Title: KETONE PYRIDINE ANALOGUES AND THEIR USE IN THE TREATMENT OF CARDIOVASCULAR DISORDERS

Abstract: The present invention relates to certain new pyridin analogues of Formula (I) to processes for preparing such compositions, for example using multi-thrombolytic agents etc, their use as medicaments in cardiovascular diseases as well as pharmaceutical compositions containing them.

Formula (I)
Ketone pyridine analogues and their use in the treatment of cardiovascular disorders

Field of the invention

The present invention provides novel pyridine compounds, their use as medicaments, compositions containing them and processes for their preparation.

Background of the invention

Platelet adhesion and aggregation are initiating events in arterial thrombosis.

Although the process of platelet adhesion to the sub-endothelial surface may have an important role to play in the repair of damaged vessel walls, the platelet aggregation that this initiates can precipitate acute thrombotic occlusion of vital vascular beds, leading to events with high morbidity such as myocardial infarction and unstable angina. The success of interventions used to prevent or alleviate these conditions, such as thrombolysis and angioplasty is also compromised by platelet mediated occlusion or re-occlusion.

Haemostasis is controlled via a tight balance between platelet aggregation, coagulation and fibrinolysis. Thrombus formation under pathological conditions, like e.g. arteriosclerotic plaque rupture, is firstly initiated by platelet adhesion, activation and aggregation. This results not only in the formation of a platelet plug but also in the exposure of negatively charged phospholipids on the outer platelet membrane promoting blood coagulation. Inhibition of the build-up of the initial platelet plug would be expected to reduce thrombus formation and reduce the number of cardiovascular events as was demonstrated by the anti-thrombotic effect of e.g. Aspirin (BMJ 1994; 308: 81-106 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy, I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients).

Platelet activation/aggregation can be induced by a variety of different agonists. However, distinct intracellular signalling pathways have to be activated to obtain full platelet aggregation, mediated via G-proteins Gq, G12/13 and G1 (Platelets, AD Michelson ed., Elsevier Science 2002, ISBN 0-12-493951-1; 197-213: D Woulfe, et al. Signal transduction during the initiation, extension, and perpetuation of platelet plug formation) In platelets, the G-protein coupled receptor P2Y12 (previously also known as the platelet $\gamma_2$,
P2T<sub>a</sub> or P2Y<sub>cyc</sub> receptor) signals via Gi, resulting in a lowering of intra-cellular cAMP and full aggregation (Nature 2001; 409: 202-207 G Hollopeter, et al. Identification of the platelet ADP receptor targeted by antithrombotic drugs.). Released ADP from dense-granules will positively feedback on the P2Y<sub>12</sub> receptor to allow full aggregation. WO 2002/098856 and WO 2004/052366 describe piperazino-carbonylmethylaminocarbonylnaphtyl or -quinolyl derivatives as ADP receptor antagonist.

Clinical evidence for the key-role of the ADP-P2Y<sub>12</sub> feedback mechanism is provided by the clinical use of clopidogrel, an thienopyridine prodrug which active metabolite selectively and irreversibly binds to the P2Y<sub>12</sub> receptor, that has shown in several clinical trials to be effective in reducing the risk for cardiovascular events in patients at risk (Lancet 1996; 348: 1329-39: CAPRIE Steering committee, A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE); N Engl J Med 2001; 345 (7): 494-502): The Clopidogrel in Unstable Angina to prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation.). In these studies, the clinical benefit with a reduced bleeding risk as compared to thienopyridines (Sem Thromb Haemostas 2005; 31 (2): 195-204 JJJ van Giezen & RG Humphries. Preclinical and clinical studies with selective reversible direct P2Y<sub>12</sub> antagonists. WO 2005/000281 describes a serie of pyrazolidine-3,5-dione derivatives and WO 2006/1 14774 describes a serie of phenyl-pyrimidine derivatives which both series have been described as P2Y<sub>12</sub> antagonists for the potential treatment of thrombosis.


WO 2001/057037 discloses some sulfonyl derivatives as platelet ADP receptor inhibitors. None of these are 2-pyridyl-5-keto derivatives.

Furthermore, in WO 2007/056219 a quinazoline dione derivative is presented as P2Y<sub>12</sub> antagonist, and in WO 2007/056167 a process for its preparation is presented.


It is an object of the present invention to provide improved, potent, reversible and selective P2Yi\textsubscript{2}-antagonists having beneficial properties as anti-thrombosis agents.

Summary of the invention

When testing a compound similar to formula I but having an ester function in R\textsubscript{i}-position, in rats and humans, unexpectedly low plasma concentrations of that compound was found but high plasma levels of the corresponding inactive free acid was also found.

We have now surprisingly found that certain pyridine compounds of Formula (I)

\begin{equation}
\text{Formula (I)}
\end{equation}

or a pharmaceutically acceptable salt thereof are reversible and selective P2Yi\textsubscript{2} antagonists, hereinafter referred to as the compounds of the invention. The compounds of the invention, having improved stability towards esterases in R\textsubscript{i}-position, unexpectedly exhibit improved beneficial properties that render them particularly suitable for use in the treatment of diseases/conditions as described below (See p.81-82). Examples of such beneficial properties are high potency, high selectivity, beneficial pharmacokinetic properties and an advantageous therapeutic window. It is believed that the unexpected high potency exhibited for certain compounds of the invention is related to the selection of
certain substituents in the Reposition, examples of such substituents are (Ci-C₃)alkylthio or hydroxy(Ci-C₃)alkyl. Furthermore, the fact that they are stable against esterase activity in Ri-position will inhibit degradation to inactive free acid in vivo. It is believed that thereby the desired plasma concentration levels of the active compound will be maintained in humans and/or animals.

Detailed description of the invention

According to the present invention there is provided a novel compound of formula (I) or a pharmaceutically acceptable salt thereof:

![Chemical structure](image)

(1)

wherein

- R₁ represents R₄C(O);

R₂ represents CN, halogen (F, Cl, Br or I), (C4-Cg)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, (C₃-Ce)cycloalkyl, heterocycl;

furthermore R₂ represents (C₂-C₃)alkyl interrupted by oxygen; furthermore R₂ represents (Ci-C3)alkyl substituted by one or more of OH, aryl, aryl(Ci-C3)alkyloxy, (C₃-Ce)cycloalkyl and heterocycl, with the proviso that any such OH group must be at least 2 carbon atoms away from any oxygen; further R₂ represents unsubstituted (Ci-C₂)alkoxy, (C₃-C₆)cycloalkyl, hydroxy(C₁-C₁₂)alkyl, (Ci-C₂)alkyloxyC(O), (Ci-C₂)alkylthioC(O), (C₁-C₁₂)alkylC(S), (Ci-C₂)alkoxyC(O), (C₃-C₆)cycloalkoxy, aryl, arylC(O), Myl(C₁-C₁₂)alkylC(O), (C₁-C₁₂)alkylsulfinyl, (C₁-C₁₂)alkylsulfonyl, unsubstituted (Ci-C₂)alkylthio, (C₃-Ce)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(Ci-C₂)alkylthio, aryl(Ci-C₂)alkylsulfinyl, aryl(Ci-C₂)alkylsulfonyl, heterocycl(Ci-C₂)alkylthio,
heterocyclyl(C1-C2)alkylsulfenyl, heterocyclyl(C1-C2)alkylsulfonyl, (C3- to C6)cycloalkyl(C1-C2)alkylthio, (C3- to C6)cycloalkyl(C1-C2)alkylsulfenyl, (C3- to C6)cycloalkyl(C1-C2)alkylsulfonyl; with the proviso that when R2 is methoxy and R3 is alkylene, then Rd is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl;

R7 represents (C1-C3)alkyl optionally interrupted by oxygen, and/or optionally substituted by OH, aryl, (C3-Ce)cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br or I) atoms; further R7 represents (C3-C6)cycloalkyl, hydroxy(C1-C2)alkyl, aryl or heterocyclyl;

Ri4 represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (C1-Cg)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and COORc; wherein R6 represents aryl, (C3-Ce)cycloalkyl, heterocyclyl or (C1-Cg)alkyl optionally substituted by one or more of halogen (F, Cl, Br or I) atom(s), OH, aryl, (C3- to C6)cycloalkyl and heterocyclyl; further R14 represents aryl, aryl(d-C8)alkyl, aryl(C1-Cs)alkoxy, heterocyclyl, a halogen (F, Cl, Br or I) atom, (C3-Ce)cycloalkyl, (C3- to C6)cycloalkyl(C1-C8)alkoxy, hydroxy(C1-C8)alkyl, (C1-C8)alkoxy, (C3-Ce)cycloalkoxy, (Ci-C8)alkylsulfenyl, (Ci-C8)alkylsulfonyl, (Ci-C8)alkylthio, (C3-C6)cycloalkylthio, or a group of formula NRa(14)b(14) in which Ra(14) and Rb(14) independently represent H, (C1- to C8)alkyl, (C1- to C8)alkylC(O), (C1- to C8)alkoxyC(O) or Ra(14) and Rb(14) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R5 is a direct bond or represents an unsubstituted or monosubstituted or polysubstituted (C1-C4)alkylene group, wherein any substituents each individually and independently are selected from (C1-C4)alkyl, (C1-C4)alkoxy, (C2-C4)alkenyl, (C2- to C4)alkynyl, (C3-Ce)cycloalkyl, carboxyl, carboxy-(C1-C4)alkyl, aryl, heterocyclyl, cyano, halogeno (F, Cl, Br or I), hydroxyl, NRa(Rc)b(Rc) in which Ra(Rc) and Rb(Rc) individually and independently from each other represents hydrogen, (C1-C4)alkyl or Ra(Rc) and Rb(Rc) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; further R5 represents imino (-NH-), N-substituted imino (-NR19-), (C1-C4)alkyleneimino or
N-substituted (Ci-C₄)alkyleneimino (-N(Rᵢ₉)-(Ci-C₄)alkylene) wherein the mentioned alkylene groups are unsubstituted or monosubstituted or polysubstituted with any substituents according to above; with the proviso that when Rᶜ is alkylene and R₂ is methoxy, then Rᵈ is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl; preferably Rᶜ represents direct bond, imino or (Ci-C₄)alkyleneimino or an unsubstituted or monosubstituted or polysubstituted (Ci-C₄)alkylene group with any substituents according to above; with the proviso that when Rᶜ is alkylene and R₂ is methoxy, then Rᵈ is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl;

Rᵢ₉ represents H or (Ci-C₄)alkyl;

Rᵈ represents (Ci-C₂)alkyl, (C₃-C₅)cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms and/or one or more of the following groups, OH, CN, (Ci-C₂)alkyl, (Ci-C₂)alkoxyC(O), (Ci-C₂)alkoxy, halogen substituted (Ci-C₂)alkyl, (C₃-C₆)cycloalkyl, aryl, heterocyclyl, (Ci-C₂)alkylsulfmyl, (Ci-C₂)alkylsulfonyl, (Ci-C₂)alkylthio, (Ci-C₂)cycloalkylthio, arylsulfmyl, arylsulfonyl, arylthio, aryl(Ci-C₂)alkylthio, aryl(Ci-C₂)alkylsulfanyl, aryl(Ci-C₂)alkylsulfonyl, heterocyclyl(Ci-C₂)alkylthio, heterocyclyl(Ci-C₂)alkylsulfmyl, heterocyclyl(Ci-C₂)alkylsulfonyl, (C₃-C₆)cycloalkyl(Ci-C₂)alkylthio, (C₃-C₆)cycloalkyl(Ci-C₂)alkylsulfmyl, (C₃-C₆)cycloalkyl(Ci-C₂)alkylsulfonyl or a group of formula NRᵃ(Rᵈ)Rᵇ(Rᵈ) in which Rᵃ(Rᵈ) and Rᵇ(Rᵈ) independently represent H, (Ci-C₂)alkyl, (Ci-C₂)alkylC(O) or Rᵃ(Rᵈ) and Rᵇ(Rᵈ) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine with the proviso that when Rᵈ is one of phenyl, 4-fluorophenyl or 4-chlorophenyl and Rᶜ is alkylene, then R₂ is not methoxy;

X represents a single bond, imino (-NH-), methylene (-CH₂-), iminomethylene (-CH₂-NH-) wherein the carbon is connected to the B-ring/ring system, methyleneimino (-NH-CH₂-) wherein the nitrogen is connected to the B-ring/ring system and any carbon and/or nitrogen in these groups may optionally be substituted with (Ci-C₆) alkyl; further X
may represent a group (-CH$_2$)$_n$ wherein $n$ = 2-6, which optionally is unsaturated and/or substituted by one or more substituent chosen among halogen, hydroxyl or (Ci-Ce)alkyl;

B is a monocyclic or bicyclic, 4 to 11-membered heterocyclic ring/ring system comprising one or more nitrogen and optionally one or more atoms selected from oxygen or sulphur, which nitrogen is connected to the pyridine-ring (according to formula I) and further the B-ring/ring system is connected to X in another of its positions; The substituent R$_{14}$ is connected to the B ring/ring system in such a way that no quarternary ammonium compounds are formed (by this connection).

An alternative embodiment of formula I is;

![Chemical structure](attachment:image.png)

wherein

- $R_1$ represents $R_7C(O)$;
- $R_2$ represents unsubstituted (Ci-C3)alkythio or unsubstituted hydroxy(Ci-C3)alkyl;
- $R_7$ represents (Ci-C$_3$)alkyl optionally interrupted by oxygen, and/or optionally substituted by OH, aryl, (C$_3$-Ce)cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br or I) atoms; further $R_7$ represents (C$_3$-Ce)cycloalkyl, hydroxy(Ci-C$_2$)alkyl, aryl or heterocyclyl;
- $R_{14}$ represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (Ci-Cg)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and
COOR<sup>e</sup>; wherein R<sup>e</sup> represents aryl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, heterocyclyl or (d-C<sub>8</sub>)alkyl optionally substituted by one or more of halogen (F, Cl, Br or I) atom(s), OH, aryl, (C<sub>5</sub>-C<sub>e</sub>)cycloalkyl and heterocyclyl; further R<sub>i4</sub> represents aryl, aryl(C-G)alkyl, aryl(C-C<sub>e</sub>)alkoxy, heterocyclyl, a halogen (F, Cl, Br or I) atom, (C<sub>5</sub>-Ce)cycloalkyl, (C<sub>5</sub>-
C<sub>6</sub>)Cycloalkyl(Ci-Cg)alkoxy, hydroxy(Ci-C<sub>g</sub>)alkyl, (Ci-Cg)alkoxy, (C<sub>3</sub>-Ce)cycloalkoxy, (Ci-C<sub>g</sub>)alkylsulfonyl, (Ci-Cg)alkylthio, (C<sub>3</sub>-C<sub>g</sub>)cycloalkylthio, or a group of formula NR<sup>a(14)</sup>R<sup>b(14)</sup> in which R<sup>a(14)</sup> and R<sup>b(14)</sup> independently represent H, (C<sub>1</sub>-
C<sub>g</sub>)alkyl, (Ci-C<sub>g</sub>)alkylC(O), (Ci-C<sub>g</sub>)alkoxyC(O) or R<sup>a(14)</sup> and R<sup>b(14)</sup> together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R<sup>e</sup> is a direct bond or represents an unsubstituted or monosubstituted or polysubstituted (Ci-C<sub>4</sub>)alkylene group, wherein any substituents each individually and independently are selected from (Ci-C<sub>4</sub>)alkyl, (Ci-C<sub>4</sub>)alkoxy, (C<sub>2</sub>-C<sub>4</sub>)alkeny1, (C<sub>2</sub>-
C<sub>4</sub>)alkynyl, (C<sub>3</sub>-Ce)cycloalkyl, carboxyl, carboxy-(Ci-C<sub>4</sub>)alkyl, aryl, heterocyclyl, cyano, halogeno (F, Cl, Br or I), hydroxyl, NR<sup>a(Rc)</sup>R<sup>b(Rc)</sup> in which R<sup>a(Rc)</sup> and R<sup>b(Rc)</sup> individually and independently from each other represents hydrogen, (Ci-C<sub>4</sub>)alkyl or R<sup>a(Rc)</sup> and R<sup>b(Rc)</sup> together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; further R<sup>e</sup> represents imino (-NH-), N-substituted imino (-NR<sub>19</sub>-), (Ci-C<sub>4</sub>)alkyleneimino or N-substituted (Ci-C<sub>4</sub>)alkyleneimino ( -N(Ri9))-((Ci-C<sub>4</sub>)alkylene) wherein the mentioned alkylene groups are unsubstituted or monosubstituted or polysubstituted with any substituents according to above; with the proviso that when R<sup>e</sup> is alkylene and R<sub>2</sub> is methoxy, then R<sup>d</sup> is not chosen from the group consisting of phenyl, 4-fluorophenyl and A-chlorophenyl; preferably R<sup>e</sup> represents direct bond, imino or (Ci-C<sub>4</sub>)alkyleneimino or an unsubstituted or monosubstituted or polysubstituted (Ci-C<sub>4</sub>)alkylene group with any substituents according to above;

R<sub>i9</sub> represents H or (Ci-C<sub>4</sub>)alkyl;

R<sup>d</sup> represents (Ci-Ci<sub>2</sub>)alkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms and/or one or more of the following groups, OH, CN, (Ci-C<sub>2</sub>)alkyl, (Ci-C<sub>2</sub>)alkoxyC(O), (Ci-C<sub>2</sub>)alkoxy, halogen substituted (Ci-Ci<sub>2</sub>)alkyl, (C<sub>3</sub>-C<sub>g</sub>)cycloalkyl,
aryl, heterocyclyl, (Ci-Ci₂)alkylsulfinyl, (Ci-Ci₂)alkylsulfonyl, (Ci-Ci₂)alkylthio, (C₃⁻
C6)cycloalkythio, arylsulfinyl, arylsulfonyl, arylthio, aryl(Ci-Ci₂)alkylthio, aryl(Ci-
Ci₂)alkylsulfinyl, aryl(Ci-Ci₂)alkylsulfonyl, heterocyclyl(Ci-Ci₂)alkylthio, heterocyclyl(Ci-Ci₂)alkylsulfinyl, heterocyclyl(Ci-Ci₂)alkylsulfonyl, (C₃⁻
C₆)cycloalkyl(Ci-Ci₂)alkylthio, (C₃⁻C₆)cycloalkyl(Ci-Ci₂)alkylsulfonyl, (C₃⁻
C₆)cycloalkyl(Ci-Ci₂)alkylthio, (C₃⁻C₆)cycloalkyl(Ci-Ci₂)alkylsulfonyl, (C₃⁻
C₆)cycloalkyl(Ci-Ci₂)alkylsulfynyl, (C₃⁻
C₆)cycloalkyl(Ci-Ci₂)alkylsulfynyl, a group of formula NRₐ(Rd)R₋(Rd) in which Rₐ(Rd) and
R₋(Rd) independently represent H, (Ci-Ci₂)alkyl, (Ci-Ci₂)alkylC(O) or Rₐ(Rd) and R₋(Rd)
together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

X represents a single bond, imino (-NH⁻), methylene (-CH₂⁻), iminomethylenel
(-CH₂-NH⁻) wherein the carbon is connected to the B-ring/ring system, methyleneimino
(-NH-CH₂⁻) wherein the nitrogen is connected to the B-ring/ring system and any carbon
and/or nitrogen in these groups may optionally be substituted with (Ci-Ci₆) alkyl; further X
may represent a group (-CH₂⁻)ₙ wherein n= 2-6, which optionally is unsaturated and/or
substituted by one or more substituent chosen among halogen, hydroxyl or (Ci-Ce)alkyl;

B is a monocyclic or bicyclic, 4 to 11-membered heterocyclic ring/ring system
comprising one or more nitrogen and optionally one or more atoms selected from oxygen
or sulphur, which nitrogen is connected to the pyridine-ring (according to formula I) and
further the B-ring/ring system is connected to X in another of its positions; the substituent
R₁₄ is connected to the B ring/ring system in such a way that no quarternary ammonium
compounds are formed (by this connection).

Preferred values of each variable group or specific embodiments of variable groups or
terms are as follows. Such values or embodiments may be used where appropriate with any
of the values, definitions, claims, aspects, embodiments or embodiments of the invention
defined hereinbefore or hereinafter. In particular, each may be used as an individual
limitation on the broadest definition of formula (I).

For the avoidance of doubt it is to be understood that where in this specification a group is
qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' the said
group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group.

It will be understood that when formula I compounds contain a chiral centre, the compounds of the invention may exist in, and be isolated in, optically active or racemic form. The invention includes any optically active or racemic form of a compound of formula I which act as P2Yi₂ receptor antagonists. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by, resolution of a racemic mixture, by chiral chromatography, synthesis from optically active starting materials or by asymmetric synthesis.

It will also be understood that the compounds of the formula I may exhibit the phenomenon of tautomerism, the present invention includes any tautomeric form of a compound of formula I which is a P2Yi₂ receptor antagonist.

It will also be understood that in so far as compounds of the present invention exist as solvates, and in particular hydrates, these are included as part of the present invention.

It is also to be understood that generic terms such as "alkyl" include both the straight chain and branched chain groups such as butyl and tert-butyl. However, when a specific term such as "butyl" is used, it is specific for the straight chain or "normal" butyl group, branched chain isomers such as "t-butyl" being referred to specifically when intended.

As used herein, when two or more groups are used in connection with each other, it means that the latter group is substituted by the immediately preceding group. For instance, aryl(Ci-C₆)alkyl means a (Ci-C₆) alkyl group substituted by an aryl group.

As used herein, the expression "alkyl optionally interrupted by oxygen" means that the optional oxygen atom is placed inside the alkyl group between two carbon atoms of the considered alkyl group, and not in any of the ends thereof.
The term "cycloalkyl" generally denotes a substituted or unsubstituted (C₃-C₆), unless other chain length specified, cyclic hydrocarbon.
When the term "cycloalkyl" denotes a substituted hydrocarbon according to above, it denotes a cyclic hydrocarbon according to above which is being substituted by one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms and/or one or more of the following groups, OH, CN, unsubstituted (Ci-Ci₂)alkyl, halogen substituted (Ci-Ci₂)alkyl, unsubstituted (Ci-Ci₂)alkoxyC(O), halogen substituted (Ci-Ci₂)alkoxyC(O), unsubstituted (Ci-Ci₂)alkoxy, halogen substituted (Ci-Ci₂)alkoxy, unsubstituted (C₃-Ce)cycloalkyl, halogen substituted (C₃-Ce)cycloalkyl, unsubstituted aryl, halogen substituted aryl, unsubstituted heterocyclyl, halogen substituted heterocyclyl, unsubstituted (Ci-Ci₂)alkylsulfinyl, halogen substituted (Ci-Ci₂)alkylsulfinyl, unsubstituted (Ci-Ci₂)alkylsulfonyl, halogen substituted (Ci-Ci₂)alkylsulfonyl, unsubstituted (Ci-Ci₂)alkythio, halogen substituted (Ci-Ci₂)alkythio, unsubstituted (C₃-Ce)cycloalkythio, halogen substituted (C₃-Ce)cycloalkythio, unsubstituted arylsulfinyl, halogen substituted arylsulfinyl, unsubstituted arylsulfonyl, halogen substituted arylsulfonyl, unsubstituted arylthio, halogen substituted arylthio, unsubstituted aryl(Ci-Ci₂)alkylthio, halogen substituted aryl(Ci-Ci₂)alkylthio, unsubstituted aryl(Ci-Ci₂)alkylsulfinyl, halogen substituted aryl(Ci-Ci₂)alkylsulfinyl, unsubstituted aryl(Ci-Ci₂)alkylsulfonyl, halogen substituted aryl(Ci-Ci₂)alkylsulfonyl, unsubstituted heterocyclyl(Ci-Ci₂)alkylthio, halogen substituted heterocyclyl(Ci-Ci₂)alkylthio, unsubstituted heterocyclyl(Ci-Ci₂)alkylsulfinyl, halogen substituted heterocyclyl(Ci-Ci₂)alkylsulfinyl, unsubstituted heterocyclyl(Ci-Ci₂)alkylsulfonyl, unsubstituted (C₃-Ce)cycloalkyl(Ci-Ci₂)alkylthio, halogen substituted (C₃-Ce)cycloalkyl(Ci-Ci₂)alkylthio, unsubstituted (C₃-Ce)cycloalkyl(Ci-Ci₂)alkylsulfinyl, halogen substituted (C₃-Ce)cycloalkyl(Ci-Ci₂)alkylsulfinyl, unsubstituted (C₃-Ce)cycloalkyl(Ci-Ci₂)alkylsulfonyl, halogen substituted (C₃-Ce)cycloalkyl(Ci-Ci₂)alkylsulfonyl or a group of formula NRᵃRᵇ in which Rᵃ and Rᵇ independently represent H, unsubstituted (Ci-Ci₂)alkyl, unsubstituted (Ci-Ci₂)alkylC(O) or Rᵃ and Rᵇ together with the nitrogen atom represent unsubstituted piperidine, unsubstituted pyrrolidine, unsubstituted azetidine or unsubstituted aziridine.
The term "alkoxy" includes both linear or branched chain groups, unless otherwise specified optionally substituted by one or more halogens (F, Cl, Br or I) or mixed halogen atoms.

The term aryl in general without other specification denotes a substituted or unsubstituted (C6-C14) aromatic hydrocarbon and includes, but is not limited to, phenyl, naphthyl, tetrahydronaphtyl, indenyl, indanyl, antracenyl, fenantrenyl, and fluorenyl. When said aryl is being substituted, it is substituted by one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms and/or one or more of the following groups, OH, CN, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkoxyC(O), halogen substituted (Ci-Ci2)alkoxyC(O), unsubstituted (Ci-Ci2)alkoxy, halogen substituted (Ci-Ci2)alkoxy, unsubstituted (C3-Ce)cycloalkyl, halogen substituted (C3-Ce)cycloalkyl, unsubstituted aryl, halogen substituted aryl, unsubstituted heterocyclyl, halogen substituted heterocyclyl, unsubstituted (Ci-Ci2)alkylsulfinyl, halogen substituted (Ci-Ci2)alkylsulfinyl, unsubstituted (Ci-Ci2)alkylsulfonyl, halogen substituted (Ci-Ci2)alkylsulfonyl, unsubstituted (Ci-Ci2)alkylthio, halogen substituted (Ci-Ci2)alkylthio, unsubstituted (C3-Ce)cycloalkylthio, halogen substituted (C3-Ce)cycloalkylthio, unsubstituted arylsulfinyl, halogen substituted arylsulfonyl, unsubstituted arylthio, halogen substituted arylthio, unsubstituted aryl(Ci-Ci2)alkylthio, halogen substituted aryl(Ci-Ci2)alkylthio, unsubstituted aryl(Ci-Ci2)alkylsulfinyl, halogen substituted aryl(Ci-Ci2)alkylsulfinyl, unsubstituted aryl(Ci-Ci2)alkylsulfonyl, halogen substituted aryl(Ci-Ci2)alkylsulfonyl, unsubstituted heterocyclyl(Ci-Ci2)alkylthio, halogen substituted heterocyclyl(Ci-Ci2)alkylthio, unsubstituted heterocyclyl(Ci-Ci2)alkylsulfonyl, halogen substituted heterocyclyl(Ci-Ci2)alkylsulfonyl, unsubstituted heterocyclyl(Ci-Ci2)alkylsulfonyl, halogen substituted heterocyclyl(Ci-Ci2)alkylsulfonyl, unsubstituted (C3-Ce)cycloalkyl(Ci-Ci2)alkylthio, halogen substituted (C3-Ce)cycloalkyl(Ci-Ci2)alkylthio, unsubstituted (C3-Ce)cycloalkyl(Ci-Ci2)alkylsulfinyl, halogen substituted (C3-Ce)cycloalkyl(Ci-Ci2)alkylsulfinyl, unsubstituted (C3-Ce)cycloalkyl(Ci-Ci2)alkylsulfonyl, halogen substituted (C3-Ce)cycloalkyl(Ci-Ci2)alkylsulfonyl or a group of formula NR^aR^b in which R^a and R^b independently represent H, unsubstituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen substituted (Ci-Ci2)alkyl, unsubstituted (Ci-Ci2)alkyl, halogen 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(Ci-Ci2)alkyl, unlabeled
Ci)alkylC(O) or R³ and R⁴ together with the nitrogen atom represent unsubstituted piperidine, unsubstituted pyrrolidine, unsubstituted azetidine or unsubstituted aziridine.

In one embodiment of the invention, the term aryl in general without other specification denotes a substituted or unsubstituted phenyl group, which when substituted is substituted by one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms and/or one or more of the following groups, OH, CN, unsubstituted (Ci-Ci)alkyl, halogen substituted (Ci-Ci)alkyl, unsubstituted (Ci-Ci)alkoxyC(O), halogen substituted (C-Ci)alkoxyC(O), unsubstituted (Ci-Ci)alkoxy, halogen substituted (Ci-Ci)alkoxy, unsubstituted (C-Ci)cycloalkyl, halogen substituted (C-Ci)cycloalkyl, unsubstituted aryl, halogen substituted aryl, unsubstituted heterocyclyl, halogen substituted heterocyclyl, unsubstituted (Ci-Ci)alkylsulfanyl, halogen substituted (Ci-Ci)alkylsulfanyl, unsubstituted (Ci-Ci)alkylsulfonyl, halogen substituted (Ci-Ci)alkylsulfonyl, unsubstituted (Ci-Ci)alkylthio, halogen substituted (Ci-Ci)alkylthio, unsubstituted (C-Ci)alkylthio, halogen substituted (C-Ci)alkylthio, unsubstituted arylsulfanyl, halogen substituted arylsulfanyl, unsubstituted arylsulfanyl, unsubstituted arylthio, halogen substituted arylthio, unsubstituted aryl(Ci-Ci)alkylthio, halogen substituted aryl(Ci-Ci)alkylthio, unsubstituted aryl(Ci-Ci)alkylsulfanyl, halogen substituted aryl(Ci-Ci)alkylsulfanyl, unsubstituted aryl(Ci-Ci)alkylsulfonyl, halogen substituted aryl(Ci-Ci)alkylsulfonyl, unsubstituted heterocyclyl(Ci-Ci)alkylthio, halogen substituted heterocyclyl(Ci-Ci)alkylthio, unsubstituted heterocyclyl(Ci-Ci)alkylsulfanyl, halogen substituted heterocyclyl(Ci-Ci)alkylsulfanyl, unsubstituted heterocyclyl(Ci-Ci)alkylsulfonyl, halogen substituted heterocyclyl(Ci-Ci)alkylsulfonyl, unsubstituted (C-Ci)cycloalkyl(Ci-Ci)alkylthio, halogen substituted (C-Ci)cycloalkyl(Ci-Ci)alkylthio, unsubstituted (C-Ci)cycloalkyl(Ci-Ci)alkylthio, halogen substituted (C-Ci)cycloalkyl(Ci-Ci)alkylthio, unsubstituted (C-Ci)cycloalkyl(Ci-Ci)alkylsulfanyl, halogen substituted (C-Ci)cycloalkyl(Ci-Ci)alkylsulfanyl, unsubstituted (C-Ci)cycloalkyl(Ci-Ci)alkylsulfonyl, halogen substituted (C-Ci)cycloalkyl(Ci-Ci)alkylsulfonyl, or a group of formula NR³R⁴ in which R³ and R⁴ independently represent H, unsubstituted (Ci-Ci)alkyl, unsubstituted (C-Ci)alkylC(O) or R³ and R⁴ together with the nitrogen atom represent unsubstituted piperidine, unsubstituted pyrrolidine, unsubstituted azetidine or unsubstituted aziridine.
The term "heterocyclyl" denotes a substituted or unsubstituted, 4- to 10-membered monocyclic or multicyclic ring system in which one or more of the atoms in the ring or rings is an element other than carbon, for example nitrogen, oxygen or sulfur, especially 4-, 5- or 6-membered aromatic or aliphatic heterocyclic groups, and includes, but is not limited to azetidine, furan, thiophene, pyrrole, pyrroline, pyrrolidine, dioxolane, oxathiolane, oxazolane, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isothiazole, oxadiazole, furazan, triazole, thiadiazole, pyran, pyridine as well as pyridine-N-oxide, piperidine, dioxane, morpholine, dithiane, oxathiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, thiadiazine, dithiazine, azaindole, azaindoline, indole, indoline, naphthyridine, benzoxadiazole, dihydrobenzodioxin, benzothiophene, benzothiadiazole, imidazothiazole, 2,3-dihydrobenzofuran, isoxazole, 3-benzisoxazole, 1,2-benzisoxazole, dihydropyrazole groups, and shall be understood to include all isomers of the above identified groups. For the above groups, e.g. azetidinyl, the term "azetidinyl" as well as "azetidinylene", etc., shall be understood to include all possible regio isomers. It is further to be understood that the term heterocyclyl may be embodied by one selection among the given possible embodiments for a variable and embodied by another (or the same) selection for another variable, e.g. R₂ when selected as heterocyclyl may be a furan, when R₄ (also when selected as heterocyclyl) may be a pyrrole.

