(54) Title: ALPHA7 NICOTINIC ACETYLCHOLINE RECEPTOR INHIBITORS

(57) Abstract: The present invention provides compounds and compositions, methods of making them, and methods of using them to modulate α7 nicotinic acetylcholine receptors and/or to treat any of a variety of disorders, diseases, and conditions. Provided compounds can affect, among other things, neurological, psychiatric and/or inflammatory systems.
ALPHA7 NICOTINIC ACETYLCHOLINE RECEPTOR INHIBITORS

Cross Reference to Related Applications

[0001] This application claims priority to United States provisional patent application serial number 61/081,211, filed July 16, 2008, the entirety of which is hereby incorporated herein by reference.

Field of the Invention

[0002] The present invention relates to compounds with α7 nicotinic acetylcholine receptor (α7 nAChR) agonistic activity, processes for their preparation, pharmaceutical compositions containing the same and the use thereof for the treatment of neurological, psychiatric, inflammatory diseases.

Background of the invention

[0003] Agents that bind to nicotinic acetylcholine receptors have been indicated as useful in the treatment and/or prophylaxis of various diseases and conditions, particularly psychotic diseases, neurodegenerative diseases involving a dysfunction of the cholinergic system, and conditions of memory and/or cognition impairment, including for example, schizophrenia, anxiety, mania, depression, manic depression, Tourette's syndrome, Parkinson's disease, Huntington's disease, cognitive disorders (such as Alzheimer's disease, Lewy Body Dementia, Amyotrophic Lateral Sclerosis, memory impairment, memory loss, cognition deficit, attention deficit, Attention Deficit Hyperactivity Disorder), and other uses such as treatment of nicotine addiction, inducing smoking cessation, treating pain (e.g. analgesic use), providing neuroprotection, and treating jetlag. See for example WO 97/30998; WO 99/03850; WO 00/42044; WO 01/36417; Holladay et al, J. Med. Chem., 40:26, 4169-94 (1997); Schmitt et al, Annual Reports Med. Chem., Chapter 5, 41-51 (2000); Stevens et al., Psychopharmacology, (1998) 136: 320-27; and Shytle et al., Molecular Psychiatry, (2002), 7, pp. 525-535.

[0004] Different heterocyclic compounds carrying a basic nitrogen and exhibiting nicotinic and muscarinic acetylcholine receptor affinity or claimed for use in Alzheimer disease
have been described, e.g. $1H$-pyrazole and pyrrole-azabicyclic compounds (WO2004013137); nicotinic acetylcholine agonists (WO2004039366); ureido-pyrazole derivatives (WO0112188); oxadiazole derivatives having acetylcholinesterase-inhibitory activity and muscarinic agonist activity (WO9313083); pyrazole-3-carboxylic acid amide derivatives as pharmaceutical compounds (WO2006077428); arylpiperidines (WO2004006924); ureidoalkypiperidines (US6605623); compounds with activity on muscarinic receptors (WO9950247). In addition, modulators of alpha7 nicotinic acetylcholine receptor are disclosed in WO06008133, in the name of the same applicant.

**Summary**

[0005] Among other things, the invention provides novel compounds acting as full or partial agonists at the $\alpha7$ nicotinic acetylcholine receptor ($\alpha7$ nAChR), pharmaceutical compositions containing the same compounds and the use thereof for the treatment of diseases that may benefit from the activation of the alpha 7 nicotinic acetylcholine receptor such as neurological, neurodegenerative, psychiatric, cognitive, immunological, inflammatory, metabolic, addiction, nociceptive, and sexual disorders, in particular Alzheimer's disease, schizophrenia, and/or others.

**Brief Description of the Drawings**

[0006] **Figure 1**: X-ray patterns of various crystal forms of hydrochloric salt.

[0007] **Figure 2**: DSC scan of various crystal forms of hydrochloric salt.

[0008] **Figure 3**: TGA of various crystal forms of hydrochloric salt.

[0009] **Figure 4**: DVS of mono-HCl salt (NO form change after DVS test).

[0010] **Figure 5**: DVS of hydrochloric salt (crystal II) (NO form change after DVS).

[0011] **Figure 6**: DVS of hydrochloric salt (crystal III) (data from pre-selection minute).

[0012] **Figure 7**: DVS of hydrochloric salt (crystal V).
[0013] **Figure 8:** Effect of pH and HCl equivalence on HCl salt formation.

[0014] **Figure 9:** Effect of pH and HCl equivalence on HCl salt formation.

[0015] **Figure 10:** Conversion of higher salts to mono-HCl crystal I 259 mg di-HCl salt was slurried in 4 volumes acetone + 0.5 volume ethanol ASDQ at room temperature. The resulting slurry gave a pH of ~2. To increase the pH, 0.02 mL NaOH 30% was added which increased the pH to 5-5.5. The slurry was stirred overnight and converted to mono-HCl. 173 mg monoHCl was obtained.

[0016] **Figure 11:** Conversion of mono-HCl to Form II by decreasing the pH (slurried overnight).

[0017] **Figure 12:** DSC scan of 5-(4-acetyl-1,4-diazepan-1-yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form I.

[0018] **Figure 13:** TGA thermogram of 5-(4-acetyl-1, 4-diazepan -yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form I.

[0019] **Figure 14:** X-ray diffraction pattern of 5-(4-acetyl-l, 4-diazepan-1 -yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form I.

[0020] **Figure 15:** DVS isothermal analysis of 5-(4-acetyl-1, 4-diazepan-1 -yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form I.

[0021] **Figure 16:** DSC scan of 5-(4-acetyl-l, 4-diazepan-1 -yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form II.

[0022] **Figure 17:** TGA thermogram of 5-(4-acetyl-l, 4-diazepan-1 -yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form II.

[0023] **Figure 18:** X-ray diffraction pattern of 5-(4-acetyl-l, 4-diazepan-1 -yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form II.

[0024] **Figure 19:** DVS isothermal analysis of 5-(4-acetyl-l, 4-diazepan-1 -yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form II.
Detailed Description of Certain Embodiments

Compounds

In certain embodiments, the invention provides a compound of Formula (I):

![Chemical structure](image)

(1)

wherein

- T is a (C3-C5) alkane-α,ω-diyi or alkene-α,ω-diyi, optionally carrying an oxo group and optionally substituted with one or more halogens; hydroxy groups; (Cl-C5) alkyl, alkoxy, fluoroalkyl, hydroxyalkyl, alkylidene, fluoroalkylidene groups; (C3-C6) cycloalkane-1,1-diyl, oxacycloalkane-1,1-diyl groups; (C3-C6) cycloalkane-1,2-diyl, oxacycloalkane-1,2-diyl groups, where the bonds of the 1,2-diyl radical form a fused ring with the T chain; and with the proviso that when T carries an oxo group this is not part of an amide bond;
- z is CH₂, N, O, S, S(O), or S(=O)₂;
- q and q’ are, independently from one another, integers from 1 to 4, with the proviso that the sum of q + q’ is no greater than 6;
- p is 0, 1, or 2;
- R’, independently from one another for p = 2, is selected from the group consisting of mono- or di- [linear, branched or cyclic (C1-C6) alkyl]aminocarbonyl; linear, branched or cyclic (C1-C6) alkyl, alkoxy, acyl;
- Q is a group of Formula

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  \[ \begin{array}{c}
    \text{N} \\
    \text{H} \\
  \end{array} \]
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- R” is C1-C3 alkyl;
- j is 0 or 1;
- R is a 5- to 10-member aromatic or heteroaromatic ring;
- m is 0, 1, 2, or 3;
Y represents, independently from one another when m is greater than 1, halogen; hydroxy; mercapto; cyano; nitro; amino; linear, branched or cyclic (C1-C6) alkyl, trihaloalkyl, di- or trihaloalkoxy, alkoxy, or alkylcarbonyl; (C3-C6) cycloalkyl-(C1-C6) alkoxy; (C3-C6) cycloalkyl-(C1-C6) alkyl; linear, branched, or cyclic (C1-C6) alkylcarbonylamino; mono- or di-, linear, branched, or cyclic (C1-C6) alkylaminocarbonyl; carbamoyl; linear, branched, or cyclic (C1-C6) alkylsulphonylamino; linear, branched, or cyclic (C1-C6) alkylsulphonyl; mono- or di-, linear, branched, or cyclic (C1-C6) alkylsulphamoyl; linear, branched or cyclic (C1-C6) alkoxy-(C1-C6) alkyl; or, when m=2, two Y substituents, together with the atoms of the R group they are attached to, may form a ring.

[0026] In certain embodiments, the invention provides compounds of Formula (I) wherein:

T is butane-1,4-diyl optionally substituted with one or more (Cl-C3) alkyl, halogen;

z is N or O;

R', independently from one another for p = 2, is selected from the group consisting of mono- or di- [linear, branched or cyclic (C1-C6) alkyl]aminocarbonyl; linear, branched or cyclic (C1-C6) alkyl, alkoxy, acyl;

Q is ;

p, q, q', R', j, R, Y and m being as defined under Formula (I);

[0027] In some embodiments, compounds of Formula (I) are those in which:

T is butane-1,4-diyl;

z is N or O;

R is selected from the group consisting of linear, branched or cyclic (C1-C6) alkyl, alkoxy, acyl;

p is 0 or 1:

Q is ;

j is 0;

R is a 5- to 10-member aromatic or heteroaromatic ring;

q, q', R, Y and m are as defined under Formula (I);
In some embodiments, compounds are those in which:

T is butane-1,4-diyl;
z is N;
p is 1;
R' is (C1-C6) acyl;

\[
\begin{array}{c}
\text{Q is } \text{ } \text{ } \\
\end{array}
\]

j is 0;
R is phenyl, pyridyl, thienyl; indolyl;
m is 0, 1 or 2;
Y represents, independently from one another when m is greater than 1, halogen; hydroxy; linear, branched or cyclic (C1-C6) alkyl, trihaloalkyl, di- or trihaloalkoxy, alkoxy; (C3-C6) cycloalkyl-(C1-C6) alkyl;
q, q' are as defined under Formula (I);

In some embodiments, the invention provides compounds, hereafter referred to as Gl of Formula (I), wherein:

T is propane-1,3-diyl optionally substituted with (C1-C3) alkyl, halogen;
z is CH₂, N, O;
Q is a group of Formula

\[
\begin{array}{c}
\text{R', p, q, q', R'', j, R,Y and m being as defined under Formula (I);}
\end{array}
\]

Within Gl, certain embodiments are those in which

T is propane-1,3-diyl optionally substituted with (Cl-C3) alkyl, halogen;
z is CH₂;

\[
\begin{array}{c}
\text{Q is } \text{ } \text{ } \\
\end{array}
\]

q and q' are, independently from one another, 1 or 2;
p is 0 or 1;
R’ is selected from the group consisting of linear, branched or cyclic (C1-C6) alkyl, alkoxy, acyl;
j is 0;
R, Y and m are as defined under Formula (I);

[0031] Within Gl, certain embodiments are those in which:

T is propane-1,3-diyl;
z is CH₂;
q and q’ are, independently from one another, 1 or 2;
p is 0 or 1;
R is selected from the group consisting of linear, branched or cyclic (C1-C6) alkyl;

\[
\begin{array}{c}
\text{Q is} \\
\text{\includegraphics[width=0.1\textwidth]{image.png}} \\
\text{j is 0;}
\end{array}
\]

R is phenyl, pyridyl, naphthyl;
m is 1 or 2;
Y represents, independently from one another when m is greater than 1, halogen; hydroxy;
linear, branched or cyclic (C1-C6) alkyl, trihaloalkyl, di- or trihaloalkoxy, alkoxy; (C3-C6)
cycloalkyl-(C1-C6) alkoxy₁.

[0032] Within this group, certain compounds are those in which Q-R is

[0033] In some embodiments, for provided compounds of formula (I):

T is propane-1,3-diyl optionally substituted with (C1-C3) alkyl, halogen;
z is CH₂;

\[
\begin{array}{c}
\text{Q is} \\
\text{\includegraphics[width=0.1\textwidth]{image.png}} \\
\text{q and q’ are, independently from one another, 1 or 2;}
\end{array}
\]
p is 0 or 1;
R’ is selected from the group consisting of linear, branched or cyclic (C1-C6) alkyl, alkoxy, acyl;
j is 0;
R, Y and m are as defined under Formula (I);

[0034] In some embodiments, compounds under Gl are those in which
T is propane-1,3-diyl;
z is \( \text{CH}_2 \);
q and q’ are, independently from one another, 1 or 2;
p is 0 or 1;
R is selected from the group consisting of linear, branched or cyclic (C1-C6) alkyl;

\[
\text{Q is}
\]

j is 0;
R is phenyl, pyridyl, naphthyl;
m is 1 or 2;
Y represents, independently from one another when m is greater than 1, halogen; hydroxy;
linear, branched or cyclic (C1-C6) alkyl, trihaloalkyl, di- or trihaloalkoxy, alkoxy; (C3-C6) cycloalkyl-(C1-C6) alkoxy.

[0035] In certain embodiments, provided compounds are those in which Q-R is Q-R is

[0036] In certain embodiments, the present invention provides a compound of formula II:

II

or a pharmaceutically acceptable salt thereof, wherein:
Ring A is a 4 to 7-membered saturated ring;
'T' is a straight or branched C_{1-6} alkylene chain; X is halogen or hydrogen; and
Ring B is a 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein
Ring B is optionally substituted with halogen; hydroxy; oxo; mercapto; cyano; nitro; amino; linear, branched or cyclic (C1-C6) alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, di- or trihaloalkoxy, alkoxy, or alkylcarbonyl; (C3-C6) cycloalkyl-(C1-C6) alkoxy; (C3-C6) cycloalkyl-(C1-C6) alkyl; linear, branched, or cyclic (C1-C6) alkylcarbonylamino; mono- or di-, linear, branched, or cyclic (C1-C6) alkyaminocarbonyl; carbamoyl; linear, branched, or cyclic (C1-C6) alkylsulphonylamino; linear, branched, or cyclic (C1-C6) alkylsulphonyl; mono- or di-, linear, branched, or cyclic (C1-C6) alkylsulphamoyl; or linear, branched or cyclic (C1-C6) alkoxy-(C1-C6) alkyl.

[0037] In certain embodiments, Ring A is a 4-membered saturated ring. In certain embodiments, Ring A is a 5-membered saturated ring. In certain embodiments, Ring A is a 6-membered saturated ring. In certain embodiments, Ring A is a 7-membered saturated ring. In certain embodiments, Ring A is a 5-6 membered saturated ring. In some embodiments, Ring A is piperidinyl. In other embodiments, Ring A is pyrrolidinyl.

[0038] In certain embodiments, the present invention provides a compound of formula II, wherein Ring B is a 6-membered monocyclic heteroaryl ring having one or two nitrogens. In some embodiments, Ring B is pyridyl. In some embodiments, Ring B is pyridyl optionally substituted with halogen or (C1-C6) alkyl, dihaloalkyl, or alkoxy. In some embodiments, Ring B is pyridin-2-yl. In some embodiments, Ring B is pyridin-3-yl. In some embodiments, Ring B is pyridin-4-yl. In some embodiments, Ring B is a pyridinone group.

[0039] In some embodiments, Ring B is an 8-10 membered bicyclic heteroaryl ring having one or two nitrogens. In certain embodiments, Ring B is a 10-membered bicyclic heteroaryl ring having one nitrogen. In some embodiments, Ring B is quinolinyl. In certain embodiments, Ring B is quinolin-6-yl or quinolin-3-yl.
In some embodiments, the X group of formula II is fluoro, chloro, or iodo. In certain embodiments, X is fluoro. In other embodiments, X is hydrogen.

In certain embodiments, T' is a straight or branched C_{1-5} alkyene chain. In certain embodiments, T' is a branched C_{2-5} alkyene chain. In some embodiments, T' is a straight C_{1-5} alkyene chain. In some embodiments, T' is a C_{2-4} alkyene chain. In some embodiments, T' is -CH$_2$CH$_2$CH$_2$-.

In certain embodiments, T' is -CH(CH$_3$)CH$_2$CH$_2$-, -C(CH$_3$)$_2$CH$_2$-, or -CH$_2$C(CH$_3$)$_2$CH$_2$-. In some embodiments, T' is -CH(CH$_3$)CH$_2$CH$_2$-. In some embodiments, T' is CH$_2$CH(CH$_3$)CH$_2$-. In some embodiments, T' is -CH$_2$C(CH$_3$)$_2$CH$_2$-.

In some embodiments, T' is other than -CH$_2$C(CH$_3$)$_2$CH$_2$-. In some embodiments, T' is other than -CH(CH$_3$)CH$_2$CH$_2$-. In some embodiments, T' is other than -C(CH$_3$)$_2$CH$_2$CH$_2$-.

In some embodiments, where T' is -CH(CH$_3$)CH$_2$CH$_2$-, Ring B is other than

. In some embodiments, where T' is -CH(CH$_3$)CH$_2$CH$_2$- and Ring B is

. X is other than hydrogen.

In some embodiments, provided compounds are of formula II-a:

![II-a](image)

wherein each of Ring A, Ring B and X is as defined above and described in classes and subclasses herein.

In some embodiments, provided compounds are of formula II-b:
wherein each of Ring A, Ring B and X is as defined above and described in classes and subclasses herein.

[0047] In some embodiments, provided compounds are of formula II-c:

wherein each of Ring A, Ring B and X is as defined above and described in classes and subclasses herein.

[0048] In some embodiments, provided compounds are of formula II-d:

wherein each of Ring A, Ring B and X is as defined above and described in classes and subclasses herein.

[0049] In some embodiments, provided compounds are of formula II-e:
wherein each of Ring A, X, and T' is as defined above and described in classes and subclasses herein; and

R^x is selected from the group consisting of halogen; hydroxy; mercapto; cyano; nitro; amino; linear, branched or cyclic (C1-C6) alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, di- or trihaloalkoxy, and alkoxy.

[0050] In some embodiments, provided compounds are of formula II-f:

\[
\text{II-f}
\]

wherein each of Ring A, X, R^x, and T' is as defined above and described in classes and subclasses herein.

[0051] In some embodiments, provided compounds are of formula II-g:

\[
\text{II-g}
\]

wherein each of Ring A, X, R^x, and T' is as defined above and described in classes and subclasses herein.

[0052] In some embodiments, provided compounds are of formula II-h:

\[
\text{II-h}
\]
wherein each of Ring A, X, and T' is as defined above and described in classes and subclasses herein.

[0053] In some embodiments, provided compounds are of formula II-j:

\[
\text{\textcircled{\(\pi\)-j}}
\]

wherein each of Ring A, X, and T' is as defined above and described in classes and subclasses herein.

[0054] In some embodiments, provided compounds are of formula II-k:

\[
\text{\textcircled{II-k}}
\]

wherein each of Ring A, Ring B, and T' is as defined above and described in classes and subclasses herein.

[0055] Exemplary compounds of formula II include those set forth below:

\[
\text{\textcircled{II-1}} \quad \text{\textcircled{II-2}} \quad \text{\textcircled{II-3}} \quad \text{\textcircled{II-4}}
\]
Additional exemplary compounds of the present invention include those set forth below:
In certain embodiments, a compound of formula II is other than 5-Piperidin-1-yl-pentanoic acid [5-(1H-indol-5-yl)-2H-pyrazol-3-yl]-amide, 5-Piperidin-1-yl-pentanoic acid (5-
In some embodiments, a compound of formula II is not one of the following:
As will be readily apparent to one skilled in the art, the unsubstituted ring nitrogen pyrazoles and imidazoles, as in the compounds of the present invention, are known to rapidly equilibrate in solution, as mixtures of both tautomers:

\[
\text{H}_3\text{N} \quad \leftrightarrow \quad \text{H}_2\text{NNH} \quad ; \\
\text{H}_2\text{NN} \quad \leftrightarrow \quad \text{HN}\text{N}
\]

in the following description therefore, where only one tautomer is indicated for compounds of Formulae (I) or (II), the other tautomer is also intended as within the scope of the present invention.

Compounds of the invention can be in the form of free bases or acid addition salts, preferably salts with pharmaceutically acceptable acids. The invention also provides separated isomers and diastereoisomers of compounds of Formulae (I) or (II), or mixtures thereof (e.g. racemic and diastereomeric mixtures), as well as isotopic compositions.

Pharmacological activity of a representative group of compounds of Formulae (I) or (II) was demonstrated in an in vitro assay utilising cells stably transfected with the alpha 7
nicotinic acetylcholine receptor and cells expressing the alpha 1 and alpha 3 nicotinic acetylcholine receptors and 5HT3 receptor as controls for selectivity.

[0062] Compounds of Formulae (I) or (II) may be provided according to the present invention in any of a variety of useful forms, for example as pharmaceutically acceptable salts, as particular crystal forms, etc. In some embodiments, prodrugs of one or more compounds of Formulae (I) or (II) are provided. Various forms of prodrugs are known in the art, for example as discussed in Bundgaard (ed.), Design of Prodrugs, Elsevier (1985); Widder et al. (ed.), Methods in Enzymology, vol. 4, Academic Press (1985); Kgrogsgaard-Larsen et al. (ed.); "Design and Application of Prodrugs", Textbook of Drug Design and Development, Chapter 5, 113-191 (1991); Bundgaard et al, Journal of Drug Delivery Reviews, 8:1-38 (1992); Bundgaard et al., J. Pharmaceutical Sciences, 77:285 et seq. (1988); and Higuchi and Stella (eds.), Prodrugs as Novel Drug Delivery Systems, American Chemical Society (1975).

Uses

[0063] Agents that bind to nicotinic acetylcholine receptors have been indicated as useful in the treatment and/or prophylaxis of various diseases and conditions, particularly psychotic diseases, neurodegenerative diseases involving a dysfunction of the cholinergic system, and conditions of memory and/or cognition impairment, including, for example, schizophrenia, anxiety, mania, depression, manic depression, Tourette's syndrome, Parkinson's disease, Huntington's disease, cognitive disorders (such as Alzheimer's disease, Lewy Body Dementia, Amyotrophic Lateral Sclerosis, memory impairment, memory loss, cognition deficit, attention deficit, Attention Deficit Hyperactivity Disorder), and other uses such as treatment of nicotine addiction, inducing smoking cessation, treating pain (i.e., analgesic use), providing neuroprotection, and treating jetlag. See, e.g., WO 97/30998; WO 99/03850; WO 00/42044; WO 01/36417; Holladay et al., J. Med. Chem., 40:26, 4169-94 (1997); Schmitt et al., Annual Reports Med. Chem., Chapter 5, 41-51 (2000); Stevens et al., Psychopharmacology, (1998) 136: 320-27; and Shytle et al., Molecular Psychiatry, (2002), 7, pp. 525-535.

[0064] Thus, in accordance with the invention, there is provided a method of treating a patient, especially a human, suffering from any of psychotic diseases, neurodegenerative diseases
involving a dysfunction of the cholinergic system, and/or conditions of memory and/or cognition impairment, including, for example, schizophrenia, anxiety, mania, depression, manic depression, Tourette's syndrome, Parkinson's disease, Huntington's disease, and/or cognitive disorders (such as Alzheimer's disease, Lewy Body Dementia, Amyotrophic Lateral Sclerosis, memory impairment, memory loss, cognition deficit, attention deficit, Attention Deficit Hyperactivity Disorder) comprising administering to the patient an effective amount of a compound according to Formulae (I) or (II).

[0065] In some embodiments, the present invention provides methods comprising the step of administering to a subject suffering from or susceptible to one or more psychotic diseases, neurodegenerative diseases involving a dysfunction of the cholinergic system, or conditions of memory or cognition impairment an effective amount of a compound of Formulae (I) or (II). In some embodiments, the present invention provides methods for improving or stabilizing cognitive function in a subject comprising administering to the subject an effective amount of a compound according to Formulae (I) or (II).

3119-31; Cubo, Neurology. (2006) 1268-71), Parkinson's disease, synucleinopathies, primary progressive aphasia, striatoniqral degeneration, Machado-Joseph disease/spinocerebellar ataxia type 3, olivopontocerebellar degenerations, Gilles De La Tourette's disease, bulbar, pseudobulbar palsy, spinal muscular atrophy, spinobulbar muscular atrophy (Kennedy's disease), primary lateral sclerosis, familial spastic paraplegia, Werdnig-Hoffmann disease, Kugelberg-Welander disease, Tay-Sach's disease, Sandhoff disease, familial spastic disease, Wohlfart-Kugelberg-Welander disease, spastic paraparesis, progressive multifocal leukoencephalopathy, prion diseases (such as Creutzfeldt- Jakob, Gerstmann- Straussler-Scheinker disease, Kuru and fatal familial insomnia), and neurodegenerative disorders resulting from cerebral ischemia or infarction including embolic occlusion and thrombotic occlusion as well as intracranial hemorrhage of any type (including, but not limited to, epidural, subdural, subarachnoid and intracerebral), and intracranial and intravertebral lesions (including, but not limited to, contusion, penetration, shear, compression and laceration).

[0067] In addition, α7nACh receptor agonists, such as the compounds of the present invention can be used to treat age-related dementia and other dementias and conditions with memory loss including age-related memory loss, senility, vascular dementia, diffuse white matter disease (Binswanger's disease), dementia of endocrine or metabolic origin, dementia of head trauma and diffuse brain damage, dementia pugilistica, alcoholism related dementia (Korsakoff Syndrome) and frontal lobe dementia. See, e.g., WO 99/62505., Tomimoto Dement Geriatr Cogn Disord. (2005), 282-8; Tohgi - J Neural Transm. (1996), 121 1-20; Casamenti, Neuroscience (1993) 465-71, Kopelman, Br J Psychiatry (1995) 154-73; Cochrane, Alcohol Alcohol. (2005) 151-4).

[0068] Amyloid precursor protein (APP) and Aβ peptides derived therefrom, e.g., Aβ1-42 and other fragments, are known to be involved in the pathology of Alzheimer's disease. The Aβ1-42 peptides are not only implicated in neurotoxicity but also are known to inhibit cholinergic transmitter function. Further, it has been determined that Aβ peptides bind to α7nACh receptors. The inflammatory reflex is an autonomic nervous system response to an inflammatory signal. Upon sensing an inflammatory stimulus, the autonomic nervous system responds through the vagus nerve by releasing acetylcholine and activating nicotinic α7 receptors on macrophages. These macrophages in turn release cytokines. Dysfunctions in this pathway
have been linked to human inflammatory diseases including rheumatoid arthritis, diabetes and sepsis. Macrophages express the nicotinic α7 receptor and it is likely this receptor that mediates the cholinergic anti-inflammatory response. See for example Czura, C. J et al., *J. Intern. Med.*, (2005) 257(2), 156-66; Wang, H. et al *Nature* (2003) 421: 384-388; de Jonge *British Journal of Pharmacology* (2007) 151, 915-929. The mammalian sperm acrosome reaction is an exocytosis process important in fertilization of the ovum by sperm. Activation of an α7 nAChR on the sperm cell has been shown to be essential for the acrosome reaction (Son, J.-H. and Meizel, S. *Biol. Reproduct.* 68: 1348-1353, 2003). In addition, nicotinic receptors have been implicated as playing a role in the body's response to alcohol ingestion. α7nACh receptor agonists such as compounds provided herein, therefore, are also useful in the treatment of these disorders, diseases, and conditions.


In accordance with the invention, there is provided a method of treating a patient, especially a human, suffering from age-related dementia and other dementias and conditions with memory loss comprising administering to the patient an effective amount of a compound according to Formulae (I) or (II).

The present invention includes methods of treating patients suffering from memory impairment due to, for example, mild cognitive impairment due to aging, Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, depression, aging, head trauma, stroke, CNS hypoxia, cerebral senility, multiinfarct dementia and other neurological conditions, as well as HIV and cardiovascular diseases, comprising administering an effective amount of a compound according to Formulae (I) or (II).

In some embodiments, the present invention provides methods comprising the step of administering to a subject suffering from or susceptible to one or more central nervous system (CNS) diseases or disorders an effective amount of a compound according to Formulae (I) or (II). In certain embodiments, the disease of disorder is selected from the group consisting of psychoses, anxiety, senile dementia, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive disorders, sleep disorders, feeding disorders, anorexia, bulimia,
binge eating disorders, panic attacks, disorders resulting from withdrawal from drug abuse, schizophrenia, gastrointestinal disorders, irritable bowel syndrome, memory disorders, Alzheimer's disease, Parkinson's disease, Huntington's chorea, schizophrenia, attention deficit hyperactive disorder, neurodegenerative diseases characterized by impaired neuronal growth, and pain.

[0074] In certain embodiments, there is provided a method of treating and/or preventing dementia in an Alzheimer's patient which comprises administering to the subject a therapeutically effective amount of a compound according to Formulae (I) or (II) to inhibit the binding of an amyloid beta peptide (preferably, Aβ1-42) with nACh receptors, preferable α7nACh receptors, most preferably, human α7nACh receptors (as well as a method for treating and/or preventing other clinical manifestations of Alzheimer's disease that include, but are not limited to, cognitive and language deficits, apraxias, depression, delusions and other neuropsychiatric symptoms and signs, and movement and gait abnormalities).

[0075] The present invention also provides methods for treating other amyloidosis diseases, for example, hereditary cerebral angiopathy, nonneuropathic hereditary amyloid, Down's syndrome, macroglobulinemia, secondary familial Mediterranean fever, Muckle-Wells syndrome, multiple myeloma, pancreatic- and cardiac-related amyloidosis, chronic hemodialysis anthropathy, and Finnish and Iowa amyloidosis.

[0076] In addition, nicotinic receptors have been implicated as playing a role in the body's response to alcohol ingestion. Thus, agonists for α7nACh receptors can be used in the treatment of alcohol withdrawal and in anti-intoxication therapy. Thus, in accordance with an embodiment of the invention there is provided a method of treating a patient for alcohol withdrawal or treating a patient with anti-intoxication therapy comprising administering to the patient an effective amount of a compound according to Formulae (I) or (II).

[0077] Agonists for the α7nACh receptor subtypes can also be used for neuroprotection against damage associated with strokes and ischemia and glutamate-induced excitotoxicity. Thus, in accordance with an embodiment of the invention there is provided a method of treating a patient to provide for neuroprotection against damage associated with strokes and ischemia and
glutamate-induced excitotoxicity comprising administering to the patient an effective amount of a compound according to Formulae (I) or (II).

[0078] Agonists for the α7nACh receptor subtypes can also be used in the treatment of nicotine addiction, inducing smoking cessation, treating pain, and treating jetlag, obesity, diabetes, sexual and fertility disorders (e.g. Premature ejaculation or vaginal dryness, see US 6448276), drug abuse (Solinas, Journal of Neuroscience (2007) 27(21), 5615-5620), and inflammation. Thus, in accordance with an embodiment of the invention there is provided a method of treating a patient suffering from nicotine addiction, pain, jetlag, obesity and/or diabetes, or a method of inducing smoking cessation in a patient comprising administering to the patient an effective amount of a compound according to Formulae (I) or (II).

[0079] The inflammatory reflex is an autonomic nervous system response to an inflammatory signal. Upon sensing an inflammatory stimulus, the autonomic nervous system responds through the vagus nerve by releasing acetylcholine and activating nicotinic α7 receptors on macrophages. These macrophages in turn release cytokines. Dysfunctions in this pathway have been linked to human inflammatory diseases including rheumatoid arthritis, diabetes and sepsis. Macrophages express the nicotinic α7 receptor and it is likely this receptor that mediates the cholinergic anti-inflammatory response. Therefore, compounds with affinity for the α7nACh receptor on macrophages may be useful for human inflammatory diseases including rheumatoid arthritis, diabetes and sepsis. See, e.g., Czura, C J et al., J. Intern. Med., (2005) 257(2), 156-66, Wang, H. et al Nature (2003) 421 : 384-388; de Jonge British Journal of Pharmacology (2007) 151, 915-929.

[0080] Thus, in accordance with an embodiment of the invention there is provided a method of treating a patient (e.g., a mammal, such as a human) suffering from an inflammatory disease, such as, but not limited to, rheumatoid arthritis, diabetes or sepsis, comprising administering to the patient an effective amount of a compound according to Formulae (I) or (II).

[0081] The mammalian sperm acrosome reaction is an exocytosis process important in fertilization of the ovum by sperm. Activation of an α7 nAChR on the sperm cell has been shown to be essential for the acrosome reaction (Son, J.--H. and Meizel, S. Biol, Reproduct. 68: 1348-1353 2003). Consequently, selective α7 agents demonstrate utility for treating fertility disorders.
[0082] In addition, due to their affinity to \( \alpha \)nACh receptors, labeled derivatives of the compounds of Formulae (I) or (II) (for example C11 or F18 labeled derivatives), can be used in neuroimaging of the receptors within, e.g., the brain. Thus, using such labeled agents in vivo imaging of the receptors can be performed using, for example PET imaging.

[0083] The condition of memory impairment is manifested by impairment of the ability to learn new information and/or the inability to recall previously learned information. Memory impairment is a primary symptom of dementia and can also be a symptom associated with such diseases as Alzheimer's disease, schizophrenia, Parkinson's disease, Huntingdon's disease, Pick's disease, Creutzfeldt-Jakob disease, HIV, cardiovascular disease, and head trauma as well as age-related cognitive decline.

[0084] Thus, in accordance with an embodiment of the invention there is provided a method of treating a patient suffering from, for example, mild cognitive impairment (MCI), vascular dementia (VaD), age-associated cognitive decline (AACD), amnesia associated w/open-heart-surgery, cardiac arrest, and/or general anesthesia, memory deficits from early exposure of anesthetic agents, sleep deprivation induced cognitive impairment, chronic fatigue syndrome, narcolepsy, AIDS-related dementia, epilepsy-related cognitive impairment, Down's syndrome, Alcoholism related dementia (Korsakoff Syndrome), drug/substance induced memory impairments, Dementia Puglistica (Boxer Syndrome), and animal dementia (e.g., dogs, cats, horses, etc.) comprising administering to the patient an effective amount of a compound according to Formulae (I) or (II).

[0085] Dosage of the compounds for use in therapy may vary depending upon, for example, the administration route, the nature and severity of the disease. In general, an acceptable pharmacological effect in humans may be obtained with daily dosages ranging from 0.01 to 200 mg/kg.

[0086] In some embodiments of the present invention, one or more compounds of Formulae (I) or (II) are administered in combination with one or more other other pharmaceutically active agents. The phrase "in combination", as used herein, refers to agents that are simultaneously administered to a subject. It will be appreciated that two or more agents are considered to be administered "in combination" whenever a subject is simultaneously
exposed to both (or more) of the agents. Each of the two or more agents may be administered according to a different schedule; it is not required that individual doses of different agents be administered at the same time, or in the same composition. Rather, so long as both (or more) agents remain in the subject's body, they are considered to be administered "in combination".

[0087] For example, compounds of Formulae (I) or (II), in forms as described herein, may be administered in combination with one or more other modulators of α7 nicotinic acetylcholine receptors. Alternatively or additionally, compounds of Formulae (I) or (II), in forms as described herein, may be administered in combination with one or more other anti-psychotic agents, pain relievers, antiinflammatories, or other pharmaceutically active agents.

[0088] Effective amounts of a wide range of other pharmaceutically active agents are well known to those skilled in the art. However, it is well within the skilled artisan's purview to determine the other pharmaceutically active agent's optimal effective amount range. The compound of Formulae (I) or (II) and the other pharmaceutically active agent can act additively or, in some embodiments, synergistically. In some embodiments of the invention, where another pharmaceutically active agent is administered to an animal, the effective amount of the compound of Formulae (I) or (II) is less than its effective amount would be where the other pharmaceutically active agent is not administered. In this case, without being bound by theory, it is believed that the compound of Formulae (I) or (II) and the other pharmaceutically active agent act synergistically. In some cases, the patient in need of treatment is being treated with one or more other pharmaceutically active agents. In some cases, the patient in need of treatment is being treated with at least two other pharmaceutically active agents.

[0089] In some embodiments, the other pharmaceutically active agent is selected from the group consisting of one or more anti-depressant agents, anti-anxiety agents, anti-psychotic agents, or cognitive enhancers. Examples of classes of antidepressants that can be used in combination with the active compounds of this invention include norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), NK-I receptor antagonists, monoamine oxidase inhibitors (MAOs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α-adrenoceptor antagonists, and atypical antidepressants. Suitable norepinephrine
reuptake inhibitors include tertiary amine tricyclics and secondary amine tricyclics. Suitable tertiary amine tricyclics and secondary amine tricyclics include amitriptyline, clomipramine, doxepin, imipramine, trimipramine, dothiepin, butriptyline, iprindole, lofepramine, nortriptyline, protriptyline, amoxapine, desipramine and maprotiline. Suitable selective serotonin reuptake inhibitors include fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine and sertraline. Examples of monoamine oxidase inhibitors include isocarboxazid, phenelzine, and tranylcypromine. Suitable reversible inhibitors of monoamine oxidase include moclobemide. Suitable serotonin and noradrenaline reuptake inhibitors of use in the present invention include venlafaxine, nefazodone, milnacipran, and duloxetine. Suitable CRF antagonists include those compounds described in International Patent Publication Nos. WO 94/13643, WO 94/13644, WO 94/13661, WO 94/13676 and WO 94/13677. Suitable atypical anti-depressants include bupropion, lithium, nefazodone, trazodone and viloxazine. Suitable NK-1 receptor antagonists include those referred to in International Patent Publication WO 01/77100.

[0090] Anti-anxiety agents that can be used in combination with the compounds of Formulae (I) or (II) include without limitation benzodiazepines and serotonin 1A (5-HT 1A) agonists or antagonists, especially 5-HT 1A partial agonists, and corticotropin releasing factor (CRF) antagonists. Exemplary suitable benzodiazepines include alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam. Exemplary suitable 5-HT 1A receptor agonists or antagonists include buspirone, flesinoxan, gepirone and ipsapirone.

[0091] Anti-psychotic agents that are used in combination with the compounds of Formulae (I) or (II) include without limitation aliphatic phethazine, a piperazine phenothiazine, a butyrophenone, a substituted benzamide, and a thioxanthine. Additional examples of such drugs include without limitation haloperidol, olanzapine, clozapine, risperidone, pimozide, aripiprazol, and ziprasidone. In some cases, the drug is an anticonvulsant, e.g., phenobarbital, phenytoin, primidone, or carbamazepine.

[0092] Cognitive enhancers that are used in combination with the compounds of Formulae (I) or (II) include, without limitation, drugs that modulate neurotransmitter levels {e.g., acetylcholinesterase or cholinesterase inhibitors, cholinergic receptor agonists or serotonin
receptor antagonists), drugs that modulate the level of soluble Aβ, amyloid fibril formation, or amyloid plaque burden (e.g., γ-secretase inhibitors, β-secretase inhibitors, antibody therapies, and degradative enzymes), and drugs that protect neuronal integrity (e.g., antioxidants, kinase inhibitors, caspase inhibitors, and hormones). Other representative candidate drugs that are co-administered with the compounds of the invention include cholinesterase inhibitors, (e.g., tacrine (COGNEX®), donepezil (ARICEPT®), rivastigmine (EXELON®) galantamine (REMINYL®), metrifonate, physostigmine, and Huperzine A), N-methyl-D-aspartate (NMDA) antagonists and agonists (e.g., dextromethorphan, memantine, dizocilpine maleate (MK-801), xenon, remacemide, eliprodil, amantadine, D-cycloserine, felbamate, ifenprodil, CP-101 606 (Pfizer), Delucemine, and compounds described in U.S. Patent Nos. 6,821,985 and 6,635,270), ampakines (e.g., cyclothiazide, aniracetam, CX-516 (Ampalex®), CX-717, CX-516, CX-614, and CX-691 (Cortex Pharmaceuticals, Inc. Irvine, CA), 7-chloro-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine S,S-dioxide (see Zivkovic et al., 1995, J. Pharmacol. Exp. Therap., 272:300-309; Thompson et al., 1995, Proc. Natl. Acad. ScL USA, 92:7667-7671), 3-bicyclo[2,2,1]hept-5-en-2-yl-6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (Yamada, et al., 1993, J. Neurosc. 13:3904-3915); 7-fluoro-3-methyl-5-ethyl-1,2,4-benzothiadiazine-S,S-dioxide; and compounds described in U.S. Patent No. 6,620,808 and International Patent Application Nos. WO 94/02475, WO 96/38414, WO 97/36907, WO 99/51240, and WO 99/42456), benzodiazepine (BZD)/GABA receptor complex modulators (e.g., progabide, gengabine, zaleplon, and compounds described in U.S. Patent No. 5,538,956, 5,260,331, and 5,422,355); serotonin antagonists (e.g., 5HT receptor modulators, 5-HT1A antagonists or agonists (including without limitation lecozotan and compounds described in U.S. Patent Nos. 6,465,482, 6,127,357, 6,469,007, and 6,586,436, and in PCT Publication No. WO 97/03982) and 5-HT6 antagonists (including without limitation compounds described in U.S. Patent Nos. 6,727,236, 6,825,212, 6,995,176, and 7,041,695)); nicotinics (e.g., niacin); muscarinics (e.g., xanomeline, CDD-0102, cevimeline, talsaclidine, oxybutyn, tolterodine, propiverine, tropium chloride and darifenacin); monoamine oxidase type B (MAO B) inhibitors (e.g., rasagiline, selegiline, deprenyl, lazabemide, safinamide, clorgyline, pargyline, N-(2-aminomethyl)-4-chlorobenzamide hydrochloride, and N-(2-aminomethyl)-5(3-fluorophenyl)-4-thiazolecarboxamide hydrochloride); phosphodiesterase (PDE) IV inhibitors (e.g., rofiumilast, arofylline, cilomilast, rolipram, RO-20-1724, theophylline, denbufylline, ARIFLO, ROFLUMILAST, CDP-840 (a tri-aryl ethane)
CP80633 (a pyrimidone), RP 73401 (Rhone-Poulenc Rorer), denbufylline (SmithKline Beecham), arofylline (Almirall), CP-77,059 (Pfizer), pyrid[2,3-d]pyridazin-5-ones (Syntex), EP-685479 (Bayer), T-440 (Tanabe Seiyaku), and SDZ-ISQ-844 (Novartis); G proteins; channel modulators; immunotherapeutics (e.g., compounds described in U.S. Patent Application Publication No. US 2005/0197356 and US 2005/0197379); anti-amyloid or amyloid lowering agents (e.g., bapineuzumab and compounds described in U.S. Patent No. 6,878,742 or U.S. Patent Application Publication Nos. US 2005/0282825 or US 2005/0282826); statins and peroxisome proliferators activated receptor (PPARS) modulators (e.g., gemfibrozil (LOPID®), fenofibrate (TRICOR®), rosiglitazone maleate (AVANDIA®), pioglitazone (Actos™), rosiglitazone (Avandia™), clofibrate and bezafibrate); cysteinyl protease inhibitors; an inhibitor of receptor for advanced glycation endproduct (RAGE) (e.g., aminoguanidine, pyridoxaminem carnosine, phenazinediamine, OPB-9195, and tenilsetam); direct or indirect neurotrophic agents (e.g., Cerebrolysin®, piracetam, oxiracetam, AIT-082 (Emilieu, 2000, Arch. Neurol. 57:454)); beta-secretase (BACE) inhibitors, α-secretase, immunophilins, caspase-3 inhibitors, Src kinase inhibitors, tissue plasminogen activator (TPA) activators, AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) modulators, M4 agonists, JNK3 inhibitors, LXR agonists, H3 antagonists, and angiotensin IV antagonists. Other cognition enhancers include, without limitation, acetyl-1-carnitine, citicholine, huperzine, DMAE (dimethylaminoethanol), Bacopa monnneiri extract, Sage extract, L-alpha glycercyl phosphoryl choline, Ginko biloba and Ginko biloba extract, Vinpocetine, DHA, nootropics including Phenyltropin, Pikatropin (from Creative Compounds, LLC, Scott City, MO), besipirdine, linopirdine, sibopirdine, estrogen and estrogenic compounds, idebenone, T-588 (Toyama Chemical, Japan), and FK960 (Fujisawa Pharmaceutical Co. Ltd.). Compounds described in U.S. Patent Nos. 5,219,857, 4,904,658, 4,624,954 and 4,665,183 are also useful as cognitive enhancers as described herein. Cognitive enhancers that act through one or more of the above mechanisms are also within the scope of this invention.

[0093] In some embodiments, the compound of Formulae (I) or (II) and cognitive enhancer act additively or, in some embodiments, synergistically. In some embodiments, where a cognitive enhancer and a compound of Formulae (I) or (II) of the invention are co-administered to an animal, the effective amount of the compound or pharmaceutically acceptable salt of the compound of the invention is less than its effective amount would be where the cognitive enhancer agent is not administered. In some embodiments, where a cognitive enhancer and a
compound of Formulae (I) or (II) are co-administered to an animal, the effective amount of the cognitive enhancer is less than its effective amount would be where the compound or pharmaceutically acceptable salt of the invention is not administered. In some embodiments, a cognitive enhancer and a compound of Formulae (I) or (II) of the invention are co-administered to an animal in doses that are less than their effective amounts would be where they were no co-administered. In these cases, without being bound by theory, it is believed that the compound of Formulae (I) or (II) and the cognitive enhancer act synergistically.

[0094] In some embodiments, the other pharmaceutically active agent is an agent useful for treating Alzheimer's disease or conditions associate with Alzheimer's disease, such as dementia. Exemplary agents useful for treating Alzheimer's disease include, without limitation, donepezil, rivastigmine, galantamine, memantine, and tacrine.

[0095] In some embodiments, the compound of Formulae (I) or (II) is administered together with another pharmaceutically active agent in a single administration or composition.

[0096] In some embodiments, a composition comprising an effective amount of the compound of Formulae (I) or (II) and an effective amount of another pharmaceutically active agent within the same composition can be administered.

[0097] In another embodiment, a composition comprising an effective amount of the compound of Formulae (I) or (II) and a separate composition comprising an effective amount of another pharmaceutically active agent can be concurrently administered. In another embodiment, an effective amount of the compound of Formulae (I) or (II) is administered prior to or subsequent to administration of an effective amount of another pharmaceutically active agent. In this embodiment, the compound of Formulae (I) or (II) is administered while the other pharmaceutically active agent exerts its therapeutic effect, or the other pharmaceutically active agent is administered while the compound of Formulae (I) or (II) exerts its preventative or therapeutic effect.

[0098] Thus, in some embodiments, the invention provides a composition comprising an effective amount of the compound of Formulae (I) or (II) of the present invention and a
pharmaceutically acceptable carrier. In some embodiments, the composition further comprises a second pharmaceutically active agent.

[0099] In another embodiment, the composition further comprises a pharmaceutically active agent selected from the group consisting of one or more other antidepressants, anti-anxiety agents, anti-psychotic agents or cognitive enhancers. Antidepressants, anti-anxiety agents, anti-psychotic agents and cognitive enhancers suitable for use in the composition include the antidepressants, anti-anxiety agents, anti-psychotic agents and cognitive enhancers provided above.

[0100] In another embodiment, the pharmaceutically acceptable carrier is suitable for oral administration and the composition comprises an oral dosage form.

[0101] In some embodiments, one or more compounds of Formulae (I) or (II) is administered in combination with antidepressant drug treatment, antipsychotic drug treatment, and/or anticonvulsant drug treatment.

[0102] In certain embodiments, a compound of Formulae (I) or (II) is administered in combination with one or more selective serotonin reuptake inhibitors (SSRIs) (for example, fluoxetine, citalopram, escitalopram oxalate, fluvoxamine maleate, paroxetine, or sertraline), tricyclic antidepressants (for example, desipramine, amitrityline, amoxipine, clomipramine, doxepin, imipramine, nortripsyline, protriptyline, trimipramine, dothiepin, butripsyline, iprindole, or lofepramine), aminoketone class compounds (for example, bupropion); in some embodiments, a compound of Formulae (I) or (II) is administered in combination with a monoamine oxidase inhibitor (MAOI) (for example, phenelzine, isocarboxazid, or tranylcypromine), a serotonin and norepinepherine reuptake inhibitor (SNRI) (for example, venlafaxine, nefazodone, milnacipran, duloxetine), a norepinephrine reuptake inhibitor (NRI) (for example, reboxetine), a partial 5-HT1A agonist (for example, buspirone), a 5-HT2A receptor antagonist (for example, nefazodone), a typical antipsychotic drug, or an atypical antipsychotic drug. Examples of such antipsychotic drugs include aliphatc phethiazine, a piperazine phenothiazine, a butyrophenone, a substituted benzamide, and a thioxanthine. Additional examples of such drugs include haloperidol, olanzapine, clozapine, risperidone, pimozone, aripiprazol, and ziprasidone. In some cases, the drug is an anticonvulsant, e.g., phenobarbital, phenytoin, primidone, or carbamazepine.
In some cases, the compound of Formulae (I) or (II) is administered in combination with at least two drugs that are antidepressant drugs, antipsychotic drugs, anticonvulsant drugs, or a combination thereof.

Pharmaceutical Compositions

[0103] In some embodiments, the present invention provides a pharmaceutical composition containing one or more compounds of Formulae (I) or (II), in association with pharmaceutically acceptable carriers and excipients. The pharmaceutical compositions can be in the form of solid, semi-solid or liquid preparations, preferably in form of solutions, suspensions, powders, granules, tablets, capsules, syrups, suppositories, aerosols or controlled delivery systems. The compositions can be administered by a variety of routes, including oral, transdermal, subcutaneous, intravenous, intramuscular, rectal and intranasal, and are preferably formulated in unit dosage form, each dosage containing from about 1 to about 1000 mg, preferably from 1 to 600 mg of the active ingredient. The compounds of the invention can be in the form of free bases or as acid addition salts, preferably salts with pharmaceutically acceptable acids. The invention also includes separated isomers and diastereomers of compounds I, or mixtures thereof (e.g. racemic mixtures). The principles and methods for the preparation of pharmaceutical compositions are described for example in Remington's Pharmaceutical Science, Mack Publishing Company, Easton (PA).

[0104] When administered to an animal, one or more compounds of Formulae (I) or (II), in any desirable form (e.g., salt form, crystal form, etc.), can be administered neat or as a component of a pharmaceutical composition that comprises a physiologically acceptable carrier or vehicle. Such a pharmaceutical composition of the invention can be prepared using standard methods, for example admixing the compound(s) and a physiologically acceptable carrier, excipient, or diluent. Admixing can be accomplished using methods well known for admixing a compound of Formulae (I) or (II) and a physiologically acceptable carrier, excipient, or diluent.

[0105] Provided pharmaceutical compositions (i.e., comprising one or more compounds of Formulae (I) or (H)), in an appropriate form, can be administered orally. Alternatively or additionally, provided pharmaceutical compositions can be administered by any other convenient
route, for example, parenterally (e.g., subcutaneously, intravenously, etc., by infusion or bolus injection, etc), by absorption through epithelial or mucocutaneous linings (e.g., oral, rectal, vaginal, and intestinal mucosa, etc., etc.). Administration can be systemic or local. Various known delivery systems, including, for example, encapsulation in liposomes, microparticles, microcapsules, and capsules, can be used.

[0106] Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdermal, rectal, by inhalation, or topical, particularly to the ears, nose, eyes, or skin. In some instances, administration will result of release of the compound (and/or one or more metabolites thereof) into the bloodstream. The mode of administration may be left to the discretion of the practitioner.

[0107] In some embodiments, provided pharmaceutical compositions are administered orally; in some embodiments, provided pharmaceutical compositions are administered intravenously.

[0108] In some embodiments, it may be desirable to administer provided pharmaceutical compositions locally. This can be achieved, for example, by local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository or edema, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

[0109] In certain embodiments, it can be desirable to introduce a compound of Formulae (I) or (II) into the central nervous system, circulatory system or gastrointestinal tract by any suitable route, including intraventricular, intrathecal injection, paraspinal injection, epidural injection, enema, and by injection adjacent to the peripheral nerve. Intraventricular injection can be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

[0110] Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or
synthetic pulmonary surfactant. In certain embodiments, the compound of Formulae (I) or (II) can be formulated as a suppository, with traditional binders and excipients such as triglycerides.

[0111] In some embodiments, one or more compounds of Formulae (I) or (II) can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533, 1990 and Treat *et al.*, *Liposomes in the Therapy of Infectious Disease and Cancer* 317-327 and 353-365, 1989).


[0113] As noted above, provided pharmaceutical compositions can optionally comprise a suitable amount of a physiologically acceptable excipient. Exemplary physiologically acceptable excipients can be liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. For example, useful physiologically acceptable excipients can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea and the like. Alternatively or additionally, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used.

[0114] In some embodiments, a physiologically acceptable excipient that is sterile when administered to an animal is utilized. Such physiologically acceptable excipients are desirably stable under the conditions of manufacture and storage and will typically be preserved against the contaminating action of microorganisms. Water is a particularly useful excipient when a
compound of Formulae (I) or (II) is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable physiologically acceptable excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. Provided pharmaceutical compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

[0115] Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups, and elixirs. A compound of Formulae (I) or (II) can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both, or pharmaceutically acceptable oils or fat. Such a liquid carrier can contain other suitable pharmaceutical additives including solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers, or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives, including sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) and their derivatives, and oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

[0116] Provided pharmaceutical compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In some embodiments, pharmaceutical compositions in the form of a capsule are provided. Other examples of suitable physiologically acceptable excipients are described in Remington's Pharmaceutical Sciences 1447-1676 (Alfonso R. Gennaro, ed., 19th ed. 1995).
In some embodiments, a compound of Formulae (I) or (II) (in an appropriate form) is formulated in accordance with routine procedures as a composition adapted for oral administration to humans. Compositions for oral delivery can be in the form of tablets, lozenges, buccal forms, troches, aqueous or oily suspensions or solutions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered compositions can contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. In powders, the carrier can be a finely divided solid, which is an admixture with the finely divided compound or pharmaceutically acceptable salt of the compound. In tablets, the compound or pharmaceutically acceptable salt of the compound is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets can contain up to about 99% of the compound or pharmaceutically acceptable salt of the compound.

Capsules may contain mixtures of one or more compounds of Formulae (I) or (II) with inert fillers and/or diluents such as pharmaceutically acceptable starches (e.g., corn, potato, or tapioca starch), sugars, artificial sweetening agents, powdered celluloses (such as crystalline and microcrystalline celluloses), flours, gelatins, gums, etc.

Tablet formulations can be made by conventional compression, wet granulation, or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents (including, but not limited to, magnesium stearate, stearic acid, sodium lauryl sulfate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, microcrystalline cellulose, sodium carboxymethyl cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, low melting waxes, and ion exchange resins.) Surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearyl alcohol, cetomacrogol emulsifying wax,
sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine.

[0120] Moreover, when in a tablet or pill form, provided pharmaceutical compositions can be coated to delay disintegration and absorption in the gastrointestinal tract, thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule can be imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time-delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, and magnesium carbonate. In some embodiments, the excipients are of pharmaceutical grade.

[0121] In some embodiments, one or more compounds of Formulae (I) or (II) (in an appropriate form) can be formulated for intravenous administration. Typically, compositions for intravenous administration comprise sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. Compositions for intravenous administration can optionally include a local anesthetic such as lignocaine to lessen pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water-free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where a compound of Formulae (I) or (II) is to be administered by infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where a compound of Formulae (I) or (II) is administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

[0122] In some embodiments, one or more compounds of Formulae (I) or (II) (in an appropriate form) can be administered transdermally through the use of a transdermal patch.
Transdermal administrations include administrations across the surface of the body and the inner linings of the bodily passages including epithelial and mucosal tissues. Such administrations can be carried out using the present in lotions, creams, foams, patches, suspensions, solutions, and suppositories (e.g., rectal or vaginal).

