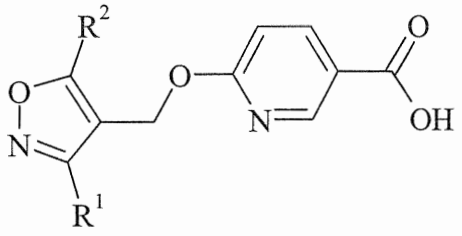
(6) The present invention further allows for a mild enzymatic hydrolysis of compounds of formula (IV) to deliver compounds of formula (I) by conventional extraction.

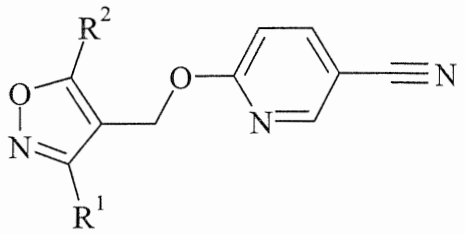
According to a first aspect, there is provided a process for the preparation of a compound of formula (I) or pharmaceutically acceptable salts thereof



(I)

wherein R^1 is phenyl optionally substituted by one or more halogen and R^2 is hydrogen, alkyl or haloalkyl; which comprises:

a) the hydrolysis of a compound of formula (IV) in a solvent, in the presence of 7 to 10 eq. of base, at a temperature between 50°C. and 60°C.,



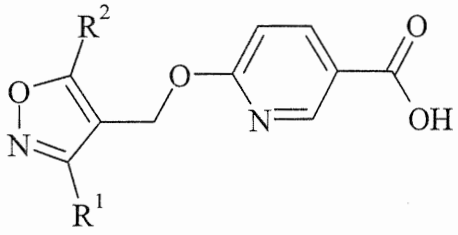
(IV),

b) removal of impurities by filtration; followed by

c) addition of an acid, in a solvent; followed by

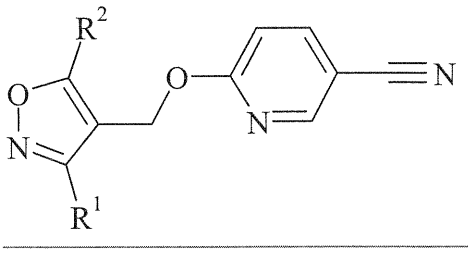
d) filtration, washing with an alcohol/water mixture and drying of the thereby obtained crystals of a compound of formula (I).

According to a second aspect, there is provided a process for the preparation of a compound of formula (I) or pharmaceutically acceptable salts thereof



(I)

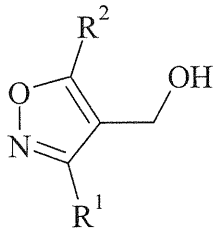
wherein R^1 is phenyl optionally substituted by one or more halogen and R^2 is hydrogen, alkyl or haloalkyl; which comprises the reaction of a compound of formula (IV)



(IV),

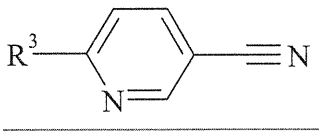
to a compound of formula (I) or pharmaceutically acceptable salts thereof

wherein further the compound of formula (V) is prepared by reaction of a compound of formula (II)



(II)

with a compound of formula (III)



(III)

wherein R^3 is a leaving group selected from halogen, -OS(O)$_2$-alkyl, or -OS(O)$_2$-aryl, in the presence of a base

wherein the compound of formula (I) is prepared in a telescoped process through reaction of a compound of formula (II) with a compound of formula (III) to a compound of formula (IV), followed by directly converting the compound of formula (IV) without isolating it to a compound of formula (I), wherein:

a) dissolution of a compound of formula (II) together with a compound of formula (III) in a solvent; followed by

b) addition of this solution to a suspension of a base in a solvent and reaction; followed by

c) quenching of the reaction; followed by

d) solvent exchange to alcohol/water; followed by

e) treatment with a base, in a solvent; followed by

f) washing the aqueous reaction mixture with a solvent to remove impurities; followed by