Generally, when cycloalkyl is substituted with aryl, heterocyclyl or another cycloalkyl, that substituent is not again substituted with another one of any one of these groups. It is not contemplated in this invention to create a "polymer" compound. Thus, e.g. -cycloalkyl-cycloalkyl, -cycloalkyl-heterocyclyl and -cycloalkyl-aryl are intended to be covered, but -cycloalkyl-cycloalkyl-cycloalkyl as well as -cycloalkyl-aryl-cycloalkyl or -cycloalkyl-heterocyclyl-aryl or even longer such chains are intended to be excluded from the invention.

When the term "heterocyclyl" denotes a substituted ring system according to above, it denotes a ring system according to above which is being substituted by
one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms and/or one or more of the following groups, OH, CN, unsubstituted (CI-Ci2)alkyl, halogen substituted
(Ci-Ci₂)alkyl, unsubstituted (C₁-C₁₂)alkoxyC(O), halogen substituted (d-Ci₂)alkoxyC(O), unsubstituted (Ci-Ci₂)alkoxy, halogen substituted (Ci-Ci₂)alkoxy, unsubstituted (C₃-C₆)cycloalkyl, halogen substituted (C₃-C₆)cycloalkyl, unsubstituted aryl, halogen substituted aryl, unsubstituted heterocyclyl, halogen substituted heterocyclyl, unsubstituted (Ci-Ci₂)alkylsulfinyl, halogen substituted (Ci-Ci₂)alkylsulfinyl, unsubstituted (C₁-Ci₂)alkylsulfonyl, halogen substituted (Ci-Ci₂)alkylsulfonyl, unsubstituted (C₁-Ci₂)alkylthio, halogen substituted (C₁-Ci₂)alkylthio, unsubstituted (C₃-Ci₆)cycloalkylthio, unsubstituted arylsulfanyl, halogen substituted arylsulfanyl, halogen substituted arylsulfonyl, halogen substituted arylthio, halogen substituted arylthio, unsubstituted aryl(Ci-Ci₂)alkylthio, halogen substituted aryl(Ci-Ci₂)alkylthio, unsubstituted aryl(Ci-Ci₂)alkylsulfinyl, halogen substituted aryl(Ci-Ci₂)alkylsulfinyl, halogen substituted aryl(Ci-Ci₂)alkylsulfonyl, halogen substituted aryl(Ci-Ci₂)alkylsulfonyl, unsubstituted heterocyclyl(Ci-Ci₂)alkylthio, halogen substituted heterocyclyl(Ci-Ci₂)alkylthio, unsubstituted heterocyclyl(Ci-Ci₂)alkylsulfinyl, halogen substituted heterocyclyl(Ci-Ci₂)alkylsulfinyl, unsubstituted heterocyclyl(Ci-Ci₂)alkylsulfonyl, halogen substituted heterocyclyl(Ci-Ci₂)alkylsulfonyl, unsubstituted heterocyclyl(Ci-Ci₂)alkylsulfonyl, unsubstituted (C₃-Ci₆)cycloalkyl(Ci-Ci₂)alkylthio, halogen substituted (C₃-Ci₆)cycloalkyl(Ci-Ci₂)alkylthio, halogen substituted (C₃-Ci₆)cycloalkyl(Ci-Ci₂)alkylsulfinyl, halogen substituted (C₃-Ci₆)cycloalkyl(Ci-Ci₂)alkylsulfinyl, unsubstituted (C₃-Ci₆)cycloalkyl(Ci-Ci₂)alkylsulfonyl, halogen substituted (C₃-Ci₆)cycloalkyl(Ci-Ci₂)alkylsulfonyl, or a group of formula NRⁿRᵇ in which Rⁿ and Rᵇ independently represent H, unsubstituted (C₁-Ci₂)alkyl, unsubstituted (Ci-Ci₂)alkylC(O) or Rⁿ and Rᵇ together with the nitrogen atom represent unsubstituted piperidine, unsubstituted pyrrolidine, unsubstituted azetidine or unsubstituted aziridine.

In another embodiment of the invention the heterocyclyl group comprises an aromatic 5-membered or 6-membered heterocyclic ring containing one, two or three heteroatoms selected from nitrogen, oxygen and sulphur, and an aromatic 5-membered or 6-membered heterocyclic ring containing one, two or three heteroatoms selected from nitrogen, oxygen and sulphur which is fused to a benzene ring;
In an alternative embodiment of the invention the heterocyclyl group is a non-aromatic 5-membered or 6-membered heterocyclic ring containing one, two or three heteroatoms selected from nitrogen, oxygen and sulphur, fused to a benzene ring.

In a further embodiment of the invention the heterocyclyl group is a group chosen among furyl, pyrrolyl, thiencyl, pyridyl, N-oxido-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, imidazolyl, oxazolyl, isooxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, benzfuranyl, quinolyl, isoquinolyl, benzimidazolyl, indolyl, benzodihydrofuranyl, benzodioxolyl (such as 1,3-benzodioxolyl), benzoxadiazone, dihydrobenzodiazone, benzo thiophene, benzo thiadiazole, imidazothiazole, 2,3-dihydrobenzofuran, isoxazole, dihydropyrazole and benz dioxan yl (such as 1,4-benzdioxan yl). More particular values include, for example, furyl, pyrrolyl, thiencyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzodiazone, dihydrobenzodiazone, benzo thiophene, benzo thiadiazole, imidazothiazole, 2,3-dihydrobenzofuran, isoxazole, 1,2-benzisoxazole, dihydropyrazole and benz dioxyan yl (such as 1,4-benz dioxyan yl).

In an even further embodiment of the invention the heterocyclyl group is a group chosen among furyl, pyrrolyl, thiencyl, pyridyl, N-oxido-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzodiazone, dihydrobenzodiazone, benzo thiophene, benzo thiadiazole, imidazothiazole, 2,3-dihydrobenzofuran, isoxazole, 1,2-benzisoxazole or dihydropyrazole.

Embodiments for $R_2$ include, for example (Ci-C3)alkyl substituted by one or more of OH, aryl, aryl(Ci-C3)alkyloxy, cycloalkyl and heterocyclyl, with the proviso that any such OH group must be at least 2 carbon atoms away from any oxygen.

In one embodiment of the invention $R_2$ is represented by unsubstituted (Ci-Cs)alkyloxy or unsubstituted (Ci-C3)alky thio, with the proviso that when $R_2$ is methoxy, and $R^c$ is alkylene, then $R^d$ is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl.

In another embodiment of the invention $R_2$ is represented by unsubstituted (Ci-C3)alkyloxy or unsubstituted (Ci-C4)alkylthio, with the proviso that when $R_2$ is methoxy,
and \( R^e \) is alkylen, then \( R^d \) is not chosen from the group consisting of phenyl, \( A \)-fluorophenyl and 4-chlorophenyl.

In a further embodiment of the invention \( R_2 \) is represented by unsubstituted \((C_1-C_3)\)alkylthio or unsubstituted hydroxy\((C_1-C_3)\)alkyl.

In an alternative further embodiment of the invention \( R_2 \) is represented by unsubstituted \((C_1-C_3)\)alkyloxy or unsubstituted hydroxy\((C_1-C_3)\)alkyl, with the proviso that when \( R_2 \) is methoxy, and \( R^e \) is alkylen, then \( R^d \) is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl.

In an even further alternative embodiment of the invention \( R_2 \) is represented by unsubstituted \((C_1-C_3)\)alkylthio.

In an utterly further alternative embodiment of the invention \( R_2 \) is represented by unsubstituted \((C_1-C_4)\)alkylthio.

It is also contemplated that \( R_2 \) may be selected from the group consisting of methylthio, ethylthio, n-propylthio, iso-propylthio, hydroxymethyl and hydroxyethyl.

It is further contemplated that \( R_2 \) may be selected from the group consisting of methylthio, ethylthio, n-propylthio, iso-propylthio, cyclopropylthio, isobutylthio, hydroxymethyl and methoxy, with the proviso that when \( R_2 \) is methoxy, and \( R^e \) is alkylen, then \( R^d \) is not chosen from the group consisting of phenyl, 4-fluorophenyl and \( A \)-chlorophenyl.

It is further contemplated that \( R_2 \) may be selected from the group consisting of methylthio, ethylthio, n-propylthio and hydroxymethyl.

It is even further contemplated that \( R_2 \) in one embodiment of the invention is methylthio.
In one embodiment of the invention \( R_7 \) is \((C_2-C_3)\text{alkyl}\). Alternatively, it is also contemplated that in another embodiment of the invention \( R_7 \) is selected among methyl, ethyl, n-propyl, isopropyl and cyclo-propyl.

In one further embodiment of the invention \( R_7 \) can be selected among n-propyl, isopropyl, or cyclo-propyl.

In an even further embodiment \( R_7 \) is chosen among methyl, ethyl and n-propyl.

In an alternative further embodiment \( R_7 \) is n-propyl.

In another further embodiment \( R_7 \) is \((C_3-C_6)\text{cycloalkyl}\).

Further embodiments for \( R_{i_4} \) include, hydrogen, amino, and \((C_{i-Ce})\text{alkyl} \) optionally substituted by one or more of OH and COOH.

In a further embodiment \( R_{i_4} \) is represented by hydrogen, or \((C_{i-Ce})\text{alkyl} \) optionally substituted by one or more of OH and COOH.

In an even further embodiment \( R_{i_4} \) is represented by hydrogen, or unsubstituted \((C_{1-Ce})\text{alkyl}\).

In one embodiment of the invention \( R_{i_4} \) represents H.

In one embodiment of the invention \( R^d \) represents \((C_{s-C_6})\text{cycloalkyl} \) optionally substituted by aryl or with one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms or represents aryl, or heterocyclyl.

In one embodiment of the invention \( R^d \) represents cyclopropyl optionally substituted by aryl or with one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms or represents aryl, or heterocyclyl.

In one embodiment of the invention \( R^d \) represents cyclopropyl optionally substituted by phenyl or with one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms.
Further embodiments for \( R^d \) includes aryl or (C\textsubscript{3}-C\textsubscript{6}) cycloalkyl optionally substituted by aryl or with one or more halogen (F, Cl, Br or I) atoms or mixed halogen, with the proviso that when \( R_2 \) is methoxy, and \( R^c \) is alkylene, then \( R^d \) is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl.

Even further embodiments for \( R^d \) includes aryl or unsubstituted (C\textsubscript{3}-C\textsubscript{6}) cycloalkyl, with the proviso that when \( R_2 \) is methoxy, and \( R^c \) is alkylene, then \( R^d \) is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl.

Another embodiment for \( R^d \) include, aryl such as phenyl and aromatic heterocyclyl such as thienyl, with the proviso that when \( R_2 \) is methoxy, and \( R^c \) is alkylene, then \( R^d \) is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl.

Other embodiments of \( R^d \) include phenyl which optionally may be substituted, with the proviso that when \( R_2 \) is methoxy, and \( R^c \) is alkylene, then \( R^d \) is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl.

In a special embodiment \( R^d \) represents aryl, heterocyclyl or (C\textsubscript{3}-C\textsubscript{6})cycloalkyl, and anyone of these groups are optionally substituted with one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms, and/or one or more of the following groups, OH, CN, (C\textsubscript{1}-C\textsubscript{2})alkyl, (Ci-C\textsubscript{2})alkoxyC(O), (Ci-C\textsubscript{2})alkoxy, halogen substituted (Ci-C\textsubscript{2})alkyl, (C\textsubscript{3}-C\textsubscript{6})cycloalkyl, aryl, heterocyclyl, (Ci-C\textsubscript{2})alkylsulfmyl, (Ci-C\textsubscript{2})alkylsulfonfyl, (Ci-C\textsubscript{2})alkylthio, (C\textsubscript{3}-C\textsubscript{6})cycloalkylthio, arylsulfmyl, arylsulfonfyl, arylthio, aryl(C\textsubscript{1}-C\textsubscript{2})alkylthio, aryl(Ci-C\textsubscript{2})alkylsulfmyl, aryl(Ci-C\textsubscript{2})alkylsulfonfyl, heterocyclyl(C\textsubscript{1}-C\textsubscript{2})alkylthio, heterocyclyl(Ci-C\textsubscript{2})alkylsulfmyl, heterocyclyl(Ci-C\textsubscript{2})alkylsulfonfyl, (C\textsubscript{3}-C\textsubscript{6})cycloalkyl(Ci-C\textsubscript{2})alkylthio, (C\textsubscript{3}-C\textsubscript{6})cycloalkyl(Ci-C\textsubscript{2})alkylsulfmyl, (C\textsubscript{3}-C\textsubscript{6})cycloalkyl(Ci-C\textsubscript{2})alkylsulfonfyl or a group of formula \( N^a R^b \) in which \( R^a \) and \( R^b \) independently represent H, (Ci-C\textsubscript{2})alkyl, (Ci-C\textsubscript{2})alkylC(O) or R\textsuperscript{c} and R\textsuperscript{c} together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine, with the proviso that when \( R_2 \) is methoxy, and \( R^c \) is alkylene, then \( R^d \) is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl.
Even further embodiments for \( R^d \) include phenyl optionally substituted at the 2,3,4,5 or 6-positions as well as any combination thereof. Example of substituents are cyano, tetrazol-5-yl, methoxy, trifluoromethoxy, methyl, trifluoromethyl, fluoro, chloro, bromo, methylsulfonyl, 3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl. Two adjacent positions (e.g. 2,3) may also be connected to form a ring. Example of such a substituent is 2-naphtyl. Further \( R^d \) also includes heteroaryls such as 2-chloro-5-thienyl, 3-bromo-5-chloro-2-thienyl, 2,1,3-benzoxadiazol-4-yl, 2,4-dimethyl-1,3-thiazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 5-chloro-3-methyl-1-benzothien-2-yl, 2,1,3-benzothiadiazol-4-yl, 2,5-dimethyl-3-furyl, 6-chloroimidazo[2,1-b][1,3]thiazol-5-yl, 2,3-dihydro-1-benzofuran-5-yl, 5-chloro-3-thienyl, 5-isoxazol-5-yl-2-thienyl, 5-isoxazol-3-yl-2-thienyl, 4-bromo-5-chloro-2-thienyl, 5-bromo-6-chloropyridin-3-yl, 5-bromo-2-thienyl, 5-pyridin-2-yl-2-thienyl, 2,5-dichloro-3-thienyl, 4,5-dichloro-2-thienyl, benzothien-3-yl, 2,5-dimethyl-3-thienyl, 3-thienyl, 5-methylisoxazol-4-yl, pyridin-3-yl, [1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]-2-thienyl, 5-chloro-1,3-dimethyl-1H-pyrazol-4-yl, 4-[(4-chlorophenyl)sulfonyl]-3-methyl-2-thienyl, 5-(methoxycarbonyl)-2-furyl and A-(methoxycarbonyl)-5-methyl-2-furyl, with the proviso that when \( R_2 \) is methoxy, and \( R^c \) is alkylene, then \( R^d \) is not chosen from the group consisting of phenyl, 4-fluorophenyl and A-chlorophenyl.

Even another further embodiment for \( R^d \) include: phenyl-1,1-(C_3-C_6)cycloalkylene with the phenyl optionally substituted at the 2,3,4,5 or 6-positions as well as any combination thereof; phenyl optionally substituted at the 2,3,4,5 or 6-positions as well as any combination thereof. Example of substituents are cyano, tetrazol-5-yl, methoxy, trifluoromethoxy, methyl, trifluoromethyl, fluoro, chloro, bromo, methylsulfonyl, nitro, 3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl. Two adjacent positions (e.g. 2,3) may also be connected to form a ring. Example of such a substituent is 2-naphtyl. Further \( R^d \) also includes heteroaryls such as 2-chloro-5-thienyl, 3-bromo-5-chloro-2-thienyl, 2,1,3-benzoxadiazol-4-yl, 2,4-dimethyl-1,3-thiazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 5-chloro-3-methyl-1-benzothien-2-yl, 2,1,3-benzothiadiazol-4-yl, 2,5-dimethyl-3-furyl, 6-chloroimidazo[2,1-b][1,3]thiazol-5-yl, 2,3-dihydro-1-benzofuran-5-yl, 5-chloro-3-thienyl, 5-isoxazol-5-yl-2-thienyl, 5-isoxazol-3-yl-2-thienyl, 4-bromo-5-chloro-2-thienyl, 5-bromo-6-chloropyridin-3-yl, 5-bromo-2-thienyl, 5-pyridin-2-yl-2-thienyl, 2,5-dichloro-3-thienyl, 4,5-dichloro-2-thienyl, benzothien-3-yl, 2,5-dimethyl-3-thienyl, 3-thienyl, 5-methylisoxazol-4-yl, pyridin-3-yl, [1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]-2-thienyl, 5-chloro-1,3-dimethyl-1H-pyrazol-4-yl, 4-[(4-chlorophenyl)sulfonyl]-3-methyl-2-thienyl, 5-(methoxycarbonyl)-2-furyl and A-(methoxycarbonyl)-5-methyl-2-furyl, with the proviso that when \( R_2 \) is methoxy, and \( R^c \) is alkylene, then \( R^d \) is not chosen from the group consisting of phenyl, 4-fluorophenyl and A-chlorophenyl.
6-chloropyridin-3-yl, 5-bromo-2-thienyl, 5-pyridin-2-yl-2-thienyl, 2,5-dichloro-3-thienyl, 4,5-dichloro-2-thienyl, benzothien-3-yl, 2,5-dimethyl-3-thienyl, 3-thienyl-2-thienyl, 5-methylisoxazol-4-yl, pyridin-3-yl, [1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]-2-thienyl, 5-chloro-1,3-dimethyl-1H-pyrazol-4-yl, 4-[(4-chlorophenyl)sulfonyl]-3-methyl-2-thienyl, 5-(methoxycarbonyl)-2-furyl and 4-(methoxycarbonyl)-5-methyl-2-furyl.

In one embodiment of the invention R⁰ represents a direct bond or an unsubstituted or monosubstituted or disubstituted (Ci-C⁴)alkylene group wherein any substituents each individually and independently are selected from (d-C⁴)alkyl, (d-C⁴)alkoxy, (C₂-C⁴)alkenyl, (C₂-C⁴)alkynyl, (C₃-C⁵)cycloalkyl, carboxyl, carboxy-(Ci-C⁴)alkyl, aryl, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br or I), hydroxyl, NRᵃ(Rᶜ)Rᵇ(Rᶜ) in which Rᵃ(Rᶜ) and Rᵇ(Rᶜ) individually and independently from each other represents hydrogen, (C₁-C⁴)alkyl or Rᵃ(Rᶜ) and Rᵇ(Rᶜ) together with the nitrogen atom represent piperidine, pyrroldine, azetidine or aziridine, and Rᵈ represents aryl, i.e R⁰Rᵈ represents an aryl-(Ci-C⁴)alkylene group with any substituents according to above, with the proviso that when R⁰ is alkylene and R₂ is methoxy, then Rᵈ is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl.

In an alternative embodiment of the invention R⁰ represents a direct bond or an unsubstituted or monosubstituted or disubstituted (Ci-C⁴)alkylene group wherein any substituents each individually and independently are selected from (Ci-C⁴)alkyl, (C₁-C⁴)alkoxy, (C₂-C⁴)alkenyl, (C₂-C⁴)alkynyl, (C₃-C⁵)cycloalkyl, carboxyl, carboxy-(Ci-C⁴)alkyl, aryl, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br or I), hydroxyl, NRᵃ(Rᶜ)Rᵇ(Rᶜ) in which Rᵃ(Rᶜ) and Rᵇ(Rᶜ) individually and independently from each other represents hydrogen, (Ci-C⁴)alkyl or Rᵃ(Rᶜ) and Rᵇ(Rᶜ) together with the nitrogen atom represent piperidine, pyrroldine, azetidine or aziridine, and Rᵈ represents aryl, i.e R⁰Rᵈ represents an aryl-(Ci-C⁴)alkylene group with any substituents according to above, with the proviso that when R⁰ is alkylene and R₂ is methoxy, then Rᵈ is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl.

In a further embodiment of the invention R⁰ represents a direct bond or an unsubstituted or monosubstituted or disubstituted (Ci-C⁴)alkylene group wherein any
substituents each individually and independently are selected from (d-C₄)alkyl, (C₁-
C₄)alkoxy, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₃-Ce)cycloalkyl, carboxyl, carboxy-(Ci-
C₄)alkyl, aryl, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br or I), hydroxyl, NRₐ[Rc]Rₐ[Rc] in which Rₐ[Rc] and Rₐ[Rc] individually and independently from each other represents hydrogen, (Ci-C₄)alkyl or Rₐ[Rc] and Rₐ[Rc] together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine, and Rₐ represents heterocyclyl, i.e. Rₐ Rₐ represents a heterocyclyl-(Ci-C₄)alkylene group with any substituents according to above.

In a further alternative embodiment of the invention Rₐ represents a direct bond or an unsubstituted or monosubstituted or disubstituted (Ci-C₃)alkylene group wherein any substituents each individually and independently are selected from (Ci-C₄)alkyl, (Ci-
C₄)alkoxy, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₃-Ce)cycloalkyl, carboxyl, carboxy-(Ci-
C₄)alkyl, aryl, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br or I), hydroxyl, NRₐ[Rc]Rₐ[Rc] in which Rₐ[Rc] and Rₐ[Rc] individually and independently from each other represents hydrogen, (Ci-C₄)alkyl or Rₐ[Rc] and Rₐ[Rc] together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine, and Rₐ represents heterocyclyl, i.e. Rₐ Rₐ represents a heterocyclyl-(Ci-C₃)alkylene group with any substituents according to above.

In a particular embodiment of the invention Rₐ represents a direct bond or a Ci-
alkylene group wherein any substituents each individually and independently are selected from (Ci-C₄)alkyl, (C₁ C₄)alkoxy, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₃-Ce)cycloalkyl, carboxyl, carboxy-(Ci-C₄)alkyl, aryl, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br or I), hydroxyl, NRₐ[Rc]Rₐ[Rc] in which Rₐ[Rc] and Rₐ[Rc] individually and independently from each other represents hydrogen, (Ci-C₄)alkyl or Rₐ[Rc] and Rₐ[Rc] together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine, and Rₐ represents aryl, i.e. Rₐ Rₐ represents an aryl-Ci-alkylene group with any substituents according to above with the proviso that when Rₐ is alkylene and R₂ is methoxy, then Rₐ is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl.

In a further particular embodiment of the invention Rₐ represents a direct bond or an unsubstituted or monosubstituted or disubstituted Ci-alkylene group wherein any substituents each individually and independently are selected from (Ci-C₄)alkyl, (Ci-
C₄alkoxy, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₃-C₆)cycloalkyl, carboxyl, carboxy-(Ci-C₄)alkyl, aryI, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br or I), hydroxyl, NRₐₑ(Rc)Rₐ₂(Rc) in which R₁₉(Rc) and Rₐ₂(Rc) individually and independently from each other represents hydrogen, (Ci-C₆)alkyl or Rₐ₃(Rc) and Rₐ₄(Rc) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine, and Rₐ₄ represents aryl, i.e., Rₐ₃Rₐ₄ represents an arylCi-alkylene group with any substituents according to above with the proviso that when Rₐ₃ is alkylene and R₂ is methoxy, then Rₐ₄ is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl.

In an even further particular embodiment of the invention Rₐ₃ represents an unsubstituted or monosubstituted or disubstituted Ci-alkylene group wherein any substituents each individually and independently are selected from (Ci-C₆)alkyl, (Ci-C₆)alkoxy, (C₂-C₄)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl, carboxyl, carboxy-(Ci-C₄)alkyl, aryI, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br or I), hydroxyl, NRₐₙ(Rc)Rₐₙ(Rc) in which Rₐₙ(Rc) and Rₐₙ(Rc) individually and independently from each other represents hydrogen, (Ci-C₆)alkyl or Rₐₙ(Rc) and Rₐₙ(Rc) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine, and Rₐₙ represents aryl, i.e., Rₐₙ Rₐₙ represents an arylCi-alkylene group with any substituents according to above with the proviso that when Rₐ₃ is alkylene and R₂ is methoxy, then Rₐ₄ is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl.

In an even further alternative particular embodiment of the invention Rₐ₃ represents a direct bond.

In one embodiment of the invention R₁₉₃ represents hydrogen or methyl.

In an alternative embodiment of the invention R₁₉ represents hydrogen.

In another embodiment of the invention R₁₉ represents methyl.

In a particular embodiment of the invention Rₐ₃ Rₐ₄ represents a benzyl group (Rₐ₃ being methylene and Rₐ₄ being phenyl), or a benzyl group which is substituted according to what is described in connection to substitution of the aryl group, with the proviso that R₂ is not methoxy.
In a most particular embodiment of the invention \( R^c R^d \) represents an aryl-1,1(C\(_3\)-C\(_6\))cycloalkylene group which is substituted according to what is described in connection to substitution of the aryl group (\( R^c \) being a direct bond and \( R^d \) an aryl-substituted 1,1(C\(_3\)-C\(_6\))cycloalkylene group).

In an alternative most particular embodiment of the invention \( R^c R^d \) represents a phenyl-1,1-cyclopropylene group which is substituted according to what is described in connection to substitution of the aryl group (\( R^c \) being a direct bond and \( R^d \) a phenyl-substituted 1,1-cyclopropylene group).

In one embodiment of the invention \( X \) represents a single bond.

In another embodiment of the invention \( X \) represents imino (-NH-) or methylene (-CH\(_2\)-). In yet another embodiment \( X \) represents imino (-NH-) . In a further embodiment \( X \) represents methylene (-CH\(_2\)-).

Suitable values for the \( B \) ring/ring system include, for example, diazepanylene, piperazinylene, piperidinylene, pyrrolidinylene and azetidinylene, wherein anyone of them may be presents in any of their isomeric forms (e.g. piperazin-tetrahydropyridazin-tetrahydropyrimidin).

Embodiments for the \( B \) ring/ring system include, for example, diazepanylene, piperazinylene, piperidinylene, pyrrolidinylene and azetidinylene. Further embodiments include these groups which are substituted with \( R^i_4 \) having a (Ci-Ce)alkyl group, wherein the (Ci-C\(_6\))alkyl group optionally is substituted with OH, COOH or COOR\(^c\) group(s), e.g. a 2-carboxyethyl group, and wherein \( R^c \) represents H, aryl, cycloalkyl, heterocyclyl or (C\(_1\)-C\(_2\))alkyl optionally substituted by one or more of halogen (F, Cl, Br or I) or mixed halogen atoms, OH, aryl, cycloalkyl and heterocyclyl.

In an alternative to the embodiment for the \( B \) ring/ring system above, the embodiment include, for example, diazepanylene, piperazinylene, piperidinylene, pyrrolidinylene or azetidinylene groups which are substituted with \( R^i_4 \) having a (Ci-
alkyl group, wherein the (Ci-C₆)alkyl group optionally is substituted with OH, COOH or COOR e group(s), e.g. a 2-carboxyethyl group, and wherein R e represents H, aryl, cycloalkyl, heterocyclyl or (Ci-Ce)alkyl optionally substituted by one or more of halogen (F, Cl, Br or I) or mixed halogen atoms, OH, aryl, cycloalkyl and heterocyclyl.

It is also contemplated that in one embodiment, the B-ring/ring system is represented by piperidinylene.

It is also further contemplated that in one embodiment, the B-ring/ring system is represented by 4-piperidin- 1-ylene.

