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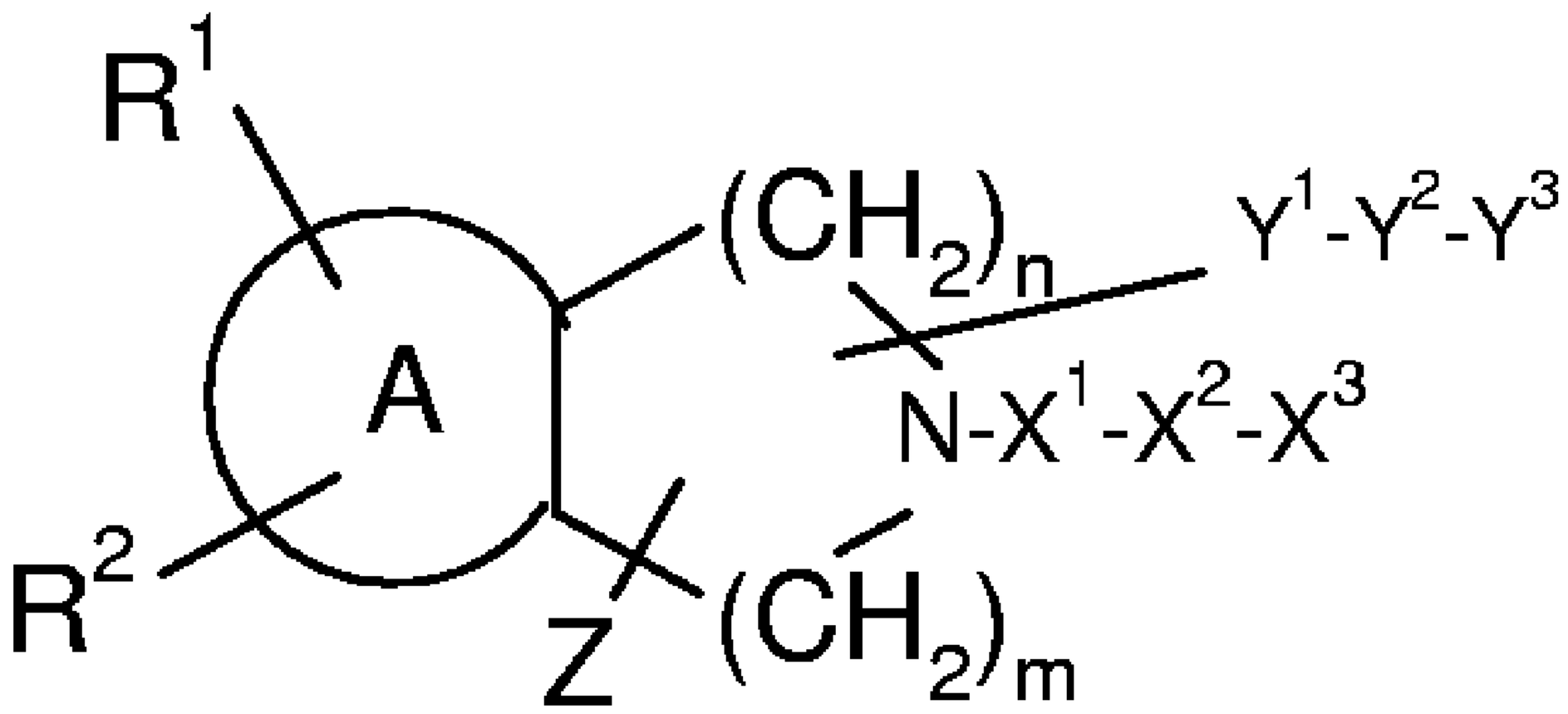
(54) Titre : NOUVELLES AMINES CYCLIQUES FUSIONNES AVEC HETEROARYLE
(54) Title: NOVEL HETEROARYL FUSED CYCLIC AMINES



(I)

(57) Abrégé/Abstract:
The invention is concerned with novel heteroaryl fused cyclic amines of formula (I) wherein A, X^1 to X^3, Y^1 to Y^3, Z, R^1, R^2, m and n are as defined in the description and in the claims, as well as physiologically acceptable salts thereof. These compounds inhibit the coagulation factor Xa and can be used as medicaments.

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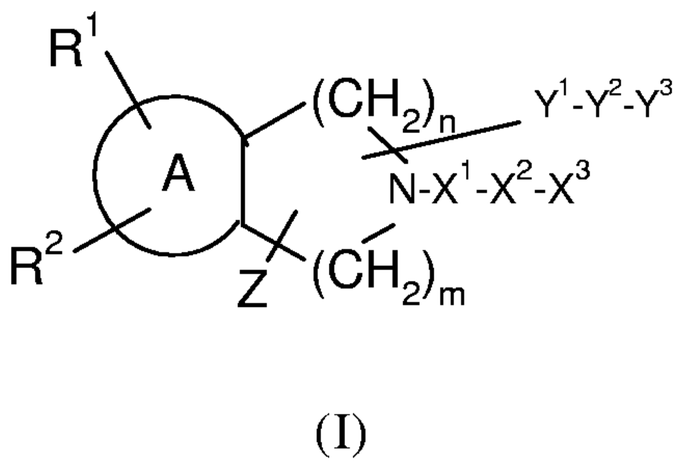
(54) Title: NOVEL HETEROARYL FUSED CYCLIC AMINES



(I)

(57) Abstract: The invention is concerned with novel heteroaryl fused cyclic amines of formula (I) wherein A, X^1 to X^3, Y^1 to Y^3, Z, R^1, R^2, m and n are as defined in the description and in the claims, as well as physiologically acceptable salts thereof. These compounds inhibit the coagulation factor Xa and can be used as medicaments.

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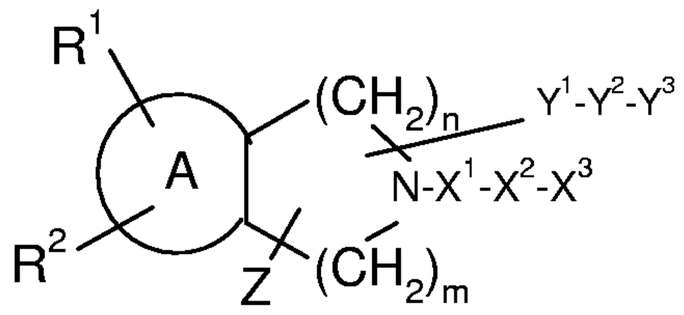
NOVEL HETEROARYL FUSED CYCLIC AMINES

The invention is concerned with novel heteroaryl fused cyclic amines of formula (I),



(I)

wherein

A is a heteroaryl ring which is a monocyclic or bicyclic aromatic ring of 5 to 12 ring atoms, containing one, two, or three ring heteroatoms selected from N, O, and S, the remaining ring atoms being C, one or two carbon atoms of said ring being optionally replaced with a carbonyl group;

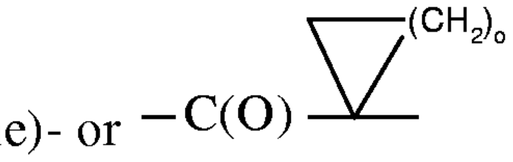
R^1 and R^2

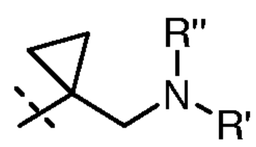
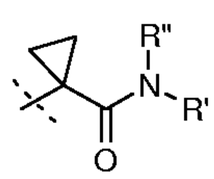
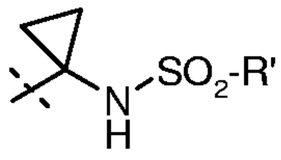
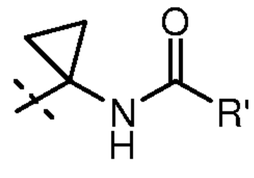
are independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, fluoro C_{1-6} alkoxy, hydroxy C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, mono or di C_{1-6} alkyl substituted amino C_{1-6} alkoxy, halogen, cyano, nitro, -N(R')-CO-(C_{1-6} alkyl optionally substituted by one or more fluorine atoms), in which R' is hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -N(R')-CO-O-(C_{1-6} alkyl optionally substituted by one or more fluorine atoms), in which R' is hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -N(R')-CO-N(R") (R"'), in which R', R" and R"' are independently hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl or -N(R')-SO_2-(C_{1-6} alkyl optionally substituted by one or more fluorine atoms), in which R' is hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl or

R^1 and R^2

are independently -SO_2-N(R')(R"), -C(O)-N(R')(R") or –N(R')(R"), in which R'

and R" are independently hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl or R' and R", together with the nitrogen atom to which they are attached, form heterocycyl;

X^1 is $-C(O)-(C_{0-6}$ alkylene$)-NR^3-(C_{0-6}$ alkylene$)-$, $-(C_{0-6}$ alkylene$)-C(O)-NR^3-(C_{0-6}$ alkylene$)-$, $-(C_{1-6}$ alkylene$)-NR^3-C(O)-(C_{0-6}$ alkylene$)-$, $-C(O)-(C_{0-6}$ alkylene$)$-, C_{0-6} alkylene, $-SO_2-(C_{0-6}$ alkylene$)$-, $-(C_{0-6}$ alkylene$)$-SO_2-$NR^3-(C_{0-6}$ alkylene$)$- or  ;

X^2 is arylene, heteroarylene or heterocyclylene, said arylene, heteroarylene and heterocyclylen being optionally substituted by one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, halogen, cyano, nitro, amino, -N(R')-CO-(C_{1-6} alkyl optionally substituted by one or more fluorine atoms), in which R' is hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -N(R')-CO-O-(C_{1-6} alkyl optionally substituted by one or more fluorine atoms), in which R' is hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -N(R')-CO-N(R") (R""), in which R', R" and R"" are independently hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -C(O)-N(R')(R"), in which R' and R" are independently hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, or R' and R", together with the nitrogen atom to which they are attached, form heterocycyl, -NR'R", in which R' and R" are independently hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, or R' and R", together with the nitrogen atom to which they are attached, form heterocycyl,  wherein R' and R" are independently C_{1-6} alkyl or fluoro C_{1-6} alkyl, or R' and R", together with the nitrogen atom to which they are attached, form heterocyclyl,  wherein R' and R" are independently C_{1-6} alkyl or fluoro C_{1-6} alkyl, or R' and R", together with the nitrogen atom to which they are attached, form heterocyclyl,  , in which R' is fluoro C_{1-6} alkyl and  , in which R' is fluoro C_{1-6} alkyl,

and one or two carbon atoms of said arylene, heteroarylene or heterocyclylene being optionally replaced with a carbonyl group;

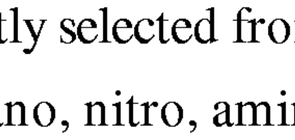
X^3 is hydrogen, aryl, heteroaryl or heterocyclyl, said aryl, heteroaryl and heterocyclyl being optionally substituted by one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, halogen, cyano, nitro, amino, mono-C_{1-6} alkyl substituted amino, di-C_{1-6} alkyl substituted amino, mono-C_{1-6} alkyl substituted amino-C_{1-6} alkyl, di-C_{1-6} alkyl substituted amino-C_{1-6} alkyl, -SO_2-C_{1-6} alkyl, -SO_2-NH_2, -SO_2-NH-C_{1-6} alkyl and -SO_2-N(C_{1-6} alkyl)$_2$,

and one or two carbon atoms of said aryl, heteroaryl and heterocyclyl being optionally replaced with a carbonyl group;

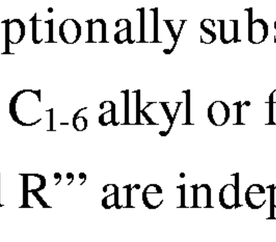
R^3 is hydrogen or C_{1-6} alkyl;

Y^1 is –(C_{0-6} alkylene)–C(O)–NR^3–(C_{0-6} alkylene)–, –(C_{0-6} alkylene)–NR^3–C(O)–(C_{0-6} alkylene)– or C_{0-6} alkylene;

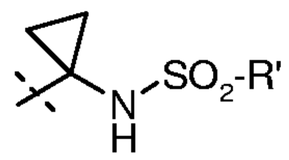
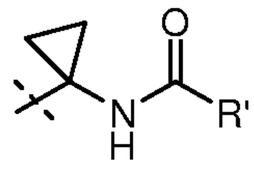
Y^2 is arylene, heteroarylene or heterocyclylene, said arylene, heteroarylene and heterocyclylene being optionally substituted by one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, halogen, cyano, nitro, amino, -N(R')-CO-(C_{1-6} alkyl optionally substituted by one or more fluorine atoms), in which R' is hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -N(R')-CO-O-(C_{1-6} alkyl optionally substituted by one or more fluorine atoms), in which R' is hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -N(R')-CO-N(R") (R"'), in which R', R" and R"' are independently hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -C(O)-N(R')(R"), in which R' and R" are independently hydrogen, C_{1-6} alkyl or halo C_{1-6} alkyl, or R' and R", together with the nitrogen atom to which they are attached, form heterocycyl, -NR'R", in which R' and R" are independently hydrogen, C_{1-6} alkyl or halo C_{1-6} alkyl, or R' and R", together with the nitrogen atom to which they are attached, form

heterocycyl, 

,in which R' and R" are independently C_{1-6} alkyl or fluoro C_{1-6} alkyl, or R' and R", together with the nitrogen atom to which they

are attached, form heterocyclyl, 

, in which R' and R" are

independently C_{1-6} alkyl or fluoro C_{1-6} alkyl, or R' and R", together with the nitrogen atom to which they are attached, form heterocyclyl,  , in which R' is fluoro C_{1-6} alkyl and  , in which R' is C_{1-6} alkyl, and one or two carbon atoms of said arylene, heteroarylene or heterocyclylene being optionally replaced with a carbonyl group;

Y^3 is hydrogen, aryl, heteroaryl or heterocyclyl, said aryl, heteroaryl and heterocyclyl being optionally substituted by one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, halogen, cyano, nitro, amino, mono-C_{1-6} alkyl substituted amino, di-C_{1-6} alkyl substituted amino, mono-C_{1-6} alkyl substituted amino-C_{1-6} alkyl, di-C_{1-6} alkyl substituted amino-C_{1-6} alkyl, $-SO_2-C_{1-6}$ alkyl, $-SO_2-NH_2$, $-SO_2-NH-C_{1-6}$ alkyl and $-SO_2-N(C_{1-6}$ alkyl$)_2$, and one or two carbon atoms of said aryl, heteroaryl and heterocyclyl being optionally replaced with a carbonyl group;

Z is attached to the same carbon atom as $-Y^1-Y^2-Y^3$, and hydrogen or C_{1-6} alkyl;

n is 0, 1 or 2;

m is 0, 1 or 2;

m+n is 2 or 3;

o is an integer from 1 to 5;

and prodrugs and pharmaceutically acceptable salts thereof.