[0123] Transdermal administration can be accomplished through the use of a transdermal patch containing one or more compounds of Formulae (I) or (II) (in an appropriate form) and a carrier that is inert to the compound or pharmaceutically acceptable salt of the compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams or ointments, pastes, gels, or occlusive devices. The creams or ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the compound or pharmaceutically acceptable salt of the compound into the blood stream, such as a semi-permeable membrane covering a reservoir containing a compound of Formulae (I) or (II) with or without a carrier, or a matrix containing the active ingredient.

[0124] One or more compounds of Formulae (I) or (II) (in an appropriate form) may be administered rectally or vaginally in the form of a conventional suppository. Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water-soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

[0125] One or more compounds of Formulae (I) or (II) (in an appropriate form) can be administered by controlled-release or sustained-release means or by delivery devices that are known to those of ordinary skill in the art. Such dosage forms can be used to provide controlled- or sustained-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release formulations known to those skilled in the art, including those described herein, can be readily
selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

[0126] In some embodiments a controlled- or sustained-release composition comprises a minimal amount of a compound of Formulae (I) or (II) to treat or prevent one or more disorders, diseases or conditions associated with activity of α7 nicotinic acetylcholine receptors. Advantages of controlled- or sustained-release compositions include extended activity of the drug, reduced dosage frequency, and increased compliance by the animal being treated. In addition, controlled- or sustained-release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the compound or a pharmaceutically acceptable salt of the compound, and can thus reduce the occurrence of adverse side effects.

[0127] Controlled- or sustained-release compositions can initially release an amount of one or more compounds of Formulae (I) or (II) that promptly produces a desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the compound to maintain this level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of the compound a body, the compound can be released from the dosage form at a rate that will replace the amount of the compound being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

[0128] In certain embodiments, provided pharmaceutical compositions deliver an amount of a compound of Formulae (I) or (II) that is effective in the treatment of one or more disorders, diseases, or conditions associated with activity (or inactivity) of α7 nicotinic acetylcholine receptors. According to the present invention, in vitro or in vivo assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed can also depend on the route of administration, the condition, the seriousness of the condition being treated, as well as various physical factors related to the individual being treated, and can be decided according to the judgment of a health-care practitioner. Equivalent dosages may be
administered over various time periods including, but not limited to, about every 2 hours, about every 6 hours, about every 8 hours, about every 12 hours, about every 24 hours, about every 36 hours, about every 48 hours, about every 72 hours, about every week, about every two weeks, about every three weeks, about every month, and about every two months. The number and frequency of dosages corresponding to a completed course of therapy will be determined according to the judgment of a health-care practitioner. Effective dosage amounts described herein typically refer to total amounts administered; that is, if more than one compound of Formulae (I) or (II) is administered, the effective dosage amounts correspond to the total amount administered.

[0129] The effective amount of a compound of Formulae (I) or (II) for use as described herein will typically range from about 0.001 mg/kg to about 600 mg/kg of body weight per day, in some embodiments, from about 1 mg/kg to about 600 mg/kg body weight per day, in another embodiment, from about 10 mg/kg to about 400 mg/kg body weight per day, in another embodiment, from about 10 mg/kg to about 200 mg/kg of body weight per day, in another embodiment, from about 10 mg/kg to about 100 mg/kg of body weight per day, in another embodiment, from about 1 mg/kg to about 10 mg/kg body weight per day, in another embodiment, from about 0.001 mg/kg to about 100 mg/kg of body weight per day, in another embodiment, from about 0.001 mg/kg to about 10 mg/kg of body weight per day, and in another embodiment, from about 0.001 mg/kg to about 1 mg/kg of body weight per day.

[0130] In some embodiments, pharmaceutical compositions are provided in unit dosage form, e.g., as a tablet, capsule, powder, solution, suspension, emulsion, granule, or suppository. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage form can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. A unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. Such unit dosage form may contain, for example, from about 0.01 mg/kg to about 250 mg/kg, and may be given in a single dose or in two or more divided doses. Variations in the dosage will necessarily occur depending upon the species, weight and condition of the patient being treated and the patient's individual response to the medicament.
In some embodiments, the unit dosage form is about 0.01 to about 1000 mg. In another embodiment, the unit dosage form is about 0.01 to about 500 mg; in another embodiment, the unit dosage form is about 0.01 to about 250 mg; in another embodiment, the unit dosage form is about 0.01 to about 100 mg; in another embodiment, the unit dosage form is about 0.01 to about 50 mg; in another embodiment, the unit dosage form is about 0.01 to about 25 mg; in another embodiment, the unit dosage form is about 0.01 to about 10 mg; in another embodiment, the unit dosage form is about 0.01 to about 5 mg; and in another embodiment, the unit dosage form is about 0.01 to about 10 mg.

A compound of Formulae (I) or (II) can be assayed in vitro or in vivo for the desired therapeutic or prophylactic activity prior to use in humans. Animal model systems can be used to demonstrate safety and efficacy.

Synthesis and Preparation

The compounds of Formulae (I) or (II) or their precursors can be prepared through a number of synthetic routes amongst which the ones illustrated in Schemes 1-5 below, whereby R” encompasses either the definition of R” in formula I or the fluorine atom bound to the pyrazole moiety of formula II:

a) Scheme 1

According to Scheme 1, an ω-haloalkanoylchloride 1 (hereby exemplified by a ω-bromoalkanoyl chloride) is reacted with a suitable heterocyclic amine 2 in a solvent such as for example but not limited to dichloromethane, dimethylformamide, dimethylacetamide, tetrahydrofurane, ethyl acetate and the like, or mixtures thereof, in the presence of a base such as for example but not limited to triethylamine, Hunig's base (diisopropylethylamine) or an inorganic base such as for example potassium carbonate, to afford the coupling amide product 3 which may or may be not isolated and purified. Amide 3 is then reacted in a suitable solvent such as but not limited to dichloromethane, dimethylformamide, or dimethylacetamide with an amine.
X, which may be or may not be used in excess, in the presence or absence of an additional base such as triethylamine or Hunig’s base to afford subject matter compounds of Formulae (I) or (II).

b) Scheme 2

According to Scheme 2, an ω-haloalkanoic acid is suitably activated using an agent such for example but not limited to as 1,1’-carbonyldiimidazole in a solvent such as for example dichloromethane, dimethylformamide or mixtures thereof and reacted with a suitable heterocyclic amine to afford the intermediate ω-haloalkanoic acid amide 3, which may or may not be isolated and purified. Amide 3 is then reacted in a suitable solvent such as but not limited to dichloromethane, dimethylformamide, or dimethylacetamide with an amine X, which may or may not be used in excess, in the presence or absence of an additional base such as triethylamine or Hunig’s base to afford subject matter compounds of Formulae (I) or (II).

c) Scheme 3

According to Scheme 3, an ω-aminoalkanoic acid is suitably activated using an agent such for example but not limited to as 1,1’-carbonyldiimidazole in a solvent such as for example dichloromethane, dimethylformamide or mixtures thereof and reacted with a suitable heterocyclic amine to afford subject matter compounds of Formulae (I) or (II).

d) Scheme 4
According to Scheme 4, an ω-aminoalkanoic acid 5 is suitably activated using an agent such for example but not limited to as 1,1′-carbonyldiimidazole in a solvent such as for example dichloromethane, dimethylformamide or mixtures thereof and reacted with a suitable bromoheterocyclic amine to afford bromoheteroarylamides of formula 7, which are then reacted further under cross-coupling conditions, for example Suzuki conditions, to afford subject matter compounds of Formulae (I) or (II).

e) Scheme 5 shows one possible route towards the synthesis of chain-substituted acids 5, precursors to compounds of Formulae (I) or (II).

[0138] According to Scheme 5, an alkyl-substituted malonic acid diester it treated with base, such as for example but not limited to sodium hydride in a solvent such as tetrahydrofuran or dimethylformamide and reacted with an α,ω-dihaloalkane. The disubstituted malonic acid diester thus obtained is hydrolysed and mono-decarboxylated by treatment with a strong acid, such as for example hydrobromic acid. Esterification is then carried out, for example by treatment with methanol and a catalytic amount of acid. Substitution of the ω-halogen may be accomplished by the use of a suitable amine heating in a solvent like toluene, but not limited to this solvent. Finally, hydrolysis of the ester function with an aqueous base affords intermediates of formula 5 which can be activated as described to afford compounds of Formulae (I) or (II).

[0139] The compounds of Formulae (I) or (II), their optical isomers or diastereomers can be purified or separated according to well-known procedures, including but not limited to chromatography with a chiral matrix and fractional crystallisation.
Exemplification

Experimental Procedures - Synthesis of compounds

General

[0140] Unless otherwise specified all nuclear magnetic resonance spectra were recorded using a Varian Mercury Plus 400 MHz spectrometer equipped with a PFG ATB Broadband probe.

[0141] HPLC-MS analyses were performed with a Waters 2795 separation module equipped with a Waters Micromass ZQ (ES ionisation) and Waters PDA 2996, using a Waters XTerra MS C18 3.5µm 2.1x50mm column. When 'methanol gradient' is specified in the Examples, a Gemini-NX 3u C18 11OA 50x2.0 mm was used.

[0142] Gradients were run using 0.1% formic acid/water and 0.1% formic acid/acetonitrile with gradient 5/95 to 95/5 with a flow of 1 mL/min; or 0.1% formic acid/water and 0.1% formic acid/methanol with gradient 5/95 to 95/5 with a flow of 0.8 mL/min ('methanol gradient') in the run time indicated in the Examples.

[0143] Preparative HLPC was run using a Waters 2767 system with a binary Gradient Module Waters 2525 pump and coupled to a Waters Micromass ZQ (ES) or Waters 2487 DAD, using a Supelco Discovery HS C18 5.0µm 10x2 1.2mm column

[0144] Preparative Chiral HLPC was run using a Waters 2767 system equipped with a Chiralcel OD-H, 2x25 cm. Gradient eluent was made of 10% methanol/ethanol 8/2 n-propyl alcohol in hexane/«-propyl alcohol.

[0145] Unless otherwise stated, all column chromatography was performed following the method of Still, C ; J. Org Chem 43, 2923 (1978). All TLC analyses were performed on silica gel
(Merck 60 F254) and spots revealed by UV visualisation at 254 nm and KMnO₄ or ninhydrin stain.

[0146] When specified for array synthesis, heating was performed on a Buchi Syncore® system.

[0147] All microwave reactions were performed in a CEM Discover oven.

**Abbreviations used throughout the Experimental Procedures**

- AcOEt: ethyl acetate
- DCM: dichloromethane
- DCE: 1,2-dichloroethane
- DMEA: N,N-dimethylethylamine
- DMF: N,N-dimethylformamide
- DMSO, dmso: dimethylsulphoxide
- DAM: N,N-dimethylacetamide
- SCX: strong cation exchanger
- TEA: triethylamine
- TFA: trifluoroacetic acid
- THF: tetrahydrofuran
- TLC: thin layer chromatography
- LC-MS: liquid chromatography - mass spectrometry
- HPLC: high performance liquid chromatography

**General 3-amino-5-aryl/heteroaryl/pyrazole synthesis**

[0148] The 3-amino-5-aryl/heteroaryl pyrazoles used in the Examples were either commercially available or synthesised using the routes shown in the scheme below:
General procedure for aryl/heteroaryl β-ketonitrile synthesis (Al):

[0149] Aryl or heteroaryl methyl carboxylate were commercially available or were synthesized according to the following standard procedure: the aryl or heteroaryl carboxylic acid (32 mmol) was dissolved in MeOH (40 mL) and sulfuric acid (1 mL) was added. The mixture was refluxed overnight, after which the solvent was evaporated under reduced pressure; the crude was dissolved in DCM and washed with saturated aqueous NaHCO₃ solution. The organic phase was dried and evaporated under reduced pressure, and the crude was used without further purification.

[0150] To a solution of an aryl or heteroaryl methyl carboxylate (6.5 mmol) in dry toluene (6 mL) under N₂, NaH (50-60% dispersion in mineral oil, 624 mg, 13 mmol) was carefully added. The mixture was heated at 80 °C and then dry CH₃CN was added dropwise (1.6 mL, 30.8 mmol). The reaction was heated for 18 hours and generally the product precipitated from the reaction mixture as Na salt.

[0151] The reaction was then allowed to cool down to room temperature and the solid formed was filtered and then dissolved in water. The solution was then acidified with 2 N HCl solution and at pH between 2-6 (depending on the ring substitution on the aryl/heteroaryl system) the product precipitated and was filtered off. If no precipitation occurred, the product was extracted with DCM.
After work-up, the products were generally used in the following step without further purification. The general yield was between 40 and 80%.

General procedure for aryl/heteroaryl β-ketonitrile synthesis (route A1 bis):

Aryl- or heteroaryl-carboxylic acid methyl esters are commercially available or were synthesized under the standard procedure, as described in general procedure A1.

To a solution of dry alkanenitrile in toluene (1 mmol/mL, 5 equiv.) cooled down to -78 °C under nitrogen, a solution of -butyllithium in -hexane (1.6 N, 3.5 equiv.) was added dropwise. The mixture was left stirring at -78 °C for 20 minutes and then a solution of the aryl or heteroaryl methyl carboxylate in toluene (0.75 mmol/mL, 1 equiv.) was added and the reaction allowed to reach room temperature. Upon reaction completion, after about 20 minutes, the mixture was cooled down to 0 °C and HCl 2 N was added to pH 2. The organic phase was recovered, dried over Na₂SO₄ and concentrated under reduced pressure, affording the title product which was generally used without further purification.

General procedure for aryl aminopyrazole synthesis (route A2):

To a solution of the β-ketonitrile (7.5 mmol), in absolute EtOH (15 mL) hydrazine monohydrate (0.44 mL, 9.0 mmol) was added and the reaction was heated at reflux for 18 hrs. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in DCM and washed with water.

The organic phase was concentrated under reduced pressure to give a crude product that was purified by SiO₂ column or by precipitation from Et₂O. Yields were generally between 65 and 90%.
Hydroxy-aryl- or hydroxy-heteroaryl-carboxylic acid to methyl ester — General procedure

[0157] 4-hydroxy-benzoic acid (usually 24.0 mmol) was dissolved in MeOH (50 mL) and sulfuric acid (1 mL/g substrate) was added. The mixture was refluxed overnight, after which the solvent was evaporated under reduced pressure; the crude was dissolved in DCM and washed with saturated NaHCO₃ to basic pH. The organic phase was dried and evaporated under reduced pressure, and the product was used without further purification. The yields were between 80 and 90%.

Hydroxy-aryl- or hydroxy-heteroaryl-carboxylic acid methyl ester to F2CHO-aryl- or heteroarylcarboxylic acid methyl ester— General procedure

[0158] Under a N₂ atmosphere, 4-hydroxy-benzoic acid methyl or ethyl ester (1.0 equiv.) and sodium chlorodifluoroacetate (1.2 equiv.) were dissolved in DMF (20-25 mL) in a two neck round bottom flask; potassium carbonate (1.2 equiv.) was added and the mixture was heated at 125 °C until complete conversion of the starting material was observed by LC-MS. The mixture was then diluted with water and extracted with DCM; the organic phase was dried and removed under reduced pressure, and the crude was purified through Si column to obtain the product (Yields from 20 to 70%).

The following Table 1 reports yields and analytical data obtained in the preparation of a series of FCHO-aryl- or F2CHO -heteroaryl-carboxylic acid methyl esters prepared according to the general procedures described above.
<table>
<thead>
<tr>
<th>Starting material</th>
<th>Methyl ester -OH</th>
<th>Methyl ester -OCHF2</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Fluoro-4-hydroxy-benzoic acid</td>
<td>C₈H₇FO₂&lt;br&gt;Yield = 85%&lt;br&gt;¹H NMR (DMSO-d₆) δ 3.78 (3H, s), 7.00-7.05 (1H, m), 7.60-7.65 (2H, m)</td>
<td>C₉H₇F₂O₂&lt;br&gt;Yield = 66%&lt;br&gt;¹H NMR (DMSO-d₆) δ 3.78 (3H, s), 6.24 (1H, m), 7.61 (1H, m), 7.64 (1H, m), 10.89 (1H, bs)</td>
</tr>
<tr>
<td>2,6-Difluoro-4-hydroxy-benzoic acid</td>
<td>C₈H₆F₂O₃&lt;br&gt;Yield = 85%&lt;br&gt;¹H NMR (DMSO-d₆) δ 3.79 (s, 3H, s), 6.53 (2H, d, J=10.8 Hz), 11.13 (1H, s)</td>
<td>C₉H₆F₄O₂&lt;br&gt;Yield = 34%&lt;br&gt;¹H NMR (DMSO-d₆) δ 3.86 (3H, s), 7.18-7.24 (2H, m), 7.42 (1H, t, J=72.4 Hz).</td>
</tr>
<tr>
<td>3,5-Dichloro-4-hydroxy-benzoic acid</td>
<td>Commercially available</td>
<td>C₉H₅Cl₂F₂O₃&lt;br&gt;Yield = 74%&lt;br&gt;¹H NMR (DMSO-d₆) δ 3.31 (3H, s), 7.22 (1H, t, J=71.6 Hz), 8.05 (2H, s).</td>
</tr>
<tr>
<td>3-Chloro-4-hydroxy-benzoic acid</td>
<td>Commercially available</td>
<td>C₉H₅ClF₂O₃&lt;br&gt;Yield = 85%&lt;br&gt;¹H NMR (DMSO-d₆) δ 3.85 (3H, s), 7.39 (1H, t, J=72.4 Hz), 7.50 (1H, t, J=8.4 Hz), 7.82-7.89 (2H, m).</td>
</tr>
<tr>
<td>4-Hydroxy-3-methoxy-benzoic acid</td>
<td>Commercially available</td>
<td>C₁₀H₁₀F₂O₄&lt;br&gt;Yield = 85%&lt;br&gt;¹H NMR (DMSO-d₆) 3.84 (3H, s), 3.87 (3H, s), 7.22 (1H, t, J=73.6 Hz), 7.29 (1H, d, J=8.4 Hz), 7.57-7.60 (2H, m).</td>
</tr>
</tbody>
</table>
3-Imidazo[1,2-a]pyridin-6-yl-3-oxo-propionitrile

[0159] The product was obtained starting from imidazo[1,2-a]pyridine-6-carboxylic acid methyl ester according to general procedure A1:

Yield: 39%

C_{10}H_{17}N_{3}O Mass (calculated) [185]; (found) [M+H^+] = 186 [M-H] = 184

LC RT = 0.23, 100% (3 min method)

^1H-NMR: (dms-o-d6): 4.72 (2H, s), 7.61-7.65 (2H, m), 7.71-7.73 (1H, m), 10.10 (1H, s).

5-Imidazo[1,2-a]pyridin-6-yl-lH-pyrazol-3-ylamine

[0160] The title compound was synthesized according to general procedure A2 starting from 3-imidazo[1,2-a]pyridin-6-yl-3-oxo-propionitrile:

Yield: 84%

C_{10}H_{17}N_{5} Mass (calculated) [199]; (found) [M+1] = 200

LCMS, (5 min method, RT=0.21 min,

NMR (^1H, 400MHz, MeOH-d{4}) 3.34 (s, 2H), 5.90 (br s, 1H), 7.57 (s, 1H), 7.63 (br s, 1H), 7.86 (s, 1H), 8.73 (s, 1H)

Chlorocynnamonitrile synthesis (route Bl)
POCl₃ (2 equiv. with respect to the aryl/heteroaryl acetophenone) were added dropwise to 4 molar equivalents of anhydrous DMF cooled down to 0 °C, at such a rate that the temperature did not exceed 10 °C. The acetophenone (1 equiv.) was then added dropwise and the reaction was allowed to reach room temperature.

The reaction was then stirred for further 30 minutes and then 0.4 mmol of hydroxylamine hydrochloride were added. The reaction was then heated up to 50 °C, after which heating was removed and additional 4 equiv. of hydroxylamine hydrochloride were added portionwise (at such a rate that the temperature never exceeded 120 °C). The reaction was then stirred until the temperature of the mixture spontaneously decreased to 25 °C. Water (100 mL) were then added and the mixture was extracted with diethyl ether. The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was used for the next step without further purification.

Aryl aminopyrazole synthesis (route B2)

To a solution of the chlorocynnamonitrile (0.5 mmol/mL, 1 equiv.) in absolute EtOH 2 equiv. of hydrazine monohydrate were added and the reaction was heated at reflux for 4 hrs. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was triturated with Et₂O, allowing to recover the title compound which was generally used without further purification.

5-(2-Trifluoromethyl-phenyl)-2H-pyrazol-S-ylamine

a) S-Oxo-S-(2-trifluoromethyl-phenyl)-propionitrile

The product was prepared according to the general procedure for aminopyrazole synthesis (route A1) from 2-trifluoromethyl-benzoic acid methyl ester (3.1 g, 14.0 mmol, 1.0 equiv.). The crude was precipitated from HCl to give the title product as a yellow solid (2.8 g, yield: 94%).
5-(2-Trifluoromethyl-phenyl)-2H-pyrazol-S-ylamine

The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude was purified through Si column (eluent: DCM) and dried to give the title product (0.6 g, 20% Yield).

5-(2,6-Dimethyl-phenyl)-2H-pyrazol-S-ylamine

a) 3-(2,6-Dimethyl-phenyl)-S-oxo-propionitrile

The product was prepared according to the general procedure for aminopyrazole synthesis (route Al), refluxing the mixture overnight and then for 2 h at 110 °C. The crude product was extracted with DCM and used in the following step without further purification (2.2 g, yield: 76%).

b) 5-(2,6-Dimethyl-phenyl)-2H-pyrazol-S-ylamine

The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude was purified through Si column (eluent: DCM) and washed with water, extracted and dried to give the title product (0.25 g, yield 10%).

\( \text{C}_{9}\text{H}_{15}\text{ClFNO} \)

\( ^1\text{H-NMR } (\text{CD}_3\text{OD}): 2.09-2.23 \text{ (6H, m); } 7.04-7.12 \text{ (2H, m); } 7.18-7.26 \text{ (2H, m).} \)

5-(2-Chloro-4-fluoro-phenyl)-2H-pyrazol-3-ylamine

a) 3-(2-Chloro-4-fluoro-phenyl)-3-oxo-propionitrile

The product was prepared according to the general procedure for aminopyrazole synthesis (route Al) from 2-chloro-4-fluoro-benzoic acid methyl ester (0.7 g, 3.7 mmol, 1.0 equiv.). The crude product was extracted with DCM and used in the following step without further purification (0.4 g, yield: 60%).

\( \text{C}_{9}\text{H}_{13}\text{ClFNO} \)
b) 5-(2-Chloro-4-fluoro-phenyl)-2H-pyrazol-5-ylamine

[0169] The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude was dissolved in DCM, washed with sat NaHCO₃, extracted and dried to give the title product (0.12 g, yield 26%).

C₉H₇ClFN₃

¹H-NMR (dmso-de): 7.03-7.53 (4H, m).

5-(5-tert-Butyl-thiophen-2-yl)-2H-pyrazol-5-ylamine

a) S-(5-tert-Butyl-thiophen-2-yl)-S-oxo-propionitrile

[0170] The product was prepared according to the general procedure for aminopyrazole synthesis (route A1) from 5-tert-Butyl-thiophene-2-carboxylic acid methyl ester (3.0 g, 15.0 mmol, 1.0 equiv.). The crude product was extracted with DCM and used in the following step without further purification (2.7 g, yield: 86%).

b) 5-(5-tert-Butyl-thiophen-2-yl)-2H-pyrazol-5-ylamine

[0171] The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude was washed with water and precipitated to give the title product (2.7 g, yield 91%).

C₁₅H₁₅N₃S

Mass (calculated) [221]; (found) [M+H⁺] =222.

LC Rt = 2.53 min, 94% (10 min method)

¹H-NMR (dmso-de): 1.26-1.29 (9H, m); 4.87 (2H, br s); 5.47 (1H, br s); 6.66-6.79 (1H, m); 6.97-7.02 (1H, m)

5-(3-Chloro-2-methyl-phenyl)-2H-pyrazol-3-ylamine

a) 2-Ethyl-benzoic acid methyl ester
2-Ethyl-benzoic acid (3.0 g, 17.6 mmol) was dissolved in MeOH (20 mL) and sulfuric acid (1 mL) was added. The mixture was refluxed overnight, after which the solvent was evaporated under reduced pressure; the crude was dissolved in DCM and washed with saturated Na₂CO₃ to basic pH. The organic phase was dried and evaporated under reduced pressure, and the product (3.1 g, yield 96%) was used without further purification.

C₉H₉ClO₂

¹H-NMR (dmsö-de): 2.48 (3H, br s); 3.82 (3H, s); 7.31 (1H, t, J=7.6 Hz); 7.63-7.67 (2H, m).

b) S-(S-Chloro-2-methyl-phenyl)-S-oxo-propionitrile

The product was prepared according to the general procedure for aminopyrazole synthesis (route Al) from 3-Chloro-2-methyl-benzoic acid methyl ester (3.1 g, 16.8 mmol, 1.0 equiv.). The crude product was precipitated from water and used in the following step without further purification (2.4 g, yield: 74%).

C₁₀H₈ClNO

¹H-NMR (dmsö-de): 2.31 (3H, br s); 4.64 (2H, br s); 7.27-7.36 (2H, m); 7.54-7.77 (1H, m).

c) 5-(3-Chloro-2-methyl-phenyl)-2H-pyrazol-3-ylamine

The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude product was purified through SiO₂ column (20 g) with gradient elution from 100% EtOAc to EtOAc-MeOH 80:20. The title product (1.3 g, yield 50%) was obtained.

C₁₀H₁₀ClN₃

Mass (calculated) [207]; (found) [M+H⁺] =208.

LC Rt = 1.96 min, 85% (10 min method)

¹H-NMR (CDCl₃): 2.41 (3H, s); 5.74 (1H, s); 7.16 (1H, t, J=8.0 Hz); 7.20-7.26 (1H, m); 7.38-7.40 (1H, m).

5-(2-Ethyl-phenyl)-2H-pyrazol-3-ylamine

a) 2-Ethyl-benzoic acid methyl ester
2-Ethyl-benzoic acid (3.0 g, 20.0 mmol) was dissolved in MeOH (20 mL) and catalytic quantity of sulfuric acid (1 mL) was added. The mixture was refluxed overnight, after that the solvent was evaporated under reduced pressure; the crude was dissolved in DCM and washed with saturated Na₂CO₃ to basic pH. The organic phase was dried and evaporated under reduced pressure, and the product (2.9 g, yield 88%) was used without further purification.

C₁₀H₁₂O₂
¹H-NMR (dmsö-de): 1.12 (3H, t, J=7.2 Hz); 2.86 (2H, q, J=7.2 Hz); 3.81 (3H, s); 7.27-7.34 (2H, m); 7.46-7.51 (1H, m); 7.73-7.75 (1H, m).

b) S-(2-Ethyl-phenyl)-S-oxo-propionitrile

The product was prepared according to the general procedure for aminopyrazole synthesis (route A1) from 2-ethyl-benzoic acid methyl ester (2.9 g, 17.6 mmol, 1.0 equiv.). The crude product was extracted with DCM as a yellow oil and used in the following step without further purification (2.8 g, yield: 92%).

CnH₁₁NO
¹H-NMR (dmsö-de): 1.10-1.18 (3H, m); 2.78 (2H, q, J=7.2 Hz); 4.67 (1H, s); 7.23-7.53 (3H, m); 7.73-7.78 (1H, m).

c) 5-(2-Ethyl-phenyl)-2H-pyrazol-3-yl-amine

The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude product was purified through SiO₂ column (20 g) with gradient elution from 100% EtOAc to EtOAc-MeOH 80:20. The title product (1.2 g, yield 40%) was obtained.

CnH₁₃N₃
Mass (calculated) [187]; (found) [M+H⁺] =188.
LC Rt = 1.58 min, 90% (10 min method)
¹H-NMR (CDCl₃): 1.15 (3H, t, J=7.6 Hz); 2.71 (2H, q, J=7.6 Hz); 5.72 (1H, s); 7.20-7.26 (1H, m); 7.29-7.35 (3H, m).
5-(4-Methoxy-phenyl)-4-methyl-2H-pyrazol-5-ylamine

a) S-(4-Methoxy-phenyl)-2-methyl-S-oxo-propionitrile

[0178] The product was prepared according to the general procedure for aminopyrazole synthesis (route A1) from 4-methoxy-benzoic acid methyl ester (3.0 mL, 18.0 mmol, 1.0 equiv.), NaH (1.4 g, 36.0 mmol, 2.0 equiv.) and propionitrile (6.1 mL, 84.9 mmol, 4.7 equiv.). The crude was purified through Si-column (eluent exane/ethyl acetate) to give 2.1 g of title product (yield: 62%).

b) 5-(4-Methoxy-phenyl)-4-methyl-2H-pyrazol-5-ylamine

[0179] The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude product was washed with basic water and dried, and the title product (1.8 g, yield 80%) was used without further purification.

CnH13N3O
Mass (calculated) [203]; (found) [M+H+] =204.
LC Rt = 1.34 min, 91% (10 min method)
1H-NMR (CDCl3): 2.03 (3H, s); 3.84 (3H, s); 6.96-6.98 (2H, m); 7.37-7.39 (2H, m).

4-Methyl-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-5-ylamine

a) 2-Methyl-3-oxo-3-(4-trifluoromethyl-phenyl)-propionitrile

[0180] The product was prepared according to the general procedure for aminopyrazole synthesis (route A1) from 4-trifluoromethyl-benzoic acid methyl ester (3.0 g, 14.7 mmol, 1.0 equiv.), NaH (1.2 g, 29.4 mmol, 2.0 equiv.) and propionitrile (4.9 mL, 69.4 mmol, 4.7 equiv.). The crude product was extracted with DCM and used in the following step without further purification (3.2 g, yield: 96%).

b) 4-Methyl-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-ylamine

[0181] The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude product was washed with basic water and dried, and the title product (2.8 g, yield 84%) was used without further purification.
C_{11}H_{10}F_{3}N_{3}
Mass (calculated) [241]; (found) [M+H^+] =242.
LC Rt = 2.34 min, 92% (10 min method)
{^1}H-NMR (CDCl_3): 2.05 (3H, s); 7.56 (2H, d, J=8.4 Hz); 7.64 (2H, d, J=8.4 Hz).

5-(4-Cyclopropylmethoxy-2-methyl-phenyl)-2H-pyrazol-5-ylamine

a) 4-Hydroxy-2-methyl-benzoic acid methyl ester

[0182] 4-Hydroxy-2-methyl-benzoic acid (4.8 g, 32.0 mmol) was dissolved in MeOH (40 mL) and catalytic quantity of sulfuric acid (1 mL) was added. The mixture was refluxed overnight, after which the solvent was evaporated under reduced pressure; the crude was dissolved in DCM and washed with saturated NaHCO_3 to basic pH. The organic phase was dried and evaporated under reduced pressure, and the product (5.0 g, yield 95%) was used without further purification.

C_{9}H_{10}O_{3}
{^1}H-NMR (dmsol-de): 2.43 (3H, s); 3.72 (3H, s); 6.62-6.64 (2H, m); 7.71-7.73 (1H, m); 10.10 (1H, s).

b) 4-Cyclopropylmethoxy-2-methyl-benzoic acid methyl ester

[0183] 4-Hydroxy-2-methyl-benzoic acid methyl ester (1.0 g, 6.0 mmol, 1.0 equiv.) was dissolved in acetone (14 mL), NaI (0.45 g, 3.0 mmol, 0.5 equiv.) and K_{2}CO_3 (1.66 g, 12.0 mmol, 2.0 equiv.) were added ad the mixture was stirred at room temperature for 20 min. (Bromomethyl)cyclopropane (0.53 mL, 5.4 mmol, 0.9 equiv.) was added, and the mixture was refluxed for 2 days. The solvent was concentrated under reduced pressure, NaOH 10% was added, and the crude was extracted with DCM and dried. 0.42 g of title product (yield 32%) were recovered and used without further purification.

C_{13}H_{16}O_{3}
{^1}H-NMR (CDCl_3): 0.23-0.34 (2H, m); 0.52-0.64 (2H, m); 1.15-1.24 (1H, m); 2.52 (3H, s); 3.75 (2H, d, J=7.2 Hz); 3.77 (3H, s); 6.64-6.66 (1H, m); 7.83-7.85 (2H, m).

c) S-(4-Cyclopropylmethoxy-2-methyl-phenyl)-S-oxo-propionitrile
The product was prepared according to the general procedure for aminopyrazole synthesis from 4-cyclopropylmethoxy-2-methyl-benzoic acid methyl ester (route Albis). 0.54 g of the title product was extracted from water and dried (yield 69%) and used directly for the next step.

d) 5-(4-Cyclopropylmethoxy-2-methyl-phenyl)-2H-pyrazol-S-ylamine

The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude product was purified through SiO\(_2\) column with gradient elution from 100% EtOAc to EtOAc-MeOH 90:10. The title product (206 mg, yield 36%) was obtained.

\[
\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}
\]

\(^1\text{H}-\text{NMR (CD}_{3}\text{OD):} 0.29-0.36 (2\text{H, m}); 0.54-0.63 (2\text{H, m}); 1.18-1.28 (1\text{H, m}); 2.33 (3\text{H, s}); 3.81 (2\text{H, d, } J=7.2 \text{ Hz}); 5.67 (1\text{H, s}); 6.74-6.80 (2\text{H, m}); 7.25 (1\text{H, d, } J=8.8 \text{ Hz}).
\]

5-(S-Chloro-4-cyclopropylmethoxy-phenyl)-2H-pyrazol-S-ylamine

a) S-Chloro-4-cyclopropylmethoxy-benzoic acid methyl ester

3-Chloro-4-hydroxy-benzoic acid methyl ester (1.1 g, 6.0 mmol, 1.0 equiv.) was dissolved in acetone (14 mL), NaI (0.45 g, 3.0 mmol, 0.5 equiv.) and K\(_2\)CO\(_3\) (1.66 g, 12.0 mmol, 2.0 equiv.) were added and the mixture was stirred at room temperature for 20 min. (Bromomethyl)cyclopropane (0.53 mL, 5.4 mmol, 0.9 equiv.) was added, and the mixture was refluxed for 2 days. The solvent was concentrated under reduced pressure, NaOH 10% was added, and the crude was extracted with DCM and dried. The title product (0.88 g, yield 32%) was recovered and used without further purification.

\[
\text{C}_{12}\text{H}_{13}\text{ClO}_3
\]

\(^1\text{H}-\text{NMR (dmso-d6):} 0.33-0.37 (2\text{H, m}); 0.55-0.60 (2\text{H, m}); 1.25-1.27 (1\text{H, m}); 3.80 (3\text{H, s}); 3.99 (2\text{H, d, } J=7.2 \text{ Hz}); 7.21 (1\text{H, s, } J=8.8 \text{ Hz}); 7.85-7.91 (2\text{H, m}).
\]
b) **S-(S-Chloro-4-cyclopropylmethoxy-phenyl)-S-oxo-propionitrile**

The product was prepared according to the general procedure from 3-Chloro-4-cyclopropylmethoxy-benzoic acid methyl ester (route Albis). 0.74 g of the title product was extracted from water and dry (yield 81%) and used directly for the next step.

---

c) **5-(S-Chloro-4-cyclopropylmethoxy-phenyl)-2H-pyrazol-S-ylamine**

The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude product was purified through SiO$_2$ column (gradient elution from 100% EtOAc to EtOAc-MeOH 90:10). 521 mg of the title product (yield 67%) were obtained.

**C$_{13}$H$_{14}$ClN$_3$O**

Mass (calculated) [263]; (found) [M+H$^+$] =264.

LC Rt = 2.51 min, 90% (10 min method)

$^1$H-NMR (CD$_3$OD): 0.25-0.29 (2H, m); 0.52-0.55 (2H, m); 1.10-1.18 (1H, m); 3.81 (2H, d, J=6.8 Hz); 5.74 (1H, s); 6.95-6.99 (1H, m); 7.24-7.30 (2H, m).

---

5-(4-Cyclopropylmethoxy-2-trifluoromethyl-phenyl)-2H-pyrazol-S-ylamine

**a) 4-hydroxy-2-trifluoromethyl-benzoic acid methyl ester**

4-hydroxy-2-trifluoromethyl-benzoic acid (5.0 g, 24.0 mmol) was dissolved in MeOH (50 mL) and a catalytic quantity of sulfuric acid was added. The mixture was refluxed overnight, after which the solvent was evaporated under reduced pressure; the crude was dissolved in DCM and washed with saturated NaHCO$_3$. The organic phase was dried and evaporated under reduced pressure, and the product was used without further purification.

**b) 4-Cyclopropylmethoxy-2-trifluoromethyl-benzoic acid methyl ester**

4-hydroxy-2-trifluoromethyl-benzoic acid methyl ester (1.1 g, 4.8 mmol, 1.0 equiv.) was dissolved in acetone (14 mL), NaI (0.5 equiv.) and K$_2$CO$_3$ (1.04 g, 2.0 equiv.) were added and the mixture was stirred at room temperature for 30 min. (Bromomethyl)cyclopropane (0.42 mL, 4.3 mmol, 0.9 equiv.) was added, and the mixture was refluxed for 2 days. The solvent was concentrated under reduced pressure, NaOH 10% was added, and it was extracted with
DCM and dried. The title product (1.21 g, yield 92%) was recovered and used without further purification.

c) S-(4-Cyclopropylmethoxy-2-trifluoromethyl-phenyl)-S-oxo-propionitrile

[0191] The product was prepared according to the general procedure (route Albis). The mixture was acidified with HCl 1M and the organic phase separated and dried, to give 1.2 g of the title product (yield 94%) which was used directly for the next step.

\[
\text{C}_{14}H_{12}F_3NO_2
\]

Mass (calculated) [283]; (found) [M+H]+=284

LC Rt = 3.86 min, 98% (10 min method)

d) 5-(4-Cyclopropylmethoxy-2-trifluoromethyl-phenyl)-2H-pyrazol-S-ylamine

[0192] The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude product was purified through SiO\(_2\) column (gradient elution from Ethyl Acetate-cycloexane 1:1 to Ethyl Acetate-MeOH 90:10). 650 mg of the title product (yield 52%) were obtained.

\[
\text{C}_{14}H_{14}F_3N_3O
\]

Mass (calculated) [297]; (found) [M+H]+=298.

LC Rt = 2.78 min, 59% (10 min method)

\(^1\text{H}-\text{NMR (CDCl}_3\): 032-0.44 (2H, m); 0.64-0.62 (2H, m); 1.22-1.37 (1H, m); 3.80-3.92 (2H, m); 5.78 (1H, s); 7.04-7.07 (1H, m); 7.24-7.26 (1H, m); 7.38-7.40 (1H, m)

5-(4-Cyclopropylmethoxy-2,3-difluoro-phenyl)-2H-pyrazol-3-ylamine

a) 4-hydroxy-2,3-difluoro-benzoic acid methyl ester

[0193] 4-hydroxy-2,3-difluoro-benzoic acid (2.0 g, 11.5 mmol) was dissolved in MeOH (20 mL) and catalytic quantity of sulfuric acid was added. The mixture was refluxed overnight, after that the solvent was evaporated under reduced pressure; the crude was dissolved in DCM and washed with saturated NaHCO\(_3\). The organic phase was dried and evaporated under reduced pressure, and the product was used without further purification.
b) 4-Cyclopropylmethoxy-2,S-difluoro-benzoic acid methyl ester

[0194] 4-Hydroxy-2,3-difluoro-benzoic acid methyl ester (0.9 g, 4.8 mmol, 1.0 equiv.) was dissolved in acetone (14 mL), NaI (0.5 equiv.) and K2CO3 (1.03 g, 2.0 equiv.) were added and the mixture was stirred at room temperature for 30 min. (Bromomethyl)cyclopropane (0.42 mL, 0.9 equiv.) was added, and the mixture was refluxed for 2 days. The solvent was concentrated under reduced pressure, NaOH 10% was added, and it was extracted with DCM and dried. The title product (0.97 g, yield 84%) was recovered and used without further purification.

c) S-(4-Cyclopropylmethoxy—2,S-difluoro-phenyl)-S-oxo-propionitrile

[0195] The product was prepared according to the general procedure (route Albis). The mixture was acidified with HCl 1 M and the organic phase separated and dried, to give 0.79 g of the title product (yield 79%) which was used directly for the next step.

\[C_{13}H_{11}F_{2}NO_2\]

Mass (calculated) [251]; (found) [M+H\(^+\)] = 252.

LC Rt = 3.53 min, 82% (10 min method)

d) 5-(4-Cyclopropylmethoxy-2,S-difluoro-phenyl)-2H-pyrazol-S-ylamine

[0196] The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude product was purified through SiO\(_2\) column (gradient elution from EtOAc-cycloexane 1:1 to EtOAc:MeOH 90:10). 810 mg of the title product (yield 97%) were obtained.

\[C_{13}H_{13}F_{2}N_3O\]

Mass (calculated) [265]; (found) [M+H\(^+\)] = 266.

LC Rt = 2.59 min, 75% (10 min method)

\(^1\)H-NMR (CDCl\(_3\)): 032-0.47 (2H, m); 0.64-0.75 (2H, m); 1.19-1.38 (1H, m); 3.67-4.15 (4H, m); 5.95 (1H, s); 6.74-6.88 (1H, m); 7.17-7.26 (1H, m);
5-(S,5-Dichloro-4-cyclopropylmethoxy-phenyl)-2H-pyrazol-Sylamine

a) S,5-Dichloro-4-Cyclopropylmethoxy-benzoic acid methyl ester

3,5-Dichloro-4-hydroxy-benzoic acid ethyl ester (1.0 g, 4.5 mmol, 1.0 equiv.) was dissolved in acetone (14 mL), NaI (0.5 equiv.) and K2CO3 (0.98 g, 9.0 mmol, 2.0 equiv.) were added and the mixture was stirred at room temperature for 30 min. (Bromomethyl)cyclopropane (0.39 mL, 4.1 mmol, 0.9 equiv.) was added, and the mixture was refluxed for 2 days. The solvent was concentrated under reduced pressure, NaOH 10% was added, and it was extracted with DCM and dried. The title product (0.98 g, yield 79%) was recovered and used without further purification.

C_{13}H_{13}Cl_2N_3O
Mass (calculated) [283]; (found) [M+H'] = 284.
LC Rt = 4.06 min, 99% (10 min method)

b) S(S,5-Dichloro-4-cyclopropylmethoxy-phenyl)-S-oxo-propionitrile

The product was prepared according to the general procedure (route Albis). The mixture was acidified with HCl 1 M and the organic phase separated and dried, to give 0.91 g of the title product (yield 90%) which was used directly for the next step.

C_{13}H_{13}Cl_2N_3O
Mass (calculated) [297]; (found) [M+H'] = 298.
LC Rt = 3.23 min, 93% (10 min method)

1H-NMR (CDCl$_3$): 0.23-0.46 (2H, m); 0.64-0.74 (2H, m); 1.30-1.48 (1H, m); 3.60-4.04 (4H, m); 5.86 (1H, s); 7.48 (2H, s)
5-(4-Cyclopropylmethoxy-3-methoxy-phenyl)-2H-pyrazol-3-ylamine

\textit{a) 4-Cyclopropylmethoxy-3-methoxy-benzoic acid methyl ester}

\[ \text{[0200]} \]

4-hydroxy-3-methoxy-benzoic acid methyl ester (1.0 g, 5.5 mmol, 1.0 equiv.) was dissolved in acetone (14 mL), NaI (0.5 equiv.) and K2CO3 (1.0 g, 2.0 equiv.) were added and the mixture was stirred at room temperature for 30 min. (Bromomethyl)cyclopropane (0.53 mL, 0.9 equiv.) was added, and the mixture was refluxed for 2 days. The solvent was concentrated under reduced pressure, NaOH 10% was added, and it was extracted with DCM and dried. The title product (1.21 g, yield 93%) was recovered and used without further purification.

\textit{b) S(4-Cyclopropylmethoxy—3-methoxy-phenyl)-3-oxo-propionitrile}

\[ \text{[0201]} \]

The product was prepared according to the general procedure (route Albis). The mixture was acidified with HCl 1 M and the organic phase separated and dried, to give 1.24 g of the title product (yield 99%) which was used directly for the next step.

\[
\text{C}_{14}\text{H}_{15}\text{NO}_3
\]

Mass (calculated) [245]; (found) [M+H+] =246.

\[
\text{LC Rt} = 3.03 \text{ min, 100% (10 min method)}
\]

\textit{c) 5-(4-Cyclopropylmethoxy-S-methoxy-phenyl)-2H-pyrazol-S-ylamine}

\[ \text{[0202]} \]

The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude product was purified through SiO\textsubscript{2} column (gradient elution from EtOAc-cycloexane 1:1 to Ethyl Acetate:MeOH 90:10). 220 mg of the title product (yield 50%) were obtained.

\[
\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_2
\]

Mass (calculated) [259]; (found) [M+H+] =260.

\[
\text{LC Rt} = 1.86 \text{ min, 93% (10 min method)}
\]

\[
\text{^1H-NMR (CDCl}_3): 027-0.43 (2H, m); 0.56-0.72 (2H, m); 1.23-1.40 (1H, m); 348 (2H, m); 3.87 (3H, s); 3.98 (2H, br s); 5.82 (1H, s); 6.85-6.89 (1H, m); 7.05-7.10 (2H, m);
\]
**S-Amino-5-(S-fluoro-phenyl)-pyrazole-l-carboxylic acid tert-butyl ester**

[0203] 3-Amino-5-(3-fluoro-phenyl)-pyrazole (5.0 g, 28.0 mmol, 1.0 equiv.) and KOH 4.5 M (50 mL, 226 mmol, 8 equiv.) were dissolved in DCM (200 mL), and di-tert-butyl dicarbonate (6.5 g, 30.0 mmol, 1.1 equiv.) was added; the mixture was stirred at room temperature until complete conversion was observed by LC-MS analysis. The organic phase was washed with saturated brine and evaporated; the crude was crystallized with MeOH, to give 7.4 g of title product (yield 95%).

C_{14}H_{16}FN_{3}O_{2}

$^1$H-NMR (dmsso-d6): 1.57 (9H, s), 5.80 (1H, s), 6.43 (2H, br s), 7.16-7.21 (1H, m), 7.41-7.47 (1H, m); 7.50-7.54 (1H, m); 7.58-7.60 (1H, m).

**S-Amino-S-o-tolyl-pyrazole-l-carboxylic acid tert-butyl ester**

[0204] 3-Amino-5-o-tolyl-pyrazole (0.5 g, 2.89 mmol, 1.0 equiv.) and KOH 4.5 M (5.1 mL, 23.1 mmol, 8.0 equiv.) were dissolved in DCM (20 mL), and Di-tert-butyl dicarbonate (0.66 g, 3.0 mmol, 1.1 equiv.) was added; the mixture was stirred at room temperature until complete conversion was observed by LC-MS analysis. The organic phase was washed with saturated brine and evaporated, to give 0.6 g of title product (yield 76%).

C_{15}H_{19}N_{3}O_{2}

Mass (calculated) [273]; (found) [M+H$^+$] =274.

LC R$\text{T} = 2.34$ min, 96% (5 min method)

**3-Amino-5-(4-trifluoromethyl-phenyl)-pyrazole-l-carboxylic acid tert-butyl ester**

[0205] 3-Amino-5-(4-trifluoromethyl-phenyl)-pyrazole (2.0 g, 8.8 mmol, 1.0 equiv.) and KOH 4.5 M (15.7 mL, 70.5 mmol, 8.0 equiv.) were dissolved in DCM (70 mL), and di-tert-butyl dicarbonate (2.02 g, 9.2 mmol, 1.1 equiv.) was added; the mixture was stirred at room temperature until complete conversion was observed by LC-MS analysis. The organic phase was washed with saturated brine and evaporated; the crude was crystallized with CH$_3$CN, to give 1.9 g of title product (yield 69%).
C_{15}H_{16}F_{3}N_{3}O_{2}

Mass (calculated) [327]; (found) [M+H^+] = 328.

LC Rt = 2.59 min, 100% (5 min method)

^1H-NMR (dms-od): 1.57 (9H, s), 5.83 (1H, s), 6.46 (2H, s), 7.74 (2H, d, J = 8.4 Hz), 7.95 (2H, d, J = 8.8 Hz)

5-Pyridin-2-yl-2H-pyrazol-5-ylamine

a) Oxo-pyridin-2-yl-acetonitrile

[0206] The product was prepared according to the general procedure for aminopyrazole synthesis (route A1) from pyridine-2-carboxylic acid methyl ester (3.0 g, 21.9 mmol, 1.0 equiv.). The crude was precipitated from HCl to give the title product as a solid (2.2 g, yield: 69%) which was used directly for the next step.

b) 5-Pyridin-2-yl-2H-pyrazol-3-ylamine

[0207] The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude product was dissolved in EtOAc, washed with NaHCO_3, dried and evaporated. NMR analysis showed that a major portion of the crude mixture was still in the opened form: the mixture was then dissolved in CH_3COOH and heated at 80 °C overnight, to allow for ring closure of the opened form. The product was then recovered as the acylated form, which was de-acylated stirring with HCl 6 N at 60 °C overnight obtaining the title product (0.816 g, yield 60%).

C_{8}H_{8}N_{4}

^1H-NMR (dms-od): 4.81 (2H, bs), 5.92 (1H, s), 7.21-7.24 (1H, m), 7.76 (2H, d), 8.51 (1H, d), 11.96 (1H, bs)

5-(S-Difluoromethoxy-phenyl)-2H-pyrazol-5-ylamine

a) 3-Difluoromethoxy-benzoic acid methyl ester

[0208] Difluoromethoxy-benzoic acid (2.0 g, 10.6 mmol, 1.0 equiv.) was dissolved in MeOH (15 mL) and a catalytic quantity of sulfuric acid was added. The mixture was refluxed overnight, after which the solvent was evaporated under reduced pressure; the crude was
dissolved in DCM and washed with saturated NaHCO₃ to basic pH. The organic phase was dried and evaporated under reduced pressure, and the title product was used without further purification (1.9 g, yield 90%).

C₉H₈F₂O₃

¹H-NMR (dmso-de): 3.86 (3H, s), 7.33 (1H, t, J = 73.6 Hz), 7.46-7.50 (1H, m), 7.59 (1H, t, J=8.0 Hz), 7.67 (1H, s); 7.82 (1H, d, J=7.6 Hz).

b) S-(S-Difluoromethoxy-phenyl)-S-oxo-propionitrile

[0209] The product was prepared according to the general procedure for aminopyrazole synthesis (route A1 bis) from 3-difluoromethoxy-benzoic acid methyl ester (1.5 g, 7.4 mmol, 1.0 equiv.). The crude was precipitated by addition of aqueous HCl to give the product which was used directly for the next step.

C₁₀H₇F₂NO₂

c) 5-(S-Difluoromethoxy-phenyl)-2H-pyrazol-S-ylamine

[0210] The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude product was purified through Si-column with gradient elution from 100% EtOAc to EtOAc-MeOH 90:10. 1.45 g of title product (yield 87%) was obtained.

C₁₀H₉F₂N₃O

¹H-NMR (dmso-de): 4.89 (2H, br s), 5.75 (1H, s), 7.02 (1H, d), 7.25 (1H, t, J= 74.0 Hz), 7.36-7.42 (2H, m), 7.48-7.50 (1H, d), 11.76 (1H, br s)

5-Pyrazolo[1,5-a]pyridin-3-yl-2H-pyrazol-3-ylamine

a) 3-Oxo-3-pyrazolo[1,5-a]pyridin-3-yl-propionitrile

[0211] To a solution of dry acetonitrile in toluene (0.66 mL, 13 mmol, 5 equiv.) cooled down to -78 °C under nitrogen, a solution of «-butyllithium in «-hexane (5.2 mL, 13 mmol, 5 equiv.) was added dropwise. The mixture was left stirring at -78 °C for 20 minutes and then a solution of pyrazolo[1,5-a]pyridine-3-carboxylic acid methyl ester (0.46 g, 2.6 mmol, 1 equiv., prepared according to the reported procedure (Anderson et al. Journal of Heterocyclic Chemistry 76)
1981, J8, 1149-1 152) in toluene was added and the reaction allowed to reach room temperature. Upon reaction completion, after about 20 minutes, the mixture was cooled down to 0 °C and HCl 2 N was added to pH 2. The organic phase was recovered, dried over Na₂SO₄ and concentrated under reduced pressure, affording the title product which was used without further purification in the following step.

b) 5-Pyrazolo[1,5-a]pyridin-S-yl-2H-pyrazol-S-ylamine

[0212] To a solution of the 3-oxo-3-pyrazolo[1,5-a]pyridin-3-yl-propionitrile (0.66 g, 3.6 mmol), in absolute EtOH (25 mL) hydrazine monohydrate (0.44 mL, 9.0 mmol) was added and the reaction was heated at reflux for 18 hours. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in DCM and washed with water.

[0213] The organic phase was concentrated under reduced pressure to give a crude product that was purified by SiO₂ column (DCM to DCM:MeOH 95:5 to 85:15 gradient), yielding the title compound in 41% Yield (0.29 g, 1.48 mmol).

C₁₀H₉N₅

¹H-NMR (dmso-de): 8.68 (s, 1H); 8.21 (s, 1H); 7.92 (s, 1H); 7.28 (s, 1H); 6.90 (s, 1H); 5.75 (s, 1H); 5.10 (s, 2H).

Mass (calculated) [199]; (found) [M+H⁺] =200.

LC Rt = 0.86 min, 92% (5 min method).

5-(6-Methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine

[0214] To a solution of dry MeCN (4.17 mL, 80.0 mmol, 2.0 equiv.) in dry THF (50 mL) cooled down to -78 °C, under N₂ atmosphere a 1.6 M solution of n-BuLi in hexane (50.0 mL, 80.0 mmol, 2.0 equiv.) was added dropwise and stirred at -78 °C for 1 hour, a white suspension formed. The mixture was allowed to reach -40 °C for 15 minutes then cooled back to -78 °C. A solution of 6-methoxy-nicotinic acid methyl ester (6.68 g, 40.0 mmol, 1.0 equiv.) in THF was added dropwise and the mixture allowed to reach room temperature and stirred overnight. A 5 N
solution of acetic acid in diethylether (18 mL, 88 mmol, 2.2 equiv.) was added and the solvent removed under vacuum.

The crude mixture was dissolved in DCM (50 mL), washed with NaHCO₃ sat. solution (2 x 20 mL). The organic phase was evaporated under vacuum to obtain a solid that was used for the next step without any further purification. To a solution of 3-(6-methoxy-pyridin-3-yl)-3-oxo-propionitrile (40.0 mmol, 1.0 equiv.), in absolute EtOH (40 mL) hydrazine monohydrate (3.88 mL, 80.0 mmol, 2.0 equiv.) was added and the reaction was heated at reflux overnight.

