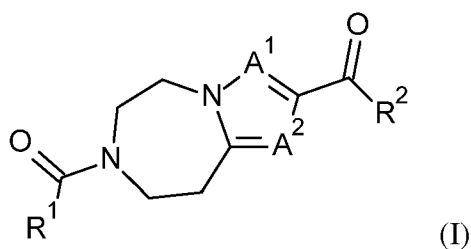


**CONDENSED [1,4]DIAZEPINE COMPOUNDS AS AUTOTAXIN (ATX)
AND LYSOPHOSPHATIDIC ACID (LPA) PRODUCTION INHIBITORS**

The present invention relates to organic compounds useful for therapy or prophylaxis in a mammal, and in particular to autotaxin (ATX) inhibitors which are inhibitors of lysophosphatidic acid (LPA) production and thus modulators of LPA levels and associated signaling, for the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, conditions of the respiratory system, vascular and cardiovascular conditions, fibrotic diseases, cancer, ocular conditions, metabolic conditions, cholestatic and other forms of chronic pruritus and acute and chronic organ transplant rejection.

The present invention provides novel compounds of formula (I)



wherein

R^1 is alkyl, haloalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylalkoxy, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isoinol-2-yl, substituted 1H-indol-2-yl or substituted benzofuran-2-yl, wherein substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylalkoxy, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isoinol-

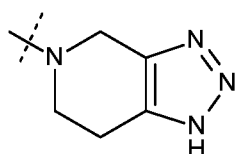
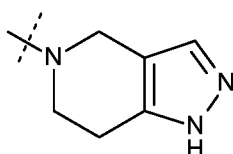
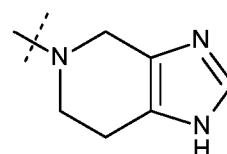
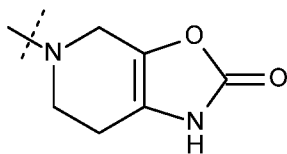
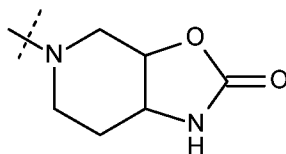
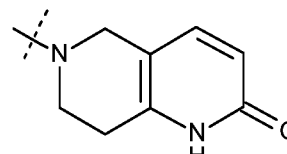
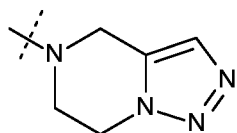
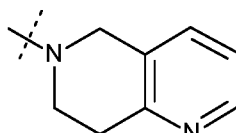
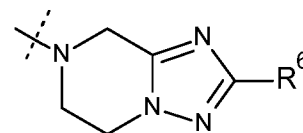
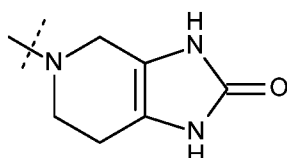
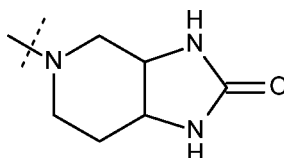
-2-

2-yl, substituted 1H-indol-2-yl and substituted benzofuran-2-yl are substituted with R^3 , R^4 and R^5 ;

A^1 is -N- or -CR⁷-;

A^2 is -N- or -CR⁸- and at least one of A^1 and A^2 is -N-;

5 R^2 is selected from the ring systems A, B, C, D, E, F, G, H, I, K and L.

**A****B****C****D****E****F****G****H****I****K****L**

R^3 , R^4 and R^5 are independently selected from H, alkyl, hydroxyalkyl, haloalkyl, hydroxyhaloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkoxy, cycloalkoxy, cycloalkoxyalkyl, cycloalkylalkoxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkoxyalkoxy, alkoxyalkoxyalkyl, heterocycloalkylalkoxy, phenyl,

substituted phenyl, pyridinyl, substituted pyridinyl, halogen, hydroxy, cyano, alkylsulfanyl, haloalkylsulfanyl, cycloalkylsulfanyl, alkylsulfinyl, haloalkylsulfinyl, cycloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, alkylcarbonylamino, substituted aminosulfonyl, substituted amino and substituted aminoalkyl, wherein substituted aminosulfonyl, substituted amino and substituted aminoalkyl are substituted on the nitrogen atom with one to two substituents independently selected from H, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl and cycloalkylcarbonyl, and wherein substituted phenyl and substituted pyridinyl are optionally substituted with one to three substituents independently selected from alkyl, halogen, haloalkyl, alkoxy and haloalkoxy;

R⁶ is H, alkyl, haloalkyl or cycloalkyl;

R⁷ and R⁸ are independently selected from H, alkyl, haloalkyl or cycloalkyl;

or pharmaceutically acceptable salts.

Autotaxin (ATX) is a secreted enzyme also called ectonucleotide pyrophosphatase / phosphodiesterase 2 or lysophospholipase D that is important for converting lysophosphatidyl choline (LPC) to the bioactive signaling molecule lysophosphatidic acid (LPA). It has been shown that plasma LPA levels are well correlated with ATX activity and hence ATX is believed to be an important source of extracellular LPA. Early experiments with a prototype ATX inhibitor have shown that such a compound is able to inhibit the LPA synthesizing activity in mouse plasma. Work conducted in the 1970s and early 1980s has demonstrated that LPA can elicit a wide range of cellular responses; including smooth muscle cell contraction, platelet activation, cell proliferation, chemotaxis and others. LPA mediates its effects via signaling to several G protein coupled receptors (GPCRs); the first members were originally denoted Edg (endothelial cell differentiation gene) receptors or ventricular zone gene-1(vzg-1) but are now called LPA receptors. The prototypic group now consists of LPA1/Edg-2/VZG-1, LPA2/Edg-4, and LPA3/Edg-7. Recently, three additional LPA receptors LPA4/p2y9/GPR23, LPA5/GPR92 and LPA6/p2Y5 have been described that are more closely related to nucleotide-selective purinergic receptors than to the prototypic LPA1-3 receptors. The ATX-LPA signaling axis is involved in a large range of physiological and pathophysiological functions, including, for example, nervous system function, vascular development, cardiovascular physiology, reproduction, immune system function, chronic inflammation, tumor metastasis and progression,

organ fibrosis as well as obesity and/or other metabolic diseases such as diabetes mellitus. Therefore, increased activity of ATX and/or increased levels of LPA, altered LPA receptor expression and altered responses to LPA may contribute to the initiation, progression and/or outcome of a number of different pathophysiological conditions related to the ATX/LPA axis.

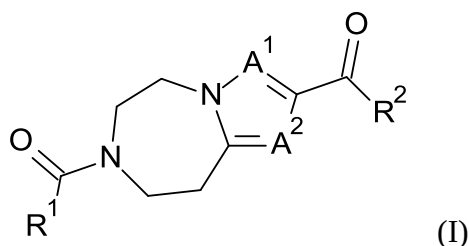
5 In accordance with the disclosure, the compounds of formula (I) or their pharmaceutically acceptable salts and esters can be used for the treatment or prophylaxis of diseases, disorders or conditions that are associated with the activity of autotaxin and/or the biological activity of lysophosphatidic acid (LPA).

10 The compounds of formula (I) or their pharmaceutically acceptable salts and esters herein inhibit autotaxin activity and therefore inhibit LPA production and modulate LPA levels and associated signaling. Autotaxin inhibitors described herein are useful as agents for the treatment or prevention of diseases or conditions in which ATX activity and/or LPA signaling participates, is involved in the etiology or pathology of the disease, or is otherwise associated with at least one symptom of the disease. The ATX-LPA axis has been implicated for example in
15 angiogenesis, chronic inflammation, autoimmune diseases, fibrotic diseases, cancer and tumor metastasis and progression, ocular conditions, metabolic conditions such as obesity and/or diabetes mellitus, conditions such as cholestatic or other forms of chronic pruritus as well as acute and chronic organ transplant rejection.

20 Objects of the embodiments disclosed herein are the compounds of formula (I) and their aforementioned salts and esters and their use as therapeutically active substances, a process for the manufacture of the said compounds, intermediates, pharmaceutical compositions, medicaments containing the said compounds, their pharmaceutically acceptable salts or esters, the use of the said compounds, salts or esters for the treatment or prophylaxis of disorders or conditions that are associated with the activity of ATX and/or the biological activity of
25 lysophosphatidic acid (LPA), particularly in the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, conditions of the respiratory system, vascular and cardiovascular conditions, fibrotic diseases, cancer, ocular conditions, metabolic conditions, cholestatic and other forms of chronic pruritus and acute and-
chronic organ transplant rejection, and the use of the said compounds, salts or esters for the
30 production of medicaments for the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, conditions of the respiratory system, vascular and cardiovascular conditions, fibrotic diseases, cancer, ocular conditions, metabolic

conditions, cholestatic and other forms of chronic pruritus and acute and chronic organ transplant rejection.

In one aspect, there is provided compounds of formula (I)



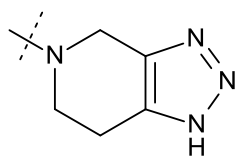
5 wherein

R^1 is alkyl, haloalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylalkoxy, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isoinol-2-yl, substituted 1H-indol-2-yl or substituted benzofuran-2-yl, wherein substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylalkoxy, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isoinol-2-yl, substituted 1H-indol-2-yl and substituted benzofuran-2-yl are substituted with R^3 , R^4 and R^5 ;

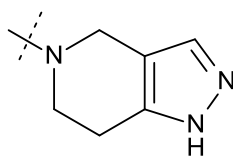
A^1 is -N- or $-CR^7$;

20 A^2 is -N- or $-CR^8$ and at least one of A^1 and A^2 is -N-;

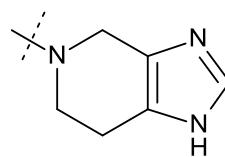
R^2 is selected from the ring systems A, B, C, D, E, F, G, H, I, K and L;



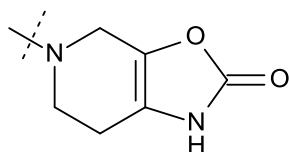
A



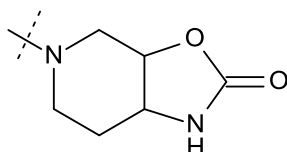
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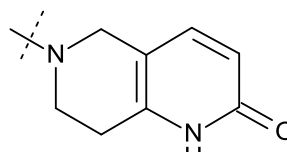
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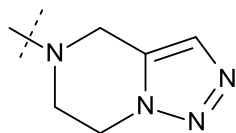
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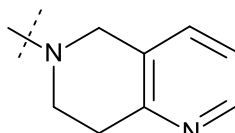
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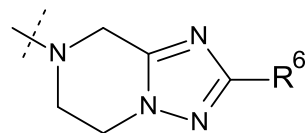
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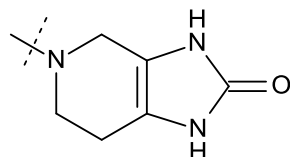
G



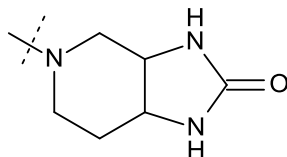
H



I



K



L

R^3 , R^4 and R^5 are independently selected from H, alkyl, hydroxyalkyl, haloalkyl, hydroxyhaloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkoxy, cycloalkoxy, cycloalkoxyalkyl, cycloalkylalkoxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkoxyalkoxy, alkoxyalkoxyalkyl, heterocycloalkylalkoxy, phenyl, substituted phenyl, pyridinyl, substituted pyridinyl, halogen, hydroxy, cyano, alkylsulfanyl, haloalkylsulfanyl, cycloalkylsulfanyl, alkylsulfinyl, haloalkylsulfinyl, cycloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, alkylcarbonylamino, substituted aminosulfonyl, substituted amino and substituted aminoalkyl, wherein substituted aminosulfonyl, substituted amino and substituted aminoalkyl are substituted on the nitrogen atom with one to two substituents independently selected from H, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl and cycloalkylcarbonyl, and wherein substituted phenyl and substituted pyridinyl are optionally

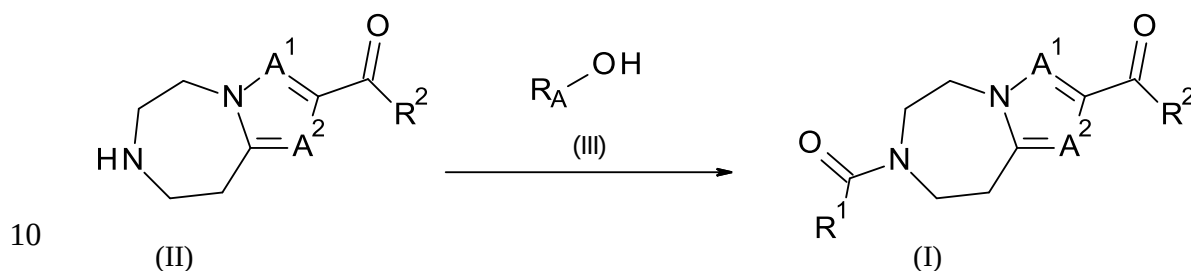
substituted with one to three substituents independently selected from alkyl, halogen, haloalkyl, alkoxy and haloalkoxy;

R^6 is H, alkyl, haloalkyl or cycloalkyl;

R^7 and R^8 are independently selected from H, alkyl, haloalkyl or cycloalkyl;

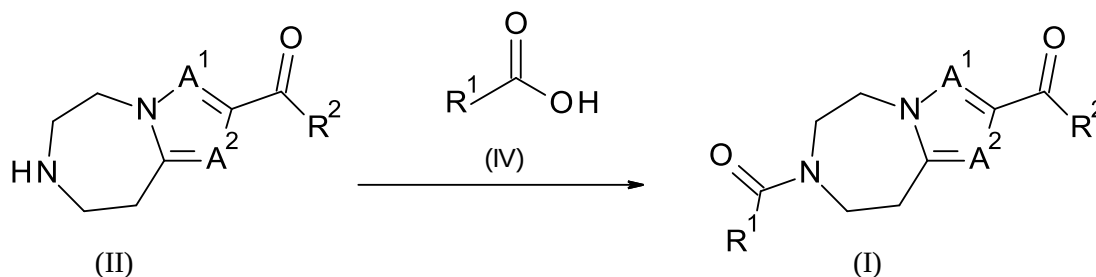
5 or pharmaceutically acceptable salts.

In another aspect, there is provided a process to prepare a compound as defined herein comprising the reaction of a compound of formula (II) in the presence of a compound of formula (III), wherein R^1 is phenylalkoxy substituted with R^3 , R^4 and R^5 , R_A is phenylalkyl substituted with R^3 , R^4 and R^5 and R^2 , R^3 , R^4 , R^5 , A^1 and A^2 are as defined herein



In another aspect, there is provided a process to prepare a compound as defined herein comprising the reaction of a compound of formula (II) in the presence of a compound of formula (IV), wherein R^1 is alkyl, haloalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted
 15 phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isoindol-2-yl, substituted 1H-indol-2-yl or substituted benzofuran-2-yl, wherein substituted cycloalkyl, substituted cycloalkylalkyl,
 20 substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isoindol-2-yl, substituted 1H-indol-2-yl and

substituted benzofuran-2-yl are substituted with R^3 , R^4 and R^5 and R^2 , R^3 , R^4 , R^5 , A^1 and A^2 are as defined herein



In another aspect, there is provided a compound as defined herein for use as therapeutically active substance.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a therapeutically inert carrier.

In another aspect, there is provided a compound as defined herein for use in the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, fibrotic diseases and acute and chronic organ transplant rejection.

In another aspect, there is provided the use of a compound as defined herein for the preparation of a medicament for the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, fibrotic diseases and acute and chronic organ transplant rejection.

The term “alkenyl” denotes a monovalent linear or branched hydrocarbon group of 2 to 7 carbon atoms with at least one double bond. In particular embodiments, alkenyl has 2 to 4 carbon atoms with at least one double bond. Examples of alkenyl include ethenyl, propenyl, prop-2-enyl, isopropenyl, n-butenyl and iso-butenyl. Particular alkenyl group is ethenyl.

The term “alkoxy” denotes a group of the formula $-O-R'$, wherein R' is an alkyl group. Examples of alkoxy group include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy and tert-butoxy. Particular alkoxy group include isopropoxy.

The term “alkoxyalkoxy” denotes an alkoxy group wherein at least one of the hydrogen atoms of the alkoxy group has been replaced by another alkoxy group. Examples of alkoxyalkoxy group include methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy and ethoxypropoxy. Particular alkoxyalkoxy groups include methoxymethoxy and methoxyethoxy.

The term “alkoxyalkoxyalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by an alkoxyalkoxy group. Examples of alkoxyalkoxyalkyl group include methoxymethoxymethyl, ethoxymethoxymethyl, methoxyethoxymethyl, ethoxyethoxymethyl, methoxypropoxymethyl, ethoxypropoxymethyl, methoxymethoxyethyl, ethoxymethoxyethyl, methoxyethoxyethyl, ethoxyethoxyethyl, methoxypropoxyethyl and ethoxypropoxyethyl.

The term “alkoxyalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by an alkoxy group. Exemplary alkoxyalkyl groups include methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, methoxypropyl, ethoxypropyl and isopropoxymethyl. Particular alkoxyalkyl group include include methoxymethyl, methoxyethyl and isopropoxymethyl.

The term “alkoxycarbonyl” denotes a group of the formula $-C(O)-R'$, wherein R' is an alkoxy group. Examples of alkoxycarbonyl groups include groups of the formula $-C(O)-R'$, wherein R' is methoxy or ethoxy. Particular alkoxycarbonyl group include groups of the formula $-C(O)-R'$, wherein R' is methoxy.

The term “alkoxyhaloalkyl” denotes a haloalkyl group wherein at least one of the hydrogen atoms of the haloalkyl group has been replaced by an alkoxy group. Exemplary alkoxyalkyl groups include methoxytrifluoroethyl, ethoxytrifluoroethyl, methoxytrifluoropropyl and ethoxytrifluoropropyl.

5 The term “alkyl” denotes a monovalent linear or branched saturated hydrocarbon group of 1 to 12 carbon atoms. In particular embodiments, alkyl has 1 to 7 carbon atoms, and in more particular embodiments 1 to 4 carbon atoms. Examples of alkyl include methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl and pentyl. Particular alkyl groups include methyl, ethyl, propyl and isopropyl. More particular alkyl groups are ethyl and isopropyl.

10 The term “alkylcarbonyl” denotes a group of the formula $-C(O)-R'$, wherein R' is an alkyl group. Examples of alkylcarbonyl groups include groups of the formula $-C(O)-R'$, wherein R' is methyl or ethyl. Particular alkylcarbonyl groups include groups of the formula $-C(O)-R'$, wherein R' is methyl.

15 The term “alkylcarbonylamino” denotes a group of the formula $-NH-C(O)-R'$, wherein R' is an alkyl group. Examples of alkylcarbonylamino groups include groups of the formula $-NH-C(O)-R'$, wherein R' is methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl or pentyl. Particular alkylcarbonylamino group include group of the formula $-NH-C(O)-R'$, wherein R' is tert-butyl.

20 The term “alkylsulfanyl” denotes a group of the formula $-S-R'$, wherein R' is an alkyl group. Examples of alkylsulfanyl groups include groups of the formula $-S-R'$, wherein R' is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl. Particular alkylsulfanyl groups include group of the formula $-S-R'$, wherein R' is methyl.

25 The term “alkylsulfinyl” denotes a group of the formula $-S(O)-R'$, wherein R' is an alkyl group. Examples of alkylsulfinyl groups include groups of the formula $-S(O)-R'$, wherein R' is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl. Particular alkylsulfinyl groups include group of the formula $-S(O)-R'$, wherein R' is methyl.

30 The term “alkylsulfonyl” denotes a group of the formula $-S(O)_2-R'$, wherein R' is an alkyl group. Examples of alkylsulfonyl groups include groups of the formula $-S(O)_2-R'$, wherein R' is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl. Particular alkylsulfonyl groups include group of the formula $-S(O)_2-R'$, wherein R' is methyl.

The term “alkylsulfonylamino” denotes a group of the formula $\text{-NH-S(O)}_2\text{-R'}$, wherein R' is an alkyl group. Examples of alkylsulfonylamino groups include groups of the formula $\text{-NH-S(O)}_2\text{-R'}$, wherein R' is methyl or ethyl. Particular a alkylsulfonylamino groups include groups of the formula $\text{-NH-S(O)}_2\text{-R'}$, wherein R' is methyl.

5 The term “amino” denotes a -NH_2 group.

The term “aminoalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by an aminogroup. Examples of aminoalkyl include aminomethyl, aminoethyl, amino-1-methyl-ethyl, aminopropyl, aminomethylpropyl and aminopropyl. Particular examples are aminomethyl and haminoethyl.

10 The term “aminosulfonyl” denotes a $\text{-S(O)}_2\text{-NH}_2$ group.

The term “carbonyl” denotes a -C(O)- group.

The term “carboxy” denotes a -COOH group.

The term “cyano” denotes a $\text{-C}\equiv\text{N}$ group.

15 The term “cycloalkoxy” denotes a group of the formula -O-R' , wherein R' is a cycloalkyl group. Examples of cycloalkoxy group include cyclopropoxy, cyclobutoxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and cyclooctyloxy. Particular cycloalkoxy group is cyclopropoxy.

20 The term “cycloalkoxyalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by a cycloalkoxy group. Examples of cycloalkoxyalkyl groups include cyclopropoxymethyl, cyclopropoxyethyl, cyclobutoxymethyl, cyclobutoxyethyl, cyclopentyloxymethyl, cyclopentyloxyethyl, cyclohexyloxymethyl, cyclohexyloxyethyl, cycloheptyloxymethyl, cycloheptyloxyethyl, cyclooctyloxymethyl and cyclooctyloxyethyl.