Further, the invention is concerned with a process and an intermediate for the manufacture of the above compounds, pharmaceutical preparations which contain such compounds, the use of these compounds for the production of pharmaceutical preparations as well as a process for the manufacture of the intermediate.

The compounds of formula (I) are active compounds and inhibit the coagulation factor Xa. These compounds consequently influence blood coagulation. They therefore inhibit the formation of thrombin and can be used for the treatment and/or prevention of thrombotic disorders, such as amongst others, arterial and venous thrombosis, deep vein

thrombosis, peripheral arterial occlusive disease (PAOD), unstable angina pectoris, myocardial infarction, coronary artery disease, pulmonary embolism, stroke (cerebral thrombosis) due to atrial fibrillation, inflammation and arteriosclerosis. They have potentially benefit in the treatment of acute vessel closure associated with thrombolytic therapy and restenosis, e.g. after transluminal coronary angioplasty (PTCA) or bypass grafting of the coronary or peripheral arteries and in the maintenance of vascular access patency in long term hemodialysis patients. F.Xa inhibitors of this invention may form part of a combination therapy with an anticoagulant with a different mode of action or with a platelet aggregation inhibitor or with a thrombolytic agent. Furthermore, these compounds have an effect on tumour cells and prevent metastases. They can therefore also be used as antitumour agents.

Other inhibitors of factor Xa had previously been suggested for the inhibition of the formation of thrombin and for the treatment of related diseases. However, there is still a need for novel factor Xa inhibitors which exhibit improved pharmacological properties, e.g. an improved selectivity towards thrombin.

The present invention provides novel compounds of formula (I) which are factor Xa inhibitors. The compounds of the present invention unexpectedly inhibit coagulation factor Xa and also exhibit improved pharmacological properties compared to other compounds already known in the art.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term "halogen" or "halo" means fluorine, chlorine, bromine and iodine, with fluorine, chlorine and bromine being preferred, and fluorine and chlorine being more preferred.

The term "C_{1-6} alkyl", alone or in combination with other groups, means a branched or straight-chain monovalent alkyl radical, having one to six carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, t-butyl. C_{1-4} alkyl is more preferred.

The term "C_{0-6} alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched divalent hydrocarbon radical of three to six carbon atoms or a bond when C is 0, e.g., methylene, ethylene, 2,2-dimethylethylene, propylene.

The term "C_{1-6} alkoxy", alone or in combination with other groups, means the group R'-O-, wherein R' is a C_{1-6} alkyl.

The term "hydroxy C_{1-6} alkoxy" means C_{1-6} alkoxy substituted by one or more hydroxy group.

The term "fluoro C_{1-6} alkyl" or "fluoro C_{1-6} alkoxy" means C_{1-6} alkyl or C_{1-6} alkoxy substituted by one or more fluorine atoms, preferably one to three fluorine atoms.

The term "aryl" means phenyl or naphthyl. Phenyl is preferred.

The term "arylene" , alone or in combination with other groups, means a divalent aryl group as defined above. 1,4-phenylene is preferred.

The term "heterocyclyl", alone or combination with other groups, means non-aromatic mono- or bi-cyclic radicals of three to eight ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or $S(O)_n$ (where n is an integer from 0 to 2), the remaining ring atoms being C. Monocyclic radicals are preferred.

The term "heterocyclylene", alone or combination with other groups, means a divalent heterocyclyl group as defined above.

The term "heteroaryl", alone or combination with other groups, means a monocyclic or bicyclic aromatic radical of 5 to 12 ring atoms, containing one, two, or three ring heteroatoms selected from N, O, and S, the remaining ring atoms being C, one or two carbon atoms of said ring being optionally replaced with a carbonyl group, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. Monocyclic radicals are preferred.

The term "heteroarylene", alone or combination with other groups, means a divalent heteroaryl group as defined above.

The term "bicyclic aromatic ring" or "bicyclic aromatic radical" contains both an aromatic monocyclic ring fused by another aromatic monocyclic ring and an aromatic monocyclic ring fused by a non-aromatic monocyclic ring. When the term "bicyclic aromatic ring" or "bicyclic aormatic radical" is used in the context of the definition of "heteroaryl" or "heteroaryl ring", at least one heteroatom must exist in the aromatic ring as a ring member. When the heteroaryl ring as A ring in formula I is a bicyclic aromatic ring, and this bicyclic aromatic ring is an aromatic monocyclic ring fused by a non-

aromatic monocyclic ring, then the aromatic ring is directly fused to the nitrogen containing ring to which $-Y^1-Y^2-Y^3$, $-X^1-X^2-X^3$ and Z are attached.

Preferred radicals for the chemical groups whose definitions are given above are those specifically exemplified in Examples.

Compounds of formula (I) can form pharmaceutically acceptable acid addition salts. Examples of such pharmaceutically acceptable salts are salts of compounds of formula (I) with physiologically compatible mineral acids, such as hydrochloric acid, sulphuric acid, sulphurous acid or phosphoric acid; or with organic acids, such as methanesulphonic acid, p-toluenesulphonic acid, acetic acid, lactic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The term "pharmaceutically acceptable salts" refers to such salts. Compounds of formula (I) in which a COOH group is present can further form salts with bases. Examples of such salts are alkaline, earth-alkaline and ammonium salts such as e.g. Na-, K-, Ca- and trimethylammoniumsalt. The term "pharmaceutically acceptable salts" also refers to such salts. Acid addition salts as described above are preferred.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "aryl group optionally substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the aryl group is substituted with an alkyl group and situations where the aryl group is not substituted with the alkyl group.

"Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

Compounds that have the same molecular Formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, if a carbon atom is bonded to four different groups, a pair of enantiomers is possible. An

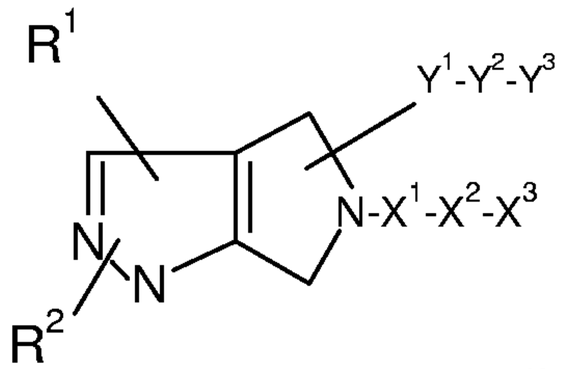
enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn, Ingold and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

The compounds of formula (I) can possess one or more asymmetric centers. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 1992).

While the broadest definition of this invention is described before, certain compounds of formula (I) are preferred.

i) A preferred compound of the invention is a compound of formula (I) wherein A is a heteroaryl ring which is a monocyclic aromatic ring of 5 or 6 ring atoms, containing one or two, preferably two ring nitrogen atoms.

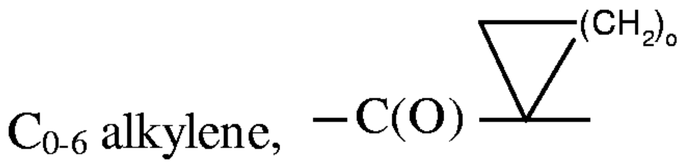
ii) Another preferred compound of the invention is a compound of formula (I) which is



(Id)

wherein X^1, X^2, X^3, Y^1, Y^2, Y^3, R^1 and R^2 are as defined before. $-Y^1-Y^2-Y^3$ is preferably located at 4 position of the pyrrolopyrazole ring.

iii) Another preferred compound of the invention is a compound of formula (I)

wherein X^1 is –C(O)-NH-, -C(O)–(C_{0-6} alkylene)-, C_{0-6} alkylene,  or –SO_2-, preferably –C(O)-NH- or -C(O)–(C_{0-6} alkylene)-, more preferably –C(O)-NH- or –C(O)-, especially –C(O)-NH-.

iv) Another preferred compound of the invention is a compound of formula (I) wherein X^2 is arylene or heteroarylene, said arylene and heteroarylene being optionally substituted by one or more substituents independently selected from the group consisting of C_{1-6} alkoxy and halogen, and X^3 is hydrogen. Preferably –X^2-X^3 forms phenyl or pyridyl, said phenyl and pyridyl being optionally substituted by one or more same or different halogen atoms. More preferably –X^2-X^3 forms 4-chlorophenyl or 5-chloropyridyn-2-yl.

v) Another preferred compound of the invention is a compound of formula (I) wherein Y^1 is –(C_{0-6} alkylene)–C(O)–NR^3–(C_{0-6} alkylene)–, preferably –C(O)–NR^3– in which R^3 is as defined before, more preferably –C(O)-NH-.

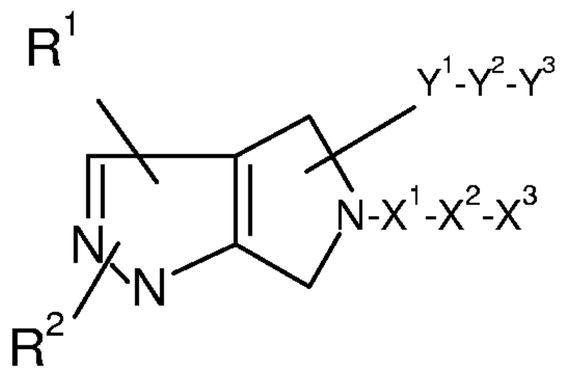
vi) Another preferred compound of the invention is a compound of formula (I) wherein Y^2 is 1,4-phenylene optionally substituted by one or more same or different halogen atoms, preferably 1,4-phenylene optionally substituted by one or more fluorine atoms, more preferably 2-fluoro-1,4 phenylene.

vii) Another preferred compound of the invention is a compound of formula (I) wherein Y^3 is heteroaryl optionally substituted by one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, halogen, cyano, nitro, amino, mono-C_{1-6} alkyl substituted amino, di-C_{1-6} alkyl substituted amino, mono-C_{1-6} alkyl substituted amino-C_{1-6} alkyl, di-C_{1-6} alkyl substituted amino-C_{1-6} alkyl, -SO_2-C_{1-6} alkyl, -SO_2-NH_2, -SO_2-NH-C_{1-6} alkyl and -SO_2-N(C_{1-6} alkyl)$_2$, and one or two carbon atoms of said heteroaryl being optionally replaced with a carbonyl group. Preferably Y^3 is unsubstituted heteroaryl which is a monocyclic aromatic ring of 5 or 6 ring atoms, containing one or two, preferably one ring nitrogen atom, and one carbon atom of said heteroaryl being optionally replaced with a carbonyl group. Preferably the ring nitrogen atom of the heteroaryl is directly attached to Y^2, and one of the ring carbon atoms next to said ring nitrogen atom is replaced with a carbonyl group. Y^3 is especially 2-oxo-2H-pyridyn-1-yl.

viii) Another preferred compound of the invention is a compound of formula (I) wherein R^1 and R^2 is hydrogen, and the other is C_{1-6} alkyl.

ix) Another preferred compound of the invention is a compound of formula (I) wherein Z is hydrogen.

x) Another preferred compound of the invention is a compound of formula (I) which is



(Id)

wherein X^1, X^2, X^3, Y^1, Y^2 and Y^3 are as defined in ii) to vii), and one of R^1 and R^2 is C_{1-6} alkyl, e.g.methyl, and at 1 position of the pyrrolopyrazole ring, and the other is hydrogen. $-Y^1-Y^2-Y^3$ is preferably located at 4 position of the pyrrolopyrazole ring.

xi) Particularly preferred compounds of the present invention are:

(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide},

(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide},

(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[2-fluoro-4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide},

(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide},

(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[2,6-difluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}.

The compounds of the present invention can be prepared, for example, by the general synthetic procedures described below.

