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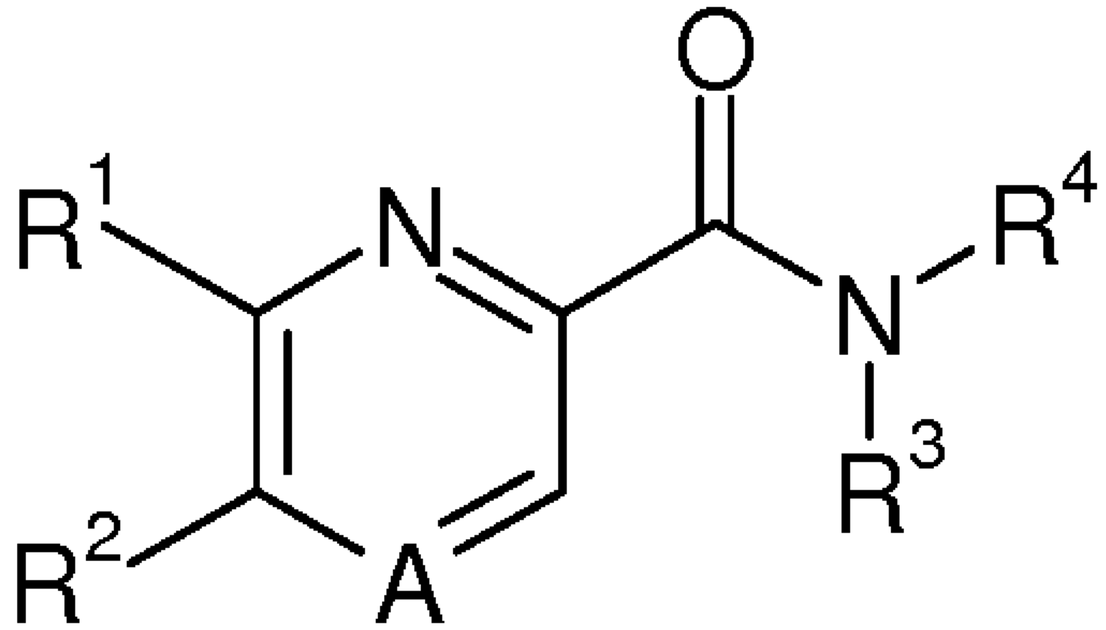
(54) **Titre : PYRIDINE-2-AMIDES UTILES COMME AGONISTES DE CB2**
(54) **Title: PYRIDINE-2-AMIDES USEFUL AS CB2 AGONISTS**



(I)

(57) **Abrégé/Abstract:**
The invention relates to a compound of formula (I) wherein A and R^1 to R^4 are defined as in the description and in the claims. The compound of formula (I) can be used as a medicament.

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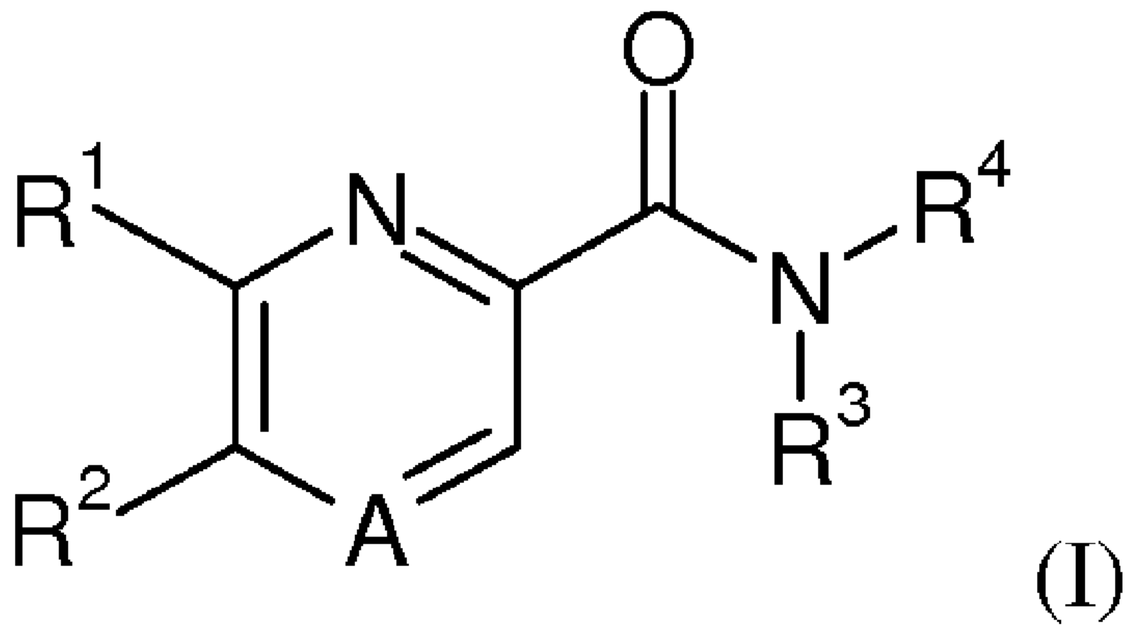
(54) Title: PYRIDINE-2-AMIDES USEFUL AS CB2 AGONISTS



(I)

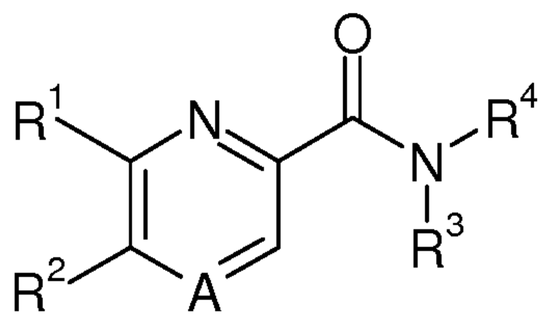
(57) Abstract: The invention relates to a compound of formula (I) wherein A and R^1 to R^4 are defined as in the description and in the claims. The compound of formula (I) can be used as a medicament.

WO 2015/150440 A1

PYRIDINE-2-AMIDES USEFUL AS CB2 AGONISTS

The present invention relates to organic compounds useful for therapy and/or prophylaxis in a mammal, and in particular to compounds that are preferential inverse agonists of the Cannabinoid Receptor 2.

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



(I)

wherein

A is -CH- or nitrogen;

R^1 is halophenyl, halophenylalkyl, haloalkoxy, halogen, alkoxyalkoxy, oxopyrrolidinyl or cycloalkylalkoxy;

R^2 is hydrogen, halophenylamino, cycloalkyl or haloazetidinyl;

one of R^3 and R^4 is hydrogen and the other one is $-(CR^5R^6)_m-(CH_2)_n-R^7$;

or R^3 and R^4 together with the nitrogen atom to which they are attached form aminocarbonylthiomorpholinyl;

R^5 and R^6 are independently selected from hydrogen and alkyl;

R^7 is 5-cycloalkyl-1,3,4-oxadiazolyl, 3-cycloalkyl-1,2,4-oxadiazolyl, 5-phenyl-1,3,4-oxadiazolyl, 3-phenyl-1,2,4-oxadiyzolyl, 5-alkyl-1,3,4-oxadiazolyl, 3-alkoxyalkoxyalkyl-1,2-oxazolyl, 1-hydroxyalkylpyrazolyl, 3-hydroxy-1-

adamantyl, alkoxycarbonylmorpholinyl, 3-oxanyloxyalkyl-1,2-oxazol-5-yl, 3-azidoalkyl-1,2-oxazol-5-yl or 5-(4-fluorophenyl)-1,3,4-oxadiazolyl;

m is 0 or 1;

n is 0 or 1;

or a pharmaceutically acceptable salt or ester thereof;

provided that 6-chloro-N-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)- 2-pyridinecarboxamide is excluded.

The compound of formula (I) is particularly useful in the treatment or prophylaxis of pain, neuropathic pain, asthma, osteoporosis, inflammation, psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, psychiatric disorders rheumatoid arthritis, psychosis and allergy.

The cannabinoid receptors are a class of cell membrane receptors belonging to the G protein-coupled receptor superfamily. There are currently two known subtypes, termed Cannabinoid Receptor 1 (CB1) and Cannabinoid Receptor 2 (CB2). The CB1 receptor is mainly expressed in the central nervous (i.e. amygdala cerebellum, hippocampus) system and to a lesser amount in the periphery. CB2, which is encoded by the CNR2 gene, is mostly expressed peripherally, on cells of the immune system, such as macrophages and T-cells (Ashton, J. C. et al. Curr Neuropharmacol 2007, 5(2), 73-80; Miller, A. M. et al. Br J Pharmacol 2008, 153(2), 299-308; Centonze, D., et al. Curr Pharm Des 2008, 14(23), 2370-42), and in the gastrointestinal system (Wright, K. L. et al. Br J Pharmacol 2008, 153(2), 263-70). The CB2 receptor is also widely distributed in the brain where it is found primarily on microglia and not neurons (Cabral, G. A. et al. Br J Pharmacol 2008, 153(2): 240-51).

The interest in CB2 receptor ligands has been steadily on the rise during the last decade (currently 30-40 patent applications/year). Evidences from different sources support the view that lipid endocannabinoid signaling through CB2 receptors represents an aspect of the mammalian protective armamentarium (Pacher, P. Prog Lipid Res 2011, 50, 193). Its modulation by either selective CB2 receptor agonists or inverse agonists/antagonists (depending on the disease and its stage) holds unique therapeutic potential in a huge number of diseases. For CB2 inverse agonists/antagonists therapeutic opportunities have been demonstrated for many pathological conditions including pain (Pasquini, S. J Med Chem 2012, 55(11): 5391), neuropathic pain (Garcia-Gutierrez, M.S. Br J Pharmacol 2012, 165(4): 951), psychiatric disorders (Garcia-Gutierrez, M.S. Br J Pharmacol 2012, 165(4): 951), psychosis (Garcia-Gutierrez, M.S. Br J Pharmacol 2012,

165(4): 951), osteoporosis and inflammation (Sophocleous, A. Calcif Tissue Int 2008, 82(Suppl. 1):Abst OC18), psychiatric diseases and psychosis (Garcia-Gutierrez, M.S. Br J Pharmacol 2012, 165(4): 951), oncology (Preet, A. Cancer Prev Res 2011, 4: 65), encephalitis and malaria (Zimmer, A. WO 2011045068), allergy and inflammation (Ueda, Y. Life Sci 2007, 80(5): 414), encephalitis and malaria (Zimmer, WO 2011045068), asthma (Lunn, C.A. J Pharmacol Exp Ther 2006, 316(2): 780), immunological disorders (Fakhfouri, G. Neuropharmacology 2012, 63(4): 653), rheumatoid arthritis (Chackalamannil, S. US 7776889), arthritis (Lunn, C.A. J Pharmacol Exp Ther 2006, 316(2): 780), and gastrointestinal disorders (Barth, F. FR 2887550),

The compounds of the invention bind to and modulate the CB2 receptor and have lower CB1 receptor activity.

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, particularly a straight or branched-chain alkyl group with 1 to 6 carbon atoms and more particularly a straight or branched-chain alkyl group with 1 to 4 carbon atoms. Examples of straight-chain and branched-chain 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, particularly methyl, ethyl, propyl, butyl and pentyl. Particular examples of alkyl are methyl, ethyl, isopropyl, butyl, isobutyl, tert.-butyl and pentyl. Methyl is a particular example of alkyl in the compound of formula (I).

The term “cycloalkyl”, alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and particularly a cycloalkyl ring with 3 to 6 carbon atoms. Examples of cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, cycloheptyl and cyclooctyl. Particular examples of “cycloalkyl” are cyclopropyl, cyclobutyl and cyclopentyl.

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. Particular “alkoxy” are methoxy, ethoxy and tert.-butoxy.

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

The term “oxo”, alone or in combination, signifies the =O group.

The terms “halogen” or “halo”, alone or in combination, signifies fluorine, chlorine, bromine or iodine and particularly fluorine, chlorine or bromine, more particularly fluorine and chlorine. The term “halo”, in combination with another group, denotes the substitution

of said group with at least one halogen, particularly substituted with one to five halogens, particularly one to four halogens, i.e. one, two, three or four halogens.

The term "haloalkyl", alone or in combination, denotes an alkyl group substituted with at least one halogen, particularly substituted with one to five halogens, particularly one to three halogens. A particular "haloalkyl" is trifluoroethyl.

The term "haloalkoxy" or "haloalkyloxy", alone or in combination, denotes an alkoxy group substituted with at least one halogen, particularly substituted with one to five halogens, particularly one to three halogens. A particular "haloalkoxy" is trifluoroethoxy.

The terms "hydroxyl" and "hydroxy", alone or in combination, signify the -OH group.

The term "carbonyl", alone or in combination, signifies the -C(O)- group.

The term "amino", alone or in combination, signifies the primary amino group (-NH2), the secondary amino group (-NH-), or the tertiary amino group (-N-).

The term "aminocarbonyl", alone or in combination, signifies the -C(O)-NH2, -C(O)-NH- or –C(O)-N- group.

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, particularly hydrochloric acid, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic 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. Particularly preferred pharmaceutically acceptable salts of compounds of formula (I) are the salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and methanesulfonic acid.

"Pharmaceutically acceptable esters" means that the compound of general formula (I) may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compounds in vivo. Examples of such compounds include physiologically acceptable and metabolically labile ester derivatives, such as methoxymethyl esters, methylthiomethyl esters and pivaloyloxymethyl esters. Additionally, any physiologically acceptable equivalents of the compound of general formula (I), similar to the metabolically labile esters, which are capable of producing the parent compound of general formula (I) in vivo, are within the scope of this invention.

If one of the starting materials or compounds of formula (I) contain 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. Wuts, 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 diastereo¬isomers, 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:

A compound or formula (I) wherein R^1 is halogen or cycloalkylalkoxy;

A compound or formula (I) wherein R^1 is chloro or cyclopropylmethoxy;

A compound or formula (I) wherein R^2 is hydrogen, halophenylamino or cycloalkyl;

A compound or formula (I) wherein R^2 is hydrogen, dichlorophenylamino or cyclopropyl;

A compound or formula (I) wherein R^2 is halophenylamino or cycloalkyl;

A compound or formula (I) wherein R^2 is dichlorophenylamino or cyclopropyl;

A compound or formula (I) wherein R^2 is hydrogen;

A compound or formula (I) wherein R^5 and R^6 are both alkyl at the same time;

A compound or formula (I) wherein R^5 and R^6 are both methyl at the same time; and

A compound or formula (I) wherein R^7 is 5-phenyl-1,3,4-oxadiyzolyl, 3-alkoxyalkoxyalkyl-1,2-oxazolyl or 3-azidoalkyl-1,2-oxazol-5-yl.

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

6-(4-chlorophenyl)-N-[1-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-yl]pyridine-2-carboxamide;

6-(4-chlorophenyl)-N-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide;

N-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]-6-(2,2,2-trifluoroethoxy)pyridine-2-carboxamide;

6-(4-chlorophenyl)-N-[2-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]pyridine-2-carboxamide;

N-[2-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]-6-(2,2,2-trifluoroethoxy)pyridine-2-carboxamide;

6-(3-chlorophenyl)-N-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide;

6-(3-chlorophenyl)-N-[1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2-methylpropan-2-yl]pyridine-2-carboxamide;

6-(3-chlorophenyl)-N-[2-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]pyridine-2-carboxamide;

6-chloro-5-(2,4-dichloroanilino)-N-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide;

6-(4-chlorophenyl)-5-cyclopropyl-N-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide;

6-(2-methoxyethoxy)-N-[2-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]pyridine-2-carboxamide;

N-[2-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]-6-(2-oxopyrrolidin-1-yl)pyridine-2-carboxamide;

6-(3-chlorophenyl)-N-[1-(5-cyclobutyl-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-yl]pyridine-2-carboxamide;

6-(2,4-dichlorophenyl)-N-[2-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide;

6-(2,4-dichlorophenyl)-N-[2-(5-methyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)-N-[3-[1-(2-methoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide;

5-cyclopropyl-6-(cyclopropylmethoxy)-N-[1-(1-hydroxy-2-methylpropan-2-yl)pyrazol-4-yl]pyridine-2-carboxamide;

5-cyclopropyl-6-(cyclopropylmethoxy)-N-[3-[1-(2-methoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide;

5-cyclopropyl-6-(cyclopropylmethoxy)-N-[3-(1-hydroxy-2-methylpropan-2-yl)-1,2-oxazol-5-yl]pyridine-2-carboxamide;

5-cyclopropyl-6-(cyclopropylmethoxy)-N-[3-[1-(2-ethoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)-N-(3-hydroxy-1-adamantyl)pyridine-2-carboxamide;

tert-butyl 2-[[[5-cyclopropyl-6-[(4-fluorophenyl)methyl]pyridine-2-carbonyl]amino]methyl]morpholine-4-carboxylate;

(3S)-4-[5-cyclopropyl-6-(cyclopropylmethoxy)pyrazine-2-carbonyl]thiomorpholine-3-carboxamide;

5-cyclopropyl-6-(cyclopropylmethoxy)-N-[3-(1-hydroxy-2-methylpropan-2-yl)-1,2-oxazol-5-yl]pyrazine-2-carboxamide;

5-cyclopropyl-6-(cyclopropylmethoxy)-N-[3-[2-methyl-1-(oxan-2-yloxy)propan-2-yl]-1,2-oxazol-5-yl]pyrazine-2-carboxamide;

N-[3-(1-azido-2-methylpropan-2-yl)-1,2-oxazol-5-yl]-5-cyclopropyl-6-(cyclopropylmethoxy)pyrazine-2-carboxamide;

6-(Cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)-N-[1-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]-2-methylpropan-2-yl]pyridine-2-carboxamide;

5-Cyclopentyl-6-(cyclopropylmethoxy)-N-[1-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]-2-methylpropan-2-yl]pyridine-2-carboxamide;

5-Cyclopentyl-6-(cyclopropylmethoxy)-N-[3-[1-(2-methoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide; and

5-Cyclopentyl-6-(cyclopropylmethoxy)-N-[3-[1-(2-ethoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide.

