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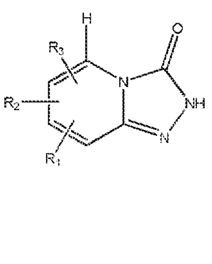
(54) **Title:** D-AMINO ACID OXIDASE ACTIVITY INHIBITING COMPOUNDS



I

(57) Abstract: Compounds of formula (I), wherein R_1 through R_3 are as defined in the claims, or pharmaceutically acceptable esters, salts, hydrates or solvates thereof, useful as DAAO inhibitors as well as pharmaceutical compositions containing them and their use as modulators of DAAO activity, D-serine levels, D-serine oxidative products and NMDA receptor activity in the nervous system of a mammalian subject are provided.

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D-AMINO ACID OXIDASE ACTIVITY INHIBITING COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to pharmacologically active triazolopyridinone compounds, or pharmaceutically acceptable esters, salts, hydrates or solvates thereof, as well as to pharmaceutical compositions containing them and to their use as modulators of D-amino acid oxidase (DAAO) activity, D-serine levels, D-serine oxidative products and N-methyl-D-aspartate (NMDA) receptor activity in the nervous system of a mammalian subject.

BACKGROUND OF THE INVENTION

NMDA receptors are ion-channel receptors found at most excitatory synapses of the nervous system. They play an important role in processes underlying learning, memory and neuroplasticity. Activation of the ligand-gated NMDA receptor requires the simultaneous binding of an excitatory amino acid glutamate as well as the binding of a co-agonist, which can either be D-serine or glycine. Additionally, at the resting potential, the channel is blocked by Mg^{2+} ions, but sufficient membrane depolarization removes the block allowing Ca^{2+} as well as Na^{+} and K^{+} ions to flow through the channel pore (Ozawa, S. et al. *Prog. Neurobiol.*, *54* (1998) 581).

Optimal NMDA signaling is pivotal for higher order cognitive functions and imbalance of this system has been proposed to play a role in several cognitive and psychotic symptoms. For example, long term potentiation (LTP), which is believed to be the molecular mechanism in learning, is mediated by NMDA receptors. While direct activation of NMDA receptors by increasing the extracellular concentration of the excitatory amino acid glutamate possesses risk of neuronal excitotoxicity, an indirect enhancement of the endogenous glutaminergic activity via NMDA receptors may offer a safer approach.

DAAO is a flavoenzyme that catalyzes the oxidative deamination of neutral and polar D-amino acids to corresponding imino acids and hydrogen peroxide. DAAO enzyme is located in peroxisomes and is expressed in both the brain and peripheral tissues. One of its endogenous substrates is D-serine, a neurotransmitter involved in NMDA receptor activation.

According to the current hypothesis, D-serine is a more relevant co-agonist for the synaptic NMDA receptors than for the extrasynaptic NMDA receptors, which prefer glycine as a co-agonist (Papouin, T. et al. *Cell, 150* (2012) 633). Especially the synaptic NMDA receptors are involved in the glutaminergic neurotransmission and are more likely to mediate neuronal excitotoxicity and cell death. Therefore, elevating the D-serine levels in the synaptic cleft via blockade of the breakdown by DAAO enzyme represents an alternative mechanism to enhance NMDA receptor activity and thus brain glutaminergic neurotransmission.

Dysfunction of central nervous system (CNS) glutamatergic signaling, more specifically the hypofunction of the NMDA receptors, has been associated with many psychiatric and neurological disorders. The most studied condition is schizophrenia based on the well-known effects of the NMDA receptor blockers ketamine and phencyclidine, which trigger schizophrenia-like condition in both healthy volunteers and preclinical animal models as well as induce the exacerbation of symptoms in patients with schizophrenia (Lahti, A. C. et al. *Neuropsychopharmacology, 25* (2001) 455).

Interestingly, decreased levels of D-serine have been observed in schizophrenic patients (Cho, S.-E. et al. *Neurosci. Lett., 634* (2016) 42) and in aging rodent brain (Billard, J.-M. *J. Pharm. Biomed. Anal., 116* (2015) 18). Besides both clinical and preclinical evidence of the involvement of NMDA receptor hypofunction in psychotic and neurocognitive symptoms of schizophrenia, recent scientific literature supports the theory that correcting the NMDA hypofunction with DAAO inhibition is a potential therapy for disorders associated with neurocognitive deficits such as dementias including Alzheimer's disease. Clinical efficacy of increased D-serine has been shown in cognitive impairment and, especially, in cognitive impairment associated with schizophrenia (Kantrowitz, J. T. et al. *Lancet Psychiatry, 2* (2015) 403). Benzoate, a weak DAAO enzyme inhibitor, has recently been studied in small scale proof of concept clinical studies. It was found to improve cognition and overall functions in patients with early phase Alzheimer's disease (Lin, C.-H. et al. *Biol. Psychiatry, 75* (2014) 678) and a variety of symptom domains and neurocognition in patients with chronic schizophrenia (Lane, H.-Y. et al. *JAMA Psychiatry, 70* (2013) 1267).

It has also been demonstrated that the increased D-serine levels facilitate the survival and function of mature neurons, which may offer disease modifying potential for DAAO enzyme inhibitors in various neurodegenerative conditions (Sultan, S. et al. *Neuron, 88* (2015) 957).

Since the role of NMDA receptors in the modulation of brain dopaminergic systems is well established, the augmentation of NMDA receptor function at the level of basal ganglia and limbic system could be beneficial in treating Parkinson's disease and related motor disorders as well as behavioral syndromes associated with this (Heresco-Levy, U. et al. *Mov. Disord., 28* (2013) 419).

DAAO enzyme inhibition may also have other than NMDA receptor function enhancing effects. Hydrogen peroxide, a product of DAAO enzyme activity, is a well-known neurotoxin, which may induce neurodegeneration and neuropathic pain through oxidative stress. Reduction of spinal hydrogen peroxide levels by inhibiting DAAO enzyme has been confirmed to exert analgesic effects in preclinical pain models, so dampening the activity of the DAAO enzyme may have therapeutic potential in treating neuropathic pain states (Xie, D. et al. *Eur. J. Med. Chem., 117* (2016) 19).

Non-limiting examples of disorders that may be treated with compounds inhibiting the DAAO enzyme include cognition-related disorders, neurodegenerative disorders and disorders associated with neuropathic pain. DAAO enzyme inhibitors are useful for treating symptoms or condition associated with NMDA receptor hypofunction such as schizophrenia, schizophreniform disorder, schizoaffective disorder and other psychotic disorders (e.g., psychotic disorder, psychosis), dementia and other cognitive disorders, anxiety disorders (e.g., generalized anxiety disorder, panic disorder), mood disorders (e.g., depressive disorders, major depressive disorders, bipolar disorders including bipolar I and II, bipolar mania, bipolar depression, apathy), posttraumatic stress disorder, eating disorders, addiction, sleep disorders, disorders usually first diagnosed in infancy, childhood or adolescence (e.g., attention-deficit disorder, autism spectrum disorders, disruptive behavior disorders), pain (e.g., neuropathic pain, inflammatory pain), neurodegenerative disorders (e.g., Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis) and motor defective syndromes including NMDA receptor hypofunction in cerebellum as well as other movement disorders.

Known inhibitors of DAAO include benzoic acid, fused heterocycles (US 2010/0029737, WO 2008/089453,WO 2010/017418, WO 2011/017634), furopyrroles (WO 2009/020814), 1,2,4-triazines (WO 2014/025993), 3-aminopyrazolines (WO 2007/093829), dihydroxy aromatic heterocycles (WO 2013/073577), hydroxyquinolinones (WO 2010/058314), pyridazinones (WO 2013/027000, WO 2014/096757), pyridinones (WO 2013/004996), pyrimidinones (WO 2013/004995), pyrrolopyridines (WO 2010/005528), selenophenes and selenazoles (WO 2009/148564), quinazolinones and pyridopyrimidinones (CN 106749045 A), benzo[d]isothiazolones (Terry-Lorenzo, R. T. et al. *J. Biomol. Screen., 20* (2015) 1218) and benzisoxazoles (WO 2005/066143, WO 2005/089753).

Several of the DAAO inhibitors known in the art are associated with very poor brain permeability.

Also triazolopyridine derivatives are known. WO 2006/138695 discloses triazolopyridinone derivatives as cannabinoid receptor 1 (CB-1) antagonists. WO 2012/003392 discloses triazolopyridinone derivatives as ion channel modulators for the treatment of cardiovascular diseases. WO 2012/150829 discloses triazolopyridinone derivatives as glycogen synthase kinase-3 (GSK-3) inhibitors. WO 2013/074390 discloses triazolopyridinone derivatives which are useful as therapeutic agents for the treatment of CNS disorders associated with phosphodiesterase 10 (PDE10). WO 2017/046318 discloses triazolopyridinone derivatives useful in treating, ameloriating or preventing viral diseases.

6-Bromo-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one has been disclosed in US 2017/0022198. 6-Chloro-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 7-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-chloro-[1,2,4]triazolo[4,3-

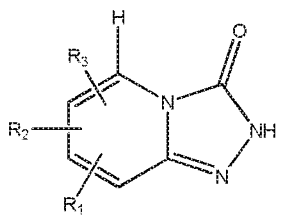
a]pyridin-3(2H)-one, 7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one and 6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one have been disclosed in Guo, C. et al. *Bioorg. Med. Chem., 22* (2014) 3414. 7-Bromo-8-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one has been disclosed in WO 2011/033265. 8-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one has been disclosed in WO 2017/046318. 7-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one has been disclosed in WO 2015/014283. 7-Bromo-8-iodo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one and 8-bromo-7-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one have been disclosed in WO 2006/138695. 6,8-Dichloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one has been disclosed in US 2004/0063580. 6-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one has been disclosed in WO 2016/057522. 8-Methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one has been disclosed in Potts, K. T. et al. *Tetrahedron, 33* (1977) 1247.

Also the following library compounds have been disclosed:

8-bromo-7-iodo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one
8-chloro-7-iodo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one
7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one
6-bromo-8-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one
8-chloro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one
8-bromo-6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one
6-bromo-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one
6-bromo-8-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one
8-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

SUMMARY OF THE INVENTION

In the first aspect, the present invention relates to compounds of formula (I),



I

wherein

R_1 and R_2 are independently H, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxy or cyano;

R_3 is fluoro, chloro, bromo, C_{1-6}alkyl, difluoromethyl or trifluoromethyl;

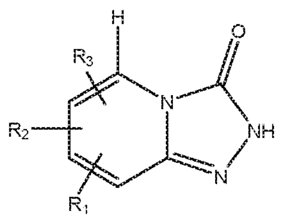
or a pharmaceutically acceptable ester, salt, hydrate or solvate thereof;

with the provisos that

a) when R_3 is chloro, bromo or C_{1-6}alkyl, R_1 and R_2 are not simultaneously H;

b) the compound is not 6-bromo-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-chloro-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 7-bromo-8-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 7-bromo-8-iodo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-bromo-7-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6,8-dichloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one or 6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.

In a further aspect, the present invention provides a compound of formula (II),



(II)

wherein

R_1 and R_2 are independently H, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxy or cyano;

R_3 is fluoro, chloro, bromo, C_{1-6}alkyl, difluoromethyl, trifluoromethyl or cyano;

or a pharmaceutically acceptable ester, salt, hydrate or solvate thereof;

for use in the treatment or prevention of a disease associated with D-amino acid oxidase.

In a further aspect, the present invention provides the use of a compound of formula (II), as defined above, for the manufacture of a medicament for the treatment or prevention of a disease associated with D-amino acid oxidase.

In a further aspect, the present invention provides a method for the treatment or prevention of a disease associated with D-amino acid oxidase comprising administering to a mammal in need of such treatment or prevention an effective amount of at least one compound of formula (II), as defined above.

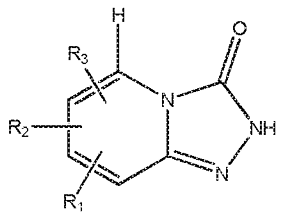
In a further aspect, the compounds of formula (I), as defined above, can be administered in combination with other compounds used for the treatment or prevention of a disease associated with D-amino acid oxidase.

In a further aspect, the present invention provides a process for the manufacture of the compounds of formula (I).

The DAAO inhibitors provided by the present invention possess enhanced brain permeability.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds of formula (I):



I

wherein

R_1 and R_2 are independently H, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxy or cyano;

R_3 is fluoro, chloro, bromo, C_{1-6}alkyl, difluoromethyl or trifluoromethyl;

or a pharmaceutically acceptable ester, salt, hydrate or solvate thereof;

with the provisos that

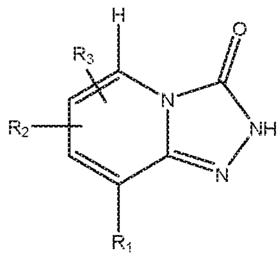
a) when R_3 is chloro, bromo or C_{1-6}alkyl, R_1 and R_2 are not simultaneously H;

b) the compound is not 6-bromo-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-chloro-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 7-bromo-8-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 7-bromo-8-iodo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-bromo-7-chloro-

[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6,8-dichloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one or 6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.

In one embodiment, the present invention relates to compounds of formula (I), wherein R_1 and R_2 are independently H, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxy or cyano;
R_3 is fluoro, chloro, bromo, C_{1-6}alkyl, difluoromethyl or trifluoromethyl;
with the provisos that
a) when R_3 is fluoro, chloro, bromo, C_{1-6}alkyl or trifluoromethyl, R_1 and R_2 are not simultaneously H;
b) the compound is not 8-bromo-7-iodo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-chloro-7-iodo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-bromo-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-bromo-8-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-chloro-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-chloro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-bromo-6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-bromo-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-bromo-8-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 7-bromo-8-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 7-bromo-8-iodo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-bromo-7-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one or 6,8-dichloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.

In one embodiment, the present invention relates to compounds of formula (III),



(III)

wherein
R_1 and R_2 are independently H, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxy or cyano;
R_3 is fluoro, chloro, bromo, C_{1-6}alkyl, difluoromethyl or trifluoromethyl.

In one embodiment, the present invention relates to compounds of formula (I), wherein R_1 and R_2 are independently H, halogen, methyl, trifluoromethyl, hydroxymethyl, cyclopropyl, methoxy or cyano;

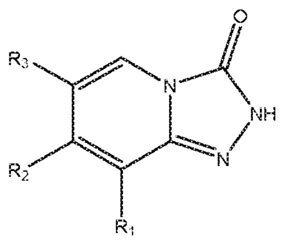
R_3 is fluoro, chloro, bromo, methyl, difluoromethyl or trifluoromethyl.

In one embodiment, the present invention relates to compounds of formula (I), wherein R_1 and R_2 are independently H, halogen, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl or cyano; R_3 is fluoro, chloro, bromo, C_{1-6}alkyl or trifluoromethyl.

In one embodiment, the present invention relates to compounds of formula (I), wherein R_1 and R_2 are independently H, halogen, haloC_{1-6}alkyl or hydroxyC_{1-6}alkyl; R_3 is fluoro, chloro, bromo, C_{1-6}alkyl or trifluoromethyl.

In one embodiment, the present invention relates to compounds of formula (I), wherein R_1 and R_2 are independently H, halogen or haloC_{1-6}alkyl; R_3 is chloro, bromo or C_{1-6}alkyl.

In one embodiment, the present invention relates to compounds of formula (IV),



(IV)

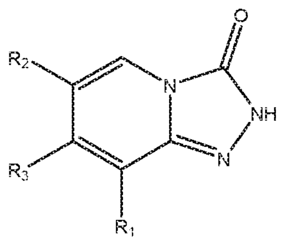
wherein

R_1 is H or halogen;

R_2 is H, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl or cyano;

R_3 is fluoro, chloro, bromo, C_{1-6}alkyl, difluoromethyl or trifluoromethyl;

or a compound of formula (V),



(V)

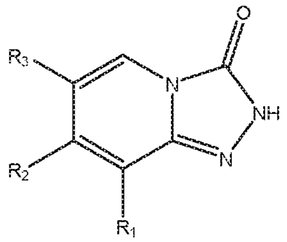
wherein

R_1 is H;

R_2 is halogen or cyano;

R_3 is chloro or C_{1-6}alkyl.

In one embodiment, the present invention relates to compounds of formula (IV),



(IV)

wherein

R_1 is H or halogen;

R_2 is H, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl or hydroxyC_{1-6}alkyl;

R_3 is fluoro, chloro, bromo, C_{1-6}alkyl, difluoromethyl or trifluoromethyl.

In one embodiment, the present invention relates to compounds of formula (IV), wherein

R_1 is H;

R_2 is halogen or C_{1-6}alkyl;

R_3 is fluoro, chloro, bromo or trifluoromethyl.