The reaction mixture was allowed to cool down to room temperature and the solvent was evaporated under reduced pressure, the residue was partitioned between EtOAc and NaHCO₃ sat. The organic phase was evaporated and the residue dissolved in MeOH and purified using an SCX cartridge (60 g, eluant DCM/MeOH (1:1), then MeOH, then 2 N methanolic ammonia). After evaporation of the solvents, 5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine was recovered in a pure form as a pale yellow solid (5.5 g, 72%).

\[ C_9H_{10}N_4O \ \text{(calculated)} \ [190]; \ (found) \ [M+H^+] = 190 \]

\[ \text{LC Rt} = 1.38 \text{ min, 100\% (5 min method)} \]

\[^{1}H\text{-NMR} \ (400 \text{ MHz, } d\text{-chloroform}, \delta): 3.96 \text{ (s, 3H); 5.86 (s, 1H); 6.79 (d, } J = 8.0 \text{ Hz, 1H); 7.72 (d, } J = 8.0 \text{ Hz, 1H); 8.36 (m, 1H).} \]

\[ 5\text{-Amino-S-(6-methoxy-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester} \]

5-(6-Methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine (3.0 g, 15.9 mmol, 1.0 equiv.) was dissolved in 120 mL of DCM. A solution of KOH 4.5 N (30 mL) was added, followed by di-tert-butyl dicarbonate (3.6 g, 16.7 mmol, 1.05 equiv.) dissolved in 8 mL of DCM. The reaction mixture was stirred at room temperature overnight. The organic phase was separated, washed with NaHCO₃ sat. solution (2 x 20 mL) and evaporated to dryness. The residue was dissolved in MeOH and purified using an SCX cartridge (60 g, eluant DCM/MeOH (1:1), then MeOH, then 2 N methanolic ammonia). After evaporation of the solvents, a brown solid was obtained. Final
trituration of the solid with pentane (50 mL) gave 5-amino-3-(6-methoxy-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester (3.3 g, 71%).

C_{14}H_{18}N_{4}O_{3}MaSs (calculated) [290]; (found) [M+H^+] = 291

LC Rt = 3.18 min, 100% (5 min method)

^1H-NMR (400 MHz, d-chloroform, δ): 1.67 (s, 9H); 3.96 (s, 3H); 5.36 (s, 2H); 5.70 (s, 1H); 6.76 (d, J = 8 Hz, 1H); 8.09 (dd, J = 4 Hz, J = 8Hz, 1H); 8.55 (d, J = 4 Hz, 1H).

**4-Fluoro-5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-ylamine**

[0218] 6-Methyl nicotinic acid (5.0 g, 36 mmol, 1.0 equiv.) was dissolved in dry THF (70 mL) under a positive nitrogen pressure, CDI (5.8 g, 36 mmol, 1.0 equiv.) was added and the reaction mixture was stirred at 40 °C for 3 hours. After that time the reaction mixture was further diluted with 80 mL of THF and cooled to -78 °C. Fluoroacetonitrile (2.1 g, 36 mmol, 1.0 equiv.) was added followed by LiHMDS 1 M in THF (72 mL, 72 mmol, 2.0 equiv.) added dropwise. After the addition, the cooling bath was removed and the resulting dark mixture was stirred for 2 hours. After this time the reaction mixture was cooled with an ice bath and 1 M aqueous HCl was added (36 mL, 36 mmol, 1.0 equiv.). The heterogeneous mixture was extracted with EtOAc. The organic layer was dried (sodium sulfate) and concentrated under reduced pressure to give crude 2-fluoro-3-(6-methyl-pyridin-3-yl)-3-oxo-propionitrile that was dissolved in EtOH (80 mL). Hydrazine monohydrate (1.35 mL, 43.2 mmol, 1.2 equiv.) was added and the mixture was heated at reflux overnight. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The crude was purified by silica column (EtOAc/MeOH 99:1) to obtain 4-fluoro-5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-ylamine (2.9 g, 55%).

C_{9}H_{9}FN_{4} Mass (calculated) [192]; found [M+H^+] = 193

LC Rt = 0.33 min (5 min method)

^1H-NMR (400 MHz d-chloroform, δ): 2.62 (s, 3H); 7.25 (m, 1H); 8.06 (m, 1H); 8.90 (m, 1H).
**5-Amino-4-fluoro-3-(6-methyl-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester**

[0219] 4-Fluoro-5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-ylamine (2.0 g, 10.4 mmol, 1.0 equiv.) was dissolved in 50 mL of DCM. A solution of 4.5 N KOH (20 mL, 8.0 equiv.) was added, followed by di-tert-butyl dicarbonate (2.38 g, 10.92 mmol, 1.05 equiv.). The reaction mixture was stirred at room temperature overnight. The organic phase was separated and evaporated to dryness. The residue purified by silica column (DCM) to afford 5-amino-4-fluoro-3-(6-methyl-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester as a pale yellow solid which was further triturated with pentane (1.9 g, 63%).

C_{14}H_{17}F_{4}NO_{2} Mass (calculated) [292]; found [M+H] = 293

Le Rt=I. 35 min (5 min method)

**5-(5-Amino-1H-pyrazol-5-yl)-1-difluoromethyl-1H-pyridin-2-one**

a) **6-Acetylamino-nicotinic acid methyl ester**

[0220] 6-Amino-nicotinic acid methyl ester (5.0 g, 32.85 mmol, 1.0 equiv.) was suspended in a 1:1 dioxane/acetic anhydride mixture (20 mL) and the suspension was heated to 100 °C for 1 hour. After reaction completion (LCMS), the reaction mixture was cooled to room temperature and poured into a flask containing 200 g of water/ice. The resulting white suspension was stirred for 1.5 hours then 6-acetylamino-nicotinic acid methyl ester was filtered and dried under suction (5.85 g, 92%).

C_{9}H_{10}N_{2}O_{3} Mass (calculated) [194]; found [M+H] = 204

Le Rt=I. 30 min (5 min method)

b) **l-Difluoromethyl-6-oxo-1,6-dihydro-pyridineS-carboxylic acid methyl ester**

[0221] To a stirred solution of 6-acetylamino-nicotinic acid methyl ester (6.5 g, 33.5 mmol, 1.0 equiv.) in anhydrous acetonitrile (130 mL) were added sodium chlorodifluoroacetate (6.63 mg, 43.5 mmol, 1.3 equiv.) and 18-crown-6 (1.77 mg, 6.7 mmol, 0.2 equiv.). The mixture
was refluxed for 16 hours under a nitrogen atmosphere. To the resulting mixture was added 1% aqueous KHSO4 (130 mL) at room temperature, and the mixture was refluxed for 5 hours. After reaction completion (LCMS), the reaction mixture was concentrated under reduced pressure to half of the initial volume, and 1-difluoromethyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester precipitated from the aqueous phase. The product was filtered and dried under vacuum at 40 °C (5.8 g, 86%).

C₈H₇F₂NO₃ Mass (calculated) [203]; found [M+H⁺] = 204

\( \text{LC R}t=1.38 \text{ min (5 min method)} \)

\( ^1\text{H NMR (400 MHz } d_6\text{-chloroform, } \delta: 3.90 (3H, s), 6.57 (1H, dd, } J = 0.8, 9.6 \text{ Hz), 7.67 (1H, t, } J = 59.9 \text{ Hz), 7.91 (1H, dd, } J = 2.4, 9.6 \text{ Hz), 8.33 (1H, d, } J = 2.4 \text{ Hz).} \)

c) 1-Difluoromethyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid

[0222] To a stirred suspension of 1-difluoromethyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (5.0 g, 24.6 mmol, 1.0 equiv.) in a 1:1 MeOH/water mixture (50 mL), solid NaOH was added portionwise (2.0 g, 50 mmol, 2.0 equiv.) and the resulting mixture was stirred at room temperature for 16 hours. After reaction completion (LCMS), 1 N aqueous HCl was added dropwise to pH 3 and the resulting suspension was stirred for 1 hour. The solid 1-difluoromethyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid was filtered, washed with water and dried under vacuum (3.8 g, 82%).

C₇H₅F₂NO₃ Mass (calculated) [189]; found [M+H⁺] = 190

\( \text{LC R}t=0.88 \text{ min (5 min method)} \)

\( ^1\text{H NMR (400 MHz } d_6\text{-DMSO, } \delta: 6.55 (1H, d, } J = 9.7 \text{ Hz), 7.82 (1H, t, } J = 60 \text{ Hz), 7.86 (1H, dd, } J = 3.0, 9.8 \text{ Hz), 8.22 (1H, d, } J = 2.3 \text{ Hz).} \)

d) 5-(5-Amino-1H-pyrazol-3-yl)-1-difluoromethyl-1H-pyridin-2-one

[0223] Cyanoacetic acid (496 mg, 5.83 mmol, 1.1 equiv.) was dissolved in anhydrous THF (30 mL) and the solution was cooled to -78 °C under nitrogen atmosphere. n-Butyllithium
(1.6 M sol. in hexane, 7.3 mL, 11.66 mmol, 2.2 equiv.) was added dropwise and the resulting suspension was stirred for 30 minutes.

[0224] 1-Difluoromethyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (1.0 g, 5.3 mmol) was treated with neat thionyl chloride (3 mL) and the mixture was stirred at 40 °C for 1 hour. The formation of the acyl chloride was monitored by LCMS. After this time, the volatiles were evaporated under reduced pressure and the crude acyl chloride was stripped with toluene (2 x 5 mL).

[0225] The solid acyl chloride was added to the previously prepared cyanoacetic acid suspension at -78 °C, then the cooling bath was removed and the mixture was allowed to warm up to room temperature overnight.

[0226] After 16 hours the reaction mixture was cooled to 0 °C and treated with 1 M aq. HCl (6 mL). EtOAc was added, the organic layer was collected, dried over Na₂SO₄ and concentrated under reduced pressure. The obtained dark oil was suspended in ethanol, treated with hydrazine monohydrate (1.35 mL, 43.2 mmol, 1.2 equiv.) and the mixture was heated at reflux overnight. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure to give 5-(5-amino-1H-pyrazol-3-yl)-1-difluoromethyl-1H-pyridin-2-one product as a dark oil (520 mg, 43%).

C₉H₈F₂N₄O Mass (calculated) [226]; found [M+H⁺] = 227

Lc Rt=0.65 min (5 min method)

5-Amino-S-quinolin-S-yl-pyrazole-l-carboxylic acid tert-butyl ester

[0227] 5-Quinolin-3-yl-2H-pyrazol-3-ylamine (3.0 g, 15.5 mmol, 1.0 equiv.) was dissolved in DCM (60 mL) and THF (10 mL) and a 4.5 N KOH solution (27 mL, 124 mmol, 8.0 equiv.) was added and the reaction was stirred for 10 minutes. Di-tertbutyl dicarbonate (3.56 g, 16.3 mmol, 1.05 equiv.) was then added and the reaction was stirred at room temperature overnight, after which the organic solvents were evaporated and EtOAc (3 x 60 mL) was used
for the extraction. The organic phases were collected, dried and evaporated, to give 5-amino-3-quinolin-3-yl-pyrazole-1-carboxylic acid tert-butyl ester as a yellow solid (3.5 g, 73%).

C_{17}H_{18}N_4O_2 Mass (calculated) [310]; found [M+H+] = 311

1H-NMR (400 MHz -Methanol, δ): 1.68 (s, 9H); 5.96 (s, 1H); 7.55 (m, 1H); 8.05 (m, 1H); 8.23 (m, 1H); 8.33 (m, 1H); 8.41 (m, 1H); 8.84 (m, 1H).

5-Amino-S-(6-methyl-pyridin-5-yl)-pyrazole-1-carboxylic acid tert-butyl ester

5-(6-Methyl-pyridin-3-yl)-2H-pyrazol-3-ylamine (1.85 g, 10.6 mmol, 1.0 equiv.) was dissolved in DCM (50 mL), 4.5 N KOH solution (19 mL, 85 mmol, 8.0 equiv.) was added and the reaction was stirred for 10 minutes. Di-tertbutyl dicarbonate (2.43 g, 11.2 mmol, 1.05 equiv.) was then added and the reaction was stirred at room temperature overnight. DCM (50 mL) was added and the organic layer separated from the aqueous phase, then washed with brine. The organic phase was collected, dried and evaporated, to give 5-amino-3-(6-methyl-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester as a yellow oil that was triturated with α-pentane and diethylether. (1.2 g, 41%).

1H-NMR (400 MHz -Methanol, δ): 1.68 (s, 9H); 2.55 (s, 3H); 5.82 (s, 1H); 7.35 (m, 1H); 8.10 (m, 1H); 8.78 (m, 1H).

4-Fluoro-5-quinolin-6-yl-2H-pyrazol-3-ylamine

Quinolin-6-carboxylic acid (5.0 g, 28.9 mmol, 1.0 equiv.) was dissolved in dry THF (120 mL) and CDI (4.6 g, 28.9 mmol, 1.0 equiv.) was added. The reaction mixture was stirred at room temperature under N₂ atmosphere for 16 hours, after which the reaction was cooled to -78 °C. THF (160 mL) and fluoroacetonitrile (1.6 mL, 28.9 mmol, 1.0 equiv.) were added, followed by 1M LiHMDS in THF (57.7 mL, 57.7 mmol, 2.0 equiv.) added dropwise. The reaction mixture was warmed to room temperature and stirred for further 16 hours. The reaction mixture was cooled to -78°C and a 5 N solution of acetic acid in diethylether (17.6 mL, 63.5
mmol, 2.2 equiv.) was added and the solvent removed under vacuum to give crude 2-fluoro-3-oxo-3-quinolin-6-yl-propionitrile was used for the next step without any further purification.

[0230] To a solution of crude 2-fluoro-3-oxo-3-quinolin-6-yl-propionitrile (23.09 mmol, 1.0 equiv.), in absolute EtOH (80 mL) hydrazine monohydrate (1.35 mL, 27.7 mmol, 1.2 equiv.) was added and the reaction was refluxed overnight. The reaction mixture was allowed to cool to room temperature, the solvent was evaporated under reduced pressure, and the residue was partitioned between EtOAc and NaHCO₃ sat. The crude was purified by silica column (EtOAc/MeOH 99:1) to give 4-fluoro-5-quinolin-6-yl-2H-pyrazol-3-ylamine (2.9 g, 55%) as a solid, contaminated by quinoline-6-carboxylic acid amide (ca. 10%, LCMS).

C₁₂H₉FN₄ Mass (calculated) [228]; found [M+H⁺] = 229

LC Rₜ=1.52 min (5 min method)

[0231] Increased purity was obtained by transforming the product into its Boc-derivative and then deprotecting again:

5-Amino-4-fluoro-3-quinolin-6-yl-pyrazole-1-carboxylic acid tert-butyl ester

[0232] 4-Fluoro-5-quinolin-6-yl-2H-pyrazol-3-ylamine (2.9 g, 12.7 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (50 mL) and di-terbutyl dicarbonate (8.3 g, 38.1 mmol, 3.0 equiv.) was added. The reaction mixture was stirred at 80 °C overnight. The solvent was evaporated and the residue purified by silica column (EtOAc/cyclohexane 0:100 to 20:80). After purification, 5-amino-4-fluoro-3-quinolin-6-yl-pyrazol-3-ylamine tert-butyl ester was obtained (1.2 g, 30%).

C₁₇H₁₇FN₄O₂ Mass (calculated) [328]; found [M+H⁺] = 329

LC Rₜ=3.13 min (5 min method)

4-Fluoro-5-quinolin-6-yl-2H-pyrazol-3-yl-ammonium hydrochloride

[0233] 5-Amino-4-fluoro-3-quinolin-6-yl-pyrazole-1-carboxylic acid tert-butyl ester (680 mg, 2.07 mmol, 1.0 equiv.) was dissolved in DCM (8 mL) and a 2 N HCl solution in diethylether
(5.2 mL, 10.4 mmol, 5.0 equiv.) was added, then the reaction was stirred at room temperature for 2 hours. The solvent was evaporated and after washing with diethylether 4-fluoro-5-quinolin-6-yl-2H-pyrazol-3-yl-ammonium hydrochloride was obtained as a solid (472 mg, quantitative).

C_{12}H_{9}FN_{4}-HCl Mass (calculated) [228]; found [M+H+] = 228

LC Rt = 3.13 min (5 min method)

4-Fluoro-5-quinolin-3-yl-2H-pyrazol-3-ylamine

[0234] Quinoline-3-carboxylic acid (5.0 g, 28.9 mmol, 1.0 equiv.) was dissolved in dry THF (120 mL), and oxalyl chloride (2.4 mL, 28.9 mmol, 1.0 equiv.) and DMF (catalytic amount) were added. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 2 hours. Then the reaction mixture was cooled to -78 °C, and fluoroacetonitrile (∼1 mL, 28.9 mmol, 1.0 equiv.) followed by a 1 M solution of LiHMDS in THF (86.6 mL, 86.6 mmol, 3 equiv.) were added dropwise. The reaction was allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was cooled to -78 °C and a 5 N solution of acetic acid in diethylether (∼11.5 mL, 57.8 mmol, 2.0 equiv.) was added. The reaction was warmed to room temperature and the solvent removed under vacuum. The obtained 2-fluoro-3-oxo-3-quinolin-3-yl-propionitrile was used for the next step without any further purification.

[0235] To a solution of 2-fluoro-3-oxo-3-quinolin-3-yl-propionitrile (28.9 mmol) in absolute EtOH (62 mL), hydrazine monohydrate (1.7 mL, 34.6 mmol, 1.2 equiv.) was added and the reaction was heated at reflux overnight. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure, the residue partitioned between EtOAc and NaHCO₃ sat. aq. solution. The organic phase was evaporated and the crude was purified by SiO₂ column (EtOAc). 4-Fluoro-5-quinolin-3-yl-2H-pyrazol-3-ylamine was obtained as a solid (∼1.0 g, 15%).

C_{12}H_{9}FN_{4} Mass (calculated) [228]; found [M+H+] = 229

LC Rt = 2.32 min (5 min method)
$^1$H-NMR (400 MHz, $^6$-methanol, $\delta$): 7.67 (m, 1H), 7.96 (m, 1H), 8.06 (m, 2H), 8.58 (m, 1H), 9.15 (m, 1H).

4-Fluoro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine

6-Methoxy-nicotinic acid (2.5 g, 16.34 mmol, 1.0 equiv.) was dissolved in dry THF (60 mL), and oxalyl chloride (1.38 mL, 16.34 mmol, 1.0 equiv.) and DMF (catalytic amount) were added. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 1.5 hours after which the reaction mixture was cooled to -78 °C; fluoroacetonitrile (0.9 mL, 16.3 mmol, 1.0 equiv.) followed by a 1 M solution of LiHMDS in THF (49.0 mL, 49.0 mmol, 3.0 equiv.) were added dropwise. The reaction was stirred at the same temperature for 2 hours and a 5 N solution of acetic acid in diethylether (6.5 mL, 32.6 mmol, 2.0 equiv.) was then added. The reaction was warmed to room temperature and the solvent removed under vacuum to afford 2-fluoro-3-(6-methoxy-pyridin-3-yl)-3-oxo-propionitrile used for the next step without any further purification.

To a solution of crude 2-fluoro-3-(6-methoxy-pyridin-3-yl)-3-oxo-propionitrile (16.3 mmol) in absolute EtOH (15 mL), hydrazine monohydrate (0.95 mL, 19.6 mmol, 1.2 equiv.) was added and the reaction was refluxed overnight. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure, then the residue partitioned between EtOAc and NaHCO$_3$ sat. aq. solution. The organic phase was separated and evaporated and the crude was purified by silica column (EtOAc). 4-Fluoro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine (2.04 g, 60%) was obtained contaminated by 6-methoxy-nicotinamide (20%, 300 mg) as a solid.

C$_9$H$_8$FN$_4$O Mass (calculated) [208]: found [M+H$^+$] = 209

LC Rt= 2.27 min (5 min method)

$^1$H-NMR (400 MHz, $d_6$-DMSO, $\delta$): 3.88 (s, 3H), 6.98 (d, 1H, $J = 8.75$ Hz), 8.00 (dd, 1H, $J = 8.68$Hz, $J = 2.55$ Hz), 8.52 (d, 1H, $J = 2.47$ Hz).
Increased purity was obtained by transforming the product into its Boc-derivative and then deprotecting again:

5-Amino-4-fluoro-3-(6-methoxy-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester

4-Fluoro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine (2.7 g, 13.0 mmol, 1.0 equiv.) was dissolved in 1,4- dioxane (45 mL) and di-terbutyl dicarbonate (5.7 g, 25.9 mmol, 2.0 equiv.) was added. The reaction mixture was stirred at 80 °C overnight. The solvent was evaporated and the crude purified by silica column (cycloexane/EtOAc 100:0 to 70:30).

5-Amino-4-fluoro-3-(6-methoxy-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester was obtained as a solid (1.3 g, 31%).

C_{14}H_{17}FN_{4}O_3 Mass (calculated) [308]; found [M+H^+] = 309

LC Rt=3.72 min (5 min method)

\^H-NMR (400 MHz, ~methanol, δ): 1.66 (s, 9H), 3.96 (m, 3H), 6.88 (dd, 1H, J = 8.8 Hz, J = 0.69 Hz), 8.11 (ddd, 1H, J = 8.74 Hz, J = 2.41 Hz, J = 0.57 Hz), 8.59 (m, 1H).

4-Fluoro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine hydrochloride

5-Amino-4-fluoro-3-(6-methoxy-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester (1.27 g, 4.1 mmol, 1.0 equiv.) was dissolved in dichloromethane (8 mL) and a 2 M solution of HCl in diethylether (4.1 mL, 8.2 mmol, 2.0 equiv.) was added. The reaction was stirred at room temperature for 16 hours. After evaporation of the solvent, the title product was obtained as a solid (1.0 g, 98%).

C_{9}H_{9}FN_{4}O Mass (calculated) [208]; found [M+H^+] = 209

LC Rt= 2.27 min (5 min method)

\^H-NMR (400 MHz, d_6-DMSO, δ): 3.88 (s, 3H), 6.98 (d, 1H, J = 8.75 Hz), 8.00 (dd, 1H, J = 8.68 Hz, J = 2.55 Hz), 8.52 (d, 1H, J = 2.47 Hz).
5-(5-Methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine

[0242] To a solution of dry CH₃CN (1.9 mL, 35.9 mmol, 2.0 equiv.) in dry THF (10 mL) cooled down to -78°C, under N₂ atmosphere a 1.6 M solution of n-BuLi in hexane (22.4 mL, 35.9 mmol, 2.0 equiv.) was added dropwise. The mixture was allowed to reach -30 °C for 10 minutes then cooled back to -78 °C. A solution of 5-methoxy-nicotinic acid methyl ester (3.0 g, 17.9 mmol, 1.0 equiv.) in THF was added dropwise and the mixture allowed to reach room temperature while stirring for 1 hour. A 5 N solution of acetic acid in diethyl ether (7.2 mL, 35.8 mmol, 2.2 equiv.) was added and the solvent removed under vacuum. The crude 3-(5-methoxy-pyridin-3-yl)-3-oxo-propionitrile was used for the next step without any further purification.

[0243] To a solution of 3-(5-methoxy-pyridin-3-yl)-3-oxo-propionitrile (17.9 mmol), in absolute EtOH (10 mL) hydrazine monohydrate (1.0 mL, 21.5 mmol, 1.2 equiv.) was added and the reaction was heated at reflux overnight. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure, the residue partitioned between EtOAc and NaHCO₃ sat. The organic phase was evaporated and the residue dissolved in MeOH, treated with charcoal and refluxed for 15 min. After filtering off the insoluble materials the solution was concentrated and the residue treated with diethyl ether. 5-(5-Methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine precipitated as a pale yellow powder (1.88 g, 55%).

C₉H₁₀N₄O Mass (calculated) [190.21]; found [M+H⁺] = 191.35
LC Rt=O. 19, 1.24 min (10 min method)

5-Amino-3-(5-methoxy-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester

[0244] 5-(5-Methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine (1.50 g, 7.9 mmol, 1.0 equiv.) was dissolved in DCM (20 mL) and 4.5 N KOH solution (14 mL, 63.1 mmol, 8.0 equiv.) was added and the reaction was stirred for 10 minutes. Then di-tertbutyl dicarbonate (1.81 g, 8.3 mmol, 1.05 equiv.) solution in DCM (5 mL) was added and reaction was stirred at room temperature overnight. DCM (50 mL) was added and the organic solvent separated from the aqueous phase, and then washed with brine. The organic phases were collected dried and
evaporated, to give 5-amino-3-(5-methoxy-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester. The product was treated with pentane and the product precipitated as a pale yellow solid (1.88 g, 82%).

\[ C_{14}H_{18}N_4O_3 \]

Mass (calculated) [290]; found [M+H\(^+\)] = 291

LC Rt = 1.52 min (5 min method)

5-(5-Fluoro-pyridin-3-yl)-2H-pyrazol-3-ylamine

[0245] 5-Fluoro-nicotinic acid (3.0 g, 21.2 mmol, 1.0 equiv.) was suspended in dry toluene (20 mL) under \( \text{N}_2 \) atmosphere and oxalyl chloride (1.8 mL, 21.2 mmol, 1.0 equiv.) was added dropwise followed by a drop of dry DMF. The mixture was heated at 40 °C for 1 hour. The solution was then cooled down to -78 °C.

[0246] In a separate flask, to a solution of dry MeCN (2.2 mL, 42.4 mmol, 2.0 equiv.) in dry THF (35 mL) cooled down to -78 °C under \( \text{N}_2 \) atmosphere, a 2.5 M solution of n-BuLi in hexane (16.6 mL, 41.5 mmol, 1.95 equiv.) was added dropwise and stirred at -78 °C for 1 hour; a white suspension formed which was added dropwise to the solution of the acyl chloride at -78 °C and allowed to reach room temperature while stirring under \( \text{N}_2 \) overnight. A 5 M solution of acetic acid in ethyl ether (9.3 mL, 46.6 mmol, 2.2 equiv.) was added and the solvent removed under vacuum. The crude was used for the next step without any further purification.

[0247] To a solution of the 3-(5-fluoro-pyridin-3-yl)-3-oxo-propionitrile (21.2 mmol), in absolute EtOH (35 mL), hydrazine monohydrate (1.20 mL, 25.5 mmol) was added and the reaction was heated at reflux for 2.5 hours. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc and washed with sat. aq. NaHCO\(_3\). The organic phase was concentrated to give a crude product that was purified by SiO\(_2\) column (EtOAc/MeOH 100:0 to 95:5).

[0248] 5-(5-Fluoro-pyridin-3-yl)-2H-pyrazol-3-ylamine was obtained as a solid (1.3 g, 34%).
C₈H₇FN₄ Mass (calculated) [178]; found [M+H⁺] = 179

LC Rt=0.95 min (5 min method)

¹H-NMR (400 MHz, D₂O, δ): 6.02 (m, 1H); 7.36 (m, 1H); 8.14 (m, 1H); 8.27 (m, 1H).

S-Amino-S-quinolin-6-yl-pyrazole-1-carboxylic acid tert-butyl ester

5-Quinolin-6-yl-2H-pyrazol-3-ylamine (1.7 g, 8.1 mmol, 1.0 equiv.) was dissolved in DCM (60 mL). A solution of 4.5 N KOH (15 mL, 63 mmol, 8.0 equiv.) was added, followed by di-tert-butyl dicarbonate (1.8 g, 8.5 mmol, 1.05 equiv.) dissolved in DCM (8 mL). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated in vacuo and the crude obtained dissolved in AcOEt (100 mL) and washed with brine (3 x 40 mL). The organic phases were collected and evaporated in vacuo to give 5-amino-3-quinolin-6-yl-pyrazole-1-carboxylic acid tert-butyl ester as a light brown solid (2.2 g, 88%).

¹H-NMR (400 MHz, D₂O, δ): 1.69 (s, 9H); 6.01 (s, 1H); 7.65 (m, 1H); 7.80 (m, 1H); 8.03 (m, 2H); 8.70 (m, 1H); 9.30 (m, 1H).
The following Table 2 shows analytical data obtained for a series of aminopyrazoles synthesised following procedures A1/A2 outlined in the general section.

**Table 2**

<table>
<thead>
<tr>
<th>Name</th>
<th>% yield</th>
<th>MF</th>
<th>MW</th>
<th>Mass found</th>
<th>LC Purity</th>
<th>LC Rt</th>
<th>LC Method (min)</th>
<th>NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-(2-Methoxy-phenyl)-2H-pyrazol-3-ylamine</td>
<td>79</td>
<td>C_{10}H_{11}N_{3}O</td>
<td>189.22</td>
<td>190</td>
<td>96</td>
<td>1.08</td>
<td>5</td>
<td>MeOD 3.92 (3H, s); 6.04 (1H, s); 6.96-7.00 (1H, m); 7.07-7.09 (1H, m); 7.28-7.32 (1H, m); 7.57-7.59 (1H, m)</td>
</tr>
<tr>
<td>5-Quinolin-6-yl-2H-pyrazol-3-ylamine</td>
<td>63</td>
<td>C_{12}H_{10}N_{4}</td>
<td>210.24</td>
<td>211</td>
<td>100</td>
<td>0.45</td>
<td>5</td>
<td>MeOD 6.08 (1H, s); 7.52-7.55 (1H, m); 8.02-8.08 (2H, m); 8.18 (1H, s); 8.35-8.37 (1H, m); 8.79-8.81 (1H, m)</td>
</tr>
<tr>
<td>5-(3-Bromo-4-methoxy-phenyl)-2H-pyrazol-3-ylamine</td>
<td>61</td>
<td>C_{10}H_{10}BrN_{3}O</td>
<td>268.11</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>^1H NMR (DMSO-d$_6$, 400 MHz) δ 3.84 (s, 1H), 6.29 (s, 1H), 7.11 (d, 1H, J=8.6 Hz), 7.59 (dd, 1H, J=2.0 Hz, J=8.6 Hz), 7.83 (d, 1H, J=2.0 Hz), 12.50 (s, 1H).</td>
</tr>
<tr>
<td>5-Pyridin-3-yl-2H-pyrazol-3-ylamine</td>
<td>27</td>
<td>C$_4$H$_3$N$_4$</td>
<td>160.18</td>
<td>161</td>
<td>100</td>
<td>0.22</td>
<td>5</td>
<td>DMSO 5.9 (2H, s, broad); 7.45-7.47 (2H, m); 8.08-8.1 (1H, m); 8.45 (1H, m, broad), 8.84 (1H, s)</td>
</tr>
<tr>
<td>5-[6-(Tetrahydro-pyran-2-yloxy)-pyridin-3-yl]-2H-pyrazol-3-ylamine</td>
<td>99</td>
<td>C$<em>{13}$H$</em>{16}$N$_{4}$O$_2$</td>
<td>260.3</td>
<td>260.2</td>
<td>94</td>
<td>1.93</td>
<td>10</td>
<td>^1H NMR (DMSO-d$_6$, 400 MHz) δ 1.67 (m, 6H), 3.53 (m, 1H), 5.45 (m, 1H), 5.65 (bs, 1H), 6.99 (d, 2H, J=8.8 Hz), 7.53 (d, 2H, J=8.8 Hz).</td>
</tr>
<tr>
<td>5-(2-Fluoro-4-trifluoromethyl-phenyl)-2H-pyrazol-3-ylamine</td>
<td>44</td>
<td>C$_{10}$H$_7$F$_4$N$_3$</td>
<td>245.18</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>^1H NMR (CDCl$_3$, 400 MHz) δ 6.10 (s, 1H), 7.42 (d, 1H, J=12.6 Hz), 7.45 (d, 1H, J=7.7 Hz), 7.73 (dd, 1H, J=7.7 Hz).</td>
</tr>
<tr>
<td>Compound</td>
<td>Formula</td>
<td>MW</td>
<td>Yield</td>
<td>Rf</td>
<td>DMF NMR (CDCl₃, 400 MHz) δ</td>
<td>DMSO NMR (CDCl₃, 400 MHz) δ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
<td>-----------</td>
<td>------</td>
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<td>-----------------------------</td>
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</tr>
<tr>
<td>5-(3-Fluoro-4-trifluoromethyl-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C₁₀H₁₃F₃N₃</td>
<td>245.18</td>
<td></td>
<td>67%</td>
<td>5.96 (s, 1H), 7.40 (d, 1H, J=11.4 Hz), 7.44 (d, 1H, J=7.8 Hz), 7.62 (d, 1H, J=7.8 Hz.)</td>
<td>2.26 (s, 3H), 7.40 (d, 1H, J=11.4 Hz), 7.44 (d, 1H, J=7.8 Hz), 7.62 (d, 1H, J=7.8 Hz.)</td>
<td></td>
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<tr>
<td>5-(2-Methyl-3-trifluoromethyl-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C₁₀H₁₀F₃N₃</td>
<td>241.22</td>
<td></td>
<td>42</td>
<td>5.96 (s, 1H), 7.40 (d, 1H, J=11.4 Hz), 7.44 (d, 1H, J=7.8 Hz), 7.62 (d, 1H, J=7.8 Hz.)</td>
<td>2.26 (s, 3H), 7.40 (d, 1H, J=11.4 Hz), 7.44 (d, 1H, J=7.8 Hz), 7.62 (d, 1H, J=7.8 Hz.)</td>
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<td>5-(4-Chloro-3-trifluoromethyl-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C₁₀H₇ClF₃N₃</td>
<td>261.64</td>
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<td>44</td>
<td>5.93 (s, 1H), 7.50 (d, 1H, J=8.34 Hz), 7.66 (d, 1H, J=8.34 Hz), 7.88 (d, 1H, J=2.0 Hz.)</td>
<td>2.26 (s, 3H), 7.40 (d, 1H, J=11.4 Hz), 7.44 (d, 1H, J=7.8 Hz), 7.62 (d, 1H, J=7.8 Hz.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-(3-Fluoro-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C₁₀H₈FN₃</td>
<td>177.18</td>
<td>178</td>
<td>69%</td>
<td>1.13</td>
<td>2.03 (s, 3H), 7.40 (d, 1H, J=11.4 Hz), 7.44 (d, 1H, J=7.8 Hz), 7.62 (d, 1H, J=7.8 Hz.)</td>
<td></td>
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<tr>
<td>5-(2-Difluoromethoxy-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C₁₀H₈F₂N₃O</td>
<td>225.20</td>
<td></td>
<td>76</td>
<td>5.79 (1H, s), 7.00-7.37 (4H, m), 7.79 (1H, d), 11.74 (1H, bs)</td>
<td>2.49 (s, 3H), 7.40 (d, 1H, J=11.4 Hz), 7.44 (d, 1H, J=7.8 Hz), 7.62 (d, 1H, J=7.8 Hz.)</td>
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<tr>
<td>5-(3-Difluoromethoxy-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C₁₀H₈F₂N₃O</td>
<td>225.20</td>
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<td>87</td>
<td>5.79 (1H, s), 7.02 (1H, d), 7.25 (1H, J=7.4 Hz), 7.36-7.42 (2H, m), 7.48-7.50 (1H, d), 11.74 (1H, bs)</td>
<td>2.49 (s, 3H), 7.40 (d, 1H, J=11.4 Hz), 7.44 (d, 1H, J=7.8 Hz), 7.62 (d, 1H, J=7.8 Hz.)</td>
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<tr>
<td>5-(2-Trifluoromethoxy-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C₁₀H₈F₃N₃O</td>
<td>243.19</td>
<td></td>
<td>57</td>
<td>5.86 (1H, s), 7.10 (1H, d), 7.32 (2H, t), 7.41 (1H, d)</td>
<td>2.49 (s, 3H), 7.40 (d, 1H, J=11.4 Hz), 7.44 (d, 1H, J=7.8 Hz), 7.62 (d, 1H, J=7.8 Hz.)</td>
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<tr>
<td>5-(3-Trifluoromethoxy-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C₁₀H₈F₃N₃O</td>
<td>243.19</td>
<td></td>
<td>59</td>
<td>5.96 (1H, s), 7.24-7.30 (3H, m), 7.55 (1H, dd)</td>
<td>2.49 (s, 3H), 7.40 (d, 1H, J=11.4 Hz), 7.44 (d, 1H, J=7.8 Hz), 7.62 (d, 1H, J=7.8 Hz.)</td>
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<td>Compound</td>
<td>Formula</td>
<td>MW</td>
<td>Multiplicity</td>
<td>J</td>
<td>DMSO</td>
<td>CDCl3</td>
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<tr>
<td>5-(4-Trifluoromethoxy-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C_{10}H_{8}F_{3}N_{3}O</td>
<td>243.19</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4.90 (2H, bs), 5.72 (1H, s), 7.32 (2H, d, J = 8), 7.73 (2H, d, J = 8.4), 11.74 (1H, bs)</td>
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<tr>
<td>5-(2,4-Difluoro-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C_{9}H_{7}F_{2}N_{3}</td>
<td>195.17</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4.97 (2H, bs), 5.67 (1H, s), 7.17 (2H, d), 7.82 (1H, bs), 11.74 (1H, bs)</td>
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<tr>
<td>5-(4-Difluoromethoxy-3-fluoro-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C_{10}H_{8}F_{3}N_{3}O</td>
<td>243.19</td>
<td>244</td>
<td>1.56</td>
<td></td>
<td>6.50 (1H, t, J = 73.2), 7.20-7.27 (2H, m), 7.30 (1H, dd, J = 11.2, J = 2.0)</td>
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<tr>
<td>5-(4-Difluoromethoxy-2,6-difluoro-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C_{10}H_{7}F_{2}N_{3}O</td>
<td>261.18</td>
<td>262</td>
<td>92%</td>
<td>1.56</td>
<td>5.61 (2H, d, J = 8), 7.35 (1H, t, J = 73.2), 11.76 (1H, bs)</td>
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<td>5-(3,5-Dichloro-4-difluoromethoxy-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C_{10}H_{7}Cl_{2}F_{2}N_{3}O</td>
<td>294.09</td>
<td>294</td>
<td>1.99</td>
<td></td>
<td>6.53 (1H, t, J = 60.0), 7.54 (2H, s)</td>
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<tr>
<td>5-(3-Chloro-4-difluoromethoxy-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C_{10}H_{7}ClF_{2}N_{3}O</td>
<td>259.64</td>
<td>260</td>
<td>97%</td>
<td>1.69</td>
<td>5</td>
<td></td>
<td></td>
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<tr>
<td>5-(4-Difluoromethoxy-3-methoxy-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C_{11}H_{11}F_{2}N_{3}O_{2}</td>
<td>255.23</td>
<td>256</td>
<td>100%</td>
<td>1.46</td>
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<tr>
<td>5-(4-Difluoromethoxy-2-methyl-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C_{11}H_{11}F_{3}N_{3}O</td>
<td>239.23</td>
<td>240</td>
<td>95%</td>
<td>1.43</td>
<td>5</td>
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</table>

**Note:** Multiplicities and Coupling Constants provided in the DMSO and CDCl3 sections refer to the chemical shifts and fine splitting patterns observed in the NMR spectra for each compound.
<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Formula</th>
<th>pKa</th>
<th>solubility</th>
<th>melting point</th>
<th>MeOD</th>
<th>DMSO-d$_6$</th>
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<tbody>
<tr>
<td>5-(5-Methyl-pyridin-3-yl)-2H-pyrazol-3-ylamine</td>
<td>C$<em>9$H$</em>{10}$N$_4$</td>
<td>174.21</td>
<td>175.21</td>
<td>100</td>
<td>0.23</td>
<td>5</td>
</tr>
<tr>
<td>5-(2-Methyl-quinolin-6-yl)-2H-pyrazol-3-ylamine</td>
<td>C$<em>{13}$H$</em>{12}$N$_4$</td>
<td>224.27</td>
<td>225.27</td>
<td>100</td>
<td>0.23-0.42</td>
<td>5</td>
</tr>
<tr>
<td>5-(6-Methoxy-naphthalen-2-yl)-2H-pyrazol-3-ylamine</td>
<td>C$<em>{14}$H$</em>{13}$N$_3$O</td>
<td>239.28</td>
<td>240.28</td>
<td>88</td>
<td>1.49</td>
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<tr>
<td>5-(2-Methoxy-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C$<em>{10}$H$</em>{11}$N$_3$O</td>
<td>189.22</td>
<td>190</td>
<td>100</td>
<td>1.07</td>
<td>10</td>
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<tr>
<td>5-(4-Trifluoromethyl-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C$_{10}$H$_8$F$_3$N$_3$</td>
<td>227.19</td>
<td>228.19</td>
<td>98</td>
<td>1.64</td>
<td>5</td>
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<tr>
<td>5-Pyridin-4-yl-2H-pyrazol-3-ylamine</td>
<td>C$_9$H$_8$N$_4$</td>
<td>160.18</td>
<td>161.18</td>
<td>100</td>
<td>0.21</td>
<td>5</td>
</tr>
<tr>
<td>5-(2-Fluoro-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C$_9$H$_8$FN$_3$</td>
<td>177.18</td>
<td>178</td>
<td>100</td>
<td>1.06</td>
<td>5</td>
</tr>
<tr>
<td>5-(5-Chloro-2-methyl-phenyl)-2H-pyrazol-3-ylamine</td>
<td>C$<em>{10}$H$</em>{10}$ClN$_3$</td>
<td>207.66</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5-(2-Methyl-3-trifluoromethyl-phenyl)-2H-pyrazol-3-ylamine</td>
<td>33</td>
<td>C₁₁H₁₀F₃N₃</td>
<td>241.22</td>
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<td>-</td>
<td>-</td>
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<td>5-(4-Fluoro-2-methyl-phenyl)-2H-pyrazol-3-ylamine</td>
<td>61</td>
<td>C₁₀H₁₀FN₃</td>
<td>191.21</td>
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<td>66</td>
<td>C₁₁H₁₃N₃</td>
<td>187.25</td>
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<td>-</td>
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<td>5-(4-Chloro-2-methyl-phenyl)-2H-pyrazol-3-ylamine</td>
<td>62</td>
<td>C₁₀H₁₀ClN₃</td>
<td>187.25</td>
<td>-</td>
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<td>5-(4-Fluoro-3-trifluoromethyl-phenyl)-2H-pyrazol-3-ylamine</td>
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<td>226.28</td>
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<td>M.p.</td>
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<td>H</td>
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<td>5-(2-Methyl-quinolin-6-yl)-2H-pyrazol-3-ylamine</td>
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<td>C$<em>{13}$H$</em>{12}$N$_4$</td>
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<td>C$<em>{12}$H$</em>{16}$N$_4$</td>
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<td>41</td>
<td>C$<em>{11}$H$</em>{10}$F$_3$N$_3$</td>
<td>241.22</td>
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<td>5-(2-Methyl-6-trifluoromethyl-pyridin-3-yl)-1H-pyrazol-3-ylamine</td>
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<td>C$<em>{10}$H$</em>{9}$F$_3$N$_4$</td>
<td>242.21</td>
<td>242.9</td>
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<td>228.18</td>
<td>228</td>
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<td>1.37</td>
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General method for the synthesis of ω-bromo-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides

A solution of ω-bromoalkanoyl chloride (15.7 mmol, 1 equiv.) in dry DMA (35 mL) was cooled to -10 °C (ice/water bath) under N₂; a solution of 5-aryl/heteroaryl-1H-pyrazol-3-ylamine (15.7 mmol, 1 equiv.) and diisopropylethylamine (15.7 mmol, 1 equiv.) in dry DMA (15 mL) is added over 30 minutes. After 2 hrs at -10 °C, completion of the reaction as monitored by LC-MS was generally observed (acylation on the pyrazole ring is also detected). The reaction is then quenched by addition of H₂O (ca. 50 mL); the thick white precipitate formed upon addition of water was recovered by filtration. Washing with Et₂O (3 X 10 mL) usually efficiently removed the byproduct of acylation on the pyrazole ring.

General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-S-yl-5-aryl)-amides

ω-Bromo-alkanoic acid [5-aryl-1H-pyrazol-3-yl]-amide (0.6 mmol, 1 equiv.) is dissolved in DMF (4 mL), sodium iodide (0.6 mmol, 1.0 equiv.) is added followed by the secondary amine (1.5 mmol, 2.5 equiv.) and diisopropylethylamine (0.6 mmol, 1 equiv.). The reaction is then stirred under N₂ at + 50 °C for 18 hrs.

Upon reaction completion (as monitored by LC-MS), the solvent is removed at reduced pressure and the resulting oily residue is dissolved in DCM (20 mL), washed with sat. Na₂CO₃ (2 X 20 mL) and sat. NaCl (2 X 20 mL); the organic layer is dried over Na₂SO₄ and the
solvent removed under reduced pressure. The title compounds were purified either by silica column or preparative HPLC.

*General synthetic method for the one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides: acylation-nucleophilic substitution*

![Chemical diagram]

[0254] To a solution of ω-bromoalkanoyl chloride (0.94 mmol, 1 equiv.) in DMA (1 mL) cooled at 0 °C is added a solution of 3-amino-5-aryl/heteroarylpyrazole (0.94 mmol, 1 equiv.) and diisopropylethylamine (1.88 mmol, 2 equiv.) in DMA (2 mL) and the reaction is stirred for 1 hour at 0 °C. The secondary amine (2.35 mmol, 2.5 equiv.) and NaI (0.94 mmol, 1 equiv.) are then added. For 3-carbon chain derivatives the reaction was generally complete after 2 hours at room temperature. For 4-carbon chain derivatives the reaction mixture was generally heated at 60 °C for 24-48 hours. Upon complete conversion of the bromo-intermediate (as monitored by LC-MS), the solvent was removed under reduced pressure. The residue was taken up in DCM (2 mL) and washed with Na₂CO₃ saturated water solution. The organic phase was concentrated under reduced pressure and the crude products were either recrystallised from CH₃CN, or purified by SiO₂ column (gradient from 100%DCM to DCM-NH₃MeOH 2 N solution 8:2) or by preparative HPLC (standard acidic conditions).

*General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-S-yl-5-aryl)-amides via the amino acid route*

![Chemical diagram]

[0255] To a solution of amine X (65 mmol) in toluene (15 mL) ethyl ω-bromoalkanoate (26 mmol) was added and the reaction mixture was refluxed for 10 hours. The mixture was
allowed to cool to room temperature and any solid present was filtered off and washed with ether. The filtrate was concentrated under reduced pressure to give the ω-aminoester which was used in the next step without further purification.

**General method for the synthesis of ω-amino acid (route C2)**

To a suspension of crude ethyl ω-aminoalkanoate from the previous step (about 25 mmol) in 15 mL of water, NaOH (1.4 g, 25 mmol) was added and the mixture was heated at reflux for 16 hours. The reaction was then allowed to cool down to room temperature, the solution was acidified at 0 °C with HCl 6 N and concentrated under reduced pressure. The residue was treated with EtOH and the sodium chloride which precipitated was filtered off. Evaporation of the solvent under reduced pressure afforded the ω-amino acid as a white solid or as a colourless oil

4-(2-Methyl-piperidin-1-yl)-butyric acid

*a)* 4-(2-Methyl-piperidin-1-yl)-butyric acid ethyl ester

The title product was prepared according to the general procedure for ω-aminoester synthesis (route C1). After filtration of the excess 2-methylpiperidine, the organic phase was concentrated under reduced pressure to give the 4.6 g of the aminoester (yield 99%) which was used in the next step without further purification.

\[
C_{12}H_{23}NO_2
\]

\[\text{H-NMR (dms-o-de): 0.94 (3H, d, J=6.0 Hz); 1.1-1.19 (4H, m); 1.31-1.40 (1H, m); 1.46-1.62 (5H, m); 1.97-2.02 (1H, m); 2.12-2.28 (5H, m); 2.52-2.59 (1H, m); 2.68-2.73 (1H, m); 4.02 (2H, q, J=7.2 Hz).}\]

\[b) 4-(2-Methyl-piperidin-1-yl)-butyric acid\]

The product was prepared according to the general procedure for ω-amino acid synthesis (route C2). Evaporation of water under reduced pressure afforded 4.1 g of the title compound (99% Yield).

\[
C_{10}H_{19}NO_2
\]
**4-(2-Methyl-pyrrolidin-1-yl)-butyric acid**

*a) 4-(2-Methyl-pyrrolidin-1-yl)-butyric acid ethyl ester*

The product was prepared according to the general procedure for ω-aminoester synthesis (route C1). After filtration of the excess 2-methylpyrrolidine, the organic phase was concentrated under reduced pressure to give 4.1 g of the aminoester as an oil (yield 99%) which was used in the next step without further purification.

C₉H₂₁NO₂

H-NMR (CDCl₃): 1.09-1.1 (3H, m); 1.23 (3H, t, J=6.8 Hz); 1.41-1.48 (2H, m); 1.63-1.95 (6H, m); 2.10-2.14 (2H, m); 2.78-2.81 (1H, m); 3.17-3.21 (2H, m); 4.10 (2H, q, J=7.2 Hz)

*b) 4-(2-Methyl-pyrrolidin-1-yl)-butyric acid*

The product was prepared according to the general procedure for ω-amino acid synthesis (route C2). Evaporation of water under reduced pressure and crystallization from acetone afforded 1.4 g of the title compound (49% Yield).

C₉H₁₇NO₂

H-NMR (dmsode): 1.31 (3H, d, J=6.4 Hz); 1.51-1.60 (1H, m); 1.81-1.91 (4H, m); 2.03-2.17 (1H, m); 2.24-2.37 (2H, m); 2.82-2.95 (1H, m); 2.97-3.02 (1H, m); 3.19-3.32 (2H, m); 3.49-3.57 (1H, m); 10.06 (1H, br s).

**4-(S)-2-Methyl-piperidin-1-yl)-butyric acid**

*a) 4-(S)-2-Methyl-piperidin-1-yl)-butyric acid ethyl ester*

The product was prepared according to the general procedure for ω-aminoester synthesis (route C1). After filtration of the excess (S)-2-methylpiperidine, the organic phase was concentrated under reduced pressure to give the 2.4 g of the aminoester (yield 92%) which was used in the next step without further purification.
C$_{12}$H$_{23}$NO$_2$

$^1$H-NMR (CDCl$_3$): 0.93 (3H, d, J=6.0 Hz); 1.10-1.21 (5H, m); 1.31-1.39 (1H, m); 1.44-1.64 (5H, m); 1.97-2.03 (1H, m); 2.11-2.25 (4H, m); 2.53-2.59 (1H, m); 2.68-2.72 (1H, m); 4.01 (2H, q, J=6.8 Hz).

b) 4((S)-2-Methyl-piperidin-1-yl)-butyric acid

[0262] The product was prepared according to the general procedure for ω-amino acid synthesis (route C2). Evaporation of water under reduced pressure afforded 1.9 g of the title compound (85% Yield).

C$_{10}$H$_{19}$NO$_2$

$^1$H-NMR (dmso-de): 1.22 (3H, d, J=6.4 Hz); 1.40-1.43 (1H, m); 1.50-1.70 (4H, m); 1.76-1.83 (3H, m); 2.26-2.33 (2H, m); 2.80-2.89 (2H, m); 2.95-3.00 (1H, m); 3.1-3.19 (2H, m).

4-((R)-2-Methyl-pyrrolidin-1-yl)-butyric acid

a) 4-((R)-2-Methyl-pyrrolidin-1-yl)-butyric acid ethyl ester

[0263] (R)-2-methyl-pyrrolidine hydrochloride (1.0 g, 8.2 mmol, 1.1 equiv.) was dissolved in 2-butanone (25 mL) and potassium carbonate (2.2 g, 15.7 mmol, 2.1 equiv.) was added. Ethyl 4-bromobutyrate (1.07 mL, 7.5 mmol, 1.0 equiv.) was added and the reaction mixture was refluxed for 2 days. The mixture was allowed to cool to room temperature and solid was filtered off and washed with ether. The filtrate was concentrated under reduced pressure to give 1.5 g of the title compound (yield 99%) which was used in the next step without further purification.

C$_n$H$_{21}$NO$_2$

$^1$H-NMR (dmso-de): 0.95 (3H, d, J=6.0 Hz); 1.15 (3H, t, J=7.2 Hz); 1.20-1.27 (1H, m); 1.56-1.64 (4H, m); 1.77-1.86 (1H, m); 1.91-1.99 (2H, m); 2.15-2.22 (1H, m); 2.25-2.30 (2H, m); 2.62-2.69 (1H, m); 2.97-3.01 (1H, m); 4.01 (2H, q, J=7.2 Hz).
b) 4-((R)-2-Methyl-pyrrolidin-1-yl)-butyric acid

The product was prepared according to the general procedure for ω-amino acid synthesis (route C2). Evaporation of water under reduced pressure afforded 1.4 g of the title compound (88% Yield) as its hydrochloride salt.

C₉H₁₃NO₂

¹H-NMR (dms-de of HCl salt): 1.34 (3H, d, J=6.4 Hz); 1.56-1.61 (1H, m); 1.83-1.92 (3H, m); 2.1-2.14 (1H, m); 2.31-2.39 (2H, m); 2.81-2.90 (1H, m); 2.95-3.04 (1H, m); 3.19-3.44 (3H, m); 3.51-3.58 (1H, m); 10.20 (1H, br s); 12.29 (1H, br s).

2-Methyl-4-(pyrrolidin-1-yl)-2-butyric acid

a) 4-Bromo-2-methyl-butyryl bromide

2-methylbutyro lactone (50 mmol, 5.0 g) and phosphorous tribromide (41 mmol, 3.7 mL) were heated at 140 °C for 2.5 hours. The reaction mixture was transferred into a Kugelrohr distillation apparatus and distilled under reduced pressure (40 mmHg, T=128 °C) to obtain 6.21 g (yield: 51%) of 4-bromo-2-methyl-butyryl bromide as a clear oil.

C₅H₈Br₂O

¹H-NMR (CDCl₃): 3.45 (2 H, t, J=6.8 Hz); 3.22-3.18 (1 H, m); 2.42-2.36 (1 H, m); 1.99-1.94 (1 H, m); 1.32 (3 H, d, J=7.2 Hz).

b) 4-Bromo-2-methyl-butyric acid methyl ester

A solution of 4-bromo-2-methyl-butyryl bromide (6.2 g, 43.0 mmol, 1.0 equiv.) in CHCl₃ (10 mL) was cooled at 0 °C. MeOH (10 mL) was slowly added and the resulting mixture stirred at room temperature for 16 hours. The solvent was evaporated and the residue dissolved in CHCl₃ and washed with water and brine. The organic layer was collected and dried with Na₂SO₄. Evaporation of the solvent gave 4-bromo-2-methyl-butyric acid methyl ester as thick oil (4.3 g, yield 51%).

C₆H₁₁BrO₂

¹H-NMR (DMSO-de): 1.19 (3H, d, J=7.2 Hz); 1.94-1.89 (2H, m); 2.29-2.23 (2H, m); 3.43-3.40 (1H, m); 3.69 (3H, s).
c) 2-Methyl-4-(pyrrolidin-1-yl)-2-butyric acid

[0267] Pyrrolidine (5.4 mL, 66 mmol) was dissolved in toluene (40 mL). 4-Bromo-2-methyl-butyric acid methyl ester (4.3 g, 22.0 mmol) was added and the reaction stirred at reflux for 2.5 hours. Removal of the solvent and of the excess amine at reduced pressure gave 2-methyl-4-(pyrrolidin-1-yl)-butyric acid methyl ester as a thick oil. The crude product was diluted with MeOH (3 mL) and 1.0 M NaOH aq solution (22 mL) was added and the reaction stirred at reflux for 18 hours.

[0268] After cooling to room temperature, the mixture was concentrated at reduced pressure to remove the organic solvent and the water. HCl 6 N was added to reach pH 4.5; subsequently EtOH was added to precipitate NaCl. After filtration the solvent was evaporated at reduced pressure (keeping the water bath at room temperature to avoid esterification) to give 4-pyrrolidin-2-methyl-butyric acid as yellow oil (3.58 g, yield 90%).