The invention particularly relates to a compound or formula (I) selected from:

6-chloro-5-(2,4-dichloroanilino)-N-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide;

5-cyclopropyl-6-(cyclopropylmethoxy)-N-[3-[1-(2-methoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide;

5-cyclopropyl-6-(cyclopropylmethoxy)-N-[3-[1-(2-ethoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide; and

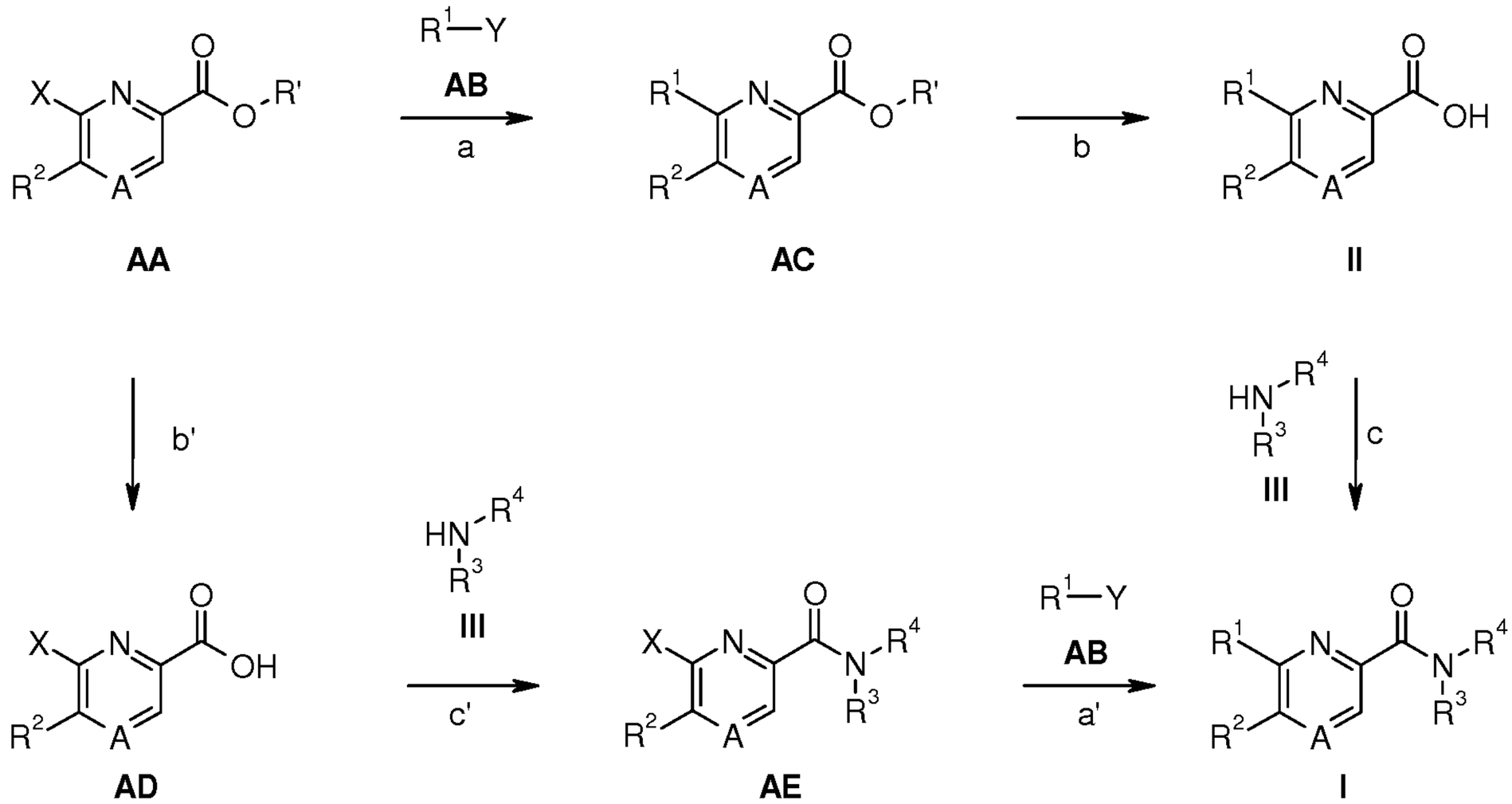
N-[3-(1-azido-2-methylpropan-2-yl)-1,2-oxazol-5-yl]-5-cyclopropyl-6-(cyclopropylmethoxy)pyrazine-2-carboxamide.

The synthesis of the compound of formula (I) can, for example, be accomplished according to the following schemes.

Unless indicated otherwise, A and R^1- R^4 have in the following schemes the meaning as defined above.

Following the procedure according to scheme 1, compound **AA** (X = Cl, Br, I or trifluoromethanesulfonate; R' = H, methyl, ethyl, isopropyl, tert. butyl or another suitable protecting group described for example in T.W. Greene et al., Protective Groups in Organic Chemistry, John Wiley and Sons Inc. New York **1999**, 3rd edition,) can be used as starting material. **AA** is either commercially available, described in the literature, can be synthesized by a person skilled in the art or as described in the experimental part.

Scheme 1



Compound **AC** can be prepared from **AA** by coupling a suitably substituted aryl or arylalkyl metal species of formula **AB** (Y is e.g. a trifluoroborate group like $[BF_3]^-K^+$, a boronic acid group $B(OH)_2$ or a boronic acid pinacol ester group) (step a), particularly an arylboronic acid or arylboronic acid ester in the presence of a suitable catalyst, in particular a palladium catalyst and more particularly palladium(II)acetate/triphenylphosphine mixtures or palladium(II)chloride-dppf (1,1'-bis(diphenylphosphino)ferrocene) complexes and a base such as triethylamine, sodium carbonate or potassium phosphate in an inert solvent such as dimethylformamide, toluene, tetrahydrofuran, acetonitrile or dimethoxyethane.

Alternatively compound **AC** can be prepared from **AA** by coupling an oxopyrrolidinyl species of formula **AB** (Y is H) (step a), in the presence of a suitable catalyst, in particular a palladium catalyst and more particularly tris(dibenzylideneacetone)dipalladium(0) complexes and a base such as triethylamine, sodium carbonate or cesium carbonate in an inert solvent such as dimethylformamide, toluene, tetrahydrofuran, acetonitrile or dimethoxyethane.

Alternatively compound **AA** can be transformed into compound **AC** by reaction with a suitably substituted primary or secondary alcohol **AB** (Y is H) in the presence of a base, for example sodium hydride or potassium hydroxide, with or without an inert solvent, for example DMF or DMSO, at temperatures ranging from room temperature to the reflux temperature of the solvent, particularly at room temperature.

The saponification of the ester of general formula **AC** (R' ≠ H) by methods well known to the ones skilled in the art - using e.g. aqueous LiOH, NaOH or KOH in tetrahydrofuran/ethanol or another suitable solvent at temperatures between 0°C and the reflux temperature of the solvent employed - leads to an acid of general formula **II** (step b).

Compound **I** can be prepared from **II** and the corresponding amine of formula **III** by suitable amide bond forming reactions (step c). These reactions are known in the art. For example coupling reagents like *N,N'*-carbonyl-diimidazole (CDI), *N,N'*-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1-[bis(dimethylamino)-methylene]-*1H*-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU), 1-hydroxy-1,2,3-benzotriazole (HOBT), O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU), and O-benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluoro-phosphate (HBTU) can be employed to affect such transformation. A convenient method is to use for example HBTU and a base, for example *N*-methylmorpholine in an inert solvent such as for example dimethylformamide at room temperature.

Alternatively esters of general formula **AA** (R' ≠ H) can be saponified by methods well known to the ones skilled in the art - using e.g. aqueous LiOH, NaOH or KOH in tetrahydrofuran/ethanol or another suitable solvent at temperatures between 0°C and the reflux temperature of the solvent employed – to give acids of general formula **AD** (step b').

Compounds **AE** can be prepared from **AD** and the corresponding amine of formula **III** by suitable amide bond forming reactions (step c'). These reactions are known in the art. For example coupling reagents like *N,N'*-carbonyl-diimidazole (CDI), *N,N'*-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1-[bis(dimethylamino)-methylene]-*1H*-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU), 1-hydroxy-1,2,3-benzotriazole (HOBT), O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) or O-benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluoro-phosphate (HBTU) can be employed to affect such transformation. A convenient method is to use for example HBTU and a base, for example *N*-methylmorpholine in an inert solvent such as for example dimethylformamide at room temperature.

Compound **I** can be prepared from **AE** by coupling a suitably substituted aryl or arylalkyl metal species of formula **AB** (Y is e.g. a trifluoroborate group like $[BF_3]^-K^+$, a boronic acid group $B(OH)_2$ or a boronic acid pinacol ester group) (step a'), particularly an arylboronic acid or arylboronic acid ester in the presence of a suitable catalyst, in particular a palladium catalyst and more particularly palladium(II)acetate/triphenylphosphine mixtures or palladium(II)chloride-dppf (1,1'-bis(diphenylphosphino)ferrocene) complexes

and a base such as triethylamine, sodium carbonate or potassium phosphate in an inert solvent such as dimethylformamide, toluene, tetrahydrofuran, acetonitrile or dimethoxyethane.

Alternatively compound **I** can be prepared from **AE** by coupling an oxopyrrolidinyl species of formula **AB** (Y is H) (step a'), in the presence of a suitable catalyst, in particular a palladium catalyst and more particularly tris(dibenzylideneacetone)dipalladium(0) complexes and a base such as triethylamine, sodium carbonate or cesium carbonate in an inert solvent such as dimethylformamide, toluene, tetrahydrofuran, acetonitrile or dimethoxyethane.

Aternatively compound **AE** can be transformed to compounds **I** by reaction with a suitably substituted primary or secondary alcohol **AB** (Y is H) in the presence of a base, for example sodium hydride or potassium hydroxide, with or without an inert solvent, for example DMF or DMSO, at temperatures ranging from room temperature to the reflux temperature of the solvent, particularly at room temperature.

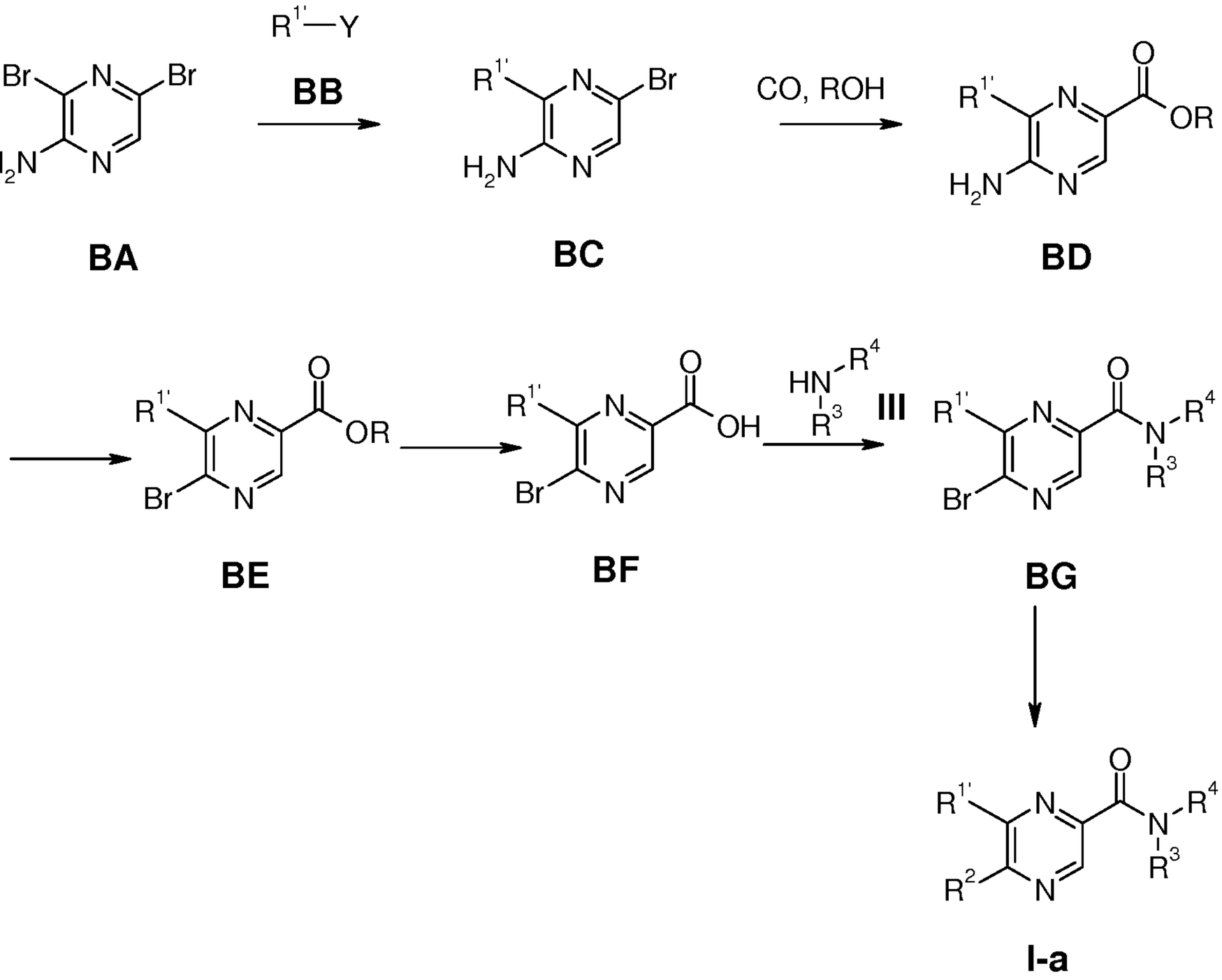
Amines **III** are either commercially available, described in the literature, can be synthesized by a person skilled in the art or as described in the experimental part.

If one of the starting materials, compounds of formulae **AA**, **AB** or **III**, 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 (P) (as described e.g. in T.W. Greene et al., Protective Groups in Organic Chemistry, John Wiley and Sons Inc. New York **1999**, 3rd edition) 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 known in the art.

If one or more compounds of formulae **AA** to **AE**, **II** or **III** contain chiral centers, compounds of formula **I** can be obtained as mixtures of diastereomers or enantiomers, which can be separated by methods well known in the art, e.g. (chiral) HPLC or crystallization. Racemic compounds can e.g. be separated into their antipodes via diastereomeric salts by crystallization or by separation of the antipodes by specific chromatographic methods using either a chiral adsorbent or a chiral eluent.

Following the procedure according to scheme 2, compound **BA** (3,5-dibromo-2-pyrazinamine, CAN 24241-18-7) can be used as starting material for the synthesis of compounds **I-a** wherein A is nitrogen and $R^{1'}$ is halophenyl, halophenylalkyl or oxopyrrolidinyl.

Scheme 2



Compound **BC**can be prepared from **BA** by coupling a suitably substituted aryl or arylalkyl metal species of formula **BB** (Y is e.g. a trifluoroborate group like $[BF_3]^-K^+$, a boronic acid acid $B(OH)_2$ or a boronic acid pinacol ester group), particularly an arylboronic acid or arylboronic acid ester in the presence of a suitable catalyst, in particular a palladium catalyst and more particularly tetrakis(triphenylphosphine)-palladium(0) and a base such as triethylamine or potassium phosphate, in particular sodium carbonate, in an inert solvent such as dimethylformamide, toluene, tetrahydrofurane, acetonitrile or in particular dimethoxyethane, at temperatures from room temperature to the boiling point of the solvent mixture.

Alternatively compound **BC** can be prepared from **BA** by coupling an oxopyrrolidinyl species of formula **BB** (Y is H), in the presence of a suitable catalyst, in particular a palladium catalyst or more particularly tris(dibenzylideneacetone)dipalladium(0) complexes, and a base such as triethylamine, sodium carbonate or cesium carbonate, in an inert solvent such as dimethylformamide, toluene, tetrahydrofuran, acetonitrile or dimethoxyethane.

Compounds of the general formula **BD** can be obtained from compounds of the general formula **BC** by palladium (II), particularly palladium(II) acetate catalyzed

carbonylation in the presence of a suitable base such as a tertiary amine base, particularly triethylamine, in a suitable solvent such as an alcohol, particularly methanol.

Compounds of the general formula **BE** can be obtained from compounds of the general formula **BD** by reaction with nitrosating agents such as a metal nitrite or an organic nitrite more particularly isoamylnitrite, in the presence of a bromide source such as hydrobromic acid or more particularly trimethylbromosilane in a suitable solvent such as halogenated hydrocarbons more particularly dibromomethane.

The saponification of the ester of general formula **BE** by methods well known to the ones skilled in the art - using e.g. aqueous LiOH, NaOH or KOH in tetrahydrofuran/ethanol or another suitable solvent at temperatures between 0°C and the reflux temperature of the solvent employed - leads to an acid of general formula **BF**.

Compound **BG** can be prepared from **BF** and the corresponding amine of formula **III** by suitable amide bond forming reactions. These reactions are known in the art. For example coupling reagents like *N,N'*-carbonyl-diimidazole (CDI), *N,N'*-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1-[bis(dimethylamino)-methylene]-*1H*-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU), 1-hydroxy-1,2,3-benzotriazole (HOBT), O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) or O-benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluoro-phosphate (HBTU) can be employed to affect such transformation. Alternative methods known in the art may commence by preparing the acid chloride from **BF** and coupling with an amine of formula **III** in the presence of a suitable base. A convenient method is to use for example 1-chloro-*N,N*,2-trimethylpropenylamine and a base, for example *N*-ethyl-*N*-isopropylpropan-2-amine (DIEA), in an inert solvent such as for example dimethylformamide at room temperature.

Amines **III** are either commercially available, described in the literature, can be synthesized by a person skilled in the art or obtained as described in the experimental part.

Compounds **I-a** wherein R^2 is cycloalkyl can be prepared from **BG** by coupling a suitably substituted cycloalkyl or cycloakenyl metal species, particularly a cyclopropyl metal species, like cyclopropylzinc(II) chloride, or cyclopropylboronic acid or cyclopropyltrifluoro-borate salts with **BG** in the presence of a suitable catalyst, particularly a palladium catalyst like tetrakis-(triphenyl-phosphine)palladium, or [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)-palladium(II) dichloride, or palladium(II)acetate, in an inert solvent such as THF or toluene at room temperature up to the reflux temperature of the solvent. The person skilled in the art will appreciate that for

coupling the cycloalkyl- or cycloalkenyl-boron species the addition of a suitable base, like potassium phosphate, is necessary for the reaction to commence. In cases where the practitioner skilled in the art chooses to couple with a cycloalkenyl metal species, like cycloalkenylboronic acid esters, compounds **I-a** will be obtained only after an additional hydrogenation step, for example by hydrogenation with hydrogen gas in the presence of a palladium catalyst, for example palladium on charcoal, in an inert solvent, for example ethanol, at suitable temperatures and pressures, particularly at ambient temperature and pressure.

Compounds **I-a** wherein R^2 is haloazetidinyl can be prepared from **BG** by reacting with the corresponding azetidine in the presence of a base, particularly DBU or triethylamine, in an inert solvent, particularly DMSO or dioxane at temperatures ranging from room temperature to 45°C.

If one of the starting materials, compounds of formula **III**, 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 (P) (as described e.g. in T.W. Greene et al., Protective Groups in Organic Chemistry, John Wiley and Sons Inc. New York **1999**, 3rd edition) 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 known in the art.

If one or more compounds of formula **III** contain chiral centers, pyridines of formula **I-a** can be obtained as mixtures of diastereomers or enantiomers, which can be separated by methods well known in the art, e.g. (chiral) HPLC or crystallization. Racemic compounds can e.g. be separated into their antipodes via diastereomeric salts by crystallization or by separation of the antipodes by specific chromatographic methods using either a chiral adsorbens or a chiral eluent.

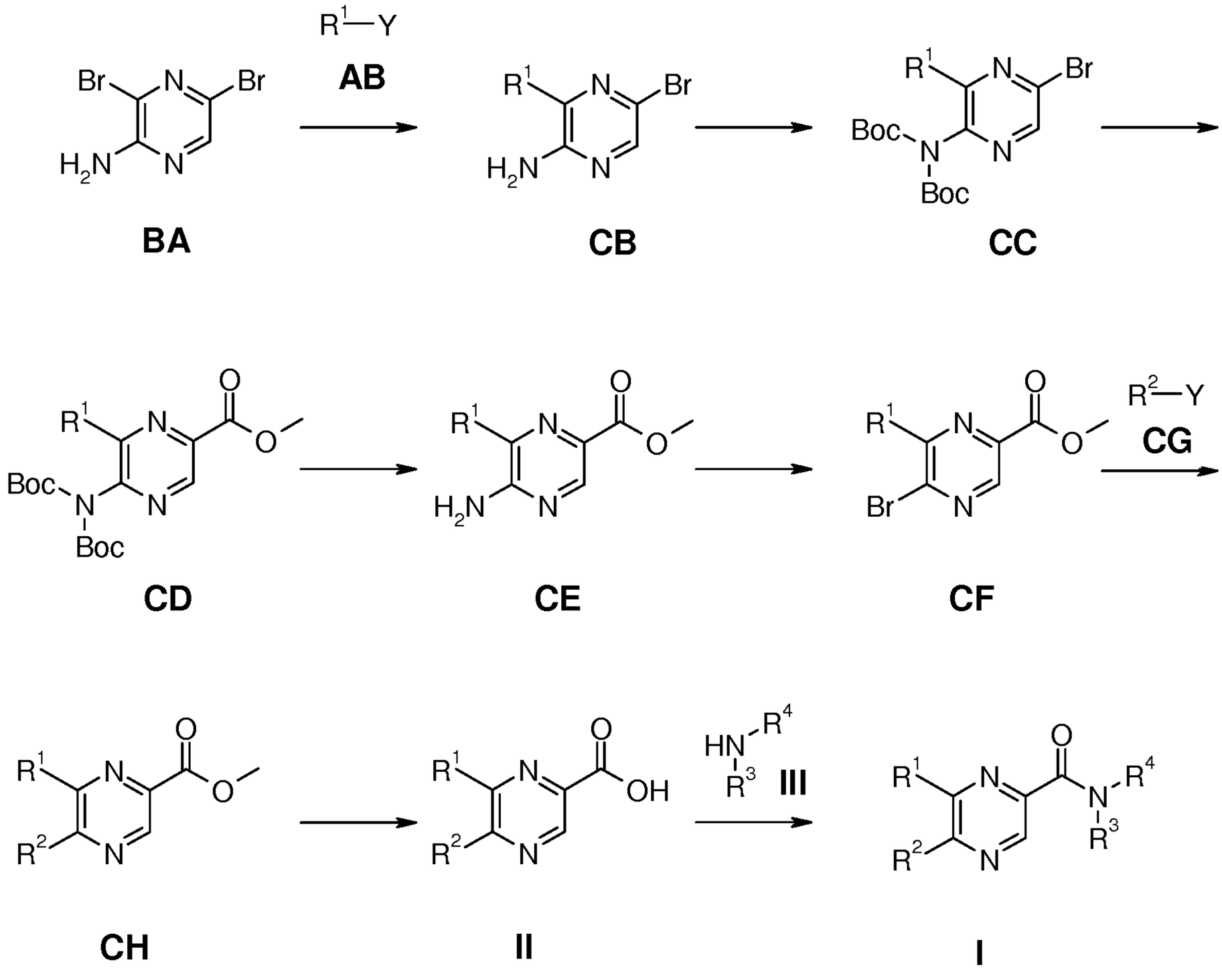
Following the procedure according to scheme 3, compound **BA** (3,5-dibromo-2-pyrazinamine, CAN 24241-18-7) can be used as starting material for the synthesis of compounds **I** where R^1 is cycloalkylalkoxy, haloalkoxy or alkoxyalkoxy.