A 2nd embodiment of formula I is defined by;

R i represents R₂C(O);

R₂ represents CN, halogen (F, Cl, Br or I), (C₄-Ce)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, (C₃-Ce)cycloalkyl, heterocyclyl; furthermore R₂ represents (C₂-C₃)alkyl interrupted by oxygen; furthermore R₂ represents (Ci-C3)alkyl substituted by one or more of OH, aryl, aryl(Ci-C3)alkyloxy, (C₃-Ce)cycloalkyl and heterocyclyl, with the proviso that any such OH group must be at least 2 carbon atoms away from any oxygen; further R₂ represents unsubstituted (Ci-Ce)alkoxy, (C₃-Ce)cycloalkyl, hydroxy(Ci-C₆)alkyl, (C₄-C₆)alkylC(O), (C₄-C₆)alkylthioC(O), (C₃-C₆)alkylC(S), (Ci-C₆)alkoxyC(O), (C₃-C₆)cycloalkoxy, aryl, aryIC(O), aryl(Ci-C₆)alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(Ci-C₆)alkylC(O), (C₁-C₆)alkylsulfonyl, (Ci-C₆)alkylsulfonyl, unsubstituted (Ci-Ce)alkylthio, (C₃-C₆)cycloalkylthio, arylsulfanyl, arylsulfonyl, arythio, aryl(d-C₆)alkylthio, aryl(Ci-Ce)alkylsulfonyl, aryl(Ci-C₆)alkylsulfonyl, heterocyclyl(Ci-C₆)alkylthio, heterocyclyl(Ci-C₆)alkylsulfanyl, heterocyclyl(Ci-C₆)alkylsulfonyl, (C₃-C₆)cycloalkyl(Ci-C₆)alkylthio, (C₃-C₆)cycloalkyl(Ci-C₆)alkylsulfonyl; with the proviso that when R₂ is methoxy and R e is alkylene, then Rd is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl;
R₇ represents (Ci-C₃)alkyl optionally interrupted by oxygen, and/or optionally substituted by OH, aryl, (C₃-Ce)cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br or I) atoms; further R₇ represents (C₃-Ce)cycloalkyl, hydroxy(Ci- Ce)alkyl, aryl or heterocyclyl;

Rᵢ₄ represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (Ci-Ce)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and COORᵢ; wherein Rᵢ represents aryl, (C₃-Ce)cycloalkyl, heterocyclyl or (d-C e)alkyl optionally substituted by one or more of halogen (F, Cl, Br or I) atom(s), OH, aryl, (C₃-Ce)cycloalkyl and heterocyclyl; further Rᵢ₄ represents aryl, aryl(Ci-C₆)alkyl, aryl(Ci- C₆)alkoxy, heterocyclyl, a halogen (F, Cl, Br or I) atom, (C₃-C₆)cycloalkyl, (C₃- C₆)Cycloalkyl(Ci-C₆)alkoxy, hydroxy(Ci-Ce)alkyl, (Ci-Ce)alkoxy, (C₃-C₆)cycloalkoxy, (Ci-C₆)alkylsulfmyl, (Ci-C₆)alkylsulfonyl, (Ci-C₆)alkylthio, (C₃-C₆)cycloalkylthio, or a group of formula NRₐ(14)Rₐ(14) in which Rₐ(14) and Rₐ(14) independently represent H, (Ci-C₆)alkyl, (Ci-C₆)alkylC(O), (Ci-C₆)alkoxyC(O) or Rₐ(14) and Rₐ(14) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

Rᵢ is a direct bond or represents an unsubstituted or monosubstituted or polysubstituted (Ci-C₄)alkylene or 1,1-(C₃-C₆)cycloalkylene group, wherein any substituents each individually and independently are selected from (Ci-C₄)alkyl, (Ci- C₄)alkoxy, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₃-Ce)cycloalkyl, carboxyl, carboxy-(Ci- C₄)alkyl, aryl, heterocyclyl, cyano, halogeno (F, Cl, Br or I), hydroxy, NRₐ(Re)Rₐ(Re) in which Rₐ(Re) and Rₐ(Re) individually and independently from each other represent hydrogen, (Ci-C₄)alkyl or Rₐ(Re) and Rₐ(Re) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; further Rᵢ represents imino (-NH-), N- substituted imino (-NR₁⁹-), (Ci-C₄)alkyleneimino or N-substituted (Ci-C₄)alkyleneimino (-N(Rᵢ₉)-((Ci-C₄)alkylene) wherein the mentioned alkylene groups are unsubstituted or monosubstituted or polysubstituted with any substituents according to above; with the proviso that when Rᵢ is alkylene and R₂ is methoxy, then R₃ is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl;
preferably R^c represents a direct bond or imino or (C_i-C_j)alkyleneimino or an 
unsubstituted or monosubstituted or polysubstituted (C_i-C_j)alkylene group with any 
substituents according to above; with the proviso that when R^c is alkylene and R_2 is 
methoxy, then R^d is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-
chlorophenyl;

R^d represents (C_i-C_j)alkyl, (C_3-C_6)cycloalkyl, aryl or heterocyclyl, and anyone of 
these groups optionally substituted with one or more halogen (F, Cl, Br or I) atoms or 
mixed halogen atoms and/or one or more of the following groups, OH, CN, (C_i-C_j)alkyl, 
(C_i-C_j)alkoxyC(O), (C_i-C_j)alkoxy, halogen substituted (C_i-C_j)alkyl, (C_3-C_6)cycloalkyl, 
aryl, heterocyclyl, (d-C_6)alkylsulfmyl, (d-C_6)alkylsulfonyl, (d-C_6)alkylthio, (C_5-C_6)
cycloalkylthio, arylsulfmyl, arylsulfonyl, arylthio, aryl(C_i-C_j)alkylthio, aryl(C_i-
C_6)alkylsulfinyl, aryl(C_i-C_6)alkylsulfonyl, heterocyclyl(C_i-C_j)alkylthio, heterocyclyl(C_i-
C_j)alkylsulfmyl, heterocyclyl(C_i-C_j)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_i-C_j)alkylthio, (C_5-
C_6)cycloalkyl(C_i-C_j)alkylsulfinyl, (C_3-C_6)cycloalkyl(C_i-C_j)alkylsulfonyl or a group of 
formula N R^a R^b in which R^a and R^b independently represent H, (C_1-C_6)alkyl, 
(C_i-C_j)alkylC(O) or R^c R^d and R^e together with the nitrogen atom represent piperidine, 
pyrroline, azetidine or aziridine with the proviso that when R^d is one of phenyl, 4-
fluorophenyl or 4-chlorophenyl and R^c is alkylene, then R_2 is not methoxy;

X represents a single bond, imino (-NH-), methylene (-CH_2-), iminomethylene 
(-CH_2-NH-) wherein the carbon is connected to the B-ring/ring system, methyleneimino 
(-NH-CH_2-) wherein the nitrogen is connected to the B-ring/ring system and any carbon 
and/or nitrogen in these groups may optionally be substituted with (C_i-C_j) alkyl; further X 
may represent a group (-CH_2-)n wherein n= 2-6, which optionally is unsaturated and/or 
substituted by one or more substituent chosen among halogen, hydroxyl or (C_i-C_j)alkyl;

B is a monocyclic or bicyclic, 4 to 11-membered heterocyclic ring/ring system 
comprising one or more nitrogen and optionally one or more atoms selected from oxygen 
or sulphur, which nitrogen is connected to the pyridine-ring (according to formula I) and
further the B-ring/ring system is connected to X in another of its positions; the substituent R$_{i4}$ is connected to the B ring/ring system in such a way that no quarternary ammonium compounds are formed (by this connection).

An alternative 2nd embodiment of formula I is defined by;

R$_i$ represents RyC(O);

R$_2$ represents unsubstituted (C$_3$-C$_4$)alkylthio or unsubstituted hydroxy(Ci-C$_3$)alkyl;

R$_7$ represents (C$_3$-C$_4$)alkyl optionally interrupted by oxygen, and/or optionally substituted by OH, aryl, (C$_3$-C$_6$)cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br or I) atoms; further R$_7$ represents (C$_3$-C$_6$)cycloalkyl, hydroxy(Ci-C$_6$)alkyl, aryl or heterocyclyl;

R$_{i4}$ represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (Ci-C$_6$)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and COOR$^e$; wherein R$^e$ represents aryl, (C$_3$-C$_6$)cycloalkyl, heterocyclyl or (Ci-C$_6$)alkyl optionally substituted by one or more of halogen (F, Cl, Br or I) atom(s), OH, aryl, (C$_3$-C$_6$)cycloalkyl and heterocyclyl; further R$_{i4}$ represents aryl, aryl(Ci-C$_6$)alkyl, aryl(Ci-C$_3$)alkoxy, heterocyclyl, a halogen (F, Cl, Br or I) atom, (C$_3$-C$_6$)cycloalkyl, (C$_3$-C$_6$)cycloalkyl(Ci-C$_6$)alkoxy, (Ci-C$_6$)alkylsulfanyl, (Ci-C$_6$)alkylsulfonyl, (Ci-C$_6$)alkylthio, (C$_3$-C$_6$)cycloalkylthio, or a group of formula NR$^a(14)$R$^b(14)$ in which R$^a(14)$ and R$^b(14)$ independently represent H, (C$_1$-C$_6$)alkyl, (Ci-C$_6$)alkylC(O), (Ci-C$_6$)alkoxyC(O) or R$^a(14)$ and R$^b(14)$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R$^e$ is a direct bond or represents an unsubstituted or monosubstituted or polysubstituted (Ci-C$_4$)alkylene or 1,1-[(C$_3$-C$_6$)cycloalkylene group, wherein any substituents each individually and independently are selected from (Ci-C$_4$)alkyl, (Ci-C$_4$)alkoxyl, (C$_2$-C$_4$)alkenyl, (C$_2$-C$_4$)alkynyl, (C$_3$-C$_6$)cycloalkyl, carboxyl, carboxy-(Ci-
C₄ alkyl, aryl, heterocyclyl, cyano, halogeno (F, Cl, Br or I), hydroxyl, NRₐ[Rc]Rₚ[Rc] in which Rₐ and Rₚ individually and independently from each other represents hydrogen, (Ci-C₄)alkyl or Rₐ[Rc] and Rₚ[Rc] together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; further Rₚ represents imino (-NH-), N-substituted imino (-NRₐ), (Ci-C₄)alkyleneimino or N-substituted (Ci-C₄)alkyleneimino (-N(Ri)-((Ci-C₄)alkylene) wherein the mentioned alkylene groups are unsubstituted or monosubstituted or polysubstituted with any substituents according to above; preferably Rₚ represents a direct bond or imino or (Ci-C₄)alkyleneimino or an unsubstituted or monosubstituted or polysubstituted (Ci-C₄)alkylene group with any substituents according to above;

Rᵢ₀ represents H or (Ci-C₄)alkyl;

Rᵈ represents (Ci-C₆)alkyl, (Ci-C₆)cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms and/or one or more of the following groups, OH, CN, (Ci-C₆)alkyl, (Ci-C₆)alkoxyC(O), (Ci-C₆)alkoxy, halogen substituted (Ci-C₆)alkyl, (Ci-C₆)cycloalkyl, aryl, heterocyclyl, (Ci-C₆)alkylsulfanyl, (Ci-C₆)alkylsulfonyl, (Ci-C₆)alkylthio, (Ci-C₆)cycloalkylthio, arylsulfanyl, arylsulfonyl, arylthio, aryl(Ci-C₆)alkylthio, aryl(Ci-C₆)alkylsulfanyl, aryl(Ci-C₆)alkylsulfonyl, heterocyclyl(Ci-C₆)alkylthio, heterocyclyl(Ci-C₆)alkylsulfanyl, heterocyclyl(d-C₆)alkylsulfonyl, (Ci-C₆)cycloalkyl(Ci-C₆)alkylthio, (Ci-C₆)cycloalkyl(Ci-C₆)alkylsulfanyl, (Ci-C₆)cycloalkyl(Ci-C₆)alkylsulfonyl or a group of formula NRᵃ[Rd]Rᵇ[Rd] in which Rᵃ[Rd] and Rᵇ[Rd] independently represent H, (Ci-C₆)alkyl, (Ci-C₆)alkylC(O) or Rᵃ[Rd] and Rᵇ[Rd] together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

X represents a single bond, imino (-NH-), methylene (-CH₂-), iminomethylene (-CH₂-NH-) wherein the carbon is connected to the B-ring/ring system, methyleneimino (-NH-CH₂-) wherein the nitrogen is connected to the B-ring/ring system and any carbon and/or nitrogen in these groups may optionally be substituted with (Ci-C₆) alkyl; further X may represent a group (-CH₂-)ₙ wherein n = 2-6, which optionally is unsaturated and/or substituted by one or more substituent chosen among halogen, hydroxyl or (Ci-Ce)alkyl;
B is a monocyclic or bicyclic, 4 to 11-membered heterocyclic ring/ring system comprising one or more nitrogen and optionally one or more atoms selected from oxygen or sulphur, which nitrogen is connected to the pyridine-ring (according to formula I) and further the B-ring/ring system is connected to X in another of its positions; the substituent $R_{i_4}$ is connected to the B ring/ring system in such a way that no quaternary ammonium compounds are formed (by this connection).

A 3rd embodiment of formula I is defined by;

$R_i$ represents $R_7\text{C(O)}$;

$R_2$ represents CN, $(C_4\text{-Ce})\text{alkyl}$ optionally interrupted by oxygen and/or optionally substituted by OH; furthermore $R_2$ represents $(C_2\text{-C3})\text{alkyl}$ interrupted by oxygen; furthermore $R_2$ represents $(C_i\text{-C}_3)\text{alkyl}$ substituted by one or more of OH, with the proviso that any such OH group must be at least 2 carbon atoms away from any oxygen; further $R_2$ represents unsubstituted $(C_i\text{-Ce})\text{alkoxy}$, $(C_3\text{-Ce})\text{cycloalkyl}$, hydroxy$(C_i\text{-Ce})\text{alkyl}$, $(C_1\text{-Ce})\text{alkoxyC(O)}$, $(C_3\text{-C}_6)\text{cycloalkoxy}$, aryl, heterocyclyl, $(C_i\text{-C}_6)\text{alkylsulfonyl}$, $(C_1\text{-C}_6)\text{alkylsulfonyl}$, unsubstituted $(C_i\text{-C}_6)\text{alkylthio}$, $(C_3\text{-C}_6)\text{cycloalkylthio}$, arylsulfanyl, arylsulfonyl, arylthio, aryl$(C_i\text{-C}_6)\text{alkylthio}$, aryl$(C_i\text{-C}_6)\text{alkylsulfonyl}$, aryl$(C_i\text{-C}_6)\text{alkylsulfonyl}$, heterocyclc$(C_i\text{-Ce})\text{alkylthio}$, heterocyclyl$(C_i\text{-C}_6)\text{alkylsulfonyl}$, heterocyclyl$(C_i\text{-Ce})\text{alkylsulfonyl}$, $(C_3\text{-C}_6)\text{cycloalkyl}(C_i\text{-Ce})\text{alkylthio}$, $(C_3\text{-C}_6)\text{cycloalkyl}(C_i\text{-C}_6)\text{alkylsulfonyl}$; with the proviso that when $R_2$ is methoxy and $R$ is alkylene, then $R_d$ is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl;

$R_7$ represents $(C_i\text{-C}_3)\text{alkyl}$ optionally interrupted by oxygen, and/or optionally substituted by OH, aryl, $(C_3\text{-Ce})\text{cycloalkyl}$, heterocyclyl or one or more halogen (F, Cl, Br or I) atoms; further $R_7$ represents $(C_3\text{-Ce})\text{cycloalkyl}$, hydroxy$(C_i\text{-Ce})\text{alkyl}$, aryl or heterocyclyl;
$R_{i_4}$ represents $H$, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (Ci-Ce)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and COOR $^e$; wherein $R^e$ represents (Ci-Ce)alkyl optionally substituted by one or more of halogen (F, Cl, Br or I) atom(s), OH, aryl, cycloalkyl and heterocycle; further $R_{i_4}$ represents a halogen (F, Cl, Br or I) atom, (C3-Ce)cycloalkyl, (Ci-Ce)alkoxy, (C3-C6)alkylalkoxy, (Ci-Ce)alkylthio, (C3-Ce)cycloalkylthio, or a group of formula $N_R^{a(i_4)} R^{b(i_4)}$ in which $R^{a(i_4)}$ and $R^{b(i_4)}$ independently represent $H$, (C1-C6)alkyl, (C1-C6)alkylC(O), (F, Cl, Br or I) atom, hydroxyl, (F, Cl, Br or I) hydroxy, (F, Cl, Br or I) alkoxy, halogen (F, Cl, Br or I), hydroxyl, NR$^{a(R^e)}$R$^{b(R^e)}$ in which $R^{a(R^e)}$ and $R^{b(R^e)}$ individually and independently from each other represent hydrogen, (Ci-C4)alkyl or R$^{a(R^e)}$ and R$^{b(R^e)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; further $R^e$ represents imino (-NH-), N-substituted imino (-NR19-), (Ci-C4)alkyleneimino or N-substituted (Ci-C4)alkyleneimino (-N(Ri9)-) or alkylene group wherein the mentioned alkylene groups are unsubstituted or monosubstituted or polysubstituted with any substituents according to above; with the proviso that when $R^e$ is alkylene and $R_2$ is methoxy, then $R^d$ is not chosen from the group consisting of phenyl, 4-fluorophenyl and A-chlorophenyl; preferably $R^e$ represents a direct bond or imino or (Ci-C4)alkyleneimino or an unsubstituted or monosubstituted or polysubstituted (Ci-C4)alkylene group with any substituents according to above; with the proviso that when $R^e$ is alkylene and $R_2$ is methoxy, then $R^d$ is not chosen from the group consisting of phenyl, 4-fluorophenyl and A-chlorophenyl; $R_{i_4}$ represents $H$ or (Ci-C4)alkyl;
$R_d$ represents (Ci-C$_6$)alkyl, (C$_3$-C$_6$)cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms and/or one or more of the following groups, OH, CN, (Ci-C$_6$)alkyl, (Ci-C$_6$)alkoxyC(O), (Ci-C$_6$)alkoxy, halogen substituted (Ci-C$_6$)alkyl, (C$_3$-C$_6$)cycloalkyl, aryl, heterocyclyl, (d-C$_6$)alkylsulfinyl, (d-C$_6$)alkylsulfonyl, (d-C$_6$)alkylthio, (C$_3$-Ce)cycloalkylthio, arylsulfanyl, arylsulfonyl, arylthio, aryl(Ci-C6)alkylthio, aryl(Ci-C6)alkylsulfinyl, aryl(Ci-C6)alkylsulfonyl, heterocyclyl(Ci-C6)alkylthio, heterocyclyl(Ci-C$_6$)alkylsulfinyl, heterocyclyl(Ci-C$_6$)alkylsulfonyl, (C$_3$-C$_6$)cycloalkyl(Ci-C$_6$)alkylthio, (C$_3$-C$_6$)cycloalkyl(Ci-C$_6$)alkylsulfinyl, (C$_3$-C$_6$)cycloalkyl(Ci-C$_6$)alkylsulfonyl or a group of formula $R^a_{b(Rd)} R^b_{d(Rd)}$ in which $R^a_{(Rd)}$ and $R^b_{(Rd)}$ independently represent H, (C$_1$-C$_6$)alkyl, (Ci-C$_e$)alkylC(O) or $R^a_{(Rd)}$ and $R^b_{(Rd)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; with the proviso that when $R_d$ is one of phenyl, 4-fluorophenyl or 4-chlorophenyl and $R^c$ is alkylene, then $R_2$ is not methoxy;

$X$ represents a single bond, imino (-NH-), methylene (-CH$_2$-), iminomethylene (-CH$_2$-NH-) wherein the carbon is connected to the B-ring/ring system, methyleneimino (-NH-CH$_2$-) wherein the nitrogen is connected to the B-ring/ring system and any carbon and/or nitrogen in these groups may optionally be substituted with (Ci-C$_6$) alkyl; further $X$ may represent a group (-CH$_2$-)$_n$ wherein $n = 2-6$, which optionally is unsaturated and/or substituted by one or more substituent chosen among halogen, hydroxyl or (Ci-C$_e$)alkyl;

$B$ is a monocyclic or bicyclic, 4 to 11-membered heterocyclic ring/ring system comprising one or more nitrogen and optionally one or more atoms selected from oxygen or sulphur, which nitrogen is connected to the pyridine-ring (according to formula I) and further the B-ring/ring system is connected to $X$ in another of its positions; the substituent $R_{i_4}$ is connected to the B ring/ring system in such a way that no quarternary ammonium compounds are formed (by this connection).

An alternative 3rd embodiment of formula I is defined by;

$R_i$ represents $R_7$C(O);
R_2 is selected from the group consisting of methylthio, ethylthio, n-propylthio, isopropylthio, hydroxymethyl and hydroxyethyl;

R_7 represents (C_1-C_4)alkyl optionally interrupted by oxygen, and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br or I) atoms; further R_7 represents (C_3-C_6)cycloalkyl, hydroxy(Ci-C_6)alkyl, aryl or heterocyclyl;

R_i4 represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (Ci-Ce)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and COOR; wherein R^e represents (Ci-Ce)alkyl optionally substituted by one or more of halogen (F, Cl, Br or I) atom(s), OH, aryl, (C_3-C_6)cycloalkyl and heterocyclyl; further R_i4 represents a halogen (F, Cl, Br or I) atom, (C_3-C_6)cycloalkyl, (Ci-Ce)alkoxy, (C_1-C_6)alkoxy, (Ci-Ce)cycloalkoxy, (Ci-Ce)alkylthio, (C_3-C_6)cycloalkylthio, or a group of formula NR^a(14)R^b(14) in which R^a(14) and R^b(14) independently represent H, (Ci-C_6)alkyl, (C_1-C_6)alkylC(O), (Ci-C_6)alkoxyC(O) or R^a(14) and R^b(14) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R^e is a direct bond or represents an unsubstituted or monosubstituted or polysubstituted (Ci-C_4)alkylene or group, wherein any substituents each individually and independently are selected from (Ci-C_4)alkyl, (Ci-C_4)alkoxy, (C_3-C_6)cycloalkyl, halogen (F, Cl, Br or I), hydroxyl, NR^a(Re)R^b(Re) in which R^a(Re) and R^b(Re) individually and independently from each other represent hydrogen, (Ci-C_4)alkyl or R^a(Re) and R^b(Re) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; further R^e represents imino (-NH-), N-substituted imino (-NR_i9-), (Ci-C_4)alkyleneimino or N-substituted (Ci-C_4)alkyleneimino (-N(Ri9)(-(Ci-C_4)alkylene)) wherein the mentioned alkylene groups are unsubstituted or monosubstituted or polysubstituted with any substituents according to above; preferably R^e represents a direct bond or imino or (Ci-C_4)alkyleneimino or an unsubstituted or monosubstituted or polysubstituted (Ci-C_4)alkylene group with any substituents according to above;
R_{i,j} represents H or \((d-C_4)alkyl;\)

R^{d} represents \((Ci-Ce)alkyl, (C_3-Ce)cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms and/or one or more of the following groups, OH, CN, \((Ci-Ce)alkyl,\)

\((Ci-C_6)alkoxyC(O), (Ci-C_6)alkoxy, halogen substituted \((d-C_6)alkyl, (C_3-C_6)cycloalkyl,\)

aryl, heterocyclyl, \((Ci-C_6)alkylsulfmyl, (Ci-C_6)alkylsulfonyl, (Ci-C_6)alkylthio, (C_3-Ce)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(Ci-C_6)alkylthio, aryl(Ci-C_6)alkylsulfmyl, aryl(d-C_6)alkylsulfonyl, heterocyclyl(Ci-C_6)alkylthio, heterocyclyl(CrC_6)alkylsulfmyl, heterocyclyl(Ci-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(Ci-C_6)alkylthio, (C_3-C_6)cycloalkyl(Ci-C_6)alkylsulfmyl, (C_3-C_6)cycloalkyl(Ci-C_6)alkylsulfonyl or a group of formula \(NR^{a(Rd)}R^{b(Rd)}\) in which \(R^{a(Rd)}\) and \(R^{b(Rd)}\) independently represent H, \((C_1-C_6)alkyl,\)

\((C_1-C_6)alkylC(O)\) or \(R^{a(Rd)}\) and \(R^{b(Rd)}\) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

X represents a single bond, imino (-NH-), methylene (-CH_2-), iminomethylene (-CH_2-NH-) wherein the carbon is connected to the B-ring/ring system, methyleneimino (-NH-CH_2-) wherein the nitrogen is connected to the B-ring/ring system and any carbon and/or nitrogen in these groups may optionally be substituted with \((Ci-C_6)alkyl;\) further X may represent a group (-CH_2-)n wherein n = 2-6, which optionally is unsaturated and/or substituted by one or more substituent chosen among halogen, hydroxyl or \((Ci-Ce)alkyl;\)

B is a monocyclic or bicyclic, 4 to 11-membered heterocyclic ring/ring system comprising one or more nitrogen and optionally one or more atoms selected from oxygen or sulphur, which nitrogen is connected to the pyridine-ring (according to formula I) and further the B-ring/ring system is connected to X in another of its positions; the substituent \(R_{i,j}\) is connected to the B ring/ring system in such a way that no quaternary ammonium compounds are formed (by this connection);

A 4th embodiment of formula I is defined by;

\(R^i\) represents \(R^iC(O);\)
R₂ represents CN, (C₄⁻Ce)alkyl optionally interrupted by oxygen and/or optionally substituted by OH; furthermore R₂ represents (C₂⁻C₃)alkyl interrupted by oxygen; furthermore R₂ represents (C₄⁻C₃)alkyl substituted by one or more of OH, with the proviso that any such OH group must be at least 2 carbon atoms away from any oxygen; further R₂ represents unsubstituted (C₁⁻Ce)alkoxy, (C₃⁻Ce)cycloalkyl, hydroxy(Ci-Ce)alkyl, (C₁⁻Ce)alkoxyC(O), (Cs-C₆)cycloalkoxy, aryl, heterocyclyl, unsubstituted (Ci-Ce)alkylthio, (C₃⁻C₆)cycloalkylthio, arylthio, aryl(Ci-C₆)alkylthio, heterocyclyl(Ci-C₆)alkylthio, (C₃⁻C₆)cycloalkyl(Ci-C₆)alkylthio; with the proviso that when R₂ is methoxy and R₃ is alkylenone, then R₄ is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl;

R₇ represents (C₃⁻Ce)alkyl optionally interrupted by oxygen, and/or optionally substituted by OH, aryl, (C₃⁻Ce)cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br or I) atoms; further R₇ represents (C₃⁻Ce)cycloalkyl;

Rᵣ represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (Ci-Ce)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH and COOH; further Rᵣ represents a halogen (F, Cl, Br or I) atom, (Ci-Ce)alkoxy, (C₃⁻Ce)cycloalkoxy, (Ci-C₆)alkylthio, (C₃⁻C₆)cycloalkylthio, or a group of formula NRᵣ(Rc) in which Rᵣ(14) and R₆(14) independently represent H or (Ci-C₆)alkyl;

Rᵣ is a direct bond or represents imino, N-substituted imino (-NR1₉-), (C₁⁻C₄)alkyleneimino or an unsubstituted or monosubstituted or polysubstituted (C₁⁻C₄)alkylene group with any substituents selected from (Ci-C₄)alkyl, (Ci-C₄)alkoxy, (C₃⁻C₆)cycloalkyl, halogen (F, Cl, Br or I), hydroxyl, NRᵣ(Rc) in which Rᵣ(Rc) and R₆(Rc) individually and independently from each other represents hydrogen, (Ci-C₄)alkyl or Rᵣ(Rc) and R₆(Rc) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine, with the proviso that when Rᵣ is alkylene and R₂ is methoxy, then R₄ is not chosen from the group consisting of phenyl, 4-fluorophenyl and 4-chlorophenyl;
R₁₀ represents H or (d-C₄)alkyl;

Rᵈ represents (Ci-Cᵉ)alkyl, (C₃-Cᵉ)cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms and/or one or more of the following groups, OH, CN, (Ci-Cᵉ)alkyl, (Ci-C₀)alkoxyC(O), (Ci-C₀)alkoxy, halogen substituted (d-C₆)alkyl, (C₃-C₀)cycloalkyl, aryl, heterocyclyl, (Ci-C₀)alkylsulfmyl, (Ci-C₀)alkylsulfonyl, (Ci-C₀)alkylthio, (C₃-Cᵉ)cycloalkylthio, arylsulfanyl, arylsulfonyl, arylthio, aryl(Ci-C₀)alkylthio, aryl(Ci-C₀)alkylsulfanyl, aryl(d-C₆)alkylsulfonyl, heterocyclyl(Ci-C₀)alkylthio, heterocyclyl(Cr C₀)alkylsulfmyl, heterocyclyl(Ci-C₀)alkylsulfonyl, (C₃-C₀)cycloalkyl(Ci-C₀)alkylthio, (C₃-C₀)cycloalkyl(Ci-C₀)alkylsulfanyl, (Cᵢ-Cᵦ)alkylC(O) or Rᵃ(Rᵈ) and Rᵇ(Rᵈ) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; with the proviso that when Rᵈ is one of phenyl, A-fluorophenyl or 4-chlorophenyl and Rᶜ is alkylene, then R₂ is not methoxy;

X represents a single bond, imino (-NH-) or methylene (-CH₂-);

B is a monocyclic or bicyclic, 4 to 11-membered heterocyclic ring/ring system comprising one or more nitrogen and optionally one or more atoms selected from oxygen or sulphur, which nitrogen is connected to the pyridine-ring (according to formula I) and further the B-ring/ring system is connected to X in another of its positions; the substituent R₁₄ is connected to the B ring/ring system in such a way that no quaternary ammonium compounds are formed (by this connection).

An alternative 4th embodiment of formula I is defined by;

Rᵢ represents Rᵢ₇C(O);

R₂ is selected from the group consisting of methylthio, ethylthio, n-propylthio and hydroxymethyl;
R₇ represents (Ci-C₃)alkyl optionally interrupted by oxygen, and/or optionally substituted by OH, aryl, (C₃-Ce)cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br or I) atoms; further R₇ represents (C₃-C₆)cycloalkyl;

Rᵢ₄ represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (Ci-Ce)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH and COOH; further Rᵢ₄ represents a halogen (F, Cl, Br or I) atom, (Ci-Ce)alkoxy, (C₃-Ce)cycloalkoxy, (Ci-C₆)alkylthio, (C₃-C₆)cycloalkylthio, or a group of formula NRᵢ(14)Rᵢ(14)Rᵢ(14) in which Rᵢ(14) and Rᵢ(14) independently represent H or (Ci-C₆)alkyl;

Rᵣ is a direct bond or represents imino, N-substituted imino (-NRᵣ), (Ci-C₄)alkyleneimino or an unsubstituted or monosubstituted or polysubstituted (Ci-C₄)alkylene group with any substituents selected from (Ci-C₄)alkyl, (Ci-C₄)alkoxy, (C₃-C₆)cycloalkyl, halogen (F, Cl, Br or I), hydroxyl, NRᵣ(Re)Rᵣ(Re) in which Re(Re) and Rᵣ(Re) individually and independently from each other represent hydrogen, (Ci-C₄)alkyl or Rᵣ(Re) and Rᵣ(Re) together with the nitrogen atom represent piperidine, pyrroline, azetidine or aziridine;

Rᵣ represents H or (Ci-C₄)alkyl;

Rᵣ represents (Ci-Ce)alkyl, (C₃-Ce)cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms and/or one or more of the following groups, OH, CN, (Ci-Ce)alkyl, (Ci-C₆)alkoxyC(O), (Ci-C₆)alkoxy, halogen substituted (Cᵣ-C₆)alkyl, (C₃-C₆)cycloalkyl, aryl, heterocyclyl, (Ci-C₆)alkylsulfinyl, (Ci-C₆)alkylsulfonyl, (Ci-C₆)alkylthio, (C₃-Ce)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(Ci-C₆)alkylthio, aryl(Ci-C₆)alkylsulfinyl, aryl(Ci-C₆)alkylsulfonyl, heterocyclyl(Ci-C₆)alkylthio, heterocyclyl(Ci-C₆)alkylsulfinyl, heterocyclyl(d-C₆)alkylsulfonyl, (C₃-C₆)cycloalkyl(Ci-C₆)alkylthio, (C₃-C₆)cycloalkyl(Ci-C₆)alkylsulfinyl or a group of formula NRᵣ(Re)Rᵣ(Re) in which Rᵣ(Re) and Rᵣ(Re) independently represent H, (Cᵣ-C₆)alkyl,
(C_1-C_6)alkylC(O) or R^a(Rd) and R^b(Rd) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

X represents a single bond, imino (-NH-) or methylene (-CH_2-); and

B is a monocyclic or bicyclic, 4 to 11-membered heterocyclic ring/ring system comprising one or more nitrogen and optionally one or more atoms selected from oxygen or sulphur, which nitrogen is connected to the pyridine-ring (according to formula I) and further the B-ring/ring system is connected to X in another of its positions; the substituent R_{14} is connected to the B ring/ring system in such a way that no quarternary ammonium compounds are formed (by this connection).

