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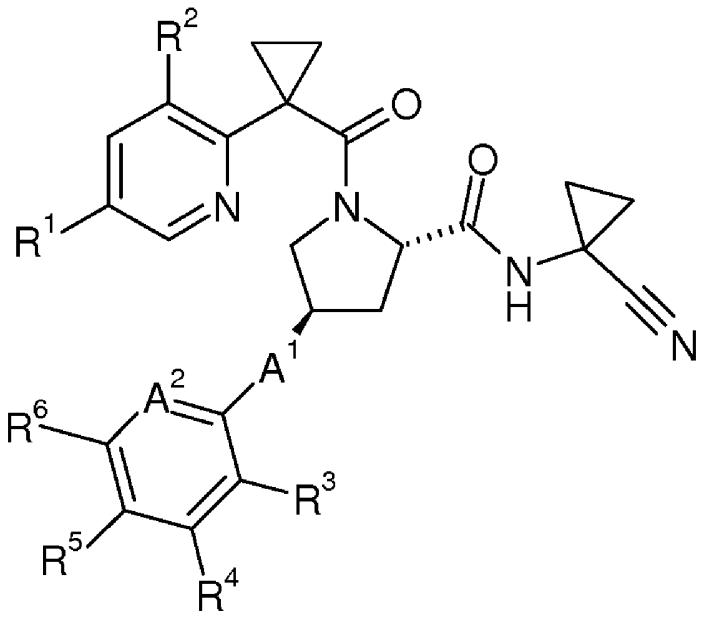
[Continued on next page]

(54) Title: NOVEL PYRIDINE DERIVATIVES

(57) Abstract: The invention relates to a compound of formula (I) wherein A^1, A^2 and R^1 to R^6 are defined as in the description and in the claims. The compound of formula (I) can be used as a medicament.



(I)

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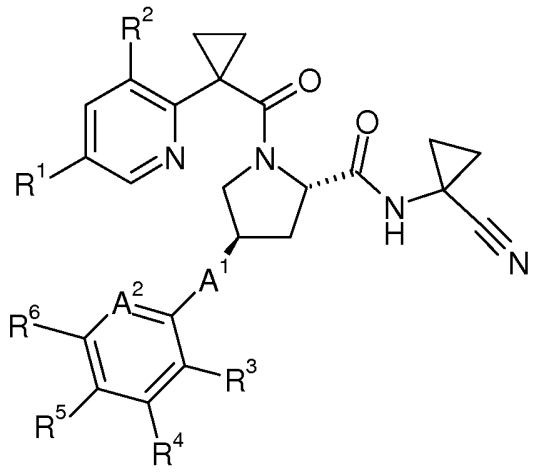
NOVEL PYRIDINE DERIVATIVES

The present invention relates to organic compounds useful for therapy and/or prophylaxis in a mammal, and in particular to compounds that are preferential inhibitors of the cysteine protease cathepsin, in particular of the cysteine protease cathepsin S or L.

The invention relates in particular to a compound of formula (I)



(I)

wherein

A^1 is -S- or -$S(O)_2$-;

A^2 is nitrogen or -(CH)-;

R^1 is halogen or haloalkyl;

R^2 is hydrogen or halogen;

R^3 is hydrogen, halogen, haloalkyl, pyrazolyl, [1,2,3]-triazolyl or [1,2,4]-triazolyl;

R^4 and R^6 are independently selected from hydrogen, alkyl, haloalkyl and halophenyl; and

R^5 is hydrogen, halogen, haloalkyl, alkoxy, haloalkoxy, alkylpyridinyl, halopyridinyl or alkylpyrazolyl;

or a pharmaceutically acceptable salt thereof.

The compounds of the invention are preferential inhibitors of the cysteine protease Cathepsin (Cat), in particular Cathepsin S or Cathepsin L and are therefore useful to treat metabolic diseases like diabetes, atherosclerosis, abdominal aortic aneurysm, peripheral arterial disease, cancer, reduction of cardiovascular events in chronic kidney disease, glomerulonephritis, age related macular degeneration, diabetic nephropathy and diabetic retinopathy. In addition, immune mediated diseases like rheumatoid arthritis, crohn's disease, multiple sclerosis, sjorgen syndrome, lupus erythematosus, neuropathic pain, diabetes type I, asthma and allergy and skin related immune disease are suitable diseases to be treated with a cathepsin S inhibitor.

Objects of the present invention are the compounds of formula (I) and their aforementioned salts per se and their use as therapeutically active substances, a process for the manufacture of the said compounds, intermediates, pharmaceutical compositions, medicaments containing the said compounds, their pharmaceutically acceptable salts, the use of the said compounds and salts for the prophylaxis and/or therapy of illnesses, especially in the treatment or prophylaxis of diabetes, atherosclerosis, abdominal aortic aneurysm, peripheral arterial disease, cancer, reduction of cardiovascular events in chronic kidney disease and diabetic nephropathy, and the use of the said compounds and salts for the production of medicaments for the treatment or prophylaxis of diabetes, atherosclerosis, abdominal aortic aneurysm, peripheral arterial disease, cancer, reduction of cardiovascular events in chronic kidney disease and diabetic nephropathy.

Mammalian cathepsins are cysteine-type proteases involved in key steps of biological and pathological events. Cathepsins are considered tractable drug targets as it is feasible to inhibit enzymatic activity with small molecules and are therefore of interest to the pharmaceutical industry (Bromme, D. (2001), 'Papain-like cysteine proteases', Curr Protoc Protein Sci, Chapter 21, Unit 21 2; Roberts, R. (2005), 'Lysosomal cysteine proteases: structure, function and inhibition of cathepsins', Drug News Perspect, 18 (10), 605-14).

Cathepsin S is prominently expressed in antigen presenting cells like macrophages and dendritic cells and smooth muscle cells (Hsing, L. C. and Rudensky, A. Y. (2005),

'The lysosomal cysteine proteases in MHC class II antigen presentation', Immunol Rev, 207, 229-41; Rudensky, A. and Beers, C. (2006), 'Lysosomal cysteine proteases and antigen presentation', Ernst Schering Res Found Workshop, (56), 81-95). While Cathepsin S is only weakly expressed in normal arterial tissue, strong upregulation is seen in atherosclerotic arteries (Liu, J., et al. (2006), 'Increased serum cathepsin S in patients with atherosclerosis and diabetes', Atherosclerosis, 186 (2), 411-9; Sukhova, G. K., et al. (1998), 'Expression of the elastolytic cathepsins S and K in human atheroma and regulation of their production in smooth muscle cells', J Clin Invest, 102 (3), 576-83).

Preclinical data suggest that the function of Cathepsin S is critical for atherosclerosis as Cathepsin S deficient mice have a reduced atherosclerosis-phenotype when tested in appropriate mouse models. In LDL-Rec deficient mice reduced lipid accumulation, elastin-fibre breakdown and chronic arterial inflammation is reported. In APO E deficient mice a significant reduction of acute plaque rupture events was reported. When chronic renal disease is introduced into CatS/In APO-E deficient mice a strong reduction of accelerated calcification is seen on top of the anti atherosclerotic activity in arteries and heart valves Aikawa, E., et al. (2009), 'Arterial and aortic valve calcification abolished by elastolytic cathepsin S deficiency in chronic renal disease', Circulation, 119 (13), 1785-94; de Nooijer, R., et al. (2009), 'Leukocyte cathepsin S is a potent regulator of both cell and matrix turnover in advanced atherosclerosis', Arterioscler Thromb Vasc Biol, 29 (2), 188-94; Rodgers, K. J., et al. (2006), 'Destabilizing role of cathepsin S in murine atherosclerotic plaques', Arterioscler Thromb Vasc Biol, 26 (4), 851-6; Sukhova et al. (2003), 'Deficiency of cathepsin S reduces atherosclerosis in LDL receptor-deficient mice', J Clin Invest, 111 (6), 897-906). This suggests a potential inhibitor of Cathepsin S would stabilise atherosclerotic plaque by reducing extracellular matrix breakdown, by reducing the proinflammatory state and by reducing accelerated calcification and subsequently its clinical manifestations.

These phenotypes described in atherosclerosis models are in agreement with known cellular functions of Cathepsin S. Firstly, Cathepsin S is involved in the degradation of extracellular matrix that stabilises the plaque. In particular, Cathepsin S has potent elastinolytic activity and can exert this at neutral pH, a feature that distinguishes Cathepsin S from all other Cathepsins. Secondly, Cathepsin S is the major protease involved in antigen processing, in particular cleavage of the invariant chain in antigen presenting cells, resulting in reduced contribution of Tcells to the chronic inflammation of the atherosclerotic tissue. Elevated inflammation results in further oxidative and proteolytic tissue damage and subsequently plaque destabilisation (Cheng, X. W., et al. (2004), 'Increased expression of elastolytic cysteine proteases, cathepsins S and K, in the neointima of balloon-injured rat carotid arteries', Am J Pathol, 164 (1), 243-51; Driessen,

C., et al. (1999), 'Cathepsin S controls the trafficking and maturation of MHC class II molecules in dendritic cells', J Cell Biol, 147 (4), 775-90; Rudensky, A. and Beers, C. (2006), 'Lysosomal cysteine proteases and antigen presentation', Ernst Schering Res Found Workshop, (56), 81-95).

The anti-inflammatory and anti-elastinolytic properties of a Cat S inhibitor make it also a prominent target for chronic obstructive pulmonary disease (Williams, A. S., et al. (2009), 'Role of cathepsin S in ozone-induced airway hyperresponsiveness and inflammation', Pulm Pharmacol Ther, 22 (1), 27-32). Furthermore due to its extracellular functions in matrix degradation, inhibition of cathepsin S will impact neointima formation and angiogenesis (Burns-Kurtis, C. L., et al. (2004), 'Cathepsin S expression is up-regulated following balloon angioplasty in the hypercholesterolemic rabbit', Cardiovasc Res, 62 (3), 610-20; Cheng, X. W., et al. (2004), 'Increased expression of elastolytic cysteine proteases, cathepsins S and K, in the neointima of balloon-injured rat carotid arteries', Am J Pathol, 164 (1), 243-51; Shi, G. P., et al. (2003), 'Deficiency of the cysteine protease cathepsin S impairs microvessel growth', Circ Res, 92 (5), 493-500; Wang, B., et al. (2006), 'Cathepsin S controls angiogenesis and tumor growth via matrix-derived angiogenic factors', J Biol Chem, 281 (9), 6020-9). An inhibitor of Cathepsin S might therefore be useful in several different disease settings.

Cathepsin S plays also a role in the reduction of tumor growth and tumor cell invasion as described by Roberta E. Burden in Clin Cancer Res 2009;15(19). In addition, nephrectomized Cathepsin S knock out mice showed a significant reduction of arterial calcification when compared to nephrectomized wild type mice. This indicates that inhibition of Cathepsin S may have a beneficial effect on the reduction of cardiovascular events in chronic kidney disease patients (Elena Aikawa, Circulation, 2009, 1785-1794).

Cathepsin L shows a broader expression profile than cathepsin S and there are also data which suggest a role of cathepsin L in atherosclerosis, e.g. LDLrec & Cat L deficient mice show a reduced atherosclerotic phenotype (Kitamoto, S., et al. (2007), 'Cathepsin L deficiency reduces diet-induced atherosclerosis in low-density lipoprotein receptor-knockout mice', Circulation, 115 (15), 2065-75). In addition, Cat L was suggested to be involved in metabolic syndrome as it controls adipogenesis and peripheral glucose tolerance. In renal disease Cathepsin L is described to regulate podocyte function by proteolytically processing dynamin and thereby proteinuria (Sever, S., et al. (2007), 'Proteolytic processing of dynamin by cytoplasmic cathepsin L is a mechanism for proteinuric kidney disease', J Clin Invest, 117 (8), 2095-104).

Tissue remodelling, extracellular matrix degradation, the generation of active neuropeptides and roles in antigen presentation in thymic epithelial cells are cellular

activities described for Cathepsin L (Funkelstein et al. (2008), (a) Major role of cathepsin L for producing the peptide hormones ACTH, β-Endorphin, and α-MSH, illustrated by protease gene knockout and expression, Journal of Biological Chemistry, 283(51), 35652-35659; (b) Cathepsin L participates in the production of neuropeptide Y in secretory vesicles, demonstrated by protease gene knockout and expression, Journal of Neurochemistry, 106(1), 384-391, Rudensky and Beers 2006).

In the present description the term "alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, in particular a straight or branched-chain alkyl group with 1 to 6 carbon atoms and particularly a straight or branched-chain alkyl group with 1 to 4 carbon atoms. Examples of straight-chain and branched C1-C8 alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, in particular methyl, ethyl, propyl, isopropyl, isobutyl and tert.-butyl, more particularly methyl.

The term "alkoxy", alone or in combination, signifies a group of the formula alkyl-O- in which the term "alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec. butoxy and tert.butoxy, in particular methoxy.

The term "oxy", alone or in combination, signifies the -O- group.

The term "halogen" or "halo", alone or in combination, signifies fluorine, chlorine, bromine or iodine.

The terms "haloalkyl" and "haloalkoxy", alone or in combination, denote an alkyl group and an alkoxy group substituted with at least one halogen, in particular substituted with one to five halogens, particularly one to three halogens. A particular "haloalkyl" is trifluoromethyl. Particular haloalkoxy are trifluoroethoxy and trifluoropropyloxy.

The term "pharmaceutically acceptable salts" refers to those salts which retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, in particular, hydrochloric acid, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxylic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcystein. In addition these salts may be prepared form addition of an inorganic base or an organic base to the

free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts. Salts derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polyamine resins. The compound of formula (I) can also be present in the form of zwitterions. Particular pharmaceutically acceptable salts of compound of formula (I) are the salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and methanesulfonic acid.

If one of the starting materials or compounds of formula (I) contains one or more functional groups which are not stable or are reactive under the reaction conditions of one or more reaction steps, appropriate protecting groups (as described e.g. in "Protective Groups in Organic Chemistry" by T. W. Greene and P. G. M. Wutts, 3rd Ed., 1999, Wiley, New York) can be introduced before the critical step applying methods well known in the art. Such protecting groups can be removed at a later stage of the synthesis using standard methods described in the literature. Examples of protecting groups are tert-butoxycarbonyl (Boc), 9-fluorenylmethyl carbamate (Fmoc), 2-trimethylsilylethyl carbamate (Teoc), carbobenzyloxy (Cbz) and p-methoxybenzyloxycarbonyl (Moz).

The compound of formula (I) can contain several asymmetric centers and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates.

The term "asymmetric carbon atom" means a carbon atom with four different substituents. According to the Cahn-Ingold-Prelog Convention an asymmetric carbon atom can be of the "R" or "S" configuration.

The invention relates in particular to the following:

A compound of formula (I) wherein A^1 is $-S(O)_2-$;

A compound of formula (I) wherein A^2 is -(CH)-;

A compound of formula (I) wherein R^1 is chloro, bromo, iodo or trifluoromethyl;

A compound of formula (I) wherein R^2 is halogen;

A compound of formula (I) wherein R^2 is chloro or fluoro;

A compound of formula (I) wherein R^3 is hydrogen, halogen or haloalkyl;

A compound of formula (I) wherein R^3 is halogen;

A compound of formula (I) wherein R^3 is chloro;

A compound of formula (I) wherein R^4 and R^6 are independently selected from hydrogen and haloalkyl;

A compound of formula (I) wherein R^4 and R^6 are independently selected from hydrogen and trifluoromethyl;

A compound of formula (I) wherein R^5 is hydrogen, alkoxy, haloalkoxy, halogen, alkylpyridinyl or alkylpyrazolyl; and

A compound of formula (I) wherein R^5 is hydrogen, methoxy, trifluoroethoxy, fluoro, trifluoropropyloxy, bromo, methylpyridinyl or mehtylpyrazolyl.

The invention further relates to a compound of formula (I) selected from:

(2S,4R)-4-(2-Chloro-4-methoxy-benzenesulfonyl)-1-[1-(5-chloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-(2-Chloro-benzenesulfonyl)-1-[1-(5-chloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(2,2,2-trifluoro-ethoxy)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-(2-Chloro-benzenesulfonyl)-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(2,2,2-trifluoro-ethoxy)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Bromo-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Bromo-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(4'-fluoro-biphenyl-3-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(3-chloro-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-4-fluorophenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(4'-fluoro-biphenyl-3-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(3-chloro-pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4S)-4-(2-Chloro-4-fluoro-benzenesulfonyl)-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(3-chloro-5-trifluoromethyl-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(5-chloro-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(6-methyl-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(3-trifluoromethyl-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(5-chloro-pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(6-methyl-pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(5-trifluoromethyl-pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(3-trifluoromethyl-pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-5-trifluoromethyl-phenylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-4-((S)-1,1,1-trifluoropropan-2-yloxy)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-5-(trifluoromethyl)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-[1-(5-Chloro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-5-trifluoromethyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-(4-Bromo-2-chloro-benzenesulfonyl)-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-4-(2-methylpyridin-4-yl)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-4-[2-Chloro-4-(2-chloro-pyridin-4-yl)-benzenesulfonyl]-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3,5-dichloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3,5-dichloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-(2-Fluoro-benzenesulfonyl)-1-[1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-fluoro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(3-Fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-pyrazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(3-Fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-[1,2,3]triazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(3-Fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-[1,2,4]triazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

((2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-pyrazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-[1,2,3]triazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide; and

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-[1,2,4]triazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide.

The invention relates in particular to a compound of formula (I) selected from:

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-(2-Chloro-benzenesulfonyl)-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(2,2,2-trifluoro-ethoxy)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Bromo-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Bromo-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-4-fluorophenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-4-((S)-1,1,1-trifluoropropan-2-yloxy)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-5-(trifluoromethyl)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-4-(4-Bromo-2-chloro-benzenesulfonyl)-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-4-(2-methylpyridin-4-yl)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3,5-dichloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide; and

(2S,4R)-4-[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3,5-dichloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide.

The compound of formula (I) can be prepared using procedures known in the art. The compound of formula (I) can also be prepared using the following procedures.

The following abbreviations are used in the present specification.

AcOEt: Ethyl acetate;

ACN: Acetonitrile;

boc: *tert*-Butyloxycarbonyl;

BOP: Benzotriazolyl-N-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate;

BOP-Cl: Bis-(2-oxo-3-oxazolidinyl)-phosphinic acid chloride;

Cbz: Carbobenzyloxy;

CDI: 1,1'-Carbonyldiimidazole;

DCM : Dichloromethane;

DIEA: Diisopropyl ethyl amine;

DMAP: 4-Dimethylaminopyridine;

DMF: N,N-Dimethylformamide;

EDCI: N-(3-Dimetylaminopropyl)-N'-ethyl-carbodiimide hydrochloride;

EtOAc: Ethyl acetate;

Fmoc: 9-Fluorenylmethyloxycarbonyl;

h: hour;

HATU: O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate;

HOBT: 1-Hydroxybenzotriazole;

Hunig's Base: Ethyl-diisopropyl-amine;

KHMDS: Potassium bis(trimethylsilyl)amide;

LDA: Lithiumdiisopropylamide;

LHMDS: Lithium bis(trimethylsilyl)amide;

mCPBA or MCPBA: meta-Chloroperoxybenzoic acid;

MeOH: Methanol;

Mes-Cl: Mesyl chloride;

min: minute;

Moz: Methoxybenzyl carbonyl;

Na_2SO_4: Sodium sulfate;

Nos-Cl: 3-Nitrobenzenesulfonyl chloride;

$Pd_2(dba)_3$: Tris(dibenzylideneacetone)dipalladium;

PyBOP: Benzotriazol-1-yl-oxytripyrrolidinephosphonium hexafluorophosphate;

TBTU: O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium terafluoroborate;

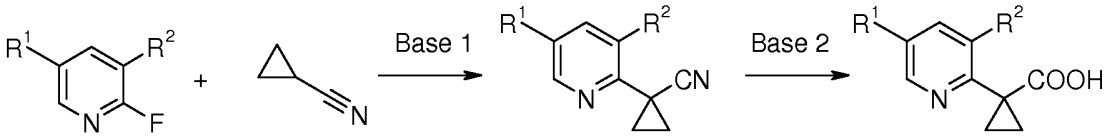
Teoc: Trimethylsilyl ethoxycarbonyl;

THF: Tetrahydrofurane;

TFA: Trifluoroacetic acid; and

Tos-Cl: Toluene-4-sulfonyl chloride.

Scheme 1

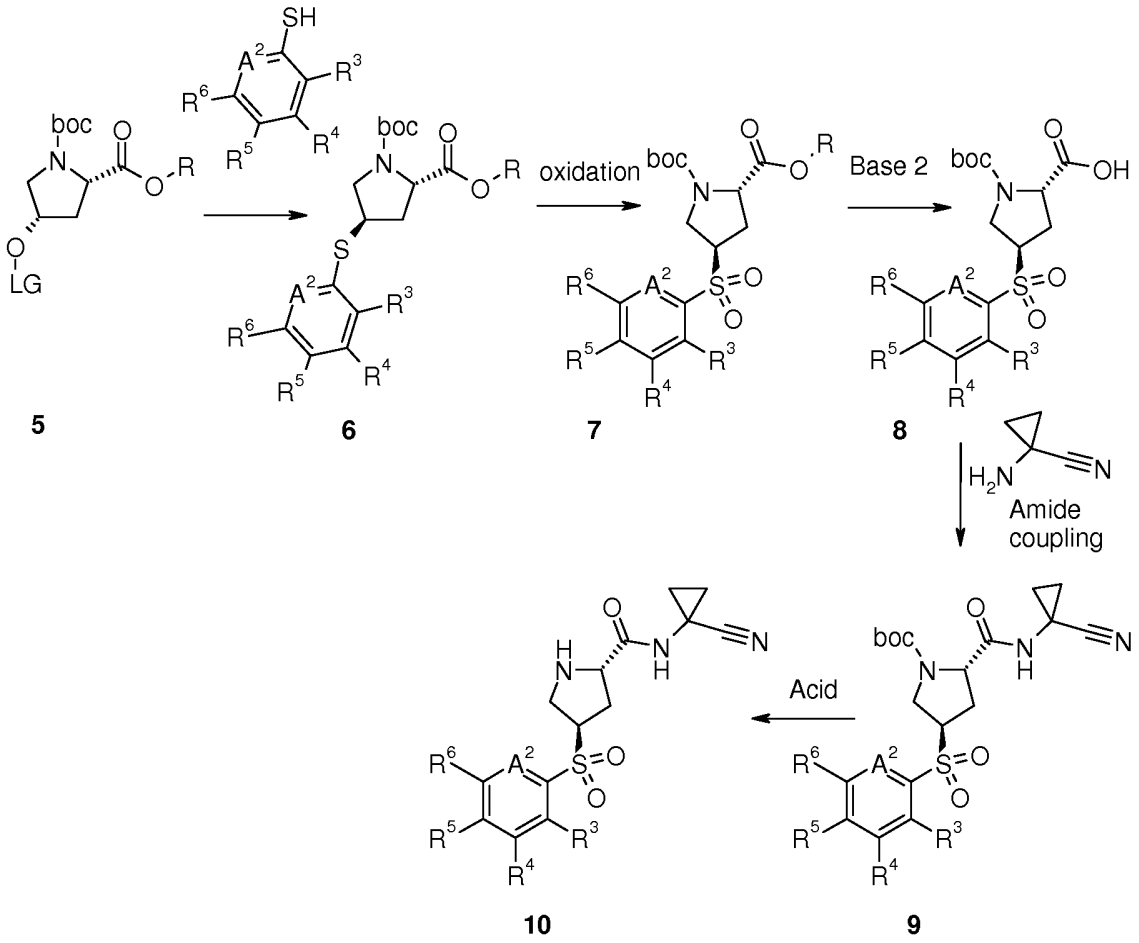


1 **2** **3** **4**

R^1-R^2 are as defined above; Base 1 is e.g. NaOtBu, KOtBu, NaH, LiHMDS, KHMDS or LDA; Base 2 is e.g. LiOH, NaOH or KOH.

A pyridine derivative such as **1** is treated with cyclopropanecarbonitrile **2** in the presence of a base (Base 1 as defined above) to yield the pyridine derivative **3**. Compound **3** is treated with a base (Base 2 as defined above) to yield the final carboxylic acid derivative **4** as free acid or as a salt thereof.

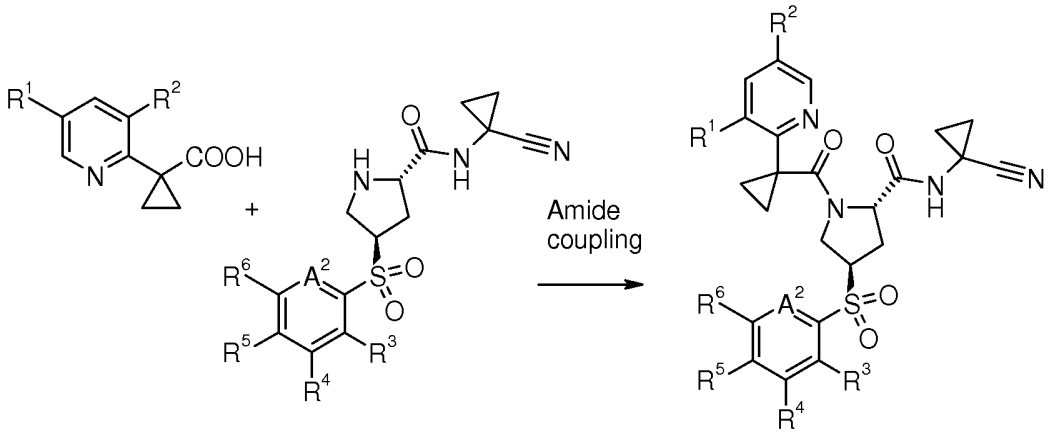
Scheme 2



LG is a leaving group such as triflate, mesylate, tosylate, brosylate or nosylate; A^2 and R^3-R^6 are as defined above; R is e.g. Methyl, Ethyl, iPropyl or Benzyl.

A Boc-protected proline derivative **5** is reacted with a phenylthiol derivative in the presence of a base such as triethyl amine, DIEA, 2,6-lutidine, etc. to yield the thioether derivative **6**. Oxidation of **6** with a peroxide reagent such as H_2O_2, oxone, mCPBA yields the sulfone derivative **7**. Saponification of the ester to the acid with a base such as LiOH, NaOH or KOH yields the corresponding carboxylic acid **8** or salts thereof. Amide coupling is accomplished by reaction of **8** with 1-aminocarbonitrile derivative and a coupling reagent, such as EDCI, CDI, BOP-Cl, TBTU, HATU, PyBOP or BOP, in the presence of a base, such as DIEA, triethyl amine or lutidine, to yield amide **9**. Finally, the Boc-protecting group is removed by treating compound **9** with an acid such as TFA, HCl in an organic solvent (e.g. AcOEt, dioxane) or formic acid to yield amine **10**.

Scheme 3

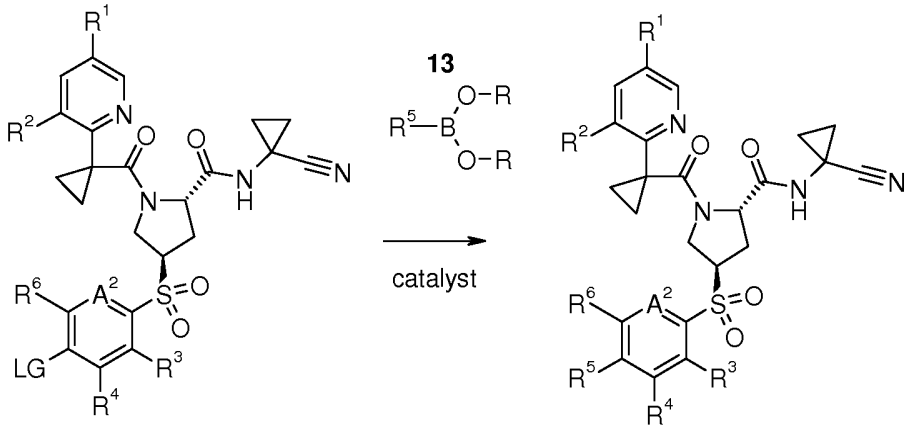


4 10 11

A^2 and R^1-R^6 are as defined above.

Carboxylic acid **4** is reacted with amine **10** in the presence of one of the amide coupling reagents, such as EDCI, CDI, BOP-Cl, TBTU, HATU, PyBOP or BOP, in the presence of a base such as DIEA, triethyl amine or 2,6-lutidine, to yield amide **11**.

Scheme 4

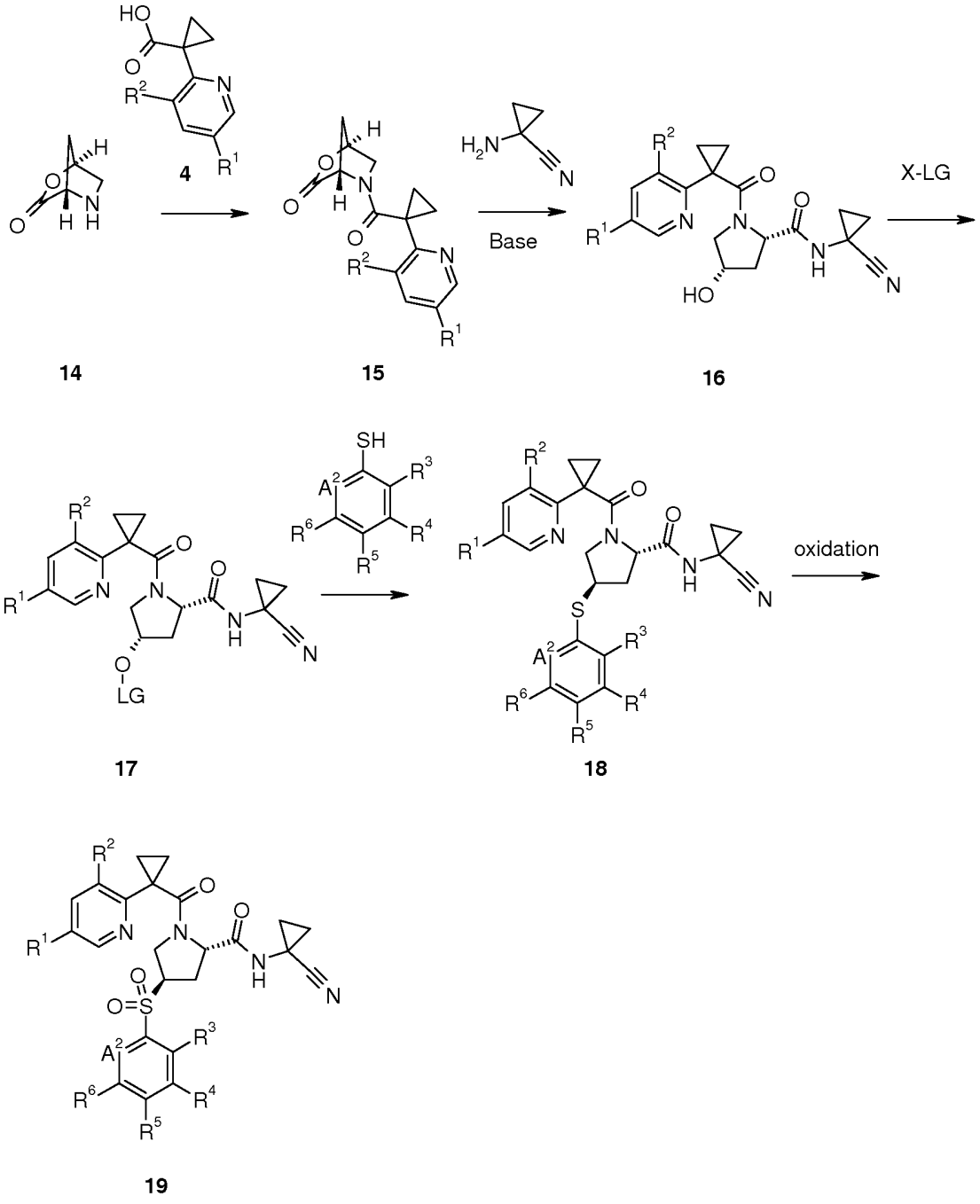


12 11

R^1-R^4 and R^6 are as defined above; LG is a leaving group such as Cl, Br, I; R^5 is phenyl, substituted phenyl, heterocyclyl or substituted heterocyclyl as defined above; R is H or methyl, or both R together with the boron atom to which they are attached form 2,4,4,5,5-pentamethyl-[1,3,2]dioxaborolane.