Compound **BA** can be transformed to compounds **CB** by reaction with a suitably substituted primary or secondary alcohol **AB** (Y is H) in the presence of a base, for example sodium hydride, with or without an inert solvent, for example DMF, at temperatures ranging from room temperature to the reflux temperature of the solvent, particularly at room temperature.

The Boc-protection of compounds of general formula **CB** by methods well known to the ones skilled in the art - using e.g. di-*tert*-butyl dicarbonate in an inert solvent,

particularly dichloromethane in the presence of a catalytic amount of base, particularly dimethylaminopyridine - leads to compounds of general formula **CC** if an excess of di-*tert*-butyl dicarbonate is employed in the reaction.

Scheme 3



Compounds of the general formula **CD** can be obtained from compounds of the general formula **CC** by palladium (II), particularly palladium(II) acetate catalyzed carbonylation in the presence of a suitable base such as a tertiary amine base, particularly triethylamine, in a suitable solvent such as an alcohol, particularly methanol.

The solvolysis of boc-protected compounds of general formula **CD** by methods well known to the ones skilled in the art - using e.g. a protic solvent, particularly methanol at elevated temperatures, particularly reflux temperature - leads to compounds of general formula **CE**.

Compounds of the general formula **CF** can be obtained from compounds of the general formula **CE** by reaction with nitrosating agents such as a metal nitrite or an organic nitrite more particularly *tert*-butyl nitrite, in the presence of a bromide source such as hydrobromic acid or more particularly trimethylbromosilane in a suitable solvent such as halogenated hydrocarbons more particularly dibromomethane.

Compounds **CH** wherein R^2 is cycloalkyl can be prepared from **CF** by coupling a suitably substituted cycloalkyl or cycloalkenyl metal species **CG** (Y is e.g. a trifluoroborate group like $[BF_3]^-K^+$, a boronic acid group $B(OH)_2$ or a boronic acid pinacol ester group) particularly a cyclopropylboronic acid or cyclopropyltrifluoro-borate salt with **CF** in the presence of a suitable catalyst, particularly a palladium catalyst like palladium(II)acetate in the presence of cyclohexylphosphine in an inert solvent such as toluene at room temperature up to the reflux temperature of the solvent in the presence of a suitable base, like potassium phosphate. In cases where the practitioner skilled in the art chooses to couple with a cycloakenyl metal species, like cycloalkenylboronic acid esters, compounds **CH** will be obtained only after an additional hydrogenation step, for example by hydrogenation with hydrogen gas in the presence of a palladium catalyst, for example palladium on charcoal, in an inert solvent, for example ethanol, at suitable temperatures and pressures, particularly at ambient temperature and pressure.

Compounds **CH** where R^2 is haloazetidinyl can be prepared from **CF** by reacting with the corresponding haloazetidine **CG** (Y is H) in the presence of a base, particularly DBU or triethylamine, in an inert solvent, particularly DMSO or dioxane at temperatures ranging from room temperature to 45 °C.

The saponification of the ester of general formula **CH** by methods well known to the ones skilled in the art - using e.g. aqueous LiOH, NaOH or KOH in tetrahydrofuran/ethanol or another suitable solvent at temperatures between 0 °C and the reflux temperature of the solvent employed - leads to the acid of general formula **II**.

Compounds of formula **II** can be further elaborated to compound **I** by coupling a compound of formula **II-c** with an amine of the formula **III** by amide coupling methods known in the art, as for example with the help of an amide coupling agent under basic conditions. For example coupling reagents like *N,N'*-carbonyl-diimidazole (CDI), *N,N'*-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1-[bis(dimethylamino)-methylene]-*1H*-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU), 1-hydroxy-1,2,3-benzotriazole (HOBT), O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) or O-benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluoro-phosphate (HBTU) can be employed to affect such transformation. A convenient method is to use for example O-benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluoro-phosphate (HBTU) and a base, for example *N*-ethyl-*N*-isopropylpropan-2-amine (DIEA) in an inert solvent such as for example dimethylformamide at room temperature. Alternative methods known in the art may commence by preparing the acid chloride from **II** and coupling with an amine of formula **III** in the presence of a suitable base.

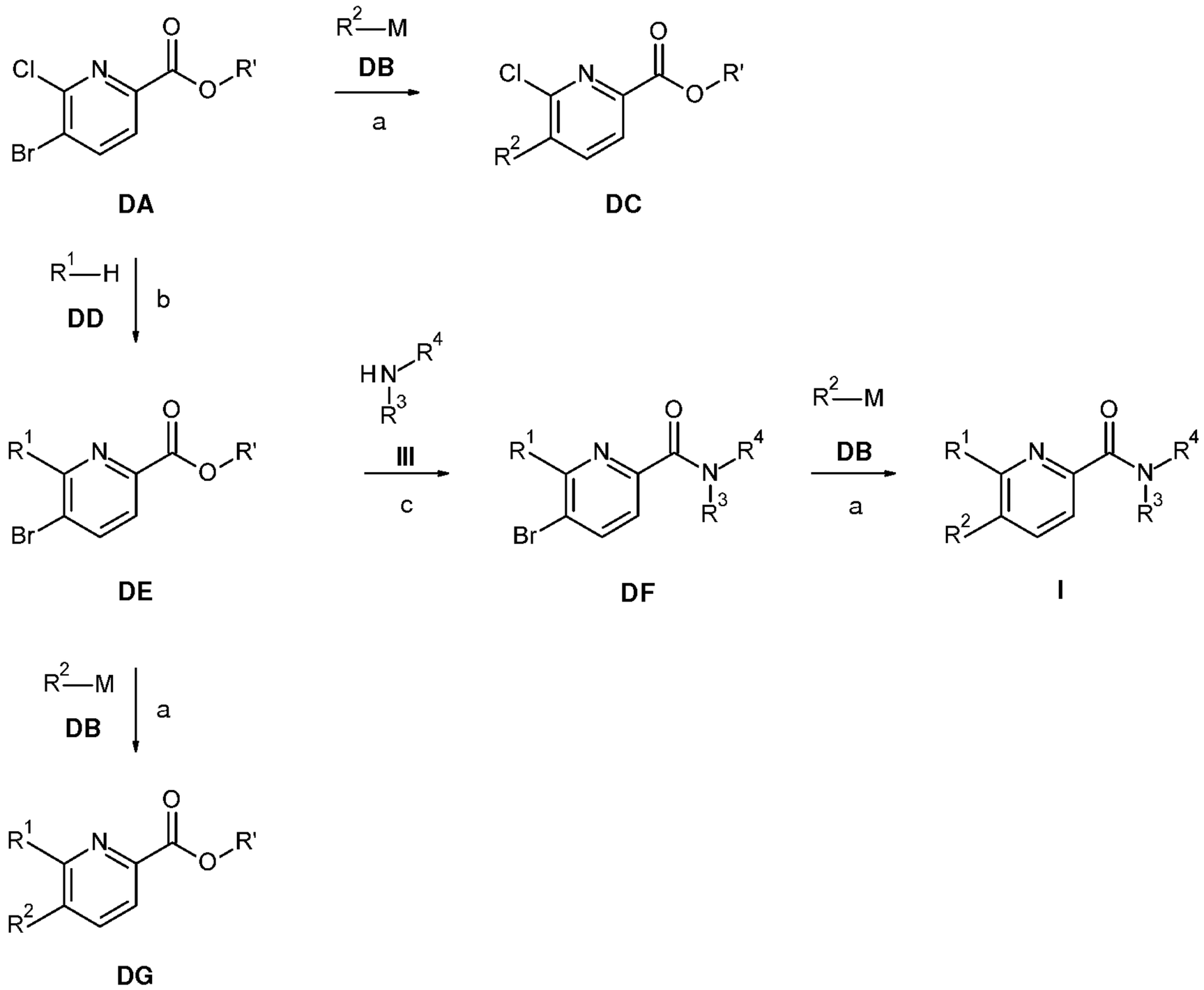
Amines **III** are either commercially available, described in the literature, can be synthesized by a person skilled in the art or obtained as described in the experimental part.

If one of the starting materials, compounds of formulae **BA**, **AB, CG** or **III**, 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 (P) (as described e.g. in T.W. Greene et al., Protective Groups in Organic Chemistry, John Wiley and Sons Inc. New York **1999**, 3rd edition) 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 known in the art.

If one or more compounds of formulae **BA**, **AB**, **CG** or **III** contain chiral centers, pyridines of formula **I** can be obtained as mixtures of diastereomers or enantiomers, which can be separated by methods well known in the art, e.g. (chiral) HPLC or crystallization. Racemic compounds can e.g. be separated into their antipodes via diastereomeric salts by crystallization or by separation of the antipodes by specific chromatographic methods using either a chiral adsorbens or a chiral eluent.

Following the procedure according to scheme 4, compound **DA** (R' = H, methyl, ethyl, isopropyl, tert. butyl or another suitable protecting group described for example in T.W. Greene et al., Protective Groups in Organic Chemistry, John Wiley and Sons Inc. New York **1999**, 3rd edition) can be used as starting material. **DA** is either commercially available (e.g. for R' = methyl: 5-bromo-6-chloro-pyridine-2-carboxylic acid methyl ester CAN 1214353-79-3), described in the literature or can be synthesized by a person skilled in the art.

Scheme 4



Compound **DC** can be prepared from **DA** by coupling a suitably substituted aryl, heteroaryl or alkenyl metal species of formula **DB** (M is e.g. a trifluoroborate group like $[BF_3]^-K^+$, a boronic acid group $B(OH)_2$ or a boronic acid pinacol ester group) (step a), e.g. an organotrifluoroborate potassium salt in the presence of a palladium catalyst such as palladium(II)acetate/butyl-1-adamantylphosphine and a base such as cesium carbonate in an inert solvent such as toluene at temperatures between 50 °C and the boiling temperature of the solvent, or an arylboronic acid or arylboronic acid ester in the presence of a suitable catalyst, in particular a palladium catalyst and more particularly palladium(II)acetate/triphenylphosphine mixtures or palladium(II)chloride-dppf (1,1'-bis(diphenylphosphino)ferrocene) complexes and a base such as triethylamine, sodium carbonate or potassium phosphate in an inert solvent such as dimethylformamide, toluene, tetrahydrofuran, acetonitrile or dimethoxyethane. Optionally, compound **DB** (M is H) can also be an amine or amide which is coupled to **DA** by methods well known to a person skilled in the art, e.g. using a palladium catalyst such as tris(dibenzylideneacetone)dipalladium / dimethylbisdiphenyl-phosphinoxanthene and a base such as cesium carbonate in a solvent such as 1,4-dioxane, preferentially at the boiling point of the solvent. Alternatively, compound **DB** can also be a sulfonamide (M is H) which undergoes a copper(I) mediated reaction with **DA** to form **DC** following

procedures described in the literature, e.g. using copper(I) iodide and 1,3-di(pyridin-2-yl)propane-1,3-dione in the presence of a base such as potassium carbonate in a solvent such as dimethylformamide at elevated temperatures preferentially at the boiling point of the solvent. Optionally, alkenyl containing R^2 residues can be transformed to the corresponding alkyl congeners **DC** using conditions described in the literature such as e.g. a hydrogenation reaction using hydrogen gas in the presence of a catalyst such as palladium on carbon in a solvent such as ethanol or ethyl acetate particularly at ambient temperature.

Compound **DC** can be further elaborated to compound **I** by: i) reaction with compound **DD** to form compound **DG** as described in steps a and a' of scheme 1; ii) saponification as described in step b of scheme 1; and iii) amide bond formation as described in step c of scheme 1.

Furthermore, compound **DA** can be converted into compound **DE** by treatment with compound **DD** as described in steps a and a' of scheme 1 (step b).

Subsequent transformation of compound **DE** into compound **DG** can be achieved as discussed for the conversion of **DA** into **DC** (step a).

Compound **DG** can be further elaborated to compound **I** by: i) saponification as described in step b of scheme 1; ii) amide bond formation as described in step c of scheme 1.

Alternatively, compound **DE** (R' = methyl, ethyl, isopropyl, tert. butyl or another suitable protecting group described for example in T.W. Greene et al., Protective Groups in Organic Chemistry, John Wiley and Sons Inc. New York **1999**, 3rd edition) can be: i) converted into its acid congener **DE** (R' = H) as described in step b of scheme 1; ii) transformed into the corresponding amide **DF** by treatment with amine **III** as described in step c of scheme 1; and iii) reacted with **DB** as described in step a to arrive at compound **I**.

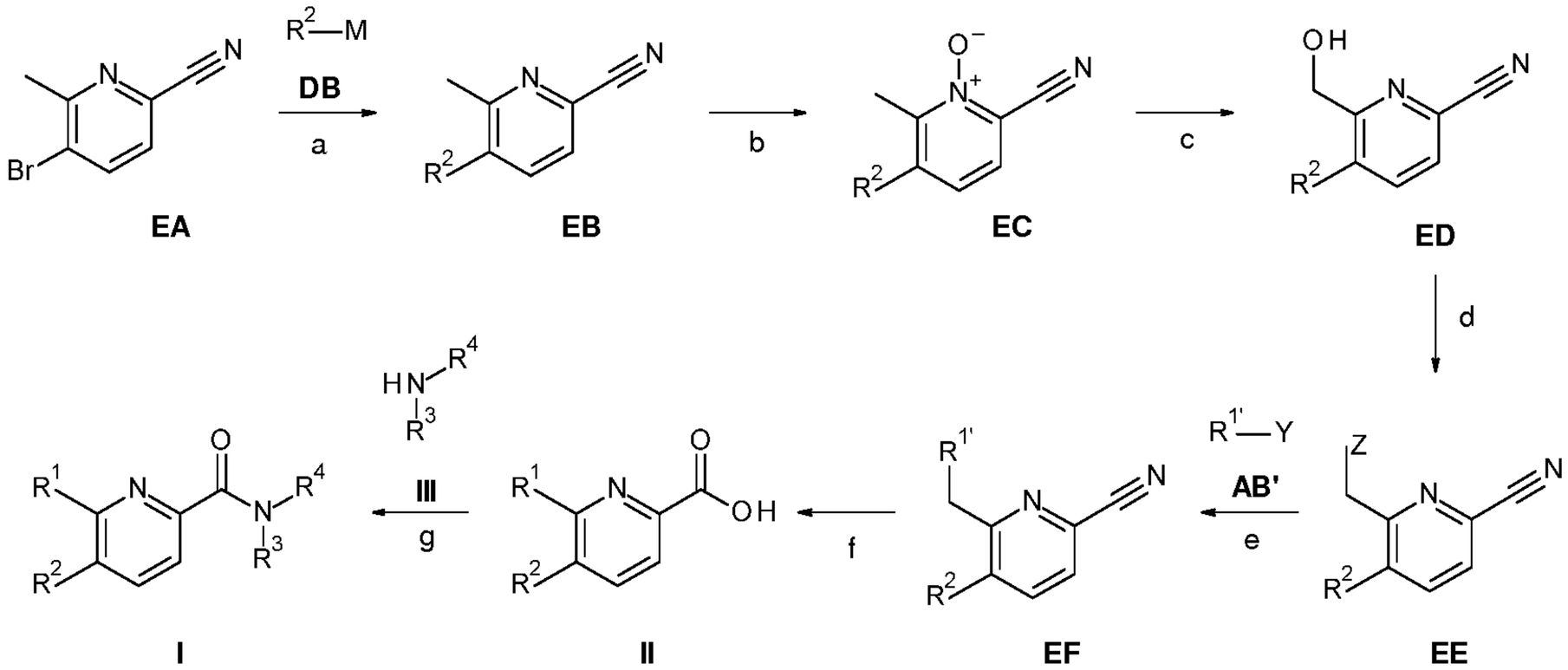
Furthermore, compound **I** can also be synthesized applying the following reaction sequence: i) saponification of compound **DA** (R' = methyl, ethyl, isopropyl, tert. butyl or another suitable protecting group described for example in T.W. Greene et al., Protective Groups in Organic Chemistry, John Wiley and Sons Inc. New York **1999**, 3rd edition) to its acid congener **DE** (R' = H) as described in step b of scheme 1; ii) conversion to the corresponding amide by treatment with amine **III** as described in step c of scheme 1; iii) reaction with compound **DB** as described in step a; and iv) reaction with compound **DD** as described in step c. Optionally step iii) and step iv) can be interchanged.

If one of the starting materials, compounds of formulae **DA, DB** or **DD** 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 (P) (as described e.g. in T.W. Greene et al., Protective Groups in Organic Chemistry, John Wiley and Sons Inc. New York **1999**, 3rd edition) 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 known in the art.

If one or more compounds of formulae **DA, DB** or **DD** contain chiral centers, picolines of formula **DC** and **DG** can be obtained as mixtures of diastereomers or enantiomers, which can be separated by methods well known in the art, e.g. (chiral) HPLC or crystallization. Racemic compounds can e.g. be separated into their antipodes via diastereomeric salts by crystallization or by separation of the antipodes by specific chromatographic methods using either a chiral adsorbent or a chiral eluent.

Following the procedure according to scheme 5, commercially available 5-bromo-6-methyl-pyridine-2-carbonitrile **EA** (CAN 1173897-86-3) can be used as starting material. In scheme 5, R^1 is benzyl or halobenzyl; $R^{1'}$ is phenyl or halophenyl.

Scheme 5



Compound **EB** can be prepared from **EA** by coupling a suitably substituted aryl, heteroaryl or alkenyl metal species of formula **DB** (Y is e.g. a trifluoroborate group like $[BF_3]^-K^+$, a boronic acid group $B(OH)_2$ or a boronic acid pinacol ester group) (step a), e.g. an organotrifluoroborate potassium salt in the presence of a palladium catalyst such as palladium(II)acetate/butyl-1-adamantylphosphine and a base such as cesium carbonate in an inert solvent such as toluene at temperatures between 50 °C and the boiling temperature of the solvent, or an arylboronic acid or arylboronic acid ester in the presence of a suitable catalyst, in particular a palladium catalyst, more particularly

palladium(II)acetate/triphenylphosphine mixtures or palladium(II)chloride-dppf (1,1'-bis(diphenylphosphino)ferrocene) complexes and a base such as triethylamine, sodium carbonate or potassium phosphate in an inert solvent such as dimethylformamide, toluene, tetrahydrofuran, acetonitrile or dimethoxyethane. Optionally, compound **DB** can also be an amine or amide (Y is H) which is coupled to **EA** by methods well known to a person skilled in the art, e.g. using a palladium catalyst such as tris(dibenzylideneacetone)dipalladium/dimethylbisdiphenyl-phosphinoxanthene and a base such as cesium carbonate in a solvent such as 1,4-dioxane preferentially at the boiling point of the solvent. Optionally, alkenyl containing R^2 residues can be transformed to the corresponding alkyl congeners **EA** using conditions described in the literature such as e.g. a hydrogenation reaction using hydrogen gas in the presence of a catalyst such as palladium on carbon in a solvent such as ethanol or ethyl acetate particularly at ambient temperature.

