1H).

Synthesis of methyl (2S)-2-(ethyl(2-thienylsulfonyl)amino)-3-hydroxy-propanoate 6H

5 A solution of **5H** (4.9 g, 18.6 mmol) in DMF (20 mL) was added with an. K₂CO₃ (1.5 mol eq, 3.85 g) and, after few minutes, 2-iodoethane (1.2 mol eq, 2.29 mL) was added and the mixture heated at 50°C for 12h. The solvent was removed under reduced pressure, water was added to the residue (150 mL) and the aqueous phase extracted with EtOAc (4x50 mL). The recombined organic phases were dried over Na₂SO₄ and
10 evaporated under reduced pressure to afford **6H** as a pale yellow oil (2.13 g, 44% yield). ¹HNMR (DMSO, 200 MHz) δ 1.17 (t, 3H, J=6.2), 3.34 (q, 2H, J=6.3), 3.49 (s, 2H), 3.76 (t, 2H, J=6.3), 4.04 (m, 1H), 4.50 (t, 1H), 5.18 (t, 1H), 7.18 (m, 1H), 7.65 (dd, 1H, J=2.1), 7.96 (dd, 1H, J=1.9).

Synthesis of 2-(ethyl(2-thienylsulfonyl)amino)prop-2-enoic acid 7H

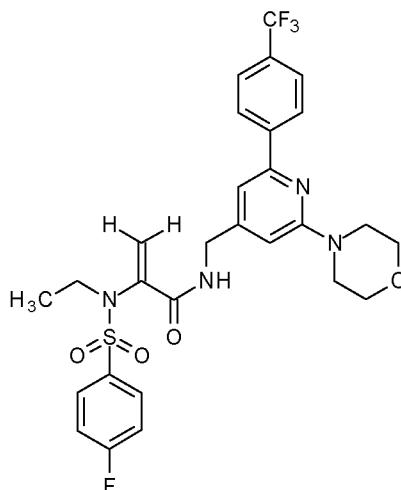
15 A solution of **6H** (2.13 g, 9.8 mmol) in dioxane (30 mL) was added with 20% NaOH aq. solution (20 mL) and the mixture heated at 80°C for 5 h. The organic solvent was removed under reduced pressure and the aqueous phase acidified with 10% HCl. The solid formed was filtered under vacuum, washed with cold water (2x25 mL) and dried to afford **7H** as white solid (135 mg, 42% yield). ¹HNMR (DMSO, 200 MHz) δ 1.02 (t, 3H, J=7.7), 3.39 (q, 2H, J=6.3), 5.67 (s, 1H), 6.34 (s, 1H), 7.21(m, 1H), 7.62 (dd, 1H, J=2.1),
20 8.00 (dd, 1H, J=1.9), 13.01(bs, 1H).

Preparation of N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-2-(ethyl(2-thienylsulfonyl)amino)prop-2-enamide Example 41

A solution of acid **7H** (0.30 g, 1.15 mmol) in THF (20 mL) was added with DEPC
25 (0.23 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes. Then [2-(N,N'-dimethylamino)-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27E** (0.371 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under

reduced pressure, water was added to the residue that is extracted with EtOAc (3x30 mL) and washed with brine (1x40 mL). The separated organic phase was dried over Na₂SO₄, evaporated to dryness and the residue was purified by flash chromatography (6/4 EtOAc/Petroleum ether) to afford a white solid (0.22 g) after crystallization from ethyl ether. Yield = 36%. ¹HNMR (DMSO, 200 MHz) δ 1.12 (t, 3H, J=6), 3.09 (s, 6H), 3.44 (m, 2H), 4.40 (d, 2H, J=4.2), 5.15 (s, 1H), 6.21 (s, 1H), 6.66 (s, 1H), 7.27 (m, 2H), 7.68 (dd, 1H, J=1.8), 7.77 (d, 2H, J=7.9), 8.06 (dd, 1H, J=2.1), 8.27 (d, 2H, J=7.8), 8.78 (bt, 1H). [M⁺] 538.02 (C₂₄H₂₅F₃N₄O₃S₂ requires 538.60).

Example 42: 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide



Synthesis of 2-morpholino-6-[4-(trifluoromethyl)phenyl]pyridine-4-carbonitrile **26B**

The nitrile **25B** (3.2 g, 14.4 mmol), 4-trifluoromethylphenylboronic acid (3.01 g, 1 mol eq), palladium acetate (65 mg, 0.02 mol eq), cesium carbonate (9.38 g, 2 mol eq), and XPhos (265 mg, 0.04 mol eq) were mixed, placed under a nitrogen atmosphere and dioxane (12 mL) was added. The mixture was heated at 100°C overnight. After cooling, the mixture was filtered through a celite pad, washed with dioxane (2 x 30 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography (7/3 Petroleum ether/EtOAc) to afford **26B** as yellow solid (1.33 g, 40% Yield). ¹HNMR

(DMSO, 400 MHz) δ 3.63 (m, 4H, J=1.9), 3.74 (m, 4H, J=2), 7.38 (s, 1H), 7.74 (s, 1H), 7.84 (d, 2H, J=8.1), 8.32 (d, 2H, J=8).

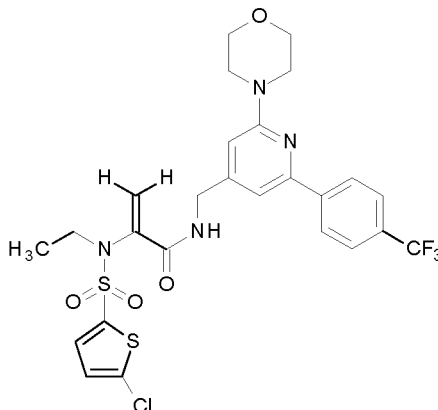
Synthesis of [2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine 27B

5 A solution of nitrile **26B** (1.33 g, 4 mmol) in diethyl ether (30 mL) was added in small amounts to a mixture of LiAlH₄ (305 mg, 2 mol eq) in diethyl ether (20 mL) stirred at 0°C. After the addition was completed, the mixture was stirred at room temperature overnight. The excess of LiAlH₄ was destroyed at 0°C by addition of small amount of water (30 mL), the solid formed was filtered off and the organic filtrate was separated,
10 washed with brine (50 mL) and dried over Na₂SO₄. The organic phase was evaporated under reduced pressure to afford **27B** as a pale yellow oil (1.34 g, quantitative yield).
¹HNMR (DMSO, 200 MHz) δ 3.54 (m, 4H), 3.76 (m, 6H), 6.87 (s, 1H), 7.38 (s, 1H), 7.81 (d, 2H, J=8), 8.27 (d, 2H, J=7.9).

Preparation of 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 42

15 A solution of acid **4B** (0.40 g, 1.46 mmol) in THF (20 mL) was added with DEPC (0.28 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes. Then [2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27B** (530 mg, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was
20 stirred at room temperature overnight. The solvent was removed under reduced pressure, water was added to the residue that is extracted with EtOAc (3x30 mL) and washed with brine (1x40 mL). The separated organic phase was dried over Na₂SO₄, evaporated to dryness and the residue was purified by flash chromatography (6/4 EtOAc/Petroleum ether) to afford a white solid (95 mg) after crystallization from ethyl ether. Yield = 12%.
25 ¹HNMR (DMSO, 200 MHz) δ 1.087 (t, 3H, J=7.8), 3.39 (q, 2H, J=7.6), 3.55 (m, 4H), 3.71 (m, 4H), 4.42 (d, 2H, J=6.2), 5.13 (s, 1H), 6.12 (s, 1H), 6.85 (s, 1H), 7.35 (s, 1H), 7.47 (t, 2H, J=8), 7.83-7.90 (m, 4H), 8.26 (d, 2H, J=8), 8.80 (bt, 1H). [M⁺] 592.33 (C₂₈H₂₈F₄N₄O₄S requires 592.60).

Example 43: 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide



5 Preparation of 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide

Example 43

A solution of acid **7I** (0.14 g, 0.47 mmol) in THF (15 mL) was added with DEPC (0.092 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes.

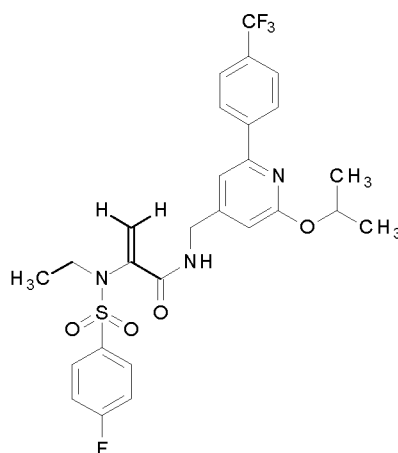
10 Then [2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27B** (0.175 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water was added to the residue that is extracted with EtOAc (3x 20mL) and washed with brine (1x30mL). The separated organic phase was dried over Na₂SO₄, evaporated to

15 dryness and the residue was purified by flash chromatography (1/1 EtOAc/Petroleum ether) to afford a white solid (90 mg) after crystallization from ethyl ether. Yield = 32%.

¹HNMR (DMSO, 200 MHz) δ 1.12 (t, 3H, J=7.2), 3.47 (m, 2H), 3.54 (m, 4H), 3.72 (m, 4H), 4.41 (d, 2H, J=6.2), 5.39 (s, 1H), 6.23 (s, 1H), 6.81 (s, 1H), 7.34 (m, 2H), 7.60 (d, 1H, J=4), 7.81 (d, 2H, J=8.1), 8.25 (d, 2H, J=8.2), 8.82 (t, 1H). [M⁺] 614.98

20 (C₂₆H₂₆ClF₃N₄O₄S₂ requires 615.09).

Example 44: 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-isopropoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide



Synthesis of 2-chloro-6-isopropoxy-pyridine-4-carbonitrile **25H**

5 A mixture of NaH 60% (05 g, 1.1 mol eq) in 2-isopropanol (15 mL) cooled at 0°C, was added in small portions with the nitrile **24** (2 g, 11.6 mmol). The reaction mixture was then heated at 60°C for 5h. Water was added (30 ml) and the aqueous phase was extracted with EtOAc (3x20 mL). The recombined organic phases were dried over sodium sulfate and evaporated under reduced pressure to afford **25H** as a pale yellow
10 viscous oil (1.82 g, 80% Yield).

¹HNMR (DMSO, 200 MHz) δ 1.31 (d, 6H, J=4), 5.18 (m, 1\H), 6.71 (s, 1H), 7.36 (s, 1H).

Synthesis of 2-isopropoxy-6-[4-(trifluoromethyl)phenyl]pyridine-4-carbonitrile **26M**

The nitrile **25H** (1.25 g, 6.4 mmol), 4-trifluoromethylphenylboronic acid (1.34 g, 1 mol eq), palladium acetate (29 mg, 0.02 mol eq), cesium carbonate (4.16 g, 2 mol eq), and XPhos (137 mg, 0.04 mol eq) were mixed, placed under a nitrogen atmosphere and dioxane (8 mL) was added. The mixture was heated at 100°C for 4h. After cooling, the mixture was filtered through a celite pad, washed with dioxane (2 x 30 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography
20 (9.5/0.5 Petroleum ether/EtOAc) to afford **26M** as yellow solid (0.65 g, 36% Yield).

¹HNMR (DMSO, 200 MHz) δ 1.37 (d, 6H, J=3.9), 5.15 (m, 1H), 6.7 (s, 1H), 7.32 (s, 1H), 7.87 (d, 2H, J=7.8), 8.33 (d, 2H, J=8).

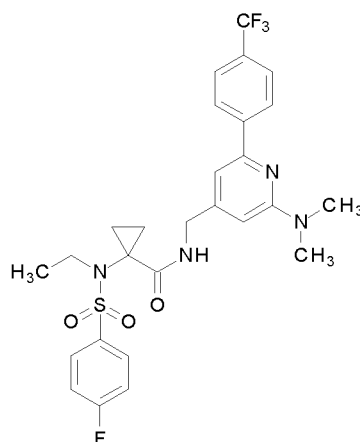
Synthesis of [2-isopropoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine 27M

5 A solution of nitrile **26M** (0.65 g, 2.14 mmol) in diethyl ether (30 mL) was added in small amounts to a mixture of LiAlH₄ (163 mg, 2 mol eq) in diethyl ether (20 mL) stirred at 0°C. After the addition was completed, the mixture was stirred at room temperature overnight. The excess of LiAlH₄ was destroyed at 0°C by addition of small amount of water (30 mL), the solid formed was filtered off and the organic filtrate was
10 separated, washed with brine (40 mL) and dried over Na₂SO₄. The organic phase was evaporated under reduced pressure to afford **27M** as a yellow oil (0.56 g, 86% yield).
¹HNMR (DMSO, 400 MHz) δ 1.28 (d, 6H, J=5.8), 3.74 (s, 2H), 5.41 (m, 1H), 6.21 (s, 1H), 6.75 (s, 1H), 7.84 (d, 2H, J=7.8), 8.27 (d, 2H, J=8).

Preparation of 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-isopropoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 44

A solution of acid **4B** (300 g, 1.09 mmol) in THF (15 mL) was added with DEPC (0.21 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes. Then [2-isopropoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27M** (370 mg, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was
20 stirred at room temperature overnight. The solvent was removed under reduced pressure, water was added to the residue that is extracted with EtOAc (3x30 mL) and washed with brine (1x40 mL). The separated organic phase was dried over Na₂SO₄, evaporated to dryness and the residue was purified by flash chromatography (3/7 EtOAc/Petroleum ether) to afford a white solid (100 mg) after crystallization from ethyl ether. Yield = 18%.
25 ¹HNMR (DMSO, 400 MHz) δ 1.08 (t, 3H, J=7.4), 1.26 (d, 6H, J=6.2), 3.39 (q, 2H), 4.40 (d, 2H, J=7.9), 5.13 (s, 1H), 5.39 (m, 1H), 6.12 (s, 1H), 6.65 (s, 1H), 7.42 (t, 3H, J=4), 7.56 (s, 1H), 7.86 (m, 4H), 8.23 (d, 2H, J=8), 8.79 (t, 1H). [M⁺] 565.02 (C₂₇H₂₇F₄N₃O₄S requires 565.58).