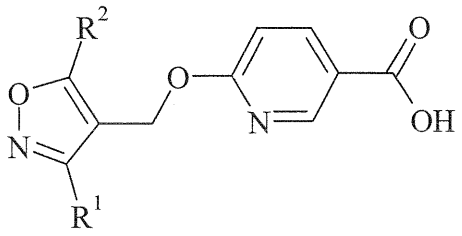
g) acidification of the aqueous phase with an acid; followed by

h) extraction of the compound of formula (I) with a solvent; followed by

i) crystallization from a solvent to yield compounds of formula (I).

Claims

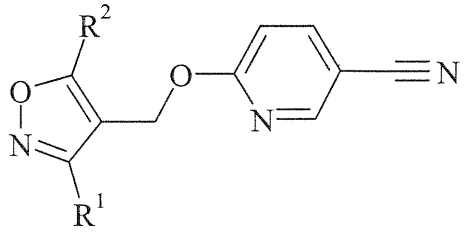
1. A process for the preparation of a compound of formula (I) or pharmaceutically acceptable salts thereof



(I)

wherein R^1 is phenyl optionally substituted by one or more halogen and R^2 is hydrogen, alkyl or haloalkyl; which comprises:

a) the hydrolysis of a compound of formula (IV) in a solvent, in the presence of 7 to 10 eq. of base, at a temperature between 50°C. and 60°C., ~~the reaction of a compound of formula (IV)~~



(IV),

b) removal of impurities by filtration; followed by

c) addition of an acid, in a solvent; followed by

d) filtration, washing with an alcohol/water mixture and drying of the thereby obtained crystals of ~~to~~ a compound of formula (I) ~~or salts thereof~~.

2. ~~A~~ The process according to claim 1, wherein R^1 is phenyl, or phenyl substituted by one fluoro, or phenyl substituted by one chloro.

3. The ~~A~~ process ~~according to any~~ of claims ~~1 or~~ 2, wherein R^1 is 4-fluoro-phenyl.

4. The ~~A~~ process ~~according to any~~ of claims ~~1 to~~ 3, wherein R^2 is hydrogen or methyl.

5. The ~~A~~ process ~~according to any~~ of claims ~~1 to~~ 4, wherein R^2 is methyl.

~~6. A process according to any of claims 1 to 5, comprising the following reaction steps:~~

~~a) hydrolysis of a compound of formula (IV) in a solvent, in the presence of a base; followed by~~

~~b) removal of impurities by filtration; followed by~~

~~c) addition of an acid, in a solvent; followed by~~

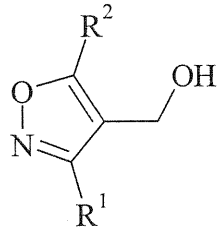
~~d) filtration, washing with an alcohol/water mixture and drying of the thereby obtained crystals of a compound of formula (I).~~

~~7~~6. The ~~A~~ process ~~according to~~ of claim ~~6~~1, wherein the solvent employed in step a) is a mixture of water with methanol, water with ethanol or water with isopropanol.

~~8~~7. The ~~A~~ process ~~according to any~~ of claim~~s 6 or 7~~1, wherein the base employed in step a) is sodium hydroxide, potassium hydroxide or lithium hydroxide.

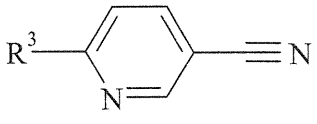
~~9~~8. The ~~A~~ process ~~according to any~~ of claim~~s 6 to 8~~1, wherein the acid employed in step c) is aqueous hydrochloric acid or aqueous sulfuric acid and wherein the solvent employed in step c) is water.