C₈H₁₇NO₂
Mass (calculated) [199]; (found) [M+H]+= 200.
LC Rt= 1.12 min; 90% (5 min method):
¹H-NMR (DMSO^δ): 2.79 (4H, m); 2.73 (2H, m); 2.37 (1H, m); 1.84 (2H, m); 1.81-1.75 (3H, br m); 1.57 (1H, m); 1.5 (3H, d, J=7.2 Hz)

2-Methyl-4-piperidin-1-yl-butyric acid

[0269] Piperidine (1.1 mL, 20.0 mmol, 3.0 equiv.) was dissolved in toluene (15 mL). 4-Bromo-2-methyl-butyric acid methyl ester (1.3 g, 6.6 mmol, 1.0 equiv.) was added and the reaction stirred at reflux for 3 hours. Removal of the solvent and of the excess amine at reduced pressure gave 4-pyrrolidin-2-methyl-butyric acid methyl ester as a thick oil. The crude product was diluted with MeOH (2 mL) and 1.0M NaOH aq solution (14 mL, 7.0 equiv.) was added and the reaction stirred at reflux for 16 hours. After cooling to room temperature, the mixture was concentrated at reduced pressure to remove the organic solvent and the water. HCl 6 N was added to reach pH 4.5; subsequently EtOH was added to precipitate NaCl. After filtration the solvent was evaporated at reduced pressure (bath at room temperature to avoid esterification) to give 4-pyrrolidin-2-methyl-butyric acid as yellow oil (0.9 g, yield 66%).
**C₁₀H₁₉NO₂**

Mass (calculated) [171]; (found) [M+H⁺] = 172.

LC Rt= 0.22 min; 90% (5 min method).

¹H-NMR (CDCl₃): 3.66 (m, 1H); 3.59 (m, 1H); 3.53 (m, 2H); 3.45 (m, 2H); 2.93 (m, 1H); 1.62-1.51 (br m, 8H); 1.10 (d, 3H, J = 7.2)

**5-[1,4]-Oxazepan-4-yl-butyric acid**

[0270] Homomorpholine (1.0 g, 7.3 mmol, 1.2 equiv.) was dissolved in toluene (15 mL) and 4-bromo-2-methyl-butyric acid methyl ester (0.9 g, 6.1 mmol, 1.0 equiv.) was added and the reaction stirred at reflux for 3 hours. Removal of the solvent and of the excess amine at reduced pressure gave the methyl ester as an oil. The crude product was diluted with H₂O (10 mL) and MeOH (2 mL) and 1.0M NaOH aq solution (0.3 g, 7.0 equiv.) was added and the reaction stirred at reflux for 18 hours. After cooling to room temperature, the mixture was concentrated at reduced pressure to remove the organic solvent and the water. HCl 6 N was added to reach pH 4; subsequently EtOH was added to precipitate NaCl. After filtration the solvent was evaporated at reduced pressure at room temperature to give 4-pyrrolidin-2-methyl-butyric acid as yellow oil (0.9 g, yield 66%).

C₉H₁₃NO₃

¹H-NMR (DMSO-de): 3.73 (m, 2H); 3.68 (m, 2H); 3.16-3.11 (m, 2H); 2.93 (m, 2H); 2.28 (m, 2H); 2.23 (m, 2H); 1.96 (m, 2H); 1.79 (m, 2H).

**4-Pyrrolidin-1-yl-butyric acid**

a) **4-Pyrrolidin-1-yl-butyric acid ethyl ester**

[0271] To a solution of pyrrolidine (8.42 mL, 102 mmol, 4.0 equiv.) in toluene (30 mL), ethyl 4-bromobutyrate (3.8 mL, 26 mmol, 1.0 equiv.) was added and the reaction mixture was refluxed for 10 hours. The mixture was allowed to cool down to room temperature, the white solid present was filtered off and washed with Et₂O. The filtrate was concentrated under reduced pressure to give the title product which was used in the next step without further purification.
b) 4-Pyrrolidin-1-yl-butyric acid hydrochloride

[0272] 4-Pyrrolidin-1-yl-butyric acid ethyl ester (about 25 mmol) was suspended in 100 mL of NaOH 10% and the mixture was heated at reflux for 10 hours. The reaction mixture was then allowed to cool to room temperature and was washed with AcOEt. The aqueous layer was recovered by extraction and acidified at 0 °C with HCl 37% to pH 4 and concentrated under reduced pressure. The residue was treated with EtOH and the sodium chloride which precipitated was filtered off. The crude was treated with Et₂O and filtered; evaporation of the solvent under reduced pressure afforded 2.5 g of the title compound as a white solid in 61% overall yield of steps a) and b).

C₈H₁₅NO₂
Mass (calculated) [157]; (found) [M+H⁺] = 158.

LC Rt = 0.21 min, 100% (5 min method)

¹H-NMR (dmso-d6 for HCl salt): 1.80-1.93 (6H, m); 2.31 (2H, t, J = 14.8); 3.03-3.11 (2H, m); 3.18-3.32 (4H, m, broad)

4-Morpholin-4-yl-butyric acid

a) 4-Morpholin-4-yl-butyric acid ethyl ester

[0273] To a solution of morpholine (8.96 mL, 102 mmol, 4.0 equiv.) in toluene (30 mL) ethyl 4-bromobutyrate (3.8 mL, 26 mmol, 1.0 equiv.) was added and the reaction mixture was refluxed for 10 hours. The mixture was allowed to cool to room temperature; the white solid present was filtered off and washed with Et₂O. The filtrate was concentrated under reduced pressure to give the title product which was used in the next step without further purification.

b) 4-Morpholin-4-yl-butyric acid

[0274] 4-Morpholin-4-yl-butyric acid ethyl ester (about 25 mmol) was suspended in 100 mL of NaOH 10%, and the mixture was heated at reflux for 10 hours. The reaction mixture was then allowed to cool down to room temperature and washed with AcOEt. The aqueous layer was recovered by extraction and acidified at 0 °C with HCl 37% to pH 4 and concentrated under reduced pressure. The residue was treated with EtOH and the sodium chloride which precipitated was filtered off. The crude was treated with acetone and filtered; evaporation of the solvent
under reduced pressure afforded 3.2 g of the title compound as a white solid in 72% overall yield of steps a) and b).

\[ \text{C}_8\text{H}_{15}\text{NO}_3 \]

Mass (calculated) [173]; (found) \([\text{M}+\text{H}^+] = 174\).

LC Rt = 0.30 min, 100% (5 min method)

\( ^1\text{H}-\text{NMR} \) (DMSO-d6 of HCl salt): 1.86-1.95 (2H, m); 2.29-2.34 (2H, m); 2.94-3.08 (4H, m); 3.34-3.38 (2H, m); 3.74-3.83 (2H, m); 3.88-3.91 (2H, m); 11.24 (1H, s)

**General method for amide coupling**

[0275] To a suspension of \( \omega \)-amino acid (7.93 mmol) in 12,2-dichloroethane (20 mL), 7V,7V'-carbonyldiimidazole (1.2 g, 7.4 mmol) was added and the mixture was stirred at room temperature for 2 hours (when all the amino acid was activated complete dissolution of the suspension was generally observed). The 3-amino-5-aryl/heteroarylpyrazole (5.29 mmol) was then added and the reaction was stirred for further 10 hours. Upon reaction completion (as monitored by LC-MS) if the formation of two isomers was observed, the mixture was heated at 50 °C until the conversion of the less stable isomer to the title compound was observed (as monitored by LC-MS). The solvent was washed with sat. Na2CO3 solution, extracted and removed under reduced pressure. The crude products were either recrystallised from CH3CN, or purified by SiO2 column or by preparative HPLC.

**4-(4-Trifluoromethoxy-phenyl)-lH-imidazol-2-ylamine**
a) N-[4-(4-Trifluoromethoxy-phenyl)-lH-imidazol-2-yl]-acetamide

[0276] Acetyl guanidine (2.6 g, 25.7 mmol, 3.0 equiv.) was dissolved in anhydrous DMF (40 mL) and 2-bromo-1-(4-trifluoromethoxy-phenyl)-ethanone (2.4 g, 8.6 mmol, 1.0 equiv.) was added; the mixture was stirred at room temperature for 4 days. DMF was removed under reduced pressure, the residue was washed with water, filtered and dried over sodium sulphate; after crystallization from MeOH 0.7 g of the title compound were recovered (yield 30%).

\[ \text{C}_{12}\text{H}_{10}\text{F}_3\text{N}_3\text{O}_2 \]

\( ^1\text{H}-\text{NMR} \) (DMSO-de): 2.14 (3H, s); 7.37-7.40 (3H, m); 7.88-7.91 (2H, m); 11.33 (1H, s); 11.78 (1H, br s).
b) 4-(4-Trifluoromethoxy-phenyl)-1H-imidazol-2-ylamine

N-[4-(4-Trifluoromethoxy-phenyl)-1H-imidazol-2-yl]-acetamide (0.7 g, 2.6 mmol, 1.0 equiv.) was dissolved in water (18 mL) and methanol (18 mL), and 20 drops of sulfuric acid were added. The reaction was refluxed for 2 days, then the mixture was dried; the residue was diluted with water, the pH adjusted to 8 with NaOH 2 N, the product was extracted with DCM and concentrated under reduced pressure to give 0.6 g of the title compound (yield 98%)

C_{10}H_{8}F_{3}N_{3}O

$^1$H-NMR (DMSO-de): 5.73 (2H, br s); 7.10 (1H, s); 7.26 (2H, d, J=8.0 Hz); 7.67-7.69 (2H, m).

S-Methyl-4-pyrrolidin-1-yl-butyric acid hydrochloride

a) (E)-S-methyl-4-pyrrolidin-1-yl-but-2-enoic acid ethyl ester

Ethyl 3-methyl-4-oxocrotonate (9.6 mL, 70.4 mmol, 1.0 equiv.) was dissolved in 400 mL of THF and cooled at 0 ºC. Pyrrolidine (5.5 mL, 66.9 mmol, 0.95 equiv.) was added dropwise at 0 ºC followed by a drop of acetic acid. The reaction mixture was allowed to warm at room temperature and stirred for 1 hour. Sodium triacetoxyborohydride (14.2 g, 66.9 mmol, 1.0 equiv.) was added and the mixture was stirred at room temperature overnight. The reaction mixture was cooled at 0 ºC and quenched with 80 mL of 1 N HCl. THF was evaporated in vacuo and the aqueous phase was washed with ethylacetate (2 x 50 mL). The aqueous phase was treated with potassium carbonate to pH 8 and extracted with EtOAc (3 x 50 mL). The organic phases were collected and evaporated in vacuo to obtain (E)-3-methyl-4-pyrrolidin-1-yl-but-2-enoic acid ethyl ester as pale yellow oil (10.58 g, 78%).

C_{11}H_{19}NO_2 Mass (calculated) [197]; (found) [M+H$^+$] = 198

LC Rt = 0.5 1 min, (3 min method)

$^1$H-NMR (400 MHz, d$_2$-chloroform, $\delta$): 1.26 (t, J = 7 Hz, 3H); 1.76 (m, 4H); 2.15 (s, 3H); 2.47 (m, 4H); 3.06 (s, 2H); 4.14 (q, J = 7 Hz, 2H); 5.87 (s, 1H).
b) S-Methyl-4-pyrrolin-1-yl-butyric acid ethyl ester

[0279] (E)-3-Methyl-4-pyrrolidin-1-yl-but-2-enoic acid ethyl ester (10.1 g, 51.3 mmol, 1.0 equiv.) was dissolved in 300 mL of MeOH and hydrogenated using H-cube (Catcart® Cartridge 10% Pd/C, 10 bar H₂, 45 °C, flow 0.8 mL/min). The organic phase was evaporated in vacuo to obtain 3-methyl-4-pyrrolidin-1-yl-butyric acid ethyl ester as pale yellow oil (9.0 g, 88%).

C₁₁H₂₁NO₂ Mass (calculated) [199]; (found) [M+H⁺] = 200

LC Rt = 0.32 min, (5 min method)

¹H-NMR (400 MHz, d-chloroform, δ): 0.95 (d, J = 6.4 Hz, 3H); 1.25 (t, J = 7.2, 3H); 1.73 (m, 4H); 2.02-2.35 (m, 4H); 2.37-2.55 (m, 5H); 4.11 (q, J = 7.2 Hz, 2H).

c) S-Methyl-4-pyrrolin-1-yl-butyric acid hydrochloride

[0280] Methyl-4-pyrrolidin-1-yl-butyric acid ethyl ester (9.0 g, 45.2 mmol, 1.0 equiv.) was dissolved in 50 mL of 6 N HCl. MeOH (2.5 mL) was added and the reaction mixture was stirred at reflux for 15 hours. The reaction mixture was evaporated in vacuo and the residual water was azeotropically removed with toluene (20 mL). The obtained dark oil was triturated with 50 mL of acetone/diethylether (1:1) to afford 3-methyl-4-pyrrolidin-1-yl-butyric acid hydrochloride as brown solid (7.62 g, 81%).

C₉H₁₇NO₂·HCl Mass (calculated) [171]; (found) [M+H⁺] = 172

LC Rt = 0.27 min, (3 min method)

¹H-NMR (400 MHz, d-DMSO, δ): 1.01 (d, J = 6.5 Hz, 3H); 1.92 (m, 4H); 2.1-2.27 (m, 2H); 2.55 (m, 1H); 2.85-3.13 (m, 4 H); 3.5 (m, 2H); 10.5 (brs, 1H); 12.3 (brs, 1H).
4-Pyrrolidin-l-yl-butyric acid hydrochloride

a) 4-Pyrrolidin-l-yl-butyric acid ethyl ester

In a four-neck round bottom flask (1 L) ethyl 4-bromobutyrate (30 mL, 212 mmol, 1 equiv.) was added dropwise to a solution of pyrrolidine (70 mL, 847 mmol, 4 equiv.) in toluene (310 mL). The reaction mixture then was refluxed for two hours with stirring. After cooling at room temperature, 200 mL of water were added and the mixture was extracted with EtOAc (3 x 200 mL). The collected organic fractions were dried over sodium sulphate filtered and evaporated under reduced pressure to give 4-pyrrolidin-1-yl-butyric acid ethyl ester as pale yellow oil. The product was used in the next step with no further purification.

Yield: 99%, 40.0 g

^1H-NMR (400 MHz, CDCl₃, δ): 1.21(m, 3H); 1.73(m, 4H); 1.80(m, 2H); 2.31 (m, 2H); 2.45 (m, 6H); 4.08(m, 2H).

b) 4-Pyrrolidin-l-yl-butyric acid hydrochloride

A mixture of methyl-4-(pyrrolidin-1-yl)butanoate (39 g, 0.22 mol) and 6 N HCl (200 mL) were refluxed for three hours under stirring in a one-neck round bottom flask (500 mL). The reaction mixture was cooled at room temperature and the solvent was evaporated. The residual water was azeotropically removed with toluene to give 4-pyrrolidin-1-yl-butyric acid hydrochloride as a off-white solid.

Yield: 65%, 28 g

^1H-NMR (400 MHz, DMSO, δ): 1.90 (m, 6H); 2.34 (m, 2H); 2.94 (m, 2H); 3.08 (m, 2H); 3.48 (m, 2H); 11.0 (s, 1H).

3-Methyl-4-piperidin-l-yl-butyric acid hydrochloride

![Chemical structure]
a) **(E/Z)-S-methyl-4-piperidin-l-yl-but-2-enoic acid ethyl ester**

Ethyl 3-methyl-4-oxocrotonate (100 mL, 0.73 mol, 1.0 equiv.) was dissolved in 1.2 L of THF and cooled at 0 °C. Piperidine (69 mL, 0.70 mmol, 0.95 equiv.) was added dropwise at 0 °C followed by a drop of acetic acid. The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. Sodium triacetoxyborohydride (156 g, 0.73 mol, 1.0 equiv.) was added portionwise and the mixture was stirred at room temperature overnight. The reaction mixture was cooled at 0 °C and quenched with 50 mL of H₂O and 200 mL of 6 N HCl. THF was evaporated in vacuo and the aqueous phase cooled at 0 °C and basified with potassium carbonate to pH 8. The aqueous phase was extracted with EtOAc (3 x 500 mL). The organic phases were collected and evaporated in vacuo to obtain (is/Z)-3-methyl-4-piperidin-1-yl-but-2-enoic acid ethyl ester as pale yellow oil (120 g, 77.5%).

C₁₂H₂INO₂ Mass (calculated) [211]: (found) [M+H⁺]= 212

LC Rt = 0.70 min, (5 min method)

¹H-NMR (400 MHz, d-chloroform, δ): 1.25 (t, J = 7.0 Hz, 3H); 1.35-1.43 (m, 2H); 1.50-1.58 (m, 4H); 2.10-2.12 (m, 3H); 2.21-2.36 (m, 4H); 2.85-2.87 (m, 2H); 4.13 (q, J = 7.0 Hz, 2H); 5.84-5.87 (m, 1H).

b) **S-Methyl-4-piperidin-l-yl-butyric acid ethyl ester**

A mixture of (is/Z)-3-Methyl-4-piperidin-1-yl-but-2-enoic acid ethyl esters (5 g, 23.7 mmol, 1.0 equiv.) was dissolved in 100 mL of ethanol; ammonium formate (7.3 g, 118.5 mmol, 5.0 equiv.) was added followed by Palladium on activated charcoal 10% (1 g, 0.97 mmol, 0.04 equiv.). The reaction mixture was stirred at reflux for 1 hour then filtered on a cellulose pad to remove the catalyst. The organic phase was evaporated in vacuo, redissolved in 100 mL of ethyl acetate and washed with NaHCO₃ saturated solution (30 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL) and the organic phases were collected together, dried and evaporated in vacuo to obtain 3-methyl-4-piperidin-1-yl-butyric acid ethyl ester as yellow oil (3.6 g, 71.3%).
1H-NMR (400 MHz, d-chloroform, δ): 0.90 (d, J = 6.7 Hz, 3H); 1.24 (t, J = 7.10, 3H); 1.32-1.41 (m, 2H); 1.45-1.54 (m, 4H); 1.96-2.07 (m, 3H); 2.12-2.29 (m, 3H); 2.29-2.39 (m, 2H); 2.40-2.47 (m, 1H); 4.10 (q, J = 7.10 Hz, 2H).

3-Methyl-4-piperidin-1-yl-butyric acid hydrochloride

Methyl-4-piperidin-1-yl-butyric acid ethyl ester (8.4 g, 39.43 mmol) was dissolved in HCl 6 N (120 mL) and the resulting solution stirred at reflux overnight. The reaction mixture was evaporated in vacuo and the residual water was azeotropically removed with toluene (20 mL). The obtained dark oil was triturated with acetone (100 mL) and filtered to afford 3-methyl-4-piperidin-1-yl-butyric acid hydrochloride as a white solid (3.8 g, 43.6%).

C10H19NO2 HCl Mass (calculated) [185]: (found) [M+H+] = 186

LC Rt = 0.32 min, (5 min method)

1H-NMR (400 MHz, ^DMSO, δ): 1.00 (d, J = 6.7 Hz, 3H); 1.59-1.93 (m, 6H); 2.10-2.19 (m, 1H); 2.30 (m, 1H); 2.49-2.57 (m, 1H); 2.74-2.92 (m, 3H); 2.92-3.02 (m, 1H); 3.36 (m, 2H); 9.85 (brs, 1H); 12.37 (brs, 1H).

2-Methyl-4-(pyrrolidin-1-yl)butanoic acid hydrochloride

a) Methyl 2-methyl-4-(pyrrolidin-1-yl)butanoate

In a four-neck round bottom flask (500 mL) a mixture of 4-chloro-2-methylbutyric acid methyl ester (12.0 mL, 86.3 mmol, 1.0 equiv.), pyrrolidine (28.5 mL, 345.2 mmol, 4.0 equiv.) and toluene (120 mL) was refluxed under stirring overnight. The reaction mixture was cooled at room temperature, filtered, diluted with EtOAc (100 mL) and washed with water (4 x 100 mL). The organic layer was dried over MgSO4, filtered and evaporated under reduced pressure to give crude methyl 2-methyl-4-(pyrrolidin-1-yl)butanoate as a pale yellow oil (13.1 g, 82%). The product was used in the next step without further purification.

TLC: (EtOAc:MeOH=9:1 + 1% of 30% aq. NH4OH) Rf = 0.35 (ninhydrin).
FTIR (Cm⁻¹): 2958, 2787, 1737, 1459, 1152.

b) 2-Methyl-4-(pyrrolidin-1-yl)butanoic acid hydrochloride

[0287] Into a one-neck round bottom flask (250 mL) a mixture of methyl 2-methyl-4-(pyrrolidin-1-yl)butanoate (13.1 g, 70.7 mmol, 1.0 equiv.) and NaOH 15% (140 mL, 516 mmol, 7.0 equiv.) was refluxed for three hour under stirring. The reaction mixture was cooled at room temperature and washed with EtOAc (3 x 100 mL). The aqueous layer was cooled at 0 °C, acidified to pH 1 with 37% aqueous HCl (50 mL) and concentrated to give a pale yellow solid. This solid was suspended in MeOH (200 mL) and filtered off. The filtrate was evaporated under reduced pressure to afford a solid that was triturated with diethylether (100 mL) and filtered to give 2-methyl-4-(pyrrolidin-1-yl)butanoic acid hydrochloride as an off white solid (12.3 g, 84%).

FTIR (Cm⁻¹): 2981, 2712, 2625, 2500, 1730, 1458, 1402, 1202, 1165, 856, 823, 622.

³H-NMR (400 MHz, d-chloroform, δ): 1.19 (s, 3H); 1.82 (m, 1H); 2.04 (m, 5H); 2.47 (m, 1H); 3.10 (m, 2H); 3.24 (m, 4H); 11.20 (brs, 1H).

2-Methyl-4-(piperidin-1-yl)butanoic acid hydrochloride

a) Methyl 2-methyl-4-(piperidin-1-yl)butanoate

[0288] In a four necked round bottom flask (500 mL) a mixture of 4-chloro-2-methylbutyric acid methyl ester (12.0 mL, 86.3 mmol, 1.0 equiv.), piperidine (34.1 mL, 345.2 mmol, 4.0 equiv.) and toluene (130 mL) was refluxed under stirring overnight. The reaction mixture was cooled at room temperature, filtered, diluted with EtOAc (100 mL) and washed with water (4 x 100 mL). The organic layer was dried over MgSO₄, filtered and evaporated under reduced pressure to give crude methyl 2-methyl-4-(piperidin-1-yl)butanoate as an orange oil (15.6 g, 90%). The product was used in the next step without further purification.

TLC: (EtOAc/MeOH 9:1 + 1% of 30% aq. NH₄OH) Rₜ = 0.33 (ninhydrin).

FTIR (Cm⁻¹): 2935, 1738, 1455, 1166.
b) 2-Methyl-4-(piperidin-1-yl)butanoic acid hydrochloride

Into a one-neck round bottom flask (250 mL) a mixture of methyl 2-methyl-4-(piperidin-1-yl)butanoate (15.6 g, 78.3 mmol, 1.0 equiv.) and 15% aqueous NaOH (150 mL, 572 mmol, 7.0 equiv.) was refluxed three hours under stirring. The reaction mixture was cooled at room temperature and washed with EtOAc (3 x 100 mL). The aqueous layer was cooled at 0 °C, acidified with 37% aqueous HCl (90 mL) and concentrated to give a white solid. This solid was suspended into an acetone/H2O mixture (95:5), refluxed under stirring for about one hour and filtered off when the suspension was still hot. The filtrate was evaporated under reduced pressure to giv 2-methyl-4-(piperidin-1-yl)butanoic acid hydrochloride as a white solid (12.2 g, 70%).

FTIR (cm⁻¹): 2945, 1731, 1434, 1183, 1156, 855, 623.

¹H-NMR (400 MHz, d-chloroform, δ): 1.24 (s, 3H); 1.4 (m, 1H); 1.94 (m, 4H); 2.22 (m, 3H); 2.64 (m, 3H); 3.06 (m, 2H); 3.57 (m, 2H); 11.9 (brs, 1H).

Example 1
5-Azepan-1-yl-pentanoic acid [5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-amide

[0290] 5-(4-Methoxy-phenyl)-1H-pyrazol-3-yl-amine (0.089 g, 0.45 mmol) is dissolved in DCE:DMF 4:1 (2.5 mL) and 5-bromovaleryl chloride (0.057 mL, 0.43 mmol) is added followed by disopropylethylamine (0.078 mL, 0.45 mmol). The reaction is stirred under N₂ at 0 °C for 1 hr. Azepane (0.152 mL, 1.35 mmol) is then added together with more disopropylethylamine (0.078 mL, 0.45 mmol). The reaction is stirred at +50 °C for 18 hrs. Upon reaction completion (as monitored by LC-MS), the solvent is removed under reduced pressure and the resulting oily residue is dissolved in DCM (20 mL), washed with sat. Na₂CO₃ (2 X 20 mL) and sat. NaCl (2 X 20 mL); the organic layer is dried over Na₂SO₄.

[0291] Purification by preparative HPLC (standard acidic conditions) gives 0.046 g of the title compound as formate salt (0.11 mmol, 25% yield)

C₂H₃N₄O₂ Mass (calculated) [370.50]; (found) [M+H⁺]=371
LC τ=1.97, 96% (10 min method)

NMR (400 MHz, DMSO-d₆): 1.79-1.71 (6H, m); 1.89 (6H, m); 3.17 (2H, t); 3.34 (2H, m); 3.82 (3H, s); 6.7 (1H, s); 6.98 (2H, d); 7.58 (2H, d); 8.26 (1H, HCOOH, s); 10.21 (1H, s).
**Example 2**

5-(4-Methyl-piperidin-l-yl)-pentanoic acid [5-(4-methoxy-phenyl)-1H-pyrazol-5-yl] amide

5-Bromo-pentanoic acid [5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]amide (0.106 g, 0.6 mmol) is dissolved in DMF (2 mL), sodium iodide (0.045g, 0.6 mmol) is added followed by 4-methylpiperidine (0.054 mL, 1.5 mmol) and diisopropylethylamine (0.052 mL, 0.6 mmol, 1 equiv.). The reaction is stirred under N₂ at + 50 °C for 18 hrs.

Upon reaction completion (as monitored by LC-MS), the solvent is removed at reduced pressure and the resulting oily residue is dissolved in DCM (20 mL), washed with sat. Na₂CO₃ (2 X 20 mL) and sat. NaCl (2 X 20 mL); the organic layer is dried over Na₂SO₄.

Purification by preparative HPLC (standard acidic conditions) gives 0.057 g of the title compound as formate salt (0.14 mmol, 45% yield).

C₂H₃O₂N Mass (calculated) [370.50]; (found) [M+H⁺]=371.26

LC Rt= 1.73, 100% (10 min method)

NMR (400 MHz, DMSO-de): 0.84 (3H, d, J=6.23 Hz); 1.13-1.07 (2H, m); 1.33-1.27 (4H, m); 1.45 (1H, m); 1.50(2H, m); 1.96 (2H, m); 2.26 (2H, m); 2.35 (2H, m); 2.88 (2H, m); 3.14 (3H, s); 6.71 (1H, s); 6.96 (2H, d); 7.6 (2H, d); 8.17 (1H, s, HCOOH); 10.13 (1H, s).

**Example 3**

5-(4-Acetyl-[1,4]diazepam-l-yl)-pentanoic acid (5-thiophen-2-yl-1H-pyrazol-5-yl)-amide

Bromovaleryl chloride (1.62 mL, 12.12 mmol) was dissolved in DMA (50 mL). To this, a solution of 5-thiophen-2-yl-2H-pyrazol-3-ylamine (2 g, 12.12 mmol) and DIEA (2.1 mL, 12.12 mmol) was added portionwise at 0 °C. The reaction mixture was left stirring 1 hour at 0°C and then for 2 hours at room temperature. After a total of 3 hours, PS-Trisamine (1 g, ~4 mmol/g) was added to the mixture and left stirring for 2 hours. Then, N-acetylhomopiperazine (4.3 g, 30.3 mmol) was added and the mixture was left stirring at room temperature for a further 60 hours. After DMA evaporation under reduced pressure, water was added (50 mL) and this was extracted with ethyl acetate (3 x 30 mL). The aqueous layer was basified with solid NaOH and extracted with ethyl acetate at pH=10 and then again at pH=1. All the organic phases were
reunited, dried and evaporated. The residue was purified by silica chromatography eluting with a gradient of ethyl acetate/methanol 9:1 up to ethyl acetate/methanol 8:2, to give the title compound as yellowish oil (800 mg, 17%).

C_{19}H_{27}N_{5}O_{2}S Mass (calculated) 389.52; (found) [M+H]+=390.1

NMR (400 MHz, CDCl₃): 1.52 (2H, m); 1.77 (2H, m); 1.82 (2H, m); 2.13+2.09 (3H, s); 2.44 (2H, m); 2.56 (2H, m); 2.62 (1H, m); 2.76-2.70 (3H, m); 3.51 (2H, m); 3.61 (1H, m); 3.64 (1H, m); 6.48 (1H, s); 6.56 (1H, s); 7.05-7.02 (2H, m); 6.9-7.26 (2H, m); 8.94 (1H, s); 9.53 (1H, s).

[0296] The title compound was converted in its hydrochloride salt by adding a solution of HCl (1.05 mL, 2 N) in diethyl ether to (5-(4-Acetyl-[1,4]diazepan-1-yl)-pentanoic acid (5-thiophen-2-yl-2H-pyrazol-3-yl)-amide (80 Omg, 2.05 mmol) suspended in MeOH (10 mL). The solution was left stirring at room temperature for 1 hour, then evaporated to dryness to yield the title compound as a yellowish powder (750 mg, 86%)

Example 4
5-(4-Acetyl-[1,4]diazepan-1-yl)-pentanoic acid [5-(4-methoxy-phenyl)-2H-pyrazol-5-yl]-amide
a) First approach
   ai) 5-Bromo-pentanoic acid [5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-amide

[0297] A solution of 5-bromovaleryl chloride (2.1 mL, 15.7 mmol, 1 equiv.) in dry DMA (35 mL) was cooled to -10 °C (ice/water bath) under N₂; a solution of 5-(4-methoxy -phenyl)-1H-pyrazol-3-ylamine (3.0 g, 15.7 mmol, 1 equiv.) and diisopropylethylamine (2.74 mL, 15.7 mmol, 1 equiv.) in dry DMA (15 mL) was added over 30 min. After 2 hrs at -10 °C, LC-MS shows completion of the reaction which was quenched by addition of H₂O (ca. 50 mL). The solid which precipitates was filtered and washed with Et₂O, to give 4.68 g of 5-bromo-pentanoic acid [5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-amide as a white powder (13.3 mmol, 85% yield).

mp= 149.5-151.5 °C.

C_{15}H_{18}BrN_{3}O_{2} Mass (calculated) 352.23; (found) [M+H^+]=352.09/354.10

LC Rt=2.07. 95% (5 min method)

NMR (400 MHz, DMSO-d₆): 1.69-1.63 (2H, m); 1.81-1.75 (2H, m); 2.29 (2H, t); 3.52 (2H, t); 3.75 (3H, s); 6.75 (1H, bs); 6.96 (2H, d); 7.6 (2H, d); 10.28 (1H, s); 12.57 (1H, s)
an) 5-(4-Acetyl-[1,4]diazepan-l-yl)-pentanoic acid [5-(4-methoxy-phenyl)-2H-pyrazol-5-ylj-amide

[0298] To 750 mg (1.96 mmol) of 5-bromo-pentanoic acid [5-(4-methoxy-phenyl)-2H-pyrazol-3-yl]-amide in 7 mL of DMA, N-acetyl-diazepine (278 mg, 1.96 mmol) and NaI (240 mg, 1.96 mmol) were added and the reaction heated at 60 °C for 18 hours. Upon complete conversion (as monitored by LC-MS) the mixture was diluted with 20 mL of DCM and washed with water. The organic phase was concentrated under reduced pressure to afford a residue which was purified with SiO₂ column (10 g) eluting with a gradient from DCM to DCM-MeOH 90:10. The title compound (380 mg) was recovered pure (yield 46%).

C₂₂H₃N₅O₂ Mass (calculated) [413]; (found) [M+H⁺]=414
LC Rt = 1.91, 100% (10 min method)
¹H-NMR (400 MHz, DMSO-de): 1.53-1.75 (4H, m), 1.90-2.15 (5H, m), 2.28-2.42 (2H, m), 2.90-3.26 (3H, m), 3.34-3.58 (3H, m), 3.71-3.88 (7H, m)

b) Second approach

hi) 5-(4-Acetyl-[1,4]diazepan-l-yl)-pentanoic acid [5-(4-methoxy-phenyl)-1H-pyrazol-3-ylj-amide (mono hydrochloride salt)

[0299] To a solution of 5-(4-methoxyphenyl)-1H-pyrazol-3-ylamine (12 g, 62.8 mmol) and N,N- diisopropylethylamine (10.96 mL, 62.8 mmol) in dry N,N-dimethylformamide (150 mL) at -10 °C was added a solution of 5-bromovaleryl chloride (8.4 mL, 62.8 mmol) in dry N,N- dimethylformamide (50 mL) slowly (-40 min) and the reaction mixture was allowed to stir at -10 to 0 °C for 8 hrs. Sodium iodide (9.44 g, 62.8 mmol) was added at 0 °C and followed by N-acetylhomopiperazine (8.24 mL, 62.8 mmol) and N,N-diisopropylethylamine (10.96 mL, 62.8 mmol) and the reaction mixture was allowed to stir at 50 °C for 18 hrs. The solvent was removed in vacuo. The residue was dissolved in methylene chloride (500 mL) and saturated aqueous sodium bicarbonate (500 mL) and the mixture was stirred at room temperature for 30 minutes. The organic layer was separated, dried over sodium sulfate, and the solvent was removed in vacuo to provide 25.8 g (99%) of 5-(4-acetyl-1,4-diazepan-1-yl)- N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide as a thick light yellow oil (crude).
Then to a solution of the crude 5-(4-acetyl-1,4-diazepan-1-yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide (as a free base) in methylene chloride (270 mL) at room temperature was added hydrogen chloride (65 mL, 1.0 M in ethyl ether) slowly. The resulting suspension was allowed to stir at room temperature for 1 hour. The solvent was removed in vacuo to afford 33 g as a yellow foam, mono hydrochloride salt. The foam was dissolved in solvents (330 mL, acetonitrile : methanol = 3 : 1) at 60-70 °C and the crystal seed was added. The mixture was slowly cooled down to the room temperature and allowed to stir at room temperature for 15 hours. The resulting precipitate was filtered and dried to give 20.5 g (72%) of the title compound as a white crystal, mono hydrochloride salt. MS [M-H]⁻ m/z 412.3; mp. 132-133 °C.

c) Third approach

ci) 3-(4-methoxyphenyl)-3-oxopropanenitrile

A solution of methyl/?-anisate in acetonitrile was cooled to -10 °C. Lithium bis(trimethylsilyl)amide (1 M in THF) was added dropwise over a minimum of 3 hr. The mixture was held at -10 to 0 °C until reaction completion. The reaction mixture was quenched with water and the pH adjusted to 3-4 with cone HCl. The mixture was stirred for 1 hr. The product was isolated by filtration, washed with water and dried in a vacuum oven. The yield was 73%.

cii) 5-(4-methoxyphenyl)-1H-pyrazol-3-amine

A suspension of 3-(4-methoxyphenyl)-3-oxopropanenitrile in ethanol was heated to 60 °C. Hydrazine hydrate was added dropwise over a minimum of 30 min at 60 °C. The resulting solution was held at 60 °C until reaction completion, generally 15-18 hr. The reaction mixture was quenched with water. Ethanol was removed by distillation to about 5 volumes. The product was isolated by filtration, washed with water and dried in a vacuum oven. The yield was 88-95%.

ciii) 5-bromo-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide

A solution of 5-(4-methoxyphenyl)-1H-pyrazol-3-amine and diisopropylethylamine in 10 volumes of a 9:1 mixture of acetonitrile:DMF was cooled to -10 °C.
5-Bromovaleryl chloride was added dropwise over a minimum of 3 hr at -10 °C. The resulting solution was held at -10 °C until reaction completion, generally 2 hr. The reaction mixture was quenched with water. The product was isolated by filtration, washed with water, TBME and suction dried. The product-wet cake was purified by re-slurring in TBME at 35 °C for a minimum of 2 hr. The yield was 70-80%.

civ) 5-(4-acetyl-1,4-diazepan-1-yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide

[0304] Bromopyrazole is mixed with K2CO3 and KI in 10 volumes of acetone at room temperature and N-acetylhomopiperazine was added over 1 hr. The reaction mixture was stirred until the reaction was complete. The mixture was filtered, removing the inorganics, washed with acetone and distilled to 2 volumes. The freebase was extracted into methyl THF/ EtOH and washed with NaCl and NaHCO3. The solvent was replaced with EtOH, a strength of the solution was determined, and 0.93 equiv. of HCl based on the available freebase was added to a mixture of acetone, ethanol and water. Careful monitoring of the pH yielded crystalline product in a 70% overall yield and the desired form 1.

d) Fourth approach

dii) 5-(4-methoxy-phenyl)-1H-pyrazol-3-ylamine

[0305] The intermediate 5-(4-methoxy-phenyl)-1H-pyrazol-3-ylamine is commercially available from Sigma-Aldrich (USA), but can be made using the following general procedure:

Aryl β-ketonitrile synthesis

[0306] To a solution of an aromatic ester (6.5 mmol) in dry toluene (6 mL), under N2, NaH (50-60% dispersion in mineral oil, 624 mg, 13 mmol) was carefully added. The mixture was heated at 80 °C and then dry CH3CN was added dropwise (1.6 mL, 30.8 mmol). The reaction was heated for 18 h and generally the product precipitated from the reaction mixture as a salt. The reaction was allowed to cool to room temperature and the solid formed was filtered and then dissolved in water. The solution was acidified with 2 N HCl solution, and upon reaching a pH between 2-4, the product precipitated and was filtered. If no precipitation occurred, the product was extracted with DCM. After aqueous workup, the products were generally pure.
enough to be used in the next step without further purification. The isolated yield was generally 40-80%.

**Aryl aminopyrazole synthesis**

[0307] To a solution of β-ketonitrile (7.5 mmol) in absolute EtOH (15 mL), hydrazine monohydrate (0.44 mL, 9.0 mmol) was added and the reaction was heated at reflux for 18 hrs. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in 20 mL of DCM and washed with water. The organic phase was concentrated to give a crude product that was purified by SiO₂ column or by precipitation from Et₂O. For example, the 2-methoxy derivative was purified by SiO₂ chromatography, eluting with a DCM/MeOH gradient (from 100% DCM to 90/10 DCM/MeOH); the 3-methoxy derivative was triturated with Et₂O. Yields were generally 65-90%.

**dii)5-bromo-pentanoic acid [5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]amide**

[0308] A solution of 5-bromovaleryl chloride (2.1 mL, 15.7 mmol) in dry dimethylacetamide (DMA) (35 mL) was cooled to -10 °C (ice water bath) under N₂; a solution of 5-(4-methoxy-phenyl)-1H-pyrazol-3-ylamine (3.0 g, 15.7 mmol) and diisopropylethylamine (2.74 mL, 15.7 mmol) in dry DMA (15 mL) was added over 30 min. After two hours at -10 °C, LCMS shows completion of the reaction (acylation on the pyrazole ring was also detected). The reaction was quenched by addition of H₂O (ca. 50 mL), and the thick white precipitate formed upon addition of water is recovered by filtration. When the reaction was allowed to reach room temperature before quenching, a putative exchange of Br with Cl caused reactivity problems in subsequent steps. Washing with Et₂O (3 x 10 mL) efficiently removed the byproduct (acylation on pyrazole ring). 4.68 g of the title compound was obtained as a white powder (13.3 mmol, 85% yield). Mp = 149.5-151.5 °C.

**diii)5-(4-acetyl-[1,4]diazepan-1-yl)-pentanoic acid [5-(4-methoxy-phenyl)-1H-pyrazol-5-yl]amide**

[0309] 5-bromo-pentanoic acid [5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]amide (1.5 g, 4.26 mmol) was dissolved in DMF (15 mL), and sodium iodide (0.64 g, 4.26 mmol) was added followed by N-acetylhomopiperazine (0.56 mL, 4.26 mmol) and diisopropylethylamine (0.74
mL, 4.26 mmol). The reaction was stirred under N₂ at 50 °C for 18 hrs. Upon reaction completion (as monitored by LCMS), the solvent was removed at reduced pressure and the resulting oily residue was dissolved in DCM (20 mL), washed with sat. Na₂CO₃ (2 x 20 mL) and sat. NaCl (2 x 20 mL), and dried over Na₂SO₄. Upon solvent removal, 1.7 g of crude product as a thick oil were obtained. The product was purified by SiO₂ chromatography (10 g cartridge-flash SI II from 1ST) employing DCM and DCM:MeOH 9:1 to yield 0.92 g of pure product and 0.52 g of less pure product. A second purification of the impure fractions using a 5 g SiO₂ cartridge was performed using the same eluent. Overall, 1.09 g of 5-(4-acetyl-[1,4]diazepan-1-yl)-pentanoic acid [5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-amide were obtained (2.64 mmol, 62% yield) as a thick light yellow oil. MS (ES+): 414.26 (M+H)+.

div) 5-(4-acetyl-[1,4]diazepan-1-yl)-pentanoic acid [5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-amide hydrochloride

[0310] 5-(4-acetyl-[1,4]diazepan-1-yl)-pentanoic acid [5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-amide (1.05 g, 2.54 mmol) was dissolved in a minimum amount of DCM (5 mL) and cooled to 0 °C. HCl (2.0 M in Et₂O, 1.4 mL, 2.89 mmol) was added and the mixture stirred at rt until precipitation of the salt was complete (about 10 min.). The solid was filtered, washed with Et₂O several times, and dried in a dessicator to yield 1.09 g of the hydrochloride salt (2.42 mmol, 95% yield). Melting point was not determined due to the extreme hygroscopicity of the sample. MS (ES+): 414.26 (M+H)+.

e) Fifth approach

ei) 5-(4-acetyl-[1,4]diazepan-1-yl)-N-[5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-pentanamide

[0311] To a cylindrical, jacketed 3 L reactor equipped with nitrogen inerting, agitator, condenser/distillation head, and temperature control, 5-bromo-pentanoic acid [5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]amide (0.15 kg, 0.426 mol), potassium carbonate (0.059 kg, 0.426 mol), potassium iodide (0.071 kg, 0.426 mol), and acetone (1.18 kg, 1.5 L) were added (at 20 °C) to form a white mixture. The mixture was stirred (235 rpm) at 25-30 °C for a minimum of 15 min. N-acetylhomopiperazine (0.062 kg, 0.057 L, 0.434 mol) was added via addition funnel to
the reactor over a minimum of 45 min., maintaining the temperature in the range of 25-30 °C. The addition funnel was rinsed with 0.05 L acetone. A white mixture persisted. The mixture was stirred (235 rpm) in the range of 25-30 °C for a minimum of 16 h, forming a white/yellow mixture. The reaction progress was monitored by HPLC and was considered complete when there was ≤ 2% of the starting material (bromopyrazole) and ≤ 2% of the iodopyrazole present.

The reactor contents were cooled to 5-15 °C over a minimum of 15 min with agitation (295 rpm) to form a white/yellow mixture that was stirred for a minimum of 1 h. To remove inorganics, the mixture was then filtered on a Buchner funnel with filter paper using house vacuum for 1.5 min. The cake was washed twice with acetone (total of 0.24 kg, 0.30 L) at 5-15 °C. The wash was combined with the mother liquor from the prior filtration and used to rinse the reactor. The filtrate was concentrated to a volume of approximately 0.45 L to form a clear solution.


eiii) Aqueous workup

To a reactor containing the material from step i, 1.5 L of a freshly made homogeneous solution of methyl THF (1.22 kg, 1.42 L) and ethanol (0.059 kg, 0.075 L) was added at 25 °C, forming a hazy solution. To this, 0.45 L of a 5% solution of sodium chloride (0.022 kg) in water (0.43 L) was added at 25 °C. The resulting mixture was heated with stirring to 30-35 °C over a minimum of 15 min., forming a clear biphasic solution. The agitation was stopped to allow the layers to settle, the product being in the upper layer. The layers were separated, keeping any emulsion in the upper organic layer. The organic layer was retained. A homogeneous 5% solution of sodium bicarbonate (0.03 kg) in water (0.57 L) at 25 °C was used to wash organic layer, stirring for a minimum of 5 min. at 10-15 °C. The agitation was stopped to allow the layers to settle, the product being in the upper layer. The layers were separated, keeping any emulsion in the upper organic layer. The organic layer was retained and concentrated to a volume of 0.35 L, forming a hazy solution. The mixture was chased with ethanol to remove residual water.

eiii) 5-(4-acetyl-[1,4]diazepan-1-yl)-N-[5-(4-methoxy-phenyl)-1H-pyrazol-5-yl]-pentanamide

HCl
To a reactor containing the material from step ii, 0.47 kg (0.60 L) of acetone was added. The resulting mixture was heated with stirring to 25-30 °C over a minimum of 10 min., forming a hazy solution. The contents of the reactor were clarified through a polypropylene pad into a tared 2 L suction flask using vacuum, maintaining the contents of the reactor at 25-30 °C. Suction was maintained until filtration stopped. The reactor and filter pad were rinsed with acetone (0.05 L) at 20-25 °C. The filtrates from the suction flask were transferred to the reactor and rinsed using acetone (0.05 L). A solution of 5% HCl (0.042 kg, 0.036 L) in acetone (0.174 L) and alcohol solution (0.0174 L of ethanol:acetone (91:9) v/v) was prepared and stirred until homogeneous at 10 °C. To the reactor, 0.05 L of water was added to form a clear solution. One third of the 5% HCl solution (0.076 L) was added to the reactor over a minimum of 20 min., maintaining the temperature in the range of 20-25 °C. A second third of the 5% HCl solution (0.076 L) was then added to the reactor over a minimum of 20 min., maintaining the temperature in the range of 20-25 °C. The contents of the reactor were seeded with 75 mg of 5-(4-acetyl-[1,4]diazepan-1-yl)-N-[5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-pentanamide HCl (e.g., Form 1), followed by the addition of the last third of 5% HCl solution (0.076 L) over a minimum of 20 min., maintaining the temperature in the range of 20-25 °C. Another 0.08 equiv. of the 5% HCl solution (0.023 L) was then added to the reactor over a minimum of 30 min., maintaining the temperature in the range of 20-25 °C. Judicious monitoring of pH was performed to attain the desired pH range of 5.2-5.8.

The mixture was stirred at 20-25 °C for a minimum of 1 h, forming a thin suspension. Acetone (0.6 L) was added over a minimum of 60 min., maintaining the temperature in the range of 20-25 °C. The mixture was stirred at 20-25 °C for a minimum of 60 min. Acetone (1.5 L) was added to the reactor over a minimum of 3 hr., maintaining the temperature in the range of 20-25 °C, forming a thick suspension. The mixture was then stirred at 20-25 °C for a minimum of 12 h. Crystallization was considered complete when there was ≤ 20% of the product present in the mother liquor.

The mixture was then filtered on a Buchner funnel (polypropylene pad) using house vacuum. A solution of water (0.009 L), acetone (0.23 L) and 0.06 L alcohol (ethanol:acetone (91:9) v/v) was stirred until homogeneous (20% ethanol, 3% water, 77% acetone overall). This solution was used to wash the filter cake twice (0.15 L x 2). A solution of
water (0.009 L), acetone (0.171 L) and 0.12 L alcohol (ethanol: acetone (91:9) v/v) was stirred until homogeneous (40% ethanol, 3% water, 57% acetone overall). This solution was used to wash the filter cake (0.30 L). The wet cake was subjected to suction under nitrogen using house vacuum and held for 30 min. after dripping stopped. Product purity was checked by HPLC and additional washing was performed if total impurities were not ≤ 2%. Product was oven dried in a vacuum oven with nitrogen bleed at 38-45 °C, maintaining vacuum at 20 torr for a minimum of 12 h until loss on drying of less than 1% was obtained. Following drying, 0.119 kg of the title compound was obtained in 62% yield (67% adjusted for aliquots removed during process; 60% when corrected for strength or purity). Melting point = 185 °C; crystal form = form 1; particle size = D90 < 89.4 μm, D50 < 19.2 μm.

f) Hydrochloride salt of 5-(4-Acetyl-[1,4]diazepan-1-yl)-pentanoic acid [5-(4-methoxy-phenyl)-2H-pyrazol-3-yl]-amide

[0317] The present Example describes the preparation of the hydrochloride salt form of 5-(4-Acetyl-[1,4]diazepan-1-yl)-pentanoic acid [5-(4-methoxy-phenyl)-2H-pyrazol-3-yl]-amide. The hydrochloric acid salt form readily adopted a solid form. Indeed, at least four different crystalline forms (i.e., polymorphs) were observed for the hydrochloric acid salt form (see below).

<table>
<thead>
<tr>
<th>Counter Ion Used</th>
<th>Solid Obtained</th>
<th>Melting Onset</th>
<th>Hygroscopicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochloric acid</td>
<td>Crystalline solid</td>
<td>185°C, 165°C, 125°C, 125°C (three peaks: about 100 and about 180; and about 200°C)</td>
<td>No, Somewhat, Yes, 2%</td>
</tr>
</tbody>
</table>

[0318] Differential scanning calorimetry data were collected for each solid form achieved using a DSC (TA instruments, model Q1000) under the following parameters: 50 mL/min purge gas (N₂); scan range 40 to 200 °C, scan rate 10 °C/min. Thermogravimetric analysis data were collected using a TGA instruments (Mettler Toledo, model TGA/SDTA 851e) under the
following parameters: 40 ml/min purge gas (N₂); scan range 30 to 250 °C, scan rate 10 °C/min.
X-ray data were acquired using an X-ray powder diffractometer (Bruker-axs, model D8 advance) having the following parameters: voltage 40 kV, current 40.0 mA, scan range (2θ) 5 to 30°, scan step size 0.01°, total scan time 33 minutes, VANTEC detector, and antiscattering slit 1 mm. Figures 1-7 show characterization data for hydrochloride salt forms.

[0319] The hydrochloride salt was polymorphic, adopting crystalline forms exhibiting DSC endotherms at 119 °C (Form III), 127 °C (Form IV), 167 °C (Form II), and 186 °C (Form I). Another form, potentially an ethanol solvate, exhibited multiple endotherms, corresponding to 1) desolvation at about 100 °C, 2) Form I at about 183 °C, and 3) possibly another polymorph at about 200 °C. The Crystal Form Table below illustrates certain characteristics of observed hydrochloride salt crystal forms:

<table>
<thead>
<tr>
<th>Crystal Form Table</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crystal Form I</strong></td>
</tr>
<tr>
<td>Mono-hydrochloride (8% HCl)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Non-hygroscopic (see Figure 4)</td>
</tr>
</tbody>
</table>

[0320] Of the various observed hydrochloride forms, only Form I (186 °C) is relatively non-hygroscopic, gaining only about 0.5% moisture when equilibrated at RH less than or equal to 70%. At 70-100% RH, Form I gains at least about 12% moisture, but loses it without significant hysteresis on decreasing RH. Evidence of a hydrochloride hydrate was not observed.

[0321] Higher degrees of hydrochloride salt were formed, depending on the amount of hydrochloric acid present in the solution during reactive crystallization. The conversion of
higher degrees of hydrochloride salt to mono-hydrochloride salt can be achieved by adjusting the pH of the solution to about pH 4-5. Further adjustment, however, can result in formation of inorganic salts. In some embodiments, pure mono-hydrochloride salt forms are produced with hydrochloride equivalence and slurry pH of <0.95 equiv. (e.g., 0.93) and pH 5.5, respectively (see, for example, Figures 8-11).

g) Characterization of Certain Crystal Forms of Hydrochloride Salt

[0322] The present Example describes characterization of two surprisingly non-hygroscopic crystal forms (Forms I and II, as described above) of a hydrochloride salt of 5-(4-Acetyl-[1,4]diazepan-1-yl)-pentanoic acid [5-(4-methoxy-phenyl)-2H-pyrazol-3-yl]-amide:

[0323] Both forms are considerably soluble in water. The melting point of Form I is 185 °C (plus or minus 2 degrees); the melting point of Form II is 166 °C (plus or minus 2 degrees).

[0324] Form I picks up moisture at relative humidity (RH) of about 50% and absorbs up to about 2% water eventually (90% RH) and loses the water as RH decreases (<50%). Form I also exhibits characteristic X-ray peaks at 2θ of 15.3 ° and 21.9 °, plus or minus about 0.3 °, depending upon the machine and measurement method utilized.

[0325] Form II picks up moisture at RH of about 20% and absorbs up to 7% water eventually (RH of 90%) and holds 2% at low RH (0%). Form II also exhibits characteristic X-ray peaks at 2θ of 20.2 ° and 24.9 °, plus or minus about 0.3 °, depending upon the machine and measurement method utilized. Differential scanning calorimetry data were collected for each solid form achieved using a DSC (TA instruments, model Q1000) under the following parameters: 50 mL/min purge gas(N2); scan range 40 to 200°C, scan rate 10 °C/min.
Thermogravimetric analysis data were collected using a TGA instruments (Mettler Toledo, model TGA/SDTA 851e) under the following parameters: 40 mL/min purge gas(N₂); scan range 30 to 250 °C, scan rate 10 °C/min.

X-ray data were acquired using an X-ray powder diffractometer (Bruker-axs, model D8 advance) having the following parameters: voltage 40 kV, current 40.0 mA, scan range (2Θ) 3.7 to 30 °, scan step size 0.01 °, total scan time 33 minutes, VANTEC detector, and antiscattering slit 1 mm.

Dynamic Vapor Sorption (DVS) was done at 26 °C.

Results of thermal studies on Crystal Forms I and II are shown in Figures 12-19.

h) Preparation of Crystal Form I of the Hydrochloride Salt of 5-(4-Acetyl-[1,4]diazepan-1-yl)-pentanoic acid [5-(4-methoxy-phenyl)-2H-pyrazol-3-yl]-amide.

The present Example describes the preparation of crystal form I of the hydrochloride salt of 5-(4-Acetyl-[1,4]diazepan-1-yl)-pentanoic acid [5-(4-methoxy-phenyl)-2H-pyrazol-3-yl]-amide.

First procedure: 6.117 mg of the free base form of 5-(4-Acetyl-[1,4]diazepan-1-yl)-pentanoic acid [5-(4-methoxy-phenyl)-2H-pyrazol-3-yl]-amide was dissolved in 1.97 mL acetone at 35 °C. A solution of 5% HCl in acetone-water was prepared by diluting 37.5% aq. HCL using acetone. 0.6 ml of 5% HCl was added slowly. 1.2 ml EtOH ASDQ (100:10 ethanol:methanol) was added slowly. The solution became milky in a few minutes; stirring was performed for around 5 minutes. 0.25 ml of 5% HCl was added slowly. After 5 minutes, 0.25 ml of 5% HCl was added slowly. After 5 minutes, 0.087 ml of 5% HCl was added slowly. The mixture was heated to about 40-50 °C. The mixture was left at room temperature while stirring overnight. Crystals were filtered and washed with 2 ml acetone, and were dried at 45 °C for about 7 hours. 505 mg of solid were recovered.