In one embodiment, the present invention relates to compounds of formula (I) selected from the group of:

6-Bromo-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one,
7-Bromo-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one,
7-Chloro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one,
6-Chloro-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one,
6-Bromo-7-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one,
7-Bromo-6-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one,
6,7-Dichloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one,
7-Bromo-6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one,
7-Chloro-6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one,
6,7-Dibromo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one,
7-(Methyl-d3)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one,
7-Methyl-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one;
or a pharmaceutically acceptable ester, salt, hydrate or solvate thereof.

The term "halo" or "halogen", as used herein as such or as part of another group, refers to fluoro, chloro, bromo or iodo.

The term "C_{1-6}alkyl", as used herein as such or as part of another group, refers to a branched or straight chain saturated hydrocarbon group having 1, 2, 3, 4, 5 or 6 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, i-propyl and t-butyl.

The term "haloC_{1-6}alkyl", as used herein, refers to at least one halogen, as defined above, bonded to the parent molecular moiety through an "C_{1-6}alkyl" group, as defined above. When there are several halogens, the halogens can be identical or different and the halogens can be attached to different carbon atoms or several halogens can be attached to the same carbon atom. HaloC_{1-6}alkyl groups include, but are not limited to, difluoromethyl, trifluoromethyl and 2-chloroethyl.

The term "hydroxyC_{1-6}alkyl", as used herein, refers to a hydroxy group bonded to the parent molecular moiety through an "C_{1-6}alkyl" group, as defined above, including, but not limited to, hydroxymethyl, 2-hydroxyethyl and 3-hydroxypropyl.

The term "C_{3-5}cycloalkyl", as used herein as such or as part of another group, refers to cyclopropyl, cyclobutyl or cyclopentyl.

The term "C_{3-5}cycloalkylC_{1-6}alkyl", as used herein, refers to a C_{3-5}cycloalkyl group, as defined above, bonded to the parent molecular moiety through an "C_{1-6}alkyl" group, as defined above, including, but not limited to, cyclopropylmethyl, cyclobutylmethyl and 2-cyclopropylethyl.

The term "C_{1-6}alkoxy", as used herein refers to an C_{1-6}alkyl group, as defined above, bonded to the parent molecular moiety through an oxygen atom including, but not limited to, methoxy, ethoxy, n-propoxy, i-propoxy and t-butoxy.

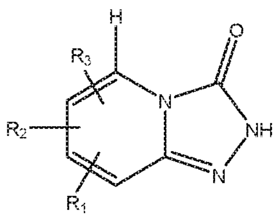
The term "pharmaceutically acceptable" describes an ingredient that is useful in preparing a pharmaceutical composition, is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes those acceptable for veterinary use as well as human pharmaceutical use.

The term "salt" means nontoxic base addition salts of the compounds of the invention which are generally prepared by reacting the acid with a suitable organic or inorganic base.

The term "hydrate" means non-covalent combinations between water and solute.

The term "solvate" means non-covalent combinations between solvent and solute. Solvents include, but are not limited to, ethanol, 2-propanol, acetonitrile and tetrahydrofuran.

In a further aspect, the present invention relates to a compound of formula (II),



(II)

wherein

R_1 and R_2 are independently H, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxy or cyano;

R_3 is fluoro, chloro, bromo, C_{1-6}alkyl, difluoromethyl, trifluoromethyl or cyano;

or a pharmaceutically acceptable ester, salt, hydrate or solvate thereof;

for use in the treatment or prevention of a disease associated with D-amino acid oxidase.

In a further aspect, the present invention relates to the use of a compound of formula (II), as defined above, for the manufacture of a medicament for the treatment or prevention of a disease associated with D-amino acid oxidase.

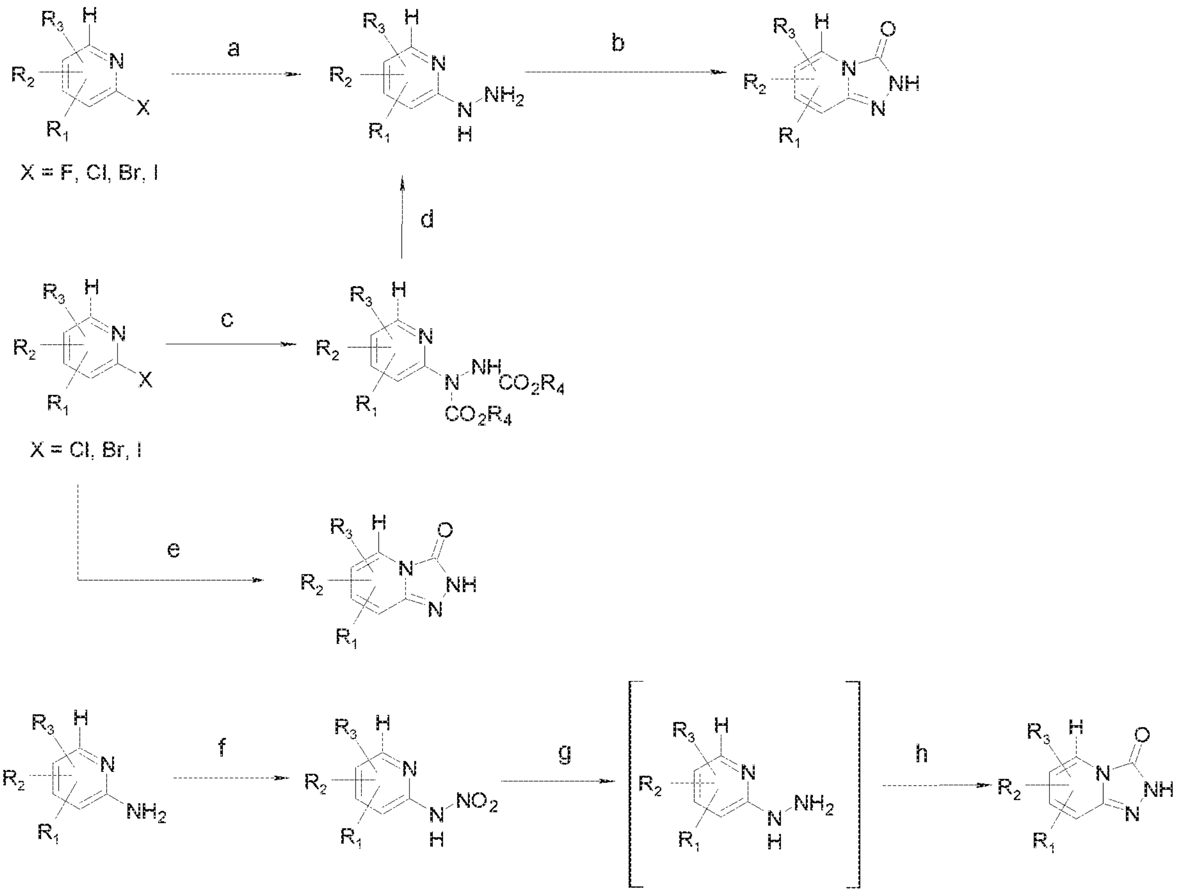
In a further aspect, the present invention relates to a method for the treatment or prevention of a disease associated with D-amino acid oxidase comprising administering to a mammal in need of such treatment or prevention an effective amount of at least one compound of formula (II), as defined above.

In one embodiment, the disease associated with D-amino acid oxidase is selected from the group of: schizophrenia, schizophreniform disorder, schizoaffective disorder and other psychotic disorders (e.g., psychotic disorder, psychosis), dementia and other cognitive disorders, anxiety disorders (e.g., generalized anxiety disorder, panic disorder), mood disorders (e.g., depressive disorders, major depressive disorders, bipolar disorders including bipolar I and II, bipolar mania, bipolar depression, apathy), posttraumatic stress disorder, eating disorders, addiction, sleep disorders, disorders usually first diagnosed in infancy, childhood or adolescence (e.g., attention-deficit disorder, autism spectrum disorders and disruptive behavior disorders), pain (e.g., neuropathic pain, inflammatory pain), neurodegenerative disorders (e.g., Parkinson's disease, Alzheimer's disease, Huntington’s disease, amyotrophic lateral sclerosis) and motor defective syndromes including NMDA receptor hypofunction in cerebellum as well as other movement disorders.

In one embodiment, the disease associated with D-amino acid oxidase is selected from the group of: schizophrenia, schizophreniform disorder, schizoaffective disorder, cognitive disorders and pain.

The invention, therefore, further relates to combination therapies wherein a compound of the invention or a pharmaceutical composition or formulation comprising a compound of the invention is administered with another therapeutic agent or agents and/or with serine, for the treatment of one or more of the conditions previously indicated. Such therapeutic agents may be selected from: antidepressants, antipsychotics, anxiolytics, anticonvulsants, mood stabilizers, $5HT_{1B}$ ligands, mGluR2 agonists, alpha 7 nicotinic agonists, chemokine receptor CCR1 inhibitors, delta opioid agonists and compounds used in the treatment of Alzheimer's disease, Parkinson's disease, migraine, stroke, neuropathic pain or nociceptive pain.

In a further aspect, the present invention provides a process for the manufacture of the compounds of formula (I) according to the following reaction route:



Step *a* can be carried out using 1-10 equivalents of hydrazine hydrate at elevated temperature in solvents, eg. methanol, ethanol, isopropanol or dioxane.

Step *b* can be carried out using 1-1.5 equivalents of carbonyl-transfer reagent, e.g., phosgene, triphosgene or carbonyl diimidazole in different solvents, e.g., THF, acetonitrile or dioxane.

Step *c* can be carried out using palladium catalyst, e.g., tris(dibenzylideneacetone)dipalladium(0) or palladium(II) acetate, suitable ligand, e.g., 1,1′-bis(diphenylphosphino)ferrocene, base, e.g., cesium carbonate or potassium carbonate, and di-tert-butyl hydrazodiformate in aprotic solvent e.g., 1,2-dichloroethane, chlorobenzene and toluene.

Step *d* can be carried out using 2-20 equivalents of HCl in ether-type solvent e.g., ether or dioxane typically in room temperature but sometimes in elevated temperatures.

Step *e* can be carried out using 2-5 equivalents of alkyl-, e.g., methyl hydrazinecarboxylate or semicarbazide at elevated temperature in alcohol, e.g., methanol, ethanol or isopropyl alcohol.

Step *f* can be carried out by nitrating the amino group with the use of 1,5-3 equivalents of nitric acid in sulphuric acid.

Step *g* and *h* can be carried out together using 1-5 equivalents of chemical reducing agents, e.g., Zn/ammonium chloride in THF/water/MeOH mixture or tin(II) chloride in acidic conditions, followed by the reaction of 1-2 equivalents of triphosgene in the same solvent system, without the isolation of intermediate.

Compounds as starting materials for step *a*, step *d*/step *f* and step *g* are either commercially available, are well-known in the literature or may be prepared using known techniques.

Pharmaceutically acceptable esters of hydroxy groups may be prepared by known methods using pharmaceutically acceptable carboxylic acids that are conventional in the field of pharmaceuticals. Representative examples of pharmaceutically acceptable esters of hydroxy groups include, but are not limited to, esters formed with acetic acid and propionic acid.

Pharmaceutically acceptable salts, such as metal salts and acid addition salts, with organic acids or inorganic acids are well known in the field of pharmaceuticals. Representative examples of pharmaceutically acceptable metal salts include, but are not limited to, lithium, sodium, potassium, calcium, magnesium, aluminum and zinc salts. Representative examples of pharmaceutically acceptable acid addition salts include, but are not limited to, chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, methane sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates and ascorbates.

The present disclosure includes within its scope all the possible isotopically labeled forms of the compounds.

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, intraarticular, intrathecal, intraperitoneal, direct intraventricular, intracerebroventicular, intramedullary injection, intracisternal injection or infusion, subcutaneous injection or implant), by inhalation spray, eye drops, or nasal, vaginal, rectal, sublingual and topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable excipients appropriate for each route of administration.

Alternatively, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly in the renal or cardiac area, often in a depot or sustained release formulation. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the organ.

The pharmaceutical compositions containing the active ingredient according to the present invention usually contain 0.01 to 500 mg of active ingredient in a single dosage unit. It is, of course possible that the amount of the active ingredient in some compositions exceeds the upper or lower limits defined above.

The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

This dosage level and regimen may be adjusted to provide the optimal therapeutic response. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition and the host undergoing therapy.

As a further aspect of the invention there is provided the pharmaceutical manufacture of medicaments containing the compounds of formula (I) or pharmaceutically acceptable esters, salts, hydrates and solvates thereof.

The pharmaceutical compositions of the present invention may be formulated as different pharmaceutical dosage forms, such as but not limited to, solid oral dosage forms like tablets (e.g., buccal, sublingual, effervescents, chewable, orodispersible, freeze dried), capsules, lozenges, pastilles, pills, orodispersible films, granules, powders; liquid oral dosage forms, such as but not limited to, solutions, emulsions, suspensions, syrups, elixires, oral drops; parenteral dosage forms, such as but not limited to, intravenous injections, intramuscular injections, subcutaneous injections; other dosage form , such as but not limited to, eye drops, semi-solid eye preparations, transdermal dosage forms, suppositories, rectal capsules, rectal solutions, emulsions and suspensions, etc.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, emulsifying, suspending, entrapping, freeze-drying, extrusion, laminating, film-casting, granulating, grinding, encapsulating, dragee-making or tabletting processes.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable excipients. Any of the well-known techniques and excipients may be used as suitable and as understood in the art.

Suitable excipients for the preparation of the dosage forms may be selected from the following categories, such as but not limited to, tablet and capsule fillers, tablet and capsule binders, release modifying agents, disintegrants, glidants, lubricants, sweetening agents, taste-masking agents, flavoring agents, coating agents, surfactants, antioxidants, buffering agents, complexing agents, emulsifying agents, lyophilization aids, microencapsulating agents, ointment bases, penetration enhancers, solubilizing agents, solvents, suppository bases, suspending agents.

In one embodiment, the invention relates to the use of specific excipients which are able to improve the solubility, dissolution, penetration, absorption or bioavailability of the active ingredient(s), such as but not limited to, hydrophilic polymers, hot melt extrusion excipients, surfactants, buffering agents, complexing agents, emulsifying agents, lyophilization aids, superdisintegrants, microencapsulating agents, penetration enhancers, solubilizing agents, co-solvents, suspending agents.

The above described ingredients and different routes of manufacture are merely representative. Other materials as well as processing techniques and the like well known in the art can also be used.

EXAMPLES

The invention is further explained in the following Examples. It should be understood that the Examples are given by way of illustration only. From the above discussion and the Examples, one skilled in the art can ascertain the essential characteristics of the invention, and without departing from the spirit and scope thereof, can make various changes and modifications to adapt the invention to various uses and conditions. As a result, the invention is not limited by the illustrative examples set forth herein below but rather defined by the claims appended hereto.

In general, the compounds of formula (I) can be prepared according to the general knowledge of one skilled in the art and/or using methods set forth in the following Example sections. Solvents, temperatures, pressures and other reaction conditions can readily be selected by one of ordinary skill in the art. Starting materials are commercially available and/or readily prepared by one skilled in the art.

The present invention will be now illustrated by the following not limiting examples.

In the following examples "room temperature" denotes a temperature in the range from 20 °C to 25 °C.

The abbreviations used in the specific examples have the following meanings:

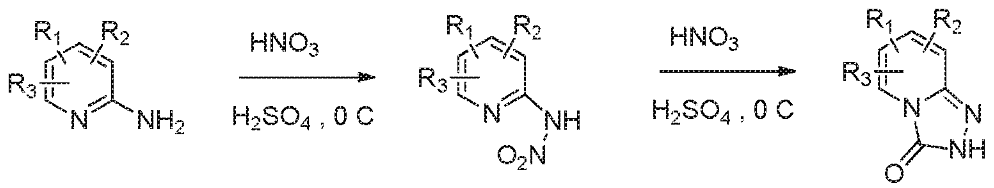
Conc.	Concentrated
DCM	Dichloromethane
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
EtOH	Ethanol

EtOAc	Ethylacetate
Et_3N	Triethylamine
IPA	Isopropylalcohol
MeOH	Methanol
rt	room temperature
THF	Tetrahydrofuran
NIS	N-iodosuccinimide
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
TFA	Trifluoroacetic acid
DAST	(Diethylamino)sulfur trifluoride
dppf	1,1´-Bis(diphenylphosphino)ferrocene
CDI	Carbonyldiimidazole
FC	Flash Column chromatography
C18	Reverse phase chromatography conditions

<u>Preparation example 1:</u>

General procedure via nitramide

<u>General procedure A</u>



a) Substituted *N*-(pyridin-2-yl)nitramide

Substituted aminopyridine (1 eq) was mixed with conc. H_2SO_4 at 0 °C. To this mixture was added dropwise a mixture of conc. HNO_3 (1.5 – 3 eq) and conc. H_2SO_4. The reaction mixture was stirred at 0 °C for 1-3 hours after which it was poured into crushed ice. Title compound was collected by filtration and dried in vacuum.