Further transformation of **EB** to **EC** can be achieved by oxidation with a suitable oxidizing reagent under conditions known to a person skilled in the art, e.g. by treatment with 3-chloro perbenzoic acid in dichloromethane at ambient temperature (step b).

Conversion of *N*-oxide **EC** to alcohol **ED** can be performed under conditions well known to a person skilled in the art, e.g. by reaction with trifluoroacetic acid anhydride in a solvent such as dichloromethane preferentially at ambient temperature and subsequent treatment with a base such as sodium hydroxide (step c).

Reactions how to convert alcohol **ED** into compound **EE** containing a leaving group (Z = Cl, Br or another suitable leaving group) are well described in the literature and known to those skilled in the art (step d). For example alcohol **ED** can be transformed to compound **EE** with Z = Br by reaction with carbon tetrabromide and triphenylphosphine in a solvent such as tetrahydrofuran at temperatures between 0 °C and the boiling point of the solvent, preferentially at 40 °C.

Conversion of compound **EE** to compound **EF** can e.g. be accomplished by coupling a suitably substituted aryl metal species of formula **AB'** (Y is e.g. a boronic acid group $B(OH)_2$ or a boronic acid pinacol ester group), particularly an arylboronic acid or arylboronic acid ester in the presence of a suitable catalyst, in particular a palladium catalyst and more particularly palladium(II)acetate/triphenylphosphine mixtures or palladium(II)chloride-dppf (1,1'-bis(diphenylphosphino)ferrocene) complexes and a base such as triethylamine, cesium carbonate or potassium phosphate in an inert solvent such as dimethylformamide, toluene, tetrahydrofuran or 1,4-dioxane (step e).

Nitrile **EF** can be hydrolyzed to acid **II** (A = CH) under acidic or basic conditions known to a person skilled in the art, e.g. by treatment with an aqueous solution of sodium hydroxide at 100 °C (step f).

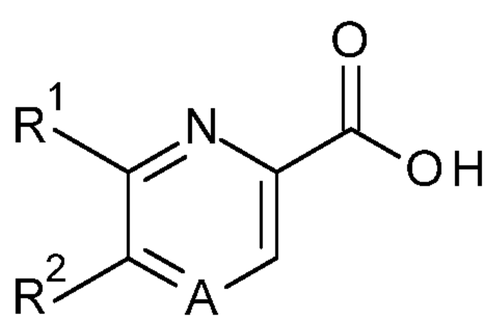
Further conversion of compound **II** to compound **I** can be done by applying amide bond formation conditions as depicted in step c of scheme 1 (step g).

If one of the starting materials, compounds of formulae **EA**, **DB**, **AB'** or **III**, 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 (P) (as described e.g. in T.W. Greene et al., Protective Groups in Organic Chemistry, John Wiley and Sons Inc. New York **1999**, 3rd edition) 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 known in the art.

If one or more compounds of formulae **EA** to **EF**, **DB**, **AB'**, **II** or **III** contain chiral centers, picolines of formula **I** can be obtained as mixtures of diastereomers or enantiomers, which can be separated by methods well known in the art, e.g. (chiral) HPLC or crystallization. Racemic compounds can e.g. be separated into their antipodes via diastereomeric salts by crystallization or by separation of the antipodes by specific chromatographic methods using either a chiral adsorbent or a chiral eluent.

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

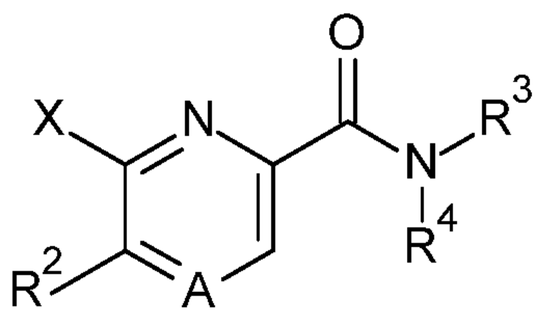
(a) the reaction of a compound of formula (A)



(A)

in the presence of NHR^3R^4, an amide coupling agent and a base, wherein A and R^1 to R^4 are as defined above;

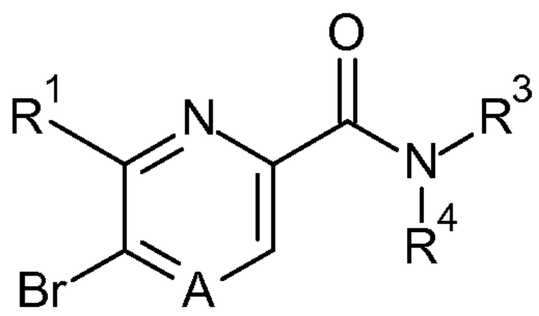
(b) the reaction of a compound of formula (B)



(B)

in the presence of R^1-Y, a palladium catalyst and a base, wherein X is Cl, Br, I or trifluoromethanesulfonate, Y is a trifluoroborate group, a boronic acid group or a boronic acid pinacol ester group, R^1 is halophenyl or halophenylalkyl and A and R^2 to R^4 are as defined above; or

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



(C)

in the presence of R^2-M, a palladium catalyst and a base, wherein R^1 is halophenyl, halophenylalkyl or oxopyrrolidinyl, R^2 is cycloalkyl, A and R^3-R^4 are as defined above and M is a trifluoroborate group, a boronic acid group or a boronic acid pinacol ester group.

In step (a), amide coupling agents for the reaction of compounds of formula (A) with amines of formula NHR^3R^4 are for example *N,N'*-carbonyldiimidazole (CDI), *N,N'*-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1-[bis(dimethylamino)-methylene]-*1H*-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU), 1-hydroxy-1,2,3-benzotriazole (HOBT), O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU), or O-benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluoro-phosphate (HBTU). Particular coupling agents are TBTU and HATU.

In step (a), suitable bases include triethylamine, *N*-methylmorpholine and particularly diisopropylethylamine.

Alternative methods known in the art may commence by preparing the acid chloride from (A) and coupling with an amine of formula NHR^3R^4 in the presence of a suitable base.

In step (b), the palladium catalyst is for example palladium(II)acetate in the presence of cyclohexylphosphine.

In step (b), the base is for example potassium phosphate.

In step (c), the palladium catalyst is for example palladium(II)acetate in the presence of butyl-1-adamantylphosphine.

In step (c), the base is for example cesium carbonate.

The invention further relates to a compound of formula (I) when manufactured according to the above process.

Another embodiment of the invention provides a pharmaceutical composition or medicament containing a compound of the invention and a therapeutically inert carrier, diluent or excipient, as well as a method of using the compounds of the invention to prepare such composition and medicament. In one example, the compound of formula (I) may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of formula (I) is formulated in an acetate buffer, at pH 5. In another embodiment, the compound of formula (I) is sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners.

The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain

components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

The invention thus also relates to:

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 treatment or prophylaxis of pain, neuropathic pain, asthma, osteoporosis, inflammation, psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, psychiatric disorders rheumatoid arthritis, psychosis or allergy;

The use of a compound of formula (I) for the preparation of a medicament for the treatment or prophylaxis of pain, neuropathic pain, asthma, osteoporosis, inflammation, psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, psychiatric disorders rheumatoid arthritis, psychosis or allergy;

A compound of formula (I) for the treatment or prophylaxis of pain, neuropathic pain, asthma, osteoporosis, inflammation, psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, psychiatric disorders rheumatoid arthritis, psychosis or allergy; and

A method for the treatment or prophylaxis of pain, neuropathic pain, asthma, osteoporosis, inflammation, psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, psychiatric disorders rheumatoid arthritis, psychosis or allergy, which method comprises administering an effective amount of a compound of formula (I) to a patient in need thereof.

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

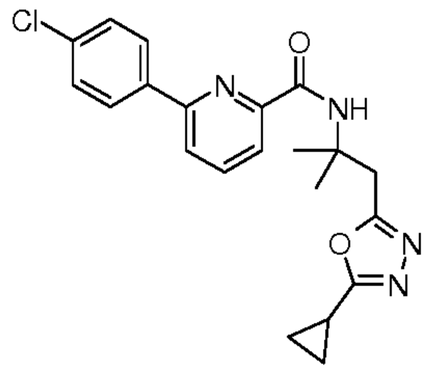
Examples

Abbreviations

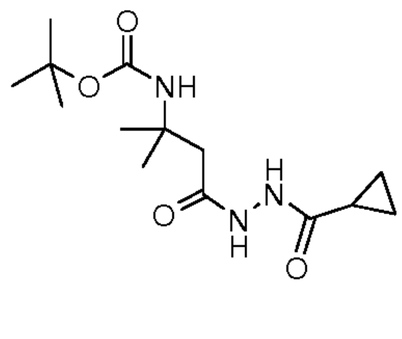
MS = mass spectrometry; EI = electron impact; ISP = ion spray, corresponds to ESI (electrospray); NMR data are reported in parts per million (δ) relative to internal tetramethylsilane and are referenced to the deuterium lock signal from the sample solvent (d_6-DMSO unless otherwise stated); coupling constants (J) are in Hertz, mp = melting point; bp = boiling point; DIEA = N-ethyl-N-isopropylpropan-2-amine; DMF = dimethylformamide; DMSO = dimethyl-sulfoxide; dppf = 1,1'-bis(diphenylphosphino)ferrocene; EtOAc = ethyl acetate, HATU = 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V); HBTU = O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate; HPLC = LC = high performance liquid chromatography; iPrOAc = isopropyl acetate; *m*-CPBA = meta-chloroperoxybenzoic acid; Rt = retention time; TBTU = O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyl-uronium-tetrafluoroborate; TEMPO = 2,2,6,6-tetra-methylpiperidine 1-oxyl radical; THF = tetrahydrofuran; tlc = thin layer chromatography.

Example 1

6-(4-Chlorophenyl)-*N*-[1-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-yl]pyridine-2-carboxamide



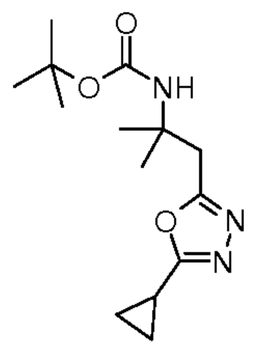
a) *tert*-Butyl *N*-[4-[2-(cyclopropanecarbonyl)hydrazinyl]-2-methyl-4-oxobutan-2-yl]carbamate



To a mixture of 3-[[(1,1-dimethylethoxy)carbonyl]amino]-3-methyl-butanoic acid (CAN 129765-95-3, 1.43 g, 6.59 mmol), DIEA (3.41 mL, 19.8 mmol) and TBTU (2.12 g, 6.59 mmol) in DMF (50 mL) was added cyclopropanecarboxylic acid hydrazide (CA 6952-93-8, 0.66 g, 6.59 mmol). The reaction mixture was stirred for 10 hours at room temperature and afterwards the solvent was removed *in vacuo*.The residue was dissolved in ethyl

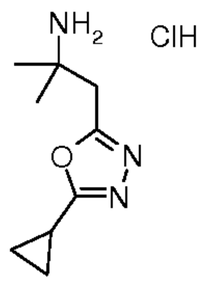
acetate (50 mL) and washed with saturated sodium bicarbonate solution (50 mL), 1 N hydrochloric acid (30 mL) and brine (30 mL). Water phases were extracted with ethyl acetate (50 mL), organic phases were pooled, dried with MgSO4, filtered and concentrated *in vacuo* to give the title compound (1.7 g, 77%) in approx. 90 % purity as yellow oil; MS (ISP): 300.2 [MH^+].

b) *tert*-Butyl *N*-[1-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-yl]carbamate



To a mixture of *tert*-butyl *N*-[4-[2-(cyclopropanecarbonyl)hydrazinyl]-2-methyl-4-oxobutan-2-yl]carbamate (1.70 g, 5.68 mmol) and triphenylphosphine (2.23 g, 8.52 mmol) in acetonitrile (60 mL) was added DIEA (2.98 mL, 17 mmol) and hexachloroethane (1.74 g, 7.38 mmol). The reaction mixture was stirred for 4 hours at room temperature and afterwards the solvent was removed *in vacuo*.The residue was dissolved in dichloromethane (80 mL) and washed with water (2x40 mL) and brine (40 mL). Water phases were extracted with dichloromethane (80 mL), organic phases were pooled, dried with MgSO4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 0% to 100% ethyl acetate in heptane) to give the title compound (1.02 g, 64%) as white solid; MS (ISP): 282.2 [MH^+].

c) 1-(5-Cyclopropyl-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-amine hydrochloride



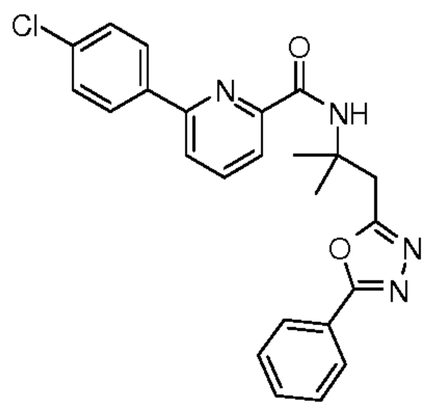
tert-Butyl *N*-[1-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-yl]carbamate (1.02 g, 3.63 mmol) was dissolved in dioxane (14 mL) and a solution of 4 N HCl in dioxane (9.1 mL, 36.3 mmol) was added. The reaction mixture was stirred for 18 hours at room temperature and afterwards diluted with *tert*-butyl methylether (50 mL). The product precipitated and was isolated by filtration and subsequent drying in vacuo to give the title compound (718 mg, 91%) as white solid; MS (ISP): 182.1 [MH^+].

d) 6-(4-Chlorophenyl)-*N*-[1-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-yl]pyridine-2-carboxamide

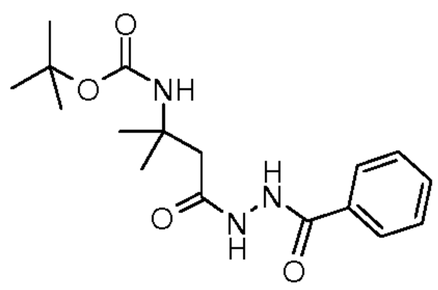
A solution of 6-(4-chlorophenyl)-2-pyridinecarboxylic acid (CAN 135432-77-8, 0.2 mmol), 1-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-amine hydrochloride (0.2 mmol), DIEA (175 µL, 1 mmol) and TBTU (77.1 mg, 0.24 mmol) in DMF (0.5 mL) was stirred for 20 h at room temperature. The crude reaction mixture was concentrated *in vacuo* by centrifugation and purified by flash chromatography (silica gel, 0% to 100% ethyl acetate in heptane) to give the title compound (64 mg, 81%) as light-yellow solid; LC-MS (UV peak area/ESI) 99%, 397.1426 [MH^+].

Example 2

6-(4-Chlorophenyl)-*N*-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide

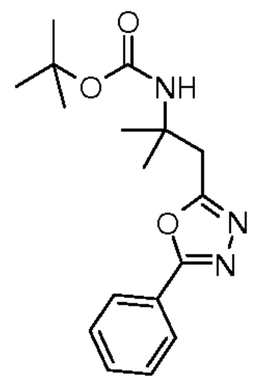


a) *tert*-Butyl N-[4-(2-benzoylhydrazinyl)-2-methyl-4-oxobutan-2-yl]carbamate



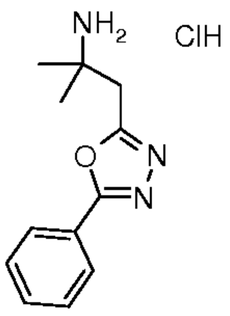
The title compound was synthesized in analogy to Example 1a, using 3-[[(1,1-dimethylethoxy)carbonyl]amino]-3-methyl-butanoic acid (CAN 129765-95-3, 1.36 g, 6.24 mmol) and benzoic acid hydrazide (CAN 613-94-5, 0.85 g, 6.24 mmol) as starting materials and isolated (1.97 g, 85%) in approx. 90% purity as orange oil, MS (ISP): 336.3 [MH^+].

b) *tert*-Butyl *N*-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]carbamate



The title compound was synthesized in analogy to Example 1b, using *tert*-butyl N-[4-(2-benzoylhydrazinyl)-2-methyl-4-oxobutan-2-yl]carbamate (Example 2a, 1.97 g, 5.87 mmol) as starting material and isolated (1.32 g, 71%) as white solid, MS (ISP): 318.1 [MH^+].

c) 2-Methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-amine hydrochloride



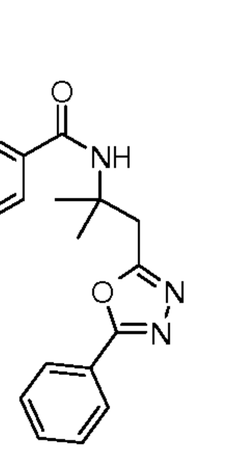
The title compound was synthesized in analogy to Example 1c, using 6 *tert*-butyl *N*-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]carbamate (Example 2b, 1.32 g, 4.16 mmol) as starting material and isolated (1.03 g, 98%) as white solid, MS (ISP): 218.1 [MH^+].

d) 6-(4-Chlorophenyl)-*N*-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide

The title compound was synthesized in analogy to Example 1d, using 6-(4-chlorophenyl)-2-pyridinecarboxylic acid (CAN 135432-77-8, 0.2 mmol) and 2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-amine hydrochloride (Example 2c, 0.2 mmol) as starting materials and isolated (71 mg, 82%) as light yellow solid, LC-MS (UV peak area/ESI) 100%, 433.1417 [MH^+].

Example 3

N-[2-Methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]-6-(2,2,2-trifluoroethoxy)pyridine-2-carboxamide



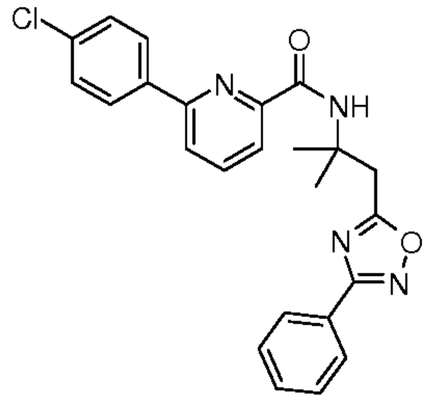
6-(2,2,2-trifluoroethoxy)-2-pyridinecarboxylic acid (CAN 1247503-48-5)

The title compound was synthesized in analogy to Example 1d, using 6-(2,2,2-trifluoroethoxy)-2-pyridinecarboxylic acid (CAN 1247503-48-5, 0.2 mmol) and 2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-amine hydrochloride (Example 2c, 0.2 mmol)

as starting materials and isolated (59 mg, 70%) as white solid, LC-MS (UV peak area/ESI) 99%, 421.1475 [MH^+].

Example 4

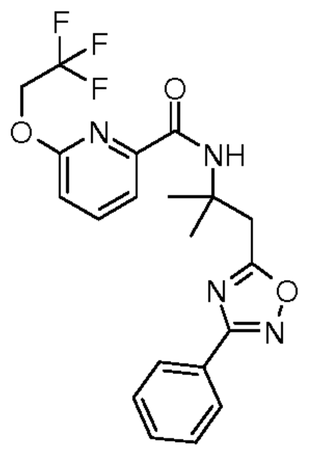
6-(4-Chlorophenyl)-N-[2-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]pyridine-2-carboxamide



The title compound was synthesized in analogy to Example 1d, using 6-(4-chlorophenyl)-2-pyridinecarboxylic acid (CAN 135432-77-8, 0.2 mmol) and α,α-dimethyl-3-phenyl-1,2,4-oxadiazole-5-ethanamine hydrochloride (1:1) (CAN 1426444-03-2, 0.2 mmol) as starting materials and isolated (83 mg, 96%) as light yellow solid, LC-MS (UV peak area/ESI) 100%, 433.1421 [MH^+].