25 The term “cycloalkyl” denotes a monovalent saturated monocyclic or bicyclic hydrocarbon group of 3 to 10 ring carbon atoms. In particular embodiments, cycloalkyl denotes a monovalent saturated monocyclic hydrocarbon group of 3 to 8 ring carbon atoms. Bicyclic means a ring system consisting of two saturated carbocycles having two carbon atoms in common. Examples for monocyclic cycloalkyl are cyclopropyl, cyclobutanyl, cyclopentyl, cyclohexyl or cycloheptyl. Examples for bicyclic cycloalkyl are bicyclo[2.2.1]heptanyl or bicyclo[2.2.2]octanyl. Particular

monocyclic cycloalkyl groups are cyclopropyl, cyclobutanyl, cyclopentyl and cyclohexyl. More particular monocyclic cycloalkyl group is cyclopropyl.

The term “cycloalkylalkoxy” denotes an alkoxy group wherein at least one of the hydrogen atoms of the alkoxy group is replaced by a cycloalkyl group. Examples of cycloalkylalkoxy include cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy, cycloheptylmethoxy and cyclooctylmethoxy.

The term “cycloalkylalkoxyalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group is replaced by a cycloalkylalkoxy group. Examples of cycloalkylalkoxyalkyl include cyclopropylmethoxymethyl, cyclopropylmethoxyethyl, cyclobutylmethoxymethyl, cyclobutylmethoxyethyl, cyclopentylmethoxyethyl, cyclopentylmethoxyethyl, cyclohexylmethoxymethyl, cyclohexylmethoxyethyl, cycloheptylmethoxymethyl, cycloheptylmethoxyethyl, cyclooctylmethoxymethyl and cyclooctylmethoxyethyl.

The term “cycloalkylalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group is replaced by a cycloalkyl group. Examples of cycloalkylalkyl include cyclopropylmethyl, cyclopropylethyl, cyclopropylbutyl, cyclobutylpropyl, 2-cyclopropylbutyl, cyclopentylbutyl, cyclohexylmethyl, cyclohexylethyl, bicyclo[4.1.0]heptanylmethyl, bicyclo[4.1.0]heptanylethyl, bicyclo[2.2.2]octanylmethyl, bicyclo[2.2.2]octanylethyl, adamantanylmethyl and adamantanylethyl. Particular examples of cycloalkylalkyl are cyclohexylmethyl, cyclohexylethyl, bicyclo[4.1.0]heptanylmethyl, bicyclo[4.1.0]heptanylethyl, bicyclo[2.2.2]octanylmethyl, bicyclo[2.2.2]octanylethyl, adamantanylmethyl and adamantanylethyl. Further particular examples cycloalkylalkyl are cyclohexylmethyl, cyclohexylethyl, bicyclo[4.1.0]heptanylmethyl, bicyclo[2.2.2]octanylmethyl, adamantanylmethyl and adamantanylethyl.

The term “cycloalkylcarbonyl” of the formula $-C(O)-R'$, wherein R' is a cycloalkyl group. Examples of cycloalkylcarbonyl groups include groups of the formula $-C(O)-R'$, wherein R' is cyclopropyl.

The term “cycloalkylsulfanyl” denotes a group of the formula $-S-R'$, wherein R' is a cycloalkyl group. Examples of cycloalkylsulfanyl groups include groups of the formula $-S-R'$, wherein R' is cyclopropyl.

The term “cycloalkylsulfinyl” denotes a group of the formula $-S(O)-R'$, wherein R' is a cycloalkyl group. Examples of cycloalkylsulfinyl groups include groups of the formula $-S(O)-R'$, wherein R' is cyclopropyl.

5 The term “cycloalkylsulfonyl” denotes a group of the formula $-S(O)_2-R'$, wherein R' is a cycloalkyl group. Examples of cycloalkylsulfonyl groups include groups of the formula $-S(O)_2-R'$, wherein R' is cyclopropyl.

10 The term “haloalkoxy” denotes an alkoxy group wherein at least one of the hydrogen atoms of the alkoxy group has been replaced by the same or different halogen atoms. The term “perhaloalkoxy” denotes an alkoxy group where all hydrogen atoms of the alkoxy group have been replaced by the same or different halogen atoms. Examples of haloalkoxy include fluoromethoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, trifluoromethylethoxy, trifluorodimethylethoxy and pentafluoroethoxy. Particular haloalkoxy group is trifluoromethoxy.

15 The term “haloalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by the same or different halogen atoms. The term “perhaloalkyl” denotes an alkyl group where all hydrogen atoms of the alkyl group have been replaced by the same or different halogen atoms. Examples of haloalkyl include fluoromethyl, difluoromethyl, trifluoromethyl, trifluoroethyl, trifluoromethylethyl and pentafluoroethyl. Particular haloalkyl group is trifluoromethyl.

20 The term “haloalkylsulfanyl” denotes a group of the formula $-S-R'$, wherein R' is a haloalkyl group. Examples of haloalkylsulfanyl groups include groups of the formula $-S-R'$, wherein R' is trifluoromethyl.

The term “haloalkylsulfinyl” denotes a group of the formula $-S(O)-R'$, wherein R' is a haloalkyl group. Examples of haloalkylsulfinyl groups include groups of the formula $-S(O)-R'$, wherein R' is trifluoromethyl.

25 The term “haloalkylsulfonyl” denotes a group of the formula $-S(O)_2-R'$, wherein R' is a haloalkyl group. Examples of haloalkylsulfonyl groups include groups of the formula $-S(O)_2-R'$, wherein R' is trifluoromethyl.

The term “halogen” and “halo” are used interchangeably herein and denote fluoro, chloro, bromo, or iodo. Particular halogen is fluoro.

The term "heterocycloalkyl" denotes a monovalent saturated or partly unsaturated mono- or bicyclic ring system of 4 to 9 ring atoms, comprising 1, 2, or 3 ring heteroatoms selected from N, O and S, the remaining ring atoms being carbon. Bicyclic means consisting of two cycles having two ring atoms in common, i.e. the bridge separating the two rings is either a single bond or a chain of one or two ring atoms. Examples for monocyclic saturated heterocycloalkyl are 4,5-dihydro-oxazolyl, oxetanyl, azetidiny, pyrrolidinyl, 2-oxo-pyrrolidin-3-yl, tetrahydrofuranly, tetrahydro-thienyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholin-4-yl, azepanyl, diazepanyl, homopiperazinyl, or oxazepanyl. Examples for bicyclic saturated heterocycloalkyl are 8-aza-bicyclo[3.2.1]octyl, quinuclidinyl, 8-oxa-3-aza-bicyclo[3.2.1]octyl, 9-aza-bicyclo[3.3.1]nonyl, 3-oxa-9-aza-bicyclo[3.3.1]nonyl, or 3-thia-9-aza-bicyclo[3.3.1]nonyl. Examples for partly unsaturated heterocycloalkyl are dihydrofuryl, imidazolinyl, dihydro-oxazolyl, tetrahydro-pyridinyl, or dihydropyranyl. Particular example of heterocycloalkyl groups is tetrahydropyranyl.

The term "heterocycloalkylalkoxy" denotes an alkoxy group wherein at least one of the hydrogen atoms of the alkoxy group is replaced by a heterocycloalkyl group. Examples of heterocycloalkylalkoxy include tetrahydropyranylmethoxy, tetrahydrofuranlymethoxy, oxetanylmethoxy, tetrahydropyranylethoxy, tetrahydrofuranylethoxy and oxetanylethoxy. Particular heterocycloalkylalkoxy is tetrahydropyranylmethoxy.

The term "hydroxy" denotes a -OH group.

The term "hydroxyalkyl" denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by a hydroxy group. Examples of hydroxyalkyl include hydroxymethyl, hydroxyethyl, hydroxy-1-methyl-ethyl, hydroxypropyl, hydroxymethylpropyl and dihydroxypropyl. Particular examples are hydroxymethyl and hydroxyethyl.

The term "hydroxyhaloalkyl" denotes a haloalkyl group wherein at least one of the hydrogen atoms of the haloalkyl group has been replaced by an hydroxy group. Exemplary hydroxyhaloalkyl groups include hydroxytrifluoroethyl and hydroxytrifluoropropyl. Particular hydroxyhaloalkyl groups include hydroxytrifluoroethyl.

The term “naphthylalkenyl” denotes an alkenyl group wherein at least one of the hydrogen atoms of the alkenyl group has been replaced a naphthynaphthyl. Particular naphthylalkenyl group is naphytlethenyl.

5 The term “naphthylalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced a naphthyl. Particular naphthylalkyl groups are naphthylmethyl, naphthylethyl and naphthylpropyl.

The term “naphthyloxyalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by a naphthyloxy group. Exemplary naphthyloxyalkyl groups include naphthyloxymethyl, naphthyloxyethyl and naphthyloxypropyl.

10 The term “phenoxy” denotes a group of the formula -O-R', wherein R' is a phenyl.

The term “phenoxyalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by a phenoxy group. Exemplary phenoxyalkyl groups include phenoxymethyl, phenoxyethyl and phenoxypropyl. Particular alkoxyalkyl group is phenoxymethyl.

15 The term “phenylalkenyl” denotes an alkenyl group wherein at least one of the hydrogen atoms of the alkenyl group has been replaced a phenyl. Particular phenylalkenyl group is phenylethenyl.

20 The term “phenylalkoxy” denotes an alkoxy group wherein at least one of the hydrogen atoms of the alkoxy group is replaced by a phenyl group. Examples of phenylalkoxy include phenylmethoxy, phenylethoxy and phenylpropoxy. Particular phenylalkoxy is phenylmethoxy.

The term “phenylalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced a phenyl. Particular phenylalkyl groups are benzyl, phenethyl and phenylpropyl. More particular phenylalkyl groups are benzyl and phenethyl. Further particular phenylalkyl group is phenethyl.

25 The term “phenylalkynyl” denotes an alkynyl group wherein at least one of the hydrogen atoms of the alkynyl group has been replaced a phenyl. Particular phenylalkynyl group is phenylethyne.

The term “phenylcycloalkyl” denotes a cycloalkyl group wherein at least one of the hydrogen atoms of the cycloalkyl group has been replaced a phenyl. Particular phenylcycloalkyl group is phenylcyclopropyl.

5 The term “pyridinylalkenyl” denotes an alkenyl group wherein at least one of the hydrogen atoms of the alkenyl group has been replaced a pyridinyl. Particular pyridinylalkenyl group is pyridinylethenyl.

10 The term “pyridinylalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced a pyridinyl. Particular pyridinylalkyl groups are pyridinylmethyl, pyridinylethyl and pyridinylpropyl. More particular pyridinylalkyl group is pyridinylethyl.

The term “pyridinylalkynyl” denotes an alkynyl group wherein at least one of the hydrogen atoms of the alkynyl group has been replaced a pyridinyl. Particular pyridinylalkynyl group is pyridinylethynyl.

15 The term “thiophenylalkenyl” denotes an alkenyl group wherein at least one of the hydrogen atoms of the alkenyl group has been replaced a thiophenyl. Particular thiophenylalkenyl group is thiophenylethenyl.

20 The term “thiophenylalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced a thiophenyl. Particular thiophenylalkyl groups are thiophenylmethyl, thiophenylethyl and thiophenylpropyl. More particular thiophenylalkyl group is thiophenylmethyl.

The term “thiophenylalkynyl” denotes an alkynyl group wherein at least one of the hydrogen atoms of the alkynyl group has been replaced a thiophenyl. Particular thiophenylalkynyl group is thiophenylethynyl.

25 The term "pharmaceutically acceptable salts" refers to those salts which retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, in particular hydrochloric acid, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid,

benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcystein and the like. In addition, these salts may be prepared by addition of an inorganic base or an organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts and the like. Salts derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polyimine resins and the like. Particular pharmaceutically acceptable salts of compounds of formula (I) are the hydrochloride salts, methanesulfonic acid salts and citric acid salts.

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

The term "protecting group" (PG) denotes a group which selectively blocks a reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotected reactive site in the meaning conventionally associated with it in synthetic chemistry. Protecting groups can be removed at the appropriate point. Exemplary protecting groups are amino-protecting groups, carboxy-protecting groups or hydroxy-protecting groups. Particular protecting groups are the tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz or Z), fluorenylmethoxycarbonyl (Fmoc) and benzyl (Bn) groups. Further particular protecting groups are the tert-butoxycarbonyl (Boc) and the fluorenylmethoxycarbonyl (Fmoc) groups. More particular protecting group is the tert-butoxycarbonyl (Boc) group.

The abbreviation uM means microMolar and is equivalent to the symbol μM .

The abbreviation uL means microliter and is equivalent to the symbol μL .

The abbreviation ug means microgram and is equivalent to the symbol μg .

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

According to the Cahn-Ingold-Prelog Convention the asymmetric carbon atom can be of the "R" or "S" configuration.

Also an embodiment of the present invention are compounds according to formula (I) as described herein and pharmaceutically acceptable salts or esters thereof, in
10 particular compounds according to formula (I) as described herein and pharmaceutically acceptable salts thereof, more particularly compounds according to formula (I) as described herein.

Another embodiment of the present invention are compounds according to formula (I) as described herein, wherein

15 R^1 is alkyl, haloalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylalkoxy, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl,
20 substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isindol-2-yl, substituted 1H-indol-2-yl or substituted benzofuran-2-yl, wherein substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylalkoxy, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted
25 pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isindol-2-yl, substituted 1H-indol-2-yl and substituted benzofuran-2-yl are substituted with R^3 , R^4 and R^5 ;

30 A^1 is -N- or -CR⁷-;

A² is -N- or -CR⁸- and at least one of A¹ and A² is -N-;

R² is selected from the ring systems A, B, C, D, E, F, G, H, I, K and L.

R³, R⁴ and R⁵ are independently selected from H, alkyl, hydroxyalkyl, haloalkyl, hydroxyhaloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkoxy, cycloalkoxy, cycloalkoxyalkyl, cycloalkylalkoxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkoxyalkoxy, alkoxyalkoxyalkyl, phenyl, substituted phenyl, pyridinyl, substituted pyridinyl, halogen, hydroxy, cyano, alkylsulfanyl, haloalkylsulfanyl, cycloalkylsulfanyl, alkylsulfinyl, haloalkylsulfinyl, cycloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, alkylcarbonylamino, substituted aminosulfonyl, substituted amino and substituted aminoalkyl, wherein substituted aminosulfonyl, substituted amino and substituted aminoalkyl are substituted on the nitrogen atom with one to two substituents independently selected from H, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl and cycloalkylcarbonyl, and wherein substituted phenyl and substituted pyridinyl are optionally substituted with one to three substituents independently selected from alkyl, halogen, haloalkyl, alkoxy and haloalkoxy;

R⁶ is H, alkyl, haloalkyl or cycloalkyl;

R⁷ and R⁸ are independently selected from H, alkyl, haloalkyl or cycloalkyl;

or pharmaceutically acceptable salts.

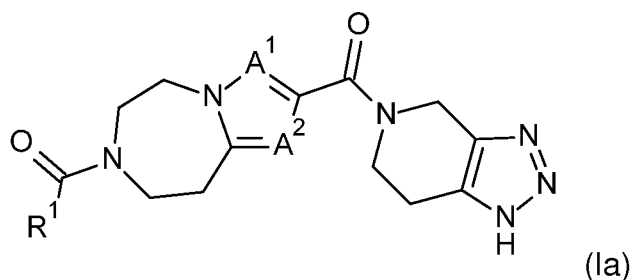
Another embodiment of the present invention are compounds according to formula (I) as described herein, wherein R¹ is substituted phenylalkyl, substituted phenoxyalkyl or substituted phenylalkoxy, wherein substituted phenylalkyl, substituted phenoxyalkyl and substituted phenylalkoxy are substituted with R³, R⁴ and R⁵.

A particular embodiment of the present invention are compounds according to formula (I) as described herein, wherein R¹ is substituted phenoxyalkyl or substituted phenylalkoxy, wherein substituted phenoxyalkyl and substituted phenylalkoxy are substituted with R³, R⁴ and R⁵.

In a further particular embodiment of the present invention are compounds according to formula (I) as described herein, wherein R¹ is phenylalkoxy substituted with R³, R⁴ and R⁵.

The present invention also relates to compounds according to formula (I) as described herein, wherein R^2 is selected from the ring systems A and O.

A particular embodiment of the present invention are compounds according to formula (I) as described herein, wherein R^2 is the ring system A and of formula (Ia).



A further embodiment of the present invention are compounds according to formula (I) as described herein, wherein A^1 is -N- and A^2 is -N- or $-CR^8$.

Another further embodiment of the present invention are compounds according to formula (I) as described herein, wherein R^3 , R^4 and R^5 are independently selected from H, alkyl, cycloalkyl, heterocycloalkylalkoxy, haloalkoxy, halogen, cyano and alkylcarbonylamino.

A particular embodiment of the present invention are compounds according to formula (I) as described herein, wherein R^3 , R^4 and R^5 are independently selected from H, alkyl, cycloalkyl, haloalkoxy, halogen, cyano and alkylcarbonylamino.

Another particular embodiment of the present invention are compounds according to formula (I) as described herein, wherein R^3 is heterocycloalkylalkoxy, haloalkoxy or cyano.

A further particular embodiment of the present invention are compounds according to formula (I) as described herein, wherein R^3 is haloalkoxy or cyano.

Another particular embodiment of the present invention are compounds according to formula (I) as described herein, wherein R^4 is H, alkyl, cycloalkyl or halogen.

A further particular embodiment of the present invention are compounds according to formula (I) as described herein, wherein R^4 is H, alkyl or halogen.

Also an embodiment of the present invention are compounds according to formula (I) as described herein, wherein R^5 is H.

Another embodiment of the present invention are compounds according to formula (I) as described herein, wherein R^7 is H.

Another embodiment of the present invention are compounds according to formula (I) as described herein, wherein R^8 is H.

5 A more particular embodiment of the present invention are compounds according to formula (I) as described herein, wherein

R^1 is substituted phenylalkoxy substituted with R^3 , R^4 and R^5 ;

A^1 is -N-;

A^2 is -N- or - CR^8 -;

10 R^2 is the ring system A.

R^3 is haloalkoxy or cyano;

R^4 is H or halogen;

R^5 is H;

R^8 is H;

15 or pharmaceutically acceptable salts.

Particular examples of compounds of formula (I) as described herein are selected from

Benzyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate;

20 Benzyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate;

[3-Fluoro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate ;

2-Fluoro-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate ;

[4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate ;

4-Cyanobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate ;

5 4-Cyano-3-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate ;

4-Cyano-2-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate ;

10 (4-Cyano-2-propan-2-ylphenyl)methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate ;

[4-Cyano-2-(2,2-dimethylpropanoylamino)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate ;

15 [4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate ;

[4-Cyano-2-(2,2-dimethylpropanoylamino)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate ;

20 [4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate ;

1-[2-(1,4,6,7-Tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]-3-[4-(trifluoromethoxy)phenyl]propan-1-one ;

25 3-Cyclopropyl-4-(2-oxo-2-(2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepin-6(5H)-yl)ethoxy)benzonitrile ;

3-Ethyl-4-(2-oxo-2-(2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepin-6(5H)-yl)ethoxy)benzonitrile ;

3-tert-Butyl-4-[2-oxo-2-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]ethoxy]benzonitrile;

and pharmaceutically acceptable salts thereof.

Also particular examples of compounds of formula (I) as described herein are
5 selected from

3-[3-fluoro-4-(trifluoromethoxy)phenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]propan-1-one;

3-(4-methoxyphenyl)-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]propan-1-one;

10 1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepin-7-yl]-3-[4-(trifluoromethoxy)phenyl]propan-1-one;

3-[3-fluoro-4-(trifluoromethoxy)phenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepin-7-yl]propan-1-one;

15 3-[3-chloro-4-(trifluoromethoxy)phenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]propan-1-one;

3-[3-chloro-4-(trifluoromethoxy)phenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepin-7-yl]propan-1-one;

20 (6-(2-cyclopropyl-6-((tetrahydro-2H-pyran-4-yl)methoxy)isonicotinoyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-d][1,4]diazepin-2-yl)(6,7-dihydro-1H-[1,2,3]triazolo[4,5-c]pyridin-5(4H)-yl)methanone;

(E)-3-[4-(difluoromethoxy)-3-fluorophenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]prop-2-en-1-one;

25 3-[4-(difluoromethoxy)-3-fluorophenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]propan-1-one;

4-methoxybenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

4-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

5 3-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

(3,4-difluorophenyl)methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate;

10 4-(difluoromethoxy)-3-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

3-fluoro-4-methoxybenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

4-methoxy-2-methylbenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

15 4-cyclopropylbenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

[2-fluoro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate;

20 [3-fluoro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate;

3-chloro-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

2-methoxy-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

25 2-methyl-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

4-(2,2,2-trifluoroethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

[3-chloro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate;

5 [3-chloro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate;

3-fluoro-4-(trifluoromethoxy)benzyl 2-((3aR,7aR)-2-oxooctahydrooxazolo[5,4-c]pyridine-5-carbonyl)-8,9-dihydro-5H-[1,2,4]triazolo[1,5-d][1,4]diazepine-7(6H)-carboxylate;

and pharmaceutically acceptable salts thereof.

10 Further

3-Fluoro-4-(Trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

[4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate;

15 [4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate;

[4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate;

20 3-tert-Butyl-4-[2-oxo-2-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]ethoxy]benzonitrile;

and pharmaceutically acceptable salts thereof.