Compound **12** is reacted with a boronic acid or ester derivative **13** in the presence of a base such as Na_2CO_3, K_2CO_3, Cs_2CO_3, KOtBu, K_3PO_4, and a catalyst known in the art for performing Suzuki reactions such as e.g. $Pd(PPh_3)_4$, $Pd_2(dba)_3$ or a Pd-source with a phosphine ligand, to yield the biaryl derivative **11**.

Scheme 5

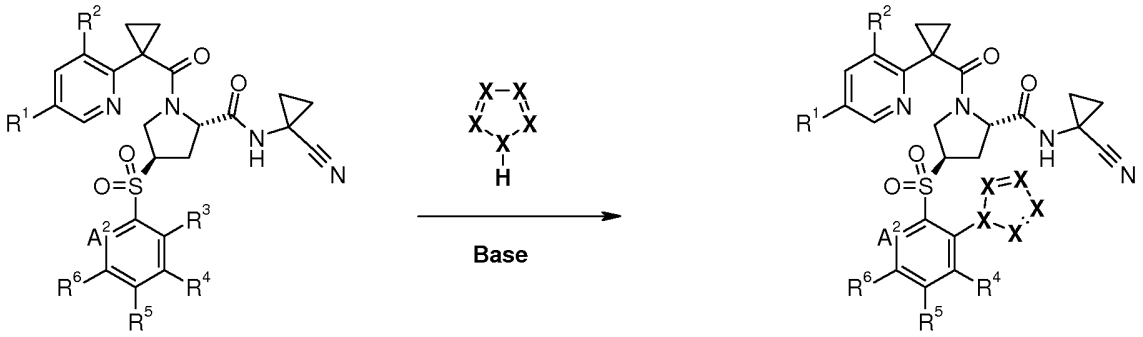


LG is a leaving group such as triflate, mesylate, tosylate, brosylate or nosylate; A^2 and R^1-R^6 are as defined above; X is F, Cl, Br, I or X = O-LG.

The aminolactone **14** or a corresponding salt thereof such as hydrochloride, hydrobromide, phosphate, hydrogenphosphate, sulfate, hydrogensulfate, methansulfonate etc. is reacted with carboxylic acid 4 in the presence of an amide coupling reagent, such as EDCI, CDI, BOP-Cl, TBTU, HATU, PyBOP or BOP, in the presence of a base such as DIEA, triethyl amine, 2,6-lutidine, or alternatively, in the presence of an acid halogenide

such as phosgene, triphosgene, oxalylchloride or thionylchloride, to yield amide **15**. Opening of the lactone **15** by an amine is performed in the presence of an appropriate base such as sodium 2-ethylhexanoate, TEA, DIEA, DMAP, 2,6-lutidine or pyridine to yield the alcohol **16**. Compound **16** is treated with X-LG in the presence of a base such as TEA, DIEA, DMAP, 2,6-lutidine or pyridine to yield the intermediate **17** which is subsequently reacted with thiols to yield the thioether **18**. Oxidation of thioether **18** to the sulfone **19** is achieved by the reaction of **18** with oxidizing reagents such as H_2O_2, oxone, MCPBA.

Scheme 6



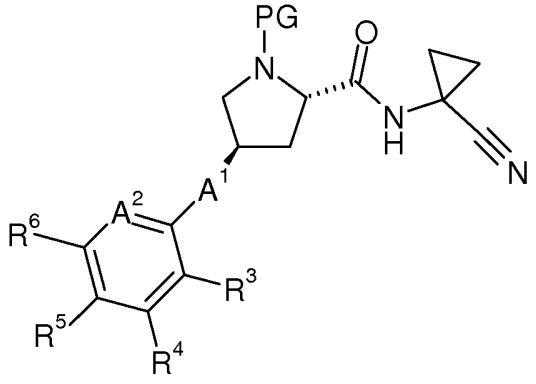
20 **21**

R^3 is a leaving group such as F, Cl, or $S(O)_2$-Me; X is either N or CH; Base is an inorganic base such as Na_2CO_3, K_2CO_3, Cs_2CO_3 or an organic base such as DIEA, triethylamine or 2,6-lutidine.

Compound **20** is dissolved in an appropriate solvent such as DMF, DMA or THF, a base as defined above and the nitrogen containing 5-membered heterocycle is added to the reaction mixture. The mixture is initially stirred at room temperature and subsequently heated to an elevated temperature from 30 - 100 °C until the reaction is completed.

The invention also relates to a process for the preparation of a compound of formula (I) as defined above, comprising one of the following steps:

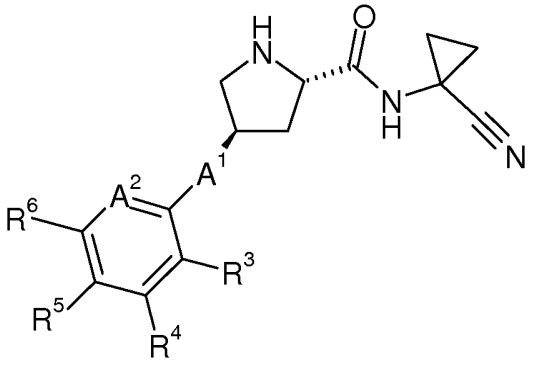
(a) The reaction of a compound of formula (A)



(A)

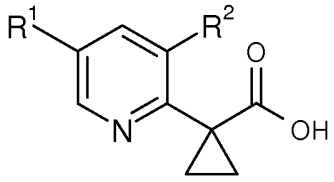
in the presence of acid, wherein A^1, A^2 and R^1 to R^6 are as defined above and wherein PG is an amine protecting group;

(b) The reaction of a compound of formula (B1)



(B1)

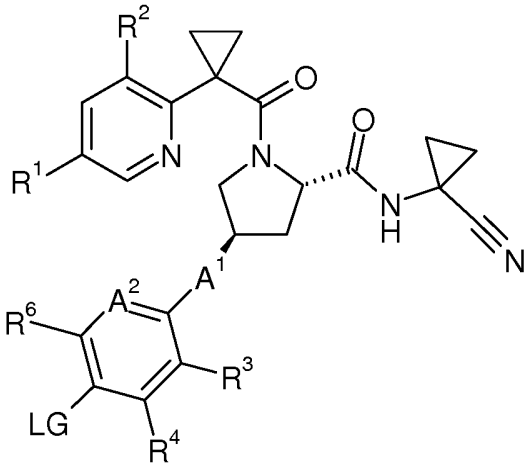
with a compound of formula (B2)



(B2)

in the presence of a base and an amide coupling agent and a base, wherein A^1, A^2 and R^1 to R^6 are as defined above;

(c) The reaction of a compound of formula (C)

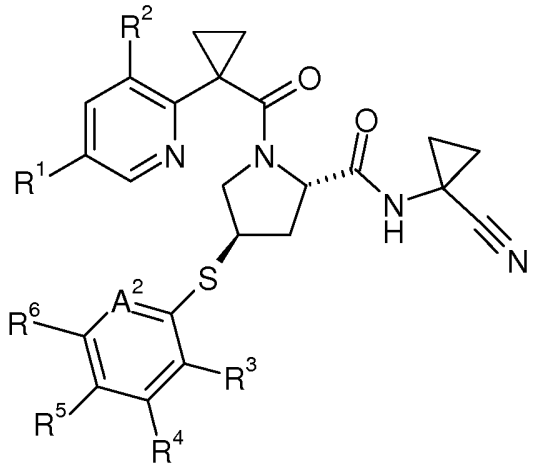


(C)

in the presence of $R^5B(OR)_2$, a base and a Suzuki catalyst, wherein wherein A^1, A^2 and R^1 to R^4 and R^6 are as defined above, LG is a leaving group, R^5 is alkylpyridinyl, halopyridinyl or alkylpyrazolyl and R is hydrogen or methyl, or both

R, together with the boron atom to which they are attached, form 2,4,4,5,5-pentamethyl-[1,3,2]dioxaborolane; or

(d) The reaction of a compound of formula (D)



(D)

in the presence of an oxidizing agent, wherein wherein A^1 and R^1 to R^6 are as defined above.

In step (a), the acid is for example TFA, HCl or formic acid.

In step (a), the amine protecting group is for example boc, Fmoc, Cbz, Teoc, benzyl or Moz.

In step (b), the amide coupling agent is for example EDCI, CDI, BOP-Cl, TBTU, HATU, PyBOP or BOP.

In step (b), the base is for example DIEA, triethyl amine or 2,6-lutidine.

In step (c), the leaving group is for example Cl, Br or I.

In step (c), the base is for example Na_2CO_3, K_2CO_3, Cs_2CO_3, KOtBu or K_3PO_4.

In step (c), the Suzuki catalyst is for example $Pd(PPh_3)_4$, $Pd_2(dba)_3$ or a Pd-source with a phosphine ligand.

In step (d), the oxidizing agent is for example H_2O_2, oxone or MCPBA.

A compound of formula (I), when manufactured according to the above process is also an object of the invention.

The compounds of formula (I) and their pharmaceutically acceptable salts can be used as medicaments (e.g. in the form of pharmaceutical preparations). The

pharmaceutical preparations can be administered internally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parentally, such as intramuscularly or intravenously (e.g. in the form of injection solutions).

The compounds of formula (I) and their pharmaceutically acceptable salts can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées and hard gelatin capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées and hard gelatin capsules.

Suitable adjuvants for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols.

Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar and glucose.

Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils.

Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid and liquid polyols.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The invention thus also relates in particular to the following:

A compound of formula (I) for use as therapeutically active substance;

A pharmaceutical composition comprising a compound of formula (I) and a therapeutically inert carrier;

The use of a compound of formula (I) for the preparation of a medicament for the treatment or prophylaxis of diabetes, atherosclerosis, abdominal aortic aneurysm, peripheral arterial disease, cancer, reduction of cardiovascular events in chronic kidney disease, diabetic nephropathy, diabetic rethinopathy or age related macular degeneration;

A compound of formula (I) for the treatment or prophylaxis of diabetes, atherosclerosis, abdominal aortic aneurysm, peripheral arterial disease, cancer, reduction of cardiovascular events in chronic kidney disease, diabetic nephropathy, diabetic rethinopathy or age related macular degeneration; and

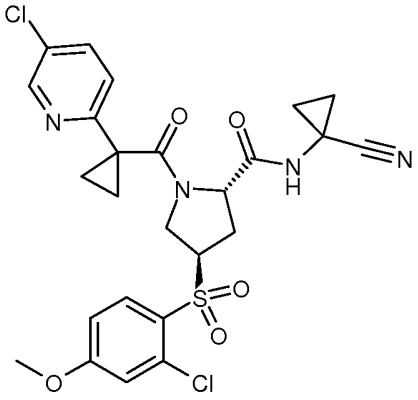
A method for the treatment or prophylaxis of diabetes, atherosclerosis, abdominal aortic aneurysm, peripheral arterial disease, cancer, reduction of cardiovascular events in chronic kidney disease, diabetic nephropathy, diabetic rethinopathy or age related macular degeneration, which method comprises administering an effective amount of a compound of formula (I).

The invention will be illustrated by the following examples which have no limiting character.

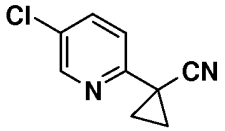
Examples

Example 1

(2S,4R)-4-(2-Chloro-4-methoxy-benzenesulfonyl)-1-[1-(5-chloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide

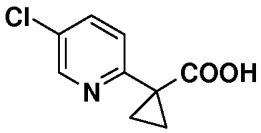


a) 1-(5-Chloro-pyridin-2-yl)-cyclopropanecarbonitrile



To a solution of 5-chloro-2-fluoropyridine (2 g, 1.53 ml, 15.2 mmol, Eq: 1.00) and cyclopropanecarbonitrile (1.02 g, 1.15 ml, 15.2 mmol, Eq: 1.00) in toluene (20.0 ml) was added dropwise over 5 min. KHMDS 0.5 M in toluene (30.4 ml, 15.2 mmol, Eq: 1.00) at 0°C. The solution turned brown. After 45 min, the reaction mixture was allowed to warm up to 22 °C and stirred for 2.5 h. Saturated aqueous NH_4Cl solution (50 ml) was then added and the aqueous phase was extracted with AcOEt (3 x 60 ml). The combined organic phases were dried over Na_2SO_4, filtered and concertrated under reduced pressure. The crude material was purified by flash chromatography (silica gel, 70 g, 0% to 20% EtOAc in heptane) to yield the title compound as a white solid (840 mg; 31 %). m/z = 179.0373 $[M+H]^+$.

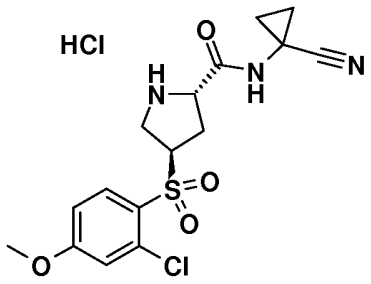
b) 1-(5-Chloro-pyridin-2-yl)-cyclopropanecarboxylic acid



Compound 1a) (600 mg, 3.36 mmol, Eq: 1.00) was dissolved in 1 % aqueous KOH solution (18 ml, 207 mg, 3.7 mmol, Eq: 1.1) . The reaction mixture was stirred 17 h at

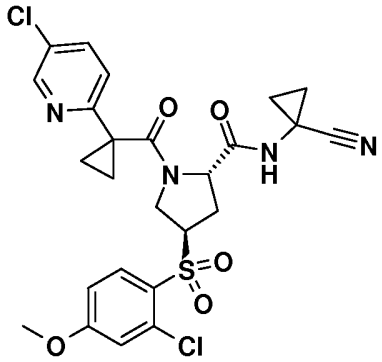
100 °C. The crude reaction mixture was concentrated in vacuo and was acidified to pH 4. The crude material was purified by preparative HPLC to yield the title compound as a white solid (339 mg; 51 %). m/z = 198.1 $[M+H]^+$.

c) (2S,4R)-4-(2-Chloro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide HCl-salt



CAS 1252640-17-7 (600 mg, 1.24 mmol, Eq: 1.00) was dissolved in HCl/dioxane (1.55 ml, 6.2 mmol, Eq: 5.00) and stirred at 22 °C for 4 h. The crude reaction mixture was concentrated in vacuo to yield a white solid (309 mg; 65 %) which was used without further purification. m/z = 384.2 $[M+H]^+$.

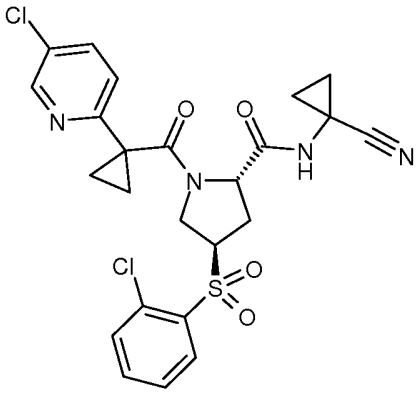
d) (2S,4R)-4-(2-Chloro-4-methoxy-benzenesulfonyl)-1-[1-(5-chloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 1b) (61.8 mg, 313 µmol, Eq: 1.20) was dissolved in DMF (2 ml). HATU (198 mg, 521 µmol, Eq: 2.00), DIEA (67.3 mg, 91.0 µl, 521 µmol, Eq: 2.00) and example 1c) (100 mg, 261 µmol, Eq: 1.00) were added to the solution and stirred at 22 °C for 15 h. The crude material was purified by preparative HPLC to yield the title compound as a white solid (106 mg; 72 %). m/z = 563.2 $[M+H]^+$.

Example 2

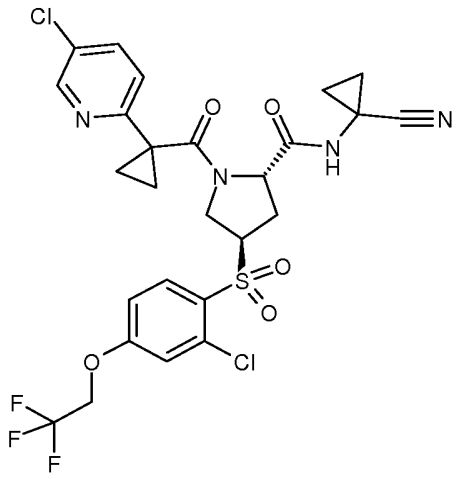
(2S,4R)-4-(2-Chloro-benzenesulfonyl)-1-[1-(5-chloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 2 was prepared in analogy to example 1 starting from CAS 1252638-10-0 to yield the title compound as a white solid (106 mg; 72 %). m/z = 533.2 $[M+H]^+$.

Example 3

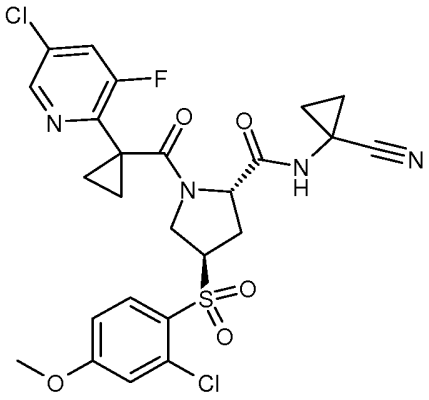
(2S,4R)-1-[1-(5-Chloro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(2,2,2-trifluoro-ethoxy)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 3 was prepared in analogy to example 1 starting from CAS 1252634-04-0 to yield the title compound as a white solid (50 mg; 36 %). m/z = 631.1 $[M+H]^+$.

Example 4

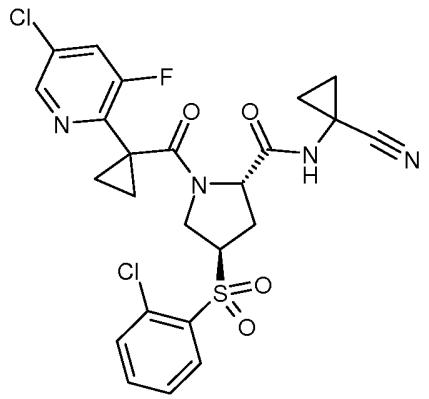
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 4 was prepared in analogy to the methods described in example 1 starting from 5-chloro-2,3-difluoropyridine and example 1c) to yield the title compound as a white solid (45 mg; 30 %). m/z = 581.1 $[M+H]^+$.

Example 5

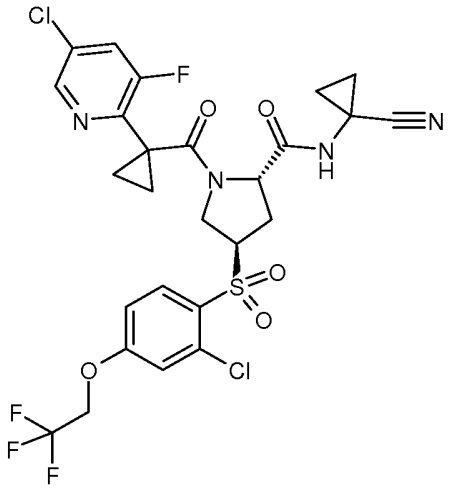
(2S,4R)-4-(2-Chloro-benzenesulfonyl)-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 5 was prepared in analogy to the methods described in example 1 starting from 5-chloro-2,3-difluoropyridine and CAS 1252638-10-0 to yield the title compound as a white solid (99 mg; 64 %). m/z = 551.1 $[M+H]^+$.

Example 6

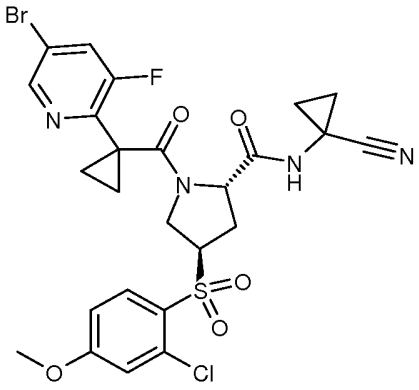
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(2,2,2-trifluoro-ethoxy)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 6 was prepared in analogy to the methods described in example 1 starting from 5-chloro-2,3-difluoropyridine and CAS 1252634-04-0 to yield the title compound as a white solid (114 mg; 79 %). m/z = 649.2 $[M+H]^+$.

Example 7

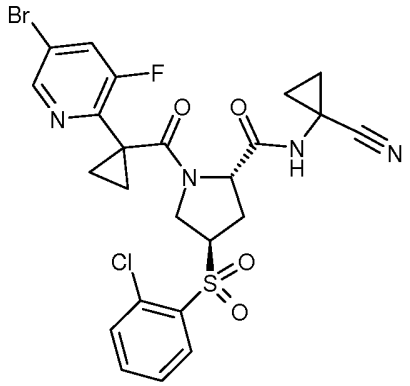
(2S,4R)-1-[1-(5-Bromo-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 7 was prepared in analogy to the methods described in example 1 starting from 5-bromo-2,3-difluoropyridine and example 1c) to yield the title compound as a white solid (14 mg; 17 %). m/z = 627.0 $[M+H]^+$.

Example 8

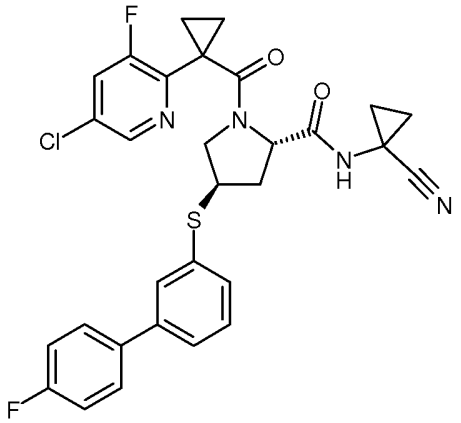
(2S,4R)-1-[1-(5-Bromo-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



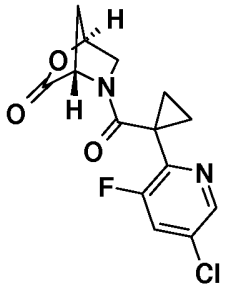
Example 8 was prepared in analogy to the methods described in example 1 starting from 5-bromo-2,3-difluoropyridine and CAS 1252638-10-0 to yield the title compound as a white foam (48 mg; 57 %). m/z = 597.0 $[M+H]^+$.

Example 9

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(4'-fluoro-biphenyl-3-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



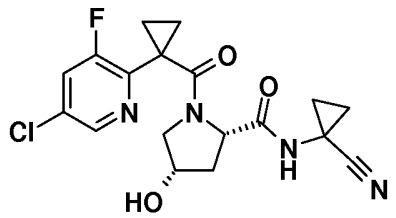
a) (1S,4S)-5-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-2-oxa-5-aza-bicyclo[2.2.1]heptan-3-one



To a milky suspension of 5-chloro-3-fluoro-pyridine-2-carboxylic acid prepared in analogy of example 1b) (670 mg, 3.11 mmol, Eq: 1.00) in toluene (6 ml) at 25 °C was

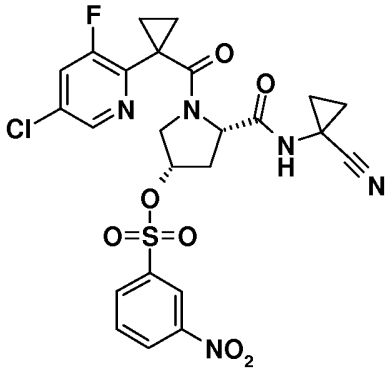
added DMF (11.4 mg, 12.0 µl, 155 µmol, Eq: 0.05). The mixture was cooled down to 0 °C, then a solution of oxalyl chloride (434 mg, 299 µl, 3.42 mmol, Eq: 1.10) in toluene (2.00 ml) was dropped in within 10 min. The reaction mixture was stirred at 0 °C for 30 min, then without cooling for 3 h. At 0 °C, (1*S*,4*S*)-2-oxa-5-aza-bicyclo[2.2.1]heptan-3-one methanesulfonate (CAS 769167-53-5) (650 mg, 3.11 mmol, Eq: 1.00) and THF (4.00 ml) were added to the reactionmixture, followed by TEA (1.18 g, 1.62 ml, 11.7 mmol, Eq: 3.75), dropped within 10 min (exothermic). The mixture was stirred at 22 °C for 16 h.The reaction mixture was poured into 20% aqueous citric acid solution (25 ml) and extracted with EtOAc (3 x 20 ml).The organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 40 g, 0% to 50% EtOAc in heptane) to yield the title compound as an orange oil (850 mg; 88 %). m/z = 311.1 $[M+H]^+$.

b) (2S,4S)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-hydroxy-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



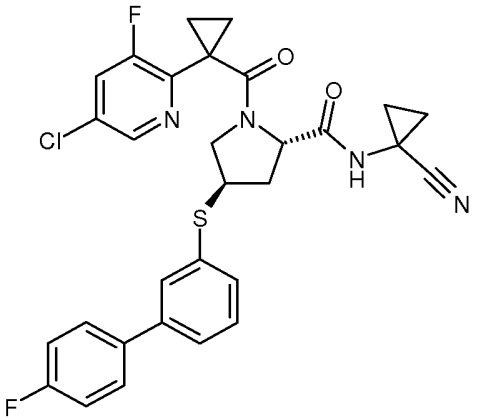
A mixture of example 9a) (850 mg, 2.74 mmol, Eq: 1.00), 1-aminocyclopropane-carbonitrile hydrochloride (422 mg, 3.56 mmol, Eq: 1.30), sodium 2-ethylhexanoate (705 mg, 4.24 mmol, Eq: 1.55) in water (3 ml) and THF (2.00 ml) was stirred at 55 °C for 18 h. To the reaction mixture were added hydrochloric acid (189 mg, 157 µl, 1.91 mmol, Eq: 0.70) and sodium chloride (1.36 g, 1.36 ml, 23.3 mmol, Eq: 8.50). The mixture was stirred for 15 min, then poured into AcOEt (25 ml) and extracted. The aqueous layer was back-extracted with AcOEt (3 x 20 ml). The organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 40 g, 0% to 90% EtOAc in heptane) to yield the title compound as white foam (560 mg; 52 %). m/z = 393.0 $[M+H]^+$.

c) 3-Nitro-benzenesulfonic acid (3S,5S)-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-5-(1-cyano-cyclopropylcarbamoyl)-pyrrolidin-3-yl ester



Example 9b) (560 mg, 1.43 mmol, Eq: 1.00) was dissolved in DCM (15 ml) and 3-nitrobenzene-1-sulfonyl chloride (335 mg, 1.51 mmol, Eq: 1.06) was added. The mixture was cooled down to 0 °C and TEA (433 mg, 596 µl, 4.28 mmol, Eq: 3.00) was slowly and carefully added with a syringe. The icebath was removed and the reaction mixture was stirred at 25 °C for 18 h. The reaction mixture was extracted with aqueous 10 % Na_2CO_3 and 0.1 N aqueous HCl solutions. The organic layers were dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash chromatography (silica gel, 40 g, 0% to 85% EtOAc in heptane) to yield the title compound as off-white solid (510 mg; 62 %). m/z = 578.0 $[M+H]^+$.

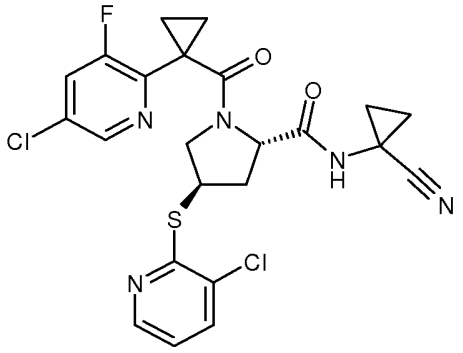
d) (2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(4'-fluoro-biphenyl-3-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 9c) (70 mg, 121 µmol, Eq: 1.00) and 4'-fluorobiphenyl-3-thiol (27.2 mg, 133 µmol, Eq: 1.10) were dissolved in propionitrile (1 ml). TEA (30.6 mg, 42.2 µl, 303 µmol, Eq: 2.50) was added and the reaction mixture was stirred at 90 °C for 3 h. The reaction mixture was poured into 0.1 M aqueous HCl solution (10 ml) and extracted with EtOAc (3 x 10 ml). The organic layers were combined, dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 10 g, 0 % to 66 % EtOAc in heptane) to yield the title compound as off-white oil (46 mg; 68%). m/z = 579.1 $[M+H]^+$.

Example 10

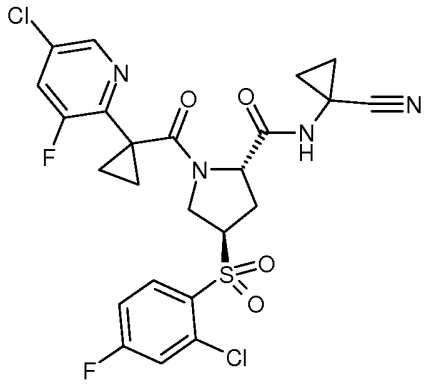
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(3-chloro-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 10 was prepared in analogy to the methods described in example 9 starting from 3-chloropyridine-2-thiol and example 9c) to yield the title compound as a light yellow oil (50 mg; 79 %). m/z = 522.0 $[M+H]^+$.

Example 11

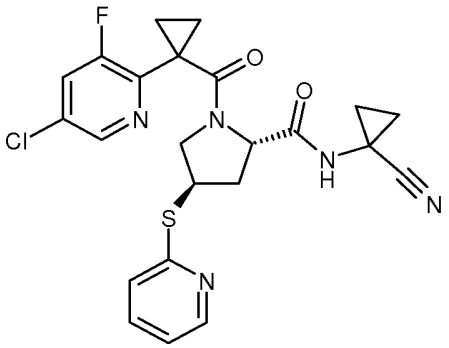
(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-4-fluorophenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide



Example 11 was prepared in analogy to the methods described in example 1 starting from 5-chloro-2,3-difluoropyridine and CAS 1252633-65-0 to yield the title compound as a white solid (46 mg; 30 %). m/z = 569.0632 $[M+H]^+$.

Example 12

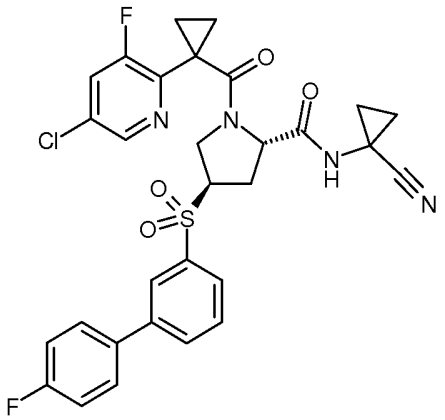
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 12 was prepared in analogy to the methods described in example 9 starting from pyridine-2-thiol and example 9c) to yield the title compound as a colorless oil (4 mg; 7 %). m/z = 486.1 $[M+H]^+$.

Example 13

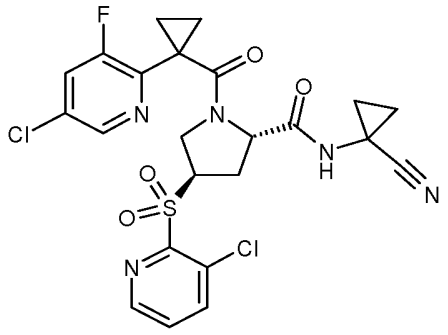
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(4'-fluoro-biphenyl-3-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 9 (41 mg, 70.8 µmol, Eq: 1.00) was dissolved in DCM (1 ml) and mCPBA (25.7 mg, 149 µmol, Eq: 2.10) was added. The reaction mixture was stirred for 3 h at 22 °C. The reaction mixture was poured into 10% aqueous Na_2CO_3 (5 ml) solution and extracted with DCM (3 x 5 ml). The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to yield the title compound as a white solid (42 mg; 97 %). m/z = 611.0 $[M+H]^+$.

Example 14

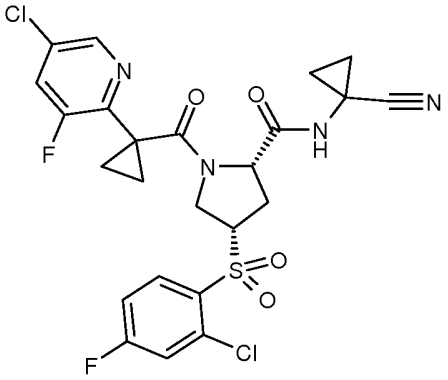
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(3-chloro-pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 14 was prepared in analogy to the methods described in example 13 starting from example 10 to yield the title compound as a white solid (44 mg; 99 %). m/z = 552.1 $[M+H]^+$.