~~10~~9. The ~~A~~ process ~~according to any~~ of claim~~s~~ 1 ~~to 9~~ wherein the compound of formula (IV) is prepared by reaction of a compound of formula (II)



(II)

with a compound of formula (III)



(III)

wherein R^3 is a leaving group selected from halogen, -$OS(O)_2$-alkyl, or -$OS(O)_2$-aryl, in the presence of a base, said process comprising:~~.~~

a) dissolution of a compound of formula (II) together with a compound of formula (III) in a solvent; followed by

b) addition of this solution to a suspension of a base in a solvent and reaction; followed by

c) neutralization by addition of an acid in a solvent; followed by

d) isolation of the compound of formula (IV) by a solvent exchange to alcohol/water and subsequent filtration and drying.

~~11~~10. ~~A~~ The process ~~according to~~of claim ~~10~~9, wherein R^3 is chloro, bromo, iodo, methanesulfonate, or toluene-4-sulfonate.

~~12~~11. The ~~A~~ process ~~according to any~~ of claim~~s 10 or 11~~, wherein R^3 is chloro.

~~13. A process according to any of claims 10 to 12, wherein the reaction of a compound of formula (II) with a compound of formula (III) to a compound of formula (IV) comprises the following reaction steps: e) dissolution of a compound of formula (II) together with a compound of formula (III) in a solvent; followed by f) addition of this solution to a suspension of a base in a solvent and reaction; followed by~~

~~g) neutralization by addition of an acid in a solvent; followed by~~

~~h) isolation of the compound of formula (IV) by a solvent exchange to alcohol/water und subsequent filtration and drying.~~

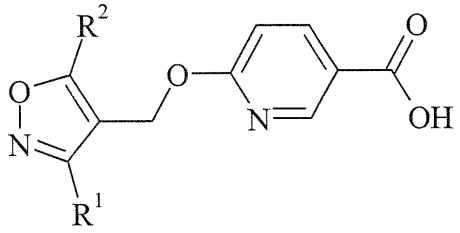
~~14~~12. The ~~A~~ process ~~according to~~of claim ~~13~~9, wherein the solvent employed in step ~~e~~a) is THF or MeTHF.

~~15~~13. The ~~A~~ process ~~according to any~~ of claim~~s 13 or 14~~9, wherein the base employed in step ~~f~~b) is sodium hydride or sodium tert-butoxide and wherein the solvent employed in step ~~f~~b) is THF or MeTHF.

~~16~~14. The ~~A~~ process ~~according to any~~ of claim~~s 13 to 15~~9, wherein the acid employed in step ~~g~~c) is citric acid and wherein the solvent employed in step ~~g~~c) is water.

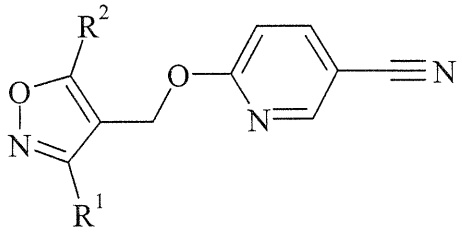
~~17~~15. The ~~A~~ process ~~according to any~~ of claim~~s 13 to 16~~9, wherein in step ~~h~~d) the solvent is exchanged to a mixture of water with methanol, water with ethanol or water with isopropanol.

~~18~~16. A process for the preparation of a ~~according to any of claims 1 to 17, wherein the~~ compound of formula (I) or pharmaceutically acceptable salts thereof



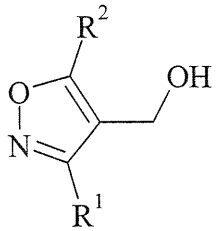
(I)

wherein R^1 is phenyl optionally substituted by one or more halogen and R^2 is hydrogen, alkyl or haloalkyl; which comprises the reaction of a compound of formula (IV)



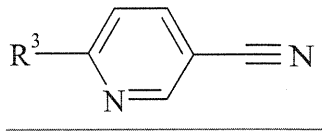
(IV),

to a compound of formula (I) or pharmaceutically acceptable salts thereof wherein further the compound of formula (V) is prepared by reaction of a compound of formula (II)



(II)

with a compound of formula (III)