Also further particular examples of compounds of formula (I) as described herein are selected from

25 (6-(2-cyclopropyl-6-((tetrahydro-2H-pyran-4-yl)methoxy)isonicotinoyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-d][1,4]diazepin-2-yl)(6,7-dihydro-1H-[1,2,3]triazolo[4,5-c]pyridin-5(4H)-yl)methanone;

(E)-3-[4-(difluoromethoxy)-3-fluorophenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]prop-2-en-1-one;

4-(difluoromethoxy)-3-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

[3-fluoro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate;

3-chloro-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

2-methyl-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

[3-chloro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate;

[3-chloro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate;

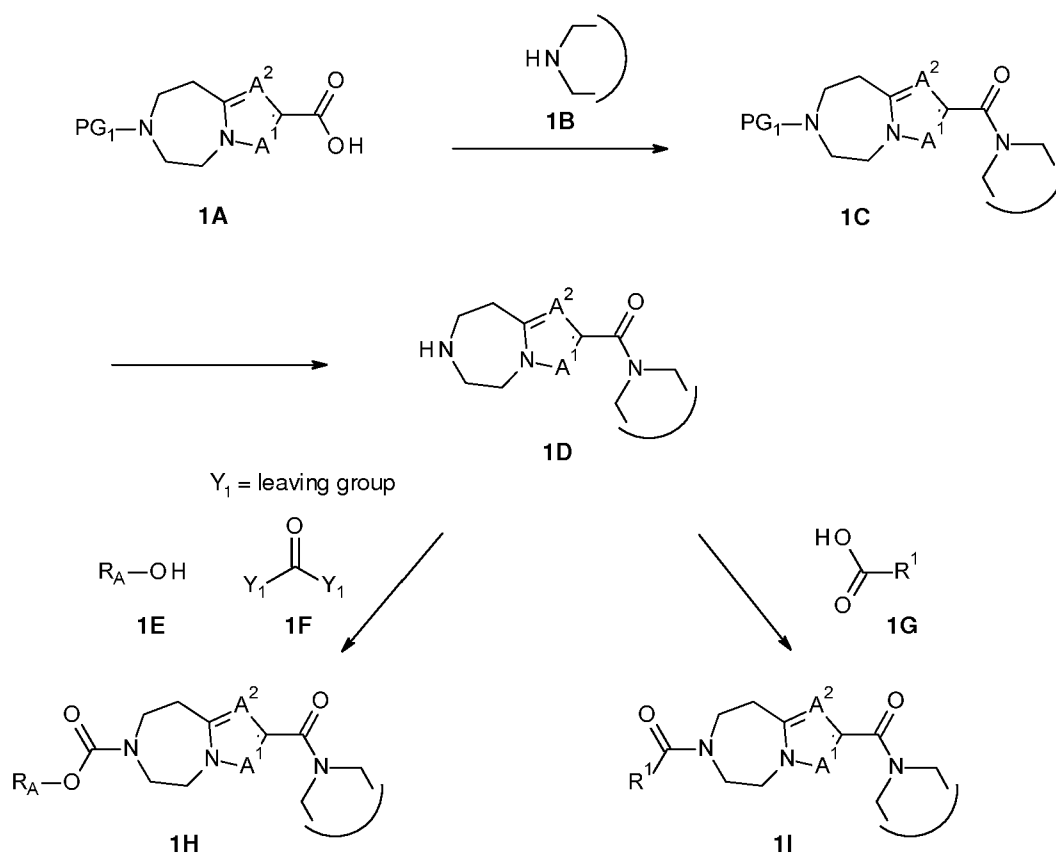
Processes for the manufacture of compounds of formula (I) as described herein are an object of the invention.

The preparation of compounds of formula (I) of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses of the invention are shown in the following general schemes. The skills required for carrying out the reactions and purifications of the resulting products are known to those persons skilled in the art. In case a mixture of enantiomers or diastereoisomers is produced during a reaction, these enantiomers or diastereoisomers can be separated by methods described herein or known to the man skilled in the art such as e.g. (chiral) chromatography or crystallization. The substituents and indices used in the following description of the processes have the significance given herein.

A general description of the invention is given in the following section and is outlined in Figures 1 - 4. To obtain compounds of formula (I), a suitably protected bicyclic carboxylic acid **1A** is treated with an appropriate cyclic secondary amine **1B** in the presence of a suitable

coupling reagent such as EDC HCl, CDI, HATU or any other peptide coupling reagent in an appropriate solvent such as DMF, THF, CH₃CN or the like at temperatures between -20°C and 100°C to provide protected amide **1C**. In the subsequent step, depending on the nature of the protecting group PG₁, various de-protection methods known to those skilled in the art can be applied to afford intermediate **1D** with PG removed. For example, a BOC protecting group can be removed by treatment with organic or aqueous acids or other known methods, whereas a Z-group is often removed by hydrogenation.

Figure 1:



10

Intermediate **1D** can now be treated with an alcohol **1E**, wherein R_A is substituted phenylalkyl, whereby **1E** has been suitably activated before for example with CDI or any other type of an activated carbonic acid derivative **1F** such as N,N'-disuccinimidyl carbonate or phosgene or the like in the presence of a base such as triethylamine, N-methylmorpholine, Huenig's base or the like to afford the first type of examples of the current invention with the

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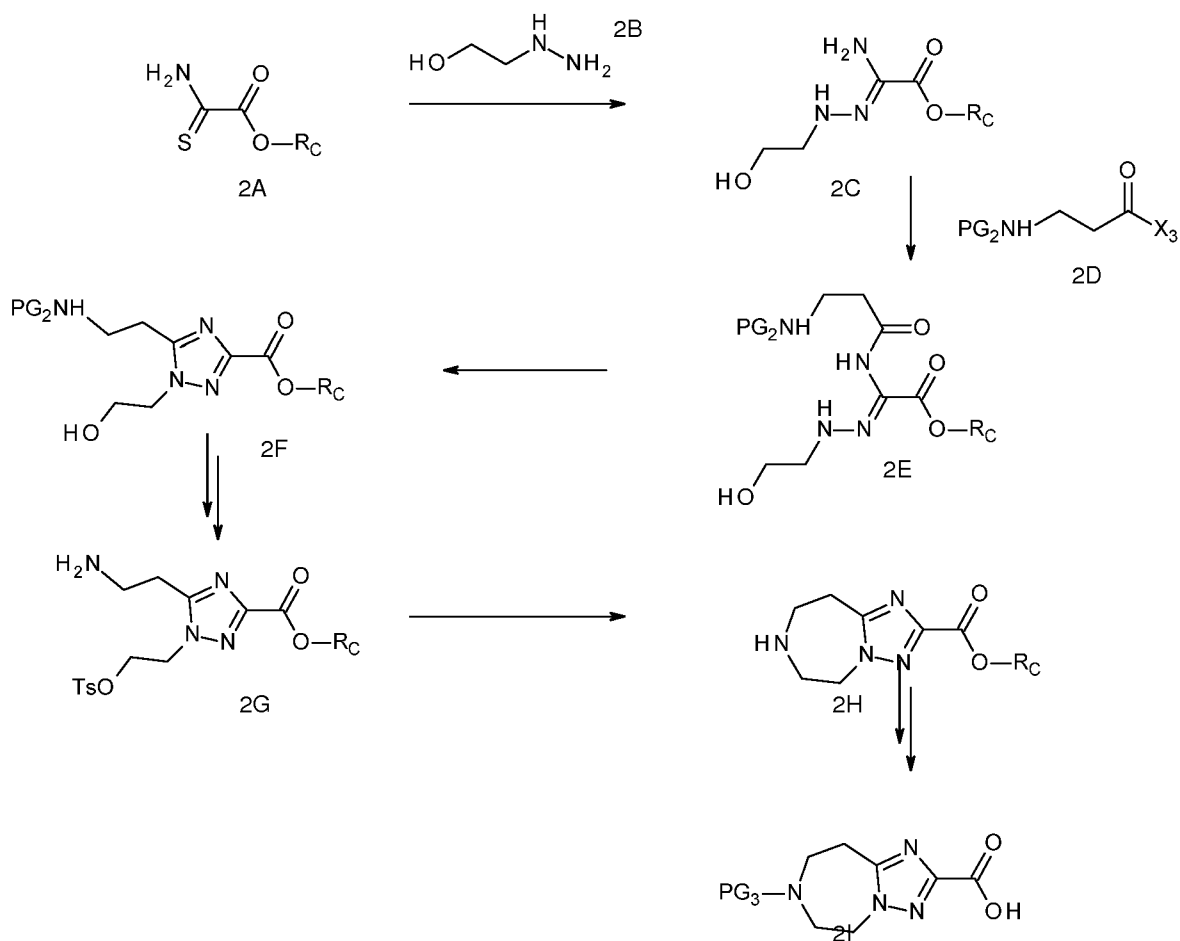
general structure **1H**. The second type of examples outlined in the current invention is represented by the general structure **1I** and can be made by treatment of intermediate **1D** with any type of free carboxylic acid **1G** (where R_B is alkyl, haloalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isoindol-2-yl, substituted 1H-indol-2-yl or substituted benzofuran-2-yl) in the presence of an activation agent such as CDI, EDC HCl or any type of peptide coupling reagent in the presence of a suitable base such as triethylamine, N-methylmorpholine, Huenig's base, NaOH, Na₂CO₃ or the like in a suitable solvent system such as DMF, CH₃CN, THF, THF/water or similar. Alternatively, any properly activated carboxylic acid derivative such as for example an acid chloride or bromide, a mixed anhydride or a p-nitrophenolate might also be used in such a reaction.

The intermediates with fused bicycles of structure **1A** or immediate precursors thereof are either described in the literature or can be made in analogy to methods described in the literature or are accessible by syntheses that can be designed by individuals skilled in the art. As an example of a synthesis of such a fused bicyclic system, the synthesis of a 6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[1,5-d][1,4]diazepine-2-carboxylic acid derivative **1A** with A¹ and A² = N (equal to a structure of formula **2I**) is outlined in Figure 2. To get access to such a material, thioamide **2A** where R_C represents for example a small alkyl group, can be treated with a substituted hydrazine of, for example, structure **2B** in a solvent such as ethanol or methanol at temperatures ranging from -20°C to the boiling point of the solvent to provide intermediate **2C**. Subsequently, intermediate **2C** can be modified with a suitably protected activated β-amino-carboxylic acid derivative **2D**, where X₃ represents a halogen or a mixed anhydride or similar, and PG₂ represents the protecting group, in the presence of an amine base such as triethylamine, Huenig's base, DMAP or the like in a solvent such as THF, DCM, diethylether or similar to give **2E**. Hydrazine derivative **2E** can be condensed to triazole **2F** by heating in an appropriate solvent such as tert-BuOH, n-BuOH or similar, at temperatures ranging up to the boiling point of the solvent or by using microwave equipment. Reaction times for such a transformation can range from minutes (i.e. in a microwave at elevated temperatures and pressures) up to several days in a standard reaction flask.

Subsequent elaboration of intermediate **2F** includes modification of the primary hydroxy group of **2F** into a better leaving group such a tosylate or mesylate or the like by treatment with the appropriate reagent in the presence of a base such as pyridine, Huenig's base, DMAP or triethylamine or similar in an appropriate solvent such as THF, DCM or similar (if required at all) at temperatures ranging from -20°C to the boiling point of the solvent. Removal of the protecting group PG₂ to afford triazole **2G** depends on the nature of PG₂. If PG₂ is for example a BOC group, it can be removed by treatment with organic or aqueous acids or other known methods; if PG₂ is a Z-group it can usually be removed by hydrogenation. In case PG₂ is yet another N-protecting group, there are other suitable de-protection conditions known to those skilled in the art that need to be applied.

Starting from intermediate **2G**, ring closure to give diazepine **2H** can be accomplished by treatment with a base such as for example triethylamine, DMAP, K₂CO₃ or similar in a suitable solvent such as DMF, CH₃CN, THF or similar at temperatures ranging from rt up to the boiling point of the solvent. If required, a suitable N-protecting group PG₃ such as a BOC group, a Z-group or any other appropriate protecting group can now be re-introduced. Compatible groups as well as conditions for introduction and removal are described for example in Green & Wuts., "Protective Groups in Organic Synthesis", John Wiley & Sons. Finally, if R_C is a small alkyl group, the free carboxylic acid **2I** is obtained from the ester precursor **2H** by hydrolysis for example in the presence of a base such as NaOH, KOH or LiOH in a solvent such as water, MeOH, EtOH, THF/water or the like at a temperature ranging from 0°C to the boiling point of the solvent to give the desired building blocks of structure **2I**. Depending on the nature of the protection group PG₃, other hydrolysis conditions known to those skilled in the art may also be applicable

Figure 2:



Suitably substituted benzyl alcohols **3B**, wherein R_D is R3, R4 and R5, as a subset of alcohols **1E**, that are used for subsequent elaboration of the central cores of formula **1A** are either

commercially available or can be made for example from the corresponding carboxylic acids, carboxylic acid esters or aldehydes **3A** ($X_4 = \text{OH}$, OR or H, respectively) by reduction with suitable reducing agents such as LAH, NaBH_4 , LiBH_4 or the like, optionally in the presence of additives such as CeCl_3 , CaCl_2 or similar, in suitable solvents such as methanol, ethanol, THF at temperatures ranging from -20 to 100°C (Figure 3).

10 Figure 3:

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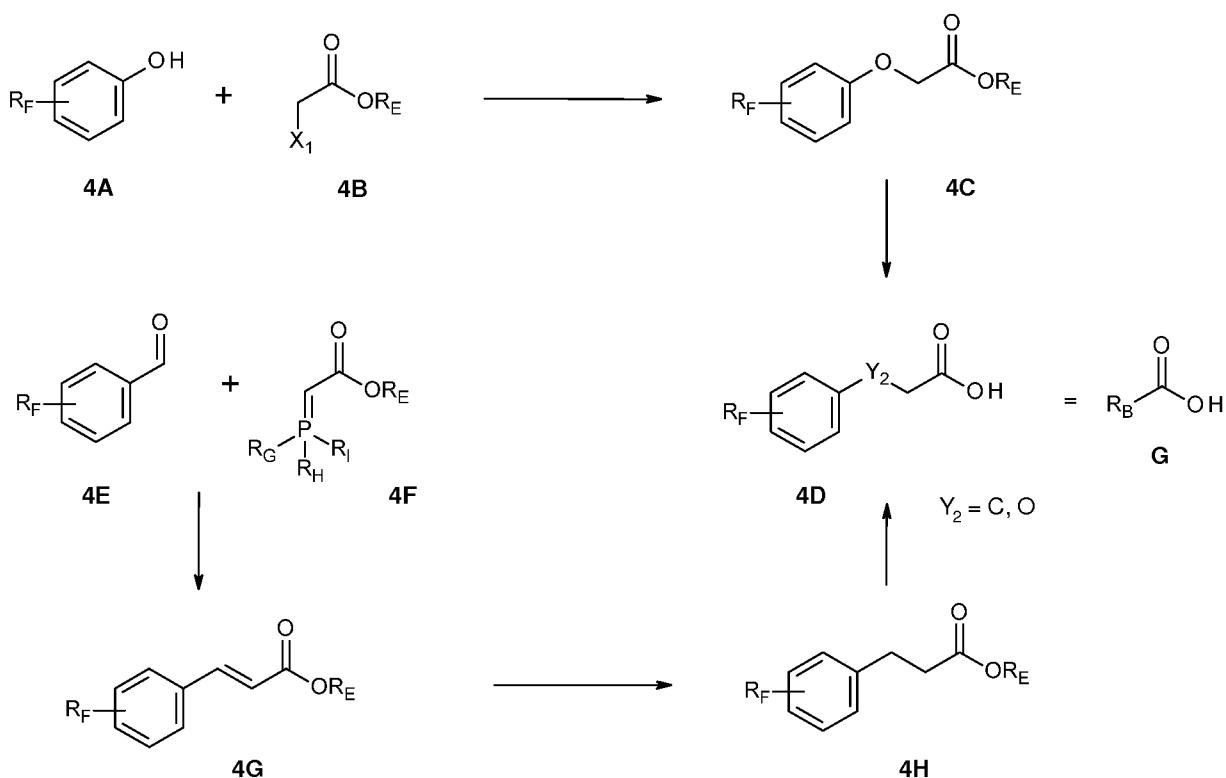
Access to suitably substituted carboxylic acids of structure **4D**, wherein R_F is R3, R4 and R5, as a subset of carboxylic acids **1G**, can be made in several ways as shown in Figure 4.

- 5 Phenoxyacetic acids **4D** with $Y_2 = O$ are accessible for example from the corresponding phenols **4A** (Figure 4, upper branch) by alkylation with an appropriate acetic acid derivative **4B** (for example an ester, when R_E is a small alkyl group) where X_1 is a suitable leaving group such as a halogen or a p-toluene sulfonate or similar to give intermediate **4C**. Such a transformation is usually made in the presence of a base such as potassium carbonate or cesium carbonate or the like in a suitable solvent such as DMF, acetone or CH_3CN at temperatures ranging from rt to the boiling point of the solvent. Similar to the conversion of **2H** to **2I**, ester **4C** can be hydrolyzed for example in the presence of a base such as NaOH, KOH or LiOH or the like to give the desired building blocks of structure **4D** with $Y_2 = O$.

- 15 Appropriately substituted 3-phenylpropionic acids of structure **4D** with $Y_2 = C$ are either commercially available or can be made as outlined in Figure 4 (lower branch). If they need to be made, they are for example accessible from the corresponding aldehydes **4E** and a Wittig reagent **4F** (a phosphor ylide which can have various substituents R_E , R_G , R_H and R_I) to produce cinnamic acid derivatives **4G**, using conditions well known to those skilled in the art. From cinnamic acid derivatives **4G**, the corresponding 3-phenylpropionic acid derivatives **4H** are made by reduction of the double bond for example by hydrogenation in the presence of a catalyst such as for example palladium on carbon, whereby different solvents or many other catalysts can be used. Subsequently, the free carboxylic acids of structure **4D** with $Y_2 = C$ are made under hydrolysis conditions as described above for the transformation of **4C** to **4D**.

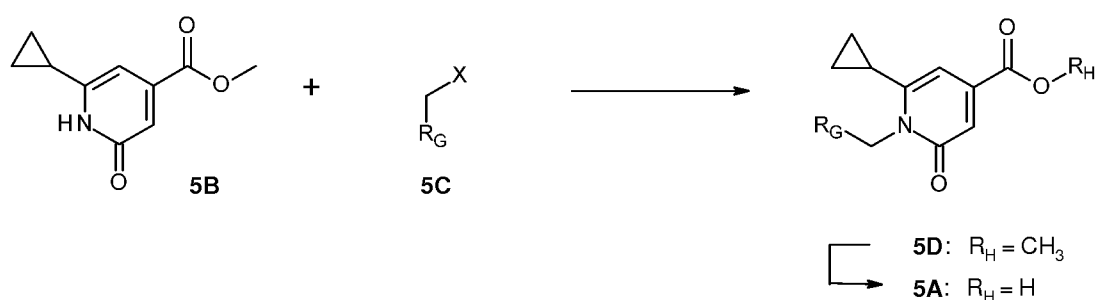
Figure 4:

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Other carboxylic acids that are needed as intermediates to prepare some of the Autotaxin inhibitors shown as examples in this application are made differently. Figure 5 shows the general route for the synthesis of appropriately substituted oxo-pyridine-4- carboxylic acids 5A:

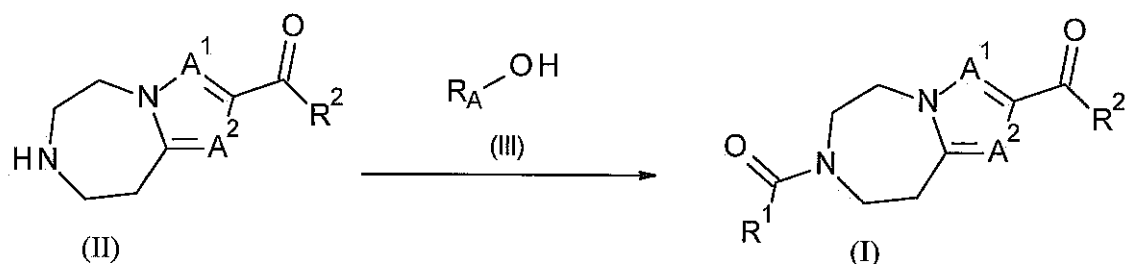
5 Figure 5:



Methyl 6-cyclopropyl-2-oxo-1H-pyridine-4-carboxylate (**5B**), for example, which is commercially available or can be made from the corresponding carboxylic acid by esterification under conditions known to those skilled in the art, can be alkylated with an appropriate alkyl halide **5C**, where X is a chloro, bromo or iodo atom, in the presence of a suitable base such as sodium hydride, lithium diisopropylamide, potassium carbonate or cesium carbonate or the like in an appropriate solvent such as DMF, THF or similar to provide the substituted pyridone

intermediate **5D**. This material is easily converted to the free carboxylic acid **5A** under hydrolytic conditions as described above, e. g. for the conversion of **4C** to **4D**.

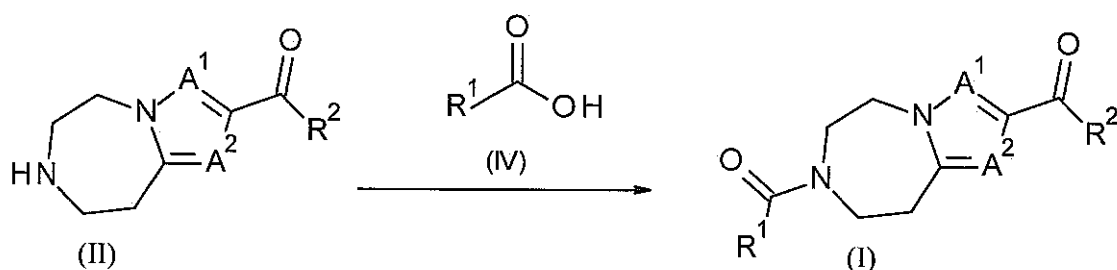
Also an embodiment of the present invention is a process to prepare a compound of formula (I) as defined above comprising the reaction of a compound of formula (II) in the presence of a compound of formula (III);



wherein R^1 is phenylalkoxy substituted with R^3 , R^4 and R^5 , R_A is phenylalkyl substituted with R^3 , R^4 and R^5 and R^2 , R^3 , R^4 , R^5 , A^1 and A^2 are as defined above.

In particular, in the presence of an activating agent such as CDI, N,N'-disuccinimidyl carbonate or phosgene, preferably N,N'-disuccinimidyl, in a solvent such as acetonitrile, in the presence of a base such as triethylamine, N-methylmorpholine or Huenig's base and at a temperature comprised between -10°C and room temperature.