Example 45: N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide

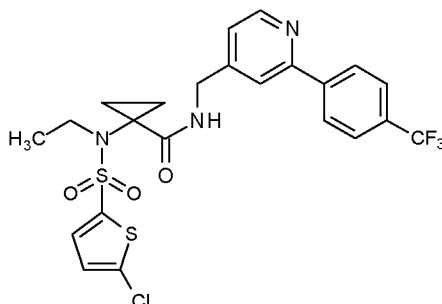


Preparation of N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide
Example 45

Acid **15B** (400 mg, 1.4 mmol) was dissolved in 20 ml of THF and at rt, then DEPC (1.3 mol equiv, 0.27 mL) and [2-(*N,N'*-dimethylamino)-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27E** (1.1 mol equiv., 450 mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. Water was added to the residue (80 mL) and extracted with EtOAc (3x30 mL). The organic phases were dried over sodium sulfate and evaporated to dryness. The residue was purified by chromatographic column (8/2 EtOAc /petroleum ether) to afford 220 mg of a white solid. Yield = 28%. ¹HNMR (DMSO, 200 MHz) δ 1.08 (bs, 2H), 1.22 (t, 3H, *J*=8.1), 1.26 (bs, 2H), 3.11 (s, 6H), 3.42 (m, 2H), 4.36 (bd, 2H), 6.63 (s, 1H), 7.2 (s, 1H), 7.42 (t, 2H, *J*=10), 7.88 (m, 4H), 8.27 (m, 3H). [*M*⁺] 564.59 (C₂₇H₂₈F₄N₄O₃S requires 564.29).

Example 46: 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide

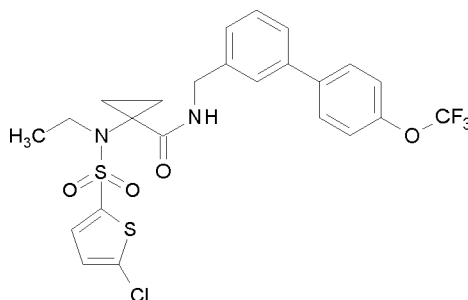
95



Preparation of 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide Example 46

Acid **18** (0.3g, 1.09 mmol) was dissolved in 15 ml of THF and at rt DEPC (1.3
 5 equiv, 0.21 mL) and [2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **21A** (1.1 mol
 equiv., 0.37 g) were added to the solution. The mixture was stirred at rt overnight then
 evaporated. The residue was dissolved in AcOEt (30 mL) and washed with water (1 X 20
 mL) and brine. The organic phase was dried over sodium sulfate and concentrated under
 vacuum. The purification of the crude by chromatographic column (EtOAc 3 /petroleum
 10 ether 7) afforded 100 mg of a white solid. Yield = 18% ¹HNMR (DMSO, 200 MHz) δ
 1.24 (m, 5H), 1.35 (m, 2H), 3.45 (m, 2H), 4.44 (d, 2H, J=6.2), 7.26 (m, 3H), 6.61 (d, 1H,
 J=2.1), 7.88 (d, 2H, J=7.8), 7.94 (s, 1H), 8.31 (d, 3H, J=8), 8.64 (d, 1H, J=4.1). [M⁺]
 543.95 (C₂₃H₂₁ClF₃N₃O₃S₂ requires 544.01).

Example 47: 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-
 15 (trifluoromethoxy)phenyl]phenyl]methyl]cyclopropanecarboxamide

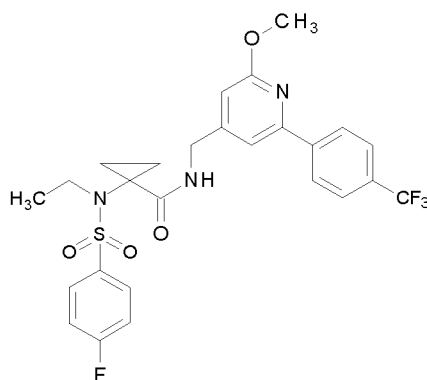


Preparation of 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl]methyl]cyclopropanecarboxamide Example 47

A solution of acid **18** (0.20 g, 0.65 mmol) in THF (15 mL) was added with DEPC (0.13
 20 mL, 1.3 mol eq) and the mixture was stirred at room temperature for 10 minutes. Then [3-

[4-(trifluoromethoxy)phenyl]phenyl]methanamine **23B** (0.19 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (45 mL) and washed with water (40 mL) and brine. The separated organic phase was dried over an. Na₂SO₄ and evaporated under reduced pressure. The residue was purified by flash chromatography (1/1 EtOAc/Petroleum ether) to afford a white solid (0.2 g). Yield = 59%, ¹HNMR (DMSO, 200 MHz) δ 1.23 (m, 5H), 1.41 (m, 2H), 3.36 (m, 2H), 4.39 (d, 2H, J=6.1), 7.25 (m, 2H), 7.45 (m, 4H), 7.57 (m, 2H), 7.79 (d, 2H, J=7.9), 8.09 (t, 1H). [M⁺] 559.31 (C₂₄H₂₂ClF₃N₂O₄S₂ requires 559.02).

Example 48: 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide

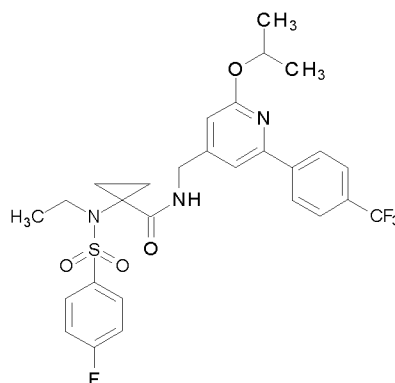


Preparation of 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide Example 48

A solution of acid **15B** (0.2 g, 0.69 mmol) in THF (20 mL) was added with DEPC (0.135 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes. Then [2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27I** (0.214 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water was added to the residue that is extracted with EtOAc (3x 30 mL) and washed with brine (1x40 mL). The separated organic phase was dried over Na₂SO₄, evaporated to dryness and the residue was purified by flash chromatography (1/1 EtOAc/Petroleum ether) to afford a white solid (170 mg) after crystallization from ethyl ether. Yield = 49%. ¹HNMR

(DMSO, 200 MHz) δ 1.08 (m, 2H), 1.22 (t, 3H, $J=6.5$), 1.25 (m, 2H), 3.42 (m, 2H), 3.96 (s, 3H), 4.39 (d, 2H, $J=6.2$), 6.75 (s, 1H), 7.41 (t, 2H, $J=7.8$), 7.61 (s, 1H), 7.91 (m, 4H), 8.32 (m, 3H). $[M^{+1}]$ 551.65 ($C_{26}H_{25}F_4N_3O_4S$ requires 551.55).

Example 49: 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-isopropoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide

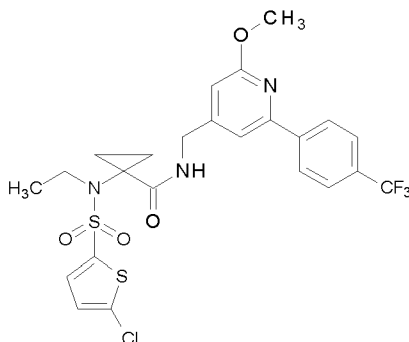


Preparation of 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-isopropoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide Example 49

A solution of acid **15B** (0.16 g, 0.55 mmol) in THF (15 mL) was added with DEPC (0.11 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes. Then [2-isopropoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27M** (0.19 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water was added to the residue that is extracted with EtOAc (3x30 mL) and washed with brine (1x40 mL). The separated organic phase was dried over Na_2SO_4 , evaporated to dryness and the residue was purified by flash chromatography (1/1 EtOAc/Petroleum ether) to afford a pale yellow solid (100 mg) after crystallization from ethyl ether. Yield = 31%. 1H NMR (DMSO, 200 MHz) δ 0.83 (m, 3H), 1.12 (m, 4H), 1.36 (d, 6H, $J=6.1$), 3.43 (m, 2H), 4.37 (d, 2H, $J=6$), 5.40 (m, 1H), 6.64 (s, 1H), 7.41 (t, 2H), 7.56 (s, 1H), 7.89 (m, 4H), 8.27 (m, 3H) $[M^{+1}]$ 579.88 ($C_{28}H_{29}F_4N_3O_4S$ requires 579.61).

Example 50: 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide

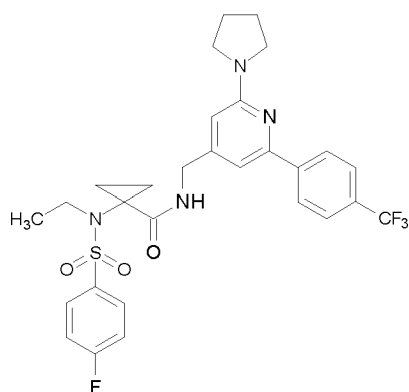
98



Preparation of 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide Example 50

A solution of acid **18** (0.3 g, 0.97 mmol) in THF (15 mL) was added with DEPC (0.19 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes. Then [2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27I** (0.22 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water was added to the residue that is extracted with EtOAc (3x 30 mL) and washed with brine (1x30 mL). The separated organic phase was dried over Na₂SO₄, evaporated to dryness and the residue was purified by flash chromatography (1/1 EtOAc/Petroleum ether) to afford a white solid (110 mg) after crystallization from ethyl ether. Yield = 26%. ¹HNMR (DMSO, 400 MHz) δ 1.21 (t, 5H, J=6.2), 1.41 (m, 2H), 3.54 (m, 2H), 3.94 (s, 3H), 4.18 (bs, 2H), 6.70 (s, 1H), 7.25 (d, 1H, J=2.1), 7.57 (d, 2H, J=2.3), 7.84 (d, 2H, J=8), 8.27 (m, 3H). [M⁺] 574.66 (C₂₄H₂₃ClF₃N₃O₄S₂ requires 574.04).

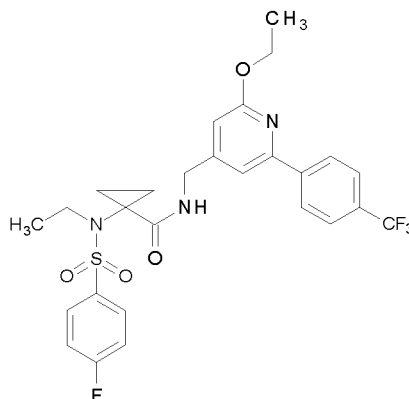
Example 51: 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide



Preparation of 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide Example 51

A solution of acid **15B** (0.3 g, 1.04 mmol) in THF (15 mL) was added with DEPC (0.20 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes. Then [2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27A** (0.36 g, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water was added to the residue that is extracted with EtOAc (3x 35 mL) and washed with brine (1x40 mL). The separated organic phase was dried over Na₂SO₄, evaporated to dryness and the residue was purified by flash chromatography (4/6 EtOAc/Petroleum ether) to afford a white solid (105 mg) after crystallization from ethyl ether. Yield = 18%. ¹HNMR (DMSO, 200 MHz) δ 1.08 (m, 2H), 1.22 (t, 3H, J=6), 1.26 (m, 2H), 1.96 (m, 4H), 3.47 (m, 6H), 4.34 (d, 2H, J=6.3), 6.43 (s, 1H), 7.17 (s, 1H), 7.46 (t, 2H, J=8), 7.86 (m, 4H), 8.20 (t, 1H), 8.27 (d, 2H, J=8). [M⁺] 590.11 (C₂₉H₃₀F₄N₄O₃S requires 590.63).

Example 52: N-[[2-ethoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide



Synthesis of 2-chloro-6-[4-(trifluoromethyl)phenyl]pyridine-4-carbonitrile 25G

A solution of compound **24** (2.5 g, 14.5 mmol) in abs. ethanol (30 mL) was added with sodium ethoxyde (1.08 mg, 1.1 mol eq) and the mixture was heated at 60°C overnight. The reaction was cooled, evaporated to dryness and then water was added (300

mL). The aqueous phase was extracted with EtOAc (3x35 mL) and the recombined organic phases were dried over sodium sulfate and evaporated under reduced pressure to afford **25G** as a pale yellow oil (1.1 g, 45% Yield). ¹HNMR (DMSO, 200 MHz) δ 1.23 (t, 3H, J=6.2), 4.24 (q, 2H, J=6.3), 7.07 (s, 1H), 7.38 (s, 1H).

5 **Synthesis of 2-ethoxy-6-[4-(trifluoromethyl)phenyl]pyridine-4-carbonitrile 26L**

The nitrile **25G** (1.1 g, 6.07 mmol), 4-trifluoromethylphenylboronic acid (1.15 g, 1 mol eq), palladium acetate (27 mg, 0.02 mol eq), cesium carbonate (3.95 g, 2 mol eq), and XPhos (116 mg, 0.04 mol eq) were mixed, placed under a nitrogen atmosphere and dioxane (7 mL) was added. The mixture was heated at 100°C for 3 h. After cooling, the
10 mixture was filtered through a celite pad, washed with dioxane (2 x 30 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography (9.5/0.5 petroleum ether/EtOAc) to afford **26L** as a pale yellow solid (620mg, 40% Yield). ¹HNMR (DMSO, 200 MHz) δ 1.38 (t, 3H, J=6.2), 4.5 (q, 2H, J=6.3), 7.40 (s, 1H), 7.89 (d, 2H, J=8), 8.14 (s, 1H), 8.36 (d, 2H, H=8).

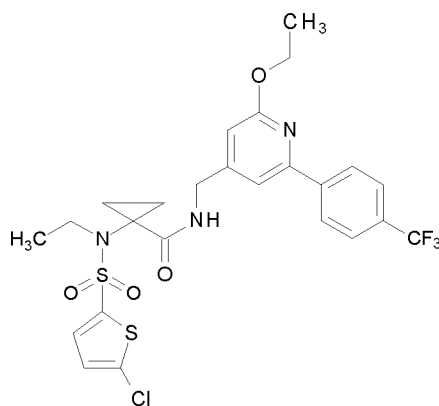
15 **Synthesis of [2-ethoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine 27L**

A solution of nitrile **26L** (620 mg, 2.1 mmol) in diethyl ether (20 mL) was added in small amounts to a mixture of LiAlH₄ (162 mg, 2 mol eq) in diethyl ether (20 mL) stirred at 0°C. After the addition was completed, the mixture was stirred at room temperature
20 overnight. The excess of LiAlH₄ was destroyed at 0°C by addition of small amount of water (30 mL), the solid formed was filtered off and the organic filtrate was separated, washed with brine (50 mL) and dried over Na₂SO₄. The organic phase was evaporated under reduced pressure to afford **27L** as a pale yellow oil (650 mg, quantitative yield). ¹HNMR (DMSO, 200 MHz) δ 1.34 (t, 3H, J=6.2), 3.30 (bs, 2H), 4.44 (q, 2H, J=6.3), 6.80
25 (s, 1H), 7.64 (s, 1H), 7.85 (d, 2H, J=7.8), 8.30 (d, 2H, J=8).