A 5th embodiment of formula I is defined by that;

R_i is n-propylcarbonyl;
R_2 is chosen from the group consisting of methoxy, methylthio, ethylthio, n-propylthio, isopropylthio, cyclopropylthio, isobutylthio and hydroxymethyl;
R_7 is n-propyl (as R_i is R_7(CO));
R_{i4} is hydrogen;
R_c is chosen from the group consisting of a single bond, methylene (-CH_2-), imino (-NH-) and methylimino (-N(CH_3)-);
R_i9 is hydrogen or methyl;
R_d is chosen from the group consisting of phenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-chloro-4-fluorophenyl, 4-methoxy-phenyl, 4-methyl-phenyl, phenyl-1,1-cyclopropylene and (trans)-phenyl-1,2-cyclopropylene;
X is a single bond; and
B is 4-piperidin-1-ylene, and the substituent R_{i4} is connected to the B ring/ring system, in such a way that no quarternary ammonium compound is formed (by this connection).

An alternative 5th embodiment of formula I is defined by that;
R_i is n-propylcarbonyl;
R₂ is chosen from the group consisting of methylthio, ethylthio, n-propylthio and hydroxymethyl;
R₇ is n-propyl (as R₁ is R₇(CO));
R₁₄ is hydrogen;
R₉ is chosen from the group consisting of a single bond, methylene (-CH₂-), imino (-NH-) and methylimino (-N(CH₃)-);
R₁₉ is hydrogen or methyl;
R₉ is chosen from the group consisting of phenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-chloro-4-fluorophenyl, 4-methoxy-phenyl, 4-methyl-phenyl, phenyl-1,1-cyclopropylene and (trans)-phenyl-1,2-cyclopropylene;
X is a single bond; and
B is 4-piperidin-l-ylen, and the substituent R₁₄ is connected to the B ring/ring system, in such a way that no quarternary ammonium compound is formed (by this connection).

In a 6th embodiment of formula (I), formula (I) is defined as being any compound(s) of formula (Ia)-(Ii):

(Ia)

(Ib)
In the above Ia to li the various values of R are as defined above and include any of the previously mentioned embodiments.

In an alternative 6th embodiment of formula (I), formula (I) is defined as being any compound(s) of formula (Ia):

In a 7th embodiment formula (I) is defined as being a compound of formula (Iaa);
In the above Iaa the various values of R (except R_{14} being H) are as defined above and include any of the previously mentioned embodiments.

Examples of specific compounds according to the invention, (embodiments of Formula I) may be selected among:

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide,

1-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(4-fluorophenyl)amino]sulfonyl)amine)piperidine-4-carboxamide,

1-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(4-fluorophenyl)(methyl)amino]sulfonyl)piperidine-4-carboxamide,

1-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(4-methoxybenzyl)sulfonyl]piperidine-4-carboxamide,

1-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(4-methylbenzyl)sulfonyl]piperidine-4-carboxamide,

1-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(2,4-difluorobenzyl)sulfonyl]piperidine-4-carboxamide,

1-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(2-fluorobenzyl)sulfonyl]piperidine-4-carboxamide,

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(2-fluorobenzyl)sulfonyl]piperidine-4-carboxamide,
1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-
{[methyl(phenyl)amino]sulfonyl}piperidine-4-carboxamide,
1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(4-
methoxybenzyl)sulfonyl]piperidine-4-carboxamide,
1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(4-
fluorobenzyl)sulfonyl]piperidine-4-carboxamide,
1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(2,4-
difluorobenzyl)sulfonyl]piperidine-4-carboxamide,
1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(4-
methylbenzyl)sulfonyl]piperidine-4-carboxamide,
N-(benzylsulfonyl)- 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-
carboxamide,
1-[5-butyryl-3-cyano-6-(hydroxymethyl)pyridin-2-yl]-N-[(1-
phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide,
1-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(1-
phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide,
1-[5-butyryl-3-cyano-6-(ethylthio)pyridin-2-yl]-N-[(1-
phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide,
1-[5-butanoyl-3-cyano-6-(propylthio)pyridin-2-yl]-N-[(1-
phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide,
1-(5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl)-N-((trans)-2-
phenylcyclopropylsulfonyl)piperidine-4-carboxamide,
1-(5-butyryl-3-cyano-6-(isobutylthio)pyridin-2-yl)-N-(1-
phenylcyclopropylsulfonyl)piperidine-4-carboxamide,
1-(5-butyryl-3-cyano-6-(isopropylthio)pyridin-2-yl)-N-(1-
phenylcyclopropylsulfonyl)piperidine-4-carboxamide and
1-(5-butyryl-3-cyano-6-(cyclopropylthio)pyridin-2-yl)-N-(1-
phenylcyclopropylsulfonyl)piperidine-4-carboxamide;
and pharmaceutically acceptable salts thereof.
Alternative examples of specific compounds according to the invention, (embodiments of Formula I) may be selected among;

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide,

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[2-fluorobenzyl)sulfonyl]piperidine-4-carboxamide,

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(methyl(phenyl)amino)sulfonyl]piperidine-4-carboxamide,

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(4-methoxybenzyl)sulfonyl]piperidine-4-carboxamide,

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(4-fluorobenzyl)sulfonyl]piperidine-4-carboxamide,

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(2,4-difluorobenzyl)sulfonyl]piperidine-4-carboxamide,

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(4-methylbenzyl)sulfonyl]piperidine-4-carboxamide,

N-(benzylsulfonyl)- 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxamide,

1-[5-butyryl-3-cyano-6-(hydroxymethyl)pyridin-2-yl]-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide,

1-[5-butyryl-3-cyano-6-(ethylthio)pyridin-2-yl]-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide, and

1-[5-butanoyl-3-cyano-6-(propylthio)pyridin-2-yl]-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide;

and pharmaceutically acceptable salts thereof.

In another alternative example the specific compound according to the invention, (embodiments of Formula I) is;

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide;

or a pharmaceutically acceptable salt thereof.
In a further alternative example the specific compound according to the invention, (embodiments of Formula I) is:

\[ 1-[5-\text{butanoyl}-3-\text{cyano}-6-(\text{propylthio})-\text{pyridin-2-yl}]-N-[(1-\text{phenylcyclopropyl})-\text{sulfonyl}]\text{piperidine-4-carboxamide}; \]

or a pharmaceutically acceptable salt thereof.

As a further option, examples of specific compounds according to the invention, (embodiments of Formula I) may be selected as one or more among:

\[ 1-(5-\text{butyryl}-3-\text{cyano}-6-(\text{methylthio})-\text{pyridin-2-yl})-N-(\text{(trans)-2-phenylcyclopropylsulfonyl})\text{piperidine-4-carboxamide} \]

\[ 1-(5-\text{butyryl}-3-\text{cyano}-6-(\text{isopropylthio})-\text{pyridin-2-yl})-N-(1-\text{phenylcyclopropylsulfonyl})\text{piperidine-4-carboxamide}; \]

and pharmaceutically acceptable salts thereof.

Processes

The following processes together with the intermediates are provided as a further feature of the present invention.

Compounds of formula (I) may be prepared by the following processes \textit{al-a9};

\textit{al}) Compounds of formula (I) in which \( R_1, R_2, B, R_i, R^c \) and \( R^d \) are defined as in formula (I) above, \( X \) is a single bond or \((-\text{CH}_2^-)\), can be formed by reacting a compound of formula (II), in which \( R_1, R_2, B \) and \( R_i \) are defined
as in formula (I) above, X is a single bond or a carbon, with a compound of formula (III) in which Rc and Rd are defined as in formula (I) above.

\[
\begin{align*}
\text{H}_2\text{NSO}_2^- \cdot \text{R}^c \cdot \text{R}^d & \quad (\text{III}) \\
\end{align*}
\]

The reaction is generally carried out in an inert organic solvent such as dichloromethane at ambient temperature. The reaction may be carried out using standard conditions or in the presence of TBTU, EDCI, PyBroP, PyBOP or the combination of EDCI and HOBr. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine or DIPEA.

**al)** Compounds of formula (I) in which \(R_1, R_2, B, \text{Ri}_4, \text{R}^c\) and \(\text{R}^d\) are defined as in formula (I) above, X is (-NH\(_2\)), (-CH\(_2\)-NH\(-\)) or a single bond connected to a nitrogen which is a member of the B ring, can be formed by reacting a compound of formula (IV), in which \(R_1, R_2, B\) and \(\text{Ri}_4\) are defined as in formula (I) above and X is (-NH\(_2\)), (-CH\(_2\)-NH\(_2\)) or a hydrogen that is connected to a nitrogen which is a member of the B-ring, with a compound of the general

\[
\begin{align*}
\end{align*}
\]
The reaction is generally carried out in an inert solvent such as DCM. The reaction may be carried out in the presence of CDI. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine, DBU or DIPEA.

\[ \text{O= C= N—SCl— R:R} \quad (\text{V}) \]

in which \( R^c \) and \( R^d \) are defined as in formula (I) above.

The reaction is generally carried out in an inert solvent such as THF. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine or DIPEA.

\[ \text{R}^d\text{R}^c\text{-SO}_2\text{NH-COOCH}_2\text{CCI}_3 \quad (\text{VI}) \]

in which \( R^c \) and \( R^d \) are defined as in formula (I) above. The reaction is generally carried out in an inert solvent such as DMA. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine or DIPEA.

\[ \text{a5) Compounds of formula (I) may also be prepared by reacting a compound of formula (VII) in which R\text{I} and R_2 are defined as in formula (I) above and L is a suitable leaving group, such as chloro, bromo, iodo, fluoro, benzotriazolylloxy(OBt), triflate (OTf) mesylate (OMs) or tosylate (OTS),} \]
with a compound of the general formula (VIII) in which B, X, R₄, Rᶜ and Rᵈ are defined as in formula (I) above.

The reaction is generally carried out in an inert solvent such as DMA. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine or DIPEA.

The reaction is generally carried out at elevated temperatures using standard equipment or in a single-node microwave oven.

For some compounds, it is advantageous to carry out the reaction in ethanol in the presence of an organic base such as triethylamine.

(a6) A compound of formula (I) in which R₁, R₂, B, R¹₄, and Rᵈ are defined as in formula (I) above and Rᶜ represents imino (-NH-) or (Cⁱ-C₄)alkylimino in which the imino group can be substituted using standard conditions or using an alkylating agent like L-R¹₉, in which R¹₉ is defined as in formula (I) above and L is a leaving group exemplified by chloro, bromo, iodo, triflate(OTf) or tosylate(OTs), to give compounds of formula (I) in which R₁, R₂, B, R¹₄, and Rᵈ are defined as in formula (I) above and Rᶜ
represents N-substituted imino (-NR₁⁻) or N-substituted (Ci-C₄)alkylimino (-N(R₁⁻H (C₁⁻C₄)alkyl), optionally in the presence of a strong base such as NaH.

\( a7 \) Compounds of formula (I) in which R₁, B, R₁₄, X, Rₑ and Rᵈ are as defined in formula (I) above, R₂ is an unsubstituted (Ci-C₂)alkoxy group defined as in formula (I) above may be prepared by reacting a compound of formula (IX)

![Chemical Structure](attachment:image.png)

(IX)

in which R₁, B, R₁₄, X, Rₑ and Rᵈ are as defined in formula (I) above with a compound of formula (X)

\[ L-R₂' \] (X)

in which R₂' is an (Ci-C₂)alkyl defined as in formula (I) above (corresponding to an R₂(Ci-C₂)alkoxy) and L is a leaving group such as chloro, bromo, iodo, triflate (OTf) or tosylate (OTs).

The reaction may be carried out in an inert organic solvent such as DCM, DMF, DMA, THF or CH₃CN. The reaction may be carried out using standard conditions or in the presence of a suitable base such as sodium hydride, DIPEA or silver carbonate or potassium carbonate. Preferentially silver carbonate is used.

The reaction may be carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.

\( a8 \) Compounds of formula (I) in which R₁, B, R₁₄, X, Rₑ and Rᵈ are as defined in formula (I) above, R₂ is an unsubstituted (Ci-C₂)alkoxy group or an unsubstituted (C₁⁻C₂)alkylthio group defined as in formula (I) above can be prepared by reacting a compound of formula (XI)
in which R₁, B, R₁₄, X, R₅ and R₆ are as defined in formula (I) above and L is a suitable leaving group such as Cl, Br, I or benzotriazolyloxy (OBt), triflate (OTf) with an unsubstituted (Ci-Ci₂)alcohol and (Ci-Ci₂)alkylthiol respectively.

The reaction may be performed using standard conditions in the presence of a palladium catalyst such as Pd(PPh₃)₄ or by using Pd(OAc)₂, Pd(OOCF₃)₂ or Pd₂(dba)₃ in combination with suitable phosphine ligands such as P(³Bu)₃, (binaphtyl)P(³Bu)₂, PPh₃ or XANTPHOS. The reaction may be carried out in an inert solvent such as DCM, DMA, DMF, THF, dioxane or toluene. Optionally in the presence of an organic or inorganic base such as CsF, Cs₂CO₃, sodium- or potassium tert-butoxide, K₃PO₄ or DIPEA.

The reaction may be carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.


The reaction may alternatively be performed without the use of a palladium catalyst in an inert organic solvent such as DCM, THF in the presence of a suitable base such as DIPEA or by using the corresponding sodium salt of the alcohol and thiol (i.e. (Ci-Ci₂)alkylO⁻Na⁺ and (Ci-Ci₂)alkylS⁻Na⁺) respectively.

The reaction may be carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.

₉Compounds of formula (I) in which R₁, B, R₁₄, X, R₅ and R₆ are as defined in formula (I) above and R₂ is a cyano group can be prepared by reacting a compound of formula (XI) defined as above and L is a suitable leaving group such as Cl, Br, I or benzotriazolyloxy (OBt), triflate (OTf) with a suitable cyanide source such as potassium cyanide, sodium cyanide, K₄[Fe(CN)₆] or zink cyanide.
The reaction may be performed using standard conditions in the presence of a palladium catalyst such as Pd(PPh\textsubscript{3})\textsubscript{4} or by using Pd(OMe\textsubscript{2})\textsubscript{2}, Pd(OCCFs)\textsubscript{2} or Pd\textsubscript{2}(dba)\textsubscript{3} in combination with suitable phosphine ligands such as P(\textsuperscript{t}Bu)\textsubscript{3}, (binaphthyl)P(\textsuperscript{t}Bu)\textsubscript{2}, PPh\textsubscript{3}, dppe, dppf or XANTPHOS. Optionally the reaction is also performed in the presence of Zink dust.

The reaction may be carried out in an inert solvent such as DCM, DMA, DMF, THF, dioxane or toluene.

The reaction is carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.


The intermediates referred to above may be prepared by, for example, the methods/processes outlined below.

\textbf{bl) The compounds of formula (II) in which R\textsubscript{i}, R\textsubscript{2}, B, and R\textsubscript{i4} are defined as in formula (I) above, X is a single bond or a carbon, may be prepared by reacting a compound of formula (VII) defined above and L is a suitable leaving group (such as fluoro, chloro, bromo, iodo, triflate (OTf), benzotriazolyloxy (OBt), mesylate (OMs) or tosylate (OTs)), with a compound of the general formula (XIII),}

![Diagram](XIII.png)

in which B and R\textsubscript{i4} are defined as in formula (I) above and X is a single bond or a carbon.

The reaction is generally carried out at elevated temperatures using standard equipment or in a single-node microwave oven. The reaction can be carried out in an inert solvent such as ethanol, DMA or a mixture of solvents such as ethanol-water. Optionally the reaction may be carried out in the presence of an organic base such as TEA or DIPEA.
b2) The compounds of formula (II) in which R_i, R_2, B and R_i_4 are defined as in formula (I) above, X is a single bond or a carbon, may be prepared by reacting a compound of formula (VII) defined above except that L is a hydroxy group with a compound of the general formula (XIII) in which B and R_i_4 are defined as in formula (I) above.

The reaction is generally carried out in an inert organic solvent such as DCM or THF at ambient temperature. The reaction is carried out in the presence of a suitable coupling reagent such as for example PyBrop or PyBOP preferentially in the presence of an organic base such as TEA or DIPEA.

Synthesis of compounds of the general formula (II), in which R_i, R_2, R_7, B and R_i_4 are defined as in formula (I) above, X is a single bond or a carbon atom also comprises the following steps (b3-b4):

b3) Reacting a compound of the general formula (XIV) with N,O-dimethylhydroxylamine.

\[
\text{(XIV)}
\]

The reaction can be performed using known reagents like CDI, EDCI or the combination of EDCI and HOBt to give a compound of the general formula (XV).

\[
\text{(XV)}
\]
b4) Reacting compounds of the general formula (XV), defined as above, with a reagent of
the general formula Rγ-MgX', in which Rγ is defined as in formula (I) above and X' is a
halogen, or a reagent of the formula Rγ-M, in which M is a metal exemplified by Zn and
Li.

Synthesis of compounds of the general formula (II), in which R1, R2, Rγ, B and R14 are
defined as in formula (I) above, X is a single bond or (CH2-) also comprises the
following steps (b5-b6):

b5) Reacting compounds of general formula (XVI)

![Diagram](image)

wherein R2, B and R14 is as defined in formula (I) above, X is a single bond or (CH2-)
and LG is a leaving group such as Cl or F with a reagent of general formula Rγ-MgX', in which Rγ is defined as in formula (I) above and X' is a halogen.

The reaction is carried out using standard conditions in an inert solvent such as THF
catalyzed by ferric acetylacetonate or other suitable ferric salts such as for example FeCl3.

The reaction may be performed at ambient temperature or preferentially at lower
temperatures for example in the range of -78 0C and 0 0C.


The reaction may alternatively be performed by using an organocopper- or
organocuprate reagent (such as for example RγCu, (Rγ)2CuLi or (Rγ)2CuMgX').

The reaction is carried out using standard conditions in an inert solvent such as DCM
or THF.

The reaction may be performed at ambient temperature or preferentially at lower
temperature for example in the range of -78 0C and 0 0C.
b6) Compounds of general formula (XVI) above can be prepared by reacting a compound of general formula (XIV) defined as above using standard conditions or with a chlorinating reagent such as oxalyl chloride, thionyl chloride or POCl₃ (e.g. when LG is Cl). Advantageously dimethylformamide may be used as catalyst. The reaction can also be performed using standard conditions with cyanuric fluoride preferentially in the presence of pyridine (e.g. when LG is F). The reaction may be performed in an inert solvent such as DCM or toluene. The reaction is carried out at ambient temperature or at elevated temperatures.

Synthesis of compounds of the general formula (II), in which Rᵢ is R₇C(O) and R₇ is a group containing a CH₂ group next to the carbonyl in Rᵢ (i.e. R₇ in this case is referred to below as Rr-CH₂) and R₂, R₇, B and R₁₄ are defined as in formula (I) above, X is a single bond or a carbon atom also comprises the following steps (b7-b8):

b7) By double decarboxylation of a compound of general formula (XVII)

![Chemical structure](XVII)

The reaction is generally carried at elevated temperature using standard equipment. Preferentially the reaction is carried out under acidic conditions in an inert solvent such as MeCN or THF.

b8) Compounds of the formula (XVII) above can be prepared by reaction of a compound of formula (XVI) with a compound of formula (XVIII)
The reaction is carried out in an inert solvent such as THF at ambient temperature in the presence of a suitable base such as sodium pentoxide or NaH. (For similar chemistry see, Asish D et al, J. Chem. Soc. Perkin Trans. I, 1989, pp 603-607 and Rathke, M et al, J. Org. Chem. 1985, pp 2622-24).

c1) Compounds of formula (IV) which are defined as above may be prepared by reacting the corresponding compound of formula (VII) which is defined above, with a compound of formula (XIX) in which B and R\textsubscript{14} are defined as in formula (I) above, X is a nitrogen, (-CH\textsubscript{2}-NH\textsubscript{2}) or a single bond connected to a nitrogen which is a member of the B ring.

The reaction is generally carried out at elevated temperatures using standard equipment or in a single-node microwave oven. The reaction can be carried out in an inert solvent such as ethanol, DMA or a mixture of solvents such as ethanol-water. Optionally the reaction may be carried out in the presence of an organic base such as TEA or DIPEA.

c2) Compounds of formula (IV) which are defined as above may be prepared by reacting the corresponding compound of formula (VII) which is defined above except that L is a hydroxy group, with a compound of formula (XIX) in which B and R\textsubscript{14} are defined as in formula (I) above, X is (-NH\textsubscript{2}), (-CH\textsubscript{2}-NH\textsubscript{2}) or a single bond connected to a nitrogen which is a member of the B ring.
The reaction is generally carried out in an inert organic solvent such as DCM or THF at ambient temperature. The reaction is carried out in the presence of a suitable coupling reagent such as for example PyBrop or PyBOP preferentially in the presence of an organic base such as TEA or DIPEA.

Synthesis of compounds of the general formula (IV), in which R₁, R₂, R₇, B, R₁₄ are defined as in formula (I) above, X is (-NH₂), (-CH₂-NH₂) or a single bond connected to a nitrogen which is a member of the B ring, comprises the following steps (c3-c4).

**c3)** Reacting a compound of the general formula (XX)

![Diagram of XX formula](image)

with N,O-dimethylhydroxylamine. The reaction can be performed using known reagents like CDI, EDCI or the combination of EDCI and HOBt to give a compound of the general formula (XXI).

![Diagram of XXI formula](image)

**c4)** A compound of the general formula (XXI), which is defined as above can be reacted with a reagent of the general formula R₇-MgX, in which R₇ is defined as in formula (I) above and X is a halogen, or a reagent of the formula R₇-M, in which M is a metal exemplified by Zn and Li, to give a compound of the general formula (IV).
Synthesis of compounds of the general formula (IV), in which \( R_1, R_2, R_7, B \) and \( R_{14} \) are defined as in formula (I) above, \( X \) is a nitrogen, (-CH\(_2\)-NH\(_2\)) or a single bond connected to a nitrogen which is a member of the B ring, also comprises the following steps (c5-c6).

5) Reacting compounds of general formula (XXII)

![Diagram of molecule XXII]

wherein \( R_2, B \) and \( R_{14} \) are as defined in formula (I) above, \( X \) is (-NH\(_2\)), (-CH\(_2\)-NH\(_2\)) or a single bond connected to a nitrogen which is a member of the B ring and LG is a leaving group such as Cl or F with a reagent of general formula \( R_7\)-MgX', in which \( R_7 \) is defined as in formula (I) above, and \( X' \) is a halogen.

The reaction is carried out using standard conditions in an inert solvent such as THF catalyzed by ferric acetylacetonate or other suitable ferric salts such as FeCl\(_3\).

The reaction may be performed at ambient temperature or preferentially at lower temperatures for example in the range of -78 °C and 0 °C.


The reaction may alternatively be performed by using an organocupper- or organocuprate reagent (such as for example \( R_7\)Cu, \( (R_7)\)\(_2\)CuLi or \( (R_7)\)\(_2\)CuMgX').

The reaction is carried out using standard conditions in an inert solvent such as DCM or THF.

The reaction may be performed at ambient temperature or preferentially at lower temperature for example in the range of -78 °C and 0 °C.


[X.X..]
c6) Compounds of general formula (XXII) above can be prepared by reacting a compound of general formula (XX) defined as above using standard reactions e.g. with a chlorinating reagent such as oxalyl chloride, thionyl chloride or POCI₃ (e.g. when LG is Cl). Advantageously dimethylformamide may be used as catalyst. The reaction can also be performed using standard conditions with cyanuric fluoride preferentially in the presence of pyridine (e.g. when LG is F).

The reaction may be performed in an inert solvent such as DCM or toluene. The reaction is carried out at ambient temperature or at elevated temperatures.

Synthesis of compounds of the general formula (IV), in which Ri is RyC(O) and R₇ is a group containing a CH₂ group next to the cabonyl in Ri (i.e. R₇ in this case is referred to below as Ry-CH₂) and R₂, B and R₁₄ are defined as in formula (I) above, X is (-NH₂), (-CH₂-NH₂) or a single bond connected to a nitrogen which is a member of the B ring, also comprises the following steps (c7-c8).

c7) By double decarboxylation of a compound of general formula (XXIII)

![Diagram](image)

The reaction is generally carried at elevated temperature using standard equipment. Preferentially the reaction is carried out under acidic conditions in an inert solvent such as MeCN or THF.

c8) Compounds of the formula (XXIII) above can be prepared by reaction of a compound of formula (XXII) with a compound of formula (XVIII)
The reaction is carried out in an inert solvent such as THF at ambient temperature in the presence of a suitable base such as sodium pentoxide or NaH.


dl) Compounds of the general formula (VII) which are defined as above can be formed by reacting a compound of formula (XXIV) using standard methods e.g. with a chlorinating reagent such as oxalyl chloride, thionyl chloride or POCl₃. Advantageously dimethylformamide may be used. The reaction may be performed in an inert solvent such as DCM. Advantageously the inert solvent is toluene.

The reaction may also be carried out with PyBOP or methyl sulfonyl chloride in the presence of a base, such as DIPEA, in an inert solvent such as DCM.

Compounds of the general formula (VIII) can be formed in one of the processes (el-e4). The compounds of formula (VIII) are advantageously isolated as a zwitterion. A ring nitrogen of compounds of formula (XIII) and (XIX) used in the below steps may be protected by a protective group such as t-butyloxycarbonyl.

el) Compounds of the general formula (VIII) in which B, R₁, R₄, R⁵ and R₆ are defined as in formula (I) above, X is a single bond or ( -CH₂-), may be formed by reacting a compound of formula (XIII) with a compound of formula (III). The reaction is
generally carried out in an inert organic solvent such as dichloromethane at ambient
temperature. The reaction may be carried out using standard conditions or in the presence
of EDCI, PyBroP or PyBOP or the combination of EDCI and HOBT. Optionally, the
reaction may be carried out in the presence of an organic base such as triethylamine or
DIPEA.

e2) Compounds of the general formula (VIII) in which B, R_{i4}, R_{c} and R_{d} are defined
as in formula (I) above, X is (-NH-), (-CH\textsubscript{2}-NH-) or a single bond connected to a nitrogen
which is a member of the B ring, can be formed by reacting a compound of formula (XIX
) defined as above with a compound of formula (V), defined as above. The reaction is
generally carried out in an inert solvent such as THF. The reaction may also be carried out
in the presence of an organic base such as triethylamine or DIPEA.

e3) Compounds of the general formula (VIII) in which B, R_{i4}, R_{c} and R_{d} defined as
in formula (I) above, X is (-NH-), (-CH\textsubscript{2}-NH-) or a single bond connected to a nitrogen
which is a member of the B ring, can also be formed by reacting a compound of formula (XIX
) with a compound of formula (VI) which is defined as above. The reaction is
generally carried out in a solvent such as DMA. This reaction may also be carried out in
the presence of an organic base such as triethylamine or DIPEA.

e4) A compound of formula (VIII) which is protected with t-butoxy carbonyl may
be transformed into a compound without the protective group using standard procedures or
a reagent such as HCl, FA or TFA.

f) Compounds of the general formula (IX) wherein R_{i1}, R_{i4}, B, X, R_{c} and R_{d} are
defined as in formula (I) may be prepared by the following steps \( f\) )-\( f\) 2 below:

\( f\) ) Reacting a compound of general formula (XXV)
Compounds of the general formula (XXV) above may be prepared by reacting a compound of the general formula (XXVI)

where B, R_i, X, R_c and R_d are as defined in formula (I) above with a compound of formula (XXVII)

The reaction is generally carried out in an inert organic solvent such as EtOH or DMSO.

The reaction is carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.

Compounds of the general formula (XXVII) defined above can be prepared by reacting a compound of the general formula (VIII) as defined above with a compound of formula (XXVIII)
using essentially the same procedure as described in [Macconi, A et. AL, J. Heterocyclic chemistry, 26, p. 1859 (1989)].

\[
\text{HN}0\text{Et (XXVIII)}
\]

\textit{f4}) Compounds of general formula (IX) above wherein \( R_1, B, R_{i4}, R^c \) and \( R^d \) are defined as in formula (I) and \( X \) is a single bond or (-CH\(_2\)-) may be prepared by reacting a compound of formula (XXIX)

\[
\text{NH}
\]

with a compound of formula (III) defined as above.

The reaction is generally carried out in an inert organic solvent such as dichloromethane at ambient temperature. The reaction may be carried out using standard conditions or in the presence of TBTU, EDCI, PyBrop or PyBOP or the combination of EDCI and HOBt. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine or DIPEA.

\textit{f5}) Compounds of general formula (XXIX) above can be made by reacting a compound of general formula (XXX)

wherein \( R_{i4} \) and \( B \) are defined as above and \( X \) is a single bond or (-CH\(_2\)-), according to any of the methods described in procedures \textit{b3}) to \textit{b8}) above.
f6) Compounds of general formula (XXX) may be prepared by reacting a compound of general formula (XXXI)

\[
\text{(XXXI)}
\]

wherin \(R_{i_4}\) and \(B\) are defined as in formula (I) and \(X\) is a single bond or (-CH\(_2\)-) with a compound of formula (XXVII) defined as above.

The reaction is generally carried out in an inert organic solvent such as EtOH or DMSO.

The reaction is carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.

P) Compounds of the general formula (XXXI) defined above can be prepared by reacting a compound of the general formula (XIII) as defined above with a compound of formula (XXVIII) using essentially the same procedure as described in [Macconi, A et. AL, J. Heterocyclic chemistry, 26, p. 1859 (1989)].

J8) Compounds of general formula (IX) above wherein \(R_1, B, R_{i_4}, R_c\) and \(R^d\) are defined as in formula (I) and \(X\) is a nitrogen, (-CH\(_2\)-NH-) or a single bond connected to a nitrogen which is a member of the B ring may be prepared by reacting a compound of formula (XXXII)

\[
\text{(XXXII)}
\]

with a compound of formula (III) defined as above.
The reaction is generally carried out in an inert solvent such as DCM. The reaction may be carried out in the presence of CDI. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine, DBU or DIPEA.

$^9f$ Compounds of general formula (IX) above wherein $R_1$, $R_i$, $R^c$ and $R^d$ are defined as in formula (I) and $X$ is (-NH-), (-CH$_2$-NH-) or a single bond connected to a nitrogen which is a member of the B ring may be prepared by reacting a compound of formula (XXXII) with a compound of general formula (V) as defined above.

The reaction is generally carried out in an inert solvent such as THF. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine or DIPEA.

$^{10f}$ Compounds of general formula (IX) above wherein $R_1$, $B$, $R_i$, $R^c$ and $R^d$ are defined as in formula (I) and $X$ is (-NH-), (-CH$_2$-NH-) or a single bond connected to a nitrogen which is a member of the B ring may be prepared by reacting a compound of formula (XXXII) with a compound of general formula (VI) as defined above.

The reaction is generally carried out in an inert solvent such as DMA. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine or DIPEA.