Another embodiment of the present invention is a process to prepare a compound of formula (I) as defined above comprising the reaction of a compound of formula (II) in the presence of a compound of formula (IV);



wherein R^1 is alkyl, haloalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted

phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isoindol-2-yl, substituted 1H-indol-2-yl or
5 substituted benzofuran-2-yl, wherein substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted
10 thiophenylalkynyl, substituted 2,3-dihydro-1H-isoindol-2-yl, substituted 1H-indol-2-yl and substituted benzofuran-2-yl are substituted with R^3 , R^4 and R^5 and R^2 , R^3 , R^4 , R^5 A^1 and A^2 are as defined above.

In particular, in the presence of an activation agent such as CDI, EDC HCl, , in a solvent such as DMF, CH_3CN , THF, THF/water, in the presence of a base such as triethylamine, N-
15 methylmorpholine, Huenig's base, NaOH, Na_2CO_3 .

Also an object of the present invention is a compound according to formula (I) as described herein for use as a therapeutically active substance.

Likewise an object of the present invention is a pharmaceutical composition comprising a compound according to formula (I) as described herein and a therapeutically inert carrier.

20 An object of the invention is the use of a compound according to formula (I) as described herein for the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, conditions of the respiratory system, vascular and cardiovascular conditions, fibrotic diseases, cancer, ocular conditions, metabolic conditions, cholestatic and other forms of chronic pruritus and acute and chronic organ transplant rejection.

25 Renal conditions include, but are not limited to, acute kidney injury and chronic renal disease with and without proteinuria including end-stage renal disease (ESRD). In more detail, this includes decreased creatinine clearance and decreased glomerular filtration rate, micro-albuminuria, albuminuria and proteinuria, glomerulosclerosis with expansion of reticulated mesangial matrix with or without significant hypercellularity (particularly diabetic nephropathy
30 and amyloidosis), focal thrombosis of glomerular capillaries (particularly thrombotic

microangiopathies), global fibrinoid necrosis, ischemic lesions, malignant nephrosclerosis (such as ischemic retraction, reduced renal blood flow and renal arteriopathy), swelling and proliferation of intracapillary (endothelial and mesangial) and/or extracapillary cells (crescents) like in glomerular nephritis entities, focal segmental glomerular sclerosis, IgA nephropathy, 5 vasculitides / systemic diseases as well as acute and chronic kidney transplant rejection.

Liver conditions include, but are not limited to, liver cirrhosis, hepatic congestion, cholestatic liver disease including pruritus, nonalcoholic steatohepatitis and acute and chronic liver transplant rejection.

10 Inflammatory conditions include, but are not limited to, arthritis, osteoarthritis, multiple sclerosis, systemic lupus erythematoses, inflammatory bowel disease, abnormal evacuation disorder and the like as well as inflammatory airways diseases such as idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD) or chronic asthma bronchiale.

Further conditions of the respiratory system include, but are not limited to, other diffuse parenchymal lung diseases of different etiologies including iatrogenic drug-induced fibrosis, 15 occupational and/or environmental induced fibrosis, systemic diseases and vasculitides, granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease, alveolar proteinosis, Langerhans cell granulomatosis, lymphangioleiomyomatosis, inherited diseases (Hermansky-Pudlak Syndrome, tuberous sclerosis, neurofibromatosis, metabolic storage disorders, familial interstitial lung disease), radiation induced fibrosis, silicosis, asbestos induced 20 pulmonary fibrosis or acute respiratory distress syndrome (ARDS).

Conditions of the nervous system include, but are not limited to, neuropathic pain, schizophrenia, neuro-inflammation (e.g. astrogliosis), peripheral and/or autonomic (diabetic) neuropathies and the like.

Vascular conditions include, but are not limited to, atherosclerosis, thrombotic vascular 25 disease as well as thrombotic microangiopathies, proliferative arteriopathy (such as swollen myointimal cells surrounded by mucinous extracellular matrix and nodular thickening), atherosclerosis, decreased vascular compliance (such as stiffness, reduced ventricular compliance and reduced vascular compliance), endothelial dysfunction and the like.

Cardiovascular conditions include, but are not limited to, acute coronary syndrome, coronary heart disease, myocardial infarction, arterial and pulmonary hypertension, cardiac arrhythmia such as atrial fibrillation, stroke and other vascular damage.

5 Fibrotic diseases include, but are not limited to myocardial and vascular fibrosis, renal fibrosis, liver fibrosis, pulmonary fibrosis, skin fibrosis, scleroderma and encapsulating peritonitis.

In a particular embodiment, the compounds of formula (I) or their pharmaceutically acceptable salts and esters can be used for the treatment or prophylaxis of organ or skin fibrosis.

10 In another embodiment, the fibrotic disease is renal tubulo-interstitial fibrosis or glomerulosclerosis.

In another embodiment, the fibrotic disease is non-alcoholic liver steatosis, liver fibrosis or liver cirrhosis.

In another embodiment, the fibrotic disease is idiopathic pulmonary fibrosis.

15 Cancer and cancer metastasis include, but are not limited to, breast cancer, ovarian cancer, lung cancer, prostate cancer, mesothelioma, glioma, hepatic carcinoma, gastrointestinal cancers and progression and metastatic aggressiveness thereof.

Ocular conditions include, but are not limited to, proliferative and non-proliferative (diabetic) retinopathy, dry and wet age-related macular degeneration (AMD), macular edema, central arterial /venous occlusion, traumatic injury, glaucoma and the like.

20 Metabolic conditions include, but are not limited to, obesity and diabetes.

In another embodiment, the compounds of formula (I) or their pharmaceutically acceptable salts and esters can be used for the treatment or prophylaxis of cholestatic or non-cholestatic chronic pruritus.

25 The present invention also relates to the use of a compound according to formula (I) as described herein for the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, fibrotic diseases and acute and chronic organ transplant rejection.

The present invention also relates to the use of a compound according to formula (I) as described herein for the treatment or prophylaxis of renal conditions, liver conditions and fibrotic diseases.

5 A particular embodiment of the present invention is a compound according to formula (I) as described herein for the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, fibrotic diseases and acute and chronic organ transplant rejection.

10 A particular embodiment of the present invention is a compound according to formula (I) as described herein for the treatment or prophylaxis of renal conditions, liver conditions and fibrotic diseases.

The present invention also relates to the use of a compound according to formula (I) as described herein for the preparation of a medicament for the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, fibrotic diseases and acute and chronic organ transplant rejection.

15 The present invention also relates to the use of a compound according to formula (I) as described herein for the preparation of a medicament for the treatment or prophylaxis of renal conditions, liver conditions and fibrotic diseases.

20 Also an object of the invention is a method for the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, fibrotic diseases and acute and chronic organ transplant rejection, which method comprises administering an effective amount of a compound according to formula (I) as described herein.

Also an object of the invention is a method for the treatment or prophylaxis of renal conditions, liver conditions and fibrotic diseases, which method comprises administering an effective amount of a compound according to formula (I) as described herein.

25 In a particular embodiment, the renal condition is selected from the group consisting of acute kidney injury, chronic kidney disease, diabetic nephropathy, acute kidney transplant rejection and chronic allograft nephropathy.

In another particular embodiment, the renal condition is acute kidney injury.

In another particular embodiment, the renal condition is chronic kidney disease.

In a further particular embodiment, the renal condition is diabetic nephropathy.

In another particular embodiment, the renal condition is acute kidney transplant rejection.

In another particular embodiment, the renal condition is chronic allograft nephropathy.

5 In a particular embodiment, the liver condition is acute and chronic liver transplant rejection

In a particular embodiment, the inflammatory condition is arthritis.

In a particular embodiment, the condition of the nervous system is neuropathic pain.

In another embodiment, the fibrotic disease is encapsulating peritonitis

10 In another embodiment, the fibrotic disease is idiopathic pulmonary fibrosis.

In another embodiment, the fibrotic disease is non-alcoholic liver steatosis, liver fibrosis or liver cirrhosis.

Also an embodiment of the present invention are compounds of formula (I) as described herein, when manufactured according to any one of the described processes.

15 Assay procedures

Production of human full length autotaxin (ATX) with and without His tag:

Autotaxin (ATX - ENPP2) cloning: cDNA was prepared from commercial human hematopoietic cells total RNA and used as template in overlapping PCR to generate a full length human ENPP2 ORF with or without a 3'-6xHis tag. These full length inserts were cloned into
20 the pcDNA3.1V5-His TOPO (Invitrogen) vector. The DNA sequences of several single clones were verified. The DNA from a correct full length clone was used to transfect Hek293 cells for verification of protein expression. The sequence of the encoded ENPP2 conforms to Swissprot entry Q13822, with or without the additional C-terminal 6xHis tag.

ATX Fermentation: Recombinant protein was produced by large-scale transient transfection in
25 20 L controlled stirred tank bioreactors (Sartorius). During cell growth and transfection,

temperature, stirrer speed, pH and dissolved oxygen concentration were maintained at 37°C, 120 rpm, 7.1 and 30% DO, respectively. FreeStyle 293-F cells (Invitrogen) were cultivated in suspension in FreeStyle 293 medium (Invitrogen) and transfected at ca. $1-1.5 \times 10^6$ cells/mL with above plasmid DNAs using X-tremeGENE Ro-1539 (commercial product, Roche
5 Diagnostics) as complexing agent. Cells were fed a concentrated nutrient solution (J Immunol Methods 194 (1996), 19, 1-199 (page 193)) and induced by sodium butyrate (2 mM) at 72 h post-transfection and harvested at 96 h post-transfection. Expression was analyzed by Western Blot, enzymatic assay and/or analytical IMAC chromatography. After cooling the cell
10 suspension to 4°C in a flow-through heat exchanger, cell separation and sterile filtration of supernatant was performed by filtration through Zeta Plus 60M02 E16 (Cuno) and Sartopore 2 XLG (Sartorius) filter units. The supernatant was stored at 4°C prior to purification.

ATX Purification: 20 liter of culture supernatant were conditioned for ultrafiltration by adding Brij 35 to a final concentration of 0.02% and by adjusting the pH to 7.0 using 1 M HCl. Then the supernatant was first microfiltered through a 0.2 µm Ultran-Pilot Open Channel PES filter
15 (Whatman) and afterwards concentrated to 1 liter through an Ultran-Pilot Screen Channel PES filter with 30 kDa MWCO (Whatman). Prior to IMAC chromatography, NiSO_4 was added to a final concentration of 1 mM. The cleared supernatant was then applied to a HisTrap column (GE Healthcare) previously equilibrated in 50 mM Na_2HPO_4 pH 7.0, 0.5 M NaCl, 10% glycerol, 0.3% CHAPS, 0.02% NaN_3 . The column was washed stepwise with the same buffer containing
20 20 mM, 40 mM and 50 mM imidazole, respectively. The protein was subsequently eluted using a linear gradient to 0.5 M imidazole in 15 column volumes. ATX containing fractions were pooled and concentrated using an Amicon cell equipped with a 30 kDa PES filter membrane. The protein was further purified by size exclusion chromatography on Superdex S-200 prep grade (XK 26/100) (GE Healthcare) in 20 mM BICINE pH 8.5, 0.15 M NaCl, 10% glycerol,
25 0.3% CHAPS, 0.02% NaN_3 . Final yield of protein after purification was 5-10 mg ATX per liter of culture supernatant. The protein was stored at -80°C.

Human ATX enzyme inhibition assay

ATX inhibition was measured by a fluorescence quenching assay using a specifically labeled substrate analogue (MR121 substrate). To obtain this MR121 substrate, BOC and TBS protected
30 6-amino-hexanoic acid (R)-3-({2-[3-(2-{2-[2-(2-amino-ethoxy)-ethoxy]-ethoxy}-ethoxy)-propionylamino]-ethoxy}-hydroxy-phosphoryloxy)-2-hydroxy-propyl ester (Ferguson et al., Org Lett 2006, 8 (10), 2023) was labeled with MR121 fluorophore (CAS 185308-24-1, 1-(3-

carboxypropyl)-11-ethyl-1,2,3,4,8,9,10,11-octahydro-dipyrido[3,2-b:2',3'-i]phenoxazin-13-ium) on the free amine of the ethanolamine side and then, after deprotection, subsequently with tryptophan on the side of the aminohexanoic acid.

Assay working solutions were made as follows:

- 5 Assay buffer (50 mM Tris-HCl, 140 mM NaCl, 5 mM KCl, 1 mM CaCl₂, 1 mM MgCl₂, 0.01% Triton-X-100, pH 8.0;
ATX solution: ATX (human His-tagged) stock solution (1.08 mg/mL in 20mM bicine, pH 8.5, 0.15 M NaCl, 10% glycerol, 0.3% CHAPS, 0.02% NaN₃), diluted to 1.4 – 2.5x final concentration in assay buffer;
- 10 MR121 substrate solution: MR121 substrate stock solution (800 μ M MR121 substrate in DMSO), diluted to 2 – 5x final concentration in assay buffer.

- Test compounds (10 mM stock in DMSO, 8 μ L) were obtained in 384 well sample plates (Corning Costar #3655) and diluted with 8 μ L DMSO. Row-wise serial dilutions were made by transferring 8 μ L cpd solution to the next row up to row O. The compound and control solutions
- 15 were mixed five times and 2 μ L were transferred to 384 well assay plates (Corning Costar # 3702). Then, 15 μ L of 41.7 nM ATX solution was added (30 nM final concentration), mixed five times and then incubated for 15 minutes at 30°C. 10 μ L of MR121 substrate solution was added (1 μ M final concentration), mixed 30 times and then incubated for 15 minutes at 30 °C. Fluorescence was then measured every 2 minutes for 1 hour (Perkin Elmer plate: vision
 - 20 multimode reader); light intensity: 2.5%; exp. time: 1.4 sec, Filter: Fluo_630/690 nm) and IC₅₀ values were calculated from these readouts.

Inhibitory activities (IC₅₀) for the examples of the present invention against ATX are given below.

Example	IC ₅₀ (μ M)
1	0.158
2	2.01
3	0.018
4	0.007
5	0.002
6	0.004
7	0.07

Example	IC ₅₀ (μ M)
8	0.06
9	0.006
10	0.018
11	0.015
12	0.067
13	0.017
14	0.014

Example	IC ₅₀ (μ M)
15	0.011
16	0.012
17	0.010
18	0.013
19	0.151
20	0.006

Example	IC ₅₀ (μM)
21	0.017
22	0.018
23	0.050
24	0.009
25	0.007
26	0.016
27	0.052
28	0.076

Example	IC ₅₀ (μM)
29	0.038
30	0.041
31	0.022
32	0.030
33	0.094
34	0.007
35	0.013
36	0.006

Example	IC ₅₀ (μM)
37	0.009
38	0.021
39	0.014
40	0.017
41	0.006
42	0.007
43	0.056

Compounds of formula (I) and their pharmaceutically acceptable salts or esters thereof as described herein have IC₅₀ values between 0.00001 μM and 1000 μM, particular compounds have IC₅₀ values between 0.0005 μM and 500 μM, further particular compounds have IC₅₀ values between 0.0005 μM and 50 μM, more particular compounds have IC₅₀ values between 0.0005 μM and 5 μM. These results have been obtained by using the enzymatic assay described above.

The compounds of formula (I) and their pharmaceutically acceptable salts can be used as medicaments (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered internally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays), rectally (e.g. in the form of suppositories) or topical ocularly (e.g. in the form of solutions, ointments, gels or water soluble polymeric inserts). However, the administration can also be effected parenterally, such as intramuscularly, intravenously, or intraocularly (e.g. in the form of sterile injection solutions).

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

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

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

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

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

Suitable adjuvants for topical ocular formulations are, for example, cyclodextrins, mannitol or many other carriers and excipients known in the art.

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

The dosage can vary in wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage
15 of about 0.1 mg to 20 mg per kg body weight, preferably about 0.5 mg to 4 mg per kg body weight (e.g. about 300 mg per person), divided into preferably 1-3 individual doses, which can consist, for example, of the same amounts, should it be appropriate. In the case of topical administration, the formulation can contain 0.001% to 15% by weight of medicament and the required dose, which can be between 0.1 and 25 mg in can be administered either by single dose
20 per day or per week, or by multiple doses (2 to 4) per day, or by multiple doses per week It will, however, be clear that the upper or lower limit given herein can be exceeded when this is shown to be indicated.

The invention is illustrated hereinafter by Examples, which have no limiting character.

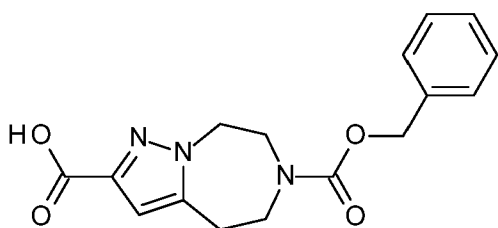
In case the preparative examples are obtained as a mixture of enantiomers, the pure
25 enantiomers can be obtained by methods described herein or by methods known to those skilled in the art, such as e.g. chiral chromatography or crystallization.

IntermediatesAbbreviations

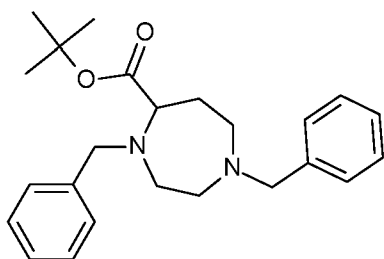
aq. = aqueous; CAS = Chemical Abstracts Service Registry Number; e.r. = enantiomeric ratio; HPLC = high performance liquid chromatography; MS = mass spectrum; NMR = nuclear magnetic resonance spectrum; sat. = saturated; rt = room temperature. Other abbreviations such as abbreviations for chemical reagents or solvents are known to those skilled in the art.

Intermediate 1:

10 **6-Phenylmethoxycarbonyl-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-2-carboxylic acid**



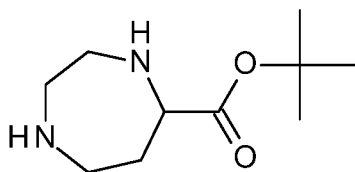
(6-*O*-benzyl 2-*O*-ethyl 4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-2,6-dicarboxylate, CAS: 1080027-19-5; synthesized in steps 1 – 7 described below) has been mentioned in Gerlach et al., PCT Int. Appl. (2008), WO 2008135526 A1 and was synthesized in analogy to Venkatesan M. A. et al., J. Med. Chem. 2006, 49, 4623.

Step 1: tert-Butyl 1,4-dibenzyl-1,4-diazepane-5-carboxylate

In a 20 mL round-bottomed flask, tert-butyl-2,4-dibromobutanoate (500 mg, [CAS: 77629-96-0]), N,N'-dibenzylethylenediamine (372 mg, [CAS: 140-28-3]) and triethylamine (460 mg) were dissolved in dichloromethane (20 mL) to give a colorless solution. The mixture was heated to 40°C for 15 hours. The reaction mixture was poured into ice/water and basified with saturated NaHCO₃ solution. The aqueous phase was then extracted two times with dichloromethane. The combined organic layers were dried over Na₂SO₄, filtered and the solvent was evaporated to dryness. The crude material was purified by flash chromatography (silica gel, gradient of ethyl acetate in heptane) to give the title compound as a light brown oil (232 mg, 35 %). MS (EI): 380.0 [M⁺].

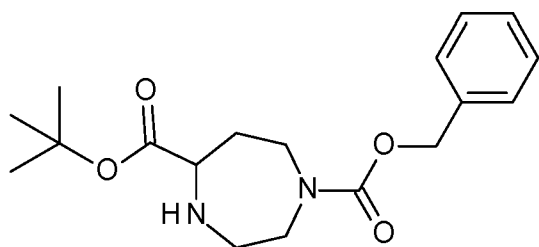
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Step 2: tert-Butyl 1,4-diazepane-5-carboxylate



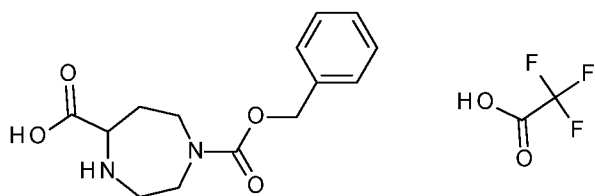
tert-Butyl 1,4-dibenzyl-1,4-diazepane-5-carboxylate (3.40 g) was dissolved in ethanol (50 mL) to give a light brown solution. Palladium on activated charcoal (800 mg, 10% Pd) was added and an atmosphere of hydrogen was introduced at room temperature. The mixture was stirred under hydrogen for 9 hours at 5 bars. The reaction mixture was filtered over dicalite speed plus (Acros Organics) and the solvent was evaporated to dryness to give the title compound as a light brown oil (1.40 g, 77 %). MS (m/e): 201.7 [M+H]⁺.

20 Step 3: 1-O-benzyl 5-O-tert-butyl 1,4-diazepane-1,5-dicarboxylate



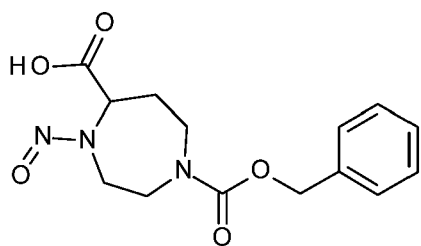
tert-Butyl 1,4-diazepane-5-carboxylate (1.055 g) was dissolved in dichloromethane (20 mL) to give a light brown solution at room temperature under an argon atmosphere. The mixture was cooled down to 0°C and a solution of dibenzyl dicarbonate (1.51 g) in dichloromethane (10 mL) was added drop wise over a period of 10 minutes. The reaction mixture was stirred for 30 minutes at 0°C and then warmed up to rt for 1.5 hours. The mixture was directly evaporated to dryness and the residue was purified by flash chromatography (silica gel, gradient of methanol in dichloromethane) to give the title compound as a light brown oil (960 mg, 52 %). MS (m/e): 335.6 [M+H]⁺.