Second procedure: 377 mg of the free base form of 5-(4-Acetyl-[1,4]diazepan-1-yl)-pentanoic acid [5-(4-methoxy-phenyl)-2H-pyrazol-3-yl]-amide was dissolved in 1.2 ml acetone at 35 °C. 0.754 ml ethanol ASDQ (100:10 ethanol:methanol) was added. A solution of
5% HCl in acetone-water was prepared by diluting 37.5% aq HCl using acetone. 0.18 ml diluted HCl solution was added slowly. A seed of crystal form I of the hydrochloride salt of 5-(4-Acetyl-[1,4]diazepan-1-yl)-pentanoic acid [5-(4-methoxy-phenyl)-2H-pyrazol-3-yl]-amide was added. 0.18 ml diluted HCl solution was added slowly. Around two minutes later, 0.18 ml diluted HCl solution was added slowly. Around two minutes later, another 0.18 ml diluted HCl solution was added slowly. The mixture was heated to about 40-50 °C, and then was left at room temperature while stirring overnight. The crystals were filtered and washed with 1.5 ml acetone, and were dried at 45 °C for about 6 hours.

Example 5
5-Piperidin-1-yl-pentanoic acid [5-(3-bromo-phenyl)-2H-pyrazol-3-yl]-amide

a) 3-(3-Bromo-phenyl)-3-chloro-acrylonitrile

[0332] To 30.9 mL of dry DMF (400 mmol) cooled down to 0°C 18.3 mL of POCl₃ (200 mmol) were added dropwise so that the temperature was always under 10°C. To the mixture 19.9 g (100 mmol) of l-(3-bromophenyl)ethanone were added dropwise and the reaction was allowed to reach room temperature.

[0333] When the addition was complete the reaction was stirred for further 30 minutes and then 2.7 g (40 mmol) of hydroxylamine hydrochloride were added and the reaction heated up to 50°C. The heating was then removed and other 27 g (400 mmol) of hydroxylamine hydrochloride were added portionwise (so that the temperature did not exceed 120 °C).

[0334] After the last addition the reaction was left stirring until the temperature of the mixture spontaneously decreased to 25 °C. Water (100 mL) was then added and the mixture was extracted with diethyl ether. The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure.

[0335] The crude product was used for the next step without further purification.

C₉H₅BrClN

¹H-NMR (400 MHz, DMSOD ᵃ) : 7.03 (s, 1H), 7.44-7.54 (m, 1H), 7.72-7.84 (m, 2H), 8.00 (br s, 1H)

Yield 68%
b) 5-(S-Bromo-phenyl)-2H-pyrazol-S-ylamine

To a solution of 3-(3-bromo-phenyl)-3-chloro-acrylonitrile (10 mmol), in absolute EtOH (20 mL) hydrazine monohydrate (1 mL, 20 mmol) was added and the reaction was heated at reflux for 4 hrs. The reaction mixture was then allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was triturated with Et₂O, allowing to recover 1.8 g of the title compound as pure product (yield 79%).

C₁₉H₂₅BrN₄O

¹H-NMR(400 MHz, DMSO-d₆): 4.58, 5.03 (1H, 2 tautomer peaks), 5.64, 5.84 (1H, 2 tautomer peaks), 7.28 (1H, s), 7.35 (1H, s), 7.53-7.65 (1H, m), 7.77 (1H, s), 11.56, 11.97 (1H, 2 tautomer peaks).

c) 5-Piperidin-1-yl-pentanoic acid [5-(S-bromo-phenyl)-2H-pyrazol-S-yl]-amide

To a solution of 5-bromo-valeryl chloride (500 µL, 3.74 mmol) in 5 mL of DMA, cooled at 0 °C, a solution of 5-(3-bromo-phenyl)-2H-pyrazol-3-ylamine (890 mg, 3.74 mmol) in 3 mL of DMA was added and the reaction left stirring for 1 h at 0 °C. Upon reaction completion the reaction was diluted with 5mL and the product was extracted with 20 mL of DCM. The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The oily product, wet of DMA, was used for the next step without further purification, assuming 100% yield.

To a solution of 5-bromo-pentanoic acid [5-(3-bromo-phenyl)-2H-pyrazol-3-yl]-amide (about 3.74 mmol) in 10 mL of DMF, Na₂CO₃ 1.23g, 7.48 mmol), piperidine (738 µL, 7.48 mmol), and NaI (561 mg, 3.74 mmol) were added and the mixture was heated at 60 °C for 5 hours. When the reaction was complete the solvent was removed under reduced pressure and the residue was diluted with DCM and washed with a saturated solution of NaHCO₃. The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified with SiO₂ column (10 g) with gradient elution from 100% DCM to DCM-NH₃ (2 N MeOH solution) 95:5 to afford the title compound (1.2 g, yield 79%).

C₁₉H₂₅BrN₄O
Mass (calculated) [405]; (found) [M+H]=405-407

LC Rt=2.48, 100% (10 min method)

\(^1\)H-NMR (400 MHz, DMSOd\(_6\)) : 1.24-1.70 (1OH, m), 2.06-2.41 (6H, m), 3.15-3.17 (2H, m), 6.96 (1H, s), 7.29-7.45 (1H, m), 7.46-7.57 (1H, m), 7.63-7.83 (1H, m), 7.94 (1H, s), 10.43 (1H, s), 12.89 (1H, s).

Example 6

5-Piperidin-1-yl-pentanoic acid [5-(lH-indol-5-yl)-2H-pyrazol-5-yl]-amide

a) 1-Triisopropylsilanyl-1H-indole-5-carboxylic acid methyl ester

[0339] To a solution of 1g of methyl indole-5-carboxylate (5.7 mmol) in 10 mL of dry DMF 273 mg of Na\(_2\)H (mineral oil dispersion 50-60%, 5.7 mmol) were added and the mixture cooled to 0 °C. Triisopropylchlorosilane (1.06 g, 5.7mmol) were added drop wise and after 1 hour LC-MS showed complete conversion of the starting material to the title product. The mixture was diluted with 30 mL of DCM and washed with saturated Na\(_2\)CO\(_3\). The organic phase was dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude was purified with SiO\(_2\) column eluting with \(\alpha\)-hexane. The title compound was obtained (500 mg, yield 26%)

C\(_{19}\)H\(_{29}\)NO\(_2\)Si

Mass (calculated) [331]; (found) [M+H]=332

LC Rt=3.39, 100% (5 min method)

\(^1\)H-NMR: (DMSO-de): 1.06 (d, 1H, J=7.52), 1.75 (quint, 3H, J=7.52), 6.75 (m, 1H), 7.48 (m, 1H), 7.60 (m, 1H), 7.72 (m, 1H), 8.25 (s, 1H).

b) S-Oxo-S-(1-triisopropylsilanyl-1H-indol-5-yl)-propionitrile

[0340] To a solution of 393 µL of anhydrous CH\(_3\)CN (7.5 mmol) in 6 mL of dry toluene cooled down to -78 °C, 5.35 mL of butyllithium in hexane solution (1.6 N) were added dropwise. The mixture was left stirring at -78 °C for 20 minutes and then a solution of 500 mg of 1-triisopropylsilanyl-1H-indole-5-carboxylic acid methyl ester (1.5 mmol) in 2 mL of dry toluene were added and the reaction allowed to reach room temperature. Upon reaction completion after about 20 minutes the mixture was cooled down to 0 °C and HCl 2 N was added to pH 2. The organic phase was separated, dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure,
affording 490 mg of title product which was used in the next step without further purification (yield = 96%).

\[ \text{C}_{20}\text{H}_{28}\text{N}_{2}\text{OSi} \]

Mass (calculated) [340]; (found) [M+H\(^+\)]=341 [M-H\(^+\)]=339

LC Rt=3.10, 89% (5 min method)

\(^1\text{H}-\text{NMR: (DMSO}_d\text{)}: 1.06 (18\text{H}, \text{d, J}=7.52), 1.76 (3\text{H}, \text{quin, J}=7.52), 4.76 (1\text{H}, \text{d}), 7.78-7.81 (1\text{H}, \text{m}), 7.48-7.52 (1\text{H}, \text{m}), 7.60-7.73 (2\text{H}, \text{m}), 8.25 (\text{s, 1H}).

c) 5-(lH-Indol-5-yl)-2H-pyrazol-3-ylamine

[0341] To a solution of 3-Oxo-3-(l-triisopropylsilanyl-1H-indol-5-yl)-propionitrile (490 mg, 1.44 mmol) in 15 mL of absolute EtOH, 720 µL of hydrazine monohydrate (14.4 mmol) were added and the reaction refluxed for 18 hours. LC-MS showed complete conversion to the aminopyrazole and also silyl deprotection. The mixture was concentrated under reduced pressure, and purified with SiO\(_2\) column (eluent gradient from 100% DCM to DCM:MeOH 9:1) to afford the title compounds (120mg, yield: 41%)

\[ \text{C}_{n}\text{H}_{10}\text{N}_4 \]

Mass (calculated) [198]; (found) [M+H\(^+\)]=199

LC Rt=0.84, 100% (3 min method)

d) 5-Piperidin-l-yl-pentanoic acid [5-(lH-indol-5-yl)-2H-pyrazol-3-yl]-amide

[0342] To a solution of 5-bromovaleryl chloride (80 µL, 0.60 mmol) in DMA (1 mL) cooled at 0 °C a solution of 5-(1H-Indol-5-yl)-2H-pyrazol-3-ylamine (120 mg, 0.60 mmol) and diisopropylethylamine (104 µL, 1.20 mmol) in DMA (2 mL) was added. The reaction was left stirring for 1 hour at 0 °C and then piperidine (119 µL,1.20 mmol) and NaI (90 mg, 0.60 mmol) were added and the mixture heated at 60°C for 5 hours, when LC-MS showed complete conversion of the bromo-intermediate and the solvent was removed under reduced pressure.

[0343] The residue was dissolved in DCM (2 mL) and washed with Na\(_2\)CO\(_3\) saturated water solution. The organic phase was concentrated under reduced pressure and the crude product was purified by prep HPLC.
Example 7

5-(4-Acetyl-[1,4]diazepan-1-yl)-pentanoic acid (5-pyridin-3-yl-2H-pyrazol-3-yl)-amide

a) 3-Oxo-3-pyridin-3-yl-propionitrile

The product was prepared according to the general procedure for aminopyrazole synthesis (route A1)

\[^1\text{H-NMR (400 MHz, MeOH-d}_4\text{): 9.07 (1H, d), 8.81 (2H, dd), 8.26 (1H, dt), 7.59 (1H, dd), 4.79 (2H, s).}\]

b) 5-Pyridin-3-yl-2H-pyrazol-3-ylamine

The product was prepared according to general procedure for aminopyrazole synthesis (route A2)

\[^1\text{H-NMR (400 MHz, MeOH-d}_4\text{): 8.82 (1H, d), 8.41 (1H, dd), 7.98 (1H, dt), 7.37 (1H, dd), 5.82 (2H, s).}\]

c) 5-(4-Acetyl-[1,4]diazepan-1-yl)-pentanoic acid (5-pyridin-3-yl-2H-pyrazol-3-yl)-amide

The product was prepared according to the general synthetic method for the one-pot synthesis of \(\omega\)-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides. The crude product was
purified with SiO$_2$ column (5 g) with gradient elution from 100% DCM to DCM-NH$_3$ (2 N MeOH solution) 95:5.

[0348] The crude was further purified by preparative HPLC to give 772 mg of pure product (yield 25%).

C$_{20}$H$_{28}$N$_6$O$_2$
Mass (calculated) [384]; (found) [M+H$^+$]=385
LC Rt= 1.91, 100% (10 min method)
$^1$H-NMR (400 MHz, MeOH-d$_4$): 8.89 (1H, d), 8.49 (1H, dd), 8.12 (1H, d), 7.48 (1H, dd), 6.81 (1H, broad), 3.60 (1H, m), 3.55 (3H, m), 2.72 (3H, m), 2.63 (1H, m), 2.55 (2H, m), 2.43 (2H, m), 2.07 (3H, s), 1.90 (1H, m), 1.80 (1H, m), 1.70 (m, 2H), 1.57 (2H, m).

Example 8
5-Piperidin-1-yl-pentanoic acid [5-(4-methoxy-phenyl)-4-methyl-2H-pyrazol-S-yl]-amide
a) S-(4-Methoxy-phenyl)-2-methyl-S-oxo-propionitrile

[0349] The product was prepared according to the general procedure for aminopyrazole synthesis (route Al).

[0350] The crude product was purified with SiO$_2$ column (10 g) with gradient elution from 100% Hexane to Hexane-AcOEt 7:3. to give 1.43 g of pure product (yield 31%).

$^1$H-NMR (400 MHz, MeOH-d$_4$): 7.97 (2H, d), 6.98 (2H, d), 4.31 (1H, q, J = 7.3 Hz), 3.89 (3H, s), 1.63 (3H, d, J = 7.3 Hz).

b) 5-(4-Methoxy-phenyl)-4-methyl-2H-pyrazol-S-ylamine

[0351] The product was prepared according to the general procedure for aminopyrazole synthesis (route A2)

[0352] The crude product was purified with SiO$_2$ column (10 g) with gradient elution from 100% DCM to DCM-MeOH 8:2. 1.0 g of pure product were obtained (yield 65%).

$^1$H-NMR (400 MHz, CDCl$_3$): 7.37 (2H, d), 6.97 (2H, d), 3.84 (3H, s), 2.03 (3H, s).
c) 5-Piperidin-1-yl-pentanoic acid [5-(4-methoxy-phenyl)-4-methyl-2H-pyrazol-3-yl]-amide

[0353] The product was prepared according to the general synthetic method for the one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides.

[0354] The crude product was purified with SiO₂ column (2 g) with gradient elution from 100% DCM to DCM-NH₃ (2N MeOH solution) 95:5.

[0355] The obtained crude was then purified again by prep-HPLC to give 54 mg of pure product (yield 7%).

C₂₂H₃₀N₆O₂
Mass (calculated) [370]; (found) [M+H⁺] =371
LC Rt= 1.61, 100% (10 min method)
¹H-NMR (400 MHz, DMSO-d₆): 9.57 (1H, s), 8.12 (1H, s), 7.47 (2H, d), 7.02 (2H, d), 3.78 (3H, s), 2.41 (4H, broad), 2.37 (2H, m), 2.29 (2H, t), 1.91 (3H, s), 1.57 (2H, m), 1.50 (6H, m), 1.38 (2H, m).

Example 9
5-Piperidin-1-yl-pentanoic acid (5-furan-2-yl-2H-pyrazol-3-yl)-amide

[0356] The product was prepared according to the general synthetic method for the one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides.

The crude product was purified by prep-HPLC (yield 15%).

C₁₆H₂₄N₆O₂
Mass (calculated) [316]; (found) [M+H⁺] =317
LC Rt= 1.53, 100% (10 min method)
¹H-NMR (400 MHz, MeOH-d₄): 8.48 (1H, s), 7.56 (1H, s), 6.70 (1H, s), 6.66 (1H, s), 6.52 (1H, m), 5.49 (1H, s), 4.88 (1H, s), 3.10 (2H, m), 2.48 (2H, m), 1.77 (10, m).

Example 10
N-[5-(4-Methoxy-phenyl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide

a) 4-Piperidin-1-yl-butyric acid ethyl ester
To a solution of piperidine (5.4 g, 65 mmol) in toluene (15 mL) ethyl 4-
bromobutyrate (3.8 mL, 26 mmol) was added and the reaction mixture was refluxed for 10 hours. The mixture was allowed to cool down to room temperature and the white solid present (piperidinium bromide) was filtered off and washed with ether. The filtrate was concentrated under reduced pressure to give the title product which was used in the next step without further purification.

\[ \text{C}_{11}\text{H}_{21}\text{NO}_2 \]

Mass (calculated) [199]; (found) [M+H\(^+\)]=200

LC Rt = 0.2, 100% (5 min method)

\(^1\text{H-NMR}\ (400 \text{ MHz, MeOH-d}_4): 1.22-1.25 \text{ (3H, m), 1.46-1.47 (2H, m), 1.57-1.63 (4H, m), 1.78-1.84 (2H, m), 2.30-2.35 (4H, m), 2.42 (4H, m, broad), 4.08-4.14 (2H, m).} \]

b) 4-Piperidin-l-yl-butyric acid

To a suspension of crude 4-piperidin-1-yl-butyric acid ethyl ester from the previous step (about 25 mmol) in 15 mL of water, NaOH (1.4 g, 25 mmol) was added and the mixture was heated at reflux for 16 hours. The reaction was then allowed to cool down to room temperature, the solution was acidified at 0°C with HCl 6 N and concentrated under reduced pressure. The residue was treated with EtOH and the sodium chloride which precipitated was filtered off. Evaporation of the solvent under reduced pressure afforded 2.8 g of the title compound as a white solid in 58% overall yield of steps a) and b)

\[ \text{C}_9\text{H}_{17}\text{NO}_2 \]

Mass (calculated) [171]; (found) [M+H\(^+\)]=172

LC Rt = 0.23, 100% (5 min method)

\(^1\text{H-NMR}\ (400 \text{ MHz, DMSO-de): 1.44-1.51 (2H, m); 1.64-1.80 (6H, m); 2.22-2.25 (2H, m); 2.75-2.78 (2H, m, broad); 2.91-2.94 (2H, m, broad); 3.30-3.40 (2H, m).} \]

c) N-[5-(4-Methoxy-phenyl)-2H-pyrazol-3-yl]-4-piperidin-l-yl-butyramide

To a suspension of 4-piperidin-1-yl-butyric acid (1.32 g, 7.93 mmol) in 12,2-
dichloroethane (20 mL), 7V,7V'-carbonyldiimidazole (1.2 g, 7.4 mmol) was added and the mixture was stirred at room temperature for 2 hours (when all the amino acid was activated complete
dissolution of the suspension was generally observed). 3-Amino-5-(4-methoxyphenyl)pyrazole (1 g, 5.29 mmol) was then added and the reaction was stirred for further 10 hours. Upon reaction completion (as monitored by LC-MS) the formation of two isomers was observed, and the mixture was heated at 50 °C until the conversion of the less stable isomer to the title compound was observed (as monitored by LC-MS). The solvent was washed with sat. Na₂CO₃ solution, extracted and removed under reduced pressure. The crude was crystallised from acetonitrile to give 1.2 g of the title compound (Yield: 70%).

**Example 11**

N-[5-(3-Methoxy-phenyl)-1H-pyrazol-3-yl]-4-morpholin-4-yl-butyramide

a) 3-(3-Methoxy-phenyl)-3-oxo-propionitrile

[0360] To a solution of commercially available 3-methoxy-benzoic acid ethyl ester (3.2 g, 18 mmol) in dry toluene (25 mL), under N₂, NaH (50-60% dispersion in mineral oil, 1.44 g, 36 mmol) was carefully added. The mixture was heated at 90 °C and anhydrous CH₃CN was added dropwise (4.45 mL, 85.2 mmol). The reaction was heated for 18 hours and the product precipitated from the reaction mixture as Na salt. The reaction was allowed to cool down to room temperature and the solid formed was filtered and washed with ether, then it was redissolved in water and the solution acidified with 2 N HCl solution to pH 3 when precipitation of title compound was observed. Filtration of the solid from the aqueous solution afforded 1.57 g of title product (50% yield).

C_{10}H_{10}NO₂

Mass (calculated) [175]; (found) [M+H⁺] =176

LC Rt = 1.69, 94% (5 min method)
b) 5-(S-Methoxy-phenyl)-2H-pyrazol-S-ylamine

5-(S-Methoxy-phenyl)-2H-pyrazol-S-ylamine

To a solution of 3-(3-methoxy-phenyl)-3-oxo-propionitrile (8.96 mmol) in absolute EtOH (20 mL) hydrazine monohydrate (0.52 mL, 15 mmol) was added and the reaction was heated at reflux for 18 hrs. The reaction mixture was then allowed to cool to room temperature and the solvent was evaporated under reduced pressure.

The crude was treated with ether and filtered, to give 1.4 g of title product (83% of yield)

C_{10}H_{11}N_{3}O

Mass (calculated) [189]; (found) [M+H^+] =190

{\text{LC Rt}} = 1.13, 100% (5 min method)

\text{^1H-NMR} (400 MHz, MeOH-d_4): 3.82 (3H, s); 5.93 (1H, s); 6.86-6.88 (1H, m); 7.19-7.31 (3H, m).

\[ )

\text{c) N-[5-(3-Methoxy-phenyl)-1H-pyrazol-3-yl]-4-morpholin-4-yl-butyramide}

N-[5-(3-Methoxy-phenyl)-1H-pyrazol-3-yl]-4-morpholin-4-yl-butyramide

A solution of 4-bromobutyryl chloride chloride (0.104 mL, 0.9 mmol) in dry DMA (1 mL) was cooled to -10 °C (ice/water bath) under N_2; 5-(3-methoxy-phenyl)-2H-pyrazol-3-ylamine (170 mg, 0.9 mmol) and diisopropylethylamine (0.315 mL, 1.8 mmol) in dry DMA (1 mL) were added. Upon complete conversion to the intermediate 4-bromo-N-[5-(3-methoxy-phenyl)-1H-pyrazol-3-yl]-butyramide (as monitored by LC-MS), morpholine (0.079 mL, 0.9 mmol) was added and the mixture was heated at 60 °C for 16 hours. The residue was dissolved in DCM (2 mL) and washed with sat. Na_2CO_3 solution. The organic phase was concentrated under reduced pressure and the crude product was purified by SiO_2 column (gradient from Acetonitrile 100% to MeCN/MeOH, NH_3 90/10). The fractions containing the title compound were collected to afford 17 mg (5.5% of yield).

C_{18}H_{24}N_{4}O_3

Mass (calculated) [344]; (found) [M+H^+] =345

{\text{LC Rt}} = 1.36, 95% (10 min method)

\text{^1H-NMR} (400 MHz, MeOH-d_4): 1.77-1.85 (2H, m); 2.34-2.40 (8H, m); 3.59-3.62 (4H, m); 3.76 (3H, s); 6.79-6.85 (2H, m); 7.15-7.29 (3H, m).
Example 12

4-Azepan-1-yl-N-[5-(S-methoxy-phenyl)-1H-pyrazol-5-yl]-butyramide

[0363] A solution of 4-bromobutyryl chloride (0.104 mL, 0.9 mmol) in dry DMA (1 mL) was cooled to -10 °C (ice/water bath) under N\textsubscript{2}; 5-(3-Methoxy-phenyl)-2H-pyrazol-3-ylamine (170 mg, 0.9 mmol) and diisopropylethylamine (0.315 mL, 1.8 mmol) in dry DMA (1 mL) was added. Upon complete conversion to the ω-bromoamide intermediate (as monitored by LC-MS) 0.101 mL of azepine were added to the solution and the mixture was left stirring at 60 °C for 16 hours.

[0364] The residue was dissolved in DCM (2 mL) and washed with saturated Na\textsubscript{2}CO\textsubscript{3} solution. The organic phase was concentrated under reduced pressure and the crude product was purified by SiO\textsubscript{2} column (gradient from acetonitrile 100\% to MeCN/MeOH, NH\textsubscript{3} 90/10). The fractions containing the title product were collected and a further purification by preparative HPLC was carried out to afford 20 mg of the title compound as its formate salt (5.5\% yield).  

C\textsubscript{20}H\textsubscript{28}N\textsubscript{4}O\textsubscript{2}  
Mass (calculated) [356]; (found) [M+H\textsuperscript{+}] =357  
LC Rt=1.71, 99\% (10 min method)  
\textsuperscript{1}H-NMR (400 MHz, MeOH-d\textsubscript{4}): 1.65-1.68 (4H, m); 1.80-1.90 (4H, m); 1.97-2.04 (2H, m); 2.49-2.52 (2H, m); 3.12-3.16 (2H, m); 3.24-3.30 (4H, m, broad); 3.75 (3H, s); 6.76 (1H, s); 6.82-6.85 (1H, m); 6.13-6.15 (2H, m); 6.23-6.27 (1H, m); 8.37 (1H, s, formate)

Example 13

4-Azepan-1-yl-N-[5-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-butyramide

[0365] Prepared following the general synthetic method for the one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides. Starting from commercially available 5-(4-fluoro-phenyl)-2H-pyrazol-3-ylamine and following the procedure, 25 mg of title compound were recovered as its formate salt after preparative HPLC purification (7\% yield).

C\textsubscript{19}H\textsubscript{25}N\textsubscript{4}O\textsubscript{F}
Mass (calculated) [344]; (found) [M+H+] = 345

LC Rt = 1.69, 100% (10 min method).

$^1$H-NMR (400 MHz, MeOH-d$_4$): 1.66-1.69 (4H, m); 1.80-1.90 (4H, m, broad); 1.97-2.05 (2H, m); 2.52-2.54 (2H, m); 3.12-3.18 (2H, m); 3.25-3.30 (4H, m, broad); 6.67 (1H, s, broad); 7.08-7.12 (2H, m); 7.59-7.63 (2H, m); 8.43 (1H, s, formate)

Example 14

$N$-[5-(6-Methyl-pyridin-$S$-$yl$)-$l$$H$-pyrazol-$S$-$yl$]-4-piperidin-$l$-$yl$-butyramide

a) 3-(6-Methyl-pyridin-3-$yl$)-3-oxo-propionitrile

The oxopropionitrile was synthesised following the general method for 3-oxopropionitriles (route AI)

$C_9$$H_8$$N_2$$O$

Mass (calculated) [160]; (found) [M+H+] = 161

LC Rt = 0.63, 100% (5 min method)

$^1$H-NMR (400 MHz, DMSO-d$_6$): 2.55 (3H, s); 4.65 (2H, s); 7.43-7.45 (m, 1); 8.13-8.16 (1H, m); 8.94-8.95 (1H, m).

b) 5-(6-Methyl-pyridin-3-$yl$)-$l$$H$-pyrazol-$3$-$yl$amine

The aminopyrazole was synthesised following the general method described in route A2

$C_9$$H_7$$N_4$

Mass (calculated) [174]; (found) [M+H+] = 175

LC Rt = 0.23, 100% (5 min method)

c) N-[5-(6-Methyl-pyridin-3-$yl$)-$l$$H$-pyrazol-$3$-$yl$]-4-piperidin-$l$-$yl$-butyramide

Prepared following the general synthetic method for the one-pot synthesis of $\omega$-amino-alkanoic acid (1H-pyrazol-3-$yl$-5-aryl)-amides to afford 19 mg (6% yield) of title compound as its formate salt after preparative HPLC purification.

$C_{18}$$H_{25}$$N_5$$O$
Mass (calculated) [327]; (found) [M+H+] = 328

LC Rt = 0.33, 100% (10 min method)

$^1$H-NMR (400 MHz, MeOH-d$_4$): 1.40-1.90 (6H, m); 2.30-2.54 (5H, m); 3.05-3.09 (4H, m); 3.20-3.24 (2H, m); 6.72 (1H, s, broad); 7.30 (1H, d, $J = 8.0$ Hz); 7.92-7.94 (1H, m); 8.35 (1H, s, formate); 8.67 (1H, s).

Example 15

$N$-[5-(5-Methyl-pyridin-$S$-yl)-1H-pyrazol-$S$-yl]-4-piperidin-$l$-yl-butyramide

a) 3-(5-Methyl-pyridin-$3$-yl)-3-oxo-propionitrile

[0369] The oxopropionitrile was synthesised following the general method for 3-oxopropionitriles (route A1)

C$_9$H$_8$N$_2$O

Mass (calculated) [160]; (found) [M+H$^+$] = 161

LC Rt = 0.63, 100% (5 min method)

$^1$H-NMR (400 MHz, MeOH-d$_4$): 2.55 (3H, s); 4.65 (2H, s); 7.43-7.45 (m, 1H); 8.13-8.16 (1H, m); 8.94-8.95 (1H, m).

b) 5-(5-Methyl-pyridin-$3$-yl)-1H-pyrazol-3-ylamine

[0370] The aminopyrazole was synthesised following the general method described in route A2

C$_9$H$_{10}$N$_4$

Mass (calculated) [174]; (found) [M+H$^+$] = 175

LC Rt = 0.23, 100% (5 min method)

c) N-[5-(5-Methyl-pyridin-$3$-yl)-1H-pyrazol-$3$-yl]-4-piperidin-$l$-yl-butyramide

[0371] Prepared following the general synthetic method for the one-pot synthesis of $\omega$-amino-alkanoic acid (1H-pyrazol-$3$-yl-$5$-aryl)-amides to afford 25 mg of the title compound as its formate salt (7.4% yield) after preparative HPLC purification.

C$_{18}$H$_{25}$N$_5$O
Example 16

4-(4-Acetyl-[1,4]diazepan-1-yl)-N-[5-(6-methoxy-naphthalen-2-yl)-1H-pyrazol-5-yl]-butyramide

a) 6-Methoxy-naphthalene^-carboxylic acid methyl ester

To a solution of 6-methoxy-naphthalene-2-carboxylic acid (1.01 g, 5 mmol) in methanol (10 mL), a catalytic amount of sulphuric acid was added. The mixture was then heated at 80°C for 8 hours. Upon reaction completion (as monitored by LCMS), the solution was slowly cooled and the precipitation of the product was observed. Filtration of the white solid afforded 1.01 g (94% yield) of title compound

\[ C_{13}H_{12}O_3 \]

Mass (calculated) [216]; (found) [M+H+] =217

LC Rt = 2.43, 100% (5 min method)

b) 3-(6-Methoxy-naphthalen-2-yl)-3-oxo-propionitrile

To a solution of 6-methoxy-naphthalene-2-carboxylic acid methyl ester (1.0 g, 4.7 mmol) in dry toluene (8 mL), NaH (0.55 mg, 9.4 mmol) were added and the mixture was heated at 90 °C. To the hot solution, acetonitrile (1.2 mL) was added dropwise. The reaction was then heated for 18 hours and the product precipitated from the reaction mixture as its sodium salt.

The reaction was allowed to cool down to room temperature and the solid formed was first filtered and washed with ether, then it was dissolved in water and the solution was acidified with HCl 2 N to pH 3, upon which precipitation of the title compound was observed. Filtration of the solid from the aqueous solution afforded 1.1 g of title compound (100% of yield).

\[ C_{13}H_{12}O_3 \]

Mass (calculated) [225]; (found) [M+H+] =226

LC Rt = 2.13, 90% (5 min method)
c) 5-(6-Methoxy-naphthalen-2-yl)-1H-pyrazol-3-ylamine

[0374] To a solution of 3-(6-methoxy-naphthalen-2-yl)-3-oxo-propionitrile (1.1 g, 4.8 mmoL) in absolute EtOH (10 mL) hydrazine monohydrate (0.96 mL, 19.2 mmol) was added and the reaction was heated at reflux for 18 hrs. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The crude was treated with ether and filtered to afford 0.95 g of title compound (83% of yield).

C_{12}H_{13}N_{3}O
Mass (calculated) [239]; (found) [M+H+] =240
LC Rt = 1.49, 90% (5 min method)

d) 4-(4-Acetyl-[1,4]diazepan-1-yl)-N-[5-(6-methoxy-naphthalen-2-yl)-1H-pyrazol-3-yl]-butyramide

[0375] Following the general method for the synthesis of ω-bromo-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides and the general method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides, purification by preparative HPLC afforded 15 mg (3% yield) of title compound as its formate salt.

C_{25}H_{31}N_{5}O_{3}
Mass (calculated) [449]; (found) [M+H+] =450
LC Rt = 1.91, 100% (10 min method)

^1H-NMR (400 MHz, MeOH-d_4): 1.88-2.0 (4H, m); 2.06 (3H, s); 2.48-2.52 (2H, m); 2.94-3.02 (2H, m); 3.08-3.18 (4H, m); 3.52-3.58 (2H, m); 3.64-3.72 (2H, m); 3.82 (3H, s); 6.78-6.82 (1H, m); 7.04-7.10 (1H, m); 7.16-7.18 (1H, m); 7.62-7.78 (3H, m); 7.98-8.02 (1H, m); 8.28 (1H, s, formate).

Example 17

5-Piperidin-1-yl-pentanoic acid [5-(S-fluoro-phenyl)-1H-pyrazol-3-yl]-amide
a) S-(S-Fluoro-phenyl)-S-oxo-propionitrile
The product was prepared according to a modification of general route A1. To a solution of methyl-3-fluorobenzoate (3 g, 18 mmol) in dry toluene (25 mL) under N₂, NaH (50-60% dispersion in mineral oil, 1.44 g, 36 mmol) was carefully added.

The mixture was heated at 90 °C and then dry CH₃CN was added dropwise (4.45 mL, 85.2 mmol). The reaction was heated for 18 hours and the product precipitated from the reaction mixture as its sodium salt. The reaction was allowed to cool down to room temperature and the solid formed was filtered, then redissolved in water, and the solution was acidified with 2 N HCl to pH 5-6, upon which precipitation was observed. Filtration of the solid from the aqueous solution afforded 2.12 g of the title compound (72% yield) which was used directly in the following step.

b) 5-(S-Fluoro-phenyl)-1H-pyrazol-5-yl-amine

The product was prepared according to a slight modification of route A2. To a solution of 3-(3-fluoro-phenyl)-3-oxo-propionitrile (1.92 g, 11.77 mmol) in absolute EtOH (32 mL) hydrazine monohydrate (0.685 mL, 14.12 mmol) was added and the reaction was heated at reflux for 2 hrs. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The crude was treated with ether and filtered to give 1.71 g of title compound were recovered (82% yield)

C₉H₇FN₃
Mass (calculated) [177]; (found) [M+H⁺] =190
LC Rt = 1.13, 69% (5 min method)

c) 5-Piperidin-1-yl-pentanoic acid [5-(3-fluoro-phenyl)-1H-pyrazol-3-yl]-amide

The product was prepared according to the general synthetic method for the one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5aryl)-amides. A solution of 5-bromovaleryl chloride (0.125 mL, 0.94 mmol) in dry DMA (1 mL) was cooled to -10 °C (ice/water bath) under N₂; 5-(3-Fluoro-phenyl)-2H-pyrazol-3-ylamine (177 mg, 0.94 mmol) and diisopropylethylamine (0.324 mL, 1.88 mmol) in dry DMA (1 ml) were added.
The reaction was left stirring for 1 h at 0 °C and then piperidine (0.232 mL, 2.35 mmol) and NaI (141 mg, 0.94 mmol) were added. The reaction mixture was heated at 60 °C, until LC-MS analysis showed complete conversion of the bromo-intermediate, upon which the reaction was cooled, the solvent was removed under reduced pressure and the residue was dissolved in DCM (2 mL) and washed with sat. Na₂CO₃ solution. The organic phase was concentrated under reduced pressure and the crude product was purified by SiO₂ column (gradient from 100% DCM to DCM-NH₃MeOH 2 N solution 8:2) followed by preparative HPLC. The fractions containing the title product were collected to afford 15 mg (4.4% of yield) as its formate salt.

C₁₉H₂₅FN₄O

Mass (calculated) [344]; (found) [M+H⁺] =345

LC Rₜ = 1.64, 100% (10 min method)

¹H-NMR (400 MHz, DMSO-d₆): 1.37-1.58 (1OH, m); 2.27-2.31 (2H, m); 2.35-2.44 (6H, m); 6.85 (1H, s); 7.14 (1H, t, J=8.6 Hz); 7.45 (1H, m), 7.53-7.55 (2H, m); 8.21 (1H, s, formate); 10.47 (1H, s).

Example 18

5-Azepan-l-yl-pentanoic acid (5-pyridin-4-yl-lH-pyrazol-3-yl)-amide

a) S-Oxo-S-pyridin-4-yl-propionitrile

The product was prepared according to a modification of route A1. To a solution of 3 g (22 mmol) of isonicotinic acid methyl ester in dry toluene (30 mL) under N₂, NaH (50-60% dispersion in mineral oil, 1.75 g, 44 mmol) was carefully added.

The mixture was heated at 90 °C and then dry CH₃CN was added dropwise (5.39 mL, 103 mmol). The reaction was heated for 18 hours and the product precipitated from the reaction mixture as the sodium salt. The reaction was allowed to cool down to room temperature and the solid formed was filtered, then it was dissolved in water and the solution was acidified with 6N HCl solution to pH 5-6 and the product extracted with DCM. The pH of the aqueous phase was adjusted again to 4-5 and another extraction with DCM afforded more product.
The organic phases were combined, dried and evaporated. The product was used directly in the following step. Yield of crude product: 58%

b) 5-Pyridin-4-yl-1H-pyrazol-3-ylamine

The product was prepared according to a modification of route A2. To a solution of 3-oxo-3-pyridin-4-yl-propionitrile (1.86 g, 12.74 mmol) in absolute EtOH (35 mL) hydrazine monohydrate (0.74 mL, 15.29 mmol) was added and the reaction was heated at reflux for 2 hours. The reaction mixture was then allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The crude product obtained was washed with ether to afford the title compound (yield: 39%).

C$_8$H$_8$N$_4$

Mass (calculated) [160]; (found) [M+H$^+$] = 161

LC Rt = 0.23, 100% (5 min method)

$^1$H-NMR (400 MHz, DMSOd$_6$): 5.02 (2H, s); 5.85 (1H, s); 7.59 (2H, d, J=6 Hz); 8.50 (2H, d, J=6 Hz); 11.93 (1H, s).

c) 5-Azepan-1-yl-pentanoic acid (5-pyridin-4-yl-1H-pyrazol-3-yl)-amide

The product was prepared according to the general synthetic method for the one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides. A solution of 5-bromoovaleryl chloride (0.125 mL, 0.94 mmol) in dry DMA (1 mL) was cooled to -10 °C (ice/water bath) under N$_2$; 5-Pyridin-4-yl-1H-pyrazol-3-ylamine (151 mg, 0.94 mmol) and diisopropylethylamine (0.324 mL, 1.88 mmol) in dry DMA (1 ml) were added. The reaction was left stirring for 1h at 0 °C and then azepane (0.265 mL, 2.35 mmol, ) and NaI (0.94 mmol, 1 equiv.) were added.

The reaction mixture was heated at 60 °C until LC-MS analysis showed complete conversion of the bromo-intermediate, at which point the reaction was cooled down and the solvent was removed under reduced pressure. The residue was dissolved in DCM (2 mL) and
washed with saturated Na₂CO₃ solution. The organic phase was concentrated under reduced pressure and the crude product was purified by SiO₂ column (gradient from 100% DCM to DCM-NH₃MeOH 2N solution 8:2); the fractions containing the title compound were collected (30 mg, 8.8% of yield).

C₁₉H₂₇N₅O
Mass (calculated) [341]; (found) [M+H⁺] = 342
LC Rt = 0.23, 100% (10 min method)

¹H-NMR (400 MHz, dmso-d₆): 1.58-1.75 (12H, m); 2.34-2.37 (2H, t, J=6.6 Hz); 3.05-3.09 (4H, m); 3.31 (2H, m); 7.09 (1H, s); 7.68 (2H, d, J=4.8 Hz); 8.59 (2H, d, J=4 Hz); 9.14 (1H, s); 10.52 (1H, s); 13.17 (1H, s).

Example 19
6-(4-Acetyl-[1,4j]diazepan-1-yl)-hexanoic acid [5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-amide

[0387] The product was prepared according to the general synthetic method for the one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides. A solution of 5-bromohexanoyl chloride (0.144 mL, 0.94 mmol) in dry DMA (1 mL) was cooled to -10 °C (ice/water bath) under N₂; 5-(4-methoxy-phenyl)-1H-pyrazol-3-ylamine (178 mg, 0.94 mmol) and diisopropylethylamine (0.324 mL, 1.88 mmol) were added in dry DMA (1 ml). The reaction was left stirring for 1h at 0 °C and then 1-[1,4j]diazepan-1-yl-ethanone (0.310 mL, 2.35 mmol, ) and NaI (0.94 mmol, 1 equiv.) were added.

[0388] The reaction mixture was heated at 60 °C until LC-MS analysis showed complete conversion of the bromo-intermediate, at which point the reaction was cooled down and the solvent was removed under reduced pressure. The residue was dissolved in DCM (2 mL) and washed with saturated Na₂CO₃ solution.

[0389] The organic phase was concentrated under reduced pressure and half of the crude was purified by SiO₂ column (gradient from 100% DCM to DCM-NH₃MeOH 2N solution 8:2). The fractions containing the title compound were collected (35 mg).

C₂₃H₃₃N₅O₃
Mass (calculated) [427]; (found) [M+H⁺] = 428
LC Rt = 1.61, 96% (10 min method)

\(^1\)H-NMR (400 MHz, dmso-d6): 1.24-1.29 (2H, m); 1.36-1.44 (2H, m); 1.54-1.58 (2H, m); 1.62-1.76 (2H, m); 1.94-1.96 (3H, m); 2.25-2.28 (2H, m); 2.35-2.41 (2H, m); 2.51-2.54 (2H, m); 2.60-2.62 (1H, m); 3.38-3.44 (5H, m); 3.77 (3H, s); 6.73 (1H, s); 6.98 (2H, d, J=8.8 Hz); 7.61 (2H, d, J=8.8); 10.32 (1H, s)

Example 20

\(N\-[5-(4-Methoxy-phenyl)-2H-pyrazol-S-yl]-2-methyl-4-piperidin-1-yl-butyramide\)

\(a\) 4-Bromo-2-methyl-butyric acid methyl ester

[0390] 4-Bromo-2-methyl-butyric acid (2.16 g, 1 equiv., prepared according to the procedure described in J.Am.Chem.Soc. 1990, 112, 2755) was dissolved in MeOH (10 mL) and a few drops of cone. H2SO4 were added. The reaction was stirred at reflux for 16 hours. After reaction completion, as monitored by LC-MS, MeOH was removed under reduced pressure, the oily residue was diluted with water, the pH adjusted to 9 with 10% NaOH, and the product was extracted with \(\text{Et}_2\text{O} (2 \times 20 \text{mL})\) and dried over \(\text{Na}_2\text{SO}_4\). The title compound was obtained as a colourless oil (1.29 g, 55% yield) after solvent removal.

\(\text{C}_6\text{H}_n\text{BrO}_2\)

NMR (400 MHz, CDCl\(_3\)): 1.19 (3H, d); 1.94-1.89 (2H, m); 2.29-2.23 (2H, m); 3.43-3.40 (1H, m); 3.69 (3H, s).

\(b\) 2-Methyl-4-piperidin-1-yl-butyric acid. HCl

[0391] 4-Methyl-2-methyl-butyric acid (2.16 g, 1 equiv.) was dissolved in toluene (15 mL) and piperidine (1.07 mL, 3 equiv.) was added; the reaction was stirred for 3 hours. After reaction completion, as monitored by LC-MS, toluene was removed under reduced pressure and the crude ester was dissolved in 1M NaOH (14 mL, 1.1 equiv.) and MeOH (2 mL). The reaction was stirred at reflux for 16 hours; after hydrolysis was complete, the reaction was concentrated under reduced pressure and the pH adjusted to 4 with 6 N HCl. EtOH was added to help precipitation of NaCl. The organic phase was filtered and EtOH removed under reduced pressure. The resulting oil was treated with 2 M HCl in \(\text{Et}_2\text{O}\) to obtain 2-methyl-4-piperidin-1-yl-butyric acid. HCl (0.96 g, 66% yield)
c) N-[5-(4-Methoxy-phenyl)-2H-pyrazol-5-yl]-2-methyl-4-piperidin-1-yl-butyramide

2-Methyl-4-piperidin-1-yl-butyric acid. HCl (0.45 g, 1.2 equiv.) was suspended in 1,2-DCE (15 mL) and triethylamine (0.29 mL, 1.2 equiv.) was added: l,l'-carbonyldiimidazole (0.303 g, 1.1 equiv.) was added in one portion and the reaction was stirred at room temperature for 2 hours. 5-(4-Methoxy-phenyl)-2H-pyrazol-3-ylamine (0.325 g, 1 equiv.) was then added and the reaction stirred at room temperature for further 16 hours. After reaction completion, as monitored by LC-MS, the solvent was removed under reduced pressure and the crude amide was purified by column chromatography (Flash-Si 10 g; CH$_3$CNMeOH 9:1, CH$_3$CN:2N NH$_3$ MeOH 9:1) to give the title compound as thick colourless oil (0.120 g, 0.33 mmol)

C$_{20}$H$_{28}$N$_4$O$_2$

Mass (calculated) [356.48]; (found) [M+H$^+$]=357.25

LC Rt=1.67, 97% (10 min method)

NMR (400 MHz, dmso-d6): 1.18 (3H, d); 1.35-1.31 (2H, m); 1.46-1.41 (4H, m); 1.77-1.72 (1H, m); 2.19-2.16 (2H, m); 2.27-2.23 (4H, m); 2.61-2.58 (2H, m); 3.76 (3H, s); 6.76 (1H, s); 6.92 (2H, d); 7.61 (2H, d); 10.33 (1H, s).

Example 21

N-[4-(4-Methoxy-phenyl)-1H-imidazol-2-yl]-4-piperidin-1-yl-butyramide

[0393] To a suspension of 4-piperidin-1-yl-butyric acid (200 mg, 1.17 mmol, 1.0 equiv.) in 1,2-dichloroethane (2 mL), 7V,7V'-carbonyldiimidazole (179.9 mg, 1.11 mmol, 0.95 equiv.) was added and the mixture was stirred at room temperature for 1 hour until complete activation of the amino acid and dissolution of the suspension. 4-(4-Methoxy-phenyl)-1H-imidazol-2-ylamine (prepared according to the procedure reported in JOC 1994, 59, 24, 7299; 110.5 g, 0.58 mmol, 0.50 equiv.) was added and the reaction stirred for 1 day at 50 °C. The slow conversion was monitored by LC-MS. Another aliquote of activated acid (4-piperidin-1-yl-butyric acid, 200 mg
and carbonyldiimidazole, 179.9 mg in 2 mL of 1,2-dichloroethane) were added and the reaction stirred for further two days at 50 °C.

[0394] The solvent was evaporated under reduced pressure and the crude mixture purified by preparative HPLC to obtain a 9:1 mixture of the product and unreacted 4-(4-methoxy-phenyl)-1H-imidazol-2-ylamine. The crude was purified by treatment with isocyanate resin and SCX column to give 78.0 mg (Yield: 39%) of the title compound as a white solid

C_{19}H_{26}N_{4}O_{2} Mass (calculated) [342]; (found) [M+H^+] =343
LC Rt = 1.00 (and solvent front), 99% (10 min method)

{^1}H-NMR (400 MHz, DMSO): 1.30-1.36 (2H, m); 1.43-1.49 (4H, m); 1.67-1.75 (2H, m); 2.22-2.34 (8H, m); 3.73 (3H, s, -OCH_3); 6.87 (2H, d, J=8.8 Hz); 7.10 (1H, s); 7.60 (2H, d, J= 8.8 Hz);
11.26 (1H, s, NHCO), 11.52 (1H, s, NH).

{^{13}}C-NMR (400 MHz, DMSO): 21.54 (1C); 23.63 (1C); 24.92 (2C); 33.24 (1C); 53.6 (1C, -OCH_3); 55.02 (2C); 57.46 (1C); 113.88 (2C); 125.18 (2C), 141.13 (1C); 157.67 (1C); 162.33 (2C); 163.66 (1C); 171.15 (1C, CO).

Example 22
N-(4-Methyl-5-o-tolyl-2H-pyrazol-3-yl)-4-pyrrolidin-1-yl-butyramide

a) 2-Methyl-3-oxo-3-o-tolyl-propionitrile

[0395] The product was prepared according to the general procedure for aminopyrazole synthesis (route Al). The mixture of methyl 2-methylbenzoate (3.0 mL, 20.0 mmol, 1.0 equiv.) and NaH (1.6 g, 40.0 mmol, 2.0 equiv.) in dry toluene (20 mL) was heated at 80 °C and then propionitrile (6.7 mL, 94.4 mmol, 4.7 equiv.) was added dropwise: the reaction was heated for 18 hours. The crude product was dissolved in water and extracted with DCM, and it was used in the following step without further purification (3.04 g, yield: 88%).

C_{n}H_{m}N_{p}O

{^1}H-NMR (dmsso-d6): 1.82 (3H, s); 2.26 (3H, s); 2.48-2.49 (1H, m); 7.10-7.42 (4H, m).
b) 4-Methyl-5-o-tolyl-2H-pyrazole-5-ylamine

The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude product was purified through SiO$_2$ column (20 g) with gradient elution from 100% ethyl acetate (EtOAc) to EtOAc-MeOH 80:20. The title product (1.2 g, 37% yield) was obtained.

C$_{19}$H$_{13}$N$_3$

Mass (calculated) [187]; (found) [M+H$^+$] =188.

LC R$_t$ = 1.33 min, 100% (10 min method)

$^1$H-NMR (dmso-d6): 1.68 (3H, s); 2.17 (3H, s); 4.36 (2H, br s); 7.14 (1H, d, J=7.2 Hz); 7.20-7.26 (3H, m); 11.24 (1H, br s).

c) N-(4-Methyl-5-o-tolyl-2H-pyrazol-3-yl)-4-pyrrolidin-1-yl-butyramide

To a suspension of 4-pyrrolidin-1-yl-butyric acid (118.0 mg, 0.8 mmol, 1.5 equiv.) in 1,2-dichloroethane (3 mL), 7V,7V'-carbonyldiimidazole (113.0 mg, 0.7 mmol, 1.4 equiv.) was added and the mixture was stirred at room temperature for 1 hour, then N,N-diisopropyl ethyl amine (87 µL, 0.5 mmol, 1.0 equiv.) was added and the mixture was stirred at room temperature for further 1 hour until complete dissolution of the suspension. 4-Methyl-5-o-tolyl-2H-pyrazol-3-ylamine (93.5 mg, 0.5 mmol, 1.0 equiv.) was added and the reaction was stirred for 18 hours, then at 50 °C for 1 day, until the conversion of the less stable ring nitrogenacylated isomer to the title compound was observed (as monitored by LC-MS). The solvent was removed under reduced pressure, the crude was purified by SiO$_2$ column to give 44.0 mg of the title compound (yield: 27%).

C$_{19}$H$_{26}$N$_4$O

Mass (calculated) [326]; (found) [M+H$^+$] =327, [M+2/2] =164.

LC R$_t$ = 1.56 min, 95% (10 min method)

$^1$H-NMR (CD$_3$OD): 1.83 (3H, s); 2.07-2.11 (6H,m); 2.22 (3H, s); 2.62 (2H,t, J=7.2 Hz); 3.27-3.39 (6H,m); 7.22-7.28 (2H, m); 7.32-7.34 (2H, m).
Example 23
N-[5-(4-Cyclopropylmethoxy-5-fluoro-phenyl)-2H-pyrazol-5-yl]-4-pyrrolidin-1-yl-butyr amide

a) S-Fluoro-4-hydroxy-benzoic acid methyl ester

[0398] 3-Fluoro-4-hydroxy-benzoic acid (5 g, 32.0 mmol) was dissolved in MeOH (50 mL) and catalytic quantity of sulfuric acid (1 mL) was added. The mixture was refluxed overnight, after which the solvent was evaporated under reduced pressure; the crude was dissolved in DCM and washed with saturated NaHCO₃ to basic pH. The organic phase was dried and evaporated under reduced pressure, and the residue was used without further purification (yield 85%).

C₈H₇FO₃
¹H-NMR (dms-o-d6): 3.78 (3H, s); 7.00-7.02 (1H, m); 7.61-7.64 (2H, m); 10.89 (1, br s).

b) 4-Cyclopropylmethoxy-S-fluoro-benzoic acid methyl ester

[0399] 3-Fluoro-4-hydroxy-benzoic acid methyl ester (1.02 g, 6.0 mmol, 1.0 equiv.) was dissolved in acetone (14 mL), NaI (0.45 g, 3.0 mmol, 0.5 equiv.) and K₂CO₃ (1.66 g, 12.0 mmol, 2.0 equiv.) were added ad the mixture was stirred at room temperature for 20 min. (Bromomethyl)cyclopropane (0.53 mL, 5.4 mmol, 0.9 equiv.) was added, and the mixture was refluxed for 2 days. The solvent was concentrated under reduced pressure, NaOH 10% was added, and it was extracted with DCM and dried.

0.91 g of title product (yield 69%) were recovered and used without further purification.

C₈H₁₃FO₃
¹H-NMR (dms-o-d6): 0.34-0.37 (2H, m); 0.57-0.62 (2H, m); 1.22-1.26 (1H, m); 3.82 (3H, s); 3.99 (2H, d, J=6.8 Hz); 7.26 (1H, t, J=8.4 Hz); 7.67-7.77 (2H, m).

C₁₂H₁₅F₁₃NO₃
¹H-NMR (dms-o-d6): 2.38-2.43 (2H, m); 3.53-3.57 (2H, m); 3.64-3.68 (1H, m); 3.83-3.87 (3H, s); 3.98 (2H, d, J=6.8 Hz); 7.26 (1H, t, J=8.4 Hz); 7.68-7.78 (2H, m).

[0400] The product was prepared according to the general procedure for aminopyrazole synthesis from 4-Cyclopropylmethoxy-3-fluoro-benzoic acid methyl ester (route Albis). 0.84 g of the title product was extracted from water and dried over sodium sulphate (yield 88%) and used directly for the next step.
d) 5-(4-Cyclopropylmethoxy-3-fluoro-phenyl)-2H-pyrazol-S-ylamine

The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude product was purified through SiO2 column with gradient elution from 100% Ethyl Acetate to EtOAc-MeOH 90:10. The title product (576 mg, 65% yield) was obtained.

C_{13}H_{14}FNO

Mass (calculated) [247]; (found) [M+H+] =248.

LC Rt = 2.19 min, 99% (10 min method)

^1H-NMR (CD_{3}OD): 0.33-0.38 (2H, m); 0.59-0.65 (2H, m); 1.22-1.31 (1H, m); 2.90-3.92 (2H, m); 7.02-7.20 (2H, m); 7.34-7.40 (2H, m).

e) N-[5-(4-Cyclopropylmethoxy-3-fluoro-phenyl)-2H-pyrazol-3-yl]-4-pyrrolidin-1-yl-butyramide

The product was prepared according to the general synthetic method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route, starting from 5-(4-Cyclopropylmethoxy-3-fluoro-phenyl)-2H-pyrazol-3-ylamine (123.5 mg, 0.5 mmol, 1.0 equiv.). 130 mg of title compound were recovered as its formate salt after preparative HPLC purification (67% yield).

C_{23}H_{27}N_{4}O_{2}F

Mass (calculated) [386]; (found) [M+H+] =387.

LC Rt = 2.01 min, 100% (10 min method)

^1H-NMR (dmso-d6 of HCOOH salt): 0.32-0.36 (2H, m); 0.56-0.61 (2H, m); 1.21-1.28 (1H, m); 1.73-1.84 (5H, m); 2.36 (2H, t, J=7.2 Hz); 2.67-2.77 (6H, m); 3.92 (3H, d, J=7.2 Hz); 6.79 (1H, s); 7.18 (1H, t, J=8.8 Hz); 7.45-7.47 (1H, m); 7.55-7.59 (1H, m); 8.19 (1H, s); 10.49 (1H, s)
Acetyl guanidine (2.6 g, 25.7 mmol, 3.0 equiv.) was dissolved in DMF anhydrous (40 mL) and 2-Bromo-1-(4-difluoromethoxy-phenyl)-ethanone (2.3 g, 8.5 mmol, 1.0 equiv.) was added; the mixture was stirred under nitrogen at room temperature for 4 days. DMF was dried; the residue was washed with water, filtered and dried. The crude was crystallized from methanol to give 1.2 g of the title compound (yield: 53%).