Preparation of N-[[2-ethoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide Example 52

A solution of acid **15B** (260 mg, 0.91 mmol) in THF (20 mL) was added with DEPC (0.18 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes. Then [2-ethoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27L** (300 mg, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water was added to the residue that is extracted with EtOAc (3x 35 mL) and washed with brine (1x40 mL). The separated organic phase was dried over Na₂SO₄, evaporated to dryness and the residue was purified by flash chromatography (4/6 EtOAc/Petroleum ether) to afford a white solid (120 mg) after crystallization from ethyl ether. Yield = 23%.
¹HNMR (DMSO, 200 MHz) δ 1.05 (t, 4H), 1.25 (t, 3H, J=6.3), 1.40 (t, 4H), 3.39 (m, 2H), 4.45 (m, 4H), 6.7 (s, 1H), 7.42 (t, 2H), 7.59 (s, 1H), 7.86 (m, 3H), 8.25 (m, 3H). [M⁺] 565.42 (C₂₇H₂₇F₄N₃O₄S requires 565.58).

Example 53: 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-ethoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide

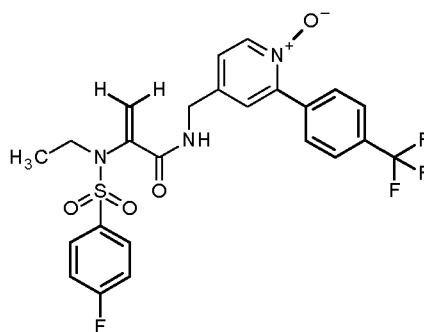


Synthesis of 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide Example 53

A solution of acid **18** (281 mg, 0.90 mmol) in THF (20 mL) was added with DEPC (0.18 mL, 1.3 mol eq) and the mixture was stirred at room temperature several minutes. Then [2-ethoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27L** (300 mg, 1.1 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, water

was added to the residue that is extracted with EtOAc (3x 35 mL) and washed with brine (1x40 mL). The separated organic phase was dried over Na₂SO₄, evaporated to dryness and the residue was purified by flash chromatography (4/6 EtOAc/Petroleum ether) to afford a white solid (130 mg) after crystallization from ethyl ether. Yield = 25%. ¹HNMR (DMSO, 200 MHz) δ 1.23(m, 4H), 1.4 (m, 6H), 3.41 (m, 2H), 4.41 (m, 4H), 6.67 (s, 1H), 7.27 (d, 1H, J=3.8), 7.58 (m, 2H), 7.86 (d, 2H, J=8), 8.28 (m, 3H). [M⁺] 587.80 (C₂₅H₂₅ClF₃N₃O₄S₂ requires 588.06).

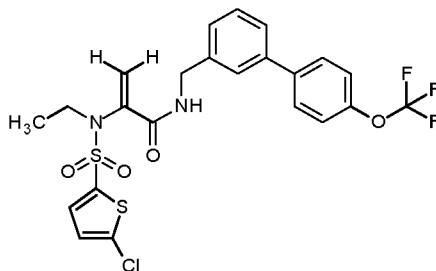
Example 54: 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[1-oxido-2-[4-(trifluoromethyl)phenyl]pyridin-1-ium-4-yl]methyl]prop-2-enamide



Preparation of 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[1-oxido-2-[4-(trifluoromethyl)phenyl]pyridin-1-ium-4-yl]methyl]prop-2-enamide Example 54

3-Chloro perbenzoic acid (1.5 mol eq, 100 mg) was added to a solution of **Example 1** (200 mg, 0.39 mmol) in CHCl₃ (10 mL) and the mixture was stirred at r.t. for 24 hours. Then 10% water solution of K₂CO₃ was added to wash the organic phase that was then dried over Na₂SO₄ and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (EtOAc 6 /petroleum ether 4) to obtain a white solid (60 mg, 29% yield). ¹HNMR (DMSO, 200 MHz) δ 1.09 (3H, t, J = 7.2Hz), 3.40 (2H, q, J = 6.8Hz), 4.40 (2H, d, J = 6Hz), 5.14 (1H, s), 6.10 (1H, s), 7.36 (1H, dd, J = 4.8 Hz, J' = 1.2 Hz), 7.46 (2H, t, J = 8.8 Hz), 7.63 (1H, d, J = 2.2 Hz), 7.83 (4H, m), 8.05 (2H, d, J = 8Hz), 8.34 (1H, d, J = 6.8Hz), 8.82 (1H, bt) [M⁺] 524.6 (C₂₄H₂₁F₄N₃O₄S requires 523.50).

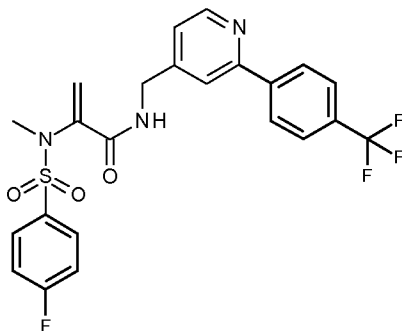
Example 55: 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl]methyl]prop-2-enamide



5 Preparation of 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl]methyl]prop-2-enamide Example 55

Acid **7I** (665mg, 2 mmol) was dissolved in 10 ml of THF and at rt DEPC (1.1 equiv, 0.3ml) and [4-(trifluoromethoxy)phenyl]phenyl]methanamine **23B** (1.1 equiv., 590mg) were added to the solution. The mixture was stirred at rt overnight then
 10 evaporated. The residue was dissolved in AcOEt (30ml) and washed with water (1 X 20ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (4:6 EtOAc:petroleum ether) afforded 200mg of a pale yellow solid. Yield = 18.3% ¹HNMR (DMSO, 200 MHz) δ 1.09 (3H, t, J = 7Hz), 3.44 (2H, q, J = 7.2Hz), 4.43 (2H, d, J = 6Hz), 5.40 (1H, s), 6.19
 15 (1H, s), 7.33 (2H, m), 7.44 (3H, m), 7.60 (3H, m), 7.75 (2H, dd, J = 8.8 Hz, J' = 2.2 Hz), 8.80 (1H, bt) [M^{+1}] 545.1 (C₂₃H₂₀ClF₃N₂O₄S₂ requires 544.99).

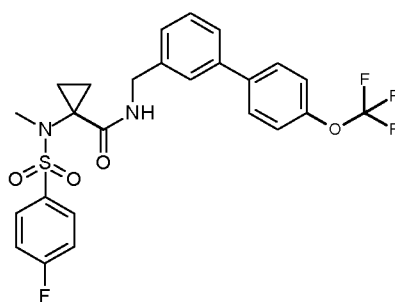
Example 56: 2-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide



Preparation of 2-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide Example 56

A solution of acid **4A** (260 mg, 1 mmol) in THF (25 mL) was added with DEPC (0.18 mL, 1.3 mol eq) and the mixture was stirred at room temperature for about 5 minutes. Then [2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **21A** (1.1 equiv., 277.5 mg) was added. The reaction mixture was then stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (30 mL) and washed with water (50 mL) and brine. The separated organic phase, after anhydrication over Na₂SO₄, was evaporated under reduced pressure and the residue was purified by flash chromatography (1:1 EtOAc:Petroleum ether) to afford a pale yellow solid (100 mg) after crystallization from a mixture of diethyl ether/petroleum ether. Yield = 49%, ¹HNMR (DMSO, 400 MHz) δ 2.93 (3H, s), 4.48 (d, 2H, J = 6 Hz), 5.08 (s, 1H), 5.87 (s, 1H), 7.35 (d, 1H), 7.37 (t, 2H, J = 8.8 Hz), 7.82 (m, 4H), 8.03 (s, 1H), 8.28 (d, 2H, J = 8.4 Hz), 8.63 (d, 1H, J = 5.2 Hz), 8.95 (bt, 1H); [M⁺] 494.47 (C₂₃H₁₉F₄N₃O₃S requires 493.47).

Example 57: 1-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl]methyl]cyclopropanecarboxamide



Synthesis of methyl 1-[methyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxylate 14A

A solution of **13A** (1g, 3.67 mmol) in DMF (15 mL) was added with an. K₂CO₃ (1.5 mol eq, 0.76 g) and, after few minutes, 2-iodomethane (1.2 mol eq, 0.81 ml) was added and the mixture was heated at 50°C for 12h. The solvent was removed under

reduced pressure, water was added to the residue (60 mL) and the aqueous phase was extracted with EtOAc (3x30 mL). The recombined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure to afford **14A** as a pale yellow oil (950 mg, 90% yield). ¹HNMR (DMSO, 200 MHz) δ 2.43 (bs, 4H), 2.88 (s, 3H), 2.90(s, 3H), 7.42 (t, 2H, J=8.2), 7.87 (m, 2H).

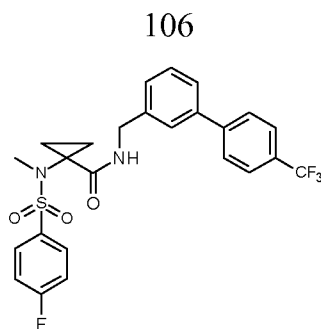
Synthesis of 1-[methyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxylic acid 15A

A solution of **14A** (1.3 g, 4.52 mmol) in dioxane (40 mL) was added with 10% NaOH aq. solution (20 mL) and the mixture was heated at 50°C overnight. The organic solvent was removed under reduced pressure and the aqueous phase was acidified with 10% HCl. The solid formed was collected by filtration, washed with water (2x20 mL) and dried to afford **15A** as white solid (1.0 g, 81% yield). ¹HNMR (DMSO, 200 MHz) δ 1.40 (bs, 4H), 2.91 (s, 3H), 7.42 (m, 2H), 7.80 (m, 2H), 12.60 (bs, 1H).

Preparation of 1-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl]methyl]cyclopropanecarboxamide Example 57

Acid **15A** (350mg, 1.28 mmol) was dissolved in 5 ml of THF and at rt DEPC (0.25 mL, 1.3 mol eq) and [3-[4-(trifluoromethoxy)phenyl]phenyl]methanamine **23B** (0.376 g, 1.1 mol eq) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30ml) and washed with water (1 X 20ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:Petroleum ether) afforded 100mg of a white solid. Yield = 15% ¹HNMR (DMSO, 200 MHz) δ 1.09 (2H, bs), 1.34 (2H, bs), 3.00 (3H, s), 4.35 (2H, d, J = 5.8 Hz), 7.43 (8H, m), 7.81 (4H, m), 8.17 (1H, bt); [M⁺] 523.9 (C₂₅H₂₂F₄N₂O₄S requires 522.51).

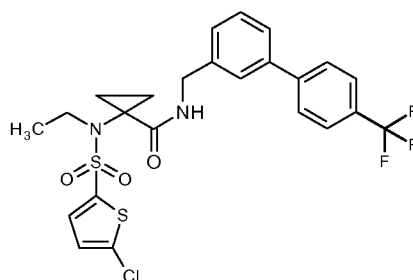
Example 58: 1-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]cyclopropanecarboxamide



Preparation of 1-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]cyclopropanecarboxamide Example 58

Acid **15A** (820mg, 3 mmol) was dissolved in 5 ml of THF and at rt DEPC (1.1 equiv, 0.5ml) and [3-[4-(trifluoromethyl)phenyl]phenyl]methanamine **23A** (1.1 equiv., 835mg) were added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30ml) and washed with water (1 X 20ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:Petroleum ether) afforded 250mg of a white solid. Yield = 16.5% ¹HNMR (DMSO, 400 MHz) δ 1.09 (2H, bs), 1.32 (2H, bs), 2.99 (3H, s), 4.34 (2H, d, J = 5.8 Hz), 7.35 (4H, m), 7.58 (2H, m), 7.80 (4H, m), 7.87 (2H, d, J = 8 Hz), 8.18 (1H, bt); [M⁺] 507.9 (C₂₅H₂₂F₄N₂O₃S requires 506.51).

Example 59: 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]cyclopropanecarboxamide

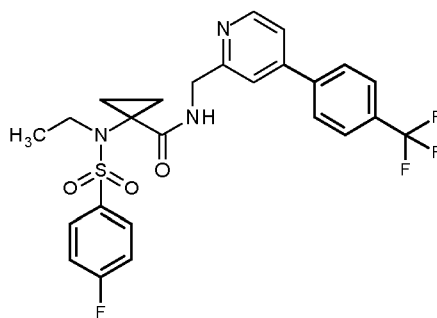


Preparation of 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]cyclopropanecarboxamide Example 59

A solution of acid **18** (0.50 g, 1.62 mmol) in THF (25 mL) was added with DEPC (0.32 mL, 1.3 mol eq) and the mixture was stirred at room temperature for 10'. [3-[4-

(trifluoromethyl)phenyl]phenyl]methanamine **23A** (1.1 equiv., 450mg) was added to the solution. The mixture was stirred at rt overnight then evaporated. The residue was dissolved in AcOEt (30ml) and washed with water (1 X 20ml) and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The purification of the crude by chromatographic column (3:7 EtOAc:Petroleum ether) afforded 350mg of a white solid. Yield = 40% ¹HNMR (DMSO, 200 MHz) δ 1.19 (5H, m), 1.41 (2H, bs), 3.39 (2H, m), 4.38 (2H, d, J = 5.8 Hz), 7.23 (1H, dd, J = 4Hz), 7.33 (1H, d), 7.41 (1H, t), 7.50 (3H, m), 7.79 (4H, dd, J = 5.8 Hz), 8.11 (1H, bs); [M⁺] 544.9 (C₂₄H₂₂ClF₃N₂O₃S₂ requires 543.02).