General procedure B

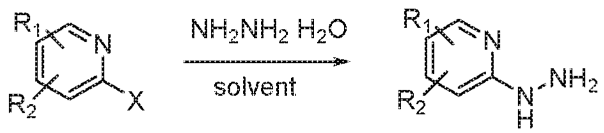
b) Substituted [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

The nitramide (1 eq) product from the general procedure A was dissolved in THF/MeOH/H_2O and NH_4Cl (5-6 eq) was added. The mixture was cooled to 0 °C in an ice bath. Powdered zinc (5-6 eq) was added and the mixture was allowed to react for 0.5 – 1.5 hour. The mixture was filtered through a pad of celite and recooled to 0 °C. Triphosgene (1.3 – 1.6 eq) was added and the reaction mixture was stirred at 0 °C. After typically 1-2 hours but sometimes overnight of reaction time, the mixture was evaporated to dryness and 1 M HCl solution was added. Crude triazolone was filtered off and dried in vacuum.

Preparation example 2:

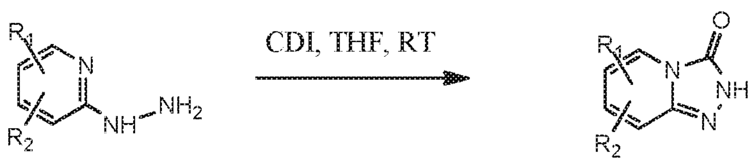
General procedure via hydrazide

General procedure C (Hydrazination, general procedure)



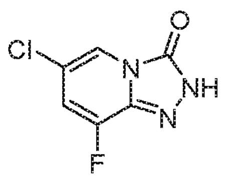
To a solution of halogenopyridine (1.0 eq) in indicated solvent at rt was added hydrazine hydrate (1-10 eq.). Reaction mixture was stirred at the indicated temperature for the indicated time. Solvents were concentrated under vacuum. Water or saline solution was then added. Precipitate that formed was filtered off, washed with water and dried under vacuum yielding 2-hydrazinylpyridine.

General procedure D (Cyclisation step with CDI)



To a solution of 2-hydrazinylpyridine (1.0 eq) in THF at rt was added at *N,N'*-carbonyldiimidazole (1.2-1.5 eq). Reaction mixture was stirred at rt for 1 hour-overnight. Solvents were concentrated under vacuum. A 1M aqueous HCl solution was added and the precipitate that formed was filtered off, washed with water and dried under vacuum yielding [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.

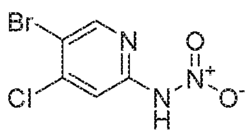
Example 1: 6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure D from 5-chloro-3-fluoro-2-hydrazinylpyridine (0.15 g, 0.93 mmol) and CDI (0.20 mg, 1.21 mmol) in THF (5 ml) with 18 hours reaction time yielding 100 mg of 6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 12.91 (br s, 1H), 7.99 (d, 1H), 7.34-7.44 (m, 1H).

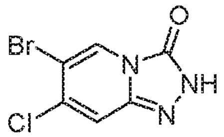
Example 2: 6-Bromo-7-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: *N*-(5-bromo-4-chloropyridin-2-yl)nitramide



The title compound was synthesised according to general procedure A from 5-bromo-4-chloropyridin-2-amine (0.50 g, 2.41 mmol) in H_2SO_4 (1 ml) and a mixture of HNO_3 (0.27 ml, 3.92 mmol) and H_2SO_4 (0.27 ml) yielding 0.57 g of *N*-(5-bromo-4-chloropyridin-2-yl)nitramide. ^{1}H NMR (DMSO-d_6) δ: 8.74 (s, 1H), 8.03 (d, 1H).

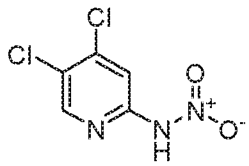
Step 2: 6-Bromo-7-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure B from *N*-(5-bromo-4-chloropyridin-2-yl)nitramide (0.35 g, 1.39 mmol), NH_4Cl (0.37 g, 6.93 mmol), Zn dust (0.45 g, 6.93 mmol) and triphosgene (0.62 g, 2.08 mmol) in THF (12 ml), MeOH (3 ml) and H_2O (3 ml). The crude product was purified by FC (C18) yielding 48 mg of 6-bromo-7-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 12.66 (br s, 1H), 8.28 (d, 1H), 7.73 (d, 1H).

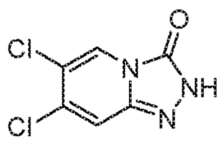
Example 3: 6,7-Dichloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: *N*-(4,5-dichloropyridin-2-yl)nitramide



The title compound was synthesised according to general procedure A from 5-bromo-4-chloropyridin-2-amine (0.50 g, 3.07 mmol) in H_2SO_4 (1.5 ml) and a mixture of HNO_3 (0.34 ml, 4.99 mmol) and H_2SO_4 (0.34 ml) yielding 0.60 g of *N*-(4,5-dichloropyridin-2-yl)nitramide. MS: *m/z* 208.0 $[M-H]^+$.

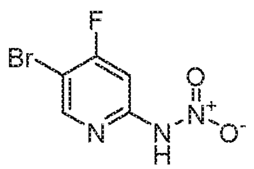
Step 2: 6,7-Dichloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure B from *N*-(4,5-dichloropyridin-2-yl)nitramide (0.35 g, 1.68 mmol), NH_4Cl (0.45 g, 8.41 mmol), Zn dust (0.55 g, 8.41 mmol) and triphosgene (0.75 g, 2.52 mmol) in THF (12 ml), MeOH (3 ml) and H_2O (3 ml). The crude product was purified by FC (C18) yielding 90 mg of 6,7-dichloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 12.74 (s, 1H), 8.27 (d, 1H), 7.75 (d, 1H).

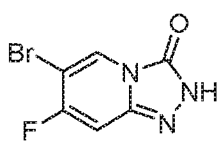
Example 4: 6-Bromo-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: *N*-(5-bromo-4-fluoropyridin-2-yl)nitramide



The title compound was synthesised according to general procedure A from 5-bromo-4-fluoropyridin-2-amine (1.00 g, 5.24 mmol) in H_2SO_4 (3 ml) and a mixture of HNO_3 (0.58 ml, 8.51 mmol) and H_2SO_4 (0.58 ml) yielding 1.07 g of *N*-(5-bromo-4-fluoropyridin-2-yl)nitramide. ^{1}H NMR (DMSO-d_6) δ: 8.71 (d, 1H), 7.82 (d, 1H).

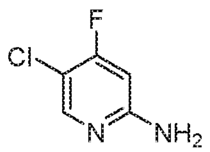
Step 2: 6-Bromo-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure B from *N*-(5-bromo-4-fluoropyridin-2-yl)nitramide (0.50 g, 2.12 mmol), NH_4Cl (0.57 g, 10.6 mmol), Zn dust (0.69 g, 10.6 mmol) and triphosgene (0.94 g, 3.18 mmol) in THF (16 ml), MeOH (4 ml) and H_2O (4 ml). The crude product was purified by FC (C18) yielding 26 mg of 6-bromo-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 12.57 (br s, 1H), 8.31 (dd, 1H), 7.35 (dd, 1H).

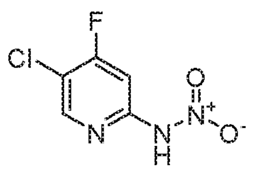
Example 5: 6-Chloro-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 5-Chloro-4-fluoropyridin-2-amine



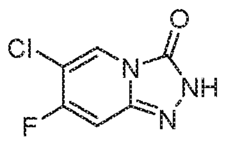
To a solution of 4-fluoropyridin-2-amine (1.00 g, 8.92 mmol) in MeCN (50 ml) at 0 °C was added NCS (0.60 g, 4.46 mmol). The resulting mixture was stirred for 1 hour at rt, cooled to 0 °C and another portion of NCS (0.60 g, 4.46 mmol) was added. The mixture was stirred for 1 hour at RT, diluted with EtOAc and washed with $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by FC (SiO_2) yielding 0.44 g of 5-chloro-4-fluoropyridin-2-amine. ^{1}H NMR (DMSO-d_6) δ: 8.00 (d, 1H), 6.45 (br s, 2H), 6.36 (d, 1H).

Step 2: *N*-(5-chloro-4-fluoropyridin-2-yl)nitramide



The title compound was synthesised according to general procedure A from 5-chloro-4-fluoropyridin-2-amine (0.44 g, 3.00 mmol) in H_2SO_4 (1.5 ml) and a mixture of HNO_3 (0.34 ml, 4.88 mmol) and H_2SO_4 (0.34 ml) yielding 0.45 g of *N*-(5-chloro-4-fluoropyridin-2-yl)nitramide. ^{1}H NMR (DMSO-d_6) δ: 8.67 (d, 1H), 7.87 (d, 1H).

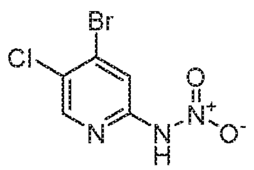
Step 3: 6-Chloro-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure B from *N*-(5-chloro-4-fluoropyridin-2-yl)nitramide (0.45 g, 2.35 mmol), NH_4Cl (0.63 g, 11.8 mmol), Zn dust (0.77 g, 11.8 mmol) and triphosgene (1.05 g, 3.52 mmol) in THF (16 ml), MeOH (4 ml) and H_2O (4 ml). The crude product was purified by FC (C18) yielding 30 mg of 6-chloro-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 12.60 (br s, 1H), 8.32 (d, 1H), 7.41 (d, 1H).

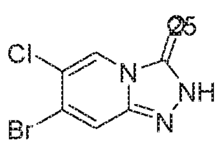
Example 6: 7-Bromo-6-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: *N*-(4-bromo-5-chloropyridin-2-yl)nitramide



The title compound was synthesised according to general procedure A from 4-bromo-5-chloropyridin-2-amine (0.83 g, 4.00 mmol) in H_2SO_4 (2.5 ml) and a mixture of HNO_3 (0.45 ml, 6.50 mmol) and H_2SO_4 (0.45 ml) yielding 1.00 g of *N*-(4-bromo-5-chloropyridin-2-yl)nitramide. ^{1}H NMR (DMSO-d_6) δ: 8.64 (s, 1H), 8.17 (s, 1H).

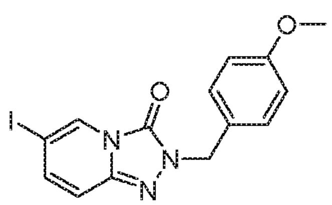
Step 2: 7-Bromo-6-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure B from *N*-(4-bromo-5-chloropyridin-2-yl)nitramide (0.50 g, 1.98 mmol), NH_4Cl (0.53 g, 9.90 mmol) and Zn dust (0.65 g, 9.90 mmol) and triphosgene (0.88 g, 2.97 mmol) in THF (16 ml), MeOH (4 ml) and H_2O (4 ml). The crude product was purified by FC (C18) yielding 12 mg of 6-chloro-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^1H NMR (DMSO-d_6) δ: 12.67 (br s, 1H), 8.22 (s, 1H), 7.90 (s, 1H).

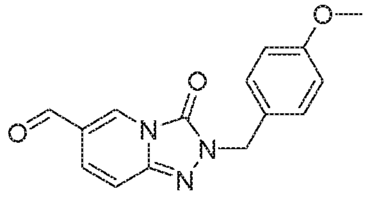
Example 7: 6-(Difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 6-Iodo-2-(4-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



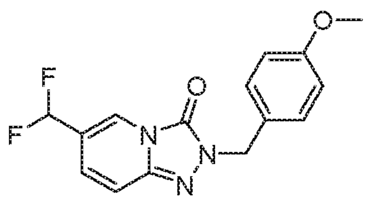
To a solution of 6-iodo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (0.21 g, 0.81 mmol; prepared as in WO 2004/043940) in DMF (3 ml) was added K_2CO_3 (0.23 g, 1.63 mmol) and 4-methoxybenzyl chloride (0.14 ml, 1.03 mmol). The resulting mixture was stirred at rt for 3 days. H_2O was added and the precipitated product was filtered off and washed with H_2O yielding 0.30 g of 6-iodo-2-(4-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^1H NMR (DMSO-d_6) δ: 8.11-8.15 (m, 1H), 7.34 (dd, 1H), 7.21-7.27 (m, 2H), 7.08 (dd, 1H), 6.86-6.92 (m, 2H), 5.01 (s, 2H), 3.72 (s, 3H).

Step 2: 2-(4-Methoxybenzyl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbaldehyde



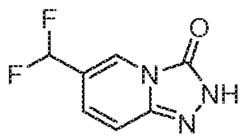
A mixture of 6-iodo-2-(4-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (0.25 g, 0.66 mmol) and THF (4 ml) was cooled to -78 °C. A 2 M solution of *i*-PrMgCl in THF (0.36 ml, 0.72 mmol) was added dropwise and the resulting solution was stirred at -78 °C for 30 min. DMF (0.31 ml, 3.94 mmol) was added and the stirring was continued for 30 min, after which the mixture was allowed to warm to rt. The mixture was stirred at rt for 2 hours and quenched with 1 M HCl. The precipitated product was filtered off and washed with water yielding 0.15 g of 2-(4-methoxybenzyl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbaldehyde. MS: *m/z* 284.3 $[M+H]^+$.

Step 3: 6-(Difluoromethyl)-2-(4-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



To a solution of 2-(4-methoxybenzyl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbaldehyde (0.13 g, 0.46 mmol) in DCM (3 ml) was added DAST (0.12 ml, 0.92 mmol). The resulting solution was stirred at rt for 18 hours. The mixture was quenched with sat. $NaHCO_3$ solution and extracted with EtOAc. The combined organic phases were washed with water and brine, dried with Na_2SO_4, filtered and evaporated to dryness yielding 0.14 g of 6-(difluoromethyl)-2-(4-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. MS: *m/z* 306.4 $[M+H]^+$.

Step 4: 6-(Difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

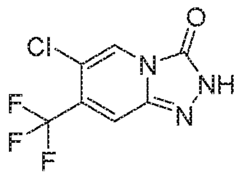


A solution of 6-(difluoromethyl)-2-(4-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (0.13 g, 0.43 mmol) in TFA (4 ml) was refluxed for 5 hours and then evaporated to dryness. The crude product was purified by FC (C18) yielding 18 mg of 6-(difluoromethyl)-

[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 12.66 (br s, 1H), 8.22-8.25 (m, 1H), 7.26-7.36 (m, 2H), 6.98 (t, 1H).

Example 8: 6-Chloro-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

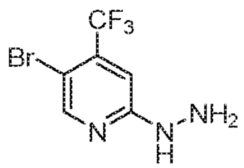
Step 1: 6-Chloro-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure D from 5-chloro-2-hydrazinyl-4-(trifluoromethyl)pyridine (0.22 g, 1.03 mmol; prepared as in WO 2011/025541) and CDI (0.22 g, 1.33 mmol) in THF (5 ml) with 18 hours reaction time yielding 0.20 g of 6-chloro-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 13.05 (br s, 1H), 8.29 (s, 1H), 7.99 (s, 1H).

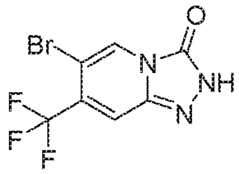
Example 9: 6-Bromo-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 5-Bromo-2-hydrazinyl-4-(trifluoromethyl)pyridine



The title compound was synthesised according to general procedure C from 5-bromo-2-chloro-4-(trifluoromethyl)pyridine (0.52 g, 2.00 mmol), hydrazine hydrate (0.87 ml, 18.0 mmol) and IPA (8 ml) at 70 °C with 11 hours reaction time. The reaction mixture was evaporated to dryness, EtOAc was added and the solids were filtered off. The filtrate was evaporated to dryness yielding 0.48 g of 5-bromo-2-hydrazinyl-4-(trifluoromethyl)pyridine. ^{1}H NMR (DMSO-d_6) δ: 8.29 (s, 1H), 8.27 (s, 1H), 7.13 (s, 1H), 4.39 (s, 2H).

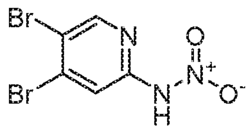
Step 2: 6-Bromo-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure D from 5-bromo-2-hydrazinyl-4-(trifluoromethyl)pyridine (0.24 g, 0.95 mmol) and CDI (0.20 g, 1.23 mmol) in THF (5 ml), with 18 hours reaction yielding 0.22 g of 6-bromo-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 13.02 (br s, 1H), 8.31 (s, 1H), 7.97 (s, 1H).