General Synthetic Procedures

Abbreviations

AcOEt: Ethyl acetate

Boc_2O : Di-tert-butyl-dicarbonate

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

BOPCl: Bis-(2-oxo-3-oxazolidinyl)-phosphinic acid chloride

tBuOMe: t-Butyldimethylether

DIPEA: Diisopropyl ethyl amine

DMA: N,N-Dimethylacetamide

DMAP: 4-Dimethylaminopyridine

DME:1,2-Dimethoxyethane

DMF: N,N-Dimethylformamide

DMSO: Dimethylsulfoxide

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

HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide, hexa-fluorophosphate

HOBT: 1-Hydroxybenzotriazole

MeOH: Methanol

TEA: Triethylamine

TFA: Trifluoroacetic acid

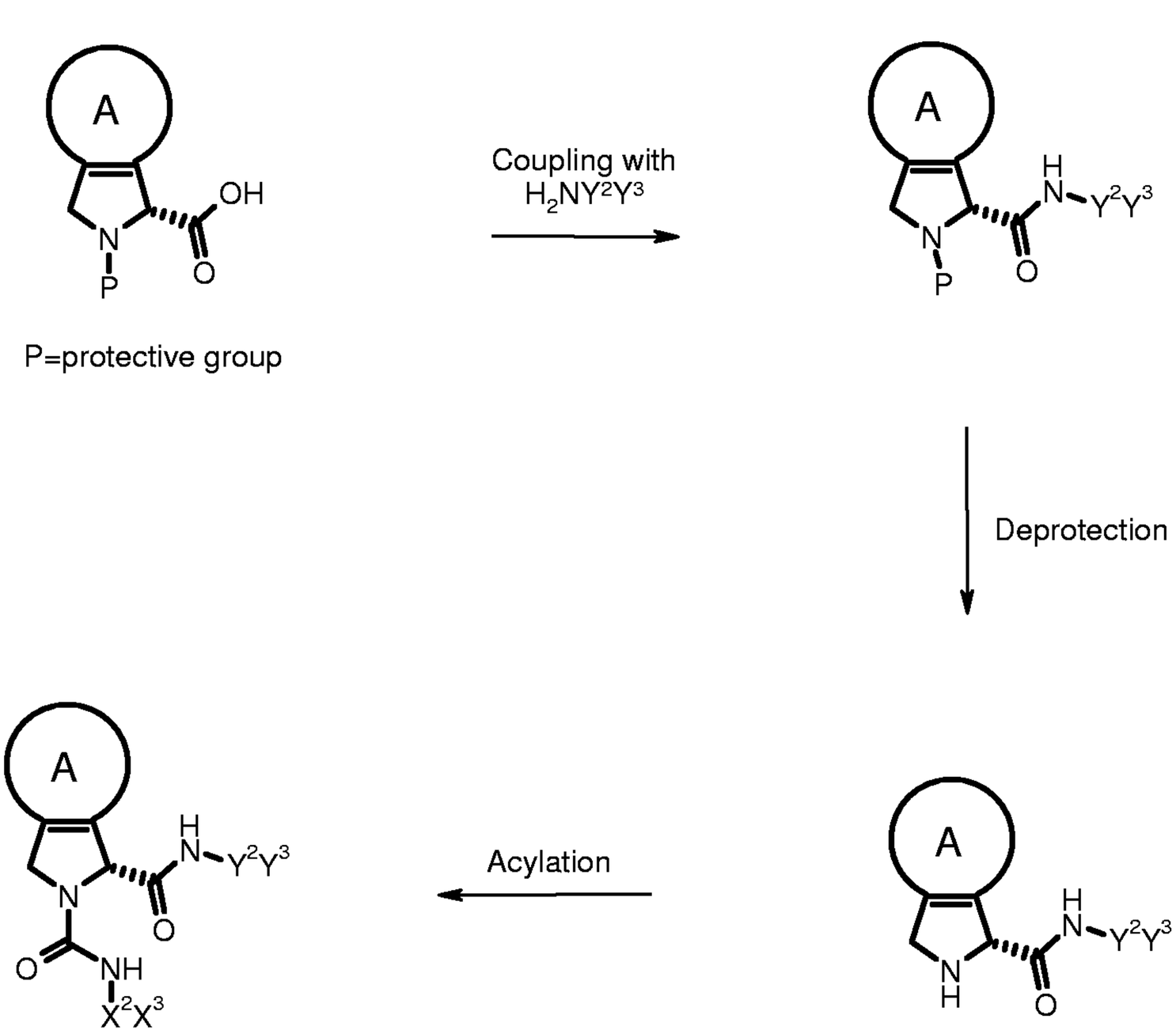
THF: Tetrahydrofuran

General procedures

Amidation: The intermediate carboxylic acid is reacted with an amine $H_2NY^2Y^3$ in a suitable solvent such as CH_2Cl_2, DMF, acetonitrile, THF. Activation is effected by an amide coupling reagent such as BOP, BOP-Cl, HATU/HOBT, EDCI/DMAP in the presence of a base like TEA, DIPEA, N-methylmorpholine etc. at 0 °C to 50 °C. Reaction times ranged from 1 hr – 72 hrs. Preferred conditions are DMF, BOPCl and DIPEA.

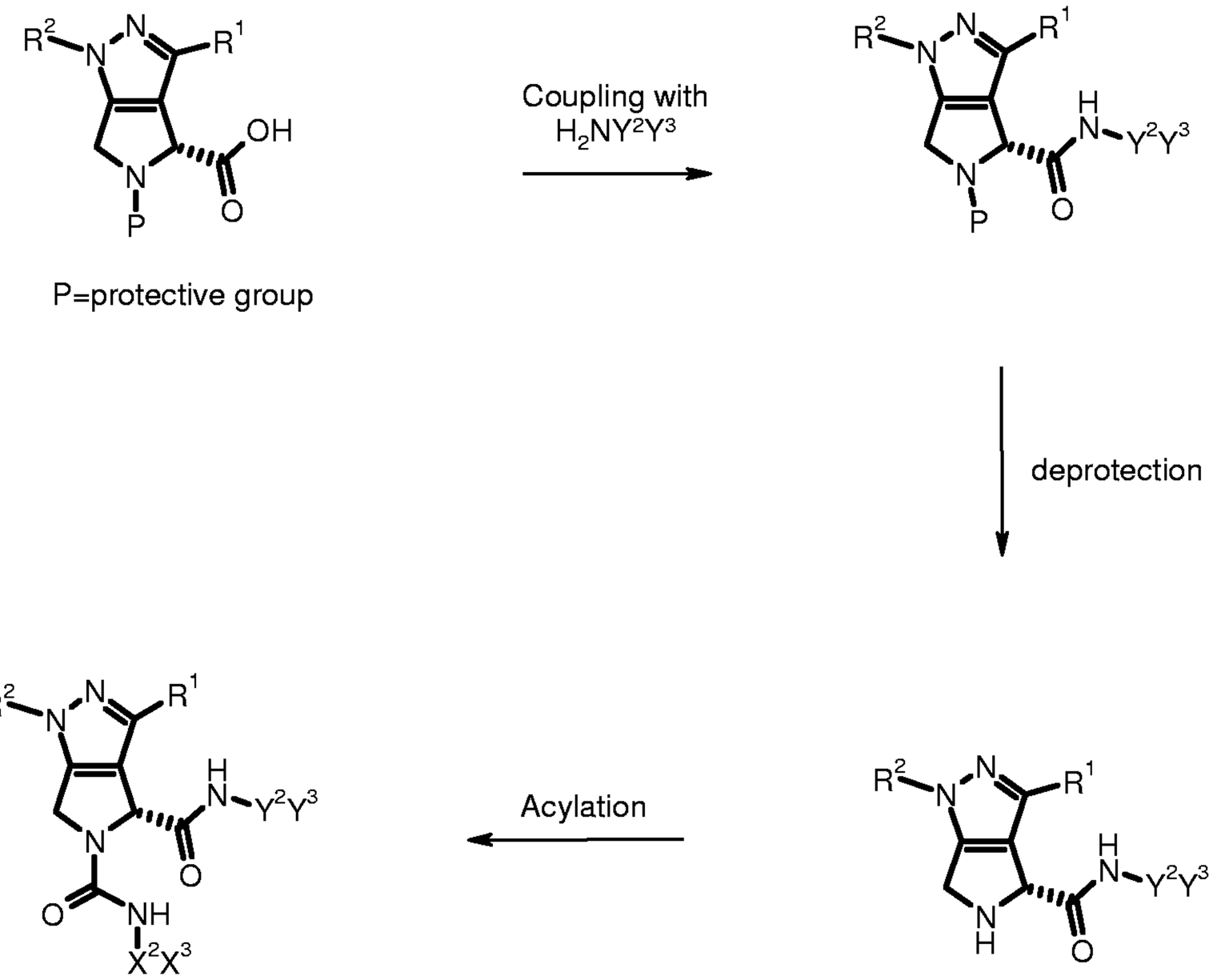
Deprotection :The intermediate is treated with a mineral acid such as HCl, HBr, H_2SO_4 or H_3PO_4 or a carbonic acid, in a solvent such as CH_2Cl_2, dioxane or HOAc at 0 to 60 °C. Preferred conditions are 4N HCl in dioxane.

Acylation : The intermediate is reacted with a substituted phenyl isocyanate in a suitable solvent such as DMF, DMSO, THF at 0 to 120 °C. Preferred conditions are DMF at 80 °C.



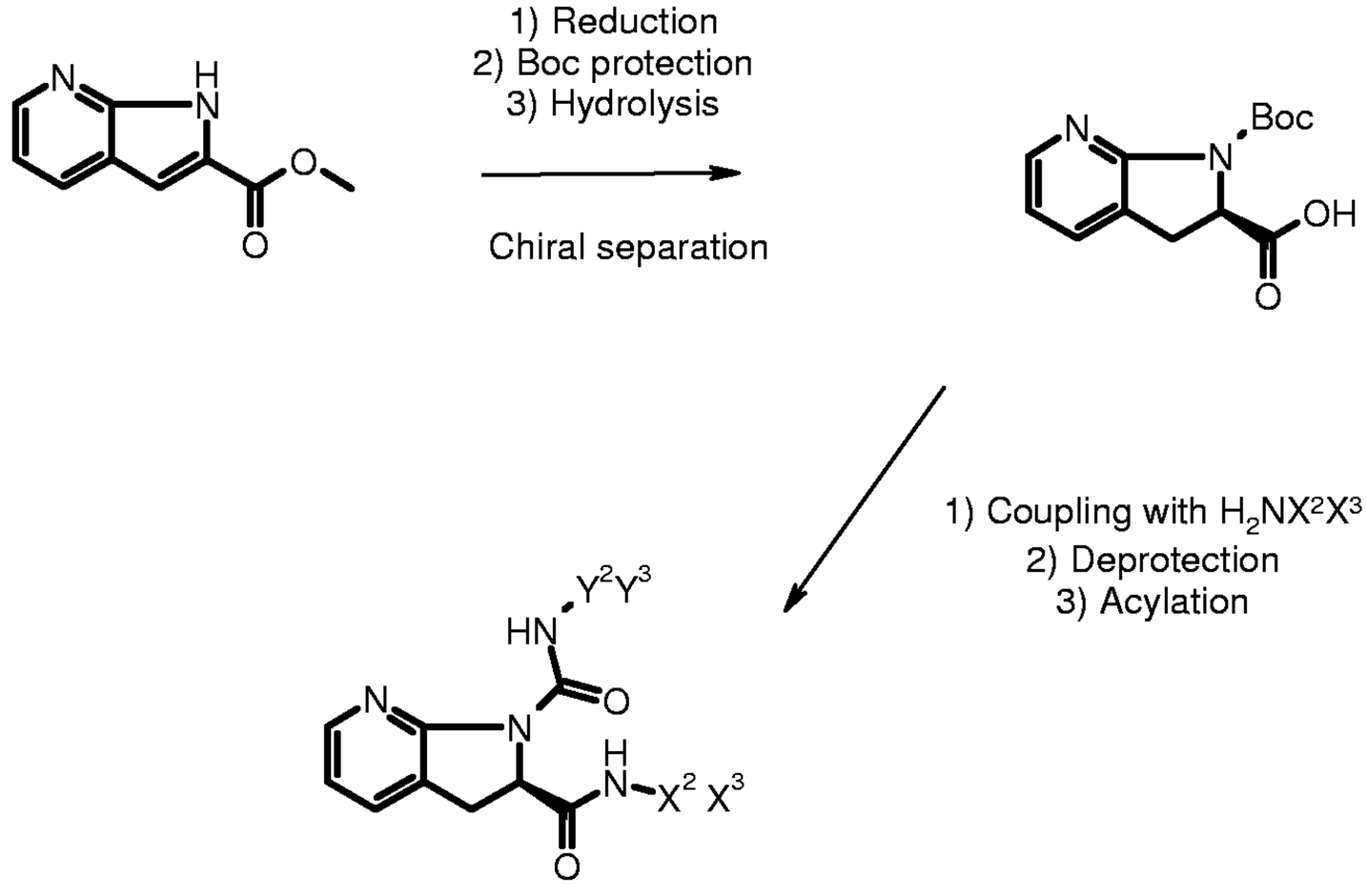
A, X^2, X^3, Y^2 and Y^3 are as defined before.