Example 60: 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[4-[4-(trifluoromethyl)phenyl]-2-pyridyl]methyl]cyclopropanecarboxamide



Synthesis of 4-[4-(trifluoromethyl)phenyl]pyridine-2-carbonitrile **20C**

4-Chloropyridine-2-carbonitrile **19B** (2.0gr, 14.44 mmol) was dissolved in 35ml of dioxane. The solution was added with cesium carbonate (6.8gr), [4-(trifluoromethyl)phenyl]boronic acid (1.2 equiv., 3.3gr) and palladium acetate/XPhos (80mg/280mg) under argon atmosphere. The mixture was stirred at 100°C for 4 hours. The reaction is filtered through a pad of celite, concentrated and crystallized from diethyl ether/ petroleum ether to give a beige solid (3.2 gr, 12.85 mmol, yield: 89%) ¹HNMR (DMSO, 400 MHz) δ 7.92 (2H, dd, J = 8.0 Hz), 8.12 (3H, m), 8.51 (1H, dd), 8.39 (1H, dd, J = 5.2Hz)

Synthesis of [4-[4-(trifluoromethyl)phenyl]-2-pyridyl]methanamine **21C**

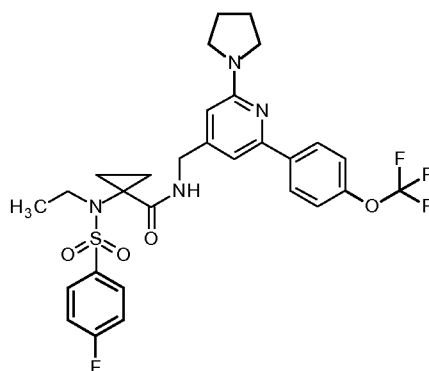
The nitrile **20C** (3.2g, 12.85 mmol) dissolved in 50 ml of diethyl ether was added dropwise to a mixture of LiAlH₄ (912mg, 2 equiv.) in diethyl ether (80mL) and stirred at

0°C. Then, the mixture was stirred at room temperature overnight. The excess of LiAlH₄ was destroyed by water addition at 0°C, the solid formed was filtered, washed with Et₂O and the filtrate was dried over Na₂SO₄ and evaporated to dryness to obtain 2.5g of the amine as a yellow oil. The amine was used for the following step without purification.

5 **Preparation of 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[4-[4-(trifluoromethyl)phenyl]-2-pyridyl]methyl]cyclopropanecarboxamide Example 60**

A solution of acid **15B** (0.5 g, 1.7 mmol) in THF (30 mL) was added with DEPC (0.34 mL, 1.3 mol eq) and the mixture was stirred at room temperature for about 5 minutes. Then [4-[4-(trifluoromethyl)phenyl]-2-pyridyl]methanamine **21C** (0.51 g, 1.18
10 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (40 mL) and washed with water (50 mL) and brine. The separated organic phase was dried over Na₂SO₄ and evaporated under reduced pressure and the residue was purified by flash chromatography (3:7 EtOAc:Petroleum ether) to
15 afford a white solid (0.18 g) after crystallization from diethyl ether. Yield = 20%, ¹HNMR (DMSO, 200 MHz) δ 1.11 (bs, 2H), 1.23 (t, 3H, J= 8), 1.26 (bs, 2H), 3.41 (bs, 2H), 4.49 (d, 2H); 7.44 (m, 2H), 7.66 (dd, 1H), 7.74 (bs, 1H), 7.90 (m, 4H), 8.02 (d, 2H, J= 8), 8.26 (bt, 3H), 8.63 (dd, 1H, J = 5.2). [M⁺] 522.53 (C₂₅H₂₃F₄N₃O₃S requires 521.53).

Example 61: 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-
20 (trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide

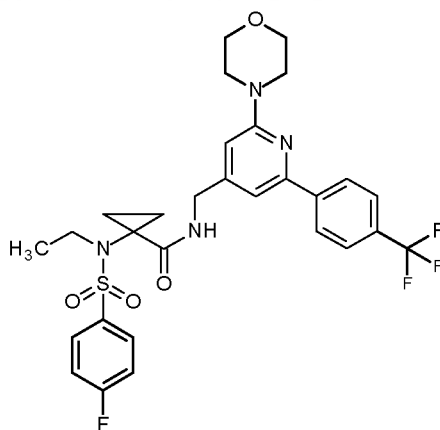


Preparation of 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide

Example 61

A solution of acid **15B** (0.5 g, 1.7 mmol) in THF (30 mL) was added with DEPC (0.34 mL, 1.3 mol eq) and the mixture was stirred at room temperature for about 5 minutes. Then [4-[4-(trifluoromethoxy)phenyl]-2-pyridyl]methanamine **27C** (0.61 g, 1.07 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (40 mL) and washed with water (50 mL) and brine. The separated organic phase was dried over Na₂SO₄ and evaporated under reduced pressure and the residue was purified by flash chromatography (3:7 EtOAc:Petroleum ether) to afford a white solid (0.18 g) after crystallization from diethyl ether. Yield = 17%, ¹HNMR (DMSO, 200 MHz) δ 1.13 (bs, 2H), 1.20 (t, 3H, J= 8), 1.25 (bs, 2H), 3.46 (bq, 2H), 4.29 (d, 2H); 6.44 (s, 1H), 7.12 (s, 1H), 7.42 (m, 4H), 7.96 (m, 2H), 8.13 (m, 3H). [M⁺] 607.53 (C₂₉H₃₀F₄N₄O₄S requires 606.63).

Example 62: 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide

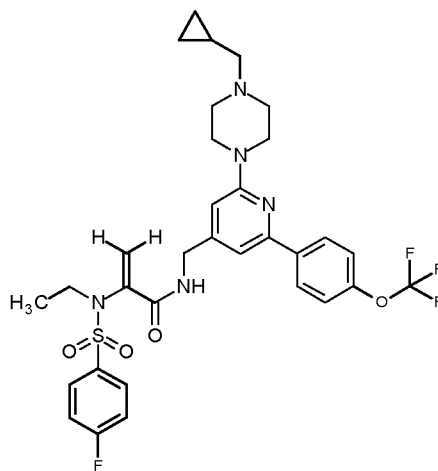


Preparation of 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide

Example 62
with solution of acid **15B** (0.5 g, 1.7 mmol) in THF (30 mL) was added with DEPC (0.34 mL, 1.3 mol eq) and the mixture was stirred at room temperature for about 5

minutes. Then [2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27D** (0.50 g, 1.04 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (40 mL) and washed with water (50 mL) and brine. The separated organic phase was dried over Na₂SO₄ and evaporated under reduced pressure and the residue was purified by flash chromatography (1:1 EtOAc:Petroleum ether) to afford a white solid (220 mg) after crystallization from diethyl ether. Yield = 21%, ¹HNMR (DMSO, 200 MHz) δ 1.10 (bs, 2H), 1.20 (t, 3H, J= 8), 1.35 (bs, 2H), 3.46 (bq, 2H), 3.55 (bt, 4H), 3.74 (bt, 4H), 4.34 (d, 2H); 6.81 (s, 1H), 7.39 (m, 3H), 7.86 (m, 4H), 8.23 (bm, 3H). [M⁺] 607.81 (C₂₉H₃₀F₄N₄O₄S requires 606.63).

Example 63: N-[[2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]-2-[ethyl-(4-fluorophenyl)sulfonylamino]prop-2-enamide



15 **Synthesis of 2-chloro-6-[4-(cyclopropylmethyl)piperazin-1-yl]pyridine-4-carbonitrile **25D****

A solution of **24** (2.5 g, 14.46 mmol) in abs. EtOH (10 mL) was added with TEA (2ml) and 4-cyclopropylmethylpiperazine (1.36 mL, 1 mol eq) and the mixture was heated at 50°C overnight. The solvent was removed under reduced pressure, water was added to the residue and the aqueous phase was extracted with EtOAc (3x40 mL). The recombined organic phase was washed with brine (1x60 mL), dried over Na₂SO₄ and

evaporated to afford **25D** as a pale yellow solid (2.4g, 8.67 mmol, 60% Yield). ¹HNMR (DMSO, 400 MHz) δ 0.08 (m, 2H), 0.46 (m, 2H), 0.84 (m, 1H), 2.20 (d, 2H, J = 6.8 Hz), 2.50 (m, 4H), 3.56 (m, 4H), 7.06 (s, 1H), 7.32 (s, 1H).

Synthesis of 2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethoxy)phenyl]pyridine-4-carbonitrile 26F

The nitrile **25D** (2.4 g, 8.67 mmol), 4-trifluoromethoxyphenylboronic acid (2.15 g, 1.1 mol eq), palladium acetate (45 mg), cesium carbonate (4.5 g, 2 mol eq), and XPhos (190 mg) were mixed, placed under a nitrogen atmosphere and dioxane (10 mL) was added. The mixture was heated at 100°C overnight. After cooling, the mixture was
10 filtered through a celite pad, washed with dioxane (2 x 20 mL) and concentrated under reduced pressure. The residue was used for the next step without further purification.

Synthesis of [2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine 27F

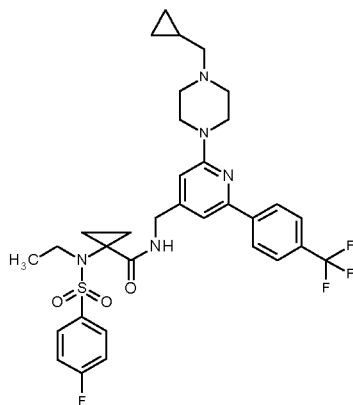
A solution of nitrile **26F** (2.5 g, 6.2 mmol) in diethyl ether (30 mL) was added in
15 small amounts to a mixture of LiAlH₄ (0.67g) in diethyl ether (30mL) stirred at 0°C. After the addition was completed, the mixture was stirred at room temperature overnight. The excess of LiAlH₄ was destroyed at 0°C by addition of small amount of water (30 mL), the solid formed was filtered off and the organic filtrate was separated, washed with brine (50 mL) and dried over Na₂SO₄. The organic phase was evaporated under reduced
20 pressure to afford **27G** as a pale yellow oil (2.0 g, 80% yield). ¹HNMR (DMSO, 200 MHz) δ 0.08 (m, 2H), 0.47 (m, 2H), 0.77 (m, 1H), 2.14 (d, 2H, J = 6.6), 2.44 (m, 4H), 2.86 (bs, 2H), 3.45 (m, 4H), 3.65 (s, 2H), 6.86 (s, 1H), 7.18 (s, 1H), 7.88 (d, 2H, J=7.8), 8.24 (d, 2H, J=8.2).

Preparation of N-[[2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]prop-2-enamide Example 63

A solution of acid **4B** (273.28mg, 1 mmol) in THF (10 mL) was added with DEPC (0.15 mL, 1.1 mol eq) and the mixture was stirred at room temperature for about 5

minutes. Then [2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methanamine **27F** (405 mg, 1.04 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (40 mL) and washed with water (50 mL) and brine. The separated organic phase was dried over Na₂SO₄ and evaporated under reduced pressure and the residue was purified by flash chromatography (9:1 EtOAc:methanol) to afford a white solid (200 mg) after crystallization from diethyl ether. Yield = 30%, ¹HNMR (DMSO, 200 MHz) δ 0.05 (m, 2H), 0.45 (bm, 2H), 0.82 (m, 1H), 1.08 (t, 3H), 2.17 (d, 2H, J = 6.4), 3.34 (bm, 4H), 3.49 (bm, 4H), 4.43 (d, 2H, J = 6.2), 5.13 (s, 1H); 6.09 (s, 1H), 6.80 (s, 1H), 7.30 (s, 1H), 7.47 (m, 4H), 7.85 (m, 4H), 8.74 (t, 1H). [M⁺] 662.90 (C₃₂H₃₅F₄N₅O₄S requires 661.71).

Example 64: N-[[2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide



Synthesis of 2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]pyridine-4-carbonitrile **26G**

The nitrile **25D** (2.4 g, 8.67 mmol), 4-trifluoromethylphenylboronic acid (2.05 g, 1.1 mol eq), palladium acetate (45 mg), cesium carbonate (4.5 g, 2 mol eq), and XPhos (190 mg) were mixed, placed under a nitrogen atmosphere and dioxane (10 mL) was added. The mixture was heated at 100°C overnight. After cooling, the mixture was

filtered through a celite pad, washed with dioxane (2 x 20 mL) and concentrated under reduced pressure. The residue was used for the next step without further purification.

Synthesis of [2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine 27G

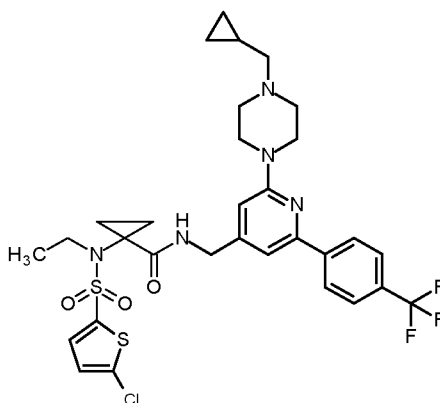
5 A solution of nitrile **26G** (2.5 g, 6.7 mmol) in diethyl ether (30 mL) was added in small amounts to a mixture of LiAlH₄ (0.67g) in diethyl ether (30mL) stirred at 0°C. After the addition was completed, the mixture was stirred at room temperature overnight. The excess of LiAlH₄ was destroyed at 0°C by addition of small amount of water (30 mL), the solid formed was filtered off and the organic filtrate was separated, washed with
10 brine (50 mL) and dried over Na₂SO₄. The organic phase was evaporated under reduced pressure to afford **27G** as a pale yellow oil (2.0 g, 80% yield). ¹HNMR (DMSO, 200 MHz) δ 0.00 (m, 2H), 0.37 (m, 2H), 0.77 (m, 1H), 2.14 (d, 2H, J = 6.6), 2.44 (m, 4H), 2.80 (bs, 2H), 3.50 (m, 4H), 3.61 (s, 2H), 6.76 (s, 1H), 7.23 (s, 1H), 7.68 (d, 2H, J=8), 8.14 (d, 2H, J=8).