Example 15

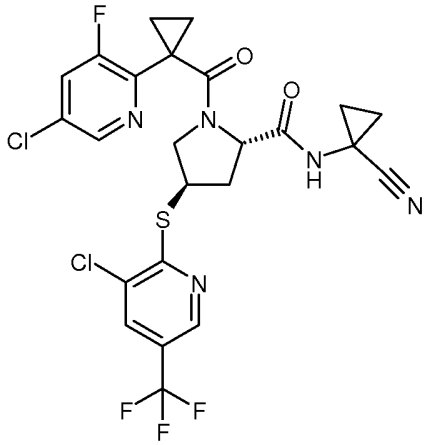
(2S,4S)-4-(2-Chloro-4-fluoro-benzenesulfonyl)-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 15 was obtained as a by-product during the synthesis of example 11 as light yellow solid (36 mg; 21 %).

Example 16

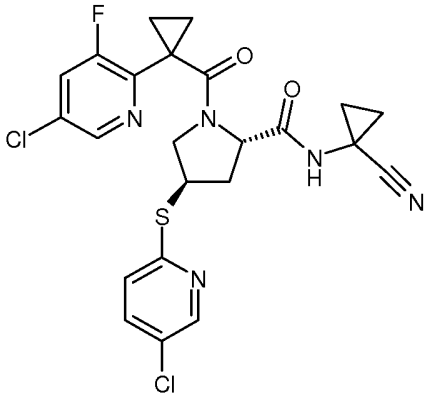
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(3-chloro-5-trifluoromethyl-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 16 was prepared in analogy to the methods described in example 9 starting from 3-chloro-5-(trifluoromethyl)pyridine-2-thiol and example 9c) to yield the title compound as a light yellow oil (4 mg; 5 %). m/z = 585.9 $[M+H]^+$.

Example 17

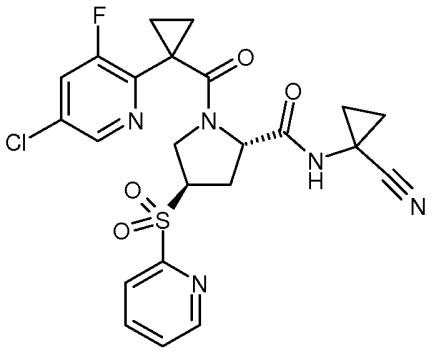
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(5-chloro-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 17 was prepared in analogy to the methods described in example 9 starting from 5-chloropyridine-2-thioland example 9c) to yield the title compound as an off-white solid (30 mg; 83 %). m/z = 522.0 $[M+H]^+$.

Example 18

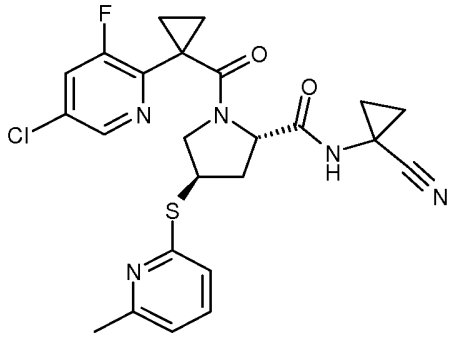
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 18 was prepared in analogy to the methods described in example 13 starting from example 10 to yield the title compound as a off-white solid (3 mg; 94 %). m/z = 518.1 $[M+H]^+$.

Example 19

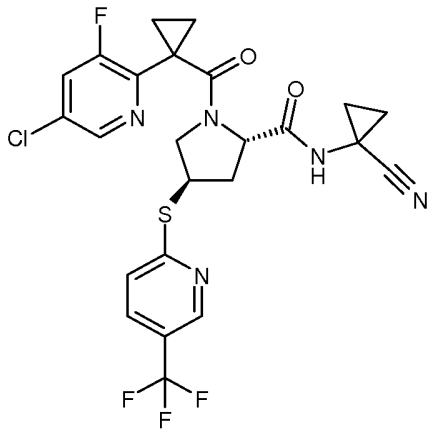
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(6-methyl-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 19 was prepared in analogy to the methods described in example 9 starting from 6-methylpyridine-2-thiol and example 9c) to yield the title compound as an off-white solid (17 mg; 49 %). m/z = 500.1 $[M+H]^+$.

Example 20

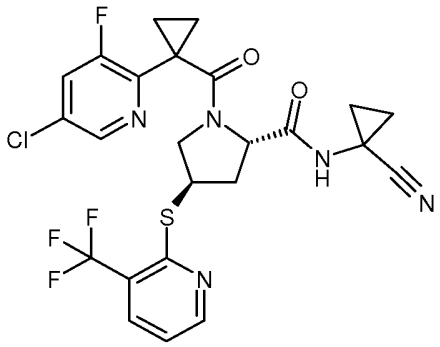
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 20 was prepared in analogy to the methods described in example 9 starting from 5-(trifluoromethyl)pyridine-2-thiol and example 9c) to yield the title compound as a light yellow solid (32 mg; 84 %). m/z = 554.1 $[M+H]^+$.

Example 21

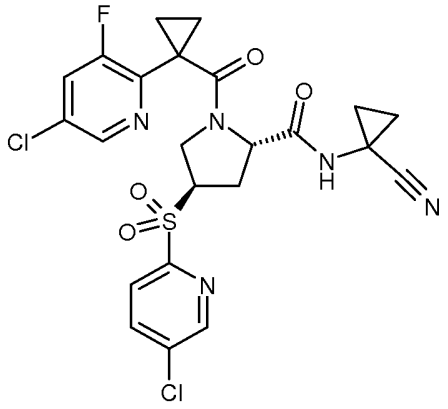
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(3-trifluoromethyl-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 21 was prepared in analogy to the methods described in example 9 starting from 3-(trifluoromethyl)pyridine-2-thiol and example 9c) to yield the title compound as a yellow solid (33 mg; 86 %). m/z = 554.1 $[M+H]^+$.

Example 22

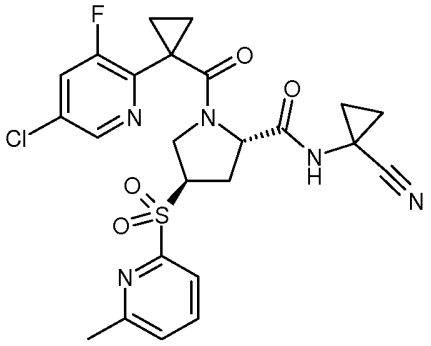
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(5-chloro-pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 22 was prepared in analogy to the methods described in example 13 starting from example 17 to yield the title compound as a white foam (22 mg; 80 %). m/z = 552.1 $[M+H]^+$.

Example 23

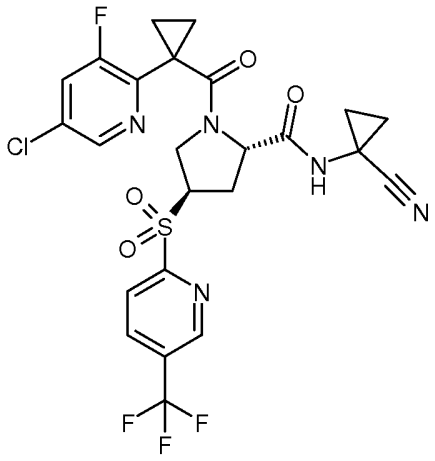
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(6-methyl-pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 23 was prepared in analogy to the methods described in example 13 starting from example 19 to yield the title compound as a white foam (13 mg; 82 %). m/z = 532.0 $[M+H]^+$.

Example 24

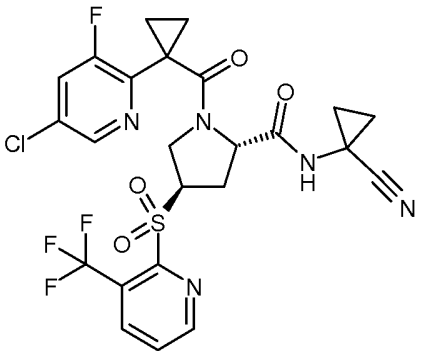
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(5-trifluoromethyl-pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 24 was prepared in analogy to the methods described in example 13 starting from example 20 to yield the title compound as a white solid (29 mg; 98 %). m/z = 585.9 $[M+H]^+$.

Example 25

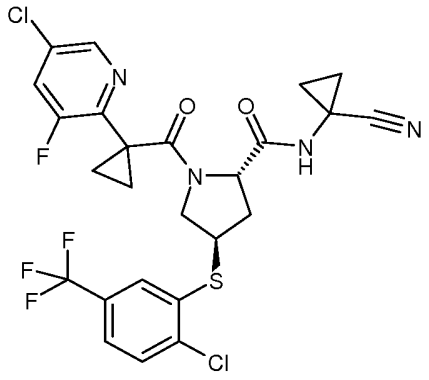
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(3-trifluoromethyl-pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 25 was prepared in analogy to the methods described in example 13 starting from example 21 to yield the title compound as a white solid (16 mg; 52 %). m/z = 585.9 $[M+H]^+$.

Example 26

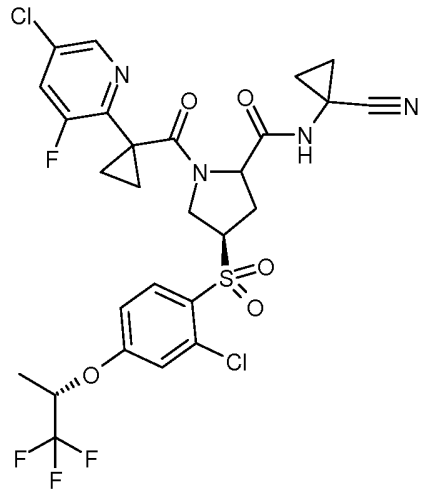
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-5-trifluoromethyl-phenylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 26 was prepared in analogy to the methods described in example 9 starting from 2-chloro-5-(trifluoromethyl)benzenethiol and example 9c) to yield the title compound as a white solid (10 mg; 25 %). m/z = 586.9 $[M+H]^+$.

Example 27

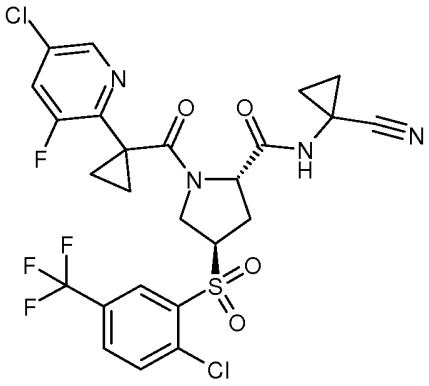
(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-4-((S)-1,1,1-trifluoropropan-2-yloxy)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide



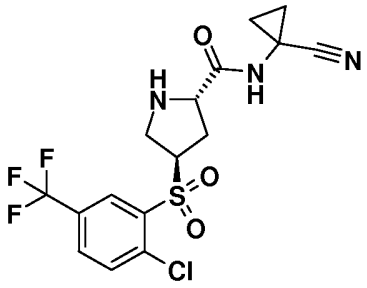
Example 11 (27 mg, 47.4 µmol, Eq: 1.00) was dissolved in DMF (1 ml). Cs_2CO_3 (23.2 mg, 71.1 µmol, Eq: 1.50) and (S)-1,1,1-trifluoropropan-2-ol (5.95 mg, 52.2 µmol, Eq: 1.10) were added to the solution and stirred at 40 °C for 4 h. The crude material was purified by preparative HPLC to yield the title compound as a white solid (17 mg; 54 %). m/z = 663.2 $[M+H]^+$.

Example 28

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-5-(trifluoromethyl)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide

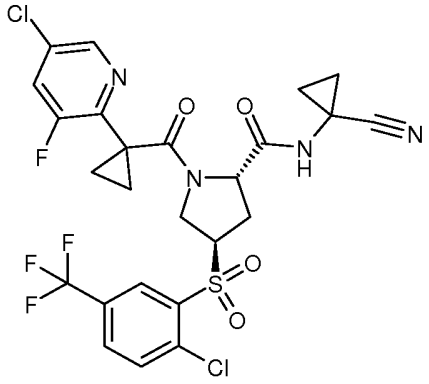


a) (2S,4R)-4-(2-Chloro-5-trifluoromethyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 28a) was prepared in analogy to the methods described for CAS 1252638-10-0 (see Haap et al.; US20100267722 and Hardegger et al.; Angewandte Chemie, International Edition, 50(1), 314-318, S314/1-S314/145; 2011) starting from 2-chloro-5-trifluormethyl-benzenethiol to yield the title compound as a light yellow solid (125 mg; 74 %) m/z = 421.9 $[M+H]^+$.

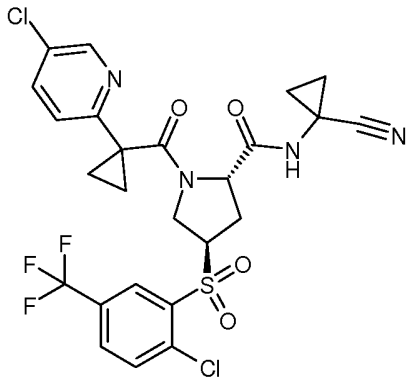
b) (2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-5-(trifluoromethyl)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide



Example 28b) was prepared in analogy to example 1 strating from example 28a) and 5-chloro-2,3-difluoropyridine to yield the title compound as a white solid (37 mg; 50 %). m/z = 619.1 $[M+H]^+$.

Example 29

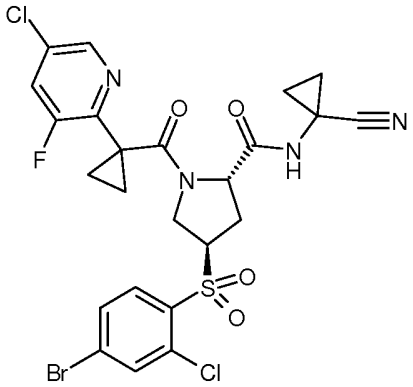
(2S,4R)-1-[1-(5-Chloro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-5-trifluoromethyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 29 was prepared in analogy to example 1 strating from example 28a) and example 1b) to yield the title compound as a white solid (37 mg; 50 %). m/z = 601.1 $[M+H]^+$.

Example 30

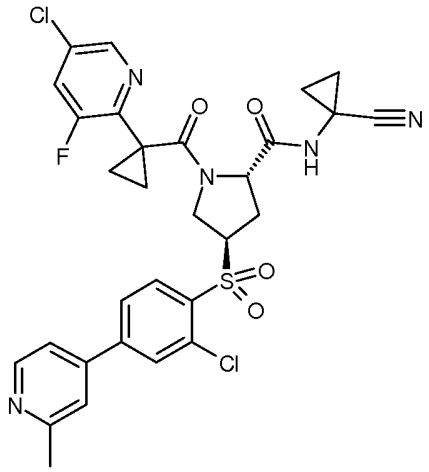
(2S,4R)-4-(4-Bromo-2-chloro-benzenesulfonyl)-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 30 was prepared in analogy to example 28 starting from 4-bromo-2-chlorobenzenethiol to yield the title compound as a white foam (860 mg; 79 %) m/z = 631.0 $[M+H]^+$.

Example 31

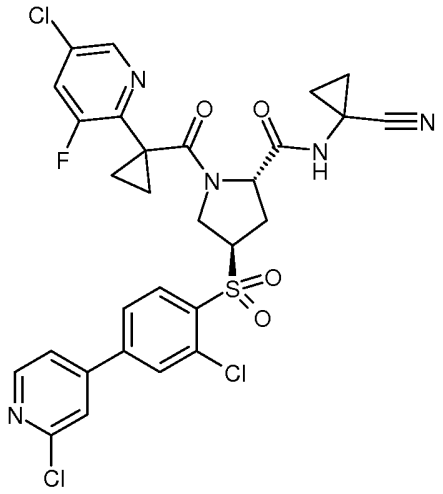
(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-4-(2-methylpyridin-4-yl)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide



Example 30 (100 mg, 159 µmol, Eq: 1.00) was dissolved in 1,2-dimethoxyethane (2 ml). 2-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (45.2 mg, 206 µmol, Eq: 1.30), triphenylphosphine (8.32 mg, 31.7 µmol, Eq: 0.20), 2 M aqueous Na_2CO_3 solution (500 µl) and $Pd(OAc)_2$ (3.56 mg, 15.9 µmol, Eq: 0.10) were added and stirred at 45 °C for 4 h. The reaction mixture was poured into 0.1 M aqueous HCl solution (10 ml) and extracted with DCM (3 x 10 ml). The organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by preparative HPLC to yield the title compound as an off-white foam (61 mg; 60 %). m/z = 642.1 $[M+H]^+$.

Example 32

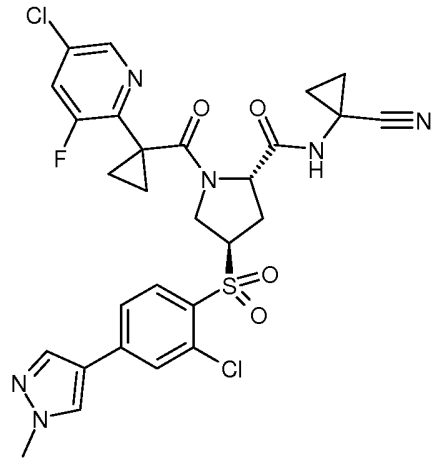
(2S,4R)-4-[2-Chloro-4-(2-chloro-pyridin-4-yl)-benzenesulfonyl]-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 32 was prepared in analogy to example 31 starting from example 30 and 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine to yield the title compound as a white solid (27 mg; 26 %) m/z = 664.1 $[M+H]^+$.

Example 33

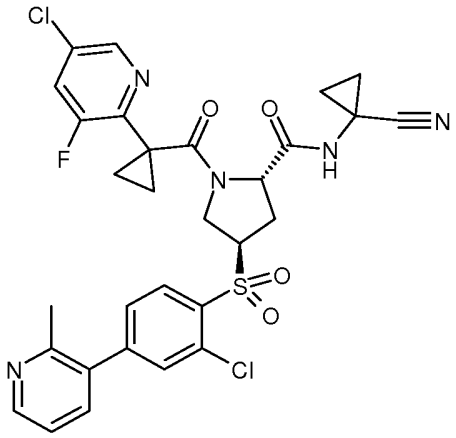
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(1-methyl-1*H*-pyrazol-4-yl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 33 was prepared in analogy to example 31 starting from example 30 and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to yield the title compound as a white solid (25 mg; 25 %). m/z = 631.1 $[M+H]^+$.

Example 34

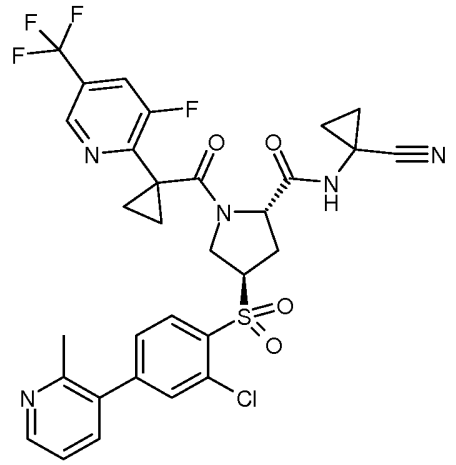
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



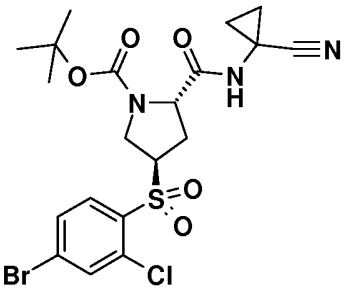
Example 34 was prepared in analogy to example 31 starting from example 30 and 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine to yield the title compound as a white foam (47 mg; 38 %) m/z = 642.2 $[M+H]^+$.

Example 35

(2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide

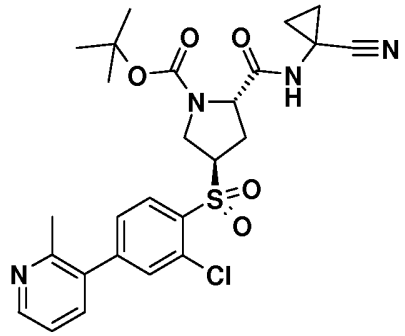


a) (2S,4R)-4-(4-Bromo-2-chloro-benzenesulfonyl)-2-(1-cyano-cyclopropylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester



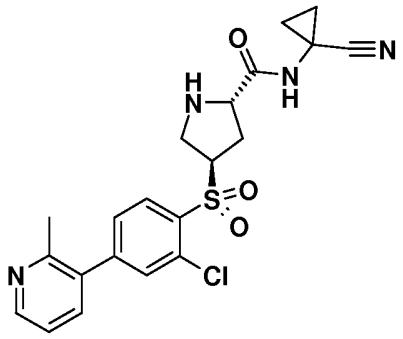
Example 35a) was prepared in analogy to the methods described for CAS 1252631-66-5 (see Haap et al.; US20100267722) starting from (2*S*,4*R*)-1,2-pyrrolidinedicarboxylic acid 4-hydroxy- 1-(1,1-dimethylethyl) ester and 4-bromo-2-chloro-benzenethiol to yield the title compound as a white solid (3.2 g; 58 %). m/z = 434.1 $[M+H\text{-}Boc]^+$.

b) (2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-2-(1-cyano-cyclopropylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester



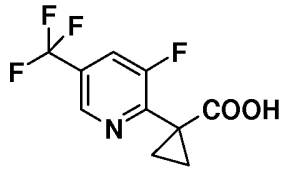
Example 35a) (700 mg, 1.31 mmol, Eq: 1.00) was dissolved in 1,2-dimethoxyethane (8 ml). 2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (345 mg, 1.58 mmol, Eq: 1.20), triphenylphosphine (68.9 mg, 263 µmol, Eq: 0.20), 2 M aqueous Na_2CO_3 solution (2 ml) and palladium (II) acetate (29.5 mg, 131 µmol, Eq: 0.10) were added and stirred at 22 °C for 24 h. After that, the reaction mixture was stirred at 50 °C for 24 h. Then, 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (57.6 mg, 263 µmol, Eq: 0.2) was added to the reaction mixture which was then stirrred at 60 °C for 6 h. The reaction mixture was poured into 0.1 M aqueous HCl solution (50 ml) and extracted with DCM (3 x 20 ml).The organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 40 g, 0% to 100% EtOAc in heptane) to yield the title compound as a light yellow oil (200 mg; 28%). m/z = 545.3 $[M+H]^+$.

c) (2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



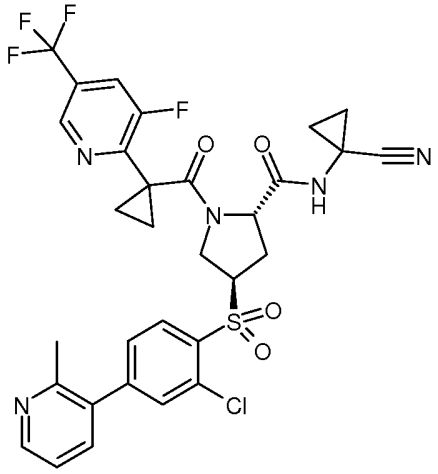
Example 35b) (200 mg, 367 µmol, Eq: 1.00) was dissolved in formic acid (2.4 g, 2 ml, 52.1 mmol, Eq: 142) and stirred at 22 °C for 15 h. The reaction mixture was adjusted carefully with icecold aqueous 10 % Na_2CO_3-solution to pH 8 and extracted with CH_2Cl_2. The water layer was washed totally 3 times with CH_2Cl_2/THF (1:1; 30 ml), the combined organic layers were dried over Na_2SO_4, filtered and evaporated to yield the title compound as a white foam (142 mg; 87 %). m/z = 445.2 $[M+H]^+$.

d) 1-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-cyclopropanecarboxylic acid



Example 35 d) was prepared in analogy to the methods described for examples 1a) and b) to yield the title compound as a light brown solid (50 mg; 41 %) m/z = 250.0 $[M+H]^+$.

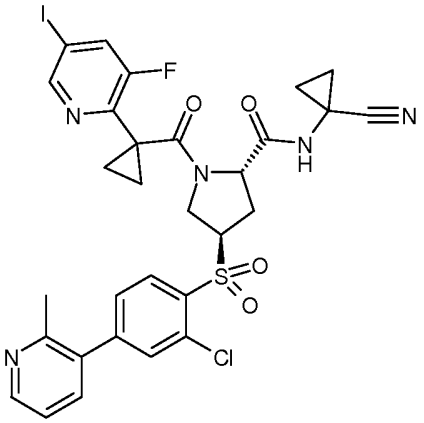
e) (2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



The title compound was prepared in analogy to example1d) starting from example 35c) (45 mg) and 35d) (30 mg) to yield an off-white solid (34 mg 50 %) m/z = 676.3 $[M+H]^+$.

Example 36

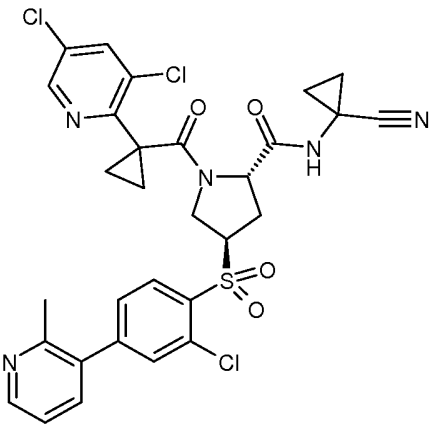
(2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 36 was prepared in analogy to example 35 starting from example 35c) and 1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarboxylic acid, which was prepared in analogy to examples 1a) and 1b), to yield the title compound as a off-white solid (35 mg; 47 %) m/z = 734.2 $[M+H]^+$.

Example 37

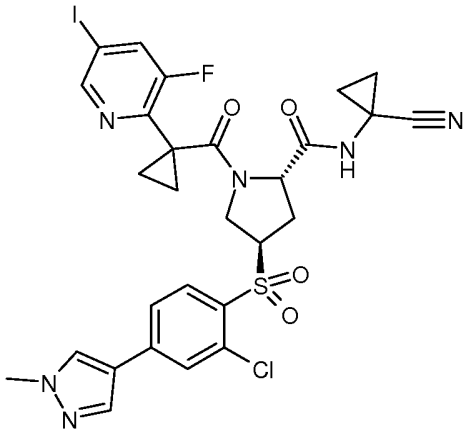
(2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3,5-dichloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



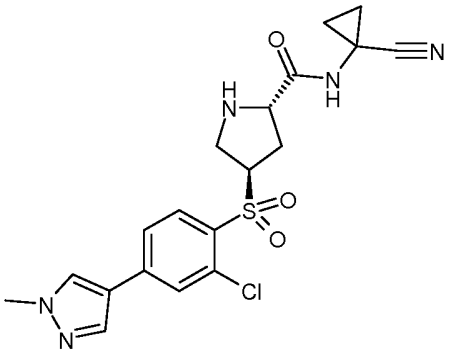
Example 37 was prepared in analogy to example 35 starting from example 35c) and 1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarboxylic acid, which was prepared in analogy to examples 1a) and 1b), to yield the title compound as an off-white solid (26 mg; 39 %) m/z = 660.2 $[M+H]^+$.

Example 38

(2S,4R)-4-[2-Chloro-4-(1-methyl-1*H*-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide

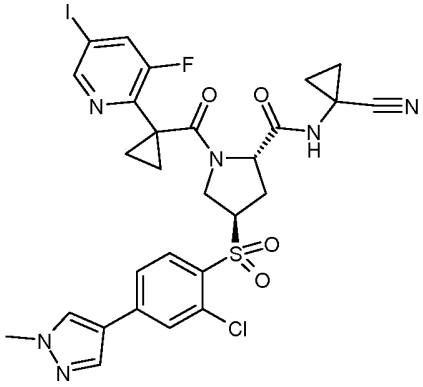


a) (2S,4R)-4-[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 38a) was prepared in analogy to example 35c) starting from examples 35a) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to yield the title compound as a light brown foam (173 mg; 95 %). m/z = 434.2 $[M+H]^+$.

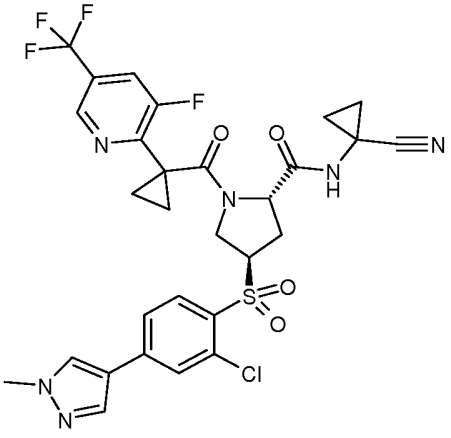
b) (2S,4R)-4-[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 38b) was prepared in analogy to example 35 starting from example 38a) and 1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarboxylic acid, which was prepared in analogy to examples 1a) and 1b), to yield the title compound as a off-white solid (40 mg; 48 %) m/z = 723.1 $[M+H]^+$.

Example 39

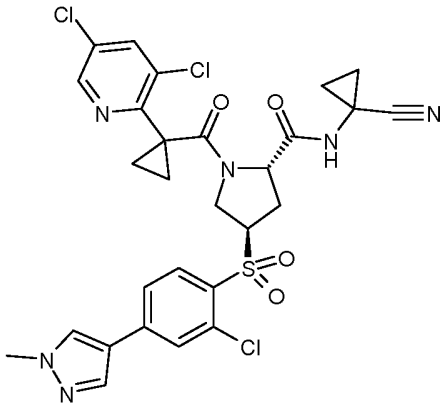
(2S,4R)-4-[2-Chloro-4-(1-methyl-1*H*-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 39 was prepared in analogy to example 38b) starting from example 38a) and 35d) to yield the title compound as a off-white solid (16 mg; 60 %). m/z = 665.1 $[M+H]^+$.

Example 40

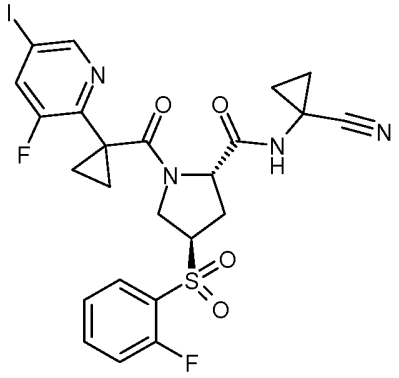
(2S,4R)-4-[2-Chloro-4-(1-methyl-1*H*-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3,5-dichloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 40 was prepared in analogy to example 35 starting from example 38a) and 1-(3,5-dichloro-pyridin-2-yl)-cyclopropanecarboxylic acid, which was prepared in analogy to examples 1a) and 1b), to yield the title compound as an off-white solid (29 mg; 39 %) m/z = 649.2 $[M+H]^+$.

Example 41

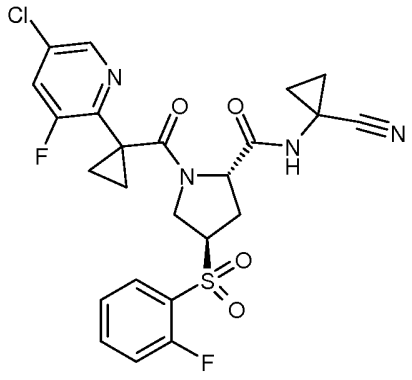
(2S,4R)-4-(2-Fluoro-benzenesulfonyl)-1-[1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 41 was prepared in analogy to example 8 starting from 2-fluorobenzenethiol and 1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarboxylic acid to yield the title compound as a white foam (328 mg; 68 %). m/z = 627.3 $[M+H]^+$.

Example 42

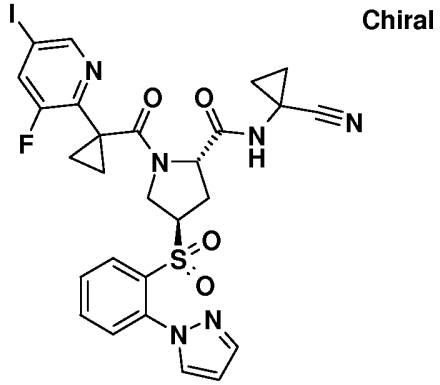
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-fluoro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



Example 42 was prepared in analogy to example 41 starting from 2-fluorobenzenethiol and 1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarboxylic acidto yield the title compound as a white foam (212 mg; 67 %). m/z = 535.4 $[M+H]^+$.