$^{11f}$ Compound of the general Formula (XXXII) above may be prepared by reacting a compound of general Formula (XXXIII)

\[
\text{(XXXIII)},
\]

wherein $R_i$ and $B$ are defined as above and $X$ is (-NH$_2$), (-CH$_2$-NH$_2$) or a single bond connected to a nitrogen which is a member of the B-ring, according to any of the methods described in procedures $^c3$) to $^c8$) above.
Compounds of general formula (XXXIII) above may be prepared by essentially the same procedure described in steps/6) above from a compound of formula (XIX) defined as above.

Compounds of general formula (II), wherein Ri, B, Ri₄, are defined as in formula (I) and R₂ is an unsubstituted (Ci-Ci₂)alkoxy group and X is a single bond or a carbon atom may be prepared by reacting a compound of formula (XXIX) as defined above, with a compound of formula (X)

\[ \text{L-R}_2' \quad (X) \]

in which R₂' is an unsubstituted (Ci-Ci₂)alkyl defined as in formula (I) above and L is a leaving group such as chloro, bromo, iodo, triflate (OTf) or tosylate (OTs).

The reaction may be carried out in an inert organic solvent such as DCM, DMF, DMA, THF or CH₃CN. The reaction may be carried out using standard conditions or in the presence of a suitable base such as sodium hydride, DIPEA or silver carbonate or potassium carbonate. Preferentially silver carbonate is used.

The reaction may be carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.

Compounds of formula (II) in which Ri, B, Ri₄ are as defined in formula (I) above and X is a single bond or a carbon atom, R₂ is an unsubstituted (Ci-Ci₂)alkoxy group or an unsubstituted (Ci-Ci₂)alkylthio group defined as in formula (I) above can be prepared by reacting a compound of formula (XXXIV)

\[ \text{XXXIV} \]

in which Ri, B, Ri₄ and X are as defined in formula (II) above and L is a suitable leaving group such as CI, Br, I benzotrazolyloxy (OBt) or triflate (OTf) with the
corresponding unsubstituted (Ci-Ci₂)alcohol and unsubstituted (Ci-Ci₂)alkylthiol respectively.

The reaction may be performed using standard conditions in the presence of a palladium catalyst such as Pd(PPh₃)₄ or by using Pd(OAc)₂, Pd(OOCCF₃)₂ or Pd₂(dba)₃ in combination with suitable phosphine ligands such as P(³Bu)₃, (binaphtyl)P(³Bu)₂, PPh₃ or XANTPHOS. The reaction may be carried out in an inert solvent such as DCM, DMA, DMF, THF, dioxane or toluene. Optionally in the presence of an organic or inorganic base such as CsF, Cs₂CO₃, sodium- or potassium tert-butoxide, K₄PO₄ or DIPEA.

The reaction may be carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.


The reaction may alternatively be performed without the use of a palladium catalyst in an inert organic solvent such as DCM, THF in the presence of a suitable base such as DIPEA or by using the corresponding sodium salt of the alcohol and thiol (i.e. (Cᵢ₋Ci₂)alkylO’Na⁺ and (Ci-Ci₂)alkylS’Na⁺) respectively.

The reaction may be carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.

g3) Compounds of formula (II) in which R₁, B, Rᵢ₄ are as defined in formula (I) above and X is a single bond or a carbon atom and Rₓ₋ is cyano group defined as in formula (I) above can be prepared by reacting a compound of formula (XXXIV) defined as above with a suitable cyanide source such as potassium cyanide, sodium cyanide, K₄[Fe(CN)₆] or zink cyanide.

The reaction may be performed using standard conditions in the presence of a palladium catalyst such as Pd(PPh₃)₄ or by using Pd(OAc)₂, Pd(OOCCF₃)₂ or Pd₂(dba)₃ in combination with suitable phosphine ligands such as P(³Bu)₃, (binaphtyl)P(³Bu)₂, PPh₃, dppf, dpppe or XANTPHOS. Optionally the reaction is also performed in the presence of Zink dust.

The reaction may be carried out in an inert solvent such as DCM, DMA, DMF, THF, dioxane or toluene.
The reaction is carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.


\textit{g4) Compounds of general formula (XXXIV) as defined above may be prepared by reacting a compound of formula (XXIX) with a halogenating reagent, such as thionylchloride, POCI$_3$ or oxalyl chloride. Optionally the reaction is performed in the presence of DMF.}

The reaction may also be carried out in an inert solvent, such as DCM, using PyBOP or trifluoromethanesulfonic anhydride, optionally in the presence of an organic base such as TEA or DIPEA at or below r.t.

\textit{g5) Compounds of general formula (IV), wherein Ri, B, R$_{14}$ are defined as in formula (I) R$_2$ is an unsubstituted (Ci-Ci2)alcoxy group and X is (-NH$_2$), (-CH$_2$-NH$_2$) or a single bond connected to a nitrogen atom which is a member of the B ring may be prepared by reacting a compound of formula (XXXII) as defined above, with a compound of formula (X)}

\[ L-R'_2 \quad (X) \]

in which R$_2'$ is an unsubstituted (Ci-Ci$_2$)alkyl defined as in formula (I) above and L is a leaving group such as chloro, bromo, iodo, triflate (OTf) or tosylate (OTs).

The reaction may be carried out in an inert organic solvent such as DCM, DMF, DMA, THF or CH$_3$CN. The reaction may be carried out using standard conditions or in the presence of a suitable base such as sodium hydride, DIPEA or silver carbonate or potassium carbonate. Preferentially silvercarbonate is used.

The reaction may be carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.

\textit{g6) Compounds of formula (IV) in which Ri, B and R$_{14}$ are as defined in formula (I) above and X is (-NH$_2$), (-CH$_2$-NH$_2$) or a single bond connected to a nitrogen atom}
which is a member of the B ring. \( R_2 \) is an unsubstituted (Ci-Ci\(_2\))alkoxy group or an unsubstituted (Ci-Ci2)alkylthio group defined as in formula (I) above can be prepared by reacting a compound of formula (XXXV)

\[
\begin{align*}
\text{H} & \quad \text{R}_1 \\
\text{L} & \quad \text{N} & \quad \text{B} \\
\text{R}_2 & \quad \text{N} & \quad \text{X} \quad (\text{XXXV})
\end{align*}
\]

in which \( \text{R}_1, \text{B} \) and \( \text{R}_{14} \) are as defined in formula (I), \( \text{X} \) is \((-\text{NH}_2), (-\text{CH}_2\text{-NH}_2)\) or a single bond connected to a nitrogen atom which is a member of the B ring and \( \text{L} \) is a suitable leaving group such as Cl, Br, I, benzotriazolyloxy (OBt) or triflate (OTf) the corresponding unsubstituted (Ci-Ci\(_2\))alcohol and unsubstituted (Ci-Ci\(_2\))alkylthiol respectively.

The reaction may be performed using standard conditions in the presence of a palladium catalyst such as \( \text{Pd}(\text{PPh}_3)_3 \) or by using \( \text{Pd}(\text{OA})c_2, \text{Pd}(\text{OCCF}_3)_2 \) or \( \text{Pd}_2(\text{dba})_3 \) in combination with suitable phosphine ligands such as \( \text{P}(\text{tBu})_3, (\text{binaphthyl})\text{P}(\text{tBu})_2, \text{PPh}_3 \) or XANTPHOS. The reaction may be carried out in an inert solvent such as DCM, DMA, DMF, THF, dioxane or toluene. Optionally in the presence of an organic or inorganic base such as CsF, Cs\(_2\)CO\(_3\), sodium- or potassium tert-butoxide, K\(_3\)PO\(_4\) or DIPEA.

The reaction may be carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.


The reaction may alternatively be performed without the use of a palladium catalyst in an inert organic solvent such as DCM, THF in the presence of a suitable base such as DIPEA or by using the corresponding sodium salt of the alcohol and thiol (i.e. (C\(_1\)-Ci\(_2\))alkyLO\(\text{Na}^+\) and (Ci-Ci\(_2\))alkylS\(\text{Na}^+\) respectively.

The reaction may be carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.
g7) Compounds of formula (IV) in which R₁, B, R₁₄ are as defined in formula (I) above and X is (-NH₂), (-CH₂-NH₂) or a single bond connected to a nitrogen atom which is a member of the B ring and R₂ is cyano group defined as in formula (I) above can be prepared by reacting a compound of formula (XXXV) defined as above with a suitable cyanide source such as potassium cyanide, sodium cyanide, K₄[Fe(CN)₆] or zink cyanide.

The reaction may be performed using standard conditions in the presence of a palladium catalyst such as Pd(PPh₃)₄ or by using Pd(OAc)₂, Pd(OOCF₃)₂ or Pd₂(dba)₃ in combination with suitable phosphine ligands such as P(⁴Bu)₃, (binaphthyl)P(⁴Bu)₂, PPh₃, dpff, dpppe or XANTPHOS. Optionally the reaction is also performed in the presence of Zink dust.

The reaction may be carried out in an inert solvent such as DCM, DMA, DMF, THF, dioxane or toluene.

The reaction is carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.


g8) Compounds of general formula (XXXV) as defined above may be prepared by reacting a compound of formula (XXXII) with a halogenating reagent, such as thionylchloride, POCl₃ or oxalyl chloride. Optionally the reaction is performed in the presence of DMF.

The reaction may also be carried out in an inert solvent, such as DCM, using PyBOP or trifluoromethanesulfonic anhydride, optionally in the presence of an organic base such as TEA or DIPEA at or below r.t.

h) Compounds of general formula (XI) as defined above may be prepared by reacting a compound of formula (IX) with a halogenating reagent, such as thionylchloride, POCl₃ or oxalyl chloride. Optionally the reaction is performed in the presence of DMF.
The reaction may also be carried out in an inert solvent, such as DCM, using PyBOP or trifluoromethanesulfonic anhydride, optionally in the presence of an organic base such as TEA or DIPEA at or below r.t.

H) The compounds of formula (XIV) in which R₂, B, and Rᵣ₄ are defined as in formula (I) above, X is a single bond or a carbon atom, may be prepared by reacting a compound of formula (XXXVI)

![Chemical Structure](attachment:image.png)

(XXXVI)

wherein R₂ is defined as in formula (I) above and L is a suitable leaving group (such as fluoro, chloro, bromo, iodo, triflate (OTf) mesylate (OMs) or tosylate (OTs)), with a compound of the general formula (XIII) defined as above.

The reaction is generally carried out at elevated temperatures using standard equipment or in a single-node microwave oven. The reaction can be carried out in an inert solvent such as ethanol, DMA or a mixture of solvents such as ethanol-water. Optionally the reaction may be carried out in the presence of an organic base such as TEA or DIPEA.

H) The compounds of formula (XIV) in which R₂, B and Rᵣ₄ are defined as in formula (I) above, X is a single bond or (-CH₂⁻), may be prepared by reacting a compound of formula (XXXVI) defined above except that L is a hydroxy group with a compound of the general formula (XIII) in which B and Rᵣ₄ are defined as in formula (I) above.

The reaction is generally carried out in an inert organic solvent such as DCM or THF at ambient temperature. The reaction is carried out in the presence of a suitable coupling reagent such as for example PyBrop or PyBOP preferentially in the presence of an organic base such as TEA or DIPEA.
13) Compounds of general formula (XIV), wherein B and R_{14} are defined as in formula (I) and R_2 is an unsubstituted (Ci-Ci_2)alkoxy group and X is a single bond or (-CH_2-) may be prepared by reacting a compound of formula (XXX) as defined above, with a compound of formula (X):

\[
L \cdot R_2' \quad (X)
\]

in which R_2' is an unsubstituted (Ci-Ci_2)alkyl defined as in formula (I) above and L is a leaving group such as chloro, bromo, iodo, triflate (OTf) or tosylate (OTs). The reaction may be carried out in an inert organic solvent such as DCM, DMF, DMA, THF or CH3CN. The reaction may be carried out using standard conditions or in the presence of a suitable base such as sodium hydride, DIPEA or silver carbonate or potassium carbonate. Preferentially silver carbonate is used.

The reaction may be carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.

14) Compounds of formula (XIV) in which B and R_{14} are as defined in formula (I) above and X is a single bond or (-CH_2-), R_2 is an unsubstituted (Ci-Ci_2)alkoxy group or an unsubstituted (Ci-Ci_2)alkylthio group defined as in formula (I) above can also be prepared by reacting a compound of formula (XXXVII):

\[
(XXXVII)
\]

in which B, R_{14} and X are as defined as above and L is a suitable leaving group such as Cl, Br, I, benzotriazolyloxy (OBt) or triflate (OTf) with the corresponding unsubstituted (Ci-Ci_2)alcohol and unsubstituted (Ci-Ci_2)alkylthiol respectively.

The reaction may be performed using standard conditions in the presence of a palladium catalyst such as Pd(PPh_3)_4 or by using Pd(OAc)_2, Pd(OOCCF_3)_2 or Pd_2(dba)_3.
in combination with suitable phosphine ligands such as \( P(\text{H}_3) \), \((\text{binaphtyl})P(\text{H}_3)\_2\), \(PPh_3\) or XANTPHOS. The reaction may be carried out in an inert solvent such as DCM, DMA, DMF, THF, dioxane or toluene. Optionally in the presence of an organic or inorganic base such as CsF, Cs_2CO_3, sodium- or potassium tert-butoxide, \( K_2\text{PO}_4\) or DIPEA.

The reaction may be carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.


The reaction may alternatively be performed without the use of a palladium catalyst in an inert organic solvent such as DCM, THF in the presence of a suitable base such as DIPEA or by using the corresponding sodium salt of the alcohol and thiol (i.e. \((\text{C}_1\text{-C}_i)_2\text{alkylO} \cdot \text{Na}^+\) and \((d\text{-C}_i)_2\text{alkylS} \cdot \text{Na}^+\) respectively.

The reaction may be carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.

\[ i5\] Compounds of formula (XIV) in which \( B \) and \( R_i\) are as defined in formula (I) above and \( X \) is a single bond or (-\(\text{CH}_2\)-), \( R_2 \) is a cyano can be prepared by reacting a compound of formula (XXXVII) defined as above with a suitable cyanide source such as potassium cyanide, sodium cyanide, \( K_4[\text{Fe(CN)}_6] \) or zink cyanide.

The reaction may be performed using standard conditions in the presence of a palladium catalyst such as \( \text{Pd}(\text{PPh}_3)\_4 \) or by using \( \text{Pd}(\text{OAc})\_2, \text{Pd}(\text{OCCF}_3)\_2 \) or \( \text{Pd}_2(\text{dba})\_3 \) in combination with suitable phosphine ligands such as \( P(\text{H}_3) \), \((\text{binaphtyl})P(\text{H}_3)\_2\), \(PPh_3\), dppf, dpppe or XANTPHOS. Optionally the reaction is also performed in the presence of Zink dust.

The reaction may be carried out in an inert solvent such as DCM, DMA, DMF, THF, dioxane or toluene.

The reaction is carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.

Compounds of general formula (XXXVII) as defined above may be prepared by reacting a compound of formula (XXX) with a halogenating reagent, such as thionyl chloride, POCI₃ or oxalyl chloride. Optionally the reaction is performed in the presence of DMF.

The reaction may also be carried out in an inert solvent, such as DCM, using PyBOP or trifluoromethanesulfonic anhydride, optionally in the presence of an organic base such as TEA or DIPEA at or below r.t.

Compounds of formula (XX) which are defined as above may be prepared by reacting the corresponding compound of formula (XXXVI) defined as above, with a compound of formula (XIX) defined as above.

The reaction is generally carried out at elevated temperatures using standard equipment or in a single-node microwave oven. The reaction can be carried out in an inert solvent such as ethanol, DMA or a mixture of solvents such as ethanol-water. Optionally the reaction may be carried out in the presence of an organic base such as TEA or DIPEA.

Compounds of formula (XX) which are defined as above may be prepared by reacting the corresponding compound of formula (XXXVI) which is defined above except that L is a hydroxy group, with a compound of formula (XIX) defined as above.

The reaction is generally carried out in an inert organic solvent such as DCM or THF at ambient temperature. The reaction is carried out in the presence of a suitable coupling reagent such as for example PyBrop preferentially in the presence of an organic base such as TEA or DIPEA.

Compounds of general formula (XX) wherein B and R₁₄ are defined as in formula (I), R₂ is an unsubstituted (Ci-Ci₂)alkoxy group and X is (-NH₂), (-CH₂-NH₂) or a single bond connected to a nitrogen atom which is a member of the B ring may be prepared by reacting a compound of formula (XXXIII) as defined above, with a compound of formula (X)

\[ \text{L-Rr (X)} \]
in which $R_2'$ is an unsubstituted (Ci-Ci$_2$)alkyl defined as in formula (I) above and L is a leaving group such as chloro, bromo, iodo, triflate (OTf) or tosylate (OTs).

The reaction may be carried out in an inert organic solvent such as DCM, DMF, DMA, THF or CH3CN. The reaction may be carried out using standard conditions or in the presence of a suitable base such as sodium hydride, DIPEA or silver carbonate or potassium carbonate. Preferentially silver carbonate is used.

The reaction may be carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.

**HO** Compounds of formula (XX) in which B and $R_{14}$ are as defined in formula (I) above and X is (-NH$_2$), (-CH$_2$-NH$_2$) or a single bond connected to a nitrogen atom which is a member of the B ring, $R_2$ is an unsubstituted (Ci-Ci$_2$)alkoxy group or an unsubstituted (Ci-Ci$_2$)alkylthio group defined as in formula (I) above can be prepared by reacting a compound of formula (XXXVIII)

![Diagram](image)

in which B and $R_{14}$ are as defined in formula (I), X is a nitrogen atom, (-CH$_2$-NH$_2$) or a single bond connected to a nitrogen atom which is a member of the B ring above and L is a suitable leaving group such as Cl, Br, I benzotriazolyloxy (OBt) or triflate (OTf) with the corresponding unsubstituted (Ci-Ci$_2$)alcohol and unsubstituted (Ci-Ci$_2$)alkylthiol respectively.

The reaction may be performed using standard conditions in the presence of a palladium catalyst such as Pd(PPh$_3$)$_4$ or by using Pd(OAc)$_2$, Pd(OOCCF$_3$)$_2$ or Pd$_2$(dba)$_3$ in combination with suitable phosphine ligands such as P(3Bu)$_3$, (binaphtyl)P(3Bu)$_2$, PPh$_3$ or XANTPHOS. The reaction may be carried out in an inert solvent such as DCM, DMA, DMF, THF, dioxane or toluene. Optionally in the presence of an organic or inorganic base such as CsF, Cs$_2$CO$_3$, sodium- or potassium tert-butoxide, K$_3$PO$_4$ or DIPEA.
The reaction may be carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.


The reaction may alternatively be performed without the use of a palladium catalyst in an inert organic solvent such as DCM, THF in the presence of a suitable base such as DIPEA or by using the corresponding sodium salt of the alcohol and thiol (i.e. \(\text{C}_1\text{Ci}_2\)alkylO \('\text{Na}^+\) and \((\text{Ci-Ci}_2)\)alkylS \('\text{Na}^+\) respectively.

The reaction may be carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.

**ill)** Compounds of formula (XX) in which B and R_i are as defined in formula (I) above and X is \((-\text{NH}_2), (-\text{CH}_2-\text{NH}_2)\) or a single bond connected to a nitrogen atom which is a member of the B ring. \(\text{R}_2\) is a cyano group can be prepared by reacting a compound of formula (XXXVIII) as defined as above with a suitable cyanide source such as potassium cyanide, sodium cyanide, \(\text{K}_4[\text{Fe(CN)}_6]\) or zinc cyanide.

The reaction may be performed using standard conditions in the presence of a palladium catalyst such as \(\text{Pd(PPh}_3)_4\) or by using \(\text{Pd(OAc)}_2\), \(\text{Pd(OOCF}_3)_2\) or \(\text{Pd}_2(\text{dba})_3\) in combination with suitable phosphine ligands such as \(\text{P(iBu)}_3\), (binaphtyl)P(iBu)_2, PPh_3, dpf, dpp or XANTPHOS. Optionally the reaction is also performed in the presence of Zink dust.

The reaction may be carried out in an inert solvent such as DCM, DMA, DMF, THF, dioxane or toluene.

The reaction is carried out at ambient temperature or at elevated temperatures using standard equipment or a single node microwave oven.


**H2)** Compounds of general formula (XXXVIII) as defined above may be prepared by reacting a compound of formula (XXXIII) with a halogenating reagent, such as
thionylchloride, POCI₃ or oxalyl chloride. Optionally the reaction is performed in the presence of DMF.

The reaction may also be carried out in an inert solvent, such as DCM, using PyBOP or trifluoromethanesulfonic anhydride, optionally in the presence of an organic base such as TEA or DIPEA at or below r.t.

The preparation of compounds of the formula (III) comprises the below processes. (jl-j3)

**jl)** A compound of the formula LR·Rᵣ wherein L is a suitable leaving group, such as chloro, bromo, iodo could be transformed to the corresponding compound (III) using a sequence of reactions using first SMOPS* (*Baskin and Wang. Tetrahedron Letters, 2002, 43, 8479-83. See esp. page 8480, left hand column.) followed by hydrolysis using a base like NaOMe in an inert solvent like DMSO at room temperature. Followed by treatment by NH₂OSO₃H and NaOAc to give a compound of formula (III).

**j2)** A compound of the formula LSO₃R₀Rᵣ wherein L is a suitable leaving group, such as chloro, bromo, iodo could be reacted with ammonium hydroxide in an inert solvent such as DCM to give a compound of formula (III).

**j3)** A compound of the formula LR·Rᵣ wherein L is a suitable leaving group, such as chloro, bromo, iodo can be transformed to the corresponding compound (III) using a sequence of reactions, first treatment with Na₂SO₃, followed by a using a reagent such as PCl₅, POCI₃ or SOCl₂ on the obtained product, and thereafter treating with ammonium hydroxide to give a compound of formula (III).

**k)** Compounds of general formula (XI) as defined above may be prepared by reacting a compound of formula (IX) with a halogenating reagent, such as thionylchloride, POCI₃ or oxalyl chloride. Optionally the reaction is performed in the presence of DMF.

The reaction may also be carried out in an inert solvent, such as DCM, using PyBOP or trifluoromethanesulfonic anhydride, optionally in the presence of an organic base such as TEA or DIPEA at or below r.t.
The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.


It will be appreciated that by those skilled in the art that the processes described above and hereinafter the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups that it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include optionally substituted and/or unsaturated alkyl groups (e.g. methyl, allyl, benzyl or tert-butyl), trialkyl silyl or diarylalkylsilyl groups (e.g. t-butyldimethylsilyl, t-butylidiphenylsilyl or trimethylsilyl) and tetrahydropyranyl. Suitable protecting groups for carboxylic acids include (Ci-Ce)alkyl, allyl or benzyl esters. Suitable protecting groups for amino include allyl, t-butyloxycarbonyl, benzylxycarbonyl, 2-(trimethylsilyl)ethoxymethyl or 2-trimethylsilylthoxycarbonyl (Teoc).

The protection and deprotection of functional groups may take place before or after any reaction in the above mentioned processes.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative, and on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This may negate, or render necessary, the need for protecting groups.
Persons skilled in the art will appreciate that starting materials for any of the above processes can in some cases be commercially available.

Persons skilled in the art will appreciate that processes could for some starting materials above be found in the general common knowledge.

The type of chemistry involved will dictate the need for protecting groups as well as sequence for accomplishing the synthesis.


Protected derivatives of the invention may be converted chemically to compounds of the invention using standard deprotection techniques (e.g. under alkaline or acidic conditions). The skilled person will also appreciate that certain compounds of formula (II)-(XXXVIII) may also be referred to as being "protected derivatives".

Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or crystallization. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. HPLC techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerization, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC, chromatography over silica or crystallization). Stereo centers may also be introduced by asymmetric synthesis, (e.g. metalloorganic reactions using chiral ligands). All stereoisomers are included within the scope of the invention. It will also be understood that some of the compounds described in the processes above may exhibit the phenomenon of tautomerism and the processes described above includes any tautomeric form.

All novel intermediates form a further aspect of the invention.
Salts of the compounds of formula (I) may be formed by reacting the free acid, or a salt thereof, or the free base, or a salt or a derivative thereof, with one or more equivalents of the appropriate base (for example ammonium hydroxide optionally substituted by Ci,C6-alkyl or an alkali metal or alkaline earth metal hydroxide) or acid (for example a hydrohalic (especially HCl), sulphuric, oxalic or phosphoric acid). The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. water, ethanol, tetrahydrofuran or diethyl ether, which may be removed *in vacuo*, or by freeze drying. The reaction may also be carried out on an ion exchange resin.

The non-toxic physiologically acceptable salts are preferred, although other salts may be useful, e.g. in isolating or purifying the product.

**Pharmacological data**

Functional inhibition of the P2Y12 receptor can be measured by in vitro assays using cell membranes from P2Y12-transfected CHO-cells, the methodology is indicated below.

**Functional inhibition of 2-Me-S-ADP induced P2Y12 signalling:** 5μg of membranes were diluted in 200 μl of 200mM NaCl, 1mM MgCl₂, 50mM HEPES (pH 7.4), 0.01% BSA, 30μg/ml saponin and 1μM GDP. To this was added an EC50 concentration of agonist (2-methyl-thio-adenosine diphosphate), the required concentration of test compound and 0.1 μCi ³⁵S-GTPyS. The reaction was allowed to proceed at 30°C for 45 min. Samples were then transferred onto GF/B filters using a cell harvester and washed with wash buffer (50mM Tris (pH 7.4), 5mM MgCl₂, 50mM NaCl). Filters were then covered with scintillant and counted for the amount of ³⁵S-GTPyS retained by the filter.

Maximum activity was that determined in the presence of the agonist and minimum activity in the absence of the agonist following subtraction of the value determined for non-specific activity. The effect of compounds at various concentrations was plotted according to the equation

\[ y = A + \frac{(B-A)}{1 + ((C/x)^n) A D} \]

and IC50 estimated where

A is the bottom plateau of the curve i.e. the final minimum y value

B is the top of the plateau of the curve i.e. the final maximum y value
C is the x value at the middle of the curve. This represents the log EC\textsubscript{50} value when A + B = 100

D is the slope factor.

x is the original known x values.

Y is the original known y values.

Most of the compounds of the invention have an activity, when tested in the functional inhibition of 2-Me-S-ADPinduced P2Y\textsubscript{i2} signalling assay described, at a concentration of around 0.5 µM or below, whereas the exemplified compounds having R\textsubscript{2} embodied by (Ci-C\textsubscript{3})alkylthio or hydroxy(Ci-C\textsubscript{3})alkyl are having an IC\textsubscript{50} of 0.05 µM or less and an average IC\textsubscript{50} of 0.02 µM.

For example the compounds described in Examples 12 and 16 gave the following test result in the functional inhibition of 2-Me-S-ADPinduced P2Y\textsubscript{i2} signalling assay described.

<table>
<thead>
<tr>
<th>IC\textsubscript{50} (µM)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 12</td>
<td>0.01</td>
</tr>
<tr>
<td>Example 16</td>
<td>0.05</td>
</tr>
</tbody>
</table>

The compounds of the invention act as P2Y\textsubscript{i2} receptor antagonists and are therefore useful in therapy. Thus, according to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy.

Thus, according to another further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use as a medicament.

In a further aspect there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treatment of a platelet aggregation disorder. In another aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the inhibition of the P2Y\textsubscript{i2} receptor.
In yet another aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use as an inhibitor of the P2Y\(_{1_2}\) receptor.

In an even further aspect there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treatment or prevention of thrombosis.

Another even further aspect of the invention is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in preventing thrombosis.

In still another aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of platelet aggregation disorder.

An alternative aspect of the invention is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in treating platelet aggregation disorder.

The compounds are useful in therapy, especially adjunctive therapy, particularly they are indicated for use as: inhibitors of platelet activation, aggregation and degranulation, promoters of platelet disaggregation, anti-thrombotic agents or in the treatment or prophylaxis of unstable angina, coronary angioplasty (PTCA), myocardial infarction, perithrombolysis, primary arterial thrombotic complications of atherosclerosis such as thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease, myocardial infarction with or without thrombolysis, arterial complications due to interventions in atherosclerotic disease such as angioplasty, endarterectomy, stent placement, coronary and other vascular graft surgery, thrombotic complications of surgical or mechanical damage such as tissue salvage following accidental or surgical trauma, reconstructive surgery including skin and muscle flaps, conditions with a diffuse thrombotic/platelet consumption component such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, thrombotic complications of septicaemia, adult respiratory distress syndrome, anti-phospholipid syndrome, heparin-induced thrombocytopenia and pre-eclampsia/eclampsia, or venous thrombosis such as deep vein thrombosis, venoocclusive disease, haematological
conditions such as myeloproliferative disease, including thrombocythaemia, sickle cell disease; or in the prevention of mechanically-induced platelet activation in vivo, such as cardio-pulmonary bypass and extracorporeal membrane oxygenation (prevention of microthromboembolism), mechanically-induced platelet activation in vitro, such as use in the preservation of blood products, e.g. platelet concentrates, or shunt occlusion such as in renal dialysis and plasmapheresis, thrombosis secondary to vascular damage/inflammation such as vasculitis, arteritis, glomerulonephritis, inflammatory bowel disease and organ graft rejection, conditions such as migraine, Raynaud's phenomenon, conditions in which platelets can contribute to the underlying inflammatory disease process in the vascular wall such as atheromatous plaque formation/progression, stenosis/restenosis and in other inflammatory conditions such as asthma, in which platelets and platelet-derived factors are implicated in the immunological disease process.

According to the invention there is further provided the use of a compound according to the invention in the manufacture of a medicament for the treatment of the above disorders. In particular the compounds of the invention are useful for treating myocardial infarction, thrombotic stroke, transient ischaemic attacks, peripheral vascular disease and angina, especially unstable angina. The invention also provides a method of treatment of the above disorders which comprises administering to a patient suffering from such a disorder a therapeutically effective amount of a compound according to the invention.

In a further aspect the invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent, adjuvant and/or carrier.

The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, pills, capsules, syrups, powders or granules, or by parenteral administration in the form of sterile parenteral solutions or suspensions, by subcutaneous administration, or by rectal administration in the form of suppositories or transdermally.

The compounds of the invention may be administered on their own or as a pharmaceutical composition comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are
compositions not containing material capable of causing an adverse, e.g. an allergic, reaction.

Dry powder formulations and pressurised HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation the compound is desirably finely divided. The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound with a carrier substance, e.g. a mono-, di- or polysaccharide, a sugar alcohol or another polyol. Suitable carriers include sugars and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres, which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, e.g. that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound with or without a carrier substance is delivered to the patient.

The pharmaceutical composition comprising the compound of the invention may conveniently be tablets, pills, capsules, syrups, powders or granules for oral administration; sterile parenteral or subcutaneous solutions, suspensions for parenteral administration or suppositories for rectal administration.

For oral administration the active compound may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved either in a readily volatile organic solvent or an aqueous solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the
compound using either the above mentioned excipients for tablets, e.g. lactose, saccharose, sorbitol, mannitol, starches, cellulose derivatives or gelatine. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The invention will be further illustrated with the following non-limiting examples:
Examples

General Experimental Procedure

Mass spectra were recorded on a Finnigan LCQ Duo ion trap mass spectrometer equipped with an electrospray interface (LC-MS) or LC-MS system consisting of a Waters ZQ using a LC-Agilent 1100 LC system.