Dihydropyrrolopyrazole Derivatives



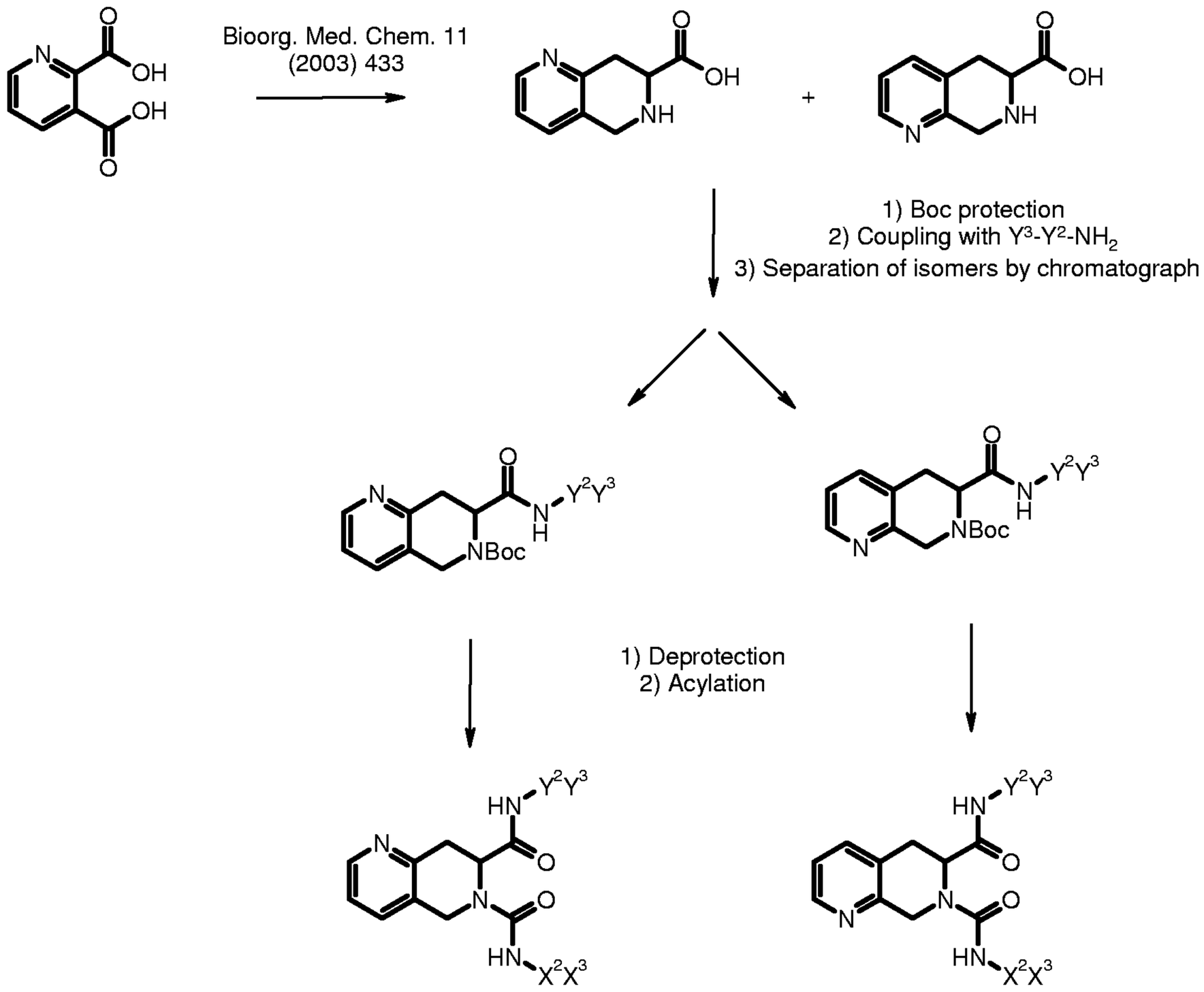
R^1, R^2, X^2, X^3, Y^2 and Y^3 are as defined before.

Azaindoline Derivatives



X^2, X^3, Y^2 and Y^3 are as defined before.

Azatetrahydroisoquinoline Derivatives



X^2, X^3, Y^2 and Y^3 are as defined before.

As described above, the compounds of formula (I) are active compounds and inhibit the coagulation factor Xa. These compounds consequently influence both platelet activation which is induced by this factor and plasmatic blood coagulation. They therefore inhibit the formation of thrombi and can be used for the treatment and/or prevention of thrombotic disorders, such as, amongst others, arterial and venous thrombosis, deep vein thrombosis, peripheral arterial occlusive disease (PAOD), unstable angina pectoris, myocardial infarction, coronary artery disease, pulmonary embolism, stroke (cerebral thrombosis) due to atrial fibrillation, inflammation and arteriosclerosis. The compounds of the present invention can also be used in the treatment of acute vessel closure

associated with thrombolytic therapy and restenosis, e.g. after transluminal coronary angioplasty (PTCA) or bypass grafting of the coronary or peripheral arteries and in the maintenance of vascular access patency in long term hemodialysis patients. F.Xa inhibitors of this invention may form part of a combination therapy with an anticoagulant with a different mode of action or with a platelet aggregation inhibitor or with a thrombolytic agent. Furthermore, these compounds have an effect on tumour cells and prevent metastases. They can therefore also be used as antitumour agents.

Prevention and/or treatment of thrombotic disorders, particularly arterial or deep vein thrombosis, is the preferred indication.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable excipient.

The invention likewise embraces compounds as described above for use as therapeutically active substances, especially as therapeutically active substances for the treatment and/or prophylaxis of diseases which are associated with the coagulation factor Xa, particularly as therapeutically active substances for the treatment and/or prophylaxis of thrombotic disorders, arterial thrombosis, venous thrombosis, deep vein thrombosis, peripheral arterial occlusive disease, unstable angina pectoris, myocardial infarction, coronary artery disease, pulmonary embolism, stroke due to atrial fibrillation, inflammation, arteriosclerosis, acute vessel closure associated with thrombolytic therapy or restenosis, and/or tumour.

In another preferred embodiment, the invention relates to a method for the therapeutic and/or prophylactic treatment of diseases which are associated with the coagulation factor Xa, particularly for the therapeutic and/or prophylactic treatment of thrombotic disorders, arterial thrombosis, venous thrombosis, deep vein thrombosis, peripheral arterial occlusive disease, unstable angina pectoris, myocardial infarction, coronary artery disease, pulmonary embolism, stroke due to atrial fibrillation, inflammation, arteriosclerosis, acute vessel closure associated with thrombolytic therapy or restenosis, and/or tumour, which method comprises administering a compound as defined above to a human being or animal.

The invention also embraces the use of compounds as defined above for the therapeutic and/or prophylactic treatment of diseases which are associated with the coagulation factor Xa, particularly for the therapeutic and/or prophylactic treatment of thrombotic disorders, arterial thrombosis, venous thrombosis, deep vein thrombosis, peripheral

arterial occlusive disease, unstable angina pectoris, myocardial infarction, coronary artery disease, pulmonary embolism, stroke due to atrial fibrillation, inflammation, arteriosclerosis, acute vessel closure associated with thrombolytic therapy or restenosis, and/or tumour.

The invention also relates to the use of compounds as described above for the preparation of medicaments for the therapeutic and/or prophylactic treatment of diseases which are asscociated with the coagulation factor Xa, particularly for the therapeutic and/or prophylactic treatment of thrombotic disorders, arterial thrombosis, venous thrombosis, deep vein thrombosis, peripheral arterial occlusive disease, unstable angina pectoris, myocardial infarction, coronary artery disease, pulmonary embolism, stroke due to atrial fibrillation, inflammation, arteriosclerosis, acute vessel closure associated with thrombolytic therapy or restenosis, and/or tumour. Such medicaments comprise a compound as described above.

The invention also relates to the process and the intermediates for manufacturing the compounds of formula (I) as well as the process for manufacturing the intermediates.

The inhibition of the coagulation factor Xa by the compounds of the present invention can be demonstrated with the aid of a chromogenic peptide substrate assay as described hereinafter.

Factor Xa activity was measured spectrophotometrically in microtiter plates in a final volume of 150 µl using the following conditions: Inhibition of human factor Xa (Enzyme Research Laboratories) was tested at an enzyme concentration of 3 nM using the chromogenic substrate S-2222 (Chromogenix AB, Mölndal, Sweden) at 200 nM. The reaction kinetics of the enzyme and the substrate were linear with both time and the enzyme concentration. The inhibitors were dissolved in DMSO and tested at various concentrations up to 100 µM. The inhibitors were diluted using HNPT buffer consisting of HEPES 100mM, NaCl 140mM, PEG 6000 0.1% and Tween 80 0.02%, pH 7.8. The cleavage of S-2222 by human factor Xa was followed at 405 nm for 5 minutes at room temperature. The velocity of the reaction was determined by the autoreader from the slope of the linear regression fit to 7 time points (1 minute). The initial velocity for each inhibitor concentration was determined by the slope of at least 4 time points in the linear phase by a linear regression fit (mOD/min^2). Apparent dissociation constants K_i were calculated according to Cheng and Prusoff [Cheng, Y. C.; Prusoff, W. H. Relationship between the inhibition constant (K_i) and the concentration of the inhibitor that causes 50 percent inhibition (IC_{50}) of an enzyme reaction. Biochem. Pharmacol. 1973, 22, 3099-

3108.] based on the IC_{50} and the respective K_m, determined previously ($K_i = IC_{50}/(1+S/K_m)$). The K_m for the substrate used was determined under the conditions of the test with at least 5 substrate concentrations ranging from 0.5 to 15 times K_m. [Lottenberg R, Hall JA, Blinder M, Binder EP, Jackson CM., The action of thrombin on peptide p-nitroanilide substrates. Substrate selectivity and examination of hydrolysis under different reaction conditions. Biochim Biophys Acta. 1983 Feb 15; 742(3):539-57]. According to Eadie [Eadie G.S. The inhibition of cholinesterase by physostigmine and prostigmine. J. Biol. Chem. 1942, 146, 85-93.], the K_m for S-2222 amounted to 613 µM.

The activity of the low molecular weight substances can, moreover, be characterized in the "prothrombin time" (PT) clotting test. The substances are prepared as a 10 mM solution in DMSO and thereafter made up to the desired dilution in the same solvent. Thereafter, 0.25 ml of human plasma (obtained from whole blood anticoagulated with 1/10 volume of 108 mM Na citrate) was placed in the instrument-specific sample container. In each case 5 µl of each dilution of the substance-dilution series was then mixed with the plasma provided. This plasma/inhibitor mixture was incubated at 37 °C for 2 minutes. Thereafter, there were pipetted to the semi-automatic device (ACL, Automated Coagulation Laboratory (Instrument Laboratory)) 50 µl of plasma/ inhibitor mixture in the measurement container. The clotting reaction was initiated by the addition of 0.1 ml of Dade®Innovin®(recombinant human tissue factor combined with calcium buffer and synthetic phospholipids, Dade Behring, Inc., Cat. B4212-50). The time up to the fibrin cross-linking was determined photooptically from the ACL. The inhibitor concentration, which brought about a doubling of the PT clotting time, was determined by fitting the data to an exponential regression (XLfit).

The compounds of the present invention can furthermore be characterised by the Activated Partial Thromboplastin time (aPTT). This coagulation test can e.g. be run on the ACL 300 Coagulation System (Instrumentation Laboratory) automatic analyzer. The substances are prepared as a 10 mM solution in DMSO and thereafter made up to the desired dilution in the same solvent. The test is performed with the Dade® Actin® FS Activated PTT reagent (purified soy phosphatides in $1.0x10^{-4}$M ellagic acid, stabilizers and preservative, Dade Behring, Inc., Cat. B4218-100). Thereafter, 0.25 ml aliquots of human plasma (obtained from whole blood anticoagulated with 1/10 volume of 108 mM Na citrate) are spiked with 5 µl of test compound in at least 6 concentrations. 50 µl plasma at 4 °C containing 1/50 vol. inhibitor in solvent are incubated with 50 µl Dade® Actin®FS Activated PTT reagent in water at 37 °C for 3 min., then 50 µl $CaCl_2.2H_2O$ 25 mM in water at 37 °C are added. The time up to the fibrin cross-linking was determined

photooptically from the ACL. The inhibitor concentration, which brought about a doubling of the APTT clotting time, was determined by fitting the data to an exponential regression (XLfit).

The K_i values of the active compounds of the present invention preferably amount to about 0.001 to 50 μM, especially about 0.001 to 1 μM. The PT values preferably amount to about 0.5 to 100 μM, especially to about 0.5 to 10 μM. The aPTT values preferably amount to about 0.5 to 100 μM, especially to about 0.5 to 10 μM.

Example	K_i [nM] factor Xa
Example 3	19
Example 16	51
Example 18	12

The compounds of formula (I) and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or suspensions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example,

vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula (I) can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 to 1000 mg, especially about 1 to 300 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the compound could be administered with one or several daily dosage units, e.g. in 1 to 3 dosage units.

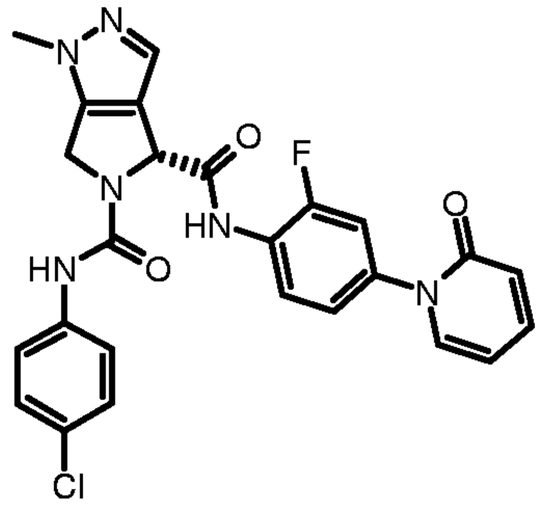
The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 1-100 mg, of a compound of formula (I).