(III)

wherein R^3 is a leaving group selected from halogen, $-OS(O)_2$-alkyl, or $-OS(O)_2$-aryl, in the presence of a base

wherein the compound of formula (I) is prepared in a telescoped process through reaction of a compound of formula (II) with a compound of formula (III) to a compound of formula (IV),

followed by directly converting the compound of formula (IV) without isolating it to a compound of formula (I), wherein:~~.~~

~~19. A telescoped process according to claim 18 comprising the following reaction steps:~~

~~r~~a) dissolution of a compound of formula (II) together with a compound of formula (III) in a solvent; followed by

~~s~~b) addition of this solution to a suspension of a base in a solvent and reaction; followed by

~~t~~c) quenching of the reaction; followed by

~~u~~d) solvent exchange to alcohol/water; followed by

~~v~~e) treatment with a base, in a solvent; followed by

~~w~~f) washing the aqueous reaction mixture with a solvent to remove impurities; followed by

~~x~~g) acidification of the aqueous phase with an acid; followed by

~~y~~h) extraction of the compound of formula (I) with a solvent; followed by

~~z~~i) crystallization from a solvent to yield compounds of formula (I).

~~20~~17. ~~A~~ The telescoped process ~~according to any~~ of claim~~s 18 to 19~~16, wherein the suspension of a base employed in step ~~s~~b) is a suspension of sodium hydride in THF or MeTHF.

~~21~~18. The ~~A~~ telescoped process ~~according to any~~ of claim~~s 18 to 20~~16, wherein the reaction is quenched with water in step c~~t~~).

~~22~~19. The ~~A~~ telescoped process ~~according to any~~ of claim~~s 18 to 21~~16, wherein the solvent exchange in step d~~u~~) is performed to a mixture of water with methanol, water with ethanol or water with isopropanol.

~~23~~20. The ~~A~~ telescoped process ~~according to any~~ of claim~~s 18 to 22~~16, wherein the base employed in step ~~v~~e) is sodium hydroxide, potassium hydroxide or lithium hydroxide and wherein the solvent employed in step ~~v~~e) is a mixture of water with methanol, water with ethanol or water with isopropanol.

~~24~~21. The ~~A~~ telescoped process ~~according to any~~ of claim~~s 18 to 23~~16, wherein the solvent employed in step f~~w~~) is toluene.

~~25~~22. The ~~A~~ telescoped process ~~according to any~~ of claim~~s 18 to 24~~16, wherein the acid employed in step ~~x~~g) is aqueous hydrochloric acid or aqueous sulfuric acid.

~~26~~23. The ~~A~~ telescoped process ~~according to any~~ of claim~~s 18 to 25~~16, wherein the solvent employed in step h~~y~~) is THF, toluene or a mixture of THF/toluene.

~~27~~24. The ~~A~~ telescoped process ~~according to any~~ of claim~~s 18 to 26~~16, wherein the solvent employed in step i~~z~~) is toluene.

~~28~~25. The ~~A~~ process ~~according to any~~ of claim~~s 1 to 27~~16, wherein the compound of formula (IV) is converted to a compound of formula (I) using a biocatalytic~~al~~ process.

~~29~~26. The ~~A~~ biocatalytic~~al~~ process ~~according to~~ of claim ~~28~~16, wherein a biocatalyst is reacted with compounds of formula (IV) in an aqueous buffer.

~~30~~27. The ~~A~~ biocatalytic~~al~~ process ~~according to any~~ of claim~~s 28 or 29~~16, wherein pH of the reaction mixture is kept constant at the selected value by the addition of a base.

~~31~~28. The ~~A~~ biocatalytic~~al~~ process ~~according to any~~ of claim~~s 28 to 30~~16, wherein the pH is kept constant with a base selected from aqueous NaOH or aqueous KOH.

~~32~~29. The ~~A~~ biocatalytic~~al~~ process ~~according to any~~ of claim~~s 28 to 31~~16, wherein the biocatalyst employed is a whole microbial cell.