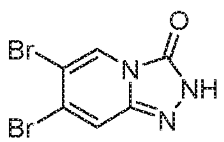
Example 10: 6,7-Dibromo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: *N*-(4,5-dibromopyridin-2-yl)nitramide



The title compound was synthesised according to general procedure A from 4,5-dibromopyridin-2-amine (0.75 g, 2.97 mmol) in H_2SO_4 (1.5 ml) and a mixture of HNO_3 (0.33 ml, 4.83 mmol) and H_2SO_4 (0.35 ml) yielding 0.85 g of *N*-(4,5-dibromopyridin-2-yl)nitramide. ^{1}H NMR (DMSO-d_6) δ: 8.71 (s, 1H), 8.16 (s, 1H).

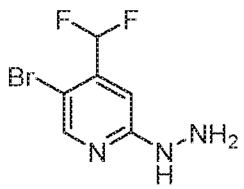
Step 2: 6,7-Dibromo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure B from *N*-(4,5-dibromopyridin-2-yl)nitramide (0.83 g, 2.80 mmol), NH_4Cl (0.75 g, 14.0 mmol), Zn dust (0.91 g, 14.0 mmol) and triphosgene (1.24 g, 4.19 mmol) in THF (25 ml), MeOH (5 ml) and H_2O (5 ml). The crude product was purified with FC (SiO_2) yielding 134 mg of 6,7-dibromo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 12.66 (br s, 1H), 8.23 (s, 1H), 7.87 (s, 1H).

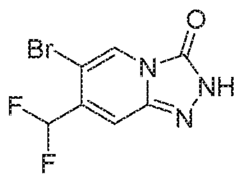
Example 11: 6-Bromo-7-(difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 5-Bromo-4-(difluoromethyl)-2-hydrazinylpyridine



The title compound was synthesised according to general procedure C from 5-bromo-2-chloro-4-(difluoromethyl)pyridine (0.10 g, 0.41 mmol), hydrazine hydrate (0.10 ml, 2.06 mmol) and IPA (1 ml) at 100 °C with 9 hours reaction time, yielding 0.08 g of 5-bromo-4-(difluoromethyl)-2-hydrazinylpyridine. ^{1}H NMR (DMSO-d_6) δ: 8.14-8.18 (m, 1H), 8.05 (s, 1H), 7.00 (t, 1H), 7.00 (s, 1H), 4.31 (s, 2H).

Step 2: 6-Bromo-7-(difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

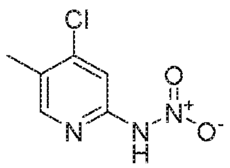


The title compound was synthesised according to general procedure D from 5-bromo-4-(difluoromethyl)-2-hydrazinylpyridine (0.07 g, 0.29 mmol) and CDI (0.06 g, 0.38 mmol) in THF (2 ml) with 1.5 hour reaction time yielding 60 mg of

6-bromo-7-(difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 12.86 (br s, 1H), 8.22-8.24 (m, 1H), 7.60-7.62 (m, 1H), 7.02 (t, 1H).

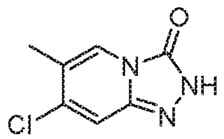
Example 12: 7-Chloro-6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: *N*-(4-chloro-5-methylpyridin-2-yl)nitramide



The title compound was synthesised according to general procedure A from 4-chloro-5-methylpyridin-2-amine (0.21 g, 1.49 mmol) in H_2SO_4 (0.8 ml) and a mixture of HNO_3 (0.17 ml, 2.44 mmol) and H_2SO_4 (0.17 ml) yielding 0.25 g of *N*-(4-chloro-5-methylpyridin-2-yl)nitramide. ^{1}H NMR (DMSO-d_6) δ: 8.30 (s, 1H), 7.87 (s, 1H), 2.30 (s, 3H).

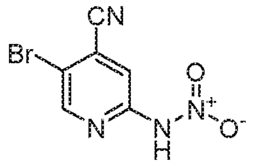
Step 2: 7-Chloro-6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure B from *N*-(4-chloro-5-methylpyridin-2-yl)nitramide (0.25 g, 1.33 mmol), NH_4Cl (0.36 g, 6.66 mmol), Zn dust (0.44 g, 6.66 mmol) and triphosgene (0.59 g, 2.00 mmol) in THF (8 ml), MeOH (2 ml) and H_2O (2 ml). The crude product was purified with FC (C18) yielding 53 mg of 7-chloro-6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 12.51 (br s, 1H), 7.85-7.87 (m, 1H), 7.49-7.51 (m, 1H), 2.17 (d, 3H).

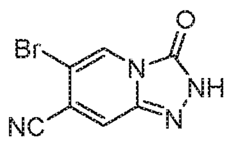
Example 13: 6-Bromo-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-7-carbonitrile

Step 1: *N*-(5-bromo-4-cyanopyridin-2-yl)nitramide



The title compound was synthesised according to general procedure A from 2-amino-5-bromoisonicotinonitrile (0.46 g, 2.32 mmol) in H_2SO_4 (1.25 ml) and a mixture of HNO_3 (0.26 ml, 3.79 mmol) and H_2SO_4 (0.25 ml) yielding 0.51 g of *N*-(5-bromo-4-cyanopyridin-2-yl)nitramide. ^{1}H NMR (DMSO-d_6) δ: 8.92 (s, 1H), 8.26 (s, 1H).

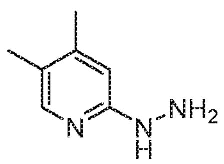
Step 2: 6-Bromo-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-7-carbonitrile



The title compound was synthesised according to general procedure B from *N*-(5-bromo-4-cyanopyridin-2-yl)nitramide (0.50 g, 2.06 mmol), NH_4Cl (0.55 g, 10.3 mmol), Zn dust (0.67 g, 10.3 mmol) and triphosgene (0.92 g, 3.09 mmol) in THF (12 ml), MeOH (3 ml) and H_2O (3 ml). The crude product was recrystallized from 1-BuOH yielding 164 mg of 6-bromo-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-7-carbonitrile. ^{1}H NMR (DMSO-d_6) δ: 13.15 (s, 1H), 8.34 (d, 1H), 8.31 (d, 1H).

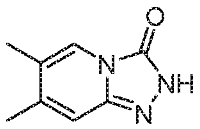
Example 14: 6,7-Dimethyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 2-Hydrazinyl-4,5-dimethylpyridine



The title compound was synthesised according to general procedure C from 2-chloro-4,5-dimethylpyridine (0.12 g, 0.85 mmol; prepared as in Kaminski, T. et al. *Eur. J. Org. Chem.* (2003) 3855), hydrazine hydrate (0.41 ml, 8.47 mmol) and EtOH (0.4 ml) at 160 °C with 42 hours reaction time yielding 0.075 g of 2-hydrazinyl-4,5-dimethylpyridine. MS: *m/z* 138.1 $[M+H]^+$.

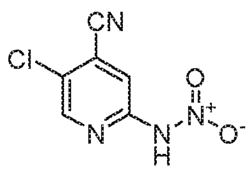
Step 2: 6,7-Dimethyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure D from 2-hydrazinyl-4,5-dimethylpyridine (0.07 g, 0.53 mmol) and CDI (0.11 g, 0.69 mmol) in THF (2 ml) with 1.5 hour reaction time. The crude product was purified with FC (C18) yielding 25 mg of 6,7-dimethyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 12.21 (br s, 1H), 7.58-7.62 (m, 1H), 6.97-7.01 (m, 1H), 2.19 (d, 3H), 2.10 (d, 3H).

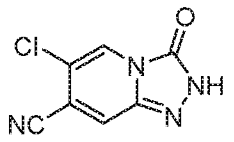
Example 15: 6-Chloro-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-7-carbonitrile

Step 1: *N*-(5-chloro-4-cyanopyridin-2-yl)nitramide



The title compound was synthesised according to general procedure A from 2-amino-5-chloroisonicotinonitrile (0.90 g, 5.86 mmol) in H_2SO_4 (3 ml) and a mixture of HNO_3 (0.66 ml, 9.55 mmol) and H_2SO_4 (0.66 ml) yielding 1.02 g of *N*-(5-chloro-4-cyanopyridin-2-yl)nitramide. ^{1}H NMR (DMSO-d_6) δ: 8.85 (d, 1H), 8.30 (d, 1H).

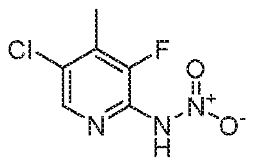
Step 2: 6-Chloro-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-7-carbonitrile



The title compound was synthesised according to general procedure B from *N*-(5-chloro-4-cyanopyridin-2-yl)nitramide (0.50 g, 2.52 mmol), NH_4Cl (0.67 g, 12.6 mmol) and Zn dust (0.82 g, 12.6 mmol) and triphosgene (1.12 g, 3.78 mmol) in THF (12 ml), MeOH (3 ml) and H_2O (3 ml). The crude product was purified with FC (C18) yielding 53 mg of 6-chloro-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-7-carbonitrile. ^1H NMR (DMSO-d_6) δ: 13.17 (br s, 1H), 8.36 (d, 1H), 8.33 (d, 1H).

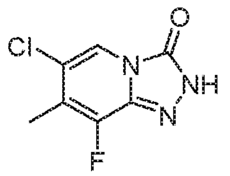
Example 16: 6-Chloro-8-fluoro-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: *N*-(5-chloro-3-fluoro-4-methylpyridin-2-yl)nitramide



The title compound was synthesised according to general procedure A from 5-chloro-3-fluoro-4-methylpyridin-2-amine (0.59 g, 3.64 mmol; prepared as in US 2011/0301193) in H_2SO_4 (3 ml) and a mixture of HNO_3 (0.41 ml, 6.01 mmol) and H_2SO_4 (0.41 ml) yielding 0.62 g of *N*-(5-chloro-3-fluoro-4-methylpyridin-2-yl)nitramide. ^1H NMR (DMSO-d_6) δ: 8.49 (s, 1H), 2.39 (d, 3H).

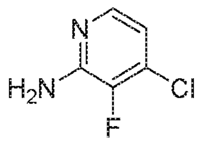
Step 2: 6-Chloro-8-fluoro-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure B from *N*-(5-chloro-3-fluoro-4-methylpyridin-2-yl)nitramide (0.60 g, 2.92 mmol), NH_4Cl (0.78 g, 14.6 mmol) and Zn dust (0.95 g, 14.6 mmol) and triphosgene (1.30 g, 4.38 mmol) in THF (24 ml), MeOH (6 ml) and H_2O (6 ml). The crude product was purified with FC (C18) yielding 131 mg of 6-chloro-8-fluoro-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^1H NMR (DMSO-d_6) δ: 12.78 (br s, 1H), 8.00-8.03 (m, 1H), 2.19-2.21 (m, 3H).

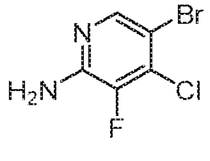
Example 17: 6-Bromo-7-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 4-Chloro-3-fluoropyridin-2-amine



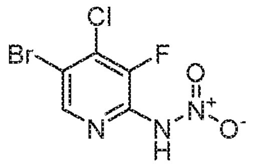
A mixture of 4-chloro-2,3-difluoropyridine (0.50 g, 3.34 mmol), IPA (3 ml), 4 M HCl in dioxane (84 µl, 0.33 mmol) and 25% NH_4OH solution (2.08 ml, 13.4 mmol) in a sealed tube was heated at 80 °C for 18 hours. The solvent was evaporated and to the residue was added H_2O and $NaHCO_3$ solution. The precipitated solid was filtered off and washed with water yielding 0.22 g of 4-chloro-3-fluoropyridin-2-amine. ^1H NMR (DMSO-d_6) δ: 7.70 (d, 1H), 6.66-6.70 (m, 1H), 6.54 (s, 2H).

Step 2: 5-Bromo-4-chloro-3-fluoropyridin-2-amine



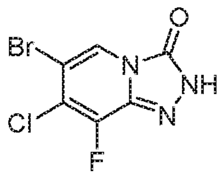
To a solution of 4-chloro-3-fluoropyridin-2-amine (0.11 g, 0.75 mmol) in MeCN (3 ml) was added NBS (0.13 g, 0.75 mmol). The resulting mixture was stirred at rt for 1 hour. EtOAc was added and the solution was washed with sat. NaHCO3 solution, H_2O and brine. The organic phase was dried with Na_2SO_4, filtered and evaporated to dryness yielding 0.15 g of 5-bromo-4-chloro-3-fluoropyridin-2-amine. MS: *m/z* 226.9 $[M+H]^+$.

Step 3: *N*-(5-bromo-4-chloro-3-fluoropyridin-2-yl)nitramide



The title compound was synthesised according to general procedure A from 5-bromo-4-chloro-3-fluoropyridin-2-amine (0.15 g, 0.67 mmol) in H_2SO_4 (0.5 ml) and a mixture of HNO_3 (91 µl, 1.33 mmol) and H_2SO_4 (90 µl) yielding 0.11 g of *N*-(5-bromo-4-chloro-3-fluoropyridin-2-yl)nitramide. MS: *m/z* 271.9 $[M+H]^+$.

Step 4: 6-Bromo-7-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

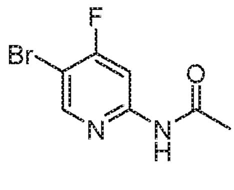


The title compound was synthesised according to general procedure B from *N*-(5-bromo-4-chloro-3-fluoropyridin-2-yl)nitramide (0.10 g, 0.37 mmol), NH_4Cl (0.10 g, 1.85 mmol), Zn dust (0.12 g, 1.85 mmol) and triphosgene (0.17 g, 0.56 mmol) in THF (5 ml), MeOH (1 ml) and H_2O (1 ml). After completion of the reaction, the mixture was extracted with EtOAc. Organic layer was extracted with 1M aqueous NaOH solution. The basic water layer was then acidified with 1M HCl solution and extracted with EtOAc. This latter organic layer was dried (Na_2SO_4) and solvents were evaporated. Purification of the evaporation residue by preparative RP HPLC afforded 10 mg of 6-bromo-7-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.

^{1}H NMR (MeOH-d_4) δ: 8.10 (d, 1H). MS: *m/z* 267.9 $[M+H]^+$.

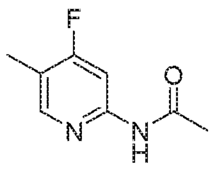
Example 18: 7-Fluoro-6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: *N*-(5-bromo-4-fluoropyridin-2-yl)acetamide



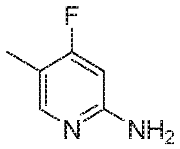
To a solution of 5-bromo-4-fluoropyridin-2-amine (2.00 g, 10.5 mmol) in pyridine (10 ml) was added acetyl chloride (1.12 ml, 15.7 mmol) dropwise. The resulting mixture was stirred at rt for 18 hours. The solvent was evaporated and to the evaporation residue was added EtOAc. The solution was washed with Na_2CO_3 solution, H_2O and brine, dried with Na_2SO_4, filtered and evaporated to dryness yielding 1.87 g of *N*-(5-bromo-4-fluoropyridin-2-yl)acetamide. ^{1}H NMR (DMSO-d_6) δ: 10.93 (s, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 2.11 (s, 3H).

Step 2: *N*-(4-fluoro-5-methylpyridin-2-yl)acetamide



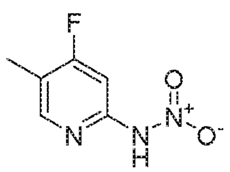
To a degassed solution of *N*-(5-bromo-4-fluoropyridin-2-yl)acetamide (1.85 g, 7.94 mmol) in 1,4-dioxane (30 ml) and H_2O (3 ml) was added K_2CO_3 (3.29 g, 23.8 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (1.67 ml, 11.9 mmol) and Pd(dppf)Cl_2 (0.29 g, 0.40 mmol). The resulting mixture was refluxed for 4 hours,allowed to cool and filtered through a pad of Celite eluting with MTBE. The filtrate was evaporated to dryness and the residue was purified by FC (SiO_2) yielding 1.05 g of still impure *N*-(4-fluoro-5-methylpyridin-2-yl)acetamide. MS: *m/z* 169.1 $[M+H]^+$.

Step 3: 4-Fluoro-5-methylpyridin-2-amine



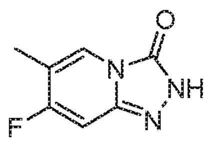
To a solution of *N*-(4-fluoro-5-methylpyridin-2-yl)acetamide (0.50 g, 2.97 mmol) in THF (5 ml) was added conc. HCl (1 ml). The resulting mixture was stirred at 60 °C for 7 hours and at rt for 18 hours and evaporated to dryness. The residue was dissolved in H_2O and pH was adjusted to 9 with 1 M NaOH solution. The aqueous mixture was extracted with EtOAc, the combined organic phases were washed with brine, dried with Na_2SO_4, filtered and evaporated yielding 0.37 g of impure 4-fluoro-5-methylpyridin-2-amine which was used in the next step without further purification. MS: *m/z* 127.3 $[M+H]^+$.