10 Step 4: 1-Phenylmethoxycarbonyl-1,4-diazepane-5-carboxylic acid 2,2,2-trifluoroacetate



1-O-benzyl 5-O-tert-butyl 1,4-diazepane-1,5-dicarboxylate (9.0 g) was dissolved in dichloromethane (90 mL) at room temperature under an argon atmosphere. Then, 2,2,2-trifluoroacetic acid (30.7 g, 20.70 mL) was added drop wise over a period of 15 minutes. The mixture was stirred at room temperature for 8 hours. The solvent was directly evaporated and the residue was dried at high vacuum to give the title compound as a crude light brown oil (11 g, 100 %, purity 95 %). MS (m/e): 279.6 [M-TFA+H]⁺.

Step 5: 4-Nitroso-1-phenylmethoxycarbonyl-1,4-diazepane-5-carboxylic acid

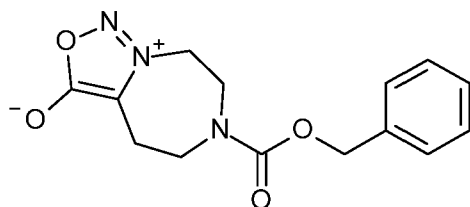


1-(Benzyloxycarbonyl)-1,4-diazepane-5-carboxylic acid 2,2,2-trifluoroacetic acid (1.448 g) was dissolved in water (11.0 mL) and tetrahydrofuran (4.0 mL) at room temperature. Then,

hydrochloric acid (37%, 337 μ L) was added dropwise over a period of 5 minutes. The light brown solution was cooled down to 0°C and sodium nitrite (251 mg) was added. The mixture was warmed up to room temperature and stirring was continued for 1 hour. The reaction mixture was poured into ice/water. The aqueous phase was then extracted two times with ethyl acetate.

- 5 The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated. The residue was dried at high vacuum to give the title compound as a crude light brown oil (966 mg, 97 %, purity 80 %). MS (m/e): 308.5 [M+H]⁺.

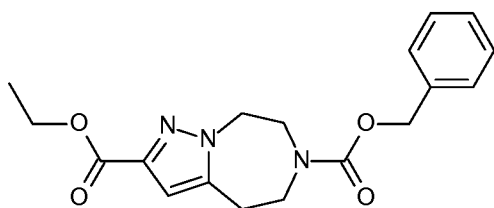
Step 6: 6-Phenylmethoxycarbonyl-4,5,7,8-tetrahydrooxadiazolo[3,4-d][1,4]diazepin-9-ium-3-
10 olate



1-(Benzyloxycarbonyl)-4-nitroso-1,4-diazepane-5-carboxylic acid (936 mg) was dissolved in acetonitrile (15 mL) at room temperature under an argon atmosphere. The mixture was cooled down to 0°C and trifluoroacetic anhydride (768 mg) was added drop wise over a period of 10
15 minutes. The mixture was warmed up to room temperature and stirring was continued for 3 hours. Then, potassium carbonate (505 mg) was added and the mixture was stirred for 30 minutes. The reaction mixture was poured into ice/water. The aqueous phase was then extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated. The crude material was purified by flash chromatography
20 (silica gel, gradient of ethyl acetate in heptane) to give the title compound as a light yellow gum (300 mg, 39 %). MS (m/e): 290.5 [M+H]⁺.

Step 7: 6-O-benzyl 2-O-ethyl 4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-2,6-dicarboxylate

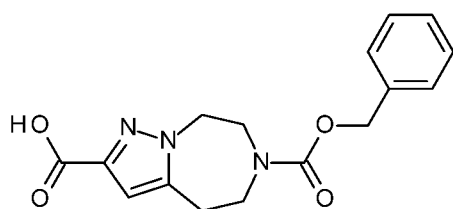
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Ethyl propiolate (284 mg) was added to a solution of 6-(benzyloxycarbonyl)-5,6,7,8-tetrahydro-4H-[1,2,3]oxadiazolo[3,4-d][1,4]diazepine-9-ium-3-olate (186 mg) in chlorobenzene (4.0 mL) at room temperature under an argon atmosphere. The mixture was heated at 150°C for 2 hours in a microwave. The reaction mixture was directly evaporated to dryness. The crude material was purified by flash chromatography (silica gel, gradient of ethyl acetate in heptane) to give the title compound as a light yellow gum (131 mg, 53 %). MS (m/e): 344.5 [M+H]⁺.

The regioisomer 6-*O*-benzyl 3-*O*-ethyl 4,5,7,8-tetrahydropyrazolo[1,5-*d*][1,4]diazepine-3,6-dicarboxylate was also isolated by flash chromatography (silica gel, gradient of ethyl acetate in heptane) as a light yellow gum (36 mg, 16 %). MS (m/e): 344.5 [M+H]⁺.

Step 8: 6-Phenylmethoxycarbonyl-4,5,7,8-tetrahydropyrazolo[1,5-*d*][1,4]diazepine-2-carboxylic acid

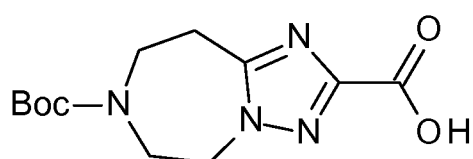


Lithium hydroxide 1M solution (9.33 mL) was added drop wise over a period of 10 minutes to a solution of 6-benzyl 2-ethyl 7,8-dihydro-4H-pyrazolo[1,5-*d*][1,4]diazepine-2,6(5H)-dicarboxylate (1.78 g) in tetrahydrofuran (20 mL) at room temperature. The mixture was stirred at room temperature for 18 hours. The reaction mixture was poured into ice/water and acidified with HCl (2M) solution to pH=1. The aqueous phase was then extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and

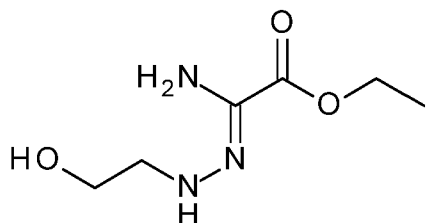
the solvent was evaporated. The residue was dried at high vacuum to give the title compound as a yellow solid (1.64 g, 95%). MS (m/e): 316.5 [M+H]⁺.

5 Intermediate 2:

4,5,7,8-tetrahydro-1,3,3a,6-tetraaza-azulene-2,6-dicarboxylic acid 6-tert-butyl ester



Step1: Ethyl (2Z)-2-amino-2-(2-hydroxyethylhydrazono)acetate

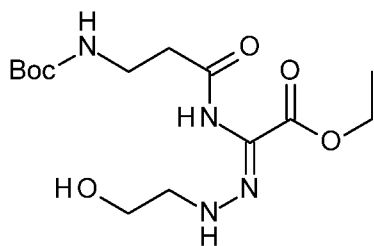


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To a solution of amino-thioxo-acetic acid ethyl ester (5.0 g,) in ethanol (160 mL) at 0°C was added 2-hydrazino-ethanol and the reaction mixture was stirred at 25°C for 2h. Volatile components were then removed *in vacuo* to get the title compound (6.58 g) as yellow sticky solid that was used in next step without any further purification. LC-MS: 175.8 [M+H]⁺.

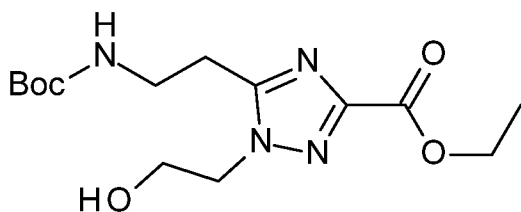
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Step 2: Ethyl (2Z)-2-[3-(tert-butoxycarbonylamino)propanoylamino]-2-(2-hydroxyethylhydrazono)acetate



To a solution of 3-tert-butoxycarbonylamino-propionic acid (7.73 g) in THF (100 mL) at -10°C were added triethyl amine (6.78 mL) and ethyl chloroformate (4.64 mL) under a nitrogen atmosphere and the reaction mixture was stirred at -10°C for 0.5h. The reaction mixture was
 5 filtered and the filtrate was then added to a solution of ethyl (2Z)-2-amino-2-(2-hydroxyethylhydrazono)acetate (6.57g) and the mixture was stirred at 25°C for 16h. Solvent was evaporated *in vacuo* and the residue was partitioned between ethyl acetate (150 mL) and water (100 mL). The organic layer was separated, and aqueous layer was re-extracted with ethyl acetate (2x100ml). The combined organic layers were washed with brine, dried over anhydrous
 10 Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography over normal silica gel (20-40%EtOAc/hexane) to get (3-tert-butoxycarbonylamino-propionylamino)-[(2-hydroxy-ethyl)-hydrazono]-acetic acid ethyl ester (5.81 g) as yellow sticky solid. LC-MS: 346.9 [M+H]⁺.

15 Step 3: Ethyl 5-[2-(tert-butoxycarbonylamino)ethyl]-1-(2-hydroxyethyl)-1,2,4-triazole-3-carboxylate

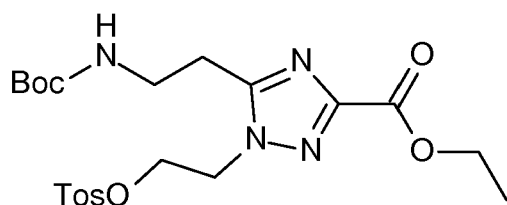


As solution of ethyl (2Z)-2-[3-(tert-butoxycarbonylamino)propanoylamino]-2-(2-hydroxyethylhydrazono)acetate (5.8 g) in n-BuOH (400 mL) was refluxed for 18h. The solvent
 20 was removed *in vacuo* and the residue was purified by column chromatography over normal silica gel using (0-4%MeOH/DCM as an eluent) to afford a mixture of 5-(2-tert-butoxycarbonylamino-ethyl)-1-(2-hydroxy-ethyl)-1H-[1,2,4]triazole-3-carboxylic acid ethyl ester and

-46-

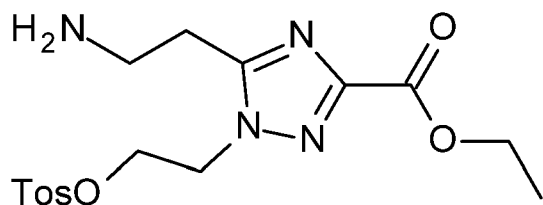
corresponding n-butyl ester (4.22 g, impure) as yellow sticky solid. LC-MS: 329.2 and 356.9 [M+H]⁺.

Step 4: Ethyl 5-(2-tert-butoxycarbonylamino-ethyl)-1-[2-(toluene-4-sulfonyloxy)-ethyl]-1H-[1, 2, 4] triazole-3-carboxylate



To a solution of 5-(2-tert-butoxycarbonylamino-ethyl)-1-(2-hydroxy-ethyl)-1H-[1,2,4]triazole-3-carboxylic acid ethyl ester (4.2 g) in DCM (100 mL) at 0°C were added triethyl amine (2.70 mL) and p-toluenesulfonyl chloride (2.92 g) and reaction mixture was stirred at 25°C for 16h. The reaction mixture was diluted with DCM (50 mL) and washed with saturated aqueous sodium bicarbonate solution (100 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography over normal silica gel (10-30%EtOAc/hexane as an eluent) to afford the title compound as a mixture of the ethyl ester and the corresponding butyl ester (1.98 g) as yellow sticky solid. LC-MS: 482.9 and 511.1 [M+H]⁺.

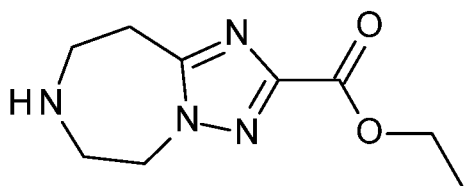
Step 5: Ethyl 5-(2-amino-ethyl)-1-(2-hydroxy-ethyl)-1H-[1, 2, 4] triazole-3-carboxylate



To a solution of ethyl 5-(2-tert-butoxycarbonylamino-ethyl)-1-[2-(toluene-4-sulfonyloxy)-ethyl]-1H-[1, 2, 4] triazole-3-carboxylate (5.17 g) in DCM (100mL) was added 4N HCl in dioxane (40 mL) and the reaction mixture was stirred at 25°C for 2h. Then the volatile components were

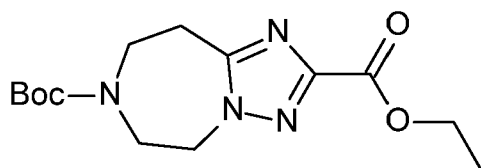
removed *in vacuo* to afford the title compound as a mixture of the ethyl ester and the corresponding butyl ester hydrochloride salts (4.42 g, crude) as brown sticky solid. LC-MS: 383.1 and 410.8 $[M+H]^+$.

5 Step 6: Ethyl 5,6,7,8-tetrahydro-4H-1,3,3a,6-tetraaza-azulene-2-carboxylate



To a suspension of ethyl 5-(2-amino-ethyl)-1-(2-hydroxy-ethyl)-1H-[1, 2, 4] triazole-3-carboxylate (4.4 g, crude) in THF (200 mL) was added drop wise triethylamine (4.44 mL) at 0°C and the reaction mixture was stirred at 60°C for 18h. Volatilities were removed *in vacuo* to get the title compound as a mixture of the ethyl ester and the corresponding butyl ester along with other impurities (2.23 g, crude) as brown sticky solid that was used in next step with out further purification. LC-MS: 211.3 and 239.0 $[M+H]^+$.

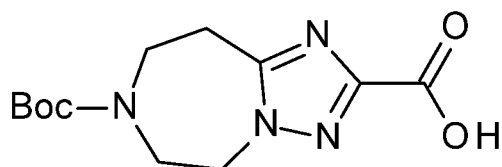
15 Step 7: 4,5,7,8-Tetrahydro-1,3,3a,6-tetraaza-azulene-2,6-dicarboxylic acid 6-tert-butyl ester 2-ethyl ester



To a suspension of ethyl 5, 6, 7, 8-tetrahydro-4H-1, 3, 3a, 6-tetraaza-azulene-2-carboxylate (2.2 g) in THF (100 mL) were added triethyl amine (2.21 mL) and di-tert-butyl carbonate (3.6 mL), and the reaction mixture was stirred at 25°C for 2h. The solvent was removed *in vacuo*, and the residue was purified by column chromatography over normal silica gel (0-5% MeOH/DCM as an eluent) to afford the title compound as a mixture of the ethyl ester and the corresponding butyl ester (1.2 g, 53.3% from ethyl 5-(2-tert-butoxycarbonylamino-ethyl)-1-[2-(toluene-4-

sulfonyloxy)-ethyl]-1H-[1,2,4] triazole-3-carboxylate, obtained in Step 4) as yellow sticky solid. LC-MS: 311.2 and 339.1 [M+H]⁺.

Step 8: 4,5,7,8-Tetrahydro-1,3,3a,6-tetraaza-azulene-2,6-dicarboxylic acid 6-tert-butyl ester



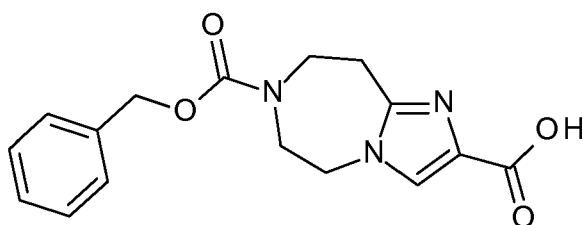
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To a solution of 4,5,7,8-tetrahydro-1,3,3a,6-tetraaza-azulene-2,6-dicarboxylic acid 6-tert-butyl ester 2-ethyl ester (1.2 g) in THF (16 mL) at 25°C was added a solution of LiOH H₂O (324 mg) in water (4 mL), and the reaction mixture was stirred at 25°C for 1h. The solvent was removed *in vacuo* and the residue was dissolved in water (30 mL) and washed with ethyl acetate. The aqueous layer was acidified with saturated aqueous citric acid solution and extracted with DCM (3x75 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by prep. HPLC to afford the title compound (228 mg, 21%) as off white solid. LC-MS: 283.3 [M+H]⁺.

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Intermediate 3:

5,6,8,9-tetrahydro-imidazo [1,2-a] [1,4] diazepine-2,7-dicarboxylic acid 7-benzyl ester:



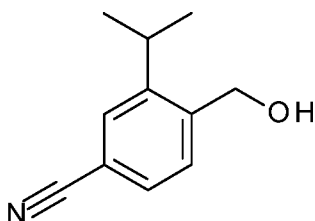
2-Formyl-5,6,8,9-tetrahydro-imidazo [1,2-a] [1,4] diazepine-7-carboxylic acid benzyl ester (500 mg), made according to the procedures described by Gerlach et al. in PCT Int. Appl. (2008), WO 2008135526 A1, was dissolved in acetone (15 mL) and water (15 mL). Then, sulphamic acid

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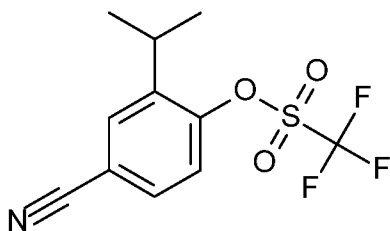
(292 mg) and NaClO₂ (211 mg) were added, and the reaction mixture was stirred at 25°C for 3h. Acetone was removed *in vacuo*, and the aqueous layer was extracted with DCM (3x50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was triturated with Et₂O and to provide an off-white solid that was dried to
5 yield 5,6,8,9-tetrahydro-imidazo [1,2-a] [1,4] diazepine-2,7-dicarboxylic acid 7-benzyl ester (**6**) (425 mg, 81%). LC-MS: 316.0 [M+H]⁺.

Intermediate 4:

10 4-(hydroxymethyl)-3-isopropyl-benzonitrile



Step1: 4-cyano-2-isopropylphenyl trifluoromethanesulfonate

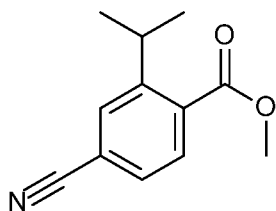


15 To a solution of pyridine (915 µl) in dichloromethane (70 mL) was added trifluoromethanesulfonic anhydride (1.75 mL) at 0 °C. The white suspension was stirred for 10 min. at 0 °C. A solution of 4-hydroxy-3-isopropylbenzonitrile (CAS: 1.52 g) in dichloromethane (40 ml) was added dropwise. The ice-bath was removed and the dark brown clear solution was stirred at rt. TLC at t = 75 min showed the reaction to be complete. The reaction mixture was
20 diluted with dichloromethane and washed with water and brine. The aq. layers were back

extracted with dichloromethane dried over magnesium sulfate filtered and evaporated. The residue was purified by flash chromatography (100 g, SiO₂; gradient heptane / dichloromethane 9 : 1 to heptane / dichloromethane 4 : 6) to afford the title compound (2.63 g, 95 %). Yellow liquid ; MS: 292.1 [M-H]⁻.

5

Step 2: Methyl 4-cyano-2-isopropylbenzoate

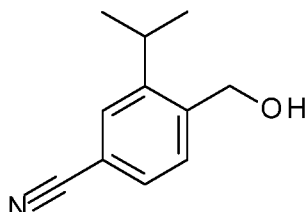


4-Cyano-2-isopropylphenyl trifluoromethanesulfonate (2.30 g) was added to an autoclave and methanol (46 mL) was added. The autoclave was set under argon and then triethylamine (2.73 mL) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex

(320 mg) were added. A CO atmosphere was introduced by repeated (3 times) evacuation and introduction of 10bar CO. The pressure was then increased to 50bar and the autoclave was kept at 110°C for 20 hrs. The reaction mixture was cooled to rt and the red solution was evaporated in vacuo. Filtration of the residue over 100 g SiO₂ column, solvent dichloromethane / heptane 1 : 1 afforded the title compound (1.23 g, 77 %). Light yellow oil, MS: 218.5 [M+H]⁺.

15

Step 3: 4-(hydroxymethyl)-3-isopropyl-benzonitrile



To a clear, light yellow solution of methyl 4-cyano-2-isopropylbenzoate (1.227 g) in tetrahydrofuran (15 mL) was added lithium borohydride (2M in THF, 9.06 mL). The reaction

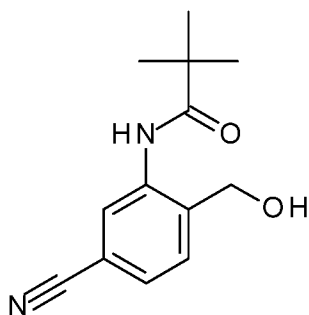
20

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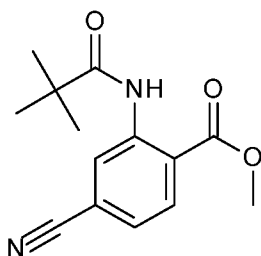
mixture was heated to reflux. TLC (dichloromethane / heptane 4 : 1) at t = 1 h showed the reaction was complete. The reaction was cooled to room temperature and 5 mL MeOH was added. After 30min, the reaction was diluted with ethyl acetate and extracted with water and brine. The aq. layers were back-extracted with ethyl acetate. The combined organic layers were
5 dried over magnesium sulfate filtered and evaporated. Chromatography (100 g, SiO₂; gradient dichloromethane to dichloromethane / methanol + 0.25 % aq. NH₄OH solution 19 : 1) afforded the title compound (802 mg, 76 %). Light yellow oil, MS: 176.2 [M+H]⁺.

10 **Intermediate 5:**

N-[5-cyano-2-(hydroxymethyl)phenyl]-2,2-dimethyl-propanamide



Step 1: Methyl 4-cyano-2-pivalamidobenzoate

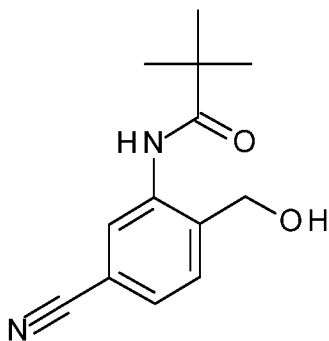


15

To a clear, red solution of methyl 2-amino-4-cyanobenzoate (CAS: 159847-83-3; 776 mg) in pyridine (6 mL) was added pivaloyl chloride (650 µl) dropwise at 0 °C. A solid precipitated. MS at t = 2 h showed the reaction to be complete. The reaction mixture was diluted with 1M aq. HCl

and extracted 2 times with ethyl acetate/ 2-methyltetrahydrofurane. The combined organic layers were washed with water, 50% Na₂CO₃ solution and brine dried over magnesium sulfate filtered and evaporated. The residue was suspended in ethyl acetate to afford the title compound (819 mg, white solid). The mother liquid was evaporated and the residue treated with tBME to afford
5 another crop of the title compound (148 mg, white solid). The products were combined to afford the title compound (967 mg, 84%). White solid. MS: 261.1 [M-H]⁻.