Example 5

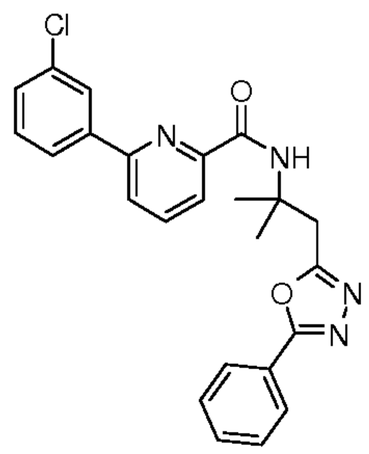
***N*-[2-Methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]-6-(2,2,2-trifluoroethoxy)pyridine-2-carboxamide**



The title compound was synthesized in analogy to Example 1d, using 6-(2,2,2-trifluoroethoxy)-2-pyridinecarboxylic acid (CAN 1247503-48-5, 0.2 mmol) and α,α-dimethyl-3-phenyl-1,2,4-oxadiazole-5-ethanamine hydrochloride (1:1) (CAN 1426444-03-2, 0.2 mmol) as starting materials and isolated (66 mg, 79%) as white solid, LC-MS (UV peak area/ESI) 98%, 421.1476 [MH^+].

Example 6

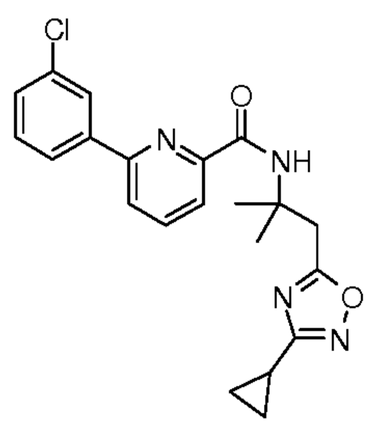
6-(3-Chlorophenyl)-*N*-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide



The title compound was synthesized in analogy to Example 1d, using 6-(3-chlorophenyl)-2-pyridinecarboxylic acid (CAN 863704-38-5, 0.2 mmol) and 2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-amine hydrochloride (Example 2c, 0.2 mmol) as starting materials and isolated (84 mg, 97%) as white solid, LC-MS (UV peak area/ESI) 95%, 433.1431 [MH^+].

Example 7

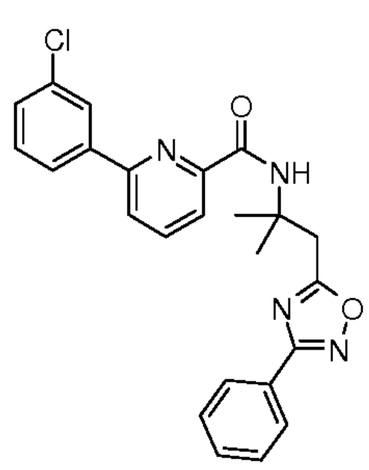
6-(3-Chlorophenyl)-*N*-[1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2-methylpropan-2-yl]pyridine-2-carboxamide



The title compound was synthesized in analogy to Example 1d, using 6-(3-chlorophenyl)-2-pyridinecarboxylic acid (CAN 863704-38-5, 0.2 mmol) and 3-cyclopropyl-α,α-dimethyl-1,2,4-oxadiazole-5-ethanamine (CAN1341734-01-7, 0.2 mmol) as starting materials and isolated (73 mg, 92%) as orange solid, LC-MS (UV peak area/ESI) 100%, 397.1434 [MH^+].

Example 8

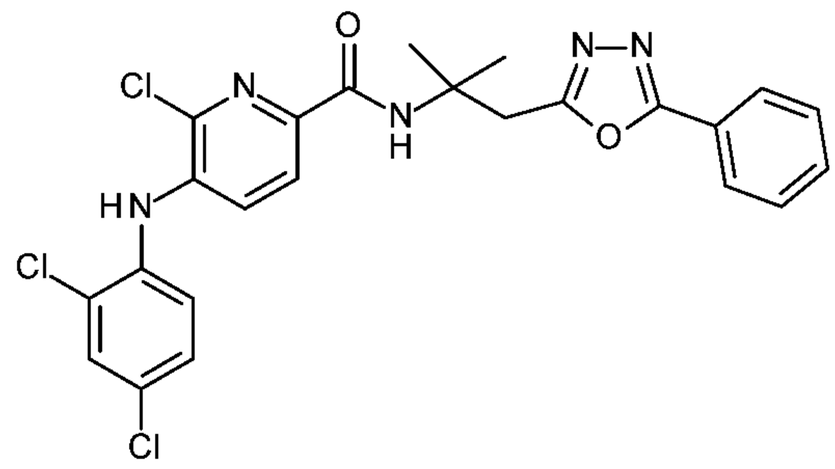
6-(3-Chlorophenyl)-*N*-[2-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]pyridine-2-carboxamide



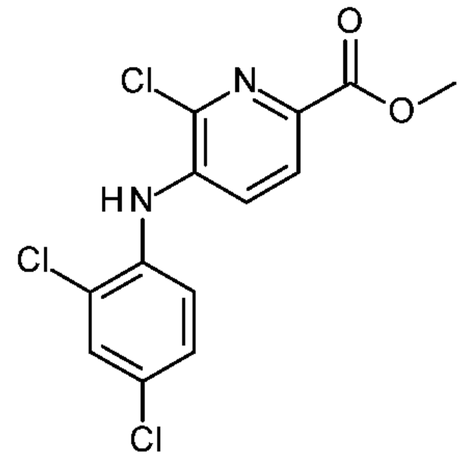
The title compound was synthesized in analogy to Example 1d, using 6-(3-chlorophenyl)-2-pyridinecarboxylic acid (CAN 863704-38-5, 0.2 mmol) and α,α-dimethyl-3-phenyl-1,2,4-oxadiazole-5-ethanamine hydrochloride (1:1) (CAN 1426444-03-2, 0.2 mmol) as starting materials and isolated (83 mg, 96%) as white solid, LC-MS (UV peak area/ESI) 100%, 433.1428 [MH^+].

Example 9

6-Chloro-5-(2,4-dichloroanilino)-*N*-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide

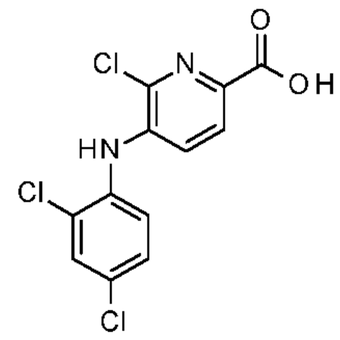


a) 6-Chloro-5-(2,4-dichloroanilino)pyridine-2-carboxylic acid methyl ester



Under an argon atmosphere a mixture of palladium(II)acetate (4.4 mg, 19 µmol) and 2-(dicyclohexylphosphino)biphenyl (13.6 mg, 39 µmol) in dioxane (1.9 mL) was stirred for 10 min at ambient temperature and added to a suspension of methyl 5,6-dichloropyridine-2-carboxylate (CAN 1214375-24-2, 100 mg, 485 µmol), 2,4-dichloroaniline (CAN 554-00-7, 78.6 mg, 485 µmol) and K_2CO_3 (1.34 g, 9.71 mmol) in dioxane (3.24 mL). The reaction mixture was heated to reflux and stirred for 20 h, poured into 20 mL ice / brine and extracted with iPrOAc (2 x 50 mL). The organic layers were washed with ice / brine (1 x 50 mL), dried over Na_2SO_4 and concentrated in vacuo to give 108 mg of a brown oil. The crude product was purified by preparative TLC (2 mm SiO_2 layer, with heptane / iPrOAc 9:1, elution with iPrOAc) to give the title compound (6 mg, 18 µmol, 4%) as brown solid.

b) 6-Chloro-5-(2,4-dichloroanilino)pyridine-2-carboxylic acid



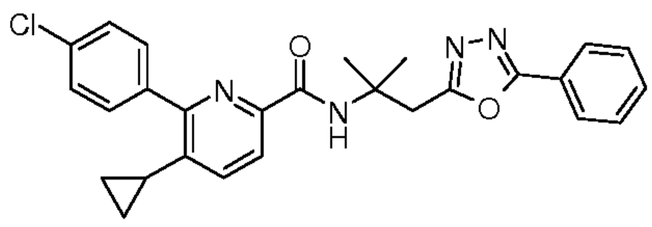
Lithium hydroxide hydrate (911 µg, 22 µmol) was added to a solution of 6-chloro-5-(2,4-dichloroanilino)pyridine-2-carboxylic acid methyl ester (6 mg, 18 µmol) in THF (49 µL) and water (25 µL). The reaction mixture was stirred at ambient temperature for 20 h, poured onto 1 M HCl / icewater (20 mL) and extracted with iPrOAc (2 x 25 mL). The combined extracts were washed with ice/water (2 x 25 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the title compound (6 mg, 19 µmol, quant.) as offwhite solid which was sufficiently pure to be used in the next reaction step, MS (ISP): 314.8 [MH^-].

c) 6-Chloro-5-(2,4-dichloroanilino)-*N*-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide

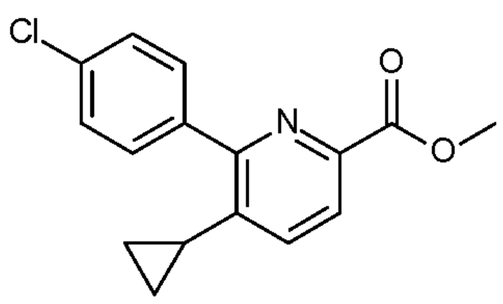
The title compound was synthesized in analogy to Example 1d, using 6-chloro-5-(2,4-dichloroanilino)pyridine-2-carboxylic acid (19 µmol) and 2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-amine hydrochloride (Example 2c, 21 µmol) as starting materials and isolated (7 mg, 57%) as colorless oil, LC-MS: 518.0724 [MH^+].

Example 10

6-(4-Chlorophenyl)-5-cyclopropyl-*N*-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide



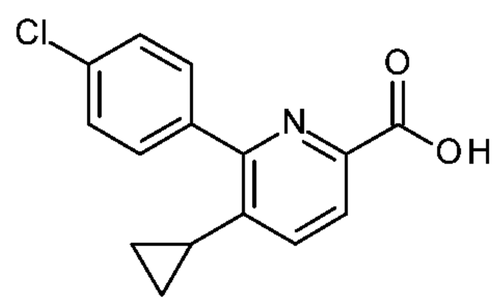
a) 6-(4-Chlorophenyl)-5-cyclopropyl-pyridine-2-carboxylic acid methyl ester



A suspension of methyl methyl 6-chloro-5-cyclopropyl-pyridine-2-carboxylate (CAN 1415898-27-9, 100 mg, 472 µmol), 4-chlorophenylboronic acid (CAN 1679-18-1, 88.7 mg, 567 µmol), 2 M aqueous sodium carbonate solution (472 µL, 945 µmol) and 1,1'-

bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (19.3 mg, 23.6 µmol) in toluene (1.5 mL) was heated to 90 °C for 30 h under an argon atmosphere. The reaction mixture was filtered through Speedex. The sovent was removed under reduced pressure to give 145 mg of brown cristals which were purified by flash-chromatographie (5g SiO_2, heptan / 0-30% iPrOAc in 75min) to give the title compound (92 mg, 68%) as off-white crystals, MS (ISP): 288.2 [MH^+].

b) 6-(4-Chlorophenyl)-5-cyclopropyl-pyridine-2-carboxylic acid



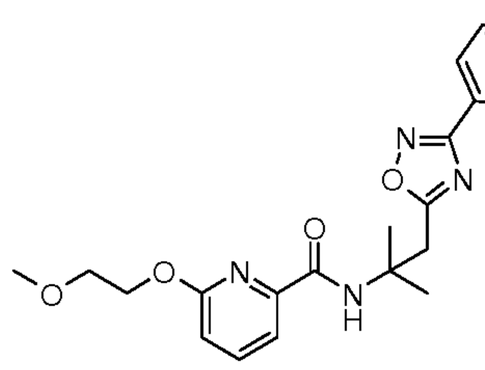
In analogy to the procedure described in Example 9 b, 6-(4-chlorophenyl)-5-cyclopropyl-pyridine-2-carboxylic acid methyl ester (313 µmol) was hydrolyzed to give the title compound (102 mg, quant.) as colorless oil, MS (ISP): 272.1 [MH^-].

c) 6-(4-Chlorophenyl)-5-cyclopropyl-*N*-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide

The title compound was synthesized in analogy to Example 1d, using 6-(4-chlorophenyl)-5-cyclopropyl-pyridine-2-carboxylic acid (37 µmol) and 2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-amine hydrochloride (Example 2c, 37 µmol) as starting materials and isolated (13 mg, 75%) as colorless oil, MS (ISP): 473.3 [MH^+].

Example 11

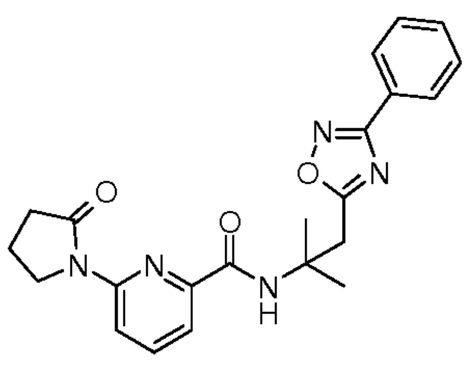
6-(2-Methoxyethoxy)-*N*-[2-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]pyridine-2-carboxamide



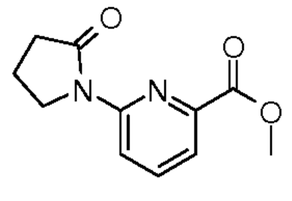
The title compound was synthesized in analogy to Example 1d, using 6-(2-methoxyethoxy)-2-pyridinecarboxylic acid (CAN 1248697-20-2, 0.1 mmol) and α,α-dimethyl-3-phenyl-1,2,4-oxadiazole-5-ethanamine hydrochloride (1:1) (CAN 1426444-03-2, 0.1 mmol) as starting materials and isolated (33 mg, 97%) as colorless oil, LC-MS (UV peak area/ESI) 100%, 397.1866 [MH^+].

Example 12

_N_-[2-Methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]-6-(2-oxopyrrolidin-1-yl)pyridine-2-carboxamide

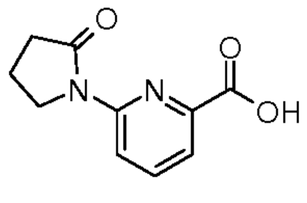


a) 6-(2-Oxopyrrolidin-1-yl)pyridine-2-carboxylic acid methylester



To a red suspension of 6-chloro-2-pyridinecarboxylic acid methyl ester (CAN 6636-55-1, 515 mg, 3 mmol), cesium carbonate (1.47 g, 4.5 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (17.4 mg, 0.03 mmol) and tris(dibenzylideneacetone)dipalladium (0) (27.5 mg, 0.03 mmol) in dioxane (5 mL) was added 2-pyrrolidone (511 mg, 6 mmol). The reaction mixture was microwaved twice for 30 minutes at 140 °C, cooled and partitioned between ethyl acetate and brine. Organic phases were pooled, dried with MgSO4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 50% ethyl acetate in heptane) to give the title compound (860 mg, quant.) as white solid that was used without further purification in the next step; LC-MS (UV peak area/ESI) 94%, 221.0922 [MH^+].

b) 6-(2-Oxopyrrolidin-1-yl)pyridine-2-carboxylic acid



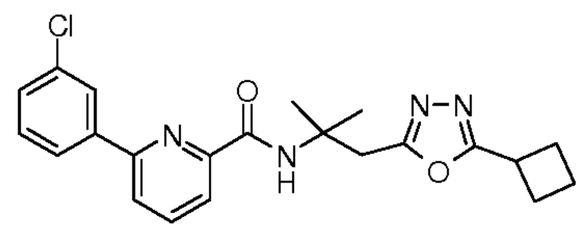
A solution of 6-(2-oxopyrrolidin-1-yl)pyridine-2-carboxylic acid methylester (911 mg, 4.11 mmol), and lithiumhydroxide (297 mg, 12. 4 mmol) in THF (85 mL) and water (25 mL) was stirred at 0 °C for 3 hours. The reaction mixture was pured onto 1 N hydrochloric acid (200 mL) and extracted with ethyl acetate (2x200 mL). Organic phases were pooled, dried with MgSO4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, ethyl acetate) to give the title compound (212 mg, 25%) as light yellow solid; MS (ISP): 204.9 [$M-H^-$].

c) *N*-[2-Methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]-6-(2-oxopyrrolidin-1-yl)pyridine-2-carboxamide

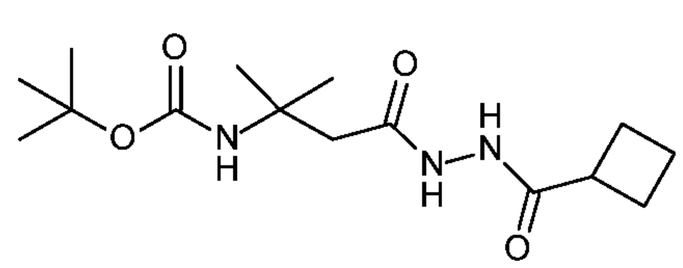
The title compound was synthesized in analogy to Example 1d, using 6-(2-oxopyrrolidin-1-yl)pyridine-2-carboxylic acid (Example 12b, 0.1 mmol) and α,α-dimethyl-3-phenyl-1,2,4-oxadiazole-5-ethanamine hydrochloride (1:1) (CAN 1426444-03-2, 0.1 mmol) as starting materials and isolated (13 mg, 28%) as colorless oil, LC-MS (UV peak area/ESI) 100%, 406.1874 [MH^+].

Example 13

6-(3-Chlorophenyl)-*N*-[1-(5-cyclobutyl-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-yl]pyridine-2-carboxamide

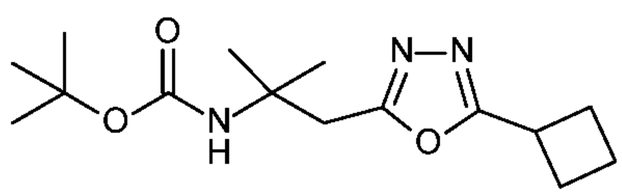


a) *tert*-Butyl 4-(2-(cyclobutanecarbonyl)hydrazinyl)-2-methyl-4-oxobutan-2-ylcarbamate



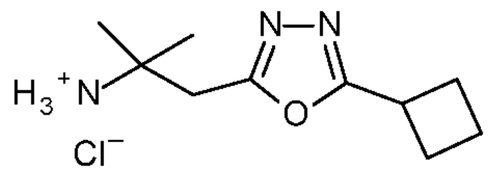
The title compound was synthesized in analogy to Example 1a, using 3-(*tert*-butoxycarbonylamino)-3-methylbutanoic acid (CAN 129765-95-3, 3.81 g, 17.5 mmol) and cyclobutanecarbohydrazide (CAN 98069-56-8, 2 g, 17.5 mmol) as starting materials and isolated (4.7 g, 86%) as off-white solid, MS (ISP): 314.2 [MH^+].

b) *tert*-Butyl 1-(5-cyclobutyl-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-ylcarbamate



The title compound was synthesized in analogy to Example 1b, using *tert*-butyl 4-(2-(cyclobutanecarbonyl)hydrazinyl)-2-methyl-4-oxobutan-2-ylcarbamate (Example 13a, 4.7 g, 15 mmol) as starting material and isolated (3.4 g, 77%) as off-white solid, MS (ISP): 296.3 [MH^+].

c) 1-(5-Cyclobutyl-1,3,4-oxadiazol-2-yl)-2-methyl-propan-2-amine hydrochloride



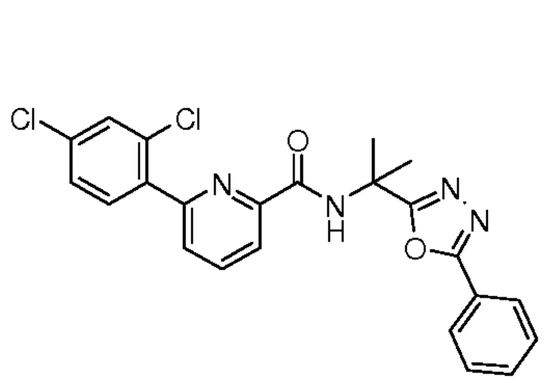
The title compound was synthesized in analogy to Example 1c, using *tert*-butyl 1-(5-cyclobutyl-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-ylcarbamate (Example 13b, 3.4 g, 11.5 mmol) as starting material and isolated (2.4 g, 90%) as white solid, MS (ISP): 196.3 [MH^+].

d) 6-(3-Chlorophenyl)-*N*-[1-(5-cyclobutyl-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-yl]pyridine-2-carboxamide

The title compound was synthesized in analogy to Example 1d, using 6-(3-chlorophenyl)-2-pyridinecarboxylic acid (CAN 863704-38-5, 64 µmol) and 1-(5-cyclobutyl-1,3,4-oxadiazol-2-yl)-2-methyl-propan-2-amine hydrochloride (77 µmol) as starting materials and isolated (7 mg, 27%) as colorless oil, MS (ISP): 411.3 [MH^+].