Step 4: *N*-(4-fluoro-5-methylpyridin-2-yl)nitramide



The title compound was synthesised according to general procedure A from impure 4-fluoro-5-methylpyridin-2-amine (0.37 g, < 2.90 mmol) in H_2SO_4 (2 ml) and a mixture of HNO_3 (0.36 ml, 5.28 mmol) and H_2SO_4 (0.36 ml) yielding 0.37 g of *N*-(4-fluoro-5-methylpyridin-2-yl)nitramide. MS: *m/z* 172.0 $[M+H]^+$.

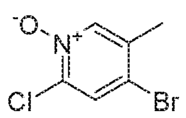
Step 5: 7-Fluoro-6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure B from *N*-(4-fluoro-5-methylpyridin-2-yl)nitramide (0.37 g, 2.19 mmol), NH_4Cl (0.59 g, 10.9 mmol), Zn dust (0.71 g, 10.9 mmol) and triphosgene (0.97 g, 0.56 mmol) in THF (15 ml), MeOH (3 ml) and H_2O (3 ml). The crude product was purified by FC (C18) yielding 5 mg of 7-fluoro-6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (MeOH-d_4) δ: 7.71-7.75 (m, 1H), 6.87 (d, 1H), 2.16-2.19 (m, 3H).

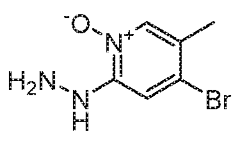
Example 19: 7-Bromo-6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 4-Bromo-2-chloro-5-methylpyridine 1-oxide



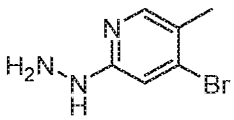
To a solution of 4-bromo-2-chloro-5-methylpyridine (0.15 g, 0.73 mmol) in DCM (5 ml) was added 77% mCPBA (0.33 g, 1.45 mmol). The resulting mixture was stirred at rt for 3 days. EtOAc was added followed by 1:1 mixture of Na_2SO_3 and Na_2CO_3 solutions. The resulting mixture was stirred vigorously for 0.5 hour and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with aq. Na_2CO_3 solution and brine, dried with Na_2SO_4, filtered and evaporated yielding 0.13 g of 4-bromo-2-chloro-5-methylpyridine 1-oxide. ^{1}H NMR ($CDCl_3$) δ: 8.20-8.23 (m, 1H), 7.66 (s, 1H), 2.31-2.34 (m, 3H).

Step 2: 4-Bromo-2-hydrazinyl-5-methylpyridine 1-oxide



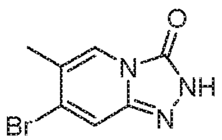
To a solution of 4-bromo-2-chloro-5-methylpyridine 1-oxide (0.13 g, 0.58 mmol) in EtOH (0.5 ml) was added hydrazine hydrate (0.50 ml, 10.2 mmol). The resulting mixture was stirred at rt for 18 hours and at 40 °C for 5 hours. The cooled mixture was filtered and the solid was washed with ice cold EtOH yielding 73 mg of 4-bromo-2-hydrazinyl-5-methylpyridine 1-oxide. ^{1}H NMR (DMSO-d_6) δ: 8.07-8.10 (m, 1H), 7.84 (s, 1H), 7.23 (s, 1H), 4.47 (d, 2H), 2.13 (d, 3H).

Step 3: 4-Bromo-2-hydrazinyl-5-methylpyridine



4-bromo-2-hydrazinyl-5-methylpyridine 1-oxide (70 mg, 0.32 mmol) was dissolved in 12% solution of $TiCl_3$ in HCl. The resulting mixture was stirred at rt for 0.5 hour. pH was adjusted to 10 with 1 M NaOH solution and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and evaporated yielding 34 mg of impure 4-bromo-2-hydrazinyl-5-methylpyridine. MS: *m/z* 204.0 $[M+H]^+$.

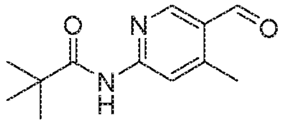
Step 4: 7-Bromo-6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure D from impure 4-bromo-2-hydrazinyl-5-methylpyridine (34 mg, < 0.17 mmol) and CDI (36 mg, 0.22 mmol) in THF (1 ml) with 18 hours reaction time. The crude product was purified using FC (C18) yielding 13 mg of 7-bromo-6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 12.50 (br s, 1H), 7.83 (s, 1H), 7.68 (s, 1H), 2.18 (d, 3H).

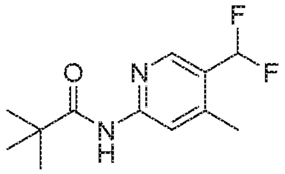
Example 20: 6-(Difluoromethyl)-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: *N*-(5-formyl-4-methylpyridin-2-yl)pivalamide



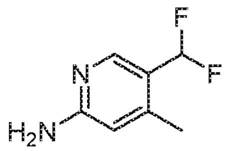
To a solution of *N*-(5-bromo-4-methylpyridin-2-yl)pivalamide (1.05 g, 3.87 mmol; prepared as in WO 2013/028474) in THF (15 ml) at -78 °C was added 2.5 M BuLi (3.87 ml, 9.68 mmol) dropwise. The resulting mixture was stirred at -78 °C for 1 hour. DMF (1.74 ml, 23.2 mmol) was added dropwise and the mixture was stirred at -78 °C for 15 minutes. Stirring was continued at rt for 2 hours and the reaction was quenched with H_2O. The mixture was extracted with EtOAc and the combined organic phases were washed with H_2O and brine, dried with Na_2SO_4, filtered and evaporated. The crude product was purified by FC (SiO2) yielding 0.28 g of *N*-(5-formyl-4-methylpyridin-2-yl)pivalamide. ^{1}H NMR (DMSO-d_6) δ: 10.23 (s, 1H), 10.13 (s, 1H), 8.73 (s, 1H), 8.06-8.08 (m, 1H), 2.60 (d, 3H), 1.25 (s, 9H).

Step 2: *N*-(5-(difluoromethyl)-4-methylpyridin-2-yl)pivalamide



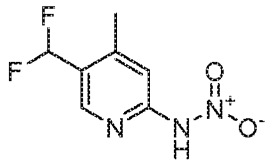
To a solution of *N*-(5-formyl-4-methylpyridin-2-yl)pivalamide (0.28 g, 1.27 mmol) in DCM (10 ml) at 0 °C was added DAST (0.50 ml, 3.81 mmol) dropwise. Stirring was continued at 0 °C for 15 minutes and at rt for 2 days. $NaHCO_3$ solution was added and stirring was continued for 15 min. Organic phase was separated and the aqueous phase was extracted with DCM. The combined organic phases were washed with aq. $NaHCO_3$ solution, H_2O and brine, dried with Na_2SO_4, filtered and evaporated yielding 0.28 g of *N*-(5-(difluoromethyl)-4-methylpyridin-2-yl)pivalamide. ^{1}H NMR (DMSO-d_6) δ: 10.00 (s, 1H), 8.40 (s, 1H), 8.04 (s, 1H), 7.16 (t, 1H), 2.41 (d, 3H), 1.24 (s, 9H).

Step 3: 5-(Difluoromethyl)-4-methylpyridin-2-amine



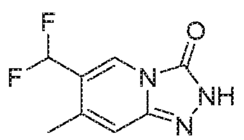
To a solution of *N*-(5-(difluoromethyl)-4-methylpyridin-2-yl)pivalamide (0.28 g, 1.16 mmol) in MeOH (3 ml) was added conc. HCl (0.5 ml). The resulting solution was heated in a sealed tube at 100 °C for 55 hours. MeOH was evaporated off and pH was adjusted to 10 with 1 M NaOH solution. The mixture was extracted with EtOAc. Combined organic phases were washed with H_2O and brine, dried with Na_2SO_4, filtered and evaporated yielding 0.12 g of impure 5-(difluoromethyl)-4-methylpyridin-2-amine. MS: *m/z* 159.3 $[M+H]^+$.

Step 4: *N*-(5-(difluoromethyl)-4-methylpyridin-2-yl)nitramide



The title compound was synthesised according to general procedure A from impure 5-(difluoromethyl)-4-methylpyridin-2-amine (0.12 g, < 0.76 mmol) in H_2SO_4 (0.75 ml) and a mixture of HNO_3 (94 µl, 1.37 mmol) and H_2SO_4 (0.10 ml) yielding 82 mg of impure *N*-(4-fluoro-5-methylpyridin-2-yl)nitramide. MS: *m/z* 204.0 $[M+H]^+$.

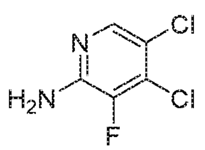
Step 5: 6-(Difluoromethyl)-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure B from impure *N*-(4-fluoro-5-methylpyridin-2-yl)nitramide (80 mg, < 0.39 mmol), NH_4Cl (0.11 g, 1.97 mmol), Zn dust (0.13 g, 1.97 mmol) and triphosgene (0.18 g, 0.59 mmol) in THF (3 ml), MeOH (0.75 ml) and H_2O (0.75 ml). The crude product was purified by FC (C18) yielding 5 mg of 6-(difluoromethyl)-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 12.49 (br s, 1H), 8.10-8.14 (m, 1H), 7.12 (s, 1H), 7.02 (t, 1H), 2.31 (s, 3H).

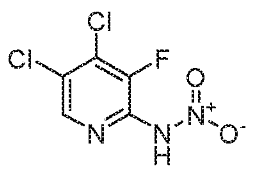
Example 21: 6,7-Dichloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 4,5-Dichloro-3-fluoropyridin-2-amine



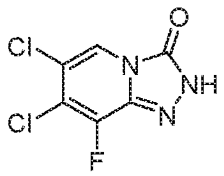
To a solution of 4-chloro-3-fluoropyridin-2-amine (0.16 g, 1.09 mmol; Example 17, Step 1) in MeCN was added NCS (0.15 g, 1.09 mmol). The resulting mixture was stirred at rt for 2 h, at 55 °C for 1.5 hour, at 70 °C for 1.5 hours and finally at rt for 18 hours. EtOAc was added and the mixture was washed twice with sat. $NaHCO_3$ solution, H_2O and brine, dried with Na_2SO4, filtered and evaporated yielding 0.14 g of 4,5-dichloro-3-fluoropyridin-2-amine. MS: *m/z* 182.9 $[M+H]^+$.

Step 2: *N*-(4,5-dichloro-3-fluoropyridin-2-yl)nitramide



The title compound was synthesised according to general procedure A from 4,5-dichloro-3-fluoropyridin-2-amine (0.14 g, 0.80 mmol) in H_2SO_4 (1 ml) and a mixture of HNO_3 (0.1 ml, 1.43 mmol) and H_2SO_4 (0.15 ml) yielding 0.11 g of *N*-(4,5-dichloro-3-fluoropyridin-2-yl)nitramide. MS: *m/z* 227.9 $[M+H]^+$.

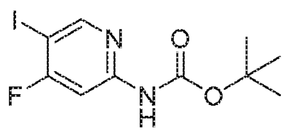
Step 3: 6,7-Dichloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure B from *N*-(4,5-dichloro-3-fluoropyridin-2-yl)nitramide (0.11 g, 0.49 mmol), NH_4Cl (0.13 g, 2.43 mmol), Zn dust (0.16 g, 2.43 mmol) and triphosgene (0.22 g, 0.73 mmol) in THF (4 ml), MeOH (1 ml) and H_2O (1 ml). The crude product was purified by FC (C18) yielding 4 mg of 6,7-dichloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (MeOH-d_4) δ: 8.03 (d, 1H).

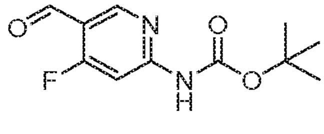
Example 22: 6-(Difluoromethyl)-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: *tert*-Butyl (4-fluoro-5-iodopyridin-2-yl)carbamate



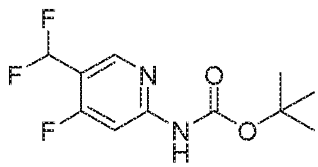
To a solution of 4-fluoro-5-iodopyridin-2-amine (2.00 g, 8.40 mmol) in *t*-BuOH (12 ml) was added di-*tert*-butyl dicarbonate (2.02 g, 9.24 mmol). The resulting mixture was stirred at 40 °C for 7 hours and at rt for 18 hours. Di-*tert*-butyl dicarbonate (2.02 g, 9.24 mmol) was added and stirring at 55 °C was continued for 8 hours. The solvent was evaporated off and the residue was recrystallized from IPA yielding 1.55 g of *tert*-butyl (4-fluoro-5-iodopyridin-2-yl)carbamate. ^{1}H NMR (DMSO-d_6) δ: 10.29 (s, 1H), 8.53 (d, 1H), 7.69 (d, 1H), 1.47 (s, 9H).

Step 2: *tert*-Butyl (4-fluoro-5-formylpyridin-2-yl)carbamate



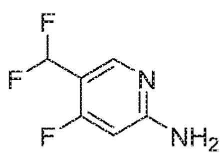
To a solution of *tert*-butyl (4-fluoro-5-iodopyridin-2-yl)carbamate (1.48 g, 4.38 mmol) in THF (15 ml) at 0 °C was added 1.3 M solution of *i*-PrMgCl·LiCl in THF (7.74 ml, 10.0 mmol) dropwise. Ater 15 minutes stirring at 0 °C DMF (3.12 ml, 41.7 mmol) was added. Stirring was continued at 0 °C for 10 minutes and at rt for 2 hours. The reaction mixture was quenched with NH_4Cl solution and extracted with EtOAc. The combined organic phases were washed with H_2O and brine, dried with Na_2SO_4, filtered and evaporated to dryness. EtOAc (15 ml) was added to the residue and the mixture was stored overnight at -18 °C. The precipitated solid was filtered off yielding 0.30 g of *tert*-butyl (4-fluoro-5-formylpyridin-2-yl)carbamate. ^1H NMR (DMSO-d_6) δ: 10.74 (s, 1H), 10.04 (s, 1H), 8.72 (d, 1H), 7.72 (d, 1H), 1.49 (s, 9H).

Step 3: *tert*-Butyl (5-(difluoromethyl)-4-fluoropyridin-2-yl)carbamate



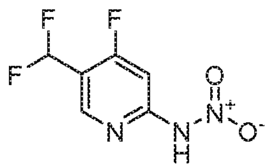
To a solution of *tert*-butyl (4-fluoro-5-formylpyridin-2-yl)carbamate (0.26 g, 1.08 mmol) in DCM (10 ml) at 0 °C was added DAST (0.43 ml, 3.25 mmol) dropwise. Stirring was continued at 0 °C for 15 minutes and at rt for 18 h. The reacton mixture was cooled to 0 °C and quenched with $NaHCO_3$ solution. After 15 minutes stirring the mixture was extracted with DCM. The combined organic phases were washed with $NaHCO_3$ solution, H_2O and brine, dried with Na_2SO_4, filtered and evaporated yielding 0.26 g of *tert*-butyl (5-(difluoromethyl)-4-fluoropyridin-2-yl)carbamate. ^1H NMR (DMSO-d_6) δ: 10.50 (s, 1H), 8.48 (d, 1H), 7.73 (d, 1H), 7.17 (t, 1H), 1.48 (s, 9H).

Step 4: 5-(Difluoromethyl)-4-fluoropyridin-2-amine



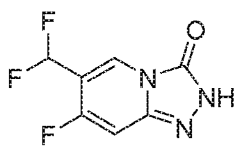
To a solution of *tert*-butyl (5-(difluoromethyl)-4-fluoropyridin-2-yl)carbamate (0.25 g, 0.95 mmol) in DCM (2 ml) was added TFA (2 ml). The resulting mixture was stirred at rt for 1.5 hours and evaporated to dryness. To the residue was added $NaHCO_3$ solution and the aqueous mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered and evaporated to dryness yielding 0.15 g of 5-(difluoromethyl)-4-fluoropyridin-2-amine. ^1H NMR (DMSO-d_6) δ: 8.05-8.12 (m, 1H), 6.96 (t, 1H), 6.78 (s, 2H), 6.25 (d, 1H).

Step 5: *N*-(5-(difluoromethyl)-4-fluoropyridin-2-yl)nitramide



The title compound was synthesised according to general procedure A from 5-(difluoromethyl)-4-fluoropyridin-2-amine (0.15 g, 0.93 mmol) in H_2SO_4 (1.5 ml) and a mixture of HNO_3 (0.11 ml, 1.67 mmol) and H_2SO_4 (0.15 ml) yielding 0.15 g of *N*-(5-(difluoromethyl)-4-fluoropyridin-2-yl)nitramide. ^1H NMR (DMSO-d_6) δ: 8.57.8.62 (m, 1H), 7.78 (d, 1H), 7.22 (t, 1H).