15 **Preparation of N-[[2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide Example 64**

A solution of acid **15B** (0.5 g, 1.7 mmol) in THF (30 mL) was added with DEPC (0.34 mL, 1.3 mol eq) and the mixture was stirred at room temperature for about 5
20 minutes. Then [2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27G** (636 mg, 1.04 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (40 mL) and washed with water (50 mL) and brine. The separated organic phase was dried over
25 Na₂SO₄ and evaporated under reduced pressure and the residue was purified by flash chromatography (9:1 EtOAc:methanol) to afford a white solid (340 mg) after crystallization from diethyl ether. Yield = 30%, ¹HNMR (DMSO, 200 MHz) δ 0.40 (m, 2H), 0.63 (bm, 2H), 0.86 (m, 1H), 1.08 (m, 2H), 1.23 (t, 3H), 1.30 (bm, 2H), 3.06 (bm,

4H), 3.39 (bm, 4H), 3.64 (bm, 2H), 4.44 (m, 4H); 6.92 (s, 1H), 7.44 (m, 3H), 7.86 (m, 4H), 8.26 (bm, 3H). $[M^{+1}]$ 660.81 ($C_{33}H_{37}F_4N_5O_3S$ requires 659.74).

Example 65: 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide

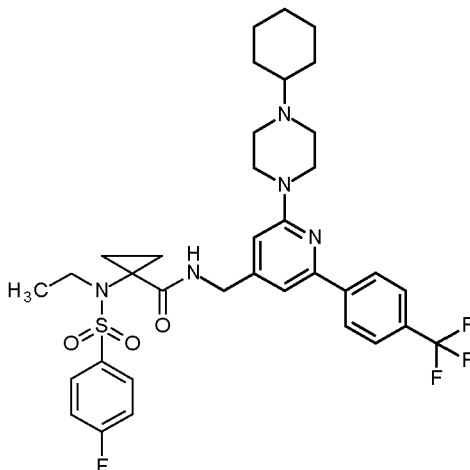


Preparation of 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide Example 65

A solution of acid **18** (463 mg, 1.5 mmol) in THF (30 mL) was added with DEPC (0.23 mL, 1.0 mol eq) and the mixture was stirred at room temperature for about 5 minutes. Then [2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27G** (560 mg, 1.04 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (40 mL) and washed with water (50 mL) and brine. The separated organic phase was dried over Na_2SO_4 and evaporated under reduced pressure and the residue was purified by flash chromatography (9:1 EtOAc:methanol) to afford a white solid (220 mg) after crystallization from diethyl ether. Yield = 21.5%, 1H NMR (DMSO, 200 MHz) δ 0.40 (m, 2H), 0.65 (bm, 2H), 0.94 (m, 1H), 1.12 (m, 2H), 1.28 (t, 3H), 1.40 (bm, 2H), 3.04 (bm, 4H), 3.39 (bm, 4H), 3.43 (bm, 2H), 3.44 (m, 4H); 4.40 (bm, 4H), 6.87 (s, 1H), 7.30 (m,

2H), 7.60 (d, 1H, $J = 3.2$), 7.82 (d, 2H, $J = 8.2$), 8.25 (bm, 3H). $[M^{+1}]$ 682.98 ($C_{31}H_{35}ClF_3N_5O_3S_2$ requires 682.22).

Example 66: N-[[2-(4-cyclohexyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide



5

Synthesis of 2-chloro-6-[4-(cyclohexyl)piperazin-1-yl]pyridine-4-carbonitrile **25E**

A solution of **24** (2.5 g, 14.46 mmol) in abs. EtOH (10 mL) was added with TEA (2 mL) and N-cyclohexylpiperazine (2.43 g, 1 mol eq) and the mixture was heated at 70°C for 4 hours. The solvent was removed under reduced pressure, water was added to the residue and the aqueous phase was extracted with EtOAc (3x40 mL). The recombined organic phase was washed with brine (1x60 mL), dried over Na_2SO_4 and evaporated to afford **25E** as a pale yellow solid (2.2g, 7.2 mmol, 49% Yield). 1H NMR (DMSO, 200 MHz) δ 1.18 (bm, 4H), 1.59 (bm, 1H), 1.74 (bm, 4H), 2.26 (bm, 2H), 2.53 (m, 4H), 3.52 (m, 4H), 7.04 (s, 1H), 7.30 (s, 1H).

15

Synthesis of 2-[4-(cyclohexyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]pyridine-4-carbonitrile **26E**

The nitrile **25E** (2.2 g, 7.2 mmol), 4-trifluoromethylphenylboronic acid (2.05 g, 1.1 mol eq), palladium acetate (45 mg), cesium carbonate (4.5 g, 2 mol eq), and XPhos (190 mg) were mixed, placed under a nitrogen atmosphere and dioxane (10 mL) was added. The mixture was heated at 100°C overnight. After cooling, the mixture was filtered

20

through a celite pad, washed with dioxane (2 x 20 mL) and concentrated under reduced pressure. The residue was a yellow oil. ¹HNMR (DMSO, 200 MHz) δ 1.14 (bm, 4H), 1.59 (bm, 1H), 1.75 (bm, 4H), 2.26 (bm, 2H), 2.58 (m, 4H), 3.62 (m, 4H), 7.33 (s, 1H), 7.66 (s, 1H), 7.82 (d, 2H, J = 8.2), 8.28 (d, 2H, J = 8.2).

5 **Synthesis of [2-[4-(cyclohexyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine 27E**

A solution of nitrile **26E** (3.2 g, 7.7 mmol) in diethyl ether (30 mL) was added in small amounts to a mixture of LiAlH₄ (800 mg) in diethyl ether (30mL) stirred at 0°C. After the addition was completed, the mixture was stirred at room temperature overnight.

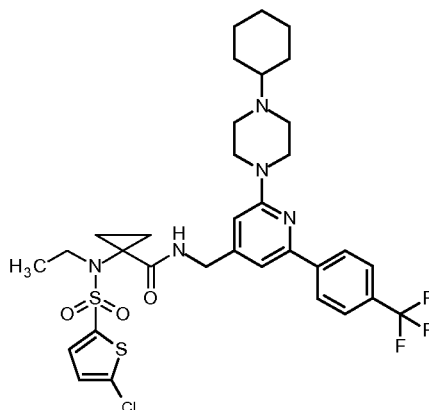
10 The excess of LiAlH₄ was destroyed at 0°C by addition of small amount of water (30 mL), the solid formed was filtered off and the organic filtrate was separated, washed with brine (50 mL) and dried over Na₂SO₄. The organic phase was evaporated under reduced pressure to afford **27E** as a pale yellow oil (1.76 g, 55% yield). ¹HNMR (DMSO, 200 MHz) δ 1.14 (bm, 4H), 1.52 (bm, 1H), 1.77 (bm, 4H), 2.26 (bm, 2H), 2.60 (m, 4H), 3.36
15 (b, 2H), 3.55 (m, 4H), 3.70 (s, 2H), 6.84 (s, 1H), 7.32 (s, 1H), 7.79 (d, 2H, J = 8.2), 8.24 (d, 2H, J = 8.2).

Preparation of N-[[2-(4-cyclohexylpiperazin-1-yl)-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide Example 66

20 A solution of acid **15B** (0.5 g, 1.7 mmol) in THF (30 mL) was added with DEPC (0.34 mL, 1.3 mol eq) and the mixture was stirred at room temperature for about 5 minutes. Then [2-[4-(cyclohexyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27E** (712 mg, 1.04 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent
25 was removed under reduced pressure, the residue was suspended in EtOAc (40 mL) and washed with water (50 mL) and brine. The separated organic phase was dried over Na₂SO₄ and evaporated under reduced pressure and the residue was purified by flash chromatography (9:1 EtOAc:methanol) to afford a white solid (140 mg) after

crystallization from diethyl ether. Yield = 20%, ^1H NMR (DMSO, 200 MHz) δ 1.18 (bm, 9H), 1.83 (bm, 4H), 2.30 (bm, 1H), 2.59 (bm, 4H), 3.34 (bm, 2H), 3.57 (bm, 4H), 4.40 (bd, 2H), 6.82 (s, 1H), 7.34 (m, 3H), 7.83 (m, 4H), 8.21 (bm, 3H). $[\text{M}^{+1}]$ 688.41 ($\text{C}_{35}\text{H}_{41}\text{F}_4\text{N}_5\text{O}_3\text{S}$ requires 687.79).

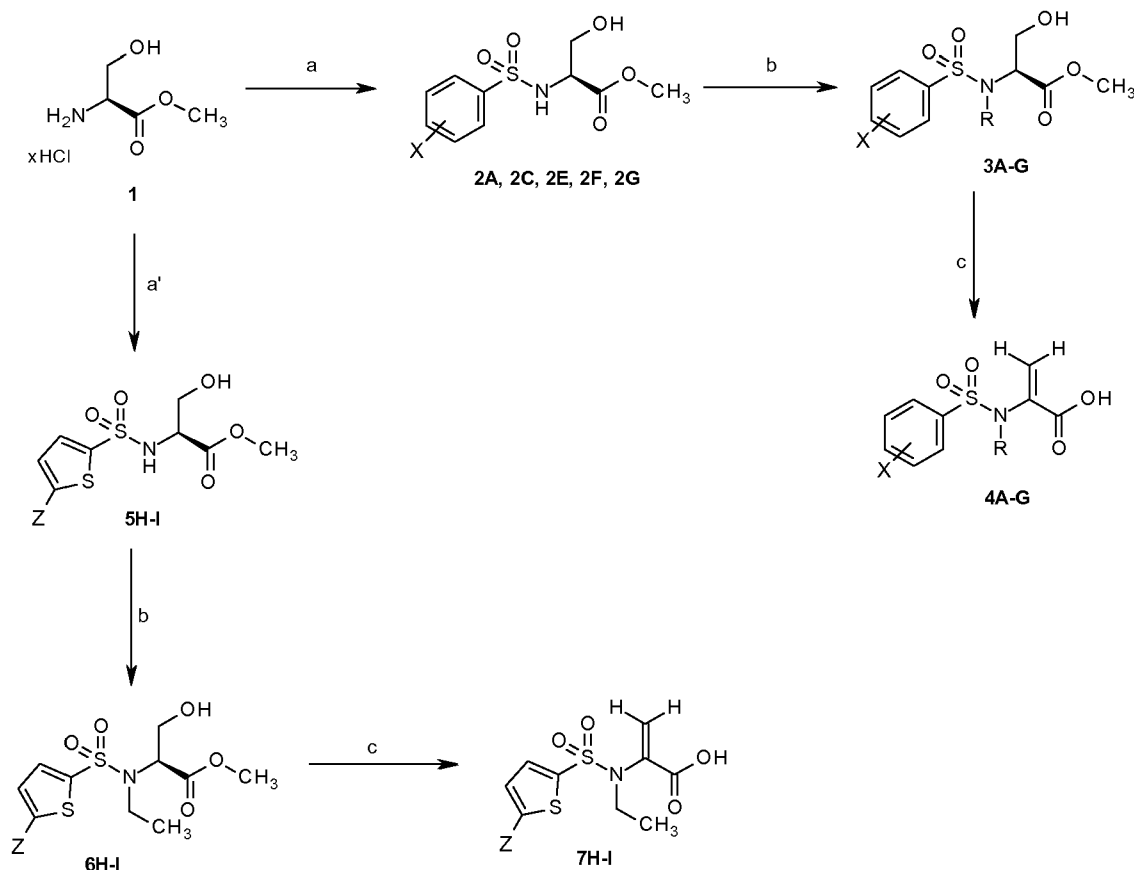
Example 67: 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-(4-cyclohexylpiperazin-1-yl)-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide



Preparation of 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-(4-cyclohexylpiperazin-1-yl)-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide Example 67

A solution of acid **18** (463 mg, 1.5 mmol) in THF (30 mL) was added with DEPC (0.23 mL, 1.0 mol eq) and the mixture was stirred at room temperature for about 5 minutes. Then [2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methanamine **27E** (628 mg, 1.04 mol eq) and a catalytic amount of TEA were added, then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (40 mL) and washed with water (50 mL) and brine. The separated organic phase was dried over Na_2SO_4 and evaporated under reduced pressure and the residue was purified by flash chromatography (9:1 EtOAc:methanol) to afford a white solid (110 mg) after crystallization from diethyl ether. Yield = 10%, ^1H NMR (DMSO, 200 MHz) δ 1.15 (bm, 9H), 1.80 (bm, 4H), 2.35 (bm, 1H), 2.59 (bm, 4H), 3.37 (bm, 2H), 3.65 (bm, 4H), 4.45

(bd, 2H), 6.89 (s, 1H), 7.35 (m, 2H), 7.60 (d, 1H, J = 3.4), 7.82 (d, 2H, J = 8), 8.25 (bm, 3H). $[M^{+}]$ 711.65 ($C_{33}H_{39}ClF_3N_5O_3S_2$ requires 710.27).

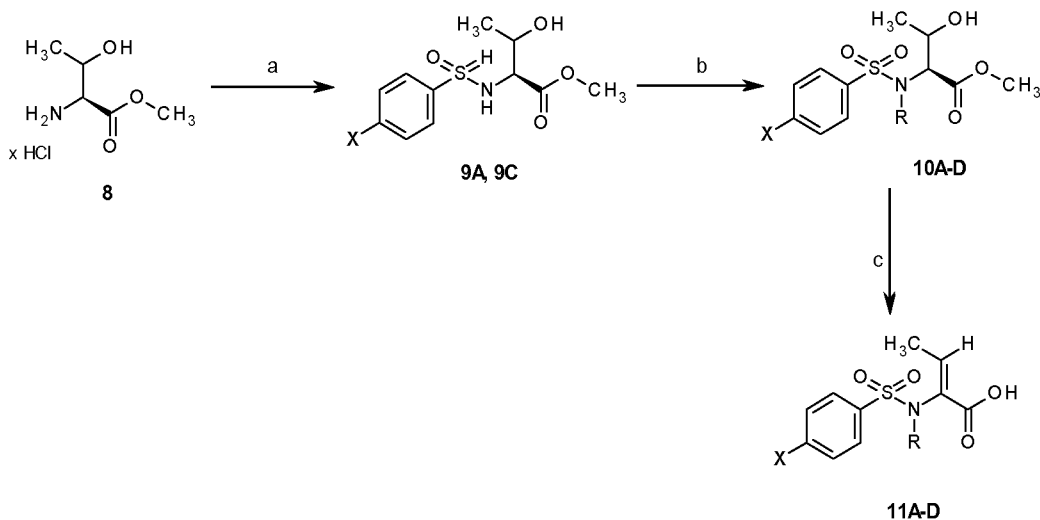
Scheme 3

5 **Reagents:** a) X-substituted-benzensulfonyl chloride, TEA, CH_2Cl_2 ; a') 5-Z-thiophene-2-sulfonylchloride, TEA, CH_2Cl_2 ; b) alkyl iodide, K_2CO_3 , DMF; c) 20% aq. NaOH or $LiOH \cdot H_2O$, THF/water - acetylchloride, Pyr.