Example 43

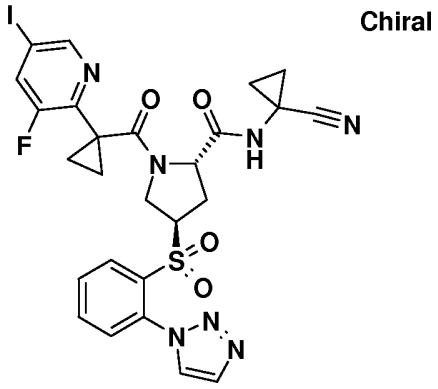
(2S,4R)-1-[1-(3-Fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-pyrazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



To a 5 mL tube were added example 41 (60 mg, 95.8 µmol, Eq: 1.00), 1H-pyrazole (9.78 mg, 144 µmol, Eq: 1.50), Cs_2CO_3 (37.4 mg, 115 µmol, Eq: 1.20) and DMF (1 ml). The reaction mixture was stirred for 24 h at 22 °C. To the reaction mixture was again 1H-pyrazole (9.78 mg, 144 µmol, Eq: 1.50) added and stirred for 24 h at 50 °C. The crude material was purified by preparative HPLC to yield the title compound as a white foam (8 mg; 12.4%). m/z = 675.0647 $[M+H]^+$.

Example 44

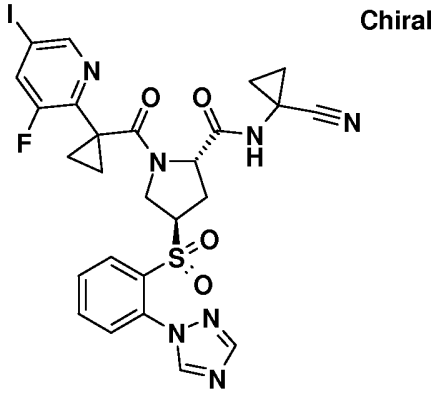
(2S,4R)-1-[1-(3-Fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-[1,2,3]triazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



To a 5 mL tube were added example 41 (60 mg, 95.8 µmol, Eq: 1.00), 1H-1,2,3-triazole (9.92 mg, 8.32 µl, 144 µmol, Eq: 1.50), Cs_2CO_3 (37.4 mg, 115 µmol, Eq: 1.20) and DMA (1 ml). The reaction mixture was stirred for 24 h at 22 °C. To the reaction mixture was again 1H-1,2,3-triazole (9.92 mg, 8.32 µl, 144 µmol, Eq: 1.50) added and stirred for 24 h at 50 °C. The crude material was purified by preparative HPLC to yield the title compound as a white foam (25 mg; 23%; purity 50-80%). m/z = 676.0638 $[M+H]^+$.

Example 45

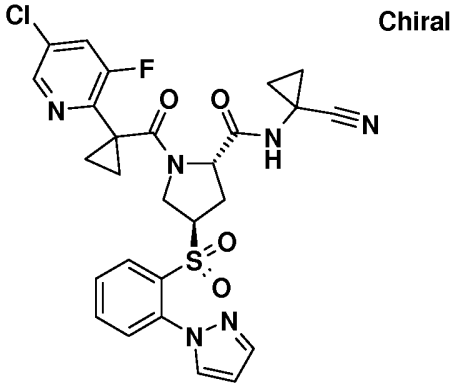
(2S,4R)-1-[1-(3-Fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-[1,2,4]triazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



To a 5 mL tube were added example 41 (60 mg, 95.8 µmol, Eq: 1.00), 1H-1,2,4-triazole (9.92 mg, 144 µmol, Eq: 1.50), 1H-1,2,4-triazole (9.92 mg, 144 µmol, Eq: 1.50) and DMA (1 ml). The reaction mixture was stirred for 24 h at 22 °C. To the reaction mixture was again 1H-1,2,4-triazole (9.92 mg, 144 µmol, Eq: 1.50) added and stirred for 24 h at 50 °C. The crude material was purified by preparative HPLC to the title compound as a white foam (15 mg; 18.8%; purity 50-80%). m/z = 676.0629 $[M+H]^+$.

Example 46

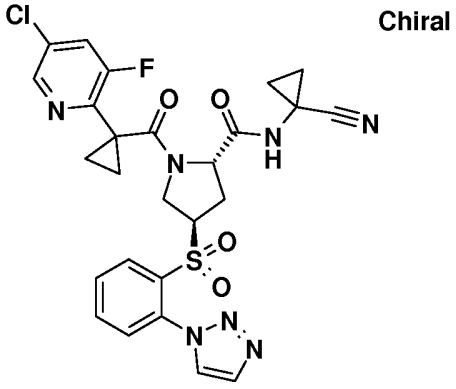
((2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-pyrazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



To a 5 mL tube were added example 42 (50 mg, 93.5 µmol, Eq: 1.00), 1H-pyrazole (9.54 mg, 140 µmol, Eq: 1.50), Cs_2CO_3 (36.5 mg, 112 µmol, Eq: 1.20) and DMA (1 ml). The reaction mixture was stirred for 24 h at 22 °C. To the reaction mixture was again 1H-pyrazole (9.54 mg, 140 µmol, Eq: 1.50) added and stirred for 24 h at 50 °C. The crude material was purified by preparative HPLC to yield the title compound as a white foam (10 mg; 15%; purity 80%). m/z = 583.1319 $[M+H]^+$.

Example 47

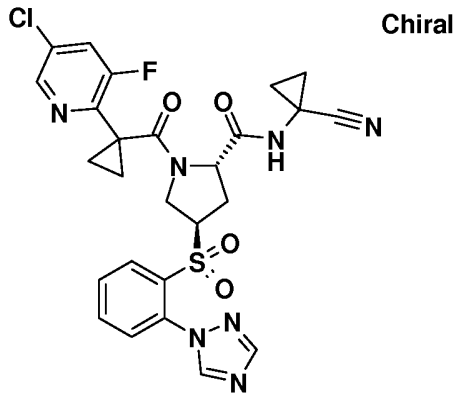
(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-[1,2,3]triazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



To a 5 mL tube were added example 42 (50 mg, 93.5 µmol, Eq: 1.00), 1H-1,2,3-triazole (9.68 mg, 8.12 µl, 140 µmol, Eq: 1.50), Cs2CO3 (36.5 mg, 112 µmol, Eq: 1.20) and DMA (1 ml). The reaction mixture was stirred for 24 h at 22 °C. To the reactionmixture was again 1H-1,2,3-triazole (9.68 mg, 8.12 µl, 140 µmol, Eq: 1.50) added and stirred for 24 h at 50 °C. The crude material was purified by preparative HPLC to yield the title compound as a white foam (10 mg; 11%; purity 60%). m/z = 584.1272 $[M+H]^+$.

Example 48

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-[1,2,4]triazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide



To a 5 mL tube were added example 42 (50 mg, 93.5 µmol, Eq: 1.00), 1H-1,2,4-triazole (9.68 mg, 140 µmol, Eq: 1.50), Cs_2CO_3 (36.5 mg, 112 µmol, Eq: 1.20) and DMA (1 ml). The reaction mixture was stirred for 24 h at 22 °C. To the reaction mixture was again 1H-1,2,4-triazole (9.68 mg, 140 µmol, Eq: 1.50) added and stirred for 24 h at 50 °C. The crude material was purified by preparative HPLC to yield the title compound as a white foam (25 mg; 35%; purity 77%). m/z = 584.1281 $[M+H]^+$.

Exemple 49

Cathepsin enzyme inhibition assay

Enzyme activity is measured by observing the increase in fluorescence intensity caused by cleavage of a peptide substrate containing a fluorophore whose emission is quenched in the intact peptide.

Assay buffer: 100 mM potassium phosphate pH 6.5, EDTA-Na 5 mM, Triton X-100 0.001%, DTT 5 mM.

Enzymes (all at 1 nM): human and mouse Cathepsin S, Cat K, Cat B, Cat L.

Substrate (20 µM): Z-Val-Val-Arg-AMC, except for Cat K which uses Z-Leu-Arg-AMC (both from Bachem).

Z = Benzyloxycarbonyl.

AMC = 7-Amino-4-Methyl-Coumarin.

DTT = dithiothreitol.

Final volume: 100 µL.

Excitation 360 nm, Emission 465 nm.

Enzyme is added to the substance dilutions in 96-well microtitre plates and the reaction is started with substrate. Fluorescence emission is measured over 20 minutes, during which time a linear increase is observed in the absence of inhibitor. IC_{50} are calculated by standard methods.

Inhibition of human Cat S, mouse Cat S, human Cat K, human Cat B, human Cat L and mouse Cat L have been measured separately. The results obtained for human Cat S and L for representative compounds of the invention are expressed in the following table in µM.

Example	IC50 h S	IC50 h L	Example	IC50 h S	IC50 h L
1	0.000606	0.4097	**25**	0.003213	13.1975
2	0.000492	0.3402	**26**	0.003466	0.0524
3	0.000825	0.429	**27**	0.001596	0.09
4	0.000393	0.0119	**28**	0.000543	0.0568
5	0.000398	0.0129	**29**	0.000618	0.3618
6	0.000675	0.0445	**30**	0.000474	0.0726
7	0.000734	0.0255	**31**	0.000505	0.0616
8	0.000438	0.0192	**32**	0.000686	0.1121
9	0.011785	0.4165	**33**	0.000375	0.0287
10	0.96365	15.8722	**34**	0.000322	0.0642

11	0.000602	0.0898	**35**	0.000768	0.0589
12	0.5941	8.2265	**36**	0.000382	0.0098
13	0.00077	0.2474	**37**	0.000779	0.0722
14	0.002844	2.117	**38**	0.000678	0.0032
15	0.011075	1.679	**39**	0.000696	0.0436
16	1.031	>25	**40**	0.000703	0.1111
17	0.2635	5.648	**41**	0.0006	0.003
18	0.00424	3.4345	**42**	0.0007	0.031
19	0.12715	4.6095	**43**	0.016985	0.0906
20	0.3926	5.0635	**44**	0.002372	1.5585
21	0.27455	10.011	**45**	0.3272	28.383
22	0.002996	1.9695	**46**	0.1587	17.445
23	0.002796	5.635	**47**	0.004268	35.2
24	0.006244	2.694	**48**	0.058535	21.1025

The compounds of the invention are preferential inhibitors of Cathepsin-S and L over Cathepsin-K and B.

The compounds according to the invention have, in the foregoing assay, an IC_{50} at Cat S and/or L which is between 0.00001 and 100 μM. Particular compounds of the invention have an IC50 at Cat S and/or L between 0.00001 and 50 μM and mor particularly between

0.00001 and 20 μM. The particular compounds of the invention have an IC_{50} in at least one of the foregoing assay below 0.09 μM.

Example A

A compound of formula (I) can be used in a manner known per se as the active ingredient for the production of tablets of the following composition:

	Per tablet
Active ingredient	200 mg
Microcrystalline cellulose	155 mg
Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	20 mg
	425 mg

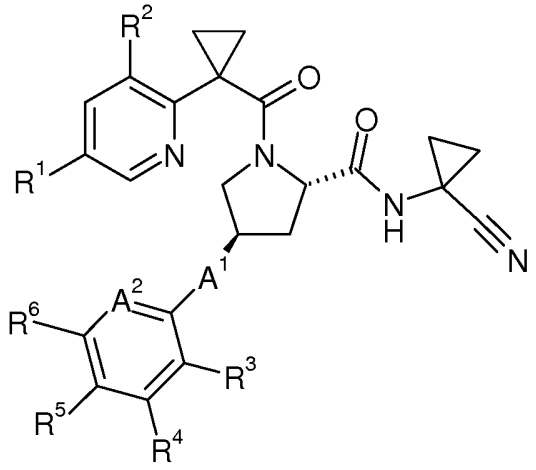
Example B

A compound of formula (I) can be used in a manner known per se as the active ingredient for the production of capsules of the following composition:

	Per capsule
Active ingredient	100.0 mg
Corn starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	0.5 mg
	220.0 mg

Claims

1. A compound of formula (I)



(I)

wherein

A^1 is -S- or $-S(O)_2-$;

A^2 is nitrogen or -(CH)-;

R^1 is halogen or haloalkyl;

R^2 is hydrogen or halogen;

R^3 is hydrogen, halogen, haloalkyl, pyrazolyl, [1,2,3]-triazolyl or [1,2,4]-triazolyl;

R^4 and R^6 are independently selected from hydrogen, alkyl, haloalkyl and halophenyl; and

R^5 is hydrogen, halogen, haloalkyl, alkoxy, haloalkoxy, alkylpyridinyl, halopyridinyl or alkylpyrazolyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein A^1 is $-S(O)_2-$.

3. A compound according to claim 1 or 2, wherein A^2 is -(CH)-.

4. A compound according to any one of claims 1 to 3, wherein R^1 is chloro, bromo, iodo or trifluoromethyl.

5. A compound according to any one of claims 1 to 4, wherein R^2 is halogen.

6. A compound according to any one of claims 1 to 5, wherein R^2 is chloro or fluoro.

7. A compound according to any one of claims 1 to 6, wherein R^3 is halogen.

8. A compound according to any one of claims 1 to 7, wherein R^3 is chloro.

9. A compound according to any one of claims 1 to 8, wherein R^4 and R^6 are independently selected from hydrogen and haloalkyl.

10. A compound according to any one of claims 1 to 9, wherein R^4 and R^6 are independently selected from hydrogen and trifluoromethyl.

11. A compound according to any one of claims 1 to 10, wherein R^5 is hydrogen, alkoxy, haloalkoxy, halogen, alkylpyridinyl or alkylpyrazolyl.

12. A compound according to any one of claims 1 to 11, wherein R^5 is hydrogen, methoxy, trifluoroethoxy, fluoro, trifluoropropyloxy, bromo, methylpyridinyl or mehtylpyrazolyl.

13. A compound according to any one of claims 1 to 12 selected from

(2S,4R)-4-(2-Chloro-4-methoxy-benzenesulfonyl)-1-[1-(5-chloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-(2-Chloro-benzenesulfonyl)-1-[1-(5-chloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(2,2,2-trifluoro-ethoxy)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-(2-Chloro-benzenesulfonyl)-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(2,2,2-trifluoro-ethoxy)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Bromo-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Bromo-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(4'-fluoro-biphenyl-3-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(3-chloro-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-4-fluorophenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(4'-fluoro-biphenyl-3-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(3-chloro-pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4S)-4-(2-Chloro-4-fluoro-benzenesulfonyl)-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(3-chloro-5-trifluoromethyl-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(5-chloro-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(6-methyl-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(3-trifluoromethyl-pyridin-2-ylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(5-chloro-pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(6-methyl-pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(5-trifluoromethyl-pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(3-trifluoromethyl-pyridine-2-sulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-5-trifluoromethyl-phenylsulfanyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-4-((S)-1,1,1-trifluoropropan-2-yloxy)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-5-(trifluoromethyl)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-[1-(5-Chloro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-5-trifluoromethyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-(4-Bromo-2-chloro-benzenesulfonyl)-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-4-(2-methylpyridin-4-yl)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-4-[2-Chloro-4-(2-chloro-pyridin-4-yl)-benzenesulfonyl]-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3,5-dichloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3,5-dichloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-(2-Fluoro-benzenesulfonyl)-1-[1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-fluoro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(3-Fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-pyrazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(3-Fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-[1,2,3]triazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(3-Fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-[1,2,4]triazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

((2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-pyrazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-[1,2,3]triazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide; and

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-[1,2,4]triazol-1-yl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide.

14. A compound according to any one of claims 1 to 13 selected from

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-(2-Chloro-benzenesulfonyl)-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(2,2,2-trifluoro-ethoxy)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Bromo-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Bromo-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-(2-chloro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-4-fluorophenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-4-((S)-1,1,1-trifluoropropan-2-yloxy)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-5-(trifluoromethyl)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-4-(4-Bromo-2-chloro-benzenesulfonyl)-1-[1-(5-chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-(1-(5-chloro-3-fluoropyridin-2-yl)cyclopropanecarbonyl)-4-(2-chloro-4-(2-methylpyridin-4-yl)phenylsulfonyl)-N-(1-cyanocyclopropyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-1-[1-(5-Chloro-3-fluoro-pyridin-2-yl)-cyclopropanecarbonyl]-4-[2-chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(2-methyl-pyridin-3-yl)-benzenesulfonyl]-1-[1-(3,5-dichloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

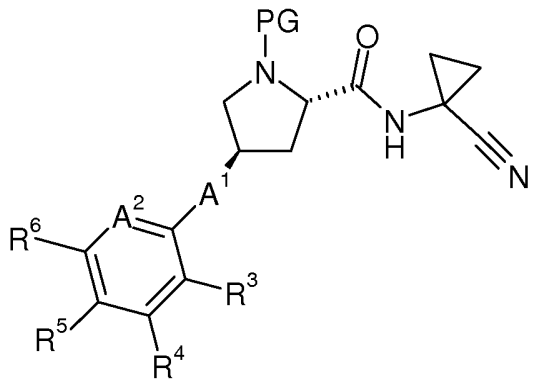
(2S,4R)-4-[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-iodo-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

(2S,4R)-4-[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide; and

(2S,4R)-4-[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1-[1-(3,5-dichloro-pyridin-2-yl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide.

15. A process for the preparation of a compound of formula (I) as defined in any one of claims 1 to 14, comprising one of the following steps:

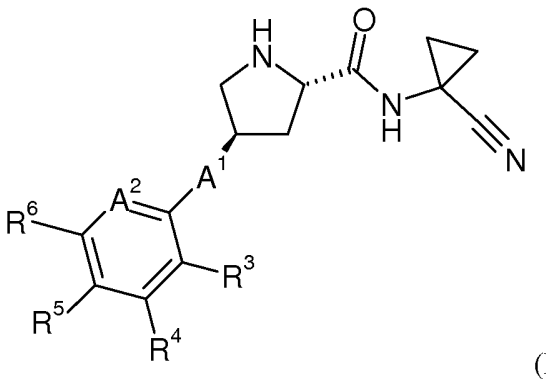
(a) The reaction of a compound of formula (A)



(A)

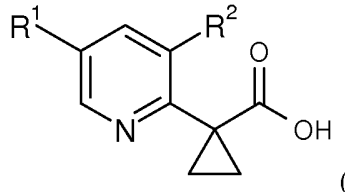
in the presence of acid, wherein A^1, A^2 and R^1 to R^6 are as defined in any one of claims 1 to 12 and wherein PG is an amine protecting group;

(b) The reaction of a compound of formula (B1)



(B1)

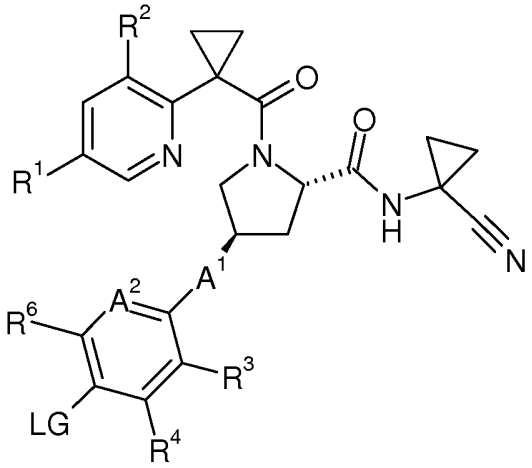
with a compound of formula (B2)



(B2)

in the presence of a base and an amide coupling agent and a base, wherein A^1, A^2 and R^1 to R^6 are as defined in any one of claims 1 to 12;

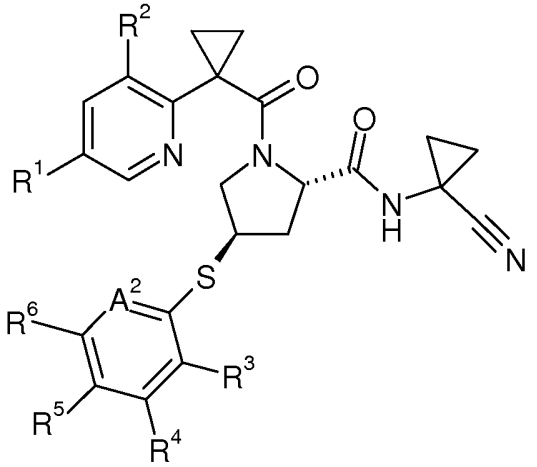
(c) The reaction of a compound of formula (C)



(C)

in the presence of $R^5B(OR)_2$, a base and a Suzuki catalyst, wherein wherein A^1, A^2 and R^1 to R^4 and R^6 are as defined in any one of claims 1 to 12, LG is a leaving group, R^5 is alkylpyridinyl, halopyridinyl or alkylpyrazolyl and R is hydrogen or methyl, or both R, together with the boron atom to which they are attached, form 2,4,4,5,5-pentamethyl-[1,3,2]dioxaborolane; or

(d) The reaction of a compound of formula (D)



(D)

in the presence of an oxidizing agent, wherein wherein A^1 and R^1 to R^6 are as defined in any one of claims 1 to 12.

16. A compound according to any one of claims 1 to 14, when manufactured according to a process of claim 15.

17. A compound according to any one of claims 1 to 14 for use as a therapeutically active substance.

18. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 14 and a therapeutically inert carrier.

19. The use of a compound according to any one of claims 1 to 14 for the preparation of a medicament for the treatment or prophylaxis of diabetes, atherosclerosis, abdominal aortic aneurysm, peripheral arterial disease or diabetic nephropathy.

20. A compound according to any one of claims 1 to 14 for the treatment or prophylaxis of diabetes, atherosclerosis, abdominal aortic aneurysm, peripheral arterial disease or diabetic nephropathy.

21. A method for the treatment or prophylaxis of diabetes, atherosclerosis, abdominal aortic aneurysm, peripheral arterial disease or diabetic nephropathy, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 14.

22. The invention as hereinbefore described.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/067218

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 A61K31/4439 A61K31/444
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/267722 A1 (SANCHEZ RUBEN ALVAREZ [FR] ET AL) 21 October 2010 (2010-10-21) Formula I,; paragraphs [0002], [0020], [0021]; claims 1,27; examples 11-32,238,288,361,368,377,420 -----	1-21
A	LEO A. HARDEGGER, BERND KUHN, BEAT SPINNLER ET AL.: "Systematische Untersuchung von Halogenbrücken in Protein-Ligand-Wechselwirkungen", ANGEW. CHEM., vol. 123, 2011, pages 329-334, XP002713287, figure 1; table 1 -----	1-21

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 September 2013	08/10/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Rudolf, Manfred

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/067218

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010267722 A1	21-10-2010	AR 076319 A1	01-06-2011
		AU 2010241084 A1	06-10-2011
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		CN 102405211 A	04-04-2012
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		EC SP11011411 A	30-11-2011
		EP 2421826 A1	29-02-2012
		JP 2012524116 A	11-10-2012
		KR 20110140136 A	30-12-2011
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		TW 201040164 A	16-11-2010
		US 2010267722 A1	21-10-2010
		WO 2010121918 A1	28-10-2010

(19)中华人民共和国国家知识产权局

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(74)专利代理机构 中科专利商标代理有限责任公司 11021
代理人 陈平 柳春琦
(51)Int.Cl.
C07D 401/14(2006.01)
A61K 31/4439(2006.01)
A61K 31/444(2006.01)

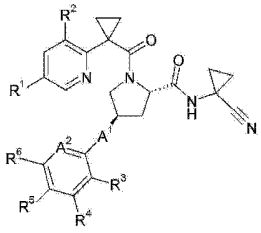
权利要求书7页 说明书46页

(54)发明名称

新吡啶衍生物

(57)摘要

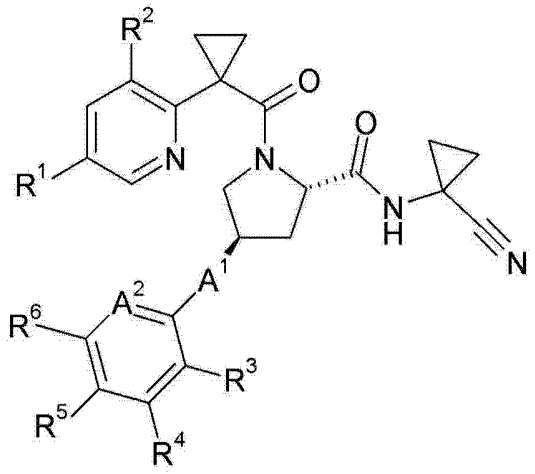
本发明涉及式(I)的化合物，其中A^1，A^2和R^1至R^6如说明书中和权利要求中所限定。式(I)的化合物可以用作药物。



(I)

CN 104583198 A

1. 式 (I) 的化合物



(I)

其中

A^1是 -S- 或 $-S(O)_2-$；

A^2是氮或 -(CH)-；

R^1是卤素或卤代烷基；

R^2是氢或卤素；

R^3是氢，卤素，卤代烷基，吡唑基，[1,2,3]- 三唑基或 [1,2,4]- 三唑基；

R^4和 R^6独立地选自氢，烷基，卤代烷基和卤代苯基；并且

R^5是氢，卤素，卤代烷基，烷氧基，卤代烷氧基，烷基吡啶基，卤代吡啶基或烷基吡唑基；

或其药用盐。

2. 根据权利要求 1 所述的化合物，其中 A^1是 $-S(O)_2-$。

3. 根据权利要求 1 或 2 所述的化合物，其中 A^2是 -(CH)-。

4. 根据权利要求 1 至 3 任一项所述的化合物，其中 R^1是氯，溴，碘或三氟甲基。

5. 根据权利要求 1 至 4 任一项所述的化合物，其中 R^2是卤素。

6. 根据权利要求 1 至 5 任一项所述的化合物，其中 R^2是氯或氟。

7. 根据权利要求 1 至 6 任一项所述的化合物，其中 R^3是卤素。

8. 根据权利要求 1 至 7 任一项所述的化合物，其中 R^3是氯。

9. 根据权利要求 1 至 8 任一项所述的化合物，其中 R^4和 R^6独立地选自氢和卤代烷基。

10. 根据权利要求 1 至 9 任一项所述的化合物，其中 R^4和 R^6独立地选自氢和三氟甲基。

11. 根据权利要求 1 至 10 任一项所述的化合物，其中 R^5是氢，烷氧基，卤代烷氧基，卤素，烷基吡啶基或烷基吡唑基。

12. 根据权利要求 1 至 11 任一项所述的化合物，其中 R^5是氢，甲氧基，三氟乙氧基，氟，三氟丙氧基，溴，甲基吡啶基或甲基吡唑基。

13. 根据权利要求 1 至 12 任一项所述的化合物，所述化合物选自

(2S,4R)-4-(2- 氯 -4- 甲氧基 - 苯磺酰基)-1-[1-(5- 氯 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺；

(2S,4R)-4-(2- 氯 - 苯磺酰基)-1-[1-(5- 氯 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺；

(2S,4R)-1-[1-(5-氯-吡啶-2-基)-环丙烷羰基]-4-[2-氯-4-(2,2,2-三氟-乙氧基)-苯磺酰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-氯-4-甲氧基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-4-(2-氯-苯磺酰基)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-[2-氯-4-(2,2,2-三氟-乙氧基)-苯磺酰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-溴-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-氯-4-甲氧基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-溴-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-氯-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(4′-氟-联苯-3-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(3-氯-吡啶-2-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-(1-(5-氯-3-氟吡啶-2-基)环丙烷羰基)-4-(2-氯-4-氟苯磺酰基)-N-(1-氰基环丙基)吡咯烷-2-甲酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(吡啶-2-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(4′-氟-联苯-3-磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(3-氯-吡啶-2-磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4S)-4-(2-氯-4-氟-苯磺酰基)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(3-氯-5-三氟甲基-吡啶-2-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(5-氯-吡啶-2-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(吡啶-2-磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(6-甲基-吡啶-2-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(5-三氟甲基-吡啶-2-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(3-三氟甲基-吡啶-2-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(5-氯-吡啶-2-磺酰

基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(6-甲基-吡啶-2-磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(5-三氟甲基-吡啶-2-磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(3-三氟甲基-吡啶-2-磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-氯-5-三氟甲基-苯基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-(1-(5-氯-3-氟吡啶-2-基)环内烷羰基)-4-(2-氯-4-((S)-1,1,1-三氟丙-2-基氧基)苯磺酰基)-N-(1-氰基环丙基)吡咯烷-2-甲酰胺；

(2S,4R)-1-(1-(5-氯-3-氟吡啶-2-基)环丙烷羰基)-4-(2-氯-5-(三氟甲基)苯磺酰基)-N-(1-氰基环丙基)吡咯烷-2-甲酰胺；

(2S,4R)-1-[1-(5-氯-吡啶-2-基)-环丙烷羰基]-4-(2-氯-5-三氟甲基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-4-(4-溴-2-氯-苯磺酰基)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-(1-(5-氯-3-氟吡啶-2-基)环丙烷羰基)-4-(2-氯-4-(2-甲基吡啶-4-基)苯磺酰基)-N-(1-氰基环丙基)吡咯烷-2-甲酰胺；

(2S,4R)-4-[2-氯-4-(2-氯-吡啶-4-基)-苯磺酰基]-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-[2-氯-4-(2-甲基-吡啶-3-基)-苯磺酰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-4-[2-氯-4-(2-甲基-吡啶-3-基)-苯磺酰基]-1-[1-(3-氟-5-三氟甲基-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-4-[2-氯-4-(2-甲基-吡啶-3-基)-苯磺酰基]-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-4-[2-氯-4-(2-甲基-吡啶-3-基)-苯磺酰基]-1-[1-(3,5-二氯-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-1-[1-(3-氟-5-三氟甲基-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-1-[1-(3,5-二氯-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-4-(2-氟-苯磺酰基)-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-氟-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

(2S,4R)-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-4-(2-吡唑-1-基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

(2S,4R)-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-4-(2-[1,2,3]三唑-1-基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

(2S,4R)-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-4-(2-[1,2,4]三唑-1-基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

((2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-吡唑-1-基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-[1,2,3]三唑-1-基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;和

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-[1,2,4]三唑-1-基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺。

14.根据权利要求1至13任一项所述的化合物,所述化合物选自

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-氯-4-甲氧基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

(2S,4R)-4-(2-氯-苯磺酰基)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-[2-氯-4-(2,2,2-三氟-乙氧基)-苯磺酰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

(2S,4R)-1-[1-(5-溴-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-氯-4-甲氧基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

(2S,4R)-1-[1-(5-溴-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-氯-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

(2S,4R)-1-(1-(5-氯-3-氟吡啶-2-基)环丙烷羰基)-4-(2-氯-4-氟苯磺酰基)-N-(1-氰基环丙基)吡咯烷-2-甲酰胺;

(2S,4R)-1-(1-(5-氯-3-氟吡啶-2-基)环丙烷羰基)-4-(2-氯-4-((S)-1,1,1-三氟丙-2-基氧基)苯磺酰基)-N-(1-氰基环丙基)吡咯烷-2-甲酰胺;

(2S,4R)-1-(1-(5-氯-3-氟吡啶-2-基)环丙烷羰基)-4-(2-氯-5-(三氟甲基)苯磺酰基)-N-(1-氰基环丙基)吡咯烷-2-甲酰胺;

(2S,4R)-4-(4-溴-2-氯-苯磺酰基)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

(2S,4R)-1-(1-(5-氯-3-氟吡啶-2-基)环丙烷羰基)-4-(2-氯-4-(2-甲基吡啶-4-基)苯磺酰基)-N-(1-氰基环丙基)吡咯烷-2-甲酰胺;

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

(2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-[2-氯-4-(2-甲基-吡啶-3-基)-苯磺酰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

(2S,4R)-4-[2-氯-4-(2-甲基-吡啶-3-基)-苯磺酰基]-1-[1-(3-氟-5-三氟甲基-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

(2S,4R)-4-[2-氯-4-(2-甲基-吡啶-3-基)-苯磺酰基]-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

(2S,4R)-4-[2-氯-4-(2-甲基-吡啶-3-基)-苯磺酰基]-1-[1-(3,5-二氯-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

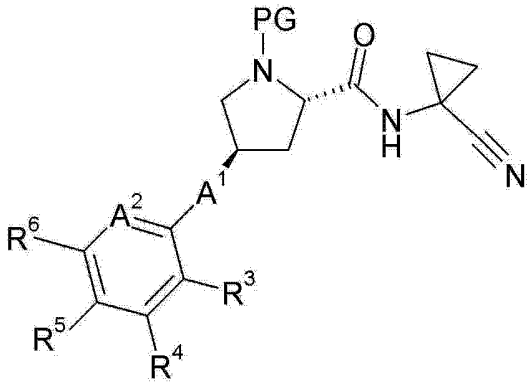
(2S,4R)-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;

(2S,4R)-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-1-[1-(3-氟-5-三氟甲基-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺;和

(2S,4R)-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-1-[1-(3,5-二氯-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺。

15.一种制备权利要求1至14任一项中限定的式(I)的化合物的方法,所述方法包括以下步骤:

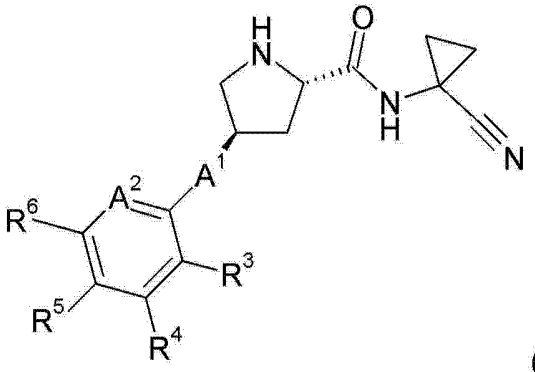
(a)在酸存在下式(A)的化合物的反应,



(A)

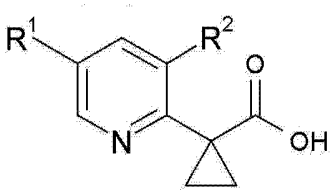
其中A^1,A^2和R^1至R^6如权利要求1至12中任一项所定义并且其中PG是胺保护基团;

(b)在碱和酰胺偶联剂和碱存在下,式(B1)的化合物



(B1)

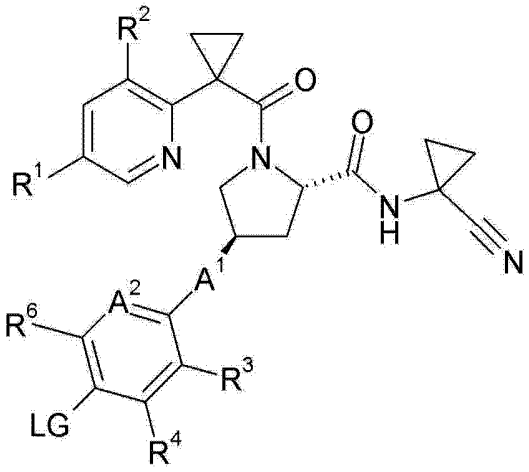
与式(B2)的化合物的反应,



(B2)

其中 A^1，A^2和 R^1至 R^6如权利要求 1 至 12 中任一项所定义；

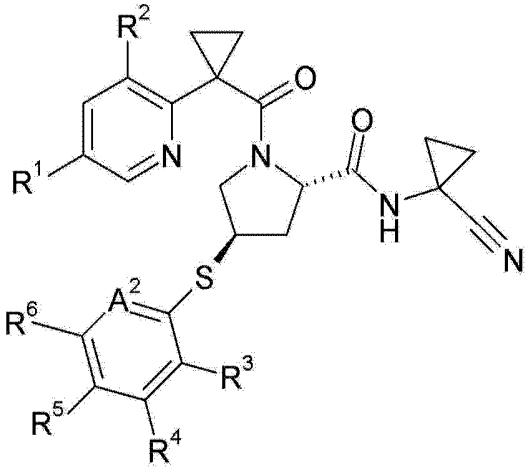
(c) 在 $R^5B(OR)_2$，碱和 Suzuki 催化剂存在下，式 (C) 的化合物的反应，



(C)

其中 A^1，A^2和 R^1至 R^4和 R^6如权利要求 1 至 12 中任一项所定义，LG 是离去基团，R^5是烷基吡啶基，卤代吡啶基或烷基吡唑基，并且 R 是氢或甲基，或两个 R 与它们所连接的硼原子一起形成 2,4,4,5,5- 五甲基 -[1,3,2] 二氧杂硼杂环戊烷；或

(d) 在氧化剂存在下，式 (D) 的化合物的反应，



(D)

其中 A^1和 R^1至 R^6如权利要求 1 至 12 中任一项所定义。

16. 根据权利要求 15 的方法制备的根据权利要求 1 至 14 任一项所述的化合物。

17. 根据权利要求 1 至 14 任一项所述的化合物，所述化合物用作治疗活性物质。

18. 一种药物组合物，所述药物组合物包含根据权利要求 1 至 14 任一项所述的化合物和治疗惰性载体。

19. 根据权利要求 1 至 14 任一项所述的化合物用于制备治疗或预防糖尿病，动脉粥样

硬化，腹主动脉瘤，外周动脉疾病或糖尿病性肾病的药物的用途。

20. 根据权利要求 1 至 14 任一项所述的化合物，所述化合物用于治疗或预防糖尿病，动脉粥样硬化，腹主动脉瘤，外周动脉疾病或糖尿病性肾病。

21. 一种治疗或预防糖尿病，动脉粥样硬化，腹主动脉瘤，外周动脉疾病或糖尿病性肾病的方法，所述方法包括给药有效量的权利要求 1 至 14 任一项中限定的化合物。

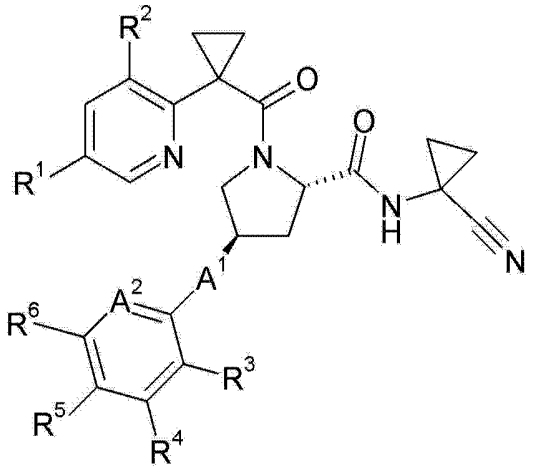
22. 如上文描述的发明。

新吡啶衍生物

[0001] 本发明涉及可用于哺乳动物中治疗和 / 或预防的有机化合物，并且特别涉及为半胱氨酸蛋白酶组织蛋白酶的优先抑制剂的化合物，特别是为半胱氨酸蛋白酶组织蛋白酶 S 或 L 的优先抑制剂的化合物。

[0002] 本发明特别涉及式 (I) 化合物

[0003]



(I)

[0004] 其中

[0005] A^1是 -S- 或 $-S(O)_2-$；

[0006] A^2是氮或 -(CH)-；

[0007] R^1是卤素或卤代烷基；

[0008] R^2是氢或卤素；

[0009] R^3是氢，卤素，卤代烷基，吡唑基，[1,2,3]- 三唑基或 [1,2,4]- 三唑基；

[0010] R^4和 R^6独立地选自氢，烷基，卤代烷基和卤代苯基；并且

[0011] R^5是氢，卤素，卤代烷基，烷氧基，卤代烷氧基，烷基吡啶基，卤代吡啶基或烷基吡唑基；

[0012] 或其药用盐。

[0013] 本发明化合物是半胱氨酸蛋白酶组织蛋白酶 (Cat) 的优先抑制剂、特别是组织蛋白酶 S 或组织蛋白酶 L 的优先抑制剂，并且因此可用于治疗代谢性疾病如糖尿病 (diabetes)，动脉粥样硬化 (atherosclerosis)，腹主动脉瘤 (abdominal aortic aneurysm)，外周动脉疾病 (peripheral arterial disease)，癌症，慢性肾病中的心血管事件的减少 (reduction of cardiovascular events in chronic kidney disease)，肾小球肾炎 (glomerulonephritis)，年龄相关性黄斑变性 (age related macular degeneration)，糖尿病性肾病 (diabetic nephropathy) 和糖尿病性视网膜病 (diabetic retinopathy)。此外，免疫介导的疾病如类风湿性关节炎 (rheumatoid arthritis)，克罗恩病 (crohn's disease)，多发性硬化 (multiple sclerosis)，斯耶格伦综合征 (sjorgen syndrome)，红斑狼疮 (lupus erythematosus)，神经性疼痛 (neuropathic pain)，I 型糖尿

病 (diabetes type I),哮喘 (asthma) 和过敏反应 (allergy) 和与皮肤有关的免疫性疾病也是适合用组织蛋白酶 S 抑制剂治疗的疾病。

[0014] 本发明的目的是式 (I) 化合物及其前述盐本身,以及它们作为治疗活性物质的用途,制备所述化合物的方法,中间体,药学组合物,包含所述化合物、其药用盐的药物,所述化合物和盐在预防和 / 或治疗疾病中的用途,特别是在治疗或预防糖尿病,动脉粥样硬化,腹主动脉瘤,外周动脉疾病,癌症,慢性肾病中的心血管事件的减少和糖尿病性肾病中的用途,以及所述化合物和盐在制备药物中的用途,所述药物用于治疗和预防糖尿病,动脉粥样硬化,腹主动脉瘤,外周动脉疾病,癌症,慢性肾病中的心血管事件的减少和糖尿病性肾病。

[0015] 哺乳动物组织蛋白酶是参与生物学和病理事件关键步骤的半胱氨酸型蛋白酶。组织蛋白酶被认为是易于驾驭的药物靶点,因为其能够用小分子化合物抑制酶活性,并且因此其也是制药行业感兴趣的 (Bromme,D. (2001), ′ Papain-like cysteine proteases′ , Curr Protoc Protein Sci,第 21 章,第 21 2 单元 ;Roberts,R. (2005), ′ Lysosomal cysteine proteases :structure,function and inhibition of cathepsins′ ,Drug News Perspect,18(10),605-14)。

[0016] 组织蛋白酶 S 在抗原呈递细胞如巨噬细胞和树突状细胞和平滑肌细胞中显著表达 (Hsing,L.C.and Rudensky,A.Y. (2005), ′ The lysosomal cysteine proteases in MHC class II antigen presentation′ , Immunol Rev,207,229-41 ;Rudensky,A.and Beers,C. (2006),′ Lysosomal cysteine proteases and antigen presentation′ ,Ernst Schering Res Found Workshop,(56),81-95)。尽管组织蛋白酶S在正常动脉组织中仅微弱表达,在动脉粥样硬化的动脉中可见到强烈上调 (Liu,J. 等 (2006), ′ Increased serum cathepsin S in patients with atherosclerosis and diabetes′ , Atherosclerosis, 186(2),411-9 ;Sukhova,G.K. 等 (1998),′ Expression of the elastolytic cathepsins S and K in human atheroma and regulation of their production in smooth muscle cells′ ,J Clin Invest,102(3),576-83)。

[0017] 临床前数据提示,组织蛋白酶 S 的功能对于动脉粥样硬化是关键性的,因为当在适当的小鼠模型中检测时,组织蛋白酶 S 缺失的小鼠具有减少的动脉粥样硬化表型。在 LDL-Rec 缺失的小鼠中,报道了减少的脂质累积,弹性纤维的分解和慢性动脉炎症。在 APO E 缺失的小鼠中,报道了急性斑块破裂事件的显著减少。当慢性肾病被引入 CatS/In APO-E 缺失的小鼠时,可以看到,除在动脉和心脏瓣膜中的抗动脉粥样硬化活性之外,加速钙化的显著减少 (Aikawa,E. 等 (2009), ′ Arterial and aortic valve calcification abolished by elastolytic cathepsin S deficiency in chronic renal disease ′ , Circulation,119(13),1785-94 ;de Nooijer,R. 等 (2009), ′ Leukocyte cathepsin S is a potent regulator of both cell and matrix turnover in advanced atherosclerosis′ , Arterioscler Thromb Vasc Biol, 29(2),188-94 ;Rodgers,K.J. 等 (2006), ′ Destabilizing role of cathepsin S in murine atherosclerotic plaques′ , Arterioscler Thromb Vasc Biol,26(4),851-6 ; Sukhova 等 (2003), ′ Deficiency of cathepsin S reduces atherosclerosis in LDL receptor-deficient mice′ , J Clin Invest,111(6),897-906)。这提示通过减少细胞外基质分解、减少促炎症状态、以及减少加速钙化,组织蛋白酶 S 的潜在抑制剂将稳定动脉粥

样硬化斑块，以及随后稳定其临床表现。

[0018] 动脉粥样硬化模型中所述的这些表型与组织蛋白酶 S 的已知细胞功能一致。首先，组织蛋白酶 S 涉及细胞外基质的降解，其使斑稳定。特别是，组织蛋白酶 S 具有强有利的解弹性蛋白 (elastinolytic) 活性并且可以在中性 pH 发挥该功能，这是组织蛋白酶 S 区别于所有其他组织蛋白酶的特征。其次，组织蛋白酶 S 是抗原呈递中涉及的主要蛋白酶，特别是抗原呈递细胞中不变链 (invariant chain) 的分裂，导致 T 细胞对动脉粥样硬化组织的慢性炎症的贡献减少。升高的炎症导致进一步的氧化性和解蛋白性组织损伤以及随后的斑不稳定化 (Cheng, X.W. 等 (2004), ′ Increased expression of elastolytic cysteine proteases, cathepsins S and K, in the neointima of balloon-injured rat carotid arteries′ ,Am J Pathol,164(1),243-51 ;Driessen,C. 等 (1999),′ Cathepsin S controls the trafficking and maturation of MHC class II molecules in dendritic cells′ ,J Cell Biol,147(4),775-90 ;Rudensky,A.and Beers,C.(2006), ′ Lysosomal cysteine proteases and antigen presentation ′ ,Ernst Schering Res Found Workshop,(56),81-95)。

[0019] Cat S 抑制剂的抗炎和抗 - 解弹性蛋白性质使其也成为慢性阻塞性肺疾 (chronic obstructive pulmonary disease) 的突出的靶点 (Williams,A.S. 等 (2009), ′ Role of cathepsin S in ozone-induced airway hyperresponsiveness and inflammation′ ,Pulm Pharmacol Ther,22(1),27-32)。此外，由于其细胞外的基质降解功能，抑制组织蛋白酶 S 将影响新内膜形成和血管新生 (Burns-Kurtis,C.L. 等 (2004),′ Cathepsin S expression is up-regulated following balloon angioplasty in the hypercholesterolemic rabbit ′ ,Cardiovasc Res,62(3),610-20 ;Cheng, X.W. 等 (2004), ′ Increased expression of elastolytic cysteine proteases, cathepsins S and K, in the neointima of balloon-injured rat carotid arteries′ ,Am J Pathol,164(1),243-51 ; Shi, G.P. 等 (2003), ′ Deficiency of the cysteine protease cathepsin S impairs microvessel growth′ ,Circ Res,92(5),493-500 ;Wang, B. 等 (2006), ′ Cathepsin S controls angiogenesis and tumor growth via matrix-derived angiogenic factors′ , J Biol Chem,281(9),6020-9)。因此，组织蛋白酶 S 的抑制剂对于数种不同的疾病定位 (setting) 可能是有用的。

[0020] 组织蛋白酶 S 还在减少肿瘤生长和肿瘤细胞侵入中起作用，如 Roberta E.Burden 在 Clin Cancer Res 2009 ;15(19) 中所述。另外，肾切除的组织蛋白酶 S 敲除小鼠与肾切除的野生型小鼠相比，表现出动脉钙化的显著减少。这表明，抑制组织蛋白酶 S 可以对减少慢性肾病患者中的心血管事件具有有益的效果 (Elena Aikawa, Circulation,2009, 1785-1794)。

[0021] 组织蛋白酶 L 显示出比组织蛋白酶 S 宽的表达分布，并且还有数据表明组织蛋白酶 L 在动脉粥样硬化中所起的作用，例如，LDLrec&Cat L 缺失小鼠表现出减少的动脉粥样硬化表型 (Kitamoto, S. 等 (2007), ′ Cathepsin L deficiency reduces diet-induced atherosclerosis in low-density lipoprotein receptor-knockout mice′ ,Circulation,115(15),2065-75)。另外，Cat L 被认为涉及代谢综合征，因为其控制脂肪生成和外周葡萄糖耐受性。在肾病中，组织蛋白酶 L 被描述为通过蛋白分解性呈递

发动蛋白和因此的蛋白尿而调节足状突细胞功能(Sever, S. 等(2007), ′ Proteolytic processing of dynamin by cytoplasmic cathepsin L is a mechanism for proteinuric kidney disease′ , J Clin Invest,117(8),2095-104)。

[0022] 组织重构、细胞外基质降解、活性神经肽的生成和胸腺上皮细胞中抗原呈递中的作用是对组织蛋白酶L描述的细胞活性(Funkelstein 等(2008), (a)′ Major role of cathepsin L for producing the peptide hormones ACTH, β-Endorphin, and α-MSH, illustrated by protease gene knockout and expression, Journal of Biological Chemistry,283(51),35652-35659 ;(b)′ Cathepsin L participates in the production of neuropeptide Y in secretory vesicles,demonstrated by protease gene knockout and expression, Journal of Neurochemistry,106(1),384-391 ;Rudensky and Beers 2006)。

[0023] 在本说明书中,术语“烷基”,单独或组合地,是指具有1至8个碳原子的直链或支链烷基,尤其是1至6个碳原子的直链或支链烷基,并特别是1至4个碳原子的直链或支链烷基。直链和支链C1-C8烷基的实例为甲基、乙基、丙基、异丙基、丁基、异丁基、叔丁基、同分异构的戊基、同分异构的己基、同分异构的庚基和同分异构的辛基,尤其是甲基、乙基、丙基、异丙基、异丁基和叔丁基,更特别是甲基。

[0024] 术语“烷氧基”,单独或组合地,是指式烷基-O-的基团,其中术语″烷基″具有之前给出的含义,例如甲氧基、乙氧基、正丙氧基、异丙氧基、正丁氧基、异丁氧基、仲丁氧基和叔丁氧基,特别是甲氧基。

[0025] 术语“氧基”,单独或组合地,是指-O-基团。

[0026] 术语“卤素”或“卤代”,单独或组合地,是指氟、氯、溴或碘。

[0027] 术语“卤代烷基”和“卤代烷氧基”,单独或组合地,表示被至少一个卤素取代,尤其是被一至五个卤素,特别是一至三个卤素替代的烷基基团和烷氧基基团。特定的“卤代烷基”是三氟甲基。特定的卤代烷氧基是三氟乙氧基和三氟丙氧基。

[0028] 术语“药用盐”是指保持游离碱或游离酸的生物学效力和性能,并且不是在生物学上或在其他方面不适宜的那些盐。所述盐用无机酸和有机酸形成,所述无机酸例如盐酸,氢溴酸,硫酸,硝酸,磷酸,特别是盐酸,所述有机酸例如乙酸,丙酸,羟基乙酸,丙酮酸,草酸(oxylic acid),马来酸,丙二酸,琥珀酸,富马酸,酒石酸,柠檬酸,苯甲酸,肉桂酸,扁桃酸,甲磺酸,乙磺酸,对甲苯磺酸,水杨酸,N-乙酰基半胱氨酸。另外,这些盐可以通过将无机碱或有机碱加入到游离酸中而制备。来自无机碱的盐包括但不限于钠,钾,锂,铵,钙,镁盐。来自有机碱的盐包括但不限于以下物质的盐:伯、仲和叔胺,取代的胺包括天然存在的取代的胺,环状胺和碱性离子交换树脂,例如异丙胺,三甲胺,二乙胺,三乙胺,三丙胺,乙醇胺,赖氨酸,精氨酸,N-乙基哌啶,哌啶,聚胺树脂。式(I)化合物还可以以两性离子形式存在。特别的式(I)化合物的药用盐是盐酸盐,氢溴酸盐,硫酸盐,磷酸盐和甲磺酸盐。

[0029] 如果原料或式(I)化合物之一含有在一步或多步反应步骤的反应条件下不稳定或反应性的一个或多个官能团,可以采用本领域熟知的方法在关键步骤之前引入合适的保护基(如,例如T.W.Greene 和P.G.M.Wutts 的“Protective Groups in Organic Chemistry”,第3版,1999, Wiley,纽约中所述)。这样的保护基团可采用文献中描述的标准方法在合成的后期除去。保护基团的实例是叔丁氧羰基(Boc),氨基甲酸9-芴基甲酯

(Fmoc)，氨基甲酸 2- 三甲基甲硅烷基乙酯 (Teoc)，苄氧羰基 (Cbz) 和对甲氧基苄氧基羰基 (Moz)。

[0030] 式 (I) 化合物可以含有几个不对称中心并且可以以光学纯对映异构体，对映异构体的混合物如，例如，外消旋物，非对映异构体的混合物，非对映异构体外消旋物或非对映异构体外消旋物的混合物的形式存在。

[0031] 术语“不对称碳原子”表示具有四个不同取代基的碳原子。按照 Cahn-Ingold-Prelog 规则，不对称碳原子可以具有“R”或“S”构型。

[0032] 本发明尤其涉及以下各项：

[0033] 式 (I) 的化合物，其中 A^1 是 $-S(O)_2-$；

[0034] 式 (I) 的化合物，其中 A^2 是 -(CH)-；

[0035] 式 (I) 的化合物，其中 R^1 是氯，溴，碘或三氟甲基；

[0036] 式 (I) 的化合物，其中 R^2 是卤素；

[0037] 式 (I) 的化合物，其中 R^2 是氯或氟；

[0038] 式 (I) 的化合物，其中 R^3 是氢，卤素或卤代烷基；

[0039] 式 (I) 的化合物，其中 R^3 是卤素；

[0040] 式 (I) 的化合物，其中 R^3 是氯；

[0041] 式 (I) 的化合物，其中 R^4 和 R^6 独立地选自氢和卤代烷基；

[0042] 式 (I) 的化合物，其中 R^4 和 R^6 独立地选自氢和三氟甲基；

[0043] 式 (I) 的化合物，其中 R^5 是氢，烷氧基，卤代烷氧基，卤素，烷基吡啶基或烷基吡唑基；和

[0044] 式 (I) 的化合物，其中 R^5 是氢，甲氧基，三氟乙氧基，氟，三氟丙氧基，溴，甲基吡啶基或甲基吡唑基。

[0045] 本发明还涉及选自以下各项的式 (I) 的化合物：

[0046] (2S,4R)-4-(2- 氯 -4- 甲氧基 - 苯磺酰基)-1-[1-(5- 氯 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺；

[0047] (2S,4R)-4-(2- 氯 - 苯磺酰基)-1-[1-(5- 氯 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺；

[0048] (2S,4R)-1-[1-(5- 氯 - 吡啶 -2- 基)- 环丙烷羰基]-4-[2- 氯 -4-(2,2,2- 三氟 - 乙氧基)- 苯磺酰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺；

[0049] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(2- 氯 -4- 甲氧基 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺；

[0050] (2S,4R)-4-(2- 氯 - 苯磺酰基)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺；

[0051] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-[2- 氯 -4-(2,2,2- 三氟 - 乙氧基)- 苯磺酰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺；

[0052] (2S,4R)-1-[1-(5- 溴 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(2- 氯 -4- 甲氧基 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺；

[0053] (2S,4R)-1-[1-(5- 溴 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(2- 氯 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺；

[0054] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(4′-氟-联苯-3-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0055] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(3-氯-吡啶-2-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0056] (2S,4R)-1-(1-(5-氯-3-氟吡啶-2-基)环丙烷羰基)-4-(2-氯-4-氟苯磺酰基)-N-(1-氰基环丙基)吡咯烷-2-甲酰胺；

[0057] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(吡啶-2-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0058] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(4′-氟-联苯-3-磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0059] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(3-氯-吡啶-2-磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0060] (2S,4S)-4-(2-氯-4-氟-苯磺酰基)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0061] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(3-氯-5-三氟甲基-吡啶-2-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0062] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(5-氯-吡啶-2-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0063] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(吡啶-2-磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0064] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(6-甲基-吡啶-2-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0065] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(5-三氟甲基-吡啶-2-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0066] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(3-三氟甲基-吡啶-2-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0067] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(5-氯-吡啶-2-磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0068] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(6-甲基-吡啶-2-磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0069] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(5-三氟甲基-吡啶-2-磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0070] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(3-三氟甲基-吡啶-2-磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0071] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-氯-5-三氟甲基-苯基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0072] (2S,4R)-1-(1-(5-氯-3-氟吡啶-2-基)环丙烷羰基)-4-(2-氯-4-((S)-1,1,1-三氟丙-2-基氧基)苯磺酰基)-N-(1-氰基环丙基)吡咯烷-2-甲酰胺；

[0073] (2S,4R)-1-(1-(5-氯-3-氟吡啶-2-基)环丙烷羰基)-4-(2-氯-5-(三氟甲基)

苯磺酰基)-N-(1-氰基环丙基)吡咯烷-2-甲酰胺；

[0074] (2S,4R)-1-[1-(5-氯-吡啶-2-基)-环丙烷羰基]-4-(2-氯-5-三氟甲基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0075] (2S,4R)-4-(4-溴-2-氯-苯磺酰基)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0076] (2S,4R)-1-(1-(5-氯-3-氟吡啶-2-基)环丙烷羰基)-4-(2-氯-4-(2-甲基吡啶-4-基)苯磺酰基)-N-(1-氰基环丙基)吡咯烷-2-甲酰胺；

[0077] (2S,4R)-4-[2-氯-4-(2-氯-吡啶-4-基)-苯磺酰基]-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0078] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0079] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-[2-氯-4-(2-甲基-吡啶-3-基)-苯磺酰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0080] (2S,4R)-4-[2-氯-4-(2-甲基-吡啶-3-基)-苯磺酰基]-1-[1-(3-氟-5-三氟甲基-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0081] (2S,4R)-4-[2-氯-4-(2-甲基-吡啶-3-基)-苯磺酰基]-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0082] (2S,4R)-4-[2-氯-4-(2-甲基-吡啶-3-基)-苯磺酰基]-1-[1-(3,5-二氯-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0083] (2S,4R)-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0084] (2S,4R)-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-1-[1-(3-氟-5-三氟甲基-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0085] (2S,4R)-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-1-[1-(3,5-二氯-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0086] (2S,4R)-4-(2-氟-苯磺酰基)-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0087] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-氟-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0088] (2S,4R)-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-4-(2-吡唑-1-基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0089] (2S,4R)-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-4-(2-[1,2,3]三唑-1-基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0090] (2S,4R)-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-4-(2-[1,2,4]三唑-1-基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0091] ((2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-吡唑-1-基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺；

[0092] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-[1,2,3]三

唑 -1- 基 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺 ;和

[0093] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(2-[1,2,4] 三唑 -1- 基 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺。

[0094] 本发明尤其涉及选自以下各项的式 (I) 的化合物 :

[0095] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(2- 氯 -4- 甲氧基 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺 ;

[0096] (2S,4R)-4-(2- 氯 - 苯磺酰基)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺 ;

[0097] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-[2- 氯 -4-(2,2,2- 三氟 - 乙氧基)- 苯磺酰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺 ;

[0098] (2S,4R)-1-[1-(5- 溴 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(2- 氯 -4- 甲氧基 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺 ;

[0099] (2S,4R)-1-[1-(5- 溴 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(2- 氯 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺 ;

[0100] (2S,4R)-1-(1-(5- 氯 -3- 氟吡啶 -2- 基) 环丙烷羰基)-4-(2- 氯 -4- 氟苯磺酰基)-N-(1- 氰基环丙基) 吡咯烷 -2- 甲酰胺 ;

[0101] (2S,4R)-1-(1-(5- 氯 -3- 氟吡啶 -2- 基) 环丙烷羰基)-4-(2- 氯 -4-((S)-1,1,1- 三氟丙 -2- 基氧基) 苯磺酰基)-N-(1- 氰基环丙基) 吡咯烷 -2- 甲酰胺 ;

[0102] (2S,4R)-1-(1-(5- 氯 -3- 氟吡啶 -2- 基) 环丙烷羰基)-4-(2- 氯 -5-(三氟甲基) 苯磺酰基)-N-(1- 氰基环丙基) 吡咯烷 -2- 甲酰胺 ;

[0103] (2S,4R)-4-(4- 溴 -2- 氯 - 苯磺酰基)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺 ;

[0104] (2S,4R)-1-(1-(5- 氯 -3- 氟吡啶 -2- 基) 环丙烷羰基)-4-(2- 氯 -4-(2- 甲基吡啶 -4- 基) 苯磺酰基)-N-(1- 氰基环丙基) 吡咯烷 -2- 甲酰胺 ;

[0105] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-[2- 氯 -4-(1- 甲基 -1H- 吡唑 -4- 基)- 苯磺酰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺 ;

[0106] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-[2- 氯 -4-(2- 甲基 - 吡啶 -3- 基)- 苯磺酰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺 ;

[0107] (2S,4R)-4-[2- 氯 -4-(2- 甲基 - 吡啶 -3- 基)- 苯磺酰基]-1-[1-(3- 氟 -5- 三氟甲基 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺 ;

[0108] (2S,4R)-4-[2- 氯 -4-(2- 甲基 - 吡啶 -3- 基)- 苯磺酰基]-1-[1-(3- 氟 -5- 碘 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺 ;

[0109] (2S,4R)-4-[2- 氯 -4-(2- 甲基 - 吡啶 -3- 基)- 苯磺酰基]-1-[1-(3,5- 二氯 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺 ;

[0110] (2S,4R)-4-[2- 氯 -4-(1- 甲基 -1H- 吡唑 -4- 基)- 苯磺酰基]-1-[1-(3- 氟 -5- 碘 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺 ;

[0111] (2S,4R)-4-[2- 氯 -4-(1- 甲基 -1H- 吡唑 -4- 基)- 苯磺酰基]-1-[1-(3- 氟 -5- 三氟甲基 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺 ;和

[0112] (2S,4R)-4-[2- 氯 -4-(1- 甲基 -1H- 吡唑 -4- 基)- 苯磺酰基]-1-[1-(3,5- 二氯 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺。

[0113] 式 (I) 的化合物可以使用本领域已知的程序制备。式 (I) 的化合物也可以使用以下程序制备。

[0114] 在本说明书中使用以下缩写。

[0115] AcOEt :乙酸乙酯 ;

[0116] ACN :乙腈 ;

[0117] boc :叔丁氧羰基 ;

[0118] BOP :苯并三唑基 -N- 氧基 - 三 (二甲基氨基)- 鏻六氟磷酸盐 ;

[0119] BOP-Cl :双 -(2- 氧代 -3- 噁唑烷基)- 次膦酰氯 ;

[0120] Cbz :苄氧羰基 ;

[0121] CDI :1,1’- 羰基二咪唑 ;

[0122] DCM :二氯甲烷

[0123] DIEA :二异丙基乙胺 ;

[0124] DMAP :4- 二甲基氨基吡啶 ;

[0125] DMF :N,N- 二甲基甲酰胺 ;

[0126] EDCI :N-(3- 二甲基氨基丙基)-N’- 乙基 - 碳二亚胺盐酸盐 ;

[0127] EtOAc :乙酸乙酯 ;

[0128] Fmoc :9- 芴甲氧羰基 ;

[0129] h :小时 ;

[0130] HATU :O-(7- 氮杂苯并三唑 -1- 基)-1,1,3,3- 四甲基脲鎓六氟磷酸盐 ;

[0131] HOBT :1- 羟基苯并三唑 ;

[0132] 许尼希碱 :乙基 - 二异丙基 - 胺

[0133] KHMDS :双 (三甲基甲硅烷基) 氨基化钾

[0134] LDA :二异丙基氨基化锂

[0135] LHMDS :双 (三甲基甲硅烷基) 氨基化锂

[0136] mCPBA 或 MCPBA :间氯过氧苯甲酸 ;

[0137] MeOH :甲醇 ;

[0138] Mes-Cl :甲磺酰氯 ;

[0139] min :分钟 ;

[0140] Moz :甲氧基苄基羰基 ;

[0141] Na_2SO_4:硫酸钠 ;

[0142] Nos-Cl :3- 硝基苯磺酰氯 ;

[0143] $Pd_2(dba)_3$:三 (二亚苄基丙酮) 二钯 ;

[0144] PyBOP :苯并三唑 -1- 基 - 氧基三吡咯烷鏻六氟磷酸盐 ;

[0145] TBTU :O-(苯并三唑 -1- 基)-N,N,N’,N’- 四甲基脲鎓四氟硼酸盐 ;

[0146] Teoc :三甲基甲硅烷基乙氧基羰基 ;

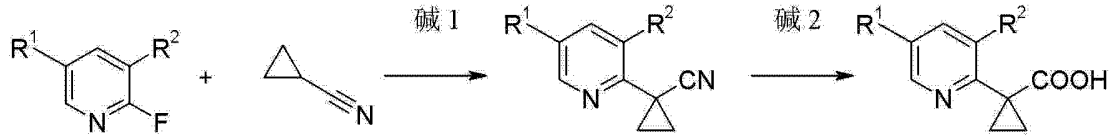
[0147] THF :四氢呋喃 ;

[0148] TFA :三氟乙酸 ;和

[0149] Tos-Cl :甲苯 -4- 磺酰氯。

[0150] 方案 1

[0151]