The following Examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

Example 1

(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide]-4-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}



A (R)-4-[2-Fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenylcarbamoyl]-1-methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-5-carboxylic acid tert-butyl ester

To a solution of (R)-1-methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-tert-butyl ester (478 mg, described in US2002/0193399), 1-(4-amino-3-fluoro-phenyl)-1H-pyridin-2-one (365 mg; CAS 536747-52-1) and DIPEA (0.46 ml) in 20 ml acetonitrile and 2 ml DMF was added BOPCl (1.366 g). The reaction mixture was stirred for 24h at rt, diluted with AcOEt and washed with 1M HCl, 1M NaOH and brine. The organic layers were dried over magnesium sulfate, evaporated and purified by chromatography (silica gel; AcOEt) to deliver the title compound as a yellow oil (510 mg). MS: 454.5 $(M+H)^+$

B (R)-1-Methyl-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole-4-carboxylic acid [2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide

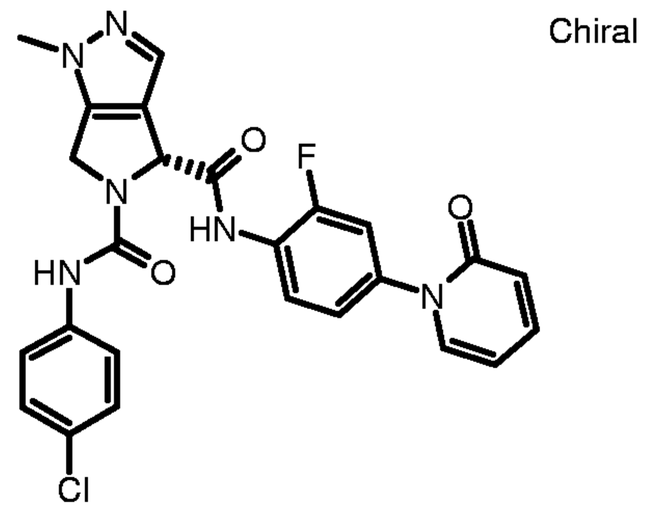
A solution of (R)-4-[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenylcarbamoyl]-1-methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-5-carboxylic acid tert-butyl ester (258 mg) in 1 ml 4M HCl/dioxane was stirred 18 h at rt. The reaction mixture was portionned between AcOEt and 1M NaOH / ice. The organic layers were washed with brine, dried over magnesium sulfate and evaporated to deliver a white residue (115 mg) of the title compound. MS: 354.3 $(M+H)^+$

C (R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}

To a solution of (R)-1-methyl-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole-4-carboxylic acid [2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide (83 mg) in 2 ml dichloromethane at 0°C, 4-chlorophenyl-isocyanate (72 mg) was added. The reaction mixture was kept for 2 hrs under ice cooling, then heptane was added and the precipitate filtrated. (R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide} was obtained as a white solid (119 mg). MS: 507.2 $(M+H)^+$

Example 2

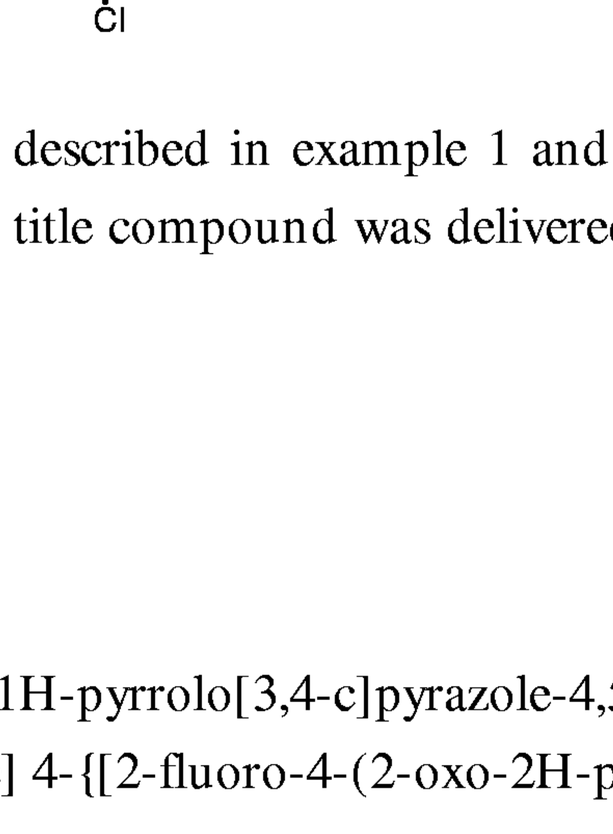
(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 4-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide} 5-[(4-methoxy-phenyl)-amide*]*



Using the same procedure described in example 1 and 4-methoxyphenyl-isocyanate as reagent in the last step, the title compound was delivered as a white solid (29 mg). MS: 503.1 $(M+H)^+$

Example 3

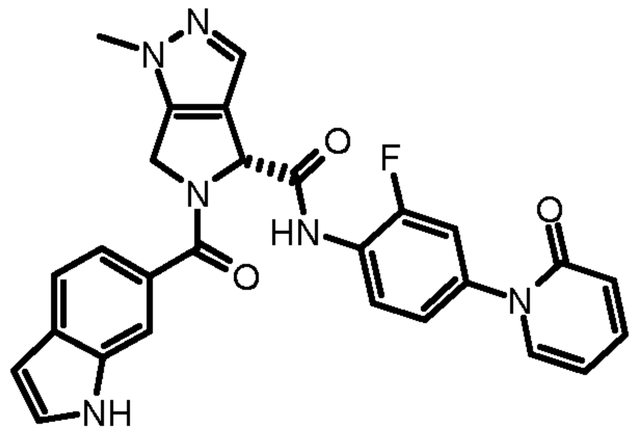
(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(5-chloro-pyridin-2-yl)-amide] 4-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}



A solution of (R)-1-Methyl-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole-4-carboxylic acid [2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide (example 1B), 36 mg), (5-chloro-pyridin-2-yl)-carbamic acid 4-nitro-phenyl ester (44 mg; CAS 536746-34-6) and DIPEA (0.042 ml) in 2 ml DMF was heated for 4hrs at 90°C. The reaction mixture was cooled, diluted with AcOEt, washed twofold with 1M NaOH, 1M HCl and brine. The aqueous layers were extracted with AcOEt, dried over magnesium sulfate, evaporated and purified by chromatography (silica gel, AcOEt) to yield the title compound as a white solid (8 mg). MS: 508.3 $(M+H)^+$

Example 4

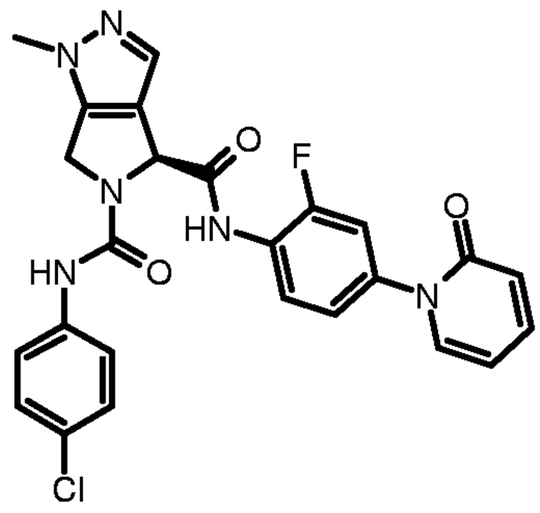
(R)-5-(1H-Indole-6-carbonyl)-1-methyl-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole-4-carboxylic acid [2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide



A solution of (R)-1-methyl-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole-4-carboxylic acid [2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide (example 1B), 38 mg), 6-indolecarboxylic acid (22 mg), 0.03 ml (DIPEA) and BOPCl (51 mg) in 2 ml acetonitrile was stirred for 2hrs at 0°C. A consecutive basic and acidic work up delivered a yellow oil which was purified by chromatography (silica gel, AcOEt). (R)-5-(1H-Indole-6-carbonyl)-1-methyl-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole-4-carboxylic acid [2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide was obtained as a white solid (13 mg). MS: 497.0 $(M+H)^+$

Example 5

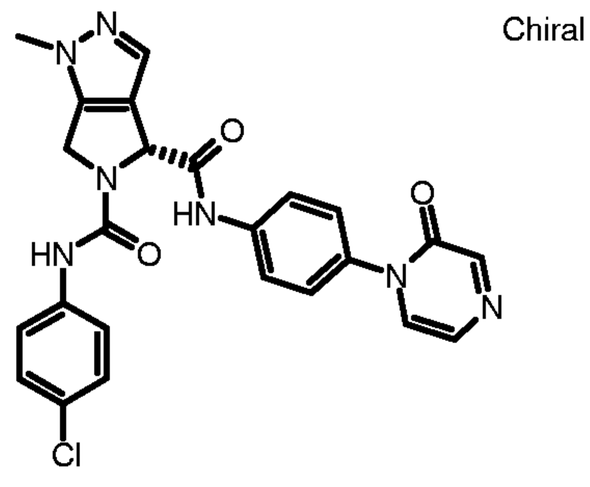
(S)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}



Using the same procedure described in example 1, but starting from (S)-1-methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-tert-butyl ester, the title compound was obtained as a white solid (14 mg). MS: 507.2 $(M+H)^+$

Example 6

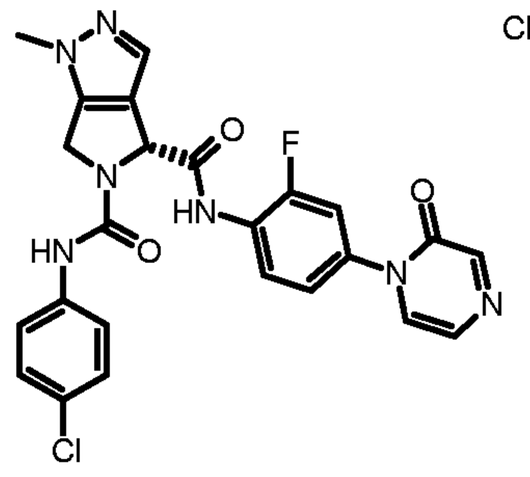
1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide}



Using the same procedure described in example 1 (with 1-(4-amino-phenyl)-1H-pyrazin-2-one, CAS 4444002-64-6) the title compound was obtained as a white solid (35 mg). MS: 490.8 $(M+H)^+$

Example 7

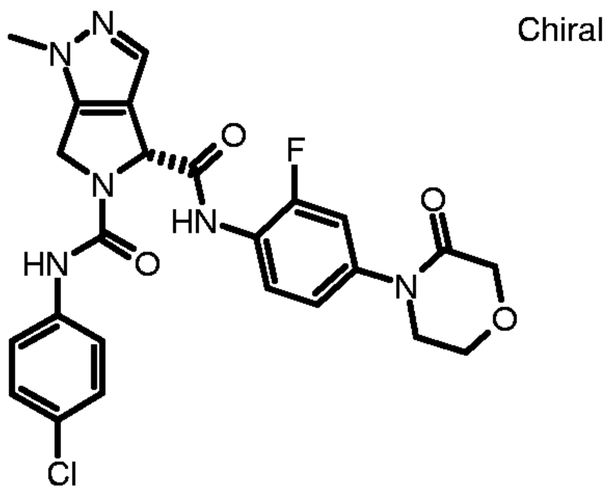
1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[2-fluoro-4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide}



Using the same procedure described in example 1 using 1-(4-amino-3-fluoro-phenyl)-1H-pyrazin-2-one (prepared from 2-fluoro-4-iodoaniline by reaction with 1H-pyrazin-2-one, Cu(I)I, N,N'-dimethylethylenediamine and cesium carbonate in dioxane at 120 °C), the title compound was obtained as a white solid (15 mg). MS: 508.0 $(M+H)^+$

Example 8

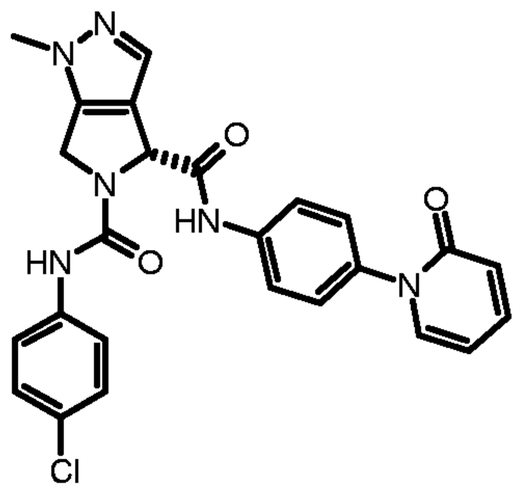
(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[2-fluoro-4-(3-oxo-morpholin-4-yl)-phenyl]-amide}



Using the same procedure described in example 1 (with 4-(4-amino-3-fluoro-phenyl)-morpholin-3-one, CAS 742073-22-9) the title compound was obtained as a white solid (88 mg). MS: 513.3 $(M+H)^+$

Example 9

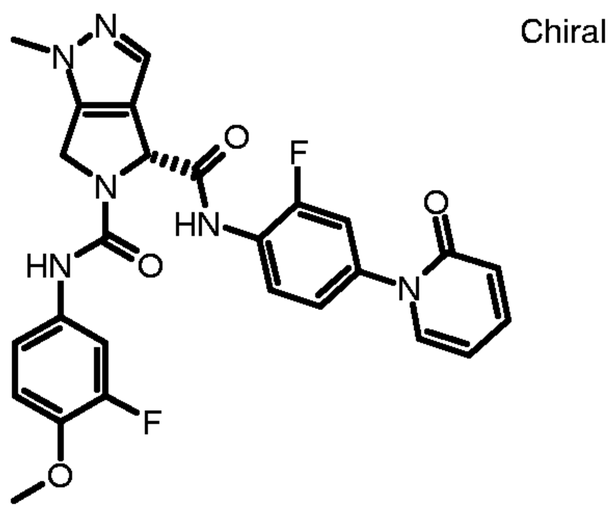
(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}