10 **Substituents:** **A**, X= 4-F and R= methyl; **B**, X= 4-F and R= ethyl; **C**, X= 4-Cl and R= methyl; **D**, X= 4-Cl and R=ethyl; **E**, X= 4- CH_3 and R= methyl; **F**, X=3-F and R= ethyl; **G**, X= 3,4-difluoro and R=ethyl.

5-7H, Z=H; **5-7I**, Z= Cl. For **2A**, **2C** and **2E**, R=H.

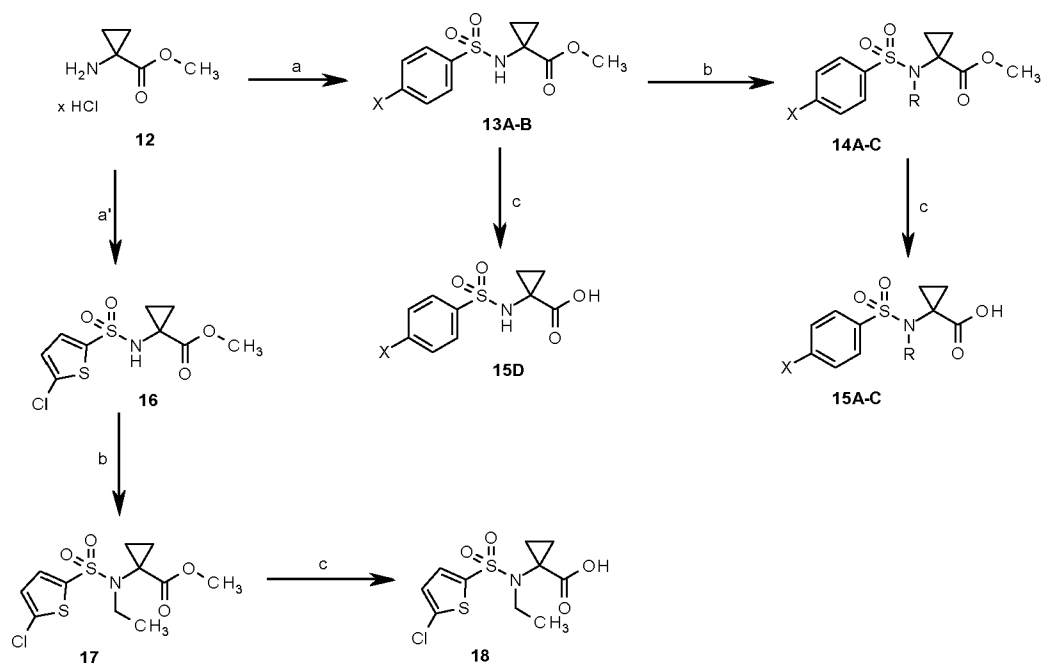
Scheme 4



Reagents: a) 4-X-benzenesulfonyl chloride, TEA, CH_2Cl_2 ; b) alkyl iodide, K_2CO_3 , DMF; c) $\text{LiOH}\cdot\text{H}_2\text{O}$, THF/water - acetyl chloride, Pyr

Substituents: **A**, X= F and R= methyl; **B**, X= F and R= ethyl; **C**, X=Cl and R= methyl; **D**, X=Cl and R=ethyl. For **9A** and **9C**, R=H.

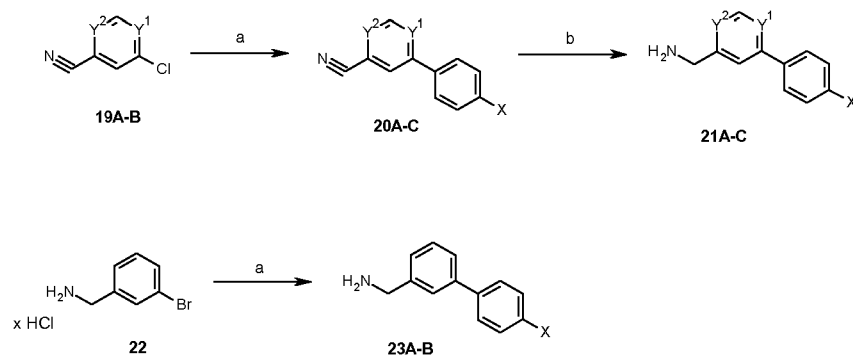
Scheme 5



Reagents: a) 4-fluoro/chlorobenzenesulfonyl chloride, TEA, CH_2Cl_2 ; a') 4-chlorothiophene-2-sulfonylchloride, TEA, CH_2Cl_2 b) 2-ethyl iodide, K_2CO_3 , DMF; c) 10% aq. NaOH or $\text{LiOH}\cdot\text{H}_2\text{O}$, THF/water.

Substituents: **A**, X= F and R= methyl; **B**, X=F and R= ethyl, **C**, X=Cl and R= ethyl. For **15D**, X=F.

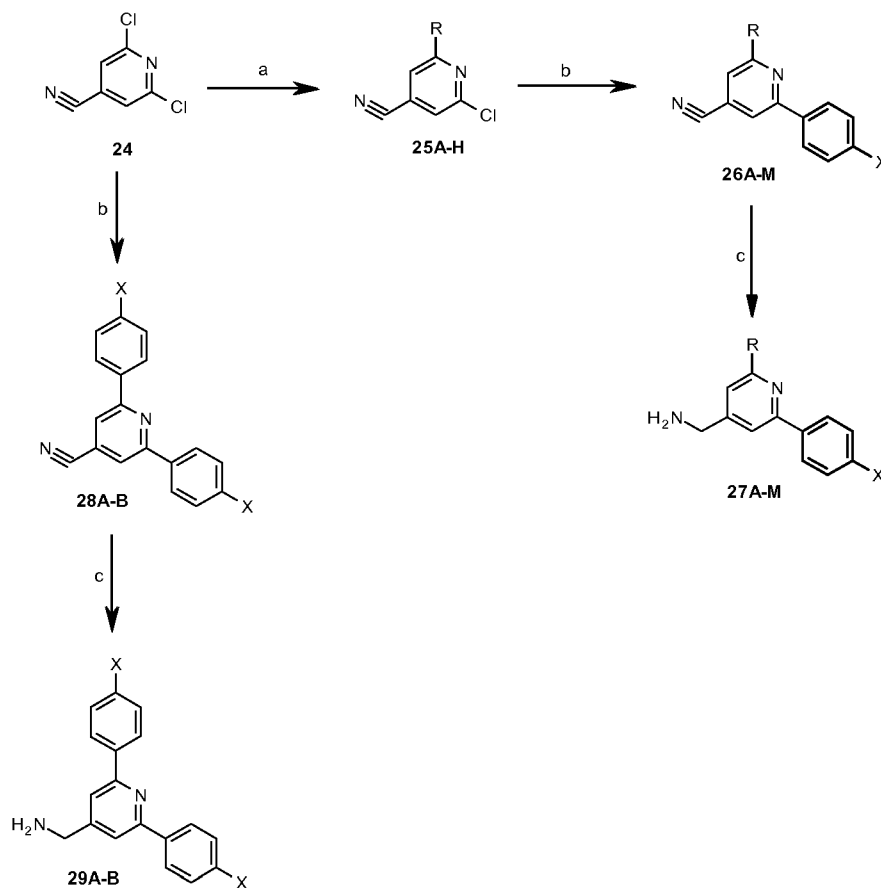
Scheme 6



Reagents: a) 4-X-Phenylboronic acid, TetrakisPd, NaHCO₃, DME, water; b) LiAlH₄, Et₂O, r.t.

Substituents: **19A**, Y¹= N, Y²= CH; **19B**, Y¹= CH, Y²= N; **20-21A**, Y¹= N, Y²= CH, X= -CF₃; **20-21B**, Y¹= N, Y²= CH, X= -OCF₃; **20-21C**, Y¹= CH, Y²= N, X= -CF₃; **23A**, X= CF₃; **23B**, X= -OCF₃

Scheme 7



Reagents: a) Pyrrolidine, morpholine, *N*-cyclopropylmethyl-piperazine, *N*-cyclohexyl-piperazine, sodiumethoxyde, EtOH, 70°C; or Examethyldiphosphoramidate,
 5 120°C, 18h; or sodiummethoxide, MeOH, 60°C; or 2-isopropanol, NaH 60%, 70°C.
 b) 4-X-Phenylboronic acid, TetrakisPd, NaHCO₃, DME, water or 4-CF₃-phenylboronic acid, Pd(OAc)₂, CsCO₃, XPhos, Dioxane, 100°C; c) LiAlH₄, Et₂O, r.t.

Substituents: **25A**, R= pyrrolidine; **25B**, R= morpholine; **25C**, R= *N,N'*-dimethylamino; **25D**, R= *N*-cyclopropylmethyl-piperazine; **25E**, R= *N*-cyclohexyl-piperazine;
 10 **25F**, R= methoxy; **25G**, R= ethoxy; **25H**, R= isopropoxy; **26-27A**, R=pyrrolidine and X= -CF₃; **26-27B**, R= morpholine and X= -CF₃; **26-27C**, R= pyrrolidine and X= -OCF₃; **26-27D**, R= morpholine and R= -OCF₃; **26-27E**, R=*N,N'*-dimethylamino and X= -CF₃; **26-27F**, R= *N*-cyclopropylmethyl-piperazine and X= -OCF₃; **26-27G**, R= *N*-cyclopropylmethyl-piperazine and X= -CF₃; **26-27H**, R= *N*-cyclohexylpiperazine and R= -CF₃; **26-27I**, R= -OCH₃ and X= -CF₃; **26-27L**, R= -
 15

OCH₂CH₃ and X= -CF₃; **26- 27M**, R= Isopropoxy and X= -CF₃; **28-29A**, X= -CF₃; **28-29B**, X= -OCF₃.

PHARMACOLOGY

Drugs and reagents were obtained from the indicated companies: PF-4840154, ionomycin, laminin, poly-L-lysine, collagenase, trypsin, L-glutamine, penicillin/streptomycin, DMEM, HBSS, mouse-NGF-7S, ARA-C, HEPES, Tween80, Complete Freund's Adjuvant (CFA) and BSA (Sigma, Italy); FBS and HS (Gibco, Italy); Fura-2-AM-ester (Vinci-Biochem, Italy) and Methylcellulose (Fluka, Switzerland). The stock concentration (10 mM) of PF-4840154, Fura-2-AM-ester, ionomycin and all tested compounds were prepared in 100% DMSO.

PF-4840154 (1μM)-induced Ca²⁺ fluorescence measurements in A549 cell line

Human lung adenocarcinoma epithelial cell line (A549) stably expressing native human TRPA1 receptors were used. The cells were cultured in medium consisting of Eagle's minimal essential medium (EMEM) supplemented with 10% fetal bovine serum (FBS), penicillin (100 IU/ml), streptomycin (100 mg/ml), L-glutamine (2 mM), sodium bicarbonate (2.5 g/L) and HEPES (24 mM). Cells were kept at 37°C in 5% CO₂/humidified air. For the experiments the cells were seeded at a density of 16,000 cells/well into 96-well black, clear-bottom plates. After 24 hours incubation the cells were loaded with medium supplemented with 2.5 mM probenecid, 3 μM of the calcium sensitive fluorescent dye Fluo-4 AM and 0.01% pluronic acid, for 30 min at 37°C. Afterwards the loading solution was aspirated and 100 μl/well of assay buffer: Hank's Balanced Salt Solution (HBSS) supplemented with 2.5 mM probenecid and 500 μM Brilliant Black (Aldrich) was added. Stock solutions (100 mM) of ligands were made in Dimethyl Sulfoxide (DMSO) and stored at -20°C. Serial dilutions of ligands for experimental use were made in HBSS buffer. After placing both plates (cell culture and compound plate) into the FlexStation II (Molecular Device, Union City, CA 94587, US), fluorescence changes were measured. On-line additions were carried out in a volume of 50 μl/well. To facilitate drug diffusion into the wells in antagonist type experiments, the

studies were performed at 36.5°C and three cycles of mixing (25 µl from each well moved up and down 3 times) were performed immediately after antagonist injection to the wells. All exemplified compounds were tested alone (to address residual agonistic activity) and against 1 µM of PF-4840154 to address inhibitory activity at the initial
5 concentration of 10 µM. For selected examples the entire inhibitory concentration-response curves were constructed and the IC₅₀ value calculated.

PF-4840154 (10µM)-induced Ca²⁺ fluorescence measurements in cultured rat dorsal root ganglia neurons

Male SD rats (~ 50 g, Charles River, Italy) were terminally anaesthetized and
10 decapitated. Dorsal root ganglia were removed and placed in cold Hank's balanced salt solution (HBSS) before being transferred to collagenase (2 mg/ml) and trypsin (1 mg/ml) for 35 min at 37°C. The ganglia, placed in cold DMEM supplemented with 10% fetal bovine serum, 10% horse serum, 2 mM L-glutamine, 100 U/ml penicillin and 100 µg/ml streptomycin, were dissociated in single cells by several passages through a series of
15 syringe needles (23G down to 25G). The medium and the ganglia were filtered to remove debris, topped up with 4 ml of DMEM medium and centrifuged (1100 rpm for 6 min). The final cell pellet was re-suspended in DMEM medium [supplemented with 100 ng/ml mouse Nerve Growth Factor (mouse-NGF-7S) and cytosine-β-D-arabinofuranoside free base (ARA-C) 2.5 µM]. The cells were plated on poly-L-lysine (8.3 µM)- and laminin (5
20 µM)-coated 25 mm glass cover slips and kept for 2 days at 37°C in a humidified incubator gassed with 5% CO₂ and air, then treated with Fura-2-AM-ester (5 µM) in a Ca²⁺ buffer solution having the following composition (mM): CaCl₂ 1.4, KCl 5.4, MgSO₄ 0.4, NaCl 135, D-glucose 5, HEPES 10 with BSA (0.1%), at pH 7.4, for 40 min at 37°C. The cells were then washed twice with the Ca²⁺ buffer solution and transferred to a chamber on the
25 stage of a Nikon eclipse TE300 microscope. Fura-2-AM-ester was excited at 340 nM and 380 nM to indicate relative [Ca²⁺]_i changes by the F₃₄₀/F₃₈₀ ratio recorded with a dynamic image analysis system (Laboratory Automation 2.0, RCS, Florence, Italy) and the cells were allowed (at least 10 min) to attain a stable fluorescence before beginning the

experiment. A calibration curve was set up using buffer containing Fura-2-AM-ester and determinant concentrations of free Ca^{2+} . This curve was then used to convert the data obtained from the F_{340}/F_{380} ratio to $[\text{Ca}^{2+}]_i$ (nM).