~~33~~30. The ~~A~~ biocatalytic~~al~~ process ~~according to any~~ of claim~~s 28 to 32~~16, wherein the biocatalyst employed is microbial strain *Fusarium poae* [ATCC 24668].

~~34~~31. The ~~A~~ biocatalytic~~al~~ process ~~according to any~~ of claim~~s 28 to 31~~16, wherein the biocatalyst employed is an enzyme.

~~35~~32. The ~~A~~ biocatalytic~~al~~ process ~~according to any~~ of claim~~s 28 to 31 and 34~~31, wherein the biocatalyst employed is a nitrilase selected from Nit-103, Nit-104, Nit-107, Nit-108, Nit-121, Nit-122, Nit-124 and Nit-127.~~;~~

~~36~~33. The ~~A~~ biocatalytic~~al~~ process ~~according to any~~ of claim~~s 28 to 35~~26, wherein the aqueous buffer used is selected from the group of N,N-bis(2-hydroxyethyl)glycine (Bicine), 4-2-hydroxyethyl-1-piperazineethanesulfonic acid (HEPES), 2-(N-morpholino)ethanesulfonic acid (MES), 3-(N-morpholino)propanesulfonic acid (MOPS), phosphate buffer saline (PBS), piperazine-N,N'-bis(2-ethanesulfonic acid) (PIPES), saline sodium citrate (SSC), 3-{[tris(hydroxymethyl)-methyl]-amino}-propanesulfonic acid (TAPS), 2-{[tris(hydroxymethyl)-methyl]-amino}ethanesulfonic acid (TES), N-tris(hydroxymethyl)-methylglycine (Tricine), and tris(hydroxymethyl)-methylamine (TRIS), or mixtures thereof.

~~37~~34. The ~~A~~ process ~~according to any~~ of claim~~s 1 to 36~~, wherein the compound of formula (IV) is selected from the group consisting of:

6-[3-(3-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinonitrile;

6-[3-(3-Chloro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinonitrile;

6-[3-(4-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinonitrile;

6-[3-(4-Chloro-phenyl)-isoxazol-4-ylmethoxy]-nicotinonitrile; and

6-[3-(4-Chloro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinonitrile.

~~38~~35. The ~~A~~ process ~~according to any~~ of claim~~s 1 to 37~~34, wherein the compound of formula (IV) is 6-[3-(4-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinonitrile.

~~39~~36. The ~~A~~ process ~~according to any~~ of claim~~s 1 to 37~~, wherein the compound of formula (I) is selected from the group consisting of:

6-(5-Methyl-3-phenyl-isoxazol-4-ylmethoxy)-nicotinic acid;

6-[3-(3-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinic acid;

6-[3-(3-Chloro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinic acid;

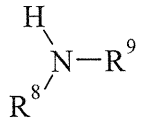
6-[3-(4-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinic acid;

6-[3-(4-Chloro-phenyl)-isoxazol-4-ylmethoxy]-nicotinic acid; and

6-[3-(4-Chloro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinic acid; and salts thereof.

~~40~~37. The ~~A~~ process ~~according to any~~ of claim~~s 1 to 39~~36, wherein the compound of formula (I) is 6-[3-(4-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinic acid; or salts thereof.

~~41~~38. The ~~A~~ process ~~according to any~~ of claim~~s 1 to 40~~, further comprising the reaction of a compound of formula (I) or salts thereof with a compound of formula (V) or salts thereof,



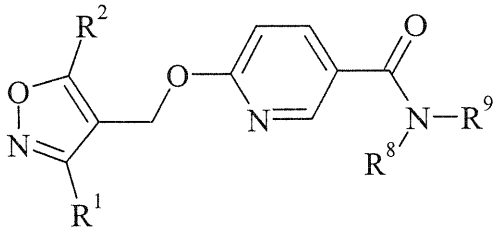
(V)

wherein R^8 and R^9 are independently selected from the group of hydrogen, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with one or more halogen, CN, alkyl, alkoxy, haloalkyl, hydroxyalkyl, hydroxy, or oxo;

or R^8 and R^9 together with the nitrogen to which they are attached to form a heterocycloalkyl or heteroaryl, wherein heterocycloalkyl and heteroaryl are optionally substituted with one or more halogen, CN, alkyl, alkoxy, haloalkyl, hydroxyalkyl, hydroxy, or oxo;

with the proviso that R^8 and R^9 are not both hydrogen;

to a compound of formula (VI) or pharmaceutically acceptable salts thereof



(VI).