Using the same procedure described in example 1 (with 1-(4-amino-phenyl)-1H-pyridin-2-one, CAS 13143-47-0) the title compound was obtained as a white solid (25 mg). MS: 489.1 $(M+H)^+$

Example 10

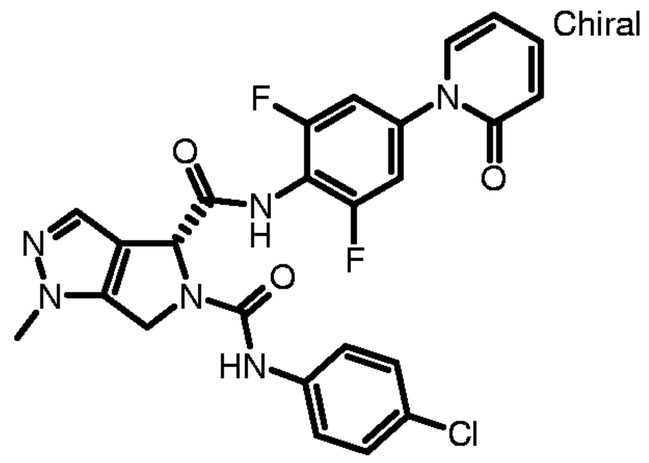
(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(3-fluoro-4-methoxy-phenyl)-amide] 4-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}



Using the same procedure described in example 3 and (3-fluoro-4-methoxy-phenyl)-carbamic acid 4-nitro-phenyl ester (prepared from 3-fluoro-4-methoxy-aniline by reaction with p-nitrophenyl chloroformat and pyridine in dichloromethane) the title compound was obtained as a white solid (26 mg). MS: 521.2 $(M+H)^+$

Example 11

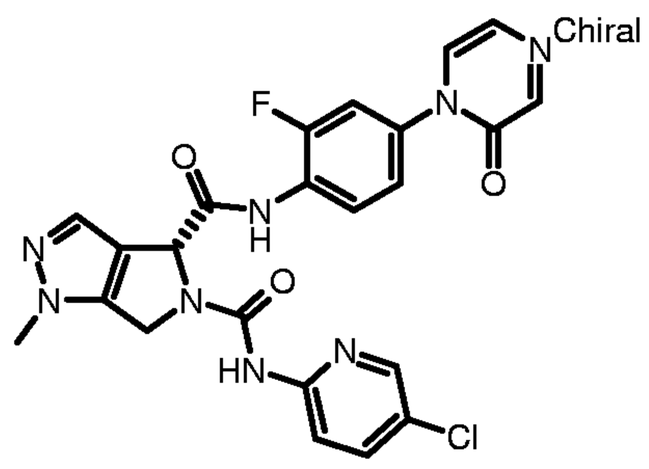
(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 5-{[2,6-difluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}



Using the same procedure described in example 1 (with 1-(4-amino-3,5-difluoro-phenyl)-
1H-pyridin-2-one prepared from 4-bromo-2.6-difluoroaniline by reaction with 2-hydroxypyridine, Cu(I)I, potassium carbonate, 8-hydroxyquinoline in DMSO at 150°C) the title compound was obtained as a white solid (110 mg). MS: 525.3 $(M+H)^+$

Example 12

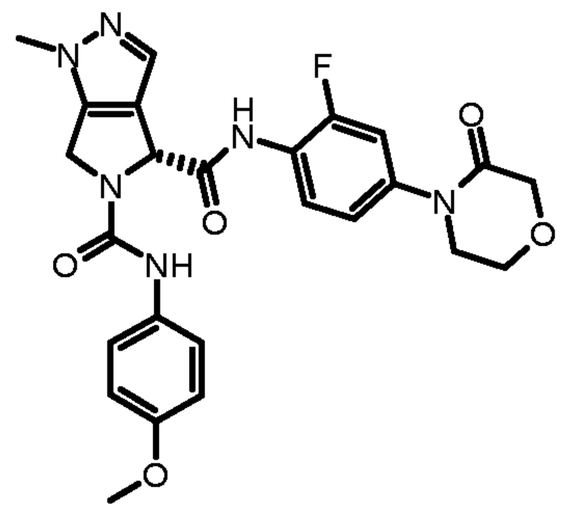
(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(5-chloro-pyridin-2-yl)-amide] 4-{[2-fluoro-4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide}



Using the same procedure described in example 1 (with 1-(4-amino-3-fluoro-phenyl)-1H-pyrazin-2-one) and for the last step following the method described in example 3, the title compound was obtained as a white solid (70 mg). MS: 509.5 $(M+H)^+$

Example 13

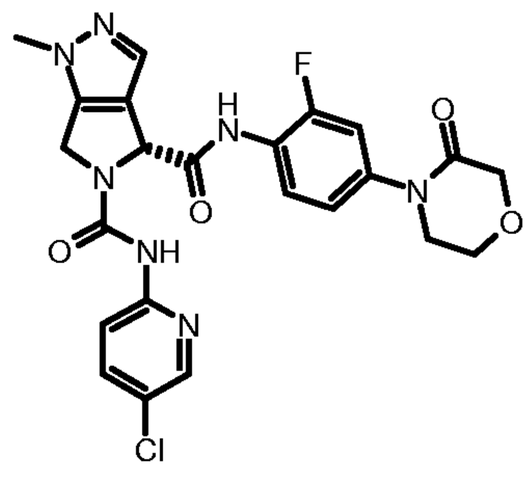
(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 4-{[2-fluoro-4-(3-oxo-morpholin-4-yl)-phenyl]-amide} 5-[(4-methoxy-phenyl)-amide]



Using the same procedure described in example 1 (with 4-(4-amino-3-fluoro-phenyl)-morpholin-3-one, CAS 742073-22-9) and using 4-methoxyphenyl-isocyanate in the last step, the title compound was obtained as a white solid (33 mg). MS: 507.4 $(M-H)^-$

Example 14

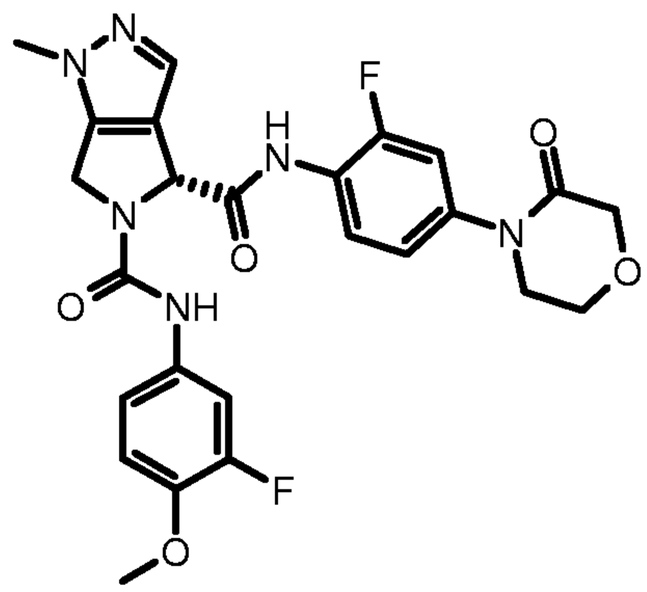
(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(5-chloro-pyridin-2-yl)-amide] 4-{[2-fluoro-4-(3-oxo-morpholin-4-yl)-phenyl]-amide}



Using the same procedure described in example 1 (with 4-(4-amino-3-fluoro-phenyl)-morpholin-3-one, CAS 742073-22-9) and in the last step the procedure described in example 3, the title compound was obtained as a white solid (27 mg). MS: 514.2 $(M+H)^+$

Example 15

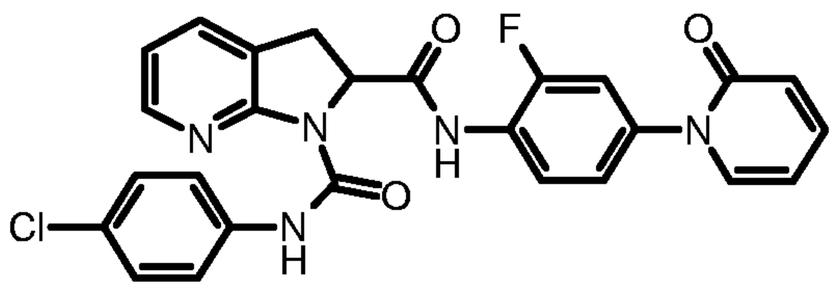
(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(3-fluoro-4-methoxy-phenyl)-amide] 4-{[2-fluoro-4-(3-oxo-morpholin-4-yl)-phenyl]-amide}



Using the same procedure described in example 1 (with 4-(4-amino-3-fluoro-phenyl)-morpholin-3-one, CAS 742073-22-9) and in the öast step the procedure described in example 3 using (3-fluoro-4-methoxy-phenyl)-carbamic acid 4-nitro-phenyl ester (prepared from 3-fluoro-4-methoxy-aniline by reaction with p-nitrophenyl chloroformat and pyridine in dichloromethane) the title compound was obtained as a white solid (26 mg). MS: 523.1 $(M+H)^+$

Example 16

2,3-Dihydro-pyrrolo[2,3-b]pyridine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}



A 2,3-Dihydro-pyrrolo[2,3-b]pyridine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester

A solution of pyrrolo[2,3-b]pyridine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (9.53 g; CAS 577711-88-7) in 240 ml ethanol was treated with 5% Pd/C 2h at 40 °C under

a hydrogene atmosphere. The reaction mixture was filtered and the title compound obtained as a yellow oil (9.3 g).

B 2,3-Dihydro-pyrrolo[2,3-b]pyridine-1,2-dicarboxylic acid 1-tert-butyl ester

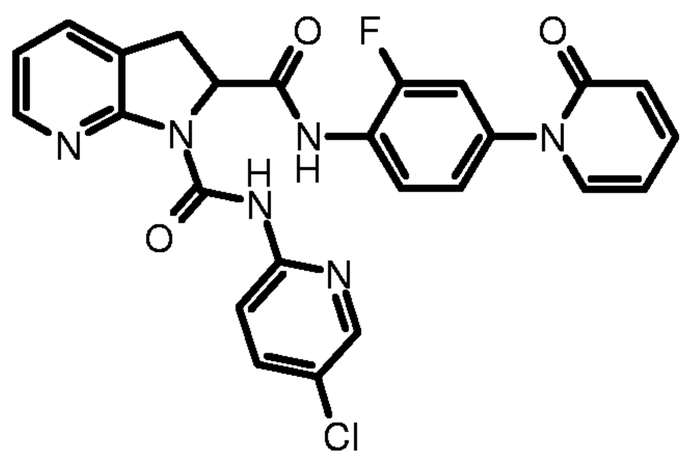
A suspension of 2,3-dihydro-pyrrolo[2,3-b]pyridine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (1 g) and lithium hydroxide (0.25 g) in 6 ml THF, 3 ml MeOH and 3 ml water was stirred 0.5h at rt. The reaction mixture was poured onto 1M HCl/ice and washed three times with dichloromethane. The aqueous layer was neutralized with 1M NaOH, evaporated to dryness and purified by chromatography (silica gel, dichloromethane/methanol, 4/1) to yield 2,3-dihydro-pyrrolo[2,3-b]pyridine-1,2-dicarboxylic acid 1-tert-butyl ester as a white solid (400 mg). MS: 263.4 $(M- H)^-$

C 2,3-Dihydro-pyrrolo[2,3-b]pyridine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}

Starting from 2,3-dihydro-pyrrolo[2,3-b]pyridine-1,2-dicarboxylic acid 1-tert-butyl ester and using the procedure described in example 1, 2,3-dihydro-pyrrolo[2,3-b]pyridine-1,2-dicarboxylic acid 1-[(4-chloro-phenyl)-amide] 2-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}was obtained as a white solid (63 mg). MS: 504.3 $(M+ H)^+$

Example 17

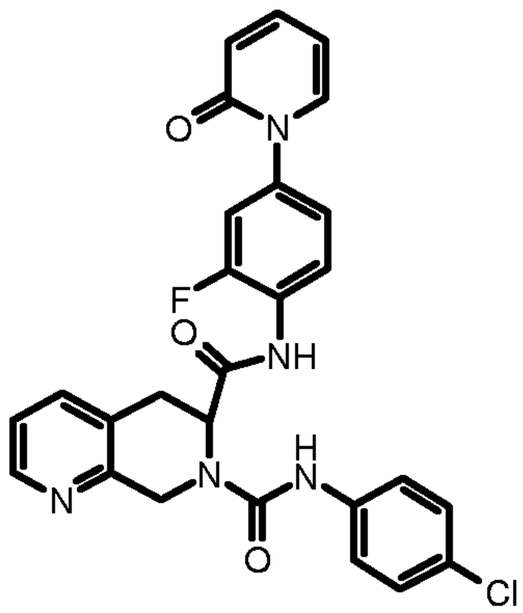
2,3-Dihydro-pyrrolo[2,3-b]pyridine-1,2-dicarboxylic acid 1-[(5-chloro-pyridin-2-yl)-amide] 2-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}



Starting from 2,3-dihydro-pyrrolo[2,3-b]pyridine-1,2-dicarboxylic acid 1-tert-butyl ester and using the procedure described in example 3, the title compound was obtained as a white solid (20 mg). MS: 505.2 $(M+ H)^+$