C_{12}H_{11}F_{2}N_{3}O_{2}

^1H-NMR (dms-o-d6): 3.40 (3H, br s); 7.10-7.47 (4H, m); 7.82 (2H, d, J=8.4 Hz); 11.32 (1H, s); 11.73 (1H, br s).

b) 4-(4-Difluoromethoxy-phenyl)-1H-imidazol-2-ylamine

N-[4-(4-Difluoromethoxy-phenyl)-1H-imidazol-2-yl]-acetamide (1.2 g, 4.5 mmol, 1.0 equiv.) was dissolved in water (30 mL) and methanol (30 mL), and 30 drops of sulfuric acid were added. The reaction was refluxed for 2 days, then the mixture was dried; the residue was diluted with water, the pH adjusted to 8 with NaOH 2N, the product was extracted with DCM and concentrated under reduced pressure to give 1.0 g of the title compound (yield: 99%).

C_{10}H_{9}F_{2}N_{3}O

^1H-NMR (dms-o-d6): 5.59 (2H, br s); 6.98-7.35 (4H, m); 7.60-7.62 (2H, m).

c) N-[4-(4-Difluoromethoxy-phenyl)-1H-imidazol-2-yl]-4-pyrrolidin-1-yl-butyramide

To a suspension of 4-pyrrolidin-1-yl-butyric acid (386 mg, 2.0 mmol, 4.0 equiv.) in 1,2-dichloroethane (3 mL), 7V,7V'-carbonyldiimidazole (300 mg, 1.8 mmol, 3.7 equiv.) and N,N-diisopropyl ethyl amine (87 µL, 0.5 mmol, 1.0 equiv.) were added and the mixture was stirred at room temperature for 1 hour until complete activation of the amino acid and dissolution of the suspension.

[4-(4-Difluoromethoxy-phenyl)-1H-imidazol-2-ylamine (112.5 mg, 0.5 mmol, 1.0 equiv.) was added; the reaction was stirred for 1 day at room temperature, then for further 2 days at 50 °C (the slow conversion was not complete and was monitored by LC-MS).
The solvent was evaporated under reduced pressure and the crude mixture purified by preparative HPLC to give 80 mg (yield: 44%) of the title compound as a white solid.

C_{18}H_{22}N_{4}O_{2}F_{2}

Mass (calculated) [364]; (found) [M+H^+]=365, [M/2] =183.

LC Rt = 1.18 min, 100% (10 min method)

$^1$H-NMR (dms-o-d6): 1.74-1.84 (6H, m); 2.38 (2H, t, J=7.6 Hz); 2.70-2.79 (6H, m); 6.99-7.37 (4H, m); 7.71 (2H, d, J=8.8 Hz); 8.23 (1H, br s)

Example 25

N-[5-(5-Chloro-2-methoxy-phenyl)-2H-pyrazol-3-yl]-4-cis-2,6-dimethyl-piperidin-l-yl)-butyramide

**a) 4-(2,6-Dimethyl-piperidin-l-yl)-butyric acid ethyl ester**

[0407] To a solution of cis-2,6-dimethylpiperidine (6.9 mL, 51.3 mmol, 2.5 equiv.) in toluene (25 mL) ethyl 4-bromobutyrate (2.9 mL, 20.5 mmol, 1 equiv.) was added and the reaction mixture was refluxed for 2 days. The mixture was allowed to cool down to room temperature and the white solid present was filtered off and washed with ether. The crude was diluted with HCl IN (8 mL, 1 equiv.), then washed with EtOAc, treated with NaOH IN (16 mL, 2 equiv.) and extracted with ethyl acetate. The title product obtained (1.51 g, yield 32%) was used in the next step without further purification.

C_{13}H_{25}NO_{2}

$^1$H-NMR (CD$_3$OD): 0.99 (6H, d, J=6.0 Hz); 1.07-1.21 (6H, m); 1.45-1.58 (5H, m); 2.20 (2H, t, J=6.8 Hz); 2.30-2.35 (2H, m); 2.53-2.57 (2H, m); 4.02 (2H, q, J=7.2 Hz).

**b) 4-(2,6-Dimethyl-piperidin-l-yl)-butyric acid**

[0408] To a suspension of 4-(2,6-dimethyl-piperidin-l-yl)-butyric acid ethyl ester (1.5 g, 6.7 mmol) in water (5 mL) and MeOH (ImL), NaOH (266 mg, 6.7 mmol, 1.0 equiv.) was added and the mixture was heated at reflux for 22 hours. The reaction was then allowed to cool down to room temperature, the pH adjusted to 4 at 0 °C with HCl 2 N and the mixture was concentrated under reduced pressure. The residue was treated with EtOH, and the sodium chloride precipitated
was filtered off. Evaporation of the solvent under reduced pressure afforded 950 mg of the title compound as a white solid (51% yield).

\[ \text{C}_n\text{H}_{21}\text{NO}_2 \]

\[ ^1\text{H-NMR (CD}_3\text{OD): } 1.28-1.34 \text{ (6H, m); } 1.46-1.74 \text{ (5H, m); } 1.81-1.91 \text{ (4H, m); } 2.36-2.40 \text{ (2H, m); } 3.20-3.27 \text{ (3H, m).} \]

\(c) \text{ N-}[5-(5-Chloro-2-methoxy-phenyl)-2H-pyrazol-3-yl]-4-((\text{cis})-2,6-dimethyl-piperidin-1-yl)-butyramide} \]

[0409] Prepared following the general synthetic method for the one-pot synthesis of \(\omega\)-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides, starting from commercially available 5-(5-Chloro-2-methoxy-phenyl)-2H-pyrazol-3-ylamine (111.8 mg, 0.5 mmol, 1.0 equiv.) and 4-(2,6-Dimethyl-piperidin-1-yl)-butyric acid (149.0 mg, 0.8 mmol, 1.5 equiv.).

[0410] Following the general procedure, 80 mg of title compound were recovered as its formate salt after preparative HPLC purification (40% yield).

\[ \text{C}_{21}\text{H}_{29}\text{N}_{4}\text{O}_2\text{Cl} \]

Mass (calculated) [404]; (found) [M+H\(^+\)] = 405

LC Rt = 2.03 min, 100% (10 min method)

\[ ^1\text{H-NMR (dmso-d}_6 \text{ of HCOOH salt): } 1.12 \text{ (6H, d, J=6.4 Hz); } 1.27-1.32 \text{ (3H, m); } 1.57-1.59 \text{ (3H, m); } 1.68-1.74 \text{ (2H, m); } 2.27-2.31 \text{ (2H, m); } 2.72-2.82 \text{ (4H, m); } 3.87 \text{ (3H, s); } 6.92 \text{ (1H, s); } 7.14 \text{ (1H, d, J=9.2 Hz); } 7.33-7.36 \text{ (1H, m); } 7.70 \text{ (1H, d, J=2.8 Hz); } 8.26 \text{ (1H, s); } 10.48 \text{ (1H, br s).} \]

**Example 26**

\(N-[5-(4-Difluoromethoxy-phenyl)-2H-pyrazol-3-yl]-4-((S)-2-methyl-pyrrolidin-1-yl)-butyramide} \)

\(a) \text{ 4-((S)-2-Methyl-pyrrolidin-1-yl)-butyric acid ethyl ester} \]

[0411] (S)-2-methyl-pyrrolidine hydrochloride (0.8 g, 6.6 mmol, 1.1 equiv.) was dissolved in 2-butane (20 mL) and potassium carbonate (1.7 g, 12.6 mmol, 2.1 equiv.) was added. Ethyl 4-bromobutyrate (0.86 mL, 6.0 mmol, 1.0 equiv.) was added and the reaction mixture was refluxed for 2 days. The mixture was allowed to cool to room temperature and any solid present was filtered off and washed with ether. The filtrate was concentrated under reduced
pressure to give 1.20 g of the title compound (yield 99%) which was used in the next step
without further purification.

CnH₂₁NO₂

¹H-NMR (dmsø-d₆): 0.95 (3H, d, J= 6.0 Hz); 1.13-1.17 (3H, m); 1.20-1.28 (1H, m); 1.59-1.64
(4H, m); 1.77-1.86 (1H, m); 1.90-2.00 (2H, m); 2.10-2.23 (1H,m); 2.25-2.31 (2H,m); 2.62-2.66
(1H,m); 2.96-2.99 (1H, m); 3.98-4.03 (2H, m).

b) 4-((S)-2-Methyl-pyrrolidin-l-yl)-butyric acid

[0412] The product was prepared according to the general procedure for ω-amino acid
synthesis (route C2). Evaporation of water under reduced pressure afforded 1.1 g of the title
compound (76% yield) as its hydrochloride salt.

C₉H₁₇NO₂

¹H-NMR (dmsø-d₆ of HCl salt): 1.22-1.27 (3H, m); 1.62-1.64 (1H, m); 2.03-2.09 (6H, m); 2.19-
2.28 (1H, m); 2.47-2.58 (1H, m); 2.86-2.92 (1H,m); 3.15-3.40 (1H, m); 3.69-3.75 (2H, m); 7.25
(1H,s).

c) N-[5-(4-Difluoromethoxy-phenyl)-2H-pyrazol-3-yl]-4-((S)-2-methyl-pyrrolidin-l-yl)-
butyramide

[0413] Prepared following the general synthetic method for the one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides, starting from 5-(4-Difluoromethoxy-phenyl)-2H-pyrazol-3-ylamine (112.5 mg, 0.5 mmol, 1.0 equiv.) and 4-((S)-2-Methyl-pyrrolidin-
l-yl)-butyric acid (155.0 mg, 0.8 mmol, 1.5 equiv.).

120 mg of title compound were recovered as its formate salt after preparative HPLC purification
(69% yield).

C₁₉H₂₄N₄O₂F₂

Mass (calculated) [378]; (found) [M+H⁺] =379

LC Rt = 1.64 min, 98% (10 min method)

¹H-NMR (dmsø-d₆ of HCOOH salt): 1.04 (3H, d, J=6.0 Hz); 1.30-1.37 (1H, m); 1.65-1.89 (5H, m);
2.16-2.26 (2H, m); 2.28-2.40 (2H, m); 2.80-2.82 (1H, m); 3.12-3.17 (2H, m); 6.79 (1H, s);
7.07-7.44 (3H, m); 7.73-7.75 (2H, m); 8.18 (1H,s); 10.44 (1H, br s)
Example 27

N-[5-(1H-Indol-3-yl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide

a) S-(1H-Indol-S-yl)-S-oxo-propionitrile

[0414] In a flask, cyanoacetic acid (5.0 g, 58.8 mmol, 1.2 equiv.) was dissolved in acetic anhydride (50 mL) and heated at 50°C. Indole (5.8 g, 50.0 mmol, 1.0 equiv.) was added and the reaction was heated at 80°C for 5 min. A white precipitate crushed out of the solution; the reaction was cooled to room temperature and then filtered. The solid obtained (620.0 mg, 85% yield) was used for the next step without further purification.

C₈H₈N₂O

¹H-NMR (dms-o-d6): 4.48 (2H, s); 7.21-7.24 (2H, m); 7.48-7.50 (1H, m); 8.12-8.14 (1H, m); 8.37 (1H, d, J=3.2 Hz); 12.17 (1H, s).

b) 5-(1H-Indol-3-yl)-2H-pyrazol-3-ylamine

[0415] To a solution of 3-(1H-indol-3-yl)-3-oxo-propionitrile (6.4 g, 34.7 mmol, 1.0 equiv.), in absolute EtOH (40 mL), hydrazine monohydrate (5.0 mL, 104.1 mmol, 3.0 equiv.) was added and the reaction was heated at reflux for 24 hours. The reaction mixture was allowed to cool to room temperature; the solid was filtered and washed with Et₂O/EtOAc 10/1 to give 3.0 g of title product (yield 74%).

C₁₀H₁₀N₄

Mass (calculated) [198]; (found) [M+H⁺]=199.

LC Rt = 0.98 min, 90% (5 min method)

¹H-NMR (dms-o-d6): 4.57 (2H, bs); 5.70 (1H, s); 7.00-7.19 (2H, m); 7.33-7.46 (1H, m); 7.59 (1H, s); 7.69-7.90 (1H, bs); 11.1 1.1 1.36 (1H, bs); 11.37-1.77 (1H, bs).

c) N-[5-(1H-Indol-3-yl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide

[0416] To a suspension of 4-piperidin-1-yl-butyric acid (621.0 mg, 3.0 mmol, 1.5 equiv.) in 1,2-dichloroethane (6 mL), 7V,7V'-carbonyldiimidazole (453.0 mg, 2.8 mmol, 1.4 equiv.) was added and the mixture was stirred at room temperature for 1 hour. 5-(1H-indol-3-yl)-2H-pyrazol-3-ylamine (400.0 mg, 2.0 mmol, 1.0 equiv.) in 1,2-dichloroethane (6 mL) was added; the
reaction was stirred at room temperature for 2 days, then 1 day at 70°C, to allow complete
migration of the acyl group from the ring nitrogen to the exocyclic nitrogen. The reaction then
was allowed to cool down to room temperature and the mixture was washed with saturated
Na₂CO₃ and evaporated under reduced pressure; the crude was purified by preparative HPLC to
give 320.0 mg (yield: 41%) of the title compound as formate salt.

C₂₀H₂₅N₅O₃
Mass (calculated) [351]; (found) [M+H⁺] =352.
LC Rt = 1.42 min, 95% (10 min method)
1H-NMR (dmsod-6 of HCOOH salt): 1.37-1.39 (2H, m); 1.50-1.54 (4H, m); 1.72-1.80 (2H, m);
2.30-2.34 (2H, m); 2.40-2.48 (6H, m); 6.78 (1H, s); 7.08-7.17 (2H, m); 7.43 (1H, d, J=7.6 Hz);
7.71 (1H, d, J=2.8 Hz); 7.76 (1H, d, J=7.6 Hz); 8.19 (1H, s); 10.39 (1H, s); 11.39 (1H, s)

Example 28
N-[5-(4-Isopropoxy-phenyl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide
a) 4-Isopropoxy-benzoic acid methyl ester

[0417] 3.0 g of 4-isopropoxy-benzoic acid (16.7 mmol, 1.0 equiv.) were dissolved in
MeOH (20 mL) and a catalytic quantity of sulfuric acid was added; the mixture was heated at
reflux for 2 days. The solvent was then evaporated and the residue was dissolved in DCM and
washed with 10% NaOH. The organic phases were dried and evaporated to give 2.2 g of title
product (yield 67%).

C₇H₁₄O₃
1H-NMR (dmsod-6): 1.25 (6H, d, J=6.4 Hz); 3.77 (3H, s); 4.67-4.70 (1H, m); 6.96-6.98 (2H, m);
7.84-7.87 (2H, m).

b) S-(4-Isopropoxy-phenyl)-S-oxo-propionitrile

[0418] To a solution of 4-Isopropoxy-benzoic acid methyl ester (2.2 g, 11.2 mmol, 1.0
equiv.) in dry toluene (15 mL) under N₂, NaH (50-60% dispersion in mineral oil, 1.1 g, 22.4
mmol, 2.0 equiv.) was added. The mixture was heated at 80°C and then dry CH₃CN was added
dropwise (2.8 mL, 56.0 mmol, 5.0 equiv.). The reaction was heated for 18 hours, then was
allowed to cool down to room temperature and acidified with HCl 2N. The organic phase was
recovered and 2.0 g of crude were obtained and it was used for cyclization without further purification.

CnH_{14}O_{3}

c) 5-(4-Isopropoxy-phenyl)-2H-pyrazol-S-ylamine

[0419] The product was prepared from 3-(4-isopropoxy-phenyl)-3-oxo-propionitrile according to general procedure for aminopyrazole synthesis (route A2). The solvent was removed under reduced pressure, water (10 mL) was added, and the title product (1.0 g, 94% yield) was precipitated as a yellow solid and used for the next step without further purification.

C_{12}H_{15}N_{3}O
Mass (calculated) [217]; (found) [M+H+] =218.
LC Rt = 1.36 min, 95% (5 min method)
{^1}H-NMR (dms-o-d6): 1.24 (6H, d, J=6.0 Hz); 4.57-4.69 (3H, br m); 5.64 (1H, s); 6.89 (2H, d, J=8.8 Hz); 7.51 (2H, d, J=8.8 Hz)

d) N-{5-(4-Isopropoxy-phenyl)-2H-pyrazol-3-yl}-4-piperidin-l-yl-butyramide

[0420] The product was prepared according to the general synthetic method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route, starting from 5-(4-isopropoxy-phenyl)-2H-pyrazol-3-ylamine (86.0 mg, 0.4 mmol, 1.0 equiv.). The crude product was purified via preparative HPLC; the title product (56.0 mg, 38% yield) was obtained as formate salt.

C_{21}H_{30}N_{4}O_{2}
Mass (calculated) [370]; (found) [M+H+] =371, [M+2/2] =165.
LC Rt = 1.91 min, 96% (10 min method)
{^1}H-NMR (dms-o-d6 of HCOOH salt): 1.25 (6H, d, J=6 Hz); 1.33-1.41 (2H, m); 1.48-1.53 (4H, m); 1.71-1.77 (2H, m); 2.29 (2H, t, J=7.2 Hz); 2.35 (2H, t, J=7.2 Hz); 2.42-2.47 (4H, m); 4.60-4.66 (1 H, m); 6.71 (1 H, s); 6.94 (2H, d, J=8.8 Hz); 7.58 (2H, d, J=8.8 Hz); 8.17 (1H, s); 10.38 (1H, s).
Example 29
N-[5-(1-Ethyl-1H-indol-3-yl)-2H-pyrazol-3-yl]-4-pyrrolidin-1-yl-butyramide

a) 1-Ethyl-1H-indole-3-carboxylic acid methyl ester

To a suspension of NaH (50-60% dispersion in mineral oil, 548.0 mg, 11.4 mmol, 2.0 equiv.) in THF (20 mL), 1H-indole-3-carboxylic acid methyl ester (1.0 g, 5.7 mmol, 1.0 equiv.) was added and after 20 min also ethyl iodide (507.0 µL, 6.3 mmol, 1.1 equiv.) was added. The reaction was heated at 70 °C for 1 h. The mixture was cooled down to 0 °C and water (10 mL) was added carefully. AcOEt was added and the organic phase was collected and concentrated, to give the crude compound that was purified through SiO2 column (10 g) with gradient elution from 100% cyclohexane to cyclohexane-EtOAc 80:20. The title product (860 mg, 74% yield) was obtained.

C12H13NO2

1H-NMR (dms-o-d6): 1.36 (3H, t, J=7.2 Hz); 3.77 (3H, s); 4.26 (2H, q, J=7.2); 7.16-7.27 (2H, m); 7.55-7.59 (1H, m); 7.97-7.99 (1H, m); 8.15 (1H, s).

b) 3-(1-Ethyl-1H-indol-3-yl)-3-oxo-propionitrile

The product was prepared according to the general procedure for aminopyrazole synthesis (route Albis) from 1-ethyl-1H-indole-3-carboxylic acid methyl ester (860.0 mg, 4.2 mmol, 1.0 equiv.). 820.0 mg of the title product (yield 91%) were obtained and used directly for the next step.

C11H12N2O

c) 5-(1-Ethyl-1H-indol-3-yl)-2H-pyrazol-3-ylamine

The product was prepared according to general procedure for aminopyrazole synthesis (route A2) starting from 3-(1-ethyl-1H-indol-3-yl)-3-oxo-propionitrile (820 mg, 3.87 mmol, 1.0 equiv.). The solvent was removed under reduced pressure; the solid residue was washed with EtOH to obtain the title product (612 mg, 70% yield).

C13H14N4

Mass (calculated) [226]; (found) [M+H+] =227.
LC Rt = 1.30 min, 69% (5 min method)

\[ \text{d) N-[5-(1-Ethyl-1H-indol-3-yl)-2H-pyrazol-3-yl]-4-pyrrolidin-l-yl-butyramide} \]

[0424] The product was prepared according to the general synthetic method for the synthesis of \( \omega \)-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route, starting from 5-(1-ethyl-1H-indol-3-yl)-2H-pyrazol-3-ylamine (99.0 mg, 0.5 mmol, 1.0 equiv.) and 4-pyrrolidin-1-yl-butyric acid (118 mg, 0.75 mmol). The crude product was purified via preparative HPLC; the title product (77.0 mg, 42% yield) was obtained as formate salt.

\( \text{C}_{21}\text{H}_{27}\text{N}_{5}\text{O} \)

Mass (calculated) [206]; (found) [M+H\(^+\)] =366.

LC Rt = 1.83 min, 99% (10 min method)

\( ^{1}\text{H-NMR (dms-o-d6 of HCOOH salt):} \) 1.38 (3H, t, \( \text{J}=7.2 \text{ Hz} \)); 1.71-1.81 (6H, m); 2.34 (2H, t \( \text{J}=7.2 \text{ Hz} \)); 2.59-2.65 (6H, m); 4.23 (2H, q, \( \text{J}=7.2 \text{ Hz} \)); 6.76 (1H, s); 7.11-7.22 (2H, m); 7.53 (1H, d, \( \text{J}=8.4 \text{ Hz} \)); 7.75-7.79 (2H,m); 8.19 (1H, br s); 10.40 (1H, s).

Example 30

\( \text{N-[5-(4-Cyclopropylmethoxy-phenyl)-2H-pyrazol-3-yl]-4-pyridin-l-yl-butyramide} \)

a) \( \text{4-Cyclopropylmethoxy-benzoic acid methyl ester} \)

[0425] 4-hydroxy-benzoic acid methyl ester (2.0 g, 13.1 mmol, 1.2 equiv.) was dissolved in acetone (20 mL), NaI (0.97 g, 6.5 mmol, 0.5 equiv.) and \( \text{K}_{2}\text{CO}_{3} \) (3.0 g, 21.8 mmol, 2.0 equiv.) were added and the mixture was stirred at room temperature for 20 min. (Bromomethyl)cyclopropane (1.1 mL, 10.3 mmol, 1.0 equiv.) was added, and the reaction was refluxed for 2 days. The solvent was concentrated under reduced pressure, NaOH 10% was added, and the product was extracted with DCM. The organic phase was dried over \( \text{Na}_{2}\text{SO}_{4} \) and the solvent evaporated under reduced pressure. The title product (1.23 g, yield 79%) was recovered and used without further purification.

\( \text{C}_{12}\text{H}_{14}\text{O}_{3} \)

Mass (calculated) [206]; (found) [M+H\(^+\)] =207.

LC Rt = 2.38 min, 86% (5 min method)
1H-NMR (dms-o-d6): 0.33-0.34 (2H, m); 0.57-0.59 (2H, m); 1.21-1.25 (1H, m); 3.81 (3H, s); 3.89 (2H, d, J=6.8 Hz); 7.02 (2H, d, J=8.8 Hz); 7.88 (2H, d, J=8.8 Hz).

b) 5-(4-Cyclopropylmethoxy-phenyl)-2H-pyrazol-3-ylamine

The product was prepared according to the general procedure (route Albis) from 4-cyclopropylmethoxy-benzoic acid methyl ester (1.17 g, 5.9 mmol, 1.0 equiv.). The reaction was allowed to cool down to room temperature, the solid formed was filtered and dissolved in H2O. The solution was acidified to pH 4 and the solid formed was filtered, affording 1.2 g of 3-(4-cyclopropylmethoxy-phenyl)-3-oxo-propionitrile that was used directly for the next step.

5-(4-Cyclopropylmethoxy-phenyl)-2H-pyrazol-3-ylamine was prepared according to general procedure for aminopyrazole synthesis (route A2). The reaction was concentrated and the residue was precipitated with water: 500 mg of the title product (37% yield) were obtained, and it was used directly for the next step.

C13H15N3O

c) N-[5-(4-Cyclopropylmethoxy-phenyl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide

The product was prepared according to the general synthetic method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route, starting from 5-(4-cyclopropylmethoxy-phenyl)-2H-pyrazol-3-ylamine (152.9 mg, 0.7 mmol, 1.0 equiv.) and 4-piperidin-1-yl-butyric acid (168 mg, 1.0 mmol, 1.5 equiv.). The crude product was purified via preparative HPLC; 72.0 mg of the title product (28% yield) was obtained as a formate salt.

C22H30N4O2

Mass (calculated) [382]; (found) [M+H+] =383.

LC Rt = 1.99 min, 100% (10 min method)

1H-NMR (dmso-d6 of HCOOH salt): 0.33-0.34 (2H, m); 0.55-0.59 (2H, m); 1.19-1.25 (1H, m); 1.38-1.40 (2H, m); 1.49-1.54 (4H, m); 1.70-1.77 (2H, m); 2.28-2.41 (8H, m); 3.84 (2H, d, J=6.8 Hz); 6.74 (1H, s); 6.97 (2H, d, J=8.8 Hz); 7.60 (2H, d, J=8.8 Hz); 8.19 (1H,s); 10.40 (1H, s).
Example 31

4-Azepan-1-yl-N-[5-(4-difluoromethoxy-phenyl)-2H-pyrazol-5-yl]-butyramide

a) 4-Azepan-1-yl-butyric acid ethyl ester

To a solution of azepane (10.2 mL, 102.0 mmol, 4.0 equiv.) in toluene (30 mL), ethyl 4-bromobutyrate (3.8 mL, 26.0 mmol, 1.0 equiv.) was added and the reaction mixture was refluxed for 10 hours. The mixture was allowed to cool to room temperature and the solid present was filtered off and washed with ether. The filtrate was concentrated under reduced pressure to give the aminoester which was used in the next step without further purification.

C_{12}H_{23}NO_2

b) 4-Azepan-1-yl-butyric acid

The product was prepared according to the general procedure for ω-amino acid synthesis (route C2). Evaporation of water under reduced pressure afforded 3.8 g of the title compound (80% yield) as its hydrochloride salt.

C_{10}H_{19}NO_2

Mass (calculated) [185]; (found) [M+H^+] =186.

LC Rt = 0.26 min, 100% (5 min method)

^1H-NMR (dms-o-d6 of HCl salt): 1.53-1.66 (4H, m); 1.77-1.91 (6H, m); 2.30 (2H, t, J=7.2 Hz); 2.98-3.09 (4H, m); 3.27-3.30 (2H, m); 10.42 (1H, br s).

c) 4-Difluoromethoxy-benzoic acid methyl ester

Under N_2 flow, 1.3 g of 4-hydroxy-benzoic acid methyl ester (8.3 mmol, 1.0 equiv.) and 1.5 g of sodium chlorodifluoroacetate (10.0 mmol, 1.2 equiv.) were dissolved in DMF (25 mL) in a two neck round bottom flask; potassium carbonate (1.4 g, 10.0 mmol, 1.2 equiv.) was added and the mixture was heated at 125 °C for 3.5 hours. The mixture was then diluted with water and extracted with DCM; organic phases were dried and evaporated, the crude was purified with Si column (eluent: cycloexane/EtOAc 80/20) to obtain 0.77 g of product (yield 46%) which was used directly for the next step.

C_{9}H_{8}F_{2}O_3
d) S-(4-Difluoromethoxy-phenyl)-S-oxo-propionitrile

The product was prepared according to the general procedure for aminopyrazole synthesis from 872.0 mg (4.3 mmol, 1.0 equiv.) of 4-difluoromethoxy-benzoic acid methyl ester (route Albis). 818.5 mg of the title product (yield 90%) were used directly for the following step.

\[ C_{10}H_7F_2NO_2 \]

\[ \text{Mass (calculated)} \ 
\[ 100\% \ (5 \text{ min method}) \]

\[ \text{LC Rt} = 1.34 \text{ min, } 100\% \ (5 \text{ min method}) \]

\[ ^{1}H\text{-NMR (dmso-d6): 4.82 (2H, br s), 5.71 (1H, s), 7.15 (2H, d, J = 8.4 Hz), 7.22 (1H, t, J = 74.0 Hz), 7.67 (2H, d, J = 8.8 Hz); 11.58 (1H, br s) \]

\[ e) 5-(4-Difluoromethoxy-phenyl)-2H-pyrazol-3-ylamine \]

The product was prepared according to the general procedure for aminopyrazole synthesis (route A2). The crude product was purified through SiO\(_2\) column with gradient elution from 100\% EtOAc to EtOAc-MeOH 80:20. The title product (826 mg, 59\% yield) was obtained.

\[ C_{10}H_9F_2N_3O \]

\[ \text{Mass (calculated)} \ [225]; \ (\text{found}) [M+H]\]^+ =226. \]

\[ \text{LC Rt} = 2.26 \text{ min, } 100\% \ (10 \text{ min method}) \]

f) 4-Azepan-1-yl-N-[5-(4-difluoromethoxy-phenyl)-2H-pyrazol-3-yl]-butyramide

The product was prepared according to the general synthetic method for the synthesis of \(\omega\)-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route, starting from 5-(4-difluoromethoxy-phenyl)-2H-pyrazol-3-ylamine (149.0 mg, 0.7 mmol, 1.0 equiv.). 90.0 mg of title compound were recovered as its formate salt after preparative HPLC purification (35\% yield).

\[ C_{20}H_{26}F_2N_4O_2 \]

\[ \text{Mass (calculated)} \ [392]; \ (\text{found}) [M+H]\]^+ =393, [M+2/2] =197. \]

\[ \text{LC Rt} = 2.26 \text{ min, } 100\% \ (10 \text{ min method}) \]

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$^1$H-NMR (dmsO-d$_6$ of HCOOH salt): 1.51-1.60 (8H, m); 1.72-1.76 (2H, m); 2.31 (2H, t, $J$=7.6 Hz); 2.56 (2H, t, $J$=7.2 Hz); 2.69 (4H, t, $J$=5.2 Hz); 6.80 (1H, s); 7.08-7.45 (3H, m); 7.73-7.76 (2H, m); 8.21 (1H, s); 10.50 (1H, br s).

**Example 32**

*Trans (±)-2-piperidin-1-ylmethyl-cyclopropanecarboxylic acid (5-o-tolyl-2H-pyrazol-3-yl)-amide*

**a)** *Trans (±)-2-piperidin-1-ylmethyl-cyclopropanecarboxylic acid ethyl ester*

[0434] Under N$_2$ atmosphere, ethyl 2-formyl-1-cyclopropanecarboxylate (3.0 g, 21.1 mmol, 1.2 equiv.) and piperidine (1.5 g, 17.6 mmol, 1.0 equiv.) were dissolved in DCM (45 mL); after 2 hours at room temperature, the mixture was cooled at 0 °C and sodium triacetoxyborohydride (5.6 g, 26.4 mmol, 1.5 equiv.) was added dropwise. The mixture was stirred at room temperature for 2.5 hours, then the organic phase was washed with NaOH aq and water to give 3.3 g of the title product (yield 89%).

C$_{12}$H$_2$INO$_2$

$^1$H-NMR (CDCl$_3$): 0.70-0.75 (1H, m); 1.20-1.38 (4H, m); 1.39-1.43 (3H, m); 1.53-1.61 (5H, m); 2.22-2.27 (1H, m); 2.34-2.43 (5H, m); 4.08-4.17 (2H, m).

**b) Trans (±)-2-piperidin-1-ylmethyl-cyclopropanecarboxylic acid**

[0435] The product was prepared according to the general procedure for $\omega$-amino acid synthesis (route C2). Evaporation of water under reduced pressure and trituration with diethyl ether afforded 1.3 g of the title compound (33% yield) as chloridrate salt.

C$_{10}$H$_{17}$NO$_2$

Mass (calculated) [183]; (found) [M+H$^+$] =184.

LC Rt = 0.19 min (5 min method)

$^1$H-NMR (dmsO-d$_6$ ofHCl salt): 0.96-1.01 (1H, m), 1.06-1.11 (1H, m), 1.27-1.41 (1H, m), 1.62-1.85 (7H, m), 2.82-3.06 (4H, m), 3.36-3.37 (2H, m), 10.88 (1H, bs), 12.38 (1H, bs)
c) Trans (±)-2-piperidin-l-ylmethyl-cyclopropanecarboxylic acid (5-o-tolyl-2H-pyrazol-3-yl)-amide

The product was prepared according to the general synthetic method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route, starting from commercially available 5-o-tolyl-2H-pyrazol-3-ylamine (152.0 mg, 0.9 mmol, 1.0 equiv.). The crude product was purified with prep HPLC and SiO$_2$ column with gradient elution from 100% CH$_3$CN to CH$_3$CN/2N NH$_3$ in MeOH 80:20. The title product (18 mg, 6% yield) was obtained.

C$_{20}$H$_{26}$N$_4$O
Mass (calculated) [338]; (found) [M+H$^+$] =339, [M+2/2]=170.
LC Rt = 1.71 min, 100% (10 min method)
$^1$H-NMR (dms-o-d6): 0.62 (1H, br s); 0.94-0.97 (1H, m); 1.27-1.37 (3H, m); 1.44-1.49 (4H, m); 1.65-1.68 (1H, m); 2.08-2.13 (1H, m); 2.30-2.35 (8H, m); 6.62 (1H, s); 7.24-7.27 (3H, m); 7.38 (1H, d, J=6.0 Hz); 10.64 (1H, s); 12.45 (1H, s).

Example 33

Trans (±)-2-piperidin-l-ylmethyl-cyclopropanecarboxylic acid [5-(2-difluoro methoxy -phenyl)-2H-pyrazol-3-yl]-amide

a) 2-Difluoromethoxy-benzoic acid methyl ester

2.0 g of 2-difluoromethoxy-benzoic acid (10.6 mmol, 1.0 equiv.) were dissolved in MeOH (15 mL) and a catalytic quantity of sulfuric acid was added; the mixture was heated at reflux overnight. The solvent was then evaporated and the residue was dissolved in DCM and washed with saturated NaHCO$_3$. The organic phase was dried and evaporated to give 1.9 g of title product (yield 87%).

C$_9$H$_8$F$_2$O$_3$
$^1$H-NMR (dms-o-d6): 3.82 (3H, s); 6.99-7.40 (2H, m); 7.31 (1H, d, J=8.4 Hz); 7.63-7.67 (1H, m); 7.82-7.84 (1H, m).
b) \textit{S-(2-Difluoromethoxy-phenyl)-S-oxo-propionitrile}

The product was prepared according to the general procedure for aminopyrazole synthesis from 1.5 g (7.4 mmol, 1.0 equiv.) of 2-Difluoromethoxy-benzoic acid methyl ester (route Albis). The crude product was used directly for the next step.

\[ \text{C}_{10}\text{H}_{7}\text{F}_{2}\text{NO}_{2} \]

c) \textit{5-(2-Difluoromethoxy-phenyl)-2H-pyrazol-S-ylamine}

The product was prepared according to general procedure for aminopyrazole synthesis (route A2). The crude product was purified through SiO\textsubscript{2} column with gradient elution from 100% EtOAc to EtOAc-MeOH 90:10. The title product (1.3 g, 76% yield) was obtained.

\[ \text{C}_{10}\text{H}_{3}\text{F}_{2}\text{N}_{3} \text{O} \]

\[ ^{1}\text{H-NMR (dms-o-d6): 4.82 (2H, bs), 5.79 (1H, s), 7.00-7.37 (4H, m), 7.79 (1H, d), 11.74 (1H, bs)} \]

d) \textit{Trans (±)-2-piperidin-1-ylmethyl-cyclopropanecarboxylic acid [5-(2-difluoro methoxy -phenyl)-2H-pyrazol-S-yl]-amide}

The product was prepared according to the general synthetic method for the synthesis of \(\omega\)-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route, starting from trans (±)-2-piperidin-1-ylmethyl-cyclopropanecarboxylic acid (99.1 mg, 0.6 mmol, 1.3 equiv.) and 5-(2-difluoromethoxy-phenyl)-2H-pyrazol-3-ylamine (125.7 mg, 0.4 mmol, 1.0 equiv.). The crude product was purified through SiO\textsubscript{2} column with gradient elution from 100% DCM to DCM-NH\textsubscript{3} in MeOH 2 N 80:20. The title product (39.9 mg, 23% yield) was obtained.

\[ \text{C}_{20}\text{H}_{24}\text{F}_{2}\text{N}_{4}\text{O}_{2} \]

Mass (calculated) [390]; (found) [M+H\textsuperscript{+}] =391.

LC Rt = 1.68 min, 100% (10 min method)

\[ ^{1}\text{H-NMR (dms-o-d6): 0.62-0.65 (1H, m); 0.96-1.00 (1H, m); 1.21-1.69 (7H, br m); 2.13 (1H, br s); 2.30-2.49 (3H, m); 3.29-3.31 (3H, m); 6.91-7.42 (5H, m); 7.72 (1H, d, J=7.2 Hz); 10.67 (1H, s); 12.68 (1H, s)} \]
Example 34

N-[5-(4-Chloro-phenyl)-2H-pyrazol-3-yl]-2-methyl-4-pyrrolidin-1-yl-butyramide

The product was prepared according to the general synthetic method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route, starting from 5-(4-Chloro-phenyl)-2H-pyrazol-3-yl-amine (58.0 mg, 0.3 mmol, 1.0 equiv.) and 2-methyl-4-pyrrolidin-1-yl-butyric acid (77.0 mg, 0.45 mmol, 1.5 equiv.). After purification with HPLC prep, 21.1 mg of title compound were recovered as formate salt (18% yield).

C_{18}H_{23}ClIN_4O
Mass (calculated) [346]; (found) [M+H^+] =347, [M+2/2]= 174.
LC Rt = 1.84 min, 100% (10 min method)

^1H-NMR (dmsod6 of HCOOH salt): 1.07 (3H, d, J=6.8 Hz); 1.47-1.52 (1H, m); 1.64-1.67 (4H, m); 1.74-1.79 (1H, m); 2.38-2.58 (4H, m); 3.79 (3H, s); 6.87-6.90 (1H, m); 7.25-7.27 (2H, m); 7.33 (1H, t, J=8.4 Hz); 10.42 (1H, br s)

Example 35

5-(4-Acetyl-[1,4]diazepan-1-yl)-2-methyl-pentanoic acid [5-(4-methoxy-phenyl)-2H-pyrazol-3-ylj-amide

a) 5-Amino-3-(4-methoxy-phenyl)-pyrazole-l-carboxylic acid tert-butyl ester

Di-tert-butyl dicarbonate (605.0 mg, 2.8 mmol, 1.0 equiv.) in DCM (3 mL) was added to a vigorously stirred mixture of 5-amino-3-(4-methoxy-phenyl)-pyrazole (500.0 mg, 2.7 mmol, 1.0 equiv.), DCM (20 mL) and KOH 4.5M aqueous solution (4.7 mL, 21.1 mmol, 8 equiv.). The mixture was stirred at room temperature for 20 hours. The organic layer was collected and washed with a water/brine 1/1 solution. Evaporation of the solvent gave a crude product purified by SiO_2 column (elution DCM), to give the title product (720 mg, yield 94%).

C_{15}H_{19}N_3O_3
Mass (calculated) [289]; (found) [M+H^+] =290
LC Rt = 1.43 min, 100% (3 min method)

^1H-NMR (dmsod6): 1.58 (9H, s); 3.78 (3H, s); 5.69 (1H, s); 6.36 (2H, s); 6.96 (2H, br d, J= 8.8 Hz); 7.68 (2H, br d, J= 8.8 Hz).
b) 2-(S-Bromo-propyl)-2-methyl-malonic acid dimethyl ester

[0443] NaH at 60% in mineral oil (1.63 g, 40.8 mmol, 1.3 equiv.) was washed three times with hexane and subsequently dried. After addition of dried THF (30mL) the suspension was cooled to 0 °C. Dimethyl methylmalonate (4.7 g, 32.3 mmol, 1.0 equiv.) was slowly and carefully added and gas development was observed. The mixture was stirred for 15 minutes and subsequently 1,3-dibromopropane (24 g, 119.0 mmol, 3.7 equiv.) was added in one portion. The mixture was allowed to reach room temperature and was then stirred for further 16 hours. NaOH 1.0 M solution was added, the crude was extracted with ethyl acetate; the organic layers were collected and dried, the obtained oil was purified by SiO₂ column (elution: cyclohexane followed by EtOAc). The title product (6.6 g, 76% yield) was obtained.

C₉H₁₅BrO₄

¹H-NMR (dmsd-d6): 1.32 (3H, s); 1.67-1.72 (2H, m); 1.861-1.90 (2H, m); 3.51 (2H, t, J= 6.4 Hz); 3.64 (6H, s).

c) 5-Bromo-2-methyl-pentanoic acid

[0444] HBr aq 48% (10 mL, 88.4 mmol) was added at room temperature to 2-(3-bromo-propyl)-2-methyl-malonic acid dimethyl ester (1.80 g, 6.74 mmol) and the mixture was stirred and heated at 120 °C for 24 hours. After cooling to room temperature, NaOH solution was added to reach pH 3 and the product was extracted using a mixture DCM:MeOH 95:5. The obtained crude (0.81 g, 62% yield) was clean enough to be used without further purification.

C₇H₁₁BrO₂

¹H-NMR (dmsd-d6): 1.05 (3H, d, J= 7.2 Hz); 1.41-1.50 (1H, m); 1.61-1.70 (2H, m); 1.75-1.83 (2H, m); 2.31-2.40 (1H, m); 3.52 (2H, dd, J= 6.8 Hz, 6.4 Hz).

d) 5-(5-Bromo-2-methyl-pentanoylamino)-S-(4-methoxy-phenyl)-pyrazole-1-carboxylic acid tert-butyl ester

[0445] Oxalyl chloride (250.0 µL, 3.0 mmol, 1.5 equiv.) was slowly added to a solution of 5-bromo-2-methyl-pentanoic acid (390.0 mg, 2.0 mmol, 1.0 equiv.) in DCM (1 mL) at room temperature and the mixture was stirred for 2 hours under nitrogen. Evaporation of solvent and excess of oxalyl chloride gave a residue which was dissolved in DCM (1 mL) and added
dropwise to a solution of 5-amino-3-(4-methoxy-phenyl)-pyrazole-1-carboxylic acid tert-butyl ester (656.0 mg, 2.3 mmol, 1.15 equiv.) and triethylamine (0.28 mL, 2.0 mmol, 1.0 equiv.) in DCM (1 mL). The mixture was stirred at room temperature for 48 hours, after which saturated NaHCO₃ solution was added and the organic layer was collected and dried. The crude was purified through SiO₂ column (elution of cyclohexane-DCM from 10:0 to 1:1) obtaining the title compound (237.0 mg, yield 25%).

C₂₁H₂₈BrN₃O₄
Mass (calculated) [466]; (found) [M+H⁺] = 467
LC Rt = 1.83 min, 92% (3 min method)
¹H-NMR (dmsø-d₆): 1.14 (3H, d, J = 6.8 Hz); 1.62 (9H, s); 1.72-1.86 (4H, m); 2.63-2.70 (1H, m); 3.55 (2H, dd, J = 6.8 Hz, 6.4 Hz); 3.78 (3H, s); 7.01 (2H, br d, J = 8.8 Hz); 7.07 (1H, s); 7.79 (2H, br d, J = 8.8 Hz); 10.09 (1H, s).

e) 5-{[5-(4-Acetyl-[1,4]-diazepan-l-yl)-2-methyl-pentanoylamino]-3-(4-methoxy-phenyl)-pyrazole-1-carboxylic acid tert-butyl ester

[0446] 5-(5-Bromo-2-methyl-pentanoylamino)-3-(4-methoxy-phenyl)-pyrazole-1-carboxylic acid tert-butyl ester (280.0 mg, 0.6 mmol, 1.0 equiv.) was dissolved in DCM (3 mL). Triethylamine (80 µL, 0.6 mmol, 1.0 equiv.) and 1-[1,4]-diazepan-1-yl-ethanone (158 µL, 170.0 mg, 1.2 mmol, 2.0 equiv.) were added and the mixture was stirred at room temperature for 24 hours, then at 50 °C for 16 hours. NaHCO₃ saturated solution was added and the organic layer separated and collected. Evaporation of the solvent gave a crude product purified using SiO₂ column (elution DCM, DCM:MeOH 99:1 to 96:4) obtaining the title product (181.3 mg, yield 54%).

C₂₈H₂₈IN₅O₅
Mass (calculated) [527]; (found) [M+H⁺] = 528
LC Rt = 1.63 min, 100% (5 min method).
¹H-NMR (dmsø-d₆): 1.13 (3H, d, J = 6.4 Hz); 1.33-1.50 (4H, m); 1.62 (9H, s); 1.65-1.81 (2H, m); 1.96 (3H, s); 2.34-2.44 (1H, m); 2.52-2.67 (3H, m); 2.98-3.13 (3H, m); 3.40-3.46 (4H, m); 3.80 (3H, s); 7.01 (2H, br d, J = 8.8 Hz); 7.06 (1H, s); 7.79 (2H, br d, J = 8.8 Hz); 10.07 (1H, s).
f) 5-(4-Acetyl-[1,4]diazepan-1-yl)-2-methyl-pentanoic acid [5-(4-methoxy-phenyl)-2H-pyrazol-3-ylj-amide

5-[5-(4-Acetyl-[1,4]diazepan-1-yl)-2-methyl-pentanoylamino]-3-(4-methoxy-phenyl)-pyrazole-1-carboxylic acid tert-butyl ester (181.0 mg, 0.34 mmol, 1.0 equiv.) was dissolved in DCM (3 mL) and HCl 4.0 M in dioxane (0.16 mL, 0.64 mmol, 1.9 equiv.) was added at room temperature. After 3 hours another 1.9 equiv. of HCl was added and the mixture stirred for 3 additional hours. NaHCO₃ saturated solution was added and the organic layer collected and dried. Evaporation of solvent gave the title product (120 mg; Yield 82%).

C₂₃H₃₃N₅O₃
Mass (calculated) [427]; (found) [M+H⁺] =428.
LC Rt = 1.58 min, 100% (10 min method)
¹H-NMR (dmso-d₆): 1.05 (3H, d, J= 6.4 Hz); 1.26-1.40 (3H, m); 1.50-1.57 (1H, m); 1.62-1.68 (1H, m); 1.70-1.76 (1H, m); 1.96 (3H, s); 2.36-2.42 (2H, m); 2.53-2.58 (2H, m); 2.59-2.62 (1H, m); 3.31-3.34 (2H, m); 3.37-3.47 (4H, m); 3.78 (3H, s); 6.80 (1H, s); 7.00 (2H, br d, J= 8.8 Hz); 7.63 (2H, br d, J= 8.8 Hz); 10.30 (1H, s); 12.6 (1H, s).

Example 36
5-(4-Acetyl-[1,4]diazepan-1-yl)-2-methyl-pentanoic acid [5-(4-chloro-phenyl)-2H-pyrazol-3-ylj-amide

a) 5-Amino-3-(4-chloro-phenyl)-pyrazole-1-carboxylic acid tert-butyl ester

To a solution of 5-Amino-3-(4-chloro-phenyl)-pyrazole (2.8 g, 14.5 mmol, 1.0 equiv.) in DCM (30 mL) potassium hydroxide (27 mL of a 4.5 M solution) and di-tert-butyl dicarbonate (3.5 g, 16.0 mmol, 1.1 equiv.) were added in sequence. The mixture was stirred at room temperature until complete conversion was observed by LC-MS analysis. The organic layer was recovered by extraction from water and dried under reduced pressure. The solid was washed with MeOH and filtered, to give 3.6 g of a white solid (yield 85%).

C₁₄H₁₀ClN₃O₂
¹H-NMR (dmso-d₆): 1.68 (9H, br s); 5.34 (2H, br s); 7.25-7.27 (1H, m); 7.35 (2H, d, J=8.4 Hz); 7.74 (2H,d, J=8.4 Hz).
b) 5-(5-Bromo-2-methyl-pentanoylamino)-S-(4-chloro-phenyl)-pyrazole-1-carboxylic acid tert-butyl ester

To a solution of 5-bromo-2-methyl-pentanoic acid (1.79 g, 9.2 mmol, 1 equiv.) in anhydrous DCM (8 mL) oxalyl chloride (1.0 mL, 12.0 mmol, 1.3 equiv.) was added dropwise and the mixture was stirred at room temperature for 16 hours. After evaporation of the solvent and the excess oxalyl chloride, the residue was dissolved in anhydrous DCM (8 mL) and a solution of 5-amino-3-(4-chloro-phenyl)-pyrazole-1-carboxylic acid tert-butyl ester (2.7 g, 9.2 mmol, 1.0 equiv.) and triethylamine (1.7 mL, 12 mmol, 1.3 equiv.) was added dropwise at 0 °C. The mixture was allowed to reach room temperature and stirred at room temperature for 24 hours, after which another 0.5 equiv. of activated 5-bromo-2-methyl-pentanoic acid was added. HCl 1 M was added; the crude was extracted with DCM and purified through SiO2 column (eluent DCM) to give 3.3 g (yield 97%) of the title product.

C₂₀H₂₅BrClN₃O₃
Mass (calculated) [370]; (found) [M+H+] =370/372.
LC Rt = 2.33, 95% (5 min method)

c) 5-(4-Acetyl-[1,4]diazepan-yl)-2-methyl-pentanoic acid [5-(4-chloro-phenyl)-2H-pyrazol-3-ylj-amide

[0450] 1-[1,4]Diazepan-1-yl-ethanone (1.4 mL, 10.8 mmol, 1.2 equiv.) was added to a solution of 5-(5-bromo-2-methyl-pentanoylamino)-3-(4-chloro-phenyl)-pyrazole-1-carboxylic acid tert-butyl ester (3.3 g, 9.0 mmol, 1.0 equiv.) and triethylamine (1.25 mL, 9.0 mmol, 1.0 equiv.) in 2-butanone (15 mL) and the mixture was stirred at reflux for 48 hours. After solvent removal, DCM (5 mL) and TFA (3 mL) were added and the mixture was stirred at room temperature for 3 hours. DCM and TFA were evaporated under reduced pressure and the crude was treated with a solution of saturated Na₂CO₃ and extracted with EtOAc. The crude was purified through SiO2 column (gradient elution from 100% DCM to DCM-NH₃ in MeOH 2N 92:8).

1.7 g (yield 44%) of the title product was recovered.
C₂₂H₃₀ClIN₅O₂
Mass (calculated) [431]; (found) [M+H+] =432.

LC Rt = 1.80 min, 90% (10 min method)

\(^1\)H-NMR (CDCl\(_3\)): 1.14-1.21 (3H, d, J = 6.58 Hz); 1.36-1.53 (1H, m); 1.53-2.0 (6H, m); 2.1 (3H, s); 2.48-3.07 (6H, m); 3.39-3.77 (4H, m); 6.93 (1H, s); 7.49 (2H, d, J= 8.0 Hz); 7.71 (2H, d, J= 8.0 Hz); 10.40 (1H, s); 12.87 (1H, s).

Example 37

4-Pyrrolidin-l-yl-pentanoic acid [5-(4-chloro-phenyl)-2H-pyrazol-5-yl]-amide

a) 4-Pyrrolidin-l-yl-pentanoic acid methyl ester

[0451] Pyrrolidine (3 mL, 36 mmol, 1.2 equiv.) was dissolved in DCM (50 mL) and methyl levulinate (4 mL, 30 mmol, 1.0 equiv.) was added. The solution was stirred at room temperature for 1 hour, then Na(OAc)\(_3\)BH (7.6 g, 36.0 mmol, 1.2 equiv.) was added. The mixture was stirred at room temperature for 16 hours, then brine was added, the crude was extracted with DCM and dried. 2.0 g of the title product were obtained (34% yield).

C\(_{10}\)H\(_{19}\)NO\(_2\)

\(^1\)H-NMR (CDCl\(_3\)): 1.04 (3H, d, J=6.4 Hz); 1.67-1.90 (6H, m); 2.26-2.43 (3H, m); 2.51-2.54 (4H, m); 3.64 (3H, s).

b) 4-Pyrrolidin-l-yl-pentanoic acid

[0452] To a suspension of 4-pyrrolidin-1-yl-pentanoic acid methyl ester (2.0 g, 10.0 mmol) in water (20 mL), NaOH (0.8 g, 20.0 mmol, 2.0 equiv.) was added and the mixture was heated at reflux for 10 hours. The reaction was then allowed to cool to room temperature, the pH was adjusted to 3 with HCl 37% and the mixture was concentrated under reduced pressure. The residue was treated with EtOH, the sodium chloride precipitated was filtered off and the solvent was evaporated under reduced pressure, affording 1.7 g of the title compound as white solid (99% yield).

C\(_9\)H\(_{17}\)NO\(_2\)

\(^1\)H-NMR (dms-o-d6): 1.22 (3H, d, J=6.4 Hz); 1.64-1.74 (1H, m); 1.81-1.96 (4H, m); 1.97-2.07 (1H, m); 2.23-2.30 (1H, m); 2.36-2.44 (1H, m); 2.97-3.02 (2H, m); 3.20-3.26 (1H, m); 3.35-3.46 (2H, m); 10.80 (1H, s)
c) 4-Pyrrolidin-1-yl-pentanoic acid [5-(4-chloro-phenyl)-2H-pyrazol-5-yl]-amide

[0453] The product was prepared according to the general synthetic method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route, starting from 5-(4-chloro-phenyl)-2H-pyrazol-3-ylamine (97.0 mg, 0.5 mmol, 1.0 equiv.) and 4-pyrrolidin-1-yl-pentanoic acid (128.0 mg, 0.7 mmol, 1.5 equiv.). The reaction was stirred at room temperature for 16 hours, then 8 hours at 50 °C, to allow the complete formation of the exocyclic nitrogen acylated isomer. After purification via preparative HPLC, 150.3 mg of title compound were recovered as formate salt (87% yield).