¹H NMR measurements were performed on Varian INOVA 400, 500 and 600 spectrometers, operating at ¹H frequencies of 400, 500 and 600 MHz respectively. Chemical shifts are given in ppm with the solvent as internal standard. Protons on heteroatoms such as NH and OH protons are only reported when detected in NMR and can therefore be missing.

The solutions for the ¹H-NMR spectra recorded for Examples 2 to 15 below are taken from a concentrated sample solved in (CH₃)₂SO and are diluted with (CD₃)₂SO. Since a substantial amount of (CH₃)₂SO is present in the sample, first a pre-scan is run and analysed to automatically suppress the (CH₃)₂SO (2.54 ppm) and H₂O (3.3 ppm) peaks. This means that in this so-called wetID experiment the intensity of peaks that reside in these areas around 3.3 ppm and 2.54 ppm is reduced. Furthermore impurities are seen in the spectrum which gives rise to a triplet at 1.12 ppm, a singlet at 2.96 and two multiplets between 2.76-2.70 ppm and 2.61-2.55 ppm. Most probably these impurities are dimethylsulfone and diethylsulfoxide.

HPLC separations were performed on a Waters YMC-ODS AQS-3 120 Angstrom 3 x 500 mm or on a Waters Delta Prep Systems using Kromasil Cg, 10 μm columns.

Straight phase chromatography was performed using Biotage silica gel 4OS, 4OM, 12i or Merck silica gel 60 (0.063-0.200mm). Flash-chromatography was performed using either standard glass- or plastic-columns or on a Biotage Horizon system

Purification Method A: The purification system and LC-MS system used in purification Method A, referred to in some of the Examples below, was Waters Fraction Lynx I
Purification System: Column: Sunfire Prep C18, 5 mm OBD, 19 x 150 mm column.
Gradient 5-95 % CH₃CN in 0.1 mM HCOOH (pH = 3). MS triggered fraction collection
was used. Mass spectra were recorded on either Micromass ZQ single quadropole or a
Micromass quattro micro, both equipped with a pneumatically assisted electrospray
interface.

Reactions performed in a microwave reactor were performed in a Personal Chemistry
Smith Creator, Smith synthesizer or an Emrys Optimizer.

IUPAC names were generated with ACD Labs Name: Release 9:00, Product version 9.04.

The GTPγS values (IC₅₀ in µM) mentioned in the examples below were measured by the
method previously described under the heading "Functional inhibition of 2-Me-S-ADP
induced P₂Y₁₂ signalling."

List of used abbreviations:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>BSA</td>
<td>Bovine Serum Albumine</td>
</tr>
<tr>
<td>CDI</td>
<td>Carbonyldiimidazole</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>dba</td>
<td>1,5-diphenylpenta- 1,4-dien-3-one</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-Diisopropylethylamine</td>
</tr>
<tr>
<td>DMA</td>
<td>N,N-Dimethylacetamide</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulphoxide</td>
</tr>
<tr>
<td>Dppf</td>
<td>1,1'-bis(diphenylphosphino)ferrocene</td>
</tr>
</tbody>
</table>
dpppe  1,5-bis(diphenylphosphino)pentane
EDCI  N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride
EtOAc  Ethyl acetate
EtOH  Ethanol
FA  formic acid
g  gram
h  hours
HEPES  [4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HFA  Hydrofluoroalkanes
HOAc  Acetic acid
HOBt  1-Hydroxybenzotriazole
HPLC  High-performance liquid chromatography
Hz  Hertz
J  Coupling constant
LC  Liquid chromatography
m  Multiplet
MeCN  acetonitrile
MeOH  Methanol
mg  milligram
MHz  Megahertz
min  minutes
mL  millilitre
mmol  millimole
MS  Mass spectra
Ms  methylsulfonyl
NMR  Nuclear magnetic resonance
OAc  acetate
OBt  H-benzo[d][1,2,3]triazol-1-yl oxy
Ph  Phenyl
PyBOP  (Benzotriazol-1-yl oxy)tri pyr r o lid in o-phosphonium hexafluorophosphate
PyBroP Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
q Quartet
r.t. Room temperature
s Singlet
sat. Saturated
SMOPS sodium 3-methoxy-3-oxopropane-1-sulfmate
t triplet
TB Tyrodes Buffer
TBTU N-[(lH-1,2,3-benzotriazol-1-yloxy) (dimethylamino)methylene]-N-methylmethanaminium tetrafluoroborate
TEA Triethylamine
Tf trifluoromethylsulfonyl
TFA Trifluoroacetic acid
THF Tetrahydrofuran
TMEDA N,N,N',N'-tetramethylethylendiamine
Ts ... p-toluenesulfonyl
XANTPHOS (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane)

**Sulfone amides**

Synthesis of sulfone amides

The synthesis of the sulfonamides used in the examples below was made with one of the three methods described below:

i) By reacting the corresponding sulfonyl chloride with ammonia in THF or MeOH or by treatment with ammonium hydroxide in methylene chloride. The sulfonamides obtained was used without further purification.

ii) By essentially following the procedure described by Seto, T. et. al. in J. Organic Chemistry, VoI 68, No 10 (2003), pp. 4123-4125.
or


**Synthesis of sulfamides.**

The different sulfamides in the Examples below were prepared by essentially the same procedure as described in Example 10(a) by replacing N-methylaniline with the appropriate amine.
Example 10(a), N-Methyl-N-phenylsulfamide

Chlorosulfonyl isocyanate (3.7 mL, 42.4 mmol) was dissolved in dry DCM (40 mL), the solution was cooled to 0 °C and tert-butanol (3.98 mL, 42.4 mmol) was added drop wise. The reaction mixture was stirred at r.t. for 2 h, the solution was cooled to 0 °C and N-methylaniline (4.61 mL, 42.4 mmol) and TEA (8.85 mL, 63.6 mmol) dissolved in dry DCM (20 mL) were added drop wise through a dropping funnel. The reaction was stirred at r.t. for 3 h, water was added and the organic phase was separated and dried (phase separator, Isolute) and concentrated in vacuo. The residue was dissolved in DCM (40 mL) and trifluoroacetic acid (32.7 mL, 423 mmol) was added. The reaction was stirred at r.t. for 20 min., the solvent was concentrated in vacuo and co-evaporated with DCM (3x). The crude product was purified by flash column chromatography, using a mixture of heptane:EtOAc 70:30 as eluent, to give N-methyl-N-phenylsulfamide. Yield: 5.96 g (76%).

$^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 3.22 (3H, s), 4.77 (2H, s), 7.28-7.33 (1H, m), 7.36-7.42 (4H, m).

MS $m/z$: 187 (M$^+$).

Example 1

l-[5-Butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[l-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide

(a) tert-Butyl l-(2-cyanoethanimidoyl)piperidine-4-carboxylate

Two microwave vials were each charged with ethyl 2-cyanoethanimidoate (See McElvain, S.M.; Schroeder, J.P.; J. Am. Chem. Soc. 71, p.40(1949)) (841 mg, 7.7 mmol), tert-butyl piperidine-4-carboxylate (926 mg, 5 mmol), DIPEA (1.94 g, 15 mmol), EtOH (7.5 mL) and heated to 100 °C for 10 minutes in a microwave oven, single node heating. Additional ethyl 2-cyanoethanimidoate (252 mg, 4.5 mmol) and DIPEA (969 mg, 7.5 mmol) was added to each vial and the stirring was continued at r.t. for 16 hours. LC-MS showed still some remaining tert-butyl piperidine-4-carboxylate and therfore ethyl 2-cyanoethanimidoate (246 mg, 2.2 mmol) was added and the mixture was again heated to
100 °C in a microwave oven for 20 minutes. The solutions from the vials was combined and used without further purification in the next step.

(b) Ethyl 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-oxo-1,2-dihydropyridine-3-carboxylate

Diethyl (ethoxymethylene)malonate (3.24 g, 15 mmol) was added to the solution from step (a) above and the reaction mixture was stirred at r.t. for 16 hours. The solvent was evaporated and NaHCO₃(sat) (50 mL) was added and the water phase extracted with DCM (3 x 50 mL). The combined organic phase was washed with brine (150 mL), dried (Na₂SO₄), filtered and evaporated to give a crude product which was purified by preparative HPLC (Kromasil Cs, 10 μm, 50.8x250 mm column, flow 50 mL/minute using a gradient of 5 to 100% CH₃CN/0.1 M NH₄OOCH) to give the desired product. Yield: 1.262 g (32%).

1H NMR (500 MHz, CDCl₃): δ 1.41 (3H, t, J = 7.1 Hz), 1.46 (9H, s), 1.75-1.86 (2H, m), 1.98-2.06 (2H, m), 2.53-2.61 (IH, m), 3.29-3.37 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 4.53-4.61 (2H, m), 8.20 (IH, s). Not unambiguous where the NH proton is.

MS m/z: 376 (M+1)

(c) Ethyl 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-\{[(trifluoromethyl)sulfonyl]oxy\}nicotinate

Tf₂(O) (0.3 mL, 1.78 mmol) was added to a cold (ice/water bath temperature) mixture of ethyl 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-oxo-1,2-dihydropyridine-3-carboxylate from step (b) above (626 mg, 1.67 mmol) and TEA (0.5 mL, 3.59 mmol) in DCM (10 mL) and the mixture was stirred for 40 minutes. The mixture was concentrated under reduced pressure and the crude product was used in the next step without further purification.

MS m/z: 508 (M+1).
(d) tert-Butyl 6-[-4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-(methylthio)nicotinate

A microwave vial was charged with ethyl 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-[(trifluoromethyl)sulfonyl]oxy]nicotinate from step (c) above (1.31 g, 2.58 mmol), sodium methanethiolate (235 mg, 3.53 mmol) and dry THF (10 mL). The reaction mixture was heated to 120 °C for 5 min. using microwave single node heating. LCMS showed complete conversion. NaHC\text{3}(aq) was added and the mixture was extracted with DCM(x3). The combined organic layer was run through a phase separator and evaporated. The crude tert-butyl 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-(methylthio)nicotinate was used without further purification assuming quantitative yield.

(e) 6-[4-(tert-Butoxycarbonyl)piperidin-1-yl]-5-cyano-2-(methylthio)nicotinic acid

A microwave vial was charged with 1M NaOH (6 mL, 6 mmol), tert-butyl 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-(methylthio)nicotinate from step (d) above (1.36 g, 3.37 mmol), THF (6 mL) and EtOH (6 mL). The reaction mixture was heated to 60 °C for 5 minutes in a single node microwave oven. The reaction mixture was concentrated under reduced pressure and acetic acid (0.36 mL, 6.29 mmol) and water was added. The solid was filtered off and washed with 2-propanol/Et\text{2}θ (1:1) and dried under reduced pressure to give the product as an off white solid (203 mg). The filtrate was evaporated, NaHCO\text{s}(aq) was added and the mixture was extracted with DCM (x3). The combined organics was run through a phase separator and evaporated. The crude product was purified by preparative HPLC (Kromasil C\text{8} 10μm, 21.5x250mm, using an increasing gradient of MeCN with a second acidic eluent H\text{2}O/MeCN/FA 95/5/0.2) to give an additional 366 mg of 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-(methylthio)nicotinic acid as a white solid. Yield: 569 mg (45%).

\text{1H} NMR (400 MHz, DMSO-d\text{6}): δ 1.39 (9H, s), 1.54 - 1.66 (2H, m), 1.87 - 1.95 (2H, m), 2.37 (3H, s), 2.54 - 2.64 (IH, m), 3.24 - 3.36 (2H, m, concealed by the DMSO signal at 3.3), 4.38 - 4.47 (2H, m), 8.20 (IH, s), 12.97 (IH, br s).

MS \text{m/z}: 378.0 (M+1), 376.2 (M-1).
(f) tert-Butyl 1-[3-cyano-5-(fluorocarbonyl)-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylate

Dry pyridine (0.15 mL, 1.86 mmol) and cyanuric fluoride (0.15 mL, 1.78 mmol) were added to a suspension of 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-(methylthio)nicotinic acid from step (e) above (569 mg, 1.51 mmol) in DCM (20 mL). The reaction mixture was stirred at r.t. for 30 minutes. LCMS showed 10% acid (sample quenched with 1% DIPEA in dry MeOH). The reaction mixture was stirred at r.t. for another 50 minutes. LCMS still showed 10% acid but 20% anhydride had been formed. Dry pyridine (0.02 mL, 0.25 mmol) and cyanuric fluoride (0.02 mL, 0.24 mmol) were added. The reaction mixture was stirred at r.t. for an additional 15 minutes. LCMS showed 4% acid left. The solid was filtered off and washed with dry DCM. Water was added to the filtrate, the organic layer was separated and the aqueous layer was extracted with DCM. The combined organics was run through a phase separator and evaporated to give the crude tert-butyl 1-[3-cyano-5-(fluorocarbonyl)-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylate as a solid. The crude was used in the next step without further purification, assuming quantitative yield.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.46 (9H, s), 1.78 - 1.90 (2H, m), 2.01 - 2.09 (2H, m), 2.49 (3H, s), 2.54 (IH, m), 3.38 - 3.48 (2H, m), 4.57 - 4.66 (2H, m), 8.18 (IH, s). ($^1$H NMR showed product/anhydride in a ratio 4:1.)

MS $m/z$ 392 (M+1). (identified as the corresponding methylester after quench with MeOH/DIPEA)

(g) tert-Butyl 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylate

Freshly prepared "Gillman-type" cuprate (3.6 mL 1.0 M solution in THF, 3.6 mmol) (the reagent was prepared from 2 eq. n-Propylmagnesium bromide (1.0 M in THF) and 1 eq. Cu(I) iodide dimethylsulfide complex at 0 °C and stirred for 10 minutes before added to the acid fluoride) was added to a cold (ice water bath temperature) stirred solution of tert-butyl 1-[3-cyano-5-(fluorocarbonyl)-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylate (1.36 g, 3.58 mmol) in dry THF (8 mL) under an atmosphere of nitrogen. The mixture was
stirred for 10 minutes at 0°C and checked by LCMS by quenching with MeOH/Et$_3$N which showed that starting material still was present (detected as the corresponding methyl ester). Addition further 0.7 equivalents (2.5 mL, 1.0 M in THF) of the cuprate reagent drove the reaction to completion.

The reaction was quenched by adding NH$_4$Cl(aq) (20mL) and EtOAc (60mL). The phases were separated and the water phase was extracted with EtOAc (20mL). The combined organic phase was dried (Na$_2$SO$_4$), filtered and evaporated to give the crude product as a dark green oil (790 mg). The crude product was purified by preparative HPLC (Kromasil C$_18$Qtm, 50 x 250mm, using an increasing gradient of MeCN with a second acidic eluent H$_2$O/MeCN/FA 95/5/0.2)) to give tert-butyl 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylate as a light yellow solid. Yield 350 mg (24%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 0.99 (3H, t, J = 7.4 Hz), 1.46 (9H, s), 1.69 - 1.78 (2H, m), 1.76 - 1.89 (2H, m), 1.98 - 2.08 (2H, m), 2.42 (3H, s), 2.50 - 2.61 (IH, m), 2.77 (2H, t, J = 7.3 Hz), 3.26 - 3.45 (2H, m), 4.54 - 4.63 (2H, m), 8.12 (IH, s).

MS $m/z$: 404 (M+1).

(h) 1-[5-Butyryl-3-cyano-6-(methylthio)pyridin-2-yl] piperidine-4-carboxylic acid

TFA (4.5 mL) was added to a cold (ice/water bath temperature) solution of tert-butyl 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylate (612 mg, 1.5 mmol) in DCM (4.5 mL) and the cooling bath was removed and the reaction was stirred at ambient temperature for 2 hours. The reaction was concentrated and CH$_2$CNZH$_2$O 1/1 (5ml) was added to initiate precipitation of the product. The solid was collected and dried to give 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylic acid as an off-white solid. Yield: 470 mg (88%).

MS $m/z$: 348 (M+1), 346 (M-I).

(i) HS-Butyryl-S-cyano-6-CmethylthioJpyridin-l-ylj-N-Kl-phenylcyclopropyljsulfonylpiperidine^a-carboxamide

DIPEA (74.2 mg, 0.574 mmol) was added to a suspension of 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylic acid (63 mg, 0.181 mmol) and PyBOP
(117 mg, 0.225 mmol) in DCM (4 mL). The reaction mixture was stirred at r.t. for 30 min. and 1-phenylcyclopropanesulfonamide (42 mg, 0.21 mmol) was added. The reaction mixture was stirred at r.t. for 2.5 h. NaHCO₃(aq) was added and the mixture was extracted with DCM (x3). The combined organics was run through a phase separator and evaporated. The crude product was purified by preparative HPLC (Kromasil C₁₀ 10 µm, 50x250 mm, using an increasing gradient of 40% to 90% MeCN with a second acidic eluent H₂O/MeCN/FA 95/5/0.2) during 30 minutes) to give l-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide as a white solid. Yield: 71 mg (75%).

¹H NMR (600 MHz, DMSO-d₆): δ 0.88 (3H, t, J = 7.4 Hz), 1.30 - 1.34 (2H, m), 1.51 - 1.58 (2H, m), 1.58 - 1.68 (2H, m), 1.74 - 1.81 (4H, m), 2.37 (3H, s), 2.51 - 2.58 (IH, m), 2.86 - 2.92 (IH, m), 3.11 - 3.18 (2H, m), 4.51 - 4.58 (2H, m), 7.35 - 7.43 (5H, m), 8.54 (IH, s), 11.36 (IH, br s).

MS m/z: 527 (M+1), 525 (M-I).

Example 2
l-(5-Butyl-3-cyano-6-methoxypyridin-2-yl)-N-[(4-fluorophenyl)amino]sulfonyl]piperidine-4-carboxamide

(a) Ethyl 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-methoxynicotinate

A microwave vial was charged with ethyl 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-oxo-1,2-dihydropyridine-3-carboxylate (See Example 1(b)) (188 mg, 0.5 mmol), methyl iodide (355 mg, 2.5 mmol), silver carbonate (276 mg, 1 mmol), DMSO (2.5 mL) and heated to 100 °C in a microwave oven, single node heating, for 20 minutes. LC-MS showed 81% of O-alkylated product along with 19% N-alkylated product. The crude product was purified by preparative HPLC (Kromasil C₁₀ 10 µm, Eluent: A: CH₃CN; B: 0.2 % HOAc in water/CH₃CN 95/5; C: 0.1 M NH₄OAc/CH₃CN 95/5. Using A/B/C 5/0/95 during injection and then eluting with a gradient going from A/B/C 5/95/0 to 100/0/0) to give the desired product. Yield: 141 mg (72%).
H NMR (400 MHz, CDCl₃): δ 1.35 (3H, t, J = 7.2 Hz), 1.46 (9H, s), 1.75-1.86 (2H, m), 1.97-2.06 (2H, m), 2.51-2.60 (IH, m), 3.27-3.37 (2H, m), 3.99 (3H, s), 4.30 (2H, q, J = 7.2 Hz), 4.51-4.60 (2H, m), 8.32 (IH, s).

MS m/z: 390 (M+1)

(b) 6-[4-(tert-Butoxycarbonyl)piperidin-1-yl]-5-cyano-2-methoxynicotinic acid

A microwave vial was charged with NaOH (0.40 g, 10 mmol), ethyl 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-methoxynicotinate (389 mg, 1 mmol) and MeCN/water (1/1, 8 mL) and the mixture was heated to 80 °C for 5 minutes using microwave single node heating. FA (1 mL) was added and the mixture was extracted with DCM (3x5 mL). The solvent was evaporated to give 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-methoxynicotinic acid which was used in the next step without further purification. Yield: 395 mg (109 %, crude).

(c) tert-Butyl l-[5-(chlorocarbonyl)-3-cyano-6-methoxypyridin-2-yl]piperidine-4-carboxylate

DMF (0.029 mL) was added dropwise (during 2-3 minutes) to a cold (ice/water bath temperature) solution of oxalyl chloride (1.24 mL, 14.66 mmol) and 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-methoxynicotinic acid (2.65 g, 7.33 mmol) in DCM (73 mL). The ice bath was removed after 5 minutes and the reaction mixture was stirred for 7 minutes at r.t.. The solvent and excess reagents were evaporated and the residue was co-evaporated twice with THF (20 mL each) to give tert-butyl l-[5-(chlorocarbonyl)-3-cyano-6-methoxypyridin-2-yl]piperidine-4-carboxylate. The crude product was used without further purification assuming quantitative yield.

(d) tert-Butyl l-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)piperidine-4-carboxylate

n-Propylmagnesium bromide (4.2 mL, 0.48 M in THF, 2 mmol) was added during 20 minutes to a cold (ice/water bath temperature) solution of tert-butyl l-[5-(chlorocarbonyl)-3-cyano-6-methoxypyridin-2-yl]piperidine-4-carboxylate (760 mg, 2.0 mmol) and ferric
acetylacetonate (35 mg, 0.1 mmol) in THF (25 mL) under an atmosphere of nitrogen. The mixture was stirred for 10 minutes and water was added to quench the reaction. The mixture was extracted with DCM (3 x 20 mL) and the combined organic phase was passed through a phase separator and evaporated to give 735 mg of the crude product. The crude product was purified by preparative HPLC. (Kromasil C18, using an increasing gradient of 60% to 95 % MeCN with a second acidic eluent H₂O/MeCN/HOAc, 95/5/0.2 during 30 minutes) to give tert-butyl 1-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)piperidine-4-carboxylate. Yield: 352 mg (45 %).

\[
\text{MS}_{m/z}: 388 (M+1)
\]

(e) 1-(5-Butyryl-3-cyano-6-methoxypyridin-2-yl)piperidine-4-carboxylic acid

A solution of tert-butyl 1-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)piperidine-4-carboxylate (253 mg, 0.653 mmol) in DCM/TFA (1/1, 2 mL) was stirred at r.t. for 4 hours. The solvent and excess TFA was evaporated to give 1-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)piperidine-4-carboxylic acid which was used without further purification assuming quantitative yield.

\[
\text{MS}_{m/z}: 330 (M-I)
\]

(f) 1-(5-Butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(4-fluorophenyl)amino]sulfamide piperidine-4-carboxamide

TBTU (154 mg, 0.48 mmol) and DIPEA (155 mg, 1.2 mmol) were added to a solution of 1-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)piperidine-4-carboxylic acid (133 mg, 0.40 mmol) in DCM (2 mL) and the mixture was stirred 0.5 hours at r.t. N-(4-fluorophenyl)sulfamide (87 mg, 0.46 mmol) was added and the reaction mixture was stirred for an additional 16 hours at r.t. LC-MS showed 54 % product and some remaining starting material (not integrated) and therefore PyBroP (28 mg, 0.06 mmol) was added and
the stirring was continued for an additional 22 hours. The crude product was purified by Purification method A (See General Experimental Procedure).

$^1$H NMR (600 MHz, (CD$_3$)$_2$SO, (CH$_3$)$_2$SO) $\delta$ 0.89 (3H, t, J = 7.4 Hz), 1.40-1.48 (2H, m), 1.52-1.60 (2H, m), 1.64-1.69 (2H, m), ca. 2.48 (IH, m)**, 2.84 (2H, t, J = 7.2 Hz), 3.11-3.19 (2H, m), 3.95 (3H, s), 4.41-4.47 (2H, m), 7.14-7.21 (4H, m), 8.22 (IH, s), 10.38 (IH, s), 1.72 (IH, s).

** From methine-H, coincides with the suppressed DMSO-signal.

MS $m/z$: 504 (M+l)

GTPyS (IC$_{50}$ µM): 0.169

** Example 3

l-(5-Butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(4-fluorophenyl)(methyl)amino]sulfonyl)piperidine-4-carboxamide

Prepared according to Example 2(f) from l-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)piperidine-4-carboxylic acid (Example 2(e)) (133 mg, 0.4 mmol) and N-(4-fluorophenyl)-N-methylsulfamide (94 mg, 0.46 mmol) to give l-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(4-fluorophenyl)(methyl)amino]sulfonyl)piperidine-4-carboxamide

Yield: 64 mg (31%)

$^1$H NMR (600 MHz, (CD$_3$)$_2$SO, (CH$_3$)$_2$SO) $\delta$ 0.89 (3H, t, J = 7.4 Hz), 1.52-1.64 (4H, m), 1.77-1.83 (2H, m), ca. 2.48 (IH, m)**, 2.84 (2H, t, J = 7.2 Hz), 3.14-3.21 (2H, m), 3.98 (3H, s), 4.52-4.58 (2H, m), 7.24-7.28 (2H, m), 7.35-7.39 (2H, m), 8.24 (IH, s), 1.68 (IH, s).

NOTE: The signal from the N-Me group is in the region 2.3-2.7 ppm where it coincides with the suppressed DMSO-signal.

** From methine-H, coincides with the suppressed DMSO-signal.

MS $m/z$: 518 (M+l)

GTPyS (IC$_{50}$ µM): 0.154
Example 4
l-(5-Butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(4-methoxybenzyl)sulfonyl]piperidine-4-carboxamide

Prepared according to Example 2(f) from l-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)piperidine-4-carboxylic acid (Example 2(e)) (133 mg, 0.4 mmol) and l-(4-methoxyphenyl)methanesulfonamide (93 mg, 0.46 mmol) to give l-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(4-methoxybenzyl)sulfonyl]piperidine-4-carboxamide

Yield: 95 mg (46%)  

** From methine-H, coincides with the suppressed DMSO-signal.

\[ MS m/z : 515 \] (M+1)

\[ \text{GTPyS (IC}_{50} \text{ µM): 0.141} \]

Example 5
l-(5-Butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(4-methylbenzyl)sulfonyl]piperidine-4-carboxamide

Prepared according to Example 2(f) from l-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)piperidine-4-carboxylic acid (Example 2(e)) (133 mg, 0.4 mmol) and l-(4-methylphenyl)methanesulfonamide (85 mg, 0.46 mmol) to give l-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(4-methylbenzyl)sulfonyl]piperidine-4-carboxamide

Yield: 78 mg (38%)

** From methine-H, coincides with the suppressed DMSO-signal.

\[ MS m/z : 499 \] (M+1)
Example 6
l-(5-Butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(4-chloro-2-fluorobenzyl)sulfonyl] piperidine-4-carboxamide

Prepared according to Example 2(f) from l-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)piperidine-4-carboxylic acid (Example 2(e)) (133 mg, 0.4 mmol) and l-(4-chloro-2-fluorophenyl)methanesulfonamide (103 mg, 0.46 mmol) to give l-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(4-chloro-2-fluorobenzyl)sulfonyl]piperidine-4-carboxamide. Yield: 87 mg (40%).

$^1$H NMR (600MHz, (CD$_3$)$_2$SO, (CH$_3$)$_2$SO) δ 0.88 (3H, t, J = 7.4 Hz), 1.52-1.59 (2H, m), 1.61-1.70 (2H, m), 1.86-1.92 (2H, m), ca. 2.48 (IH, m)**, 2.84 (2H, t, J = 7.2 Hz), 3.16-3.24 (2H, m), 3.98 (3H, s), 4.54-4.60 (2H, m), 4.76 (2H, s), 7.36-7.40 (IH, m), 7.42-7.46 (IH, m), 7.51-7.55 (IH, m), 8.24 (IH, s).

** From methine-H, coincides with the suppressed DMSO-signal.

MS $m/z$: 537 (M+1)

GTPyS(IC$_{50}$ µM): 0.0838

Example 7
l-(5-Butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(2,4-difluorobenzyl)sulfonyl]piperidine-4-carboxamide

Prepared according to Example 2(f) from l-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)piperidine-4-carboxylic acid (Example 2(e)) (133 mg, 0.4 mmol) and l-(2,4-difluorophenyl)methanesulfonamide (95 mg, 0.46 mmol) to give l-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(2,4-difluorobenzyl)sulfonyl]piperidine-4-carboxamide. Yield: 64 mg (29%).

$^1$H NMR (600MHz, (CD$_3$)$_2$SO, (CH$_3$)$_2$SO) δ 0.89 (3H, t, J = 7.4 Hz), 1.53-1.60 (2H, m), 1.62-1.70 (2H, m), 1.86-1.92 (2H, m), ca. 2.48 (IH, m)**, 2.84 (2H, t, J = 7.2 Hz), 3.18-3.24 (2H, m), 3.98 (3H, s), 4.55-4.61 (2H, m), 4.74 (2H, s), 7.15-7.20 (IH, m), 7.32-7.36 (IH, m), 7.44-7.50 (IH, m), 8.25 (IH, s).
From methine-H, coincides with the suppressed DMSO-signal.

\[ M^+ /z : 521 \ (M+1) \]

GTPyS(IC\(_{50}\ \mu M\)): 0.0636

** Example 8 **

1-(5-Butyryl-3-cyano-6-methoxypyridin-2-yl)-N-(2-fluorobenzyl)sulfonyl]piperidine-4-carboxamide

Prepared according to Example 2(f) from 1-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)piperidine-4-carboxylic acid (Example 2(e)) (133 mg, 0.4 mmol) and 1-(2-fluorophenyl)methanesulfonamide (87 mg, 0.46 mmol) to give 1-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)-N-(2-fluorobenzyl)sulfonyl]piperidine-4-carboxamide. Yield: 59 mg (28%).

\[ \deltaH \text{ NMR (600MHz, (CD\(_3\))_2SO, (CH}_3)_2SO) \delta 0.88 \ (3H, t, J = 7.4 \text{ Hz}), 1.51-1.59 \ (2H, m), 1.62-1.70 \ (2H, m), 1.85-1.92 \ (2H, m), \text{ ca. 2.48 (IH, m)**, 2.84 (2H, t, J = 7.2 \text{ Hz}), 3.16-3.23 \ (2H, m), 3.97 \ (3H, s), 4.54-4.60 \ (2H, m), 4.75 \ (2H, s), 7.23-7.29 \ (2H, m), 7.38-7.42 \ (IH, m), 7.43-7.48 \ (IH, m), 8.24 \ (IH, s).} \]

** From methine-H, coincides with the suppressed DMSO-signal.**

\[ M^+ /z : 503 \ (M+1) \]

GTPyS(IC\(_{50}\ \mu M\)): 0.0875

** Example 9 **

HS-Butyryl-S-cyano-6-Cmethylthio]pyridin-l-ylj-N-Kl-fluorobenzyl)sulf]nyl]piperidine-4-carboxamide

A mixture of l-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylic acid (Example l(h)) (48 mg, 0.14 mmol), TBTU (55 mg, 0.17 mmol) and TEA (71 mg, 0.7 mmol) in DCM (2 mL) was stirred for 1.5 hours at r.t. before 1-(2-fluorophenyl)methanesulfonamide (26 mg, 0.14 mmol) was added. The slurry was stirred at r.t. over night (LCMS showed only startingmaterial). DMF (0.5 mL) was added to dissolve the slurry and the mixture was stirred for an additional 2.5 hours (LCMS showed about 40 % startingmaterial left). Therefore, an additional amount of PyBOP (44 mg, 0.084
mmol) was added and the stirring was continued until all starting material had been converted to product (2 hours). Water containing 2% HOAc was added and the organic phase was separated and evaporated to give a crude product that was purified by purification method A (See General Experimental Procedure). This gave pure 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(2-fluorobenzyl)sulfonyl]piperidine-4-carboxamide. Yield: 51 mg (71%).

\[ ^1H \text{NMR (500 MHz, CDCl}_3) \delta 3.22 (3H, s), 4.77 (2H, s), 7.28-7.33 (1H, m), 7.36-7.42 (4H, m). \]

MS m/z: 519 (M+1), 517 (M-I).