~~42~~39. The ~~A~~ process according to claim ~~41~~38, wherein the reaction is selected from the group consisting of~~comprising~~:

i) the reaction of a compound of formula (I) or salts thereof, in a solvent, such as DMF, in the presence of TBTU and DIPEA, together with a compound of formula (V), in a solvent, such as methanol, to give a compound of formula (VI); or

ii) the reaction of a compound of formula (I) or salts thereof, in a solvent, such as THF, in the presence of HOBT, DIPEA and EDAC, together with a compound of formula (V), to give a compound of formula (VI); or

iii) the reaction of a compound of formula (I) or salts thereof, in a solvent, such as DMF or THF, in the presence of CDI, together with a compound of formula (V), in a solvent, to give a compound of formula (VI); or

iv) the reaction of a compound of formula (I) or salts or esters thereof, in a solvent, such as toluene, in the presence of Me_3Al, together with a compound of formula (V), in a solvent, such as dioxane, to give a compound of formula (VI); or

v) the reaction of a compound of formula (I) or salts or esters thereof, in a solvent, such as toluene, in the presence of TBD, together with a compound of formula (V), to give a compound of formula (VI); or

vi) the reaction of a compound of formula (I) or salts thereof, in a solvent, such as THF, in the presence of CDI, with or without DMAP, and a base such as triethylamine (TEA), together with a compound of formula (V), to give a compound of formula (VI).

~~43~~40. ~~The A~~ process ~~according to any~~ of claim~~s 41 or 42~~38, wherein the compound of formula (V) is employed in a salt form, in particularly as a hydrochloric salt, which is converted to the free base of the compound of formula (V) by reaction with lithium tert-butoxide (LiOtBu), in a solvent prior to reaction with a compound of formula (I).

~~44~~41. ~~The A~~ process ~~according to any~~ of claim~~s 41 to 43~~38, wherein R^8 is isopropyl, trifluoroethyl, hydroxypropyl, cyclopropyl, cyclopropylmethyl, tetrahydropyranyl, isoxazolylmethyl substituted by isopropyl, phenyl substituted by fluoro, pyrazolyl substituted by methyl, or pyridinylmethyl.

~~45~~42. ~~The A~~ process ~~according to any~~ of claim~~s 41 to 44~~38, wherein R^9 is hydrogen or methyl.

~~46~~43. ~~The A~~ process ~~according to any~~ of claim~~s 41 to 43~~38, wherein R^8 and R^9 together with the nitrogen to which they are attached to form thiazolidinyl, piperidinyl substituted by hydroxy, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholin-4-yl, or 5,6-Dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl.

~~47~~44. ~~The A~~ process ~~according to any~~ of claim~~s 41 to 43 and 46~~43, wherein R^8 and R^9 together with the nitrogen to which they are attached to form morpholinyl, or 1,1-dioxo-thiomorpholin-4-yl.

~~48~~45. ~~The A~~ process ~~according to any~~ of claim~~s 41 to 43 and 46 and 47~~44, wherein the compound of formula (V) is thiomorpholine-1,1-dioxide or thiomorpholine-1,1-dioxide HCl.