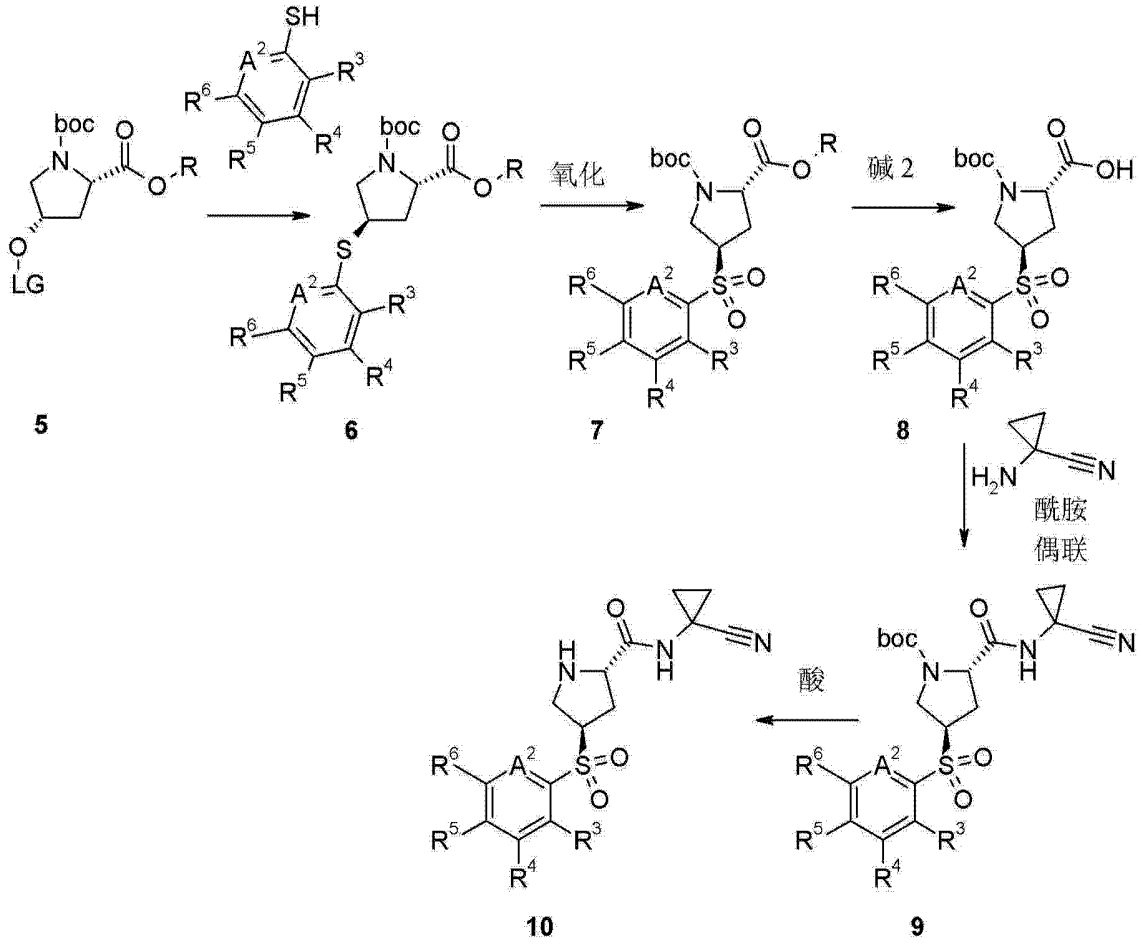
1 2 3 4

[0152] R^1-R^2如上文定义 ;碱 1 是例如 NaOtBu, KOtBu, NaH, LiHMDS, KHMDS 或 LDA ;碱 2 是例如 LiOH, NaOH 或 KOH。

[0153] 在碱 (如上文定义的碱 1) 存在下将吡啶衍生物如 1 用环丙烷甲腈 2 处理获得吡啶衍生物 3。将化合物 3 用碱 (如上文定义的碱 2) 处理, 获得最终的羧酸衍生物 4, 为游离酸或为其盐。

[0154] 方案 2

[0155]



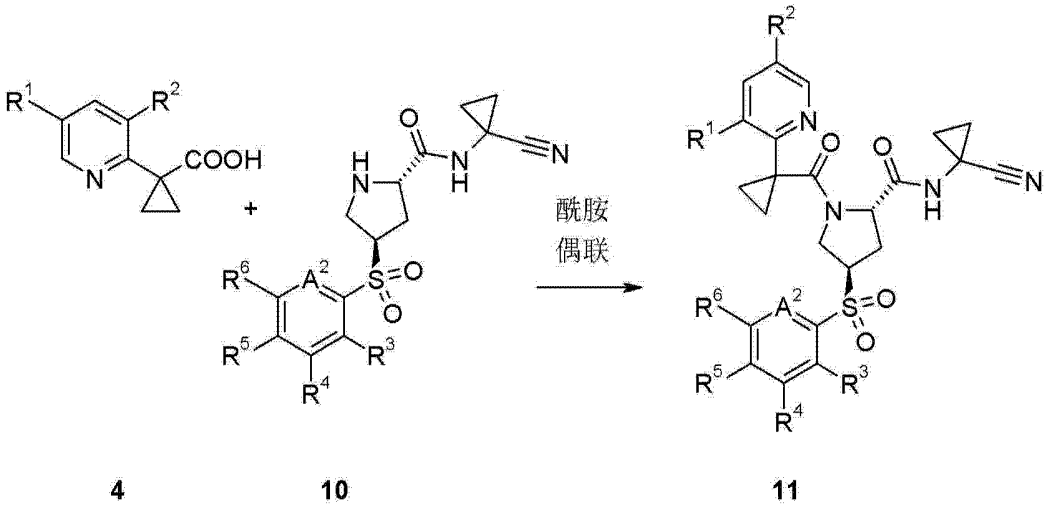
5 6 7 8 9 10

[0156] LG 是离去基团诸如三氟甲磺酸根、甲磺酸根、甲苯磺酸根、对溴苯磺酸根或硝基苯磺酸根 (nosylate) ;A^2和 R^3-R^6如上文定义 ;R 是例如甲基, 乙基, 异丙基或苄基。

[0157] 将Boc保护的脯氨酸衍生物5与苯基硫醇衍生物在碱如三乙胺、DIEA、2,6-二甲基吡啶等存在下反应以产生硫醚衍生物6。6用过氧化物试剂如H_2O_2、过硫酸氢钾制剂、mCPBA的氧化产生砜衍生物7。用碱如LiOH,NaOH或KOH将酯皂化为酸,产生相应羧酸8或其盐。通过将8与1-氨基甲腈衍生物与偶联剂,如EDCI,CDI,BOP-Cl,TBTU,HATU,PyBOP或BOP,在碱如DIEA,三乙胺或二甲基吡啶存在下反应完成酰胺偶联,从而产生酰胺9。最后,通过用酸如如TFA,HCl在有机溶剂(例如AcOEt,二噁烷)中或甲酸处理化合物9去除Boc-保护基团,产生胺10。

[0158] 方案3

[0159]



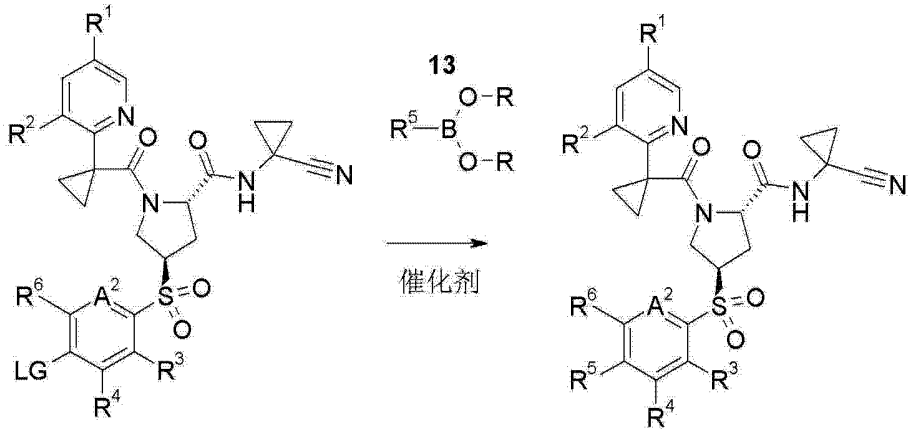
4 10 11

[0160] A^2和R^1-R^6如上文中定义。

[0161] 将羧酸4与胺10在酰胺偶联剂之一如EDCI,CDI,BOP-Cl,TBTU,HATU,PyBOP或BOP存在下,在碱诸如DIEA,三乙胺或2,6-二甲基吡啶存在下反应,产生酰胺11。

[0162] 方案4

[0163]



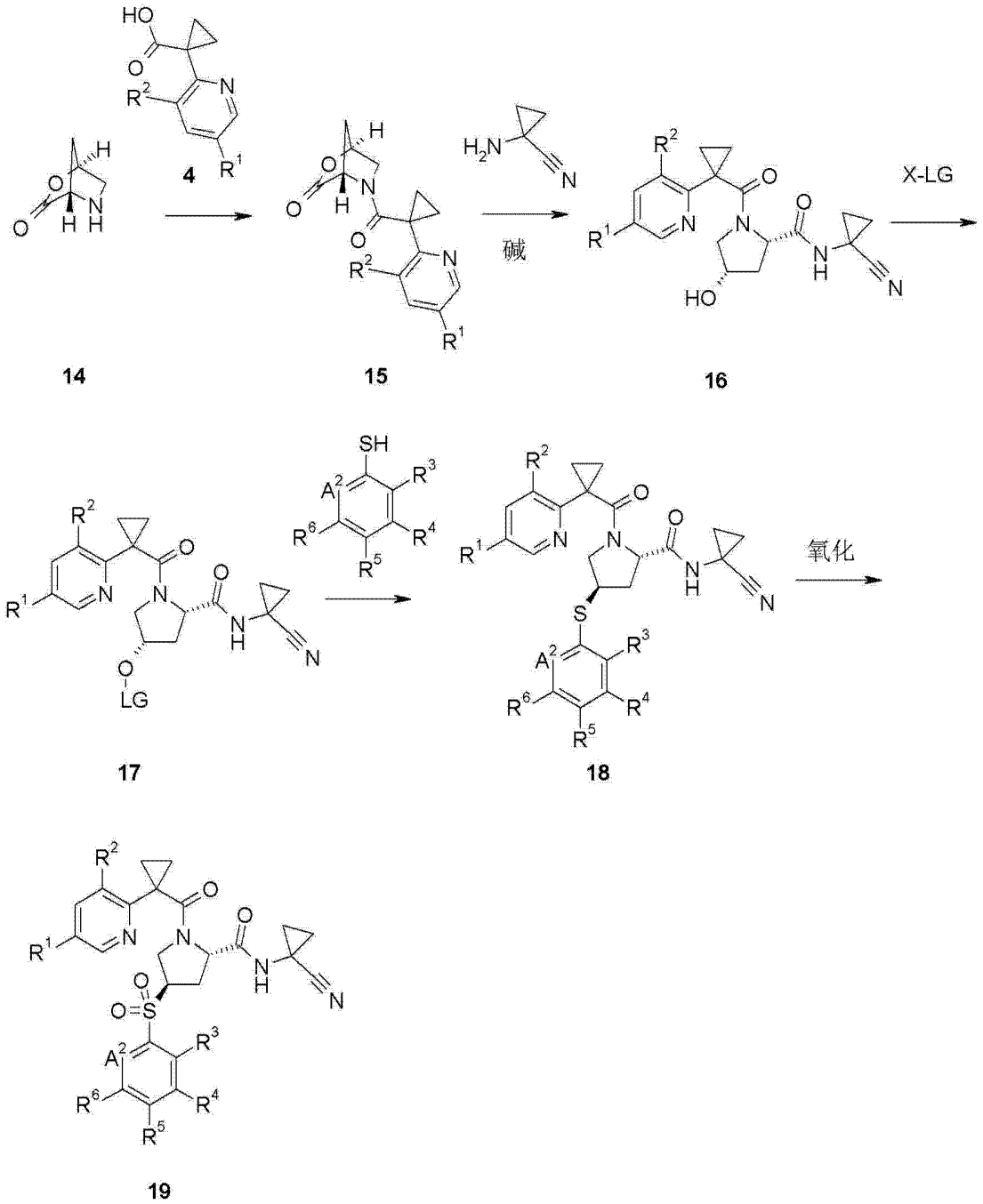
12 11

[0164] R^1-R^4和R^6如上文定义;LG是离去基团如Cl,Br,I;R^5是如上文定义的苯基,取代的苯基,杂环基或取代的杂环基;R是H或甲基,或两个R与其连接的硼原子一起形成2,4,4,5,5-五甲基-[1,3,2]二氧杂硼杂环戊烷。

[0165] 将化合物 12 与硼酸或酯衍生物 13 在碱如 Na_2CO_3，K_2CO_3，Cs_2CO_3，KOtBu，K_3PO_4，和本领域已知的用于进行 Suzuki 反应的催化剂如例如 $Pd(PPh_3)_4$，$Pd_2(dba)_3$或具有膦配体的 Pd- 源存在下反应，产生联芳衍生物 11。

[0166] 方案 5

[0167]



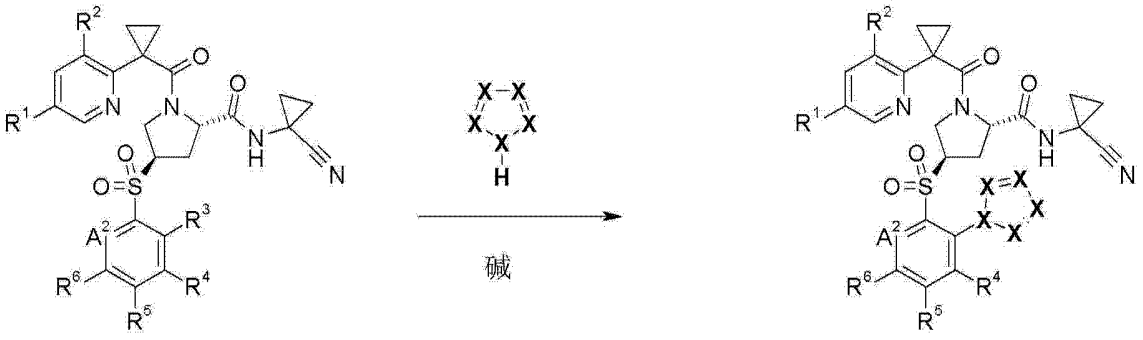
[0168] LG 是离去基团如三氟甲磺酸根、甲磺酸根、甲苯磺酸根、对溴苯磺酸根或硝基苯磺酸根；A^2和 R^1-R^6如上文定义；X 是 F，Cl，Br，I 或 X = O-LG。

[0169] 将氨基内酯 14 或其相应盐如盐酸盐、氢溴酸盐、磷酸盐、磷酸氢盐、硫酸盐、硫酸氢盐、甲磺酸盐等与羧酸 4 在酰胺偶联剂如 EDCI，CDI，BOP-Cl，TBTU，HATU，PyBOP 或 BOP 存在下，在碱如 DIEA，三乙胺，2，6- 二甲基吡啶存在下，或备选地在酰卤如光气，三光气，草酰

氯或亚硫酰氯存在下反应，产生酰胺 15。由胺打开内酯 15 在适当的碱如 2- 乙基己酸钠，TEA，DIEA，DMAP，2，6- 二甲基吡啶或吡啶存在下进行，产生醇 16。将化合物 16 在碱如 TEA，DIEA，DMAP，2，6- 二甲基吡啶或吡啶存在下用 X-LG 处理，产生中间体 17，随后将其与硫醇反应，产生硫醚 18。硫醚 18 至砜 19 的氧化通过将 18 与氧化剂如 H_2O_2，过硫酸氢钾制剂，MCPBA 反应实现。

[0170] 方案 6

[0171]



20 21

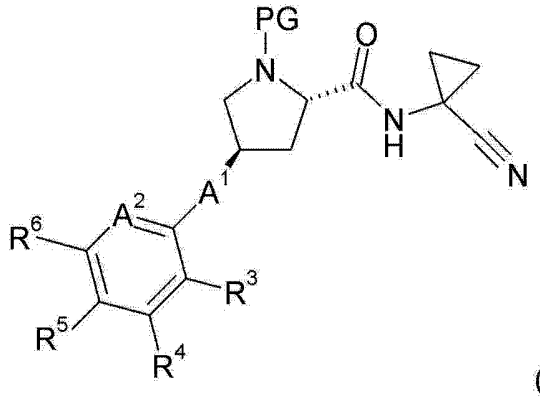
[0172] R^3是离去基团如 F，Cl，或 S(O) $_2$-Me ；X 或是 N 或是 CH ；碱是无机碱如 Na_2CO_3，K_2CO_3，Cs_2CO_3或有机碱如 DIEA，三乙胺或 2，6- 二甲基吡啶。

[0173] 将化合物 20 溶解在适当溶剂如 DMF，DMA 或 THF 中，将如上文定义的碱和含氮 5- 元杂环加入反应混合物中。最初将混合物在室温搅拌并随后加热至从 30-100℃升高的温度，直到反应完成。

[0174] 本发明还涉及一种用于制备如上所定义的式 (I) 的化合物的方法，所述方法包括以下步骤中的一个 ：

[0175] (a) 在酸存在下，式 (A) 的化合物的反应，

[0176]

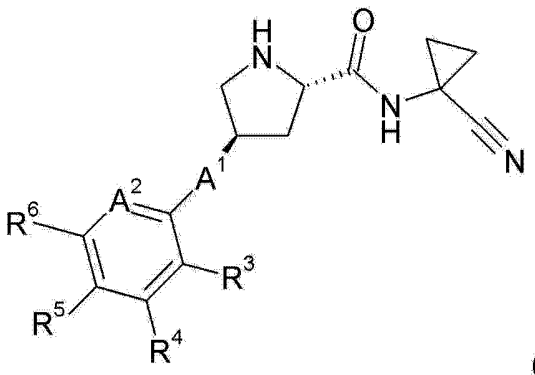


(A)

[0177] 其中 A^1，A^2和 R^1至 R^6如上文定义并且其中 PG 是胺保护基团 ；

[0178] (b) 在碱和酰胺偶联剂和碱存在下，式 (B1) 的化合物

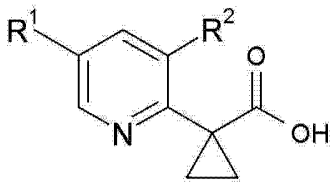
[0179]



(B1)

[0180] 与式 (B2) 的化合物的反应，

[0181]

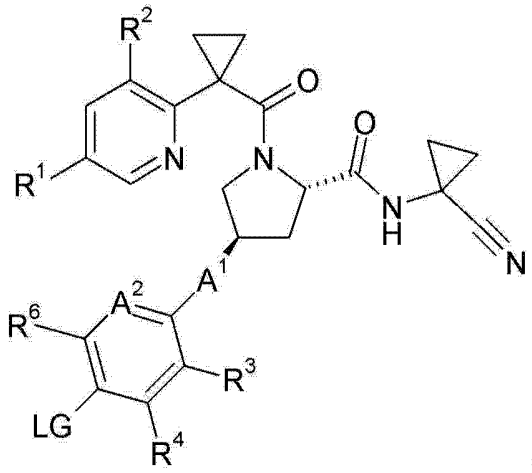


(B2)

[0182] 其中 A^1，A^2 和 R^1 至 R^6 如上文定义；

[0183] (c) 在 $R^5B(OR)_2$，碱和 Suzuki 催化剂存在下，式 (C) 的化合物的反应，

[0184]

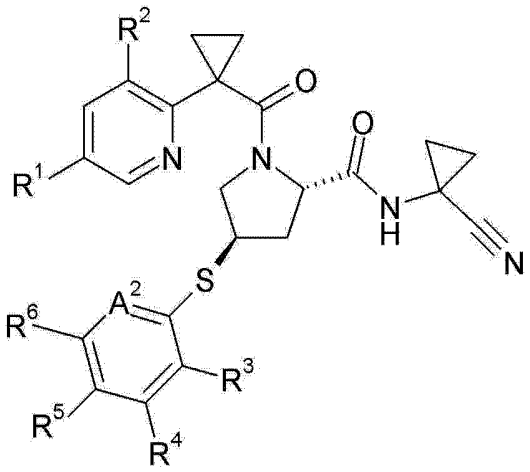


(C)

[0185] 其中 A^1，A^2 和 R^1 至 R^4 和 R^6 如上文定义，LG 是离去基团，R^5 是烷基吡啶基，卤代吡啶基或烷基吡唑基，并且 R 是氢或甲基，或两个 R 与其连接的硼原子一起形成 2,4,4,5,5- 五甲基 -[1,3,2] 二氧杂硼杂环戊烷；或

[0186] (d) 在氧化剂存在下，式 (D) 的化合物的反应，

[0187]



(D)

[0188] 其中其中 A^1和 R^1至 R^5如上文定义。

[0189] 步骤 (a) 中，酸是例如 TFA，HCl 或甲酸。

[0190] 步骤 (a) 中，胺保护基团是例如 boc，Fmoc，Cbz，Teoc，苄基或 Moz。

[0191] 步骤 (b) 中，酰胺偶联剂是例如 EDCI，CDI，BOP-Cl，TBTU，HATU，PyBOP 或 BOP。

[0192] 步骤 (b) 中，碱是例如 DIEA，三乙胺或 2,6- 二甲基吡啶。

[0193] 步骤 (c) 中，离去基团是例如 Cl，Br 或 I。

[0194] 步骤 (c) 中，碱是例如 Na_2CO_3，K_2CO_3，Cs_2CO_3，KOtBu 或 K_3PO_4。

[0195] 步骤 (c) 中，Suzuki 催化剂例如 $Pd(PPh_3)_4$，$Pd_2(dba)_3$或具有膦配体的 Pd- 源。

[0196] 步骤 (d) 中，氧化剂是例如 H_2O_2，过硫酸氢钾制剂或 MCPBA。

[0197] 根据本发明的以上方法制备的式 (I) 的化合物也是本发明的目的。

[0198] 式 (I) 的化合物和它们的药用盐可以作为药物使用（例如以药物制剂的形式）。可以将该药物制剂内服给药，如经口（例如以片剂、包衣片剂、糖锭剂、硬和软明胶胶囊、溶液、乳剂或混悬剂）的形式、经鼻（例如以鼻喷雾剂的形式）或经直肠（例如以栓剂的形式）。然而，给药还可以肠胃外实现，如肌肉内或静脉内（例如以注射液的形式）。

[0199] 式 (I) 的化合物和它们的药用盐可与药学上惰性的无机或有机辅剂一起加工用于片剂、包衣片剂、糖锭剂和硬明胶胶囊的制造。可以使用乳糖、玉米淀粉或其衍生物、滑石、硬脂酸或其盐等，例如，作为用于片剂、糖锭剂和硬明胶胶囊的这种辅剂。

[0200] 用于软明胶胶囊的合适的辅剂是，例如，植物油、蜡、脂肪、半固体物质和液体多元醇。

[0201] 用于制备溶液和糖浆的合适的辅剂是，例如，水、多元醇、蔗糖、转化糖和葡萄糖。

[0202] 用于注射液的合适的辅剂是，例如，水、醇、多元醇、甘油和植物油。

[0203] 用于栓剂的合适的辅剂是，例如，天然或硬化油、蜡、脂肪、半固体和液体多元醇。

[0204] 此外，药物制剂可以含有防腐剂、增溶剂、粘度增加物质、稳定剂、润湿剂、乳化剂、甜味剂、着色剂、食用香料、用于改变渗透压的盐、缓冲剂、掩蔽剂或抗氧化剂。它们仍然还可以含有其他的治疗上有价值的物质。

[0205] 本发明因此还特别涉及以下各项：

[0206] 式 (I) 的化合物，所述式 (I) 的化合物用作治疗活性物质；

[0207] 一种药物组合物，所述药物组合物包含式 (I) 的化合物和治疗惰性载体；

[0208] 式 (I) 的化合物在制备药物中的用途，所述药物用于治疗或预防糖尿病，动脉粥样硬化，腹主动脉瘤，外周动脉疾病，癌症，慢性肾病中的心血管事件的减少，糖尿病性肾病，糖尿病性视网膜病或老年性黄斑变性；

[0209] 式 (I) 的化合物，所述式 (I) 的化合物用于治疗或预防糖尿病，动脉粥样硬化，腹主动脉瘤，外周动脉疾病，癌症，慢性肾病中的心血管事件的减少，糖尿病性肾病，糖尿病性视网膜病或老年性黄斑变性；和

[0210] 一种用于治疗或预防糖尿病，动脉粥样硬化，腹主动脉瘤，外周动脉疾病，癌症，慢性肾病中心血管事件的减少，糖尿病性肾病，糖尿病性视网膜病或老年性黄斑变性的方法，所述方法包括给药有效量的式 (I) 的化合物。

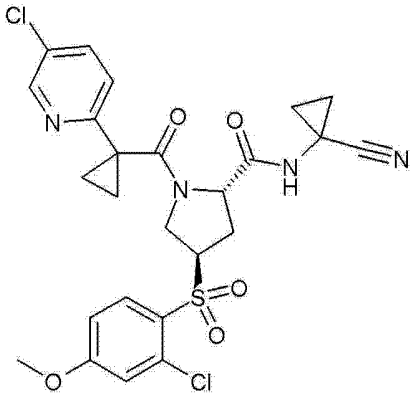
[0211] 将用不具有限制特性的以下实施例描述本发明。

[0212] 实施例

[0213] 实施例 1

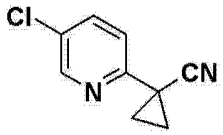
[0214] (2S,4R)-4-(2- 氯 -4- 甲氧基 - 苯磺酰基)-1-[1-(5- 氯 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0215]



[0216] a)1-(5- 氯 - 吡啶 -2- 基)- 环丙烷甲腈

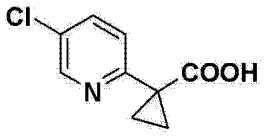
[0217]



[0218] 在 0℃向 5- 氯 -2- 氟吡啶 (2g,1.53ml,15.2mmol,Eq :1.00) 和环丙烷甲腈 (1.02g,1.15ml,15.2mmol,Eq :1.00) 在甲苯 (20.0ml) 中的溶液经 5min 逐滴加入在甲苯中的 KHMDS 0.5M(30.4ml,15.2mmol,Eq :1.00)。溶液变成棕色。45min 之后，将反应混合物加温至 22℃并搅拌 2.5h。随后加入饱和 NH_4Cl 水溶液 (50ml) 并且将水相用 AcOEt(3x 60ml) 萃取。将合并的有机相经 Na_2SO_4 干燥，过滤并在减压下浓缩。将粗制材料通过急骤色谱 (硅胶，70g，庚烷中 0％至 20％ EtOAc) 纯化，获得标题化合物，为白色固体 (840mg ;31％)。m/z ＝ 179.0373$[M+H]^+$。

[0219] b)1-(5- 氯 - 吡啶 -2- 基)- 环丙烷甲酸

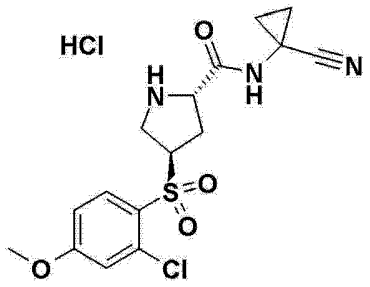
[0220]



[0221] 将化合物 1a)(600mg,3.36mmol,Eq :1.00) 溶解在 1％ KOH 水溶液 (18ml,207mg,3.7mmol,Eq :1.1) 中。将反应混合物在 100℃搅拌 17h。将粗反应混合物在真空中浓缩并酸化至 pH 4。将粗制材料通过制备型 HPLC 纯化,获得标题化合物,为白色固体 (339mg ;51％)。m/z ＝ 198.1[M+H]$^+$。

[0222] c)(2S,4R)-4-(2- 氯 -4- 甲氧基 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺 HCl- 盐

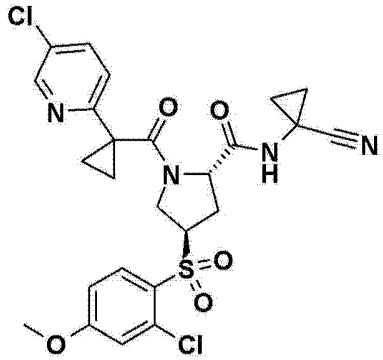
[0223]



[0224] 将 CAS 1252640-17-7(600mg,1.24mmol,Eq :1.00) 溶解在 HCl/ 二噁烷 (1.55ml,6.2mmol,Eq :5.00) 中并在 22℃搅拌 4h。将粗反应混合物在真空中浓缩,获得白色固体 (309mg ;65％),其无需进一步纯化即使用。m/z ＝ 384.2[M+H]$^+$。

[0225] d)(2S,4R)-4-(2- 氯 -4- 甲氧基 - 苯磺酰基)-1-[1-(5- 氯 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0226]

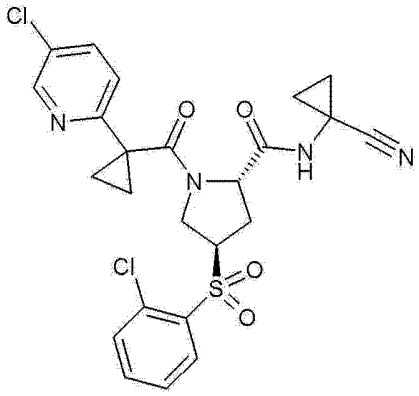


[0227] 将实施例 1b)(61.8mg,313μmol,Eq :1.20) 溶解在 DMF(2ml) 中。将 HATU(198mg,521μmol,Eq :2.00),DIEA(67.3mg,91.0μl,521μmol,Eq :2.00) 和实施例 1c)(100mg,261μmol,Eq :1.00) 加入溶液中并在 22℃搅拌 15h。将粗制材料通过制备型 HPLC 纯化,获得标题化合物,为白色固体 (106mg ;72％)。m/z ＝ 563.2[M+H]$^+$。

[0228] 实施例 2

[0229] (2S,4R)-4-(2- 氯 - 苯磺酰基)-1-[1-(5- 氯 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0230]

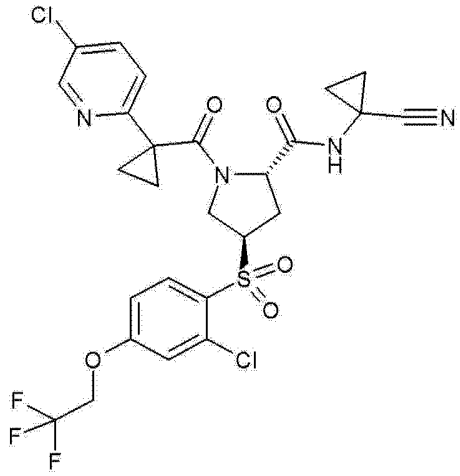


[0231] 类似于实施例 1 从 CAS 1252638-10-0 开始制备实施例 2，获得标题化合物，为白色固体 (106mg ;72％)。m/z ＝ 533.2[M+H]$^+$。

[0232] 实施例 3

[0233] (2S,4R)-1-[1-(5- 氯 - 吡啶 -2- 基)- 环丙烷羰基]-4-[2- 氯 -4-(2,2,2- 三氟 - 乙氧基)- 苯磺酰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0234]

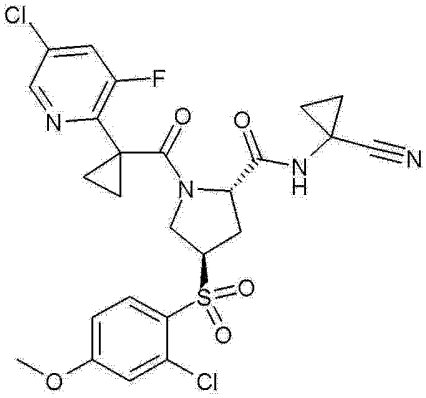


[0235] 类似于实施例 1 从 CAS 1252634-04-0 开始制备实施例 3，获得标题化合物，为白色固体 (50mg ;36％)。m/z ＝ 631.1[M+H]$^+$。

[0236] 实施例 4

[0237] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(2- 氯 -4- 甲氧基 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0238]

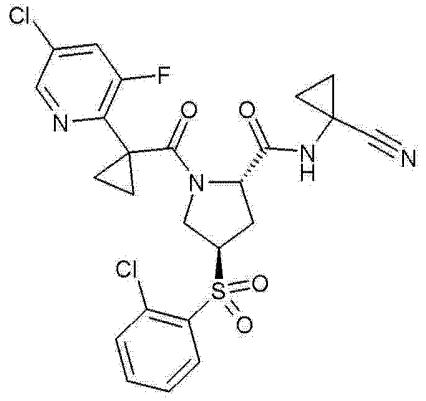


[0239] 类似于实施例 1 中描述的方法，从 5- 氯 -2,3- 二氟吡啶和实施例 1c) 开始制备实施例 4，获得标题化合物，为白色固体 (45mg ;30％)。m/z ＝ 581.1[M+H]$^+$。