Example 14

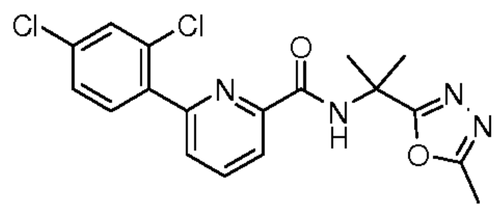
6-(2,4-Dichlorophenyl)-*N*-[2-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide



The title compound (7 mg, 70%) was synthesized in analogy to Example 1d, using 6-(2,4-dichlorophenyl)-2-pyridinecarboxylic acid (CAN 1261912-00-8, 22 µmol) and α,α-dimethyl-5-phenyl-1,3,4-oxadiazole-2-methanamine (CAN 68176-04-5, 24 µmol) as starting materials, LC-MS (EI): 453.0 [MH^+]. ^{1}H NMR (300 MHz, *$CDCl_3$*): δ 8.66 (bs, 1H), 8.13 (dd, 1H, J_1 = 7.5 Hz, J_2 = 0.9 Hz), 8.04 - 8.00 (m, 2H), 7.93 (t, 1H, J = 7.8 Hz), 7.78 (dd, 1H, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 7.62 - 7.40 (m, 6H), 1.98 (s, 6H).

Example 15

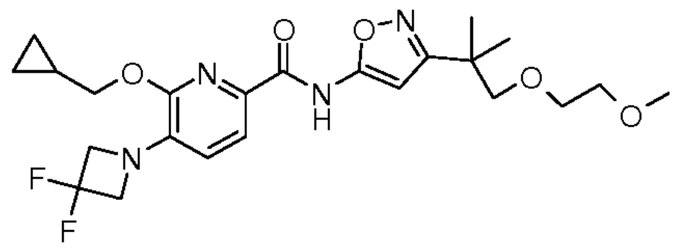
6-(2,4-Dichlorophenyl)-*N*-[2-(5-methyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide



The title compound (2 mg, 23%) was synthesized in analogy to Example 1d, using 6-(2,4-dichlorophenyl)-2-pyridinecarboxylic acid (CAN 1261912-00-8, 22 µmol) and α,α,5-trimethyl-1,3,4-oxadiazole-2-methanamine (CAN 1368716-09-9, 24 µmol) as starting materials, LC-MS (EI): 390.7 [MH^+]. ^{1}H NMR (300 MHz, *$CDCl_3$*): δ 8.56 (bs, 1H), 8.13 (dd, 1H, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 7.93 (t, 1H, J = 7.8 Hz), 7.78 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.2 Hz), 7.59 - 7.54(m, 2H), 7.41 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.8 Hz), 2.52 (s, 3H), 1.89 (s, 6H).

Example 16

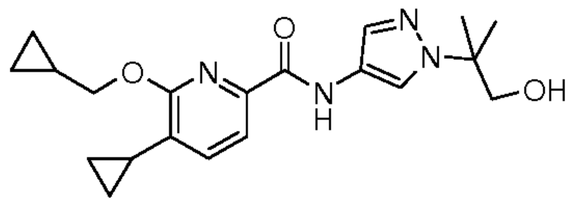
6-(Cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)-*N*-[3-[1-(2-methoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide



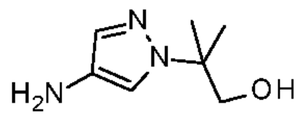
The title compound (20 mg, 12%) was synthesized in analogy to Example 1d, using 6-(cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)pyridine-2-carboxylic acid (CAN 1415898-88-2, 351 µmol) and 3-[2-(2-methoxyethoxy)-1,1-dimethyl-ethyl]isoxazol-5-amine (CAN 1218915-72-0, 383 µmol) as starting materials, LC-MS (EI): 481.2 [MH^+]. ^{1}H NMR (300 MHz, CD_3OD): δ 7.68 (d, 1H, J = 7.8 Hz), 6.80 (d, 1H, J = 7.8 Hz), 6.45 (s, 1H), 4.44 (t, 4H, J = 12.0 Hz), 4.29 (d, 2H, J = 7.2Hz), 3.60 - 3.50 (m, 6H), 3.34 (s, 3H), 1.40 - 1.25 (m, 7H), 0.70 - 0.60 (m, 2H), 0.45 - 0.38 (m, 2H).

Example 17

5-Cyclopropyl-6-(cyclopropylmethoxy)-*N*-[1-(1-hydroxy-2-methylpropan-2-yl)pyrazol-4-yl]pyridine-2-carboxamide



a) 2-(4-Aminopyrazol-1-yl)-2-methyl-propan-1-ol



To a solution of 5-hydroxy-4,4-dimethyl-3-oxo-pentanenitrile (CAN 489432-33-9, 5 g, 35 mmol) and NaOH (2.6 g, 65 mmol) in water (100 mL) is added $NH_2OH.HCl$ (2.8 g, 41 mmol). The mixture is heated to 100 °C for 12 hours. After this time, the reaction mixture

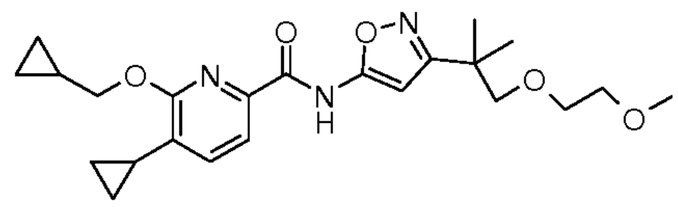
was cooled to room temperature and extracted with EtOAc (3 x 150 mL), the organic layers were combined and washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound (2 g, 36%) as yellow solid, LC-MS (EI): 157.2 [MH^+].

b) 5-Cyclopropyl-6-(cyclopropylmethoxy)-N-[1-(1-hydroxy-2-methylpropan-2-yl)pyrazol-4-yl]pyridine-2-carboxamide

The title compound (102 mg, 80%) was synthesized in analogy to Example 1d, using 5-cyclopropyl-6-(cyclopropylmethoxy)pyridine-2-carboxylic acid (CAN 1415898-71-3, 342 µmol) and 2-(4-aminopyrazol-1-yl)-2-methyl-propan-1-ol (373 µmol) as starting materials, LC-MS: 371.2 [MH^+]. ^{1}H NMR (300 MHz, *CD_3OD*): δ 8.18 (s, 1H), 7.81 (s, 1H), 7.63 (d, 1H, J = 7.5 Hz), 7.35 (d, 1H, J = 7.5 Hz), 4.38 (d, 2H, J = 7.8 Hz), 3.74 (s, 2H), 2.25 - 2.15 (m, 1H), 1.57 (s, 6H), 1.40 - 1.20 (m, 1H), 1.05 - 0.43 (m, 8H).

Example 18

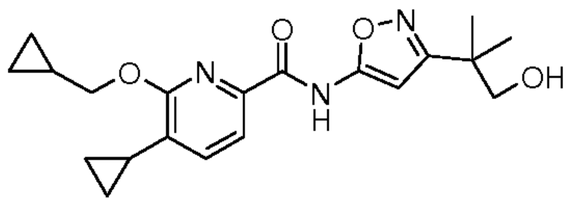
5-Cyclopropyl-6-(cyclopropylmethoxy)-*N*-[3-[1-(2-methoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide



The title compound (20 mg, 11%) was synthesized in analogy to Example 1d, using 5-cyclopropyl-6-(cyclopropylmethoxy)pyridine-2-carboxylic acid (CAN 1415898-71-3, 429 µmol) and 3-[2-(2-methoxyethoxy)-1,1-dimethyl-ethyl]isoxazol-5-amine (CAN 1218915-72-0, 468 µmol) as starting materials, LC-MS: 430.2 [MH^+]. ^{1}H NMR (300 MHz, CD_3OD): δ 7.67 (dd, 1H, J_1 = 7.5 Hz, J_2 = 0.3 Hz), 7.35 (d, 1H, J = 7.2 Hz), 6.49 (s, 1H), 4.36 (d, 2H, J = 7.2 Hz), 3.60 - 3.50 (m, 6H), 3.34 - 3.30 (m, 3H), 2.25 - 2.15 (m, 1H), 1.40 - 1.20 (m, 7H), 1.08 - 1.02 (m, 2H), 0.83 - 0.78 (m, 2H), 0.67 - 0.61 (m, 2H), 0.46 - 0.43 (m, 2H).

Example 19

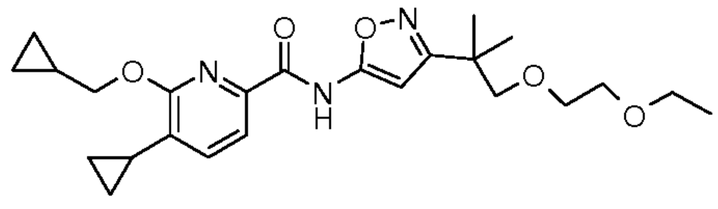
5-Cyclopropyl-6-(cyclopropylmethoxy)-*N*-[3-(1-hydroxy-2-methylpropan-2-yl)-1,2-oxazol-5-yl]pyridine-2-carboxamide



The title compound (25 mg, 16%) was synthesized in analogy to Example 1d, using 5-cyclopropyl-6-(cyclopropylmethoxy)pyridine-2-carboxylic acid (CAN 1415898-71-3, 429 µmol) and 2-(5-aminoisoxazol-3-yl)-2-methyl-propan-1-ol (CAN 1188910-70-4, 468 µmol) as starting materials, LC-MS: 372.1 [MH^+]. ^1H NMR (300 MHz, CD_3OD): δ 7.59 (d, 1H, J = 7.8 Hz), 7.29 (d, 1H, J = 7.8 Hz), 6.39 (s, 1H), 4.28 (d, 2H, J = 7.2 Hz), 3.51 (s, 2H), 2.15 - 2.10 (m, 1H), 1.30 - 1.10 (m, 7H), 1.00 - 0.93 (m, 2H), 0.75 - 0.69 (m, 2H), 0.59 - 0.52 (m, 2H), 0.36 - 0.33 (m, 2H).

Example 20

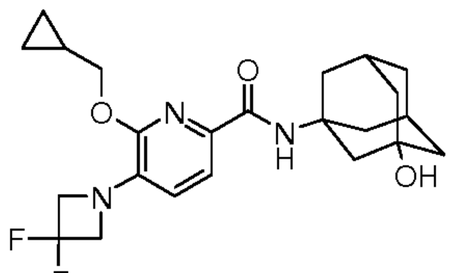
5-Cyclopropyl-6-(cyclopropylmethoxy)-*N*-[3-[1-(2-ethoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide



The title compound (25 mg, 13%) was synthesized in analogy to Example 1d, using 5-cyclopropyl-6-(cyclopropylmethoxy)pyridine-2-carboxylic acid (CAN 1415898-71-3, 429 µmol) and 3-[2-(2-ethoxyethoxy)-1,1-dimethyl-ethyl]isoxazol-5-amine (CAN 1218915-74-2, 468 µmol) as starting materials, LC-MS: 444.3 [MH^+]. ^1H NMR (300 MHz, CD_3OD): δ 7.54 (d, 1H, J = 7.5 Hz), 7.23 (d, 1H, J = 7.5 Hz), 6.39 (s, 1H), 4.24 (d, 2H, J = 6.9 Hz), 3.48 - 3.36 (m, 8H), 2.20 - 2.00 (m, 1H), 1.30 - 1.05 (m, 7H), 1.05 (t, 3H, J = 7.2 Hz), 0.96 - 0.91 (m, 2H), 0.72 - 0.67 (m, 2H), 0.56 - 0.50 (m, 2H), 0.35 - 0.30 (m, 2H).

Example 21

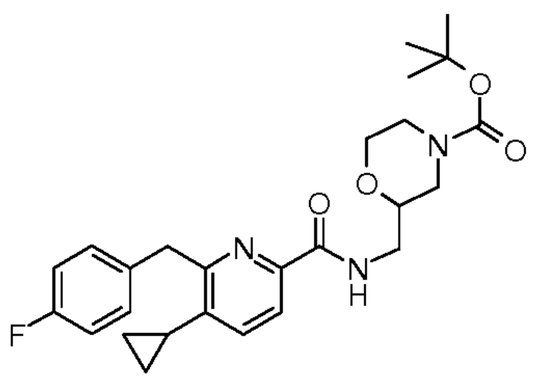
6-(Cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)-*N*-(3-hydroxy-1-adamantyl)pyridine-2-carboxamide



The title compound (8 mg, 53%) was synthesized in analogy to Example 1d, using 6-(cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)pyridine-2-carboxylic acid (CAN 1415898-88-2, 35 µmol) and 3-aminoadamantan-1-ol (CAN 702-82-9, 42 µmol) as starting materials and isolated as white solid, MS (ESI): 434.5 [MH^+].

Example 22

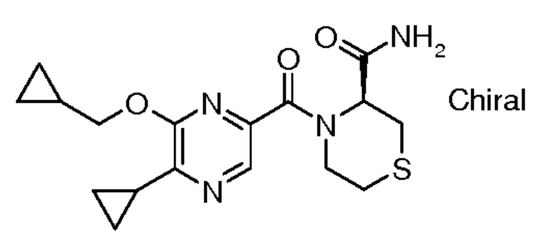
tert-Butyl 2-[[[5-cyclopropyl-6-[(4-fluorophenyl)methyl]pyridine-2-carbonyl]amino]methyl]morpholine-4-carboxylate



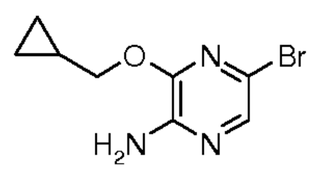
The title compound (132 mg, 51%) was synthesized in analogy to Example 1d, using 5-cyclopropyl-6-[(4-fluorophenyl)methyl]pyridine-2-carboxylic acid (CAN 1415899-48-7, 553 µmol) and tert-butyl 2-(aminomethyl)morpholine-4-carboxylate (CAN 140645-53-0, 664 µmol) as starting materials and isolated as colorless oil, MS (ESI): 470.5 [MH^+].

Example 23

(+)-4-[5-Cyclopropyl-6-(cyclopropylmethoxy)pyrazine-2-carbonyl]thiomorpholine-3-carboxamide

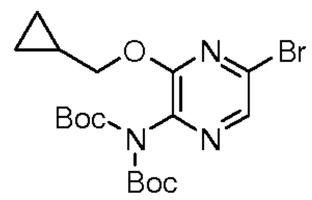


a) 5-Bromo-3-cyclopropylmethoxy-pyrazin-2-ylamine



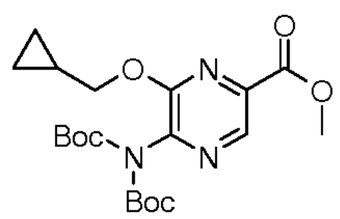
To a solution of cyclopropyl-methanol (16.47 mL, 205.62 mmol) in dimethyl sulfoxide (200 mL) was added sodium hydride (60% in oil, 4.93 g, 205.62 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 2 hours. To this suspension was added 3,5-dibromo-pyrazin-2-ylamine (20 g, 79.09 mmol) in dimethyl sulfoxide (40 mL) and the mixture was stirred at ambient temperature for 12 hours. The mixture was partitioned between water (300 mL) and ethyl acetate and the organic phase was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by chromatography (silica gel, 500 g, 10% ethyl acetate in hexane) to give the desired product (14 g, 72.52%) as yellow solid; LC-MS (UV peak area, ESI) 94.69%, 244.0 [MH^+].

b) Di-*tert*-butyl[5-bromo-3-(cyclopropylmethoxy)pyrazin-2-yl]imidodicarbonate



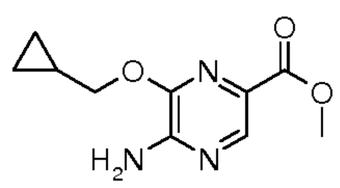
To a solution of 5-bromo-3-cyclopropylmethoxy-pyrazin-2-ylamine (30 g, 122.91 mmol) in dichloromethane (200 mL) were added di-*tert*-butyl dicarbonate (67.7 mL, 307.26 mmol) and 4-dimethylaminopyridine (1.49 g, 12.29 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The mixture was partitioned between water (300 mL) and dichloromethane and the organic phase was separated, washed with brine, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by chromatography (silica gel, 600 g, 5%-7% ethyl acetate in hexane) to give the desired product (45 g, 82.77%) as yellow oil; LC-MS (UV peak area, ESI) 94.69%, 445.0 [MH^+].

c) Methyl 5-[bis(*tert*-butoxycarbonyl)amino]-6-(cyclopropylmethoxy)pyrazine-2-carboxylate



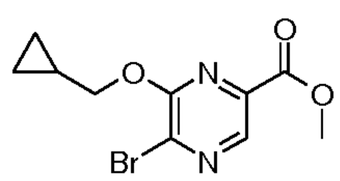
To a solution of di-*tert*-butyl[5-bromo-3-(cyclopropylmethoxy)pyrazin-2-yl]imido-dicarbonate (20 g, 45.05 mmol) in methanol (200 mL) was added $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ (4.04 g, 4.95 mmol) and triethylamine (9.5 mL, 67.57 mmol) and the mixture was stirred under an atmosphere of 32 bar carbon monoxide at 80°C for 5 hours. After expansion and cooling, the solid was removed by filtration. The organic phase was separated, washed with brine (300 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by chromatography (Combi-Flash, 120 g, 15%-20% ethyl acetate in hexane) to give the desired product (14 g, 73.68%) as yellow semi-solid; LC-MS (UV peak area, ESI) 96.14%, 424.4 [MH^+].

d) 5-Amino-6-cyclopropylmethoxy-pyrazine-2-carboxylic acid methyl ester



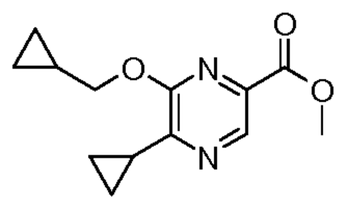
Methyl 5-[bis(*tert*-butoxycarbonyl)amino]-6-(cyclopropylmethoxy)pyrazine-2-carboxylate (15 g, 35.46 mmol) was suspended in methanol (150 mL) and water (225 mL) and the mixture was heated at 100°C for 12 hours. After cooling, white solid was formed, filtered and dried *in vacuo* to give the title compound (5.7 g, 72.15%) as off white solid; LC-MS (UV peak area, ESI) 99.68%, 224.2 [MH^+].