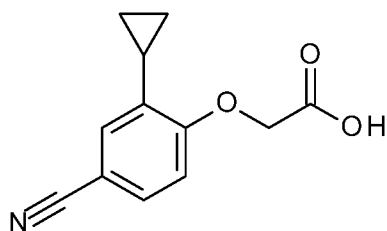
Step 2: N-[5-cyano-2-(hydroxymethyl)phenyl]-2,2-dimethyl-propanamide



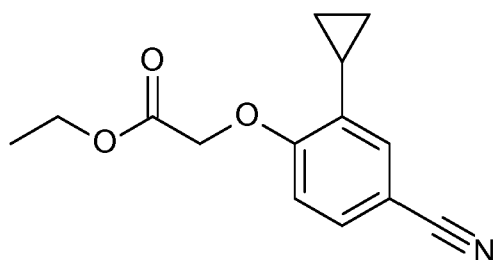
10 To a white suspension of methyl 4-cyano-2-pivalamidobenzoate (335 mg) in tetrahydrofuran (6.0 mL) was added a solution of calcium chloride (286 mg) in ethanol (6.0 mL) under argon. Sodium borohydride (195 mg) was added in 3 portions over a period of 20 minutes. TLC at t = 4 h showed the reaction to be complete. The reaction mixture was poured onto ice/water and sat. NH₄Cl solution. The aq. layer was extracted two times with ethyl acetate. The combined organic
15 layers were washed with brine, dried over magnesium sulfate, filtered and evaporated. Chromatography (50 g, SiO₂, gradient dichloromethane to dichloromethane/ methanol 9:1) afforded the title compound (257 mg, 86 %). White solid, MS: 233.2 [M+H]⁺.

20 Intermediate 6:

2-(4-cyano-2-cyclopropylphenoxy)acetic acid

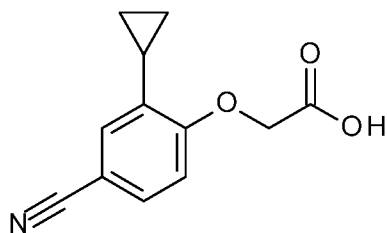


Step 1: Ethyl 2-(4-cyano-2-cyclopropylphenoxy)acetate



- 5 3-Cyclopropyl-4-hydroxybenzonitrile (140 mg) was dissolved in acetone (5 mL) at rt under an argon atmosphere. Potassium carbonate (122 mg) and ethyl 2-bromoacetate (97 μ L) were successively added to the mixture. The reaction mixture was heated to reflux for 3 hours and then cooled down to rt. The solvent was evaporated and the residue was poured into brine and ethyl acetate and the layers were separated. The aqueous layer was extracted twice with
- 10 additional ethyl acetate. The organic layers were combined washed once with brine, dried over Na_2SO_4 , filtered, evaporated and dried at high vacuum to give the crude product as a yellow viscous oil that was used without further purification (210 mg, 88 %).

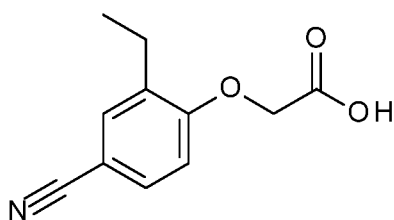
Step 2: 2-(4-cyano-2-cyclopropylphenoxy)acetic acid



Lithium hydroxide 1M solution (1.47 mL) was added drop wise over a period of 5 minutes to a solution of ethyl 2-(4-cyano-2-cyclopropylphenoxy)acetate (200 mg) in THF (4.0 ml) at room temperature. The mixture was stirred at room temperature for 5 hours. The reaction mixture was poured into ice/water and acidified with HCl 2M solution to pH=1. The aqueous phase was then
5 extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and the solvent was evaporated. The residue was dried at high vacuum to give the title compound as a yellow solid (170 mg, 96 %). MS (m/e): 216.1 [M-H]⁻.

10 **Intermediate 7:**

2-(4-cyano-2-ethylphenoxy)acetic acid

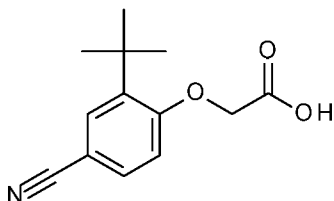


This material was made in analogy to Intermediate 6 from 3-ethyl-4-hydroxybenzonitrile (CAS: 4997-55-1)

15

Intermediate 8:

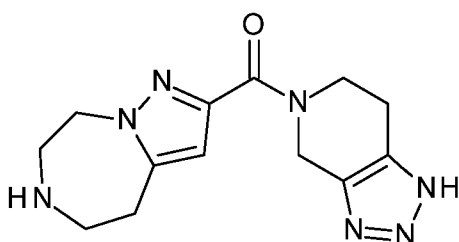
2-(2-tert-butyl-4-cyanophenoxy)acetic acid



This material was made in analogy to Intermediate 7 from 3-tert-butyl-4-hydroxybenzonitrile
20 (CAS: 4910-04-7)

Intermediate 9:

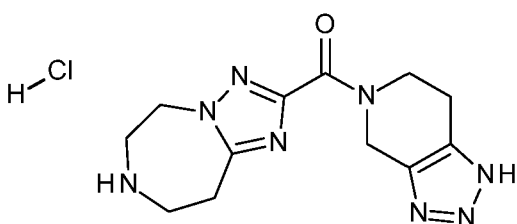
5,6,7,8-Tetrahydro-4H-pyrazolo[1,5-d][1,4]diazepin-2-yl(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridin-5-yl)methanone



The synthesis of Intermediate 9 is described in Example 3, Step 1.

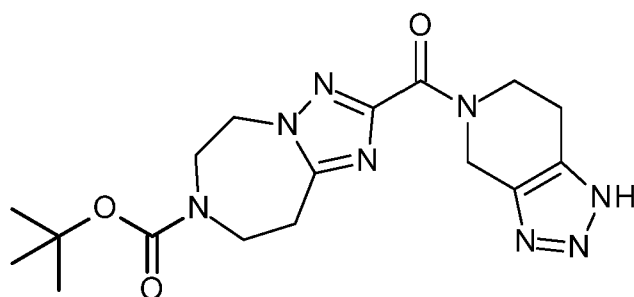
Intermediate 10:

1,4,6,7-tetrahydrotriazolo[4,5-c]pyridin-5-yl(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[1,5-d][1,4]diazepin-2-yl)methanone hydrochloride



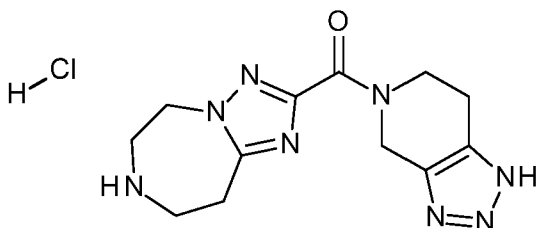
Step 1: Tert-butyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate

-56-



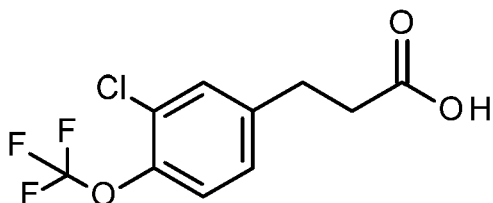
In a 20 mL round-bottom flask, 7-(tert-butoxycarbonyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[1,5-d][1,4]diazepine-2-carboxylic acid (Intermediate 9, 450 mg) and 4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine (207 mg) were combined with DMF (12.9 mL) to
 5 give a white suspension. N-ethyldiisopropylamine (587 mg) was added dropwise over a period of 2 minutes at room temperature. Then, HATU (638 mg) was added and the reaction mixture was stirred for 15 h at rt. The mixture was poured into ice/water and the aqueous phase was extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated. The residue was once again evaporated with toluene.
 10 The crude material was purified by flash chromatography (silica gel, 20 g, 0% to 10% MeOH in CH₂Cl₂) to give a white foam (310 mg). MS: 389.3 [M+H]⁺.

Step 2: 1,4,6,7-tetrahydrotriazolo[4,5-c]pyridin-5-yl(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[1,5-d][1,4]diazepin-2-yl)methanone hydrochloride

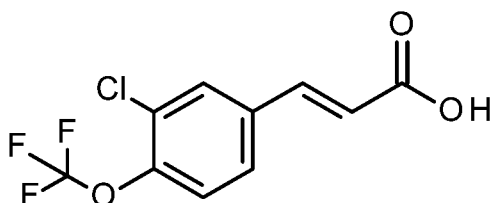


15

In a 20 mL round-bottom flask, tert-butyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-8,9-dihydro-5H-[1,2,4]triazolo[1,5-d][1,4]diazepine-7(6H)-carboxylate (230 mg) and 5N HCl in 2-propanol (5 mL) were combined to give a white suspension. The reaction mixture was heated to 50°C with stirring for 2 hours. The reaction mixture was then
 20 cooled and concentrated *in vacuo* to give a crude salt (190 mg) which was used without further purification. MS: 289.1 [M+H]⁺.

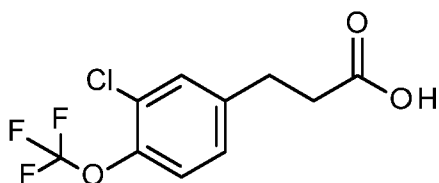
Intermediate 11:**3-[3-chloro-4-(trifluoromethoxy)phenyl]propanoic acid**

5

Step 1: (E)-3-[3-chloro-4-(trifluoromethoxy)phenyl]prop-2-enoic acid

In a 20 mL round-bottom flask, 3-chloro-4-(trifluoromethoxy)benzaldehyde (CAS: 83279-39-4, 500 mg), malonic acid (510 mg) and piperidine (22.0 μ L) were combined with pyridine (3.0 mL) to give a colorless solution. The mixture was then heated to reflux for 5 h. The reaction mixture was cooled, poured into ice/water and acidified with 2N HCl. The aqueous phase was extracted 2 times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and evaporated. The crude material was purified by flash chromatography (silica gel, 20 g, 0% to 10% MeOH in CH_2Cl_2) to provide the title compound as a white solid (400 mg). MS: 265.1 $[\text{M}-\text{H}]^-$.

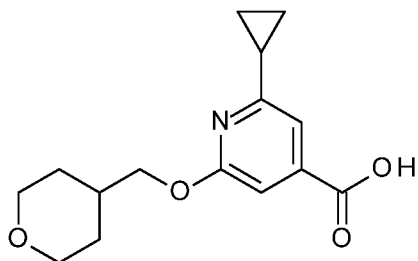
Step 2: 3-[3-chloro-4-(trifluoromethoxy)phenyl]propanoic acid



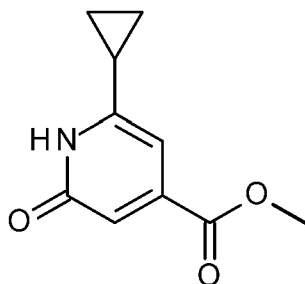
In a 50 mL three-neck flask, (E)-3-[3-chloro-4-(trifluoromethoxy)phenyl]prop-2-enoic acid (300 mg) was combined with ethyl acetate (10 mL) to give a colorless solution. Palladium on charcoal (10% Pd, 40 mg) was added and the mixture was then hydrogenated for 30min, where TLC
5 analysis showed no residual starting material. The reaction mixture was filtered through celite and was then concentrated *in vacuo* to give a light yellow solid (300 mg) which was used without further purification. MS: 267.3 [M-H]⁻.

Intermediate 12:

10 **2-Cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carboxylic acid**

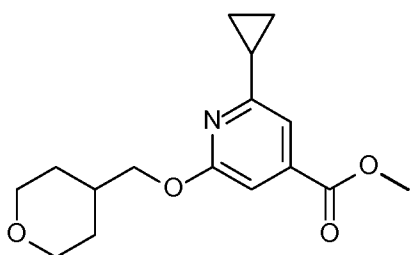


Step 1: Methyl 6-cyclopropyl-2-oxo-1,2-dihydropyridine-4-carboxylate



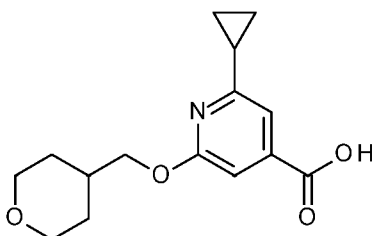
A suspension of 6-cyclopropyl-2-oxo-1,2-dihydropyridine-4-carboxylic acid (CAS: 150190-28-6; 400 mg) in methanol (4 mL) and sulfuric acid (12 μ L) was heated at 70°C for 48 h. The mixture was then concentrated *in vacuo*. The residue was suspended in dichloromethane (10 mL), then insoluble material was removed by filtration and the filtrate was evaporated to produce the title compound (427 mg) as a light brown semisolid. MS: 194.1 [M+H]⁺.

Step 2: Methyl 2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carboxylate



To suspension of methyl 6-cyclopropyl-2-oxo-1,2-dihydropyridine-4-carboxylate (212 mg) in acetonitrile (5 mL) were added potassium carbonate (455 mg) and 4-(iodomethyl)tetrahydro-2H-pyran (CAS: 101691-94-5; 744 mg) with stirring. The reaction mixture was heated at 80°C for 16 h and was then evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel; heptane–ethyl acetate gradient) to produce the title compound as a colorless oil (188 mg). MS: 292.2 [M+H]⁺.

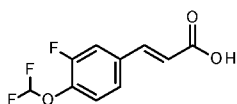
Step 3: 2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carboxylic acid



To a solution of methyl 2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carboxylate (184 mg) in tetrahydrofuran (2 mL) and water (2 mL) was added lithium hydroxide monohydrate (53.0 mg, 1.26 mmol) and the resulting mixture was stirred at room temperature for 16 h. The mixture was

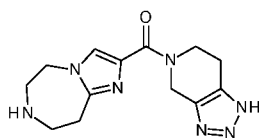
partially evaporated in order to remove the tetrahydrofuran. The aqueous phase was partitioned between 1 M aq. hydrochloric acid solution and ethyl acetate. The layers were separated and the organic layer was washed with brine, dried over magnesium sulfate, filtered and evaporated to give the title compound as a colorless oil (218 mg). MS: 276.1 $[M-H]^-$.

5

Intermediate 13:**(E)-3-[4-(difluoromethoxy)-3-fluoro-phenyl]prop-2-enoic acid**

This material was made in analogy to Intermediate 11, Step 1 from 4-(difluoromethoxy)-3-fluorobenzaldehyde (CAS: 1214379-56-2, 1.54 g). MS: 233.1 $[M+H]^+$.

10

Intermediate 14:**6,7,8,9-tetrahydro-5H-imidazo[1,2-d][1,4]diazepin-2-yl(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridin-5-yl)methanone**

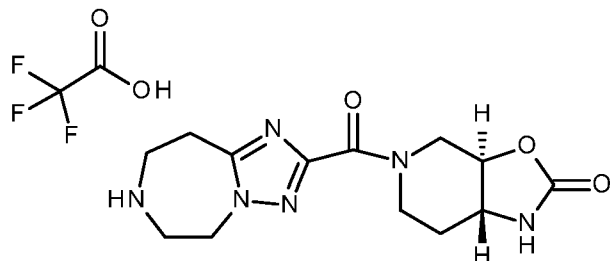
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This material was made in analogy to Example 3, Step 1, by hydrogenation of benzyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate (obtained in Example 2) to give the title compound 6,7,8,9-tetrahydro-5H-imidazo[1,2-d][1,4]diazepin-2-yl(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridin-5-yl)methanone as a colorless powder. MS: 288.2 $[M+H]^+$.

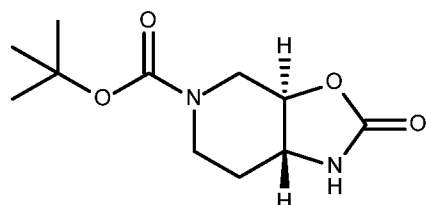
20

Intermediate 15:

(3aR,7aR)-5-(6,7,8,9-Tetrahydro-5H-[1,2,4]triazolo[1,5-d][1,4]diazepine-2-carbonyl)hexahydro-[1,3]oxazolo[5,4-c]pyridin-2(1H)-one 2,2,2-trifluoroacetate

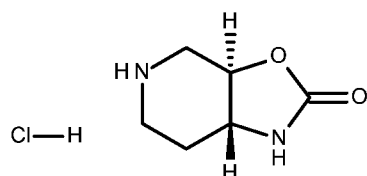


Step 1: tert-Butyl (3aR,7aR)-2-oxo-1,3a,4,6,7,7a-hexahydro-[1,3]oxazolo[5,4-c]pyridine-5-carboxylate



To a solution of (3R,4R)-tert-butyl 4-amino-3-hydroxypiperidine-1-carboxylate (CAS: 1007596-95-3, 510 mg) in DMF (8.0 mL) was added imidazole (161 mg) and then 1,1'-carbonyldiimidazole (382 mg) at room temperature under an argon atmosphere. The mixture was stirred at room temperature for 18 hours. Then, the reaction mixture was poured into ice/water and the aqueous layer was extracted twice with ethyl acetate. The organic layers were washed once with brine, dried over Na₂SO₄, filtered and evaporated. The residue was once again evaporated with toluene. The crude material was purified by flash chromatography (silica gel, 20g cartridge, 0% to 5% methanol in dichloromethane) to provide the title compound as a white solid (460 mg). MS: 187.0 [M-56 (isobutylene) +H]⁺.

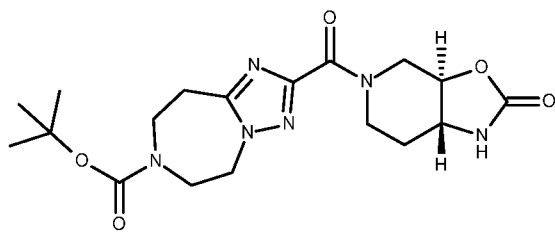
Step 2: (3aR,7aR)-3a,4,5,6,7,7a-hexahydro-1H-[1,3]oxazolo[5,4-c]pyridin-2-one hydrochloride



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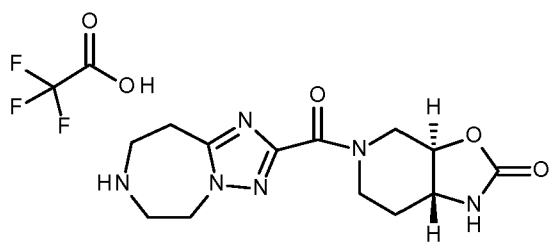
tert-Butyl (3*aR*,7*aR*)-2-oxo-1,3*a*,4,6,7,7*a*-hexahydro-[1,3]oxazolo[5,4-*c*]pyridine-5-carboxylate (458 mg) was combined with hydrochloric acid (approx. 5M - 6M in isopropanol, 6.87 mL) and the mixture was stirred at room temperature for 19 hours. The reaction mixture was then directly evaporated to dryness. The white residue was combined with ethyl acetate (8 mL) and the suspension was stirred at room temperature for 1 hour. The colorless solid was isolated by filtration, washed with ethyl acetate and dried at high vacuum to provide the title compound (279 mg). MS: 143.0 [M+H]⁺ (free base).

Step 3: tert-Butyl 2-[(3*aR*,7*aR*)-2-oxo-1,3*a*,4,6,7,7*a*-hexahydro-[1,3]oxazolo[5,4-*c*]pyridine-5-carbonyl]-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-*d*][1,4]diazepine-7-carboxylate



In a 50 mL round-bottom flask, (3*aR*,7*aR*)-3*a*,4,5,6,7,7*a*-hexahydro-1*H*-[1,3]oxazolo[5,4-*c*]pyridin-2-one hydrochloride (225 mg), 4-methylmorpholine (382 mg) and 4,5,7,8-tetrahydro-1,3,3*a*,6-tetraaza-azulene-2,6-dicarboxylic acid 6-tert-butyl ester (Intermediate 2, 391 mg) were combined with DMF (10.0 mL) to give a light yellow solution. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (483 mg) and 1-hydroxybenzotriazole hydrate (340 mg) were added and the reaction mixture was stirred for 16 hours at room temperature. The mixture was poured into ice/water and was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated. The residue was once again evaporated with toluene. The crude material was purified by flash chromatography (silica gel, 50g cartridge, 0% to 10% methanol in dichloromethane) to provide the title compound as a colorless solid (491 mg). MS: 351.2 [M-56 (isobutylene) +H]⁺.

Step 4: (3*aR*,7*aR*)-5-(6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[1,5-*d*][1,4]diazepine-2-carbonyl)hexahydro-[1,3]oxazolo[5,4-*c*]pyridin-2(1*H*)-one 2,2,2-trifluoroacetate

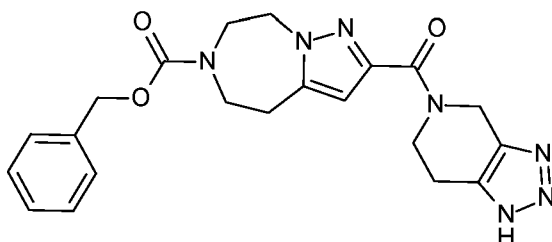


tert-Butyl 2-[(3aR,7aR)-2-oxo-1,3a,4,6,7,7a-hexahydro-[1,3]oxazolo[5,4-c]pyridine-5-carbonyl]-
5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate (50 mg) was dissolved in
dichloromethane (5.0 mL) at room temperature under an argon atmosphere. Then, 2,2,2-
5 trifluoroacetic acid (140 mg) was added dropwise over a period of 5 minutes and the mixture
was stirred at room temperature for 3 hours. More 2,2,2-trifluoroacetic acid (42.1 mg) was
slowly added and stirring was continued at room temperature for another 17 hours. Then, the
solvent was removed by evaporation and residual TFA was removed by addition and evaporation
of toluene. Following evaporation, the residue was dried at high vacuum to provide a light
10 yellow gum (68 mg) that was used without further purification. MS: 307.2 [M +H]⁺ (free base).