[0240] 实施例 5

[0241] (2S,4R)-4-(2- 氯 - 苯磺酰基)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0242]

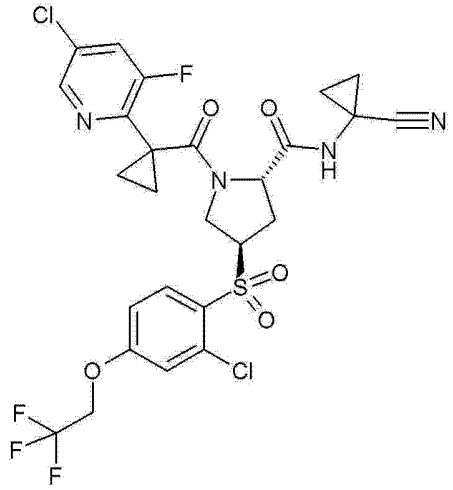


[0243] 类似于实施例 1 中描述的方法，从 5- 氯 -2,3- 二氟吡啶和 CAS1252638-10-0 开始制备实施例 5，获得标题化合物，为白色固体 (99mg ;64％)。m/z ＝ 551.1[M+H]$^+$。

[0244] 实施例 6

[0245] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-[2- 氯 -4-(2,2,2- 三氟 - 乙氧基)- 苯磺酰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0246]

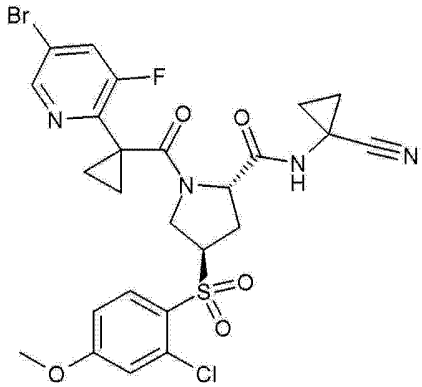


[0247] 类似于实施例 1 中描述的方法，从 5- 氯 -2,3- 二氟吡啶和 CAS1252634-04-0 开始制备实施例 6，获得标题化合物，为白色固体 (114mg ;79％)。m/z ＝ 649.2[M+H]$^+$。

[0248] 实施例 7

[0249] (2S,4R)-1-[1-(5- 溴 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(2- 氯 -4- 甲氧基 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0250]

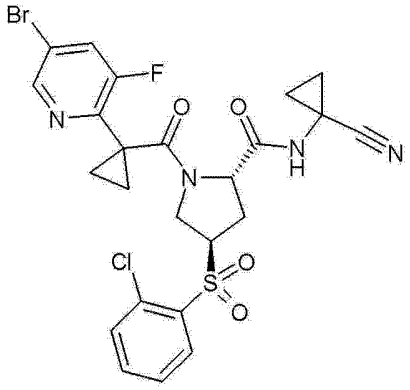


[0251] 类似于实施例 1 中描述的方法，从 5- 溴 -2,3- 二氟吡啶和实施例 1c) 开始制备实施例 7，获得标题化合物，为白色固体 (14mg ;17％)。m/z ＝ 627.0[M+H]$^+$。

[0252] 实施例 8

[0253] (2S,4R)-1-[1-(5- 溴 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(2- 氯 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0254]

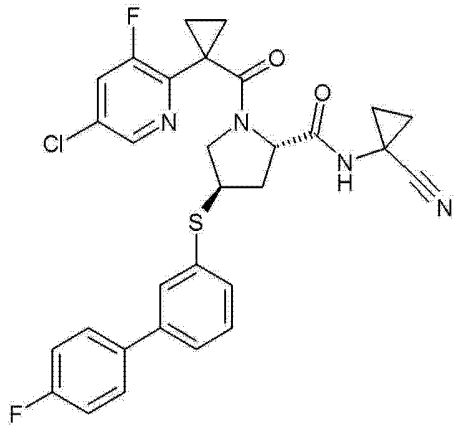


[0255] 类似于实施例 1 中描述的方法，从 5- 溴 -2,3- 二氟吡啶和 CAS1252638-10-0 开始制备实施例 8，获得标题化合物，为白色泡沫 (48mg ;57％)。m/z ＝ 597.0[M+H]$^+$。

[0256] 实施例 9

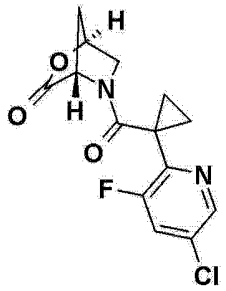
[0257] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(4′ - 氟 - 联苯 -3- 基硫基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0258]



[0259] a)(1S,4S)-5-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-2- 氧杂 -5- 氮杂 - 双环 [2.2.1] 庚 -3- 酮

[0260]

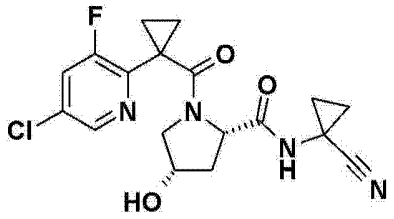


[0261] 在 25℃，向类似于实施例 1b) 制备的 5- 氯 -3- 氟 - 吡啶 -2- 甲酸 (670mg, 3.11mmol，Eq :1.00) 在甲苯 (6ml) 中的乳状悬浮液中，加入 DMF(11.4mg,12.0μl, 155μmol，Eq :0.05)。将混合物冷却至 0℃，随后在 10min 内滴入草酰氯 (434mg,299μl, 3.42mmol,Eq :1.10) 在甲苯 (2.00ml) 中的溶液。将反应混合物在 0℃搅拌 30min，然后无冷却下搅拌 3h。在 0℃，将 (1S,4S)-2- 氧杂 -5- 氮杂 - 双环 [2.2.1] 庚 -3- 酮甲磺酸酯 (CAS 769167-53-5)(650mg,3.11mmol，Eq :1.00) 和 THF(4.00ml) 加入反应混合物，接着在 10min

内滴入 TEA(1.18g,1.62ml,11.7mmol,Eq :3.75)(放热的)。将混合物在 22℃搅拌 16h。将反应混合物倒入 20％柠檬酸水溶液 (25ml) 中并用 EtOAc(3x20ml) 萃取。将有机层经 Na_2SO_4 干燥并在真空中浓缩。将粗制材料通过急骤色谱 (硅胶,40g,庚烷中 0％至 50％ EtOAc) 纯化,获得标题化合物,为橙色油状物 (850mg ;88％)。m/z ＝ 311.1[M+H]$^+$。

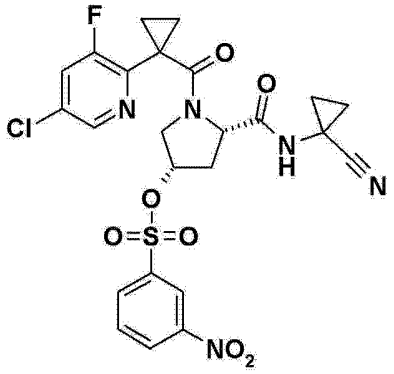
[0262] b)(2S,4S)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 甚)- 环丙烷羰基]-4- 羟基 - 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0263]



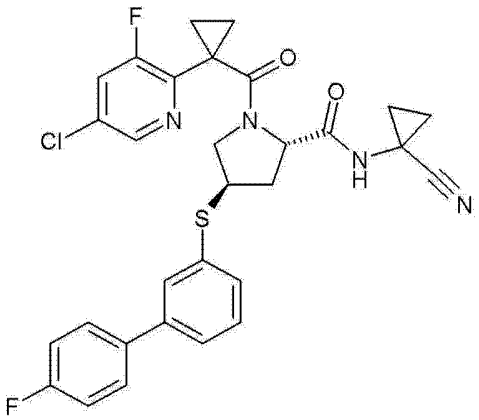
[0264] 将实施例 9a)(850mg,2.74mmol, Eq :1.00),1- 氨基环丙烷甲腈盐酸盐 (422mg,3.56mmol, Eq :1.30),2- 乙基己酸钠 (705mg,4.24mmol, Eq :1.55) 在水 (3ml) 和 THF(2.00ml) 中的混合物在 55℃搅拌 18h。向反应混合物加入盐酸 (189mg,157μl,1.91mmol,Eq :0.70) 和氯化钠 (1.36g,1.36ml,23.3mmol,Eq :8.50)。将混合物搅拌 15min,随后倒入 AcOEt(25ml) 中并萃取。将水层用 AcOEt(3x20ml) 反萃取。将有机层经 Na_2SO_4 干燥并在真空中浓缩。将粗制材料通过急骤色谱 (硅胶,40g,庚烷中 0％至 90％ EtOAc) 纯化,获得标题化合物,为白色泡沫 (560mg ;52％)。m/z ＝ 393.0[M+H]$^+$。c)3- 硝基 - 苯磺酸 (3S,5S)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-5-(1- 氰基 - 环丙基氨甲酰基)- 吡咯烷 -3- 基酯

[0265]



[0266] 将实施例 9b)(560mg,1.43mmol, Eq :1.00) 溶解在 DCM(15ml) 中并加入 3- 硝基苯 -1- 磺酰氯 (335mg,1.51mmol, Eq :1.06)。将混合物冷却至 0℃并且用注射器缓慢且小心地加入 TEA(433mg,596μl,4.28mmol, Eq :3.00)。去除冰浴并将反应混合物在 25℃搅拌 18h。将反应混合物用 10％ Na_2CO_3 水溶液和 0.1N HCl 水溶液萃取。将有机层经 Na_2SO_4 干燥,过滤并蒸发。将粗制材料通过急骤色谱 (硅胶,40g,庚烷中 0％至 85％ EtOAc) 纯化,获得标题化合物,为灰白色固体 (510mg ;62％)。m/z ＝ 578.0[M+H]$^+$。d)(2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(4′ - 氯 - 联苯 -3- 基硫基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0267]

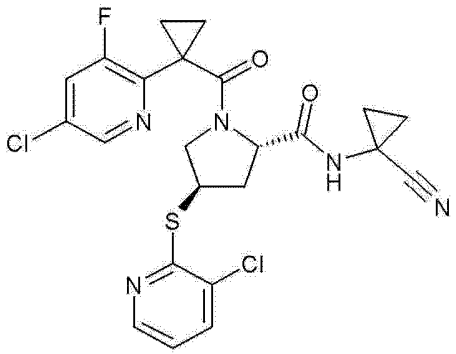


[0268] 将实施例 9c)(70mg,121μmol,Eq:1.00)和 4′-氟联苯-3-硫醇(27.2mg,133μmol,Eq:1.10)溶解在丙腈(1ml)中。加入 TEA(30.6mg,42.2μl,303μmol,Eq:2.50)并将反应混合物在 90℃搅拌 3h。将反应混合物倒入 0.1M HCl 水溶液(10ml)中并用 EtOAc(3x10ml)萃取。将有机层合并,经 Na_2SO_4 干燥并在真空中浓缩。将粗制材料通过急骤色谱(硅胶,10g,庚烷中 0%至 66% EtOAc)纯化,获得标题化合物,为米黄色油状物(46mg;68%)。m/z = 579.1[M+H]$^+$。

[0269] 实施例 10

[0270] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(3-氯-吡啶-2-基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺

[0271]

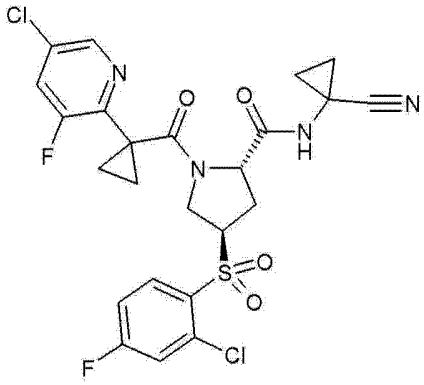


[0272] 类似于实施例 9 中描述的方法,从 3-氯吡啶-2-硫醇和实施例 9c)开始制备实施例 10,获得标题化合物,为浅黄色油状物(50mg;79%)。m/z = 522.0[M+H]$^+$。

[0273] 实施例 11

[0274] (2S,4R)-1-(1-(5-氯-3-氟吡啶-2-基)环丙烷羰基)-4-(2-氯-4-氟苯磺酰基)-N-(1-氰基环丙基)吡咯烷-2-甲酰胺

[0275]

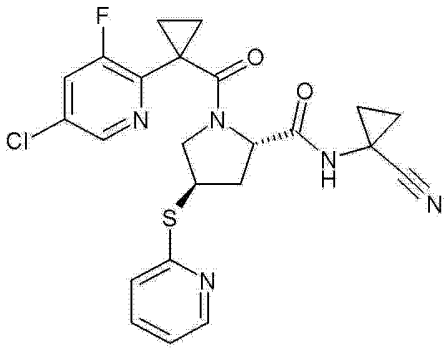


[0276] 类似于实施例 1 中描述的方法，从 5- 氯 -2,3- 二氟吡啶和 CAS1252633-65-0 开始制备实施例 11，获得标题化合物，为白色固体 (46mg ;30％)。m/z ＝ 569.0632[M+H]$^+$。

[0277] 实施例 12

[0278] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(吡啶 -2- 基硫基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0279]

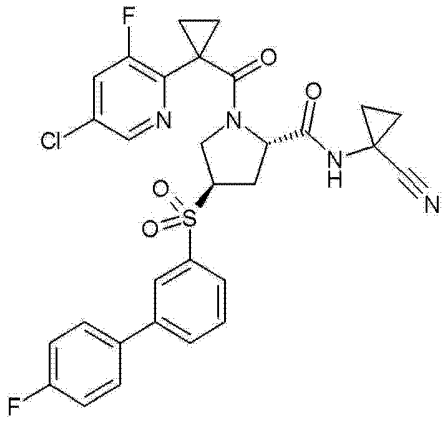


[0280] 类似于实施例 9 中描述的方法，从吡啶 -2- 硫醇和实施例 9c) 开始制备实施例 12，获得标题化合物，为无色油状物 (4mg ;7％)。m/z ＝ 486.1[M+H]$^+$。

[0281] 实施例 13

[0282] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(4′ - 氟 - 联苯 -3- 磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0283]



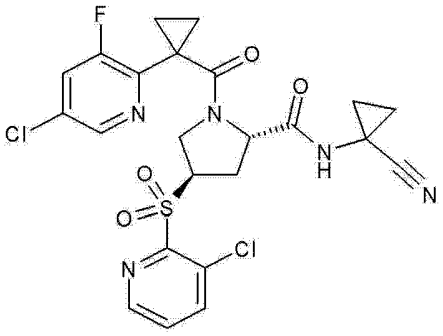
[0284] 将实施例 9(41mg,70.8μmol,Eq :1.00) 溶解在 DCM(1ml) 中并加入 mCPBA(25.7mg,149μmol,Eq :2.10)。将反应混合物在 22℃搅拌 3h。将反应混合物倒入 10％ Na_2CO_3(5ml)

水溶液中并用 DCM(3x5ml) 萃取。将有机层经 Na_2SO_4 干燥，过滤并在真空中浓缩，获得标题化合物，为白色固体 (42mg ;97％)。m/z ＝ 611.0$[M+H]^+$。

[0285] 实施例 14

[0286] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(3- 氯 - 吡啶 -2- 磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0287]

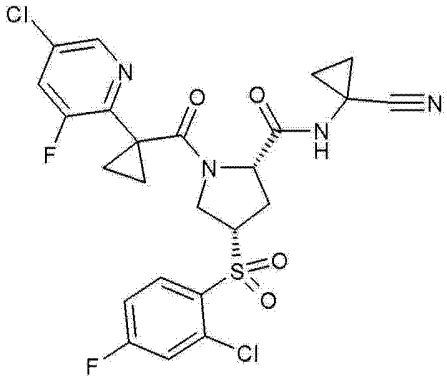


[0288] 类似于实施例 13 中描述的方法，从实施例 10 开始制备实施例 14，获得标题化合物，为白色固体 (44mg ;99％)。m/z ＝ 552.1$[M+H]^+$。

[0289] 实施例 15

[0290] (2S,4S)-4-(2- 氯 -4- 氟 - 苯磺酰基)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0291]

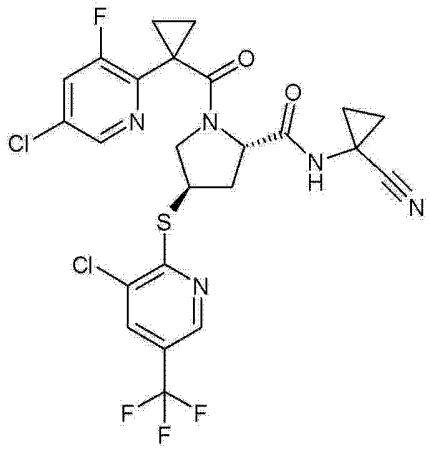


[0292] 获得实施例 15，为实施例 11 合成过程中的副产物，为浅黄色固体 (36mg ;21％)。

[0293] 实施例 16

[0294] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(3- 氯 -5- 三氟甲基 - 吡啶 -2- 基硫基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0295]

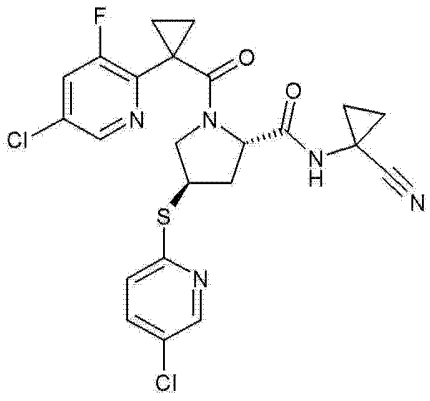


[0296] 类似于实施例 9 中描述的方法，从 3- 氯 -5-(三氟甲基) 吡啶 -2- 硫醇和实施例 9c) 开始制备实施例 16，获得标题化合物，为浅黄色油状物 (4mg ;5％)。m/z ＝ 585.9[M+H]$^+$。

[0297] 实施例 17

[0298] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(5- 氯 - 吡啶 -2- 基硫基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0299]

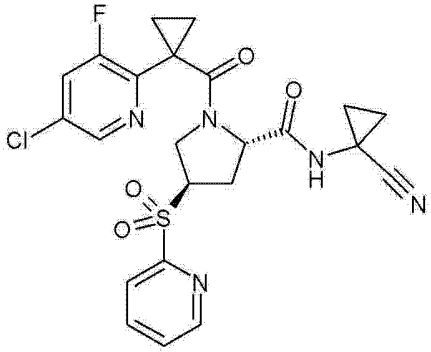


[0300] 类似于实施例 9 中描述的方法，从 5- 氯吡啶 -2- 硫醇和实施例 9c) 开始制备实施例 17，获得标题化合物，为灰白色固体 (30mg ;83％)。m/z ＝ 522.0[M+H]$^+$。

[0301] 实施例 18

[0302] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(吡啶 -2- 磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0303]



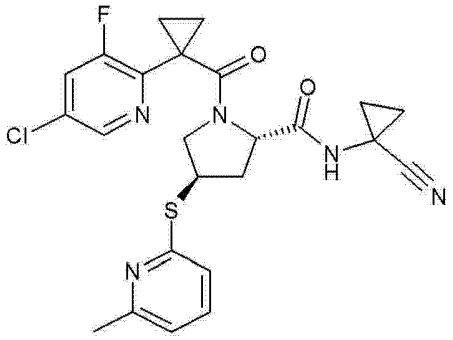
[0304] 类似于实施例 13 中描述的方法，从实施例 10 开始制备实施例 18，获得标题化合

物，为灰白色固体 (3mg ;94％)。m/z ＝ 518.1[M+H]$^+$。

[0305] 实施例 19

[0306] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(6- 甲基 - 吡啶 -2- 基硫基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0307]

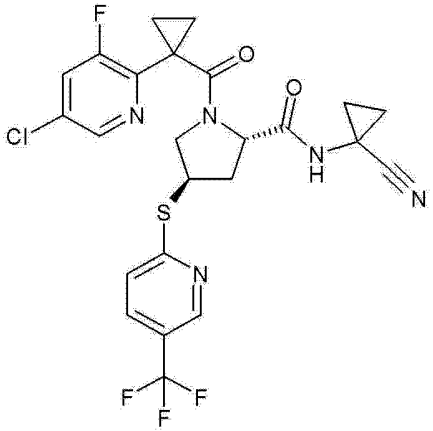


[0308] 类似于实施例 9 中描述的方法，从 6- 甲基吡啶 -2- 硫醇和实施例 9c) 开始制备实施例 19，获得标题化合物，为灰白色固体 (17mg ;49％)。m/z ＝ 500.1[M+H]$^+$。

[0309] 实施例 20

[0310] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(5- 三氟甲基 - 吡啶 -2- 基硫基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0311]

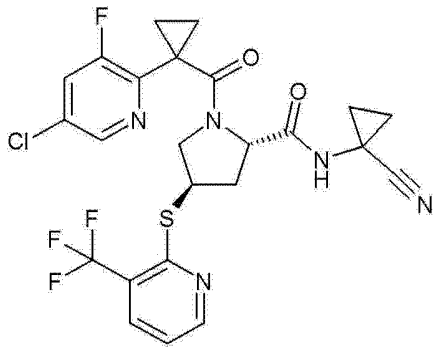


[0312] 类似于实施例 9 中描述的方法，从 5-(三氟甲基) 吡啶 -2- 硫醇和实施例 9c) 开始制备实施例 20，获得标题化合物，为浅黄色固体 (32mg ;84％)。m/z ＝ 554.1[M+H]$^+$。

[0313] 实施例 21

[0314] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(3- 三氟甲基 - 吡啶 -2- 基硫基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0315]

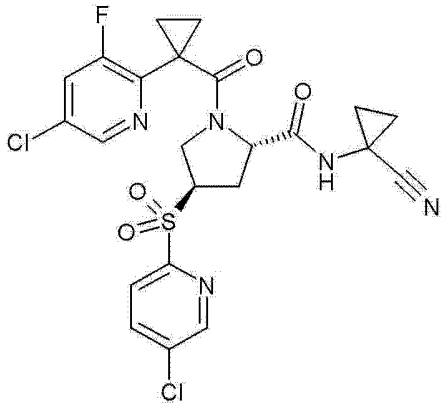


[0316] 类似于实施例 9 中描述的方法，从 3-（三氟甲基）吡啶 -2- 硫醇和实施例 9c）开始制备实施例 21，获得标题化合物，为黄色固体（33mg ；86％）。m/z ＝ 554.1[M+H]$^+$。

[0317] 实施例 22

[0318] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(5- 氯 - 吡啶 -2- 磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0319]

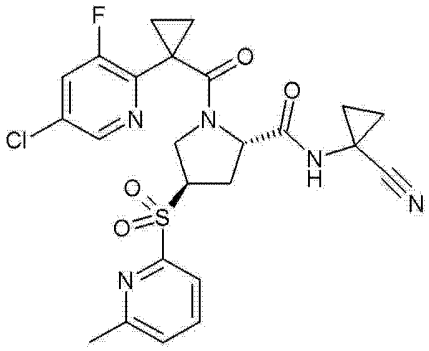


[0320] 类似于实施例 13 中描述的方法从实施例 17 开始制备实施例 22，获得标题化合物，为白色泡沫（22mg ；80％）。m/z ＝ 552.1[M+H]$^+$。

[0321] 实施例 23

[0322] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(6- 甲基 - 吡啶 -2- 磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0323]

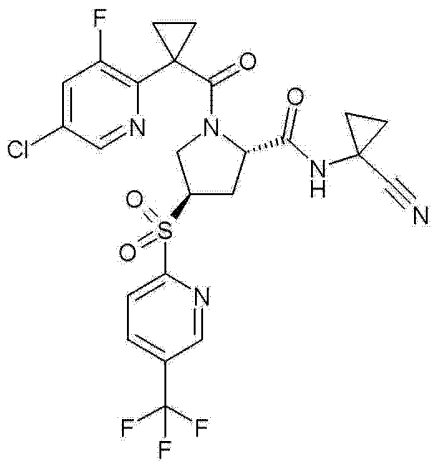


[0324] 类似于实施例 13 中描述的方法，从实施例 19 开始制备实施例 23，获得标题化合物，为白色泡沫（13mg ；82％）。m/z ＝ 532.0[M+H]$^+$。

[0325] 实施例 24

[0326] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(5-三氟甲基-吡啶-2-磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺

[0327]

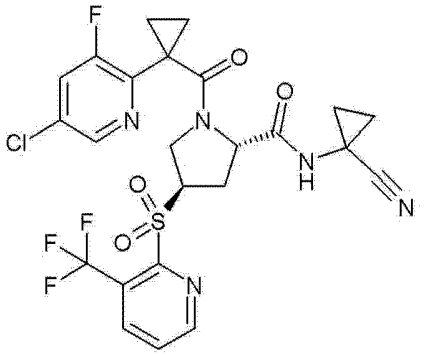


[0328] 类似于实施例13中描述的方法,从实施例20开始制备实施例24,获得标题化合物,为白色固体(29mg;98%)。m/z = 585.9[M+H]$^+$。

[0329] 实施例25

[0330] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(3-三氟甲基-吡啶-2-磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺

[0331]

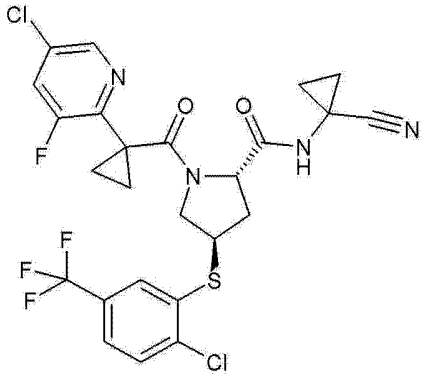


[0332] 类似于实施例13中描述的方法,从实施例21开始制备实施例25,获得标题化合物,为白色固体(16mg;52%)。m/z = 585.9[M+H]$^+$。

[0333] 实施例26

[0334] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-氯-5-三氟甲基-苯基硫基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺

[0335]

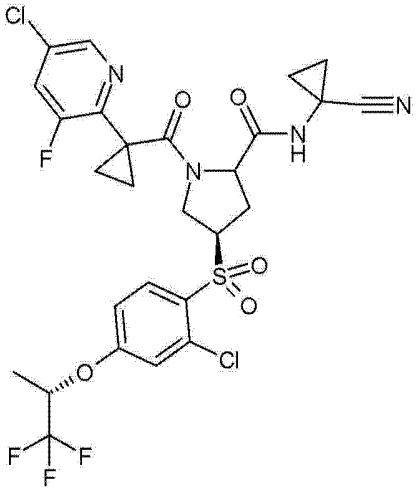


[0336] 类似于实施例 9 中描述的方法，从 2- 氯 -5-(三氟甲基) 苯硫酚和实施例 9c) 开始制备实施例 26，获得标题化合物，为白色固体 (10mg ;25%)。m/z = 586.9[M+H]$^+$。

[0337] 实施例 27

[0338] (2S,4R)-1-(1-(5- 氯 -3- 氟吡啶 -2- 基) 环丙烷羰基)-4-(2- 氯 -4-((S)-1,1,1- 三氟丙 -2- 基氧基) 苯磺酰基)-N-(1- 氰基环丙基) 吡咯烷 -2- 甲酰胺

[0339]

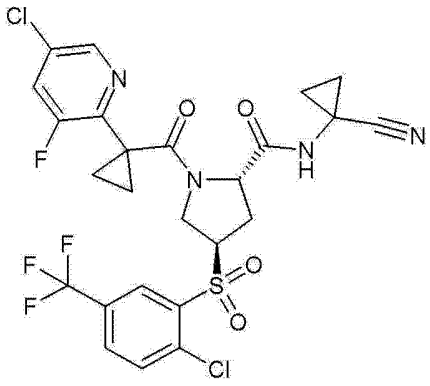


[0340] 将实施例 11(27mg,47.4μmol,Eq :1.00) 溶解在 DMF(1ml) 中。将 Cs_2CO_3(23.2mg,71.1μmol,Eq :1.50) 和 (S)-1,1,1- 三氟丙 -2- 醇 (5.95mg,52.2μmol,Eq :1.10) 加入到溶液中并在 40℃搅拌 4h。将粗制材料通过制备型 HPLC 纯化，获得标题化合物，为白色固体 (17mg ;54%)。m/z = 663.2[M+H]$^+$。

[0341] 实施例 28

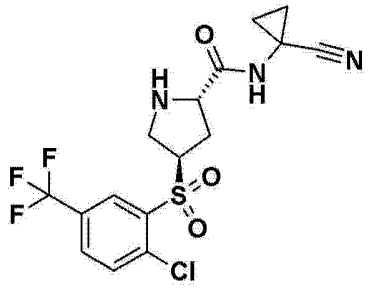
[0342] (2S,4R)-1-(1-(5- 氯 -3- 氟吡啶 -2- 基) 环丙烷羰基)-4-(2- 氯 -5-(三氟甲基) 苯磺酰基)-N-(1- 氰基环丙基) 吡咯烷 -2- 甲酰胺

[0343]



[0344] a)(2S,4R)-4-(2-氯-5-三氟甲基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺

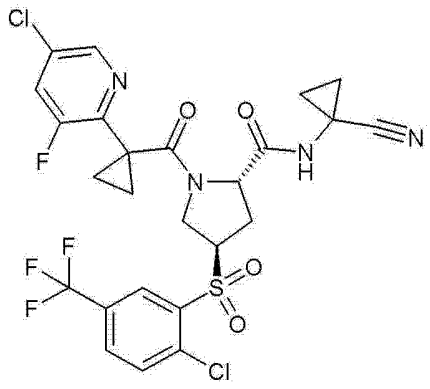
[0345]



[0346] 类似于对 CAS 1252638-10-0 所描述的方法(参见 Haap 等人;US20100267722 和 Hardegger 等人;Angewandte Chemie,国际版,50(1),314-318,S314/1-S314/145;2011),从 2-氯-5-三氟甲基-苯硫酚开始制备实施例 28a),获得标题化合物,为浅黄色固体(125mg;74%)m/z = 421.9[M+H]+。

[0347] b)(2S,4R)-1-(1-(5-氯-3-氟吡啶-2-基)环丙烷羰基)-4-(2-氯-5-(三氟甲基)苯磺酰基)-N-(1-氰基环丙基)吡咯烷-2-甲酰胺

[0348]

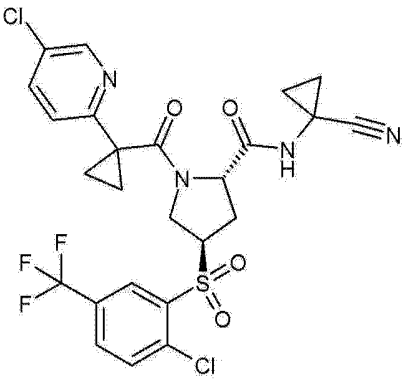


[0349] 类似于实施例 1,从实施例 28a)和 5-氯-2,3-二氟吡啶开始制备实施例 28b),获得标题化合物,为白色固体(37mg;50%)。m/z = 619.1[M+H]+。

[0350] 实施例 29

[0351] (2S,4R)-1-[1-(5-氯-吡啶-2-基)-环丙烷羰基]-4-(2-氯-5-三氟甲基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺

[0352]

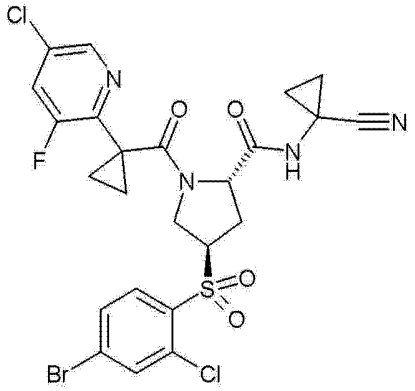


[0353] 类似于实施例 1，从实施例 28a) 和实施例 1b) 开始制备实施例 29，获得标题化合物，为白色固体 (37mg ；50％)。m/z ＝ 601.1[M+H]$^+$。

[0354] 实施例 30

[0355] (2S，4R)-4-(4- 溴 -2- 氯 - 苯磺酰基)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0356]

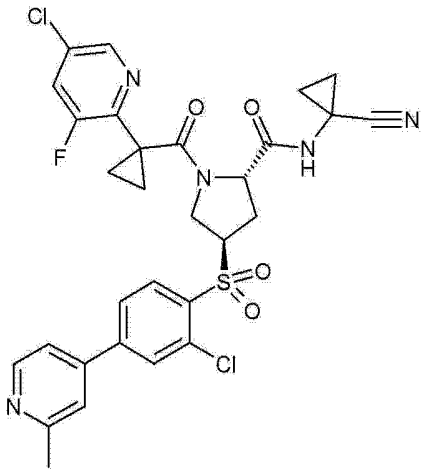


[0357] 类似于实施例 28，从 4- 溴 -2- 氯苯硫酚开始制备实施例 30，获得标题化合物，为白色泡沫 (860mg ；79％)m/z ＝ 631.0[M+H]$^+$。