e) 5-Bromo-6-cyclopropylmethoxy-pyrazine-2-carboxylic acid methyl ester



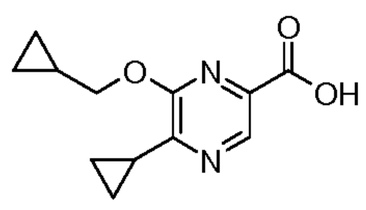
5-Amino-6-cyclopropylmethoxy-pyrazine-2-carboxylic acid methyl ester (10 g, 44.84 mmol) was suspended in dibromomethane (150 mL). To this suspension were added trimethylsilyl bromide (14.8 mL, 112.11 mmol) followed by *tert*-butyl nitrite (57.5 mL, 448.43 mmol) at 0°C and the mixture was stirred at that temperature for 3 hours. The mixture was partitioned between water (190 mL) and ethyl acetate and the organic phase was washed with brine (200 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by chromatography (Combi-Flash, 80 g, 20% ethyl acetate in hexane) to give the desired product (6.3 g, 46.6%) as white solid; LC-MS (UV peak area, ESI) 90.68%, 287.2 [MH^+].

f) 5-Cyclopropyl-6-cyclopropylmethoxy-pyrazine-2-carboxylic acid methyl ester



5-Bromo-6-cyclopropylmethoxy-pyrazine-2-carboxylic acid methyl ester (5 g, 17.42 mmol), potassium phosphate tribasic (12.9 g, 60.98 mmol) and palladium(II)acetate (389 mg, 1.74 µmol) were dissolved in toluene (45 mL) and water (5 mL) and the reaction mixture was degassed with argon for 15 minutes. Cyclopropylboronic acid (2.9 g, 34.84 mmol) and tricyclohexylphosphine (0.487 g, 1.74 mmol) were added and the reaction mixture was stirred at 60°C for 16 hours. The mixture was partitioned between water and ethyl acetate and the organic phase was washed with brine (100 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by chromatography (Combi-Flash, 80 g, 10%-15% ethyl acetate in hexane) to give the desired product (2.6 g, 60.11%) as white solid; LC-MS (UV peak area, ESI) 98.87%, 249.2 [MH^+].

g) 5-Cyclopropyl-6-cyclopropylmethoxy-pyrazine-2-carboxylic acid



To a solution of 5-cyclopropyl-6-cyclopropylmethoxy-pyrazine-2-carboxylic acid methyl ester (7 g, 28.23 mmol) in THF (20 mL) and H_2O (10 mL) was added lithium hydroxide (1.54 g, 26.69 mmol) and the mixture was stirred at ambient temperature for 4.5 hours. Solvent was concentrated *in vacuo* and residue was diluted with H_2O (20 mL). The aqueous phase was acidified with hydrochloric acid (1M, pH~ 2-3) and the solid was separated. The solid was triturated with toluene (25ml) and dried *in vacuo* to give the title compound (5.3 g, 86.6%) as white crystalline solid; LC-MS (UV peak area, ESI) 93.2%, 233.2 [$M-H^-$].

h) 4-[5-Cyclopropyl-6-(cyclopropylmethoxy)pyrazine-2-carbonyl]thiomorpholine-3-carboxamide

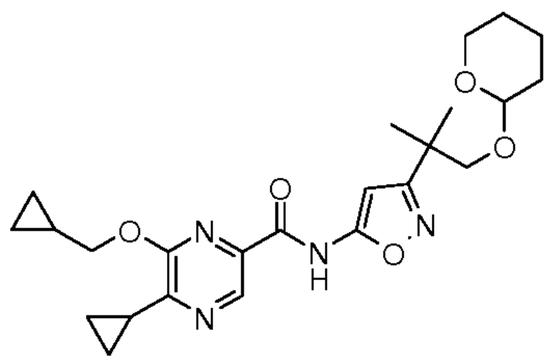
The title compound was synthesized in analogy to Example 1d, using 5-cyclopropyl-6-cyclopropylmethoxy-pyrazine-2-carboxylic acid (Example 23g, 0.43 mmol) and 3-thiomorpholinecarboxamide (CAN 103742-31-0, 0.43 mmol) as starting materials and isolated (134 mg, 87%) as light yellow solid, LC-MS (UV peak area/ESI) 100%, 363.1490 [MH^+].

i) (+)-4-[5-Cyclopropyl-6-(cyclopropylmethoxy)pyrazine-2-carbonyl]thiomorpholine-3-carboxamide

Racemic 4-[5-cyclopropyl-6-(cyclopropylmethoxy)pyrazine-2-carbonyl]thiomorpholine-3-carboxamide (Example 23h, 108 mg) was subjected to chiral chromatography (Reprosil chiral NR, 30% ethanol in heptane) to give the title compound (46 mg, 43%) as light yellow solid; LC-MS (UV peak area/ESI) 100%, 363.1490 [MH^+]; (+) enantiomer, $\alpha_D^{20}(MeOH) = +41.3°$.

Example 24

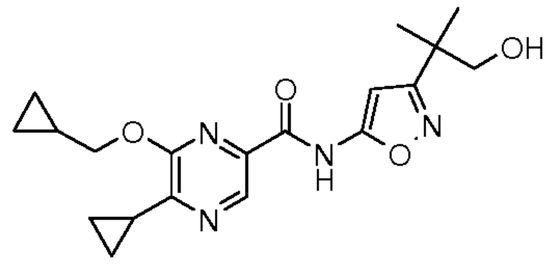
5-Cyclopropyl-6-(cyclopropylmethoxy)-*N*-[3-[2-methyl-1-(oxan-2-yloxy)propan-2-yl]-1,2-oxazol-5-yl]pyrazine-2-carboxamide



To a stirred solution of 5-cyclopropyl-6-cyclopropylmethoxy-pyrazine-2-carboxylic acid (Example 23g, 100mg, 0.427mmol) and 3-[1,1-dimethyl-2-[(tetrahydro-2*H*-pyran-2-yl)oxy]ethyl]-5-isoxazolamine (CAN 1218915-54-8, 153.34mg, 0.641mmol) in pyridine (3 mL) was added POCl3 at 0 °C and was stirred for 3 hours at room temperature. After completion of the reaction, the reaction mixture was evaporated *in vacuo*, diluted with ethyl acetate and washed with water. The organic phase was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica column chromatography using 20% ethyl acetate in hexane to give the title compound (110mg, 56%) as light yellow solid; LC-MS (UV peak area, ESI) 98.4%, 457.2 [MH^+].

Example 25

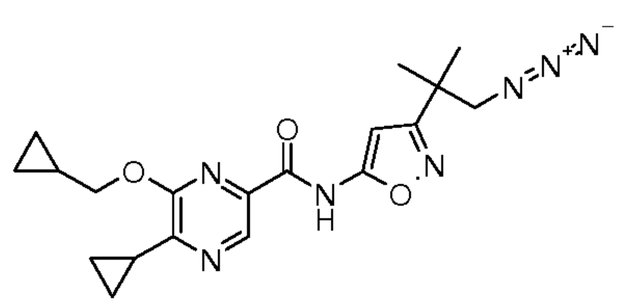
5-Cyclopropyl-6-(cyclopropylmethoxy)-*N*-[3-(1-hydroxy-2-methylpropan-2-yl)-1,2-oxazol-5-yl]pyrazine-2-carboxamide



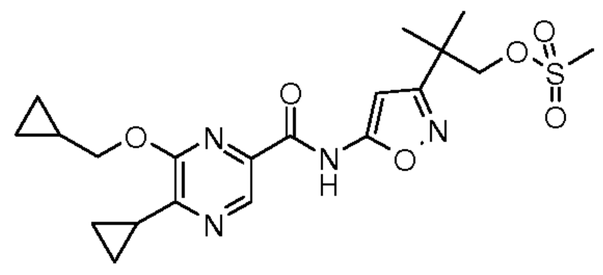
To a stirred solution of 5-cyclopropyl-6-(cyclopropylmethoxy)-*N*-[3-[2-methyl-1-(oxan-2-yloxy)propan-2-yl]-1,2-oxazol-5-yl]pyrazine-2-carboxamide (Example 24, 1.0 g, 1.972 mmol) in ethanol (20 mL) was added pyridinium p-toluenesulfonate (0.149 g, 0.592 mmol) and the mixture heated to 70 °C for 1 hour. After completion of the reaction, the solvent was removed *in vacuo*. The residue was purified by silica column chromatography using 30% ethyl acetate in hexane to give the title compound (600 mg, 82%) as white solid; LC-MS (UV peak area, ESI) 98.9%, 373.0 [MH^+].

Example 26

***N*-[3-(1-Azido-2-methylpropan-2-yl)-1,2-oxazol-5-yl]-5-cyclopropyl-6-(cyclopropylmethoxy)pyrazine-2-carboxamide**



a) [2-[5-[[5-Cyclopropyl-6-(cyclopropylmethoxy)pyrazine-2-carbonyl]amino]-1,2-oxazol-3-yl]-2-methylpropyl] methanesulfonate



To a stirred solution 5-cyclopropyl-6-(cyclopropylmethoxy)-*N*-[3-(1-hydroxy-2-methylpropan-2-yl)-1,2-oxazol-5-yl]pyrazine-2-carboxamide (Example 25, 400 mg, 1.075 mmol) in DCM (15 mL) were added triethylamine (0.724 mL, 5.376 mmol) and mesyl chloride (0.166 mL, 2.151mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, the reaction mixture was diluted with DCM and washed with aqueous saturated sodium bicarbonate solution. The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. The residue

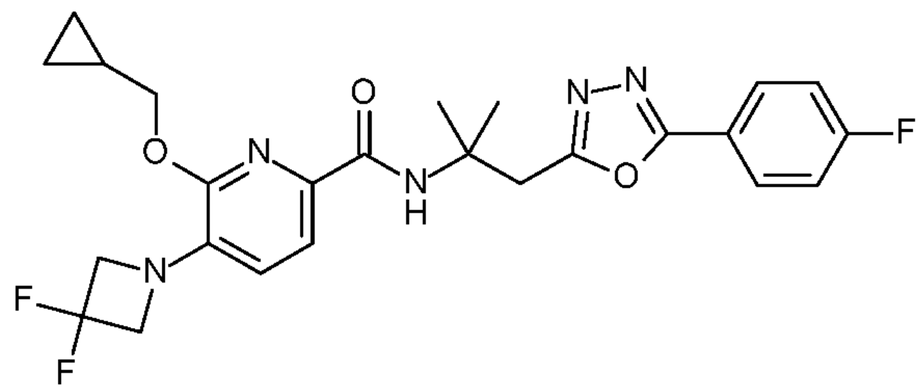
consisted mostly of the title compound (450 mg) as a brown sticky liquid which was directly used for next step; LC-MS (UV peak area, ESI) 93.5%, 451.1 [MH^+].

b) *N*-[3-(1-Azido-2-methylpropan-2-yl)-1,2-oxazol-5-yl]-5-cyclopropyl-6-(cyclopropylmethoxy)pyrazine-2-carboxamide

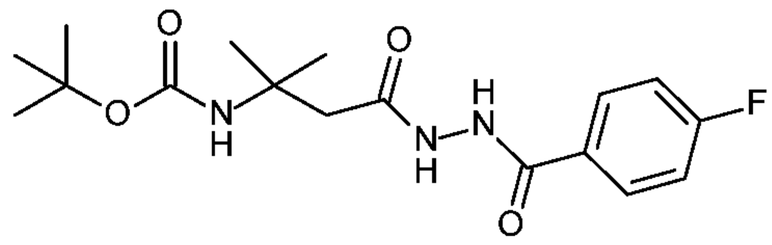
To a stirred solution of [2-[5-[[5-cyclopropyl-6-(cyclopropylmethoxy)pyrazine-2-carbonyl]amino]-1,2-oxazol-3-yl]-2-methylpropyl] methanesulfonate (Example 26a, 200 mg, crude) in DMF (2 mL) was added sodium azide (144.4 mg, 2.22 mmol) and heated to 120 °C in sealed tube for 16 hours. After completion of the reaction, the reaction mixture was cooled to room temperature then diluted with ethyl acetate and washed with water. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by l silica column chromatography using 20% ethyl acetate in hexane to give the title compound (60mg, 32% after two steps) as white solid; LC-MS (UV peak area, ESI) 99.7%, 398.2 [MH^+].

Example 27

6-(Cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)-N-[1-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]-2-methylpropan-2-yl]pyridine-2-carboxamide

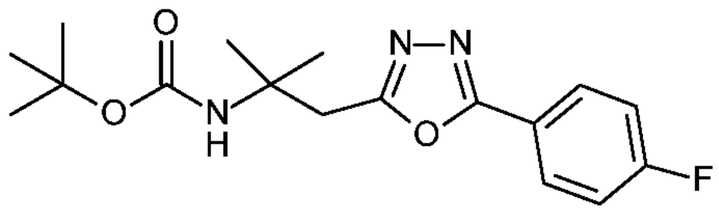


a) *tert*-Butyl 4-(2-(4-fluorobenzoyl)hydrazinyl)-2-methyl-4-oxobutan-2-ylcarbamate



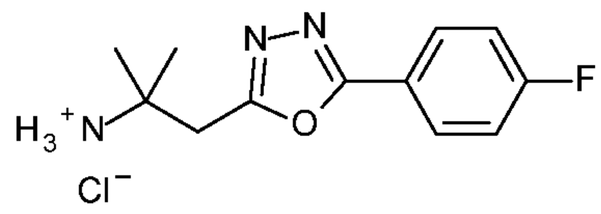
The title compound was synthesized in analogy to Example 1a, using 3-(*tert*-butoxycarbonylamino)-3-methylbutanoic acid (CAN 129765-95-3, 3 g, 13.8 mmol) and 4-fluorobenzohydrazide (CAN 456-06-4, 2.1 g, 13.8 mmol) as starting materials and isolated (1.3 g, 26%) as yellow oil, MS (ISP): 354.3 [MH^+].

b) *tert*-butyl 1-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-ylcarbamate



The title compound was synthesized in analogy to Example 1b, using *tert*-butyl 4-(2-(4-fluorobenzoyl)hydrazinyl)-2-methyl-4-oxobutan-2-ylcarbamate (Example 27a, 1.3 g, 3.7 mmol) as starting material and isolated (0.99 g, 81%) as white solid, MS (ISP): 336.3 [MH^+].

c) 1-(5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-amine hydrochloride



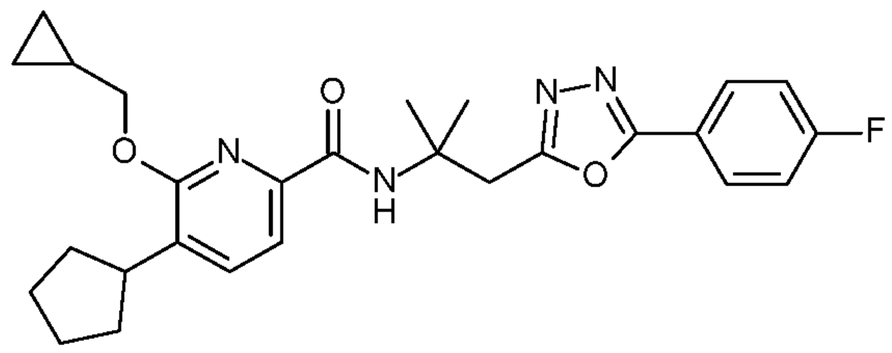
The title compound was synthesized in analogy to Example 1c, using , *tert*-butyl 1-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-ylcarbamate (Example 27b, 0.98 g, 2.9 mmol) as starting material and isolated (620 mg, 78%), MS (ESI): 236.2 [MH^+].

d) 6-(Cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)-N-[1-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]-2-methylpropan-2-yl]pyridine-2-carboxamide

To a solution of 6-(cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)pyridine-2-carboxylic acid (CAN 1415898-88-2, 20 mg, 70.4 µmol) in dichloromethane (1 mL) was added DIPEA (22.7 mg, 30.7 µL, 176 µmol) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholin-4-ium chloride (21.4 mg, 77.4 µmol). The mixture was stirred for 30 min at ambient temperature, then 1-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-amine hydrochloride (Example 27c, 16.6 mg, 70.4 µmol) was added. The reaction mixture was stirred at ambient temperature over night, diluted with dichloromethane (8 mL) and washed with 1 M aq. $NaHCO_3$ solution (3 x 10 mL), water (10 mL) and brine (15 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (10 g SiO_2, heptane / EtOAc 4:1 to 1:1) gave the title compound (19.7 mg, 56%), MS (ESI): 502.6 [MH^+].

Example 28

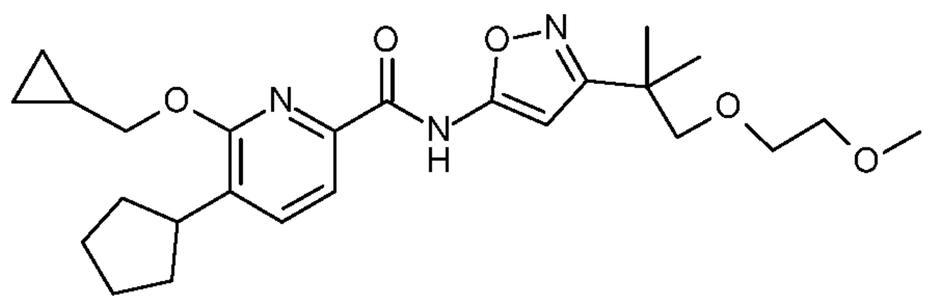
5-Cyclopentyl-6-(cyclopropylmethoxy)-N-[1-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]-2-methylpropan-2-yl]pyridine-2-carboxamide



The title compound was synthesized in analogy to the procedure described in Example 27d, using 5-cyclopentyl-6-(cyclopropylmethoxy)pyridine-2-carboxylic acid (CAN 1415898-70-2, 20 mg, 77 µmol) and 1-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-amine hydrochloride (Example 27c, 23 mg, 85 µmol) and isolated (18 mg, 49%), LC-MS (ESI): 479.7 [MH^+].

Example 29

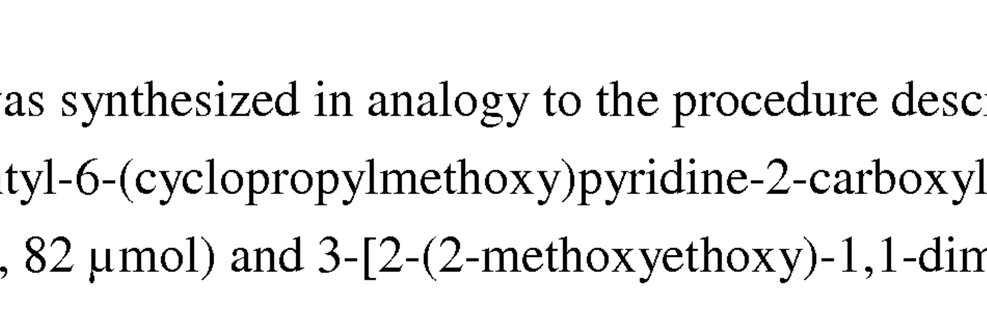
5-Cyclopentyl-6-(cyclopropylmethoxy)-N-[3-[1-(2-methoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide



The title compound was synthesized in analogy to the procedure described in Example 27d, using 5-cyclopentyl-6-(cyclopropylmethoxy)pyridine-2-carboxylic acid (CAN 1415898-70-2, 21 mg, 82 µmol) and 3-[2-(2-methoxyethoxy)-1,1-dimethyl-ethyl]isoxazol-5-amine (CAN 1218915-72-0, 18 mg, 82 µmol) and isolated (10 mg, 26%) as colorless oil, LC-MS (ESI): 458.7 [MH^+].