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ExamplesExample 1

Benzyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate



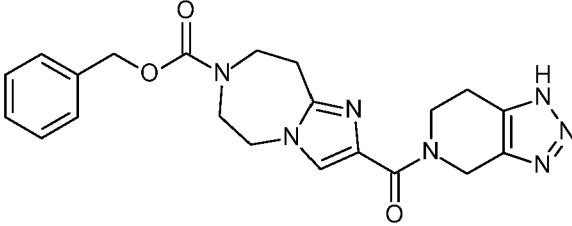
5

4-Methylmorpholine (1.56 g) was added drop wise over a period of 5 minutes to a suspension of 6-(benzyloxycarbonyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-d][1,4]diazepine-2-carboxylic acid (Intermediate 1, 1.62 g) and 4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine (702 mg, [CAS: 706757-05-3]) in dimethylformamide (20 mL) at room temperature under an argon atmosphere.

10 Then, HATU (2.17 g) was added in four portions. The mixture was stirred at room temperature for 17 hours. The reaction mixture was poured into ice/water. The aqueous phase was then extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated. The residue was once again evaporated with toluene. The crude material was purified by flash chromatography (silica gel, 0% to 100% ethyl acetate in
15 heptane and then CH₂Cl₂/MeOH=96/4) to give the title compound as a off-white foam (1.40 g, 62 %). MS (m/e): 422.6 [M+H⁺].

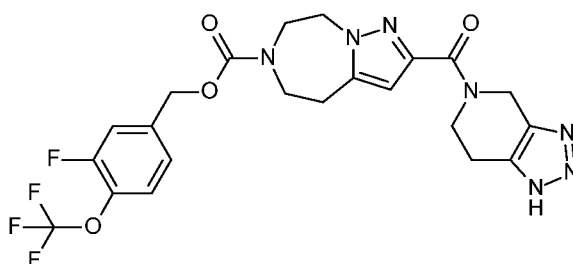
The following Example 2 was synthesized from the suitable building block/intermediate in analogy to Example 1:

20

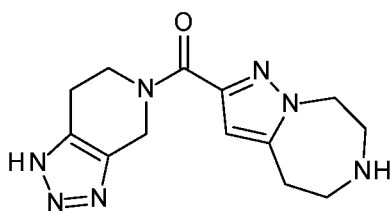
Ex.	Systematic Name	Building block / intermediate	MS, m/e
2	benzyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate 	Intermediate 3	422.2 [M+H] ⁺

Example 3

- 5 [3-Fluoro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate

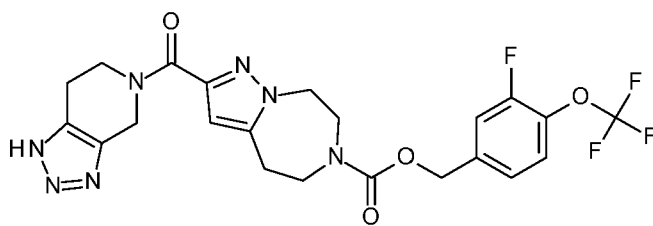


Step 1: 5,6,7,8-Tetrahydro-4H-pyrazolo[1,5-d][1,4]diazepin-2-yl(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridin-5-yl)methanone



Benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate (1.40 g, obtained in Example 1) was dissolved in methanol (10 mL) to give a colorless solution. Palladium on activated charcoal (140 mg, 10% Pd) was added and an atmosphere of hydrogen was introduced at rt. The mixture was stirred under hydrogen for 16 hours. The reaction mixture was filtered over dicalite speed plus (Acros Organics) and the solvent was evaporated to dryness to give the title compound as a colorless oil (910 mg, 94 %). MS (m/e): 288.2 [M+H⁺].

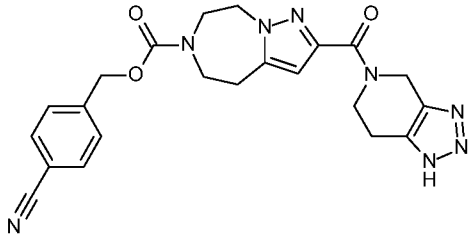
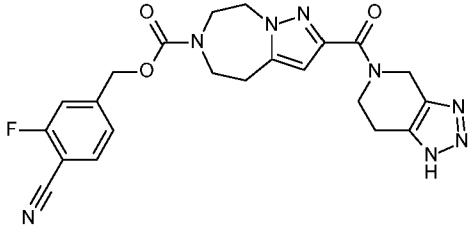
10 Step 2: [3-Fluoro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate

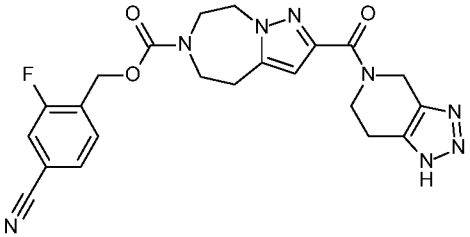
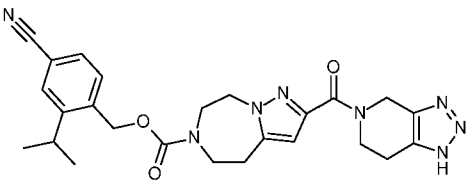


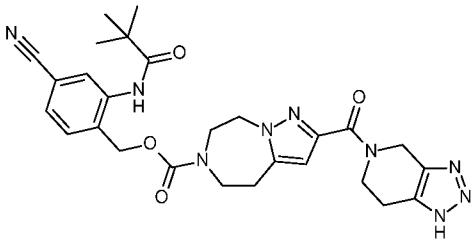
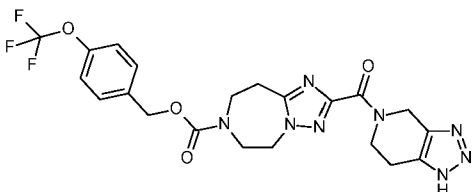
Triethylamine (31.7 mg) was added to a solution of (3-fluoro-4-(trifluoromethoxy)phenyl)methanol (CAS: 886498-99-3, 98.7 mg) in acetonitrile (8.0 mL) at room temperature under an argon atmosphere. Then, N,N'-disuccinimidyl carbonate (120 mg) was added and the colorless solution was stirred at room temperature for 3 hours to give the activated alcohol. (6,7-dihydro-1H-[1,2,3]triazolo[4,5-c]pyridin-5(4H)-yl)(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-d][1,4]diazepin-2-yl)methanone (90 mg) and triethylamine (95.1 mg) were added to the colorless solution and the mixture was stirred at room temperature for 18 h. The reaction mixture was poured into ice/water and the aqueous phase was extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated. Toluene was added and the solvent was once again evaporated. The crude material was purified by flash chromatography (silica gel, gradient of ethyl acetate in heptane) to give the title compound as a white solid (53 mg, 32 %). MS (m/e): 524.6 [M+H]⁺.

The following Examples 4 – 13 were synthesized from the suitable building block and the corresponding substituted benzyl alcohol in analogy to Example 2, Step 2:

Ex.	Systematic Name	Building block / intermediate	Benzyl alcohol	MS, m/e
4	2-Fluoro-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate	Intermediate 9	(2-fluoro-4-(trifluoromethoxy)-phenyl)-methanol CAS: 1240257-07-1	524.5 [M+H] ⁺
5	[4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate	Intermediate 9	(4-trifluoromethoxy-phenyl)methanol CAS: 1736-74-9	506.3 [M+H] ⁺

Ex.	Systematic Name	Building block / intermediate	Benzyl alcohol	MS, m/e
6	4-Cyanobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate 	Intermediate 9	4-(hydroxymethyl)-benzonitrile CAS: 874-89-5	447.2 [M+H]⁺
7	4-Cyano-3-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate 	Intermediate 9	2-Fluoro-4-(hydroxymethyl)-benzonitrile CAS: 222978-02-1	465.2 [M+H]⁺

Ex.	Systematic Name	Building block / intermediate	Benzyl alcohol	MS, m/e
8	4-Cyano-2-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate 	Intermediate 9	3-Fluoro-4-(hydroxymethyl)-benzonitrile CAS: 219873-06-0	465.3 [M+H]⁺
9	(4-Cyano-2-propan-2-ylphenyl)methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate 	Intermediate 9	4-(hydroxymethyl)-3-isopropyl-benzonitrile (Intermediate 4)	489.4 [M+H]⁺

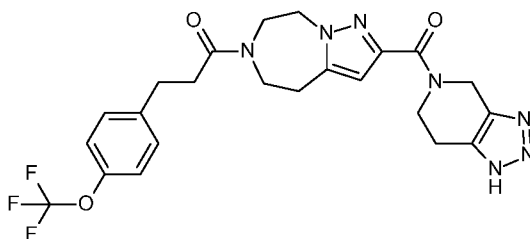
Ex.	Systematic Name	Building block / intermediate	Benzyl alcohol	MS, m/e
10	[4-Cyano-2-(2,2-dimethylpropanoylamino)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate 	Intermediate 9	N-[5-cyano-2-(hydroxymethyl)-phenyl]-2,2-dimethylpropanamide (Intermediate 5)	546.4 [M+H]⁺
11	[4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate 	Intermediate 2	(4-trifluoromethoxy-phenyl)methanol CAS: 1736-74-9	507.3 [M+H]⁺

Ex.	Systematic Name	Building block / intermediate	Benzyl alcohol	MS, m/e
12	[4-Cyano-2-(2,2-dimethylpropanoylamino)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate	Intermediate 2	N-[5-cyano-2-(hydroxymethyl)-phenyl]-2,2-dimethylpropanamide (Intermediate 5)	547.4 [M+H] ⁺
13	[4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate	Intermediate 3	(4-trifluoromethoxy-phenyl)methanol CAS: 1736-74-9	506.2 [M+H] ⁺

Example 14

1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]-3-[4-(trifluoromethoxy)phenyl]propan-1-one

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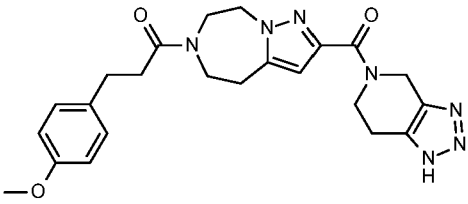
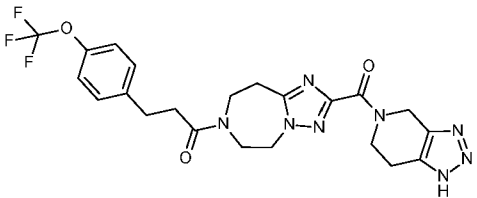
4-Methylmorpholine (84.5 mg) was added drop wise over a period of 5 minutes to a suspension of (6,7-dihydro-1H-[1,2,3]triazolo[4,5-c]pyridin-5(4H)-yl)(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-d][1,4]diazepin-2-yl)methanone (Intermediate 9, 80 mg) and 3-(4-

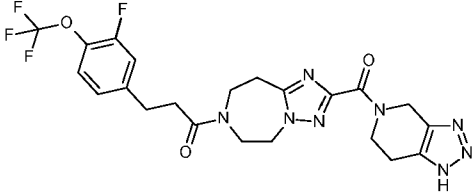
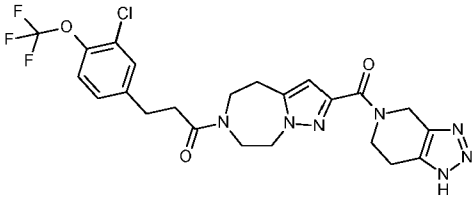
- 5 (trifluoromethoxy)phenyl)propanoic acid (CAS: 886499-74-7; 71.7 mg,) in dimethylformamide (4.0 mL) at room temperature under an argon atmosphere. The mixture was cooled down to 0°C and HATU (117 mg) was added. The mixture was warmed up to room temperature for 17 h. The reaction mixture was poured into ice/water and the aqueous phase was then extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄,
10 filtered and evaporated. Toluene was added and the mixture was once again evaporated. The crude material was purified by flash chromatography (silica gel, gradient of ethyl acetate in heptane) to give the title compound as a white solid (13 mg, 10 %). MS (m/e): 504.6 [M+H]⁺

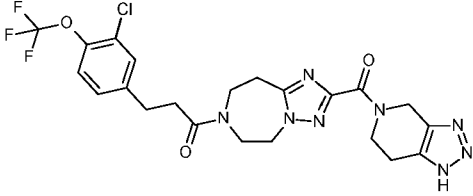
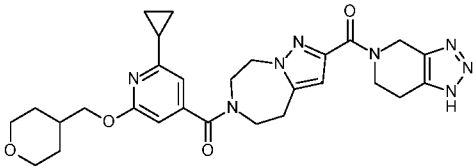
- The following Examples 15 – 17 were synthesized in analogy to Example 10 from Intermediate
15 9 and the corresponding substituted carboxylic acids:

Ex.	Systematic Name	Building block	Carboxylic acid	MS, m/e
15	3-Cyclopropyl-4-(2-oxo-2-(2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepin-6(5H)-yl)ethoxy)benzonitrile	Intermediate 9	2-(4-cyano-2-cyclopropylphenoxy)acetic acid (Intermediate 6)	487.4 [M+H] ⁺
16	3-Ethyl-4-(2-oxo-2-(2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepin-6(5H)-yl)ethoxy)benzonitrile	Intermediate 9	2-(4-cyano-2-ethylphenoxy)-acetic acid (Intermediate 7)	475.4 [M+H] ⁺

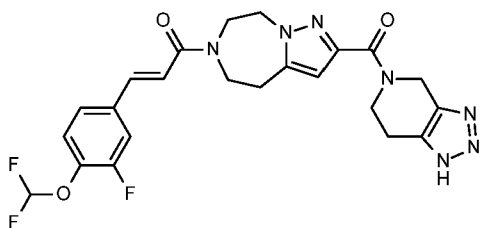
Ex.	Systematic Name	Building block	Carboxylic acid	MS, m/e
17	3-tert-Butyl-4-[2-oxo-2-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]ethoxy]benzonitrile	Intermediate 9	2-(2-tert-butyl-4-cyanophenoxy)-acetic acid (Intermediate 8)	503.4 [M+H] ⁺
18	3-[3-fluoro-4-(trifluoromethoxy)phenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]propan-1-one	Intermediate 9	3-[3-fluoro-4-(trifluoromethoxy)phenyl]propanoic acid CAS: 1261616-38-9 Made according to WO2014048865	522.2 [M+H] +

Ex.	Systematic Name	Building block	Carboxylic acid	MS, m/e
19	3-(4-methoxyphenyl)-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]propan-1-one 	Intermediate 9	3-(4-methoxyphenyl)propanoic acid CAS: 1929-29-9	450.3 [M+H] +
20	1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepin-7-yl]-3-[4-(trifluoromethoxy)phenyl]propan-1-one 	Intermediate 10	3-(4-(trifluoromethoxy)phenyl)propanoic acid CAS: 886499-74-7	505.2 [M+H] +

Ex.	Systematic Name	Building block	Carboxylic acid	MS, m/e
21	3-[3-fluoro-4-(trifluoromethoxy)phenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepin-7-yl]propan-1-one 	Intermediate 10	3-[3-fluoro-4-(trifluoromethoxy)phenyl]propanoic acid CAS: 1261616-38-9 Made according to WO2014048865	523.3 [M+H] +
22	3-[3-chloro-4-(trifluoromethoxy)phenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]propan-1-one 	Intermediate 9	3-[3-chloro-4-(trifluoromethoxy)phenyl]propanoic acid CAS: 1261873-29-3 Intermediate 11	538.3 [M+H] +

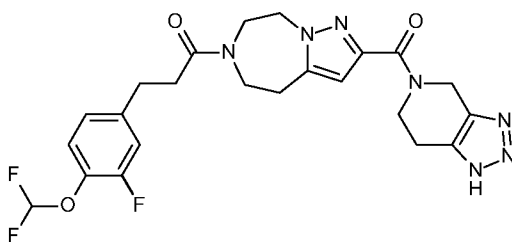
Ex.	Systematic Name	Building block	Carboxylic acid	MS, m/e
23	3-[3-chloro-4-(trifluoromethoxy)phenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepin-7-yl]propan-1-one 	Intermediate 10	3-[3-chloro-4-(trifluoromethoxy)phenyl]propanoic acid CAS: 1261873-29-3 Intermediate 11	539.3 [M+H] +
24	(6-(2-cyclopropyl-6-((tetrahydro-2H-pyran-4-yl)methoxy)isonicotinoyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-d][1,4]diazepin-2-yl)(6,7-dihydro-1H-[1,2,3]triazolo[4,5-c]pyridin-5(4H)-yl)methanone 	Intermediate 9	Intermediate 12	547.3 [M+H] +

Ex.	Systematic Name	Building block	Carboxylic acid	MS, m/e
25	(E)-3-[4-(difluoromethoxy)-3-fluorophenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]prop-2-en-1-one	Intermediate 9	(E)-3-[4-(difluoromethoxy)-3-fluorophenyl]prop-2-enoic acid Intermediate 13 (CAS: 1262013-95-5)	502.2 [M+H] +



Example 26

3-[4-(difluoromethoxy)-3-fluorophenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]propan-1-one



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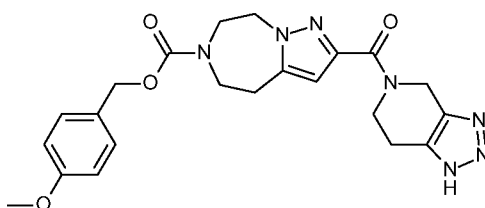
In a 25 mL three-neck flask, (*E*)-3-[4-(difluoromethoxy)-3-fluorophenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]prop-2-en-1-one (Example 25, 35 mg) was combined with EtOH (5 mL) to give a colorless solution. The mixture was degassed and Pd/C (10% Pd, 20 mg) was added under nitrogen, followed by introduction of a hydrogen atmosphere. Then, the mixture was allowed to stir at room temperature over night. Hydrogen was then removed and the reaction mixture was filtered through celite. The filtrate was evaporated to give a crude material as a white foam. This residue

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was purified by flash chromatography (silica gel, 10g, 0% to 50% MeOH in DCM) to give the title compound as a white foam (20 mg). MS: 504.2 [M+H]⁺.

Example 27

5 **4-methoxybenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate**



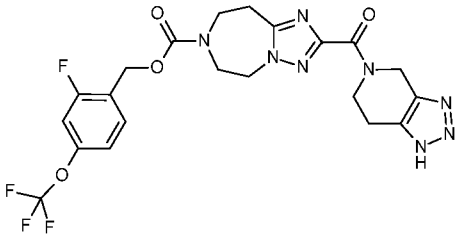
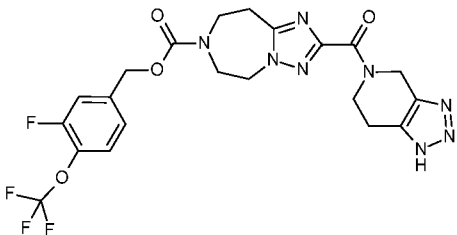
This material was made in analogy to Example 3, Step 2, from 5,6,7,8-tetrahydro-4H-pyrazolo[1,5-d][1,4]diazepin-2-yl(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridin-5-yl)methanone
10 (Intermediate 9) and (4-methoxyphenyl)methanol (CAS: 105-13-5). MS: 452.3 [M+H]⁺.