[0358] 实施例 31

[0359] (2S，4R)-1-(1-(5- 氯 -3- 氟吡啶 -2- 基) 环丙烷羰基)-4-(2- 氯 -4-(2- 甲基吡啶 -4- 基) 苯磺酰基)-N-(1- 氰基环丙基) 吡咯烷 -2- 甲酰胺

[0360]

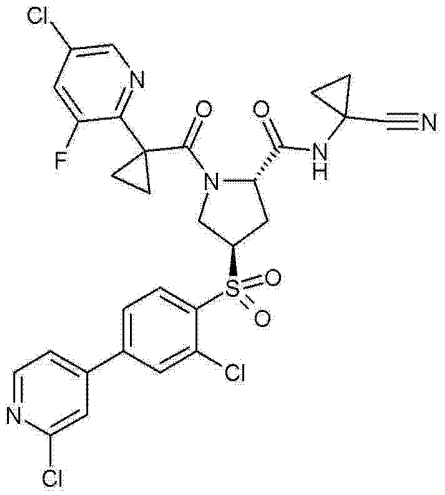


[0361] 将实施例 30(100mg,159μmol,Eq:1.00)溶解在 1,2-二甲氧基乙烷(2ml)中。将 2-甲基-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶(45.2mg,206μmol,Eq:1.30),三苯基膦(8.32mg,31.7μmol,Eq:0.20),2M Na_2CO_3水溶液(500μl)和 Pd(OAc)2(3.56mg,15.9μmol,Eq:0.10)加入并在 45℃搅拌 4h。将反应混合物倒入 0.1M HCl 水溶液(10ml)中并用 DCM(3x10ml)萃取。将有机层经 Na_2SO_4干燥并在真空中浓缩。将粗制材料通过制备型 HPLC 纯化,获得标题化合物,为灰白色泡沫(61mg;60%)。m/z = 642.1[M+H]$^+$。

[0362] 实施例 32

[0363] (2S,4R)-4-[2-氯-4-(2-氯-吡啶-4-基)-苯磺酰基]-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺

[0364]

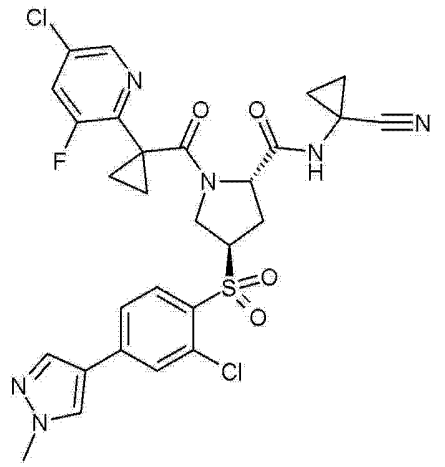


[0365] 类似于实施例 31,从实施例 30 和 2-氯-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶开始制备实施例 32,获得标题化合物,为白色固体(27mg;26%)m/z = 664.1[M+H]$^+$。

[0366] 实施例 33

[0367] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺

[0368]

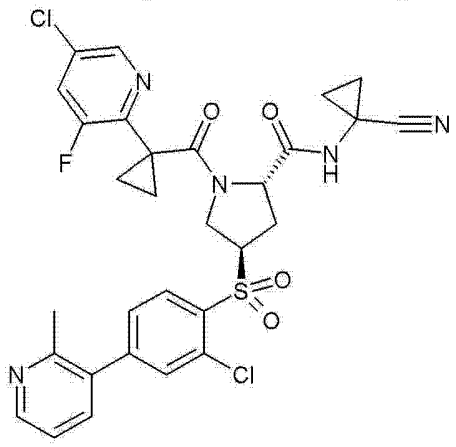


[0369] 类似于实施例 31，从实施例 30 和 1- 甲基 -4-(4,4,5,5- 四甲基 -1,3,2- 二氧杂硼杂环戊烷 -2- 基)-1H- 吡唑开始制备实施例 33，获得标题化合物，为白色固体 (25mg ；25％)。m/z ＝ 631.1[M+H]$^+$。

[0370] 实施例 34

[0371] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-[2- 氯 -4-(2- 甲基 - 吡啶 -3- 基)- 苯磺酰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0372]

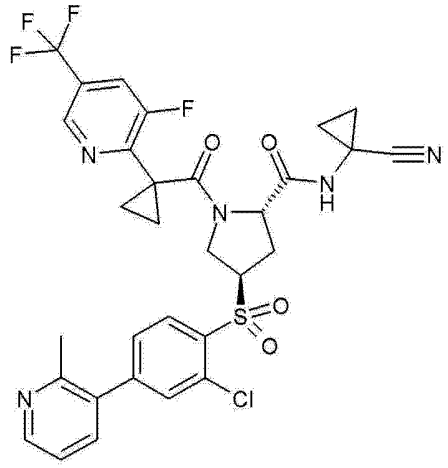


[0373] 类似于实施例 31，从实施例 30 和 2- 甲基 -3-(4,4,5,5- 四甲基 -1,3,2- 二氧杂硼杂环戊烷 -2- 基) 吡啶开始制备实施例 34，获得标题化合物，为白色泡沫 (47mg ；38％)m/z ＝ 642.2[M+H]$^+$。

[0374] 实施例 35

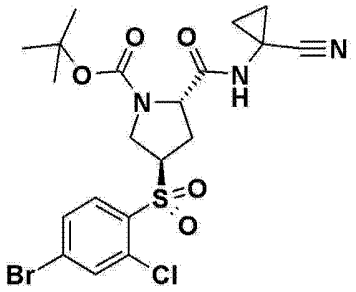
[0375] (2S,4R)-4-[2- 氯 -4-(2- 甲基 - 吡啶 -3- 基)- 苯磺酰基]-1-[1-(3- 氟 -5- 三氟甲基 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0376]



[0377] a) (2S,4R)-4-(4- 溴 -2- 氯 - 苯磺酰基)-2-(1- 氰基 - 环丙基氨甲酰基)- 吡咯烷 -1- 甲酸叔丁酯

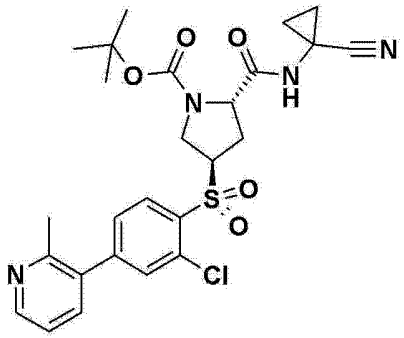
[0378]



[0379] 类似于描述 CAS 1252631-66-5 的方法（见 Haap 等人 ;US20100267722），从 (2S, 4R)-1,2- 吡咯烷二甲酸 4- 羟基 -1-(1,1- 二甲基乙基）酯和 4- 溴 -2- 氯 - 苯硫酚制备实施例 35a)，获得标题化合物，为白色固体 (3.2g ;58%）。m/z = 434.1[M+H-Boc]$^+$。

[0380] b)(2S,4R)-4-[2- 氯 -4-(2- 甲基 - 吡啶 -3- 基)- 苯磺酰基]-2-(1- 氰基 - 环丙基氨甲酰基)- 吡咯烷 -1- 甲酸叔丁酯

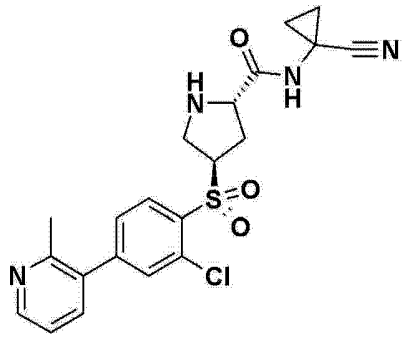
[0381]



[0382] 将实施例 35a)(700mg,1.31mmol, Eq :1.00) 溶解在 1,2- 二甲氧基乙烷 (8ml) 中。加入 2- 甲基 -3-(4,4,5,5- 四甲基 -1,3,2- 二氧杂硼杂环戊烷 -2- 基）吡啶 (345mg, 1.58mmol,Eq :1.20)，三苯基膦 (68.9mg,263μmol,Eq :0.20)，2M Na_2CO_3 水溶液 (2ml) 和乙酸钯 (II)(29.5mg,131μmol,Eq :0.10) 并在 22℃搅拌 24h。之后，将反应混合物在 50℃搅拌 24h。随后，将 2- 甲基 -3-(4,4,5,5- 四甲基 -1,3,2- 二氧杂硼杂环戊烷 -2- 基）吡啶 (57.6mg,263μmol, Eq :0.2) 加入反应混合物中，然后将其在 60℃搅拌 6h。将反应混合物倒入 0.1M HCl 水溶液 (50ml) 中并用 DCM(3x20ml) 萃取。将有机层经 Na_2SO_4 干燥并在真空中浓缩。将粗制材料通过急骤色谱（硅胶，40g，庚烷中 0% 至 100% EtOAc) 纯化，获得标题化合物，为浅黄色油状物 (200mg ;28%）。m/z = 545.3[M+H]$^+$。

[0383] c)(2S,4R)-4-[2- 氯 -4-(2- 甲基 - 吡啶 -3- 基)- 苯磺酰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

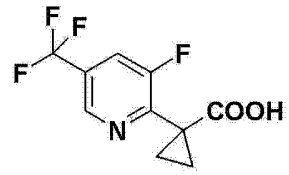
[0384]



[0385] 将实施例 35b)(200mg,367 μ mol,Eq :1.00) 溶解在甲酸 (2.4g,2ml,52.1mmol,Eq : 142) 中并在 22℃搅拌 15h。将反应混合物用冰冷的 10% Na_2CO_3- 水溶液小心调节至 pH8 并用 CH_2Cl_2萃取。将水层用 CH_2Cl_2/THF(1 :1 ;30ml) 总共洗涤 3 次,将合并的有机层经 Na_2SO_4 干燥,过滤并蒸发,获得标题化合物,为白色泡沫 (142mg ;87%)。m/z = 445.2$[M+H]^+$。

[0386] d)1-(3- 氯 -5- 三氟甲基 - 吡啶 -2- 基)- 环丙烷甲酸

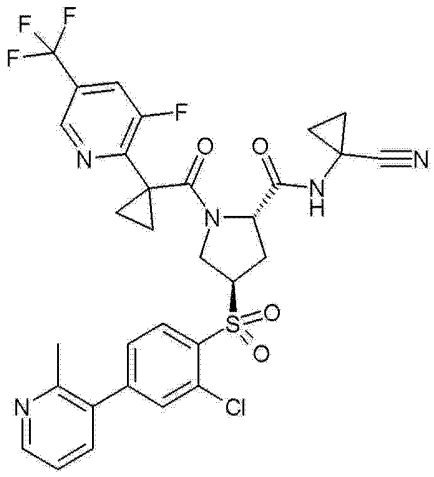
[0387]



[0388] 类似于对实施例 1a) 和 b) 所描述的方法制备实施例 35d),获得标题化合物,为浅棕色固体 (50mg ;41%)m/z = 250.0$[M+H]^+$。

[0389] e)(2S,4R)-4-[2- 氯 -4-(2- 甲基 - 吡啶 -3- 基)- 苯磺酰基]-1-[1-(3- 氟 -5- 三氟甲基 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰甚 - 环丙基)- 酰胺

[0390]

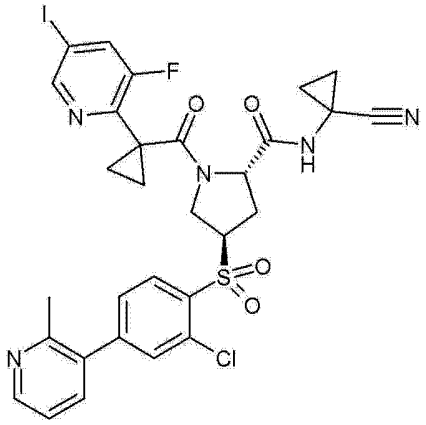


[0391] 类似于实施例 1d),从实施例 35c)(45mg) 和 35d)(30mg) 开始制备标题化合物,获得灰白色固体 (34mg50%)m/z = 676.3$[M+H]^+$。

[0392] 实施例 36

[0393] (2S,4R)-4-[2- 氯 -4-(2- 甲基 - 吡啶 -3- 基)- 苯磺酰基]-1-[1-(3- 氟 -5- 碘 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0394]

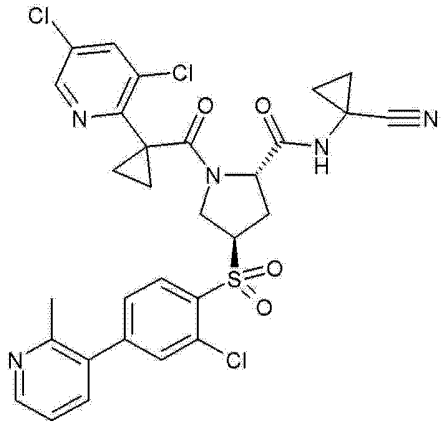


[0395] 类似于实施例35，从实施例35c）和类似于实施例1a）和1b）制备的1-(3-氟-5-碘-吡啶-2-基)-环丙烷甲酸开始制备实施例36，获得标题化合物，为灰白色固体（35mg；47％）m/z = 734.2[M+H]$^+$。

[0396] 实施例37

[0397] (2S,4R)-4-[2-氯-4-(2-甲基-吡啶-3-基)-苯磺酰基]-1-[1-(3,5-二氯-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺

[0398]

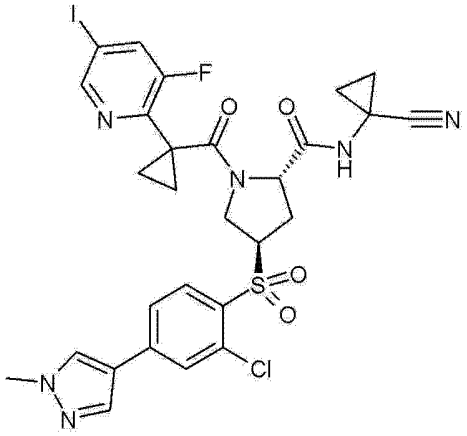


[0399] 类似于实施例35，从实施例35c）和类似于实施例1a）和1b）制备的1-(5-氯-3-氟-吡啶-2-基)-环丙烷甲酸开始制备实施例37，获得标题化合物，为灰白色固体（26mg；39％）m/z = 660.2[M+H]$^+$。

[0400] 实施例38

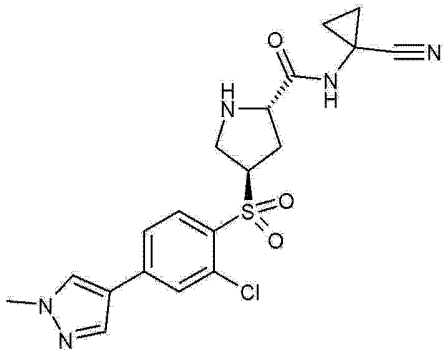
[0401] (2S,4R)-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺

[0402]



[0403] a)(2S,4R)-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺

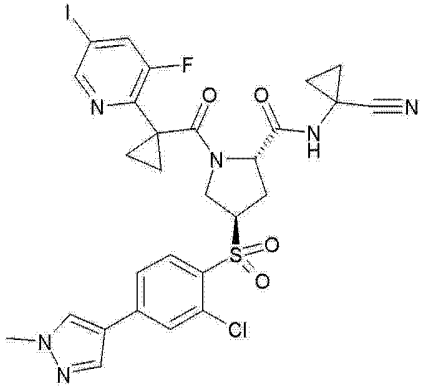
[0404]



[0405] 类似于实施例35c),从实施例35a)和1-甲基-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1H-吡唑开始制备实施例38a),获得标题化合物,为浅棕色泡沫(173mg;95%)。m/z = 434.2[M+H]$^+$。

[0406] b)(2S,4R)-4-[2-氯-4-(1-甲基-1H-吡唑-4-基)-苯磺酰基]-1-[1-(3-氟-5-碘-吡啶-2-基)-环丙烷羰基]-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺

[0407]

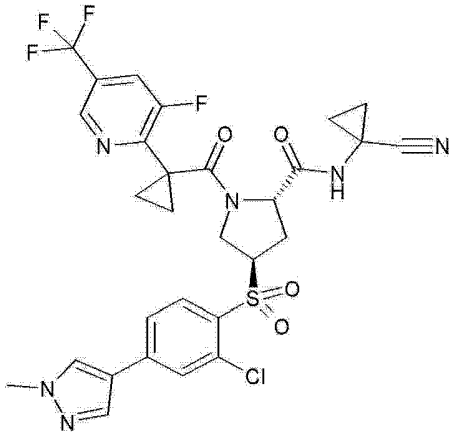


[0408] 类似于实施例35,从实施例38a)和类似于实施例1a)和1b)制备的1-(3-氟-5-碘-吡啶-2-基)-环丙烷甲酸开始制备实施例38b),获得标题化合物,为灰白色固体(40mg;48%)m/z = 723.1[M+H]$^+$。

[0409] 实施例 39

[0410] (2S,4R)-4-[2- 氯 -4-(1- 甲基 -1H- 吡唑 -4- 基)- 苯磺酰基]-1-[1-(3- 氟 -5- 三氟甲基 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0411]

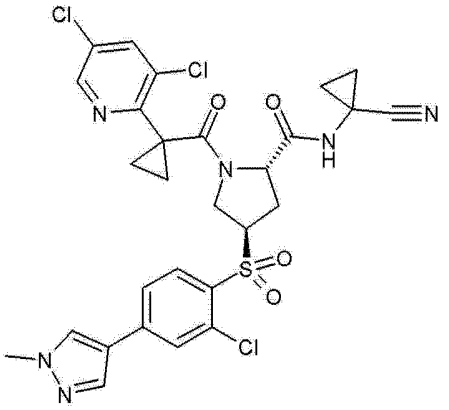


[0412] 类似于实施例 38b),从实施例 38a) 和 35d) 开始制备实施例 39,获得标题化合物,为灰白色固体 (16mg ;60%)。m/z = 665.1[M+H]$^+$。

[0413] 实施例 40

[0414] (2S,4R)-4-[2- 氯 -4-(1- 甲基 -1H- 吡唑 -4- 基)- 苯磺酰基]-1-[1-(3,5- 二氯 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0415]

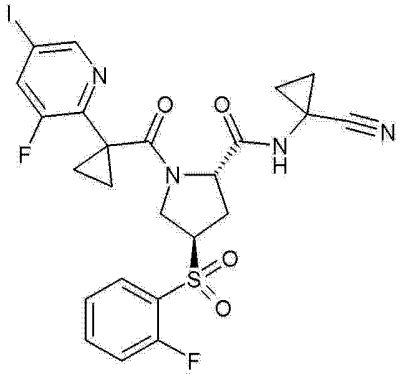


[0416] 类似于实施例 35,从实施例 38a) 和类似于实施例 1a) 和 1b) 制备的 1-(3,5- 二氯 - 吡啶 -2- 基)- 环丙烷甲酸开始制备实施例 40,获得标题化合物,为灰白色固体 (29mg ; 39%)m/z = 649.2[M+H]$^+$。

[0417] 实施例 41

[0418] (2S,4R)-4-(2- 氟 - 苯磺酰基)-1-[1-(3- 氟 -5- 碘 - 吡啶 -2- 基)- 环丙烷羰基]- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0419]

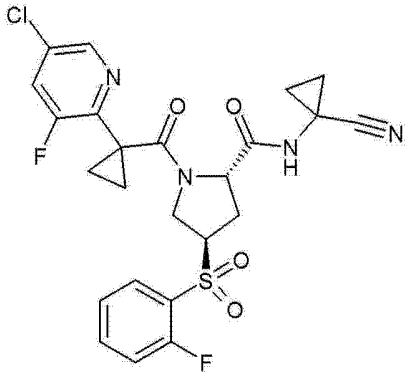


[0420] 类似于实施例 8，从 2- 氟苯硫酚和 1-(3- 氟 -5- 碘 - 吡啶 -2- 基)- 环丙烷甲酸开始制备实施例 41，获得标题化合物，为白色泡沫 (328mg ;68％)。m/z ＝ 627.3[M+H]$^+$。

[0421] 实施例 42

[0422] (2S,4R)-1-[1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷羰基]-4-(2- 氟 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0423]

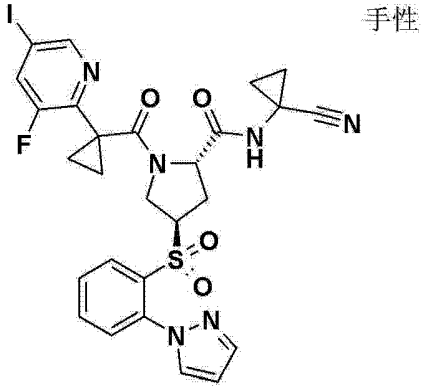


[0424] 类似于实施例 41，从 2- 氟苯硫酚和 1-(5- 氯 -3- 氟 - 吡啶 -2- 基)- 环丙烷甲酸开始制备实施例 42，获得标题化合物，为白色泡沫 (212mg ;67％)。m/z ＝ 535.4[M+H]$^+$。

[0425] 实施例 43

[0426] (2S,4R)-1-[1-(3- 氟 -5- 碘 - 吡啶 -2- 基)- 环丙烷羰基]-4-(2- 吡唑 -1- 基 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0427]



手性

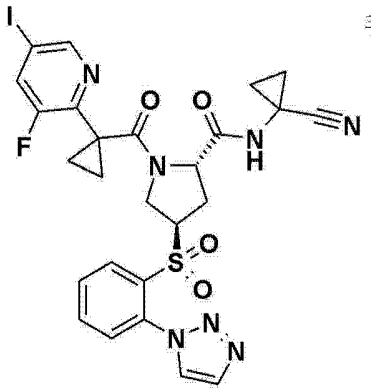
[0428] 向 5mL 管中加入实施例 41(60mg,95.8μmol，Eq :1.00)，1H- 吡唑 (9.78mg，144μmol，Eq :1.50)，Cs_2CO_3(37.4mg，115μmol，Eq :1.20) 和 DMF(1ml)。将反应混合物在

22℃搅拌 24h。再向反应混合物加入 1H- 吡唑 (9.78mg,144μmol,Eq :1.50) 并在 50℃搅拌 24h。将粗制材料通过制备型 HPLC 纯化,获得标题化合物,为白色泡沫 (8mg ;12.4%)。m/z = 675.0647[M+H]$^+$。

[0429] 实施例 44

[0430] (2S,4R)-1-[1-(3- 氟 -5- 碘 - 吡啶 -2- 基)- 环丙烷羰基]-4-(2-[1,2,3] 三唑 -1- 基 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0431]

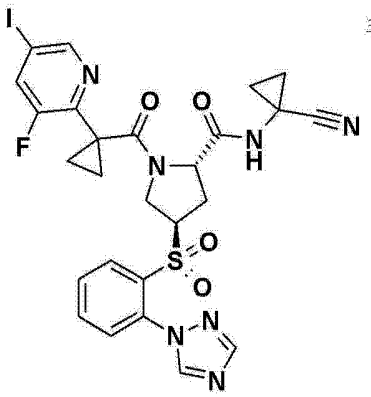


[0432] 向 5mL 管中加入实施例 41(60mg,95.8μmol,Eq :1.00),1H-1,2,3- 三唑 (9.92mg,8.32μl,144μmol,Eq :1.50),Cs_2CO_3(37.4mg,115μmol,Eq :1.20) 和 DMA(1ml)。将反应混合物在 22℃搅拌 24h。再向反应混合物中加入 1H-1,2,3- 三唑 (9.92mg,8.32μl,144μmol,Eq :1.50) 并在 50℃搅拌 24h。将粗制材料通过制备型 HPLC 纯化,获得标题化合物,为白色泡沫 (25mg ;23% ;纯度 50-80%)。m/z = 676.0638[M+H]$^+$。

[0433] 实施例 45

[0434] (2S,4R)-1-[1-(3- 氟 -5- 碘 - 吡啶 -2- 基)- 环丙烷羰基]-4-(2-[1,2,4] 三唑 -1- 基 - 苯磺酰基)- 吡咯烷 -2- 甲酸 (1- 氰基 - 环丙基)- 酰胺

[0435]

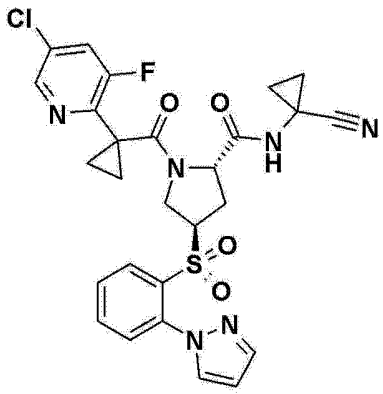


[0436] 向 5mL 管中加入实施例 41(60mg,95.8μmol,Eq :1.00),1H-1,2,4- 三唑 (9.92mg,144μmol, Eq :1.50),1H-1,2,4- 三唑 (9.92mg,144μmol, Eq :1.50) 和 DMA(1ml)。将反应混合物在 22℃搅拌 24h。再向反应混合物中加入 1H-1,2,4- 三唑 (9.92mg,144μmol, Eq :1.50) 并在 50℃搅拌 24h。将粗制材料通过制备型 HPLC 纯化,得到标题化合物,为白色泡沫 (15mg ;18.8% ;纯度 50-80%)。m/z = 676.0629[M+H]$^+$。

[0437] 实施例 46

[0438] ((2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-吡唑-1-基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺

[0439]



[0440] 向5mL管中加入实施例42(50mg,93.5μmol,Eq:1.00),1H-吡唑(9.54mg,140μmol,Eq:1.50),Cs_2CO_3(36.5mg,112μmol,Eq:1.20)和DMA(1ml)。将反应混合物在22℃搅拌24h。再向反应混合物加入1H-吡唑(9.54mg,140μmol,Eq:1.50)并在50℃搅拌24h。将粗制材料通过制备型HPLC纯化,获得标题化合物,为白色泡沫(10mg;15%;纯度80%)。m/z = 583.1319$[M+H]^+$。

[0441] 实施例47

[0442] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-[1,2,3]三唑-1-基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺

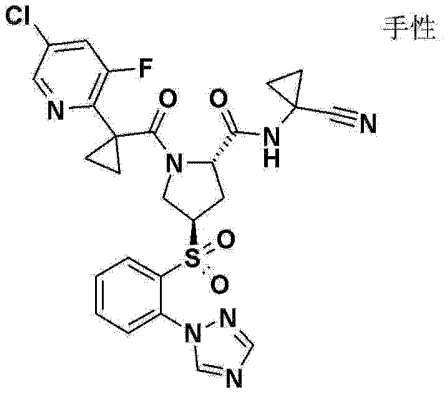
[0443]

[0444] 向5mL管中加入实施例42(50mg,93.5μmol,Eq:1.00),1H-1,2,3-三唑(9.68mg,8.12μl,140μmol,Eq:1.50),Cs2CO3(36.5mg,112μmol,Eq:1.20)和DMA(1ml)。将反应混合物在22℃搅拌24h。再向反应混合物加入1H-1,2,3-三唑(9.68mg,8.12μl,140μmol,Eq:1.50)并在50℃搅拌24h。将粗制材料通过制备型HPLC纯化,获得标题化合物,为白色泡沫(10mg;11%;纯度60%)。m/z = 584.1272$[M+H]^+$。

[0445] 实施例48

[0446] (2S,4R)-1-[1-(5-氯-3-氟-吡啶-2-基)-环丙烷羰基]-4-(2-[1,2,4]三唑-1-基-苯磺酰基)-吡咯烷-2-甲酸(1-氰基-环丙基)-酰胺

[0447]



[0448] 向 5mL 管中加入实施例 42(50mg,93.5μmol,Eq:1.00),1H-1,2,4-三唑 (9.68mg,140μmol,Eq:1.50),Cs_2CO_3(36.5mg,112μmol,Eq:1.20) 和 DMA(1ml)。将反应混合物在 22℃搅拌 24h。再向反应混合物加入 1H-1,2,4-三唑 (9.68mg,140μmol,Eq:1.50) 并在 50℃搅拌 24h。将粗制材料通过制备型 HPLC 纯化,获得标题化合物,为白色泡沫 (25mg;35%;纯度 77%)。m/z = 584.1281$[M+H]^+$。

[0449] 实施例 49

[0450] 组织蛋白酶的酶抑制测定

[0451] 通过观察由含荧光团的肽底物的分解造成的荧光强度的增加,测量酶活性,所述荧光团的(光)发射是在完整的肽中被猝灭的。

[0452] 测定缓冲液:100mM 磷酸钾 pH6.5,EDTA-Na5mM,Triton X-1000.001%,DTT5mM。

[0453] 酶(均为 1nM):人和小鼠组织蛋白酶 S、Cat K、Cat B、Cat L

[0454] 底物 (20μM):Z-Val-Val-Arg-AMC,Cat K 除外,其使用 Z-Leu-Arg-AMC(均来自 Bachem)。

[0455] Z =苄氧羰基。

[0456] AMC = 7-氨基 -4-甲基 - 香豆素。

[0457] DTT =二硫苏糖醇

[0458] 最终体积:100μL。

[0459] 激发 360nm,发射 465nm。

[0460] 将酶加入到在 96 孔微滴定板中的物质稀释物中,并且用底物启动反应。测量荧光发射 20 分钟,期间,在没有抑制剂的情况下观察到线性升高。采用标准方法计算 IC_{50}。

[0461] 分别测定对人 Cat S、小鼠 Cat S、人 Cat K、人 Cat B、人 Cat L 和小鼠 Cat L 的抑制性。本发明的代表性化合物对人 Cat S 和 L 的所得结果以 μM 列在下表中。

[0462]

实施例	IC50 h S	IC50 h L	实施例	IC50 h S	IC50 h L
1	0.000606	0.4097	**25**	0.003213	13.1975
2	0.000492	0.3402	**26**	0.003466	0.0524
3	0.000825	0.429	**27**	0.001596	0.09
4	0.000393	0.0119	**28**	0.000543	0.0568
5	0.000398	0.0129	**29**	0.000618	0.3618
6	0.000675	0.0445	**30**	0.000474	0.0726
7	0.000734	0.0255	**31**	0.000505	0.0616
8	0.000438	0.0192	**32**	0.000686	0.1121
9	0.011785	0.4165	**33**	0.000375	0.0287
10	0.96365	15.8722	**34**	0.000322	0.0642
11	0.000602	0.0898	**35**	0.000768	0.0589
12	0.5941	8.2265	**36**	0.000382	0.0098
13	0.00077	0.2474	**37**	0.000779	0.0722
14	0.002844	2.117	**38**	0.000678	0.0032
15	0.011075	1.679	**39**	0.000696	0.0436
16	1.031	>25	**40**	0.000703	0.1111
17	0.2635	5.648	**41**	0.0006	0.003

[0463]

18	0.00424	3.4345	**42**	0.0007	0.031
19	0.12715	4.6095	**43**	0.016985	0.0906
20	0.3926	5.0635	**44**	0.002372	1.5585
21	0.27455	10.011	**45**	0.3272	28.383
22	0.002996	1.9695	**46**	0.1587	17.445
23	0.002796	5.635	**47**	0.004268	35.2
24	0.006244	2.694	**48**	0.058535	21.1025

[0464] 本发明的化合物是对组织蛋白酶 S 和 L 比对组织蛋白酶 K 和 B 优先的抑制剂。

[0465] 在以上试验中，根据本发明的化合物对 Cat S 和 / 或 L 具有 0.00001 至 100 μ M 的 IC_{50}。本发明的特定化合物对 Cat S 和 / 或 L 具有 0.00001 至 50 μ M 和更特别为 0.00001 至 20 μ M 的 IC50。本发明的特定化合物在以上试验的至少一个中具有低于 0.09 μ M 的 IC_{50}。

[0466] 实施例 A

[0467] 式 (I) 化合物可以作为活性成分以本身已知方式用于制备具有下列组成的片剂：

[0468]

	每片
活性成分	200 mg
微晶纤维素	155 mg
玉米淀粉	25 mg
滑石	25 mg
羟丙基甲基纤维素	20 mg

[0469]

425 mg

[0470] 实施例 B

[0471] 式 (I) 化合物可以作为活性成分以本身已知方式用于制备具有下列组成的胶囊：

[0472]

	每胶囊
活性成分	100.0 mg
玉米淀粉	20.0 mg
乳糖	95.0 mg
滑石	4.5 mg
硬脂酸镁	0.5 mg
	220.0 mg