Example 30

5-Cyclopentyl-6-(cyclopropylmethoxy)-N-[3-[1-(2-ethoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide



The title compound was synthesized in analogy to the procedure described in Example 27d, using 5-cyclopentyl-6-(cyclopropylmethoxy)pyridine-2-carboxylic acid (CAN 1415898-70-2, 22 mg, 83 µmol) and 3-[2-(2-ethoxyethoxy)-1,1-dimethyl-ethyl]isoxazol-5-

amine (CAN 1218915-74-2, 19 mg, 83 μmol) and isolated (10 mg, 25%), LC-MS (ESI): 472.8 [MH^+].

Example 31

Pharmacological tests

The following tests were carried out in order to determine the activity of the compounds of formula I:

Radioligand binding assay

The affinity of the compounds of the invention for cannabinoid CB1 receptors was determined using recommended amounts of membrane preparations (PerkinElmer) of human embryonic kidney (HEK) cells expressing the human CNR1 or CNR2 receptors in conjunction with 1.5 or 2.6 nM [3H]-CP-55,940 (Perkin Elmer) as radioligand, respectively. Binding was performed in binding buffer (50 mM Tris, 5 mM MgCl2, 2.5 mM EDTA, and 0.5% (wt/vol) fatty acid free BSA, pH 7.4 for CB1 receptor and 50 mM Tris, 5 mM MgCl2, 2.5 mM EGTA, and 0.1% (wt/vol) fatty acid free BSA, pH 7.4 for CB2 receptor) in a total volume of 0.2 ml for 1h at 30°C shaking. The reaction was terminated by rapid filtration through microfiltration plates coated with 0.5% polyethylenimine (UniFilter GF/B filter plate; Packard). Bound radioactivity was analyzed for Ki using nonlinear regression analysis (Activity Base, ID Business Solution, Limited), with the Kd values for [3H]CP55,940 determined from saturation experiments. The compounds of formula (I) show an excellent affinity for the CB2 receptor.

The compounds according to formula (I) have an activity in the above assay (Ki) between 0.5 nM and 10 μM. Particular compounds of formula (I) have an activity in the above assay (Ki) between 0.5 nM and 3 μM. Other particular compounds of formula (I) have an activity in the above assay (Ki) between 0.5 nM and 100 nM.

cAMP Assay

CHO cells expressing human CB1 or CB2 receptors are seeded 17-24 hours prior to the experiment 50.000 cells per well in a black 96 well plate with flat clear bottom (Corning Costar #3904) in DMEM (Invitrogen No. 31331), 1x HT supplement, with 10 % fetal calf serum and incubated at 5% CO_2 and 37°C in a humidified incubator. The growth medium was exchanged with Krebs Ringer Bicarbonate buffer with 1 mM IBMX and incubated at 30°C for 30 min. Compounds were added to a final assay volume of 100 μl and incubated for 30 min at 30°C. Using the cAMP-Nano-TRF detection kit the assay (Roche Diagnostics) was stopped by the addition of 50 μl lysis reagent (Tris, NaCl, 1.5% Triton

X100, 2.5% NP40, 10% NaN_3) and 50 µl detection solutions (20 µM mAb Alexa700-cAMP 1:1, and 48 µM Ruthenium-2-AHA-cAMP) and shaken for 2h at room temperature. The time-resolved energy transfer is measured by a TRF reader (Evotec Technologies GmbH), equipped with a ND:YAG laser as excitation source. The plate is measured twice with the excitation at 355 nm and at the emission with a delay of 100 ns and a gate of 100 ns, total exposure time 10s at 730 (bandwidth 30 nm) or 645 nm (bandwidth 75 nm), respectively. The FRET signal is calculated as follows: FRET = T730-Alexa730-P(T645-B645) with P = Ru730-B730/Ru645-B645, where T730 is the test well measured at 730 nM, T645 is the test well measured at 645 nm, B730 and B645 are the buffer controls at 730 nm and 645 nm, respectively. cAMP content is determined from the function of a standard curve spanning from 10 µM to 0.13 nM cAMP.

EC_{50} values were determined using Activity Base analysis (ID Business Solution, Limited). The EC_{50} values for a wide range of cannabinoid agonists generated from this assay for reference compounds were in agreement with the values published in the scientific literature.

In the foregoing assay, the compounds according to the invention have a human CB2 EC_{50} which is between 0.5 nM and 10 µM. Particular compounds according to the invention have a human CB2 EC_{50} between 0.5 nM and 1 µM. Further particular compounds according to the invention have a human CB2 EC_{50} between 0.5 nM and 100 nM. They exhibit at least 10 fold selectivity against the human CB1 receptor in, either both of the radioligand and cAMP assay, or in one of these two assays.

Results obtained for representative compounds of the invention are given in the following table.

Example	**cAMP assay human CB2 EC_{50} [µM]**
1	0.4965
2	0.1646
3	0.1321
4	0.3394
5	0.5537
6	0.1822
7	0.2438
8	0.1945
9	0.0367
10	0.2647
11	0.5735
12	0.6621

Example	cAMP assay human CB2 EC_{50} [µM]
13	0.2939
14	0.2271
15	0.1070
16	0.2185
17	0.2236
18	0.0352
19	0.1387
20	0.0225
21	0.0816
22	0.1008
23	0.5893
24	0.0752
25	0.0516
26	0.0124
27	2.889
28	2.758
29	0.175
30	0.176

Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet	
Kernel:		
Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg

Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxide (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

The active ingredient is sieved and mixed with microcrystalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidone in water. The granulate is then mixed with sodium starch glycolate and magnesium stearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aq. solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

The components are sieved and mixed and filled into capsules of size 2.

Example C

Injection solutions can have the following composition:

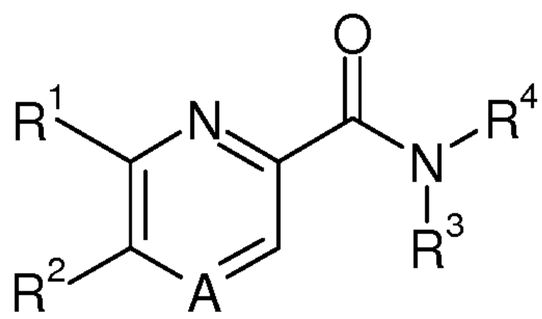
Compound of formula (I)	3.0 mg

Polyethylene glycol 400	150.0 mg
Acetic acid	q.s. ad pH 5.0
Water for injection solutions	ad 1.0 ml

The active ingredient is dissolved in a mixture of Polyethylene glycol 400 and water for injection (part). The pH is adjusted to 5.0 by addition of acetic acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Claims

1. A compound of formula (I)



(I)

wherein

A is -CH- or nitrogen;

R^1 is halophenyl, halophenylalkyl, haloalkoxy, halogen, alkoxyalkoxy, oxopyrrolidinyl or cycloalkylalkoxy;

R^2 is hydrogen, halophenylamino, cycloalkyl or haloazetidinyl;

one of R^3 and R^4 is hydrogen and the other one is $-(CR^5R^6)_m-(CH_2)_n-R^7$;

or R^3 and R^4 together with the nitrogen atom to which they are attached form aminocarbonylthiomorpholinyl;

R^5 and R^6 are independently selected from hydrogen and alkyl;

R^7 is 5-cycloalkyl-1,3,4-oxadiazolyl, 3-cycloalkyl-1,2,4-oxadiazolyl, 5-phenyl-1,3,4-oxadiazolyl, 3-phenyl-1,2,4-oxadiyzolyl, 5-alkyl-1,3,4-oxadiazolyl, 3-alkoxyalkoxyalkyl-1,2-oxazolyl, 1-hydroxyalkylpyrazolyl, 3-hydroxy-1-adamantyl, alkoxycarbonylmorpholinyl, 3-oxanyloxyalkyl-1,2-oxazol-5-yl, 3-azidoalkyl-1,2-oxazol-5-yl or 5-(4-fluorophenyl)-1,3,4-oxadiazolyl;

m is 0 or 1;

n is 0 or 1;

or a pharmaceutically acceptable salt or ester thereof;

provided that 6-chloro-N-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)- 2-pyridinecarboxamide is excluded.

2. A compound according to claim 1, wherein R^1 is halogen or cycloalkylalkoxy.

3. A compound according to claim 1 or 2, wherein R^1 is chloro or cyclopropylmethoxy.

4. A compound according to any one of claims 1 to 3, wherein R^2 is halophenylamino or cycloalkyl.

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

6. A compound according to any one of claims 1 to 5, wherein R^5 and R^6 are both alkyl at the same time.

7. A compound according to any one of claims 1 to 6, wherein R^5 and R^6 are both methyl at the same time.

8. A compound according to any one of claims 1 to 7, wherein R^7 is 5-phenyl-1,3,4-oxadiyzolyl, 3-alkoxyalkoxyalkyl-1,2-oxazolyl or 3-azidoalkyl-1,2-oxazol-5-yl.

9. A compound according to any one of claims 1 to 8 selected from

6-(4-chlorophenyl)-N-[1-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-yl]pyridine-2-carboxamide;

6-(4-chlorophenyl)-N-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide;

N-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]-6-(2,2,2-trifluoroethoxy)pyridine-2-carboxamide;

6-(4-chlorophenyl)-N-[2-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]pyridine-2-carboxamide;

N-[2-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]-6-(2,2,2-trifluoroethoxy)pyridine-2-carboxamide;

6-(3-chlorophenyl)-N-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide;

6-(3-chlorophenyl)-N-[1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2-methylpropan-2-yl]pyridine-2-carboxamide;

6-(3-chlorophenyl)-N-[2-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]pyridine-2-carboxamide;

6-chloro-5-(2,4-dichloroanilino)-N-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide;

6-(4-chlorophenyl)-5-cyclopropyl-N-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide;

6-(2-methoxyethoxy)-N-[2-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]pyridine-2-carboxamide;

N-[2-methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]-6-(2-oxopyrrolidin-1-yl)pyridine-2-carboxamide;

6-(3-chlorophenyl)-N-[1-(5-cyclobutyl-1,3,4-oxadiazol-2-yl)-2-methylpropan-2-yl]pyridine-2-carboxamide;

6-(2,4-dichlorophenyl)-N-[2-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide;

6-(2,4-dichlorophenyl)-N-[2-(5-methyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)-N-[3-[1-(2-methoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide;

5-cyclopropyl-6-(cyclopropylmethoxy)-N-[1-(1-hydroxy-2-methylpropan-2-yl)pyrazol-4-yl]pyridine-2-carboxamide;

5-cyclopropyl-6-(cyclopropylmethoxy)-N-[3-[1-(2-methoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide;

5-cyclopropyl-6-(cyclopropylmethoxy)-N-[3-(1-hydroxy-2-methylpropan-2-yl)-1,2-oxazol-5-yl]pyridine-2-carboxamide;

5-cyclopropyl-6-(cyclopropylmethoxy)-N-[3-[1-(2-ethoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)-N-(3-hydroxy-1-adamantyl)pyridine-2-carboxamide;

tert-butyl 2-[[[5-cyclopropyl-6-[(4-fluorophenyl)methyl]pyridine-2-carbonyl]amino]methyl]morpholine-4-carboxylate;

(3S)-4-[5-cyclopropyl-6-(cyclopropylmethoxy)pyrazine-2-carbonyl]thiomorpholine-3-carboxamide;

5-cyclopropyl-6-(cyclopropylmethoxy)-N-[3-(1-hydroxy-2-methylpropan-2-yl)-1,2-oxazol-5-yl]pyrazine-2-carboxamide;

5-cyclopropyl-6-(cyclopropylmethoxy)-N-[3-[2-methyl-1-(oxan-2-yloxy)propan-2-yl]-1,2-oxazol-5-yl]pyrazine-2-carboxamide;

N-[3-(1-azido-2-methylpropan-2-yl)-1,2-oxazol-5-yl]-5-cyclopropyl-6-(cyclopropylmethoxy)pyrazine-2-carboxamide;

6-(Cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)-N-[1-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]-2-methylpropan-2-yl]pyridine-2-carboxamide;

5-Cyclopentyl-6-(cyclopropylmethoxy)-N-[1-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]-2-methylpropan-2-yl]pyridine-2-carboxamide;

5-Cyclopentyl-6-(cyclopropylmethoxy)-N-[3-[1-(2-methoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide; and

5-Cyclopentyl-6-(cyclopropylmethoxy)-N-[3-[1-(2-ethoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide.

10. A compound according to any one of claims 1 to 9 selected from

6-chloro-5-(2,4-dichloroanilino)-N-[2-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine-2-carboxamide;

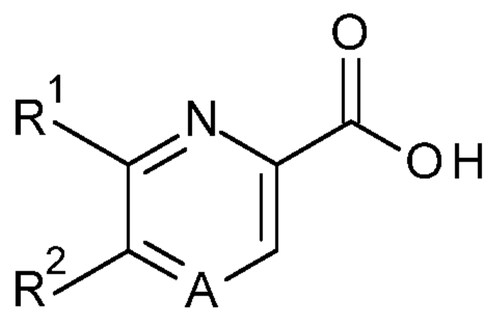
5-cyclopropyl-6-(cyclopropylmethoxy)-N-[3-[1-(2-methoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide;

5-cyclopropyl-6-(cyclopropylmethoxy)-N-[3-[1-(2-ethoxyethoxy)-2-methylpropan-2-yl]-1,2-oxazol-5-yl]pyridine-2-carboxamide; and

N-[3-(1-azido-2-methylpropan-2-yl)-1,2-oxazol-5-yl]-5-cyclopropyl-6-(cyclopropylmethoxy)pyrazine-2-carboxamide.

11. A process for the preparation of a compound according to any one of claims 1 to 10, comprising one of the following steps:

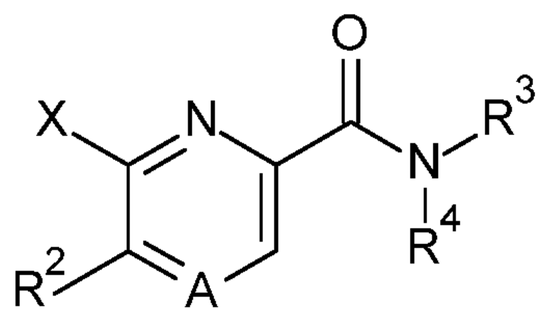
(a) the reaction of a compound of formula (A)



(A)

in the presence of NHR^3R^4, an amide coupling agent and a base, wherein A and R^1 to R^4 are as defined in any one of claims 1 to 8;

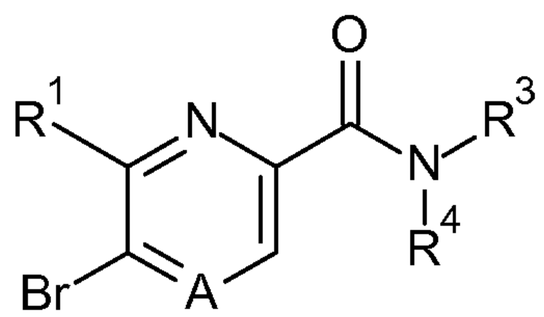
(b) the reaction of a compound of formula (B)



(B)

in the presence of R^1-Y, a palladium catalyst and a base, wherein X is Cl, Br, I or trifluoromethanesulfonate, Y is a trifluoroborate group, a boronic acid group or a boronic acid pinacol ester group, R^1 is halophenyl or halophenylalkyl and A and R^2 to R^4 are as defined in any one of claims 1 to 8; or

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



(C)

in the presence of R^2-M, a palladium catalyst and a base, wherein R^1 is halophenyl, halophenylalkyl or oxopyrrolidinyl, R^2 is cycloalkyl, A and R^3-R^4 are as defined in any one of claims 1 to 8 and M is a trifluoroborate group, a boronic acid group or a boronic acid pinacol ester group.

12. A compound according to any one of claims 1 to 10, when manufactured according to a process of claim 11.

13. A compound according to any one of claims 1 to 10 for use as therapeutically active substance.

14. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 10 and a therapeutically inert carrier.

15. The use of a compound according to any one of claims 1 to 10 for the treatment or prophylaxis of pain, neuropathic pain, asthma, osteoporosis, inflammation, psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, psychiatric disorders rheumatoid arthritis, psychosis or allergy.

16. The use of a compound according to any one of claims 1 to 10 for the preparation of a medicament for the treatment or prophylaxis of pain, neuropathic pain, asthma, osteoporosis, inflammation, psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, psychiatric disorders rheumatoid arthritis, psychosis or allergy.

17. A compound according to any one of claims 1 to 10 for the treatment or prophylaxis of pain, neuropathic pain, asthma, osteoporosis, inflammation, psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, psychiatric disorders rheumatoid arthritis, psychosis or allergy.

18. A method for the treatment or prophylaxis of pain, neuropathic pain, asthma, osteoporosis, inflammation, psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, psychiatric disorders rheumatoid arthritis, psychosis or allergy, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 10 to a patient in need thereof.

19. The invention as hereinbefore described.

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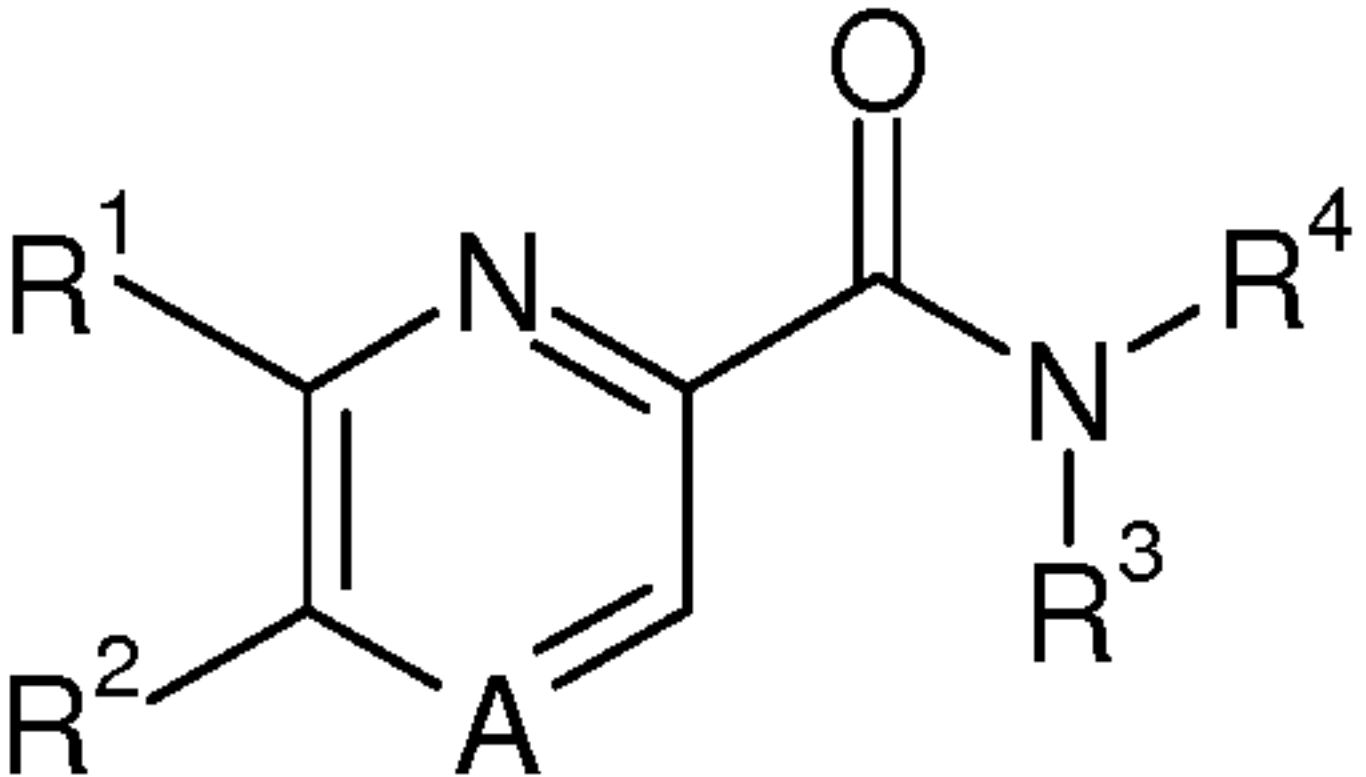

(I)