~~49~~46. ~~The A~~ process ~~according to any~~ of claim~~s 41 to 48~~38, wherein the compound of formula (VI) is selected from the group consisting of:

5047. The A process according to any of claims 41 to 4946, wherein the compound of formula (VI) is selected from the group consisting of:

6-[3-(4-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-N-(tetrahydro-pyran-4-yl)-nicotinamide;

(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone;

6-[3-(4-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-N-isopropyl-nicotinamide;

N-Cyclopropylmethyl-6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinamide;

{6-[3-(4-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-morpholin-4-yl-methanone; and

6-[3-(4-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-N-(2,2,2-trifluoro-ethyl)-nicotinamide; and pharmaceutically acceptable salts thereof.

5148. The A process according to any of claims 41 to 5047, wherein the compound of formula (VI) is (1,1-dioxo-1λ^6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone; or pharmaceutically acceptable salts thereof.

5249. A process for the preparation of a compound of formula (VI) according to any of claims 41 to 5138, comprising the reaction of a compound of formula (II) with a compound of formula (III) to a compound of formula (IV),

followed by the reaction of the compound of formula (IV) to a compound of formula (I),

followed by the reaction of the compound of formula (I) with a compound of formula (V) to a compound of formula (VI);

wherein the compound of formula (II) is 3-(4-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethanol,

wherein the compound of formula (III) is 6-chloronicotinonitrile,

wherein the compound of formula (IV) is 6-[3-(4-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinonitrile,

wherein the compound of formula (I) is 6-[3-(4-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinic acid, or salts thereof;

wherein the compound of formula (V) is thiomorpholine-1,1-dioxide, or salts thereof;

wherein the compound of formula (VI) is (1,1-dioxo-1λ^6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone, or pharmaceutically acceptable salts thereof.

5350. Compounds obtainable by a process according to any of claims 1 to 52. The process of claim 16, wherein the compound of formula (IV) is selected from the group consisting of:

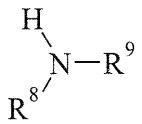
6-[3-(3-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinonitrile;
6-[3-(3-Chloro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinonitrile;
6-[3-(4-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinonitrile;
6-[3-(4-Chloro-phenyl)-isoxazol-4-ylmethoxy]-nicotinonitrile; and
6-[3-(4-Chloro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinonitrile.

51. The process of claim 50, wherein the compound of formula (IV) is 6-[3-(4-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinonitrile.

52. The process of claim 51, wherein the compound of formula (I) is selected from the group consisting of:
6-(5-Methyl-3-phenyl-isoxazol-4-ylmethoxy)-nicotinic acid;
6-[3-(3-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinic acid;
6-[3-(3-Chloro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinic acid;
6-[3-(4-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinic acid;
6-[3-(4-Chloro-phenyl)-isoxazol-4-ylmethoxy]-nicotinic acid; and
6-[3-(4-Chloro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinic acid; and salts thereof.

53. The process of claim 52, wherein the compound of formula (I) is 6-[3-(4-Fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-nicotinic acid; or salts thereof.

54. The process of claim 16, further comprising the reaction of a compound of formula (I) or salts thereof, with a compound of formula (V) or salts thereof,



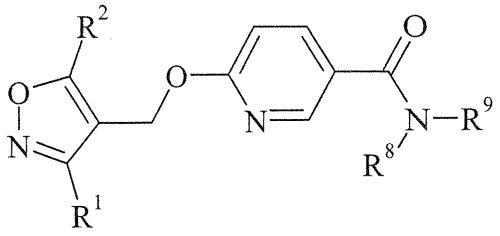
(V)

wherein R^8 and R^9 are independently selected from the group of hydrogen, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with one or more halogen, CN, alkyl, alkoxy, haloalkyl, hydroxyalkyl, hydroxy, or oxo;

or R^8 and R^9 together with the nitrogen to which they are attached to form a heterocycloalkyl or heteroaryl, wherein heterocycloalkyl and heteroaryl are optionally substituted with one or more halogen, CN, alkyl, alkoxy, haloalkyl, hydroxyalkyl, hydroxy, or oxo;

with the proviso that R^8 and R^9 are not both hydrogen;

to a compound of formula (VI) or pharmaceutically acceptable salts thereof



(VI).