Example 18

5,8-Dihydro-6H-[1,7]naphthyridine-6,7-dicarboxylic acid 7-[(4-chloro-phenyl)-amide] 6-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}



A 5,8-Dihydro-6H-[1,7]naphthyridine-6,7-dicarboxylic acid 7-tert-butyl ester and 7,8-Dihydro-5H-[1,6]naphthyridine-6,7-dicarboxylic acid 6-tert-butyl ester

To a solution of 5,6,7,8-tetrahydro-[1,7]naphthyridine-6-carboxylic acid methyl ester hydrochloride and 5,6,7,8-tetrahydro-[1,6]naphthyridine-7-carboxylic acid methyl ester hydrochloride (500 mg)) in 12 ml acetonitrile and 1 ml water under ice cooling, were added successively Boc_2O (478 mg), triethylamine (1.11 ml) and DMAP (12 mg). The reaction mixture was stirred 2h at rt, evaporated and purified by chromatography (silica gel, dichloromethane/methanol, 4/1) to yield a mixture of the two compounds as a yellow residue (313 mg). MS: 277.4 $(M- H)^-$

B 7-[2-Fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenylcarbamoyl]-7,8-dihydro-5H-[1,6]naphthy-ridine-6-carboxylic acid tert-butyl ester and 6-[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenylcarbamoyl]-5,8-dihydro-6H-[1,7]naphthyridine-7-carboxylic acid tert-butyl ester

To a solution of the above mixture (707 mg) in 20 ml THF was added lithium hydroxide (58 mg) and vigourously stirred for 15 min. Then, molecular sieves was added, followed by

N-methylmorpholine (0.84 ml). The reaction mixture was cooled, treated with isobutyl chloroformate (0.49 ml) and stirred for 30 min. After addition of 1-(4-amino-3-fluoro-phenyl)-1H-pyridin-2-one (622 mg; CAS 536747-52-1), the suspension was kept for 1h at 0^oC and for 18hrs at rt. The reaction mixture was evaporated and filtrated. The residue was diluted with dichloromethane and washed with water and brine. The organic layers were dried over magnesium sulfate, evaporated and purified by chromatography (silica

gel, AcOEt/MeOH, 50:1) to deliver the two isomers. 6-[2-Fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenylcarbamoyl]-5,8-dihydro-6H-[1,7]naphthyridine-7-carboxylic acid tert-butyl ester was obtained as a white solid (205 mg; Rf=0.5, AcOEt/MeOH 19:1) and 7-[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenylcarbamoyl]-7,8-dihydro-5H-[1,6]naph-thyridine-6-carboxylic acid tert-butyl ester as a light yellow solid (351 mg; Rf=0.4, AcOEt/MeOH 19:1). MS: 465.5 $(M+ H)^+$

C 5,6,7,8-Tetrahydro-[1,7]naphthyridine-6-carboxylic acid [2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide

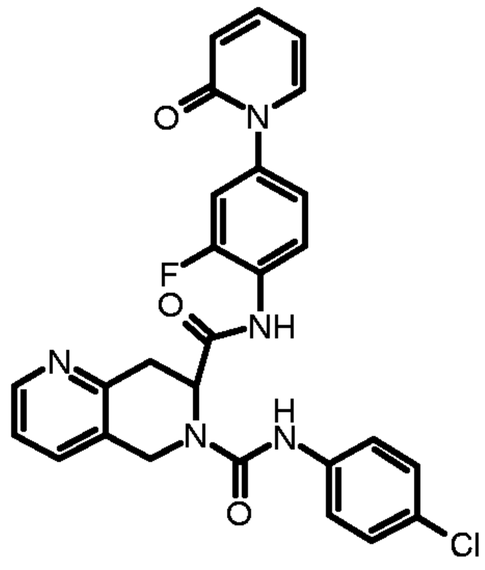
A solution of 7-[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenylcarbamoyl]-7,8-dihydro-5H-[1,6]naphthyridine-6-carboxylic acid tert-butyl ester (310 mg) in 8 ml dichloromethane and 1.53 ml TFA was stirred for 4hrs at rt. The reaction mixture was poured onto 1M NaOH/ice and extracted twice with dichloromethane. The organic layers were dried over magnesium sulfate, evaporated and purified by chromatography (silica gel, AcOEt/methanol 9:1) to deliver the title compound as a light yellow solid (151 mg). MS: 365.5 $(M+ H)^+$

D 5,8-Dihydro-6H-[1,7]naphthyridine-6,7-dicarboxylic acid 7-[(4-chloro-phenyl)-amide] 6-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}

To a solution of 5,6,7,8-tetrahydro-[1,7]naphthyridine-6-carboxylic acid [2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide (40 mg) in 4 ml THF at -78°C, was added a solution of 4-chlorophenylisocyannate in 2 ml THF. After 30 mn, the reaction mixture was kept at rt for 1h, diluted with heptane and the white precipitate of the title compound was filtered (38 mg). MS: 518.5 $(M+ H)^+$

Example 19

7,8-Dihydro-5H-[1,6]naphthyridine-6,7-dicarboxylic acid 6-[(4-chloro-phenyl)-amide] 7-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}



A 5,6,7,8-Tetrahydro-[1,6]naphthyridine-7-carboxylic acid [2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide

A solution of 6-[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenylcarbamoyl]-5,8-dihydro-6H-[1,7]naphthyridine-7-carboxylic acid tert-butyl ester (170 mg; example 16B) in 5 ml dichloromethane and 0.84 ml TFA was stirred for 4hrs at rt. The reaction mixture was poured onto 1M NaOH/ice and extracted twice with dichloromethane. The organic layers were dried over magnesium sulfate and evaporated to deliver the title compound as a white foam (123 mg). MS: 365.5 $(M+H)^+$

B 7,8-Dihydro-5H-[1,6]naphthyridine-6,7-dicarboxylic acid 6-[(4-chloro-phenyl)-amide] 7-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}

This compound prepared from 5,6,7,8-tetrahydro-[1,6]naphthyridine-7-carboxylic acid [2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide with the procedure described in example 16D) was obtained as a white solid (50 mg). MS: 518.5 $(M+H)^+$

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 oxyde (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

The active ingredient is sieved and mixed with microcristalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidon in water. The granulate is mixed with sodium starch glycolate and magesiumstearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aqueous 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 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.

Example D

Soft gelatin capsules containing the following ingredients can be manufactured in a conventional manner:

Capsule contents	
Compound of formula (I)	5.0 mg
Yellow wax	8.0 mg
Hydrogenated Soya bean oil	8.0 mg
Partially hydrogenated plant oils	34.0 mg
Soya bean oil	110.0 mg
Weight of capsule contents	165.0 mg
Gelatin capsule	
Gelatin	75.0 mg
Glycerol 85 %	32.0 mg
Karion 83	8.0 mg (dry matter)
Titan dioxide	0.4 mg
Iron oxide yellow	1.1 mg

The active ingredient is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

Example E

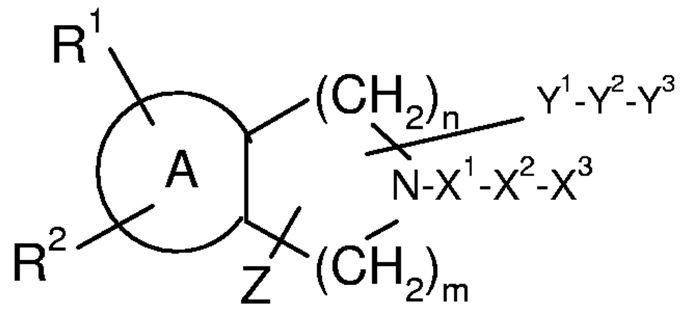
Sachets containing the following ingredients can be manufactured in a conventional manner:

Compound of formula (I)	50.0 mg
Lactose, fine powder	1015.0 mg
Microcristalline cellulose (AVICEL PH 102)	1400.0 mg
Sodium carboxymethyl cellulose	14.0 mg
Polyvinylpyrrolidon K 30	10.0 mg
Magnesiumstearate	10.0 mg
Flavoring additives	1.0 mg

The active ingredient is mixed with lactose, microcristalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidon in water. The granulate is mixed with magnesiumstearate and the flavouring additives and filled into sachets.

Claims

1. Compounds of formula (I)



(I)

wherein

A is a heteroaryl ring which is a monocyclic or bicyclic aromatic ring of 5 to 12 ring atoms, containing one, two, or three ring heteroatoms selected from N, O, and S, the remaining ring atoms being C, one or two carbon atoms of said ring being optionally replaced with a carbonyl group;

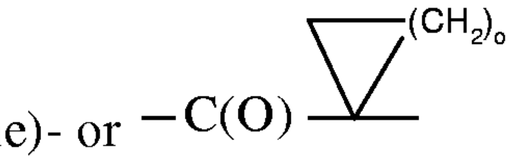
R^1 and R^2

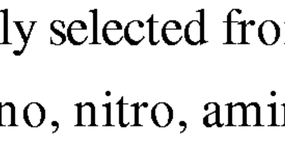
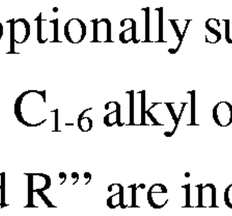
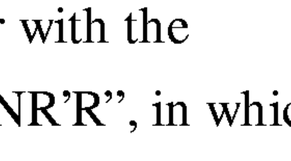
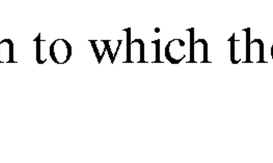
are independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, fluoro C_{1-6} alkoxy,

hydroxy C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, mono or di C_{1-6} alkyl substituted amino C_{1-6} alkoxy, halogen, cyano, nitro, -N(R')-CO-(C_{1-6} alkyl optionally substituted by one or more fluorine atoms), in which R' is hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -N(R')-CO-O-(C_{1-6} alkyl optionally substituted by one or more fluorine atoms), in which R' is hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -N(R')-CO-N(R") (R""), in which R', R" and R"" are independently hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl or -N(R')-SO_2-(C_{1-6} alkyl optionally substituted by one or more fluorine atoms), in which R' is hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl or

R^1 and R^2

are independently -SO_2-N(R')(R"), -C(O)-N(R')(R") or –N(R')(R"), in which R' and R" are independently hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl or R' and R", together with the nitrogen atom to which they are attached, form heterocycyl;

X^1 is $-C(O)-(C_{0-6}$ alkylene$)-NR^3-(C_{0-6}$ alkylene$)-$, $-(C_{0-6}$ alkylene$)-C(O)-NR^3-(C_{0-6}$ alkylene$)-$, $-(C_{1-6}$ alkylene$)-NR^3-C(O)-(C_{0-6}$ alkylene$)-$, $-C(O)-(C_{0-6}$ alkylene$)$-, C_{0-6} alkylene, $-SO_2-(C_{0-6}$ alkylene$)$-, $-(C_{0-6}$ alkylene$)$-SO_2-NR^3- (C_{0-6} alkylene$)$- or  ;

X^2 is arylene, heteroarylene or heterocyclylene, said arylene, heteroarylene and heterocyclylen being optionally substituted by one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, halogen, cyano, nitro, amino, -N(R')-CO-(C_{1-6} alkyl optionally substituted by one or more fluorine atoms), in which R' is hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -N(R')-CO-O-(C_{1-6} alkyl optionally substituted by one or more fluorine atoms), in which R' is hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -N(R')-CO-N(R") (R"'), in which R', R" and R"' are independently hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -C(O)-N(R')(R"), in which R' and R" are independently hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, or R' and R", together with the nitrogen atom to which they are attached, form heterocycyl, -NR'R", in which R' and R" are independently hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, or R' and R", together with the nitrogen atom to which they are attached, form heterocycyl,  wherein R' and R" are independently C_{1-6} alkyl or fluoro C_{1-6} alkyl, or R' and R", together with the nitrogen atom to which they are attached, form heterocyclyl,  wherein R' and R" are independently C_{1-6} alkyl or fluoro C_{1-6} alkyl, or R' and R", together with the nitrogen atom to which they are attached, form heterocyclyl,  , in which R' is fluoro C_{1-6} alkyl and  , in which R' is fluoro C_{1-6} alkyl,

and one or two carbon atoms of said arylene, heteroarylene or heterocyclylene being optionally replaced with a carbonyl group;

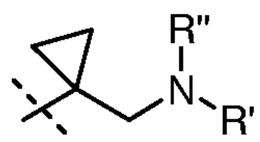
X^3 is hydrogen, aryl, heteroaryl or heterocyclyl, said aryl, heteroaryl and heterocyclyl being optionally substituted by one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, halogen, cyano, nitro, amino, mono-C_{1-6} alkyl substituted amino, di-C_{1-6} alkyl substituted amino, mono-C_{1-6} alkyl substituted amino-C_{1-6} alkyl, di-C_{1-6} alkyl substituted amino-C_{1-6} alkyl, -SO_2-C_{1-6} alkyl, -SO_2-NH_2, -SO_2-NH-C_{1-6} alkyl and -SO_2-N(C_{1-6} alkyl)$_2$,

and one or two carbon atoms of said aryl, heteroaryl and heterocyclyl being optionally replaced with a carbonyl group;

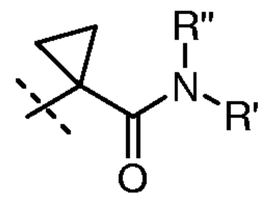
R^3 is hydrogen or C_{1-6} alkyl;