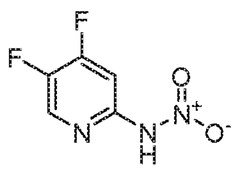
Step 6: 6-(Difluoromethyl)-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure B from *N*-(5-(difluoromethyl)-4-fluoropyridin-2-yl)nitramide (0.14 g, 0.68 mmol), NH_4Cl (0.18 g, 3.38 mmol), Zn dust (0.22 g, 3.38 mmol) and triphosgene (0.30 g, 1.01 mmol) in THF (5 ml), MeOH (1.2 ml) and H_2O (1.2 ml). The crude product was extracted from acidic aqueous phase with EtOAc (no precipitate). The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered and evaporated. The obtained crude product was purified by FC (C18) yielding 40 mg of 6-(difluoromethyl)-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 12.64 (s, 1H), 8.33-8.40 (m, 1H), 7.32 (d, 1H), 7.05 (t, 1H).

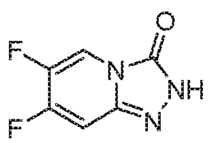
Example 23: 6,7-Difluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: *N*-(4,5-difluoropyridin-2-yl)nitramide



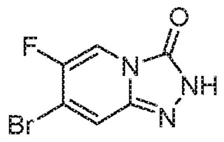
The title compound was synthesised according to general procedure A from 4,5-difluoropyridin-2-amine (0.23 g, 1.77 mmol) in H_2SO_4 (1.5 ml) and a mixture of HNO_3 (0.20 ml, 2.92 mmol) and H_2SO_4 (0.22 ml). After pouring to ice the aqueous mixture was extracted with EtOAc and the combined organic extracts were washed with H_2O and brine, dried with Na_2SO_4, filtered and evaporated yielding 0.30 g of *N*-(4,5-difluoropyridin-2-yl)nitramide. ^{1}H NMR (DMSO-d_6) δ: 8.26-8.34 (m, 1H), 7.58-7.68 (m, 1H).

Step 2: 6,7-Difluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure B from *N*-(4,5-difluoropyridin-2-yl)nitramide (0.29 g, 1.66 mmol), NH_4Cl (0.44 g, 8.28 mmol), Zn dust (0.54 g, 8.28 mmol) and triphosgene (0.74 g, 2.48 mmol) in THF (8 ml), MeOH (2 ml) and H_2O (2 ml). The precipitated product was filtered off yielding 85 mg of 6,7-difluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 12.78 (br s, 1H), 7.80-7.86 (m, 1H), 6.76-6.85 (m, 1H).

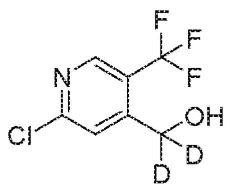
Example 24: 7-Bromo-6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



To a solution of 4-bromo-2,5-difluoropyridine (0.10 g, 0.52 mmol) in IPA (1 ml) was added 4 M HCl in 1,4-dioxane (13 µl, 0.05 mmol) and hydrazine hydrate (75 µl, 1.55 mmol). The resulting mixture was stirred at 80 °C for 9 hours, followed by 18 hours at rt. H_2O was added and the mixture was extracted with EtOAc. The combine organic phases were washed with brine, dried with Na_2SO_4 and filtered. The solution was concentrated to about 7 ml and THF (6 ml) was added. The mixture was cooled to 0 °C and triphosgene (0.15 g, 0.52 mmol) was added. The resulting mixture was stirred at 0 °C for 1 hour. The solvents were evaporated off and 1 M HCl was added. The precipitated solid was filtered off and washed with H_2O yielding 25 mg of 7-bromo-6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^1H NMR (600 MHz, DMSO-d_6) δ: 12.73 (br s, 1H), 8.22 (d, 1H), 7.89 (d, 1H).

Example 25: 7-(Methyl-d_3)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

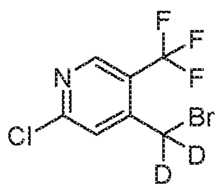
Step 1: (2-Chloro-5-(trifluoromethyl)pyridin-4-yl)methan-d_2-ol



To a solution of methyl 2-chloro-5-(trifluoromethyl)isonicotinate (2.97 g, 12.4 mmol) in THF (40 ml) and MeOH-d_4 (7 ml) at 0 °C was added $NaBD_4$ (1.04 g, 24.8 mmol). The resulting mixture was stirred at rt for 15 min and $NaBD_4$ (0.26 g, 6.20 mmol) was added. After 1 hour, H_2O and NH_4Cl solution were added and the resulting mixture was extracted with EtOAc. The combined organic phases were washed with H_2O and brine, dried with Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by FC (SiO_2)

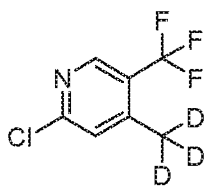
yielding 2.13 g of (2-chloro-5-(trifluoromethyl)pyridin-4-yl)methan-*d*$_2$-ol. [1]H NMR ($CDCl_3$) δ: 8.58-8.61 (m, 1H), 7.83-7.84 (m, 1H), 2.15-2.17 (m, 1H).

Step 2: 4-(Bromomethyl-*d*$_2$)-2-chloro-5-(trifluoromethyl)pyridine



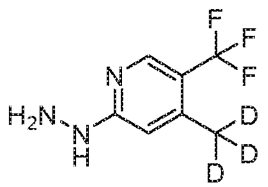
To a solution of (2-chloro-5-(trifluoromethyl)pyridin-4-yl)methan-*d*$_2$-ol (1.18 g, 5.52 mmol) in DCM (15 ml) at 0 °C was added PPh_3 (1.61 g, 6.14 mmol) and the resulting mixture was stirred for 10 minutes. NBS (1.09 g, 6.14 mmol) was added in portions. The resulting mixture was stirred at 0 °C for 1.5 hour and evaporated to dryness. The title compound was isolated with FC (SiO_2) yielding 1.59 g of 4-(bromomethyl-*d*$_2$)-2-chloro-5-(trifluoromethyl)pyridine. [1]H NMR ($CDCl_3$) δ: 8.64-8.67 (m, 1H), 7.59-7.61 (m, 1H).

Step 3: 2-Chloro-4-(methyl-*d*$_3$)-5-(trifluoromethyl)pyridine



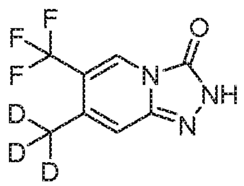
To a mixture of LiAlD4 (0.15 g, 3.62 mmol) in THF (10 ml) at 0 °C was added dropwise a solution of 4-(bromomethyl-*d*$_2$)-2-chloro-5-(trifluoromethyl)pyridine (1.00 g, 3.62 mmol) in THF (10 ml). The resulting mixture was stirred at rt for 1 hour and cooled to 0 °C. $NaHSO_4$ solution (1M) was added until the pH of the solution was 5. The resulting mixture was extraxted with DCM. The combined organic phases were washed with H_2O and brine, dried with Na_2SO_4, filtered and evaporated to dryness yielding 0.62 g of 2-chloro-4-(methyl-*d*$_3$)-5-(trifluoromethyl)pyridine. [1]H NMR ($CDCl_3$) δ: 8.57-8.59 (m, 1H), 7.28-7.30 (m, 1H).

Step 4: 2-Hydrazinyl-4-(methyl-*d*$_3$)-5-(trifluoromethyl)pyridine



The title compound was synthesised according to general procedure C from 2-chloro-4-(methyl-d_3)-5-(trifluoromethyl)pyridine (0.62 g, 3.12 mmol) and hydrazine hydrate (1.51 ml, 31.2 mmol) in IPA (6 ml) in a sealed tube at 110 °C with 1h reaction time yielding 0.53 g of 2-hydrazinyl-4-(methyl-d_3)-5-(trifluoromethyl)pyridine. ^{1}H NMR (DMSO-d_6) δ: 8.16 (s, 1H), 8.15 (s, 1H), 6.66 (s, 1H), 4.30 (br s, 2H).

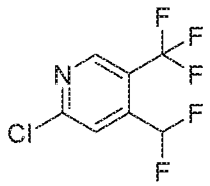
Step 5: 7-(Methyl-d_3)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure D from 2-hydrazinyl-4-(methyl-d_3)-5-(trifluoromethyl)pyridine (0.53 g, 2.73 mmol) and CDI (0.53 g, 3.28 mmol) in THF (15 ml) with 1 hour reaction time. The crude product was purified by FC (C18) yielding 0.32 g of 7-(methyl-d_3)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d_6) δ: 12.61 (br s, 1H), 8.12-8.15 (m, 1H), 7.24 (s, 1H).

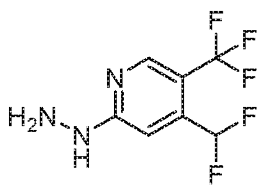
Example 26: 7-(Difluoromethyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 2-Chloro-4-(difluoromethyl)-5-(trifluoromethyl)pyridine



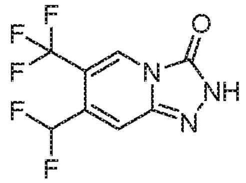
To a solution of 2-chloro-5-(trifluoromethyl)isonicotinaldehyde (0.10 g, 0.48 mmol) in DCM (4 ml) at 0 °C was added DAST (0.13 ml, 0.95 mmol) dropwise. The resulting mixture was stirred at 0 °C for 0.5 hour and at rt 18 hours. The reaction mixture was cooled in ice bath and quenched with sat. $NaHCO_3$ solution. The aqueous phase was extracted twice with DCM. The combined organic phases were washed with H_2O and brine, dried with Na_2SO_4, filtered and evaporated to dryness yielding 0.12 g of crude 2-chloro-4-(difluoromethyl)-5-(trifluoromethyl)pyridine. ^{1}H NMR (DMSO-d6) δ: 9.05-8.99 (m, 1H), 8.07-8.02 (m, 1H), 7.35 (t, 1H).

Step 2: 4-(Difluoromethyl)-2-hydrazinyl-5-(trifluoromethyl)pyridine



The title compound was synthesised according to general procedure C from 2-chloro-4-(difluoromethyl)-5-(trifluoromethyl)pyridine (0.11 g, 0.48 mmol), hydrazine hydrate (0.18 ml, 3.80 mmol) and IPA (1 ml) at 100 °C with 1 hour reaction time. The reaction mixture was evaporated to dryness, EtOAc was added and the solution was washed with H_2O and brine, dried with Na_2SO_4, filtered and evaporated to dryness yielding 0.10 g of 4-(difluoromethyl)-2-hydrazinyl-5-(trifluoromethyl)pyridine. ^{1}H NMR (DMSO-d6) δ: 8.73 (br s, 1H), 8.36 (br s, 1H), 7.13 (t, 1H), 7.06 (br s, 1H), 4.53 (br s, 2H).

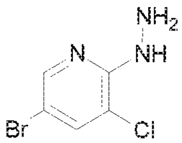
Step 3: 7-(Difluoromethyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure D from 4-(difluoromethyl)-2-hydrazinyl-5-(trifluoromethyl)pyridine (0.10 g, 0.44 mmol) and CDI (86 mg, 0.53 mmol) in THF (3 ml), with 18 hours reaction yielding 70 mg of 7-(difluoromethyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (400MHz, DMSO-d6) δ: 13.01 (br s, 1H), 8.35-8.28 (m, 1H), 7.78-7.72 (m, 1H), 7.09 (t, 1H).

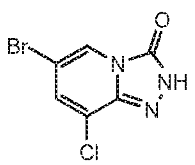
Example 27: 6-bromo-8-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 5-bromo-3-chloro-2-hydrazinylpyridine



To a solution of 5-bromo-2,3-dichloropyridine (500 mg, 2.20 mmol) in EtOH (5 mL) was added hydrazine hydrate (0.33 mL, 6.61 mmol) and the reaction mixture was stirred at 80 °C for 24 hours. After completion of the reaction, it was concentrated under reduced pressure at 25 °C. The resulting crude mass was triturated with EtOH (1 mL) at 0 °C. The solid precipitate was filtered, washed with Et_2O (2 mL) and dried under reduced pressure to get 480 mg of 5-bromo-3-chloro-2-hydrazinylpyridine. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.14 (s, 1H), 7.92 (s, 1H), 7.86 (s, 1H), 4.24 (brs, 2H). LCMS: [M+H] = 222.1.

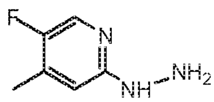
Step 2: 6-bromo-8-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure D from 5-bromo-3-chloro-2-hydrazinylpyridine (101 mg, 0.45 mmol), CDI (88 mg, 0.54 mmol) in THF (3 ml) yielding 71 mg of 6-bromo-8-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.
MS: *m/z* 250 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ: 12.87 (br s, 1H), 8.13 (d, 1H), 7.65 (d, 1H)

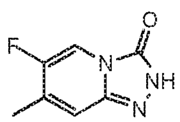
Example 28: 6-fluoro-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 5-fluoro-2-hydrazinyl-4-methylpyridine



To a solution of 2-chloro-5-fluoro-4-methylpyridine (200 mg, 1.4 mmol) in *n*-butanol (2 ml) at rt was added hydrazine hydrate (0.7 ml, 13.7 mmol). Reaction mixture was stirred at 150 °C for 7 hours, then at 160 °C for 22 hours. Solvents were evaporated under vacuum. Water was added to the mixture. Precipitate formed was filtered off, washed with water and dried under vacuum yielding 66 mg of 5-fluoro-2-hydrazinyl-4-methylpyridine and 2-chloro-5-hydrazinyl-4-methylpyridine as a 8/2 mixture.
MS: *m/z* 142 $[M+H]^+$.

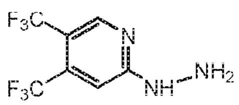
Step 2: 6-fluoro-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure D from the mixture of 5-fluoro-2-hydrazinyl-4-methylpyridine and 2-chloro-5-hydrazinyl-4-methylpyridine (66 mg, 0.46 mmol) and CDI (91 mg, 0.56 mmol) in THF (3 ml) yielding 30 mg of 6-fluoro-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.
MS: *m/z* 168 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ: 12.46 (br s, 1H), 7.96 (d, 1H), 7.17 (m, 1H), 2.17-2.26 (m, 3H)

Example 29: 6,7-bis(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

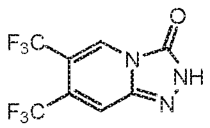
Step 1: 2-hydrazinyl-4,5-bis(trifluoromethyl)pyridine



To a solution of 2-chloro-4,5-bis(trifluoromethyl)pyridine (212 mg, 0.85 mmol) in 2-propanol (2 ml) at rt was added hydrazine hydrate (425 mg, 8.5 mmol). Reaction mixture was stirred at 150 °C for 2 hours. Solvents were evaporated under vacuum. Water was added and the mixture was stirred at rt overnight. Precipitate that formed was filtered off, washed with water and dried under vacuum yielding 46 mg of 2-hydrazinyl-4,5-bis(trifluoromethyl)pyridine.

MS: m/z 246 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ: 8.99 (br s, 1H), 8.47 (s, 1H), 7.19 (br s, 1H), 4.60 (br s, 2H)

Step 2: 6,7-bis(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

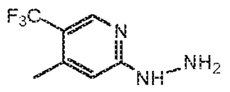


The title compound was synthesised according to general procedure D from 2-hydrazinyl-4,5-bis(trifluoromethyl)pyridine (46 mg, 0.19 mmol) and CDI (37 mg, 0.22 mmol) in THF (3 ml), with stirring at rt for 4 days. Then CDI (15 mg, 0.10 mmol) was added and the mixture was stirred at 40 °C for 2 more hours. General work-up yielded 18 mg of 6,7-bis(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.

MS: m/z 272 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ: 13.16 (br s, 1H), 8.37 (s, 1H), 8.09 (s, 1H)

Example 30: 7-methyl-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

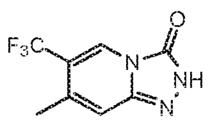
Step 1: 2-hydrazinyl-4-methyl-5-(trifluoromethyl)pyridine



To a solution of 2-chloro-4-methyl-5-(trifluoromethyl)pyridine (200 mg, 1.02 mmol) in 2-propanol (3 ml) at rt was added hydrazine hydrate (0.5 ml, 10.2 mmol). Reaction mixture was heated up to 100 °C for 2 hours, then heated up to 120 °C in a microwave reactor and stirred for 0.5 hour. Solvents were evaporated under vacuum. Water was added and the precipitate formed was filtered off, washed with water and dried under vacuum yielding 150 mg of 2-hydrazinyl-4-methyl-5-(trifluoromethyl)pyridine.

MS: *m/z* 192 $[M+H]^+$. ^{1}H NMR (DMSO-d_6) δ: 8.16 (s, 1H), 8.15 (d, 1H), 6.66 (s, 1H), 4.30 (s, 2H), 2.28-2.31 (m, 3H)

Step 2: 7-methyl-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

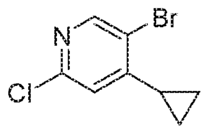


The title compound was synthesised according to general procedure D from 2-hydrazinyl-4-methyl-5-(trifluoromethyl)pyridine (148 mg, 0.77 mmol), CDI (151 mg, 0.93 mmol) in THF (3 ml). Resulting crude compound was dissolved in 1M aqueous NaOH solution and washed 3-times with EtOAc. Aqueous layer was acidifed with conc. HCl. Precipitate formed was filtered off, washed with water and dried under vacuum yielding 67 mg of 7-methyl-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.