C_{18}H_{23}ClN_{4}O
Mass (calculated) [346]; (found) [M+H]={347}.  
LC Rt = 1.69 min, 100% (10 min method)

^{1}H-NMR (dms-o-d6 on the formate salt): 1.11 (3H, d, J=6.4 Hz); 1.63-1.80 (5H, m); 1.90-1.99 (1H, s); 2.29-2.42 (2H, m); 2.80-2.86 (5H, m); 6.82 (1H, s); 7.46-7.49 (2H, m); 7.70-7.73 (2H, m); 8.19 (1H, s); 10.55 (1H, br s)

Table 3- Examples 38-372

[0454] Table 3 shows a selection of the compounds synthesised, which were prepared according to the method indicated in the last column of the table and discussed in detail in the Experimental Procedures with the synthesis of Examples 1-37. When the compound is indicated as the HCl salt, the salt was formed by dissolution of the free base in methanol and addition of 1 equiv. IM HCl in ether followed by evaporation of the solvents. When the compound is indicated as HCOOH (formic acid) salt, the compound was purified by preparative HPLC.
<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>Structure</th>
<th>Salt</th>
<th>Parent Formula</th>
<th>Parent MW</th>
<th>Mass found</th>
<th>LC purity %</th>
<th>LC Rt (min)</th>
<th>LC method (min)</th>
<th>Synthetic Method</th>
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<td>356.46</td>
<td>357</td>
<td>100</td>
<td>1.64</td>
<td>10</td>
<td>one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides</td>
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<td>418</td>
<td>100</td>
<td>1.74</td>
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<td>328.15</td>
<td>99</td>
<td>0.23</td>
<td>10</td>
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</tr>
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<td>317.18</td>
<td>99</td>
<td>Solve nt Front 1.53</td>
<td>10</td>
<td>one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides</td>
</tr>
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<td><img src="image5" alt="Structure" /></td>
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![Structures](image-url)
<p>| 53 | <img src="image1.png" alt="Chemical Structure" /> | C18H25N5O | 327.42 | 328 | 95 | 0.21 | 10 | Route A1/A2 for aminopyrazole; one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides |
| 54 | <img src="image2.png" alt="Chemical Structure" /> | C19H25N4OCl | 360.88 | 361 | 100 | 1.88 | 10 | one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides |
| 55 | <img src="image3.png" alt="Chemical Structure" /> | C20H25N4OF3 | 394.43 | 395 | 100 | 2.09 | 10 | Route A1/A2 for aminopyrazole; one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides |
| 56 | <img src="image4.png" alt="Chemical Structure" /> | C20H26N4O4 | 386 | 387 | 100 | 0.24 and 1.40 | 10 | one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides |</p>
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<td><img src="image" alt="Structure 58" /></td>
<td><img src="image" alt="Structure 59" /></td>
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*one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides*
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**Route A1/A2 for aminopyrazole; one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides**
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Route A1/A2 for aminopyrazole; one-pot synthesis of \( \omega \)-amino-alkanoic acid \((1H\text{-}pyrazol\text{-}3\text{-}yl\text{-}5\text{-}aryl)\text{-}amides \)

one-pot synthesis of \( \omega \)-amino-alkanoic acid \((1H\text{-}pyrazol\text{-}3\text{-}yl\text{-}5\text{-}aryl)\text{-}amides \)

one-pot synthesis of \( \omega \)-amino-alkanoic acid \((1H\text{-}pyrazol\text{-}3\text{-}yl\text{-}5\text{-}aryl)\text{-}amides \)

one-pot synthesis of \( \omega \)-amino-alkanoic acid \((1H\text{-}pyrazol\text{-}3\text{-}yl\text{-}5\text{-}aryl)\text{-}amides \)

one-pot synthesis of \( \omega \)-amino-alkanoic acid \((1H\text{-}pyrazol\text{-}3\text{-}yl\text{-}5\text{-}aryl)\text{-}amides \)
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General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route.
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|   | 10 | General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route | General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route | General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route | General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
<p>| 132 | <img src="image1" alt="Chemical Structure" /> | HCOOH | C20H28N4O | 340.46 | 341.46 | 96 | 1.73 | 10 | General method for the synthesis of γ-aminooalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |
| 133 | <img src="image2" alt="Chemical Structure" /> | N | C21H30N4O2 | 370.49 | 371.49 | 99 | 2.18 | 10 | General method for the synthesis of γ-aminooalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |
| 134 | <img src="image3" alt="Chemical Structure" /> | HCOOH | C18H23N4O3Cl | 378.85 | 379.85 | 99 | 1.71 | 10 | General method for the synthesis of γ-aminooalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |
| 135 | <img src="image4" alt="Chemical Structure" /> | HCOOH | C17H22N4O2 | 314.38 | 315.38 | 99 | Double peak 0.24 1.28 | 10 | General method for the synthesis of γ-aminooalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |</p>
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General method for the synthesis of 6-aminomethyleneindoline derivatives via the amino acid route.
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Route A1/A2 for aminopyrazole: general method for the synthesis of o-aminoalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route.
<p>| 142 | ![Chemical Structure 1] | C21H29N5O3 | 399.49 | 400 | 98 | 1.01 | 10 | Route A1/A2 for aminopyrazole general method for the synthesis of o-aminoalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |
| 143 | ![Chemical Structure 2] | HCOOH | C18H24N4O2 | 328.41 | 329, 258, 165 | 100 | 1.48 | 10 | Route A1/A2 for aminopyrazole general method for the synthesis of o-aminoalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |
| 144 | ![Chemical Structure 3] | HCOOH | C18H24N4O3 | 344.41 | 345, 173, 258 | 99 | 1.36 | 10 | Route A1/A2 for aminopyrazole general method for the synthesis of o-aminoalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |</p>
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![Chemical Structures](image-url)
| 160 | ![Chemical Structure] | **HCOOH** | **C18H24N4O** | 312.41 | 313, 157 | 99 | 2.38 | 10 | **Route A1/A2 for aminopyrazole:**
e general method for the synthesis of o-amino-
alkanoic acid (1H-pyrazol-3-
yl-5-aryl)-amides via the
amino acid route |
| 161 | ![Chemical Structure] | **HCOOH** | **C18H23N4O3Cl** | 378.85 | 379, 291, 190 | 100 | 1.58 | 10 | **Route A1/A2 for aminopyrazole:**
e general method for the synthesis of o-amino-
alkanoic acid (1H-pyrazol-3-
yl-5-aryl)-amides via the
amino acid route |
| 162 | ![Chemical Structure] | **HCOOH** | **C18H23N4O3F** | 362.40 | 363, 276, 182 | 100 | 1.48 | 10 | **Route A1/A2 for aminopyrazole:**
e general method for the synthesis of o-amino-
alkanoic acid (1H-pyrazol-3-
yl-5-aryl)-amides via the
amino acid route |
<p>| 163 | <img src="image1.png" alt="Chemical Structure" /> | C18H23N4O3F | 362.40 | 363, 276, 182 | 100 | 1.39 | 10 | Route A1/A2 for aminopyrazole general method for the synthesis of ω-aminoalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |
| 164 | <img src="image2.png" alt="Chemical Structure" /> | HCOOH | C22H26N4O3 | 394.47 | 395, 308, 198 | 100 | 1.86 | 10 | Route A1/A2 for aminopyrazole general method for the synthesis of ω-aminoalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |
| 165 | <img src="image3.png" alt="Chemical Structure" /> | HCOOH | C17H20N4O2Cl2 | 383.27 | 383, 192 | 100 | 1.78 | 10 | Route A1/A2 for aminopyrazole general method for the synthesis of ω-aminoalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |</p>
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<td>359, 258</td>
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![Chemical Structures](image)
<p>| 190 | <img src="image1.png" alt="Chemical Structure 1" /> | HCOOH | C20H25N5O | 351.45 | 352, 177, 267 | 95 | 1.46 | 10 | Route A1/A2 for aminopyrazole: general method for the synthesis of α-aminoalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |
| 191 | <img src="image2.png" alt="Chemical Structure 2" /> | HCOOH | C20H25N5O | 351.45 | 352, 177, 267 | 93 | 1.49 | 10 | Route A1/A2 for aminopyrazole: general method for the synthesis of α-aminoalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |
| 192 | <img src="image3.png" alt="Chemical Structure 3" /> | HCOOH | C20H25N5O | 351.45 | 352, 177, 267 | 98 | 1.61 | 10 | Route A1/A2 for aminopyrazole: general method for the synthesis of α-aminoalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |
| 193 | <img src="image1" alt="Chemical Structure" /> | C20H28N4O2 | 356.46 | 357.158 | 100 | 1.81 | 10 | Route A1/A2 for aminopyrazole: general method for the synthesis of o-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |
| 194 | <img src="image2" alt="Chemical Structure" /> | C20H28N4O3 | 372.46 | 373.166 | 100 | 1.69 | 10 | Route A1/A2 for aminopyrazole: general method for the synthesis of o-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |
| 195 | <img src="image3" alt="Chemical Structure" /> | HCOOH | C22H32N4O2 | 384.52 | 385.172 | 100 | 2.08 | 10 | Route A1/A2 for aminopyrazole: general method for the synthesis of o-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |
| 196 | ![Chemical Structure 1] | C22H32N4O2 | 384.52 | 385,172 | 100 | 2.06 | 10 | <strong>Route A1/A2 for aminopyrazole; general method for the synthesis of α-aminoalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route</strong> |
| 197 | ![Chemical Structure 2] | HCOOH | C19H24N6O | 352.43 | 353 | 95 | 0.23 | 10 | <strong>Route A1/A2 for aminopyrazole; general method for the synthesis of α-aminoalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route</strong> |
| 198 | ![Chemical Structure 3] | HCOOH | C20H26N6O | 366.46 | 367,184 | 95 | 0.23 | 10 | <strong>Route A1/A2 for aminopyrazole; general method for the synthesis of α-aminoalkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route</strong> |</p>
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Route A1/A2 for aminopyrazole: general method for the synthesis of o-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route.
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Route A1/A2 for aminopyrazole general method for the synthesis of \(\alpha\)-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route.
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Route A1/A2 for aminopyrazole: general method for the synthesis of \(\sigma\)-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
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| Route A1/A2 for aminopyrazole
gener method for the synthesis of o-amino-alkanoic acid
(1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route | Route A1/A2 for aminopyrazole
gener method for the synthesis of o-amino-alkanoic acid
(1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route | Route A1/A2 for aminopyrazole
gener method for the synthesis of o-amino-alkanoic acid
(1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route |
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246
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Route A1/A2 for aminopyrazole: general method for the synthesis of α-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route.
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<td>(H-pyrazol-3-yl-5-aryl)</td>
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<td>1.84</td>
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![Chemical structures](image-url)
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Route A1/A2 for aminopyrazole general method for the synthesis of o-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route.
<table>
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<th>327, 164</th>
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<td>100</td>
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<td>General Method for the Synthesis of O-Aminoalkanoic Acid (H-Pyrazol-3-Yl-5-Aryl)-Amides via the Amino Acid Route</td>
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<td>General Method for the Synthesis of O-Aminoalkanoic Acid (H-Pyrazol-3-Yl-5-Aryl)-Amides via the Amino Acid Route</td>
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<td>General Method for the Synthesis of O-Aminoalkanoic Acid (H-Pyrazol-3-Yl-5-Aryl)-Amides via the Amino Acid Route</td>
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<td>362</td>
<td><img src="image2.png" alt="Structural Diagram" /></td>
<td>363</td>
<td><img src="image3.png" alt="Structural Diagram" /></td>
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<td>Route A1/A2 for aminopyrazole: general method for the synthesis of Ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route</td>
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<td>378, 189</td>
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<td>Route A1/A2 for aminopyrazole: general method for the synthesis of Ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route</td>
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<td>364, 182</td>
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<td>1.35</td>
<td>10</td>
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<td>1.07</td>
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</table>
|   | Route A1/A2 for aminopyrazole: general method for the synthesis of o-amino-
|   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |
| 371 | ![Chemical Structure](image2) |   |   | C17H23N5O | 313.40 | 314, 157 | 95 | 0.22 | 10 |
|   | Route A1/A2 for aminopyrazole: general method for the synthesis of o-amino-
|   |   |   |   |   |   |   |   |   |   |
| 372 | ![Chemical Structure](image3) |   |   | HCOOH | C19H24N5OF3 | 395.42 | 396 | 96 | 5.27 | 10 |
|   | Route A1/A2 for aminopyrazole: general method for the synthesis of o-amino-
|   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |
The following general procedures were used for Examples 373 and 374.

General procedure for 5-amino-3-(6-methyl-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester

i) General procedure for aryl/heteroaryl β-ketonitrile synthesis

[0455] Aryl or heteroaryl methyl carboxylate were commercially available or were synthesized according to the following standard procedure: the aryl or heteroaryl carboxylic acid (32 mmol) was dissolved in MeOH (40 mL) and sulfuric acid (1 mL) was added. The mixture was refluxed overnight, after which the solvent was evaporated under reduced pressure; the crude was dissolved in DCM and washed with saturated aqueous NaHCO₃ solution. The organic phase was dried and evaporated under reduced pressure, and the crude was used without further purification.

[0456] To a solution of an aryl or heteroaryl methyl carboxylate (6.5 mmol) in dry toluene (6 mL) under N₂, NaH (50-60% dispersion in mineral oil, 624 mg, 13 mmol) was carefully added. The mixture was heated at 80 °C and then dry CH₂CN was added dropwise (1.6 mL, 30.8 mmol). The reaction was heated for 18 hours and generally the product precipitated from the reaction mixture as a Na salt.

[0457] The reaction was then allowed to cool down to room temperature and the solid formed was filtered and then dissolved in water. The solution was then acidified with 2 N HCl solution and at pH between 2-6 (depending on the ring substitution on the aryl/heteroaryl system) the product precipitated and was filtered off. If no precipitation occurred, the product was extracted with DCM.

After work-up, the products were generally used in the following step without further purification. The general yield was between 40 and 80%.

3-(6-Methyl-pyridin-3-yl)-3-oxo-propionitrile

C₉H₈N₂O

Mass (calculated) [160]; (found) [M+H⁺] =161

LC Rt = 0.63, 100% (5 min method)
\textbf{General procedure for aryl aminopyrazole synthesis}

To a solution of 3-(6-methyl-pyridin-3-yl)-3-oxo-propionitrile (7.5 mmol), in absolute EtOH (15 mL) hydrazine monohydrate (0.44 mL, 9.0 mmol) was added and the reaction was heated at reflux for 18 hrs. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in DCM and washed with water.

The organic phase was concentrated under reduced pressure to give a crude product that was purified by SiO$_2$ column or by precipitation from Et$_2$O. Yields were generally between 65 and 90%.

\textit{a) 5-(6-Methyl-pyridin-S-yl)-1H-pyrazol-S-ylamine}

C$_9$H$_{10}$N$_4$

Mass (calculated) [174]; (found) [M+H$^+$] = 175

LC Rt = 0.23, 100% (5 min method)

$^1$H-NMR (400 MHz, DMSO-$d_6$): 2.43 (s, 3H); 4.86 (s, 2H); 5.75 (s, 1H); 7.22 (d, J=8.0 Hz, 1H); 7.87 (dd, J=8.0, 2.3 Hz, 1H); 8.71 (d, J=2.2 Hz, 1H); 11.72 (s, 1H)

\textit{b) 5-amino-S-(6-methyl-pyridin-S-yl)-pyrazole-l-carboxylic acid tert-butyl ester}

To a mixture of 5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-ylamine (1.48 g, 1.0 equiv.) and KOH 4.5 N (15.1 mL, 8 equiv.) in 50 mL of DCM, (BOC)$_2$O (1.95 g, 1.05 equiv.) in 5 mL of DCM was added. The mixture was stirred overnight at RT.

The organic phase was separated and washed with water. The solvent was dried and evaporated affording the title product (1.97 g, 84% yield) obtained as a solid.

C$_{14}$H$_{18}$N$_4$O$_2$ Mass

$^1$H-NMR (400 MHz, CDC13): 1.68 (s, 9H); 2.60 (m, 3H), 5.41 (s, 2H), 5.75 (s, 1H), 7.20 (m, 1H), 8.09 (m, 1H), 8.83 (m, 1H).

\textit{Example 373}

2-Methyl-N-[5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-4-pyrrolidin-l-yl-butyramide
a) 4-Bromo-2-methyl-butyric acid methyl ester

[0462] 3-Methyl-dihydro-furan-2-one (5.0 g, 1.20 equiv.) was heated at 140 °C in neat PBr₃ (3.90 mL, 1.0 equiv.) for 2 hrs. The reaction mixture was transferred to a Kugelrohr apparatus and distilled under reduced pressure (130 °C at 40 mm Hg). The product was then transferred in a flask, dissolved in DCM (10 mL) and cooled with an ice bath to 0 °C. The mixture was treated slowly with CH₃OH (10 mL), due to the strong exotherm produced. The reaction mixture was stirred under nitrogen for 24 hrs and the solvents evaporated in vacuo. The title product (6.10 g, 75% yield) was obtained as an oil.

C₆H₇BrO₂

¹H-NMR (400 MHz, CDC1₃): 1.19 (d, J=7.09 Hz, 3H); 1.92 (m, 1H), 2.25 (m, 1H), 2.70 (m, 1H), 3.40 (m, 2H), 3.68 (s, 3H).

b) 2-Methyl-4-pyrrolidin-1-yl-butyric acid methyl ester

[0463] 4-Bromo-2-methyl-butyric acid methyl ester (3.0 g, 1.0 equiv.) was dissolved in toluene (20 mL), treated with pyrrolidine (3.82 mL, 3.0 equiv.) and heated at reflux overnight. After cooling, the insoluble material was filtered off, the solvent evaporated and the residue purified by silica gel chromatography (eluent AcOEtICH₃OH with 2 N NH₃ 95:5).

The title product (1.01 g, 36%) was obtained as an oil.

C₁₀H₁₉NO₂ Mass (calculated) [185.27]; found [M+H⁺] = 186.2

Lc Rt = 0.20 min

c) 2-Methyl-4-pyrrolidin-1-yl-butyric acid hydrochloride
2-Methyl-4-pyrrolidin-1-yl-butyric acid methyl ester (1.01 g) was dissolved in HCl aq 6 N (5 mL) and heated at reflux temperature overnight. The reaction mixture was cooled to room temperature and evaporated to dryness. The residue was triturated with Et₂O and the solid recovered by filtration. The title product (1.10 g, 95%) was obtained as a solid.

**Example 374**

2-Methyl-5-[1, 4]oxazepan-4-yl-pentanoic acid [5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-amide
a) 2-(S-Bromo-propyl)-2-methyl-malonic acid dimethyl ester

Sodium hydride (60% in mineral oil, 1.63 g, 1.3 equiv.) was washed three times with hexane and subsequently dried. After addition of dried THF (30 mL) the suspension was cooled to 0 °C. Dimethyl methylmalonate (4.7 g, 1.0 equiv.) was slowly added and gas development was observed. The mixture was stirred for 15 minutes and subsequently 1,3-dibromopropane (24 g, 3.7 equiv.) was added in one portion. The mixture was allowed to reach room temperature and was then stirred for further 16 hours. NaOH 1.0 M solution was added, the crude was extracted with ethyl acetate; the organic layers were collected and dried, the obtained oil was purified by silica gel chromatography (elution: 100% cyclohexane followed by 100% EtOAc). The title product (6.6 g, 76% yield) was obtained as an oil.

$^1$H-NMR (dmso-d6): 1.32 (3H, s); 1.67-1.72 (2H, m); 1.861-1.90 (2H, m); 3.51 (2H, t, J= 6.4 Hz); 3.64 (6H, s).
b) 5-Bromo-2-methyl-pentanoic acid methyl ester

[0467] 
Aqueous HBr 48% (60 mL, 16.5 equiv.) was added at room temperature to 2-(3-bromo-propyl)-2-methyl-malonic acid dimethyl ester (8.6 g, 1.0 equiv.) and the mixture was stirred and heated at 110 °C for 7 hours, then at room temperature for 15 hours and then again at 110 °C for 9 h. After cooling to room temperature, NaOH 15% was added to reach pH 4 and the product was extracted using a mixture DCM:MeOH 95:5. The organic phase was evaporated to dryness.

[0468] 
The product obtained was dissolved in methanol prior to re-evaporation in vacuo to give the title product (3.37 g, 47% yield) as an oil.

1H-NMR (400 MHz, Acetone-\textit{d}/6): 1.13 (d, J=8.4 Hz, 3H); 1.56 (m, 1H); 1.79 (m, 3H); 2.49 (q, J=6.9 Hz, 1H); 3.49 (t, J=6.6 Hz, 2H); 3.64 (s, 3H).

c) 2-Methyl-5-[\textit{l},4]oxazepan-4-yl-pentanoic acid methyl ester

[0469] 
5-Bromo-2-methyl-pentanoic acid methyl ester (2.63 g, 1.0 equiv.), [\textit{l},4]oxazepane hydrochloride (1.72 g, 1.0 equiv.), triethylamine (2.54 g, 3.50 mL, 2.0 equiv.) and sodium iodide (1.87 g, 1.0 equiv.) were mixed in 2-butanone (30 mL) and the mixture was heated at 50 °C overnight under a nitrogen atmosphere.

[0470] 
The resulting suspension was diluted with ethyl acetate and the product was extracted with HCl 2 N. After basification of the aqueous phase by NaOH 2 N the product was extracted with ethyl acetate. The organic phase was then dried and evaporated.

[0471] 
The crude product was purified by silica gel chromatography (DCM to DCM: NH\textsubscript{3} in MeOH 2N 95:5). The title product was obtained (1.82 g, 63% yield) as an oil.

1H-NMR (400 MHz, DMSO-\textit{d}/6): 1.06 (d, J=7.0 Hz, 3H); 1.44 (m, 4H); 1.82 (m, 2H); 2.60 (m, 8H); 3.61 (m, 6H).

d) 2-Methyl-5-[\textit{l},4]oxazepan-4-yl-pentanoic acid hydrochloric salt

[0472] 
2-Methyl-5-[\textit{l},4]oxazepan-4-yl-pentanoic acid methyl ester (1.8 g, 1.0 equiv.) was dissolved in 20 mL of HCl 6 N and the mixture was heated at reflux temperature overnight.
The solvent was then evaporated and the residue was washed with diethyl ether to give the title product (650 mg, 33 % yield) as a solid.

$^1$H-NMR (400 MHz, DMSO-$d_6$): 1.05 (d, J=7.0 Hz, 3H); 1.32 (m, 1H); 1.53 (m, 1H); 1.66 (m, 2H); 1.96 (m, 1H); 2.19 (m, 1H); 2.33 (q, J=6.9 Hz, 1H); 3.13 (m, 4H); 3.41 (m, 2H); 3.70 (m, 4H).

e) 5-(2-Methyl-5-[1,4]oxazepan-4-yl-pentanoylamino)-S-(6-methyl-pyridin-5-yl)-pyrazole-1-carboxylic acid tert-butyl ester

2-Methyl-5-[1,4]oxazepan-4-yl-pentanoic acid hydrochloride salt (640 mg, 1.0 equiv.) was suspended in 5 mL of acetonitrile. Oxalyl chloride (320 µL, 1.5 equiv.) was added and the suspension stirred for 5.5 hrs at RT under a nitrogen atmosphere. The acid activation was checked by LCMS quenching a small sample with CH$_3$OH and detecting the formation of the methyl ester. Since the acid was not totally converted, a further equivalent of oxalyl chloride was added and the mixture was stirred overnight at RT.

The solution was then cooled at 0 °C and 5-amino-3-(6-methyl-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester (700 mg, 1.0 equiv.) was then added and the mixture was stirred at room temperature for 5 hours under a nitrogen atmosphere.

The solution obtained was used for the following step without any further purification.

C$_{25}$H$_{37}$N$_5$O$_4$MaSs (calculated) [471.60]; found [M+H$^+$] = 472.15

Lc Rt (5 min) = 1.17

f) 2-Methyl-5-[1,4]oxazepan-4-yl-pentanoic acid [5-(6-methyl-pyridin-5-yl)-2H-pyrazol-5-yl]-amide

To the previously prepared solution, HCl 2 N in diethyl ether (3.6 mL, 2.8 equiv.) was added and the mixture was stirred until LCMS showed complete deprotection.

The solvent was then evaporated and the product partitioned between ethyl acetate/saturated Na$_2$CO$_3$. The organic phase was dried and evaporated. The crude product was
then purified by silica gel chromatography (EtOAc to EtOAc:NH$_3$ 2 N in MeOH 90:10). The title product was (390 mg, 41% yield over two steps) as a solid.

C$_{20}$H$_{29}$N$_5$O$_4$MaSs (calculated) [371.49]; found [M+H$^+$] = 372.10

Le Rtz (10 min) = 0.22

$^1$H-NMR (400 MHz, DMSO-$d_6$): 1.04 (d, J=6.6 Hz, 3H); 1.43 (m, 4H); 1.74 (m, 2H); 2.39 (m, 1H); 2.46 (s, 3H); 2.54 (m, 5H); 3.54 (m, 3H); 3.61 (t, J=3.6 Hz, 2H); 6.95 (s, 1H); 7.31 (d, J=8.1 Hz, 1H); 7.95 (d, J=8.0 Hz, 1H); 8.78 (s, 1H); 10.37 (s, 1H); 12.86 (s, 1H).

Example 375

N-[5-(6-Methoxy-pyridin-3-yl)-2H-pyrazol-5-yl]-4-piperidin-1-yl-butyramide

\[
\begin{align*}
\text{NIPB} & \quad + \quad \text{Pyrazole} \\
\text{HC} & \quad \rightarrow \quad \text{NIPB} \\
\text{Et}_2O & \quad \text{HCl}
\end{align*}
\]

4-Piperidin-1-yl-butyric acid hydrochloride (139 mg, 0.67 mmol, 1.3 equiv.) was suspended in anhydrous DCM (2 mL) under a nitrogen atmosphere. Ethyl diisopropylamine (117 µL, 0.67 mmol, 1.3 equiv.) was added followed by oxalyl chloride (54 µL, 0.65 mmol, 1.25 equiv.) and a drop of DMF. After stirring for 1 hour the conversion of the acid to the corresponding acyl chloride was complete and 5-amino-3-(6-methoxy-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester was added (150 mg, 0.52 mmol, 1.0 equiv.). The reaction was stirred overnight at room temperature. HCl (2 N solution in diethylether, 0.57 mL, 1.04 mmol, 2
equiv.) was added and after stirring 1 hour at room temperature the Boc deprotection was complete. After evaporation of the solvent, the mixture was purified by preparative HPLC and by silica gel chromatography (DCM/2 N methanolic ammonia 100:0 to 90:10) to give N-[5-(6-Methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide as a solid (68 mg, 38.3%).

C_{18}H_{25}N_{5}O_{2} Mass (calculated) [343]; found [M+H]+=344

LC Rt= 1.41 min (10 min method)

^1H-NMR (400 MHz, ^-methanol, δ): 1.47 (m, 2H); 1.63 (m, 4H); 1.9 (m, 2H); 2.46 (m, 8H); 3.93 (s, 3H); 6.86 (d, J = 8.8 Hz, 1H); 7.95 (m, 1H); 8.46 (m, 1H).

Example 376

N-[5-(6-Methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-2-methyl-4-piperidin-1-yl-butyramide formic acid salt

[0480] 2-Methyl-4-piperidin-1-yl-butyric acid hydrochloride (171 mg, 0.78 mmol, 1.5 equiv.) was suspended in dry DCM (3 mL) under nitrogen. Ethyl-diisopropyl-amine (135 µL, 0.78 mmol, 1.5 equiv.) was added followed by oxalyl chloride (63 µL, 0.75 mmol, 1.45 equiv.) and a drop of DMF. After stirring for 2 hours the conversion of the acid to the corresponding acyl chloride was completed and 5-amino-3-(6-methoxy-pyridin-3-yl)-pyrazole-1-carboxylic
Acid tert-butyl ester was added (150 mg, 0.52 mmol, 1.0 equiv.). The reaction was stirred overnight at room temperature. Trifluoroacetic acid (2 mL) was added and after stirring 2 hours at room temperature the deprotection was complete. After evaporation of the solvent the mixture was purified by preparative HPLC to give N-[5-(6-Methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-2-methyl-4-piperidin-1-yl-butramide formic acid salt (131 mg, 63%) as a solid.

C_{19}H_{27}N_{5}O_{2}-HCOOH (parent mass, calculated) [357]; found [M+H^+]=358

Le R_l=1.47 min (10 min method)

$^1$H-NMR (400 MHz, $^-$-methanol, $\delta$): 1.31 (d, $J=7.29$ Hz, 3H); 1.66 (m, 2H); 1.84 (m, 6H); 2.1 (m, 1H); 2.63 (m, 2H); 3.0 (m, 4H); 3.94 (s, 3H); 6.74 (brs, 1H); 6.87 (m, 1H); 7.95 (m, 1H); 8.45 (m, 1H); 8.48 (s, 1H).

Example 377

N-[5-(6-Methoxy-pyridin-5-yl)-2H-pyrazol-5-yl]-2-methyl-4-pyrrolidine-1-ylbutramide formic acid salt
0.78 mmol, 1.5 equiv.) was added followed by oxalyl chloride (63.4 µL, 0.75 mmol, 1.45 equiv.) and a drop of DMF. After stirring for 2 hours the conversion of the acid to the corresponding acyl chloride was complete and 5-amino-3-(6-methoxy-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester was added (150 mg, 0.52 mmol, 1.0 equiv.). The reaction was stirred overnight at room temperature. LCMS analysis showed the presence of unreacted aminopyrazole thus another equivalent of activated 2-methyl-4-pyrrolidin-1-yl-butyric acid was added (0.52 mmol, 1.0 equiv.). The reaction was stirred overnight at room temperature. Trifluoroacetic acid (2 mL) was added and after stirring 2 hours at room temperature the deprotection was complete. After evaporation of the solvent the mixture was purified by silica gel chromatography (DCM/2 N methanolic ammonia 100:0 to 90:10) followed by preparative HPLC to give N-[5-(6-Methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-2-methyl-4-pyrrolidin-1-yl-butyramide formic acid salt (59 mg, 30%) a solid.

C_{18}H_{25}N_{5}O_{2}-HCOOH (parent mass, calculated) [343]; found [M+H]+=344.

Lc Rt=I. 35 min (10 min method)

$^1$H-NMR (400 MHz, $^-$methanol, δ): 1.30 (d, J = 6.98 Hz, 3H); 1.87 (m, 1H); 2.07 (m, 5H); 2.65 (m,1H); 3.13 (m, 1H); 3.25 (m, 1H); 3.28-3.42 (m, 4H); 3.94 (s, 3H); 6.74 (brs, 1H); 6.87 (m, 1H); 7.95 (m,1H); 8.45 (s, 1H).

Example 378

2-Methyl-4-pyrrolidin-l-yl-N-(5-quinolin-3-yl-2H-pyrazol-3-yl)-butyramide
2-Methyl-4-pyrrolidin-1-yl-butyric acid hydrochloride (107 mg, 0.52 mmol, 1.5 equiv.) was suspended in dry MeCN (3 mL) under nitrogen. Oxalyl chloride (42 µL, 0.50 mmol, 1.45 equiv.) was added followed by a drop of DMF. After stirring for 1 hour conversion of the acid to the corresponding acyl chloride was complete and 5-amino-3-quinolin-3-yl-pyrazole-I-carboxylic acid tert-butyl ester was added (107 mg, 0.35 mmol, 1.0 equiv.). The reaction was stirred at room temperature for 2 hours. Trifluoroacetic acid (1 mL) was added and after stirring 2 hours at room temperature the deprotection was complete. After evaporation of the solvent the mixture was purified by preparative HPLC followed by silica gel chromatography (MeCN/2 N methanolic ammonia 100:0 to 80:20) to give 2-methyl-4-pyrrolidin-1-yl-N-(5-quinolin-3-yl-2H-pyrazol-3-yl)-butyramide (60 mg, 48%) as a solid.

C_{21}H_{25}N_5O Mass (calculated) [363]; found [M+H^+] = 364

Lc Rt= 1.05 min (10 min method)

^1H-NMR (400 MHz, ^^-methanol, δ): 1.286 (d, J = 6.86 Hz, 3H); 1.79 (m, 1H); 1.93 (m, 4H); 2.04 (m, 1H); 2.64 (m, 1H); 2.80 (m, 1H); 2.87-2.99 (m, 5H); 6.97 (brs, 1H); 7.57 (m, 1H); 8.06-8.15 (m, 2H); 8.26 (m, 1H); 8.41 (m, 1H); 8.85 (m, 1H).
Example 3 7 9

N-[5-(6-Methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-3-methyl-4-piperidin-1-yl-butyramide formic acid salt

3-Methyl-4-piperidin-1-yl-butyric acid hydrochloride (114 mg, 0.52 mmol, 1.5 equiv.) was suspended in dry MeCN (3 mL) under nitrogen. Oxalyl chloride (42 µL, 0.50 mmol, 1.45 equiv.) was added followed by a drop of DMF. After stirring for 1 hour the conversion of the acid to the corresponding acyl chloride was completed and 5-amino-3-(6-methoxy-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester was added (100 mg, 0.34 mmol, 1.0 equiv.). The reaction was stirred overnight at room temperature. HCl (2 N solution in diethyleter, 0.23 mL, 0.68 mmol, 2 equiv.) was added and after stirring 1 hour at room temperature the deprotection was complete. After evaporation of the solvent the mixture was purified by preparative HPLC to give N-[5-(6-Methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-3-methyl-4-piperidin-1-yl-butyramide formic acid salt (70 mg, 50%) as a solid.

C_{19}H_{27}N_{5}O_{2}-HCOOH (parent mass, calculated) [357]; found [M+H^+] = 358

H-NMR (400 MHz, ^-methanol, δ): 1.12 (d, J = 6.86 Hz, 3H); 1.70 (m, 2H); 1.9 (m, 5H); 2.54 (m, 1H); 2.58-2.64 (m, 2H); 3.0-3.14 (m, 4H); 3.24 (m, 1H); 3.94 (s, 3H); 6.76 (s, 1H); 6.88 (d, J = 8.67, 1H); 7.96 (dd, J = 8.67 J = 2.46, 1H); 8.42 (s, 1H); 8.46 (d, J = 2.46, 1H):
Example 380

*S-Methyl-4-piperidin-l-yl-N-(5-quinolin-6-yl-2H-pyrazol-3-yl)-butyramide formic acid salt*

3-Methyl-4-piperidin-1-yl-butyric acid hydrochloride (114 mg, 0.52 mmol, 1.5 equiv.) was suspended in dry MeCN (3 mL) under nitrogen. Oxalyl chloride (42 µL, 0.50 mmol, 1.45 equiv.) was added followed by a drop of DMF. After stirring for 1 hour conversion of the acid to the corresponding acyl chloride was complete and 5-amino-3-quinolin-6-yl-pyrazole-1-carboxylic acid tert-buty l ester was added (106 mg, 0.35 mmol, 1.0 equiv.). The reaction was stirred overnight at room temperature. HCl (2N solution in diethylether, 0.35 mL, 0.70 mmol, 2.0 equiv.) was added and deprotection was complete after stirring for 1 hour at room temperature. After evaporation of the solvent the mixture was purified by preparative HPLC to give 3-methyl-4-piperidin-1-yl-N-(5-quinolin-6-yl-2H-pyrazol-3-yl)-butyramide formic acid salt (84 mg, 58%) was obtained as a solid.

C_{22}H_{27}N_{5}O-HCOOH (parent mass, calculated) [377]; found [M+H^+]=378

Lc Rt= 1.47 min (10 min method)

^1H-NMR (400 MHz, ^-methanol, δ): 1.14 ((L, J = 6.86 Hz, 3H); 1.71 (m, 3H); 1.92 (m, 4H); 2.57 (m, 1H); 2.61-2.67 (m, 2H); 3.0-3.16 (m, 4H); 3.2 (m, 1H); 7.02 (bs, 1H); 7.67 (m, 1H); 7.80 (m, 1H); 8.03 (m, 2H); 8.41 (s, 1H); 8.64 (m, 1H); 9.21 (m, 1H).
Example 381

3-Methyl-4-piperidin-1-yl-N-(5-quinolin-3-yl-2H-pyrazol-3-yl)-butyramide formic acid salt

3-Methyl-4-piperidin-1-yl-butyric acid hydrochloride (107 mg, 0.48 mmol, 1.5 equiv.) was suspended in dry MeCN (2 mL) under nitrogen. Oxalyl chloride (40 µL, 0.47 mmol, 1.45 equiv.) was added followed by a drop of DMF. After stirring for 1 hour conversion of the acid to the corresponding acyl chloride was complete and 5-amino-3-quinolin-3-yl-pyrazole I-carboxylic acid tert-butyl ester was added (100 mg, 0.32 mmol, 1.0 equiv.). The reaction was stirred overnight at room temperature. TFA (2 mL) was added and the deprotection was complete after stirring 1 hour at room temperature. After evaporation of the solvent the mixture was purified by preparative HPLC to give 3-methyl-4-piperidin-1-yl-N-(5-quinolin-3-yl-2H-pyrazol-3-yl)-butyramide formic acid salt (46 mg, 33%) as a solid.

C_{22}H_{27}N_{5}O-HCOOH (parent mass, calculated) [377]; found [M+H^+] = 378

Lc Rt= 1.15 min (10 min method)

$^1$H-NMR (400 MHz, $^+$-methanol, δ): 1.14 (d, $J = 6.8$ Hz, 3H); 1.71 (m, 3H); 1.92 (m, 4H); 2.5 (m, 1H); 2.61-2.66 (m, 2H); 3.0-3.13 (m, 4H); 3.2 (m, 1H); 7.00 (brs, 1H); 7.58 (m, 1H); 8.07-8.14 (m, 2H); 8.27 (s, 1H); 8.39-8.46 (m, 2H); 8.84-8.87 (m, 1H).
Example 382

**N-[5-(5-Methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-3-methyl-4-piperidin-1-yl-butyramide formic acid salt**

![Chemical Structure]

3-Methyl-4-piperidin-1-yl-butyric acid hydrochloride (114 mg, 0.52 mmol, 1.5 equiv.) was suspended in dry MeCN (3 mL) under nitrogen. Oxalyl chloride (42 µL, 0.50 mmol, 1.45 equiv.) was added followed by a drop of DMF. After stirring for 1 hour conversion of the acid to the corresponding acyl chloride was complete and 5-amino-3-(5-methoxy-pyridin-3-yl)pyrazole-1-carboxylic acid tert-butyl ester was added (100 mg, 0.35 mmol, 1.0 equiv.). The reaction was stirred overnight at room temperature. HCl (2 N solution in diethylether, 0.35 mL, 0.70 mmol, 2.0 equiv.) was added and after stirring 1 hour at room temperature the deprotection was complete. After evaporation of the solvent the mixture was purified by preparative HPLC to give N-[5-(5-methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-3-methyl-4-piperidin-1-yl-butyramide formic acid salt (28 mg, 20%) as a solid.

**C_{19}H_{27}N_{5}O_{2}-HCOOH** (parent mass, calculated) [357]; found [M+H^+] = 358

Le Rт= 1.10 min (10 min method)

^1H-NMR (400 MHz, ^^-methanol, δ): 1.12 (d, J = 6.72 Hz, 3H); 1.69 (m, 3H); 1.89 (m, 4H); 2.48-2.58 (m, 1H); 2.58-2.63 (m, 2H); 2.97-3.10 (m, 4H); 3.2 (m, 1H); 3.00 (s, 3H); 6.88 (brs, 1H); 7.69-7.72 (m, 1H); 8.20-8.23 (m, 1H); 8.47 (s, 1H).
Example 383

*N-[5-(6-Methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-3-methyl-4-pyrrolidin-1-yl-butyramide*

3-Methyl-4-pyrrolidin-1-yl-butyric acid hydrochloride (963 mg, 4.65 mmol, 1.55 equiv.) was suspended in dry MeCN (30 mL) under nitrogen. Oxalyl chloride (381 µL, 4.5 mmol, 1.5 equiv.) was added followed by a drop of DMF. After stirring for 2 hours conversion of the acid to the corresponding acyl chloride was complete and 5-amino-3-(6-methoxy-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester was added (870 mg, 3.0 mmol, 1.0 equiv.). The reaction was stirred overnight at room temperature. HCl (2 N solution in diethylether, 3.0 mL, 6.0 mmol, 2 equiv.) was added and after stirring 1 hour at room temperature the deprotection was complete. After evaporation of the solvent the mixture was made basic with NaHCO₃ sat. aqueous solution (20 mL) and extracted with DCM (3 x 50 mL). The organic phases were combined, dried and evaporated *in vacuo*. The mixture was purified by silica gel chromatography (MeCN/2 N methanolic ammonia 100:0 to 90:10) to give *N-[5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-3-methyl-4-pyrrolidin-1-yl-butyramide* (335 mg, 33%) as a solid.

C₁₈H₂₅N₅O₂ Mass (calculated) [343]; found [M+H⁺]=344

LC Rt=2.33 min (10 min method, methanol gradient)

¹H-NMR (400 MHz, ³¹methanol, δ): 1.03 (d, J = 6.7 Hz, 3H); 1.82 (m, 4H); 2.20-2.32 (m, 2H); 2.38-2.47 (m, 1H); 2.47-2.57 (m, 2H); 2.56-2.72 (m, 4H); 3.94 (s, 3H); 6.78 (brs, 1H); 6.87 (m, 1H); 7.96 (m, 1H); 8.46 (m, 1H).
Example 384

*N*-[5-(1-Difluoromethyl-6-oxo-1,6-dihydro-pyridin-5-yl)-1H-pyrazol-5-yl]-4-piperidin-1-yl-butyramide

![Chemical Structure](image)

[0488] To a suspension of 4-piperidin-1-yl-butyric acid hydrochloride (118 mg, 0.57 mmol, 1.3 equiv.) in DMF (0.5 mL), CDI (89 mg, 0.55 mmol, 1.25 equiv.) was added. The mixture was stirred at room temperature for 2 hours, then at 40 °C overnight until complete activation of the amino acid (LCMS). The mixture was diluted with further DMF (0.5 mL), 5-(5-amino-1H-pyrazol-3-yl)-1-difluoromethyl-1H-pyridin-2-one (100 mg, 0.44 mmol, 1.0 equiv.) was added and the reaction was stirred for 24 hours at 40 °C. The solvent was evaporated and the crude product was purified by preparative HPLC, followed by silica column (MeCN/2 N methanolic ammonia 100:0 to 80:20) to give *N*-[5-(1-difluoromethyl-6-oxo-1,6-dihydro-pyridin-3-yl)-1H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide (22 mg, 13%) as a solid.

C_{18}H_{23}F_{2}N_{5}O_{2} Mass (calculated) [379]; found [M+H+] = 380

LCMS Rt= 0.21 min (10 min method)

{\textsuperscript{1}H}-NMR (400 MHz, *d*-methanol, δ): 1.38 (m, 2H), 1.53 (m, 4H), 1.83 (m, 2H), 2.40 (m, 8H), 6.56 (m, 1H), 7.71 (t, 1H, J = 60 Hz); 7.84 (m, 1H), 7.98 (m, 1H).

Example 385

*N*-[4-Fluoro-5-(6-methyl-pyridin-5-yl)-1H-pyrazol-5-yl]-4-piperidin-1-yl-butyramide formic acid salt

![Chemical Structure](image)
To a suspension of 4-piperidin-1-yl-butyric acid hydrochloride (118 mg, 0.57 mmol, 1.0 equiv.) in DCE (3 mL), CDI (93 mg, 0.57 mmol, 1.0 equiv.) was added. The mixture was stirred at 40 °C for 2 hours until complete activation of the amino acid. 4-Fluoro-5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-ylamine (110 mg, 0.57 mmol, 1.0 equiv.) was added and the reaction was stirred overnight at 40 °C. The solvent was evaporated and the crude product was purified by preparative HPLC to give N-[4-fluoro-5-(6-methyl-pyridin-3-yl)-1H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide formic acid salt (41 mg, 21%) as a solid.

C_{18}H_{24}FN_{5}O-HCOOH (parent mass, calculated) [345]; found [M+H+] = 346

Lc Rt=0.18 min (10 min method)

\(^1\)H-NMR (400 MHz, d\(_6\)-DMSO, δ): 1.40 (m, 2H); 1.55 (m, 4H); 1.78 (m, 2H); 2.35 (m, 2H); 2.49 (s, 3H); 2.54 (m, 2H); 2.60 (m, 2H); 7.37 (m, 1H); 7.92 (m, 1H); 8.14 (s, 1H); 8.75 (m, 1H).

**Example 386**

N-[4-Fluoro-5-(6-methyl-pyridin-S-yl)-2H-pyrazol-S-yl]-S-methyl-4-piperidin-1-yl-butyramide formic acid salt

To a suspension of 3-methyl-4-piperidin-1-yl-butyric acid hydrochloride (827 mg, 3.74 mmol, 1.2 equiv.) in DCE (4 mL), CDI (581 mg, 3.59 mmol, 1.15 equiv.) was added. The mixture was stirred at 40 °C for 2 hours until complete activation of the amino acid. The mixture was further diluted with DCE (4 mL) and 4-fluoro-5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-ylamine (600 mg, 3.12 mmol, 1.0 equiv.) was added. The reaction was stirred overnight at 40 °C. The solvent was evaporated and the crude product was purified by preparative HPLC to give N-[4-fluoro-5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-methyl-4-piperidin-1-yl-butyramide formic acid salt (178 mg, 16%) as a solid.

C_{19}H_{26}FN_{5}O-HCOOH (parent mass, calculated) [359]; found [M+H+] = 360
Lc Rt=0.97 min (10 min method, methanol gradient)

$^1$H-NMR (400 MHz, $d_6$-DMSO): 0.89 (d, $J = 6.05$ Hz, 3H); 1.36 (m, 2H); 1.48 (m, 4H); 2.08 (m, 1H); 2.15 (m, 3H); 2.36 (m, 5H); 2.49 (s, 3H); 7.37 (m, 1H); 7.93 (m, 1H); 8.14 (s, 1H); 8.76 (m, 1H).

Example 387

$N$-[4-Fluoro-5-(6-methyl-pyridin-3-yl)-1H-pyrazol-3-yl]-3-methyl-4-pyrrolidin-1-yl-butyramide formic acid salt

[0491] To a suspension of 3-methyl-4-pyrrolidin-1-yl-butyric acid hydrochloride (496 mg, 2.39 mmol, 1.15 equiv.) in DMF (2 mL), CDI (370 mg, 2.28 mmol, 1.10 equiv.) was added. The mixture was stirred at 40 °C for 2 hours until complete activation of the amino acid. 4-Fluoro-5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-ylamine (600 mg, 3.12 mmol, 1 equiv.) was added and the reaction was stirred 2 hours at room temperature and then overnight at 40 °C. The reaction mixture was purified by prep HPLC without workup to give $N$-[4-fluoro-5-(6-methyl-pyridin-3-yl)-1H-pyrazol-3-yl]-3-methyl-4-pyrrolidin-1-yl-butyramide formic acid salt (74 mg, 22%) as a solid.

$C_{18}H_{24}FN_5O$-HCOOH (parent mass, calculated) [345]; found [M+H$^+$]=346

Lc Rt=0.67 min (10 min method, methanol gradient)

$^1$H-NMR (400 MHz, $d_6$-DMSO): 0.92 (d, $J = 6.05$ Hz, 3H); 1.69 (m, 5H); 2.08 (m, 3H); 2.33 (m, 5H); 2.49 (s, 3H); 7.37 (m, 1H); 7.93 (m, 1H); 8.15 (s, 1H); 8.76 (m, 1H).

Example 388

$N$-[4-Fluoro-5-(6-methyl-pyridin-3-yl)-1H-pyrazol-3-yl]-2-methyl-4-pyrrolidin-1-yl-butyramide
2-Methyl-4-pyrrolidin-1-yl-butyric acid hydrochloride (126 mg, 0.61 mmol, 1.2 equiv.) was suspended in DCM under nitrogen, oxalyl chloride (52 µL, 0.61 mmol, 1.05 equiv.) was added followed by a drop of DMF. After stirring for 15 min conversion of the acid to the corresponding acyl chloride was complete and 5-amino-4-fluoro-3-(6-methyl-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester was added (150 mg, 0.51 mmol, 1.0 equiv.). The reaction was stirred overnight at room temperature. HCl (2 N solution in diethylether, 0.3 mL, 0.60 mmol, 1.2 equiv.) was added and after stirring overnight at room temperature the deprotection was complete. After evaporation of the solvent, the mixture was purified by silica gel chromatography (eluent MeCN/2 N methanolic ammonia 100:0 to 80:20) to give N-[4-fluoro-5-(6-methyl-pyridin-3-yl)-1H-pyrazol-3-yl]-2-methyl-4-pyrrolidin-1-yl-butyramide (20 mg, 13%) as a solid.

C_{18}H_{24}FN_{5}O Mass (calculated) [345]; found [M+H^+]=346

Lc Rt=0.21 min (10 min method)

^1H-NMR (400 MHz, ^-methanol): 1.16 (d, J = 7.01 Hz, 3H); 1.63 (m, 1H); 1.74 (m, 4H); 1.88 (m, 1H); 2.47 (s, 3H); 2.54 (m, 7H); 7.32 (m, 1H); 7.95 (m, 1H); 8.67 (m, 1H).

Example 389

N-[4-Fluoro-5-(6-methyl-pyridin-3-yl)-1H-pyrazol-3-yl]-2-methyl-4-piperidin-1-yl-butyramide

2-Methyl-4-piperidin-1-yl-butyric acid hydrochloride (114 mg, 0.61 mmol, 1.2 equiv.), was suspended in DCM under nitrogen, oxalyl chloride (52 µL, 0.61 mmol, 1.05 equiv.)
was added followed by a drop of DMF. After stirring for 15 min conversion of the acid to the corresponding acyl chloride was complete and 5-amino-4-fluoro-3-(6-methyl-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester was added (150 mg, 0.51 mmol, 1.0 equiv.). The reaction was stirred overnight at room temperature. HCl (2 N solution in diethylether, 0.3 mL, 0.60 mmol, 1.2 equiv.) was added and after stirring overnight at room temperature the deprotection was complete. After evaporation of the solvent the mixture was purified by silica gel chromatography (eluent MeCN/2 N methanolic ammonia 100:0 to 80:20) to give N-[4-fluoro-5-(6-methyl-pyridin-3-yl)-1H-pyrazol-3-yl]-2-methyl-4-piperidin-1-yl-butyramide (30 mg, 16%) as a solid.

C_{19}H_{26}FN_{5}O Mass (calculated) [359]; found [M+H^{+}]=360

LCMS Rt=0.21 min (10 min method)

$^1$H-NMR (400 MHz, ^-methanol): 1.24 (d, J = 7.01 Hz, 3H); 1.82 (m, 6H); 2.03 (m, 1H); 2.48 (s, 3H); 2.60 (m, 1H); 2.87 (m, 3H); 2.99 (m, 1H); 3.01 (m, 1H); 3.45 (m, 2H); 7.33 (m, 1H); 7.94 (m, 1H); 8.09 (s, 1H); 8.66 (m, 1H).

Example 390

2-Methyl-4-piperidin-1-yl-N-(5-quinolin-3-yl-2H-pyrazol-3-yl)-butyramideformic acid salt

[0494] 2-Methyl-4-pyperidin-1-yl-butyric acid hydrochloride (160 mg, 0.73 mmol, 1.5 equiv.), was suspended in DCM (4 mL) under nitrogen, oxalyl chloride (44 µL, 0.51 mmol, 1.05 equiv.) was added followed by a drop of DMF. After stirring for 60 min the conversion of the acid to the corresponding acyl chloride was complete and 5-amino-3-quino lin-3-yl-pyrazo le-1-carboxylic acid tert-butyl ester was added (150 mg, 0.48 mmol, 1.0 equiv.). The reaction was stirred overnight at room temperature. HCl (2 N solution in diethylether, 0.3 mL, 0.58 mmol, 1.2 equiv.) was added and after stirring overnight at room temperature the Boc deprotection was complete. After evaporation of the solvent the mixture was purified by preparative HPLC to give
2-methyl-4-piperidin-1-yl-N-(5-quinolin-3-yl-2H-pyrazol-3-yl)-butyramide formic acid salt (81 mg, 40%) as a solid.

C_{22}H_{27}N_{5}O-HCOOH (parent mass, calculated) [377]; found [M+H^+] = 378

LC Rt = 0.21, 1.12 min (10 min method)

\textsuperscript{1}H-NMR (400 MHz, \textsuperscript{^-}C-DMSO): 1.23 (d, J = 8.0 Hz, 3H); 1.57 (m, 2H); 1.75 (m, 5H); 2.04 (m, 1H); 2.57 (m, 1H); 3.01 (m, 6H); 6.88 (brs, 1H); 7.48 (m, 1H); 8.01 (m, 2H); 8.33 (m, 1H); 8.37 (m, 1H); 8.76 (m, 1H).

Example 391

\textit{N-(4-Fluoro-5-quinolin-6-yl-2H-pyrazol-3-yl)-4-pyrrolidin-1-yl-butyramide formic acid salt}

[0495] To a suspension of 4-pyrrolidin-1-yl-butyric acid (222 mg, 1.15 mmol, 1.6 equiv.) in DCE (5 mL), CDI (180.8 mg, 1.11 mmol, 1.55 equiv.) was added and the mixture stirred at room temperature for 1 hour until complete activation of the amino acid. 4-Fluoro-5-quinolin-6-yl-2H-pyrazol-3-yl-ammonium hydrochloride (190.0 g, 0.72 mmol, 1.0 equiv.) Et\textsubscript{3}N (100 µL, 0.72 mmol, 1.0 equiv.) were added and the reaction stirred for 3 hours at room temperature then at 50 °C overnight. After evaporation of the solvent the crude product was purified by preparative HPLC to give \textit{N-(4-fluoro-5-quinolin-6-yl-2H-pyrazol-3-yl)-4-pyrrolidin-1-yl-butyramide formic acid salt} (189 mg, 63%) as a solid.

C_{20}H_{22}FN_{5}O-HCOOH (parent mass, calculated) [367]; found [M+H^+] = 368

LC Rt = 1.30 min (10 min method, methanol gradient)

\textsuperscript{1}H-NMR (400 MHz, \textsuperscript{6}D-DMSO): 1.70 (m, 4H); 1.78 (m, 2H); 2.39 (m, 2H); 2.56 (m, 6H); 7.56 (m, 1H); 8.10 (m, 2H); 8.28 (m, 1H); 8.43 (m, 1H); 8.90 (m, 1H); 10.12 (brs, 1H).
Example 392

N-(4-Fluoro-5-quinolin-6-yl-2H-pyrazol-3-yl)-4-piperidin-1-yl-butyramide formic acid salt

[0496] To a suspension of 4-piperidin-1-yl-butyric acid (540 mg, 2.60 mmol, 1.6 equiv.) in DCE (5 mL), CDI (408 mg, 2.52 mmol, 1.55 equiv.) was added and the mixture stirred at 50 °C for 2 hours until complete activation of the amino acid. 4-Fluoro-5-quinolin-6-yl-2H-pyrazol-3-yl-ammonium hydrochloric acid salt (430 mg, 1.62 mmol, 1.0 equiv.) and Et3N (226 µL, 1.62 mmol, 1.0 equiv.) were added and the reaction stirred for 1 hour at room temperature then at 50 °C overnight. After evaporation of the solvent the crude product was purified using C18 reverse chromatography (water/methanol 95:5, 0.1% HCOOH) to give N-(4-fluoro-5-quinolin-6-yl-2H-pyrazol-3-yl)-4-piperidin-1-yl-butyramide formic acid salt (330 mg, 48%) as a solid.

C21H24FN5O HCOOH (parent mass, calculated) [381]; found [M+H+] = 382

LC Rt=1.63 min (10 min method, methanol gradient)

1H-NMR (400 MHz, D-methanol): 1.59 (m, 2H); 1.76 (m, 4H); 2.01 (m, 2H); 2.54 (m, 2H); 3.04 (m, 2H); 3.11 (m, 4H); 7.52 (m, 1H); 8.04 (m, 2H); 8.19 (m, 1H); 8.34 (m, 1H); 8.41 (s, 1H); 8.79 (m, 1H).

Example 393

N-(4-Fluoro-5-quinolin-6-yl-2H-pyrazol-3-yl)-3-methyl-4-pyrrolidin-1-yl-butyramide formic acid salt

[0497] To a suspension of 3-methyl-4-pyrrolidin-1-yl-butyric acid hydrochloride (540 mg, 2.60 mmol, 1.6 equiv.) in DCE (5 mL), and CDI (408 mg, 2.52 mmol, 1.55 equiv.) were
added and the mixture stirred at 50 °C for 2 hours until complete activation of the amino acid. 4-Fluoro-5-quinolin-6-yl-2H-pyrazol-3-yl-ammonium hydrochloride (430 mg, 1.62 mmol, 1.0 equiv.) and Et$_3$N (226 µL, 1.62 mmol, 1.0 equiv.) were added and the reaction stirred for 1 hour at room temperature then at 50 °C overnight. After 16 hours a second portion of 3-methyl-4-pyrrolidin-1-yl-butyric acid hydrochloride (169 mg, 0.81 mmol, 0.5 equiv.) was activated with CDI (126 mg, 0.76 mmol), and then added to the reaction mixture that was stirred for further 3 hours at 50 °C. After evaporation of the solvent the crude product was purified using C18 reverse chromatography (water/MeOH 95:5, 0.1% HCOOH) to give N-(4-fluoro-5-quinolin-6-yl-2H-pyrazol-3-yl)-3-methyl-4-pyrrolidin-1-yl-butyramide formic acid salt (203 mg, 18%) as a solid.