GTPyS (IC\text{50 µM}): 0.0101

**Example 10**

1-[5-Butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(methyl(phenyl)amino)sulfonyl]piperidine-4-carboxamide

(a) N-Methyl-N-phenylsulfamide

Chlorosulfonyl isocyanate (3.7 mL, 42.4 mmol) was dissolved in dry DCM (40 mL), the solution was cooled to 0 °C and tert-butanol (3.98 mL, 42.4 mmol) was added drop wise. The reaction mixture was stirred at r.t. for 2h, the solution was cooled to 0 °C and N-methylaniline (4.61 mL, 42.4 mmol) and TEA (8.85 mL, 63.6 mmol) dissolved in dry DCM (20 mL) were added drop wise through a dropping funnel. The reaction was stirred at r.t. for 3h, water was added and the organic phase was separated and dried (phase separator, Isolute) and concentrated in vacuo. The residue was dissolved in DCM (40 mL) and trifluoroacetic acid (32.7 mL, 423 mmol) was added. The reaction was stirred at r.t. for 20 min., the solvent was concentrated in vacuo and co-evaporated with DCM (3x). The crude product was purified with flash column chromatography, using a mixture of heptane:EtOAc 70:30 as eluent, to give N-methyl-N-phenylsulfamide. Yield: 5.96 g (76%).

\[ ^1H \text{NMR (500 MHz, CDCl}_3) d 3.22 (3H, s), 4.77 (2H, s), 7.28-7.33 (1H, m), 7.36-7.42 (4H, m). \]
MS $^{m/z}$: 187 (M+1).

(b) 1-[5-Butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[[methyl(phenyl)amino]sulfonyl]piperidine-4-carboxamide

Prepared according to Example 9 from 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylic acid (Example 1(h)) (48 mg, 0.14 mmol) and N-Methyl-N-phenylsulfamide (32 mg, 0.17 mmol) to give 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[[methyl(phenyl)amino]sulfonyl]piperidine-4-carboxamide. Yield: 4.9 mg (6%).

$^1$H NMR (600MHz, (CD$_3$)$_2$SO, (CH$_3$)$_2$SO) $\delta$ 0.86 (3H, t, J = 7.3 Hz), 1.49 - 1.59 (2H, m), 1.67 - 1.76 (2H, m), 2.04 (3H, s), 2.18 (3H, s) but there is another singlet close to this one at 2.21 due to WET-pulse, 2.54 - 2.58 (IH, m), 2.84 (2H, t, J = 7.2 Hz), 2.96 - 3.01 (2H, m), 3.12 - 3.20 (2H, m), 4.44 - 4.53 (2H, m), 7.22 - 7.33 (3H, m), 7.35 - 7.39 (2H, m), 8.52 (IH, s), 11.61 - 11.66 (IH, m).

MS $^{m/z}$: 516 (M+l), 514 (M-I).

GTPyS(IC$_{50}$ µM): 0.0175

Example 11

1-[5-Butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(4-methoxybenzyl)sulfonyl] piperidine-4-carboxamide

Prepared according to Example 9 from 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylic acid (Example 1(h)) (48 mg, 0.14 mmol) and 1-(4-methoxyphenyl)methanesulfonamide (28 mg, 0.14 mmol) to give 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(4-methoxybenzyl)sulfonyl]piperidine-4-carboxamide. Yield: 47 mg (63%).

$^1$H NMR (600MHz, (CD$_3$)$_2$SO, (CH$_3$)$_2$SO) $\delta$ 0.86 (3H, t, J = 7.5 Hz), 1.49 - 1.57 (2H, m), 1.60 - 1.69 (2H, m), 1.79 - 1.86 (2H, m), 2.35 (3H, s), 2.57 - 2.62 (IH, m), 2.85 (2H, t, J = 7.2 Hz), 3.14 - 3.22 (2H, m), 3.72 (3H, s), 4.52 - 4.57 (2H, m), 4.58 (2H, s), 6.92 (2H, d, J = 8.5 Hz), 7.17 (2H, d, J = 8.5 Hz), 8.54 (IH, s), 11.52 (IH, s).

MS $^{m/z}$: 531 (M+l), 529 (M-I).

GTPyS(IC$_{50}$ µM): 0.0268
Example 12

1-[5-Butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[4-fluorobenzyl)sulfonyl]piperidine-4-carboxamide

Prepared according to Example 9 from 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylic acid (Example 1(h)) (48 mg, 0.14 mmol) and 1-(4-fluorophenyl)methanesulfonamide (26 mg, 0.14 mmol) to give 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[4-fluorobenzyl)sulfonyl]piperidine-4-carboxamide. Yield: 59 mg (81%).

1H NMR (600MHz, (CD$_3$)$_2$SO, (CH$_3$)$_2$SO) δ 0.86 (3H, t, J = 7.5 Hz), 1.49 - 1.57 (2H, m), 1.59 - 1.66 (2H, m), 1.79 - 1.85 (2H, m), 2.35 (3H, s), 2.55 - 2.62 (IH, m), 2.85 (2H, t, J = 7.2 Hz), 3.13 - 3.21 (2H, m), 4.51 - 4.58 (2H, m), 4.67 (2H, s), 7.18 - 7.24 (2H, m), 7.28 - 7.32 (2H, m), 8.54 (IH, s), 11.59 (IH, s)

MS m/z: 519 (M+1), 517 (M-I).

GTPyS(IC$_{50}$ µM): 0.0130

Example 13

1-[5-Butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[2,4-difluorobenzyl)sulfonyl]piperidine-4-carboxamide

Prepared according to Example 9 from 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylic acid (Example 1(h)) (48 mg, 0.14 mmol) and 1-(2,4-difluorophenyl)methanesulfonamide (29 mg, 0.14 mmol) to give 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[2,4-difluorobenzyl)sulfonyl]piperidine-4-carboxamide. Yield: 19 mg (25%).

1H NMR (600MHz, (CD$_3$)$_2$SO, (CH$_3$)$_2$SO) δ 0.86 (3H, t, J = 7.3 Hz), 1.49 - 1.57 (2H, m), 1.60 - 1.69 (2H, m), 1.82 - 1.90 (2H, m), 2.04 (3H, s), 2.58 - 2.62 (IH, m), 2.85 (2H, t, J = 7.2 Hz), 3.14 - 3.24 (2H, m), 4.52 - 4.58 (2H, m), 4.70 (2H, s), 7.11 - 7.17 (IH, m), 7.26 - 7.33 (IH, m), 7.40 - 7.47 (IH, m), 8.53 (IH, s), 11.73 (IH, s)

MS m/z: 537 (M+1), 535 (M-I).

GTPyS(IC$_{50}$ µM): 0.0355
Example 14

l-[5-Butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(4-methylbenzyl)sulfonyl]piperidine-4-carboxamide

Prepared according to Example 9 from l-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylic acid (Example 1(h)) (48 mg, 0.14 mmol) and l-(4-methylphenyl)methanesulfonamide (26 mg, 0.14 mmol) to give l-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(4-methylbenzyl)sulfonyl]piperidine-4-carboxamide. Yield: 29 mg (40%).

1H NMR (600 MHz, (CD$_3$)$_2$SO, (CH$_3$)$_2$SO) δ 0.86 (3H, t, J = 7.3 Hz), 1.49 - 1.57 (2H, m), 1.59 - 1.69 (2H, m), 1.78 - 1.86 (2H, m), 2.54 - 2.62 (IH, m), 2.77 (3H, s), 2.85 (2H, t, J = 7.2 Hz), 3.13 - 3.22 (2H, m), 4.52 - 4.57 (2H, m), 4.60 (2H, s), 7.14 (2H, d, J = 8.2 Hz), 7.17 (2H, d, J = 7.9 Hz), 8.54 (IH, s), 11.53 (IH, s). 3 Hydrogens (thiometyl) difficult to detect due to the wet NMR recording.

MS m/z: 515 (M+1), 513 (M-I).

GTPyS(IC$_{50}$ µM): 0.0852

Example 15

N-(Benzylsulfonyl)-l-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxamide

Prepared according to Example 9 from l-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylic acid (Example 1(h)) (48 mg, 0.14 mmol) and 1-(phenyl)methanesulfonamide (24 mg, 0.14 mmol) to give N-(benzylsulfonyl)-l-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxamide. Yield: 56 mg (80%).

1H NMR (600 MHz, (CD$_3$)$_2$SO, (CH$_3$)$_2$SO) δ 0.87 (3H, t, J = 7.5 Hz), 1.49 - 1.57 (2H, m), 1.59 - 1.69 (2H, m), 1.78 - 1.86 (2H, m), 2.54 - 2.60 (IH, m), 2.85 (2H, t, J = 7.2 Hz), 3.13 - 3.22 (2H, m), 4.51 - 4.57 (2H, m), 4.66 (2H, s), 7.24 - 7.28 (2H, m), 7.34 - 7.39 (3H, m), 7.39 (3H, s), 8.54 (IH, s), 8.54 (IH, s).

MS m/z: 501 (M+1), 499 (M-I).

GTPyS(IC$_{50}$ µM): 0.0170
Example 16
1-[5-Butyryl-3-cyano-6-(hydroxymethyl)pyridin-2-yl]-N-[1-phenylcyclopropylsulfonyl]piperidine^-carboxamide

(a) Ethyl 4-[(3,4-dimethoxybenzyl)oxy]-3-oxobutanoate

Prepared essentially according to the procedure described by Yasohara Y et al, (Tetrahedron assymetry, 12(2001) pp. 1713-18) replacing bensylalcohol for (3,4-dimethoxyphenyl)methanol. Yield: 9.65 g (44%).

$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 1.17 (3H, t, $J = 7.3$ Hz), 3.57 (2H, s), 3.75 (3H, s), 3.76 (3H, s), 4.08 (2H, q, $J = 7.2$ Hz), 4.20 (2H, s), 4.44 (2H, s), 6.84 - 6.96 (3H, m)

MS $m/z$: 295 (M-I)

(b) Ethyl 4-[(3,4-dimethoxybenzyl)oxy]-2-[(dimethylamino)methylene]-3-oxobutanoate

1,1-Dimethoxy-N,N-dimethylmethanamine was added to a solution of ethyl 4-[(3,4-dimethoxybenzyl)oxy]-3-oxobutanoate in EtOH (40 mL) at r.t. (N2-atmosphere) and the pale yellow mixture was stirred over night (17 hours, LC-MS showed complete conversion). The solvent and excess reagents were evaporated and the crude product (red oil) was used without further purification in the next step.

(c) Ethyl 5-cyano-2-[(3,4-dimethoxybenzyl)oxy]methyl]-6-oxo-1,6-dihydropyridine-3-carboxylate

Malonitrile (5.44 g, 82.4 mmol) dissolved in EtOH (absolut, 20 mL) was added to a solution of ethyl 4-[(3,4-dimethoxybenzyl)oxy]-2-[(dimethylamino)methylene]-3-oxobutanoate (26.32 g, 74.9 mmol, from above) and TEA (758 mg, 7.49 mmol) in EtOH (40 mL) at r.t. (slightly exotermic) under an N2-atm. The agitation had stopped after 15 minutes and EtOH (40 mL) was added to allow stirring and the stirring of the slurry was continued over night (27 hours). The reaction was quenched by adding HOAc (5.4 g, 89.9
mmol, a thick precipitate was formed) and water (200 mL). The thick brownish precipitate was filtered off and washed with water (3 x 150 mL), water / EtOH (2/1, 150 mL) (a green solid) and Et₂O (100 mL + 150 mL) (a light green-grey coloured solid). The solid was dried in vacuo at 70 °C to give ethyl 5-cyano-2-[[3,4-dimethoxybenzyl]oxy]methyl]-6-oxo-1,6-dihydropyridine-3-carboxylate of the product as a light green-grey solid. Yield 18.5 g (66 %).

^1H NMR (500 MHz, DMSO-d₆) δ 1.26 (3H, t, J = 7.1 Hz), 3.74 (6H, d, J = 3.1 Hz), 4.20 (2H, q, J = 7.1 Hz), 4.53 (2H, s), 4.80 (2H, s), 6.86 - 7.00 (3H, m), 8.42 (1H, s)

MS m/z: 390 (M+NH₄), 371 (M-I)

(c) Ethyl 6-(benzyloxy)-5-cyano-2-[[3,4-dimethoxybenzyl]oxy]methyl]nicotinate

Benzylbromide (12.75 g, 74.5 mmol) was added to a slurry of ethyl 5-cyano-2-[[3,4-dimethoxybenzyl]oxy]methyl]-6-oxo-1,6-dihydropyridine-3-carboxylate (18.5 g, 49.7 mmol) and K₂CO₃ (13.73 g, 99.4 mmol) in CH₃CN (400 mL) and the mixture was heated to reflux for 4.5 hours. The reaction was filtered and the solvent was evaporated. The residue was dissolved in EtOAc (400 mL) and the organic phase was washed with water (40 mL). The phases were separated (slow phase separation) and the organic phase was dried (MgSO₄), filtered and evaporated to give 27.3 g of the crude product as a black oil (the crude product contained both O- (Rf= 0.36, diethyl ether/petroleum ether 6/4) and N-alkylated (Rf= 0.14 diethyl ether/petroleum ether 6/4) products). The crude product was purified by flash chromatography on silica. (1000 g, SiO₂, Eluent: 1400 mL 1/1, 3500 mL 6/4, 1400 mL 7/3, 1400 mL 4/1, 700 mL 9/1 and 1400 mL 100/0 of diethyl ether/petroleum ether). The fractions with Rf= 0.36 was collected and evaporated to give ethyl 6-(benzyloxy)-5-cyano-2-[[3,4-dimethoxybenzyl]oxy]methyl]nicotinate as a light yellow solid. Yield: 12.02 g (52%)

^1H NMR (400 MHz, DMSO-d₆) δ 1.27 (3H, t), 3.68 (3H, s), 3.70 (3H, s), 4.25 (2H, m), 4.47 (2H, s), 4.86 (2H, s), 5.55 (2H, s), 6.79 (3H, m), 7.31-7.40 (3H, m), 7.46-7.50 (2H, m), 8.58 (1H, s).

MS m/z: 463 (M+1).

(d) 6-(Benzyloxy)-5-cyano-2-[[3,4-dimethoxybenzyl]oxy]methyl] nicotinic acid
NaOH (1.68 g, 42 mmol) dissolved in water (40 mL) was added to a solution of ethyl 6-(benzyloxy)-5-cyano-2-\{[(3,4-dimethoxybenzyl)oxy]methyl\}nicotinate (12.0 g, 25.9 mmol) in CH₃CN (60 mL) at r.t. (2 phase system slurry in the upper layer) and the mixture was heated to 55 °C (bath temp) for 1 hour (the reaction mixture was homogenous after 5 minutes, LC-MS showed complete conversion). The organic solvent was evaporated and water (30 mL) was added followed by acetic acid (2.4 mL) dropwise during stirring. The precipitated product was taken up in DCM (200 mL). The water phase was extracted with an additional 30 mL DCM. The combined organic phase was passed through a phase separator and evaporated to give the crude product as an oil. The crude product was triturated by adding 5-10 mL Et₂O/100 mL Petroleum ether while stirring which gave the product as a solid. The solid was filtered off, washed with Peth. ether and dried in vacuo over night to give 6-(benzyloxy)-5-cyano-2-\{[(3,4-dimethoxybenzyl)oxy]methyl\}nicotinic acid as an off white solid. Yield: 10.66 g (95%).

$^1$H NMR (400 MHz, DMSO-d$_6$) δ 3.69 (3H, s), 3.71 (3H, s), 4.50 (2H, s), 4.92 (2H, s), 5.57 (2H, s), 6.81-6.93 (3H, m), 7.32-7.41 (3H, m), 7.47-7.51 (2H, m), 8.58 (IH, s), 13.48 (IH, bs).

MS $^{m/z}$: 435 (M+1), 433 (M-I).

(c) 6-(Benzyloxy)-5-cyano-2-\{[(3,4-dimethoxybenzyl)oxy]methyl\}nicotinoyl fluoride

Cyanuric fluoride (4.54 g, 33.6 mmol) was added (during about 2 minutes) to a solution of 6-(benzyloxy)-5-cyano-2-\{[(3,4-dimethoxybenzyl)oxy]methyl\}nicotinic acid and pyridine (2.66 g, 33.6 mmol) in DCM (100 mL) at 0 °C and the reaction was allowed to reach r.t. and stirred for 1 hour and 15 minutes.

The reaction mixture was filtered and DCM (80 mL) was added to the solution and the organic phase was washed with water (2x20 mL). The organic phase was passed through a phase separator and the solvent was evaporated and the product was dried under vaccum over night to give 6-(benzyloxy)-5-cyano-2-\{[(3,4-dimethoxybenzyl)oxy]methyl\}nicotinoyl fluoride as a brown solid. The crude product was used without further purification in the next step. Yield: 9.38g (96 %).
(f) 2-(Benzyloxy)-5-butyryl-6-[(3,4-dimethoxybenzyl)oxy]methyl nicotinonitrile

n-Propylmagnesium bromide (0.88 + 0.4 mL, 1.25 M in THF, 1.6 mmol) was added dropwise to a cold solution (not completely homogenous) of 6-(benzyloxy)-5-cyano-2-[(3,4-dimethoxybenzyl)oxy]methyl nicotinoyl fluoride (436 mg, 1 mmol) and ferric acetylacetonate (14 mg, 0.04 mmol) in THF (10 mL) at 0 °C (red solution before addition, at the end of the addition the mixture took a much darker brownish color, after a few minutes the mixture changed to red again). The mixture was stirred for 10 minutes and the reaction was quenched by adding NH$_4$Cl (5 mL). Added EtOAc (50 mL) and water (5 mL). Extracted and separated the phases. The water phase was extracted with an additional 10 mL EtOAc. The combined organic phase was washed with brine and dried (Na$_2$SO$_4$). Filtration followed by evaporation gave 403 mg of the crude product as a brown-red oil. Purification was done by preparative HPLC (Kromasil C$_8$, column dimensions: 250 x 50 mm ID; Mobile-phase A water/MeCN/FA 95/5/0.2, Mobile-phase B MeCN. Gradient 30% to 95% of mobile-phase B in mobile phase A over 35 minutes. Fraction volume 50 mL). The relevant fractions were collected and evaporated to give 2-(benzyloxy)-5-butyryl-6-[(3,4-dimethoxybenzyl)oxy]methyl nicotinonitrile. Yield: 150 mg (33%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 0.95 (3H, t), 1.68 (2H, sextett), 2.77 (2H, t), 3.87 (6H, s), 4.53 (2H, s), 4.84 (2H, s), 5.58 (2H, s), 6.80-6.87 (2H, m), 6.88-6.90 (IH, m), 7.30-7.39 (3H, m), 7.45 (2H, m), 8.58 (IH, s).

MS $^m/z$: 461 (M+1), 459 (M-I).
(g) 5-Butyryl-6-\{[(3,4-dimethoxybenzyl)oxy]methyl\}-2-oxo-1,2-dihydropyridine-3-carbonitrile

Pd/C (5 weight % Pd, 50 % water, 497 mg, 5 mol % Pd) sluried in EtOH (3 mL) was added to a solution of 2-(benzyloxy)-5-butyryl-6-\{[(3,4-dimethoxybenzyl)oxy]methyl\}nicotinonitrile (1.075 g, 2.33 mmol) in MeOH/THF (60 mL 1/1) and the mixture was hydrogenated at atmospheric pressure for 1 hour. The mixture was filtered through HYFLO, washed with MeOH and evaporated (precipitation occured during evaporation, possibly when THF evaporated). This gave 797 mg of the crude product as a yellow solid.

Purification was done by preparative reverse phase HPLC (Kromasil C\textsubscript{8} column dimensions: 250 x 50 mm ID; Mobile-phase A water/MeCN/FA 95/5/0.2, Mobile-phase B MeCN. Gradient 20\% to 70\% of Mobile-phase B in Mobile phase A over 30 minutes. Fraction volume 50 mL; detection at 330 nM). The relevant fractions were collected and the MeCN was evaporated. The precipitated product was extracted into DCM (100 mL). The organic phase was washed with NaHCO\textsubscript{3}(saturated) (20 mL), passed through a phase separator and evaporated to give pure 5-butyryl-6-\{[(3,4-dimethoxybenzyl)oxy]methyl\}-2-oxo-1,2-dihydropyridine-3-carbonitrile as a light yellow solid. Yield: 359 mg (41\%).

\textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) \\begin{align*}
\delta & \quad \text{0.86 (3H, m),} \\
& \quad \text{1.50 (2H, sextett),} \\
& \quad \text{2.80 (2H, t),} \\
& \quad \text{3.73 (3H, s),} \\
& \quad \text{3.74 (3H, s),} \\
& \quad \text{4.52 (2H, s),} \\
& \quad \text{4.73 (2H, s),} \\
& \quad \text{6.85-6.92 (2H, m),} \\
& \quad \text{6.98 (IH, s),} \\
& \quad \text{8.68 (IH, s),} \\
& \quad \text{12.23 (IH, bs).}
\end{align*}

MS \text{m/z}: 369 (M-I).

(h) tert-Butyl 1-(5-butyryl-3-cyano-6-\{[(3,4-dimethoxybenzyl)oxy]methyl\}pyridin-2-yl)piperidine-4-carboxylate

5-butyryl-6-\{[(3,4-dimethoxybenzyl)oxy]methyl\} -2-oxo-1,2-dihydropyridine-3 -carbonitrile (200mg, 0.54mmol), was charged together with PyBOP (337mg, 0.81mmol, 1.2 eq.) and DIPEA (470\µL, 5 eq.) in DCM (2 mL) and stirred at 22\° C for 30 minutes before tert-butyl piperidine-4-carboxylate (300 mg, 0.81mmol, 1 eq.), was added. The reaction mixture was stirred over night. Formic acid ca 2\% in water was added and the organic phase was separated (Phase Separator) and concentrated to give 976 mg of a
yellow oil. Purification by preparative HPLC (Kromasil Cg, using an increasing gradient of MeCN in water/0.2 % FA) gave tert-butyl 1-(5-butyryl-3-cyano-6-([(3,4-dimethoxybenzyl)oxy]methyl)pyridin-2-yl)piperidine-4-carboxylate as a light yellow oil. Yield: 239 mg (89%).

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \] \( \delta \) 0.96 (3H, t, J = 7.4 Hz), 1.45 (9H, s), 1.63 - 1.73 (2H, m), 1.75 - 1.86 (2H, m), 1.94 - 2.05 (2H, m), 2.47 - 2.58 (IH, m), 2.73 - 2.77 (2H, m), 3.27 - 3.34 (2H, m), 3.87 (3H, s), 3.88 (3H, s), 4.55 - 4.64 (2H, m), 4.84 (2H, s), 6.78 - 6.94 (3H, m), 8.08 (IH, s).

MS \( m/z \): 538 (M+1), 536 (M-I).

(i) 1-[5-Butyryl-3-cyano-6-(hydroxymethyl)pyridin-2-yl] piperidine-4-carboxylic acid

TFA (2 mL) was added to a solution of tert-butyl 1-(5-butyryl-3-cyano-6-([(3,4-dimethoxybenzyl)oxy]methyl)pyridin-2-yl)piperidine-4-carboxylate (239 mg, 0.44 mmol) in DCM (2 mL) at 0 °C. The reaction was stirred for 15 minutes and then left at r.t. for 1 hour. The solvent was evaporated and the crude product was purified by preparative-HPLC to give 1-[5-butyryl-3-cyano-6-(hydroxymethyl)pyridin-2-yl]piperidine-4-carboxylic acid as a light yellow solid. Yield: 36mg (25%)  

\[ ^1H \text{NMR (400 MHz, DMSO-d}_6 \] \( \delta \) 0.88 (3H, t, J = 7.4 Hz), 1.49 - 1.57 (2H, m), 1.57 - 1.67 (2H, m), 1.85 - 1.98 (2H, m), 2.55 - 2.63 (IH, m), 2.86 (2H, t, J = 7.1 Hz), 4.46 - 4.56 (2H, m), 4.64 - 4.71 (2H, m), 4.77 - 4.81 (2H, m), 8.52 (IH, s), 12.21 - 12.44 (IH, m).

MS \( m/z \): 332 (M+1), 330 (M-I).

(j) 1-[5-Butyryl-3-cyano-6-(hydroxymethyl)pyridin-2-yl]-N-[(1-phenylcyclopropyl)sulfonyl] piperidine-4-carboxamide

A mixture of 1-[5-butyryl-3-cyano-6-(hydroxymethyl)pyridin-2-yl]piperidine-4-carboxylic acid (35 mg, 0.11 mmol), PyBOP (66 mg, 0.13 mmol, 1.2 eq.), 1-phenylcyclopropanesulfonamide (22 mg, 0.11 mmol) and DIPEA (92 µL, 5 eq.) in DCM (1mL) was stirred at r.t. for 2 hours (ca 60% conversion according to LC-MS). An additional amount of PyBOP (30 mg) and 1-phenylcyclopropanesulfonamide (15 mg) and DIPEA (50 µL) were added and the reaction mixture was stirred over night. Formic acid ca
2% in water was added and the organic phase was separated (Phase Separator) and concentrated to a crude product which was purified by preparative HPLC (Kromasil Cs, using an increasing gradient of MeCN in water/0.2 % FA) to give 1-[5-butyryl-3-cyano-6-(hydroxymethyl)pyridin-2-yl]-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide as a light yellow solid. Yield: 37 mg (69%).

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 0.88 (3H, t, J = 7.4 Hz), 1.29 - 1.37 (2H, m), 1.50 - 1.57 (2H, m), 1.59 - 1.69 (2H, m), 1.73 - 1.83 (4H, m), 2.52 - 2.56 (IH, m), 2.87 (2H, t, J = 7.2 Hz), 3.05 - 3.18 (2H, m), 4.55 - 4.65 (2H, m), 4.69 (2H, s), 4.76 - 4.84 (IH, m), 7.28 - 7.48 (5H, m), 8.54 (IH, s), 8.54 (IH, s).

MS $m/z$: 511 (M+1), 509 (M-I).

GTPyS(IC$_{50}$µM): 0.049

Example 17

1-(5-Butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(1-phenylcyclopropyl)sulfonyl] piperidine-4-carboxamide

Prepared according to Example 1(i) from 1-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)piperidine-4-carboxylic acid (Example 2(e)) (50 mg, 0.15 mmol) and 1-phenylcyclopropanesulfonamide (33 mg, 0.17 mmol) to give 1-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide. Yield: 58 mg (75%).

$^1$H NMR (600 MHz, DMSO-d$_6$): $\delta$ 0.87 (3H, t, J = 7.4 Hz), 1.29 - 1.33 (2H, m), 1.50 - 1.57 (2H, m), 1.57 - 1.65 (2H, m), 1.74 - 1.80 (4H, m), 2.50 - 2.56 (IH, m), 2.82 (2H, t, J = 7.1 Hz), 3.09 - 3.17 (2H, m), 3.96 (3H, s), 4.50 - 4.57 (2H, m), 7.35 - 7.42 (5H, m), 8.21 (IH, s), 11.36 (IH, br s).

MS $m/z$: 511 (M+1), 509 (M-I).

GTPyS(IC$_{50}$µM): 0.248
Example 18

(a) l-(5-butyryl-3-cyano-6-oxo-1,6-dihydropyridin-2-yl)piperidine-4-carboxylic acid

1 M tribromoborane (BBr3) solution in DCM (2.0 mL, 2.0 mmol) was added drop wise to a cooled solution of tert-butyl l-(5-butyryl-3-cyano-6-methoxypyridin-2-yl)piperidine-4-carboxylate (520 mg, 1.34 mmol, prepared according to example 2 (d)) in dry DCM (10 mL) at 0°C under N2-atm. The reaction mixture was stirred at 0°C for 1h 40min. Water and NaHCO3(aq) were added and the mixture was extracted with DCM (x3). The combined organics was run through a phase separator and evaporated (mostly containing the corresponding methylester by-product). The aqueous phase was made acidic by addition of 6 M HCl and extracted with DCM (x3). The combined organics was run through a phase separator and evaporated (mostly containing the acid product). The two crudes were purified by preparative HPLC (Kromasil Cg 1.0µm, 50x250mm, using an increasing gradient of 30% to 80 % MeCN with a second acidic eluent H2O/MeCN/FA 95/5/0.2) during 30 minutes) to give l-(5-butyryl-3-cyano-6-oxo-1,6-dihydropyridin-2-yl)piperidine-4-carboxylic acid as a solid. Yield: 146 mg (34%). The methyl l-(5-butyryl-3-cyano-6-oxo-1,6-dihydropyridin-2-yl)piperidine-4-carboxylate was also isolated as a solid. Yield: 154 mg (35%).

MS m/z: 318 (M+1), 316 (M-I).

(b) l-(6-(1H-benzo[d][1,2,3]triazol-1-yl oxy)-5-butyryl-3-cyanopyridin-2-yl)-N-(1-phenylcyclopropylsulfonyl)piperidine^-carboxamide

A mixture of l-(5-butyryl-3-cyano-6-oxo-1,6-dihydropyridin-2-yl)piperidine-4-carboxylic acid (146 mg, 0.46 mmol), PyBop (563 mg, 1.08 mmol), DIPEA (0.4 mL, 297 mg, 2.30 mmol) in DCM (8 mL) was stirred at r.t for 20min and 1-phenylcyclopropane-1-sulfonamide (91 mg, 0.46 mmol) was added. The reaction mixture was stirred at r.t over night. NaHCO3(aq) was added and the mixture was extracted with DCM (x3). The combined organics was run through a phase separator and evaporated. The crude product was purified by preparative HPLC (Kromasil Cg 1.0µm, 50x250mm, using an increasing gradient of 30% to 80 % MeCN with a second acidic eluent H2O/MeCN/FA 95/5/0.2) during 30 minutes) to give l-(6-(1H-benzo[d][1,2,3]triazol-1-yl oxy)-5-butyryl-3-
cyanopyridin-2-yl)-N-(1-phenylcyclopropylsulfonyl)piperidine-4-carboxamide as a white solid. Yield: 230 mg (81%).

MS \( m/z \): 614 (M+l), 612 (M-I).

(c) HS-Butyryl-S-cyano-6-Cethythiojpyridin-l-ylj-N-Kl-phenylcyclopropyljsulfonyljpiperidine\^ carboxamide

Ethanethiol (0.5 mL, 420 mg, 6.75 mmol) was added to a solution of 1-(6-(1H-benzo[d][1,2,3]triazol-1-yl)oxy)-5-butyryl-3-cyanopyridin-2-yl)-N-(1-phenylcyclopropylsulfonyl)piperidine-4-carboxamide (153 mg, 0.25 mmol) in EtOH (3 mL) and DIPEA (0.1 mL, 74.2 mg, 0.57 mmol). The reaction mixture was heated to 120°C for 10 min in a single node microwave oven. LCMS showed starting material left.