MS: *m/z* 218 $[M+H]^+$. ^{1}H NMR (DMSO-d_6) δ: 12.60 (br s, 1H), 8.13 (s, 1H), 7.24 (s, 1H), 2.31 (s, 3H)

Example 31: 6-bromo-7-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

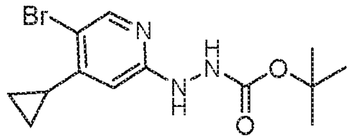
Step 1: 5-bromo-2-chloro-4-cyclopropylpyridine



To a degassed solution of 5-bromo-2-chloro-4-iodopyridine (1 g, 3.14 mmol) in dioxane/water (15 mL, 8:2) was added cyclopropaneboronic acid (0.54 g, 6.28 mmol), K_2CO_3 (0.85 g, 6.28 mmol) and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.45 g, 0.062 mmol) and the reaction mixture was stirred at 80 °C for 12 hours. After completion of the reaction, it was diluted with EtOAc (50 mL) and filtered through celite. The organic layer was washed with water (25 mL), dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (silica gel) to get 550 mg of 2,5-dichloro-4-cyclopropylpyridine.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.50 (s, 1H), 7.11 (s, 1H), 2.13-2.17 (m, 1H), 1.12-1.17 (m, 2H), 0.96-0.97 (m, 2H). LCMS: [M+H]=232.9.

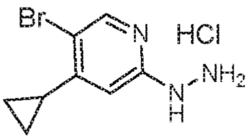
Step 2: tert-butyl-2-(5-bromo-4-cyclopropylpyridin-2-yl)hydrazine-1-carboxylate



To a solution of 5-bromo-2-chloro-4-cyclopropylpyridine (0.25 mg, 1.07 mmol) in EtOH (10 mL) was added hydrazine hydrate (0.26 mL, 5.37 mmol) and the reaction mixture was stirred at 130 °C for 2 hours in a microwave reactor (Biotage). The reaction mixture was concentrated under reduced pressure. The resulting crude mass was dissolved in THF (5 mL, Et_3N (0.45 mL, 3.23 mmol) and di-tert-butyl dicarbonate (2.3 mL, 10.7 mmol) were added and the reaction mixture was stirred at rt for 5 hours. After completion of the reaction, the reaction mixture was diluted with EtOAc (50 mL), washed with water (25 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (silica gel) to get 130 mg of tert-butyl 2-(5-bromo-4-cyclopropylpyridin-2-yl)hydrazine-1-carboxylate.

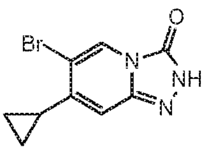
^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.79 (s, 1H), 8.24 (s, 1H), 8.07 (s, 1H), 6.03 (s, 1H), 2.03-2.07 (m, 1H), 1.43 (s, 9H), 1.06-1.11 (m, 2H), 0.63-0.64 (m, 2H). LCMS: [M+2H]= 329.9.

Step 3: 5-bromo-4-cyclopropyl-2-hydrazinylpyridine hydrochloride



To a solution of tert-butyl 2-(5-bromo-4-cyclopropylpyridin-2-yl)hydrazine-1-carboxylate (130 mg, 0.039 mmol) in dioxane (2 mL) was added 4M HCl in dioxane (5 mL) at 0 °C and the reaction mixture was stirred at rt for 4 hours. After completion of the reaction, it was concentrated under reduced pressure to give 85 mg of 5-bromo-4-cyclopropyl-2-hydrazinylpyridine hydrochloride. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.03 (s, 3H), 9.10 (s, 1H), 8.31 (s, 1H), 6.43 (s, 1H), 2.10-2.14 (m, 1H), 1.11-1.16 (m, 2H), 0.76-0.78 (m, 2H). LCMS: [M+H]= 228.2.

Step 4: 6-bromo-7-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

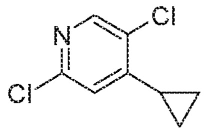


The title compound was synthesised according to general procedure D from 5-bromo-4-cyclopropyl-2-hydrazinylpyridine hydrochloride 69 mg, 0.26 mmol) and CDI (51 mg, 0.31 mmol) in THF (3 ml), with addition of NEt_3 (26 mg, 0.26 mmol) yielding 38 mg of 6-bromo-7-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.

MS: m/z 256 $[M+H]^+$. ^{1}H NMR (DMSO-d_6) δ: 12.45 (s, 1H), 8.07 (d, 1H), 6.91 (m, 1H), 1.92-1.99 (m, 1H), 0.97-1.02 (m, 2H), 0.74-0.84 (m, 2H)

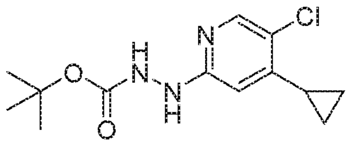
Example 32: 6-chloro-7-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 2,5-dichloro-4-cyclopropylpyridine



To a degassed solution of 4-bromo-2,5-dichloropyridine (1.5 g, 6.63 mmol) in toluene/water (10 mL, 8:2) was added cyclopropaneboronic acid (0.85 g, 9.95 mmol), potassium phosphate tribasic (2.81 g, 13.27 mmol), tricyclohexyl phosphine (2.23 g, 7.96 mmol) and palladium acetate (0.29 g, 1.32 mmol) and the reaction mixture was stirred at 140 °C for 3 hours in a microwave initiator (Biotage). After completion of the reaction, it was diluted with EtOAc (50 mL) and filtered through celite. The organic layer was washed with water (25 mL), dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (silica gel) to get 700 mg of 2,5-dichloro-4-cyclopropylpyridine. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.40 (s, 1H), 7.14 (s, 1H), 2.09-2.12 (m, 1H), 1.16 (t, 2H), 0.97 (t, 2H). LCMS: [M+H]= 187.9.

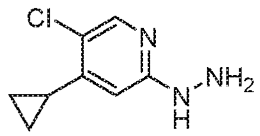
Step 2: tert-butyl 2-(5-chloro-4-cyclopropylpyridin-2-yl)hydrazine-1-carboxylate



To a solution of 2,5-dichloro-4-cyclopropylpyridine (700 mg, 3.70 mmol) in EtOH (10 mL) at rt was added hydrazine hydrate (2.2 mL, 4.28 mmol) and the reaction mixture stirred at 140 °C for 1 hour in a microwave reactor (Biotage). After completion of the reaction, the reaction mixture was concentrated under reduced pressure at 20 °C. The resulting crude mass was dissolved in THF (10 mL), Et_3N (1.87 mL, 18.51 mmol) and di-tert-butyl dicarbonate (4.0 mL, 18.51 mmol) were added at 0 °C and the reaction mixture was stirred at rt for 16 hours. After completion of the reaction, the reaction mixture was diluted with DCM (25 mL) and washed with water (10 ml) dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (silica gel) to get 350 mg of tert-butyl 2-(5-chloro-4-cyclopropylpyridin-2-

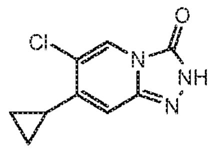
yl)hydrazine-1-carboxylate. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.78 (s, 1H), 8.20 (s, 1H), 7.98 (s, 1H), 6.02 (s, 1H), 2.08-2.12 (m, 1H), 1.40 (s, 9H), 1.07-1.11 (m, 2H), 0.63-0.65 (m, 2H). LCMS: [M+H]= 284.0.

Step 3: 5-chloro-4-cyclopropyl-2-hydrazinylpyridine hydrochloride



To a solution of tert-butyl 2-(5-chloro-4-cyclopropylpyridin-2-yl)hydrazine-1-carboxylate (210 mg, 0.0074 mmol) in Et_2O (2 mL) was added 4M HCl in Et_2O (5 mL) at 0 °C and the reaction mixture was stirred at rt for 4 hours. After completion of the reaction, it was concentrated under reduced pressure to get 160 mg of 5-chloro-4-cyclopropyl-2-hydrazinylpyridine hydrochloride. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.09 (s, 3H), 9.14 (s, 1H), 8.20 (s, 1H), 6.45 (s, 1H), 2.13-2.17 (m, 1H), 1.11-1.16 (m, 2H), 0.73-0.77 (m, 2H). LCMS: [M+H]=284.2.

Step 4: 6-chloro-7-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

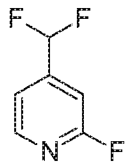


The title compound was synthesised according to general procedure D from 5-bromo-4-cyclopropyl-2-hydrazinylpyridine hydrochloride (70 mg, 0.32 mmol) and CDI (62 mg, 0.38 mmol) in THF (3 ml), with addition of NEt_3 (32 mg, 0.32 mmol) yielding 27 mg of 6-chloro-7-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.

MS: *m/z* 210 $[M+H]^+$. ^{1}H NMR (DMSO-d_6) δ: 12.46 (s, 1H), 8.00 (d, 1H), 6.92 (m, 1H), 1.96-2.01 (m, 1H), 0.99-1.02 (m, 2H), 0.80-0.82 (m, 2H)

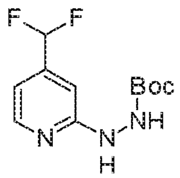
Example 33: 7-(difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 4-(difluoromethyl)-2-fluoropyridine



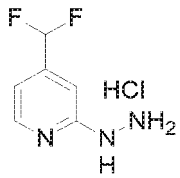
To a solution of 2-fluoroisonicotinaldehyde (1.7 g, 13.6 mmol) in DCM (20 ml) was added DAST (4.4 mL, 34.2 mmol) at 0 °C and the reaction mixture was stirred at rt for 12 hours. After completion of the reaction, the reaction mixture was diluted with DCM (50 mL), washed with water (10 mL), dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (silica gel) to get 0.8 g of 4-(difluoromethyl)-2-fluoropyridine. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.45 (d, 1H), 7.57 (d, 1H), 7.44 (s, 1H), 7.15 (t, 1H).

Step 2: tert-butyl 2-(4-(difluoromethyl)pyridin-2-yl)hydrazine-1-carboxylate



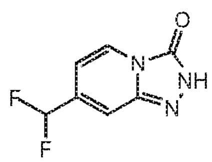
To a solution of 4-(difluoromethyl)-2-fluoropyridine (800 mg, 5.440 mmol) in EtOH (10 ml) was added hydrazine hydrate (1.3 mL, 27.2 mmol) at rt and the reaction mixture stirred at 80 °C for 12 hours. After completion of the reaction, it was concentrated under reduced pressure. The resulting crude mass was dissolved in THF (10 ml), Et_3N (2.2 mL, 16.3 mmol) and di-tert-butyl dicarbonate (9.4 mL, 43.5 mmol) were added at 0 °C and the reaction mixture was stirred at rt for 16 hours. After completion of the reaction, the reaction mixture was diluted with EtOAc (30 mL), washed with water (25 mL), dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (silica gel) to get 550 mg of tert-butyl 2-(4-(difluoromethyl)pyridin-2-yl)hydrazine-1-carboxylate. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.89 (s, 1H), 8.51 (s, 1H), 8.18 (d, 1H), 6.98 (t, 1H), 6.80 (d, 1H), 6.62 (s, 1H), 1.41 (s, 9H) LCMS: [M+H]=260.0.

Step 3: tert-butyl 2-(4-(difluoromethyl)pyridin-2-yl)hydrazine-1-carboxylate hydrochloride



To a solution of tert-butyl 2-(4-(difluoromethyl)pyridin-2-yl)hydrazine-1-carboxylate (500 mg, 0.039 mmol) in dioxane (5 ml) was added 4M HCl in dioxane (5 ml) at 0 °C and the reaction mixture was stirred at rt for 4 hours. After completion of the reaction, it was concentrated under reduced pressure to get 450 mg of tert-butyl 2-(4-(difluoromethyl)pyridin-2-yl)hydrazine-1-carboxylate hydrochloride. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 9.82 (s, 3H), 8.33 (d, 1H), 6.94-7.22 (m, 3H). LCMS: [M+H]=160.2

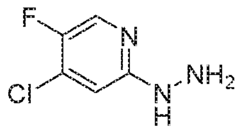
Step 4: 7-(difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure D from 4-(difluoromethyl)-2-hydrazinylpyridine hydrochloride OS-037 (100 mg, 0.51 mmol) and CDI (99 mg, 0.61 mmol) in THF (3 ml), with addition of Et_3N (52 mg, 0.51 mmol) yielding 53 mg of 7-(difluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.
MS: m/z 186 $[M+H]^+$. ^{1}H NMR (DMSO-d_6) δ: 12.74 (br s, 1H), 7.94 (d, 1H), 7.51 (s, 1H), 6.97 (t, 1H), 6.63 (d, 1H)

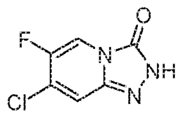
Example 34: 7-chloro-6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 4-chloro-5-fluoro-2-hydrazineylpyridine



To a solution of 4-chloro-2,5-difluoropyridine (200 mg, 1.33 mmol) and 4M HCl in dioxane (0.33 ml, 1.33 mmol) in 2-propanol (3 ml) was added hydrazine hydrate (134 mg, 2.68 mmol). Reaction mixture was stirred at rt for 1 month. Solvents were evaporated under vacuum. Aqueous $NaHCO_3$ solution was added to the mixture. Precipitate formed was filtered off, washed with water and dried under vacuum yielding 51 mg of 4-chloro-5-fluoro-2-hydrazinylpyridine and 2,5-difluoro-4-hydrazinylpyridine as a 1/1 mixture. MS: *m/z* 162 $[M+H]^+$. ^{1}H NMR (DMSO-d_6) δ: 8.19 (br s, 1H), 8.09 (d, 1H), 7.70 (d, 1H), 7.66 (d, 1H), 6.88 (d, 1H), 6.55 (d, 1H), 4.39 (d, 2H), 4.21 (br s, 2H)

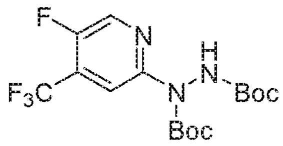
Step 2: 7-chloro-6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



To a solution containing the mixture of 4-chloro-5-fluoro-2-hydrazinylpyridine and 2,5-difluoro-4-hydrazinylpyridine (50 mg, 0.31 mmol) in THF (3 ml) at 0°C was added triphosgene (92 mg, 0.31 mmol). Reaction mixture was stirred at 0°C for 1 hour. Solvents were evaporated under vacuum. A solution of 1M aqueous HCl was then added and the mixture was extracted 3 times with EtOAc. Organic layers were concentrated under vacuum. Evaporation residue was dissolved in 1M NaOH solution and extracted twice with EtOAc. Aqueous phase was acidified with conc. HCl and extracted twice with EtOAc. Organic layers were dried and concentrated under vacuum. Evaporation residue was stirred in Et_2O, filtered off and dried under vacuum yielding 11 mg of pure 7-chloro-6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. MS: *m/z* 188 $[M+H]^+$. ^{1}H NMR (DMSO-d_6) δ: 12.71 (br s, 1H), 8.27 (dd, 1H), 7.75 (dd, 1H)

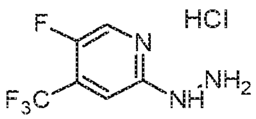
Example 35: 6-fluoro-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: di-tert-butyl 1-(5-fluoro-4-(trifluoromethyl)pyridin-2-yl)hydrazine-1,2-dicarboxylate



A solution of di-tert-butyl hydrazine-1,2-dicarboxylate (116 mg, 0.50 mmol), dppf (28 mg, 0.05 mmol) and Cs_2CO_3 (180 mg, 0.55 mmol) in toluene (3 ml) was degassed under inert atmosphere for 15 minutes at RT. 2-Chloro-5-fluoro-4-(trifluoromethyl)pyridine (100 mg, 0.50 mmol) and $Pd_2(dba)_3$ (46 mg, 0.05 mmol) were added, mixture was degassed again for 10 minutes, heated up to 100°C and stirred for 4 hours. Reaction mixture was diluted in EtOAc, washed with water and brine and concentrated under vacuum. Crude product was purified by reverse phase flash column chromatography (CH_3CN/MeOH/water) yielding 61 mg of di-tert-butyl 1-(5-fluoro-4-(trifluoromethyl)pyridin-2-yl)hydrazine-1,2-dicarboxylate. MS: *m/z* 396 $[M+H]^+$.