C$_{21}$H$_{24}$F$_{N_5}$O-HCOOH (parent mass, calculated) [381]; found [M+H$^+$] = 382

LC Rt=1.62 min (10 min method, methanol gradient)

$^1$H-NMR (400 MHz, ^-$^-$methanol ): 1.08 (d, J = 6.8 Hz, 3H); 2.01 (m, 4H); 2.37-2.56 (m, 3H); 3.05 (m, 1H); 3.16-3.38 (m, 5H); 7.51 (m, 1H); 8.04 (m, 2H); 8.19 (m, 1H); 8.34 (m, 1H); 8.37 (s, 1H); 8.79 (m, 1H).

Example 394

N-(4-Fluoro-5-quinolin-6-yl-2H-pyrazol-3-yl)-3-methyl-4-piperidin-1-yl-butyramideformic acid salt

[0498] To a suspension of 3-methyl-4-piperidin-1-yl-butyric acid hydrochloride (487 mg, 2.20 mmol, 1.6 equiv.) in DCE (5 mL), CDI (346 mg, 2.13 mmol, 1.55 equiv.) was added and the mixture stirred at 50 °C for 2 hours until complete activation of the amino acid. 4-Fluoro-5-quinolin-6-yl-2H-pyrazol-3-yl-ammonium hydrochloride (500 mg, 1.89 mmol, 1.0 equiv.) and Et$_3$N (192 µL, 1.89 mmol, 1.0 equiv.) were added and the reaction stirred for 1 hour at room temperature then at 50 °C overnight. After 16 hours a second portion of 3-methyl-4-piperidin-1-yl-butyric acid hydrochloride (152 mg, 0.69 mmol, 0.5 equiv.) was activated with CDI (109 mg,
0.67 mmol), and then added to the reaction mixture that was stirred for further 3 hours at 50 °C. After evaporation of the solvent the crude product was purified using C18 reverse chromatography (water/MeOH 95:5, 0.1% HCOOH) to give N-(4-fluoro-5-quinolin-6-yl-2H-pyrazol-3-yl)-3-methyl-4-piperidin-1-yl-butyramide formic acid salt (330 mg, 48%) as a solid.

C_{22}H_{26}FN_{5}O-HCOOH (parent mass, calculated) [395]; found [M+H^+] = 396

LC Rt = 1.92 min (10 min method, methanol gradient)

^1H-NMR (400 MHz, ^{-}-methanol, δ): 1.06 (d, J = 6.8 Hz, 3H); 1.57 (m, 2H); 1.77 (m, 4H); 2.46 (m, 1H); 2.54 (m, 2H); 2.87-3.21 (m, 6H); 7.51 (m, 1H); 8.04 (m, 2H); 8.20 (m, 1H); 8.34 (m, 1H); 8.41 (s, 1H); 8.79 (m, 1H).

Example 395

N-(4-Fluoro-5-quinolin-5-yl-2H-pyrazol-5-yl)-4-piperidin-1-yl-butyramide formic acid salt

To a suspension of 4-piperidin-1-yl-butyric acid hydrochloride (473 mg, 2.28 mmol, 1.3 equiv.) in DCE (3 mL), CDI (355 mg, 2.19 mmol, 1.25 equiv.) was added. The mixture was stirred at room temperature overnight until complete activation of the amino acid. 4-Fluoro-5-quinolin-3-yl-2H-pyrazol-3-ylamine (400 mg, 1.75 mmol, 1.0 equiv.) and DCE (3 mL) were added and the reaction was stirred for 10 hours at 40 °C. After evaporation of the solvent the crude product was purified by preparative HPLC to give N-(4-fluoro-5-quinolin-3-yl-2H-pyrazol-3-yl)-4-piperidin-1-yl-butyramide formic acid salt. (480 mg, 70%) as a solid.

C_{21}H_{24}FN_{5}O-HCOOH (parent mass, calculated) [381]; found [M+H^+] = 382

LC Rt = 2.40 min (10 min method, methanol gradient)
Example 396

N-(4-Fluoro-5-quinolin-3-yl-2H-pyrazol-3-yl)-4-pyrrolidin-1-yl-butramide formic acid salt

![Structure of N-(4-Fluoro-5-quinolin-3-yl-2H-pyrazol-3-yl)-4-pyrrolidin-1-yl-butramide formic acid salt]

[0500] To a suspension of 4-pyrrolidin-1-yl-butric acid hydrochloride (354 mg, 1.71 mmol, 1.3 equiv.) in DCE (3 mL), CDI (267 mg, 1.64 mmol, 1.25 equiv.) was added. The mixture was stirred at room temperature for 10 hours until complete activation of the amino acid. 4-Fluoro-5-quinolin-3-yl-2H-pyrazol-3-ylamine (300 mg, 1.31 mmol, 1.0 equiv.) and DCE (3 mL) were added and the reaction was stirred overnight at 40 °C. After evaporation of the solvent the crude product was purified by preparative HPLC to give N-(4-fluoro-5-quinolin-3-yl-2H-pyrazol-3-yl)-4-pyrrolidin-1-yl-butramide formic acid salt (300 mg, 62%) as a solid.

C_{20}H_{22}FN_{5}O-HCOOH (parent mass, calculated) [367]; found [M+H+] =368

LC Rt= 2.15 min (10 min method, methanol gradient)

Example 397

N-(4-Fluoro-5-quinolin-3-yl-2H-pyrazol-3-yl)-3-methyl-4-pyrrolidin-1-yl-butramide formic acid salt
To a suspension of 3-methyl-4-pyrrolidin-1-yl-butyric acid hydrochloride (355 mg, 1.71 mmol, 1.3 equiv.) in DCE (3 mL), CDI (267 mg, 1.64 mmol, 1.25 equiv.) was added. The mixture was stirred at room temperature for 10 hours until complete activation of the amino acid. 4-Fluoro-5-quinolin-3-yl-2H-pyrazol-3-ylamine (300 mg, 1.31 mmol, 1.0 equiv.) and DCE (3 mL) were added and the reaction was stirred overnight at 40 °C. After this time the LC/MS analysis showed 50% of conversion. A second batch of 3-methyl-4-pyrrolidin-1-yl-butyric acid hydrochloride (218 mg, 1.05 mmol, 0.8 equiv.) activated with CDI (160 mg, 0.98 mmol, 0.75 equiv.) was added. After stirring over weekend at room temperature, the reaction was worked up. After evaporation of the solvent the crude product was purified by preparative HPLC to give N-(4-fluoro-5-quinolin-3-yl-2H-pyrazol-3-yl)-3-methyl-4-pyrrolidin-1-yl-butyramide formic acid salt (201 mg, 40%) as a solid.

C_{21}H_{24}FN_{5}O-HCOOH (parent mass, calculated) [381]; found [M+H^+] =382

LC Rt= 2.47 min (10 min method, methanol gradient)

^1H-NMR (400 MHz, d_6-OMSO, δ): 0.94 (d, 3H, J = 6.18 Hz), 1.69 (m, 4H), 2.05-2.19 (m, 2H), 2.29-2.59 (m, 7H), 7.65 (m, 1H), 7.78 (m, 1H), 8.05 (m, 2H), 8.19 (s,1H), 8.60 (m, 1H), 9.24 (m, 1H), 10.19 (brs, 1H).

Example 398

N-(4-Fluoro-5-quinolin-S-yl-2H-pyrazol-S-yl)-S-methyl-4-piperidin-1-yl-butyramideformic acid salt

C_{21}H_{24}FN_{5}O-HCOOH (parent mass, calculated) [381]; found [M+H^+] =382

LC Rt= 2.47 min (10 min method, methanol gradient)

^1H-NMR (400 MHz, d_6-OMSO, δ): 0.94 (d, 3H, J = 6.18 Hz), 1.69 (m, 4H), 2.05-2.19 (m, 2H), 2.29-2.59 (m, 7H), 7.65 (m, 1H), 7.78 (m, 1H), 8.05 (m, 2H), 8.19 (s,1H), 8.60 (m, 1H), 9.24 (m, 1H), 10.19 (brs, 1H).

Example 398

N-(4-Fluoro-5-quinolin-S-yl-2H-pyrazol-S-yl)-S-methyl-4-piperidin-1-yl-butyramideformic acid salt
To a suspension of 3-methyl-4-piperidin-1-yl-butyric acid (141 mg, 0.64 mmol, 1.3 equiv.) in DCE (2 mL), CDI (100 mg, 0.62 mmol, 1.25 equiv.) was added. The mixture was stirred at 40 °C for 1.5 hours until complete activation of the amino acid. 4-Fluoro-5-quinolin-3-yl-2H-pyrazol-3-ylamine hydrochloride (130 mg, 0.49 mmol, 1.0 equiv.), Et$_3$N (0.137 mL, 0.98 mmol, 2.0 equiv.) and DCE (2 mL) were added and the reaction was stirred at 40 °C for 10 hours and then at room temperature for 2 days. After evaporation of the solvent the crude product was purified by preparative HPLC to give N-(4-fluoro-5-quinolin-3-yl-2H-pyrazol-3-yl)-3-methyl-4-piperidin-1-yl-butyramide formic acid salt (72 mg, 33%) as a solid.

C$_{22}$H$_{26}$FN$_5$O-HCOOH (parent mass, calculated) [395]; found [M+H$^+$]=396

LC Rt= 2.80 min (10 min method, methanol gradient)

$^1$H-NMR (400 MHz, $^-$methanol, $\delta$): 1.07 (d, 3H, $J = 6.67$ Hz), 1.59 (brs, 2H), 1.73-1.84 (m, 4H), 2.42-2.59 (m, 3H), 2.90-3.22 (m, 6H), 7.59 (m, 1H), 7.73 (m, 1H), 7.95 (m, 2H), 8.33 (s, 1H), 8.55 (m, 1H), 9.13 (brs, 1H).

Example 399

$N$-[4-Fluoro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramideformic acid salt

[0503] To a suspension of 4-piperidin-1-yl-butyric acid hydrochloride (331 mg, 1.59 mmol, 1.3 equiv.) in DCE (2 mL), CDI (248 mg, 1.53 mmol, 1.25 equiv.) was added. The mixture was stirred at 40 °C for 2 hours until complete activation of the amino acid. 4-Fluoro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine (255 mg, 1.22 mmol, 1 equiv.) and DCE (2 mL) were added and the reaction was stirred overnight at 40 °C. The solvent was evaporated and the crude product was purified by prep HPLC. After the evaporation of the solvent, the obtained
solid was triturated with acetone and dried. N-[4-Fluoro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide formic acid salt was obtained as a solid (136 mg, 31%).

C\textsubscript{18}H\textsubscript{24}FN\textsubscript{5}O\textsubscript{2}-HCOOH (parent mass, calculated) [361]; found [M+H\textsuperscript{+}]\textasciitilde362

LC Rt= 2.32 min (10 min method, methanol gradient)

\textsuperscript{1}H-NMR (400 MHz, \textsuperscript{^-}methanol, \textgreek{d}): 1.84 (m, 3H), 2.09 (m, 2H), 2.61 (t, 2H, \textit{J} = 6.74 Hz), 3.05-3.34 (m, 7H), 3.96 (s, 3H), 6.92 (m, 1H), 7.98 (m, 1H), 8.45-8.54 (m, 2H).

**Example 400**

\textit{N-[4-Fluoro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-4-pyrrolidin-1-yl-butyramide formic acid salt}

![Chemical structure]

[0504] To a suspension of 4-pyrrolidin-1-yl-butyric acid hydrochloride (308 mg, 1.59 mmol, 1.3 equiv.) in DCE (2 mL), CDI (248 mg, 1.53 mmol, 1.25 equiv.) was added. The mixture was stirred at 40 °C for 2 hours until complete activation of the amino acid. 4-Fluoro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine (255 mg, 1.22 mmol, 1 equiv.) and DCE (2 mL) were added and the reaction was stirred overnight at 40 °C. After evaporation of the solvent the crude product was purified by prep HPLC to give \textit{N-[4-fluoro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-4-pyrrolidin-1-yl-butyramide formic acid salt} (264.4 mg, 62%) as a solid.

C\textsubscript{17}H\textsubscript{22}FN\textsubscript{5}O\textsubscript{2}-HCOOH (parent mass, calculated) [347]; found [M+H\textsuperscript{+}]\textasciitilde348

LC Rt= 2.12 min (10 min method, methanol gradient)

\textsuperscript{1}H-NMR (400 MHz, \textsuperscript{^-}methanol, \textgreek{d}): 2.02-2.14 (m, 6H), 2.60 (t, 2H, \textit{J} = 6.52 Hz), 3.23 (t, 2H, \textit{J} = 8.01), 3.95 (s, 3H), 3.28-3.39 (m, 4H), 6.91 (m, 1H), 7.97 (m, 1H), 8.47 (m, 1H), 8.51 (m, 1H).
Example 401

\[ \text{N-[4-Fluro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-3-methyl-4-piperidin-1-yl-butyramide formic acid salt} \]

![Chemical Structure](image)

[0505] To a suspension of 3-methyl-4-piperidin-1-yl-butyric acid (543 mg, 2.46 mmol, 1.2 equiv.) in DCE (4 mL), CDI (415 mg, 2.56 mmol, 1.25 equiv.) was added. The mixture was stirred at 40 °C for 1.5 hours until complete activation of the amino acid. 4-Fluoro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine hydrochloride (500 mg, 2.05 mmol, 1.0 equiv.), Et\(\text{N} \) (0.57 mL, 4.09 mmol, 2 equiv.) and DCE (4 mL) were added and the reaction mixture was stirred at room temperature for 2 days. After evaporation of the solvent the crude product was purified by C18 reverse chromatography (water/MeOH 0.1% HCOOH 90:10) to give N-[4-fluoro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-3-methyl-4-piperidin-1-yl-butyramide formic acid salt (456 mg, 53%) as a solid.

\( \text{C}_{19}\text{H}_{26}\text{FN}_5\text{O}_2\cdot\text{HCOOH} \) (parent mass, calculated) [375]; found [M+H\(^+\)] =376.

LC Rt= 2.57 min (10 min method, methanol gradient)

\( ^1\text{H-NMR} \) (400 MHz, ^\text{\textasciitilde}methanol, \( \delta \)): 1.14 (d, 3H, \( J = 6.63 \) Hz), 1.67 (brs, 2H), 1.88 (m, 2H), 2.48-2.69 (m, 3H), 3.00-3.44 (m, 6H), 3.95 (s, 3H), 6.91 (m, 1H), 7.97 (dd, 1H, \( J = 8.78 \) Hz, \( J = 2.54 \)), 8.44 (s, 1H), 8.48 (m, 1H).

Example 402

\[ \text{N-[4-Fluro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-3-methyl-4-pyrrolidin-1-yl-butyramide formic acid salt} \]
To a suspension of 3-methyl-4-pyrrolidin-1-yl-butyric acid (636 mg, 3.07 mmol, 1.5 equiv.) in DCE (4 mL), CDI (602 mg, 3.71 mmol, 1.45 equiv.) was added. The mixture was stirred at 40 °C for 1.5 until complete activation of the amino acid. 4-Fluoro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine hydrochloride (500 mg, 2.05 mmol, 1.0 equiv.), Et$_3$N (0.57 mL, 4.09 mmol, 2.0 equiv.) and DCE (4 mL) were added and the reaction was stirred at room temperature for 2 days. After evaporation of the solvent the crude product was purified by C18 reverse chromatography (water/MeOH 0.1% HCOOH 90:10) to give N-[4-fluoro-5-(6-methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-3-methyl-4-pyrrolidin-1-yl-butyramide formic acid salt (418 mg, 50%) as a solid.

C$_{18}$H$_{24}$F$_N$O$_5$HCOOH (parent mass, calculated) [361]: found [M+H$^+$] = 362

LC Rt= 2.27 min (10 min method, methanol gradient)

$^1$H-NMR (400 MHz, $^-$methanol, $\delta$): 1.17 (d, 3H, $J = 6.70$ Hz), 2.09 (m, 4H), 2.42-2.65 (m, 3H), 3.1-3.18 (m, 1H), 3.22-3.29 (m, 1H), 3.40 (brs, 4H), 3.95 (s, 3H), 6.91 (m, 1H), 7.98 (dd, 1H, $J = 8.69$ Hz, $J = 2.51$ Hz), 8.48 (m, 2H).

Example 403

3-Methyl-N-[5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-4-pyrrolidin-1-yl-butyramide

[0507] To a suspension of 3-methyl-4-pyrrolidin-1-yl-butyric acid (135 mg, 0.65 mmol, 1.3 equiv.) in MeCN (3 mL), under nitrogen atmosphere, oxalyl chloride (53 µL, 0.63 mmol, 1.26 equiv.) and DMF (catalytic amount) were added. The reaction mixture was stirred for 1...
hour at room temperature until complete activation of the amino acid. 5-Amino-3-(6-methyl-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester (137 mg, 0.50 mmol, 1.0 equiv.) was added. The reaction was stirred overnight at room temperature. HCl (2 N solution in diethylether, 0.5 mL, 1.0 mmol, 2.0 equiv.) was added and the reaction mixture was stirred for 10 hours at room temperature until complete deprotection. After evaporation of the solvent, the mixture was purified by preparative HPLC followed by silica chromatography (EtOAc/2 N NH₃ in MeOH 100:0 to 90:10) to give 3-methyl-N-[5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-4-pyrrolidin-1-yl-butyramide (59 mg, 36%) as a solid.

C₁₈H₂₅N₅O Mass (calculated) [327]; found [M+H⁺]=328

Lc Rt= 0.20 min (10 min method, methanol gradient)

¹H-NMR (400 MHz, ^-methanol, δ): 1.03 (d, 3H, J = 6.36 Hz), 1.80 (m, 4H), 2.18-2.68 (m, 13H), 6.79 (brs, 1H), 7.37 (m, 1H), 8.02 (m, 1H), 8.74 (m, 1H).

Example 404

S-Methyl-4-pyrrolidin-l-yl-N-(5-quinolin-S-yl-2H-pyrazol-3-yl)-butyramide

[0508] To a suspension of 3-methyl-4-pyrrolidin-1-yl-butyric acid (135 mg, 0.65 mmol, 1.3 equiv.) in MeCN (3 mL), under nitrogen atmosphere, oxalyl chloride (53 µL, 0.63 mmol, 1.26 equiv.) and DMF (catalytic amount) were added. The reaction mixture was stirred for 1 hour at room temperature until complete activation of the amino acid. 5-Amino-3-quinolin-3-yl-pyrazole-1-carboxylic acid tert-butyl ester (155 mg, 0.50 mmol, 1.0 equiv.) was added. The reaction was stirred overnight at room temperature. HCl (2 N solution in diethylether, 0.5 mL, 1.0 mmol, 2.0 equiv.) was added and the reaction mixture was stirred for 10 hours at room temperature until complete Boc deprotection. After evaporation of the solvent the mixture was purified by prep HPLC followed by silica chromatography column (EtOAc/ 2 N NH₃ in MeOH
100:0 to 90:10) to give 3-methyl-4-pyrrolidin-1-yl-N-(5-quinolin-3-yl-2H-pyrazol-3-yl)-butyramide (60.4 mg, 33%) as a solid.

C\textsubscript{2}I\textsubscript{H}\textsubscript{25}N\textsubscript{5}O Mass (calculated) \[363\]; found [M+H\textsuperscript{+}]=364

Lc Rt= 0.98 min (10 min method, methanol gradient)

\textsuperscript{1}H-NMR (400 MHz, \textsuperscript{1}H\textsubscript{8}methanol, \textdagger): 0.95 (d, 3H, J = 6.96 Hz), 1.71 (m, 4H), 2.09-2.32 (m, 3H), 2.37-2.57 (m, 6H), 6.87 (brs, 1H), 7.48 (m, 1H), 7.97-8.07 (m, 2H), 8.17 (m, 1H), 8.33 (m, 1H), 8.75 (dd, 1H, J = 4.43 Hz, J = 1.64 Hz).

Example 405

3-Methyl-4-pyrrolidin-1-yl-N-(5-quinolin-6-yl-2H-pyrazol-3-yl)-butyramide

\begin{center}
\textbf{[0509]} To a suspension of 3-methyl-4-pyrrolidin-1-yl-butyric acid (135 mg, 0.65 mmol, 1.3 equiv.) in MeCN (3 mL), under nitrogen atmosphere, oxalyl chloride (53 \textmu L, 0.63 mmol, 1.26 equiv.) and DMF (catalytic amount) were added. The reaction mixture was stirred for 1 hour at room temperature until complete activation of the amino acid. 5-Amino-3-quinolin-6-yl-pyrazole-1-carboxylic acid tert-butyl ester (155 mg, 0.50 mmol, 1.0 equiv.) was added. The reaction was stirred overnight at room temperature. HCl (2 N solution in diethylether, 0.5 mL, 1.0 mmol, 2.0 equiv.) was added and the reaction mixture was stirred for 10 hours at room temperature until complete deprotection. After evaporation of the solvent the mixture was purified by prep HPLC and then SiO\textsubscript{2} column (EtOAc/ 2 N NH\textsubscript{3} in MeOH 100:0 to 90:10) to give 3-methyl-4-pyrrolidin-1-yl-N-(5-quinolin-6-yl-2H-pyrazol-3-yl)-butyramide. (84.4 mg, 46 %) as a solid.

C\textsubscript{2}I\textsubscript{H}\textsubscript{25}N\textsubscript{5}O Mass (calculated) \[363\]; found [M+H\textsuperscript{+}]=364
\end{center}
Le Rt= 1.38 min (10 min method, methanol gradient)

$^1$H-NMR (400 MHz, $^{$-}$$methanol, $^{$\delta$$}$): 1.04 (d, 3H, $^{$J$$}$ = 6.70 Hz), 1.80 (m, 4H), 2.19-2.41 (m, 3H), 2.45-2.67 (m, 6H), 6.93 (brs, m), 7.66 (m, 1H), 7.79 (m, 1H), 8.03 (m, 2H), 8.63 (m, 1H), 9.23 (m, 1H).

Example 406

$N$-[5-(5-Methoxy-pyridin-$S$-yl)-2H-pyrazol-$S$-yl]-$S$-methyl-4-pyrrolidin-$l$-yl-butyramide

[0510] To a suspension of 3-methyl-4-pyrrolidin-$l$-yl-butyric acid (135 mg, 0.65 mmol, 1.3 equiv.) in MeCN (3 mL), under nitrogen atmosphere, oxalyl chloride (53 $\mu$L, 0.63 mmol, 1.26 equiv.) and DMF (catalytic amount) were added. The reaction mixture was stirred for 1 hour at room temperature until complete activation of the amino acid. 5-Amino-3-(5-methoxy-pyridin-$3$-yl)-pyrazole-1-carboxylic acid tert-butyl ester (145 mg, 0.50 mmol, 1.0 equiv.) was added. The reaction was stirred overnight at room temperature. HCl (2 N solution in diethylether, 0.5 mL, 1.0 mmol, 2.0 equiv.) was added and the reaction mixture was stirred for 10 hours at room temperature until complete deprotection. After evaporation of the solvent the mixture was purified by prep HPLC and then SiO$_2$ column (EtOAc/ 2 N NH$_3$ in MeOH 100:0 to 90:10) to give $N$-[5-(5-Methoxy-pyridin-$3$-yl)-2H-pyrazol-$3$-yl]-3-methyl-4-pyrrolidin-$l$-yl-butyramide (63.3 mg, 37 %) as a solid.

C$_{18}$H$_{25}$N$_5$O Mass (calculated) [343]; found [M$+$H$^+$]= 344

Le Rt= 0.88 min (10 min method, methanol gradient)

$^1$H-NMR (400 MHz, $^{$-}$$methanol): 1.02 (d, 2H, $^{$J$$}$ = 6.62 Hz), 1.82 (m, 4H), 2.33-2.20 (m, 3H), 2.47-2.37 (m, 1H), 2.72-2.48 (m, 5H), 3.94 (s, 3H), 7.71 (m, 1H), 8.20 (m, 1H), 8.47 (m, 1H).
Example 407

**N-[5-(5-Methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide formic acid salt**

![Chemical Structure](image)

[0511] To a suspension of 4-piperidin-1-yl-butyric acid hydrochloride (164 mg, 0.79 mmol, 1.5 equiv.) in DCE (5 mL), Et$_3$N (110 µL, 0.79 mmol, 1.5 equiv.) and CDI (111 mg, 0.68 mmol, 1.30 equiv.) were added and the mixture stirred at room temperature for 1 hour until complete activation of the amino acid. 5-(5-Methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine (100 mg, 0.53 mmol, 1.0 equiv.) was added and the reaction stirred for 3 hours at room temperature then at 50 °C overnight. After evaporation of the solvent the crude product was purified by preparative HPLC to give N-[5-(5-methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide formic acid salt (61 mg, 29%) obtained as a solid.

C$_{18}$H$_{25}$N$_5$O$_2$-HCOOH Mass (parent, calculated) [343]; found [M+H$^+$]=344

LC Rt=0.18, 0.87 min (10 min method)

$^1$H-NMR (400 MHz, $^-$methanol, δ): 1.65 (m, 2H); 1.86 (m, 4H); 2.09 (m, 2H); 2.58 (m, 2H); 3.12 (m, 6H); 3.92 (m, 3H); 6.83 (brs, 1H); 7.66 (m, 1H); 8.18 (m, 1H); 8.46 (m, 2H).

Example 408

**N-[5-(5-Methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-4-pyrrolidin-1-yl-butyramideformic acid salt**

![Chemical Structure](image)

[0512] To a suspension of 4-pyrrolidin-1-yl-butyric acid hydrochloride (153 mg, 0.79 mmol, 1.5 equiv.) in DCE (5 mL), Et$_3$N (110 µL, 0.79 mmol, 1.5 equiv.) and CDI (111 mg, 0.68
mmol, 1.30 equiv.) were added and the mixture stirred at room temperature for 1 hour until complete activation of the amino acid. 5-(5-Methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine was (100 mg, 0.53 mmol, 1.0 equiv.) added and the reaction stirred for 3 hours at room temperature then at 50 °C overnight. After evaporation of the solvent the crude product was purified by preparative HPLC to give N-[5-(5-methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-4-pyrrolidin-1-yl-butyramide formic acid salt (43 mg, 22%) as a solid.

C_{14}H_{23}N_{5}O_{2}-HCOOH (parent mass, calculated) [329]; found [M+H^+] = 330

LC Rt=0.20, 0.63 min (10 min method)

^1H-NMR (400 MHz, ^-methanol, δ): 2.09 (m, 6H); 2.58 (m, 2H); 3.26 (m, 2H); 3.38 (m, 4H); 3.94 (s, 3H); 6.82 (brs, 1H); 7.70 (m, 1H); 8.21 (m, 1H); 8.46 (m, 2H).

Example 409

N-[5-(5-Fluoro-pyridin-3-yl)-2H-pyrazol-3-yl]-4-pyrrolidin-1-yl-butyramide

To a suspension of 4-pyrrolidin-1-yl-butyric acid hydrochloride (163 mg, 0.84 mmol, 1.5 equiv.) in DCE (2 mL), Et₃N (117 µl, 0.84 mmol, 1.5 equiv.) and CDI (118 mg, 0.73 mmol, 1.30 equiv.) were added and the mixture stirred at room temperature for 1 hour until complete activation of the amino acid. 5-(5-Fluoro-pyridin-3-yl)-2H-pyrazol-3-ylamine (100 mg, 0.56 mmol, 1.0 equiv.) was added and the reaction stirred for 3 hours at room temperature then at 50 °C overnight. After evaporation of the solvent the mixture was purified by silica gel chromatography (EtOAc/MeOH with 2N NH₃ 100:0 to 90:10) to give N-[5-(5-Fluoro-pyridin-3-yl)-2H-pyrazol-3-yl]-4-pyrrolidin-1-yl-butyramide (30 mg, 17%) as a solid.

C_{16}H_{20}FN_{5}O Mass (calculated) [317]; found [M+H^+] = 318
LC Rt=0.20, 1.00 min (10 min method)

$^1$H-NMR (400 MHz, $^-$methanol): 1.60 (m, 2H); 1.78 (m, 4H); 2.01 (m, 2H); 2.50 (m, 2H); 3.07 (m, 4H); 6.77 (brs, 1H); 7.32 (m, 1H); 8.09 (m, 1H); 8.20 (m, 1H); 8.29 (s, 1H).

Example 410

$N$-[5-(5-Fluoro-pyridin-3-yl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide

\[
\text{CDI} + \text{N-(5-(5-Fluoro-pyridin-3-yl)-2H-pyrazol-3-yl)-4-piperidin-1-yl-butyramide} \rightarrow \text{Product}
\]

[0514] To a suspension of 4-piperidin-1-yl-butyric acid hydrochloride (0.80 g, 3.86 mmol, 1.3 equiv.) in DCE (20 mL), CDI (0.60 g, 3.7 mmol, 1.25 equiv.) was added and the mixture was stirred and heated at 40 °C for 2 hours. 5-(5-Fluoro-pyridin-3-yl)-2H-pyrazol-3-ylamine (0.60 g, 2.97 mmol, 1.0 equiv.) was added and the reaction was stirred for 1 hour at room temperature then overnight at 50 °C.

After evaporation of the solvent, the crude was dissolved in MeOH and loaded onto an NH$_2$ cartridge. The fractions containing the product were collected and evaporated.

The crude was purified by silica column (MeCN/MeOH, 2N NH3 100:0 to 80:20) to give $N$-[5-(5-fluoro-pyridin-3-yl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide (650 mg, 66%) as a solid.

C$_{17}$H$_{22}$FN$_5$O Mass (calculated) [331]; (found) [M+H$^+$] = 332

LC Rt = 1.77 min, (10 min method)

$^1$H-NMR (400 MHz, $^-$methanol, $\delta$): 1.64 (m, 2H); 1.81 (m, 4H); 2.06 (m, 2H); 2.56 (m, 2H); 3.03 (m, 6H); 6.89 (brs, 1H); 7.41 (m, 1H); 8.18 (m, 1H); 8.30 (m, 1H).
Example 411

2-Methyl-4-pyrrolidin-1-yl-N-(5-quinolin-6-yl-2H-pyrazol-3-yl)-butyramide formic acid salt

[0515] 2-Methyl-4-pyrrolidin-1-yl-butric acid hydrochloride (100 mg, 0.58 mmol, 1.0 equiv.), was suspended in MeCN under nitrogen atmosphere. Oxalyl chloride (52 µL, 0.61 mmol, 1.05 equiv.) was added followed by a drop of DMF. After stirring for 1 hour the conversion of the acid to the corresponding acyl chloride was complete and 5-amino-3-quinolin-6-yl-pyrazole-1-carboxylic acid tert-butyl ester was added (160 mg, 0.58 mmol, 1.0 equiv.). The reaction was stirred overnight at room temperature. HCl (2 N solution in diethylether, 0.35 mL, 0.7 mmol, 1.2 equiv.) was added and after stirring overnight at room temperature the deprotection was complete. After evaporation of the solvent the mixture was partitioned between AcOEt and NaHCO₃ sat. aqueous solution, the organic phase was collected, evaporated and purified by preparative HPLC to give 2-methyl-4-pyrrolidin-1-yl-N-(5-quinolin-6-yl-2H-pyrazol-3-yl)-butyramide (470 mg, 58%) as a solid.

\[
\text{C}_{21}\text{H}_{25}\text{N}_{5}\text{O}-\text{HCOOH (parent mass, calculated) [363]; found [M+H^+] = 364}
\]

Lc Rt=1. 33 min (10 min method)

\[\text{^1H-NMR (400 MHz, d-chloroform, } \delta: 1.11 (d, J = 4.0 Hz, 3H); 1.58 (m, 1H); 1.72 (m, 4H); 1.84 (m, 1H); 2.60 (m, 3H); 2.66 (m, 4H); 7.06 (brs, 1H); 7.63 (dd, J = 8 Hz, J = 8 Hz, 1H); 7.75 (dd, J = 8 Hz, J = 8 Hz, 1H); 8.00 (dd, J = 8 Hz, J = 8 Hz, 2H); 8.23 (s, 1H); 8.66 (s, 1H); 9.28 (s, 1H); 10.71 (brs, 1H).}\]
Example 412

3-Methyl-N-[5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide

4-Piperidin-1-yl-butyric acid hydrochloride (114 mg, 0.52 mmol, 1.5 equiv.), was suspended in MeCN under nitrogen. Oxalyl chloride (44 µL, 0.52 mmol, 1.45 equiv.) was added followed by a drop of DMF. After stirring for 1 hour conversion of the acid to the corresponding acyl chloride was complete and 5-amino-3-(6-methyl-pyridin-3-yl)-pyrazole-1-carboxylic acid tert-butyl ester was added (94 mg, 0.35 mmol, 1.0 equiv.). The reaction was stirred overnight at room temperature. HCl (2 N solution in diethylether, 0.35 mL, 0.7 mmol, 1.2 equiv.) was then added and after stirring overnight at room temperature the deprotection was complete. After evaporation of the solvent the mixture was dissolved in 4 mL of 2 N methanolic ammonia and the solvent evaporated. The crude material was then purified by silica column (MeCN/MeOH, 2 N NH₃ 100:0 to 95:5) to give 3-methyl-N-[5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide (24 mg, 20%) as a solid.

C₁₉H₂₇N₅O Mass (calculated) [341]; found [M+H⁺]=342

Lc Rt=0.22, 0.48 min (10 min method)

¹H-NMR (400 MHz, ¹H-methanol, δ): 0.91 (d, J = 6.0 Hz, 3H); 1.36 (m, 2H); 1.51 (m, 2H); 2.03-2.44 (m, 8H); 2.46 (s, 3H); 6.85 (brs, 1H); 7.28 (m, 1H); 7.93 (m, 1H); 8.65 (s, 1H).
Example 413

\[ \text{N-[4-Fluoro-5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-4-pyrrolidin-1-yl-butyramide hydrochloric salt} \]

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{N} & \quad \text{F} \\
\text{C} & \quad \text{H}_2 \\
\text{O} & \quad \text{HCl}
\end{align*}
\]

[0517] To a suspension of 3-methyl-4-piperidin-1-yl-butyric acid hydrochloride (452 mg, 2.34 mmol, 1.5 equiv.) in DCE (6 mL), CDI (329 mg, 2.03 mmol, 1.3 equiv.) was added. The mixture was stirred at room temperature until complete activation of the amino acid. 4-Fluoro-5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-ylamine (300 mg, 1.56 mmol, 1.0 equiv.) was added and the reaction stirred overnight at 40 °C. The solvent was evaporated and the crude product purified by silica column (eluent DCM/MeOH with 2 N NH₃ 100:0 to 9:1). The product obtained was crystallized from MeCN. The pure product was dissolved in MeOH and 2N HCl in MeOH (84 μL, 1.2 equiv.) was added, the solvent was evaporated to give \( \text{N-[4-fluoro-5-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-4-pyrrolidin-1-yl-butyramide hydrochloric salt} \) (52 mg, 9%) as a solid.

\( \text{C}_{17}\text{H}_{22}\text{FN}_{5}\text{O HCl} \) (parent mass, calculated) [331]; found [M+H⁺] = 332

\( \text{LC Rt}=0.21 \text{ min (10 min method)} \)

\(^1\text{H-NMR (400 MHz, } d_6-\text{DMSO): } 1.74 \text{ (m, 4H); 1.80 (m, 2H); 2.38 (m, 2H); 2.49 (s, 3H); 2.67 (m, 6H); 7.37 (m, 1H); 7.93 (m, 1H); 8.76 (m, 1H); 10.10 (brs, 1H).} \)

Example 414

\( \text{N-[5-(6-Methoxy-pyridin-3-yl)-2H-pyrazol-3-yl]-4-pyrrolidin-1-yl-butyramide} \)

316
To a suspension of 4-pyrrolidin-1-yl-butyric acid hydrochloride (0.73 g, 3.80 mmol, 1.3 equiv.) in DCE (15 mL), CDI (0.59 g, 3.65 mmol, 1.25 equiv.) was added and the mixture was stirred and heated at 40 °C for 2 hours (complete activation of the acid was checked by LCMS analysis quenching a reaction sample with MeOH). 5-(6-Methoxy-pyridin-3-yl)-2H-pyrazol-3-ylamine (0.56 g, 2.93 mmol, 1.0 equiv.) was then added and the reaction was stirred for 1 hour at room temperature then overnight at 50 °C. The solvent was evaporated and the crude dissolved in MeOH and loaded onto an NH2 cartridge. The fractions containing the product were collected and evaporated. The crude was purified by silica column (CH3CN: MeOH, 2 N NH3).

Yield: 70%, 670 mg

C_{17}H_{23}N_5O_2 Mass (calculated) [329.41]; (found) [M+H+] = 330.08

LC Rt = 2.05 min, 100% (10 min method)

^1H-NMR (400 MHz, ^^-methanol, δ): 1.84 (m, 4H); 1.94 (m, 2H); 2.45 (m, 2H); 2.65 (m, 6H); 3.94 (m, 3H); 6.73 (brs, 1H); 6.87 (m, 1H); 7.96 (m, 1H); 8.46 (m, 1H).

Example 415

N-[5-(5-Fluoro-pyridin-S-yl)-2H-pyrazol-S-yl]-S-methyl-4-pyrrolidin-1-yl-butyramide formic acid salt
To a suspension of 3-methyl-4-pyrrolidin-1-yl-butyric acid (429 mg, 2.06 mmol, 1.5 equiv.) in DCE (4 mL), CDI (324 mg, 2.00 mmol, 1.45 equiv.) was added. The mixture was stirred at 40 °C for 1.5 h until complete activation of the amino acid. 5-(5-Fluoro-pyridin-3-yl)-2H-pyrazol-3-ylamine (245 mg, 1.38 mmol, 1.0 equiv.), and DCE (4 mL) were added and the reaction mixture was stirred at 40 °C for 12 h. After evaporation of the solvent the crude product was purified by preparative HPLC to give N-[5-(5-fluoro-pyridin-3-yl)-2H-pyrazol-3-yl]-3-methyl-4-pyrrolidin-1-yl-butyramide formic acid salt (125 mg, 25%) as a solid.

C_{17}H_{22}FN_{5}O-HCOOH (parent mass, calculated) [331]; found [M+H+] = 332.

LC Rt= 1.68 min (10 min method, methanol gradient)

^1H-NMR (400 MHz, ^1H-methanol, δ): 1.14 (d, 3H, J = 6.6 Hz), 2.10 (m, 4H); 2.48-2.69 (m, 3H), 3.14 (m, 1H), 3.25 (m, 2H), 3.40 (m, 3H), 6.88 (brs, 1H), 7.41 (m, 1H), 8.18 (m, 1H); 8.30 (m, 1H); 8.46 (s, 1H).

Example 416

N-[5-(5-Fluoro-pyridin-S-yl)-2H-pyrazol-S-yl]-S-methyl-4-piperidin-l-yl-butyramideformic acid salt

To a suspension of 3-methyl-4-piperidin-1-yl-butyric acid (456 mg, 2.06 mmol, 1.5 equiv.) in DCE (4 mL), CDI (324 mg, 2.00 mmol, 1.45 equiv.) was added. The mixture was stirred at 40 °C for 1.5 h until complete activation of the amino acid. 5-(5-Fluoro-pyridin-3-yl)-2H-pyrazol-3-ylamine (245 mg, 1.38 mmol, 1.0 equiv.), and DCE (4 mL) were added and the reaction mixture was stirred at 40 °C for 12 h. After evaporation of the solvent the crude product
was purified by preparative HPLC to give N-[5-(5-fluoro-pyridin-3-yl)-2H-pyrazol-3-yl]-3-methyl-4-piperidin-1-yl-butyramide formic acid salt (272 mg, 50%) as a solid.

C$_{15}$H$_{24}$FN$_5$O-HCOOH (parent mass, calculated) [345]; found [M+H$^+$] =346.

LC Rt= 1.95 min (10 min method, methanol gradient)

$^1$H-NMR (400 MHz, $^-$methanol, $\delta$): 1.13 (d, 3H, J = 6.6 Hz), 1.68 (m, 2H), 1.88 (m, 4H), 2.45-2.65 (m, 3H), 2.97-3.36 (m, 6H), 6.90 (brs, 1H), 7.41 (m, 1H), 7.19 (m, 1H), 8.30 (m, 1H); 8.49 (s, 1H).

**Example 417**

2-Methyl-4-piperidin-1-yl-N-(5-quinolin-6-yl-1H-pyrazol-5-yl)-butyramide

2-Methyl-4-piperidin-1-yl-butyric acid hydrochloride (171 mg, 0.78 mmol, 1.5 equiv.) was suspended in dry DCM (3 mL) under nitrogen. Ethyl-diisopropyl-amine (135 µL, 0.78 mmol, 1.5 equiv.) was added followed by oxalyl chloride (63 µL, 0.75 mmol, 1.45 equiv.) and a drop of DMF. After stirring for 2 hours the conversion of the acid to the corresponding acyl chloride was complete and 5-amino-3-quinolin-6-yl-pyrazole-1-carboxylic acid tert-butyl ester was added (160 mg, 0.52 mmol, 1.0 equiv.). The reaction was stirred overnight at room temperature. Trifluoroacetic acid (2 mL) was added and after stirring 2 hours at room temperature the deprotection was complete. After evaporation of the solvent the mixture was purified by preparative HPLC to give 2-methyl-4-piperidin-1-yl-N-(5-quinolin-6-yl-1H-pyrazol-3-yl)-butyramide formic acid salt. The product was dissolved in ethyl acetate (20 mL), washed
with NaHCO₃ sat. solution (2 x 5 mL) and with brine (2 x 5 mL). The organic phase was dried and evaporated in vacuo to give 2-methyl-4-piperidin-1-yl-N-(5-quinolin-6-yl-1H-pyrazol-3-yl)-butyramide (135 mg, 69%) as a solid.

C₂₂H₂₇N₅O Mass (calculated) [377]; found [M+H⁺]=378

Lc Rt= 1.43 min (10 min method)

¹H-NMR (400 MHz, D-methanol, δ): 1.25 (d, J = 7.0 Hz, 3H); 1.47 (m, 2H); 1.61 (m, 4H); 1.69 (m, 1H); 1.96 (m, 1H); 2.47 (m, 7H); 6.96 (brs, 1H); 7.65 (m, 1H); 7.79 (m, 1H); 8.0 (m, 2H); 8.62 (m, 1H); 9.22 (m, 1H).

**Biological activity**

*Cloning of alpha7 nicotinic acetylcholine receptor and generation of stable recombinant alpha7 nAChR expressing cell lines*

[0522] Full length cDNAs encoding the alpha7 nicotinic acetylcholine receptor were cloned from a rat brain cDNA library using standard molecular biology techniques. Rat GH4C1 cells were then transfected with the rat receptor, cloned and analyzed for functional alpha7 nicotinic receptor expression employing a FLIPR assay to measure changes in intracellular calcium concentrations. Cell clones showing the highest calcium-mediated fluorescence signals upon agonist (nicotine) application were further subcloned and subsequently stained with Texas red-labelled α-bungarotoxin (BgTX) to analyse the level and homogeneity of alpha7 nicotinic acetylcholine receptor expression using confocal microscopy. Three cell lines were then expanded and one characterised pharmacologically (see Table 4 below) prior to its subsequent use for compound screening.

*Table 4 - Pharmacological characterisation of alpha7 nAChR stably expressed in GH4C1 cells using the functional FLIPR assay*

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC₅₀ [microM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>3.05 ± 0.08 (n=4)</td>
</tr>
<tr>
<td>Choline</td>
<td>24.22 ± 8.30 (n=2)</td>
</tr>
</tbody>
</table>
Development of a functional FLIPR assay for primary screening

A robust functional FLIPR assay ($Z' = 0.68$) employing the stable recombinant GH4C1 cell line was developed to screen the alpha7 nicotinic acetylcholine receptor. The FLIPR system allows the measurements of real time Ca$^{2+}$-concentration changes in living cells using a Ca$^{2+}$ sensitive fluorescence dye (such as Fluo4). This instrument enables the screening for agonists and antagonists for alpha 7 nAChR channels stably expressed in GH4C1 cells.

Cell culture

GH4C1 cells stably transfected with rat- alpha7-nAChR (see above) were used. These cells are poorly adherent and therefore pretreatment of flasks and plates with poly-D-lysine was carried out. Cells are grown in 150 cm$^2$-T-flasks, filled with 30 ml of medium at 37°C and 5% CO$_2$.

Data analysis

EC50 and IC50 values were calculated using the IDBS XLfit 4.1 software package employing a sigmoidal concentration-response (variable slope) equation:

$$Y = \text{Bottom} + \left(\frac{\text{Top-Bottom}}{1+(EC_{50}/X)^{\text{HillSlope}}}ight)$$

Assay validation

The functional FLIPR assay was validated with the alpha7 nAChR agonists nicotine, cytisine, DMPP, epibatidine, choline and acetylcholine. Concentration-response curves were obtained in the concentration range from 0.001 to 30 microM. The resulting EC50 values are listed in Table 2 and the obtained rank order of agonists is in agreement with published data (Quik et al, 1997, *Mol. Pharmacol.*, 51, 499-506).
The assay was further validated with the specific alpha7 nAChR antagonist MLA (methyllycaconitine), which was used in the concentration range between 1 microM to 0.01 nM, together with a competing nicotine concentration of 10 microM. The IC50 value was calculated as 1.31±0.43 nM in nine independent experiments.

Development of functional FLIPR assays for selectivity testing

Functional FLIPR assays were developed in order to test the selectivity of compounds against the alphal (muscular) and alpha3 (ganglionic) nACh receptors and the structurally related 5-HT3 receptor. For determination of activity at alphal receptors natively expressed in the rhabdomyosarcoma derived TE 671 cell line an assay employing membrane potential sensitive dyes was used, whereas alpha3 selectivity was determined by a calcium-monitoring assays using the native SH-SY5Y cell line. In order to test selectivity against the 5-HT3 receptor, a recombinant cell line was constructed expressing the human 5-HT3A receptor in HEK 293 cells and a calcium-monitoring FLIPR assay employed.

Screening of compounds

The compounds were tested using the functional FLIPR primary screening assay employing the stable recombinant GH4C1 cell line expressing the alpha7 nAChR. Hits identified were validated further by generation of concentration-response curves. The potency of compounds from Examples 1-417 as measured in the functional FLIPR screening assay was found to range between 10 nM and 10 microM, with the majority showing a potency ranging between 100 nM and 5 microM.

The compounds were also demonstrated to be selective against the alphal nAChR, alpha3 nAChR and 5HT3 receptors.

While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.
Claims

What is claimed is:

1. A compound of formula II:

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a 4 to 7-membered saturated ring;

T' is a straight or branched C₁₋₆ alkylene chain;

X is halogen or hydrogen; and

Ring B is a 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein Ring B is optionally substituted with halogen; hydroxy; oxo; mercapto; cyano; nitro; amino; linear, branched or cyclic (C₁-C₆) alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, di- or trihaloalkoxy, alkoxy, or alkylcarbonyl; (C₃-C₆) cycloalkyl-(C₁-C₆) alkoxy; (C₃-C₆) cycloalkyl-(C₁-C₆) alkyl; linear, branched, or cyclic (C₁-C₆) alkylcarbonylamino; mono- or di-, linear, branched, or cyclic (C₁-C₆) alkylaminocarbonyl; carbamoyl; linear, branched, or cyclic (C₁-C₆) alkylsulphonylamino; mono- or di-, linear, branched, or cyclic (C₁-C₆) alkylsulphamoyl; or linear, branched or cyclic (C₁-C₆) alkoxy-(C₁-C₆) alkyl;

with the proviso that the compound is not 5-piperidin-1-yl-pentanoic acid [5-(1H-indol-5-yl)-2H-pyrazol-3-yl]-amide, 5-piperidin-1-yl-pentanoic acid (5-furan-2-yl-2H-pyrazol-3-yl)-amide, N-[5-(6-methyl-pyridin-3-yl)-1H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide, N-[5-(5-methyl-pyridin-3-yl)-1H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide, 5-azepan-1-yl-pentanoic acid (5-pyridin-4-yl-1H-pyrazol-3-yl)-amide, N-[5-(1H-indol-3-yl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide, N-[5-(1-ethyl-1H-indol-3-yl)-2H-pyrazol-3-yl]-4-pyrrolidin-1-yl-butyramide, or one of the following:
2. The compound of claim 1, wherein Ring A is a 5-6 membered saturated ring.

3. The compound of claim 2, wherein Ring A is piperidinyl.

4. The compound of claim 2, wherein Ring A is pyrrolidinyl.

5. The compound of claim 1, wherein Ring B is a 6-membered monocyclic heteroaryl ring having one or two nitrogens.

6. The compound of claim 5, wherein Ring B is pyridyl.

7. The compound of claim 6, wherein Ring B is pyridyl optionally substituted with halogen or (C1-C6) alkyl, dihaloalkyl, or alkoxy.

8. The compound of claim 1, wherein Ring B is an 8-10 membered bicyclic heteroaryl ring having one or two nitrogens.

9. The compound of claim 8, wherein Ring B is a 10-membered bicyclic heteroaryl ring having one nitrogen.
10. The compound of claim 9, wherein Ring B is quinolinyl.

11. The compound of claim 1, wherein X is halogen.

12. The compound of claim 11, wherein X is fluoro.

13. The compound of claim 1, wherein X is hydrogen.

14. The compound of claim 1, wherein T' is a C2-5 alkylene chain.

15. The compound of claim 14, wherein T' is selected from the group consisting of -CH₂CH₂CH₂-, -CH(CH₃)CH₂CH₂-, -C(CH₃)₂CH₂CH₂-, -CH₂CH(CH₃)CH₂-, and -CH₂C(CH₃)₂CH₂-.

16. The compound of claim 1, wherein the compound is of formula II-a, II-b, II-c, II-d, II-e, II-f, II-g, II-h, II-j, or II-k:
wherein $R^x$ is selected from the group consisting of halogen; hydroxy; mercapto; cyano; nitro; amino; linear, branched or cyclic (Cl-C6) alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, di- or trihaloalkoxy, and alkoxy.

17. The compound of claim 1, wherein the compound is selected from the group consisting of:
18. A compound selected from the group consisting of:
19. A pharmaceutical composition comprising:

and
a therapeutically effective amount of a compound of any one of claims 1 through 18; and at least one pharmaceutically acceptable carrier or excipient.

20. The pharmaceutical composition of claim 19, which composition is formulated for oral delivery.

21. A method comprising the step of:
administering to a subject suffering from or susceptible to one or more psychotic diseases, neurodegenerative diseases involving a dysfunction of the cholinergic system, or conditions of memory or cognition impairment a pharmaceutical composition comprising:
a therapeutically effective amount of a compound of any one of claims 1 through 18; and at least one pharmaceutically acceptable carrier or excipient.

22. A method for improving or stabilizing cognitive function in a subject comprising administering to the subject a pharmaceutical composition comprising:
a therapeutically effective amount of a compound of any one of claims 1 through 18; and at least one pharmaceutically acceptable carrier or excipient.

23. A method comprising the step of:
administering to a subject suffering from or susceptible to one or more central nervous system (CNS) diseases or disorders a pharmaceutical composition comprising:
a therapeutically effective amount of a compound of any one of claims 1 through 18; and at least one pharmaceutically acceptable carrier or excipient.

24. The method of claim 23, wherein the disease or disorder is selected from the group consisting of psychoses, anxiety, senile dementia, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive disorders, sleep disorders, feeding disorders, anorexia, bulimia, binge eating disorders, panic attacks, disorders resulting from withdrawal from drug abuse, schizophrenia, gastrointestinal disorders, irritable bowel syndrome, memory disorders, Alzheimer's disease, Parkinson's disease, Huntington's chorea, schizophrenia, attention deficit
hyperactive disorder, neurodegenerative diseases characterized by impaired neuronal growth, and pain.
Figure 1
X-ray Patterns of various crystal forms of hydrochloric salt
Figure 2
DSC scan of various crystal forms of hydrochloric salt
Figure 3
TGA of various crystal forms of hydrochloric salt

Form I
Step -68.8856e-03 %
Step -5.5866e-03 mg
26.01.2007 12:01:34
8.1100 mg

Crystal III
Step -2.9271 %
Step -0.2678 mg
19.01.2007 15:27:30
9.1500 mg

Crystal V
Step -6.9451 %
Step -0.6181 mg
19.02.2007 15:05:40
8.9000 mg
Figure 4
DVS of mono-HCl salt (NO form change after DVS test)
Figure 5
DVS of hydrochloric salt (crystal II) (NO form change after DVS)
Figure 6
DVS of hydrochloric salt (crystal III)
(data from pre-selection minute)
Figure 7
DVS of hydrochloric salt (crystal V )

![Graph showing change in mass versus relative humidity.](image-url)
Figure 8
Formation of mono-HCl salt and the effect of HCl eq.
Figure 9
Effect of pH and HCl equivalence on HCl salt formation

![Graph showing heat flow against temperature for different pH levels and HCl equivalence.](image-url)
Figure 10
Conversion of higher salts to mono-HCl salt crystal
Form I
Figure 11

Conversion of mono-HCl to Form II by decreasing the pH (slurried overnight)

pH adjustment from ~4 to ~2 by adding 0.2 eq. HCl

Heat Flow (W/g)

Exo Up

Temperature (°C)

Universal V4

91.83°C 14.34 J/g
106.87°C
168.24°C 20.51 J/g
175.26°C
180.97°C 14.99 J/g
184.14°C 98.47 J/g
188.18°C
189.61°C
Figure 12
DSC scan of 5-(4-acetyl-1,4-diazepan-1yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form I
Figure 13
TGA thermogram of 5-(4-acetyl-1,4-diazepan-1-yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form I
Figure 14
X-ray Diffraction pattern of 5-(4-acetyl-1,4-diazepan-1-yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form I
Figure 15
DVS isothermal analysis of 5-(4-acetyl-1,4-diazepan-1-yl) -N-(5-4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form I
Figure 16
DSC scan of 5-(4-acetyl-1,4-diazepan-1yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form II
Figure 17
TGA thermogram of 5-(4-acetyl-1,4-diazepan-1-yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form II
Figure 18
X-ray Diffraction pattern of 5-(4-acetyl-1,4-diazepan-1-yl)-N-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form II
Figure 19
DVS isothermal analysis of 5-(4-acetyl-1,4-diazepan-1-yl) -N-(5-4-methoxyphenyl)-1H-pyrazol-3-yl)pentanamide hydrochloric salt Form II
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D231/40 C07D401/04 C07D405/04 C07D409/04 C07D471/04

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , BEILSTEIN Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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**D**

Further documents are listed in the continuation of Box C

**X** See patent family annex

* Special categories of cited documents

'A' document defining the general state of the art which is not considered to be of particular relevance
'E' earlier document but published on or after the international filing date
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Date of the actual completion of the international search: 13 October 2009

Date of mailing of the international search report: 27/10/2009

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### INTERNATIONAL SEARCH REPORT

**Information on patent family members**

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