Ethanethiol (0.5 mL, 420 mg, 6.75 mmol) was added and the reaction mixture was heated to 120°C for 20 min in a single node microwave oven. NaHCO\(_3\) (aq) was added and the mixture was extracted with DCM (x3). The combined organics was run through a phase separator and evaporated. The crude product was purified by preparative HPLC (Kromasil C\(_8\) 1\(\mu\)m, 20x250 mm, using an increasing gradient of 40% to 80% MeCN with a second acidic eluent H\(_2\)O/MeCN/FA 95/5/0.2) during 25 minutes) to give 1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide as a white solid. Yield: 60 mg (45%).

\(^1\)H NMR (600 MHz, DMSO-d\(_6\)) : \( \delta \) 0.88 (3H, t, \( J = 7.4 \) Hz), 1.26 (3H, t, \( J = 7.3 \) Hz), 1.29 - 1.33 (2H, m), 1.52 - 1.59 (2H, m), 1.59 - 1.67 (2H, m), 1.75 - 1.82 (4H, m), 2.52 - 2.58 (IH, m), 2.84 (2H, t, \( J = 7.1 \) Hz), 3.01 (2H, q, \( J = 7.3 \) Hz), 3.14 - 3.20 (2H, m), 4.48 - 4.54 (2H, m), 7.33 - 7.38 (3H, m), 7.39 - 7.43 (2H, m), 8.48 (IH, s), 11.23 (IH, br s).

MS \( m/z \): 541 (M+l), 539 (M-I).

GTPyS(IC\(_{50}\) µM): 0.017
Example 19

l- [5-Butyryl-3-cyano-6-(propylthio)pyridin-2-yl]-N-[(l-phenylcyclopropyl)sulfonyl]piperidine^carboxamide

Prepared according to Example 18(c) from 1-(6-(lH-benzo[d][1,2,3]triazol-l-yloxy)-5-butyryl-3-cyanopyridin-2-yl)-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide (Example 18(b)) (77 mg, 0.13 mmol) and propane-1-thiol (1.0 mL, 841 mg, 11.0 mmol) to give l-[5-Butyryl-3-cyano-6-(propylthio)pyridin-2-yl]-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide as a white solid. Yield: 31.1 mg (45%).

^H NMR (600 MHz, DMSO-d$_6$); δ 0.88 (3H, t, J = 7.4 Hz), 0.97 (3H, t, J = 7.3 Hz), 1.29 - 1.33 (2H, m), 1.52 - 1.59 (2H, m), 1.59 - 1.67 (4H, m), 1.76 - 1.82 (4H, m), 2.52 - 2.59 (IH, m), 2.84 (2H, t, J = 7.2 Hz), 2.98 (2H, t, J = 7.3 Hz), 3.15 - 3.20 (2H, m), 4.48 - 4.54 (2H, m), 7.34 - 7.38 (3H, m), 7.39 - 7.43 (2H, m), 8.47 (IH, s), 11.23 (IH, br s).

MS $m/z$: 555 (M+l), 553 (M-I).

GTPyS(IC$_{50}$ µM): 0.032

Example 20

l-(5-Butyryl-3-cyano-6-(methylthio)pyridin-2-yl)-N-((trans)-2-phenylcyclopropylsulfonyl)piperidine^carboxamide

DIPEA (74.2 mg, 0.574 mmol) was added to a suspension of l-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxylic acid (See Example 1(h)) (42 mg, 0.12 mmol) and PyBOP (92 mg, 0.28 mmol) in DCM (4 mL). The reaction mixture was stirred at r.t. for 15 min. and (trans)-2-phenylcyclopropane-1-sulfonamide (23.8 mg, 0.12 mmol) was added. The reaction mixture was stirred at r.t. over night. NaHCO$_3$(aq) was added and the mixture was extracted with DCM (x3). The combined organics was run through a phase separator and evaporated. The crude product was purified by preparative HPLC (Kromasil C$_8$ 1µm, 50x250 ID mm, using an increasing gradient of 20% to 80 % MeCN with a second acidic eluent H$_2$CVMeCNZFA 95/5/0.2 during 20 minutes with a flow of 19 mL/min) to give l-(5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl)-N-((trans)-2-phenylcyclopropylsulfonyl)piperidine-4-carboxamide as a solid. Yield: 64 mg (46%).
$^1$H NMR (600 MHz, DMSO-d$_6$): δ 0.86 (3H, t), 1.49 - 1.55 (2H, m), 1.55 - 1.64 (3H, m), 1.64 - 1.69 (IH, m), 1.83 - 1.90 (2H, m), 2.32 (3H, s), 2.63 - 2.70 (2H, m), 2.84 (2H, t), 3.11 - 3.16 (2H, m), 3.18 - 3.26 (2H, m), 4.46 - 4.53 (2H, m), 7.14 - 7.17 (2H, m), 7.17 - 7.21 (IH, m), 7.23 - 7.28 (2H, m), 8.51 (IH, s), 11.87 (IH, br s).

MS $^{m/z}$: 527 (M+1), 525 (M-I).

GTPyS (IC$_{50}$ µM): 0.081

Example 2.1

1-(5-Butyryl-3-cyano-6-(isobutylthio)pyridin-2-yl)-N-((1-phenylcyclopropylsulfonyl)piperidine^-carboxamide

1-(6-(1H-Benz[d][1,2,3]triazol-1-ylxylo)-5-butyryl-3-cyanopyridin-2-yl)-N-(1-phenylcyclopropylsulfonyl)piperidine-4-carboxamide (See Example 18(b)) (48 mg, 0.08 mmol) was dissolved in THF (3 mL) and 2-methylpropane-1-thiol (0.5 mL, 4.62 mmol) was added. The reaction mixture was heated to 120 °C for 30 min in a single node microwave oven. LCMS showed product/starting material in a ratio 1:6. The reaction mixture was heated again to 120 °C for 30 min, but failure with the microwave oven led to heating to 220 °C. NaHCO$_3$(aq) was added and the mixture was extracted with DCM (x3). The combined organics was run through a phase separator and evaporated. The crude product was purified by preparative HPLC (Kromasil C$_8$ 10 µm, 250x20 ID mm using an increasing gradient of 30-90% MeCN with a second acidic eluent H$_2$O/MeCN/FA 95/5/0.2 over 25 minutes with a flow of 19 mL/min) to give 1-(5-butyryl-3-cyano-6-(isobutylthio)pyridin-2-yl)-N-(1-phenylcyclopropylsulfonyl)piperidine-4-carboxamide as a solid. Yield: 4.3 mg (10%).

$^1$H NMR (400 MHz, DMSO-d$_6$): δ 0.88 (3H, t), 0.98 (6H, d, J = 6.6 Hz), 1.24 - 1.30 (2H, m), 1.49 - 1.67 (4H, m), 1.72 - 1.81 (4H, m), 1.81 - 1.93 (IH, m), 2.50 - 2.55 (IH, m), 2.85 (2H, t), 2.90 (2H, d), 3.13 - 3.23 (2H, m), 4.47 - 4.55 (2H, m), 7.31 - 7.37 (3H, m), 7.37 - 7.44 (2H, m), 8.52 (IH, s), 11.35 (IH, br s).

MS $^{m/z}$: 569 (M+1), 567 (M-I).

GTPyS (IC$_{50}$ µM): 0.025
Example 22

l-(5-Butyryl-3-cyano-6-(isopropylthio)pyridin-2-yl)-N-(l-phenylcyclopropylsulfonyl)piperidine^-carboxamide

Propane-2-thiol (0.050 mL, 0.53 mmol) was added to a suspension of sodium 2-methylbutan-2-olate (32 mg, 0.28 mmol) in dry THF (5 mL) at r.t. The mixture was stirred at r.t. for 20 minutes and l-(6-(1H-benzo[d][1,2,3]triazol-1-yl)-5-butyryl-3-cyanopyridin-2-yl)-N-(1-phenylcyclopropylsulfonyl)piperidine-4-carboxamide (See Example 18(b)) (50 mg, 0.08 mmol) dissolved in dry THF (5 mL) was added. The reaction mixture was stirred at r.t. for 1 hour. NaHCO\textsubscript{3} (aq) was added and the reaction mixture was extracted with DCM (x3). The combined organics was run through a phase separator and evaporated. The crude product was purified by preparative HPLC (Kromasil C\textsubscript{g}10 µm, 250x20 ID mm using a gradient of 40-90% MeCN with a second acidic eluant H2O/MeCN/FA 95/5/0.2 buffer over 20 minutes with a flow of 19 mL/min.) to give l-(5-butyryl-3-cyano-6-(isopropylthio)pyridin-2-yl)-N-(1-phenylcyclopropylsulfonyl)piperidine-4-carboxamide as a white solid. Yield: 33 mg (73%).

\textit{IH NMR} (600 MHz, DMSO-d6): \textit{δ} 0.86 (3H, t), 1.30 (6H, d), 1.48 - 1.56 (2H, m), 1.56 - 1.65 (2H, m), 1.74 - 1.79 (4H, m), 2.50 - 2.56 (IH, m), 2.83 (2H, t), 3.11 - 3.18 (2H, m), 3.83 (IH, septet), 4.49 - 4.55 (2H, m), 7.33 - 7.37 (3H, m), 7.37 - 7.41 (2H, m), 8.49 (IH, s), 11.35 (IH, br s).

\textit{MS m/Z}: 555 (M+), 553 (M-1).

GTPyS(IC\textsubscript{50} µM): 0.018

Example 23

l-(5-Butyryl-3-cyano-6-(cyclopropylthio)pyridin-2-yl)-N-(l-phenylcyclopropylsulfonyl)piperidine^-carboxamide

Cyclopropanethiol (2.200 mL of a ca 0.3 M solution in THF/Et2O, 0.66 mmol, See Dixon, D.A., JACS, 1992, No. 9, pp. 3492-99) was added to sodium 2-methylbutan-2-olate (0.077 g, 0.66 mmol) in THF (8 mL) and the mixture was stirred at r.t. for 5 minutes (a precipitate was formed). l-(6-(1H-benzo[d][1,2,3]triazol-1-yl)-oxy)-5-butyryl-3-
cyanopyridin-2-yl)-N-(1-phenylcyclopropylsulfonyl)piperidine-4-carboxamide (Example 18(b)) (0.135 g, 0.22 mmol) dissolved in THF (10 mL) was added and the mixture was stirred at r.t. for 40 minutes. NaHCO3(sat) (20 mL) was added and the mixture was extracted with DCM (40 + 30 mL). The combined organic phase was washed with Brine (10 mL) and dried (MgSO₄). Filtration followed by evaporation gave the crude product as an oil which was purified by preparative HPLC (Kromasil C₈ column (10 µm 250x50 ID mm) using a gradient of 40-90% MeCN with a second acidic eluant H₂CVMeCNZFA 95/5/0.2 over 30 minutes with a flow of 100 mL/min) to give l-(5-butyryl-3-cyano-6-(cyclopropylthio)pyridin-2-yl)-N-(l-phenylcyclopropylsulfonyl)piperidine-4-carboxamide as a solid. Yield: 64 mg (53%).

¹H NMR (600 MHz, DMSO-d₆): δ 0.5-0.56 (2H, m), 0.87 (3H, t), 1.01-1.08 (2H, m), 1.48-1.69 (4H, m), 1.74-1.82 (4H, m), 2.20-2.28 (IH, m), 2.4-2.59 (2H, m), 2.85 (2H, t), 3.12-3.23 (2H, m), 4.6-4.69 (2H, m), 7.33-7.43 (5H, m), 8.53 (IH, s), 11.36 (IH, br. s). One proton is overlapping with the watersignal in the DMSO-d₆ at 3.0 ppm.

MS m/z: 553 (M+1), 551 (M-I).

Example 24

Bioavailability study

The oral bioavailability of the compound (Example 1) l-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(l-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide in rats, administrated as a solution was evaluated in rats, by comparing with intravenous administration of the same solution.

The solution was prepared as a saline solution comprising the active compound.

Two rats were used both for i.v and p.o. administration in this study.

Two days prior to dosing, the rats were prepared by cannulation of the left carotid artery for blood sampling and, for the i.v. administration rats, by cannulation of the right jugular vein.
The catheters were filled with heparin (100 IU/mL), exteriorised at the nape of the neck and sealed. The surgery was performed under isoflurane (Forene®, Abbott) anaesthesia. After surgery the rats were housed individually and had free access to food and water. About 16 hours prior to dosing the animals were deprived of food, and fasting until 4 hours after dosing. The rats had free access to drinking water during the experiment. A cage card number identified the rats.

The p.o. test formulation was administered orally by gavage, with the dose being 5 µmol/kg, whereas the intravenously administered dose was given in the jugular vein, with the dose being 2 µmol/kg.

At pre-defined time points, blood samples of about 0.150 mL were withdrawn from the carotid artery, up to 24 h after dosing. About 10 samples were withdrawn. The blood samples were collected in heparinized plastic tubes and centrifuged, within 30 minutes, for five minutes at 10 000 g and +4°C. The plasma was transferred to a 96-well plate and stored at -20°C until analysis.

The plasma concentrations of the test item were determined by liquid chromatography and mass-spectrometric detection. The concentrations of the test item in the formulation were confirmed by liquid chromatography and mass-spectrometric detection.

Calculations
The area under the plasma concentration-time curve following oral and intravenous administration, AUC(o-t), was calculated using a combination of the linear and logarithmic trapezoidal rule from the time of administration to the sampling time with the last determinable plasma concentration. For the intravenous bolus dose, the concentration at time zero, C(O), was estimated by log linear regression of the first two concentration-time points. The AUC(O-t) was extrapolated to AUC by adding C/t/k. C/t is the predicted plasma concentration at the time of the last plasma sample with a determinable concentration, and k is the apparent terminal rate constant. C/t and k were obtained by linear least squares
regression analysis of the logarithm of the last 3 to 5 plasma concentrations versus time. The apparent terminal half-life ($t_{1/2}$) was calculated as $\ln 2/k$.

The bioavailability ($F$) was calculated as

$$F = \frac{\text{AUC}_{p.o.} \cdot \text{X} \cdot \text{mean}}{\text{AUC}_{p.o.} \cdot \text{X} \cdot \text{mean} \cdot \text{D} \cdot \text{Se}_{p.o.}} \times 100\%.$$

The results obtained were:

<table>
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<th>Animal</th>
<th>$\text{AUC}_{L.V.}$ (µM'h)</th>
<th>$\text{AUC}_{p.o.}$ (µM'h)</th>
<th>$F$ (%)</th>
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<tr>
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<td></td>
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<tr>
<td>Average</td>
<td>3.64</td>
<td>35.2</td>
<td></td>
</tr>
</tbody>
</table>
1. A compound of formula I or a pharmaceutically acceptable salt thereof:

\[
\text{(I)}
\]

wherein

- \( R_i \) represents \( R_y C(O) \);
- \( R_2 \) represents unsubstituted (\( C_3-C_6 \))alkylthio or unsubstituted hydroxy(\( C_3 \))alkyl;
- \( R_7 \) represents (\( C_3-C_6 \))alkyl optionally interrupted by oxygen, and/or optionally substituted by OH, aryl, (\( C_3-C_6 \))cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br or I) atoms; further \( R_7 \) represents (\( C_3-C_6 \))cycloalkyl, hydroxy(\( C_3-C_2 \))alkyl, aryl or heterocyclyl;
- \( R_{i4} \) represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (\( C\_3-C\_6 \))alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and COOR\( ^e \); wherein \( R^e \) represents aryl, (\( C_3-C_6 \))cycloalkyl, heterocyclyl or (\( C\_3-C\_6 \))alkyl optionally substituted by one or more of halogen (F, Cl, Br or I) atom(s), OH, aryl, (\( C_3-C_6 \))cycloalkyl and heterocyclyl; further \( R_{i4} \) represents aryl, aryl(\( C\_3-C\_6 \))alkyl, aryl(\( C\_3-C_3 \))alkoxy, heterocyclyl, a halogen (F, Cl, Br or I) atom, (\( C_3-C_6 \))cycloalkyl, (\( C_3-C_6 \))cycloalkyl(\( C\_3-C_8 \))alkoxy, hydroxy(\( C\_3-C_7 \))alkyl, (\( C\_3-C_6 \))alkoxy, (\( C_3-C_6 \))cycloalkoxy, (\( C\_3-C_6 \))alkylsulfonyl, (\( C\_3-C_6 \))alkylsulfonanyl, (\( C\_3-C_8 \))alkylthio, (\( C\_3-C_6 \))cycloalkylthio, or a...
group of formula \( NR^{a(14)}R^{b(14)} \) in which \( R^{a(14)} \) and \( R^{b(14)} \) independently represent \( H, (C_1-C_8)alkyl, (Ci-C_8)alkylC(O), (Ci-C_8)alkoxyC(O) \) or \( R^{a(14)} \) and \( R^{b(14)} \) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

\( R^c \) is a direct bond or represents an unsubstituted or monosubstituted or polysubstituted \((Ci-C_4)alkylene\) group, wherein any substituents each individually and independently are selected from \((Ci-C_4)alkyl, (Ci-C_4)alkoxy, \) \( \text{oxy}-(Ci-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_3-Ce)cycloalkyl, \) carboxyl, carboxy-(\(Ci-C_4)alkyl, \) aryl, heterocyclyl, cyano, halogeno (\(F, Cl, Br \) or I), hydroxyl, \( NR^{a(Rc)}R^{b(Rc)} \) in which \( R^{a(Rc)} \) and \( R^{b(Rc)} \) individually and independently from each other represents hydrogen, \((Ci-C_4)alkyl \) or \( R^{a(Rc)} \) and \( R^{b(Rc)} \) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; further \( R^c \) represents imino (-NH-), \( N \)-substituted imino (-NR19-), \((C_1-C_4)alkyleneimino \) or \( N \)-substituted \((Ci-C_4)alkyleneimino \) (\( -N(Ri)_g-(\text{(Ci-C_4)alkylene}) \) wherein the mentioned alkylene groups are unsubstituted or monosubstituted or polysubstituted with any substituents according to above;

\( R_{i_g} \) represents \( H \) or \((d-C_{4})alkyl\);

\( R^d \) represents \((Ci-C_i)alkyl, (C_3-C_g)cycloalkyl, \) aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (\(F, Cl, Br \) or I) atoms or mixed halogen atoms and/or one or more of the following groups, OH, CN, \((Ci-C_i)alkyl, (Ci-C_i)alkoxyC(O), (Ci-C_i)alkoxy, \) halogen substituted \((Ci-C_i)alkyl, (C_3-C_6)cycloalkyl, \) aryl, heterocyclyl, \((Ci-C_i)alkylsulfmyl, (Ci-C_i)alkylsulfonyl, (Ci-C_i)alkylthio, (C_3-Ce)cycloalkylthio, \) arylsulfenyl, arylsulfonyl, arylthio, aryl(Ci-C_i)alkylthio, aryl(Ci-C_i)cycloalkylthio, \( \text{heterocyclyl}(Ci-C_i)alkylsulfonyl, \) \( \text{heterocyclyl}(Ci-C_i)cycloalkylsulfenyl, \) \( \text{heterocyclyl}(Ci-C_i)cycloalkylsulfonyl, \) \( C_3-cycloalkyl(Ci-C_i)alkylthio, (C_3-C_g)cycloalkyl(Ci-C_i)alkylsulfmyl, (C_3-C_g)cycloalkyl(Ci-C_i)alkylsulfonyl \) or a group of formula \( NR^{a(Rd)}R^{b(Rd)} \) in which \( R^{a(Rd)} \) and \( R^{b(Rd)} \) independently represent \( H, (Ci-C_i)alkyl, (Ci-C_i)alkylC(O) \) or \( R^{a(Rd)} \) and \( R^{b(Rd)} \) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

\( X \) represents a single bond, imino (-NH-), methylene (-CH_2-), iminomethylene (-CH_2-NH-) wherein the carbon is connected to the B-ring/ring system, methyleneimino (-
NH-CH₂-) wherein the nitrogen is connected to the B-ring/ring system and any carbon
and/or nitrogen in these groups may optionally be substituted with (Ci-C₆) alkyl; further X
may represent a group (-CH₂-)n wherein n= 2-6, which optionally is unsaturated and/or
substituted by one or more substituent chosen among halogen, hydroxyl or (Ci-Ce)alkyl;
and

B is a monocyclic or bicyclic, 4 to 11-membered heterocyclic ring/ring system
comprising one or more nitrogen and optionally one or more atoms selected from oxygen
or sulphur, which nitrogen is connected to the pyridine-ring (according to formula I) and
further the B-ring/ring system is connected to X in another of its positions; the substituent
Rᵢ₄ is connected to the B ring/ring system in such a way that no quarternary ammonium
compounds are formed (by this connection).

2. A compound according to claim 1 wherein
R₇ represents unsubstituted (Ci-C₃)alkylthio or unsubstituted hydroxy(Ci-C₃)alkyl;

R₇ represents (Ci-C₃)alkyl optionally interrupted by oxygen, and/or optionally
substituted by OH, aryl, (C₃-C₆)cycloalkyl, heterocyclic or one or more halogen (F, Cl, Br
or I) atoms; further R₇ represents (C₃-Ce)cycloalkyl, hydroxy(Ci-Ce)alkyl, aryl or
heterocyclyl;

Rᵢ₄ represents H, OH with the proviso that the OH group must be at least 2 carbon
atoms away from any heteroatom in the B ring/ring system, (Ci-Ce)alkyl optionally
interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and
COORₓ; wherein Rₓ represents aryl, (C₃-C₆)cycloalkyl, heterocyclic or (d-C₃₋₆)alkyl
optionally substituted by one or more of halogen (F, Cl, Br or I) atom(s), OH, aryl,
cycloalkyl and heterocyclyl; further Rᵢ₄ represents aryl, aryl(Ci-Ce)alkyl, aryl(Ci-
Cs)alkoxy, heterocyclyl, a halogen (F, Cl, Br or I) atom, (C₃-Ce)cycloalkyl, (C₃₋₆)
cycloalkyl(Ci-Ce)alkoxy, hydroxy(Ci-Ce)alkyl, (Ci-Ce)alkoxy, (C₃-Ce)cycloalkoxy,
(Ci-C₆)alkylsulfmyl, (Ci-C₆)alkylsulfonyl, (Ci-C₆)alkylthio, (C₃-C₆)cycloalkylthio, or a
group of formula NRᵃ⁽¹⁴⁾Rᵇ⁽¹⁴⁾ in which Rᵃ⁽¹⁴⁾ and Rᵇ⁽¹⁴⁾ independently represent H, (Ci-
C₆)alkyl, (Ci-C₆)alkylC(O), (Ci-C₆)alkoxyC(O) or Rₐ(14) and Rₚ(14) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; and

Rᵈ represents (Ci-Ce)alkyl, (C₃-Ce)cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br or I) atoms or mixed halogen atoms and/or one or more of the following groups, OH, CN, (Ci-Ce)alkyl, (Ci-C₆)alkoxyC(O), (Ci-C₆)alkoxy, halogen substituted (d-C₆)alkyl, (C₃-C₆)cycloalkyl, aryl, heterocyclyl, (Ci-C₆)alkylsulfinyl, (Ci-C₆)alkylsulfonyl, (Ci-C₆)alkylthio, (C₃-Ce)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(Ci-Ce)alkylthio, aryl(Ci-C₆)cycloalkylthio, aryl(Ci-C₆)alkylsulfinyl, aryl(Ci-C₆)alkylsulfonyl, heterocyclyl(Ci-C₆)alkylthio, heterocyclyl(Ci-C₆)cycloalkylthio, heterocyclyl(Ci-C₆)cycloalkylsulfinyl, (C₃-C₆)cycloalkyl(Ci-C₆)alkylsulfinyl, (C₃-C₆)cycloalkyl(Ci-C₆)alkylsulfonyl, (C₃-C₆)cycloalkyl(Ci-C₆)alkylthio, or a group of formula N Rᵃ(4) Rᵇ(4) in which Rᵃ(4) and Rᵇ(4) independently represent H, (C₁-C₆)alkyl, (Ci-C₆)alkylC(O) or Rᵃ(4) and Rᵇ(4) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

3. A compound according to claim 2 wherein;

R₂ is selected from the group consisting of methylthio, ethylthio, n-propylthio, iso-propylthio, hydroxymethyl and hydroxyethyl;

Rⁱ₄ represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (Ci-Ce)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and COOᵉ wherein Rᵉ represents (Ci-Ce)alkyl optionally substituted by one or more of halogen (F, Cl, Br or I) atom(s), OH, aryl, (C₃-C₆)cycloalkyl and heterocyclyl; further Rⁱ₄ represents a halogen (F, Cl, Br or I) atom, (C₃-Ce)cycloalkyl, (Ci-Ce)alkoxy, (C₃-Ce)cycloalkoxy, (Ci-Ce)alkylthio, (C₃-Ce)cycloalkylthio, or a group of formula N Rᵃ(4) Rᵇ(4) in which Rᵃ(4) and Rᵇ(4) independently represent H, (C₁-C₆)alkyl, (C₁-C₆)alkylC(O), (C₁-C₆)alkoxyC(O) or Rᵃ(4) and Rᵇ(4) together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;
Rc is a direct bond or represents an unsubstituted or monosubstituted or polysubstituted (Ci-C4)alkylene or group, wherein any substituents each individually and independently are selected from (Ci-C4)alkyl, (Ci-C4)alkoxy, (C3-C6)cycloalkyl, halogen (F, Cl, Br or I), hydroxyl, NRa(Rc)Rb(Rc) in which Ra(Rc) and Rb(Rc) individually and independently from each other represents hydrogen, (Ci-C4)alkyl or RaRc and RbRc together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; further Rc represents imino (-NH-), N-substituted imino (-NR19-), (Ci-C4)alkyleneimino or N-substituted (Ci-C4)alkyleneimino (-N(R19)-((Ci-C4)alkylene) wherein the mentioned alkylene groups are unsubstituted or monosubstituted or polysubstituted with any substituents according to above;

4. A compound according to claim 3 wherein;
   Rc is selected from the group consisting of methylthio, ethylthio, n-propylthio and hydroxymethyl;

R7 represents (Ci-C3)alkyl optionally interrupted by oxygen, and/or optionally substituted by OH, aryl, (C3-C6)cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br or I) atoms; further R7 represents (C3-C6)cycloalkyl;

R14 represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (Ci-Ce)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH and COOH; further R14 represents a halogen (F, Cl, Br or I) atom, (Ci-Ce)alkoxy, (C3-Ce)cycloalkoxy, (Ci-C6)alkylthio, (C3-C6)cycloalkylthio, or a group of formula NRa(14)Rb(14) in which Ra(14) and Rb(14) independently represent H or (d-C6)alkyl;

Rc is a direct bond or represents imino, N-substituted imino (-NR19-), (Ci-C4)alkyleneimino or an unsubstituted or monosubstituted or polysubstituted (Ci-C4)alkylene group with any substituents according to above; and

X represents a single bond, imino (-NH-) or methylene (-CH2-).
5. A compound according to claim 4 wherein;
   \( R_i \) is n-propylcarbonyl;
   \( R_2 \) is chosen from the group consisting of methylthio, ethylthio, n-propylthio and hydroxymethyl;
   \( R_7 \) is n-propyl;
   \( R_{14} \) is hydrogen;
   \( R^e \) is chosen from the group consisting of a single bond, methylene (-CH\(_2\)-), imino (-NH-) and methylimino (-N(CH\(_3\))-);
   \( R^g \) is hydrogen or methyl;
   \( R^d \) is chosen from the group consisting of phenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-chloro-4-fluorophenyl, 4-methoxy-phenyl, 4-metyl-phenyl and phenyl-1,1-cyclopropylene;
   \( X \) is a single bond; and
   \( B \) is 4-piperidin-l-ylene, and the substituent \( R_{14} \) is connected to the \( B \) ring/ring system, in such a way that no quarternary ammonium compound is formed (by this connection).

6. A compound according to any one of claims 1-5 which is of the formula (Ia):

\[ \text{(Ia)} \]

7. A compound according to any one of claims 1-5, which is of the formula (Iaa):
8. A compound according to claim 1 selected from:

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(2-fluorobenzyl)sulfonyl]piperidine-4-carboxamide

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(methyl(phenyl)amino)sulfonyl]piperidine-4-carboxamide

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(4-methoxybenzyl)sulfonyl]piperidine-4-carboxamide

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(4-fluorobenzyl)sulfonyl]piperidine-4-carboxamide

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(2,4-difluorobenzyl)sulfonyl]piperidine-4-carboxamide

1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[(4-methylbenzyl)sulfonyl]piperidine-4-carboxamide

N-(benzylsulfonyl)-1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]piperidine-4-carboxamide

1-[5-butyryl-3-cyano-6-(hydroxymethyl)pyridin-2-yl]-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide

1-[5-butyryl-3-cyano-6-(ethylthio)pyridin-2-yl]-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide

1-[5-butanoyl-3-cyano-6-(propylthio)pyridin-2-yl]-N-[(1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide;

and pharmaceutically acceptable salts thereof.
9. A compound according to claim 1 being;
   1-[5-butyryl-3-cyano-6-(methylthio)pyridin-2-yl]-N-[1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide;
   or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 1 being;
    1-[5-butanoyl-3-cyano-6-(propylthio)pyridin-2-yl]-N-[1-phenylcyclopropyl)sulfonyl]piperidine-4-carboxamide;
    or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound according to any one of claims 1-10 in combination with pharmaceutically acceptable adjuvants, diluents and/or carriers.

12. A compound according to any one of claims 1-10 for use in therapy.

13. Use of a compound according to any one of claims 1-10 for the manufacture of a medicament for treatment of platelet aggregation disorder.

14. Use of a compound according to any one of claims 1-10 for the manufacture of a medicament for the inhibition of the P2Y_{12} receptor.

15. A method of treatment of a platelet aggregation disorder comprising administering to a patient suffering from such a disorder a therapeutically effective amount of a compound according to any one of claims 1-10.
A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, A61K, A61P

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

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM. ABS DATA AND CROSSFIRE DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
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  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"Z" document member of the same patent family

Date of the actual completion of the international search: 6 October 2009
Date of mailing of the international search report: 09-10-2009

Name and mailing address of the ISA/Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer
Cecilia Tham / Eo
Telephone No. +46 8 782 25 00
# INTERNATIONAL SEARCH REPORT

**Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: 15 because they relate to subject matter not required to be searched by this Authority, namely:
   
   Claim 15 relates to a method for treatment of the human by therapy, see PCT rule 39.1(iv). Nevertheless, a search has been made for this claim. The search has been directed to the technical content of the claim.

2. ☑ Claims Nos.:
   
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. [-J As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☑ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.
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International patent classification (IPC)
C01O 401/04 (2006.01)
A61K 31/4545 (2006.01)
A61P 7/02 (2006.01)

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Use the application number as username. The password is IINPZOQZHS.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.
## INTERNATIONAL SEARCH REPORT

**Information on patent family members**

**PCT/SE2009/050875**

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