All exemplified compounds were tested at the concentration of 10 μM against the calcium uptake induced by 10 μM PF-4840154. For selected examples, the entire concentration response curves were constructed and the respective IC_{50} value calculated.

Agonist (PF-4840154)-induced mechanical hyperalgesia in rats

The method is used to investigate the anti-hyperalgesic effects of the compounds listed in the present invention following agonist (PF-4840154)-induced hyperalgesic responses. The activity is indicative of TRPA1 receptor occupancy following oral dosing. Specifically, male SD rats (Charles River, Italy) weighing 70-100 g. were used. The anti-hyperalgesic effects were investigated using the electronic dynamometer test. PF-4840154 (Sigma, USA) was used to induce mechanical hyperalgesia. Local, intraplantar injection of PF-4840154 at 0.05nmol/50 μl /paw caused the reduction of the hind paw withdrawal response induced by mechanical stimuli. Mechanical stimulation was induced in basal condition and 30, 60, 120, 180 and 240 minutes after the oral administration of the antagonists dissolved in 2.5% DMSO and 30% Solutol. Compounds were orally administered (30 $\mu\text{mol/kg/10ml}$) to rats 1 hour before the injection of PF-4840154 into the plantar surface of a rat's hind using a micro syringe.

Oxaliplatin-induced mechanical hyperalgesia in rats

The method described by Nassini et al. (*Pain*, 2011, 152(7), 1621-31) was used with minor modifications. Restrained rats were treated with a single intravenous bolus injection of oxaliplatin (2.5 mg/kg) dissolved in normal saline. This approach was sufficient to elicit reproducible allodynic behaviour evident 3 days post injection and during the day thereafter. For convenience all acute experiments were conducted 7 days post injection when compounds were orally administered at 30 $\mu\text{mol/kg}$.

RESULTS

PF-4840154 (1 μM)-induced Ca^{2+} fluorescence measurements in cultured A549

cell line

PF-4840154 (1 μ M) increased $[Ca^{2+}]$ in the vast majority (95%) of cultured cells which were thereby identified as TRPA1 expressing cells. All synthesized derivatives were initially tested at the final concentration of 10 μ M and then, most active compounds were further investigated to determine their respective potency evaluating the IC₅₀ value defined as the concentration eliciting 50% inhibition under the experimental condition used. The compounds were able to effectively inhibit calcium uptake and several exhibited an inhibitory activity at the tested concentration comprised between 80% and 100% of agonist response. Several derivatives among those of Examples 1-67 showed IC₅₀ values < 50nM.

The IC₅₀ values of the compounds of Examples 1, 7, 10, 11, 12, 14, 15, 34, 37, 38, 39, 40, 43, 44, 50, 51, 53, 55 and 59 calculated against PF-4840154-evoked $[Ca^{2+}]_i$ mobilization were 15, 36, 25, 17, 33, 40, 22, 25, 18, 17, 20, 16, 48, 18, 19, 41, 17, 31, 38nM, respectively.

Tables 1, describes the calcium assay data obtained in A549 cells for exemplified compounds of Formula I.

Table 1

Example	% inhibition at 10μM	IC₅₀ (nM)
1	100%	15
2	98%	135
3	95%	93
4	98%	78
5	99%	100
6	100%	355
7	100%	36
8	100%	76
9	98%	68
10	99%	25

11	99%	17
12	100%	33
13	99%	182

(continued)

14	100%	40
15	100%	22
16	99%	457
17	98%	120
18	100%	93
19	100%	74
20	96%	251
21	100%	323
22	97%	246
23	98%	437
24	97%	724
25	100%	76
26	100%	151
27	100%	135
28	100%	129
29	100%	138
30	100%	100
31	100%	57
32	80%	>4μM
33	55%	>2μM
34	100%	25
35	100%	58
36	100%	118
37	100%	18
38	100%	17
39	100%	20
40	100%	16
41	96%	135
42	100%	104
43	100%	48
44	100%	18
45	100%	151
46	97%	63
47	96%	113
48	96%	260
49	98%	95
50	100%	19
51	100%	41
52	99%	87
53	100%	17
54	47%	>10μM
55	100%	31
56	100%	275
57	97%	275
58	100%	160
59	99%	38
60	100%	423

(continued)

61	95%	784
62	100%	660
63	99%	175
64	99%	338
65	100%	327
66	93%	1.5μM
67	95%	590

PF-4840154 (10 μ M)-induced Ca^{2+} fluorescence measurements in cultured primary dorsal root rat neurons

As mentioned above, selected compounds were also characterized with respect to their specific activity on PF-4840154-induced $[\text{Ca}^{2+}]_i$ mobilization in primary culture of rat dorsal ganglia neurons. In this assay, Examples 1, 7, 10, 11, 14, 15, 19 and 38 had estimated IC_{50} of 14, 29, 47, 20, 60, 32, 68 nM, and 14 respectively.

Tables 2 below, describes the calcium assay data obtained in primary culture of rat dorsal ganglia neurons of selected compounds of formula I.

Table 2

Example	IC₅₀ (nM)
1	14
7	29
10	47
11	20
14	60
15	32
19	68
38	14

Agonist (PF-4840154)-induced mechanical hyperalgesia in rats

The more potent antagonists were orally administered at 30 $\mu\text{mol/kg}$ to rats and their anti-hyperalgesic activity tested against PF-4840154 administered intraplantary at the dose of 0.05 nmol/50 $\mu\text{l/paw}$. Examples 1, 4, 5, 7, 10, 11, 14, 15, 19, 26, 30, 37, 38, 50, 51, 53 and 59 were able to effectively counteract PF-4840154 producing a robust and long-lasting reversal of mechanical allodynia showing 80, 67, 76, 74, 63, 72, 75, 72, 74, 64, 82, 95, 87, 76, 76, 89 and 111 % of reversal, respectively.

Tables 3 below, describes the anti-hyperalgesic activity of selected examples of Formula I in PF-4840154-induced hyperalgesic responses.

Table 3

5

Example	Maximal inhibition (%)
1	80
4	67
5	76
7	74
10	63
11	72
14	75
15	72
19	74
26	64
30	82
37	95
38	87
50	76
51	76
53	89
59	111

Oxaliplatin-induced mechanical hyperalgesia in rats

The more potent antagonists were orally administered at 30 $\mu\text{mol/kg}$ to rats 7 days post intravenous injection of oxaliplatin at the dose of 2.5mg/kg and their anti-nociceptive effect was measured. Examples 1, 34, 37, 40, 50, 51, 53 and 59 were able to effectively counteract the oxaliplatin effect producing a robust and long-lasting reversal of mechanical allodynia showing 97, 71, 82, 103, 82, 65, 83 and 67% of reversal, respectively.

Tables 4 below, describes the anti-hyperalgesic activity of selected examples of Formula I in oxaliplatin-induced mechanical hyperalgesia.

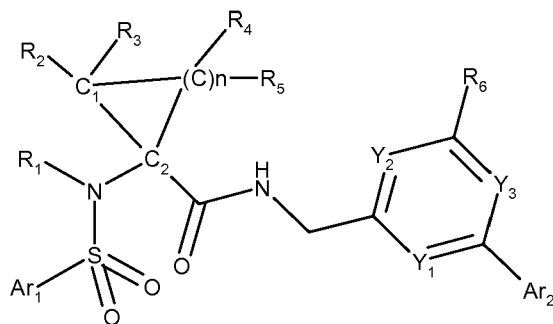
15

Table 4

Example	Maximal inhibition (%)
1	97
34	71
37	82
40	103
50	82
51	65
53	83
59	67

CLAIMS

1. A compound of formula (I)



(I)

5

wherein:

Ar₁ is:

i) phenyl substituted with 0, 1, 2 or 3 substituents R_a; or

ii) a 5- or 6-membered monocyclic aromatic heterocycle ring optionally
 10 substituted with one or two substituents R_a; where each R_a is independently halo, -C₁₋₄alkyl, -OC₁₋₄alkyl, -CN, -CF₃, -OCF₃, -NO₂, -C(O)C₁₋₄alkyl or -CO₂H;

Ar₂ is:

i) phenyl substituted with 0, 1, 2 or 3 substituents R_b; where each R_b is
 independently halo, -C₁₋₄alkyl, -C(O)NR_cR_d, -OC₁₋₄alkyl, -OC₀₋₄alkylCF₃, -CN, -CF₃, -
 15 OCF₂H, -NO₂, -NR_cR_d, -S(O)₀₋₂C₁₋₄alkyl, -C(O)C₁₋₄alkyl, S(O)(O)NH₂, -(CH₂)₀₋₂-
 morpholinyl, piperidin-1-yl, piperazinyl, said piperazinyl being optionally substituted
 with a methyl, or two R_b substituents on adjacent carbon atoms taken together form -
 O(CH₂)₁₋₂O-;

ii) pyridyl substituted with 0, 1 or 2 substituents R_e; where each R_e is
 20 independently selected from halo, -C₁₋₄alkyl, -OC₁₋₄alkyl, -CF₃, -NR_cR_d or 4-morpholinyl;
 or

iii) a bicyclic 9-11-membered aromatic heterocycle, optionally substituted with 1

substituent R_f , where R_f is $-C_{1-4}$ alkyl;

R_c and R_d are each independently selected from H or $-C_{1-4}$ alkyl;

R_1 is H, C_{1-4} alkyl-O- C_{1-4} alkyl, or C_{1-4} alkyl optionally substituted with halo;

R_2 , R_3 , R_4 , and R_5 are each independently H, halo or $-C_{1-4}$ alkyl;

5 n is 0 or 1 providing that when n is 1 the bond between C1 and C2 is single and when n is 0 the bond between C1 and C2 is double;

each Y_1 , Y_2 and Y_3 is independently CH or N;

R_6 is

i) H, $-C_{1-4}$ alkyl, $-CF_3$, $-OR_z$ or $-NR_hR_i$;

10 where R_h is selected from:

a) H, $-C_{0-4}$ alkyl CF_3 , $-C_{1-4}$ alkyl- $N(CH_3)_2$, saturated C_{3-7} cycloalkyl or $-C_{1-4}$ alkyl-monocyclic heteroaryl ring;

b) $-C_{1-5}$ alkyl optionally substituted with OH;

c) $-C_{1-4}$ alkyl-heterocycloalkyl, wherein said heterocycloalkyl is optionally
15 substituted with $-C_{1-4}$ alkyl; or

d) $-C_{0-4}$ alkyl-phenyl, said phenyl being optionally substituted with one or two R_j moieties; where each R_j is independently halo, $-OC_{1-4}$ alkyl,

R_z is $-C_{1-4}$ alkyl, $-C_{1-4}$ alkyl CF_3 or $-C_{1-4}$ alkyl-heterocycloalkyl;

ii) 1-pyrrolidinyl optionally substituted with a moiety selected from the group
20 consisting of $-NR_kR_i$ and $-C_{1-4}$ alkyl, said $-C_{1-4}$ alkyl optionally substituted with -OH;

iii) 1-piperidinyl optionally substituted with $-C_{1-4}$ alkyl, $-C(O)NH_2$, $-CO_2C_{1-4}$ alkyl or $-C_{0-4}$ alkyl-phenyl;

iv) piperazinyl optionally substituted with $-C_{1-5}$ alkyl, $-OC_{1-4}$ alkyl, $-C_{0-4}$ alkylpyridyl, $-C_{0-4}$ alkyl-1-methyl-piperidin-4-yl, $-C_{0-4}$ alkyl NR_kR_i or
25 $-C_{0-4}$ alkyl-phenyl, said phenyl being optionally substituted with one or two R_T substituents; where each R_T substituent is selected from the group consisting of halo, -
 OCF_3 , $-C_{1-4}$ alkyl, $-OC_{1-4}$ alkyl, $-CO_2C_{1-4}$ alkyl, $-C(O)C_{1-4}$ alkyl and $-C_{0-4}$ alkyl NR_kR_i , or two
 R_T substituents on adjacent carbon atoms taken together form $-O(CH_2)_{1-2}O-$;

v) phenyl optionally substituted with halo, $-\text{CF}_3$, $-\text{OCF}_3$;

vi) pyridyl;

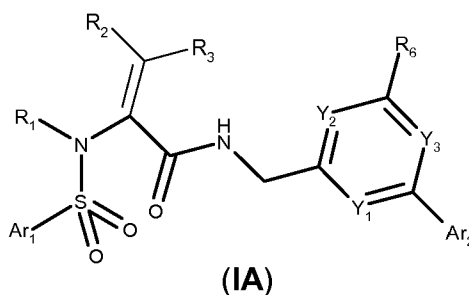
vii) morpholin-yl;

R_k is H, $-\text{C}_{1-4}\text{alkyl}$ or $-\text{C}(\text{O})_{1-2}\text{C}_{1-4}\text{alkyl}$;

5 R_i is H or $\text{C}_{1-4}\text{alkyl}$;

N-oxides, isomers, enantiomers, racemic mixtures and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 of formula (IA)



10

wherein:

Ar_1 is:

i) phenyl substituted with 0, 1, 2 or 3 substituents R_a ; or

15 ii) a 5-6-membered monocyclic aromatic heterocycle ring, optionally substituted with one or two substituents R_a ; where each R_a is independently halo, $-\text{C}_{1-4}\text{alkyl}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$ or $-\text{CO}_2\text{H}$;

Ar_2 is:

20 i) phenyl substituted with 0, 1, 2 or 3 substituents R_b ; where each R_b is independently halo, $-\text{C}_{1-4}\text{alkyl}$, $-\text{C}(\text{O})\text{NR}_c\text{R}_d$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{OC}_{0-4}\text{alkylCF}_3$, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_2\text{H}$, $-\text{NO}_2$, $-\text{NR}_c\text{R}_d$, $-\text{S}(\text{O})_{0-2}\text{C}_{1-4}\text{alkyl}$, $-\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$, $\text{S}(\text{O})(\text{O})\text{NH}_2$, $-(\text{CH}_2)_{0-2}\text{-morpholinyl}$, piperidin-1-yl, piperazinyl, said piperazinyl being optionally substituted with a methyl, or two R_b substituents on adjacent carbon atoms taken together form $-\text{O}(\text{CH}_2)_{1-2}\text{O}-$;

25 ii) pyridyl substituted with 0, 1 or 2 substituents R_e ; where each R_e is independently selected from halo, $-\text{C}_{1-4}\text{alkyl}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{CF}_3$, $-\text{NR}_c\text{R}_d$ or 4-morpholinyl;

or

iii) a bicyclic 9-11-membered aromatic heterocycle optionally substituted with 1 substituent R_f , where R_f is $-C_{1-4}alkyl$;

R_c and R_d are each independently selected from H or $-C_{1-4}alkyl$;

5 R_1 is H, $C_{1-4}alkyl-O-C_{1-4}alkyl$, or $C_{1-4}alkyl$ optionally substituted with halo;

R_2 and R_3 are each independently H, halo or $-C_{1-4}alkyl$;

each Y_1 , Y_2 and Y_3 is independently CH or N;

R_6 is

i) H, $-C_{1-4}alkyl$, $-CF_3$, $-OR_z$ or $-NR_hR_i$;

10 where R_h is selected from:

a) H, $-C_{0-4}alkylCF_3$, $-C_{1-4}alkyl-N(CH_3)_2$, saturated $C_{3-7}cycloalkyl$ or $-C_{1-4}alkyl-monocyclic\ heteroaryl\ ring$;

b) $-C_{1-5}alkyl$ optionally substituted with OH;

c) $-C_{1-4}alkyl-heterocycloalkyl$, wherein said heterocycloalkyl is optionally
15 substituted with $-C_{1-4}alkyl$; or

d) $-C_{0-4}alkyl-phenyl$, said phenyl being optionally substituted with one or two R_j moieties; where each R_j is independently halo, $-OC_{1-4}alkyl$,

R_z is $-C_{1-4}alkyl$, $-C_{1-4}alkylCF_3$ or $-C_{1-4}alkyl-heterocycloalkyl$;

ii) 1-pyrrolidinyl optionally substituted with a moiety selected from the group
20 consisting of $-NR_kR_i$ and $-C_{1-4}alkyl$, said $-C_{1-4}alkyl$ optionally substituted with $-OH$;

iii) 1-piperidinyl optionally substituted with $-C_{1-4}alkyl$, $-C(O)NH_2$, $-CO_2C_{1-4}alkyl$ or $-C_{0-4}alkyl-phenyl$;

iv) piperazinyl optionally substituted with $-C_{1-5}alkyl$, $-OC_{1-4}alkyl$, $-C_{0-4}alkylpyridyl$, $-C_{0-4}alkyl-1-methyl-piperidin-4-yl$, $-C_{0-4}alkylNR_kR_i$ or
25 $-C_{0-4}alkyl-phenyl$, said phenyl being optionally substituted with one or two R_T substituents; where each R_T substituent is selected from the group consisting of halo, $-OCF_3$, $-C_{1-4}alkyl$, $-OC_{1-4}alkyl$, $-CO_2C_{1-4}alkyl$, $-C(O)C_{1-4}alkyl$ and $-C_{0-4}alkylNR_kR_i$, or two R_T substituents on adjacent carbon atoms taken together form $-O(CH_2)_{1-2}O-$;

v) phenyl optionally substituted with halo, -CF₃, -OCF₃;

vi) pyridyl;

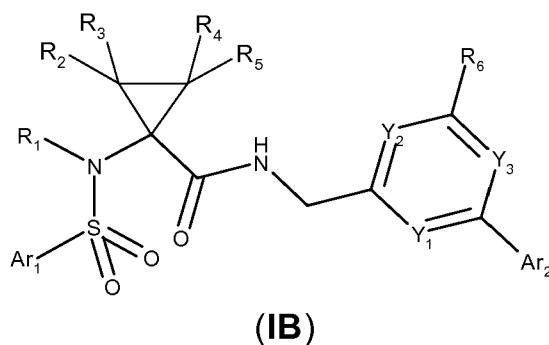
vii) morpholin-yl;

R_k is H, -C₁₋₄alkyl or -C(O)₁₋₂C₁₋₄alkyl;

5 R_i is H or C₁₋₄alkyl;

N-oxides, isomers, enantiomers, racemic mixtures and pharmaceutically acceptable salts thereof.

3. A compound according to claim 1 of formula **(IB)**



10

wherein:

Ar₁ is:

i) phenyl substituted with 0, 1, 2 or 3 substituents R_a; or

15 ii) a 5- or 6-membered monocyclic aromatic heterocycle ring, optionally substituted with one or two substituents R_a; where each R_a is independently halo, -C₁₋₄alkyl, -OC₁₋₄alkyl, -CN, -CF₃, -OCF₃, -NO₂, -C(O)C₁₋₄alkyl or -CO₂H;

Ar₂ is:

20 i) phenyl substituted with 0, 1, 2 or 3 substituents R_b; where each R_b is independently halo, -C₁₋₄alkyl, -C(O)NR_cR_d, -OC₁₋₄alkyl, -OC₀₋₄alkylCF₃, -CN, -CF₃, -OCF₂H, -NO₂, -NR_cR_d, -S(O)₀₋₂C₁₋₄alkyl, -C(O)C₁₋₄alkyl, S(O)(O)NH₂, -(CH₂)₀₋₂-morpholinyl, piperidin-1-yl, piperazinyl, said piperazinyl being optionally substituted with a methyl, or two R_b substituents on adjacent carbon atoms taken together form -O(CH₂)₁₋₂O-;

ii) pyridyl substituted with 0, 1 or 2 substituents R_c; where each R_c is

independently selected from halo, -C₁₋₄alkyl, -OC₁₋₄alkyl, -CF₃, -NR_cR_d or 4-morpholinyl;
or

iii) a bicyclic 9-11-membered aromatic heterocycle optionally substituted with 1 substituent R_f, where R_f is -C₁₋₄alkyl;

5 R_c and R_d are each independently selected from H or -C₁₋₄alkyl;

R₁ is H, C₁₋₄alkyl-O-C₁₋₄alkyl, or C₁₋₄alkyl optionally substituted with halo;

R₂, R₃, R₄, and R₅ are each independently H, halo or -C₁₋₄alkyl;

each Y₁, Y₂ and Y₃ is independently CH or N;

R₆ is

10 i) H, -C₁₋₄alkyl, -CF₃, -OR_z or -NR_hR_i;

where R_h is selected from

a) H, -C₀₋₄alkylCF₃, -C₁₋₄alkyl-N(CH₃)₂, saturated C₃₋₇cycloalkyl or -C₁₋₄alkyl-monocyclic heteroaryl ring;

b) -C₁₋₅alkyl optionally substituted with OH;

15 c) -C₁₋₄alkyl-heterocycloalkyl, wherein said heterocycloalkyl is optionally substituted with -C₁₋₄alkyl; or

d) -C₀₋₄alkyl-phenyl, said phenyl being optionally substituted with one or two R_j moieties; where each R_j is independently halo, -OC₁₋₄alkyl,

R_z is -C₁₋₄alkyl, -C₁₋₄alkylCF₃ or -C₁₋₄alkyl-heterocycloalkyl;

20 ii) 1-pyrrolidinyl optionally substituted with a moiety selected from the group consisting of -NR_kR_i and -C₁₋₄alkyl, said -C₁₋₄alkyl optionally substituted with -OH;

iii) 1-piperidinyl optionally substituted with -C₁₋₄alkyl, -C(O)NH₂, -CO₂C₁₋₄alkyl or -C₀₋₄alkyl-phenyl;

25 iv) piperazinyl optionally substituted with -C₁₋₅alkyl, -OC₁₋₄alkyl, -C₀₋₄alkylpyridyl, -C₀₋₄alkyl-1-methyl-piperidin-4-yl, -C₀₋₄alkylNR_kR_i or -C₀₋₄alkyl-phenyl, said phenyl being optionally substituted with one or two R_T substituents; where each R_T substituent is selected from the group consisting of halo, -OCF₃, -C₁₋₄alkyl, -OC₁₋₄alkyl, -CO₂C₁₋₄alkyl, -C(O)C₁₋₄alkyl and -C₀₋₄alkylNR_kR_i, or two

R_T substituents on adjacent carbon atoms taken together form -O(CH₂)₁₋₂O-;

v) phenyl optionally substituted with halo, CF₃;

vi) pyridyl;

vii) morpholin-yl;

5 R_k is H, -C₁₋₄alkyl or -C(O)₁₋₂C₁₋₄alkyl;

R_i is H or C₁₋₄alkyl;

N-oxides, isomers, enantiomers, racemic mixtures and pharmaceutically acceptable salts thereof.

4. A compound according to claims 1-3 wherein each Y₁, Y₂ are CH and Y₃ is N.

10 5. A compound according to claims 1-3 wherein each Y₁, Y₂ and Y₃ are CH.

6. A compound according to claim 4 or 5 wherein:

Ar₁ is:

i) phenyl substituted with one substituent R_a; where R_a is halo, or -C₁₋₄alkyl;

ii) a thienyl ring optionally substituted with one substituents R_a: where R_a is

15 halo;

Ar₂ is:

i) phenyl substituted with 1 substituent R_b; where R_b is -OC₀₋₄alkylCF₃;

R₁ is H or C₁₋₄ alkyl optionally substituted with halo;

R₂, R₃, R₄, and R₅ are each independently H, or -C₁₋₄alkyl;

20 R₆ is:

i) H;

ii) 1-pyrrolidinyl;

iii) phenyl optionally substituted with -CF₃ or -OCF₃;

iv) morpholin-yl.

25 7. A compound according to any of the proceeding claims, selected from:

2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;

2-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-

- pyridyl]methyl]prop-2-enamide;
2-[(4-fluorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
5 2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
2-(methyl(p-tolylsulfonyl)amino)-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
10 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]prop-2-enamide;
2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]prop-2-enamide;
2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]prop-2-enamide;
15 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl]methyl]prop-2-enamide;
2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl]methyl]prop-2-enamide;
20 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
25 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[2-morpholino-6-[4-

- (trifluoromethoxy)phenyl]-4-pyridyl)methyl]prop-2-enamide;
2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]prop-2-enamide;
2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]prop-2-enamide;
- 5 N-[[2,6-bis[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]-2-[(4-chlorophenyl)sulfonyl-ethyl-amino]prop-2-enamide;
N-[[2,6-bis[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]-2-[(4-chlorophenyl)sulfonyl-methyl-amino]prop-2-enamide;
- 10 (Z)-2-[(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]but-2-enamide;
(Z)-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]but-2-enamide;
(Z)-2-[(4-chlorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl)methyl]but-2-enamide;
- 15 (Z)-2-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl)methyl]but-2-enamide;
1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
- 20 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
1-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethoxy)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
- 25 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl)methyl]cyclopropanecarboxamide;
1-[(4-chlorophenyl)sulfonyl-ethyl-amino]-N-[[3-[4-

- (trifluoromethyl)phenyl]phenyl)methyl]cyclopropanecarboxamide;
 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl)methyl]cyclopropanecarboxamide;
 1-[(4-fluorophenyl)sulfonylamino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
 5 1-[(4-fluorophenyl)sulfonylamino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
 10 2-[(3,4-difluorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
 2-[(3-difluorophenyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
 N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]prop-2-enamide;
 15 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
 20 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
 N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-2-(ethyl(2-thienylsulfonyl)amino)prop-2-enamide;
 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
 25 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]prop-2-enamide;
 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-isopropoxy-6-[4-

- (trifluoromethyl)phenyl]-4-pyridyl)methyl]prop-2-enamide;
 N-[[2-dimethylamino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide;
 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-
 5 pyridyl)methyl]cyclopropanecarboxamide;
 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl)methyl]cyclopropanecarboxamide;
 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
 10 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-isopropoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-methoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
 15 (trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
 N-[[2-ethoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide;
 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-ethoxy-6-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]cyclopropanecarboxamide;
 20 2-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[1-oxido-2-[4-(trifluoromethyl)phenyl]pyridin-1-ium-4-yl)methyl]prop-2-enamide;
 2-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl)methyl]prop-2-enamide;
 2-[4-(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[2-[4-(trifluoromethyl)phenyl]-4-pyridyl)methyl]prop-2-enamide;
 25 1-[4-(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-(trifluoromethoxy)phenyl]phenyl)methyl]cyclopropanecarboxamide;
 1-[4-(4-fluorophenyl)sulfonyl-methyl-amino]-N-[[3-[4-

- (trifluoromethyl)phenyl]phenyl)methyl]cyclopropanecarboxamide;
 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[3-[4-(trifluoromethyl)phenyl]phenyl)methyl]cyclopropanecarboxamide;
 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[4-[4-(trifluoromethyl)phenyl]-2-pyridyl]methyl]cyclopropanecarboxamide;
 5 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-pyrrolidin-1-yl-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
 1-[ethyl-(4-fluorophenyl)sulfonyl-amino]-N-[[2-morpholino-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
 10 N-[[2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethoxy)phenyl]-4-pyridyl]methyl]-2-[ethyl-(4-fluorophenyl)sulfonyl-amino]prop-2-enamide;
 N-[[2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide;
 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-[4-(cyclopropylmethyl)piperazin-1-yl]-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide;
 15 N-[[2-(4-cyclohexylpiperazin-1-yl)-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]-1-[ethyl-(4-fluorophenyl)sulfonyl-amino]cyclopropanecarboxamide;
 1-[(5-chloro-2-thienyl)sulfonyl-ethyl-amino]-N-[[2-(4-cyclohexylpiperazin-1-yl)-6-[4-(trifluoromethyl)phenyl]-4-pyridyl]methyl]cyclopropanecarboxamide.
- 20 8. Pharmaceutical compositions comprising one or more compounds of claims 1-7 as the active ingredient.
9. The compounds of claims 1-7 for use as TRPA1 antagonists.
10. The compounds of claims 1-7 for use in the treatment of pain and inflammatory diseases. including airways disorders such as asthma, chronic cough and COPD.