Y^1 is –(C_{0-6} alkylene)–C(O)–NR^3–(C_{0-6} alkylene)–, –(C_{0-6} alkylene)–NR^3–C(O)–(C_{0-6} alkylene)– or C_{0-6} alkylene;

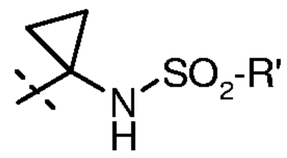
Y^2 is arylene, heteroarylene or heterocyclylene, said arylene, heteroarylene and heterocyclylene being optionally substituted by one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, halogen, cyano, nitro, amino, -N(R')-CO-(C_{1-6} alkyl optionally substituted by one or more fluorine atoms), in which R' is hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -N(R')-CO-O-(C_{1-6} alkyl optionally substituted by one or more fluorine atoms), in which R' is hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -N(R')-CO-N(R") (R"'), in which R', R" and R"' are independently hydrogen, C_{1-6} alkyl or fluoro C_{1-6} alkyl, -C(O)-N(R')(R"), in which R' and R" are independently hydrogen, C_{1-6} alkyl or halo C_{1-6} alkyl, or R' and R", together with the nitrogen atom to which they are attached, form heterocyclyl, -NR'R", in which R' and R" are independently hydrogen, C_{1-6} alkyl or halo C_{1-6} alkyl, or R' and R", together with the nitrogen atom to which they are attached, form

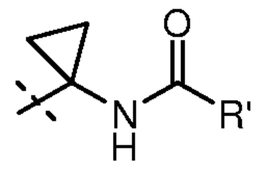


heterocyclyl, ,in which R' and R" are independently C_{1-6} alkyl or fluoro C_{1-6} alkyl, or R' and R", together with the nitrogen atom to which they



are attached, form heterocyclyl, , in which R' and R" are independently C_{1-6} alkyl or fluoro C_{1-6} alkyl, or R' and R", together with the

nitrogen atom to which they are attached, form heterocyclyl,  ,

in which R' is fluoro C_{1-6} alkyl and  , in which R' is C_{1-6} alkyl,

and one or two carbon atoms of said arylene, heteroarylene or heterocyclylene being optionally replaced with a carbonyl group;

Y^3 is hydrogen, aryl, heteroaryl or heterocyclyl, said aryl, heteroaryl and heterocyclyl being optionally substituted by one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, halogen, cyano, nitro, amino, mono-C_{1-6} alkyl substituted amino, di-C_{1-6} alkyl substituted amino, mono-C_{1-6} alkyl substituted amino-C_{1-6} alkyl, di-C_{1-6} alkyl substituted amino-C_{1-6} alkyl, $-SO_2-C_{1-6}$ alkyl, $-SO_2-NH_2$, $-SO_2-NH-C_{1-6}$ alkyl and $-SO_2-N(C_{1-6}\text{ alkyl})_2$, and one or two carbon atoms of said aryl, heteroaryl and heterocyclyl being optionally replaced with a carbonyl group;

Z is attached to the same carbon atom as $-Y^1-Y^2-Y^3$, and hydrogen or C_{1-6} alkyl;

n is 0, 1 or 2;

m is 0, 1 or 2;

m+n is 2 or 3;

o is an integer from 1 to 5;

and prodrugs and pharmaceutically acceptable salts thereof;

wherein,

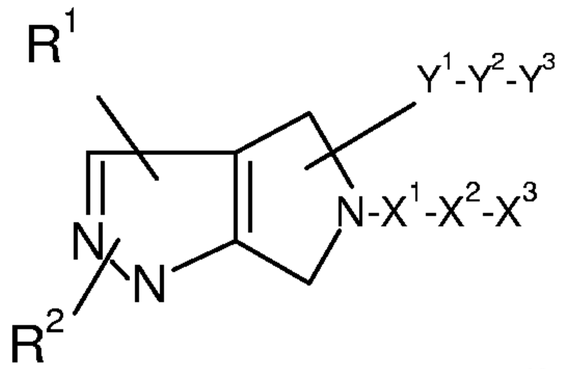
unless otherwise indicated,

the term "aryl" means phenyl or naphthyl;

the term "heteroaryl" means a monocyclic or bicyclic aromatic radical of 5 to 12 ring atoms, containing one, two, or three ring heteroatoms selected from N, O, and S, the remaining ring atoms being C, one or two carbon atoms of said ring being optionally replaced with a carbonyl group, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring;

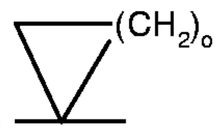
the term "heterocyclyl" means non-aromatic mono- or bi-cyclic radicals of three to eight ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or $S(O)_n$ (where n is an integer from 0 to 2), the remaining ring atoms being C.

2. The compounds according to claim 1, which are



(Id)

wherein X^1, X^2, X^3, Y^1, Y^2, Y^3, R^1 and R^2 are as defined in claim 1.

3. The compounds according to any one of claims 1 to 2, wherein X^1 is –C(O)-NH-, -C(O)–(C_{0-6} alkylene)-, C_{0-6} alkylene, 

or $–SO_2$-.

4. The compounds according to any one of claims 1 to 3, wherein X^1 is –C(O)-NH- or –C(O)-.

5. The compounds according to any one of claims 1 to 4, wherein X^1 is –C(O)-NH-.

6. The compounds according to any one of claims 1 to 5, wherein X^2 is arylene or heteroarylene, said arylene and heteroarylene being optionally substituted by one or more substituents independently selected from the group consisting of C_{1-6} alkoxy and halogen, and X^3 is hydrogen.

7. The compounds according to any one of claims 1 to 6, wherein $–X^2$-X^3 forms phenyl or pyridyl, said phenyl and pyridyl being optionally substituted by one or more same or different halogen atoms.

8. The compounds according to any one of claims 1 to 7, wherein $-X^2-X^3$ forms 4-chlorophenyl or 5-chloropyridyn-2-yl.

9. The compounds according to any one of claims 1 to 8, wherein Y^1 is –C(O)-NH-.

10. The compounds according to any one of claims 1 to 9, wherein Y^2 is 1,4-phenylene optionally substituted by one or more same or different halogen atoms.

11. The compounds according to any one of claims 1 to 10, wherein Y^2 is 2-fluoro-1,4 phenylene.

12. The compounds according to any one of claims 1 to 11, wherein Y^3 is heteroaryl optionally substituted by one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, halogen, cyano, nitro, amino, mono-C_{1-6} alkyl substituted amino, di-C_{1-6} alkyl substituted amino, mono-C_{1-6} alkyl substituted amino-C_{1-6} alkyl, di-C_{1-6} alkyl substituted amino-C_{1-6} alkyl, -SO_2-C_{1-6} alkyl, -SO_2-NH_2, -SO_2-NH-C_{1-6} alkyl and -SO_2-N(C_{1-6} alkyl)$_2$, and one or two carbon atoms of said heteroaryl being optionally replaced with a carbonyl group.

13. The compounds according to any one of claims 1 to 12, wherein Y^3 is 2-oxo-2H-pyridyn-1-yl.

14. The compounds according to any one of claims 1 to 13, wherein one of R^1 and R^2 is hydrogen, and the other is C_{1-6} alkyl.

15. The compounds according to any one of claims 2 to 14, wherein one of R^1 and R^2 is C_{1-6} alkyl and at 1 position of the pyrrolopyrazole ring, and the other is hydrogen.

16. The compounds according to any one of claims 2 to 15, wherein one of R^1 and R^2 is methyl and at 1 position of the pyrrolopyrazole ring, and the other is hydrogen.

17. The compounds according to claim 1, which is

(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide},

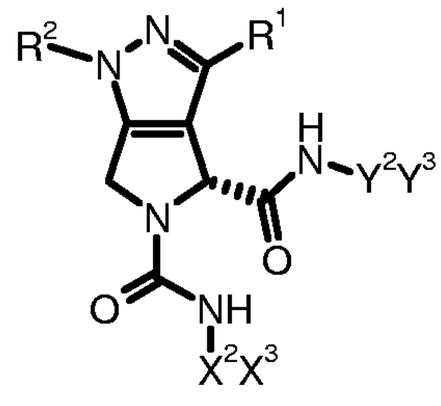
(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide},

(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[2-fluoro-4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide},

(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide} or

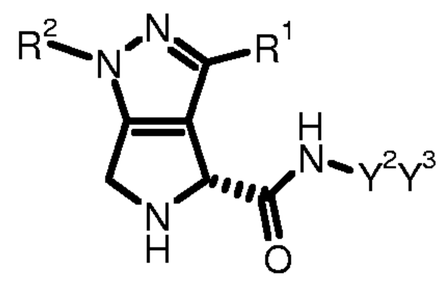
(R)-1-Methyl-4,6-dihydro-1H-pyrrolo[3,4-c]pyrazole-4,5-dicarboxylic acid 5-[(4-chloro-phenyl)-amide] 4-{[2,6-difluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide}.

18. A process for preparaing compounds of Formula (I'),



(I')

comprising a step of acylating compounds of Formula (II)



(II)

wherein X^2, X^3, Y^2, Y^3, R^1 and R^2 are as defined in claim 1.

19. Pharmaceutical compositions comprising a compound according to any of claims 1 to 17 and a pharmaceutically acceptable excipient.

20. The compounds according to any one of claims 1 to 17 for use as therapeutic active substances.

21. The compounds according to any one of claims 1 to 17 for use as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with the coagulation factor Xa.

22. Use of compounds according to any of claims 1 to 17 for the preparation of medicaments for the therapeutic and/or prophylactic treatment of diseases which are associated with the coagulation factor Xa.

23. The use according to claim 21, wherein the disease is thrombotic disorders, arterial thrombosis, venous thrombosis, deep vein thrombosis, peripheral arterial occlusive disease, unstable angina pectoris, myocardial infarction, coronary artery disease, pulmonary embolism, stroke due to atrial fibrillation, inflammation, arteriosclerosis, acute vessel closure associated with thrombolytic therapy or restenosis, and/or tumour.

24. The invention as hereinbefore defined, particularly with reference to the new compounds, intermediates, medicaments, uses and processes.

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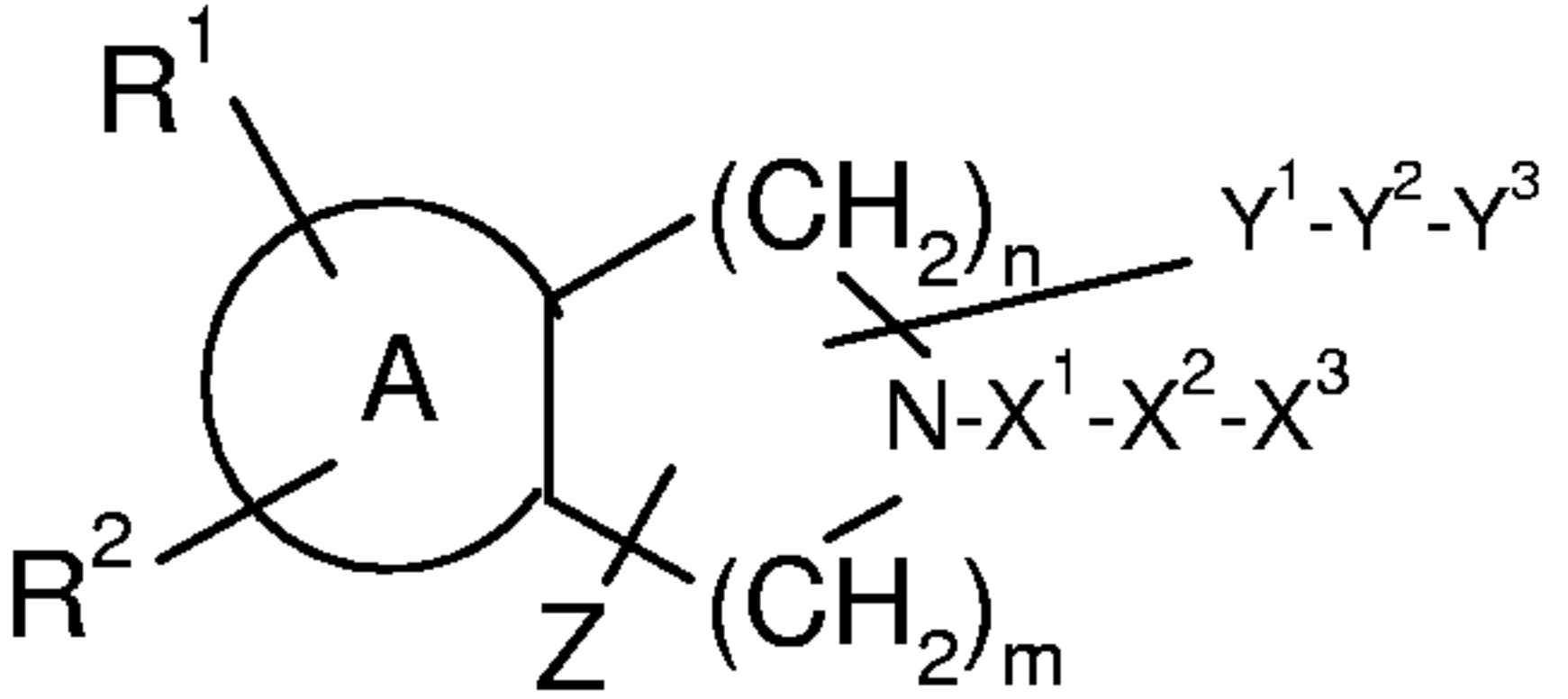

(I)