The following Examples 28 – 43 were synthesized from the suitable building block and the corresponding substituted benzyl alcohol in analogy to Example 27:

Ex.	Systematic Name	Building block / intermediate	Benzyl alcohol	MS, m/e
28	4-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate	Intermediate 9	(4-fluorophenyl) methanol CAS: 459-56-3	440.2 [M+H] ⁺
29	3-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate	Intermediate 9	(3-fluorophenyl) methanol CAS: 456-47-3	440.3 [M+H] ⁺
30	(3,4-difluorophenyl)methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate	Intermediate 9	(3,4-difluorophenyl) methanol CAS: 85118-05-4	458.3 [M+H] ⁺

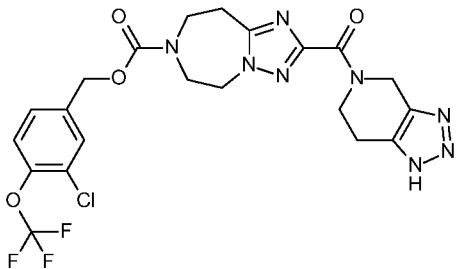
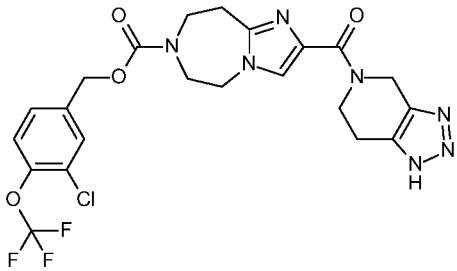
Ex.	Systematic Name	Building block / intermediate	Benzyl alcohol	MS, m/e
31	4-(difluoromethoxy)-3-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate	Intermediate 9	[4-(difluoromethoxy)-3-fluorophenyl]methanol CAS: 1242252-59-0 Made according to WO 2014048865	506.3 [M+H] ⁺
32	3-fluoro-4-methoxybenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate	Intermediate 9	[3-fluoro-4-methoxyphenyl]methanol CAS: 96047-32-4	470.3 [M+H] ⁺

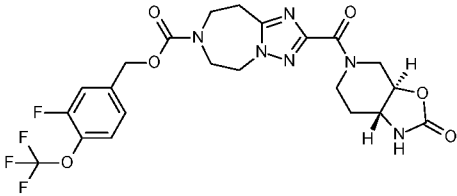
Ex.	Systematic Name	Building block / intermediate	Benzyl alcohol	MS, m/e
33	4-methoxy-2-methylbenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate	Intermediate 9	[4-(methoxy)-2-methyl-phenyl]methanol CAS: 52289-55-1	466.4 [M+H] ⁺
34	4-cyclopropylbenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate	Intermediate 9	(4-cyclopropyl-phenyl)methanol CAS: 454678-87-6	462.4 [M+H] ⁺

Ex.	Systematic Name	Building block / intermediate	Benzyl alcohol	MS, m/e
35	[2-fluoro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate 	Intermediate 10	[2-fluoro-4-(trifluoromethoxy)phenyl]methanol CAS: 1240257-07-1	525.3 [M+H]⁺
36	[3-fluoro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate 	Intermediate 10	[3-fluoro-4-(trifluoromethoxy)phenyl]methanol CAS: 886498-99-3	525.2 [M+H]⁺

Ex.	Systematic Name	Building block / intermediate	Benzyl alcohol	MS, m/e
37	3-chloro-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate	Intermediate 9	[3-chloro-4-(trifluoromethoxy)phenyl]methanol CAS: 56456-48-5	540.2 [M+H] ⁺
38	2-methoxy-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate	Intermediate 9	[2-methoxy-4-(trifluoromethoxy)phenyl]methanol CAS: 886500-30-7	536.2 [M+H] ⁺

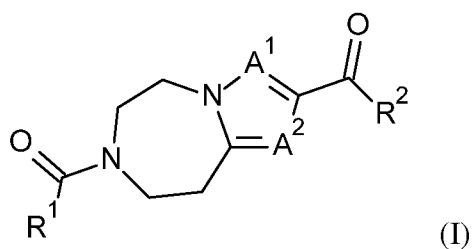
Ex.	Systematic Name	Building block / intermediate	Benzyl alcohol	MS, m/e
39	2-methyl-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate	Intermediate 9	[2-methyl-4-(trifluoromethoxy)phenyl]methanol CAS: 261951-94-4	520.2 [M+H] ⁺
40	4-(2,2,2-trifluoroethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate	Intermediate 9	[4-(2,2,2-trifluoroethoxy)phenyl]methanol CAS: 1020949-12-5	520.2 [M+H] ⁺

Ex.	Systematic Name	Building block / intermediate	Benzyl alcohol	MS, m/e
41	[3-chloro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate 	Intermediate 10	[3-chloro-4-(trifluoromethoxy)phenyl]methanol CAS: 56456-48-5	541.3 $[M+H]^+$
42	[3-chloro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate 	Intermediate 14	[3-chloro-4-(trifluoromethoxy)phenyl]methanol CAS: 56456-48-5	540.3 $[M+H]^+$

Ex.	Systematic Name	Building block / intermediate	Benzyl alcohol	MS, m/e
43	3-fluoro-4-(trifluoromethoxy)benzyl 2-((3aR,7aR)-2-oxooctahydrooxazolo[5,4-c]pyridine-5-carbonyl)-8,9-dihydro-5H-[1,2,4]triazolo[1,5-d][1,4]diazepine-7(6H)-carboxylate 	Intermediate 15	[3-fluoro-4-(trifluoromethoxy)phenyl]methanol CAS: 886498-99-3	543.3 [M+H]⁺

Claims

1. Compounds of formula (I)



wherein

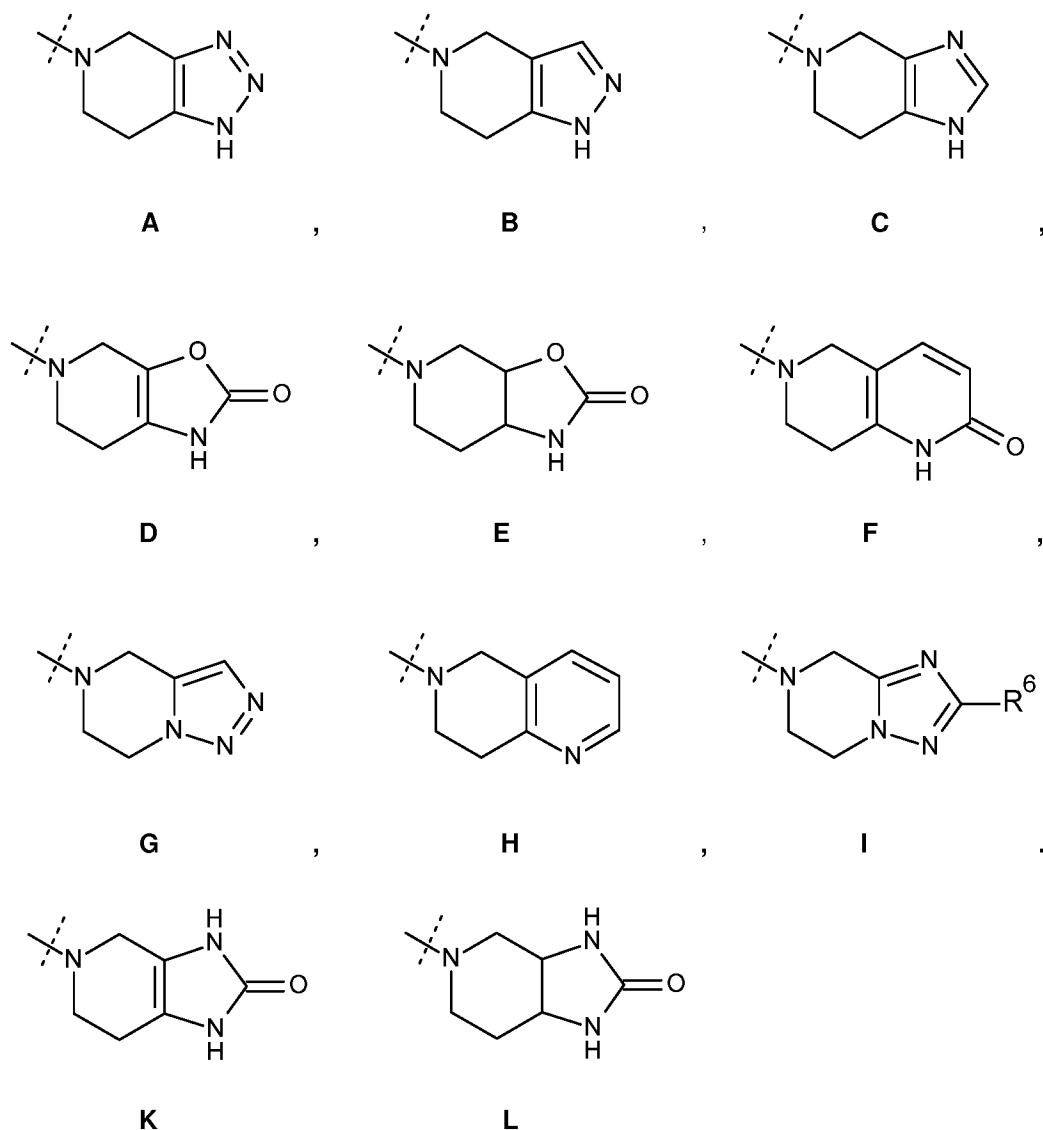
5 R^1 is alkyl, haloalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylalkoxy, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isindol-2-yl, substituted 1H-indol-2-yl or substituted benzofuran-2-yl, wherein substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylalkoxy, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isindol-2-yl, substituted 1H-indol-2-yl and substituted benzofuran-2-yl are substituted with R^3 , R^4 and R^5 ;

20 A^1 is -N- or $-CR^7-$;

A^2 is -N- or $-CR^8-$ and at least one of A^1 and A^2 is -N-;

R^2 is selected from the ring systems A, B, C, D, E, F, G, H, I, K and L.

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R^3 , R^4 and R^5 are independently selected from H, alkyl, hydroxyalkyl, haloalkyl, hydroxyhaloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkoxy, cycloalkoxy, cycloalkoxyalkyl, cycloalkylalkoxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkoxyalkoxy, alkoxyalkoxyalkyl, heterocycloalkylalkoxy, phenyl, substituted phenyl, pyridinyl, substituted pyridinyl, halogen, hydroxy, cyano, alkylsulfanyl, haloalkylsulfanyl, cycloalkylsulfanyl, alkylsulfinyl, haloalkylsulfinyl, cycloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, alkylcarbonylamino, substituted aminosulfonyl, substituted amino and substituted aminoalkyl, wherein substituted aminosulfonyl, substituted amino and substituted aminoalkyl are substituted on the nitrogen atom with one to two substituents independently selected from H, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl and cycloalkylcarbonyl, and wherein substituted phenyl

and substituted pyridinyl are optionally substituted with one to three substituents independently selected from alkyl, halogen, haloalkyl, alkoxy and haloalkoxy;

R⁶ is H, alkyl, haloalkyl or cycloalkyl;

R⁷ and R⁸ are independently selected from H, alkyl, haloalkyl or cycloalkyl;

5 or pharmaceutically acceptable salts.

2. A compound according to claim 1, wherein

10 R¹ is alkyl, haloalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylalkoxy, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isindol-2-yl, substituted 1H-indol-2-yl or substituted benzofuran-2-yl, wherein substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted
15 phenylalkyl, substituted phenoxyalkyl, substituted phenylalkoxy, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isindol-
20 2-yl, substituted 1H-indol-2-yl and substituted benzofuran-2-yl are substituted with R³, R⁴ and R⁵;

A¹ is -N- or -CR⁷-;

A² is -N- or -CR⁸- and at least one of A¹ and A² is -N-;

R² is selected from the ring systems A, B, C, D, E, F, G, H, I, K and L.

25 R³, R⁴ and R⁵ are independently selected from H, alkyl, hydroxyalkyl, haloalkyl, hydroxyhaloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkoxy, cycloalkoxy, cycloalkoxyalkyl, cycloalkylalkoxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkoxyalkoxy, alkoxyalkoxyalkyl, phenyl, substituted phenyl,

pyridinyl, substituted pyridinyl, halogen, hydroxy, cyano, alkylsulfanyl, haloalkylsulfanyl, cycloalkylsulfanyl, alkylsulfinyl, haloalkylsulfinyl, cycloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, alkylcarbonylamino, substituted aminosulfonyl, substituted amino and substituted aminoalkyl, wherein substituted aminosulfonyl, substituted amino and substituted aminoalkyl are substituted on the nitrogen atom with one to two substituents independently selected from H, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl and cycloalkylcarbonyl, and wherein substituted phenyl and substituted pyridinyl are optionally substituted with one to three substituents independently selected from alkyl, halogen, haloalkyl, alkoxy and haloalkoxy;

R^6 is H, alkyl, haloalkyl or cycloalkyl;

R^7 and R^8 are independently selected from H, alkyl, haloalkyl or cycloalkyl;

or pharmaceutically acceptable salts.

3. A compound according to claim 1 or 2, wherein R^1 is substituted phenylalkyl, substituted phenoxyalkyl or substituted phenylalkoxy, wherein substituted phenylalkyl, substituted phenoxyalkyl and substituted phenylalkoxy are substituted with R^3 , R^4 and R^5 ;
4. A compound according to any one of claims 1 to 3, wherein R^1 is substituted phenoxyalkyl or substituted phenylalkoxy, wherein substituted phenoxyalkyl and substituted phenylalkoxy are substituted with R^3 , R^4 and R^5 ;
5. A compound according to any one of claims 1 to 4, wherein R^1 is phenylalkoxy substituted with R^3 , R^4 and R^5 ;
6. A compound according to any one of claims 1 to 5, wherein R^2 is the ring system A.
7. A compound according to any one of claims 1 to 6, wherein A^1 is -N- and A^2 is -N- or -CR⁸-.

8. A compound according to any one of claims 1 to 7, wherein R^3 , R^4 and R^5 are independently selected from H, alkyl, cycloalkyl, heterocycloalkylalkoxy, haloalkoxy, halogen, cyano and alkylcarbonylamino.
9. A compound according to any one of claims 1 to 8, wherein R^3 , R^4 and R^5 are independently selected from H, alkyl, cycloalkyl, haloalkoxy, halogen, cyano and alkylcarbonylamino.
10. A compound according to any one of claims 1 to 9, wherein R^3 is heterocycloalkylalkoxy, haloalkoxy or cyano.
11. A compound according to any one of claims 1 to 10, wherein R^3 is haloalkoxy or cyano.
12. A compound according to any one of claims 1 to 11, wherein R^4 is H, alkyl, cycloalkyl or halogen.
13. A compound according to any one of claims 1 to 12, wherein R^4 is H, alkyl or halogen.
14. A compound according to any one of claims 1 to 13, wherein R^5 is H.
15. A compound according to any one of claims 1 to 14, wherein R^7 is H.
16. A compound according to any one of claims 1 to 15, wherein R^8 is H.
17. A compound according to any one of claims 1 to 16, wherein

R^1 is substituted phenylalkoxy substituted with R^3 , R^4 and R^5 ;

A^1 is -N-;

A^2 is -N- or -CR⁸-;

R^2 is the ring system A.

R^3 is haloalkoxy or cyano;

R^4 is H or halogen;

R^5 is H;

R^8 is H;

or pharmaceutically acceptable salts.

18. A compound according to any one of claims 1 to 17, selected from

Benzyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate;

Benzyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate;

[3-Fluoro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate ;

2-Fluoro-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate ;

[4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate ;

4-Cyanobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate ;

4-Cyano-3-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate ;

4-Cyano-2-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate ;

(4-Cyano-2-propan-2-ylphenyl)methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate ;

[4-Cyano-2-(2,2-dimethylpropanoylamino)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate ;

[4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate ;

[4-Cyano-2-(2,2-dimethylpropanoylamino)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate ;

[4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate ;

1-[2-(1,4,6,7-Tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]-3-[4-(trifluoromethoxy)phenyl]propan-1-one;

3-Cyclopropyl-4-(2-oxo-2-(2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepin-6(5H)-yl)ethoxy)benzonitrile ;

3-Ethyl-4-(2-oxo-2-(2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepin-6(5H)-yl)ethoxy)benzonitrile ;

3-tert-Butyl-4-[2-oxo-2-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]ethoxy]benzonitrile;

3-[3-fluoro-4-(trifluoromethoxy)phenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]propan-1-one;

3-(4-methoxyphenyl)-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]propan-1-one;

1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepin-7-yl]-3-[4-(trifluoromethoxy)phenyl]propan-1-one;

3-[3-fluoro-4-(trifluoromethoxy)phenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepin-7-yl]propan-1-one;

3-[3-chloro-4-(trifluoromethoxy)phenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]propan-1-one;

3-[3-chloro-4-(trifluoromethoxy)phenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepin-7-yl]propan-1-one;

(6-(2-cyclopropyl-6-((tetrahydro-2H-pyran-4-yl)methoxy)isonicotinoyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-d][1,4]diazepin-2-yl)(6,7-dihydro-1H-[1,2,3]triazolo[4,5-c]pyridin-5(4H)-yl)methanone;

(E)-3-[4-(difluoromethoxy)-3-fluorophenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]prop-2-en-1-one;

3-[4-(difluoromethoxy)-3-fluorophenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]propan-1-one;

4-methoxybenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

4-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

3-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

(3,4-difluorophenyl)methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate;

4-(difluoromethoxy)-3-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

3-fluoro-4-methoxybenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

4-methoxy-2-methylbenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

4-cyclopropylbenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

[2-fluoro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate;

[3-fluoro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate;

3-chloro-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

2-methoxy-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

2-methyl-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

4-(2,2,2-trifluoroethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

[3-chloro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate;

[3-chloro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate;

3-fluoro-4-(trifluoromethoxy)benzyl 2-((3aR,7aR)-2-oxooctahydrooxazolo[5,4-c]pyridine-5-carbonyl)-8,9-dihydro-5H-[1,2,4]triazolo[1,5-d][1,4]diazepine-7(6H)-carboxylate;

and pharmaceutically acceptable salts thereof.

19. A compound according to any one of claims 1 to 18, selected from

Benzyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate;

Benzyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate;

[3-Fluoro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate ;

2-Fluoro-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate ;

[4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate ;

4-Cyanobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate ;

4-Cyano-3-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate ;

4-Cyano-2-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate ;

(4-Cyano-2-propan-2-ylphenyl)methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate ;

[4-Cyano-2-(2,2-dimethylpropanoylamino)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate ;

[4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate ;

[4-Cyano-2-(2,2-dimethylpropanoylamino)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate ;

[4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate ;

1-[2-(1,4,6,7-Tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]-3-[4-(trifluoromethoxy)phenyl]propan-1-one;

3-Cyclopropyl-4-(2-oxo-2-(2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepin-6(5H)-yl)ethoxy)benzonitrile ;

3-Ethyl-4-(2-oxo-2-(2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepin-6(5H)-yl)ethoxy)benzonitrile ;

3-tert-Butyl-4-[2-oxo-2-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]ethoxy]benzonitrile;

and pharmaceutically acceptable salts thereof.

20. A compound according to any one of claims 1 to 18, selected from

(6-(2-cyclopropyl-6-((tetrahydro-2H-pyran-4-yl)methoxy)isonicotinoyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-d][1,4]diazepin-2-yl)(6,7-dihydro-1H-[1,2,3]triazolo[4,5-c]pyridin-5(4H)-yl)methanone;

(E)-3-[4-(difluoromethoxy)-3-fluorophenyl]-1-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]prop-2-en-1-one;

4-(difluoromethoxy)-3-fluorobenzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

[3-fluoro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate;

3-chloro-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

2-methyl-4-(trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

[3-chloro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate;

[3-chloro-4-(trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate;

and pharmaceutically acceptable salts thereof.

21. A compound according to any one of claims 1 to 19, selected from

3-Fluoro-4-(Trifluoromethoxy)benzyl 2-(4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridine-5-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-d][1,4]diazepine-6(5H)-carboxylate;

[4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepine-6-carboxylate;

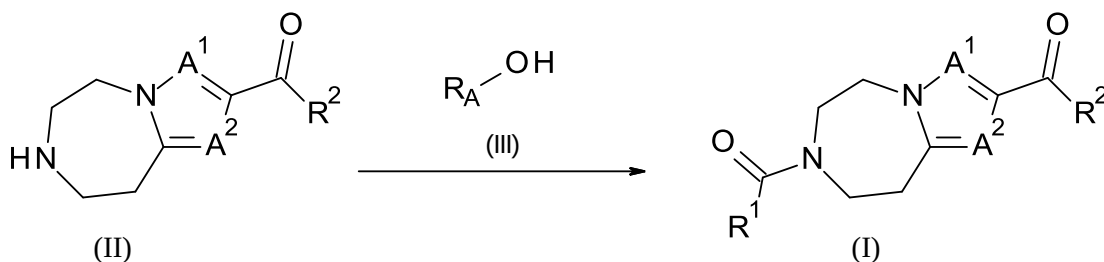
[4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydro-[1,2,4]triazolo[1,5-d][1,4]diazepine-7-carboxylate;

[4-(Trifluoromethoxy)phenyl]methyl 2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-5,6,8,9-tetrahydroimidazo[1,2-d][1,4]diazepine-7-carboxylate;

3-tert-Butyl-4-[2-oxo-2-[2-(1,4,6,7-tetrahydrotriazolo[4,5-c]pyridine-5-carbonyl)-4,5,7,8-tetrahydropyrazolo[1,5-d][1,4]diazepin-6-yl]ethoxy]benzonitrile;

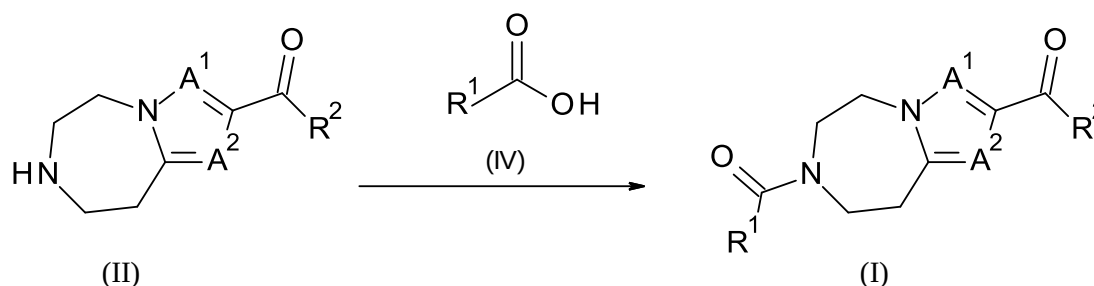
and pharmaceutically acceptable salts thereof.

22. A process to prepare a compound according to any one of claims 1 to 21 comprising the reaction of a compound of formula (II) in the presence of a compound of formula (III), wherein R^1 is phenylalkoxy substituted with R^3 , R^4 and R^5 , R_A is phenylalkyl substituted with R^3 , R^4 and R^5 and R^2 , R^3 , R^4 , R^5 , A^1 and A^2 are as defined in any one of claim 1 to 17



23. A process to prepare a compound according to any one of claims 1 to 21 comprising the reaction of a compound of formula (II) in the presence of a compound of formula (IV), wherein R^1 is alkyl, haloalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isindol-2-yl, substituted 1H-indol-2-yl or substituted benzofuran-2-yl, wherein substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted

phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isindol-2-yl, substituted 1H-indol-2-yl and substituted benzofuran-2-yl are substituted with R^3 , R^4 and R^5 and R^2 , R^3 , R^4 , R^5 A^1 and A^2 are as defined in any one of claim 1 to 17



24. A compound according to any one of claims 1 to 21 for use as therapeutically active substance.
25. A pharmaceutical composition comprising a compound according to any one of claims 1 to 21 and a therapeutically inert carrier.
26. A compound according to any one of claims 1 to 21 for use in the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, fibrotic diseases and acute and chronic organ transplant rejection.
27. The use of a compound according to any one of claims 1 to 21 for the preparation of a medicament for the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, fibrotic diseases and acute and chronic organ transplant rejection.