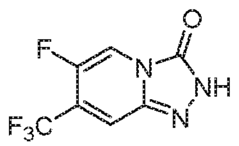
Step 2: 5-Fluoro-2-hydrazinyl-4-(trifluoromethyl)pyridine hydrochloride



To a solution of di-tert-butyl 1-(5-fluoro-4-(trifluoromethyl)pyridin-2-yl)hydrazine-1,2-dicarboxylate (222 mg, 0.56 mmol) in Et_2O (15 ml) at rt was added 1M HCl in Et_2O (11.2 ml, 11.2 mmol added in 2 batches). Reaction mixture was stirred at rt for 2 x 24 hours. Solvents were evaporated to dryness. Residue was taken back in minimum of Et_2O, precipite formed was filtered off and dried under vacuum yielding 89 mg of tert-butyl 1-(5-fluoro-4-(trifluoromethyl)pyridin-2-yl)hydrazinecarboxylate hydrochloride. Compound was dissolved in 4M HCl in dioxane (2.2 ml added in 3 batches). Reaction mixture was stirred at rt for 2 x 24 hours and finaly stirred at 50 °C for 8 hours. Solvents were evaporated under vacuum. 5-Fluoro-2-hydrazinyl-4-(trifluoromethyl)pyridine hydrochloride obtained (42 mg) was used directly in the next step.

MS: m/z 196 $[M+H]^+$.

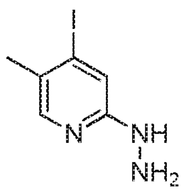
Step 3: 6-fluoro-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure D from 5-Fluoro-2-hydrazinyl-4-(trifluoromethyl)pyridine hydrochloride (42 mg, 0.21 mmol) and CDI (42 mg, 0.26 mmol) in THF (2 ml). Resulting crude compound was dissolved in 1M aqueous NaOH solution and washed twice with EtOAc. Aqueous layer was acidifed with conc. HCl and extracted with EtOAc. Organic layer was dried, concentrated under vaccum yielding 6.1 mg of pure 6-fluoro-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.
MS: m/z 222 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ: 13.07 (br s, 1H), 8.37 (d, 1H), 8.02 (d, 1H)

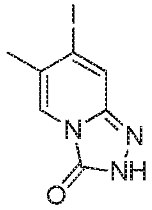
Example 36: 7-Iodo-6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 2-Hydrazinyl-4-iodo-5-methylpyridine



A mixture of 2-fluoro-4-iodo-5-methylpyridine (0.237 g, 1.0 mmol), 2-propanol (0.4 mL) and hydrazine hydrate (0.125 mL, 2.0 mmol) was heated at 80 °C for 4 hours. More hydrazine hydrate (0.05 mL, 0.8 mmol) was added and heating was continued for another seven hours. The mixture was concentrated and dried under vacuum to provide the title compound (0.17 g). ^1H NMR (DMSO-d_6) δ: 7.82 (s, 1H), 7.32 (s, 1H), 7.25 (s, 1H), 4.10 (br s, 2H), 2.16 (s, 3H).

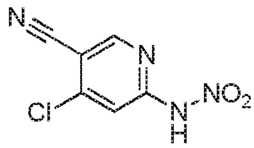
Step 2: 7-Iodo-6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



A flask was charged with 2-hydrazinyl-4-iodo-5-methylpyridine (0.17 g, 0.68 mmol), THF (5 mL) and *N,N'*-carbonyldiimidazole (0.166 g, 1.02 mmol). The mixture was stirred for one hour. 1 M HCl solution (5 mL) was added and organic solvent was evaporated under vacuum. Title compound was filtered out and dried under vacuum (0.056 g). ^{1}H NMR (DMSO-d$_6$) δ: 12.44 (br s, 1H), 7.91 (s, 1H), 7.76-7.79 (m, 1H), 2.19 (d, 3H). LC-MS *m/z* 276.0 (M+H)$^+$.

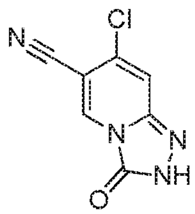
Example 37: 7-Chloro-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonitrile

Step 1: *N*-(4-Chloro-5-cyanopyridin-2-yl)nitramide



Title compound was synthesised according to General procedure A from 6-amino-4-chloronicotinonitrile (0.80 g, 5.2 mmol) in H_2SO_4 (4.5 mL) and a mixture of HNO_3 (0.44 mL, 10.5 mmol) and H_2SO_4 (0.7 mL) yielding 0.36 g of *N*-(4-chloro-5-cyanopyridin-2-yl)nitramide. LC-MS *m/z* 199.0 (M+H)$^+$.

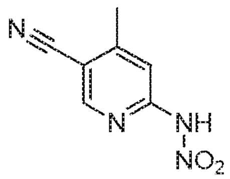
Step 2: 7-Chloro-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonitrile



Title compound was synthesised according to General procedure B from *N*-(4-chloro-5-cyanopyridin-2-yl)nitramide (0.36 g, 1.8 mmol), NH_4Cl (0.485 g, 9.1 mmol), Zn dust (0.593 g, 9.1 mmol) and triphosgene (0.807 g, 2.7 mmol) in THF (8 mL), MeOH (1.5 mL) and H_2O (2 mL). Crude material was purified by column chromatography (C18 on silica, H_2O/MeCN) yielding 0.013 g of 7-chloro-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonitrile. ^1H NMR (DMSO-d_6) δ: 12.82 (br s, 1H), 8.93 (d, 1H), 7.73 (d, 1H). LC-MS m/z 195.0 $(M+H)^+$.

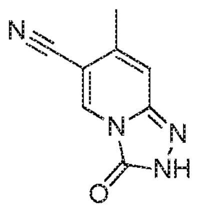
Example 38: 7-Methyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonitrile

Step 1: *N*-(5-cyano-4-methylpyridin-2-yl)nitramide



Title compound was synthesised according to General procedure A from 6-amino-4-methylnicotinonitrile (1.40 g, 10.5 mmol) in H_2SO_4 (9 mL) and a mixture of HNO_3 (0.88 mL, 21.0 mmol) and H_2SO_4 (1.5 mL) yielding 0.9 g of *N*-(5-cyano-4-methylpyridin-2-yl)nitramide. LC-MS m/z 179.0 $(M+H)^+$.

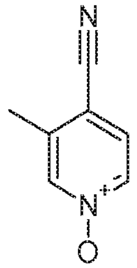
Step 2: 7-Methyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonitrile



Title compound was synthesised according to General procedure B from *N*-(5-cyano-4-methylpyridin-2-yl)nitramide (0.97 g, 5.4 mmol), NH_4Cl (1.46 g, 27.2 mmol), Zn dust (1.78 g, 27.2 mmol) and triphosgene (2.42 g, 8.2 mmol) in THF (40 mL), MeOH (10 mL) and H_2O (10 mL). Crude precipitate was dissolved in 0.5 M NaOH solution and extracted with EtOAc. The aqueous layer was acidified with conc. HCl. Title compound was filtered out, washed with water and dried under vacuum (0.177 g). ^{1}H NMR (DMSO-d_6) δ: 12.60 (br s, 1H), 8.70 (d, 1H), 7.18-7.20 (m, 1H), 2.31 (d, 3H). LC-MS *m/z* 175.1 $(M+H)^+$.

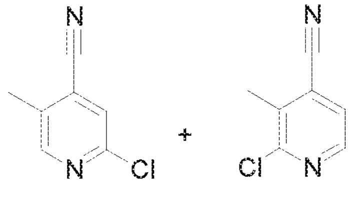
Example 39: 6-Methyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-7-carbonitrile

Step 1: 4-Cyano-3-methylpyridine 1-oxide



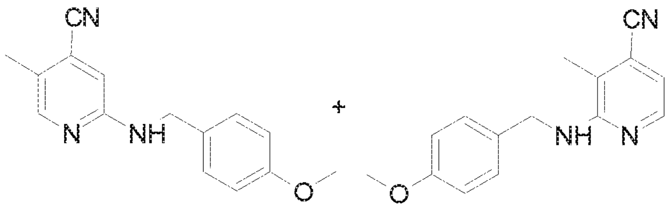
To a stirred solution of 3-methylpyridine-4-carbonitrile (2.0 g, 16.9 mmol) in dry CH_2Cl_2 (100 mL) was added m-CPBA (14.56 g, 84.4 mmol) at 0 °C. The reaction mixture was stirred at rt for 16 hours. After completion of the reaction, the reaction mixture was poured onto ice and 10% $NaHCO_3$ solution. Aqueous layer was extracted with 10% methanol in CH_2Cl_2, combined organic layers were dried over anh. Na_2SO_4 and concentrated under vacuum. The resulting material was purified by column chromatography (silica gel) to give 1.6 g of title compound. ^{1}H-NMR (DMSO-d_6) δ: 8.42 (s, 1H), 8.24 (d, 1H), 7.86 (d, 1H), 2.39 (s, 3H).

Step 2: 2-Chloro-5-methylisonicotinonitrile



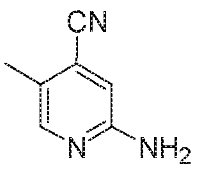
Cooled $POCl_3$ (16 mL) was added dropwise to 4-cyano-3-methylpyridine 1-oxide (1.6 g, 12 mmol) at 0 °C and the resulting reaction mass was heated at 70 °C for 16 hours. After completion of reaction, the reaction mixture was poured into ice water, neutralised with 10% $NaHCO_3$ solution and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (silica gel) to give a mixture of title compound and 2-chloro-3-methylisonicotinonitrile (1.15 g). GC-MS *m/z* 152.0 $(M+H)^+$.

Step 3: 2-((4-methoxybenzyl) amino)-5-methylisonicotinonitrile



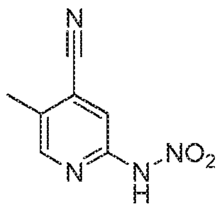
To a stirred solution of 2-chloro-5-methylisonicotinonitrile and 2-chloro-3-methylisonicotinonitrile (1.15 g, 7.6 mmol) in toluene (10 mL) was added sodium *tert*-butoxide (2.18 g, 22.7 mmol) and *p*-methoxy benzylamine 2.07 g, 15.1 mmol) at rt. After 10 minutes, BINAP (0.939 g, 1.5 mmol) and palladium acetate (0.168 g, 0.76 mmol) were added and the reaction mixture was stirred at 50 °C for 4 hours. After completion of the reaction the mixture was diluted with EtOAc, washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (silica gel) to give 0.55 g of title compound. ^{1}H-NMR (DMSO-d_6) δ: 8.07 (s, 1H), 7.30 (s, 1H), 7.25 (d, 1H), 7.23 (d, 1H), 6.88 (d, 1H), 6.86 (d, 1H), 6.81 (t, 1H), 4.38 (d, 2H), 3.72 (s, 3H), 2.22 (s, 3H).

Step 4: 2-amino-5-methylisonicotinonitrile



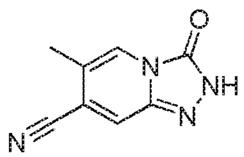
A solution of 2-chloro-5-methylisonicotinonitrile (550 mg, 2.17 mmol) in TFA (8 mL) was heated at 50 °C for 8 hours. After completion of the reaction, the mixture was poured onto ice water and neutralised with 10% $NaHCO_3$ solution. The mixture was extracted with ethyl acetate, dried over anh. Na_2SO_4 and concentrated under reduced pressure. The resulting material was purified by column chromatography (silica gel) to give 0.19 g of title compound. ^{1}H-NMR (DMSO-d_6) δ: 8.02 (s, 1H), 6.71 (s, 1H), 6.26 (s, 2H), 2.23 (s, 3H).

Step 5: *N*-(4-cyano-5-methylpyridin-2-yl)nitramide



Title compound was synthesised according to General procedure A from 2-amino-5-methylisonicotinonitrile (0.19 g, 1.4 mmol) in H_2SO_4 (1.5 mL) and a mixture of HNO_3 (0.20 mL, 2.9 mmol) and H_2SO_4 (0.3 mL) yielding 0.22 g of *N*-(4-cyano-5-methylpyridin-2-yl)nitramide. LC-MS *m/z* 179.1 $(M+H)^+$.

Step 6: 6-Methyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridine-7-carbonitrile

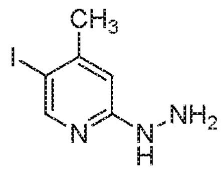


Title compound was synthesised according to General procedure B from *N*-(4-cyano-5-methylpyridin-2-yl)nitramide (0.22 g, 1.2 mmol), NH_4Cl (0.33 g, 6.2 mmol), Zn dust (0.40 g, 6.2 mmol) and triphosgene (0.55 g, 1.9 mmol) in THF (6 mL), MeOH (1.5 mL) and H_2O (1.5 mL). Crude precipitate was dissolved in 0.5 M NaOH solution and the solution was extracted with EtOAc. The aqueous layer was acidified with conc. HCl. Title compound was filtered out, washed with water and dried under vacuum (0.020 g). ^{1}H NMR

(DMSO-d_6) δ: 12.97 (s, 1H), 8.13 (d, 1H), 7.87-7.94 (m, 1H), 2.23-2.24 (m, 3H). LC-MS *m/z* 175.1 $(M+H)^+$.

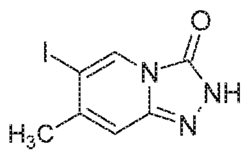
Example 40: 6-Iodo-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 2-Hydrazinyl-5-iodo-4-methylpyridine



Hydrazine monohydrate (190 mg, 3.80 mmol) was added to a solution of 2-fluoro-5-iodo-4-methylpyridine (300 mg, 1.27 mmol) in dioxane (3 mL). The reaction mixture was stirred at 80 °C for 6 hours, then at 90 °C for 7.5 hours. After completion of the reaction, water was added. The precipitate formed was filtered off, washed with water and dried under vacuum at 40°C yielding 183 mg of 2-hydrazinyl-5-iodo-4-methylpyridine. ^1H NMR (400 MHz, DMSO-d_6) δ: 8.15 (s, 1H), 7.51 (s, 1H), 6.74 (s, 1H), 4.14 (br s, 2H), 2.22 (s, 3H).

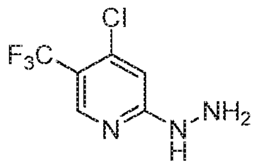
Step 2: 6-Iodo-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



N,N'-Carbonyldiimidazole (155 mg, 0.96 mmol) was added to a solution of 2-hydrazinyl-5-iodo-4-methylpyridine (183 mg, 0.74 mmol) in THF (4 mL) at rt. The reaction mixture was stirred at rt for 1 hour. After completion of the reaction, water was added. The precipitate formed was filtered off, washed with water and dried under vacuum at 40 °C yielding 6-iodo-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. More product was precipitated from the mother solution after evaporation of THF. Total yield 139 mg. ^1H NMR (400 MHz, DMSO-d_6) δ: 12.38 (br s, 1H), 8.11 (s, 1H), 7.21 (s, 1H), 2.28 (s, 3H).

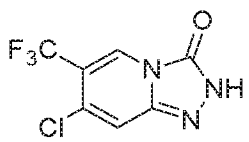
Example 41: 7-Chloro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 4-Chloro-2-hydrazinyl-5-(trifluoromethyl)pyridine



Hydrazine monohydrate (75 mg, 1.50 mmol) was added to a solution of 4-chloro-2-fluoro-5-(trifluoromethyl)pyridine (100 mg, 0.50 mmol) in dioxane (1.2 mL). The reaction mixture was stirred at rt for 2.5 hours. After completion of the reaction, water was added to the mixture and dioxane was evaporated. The precipitate formed was filtered off, washed with water and dried under vacuum at 40 °C yielding 73 mg of 4-chloro-2-hydrazinyl-5-(trifluoromethyl)pyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.64 (s, 1H), 8.28 (s, 1H), 6.91 (br s, 1H), 4.48 (s, 2H).

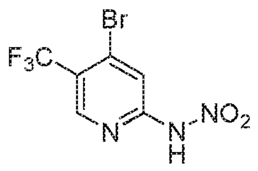
Step 2: 7-Chloro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



N,N'-Carbonyldiimidazole (72 mg, 0.45 mmol) was added to a solution of 4-chloro-2-hydrazinyl-5-(trifluoromethyl)pyridine (70 mg, 0.33 mmol) in THF (2.5 mL) at rt. The reaction mixture was stirred at rt for 2 hours. After completion of the reaction, aq. 1 M HCl solution was added. The precipitate formed was filtered off, washed with water and dried under vacuum at 40°C. The crude material was dissolved in 1 mL of 1 M NaOH solution. The water solution was washed twice with EtOAc and then acidified (pH 2-3) with 6 M HCl solution. The precipitate formed was filtered off, washed with water and dried under vacuum at 40 °C yielding 20 mg of 7-chloro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 12.84 (s, 1H), 8.31 (s, 1H), 7.76 (s, 1H).

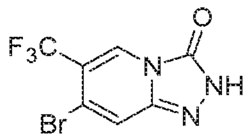
Example 42: 7-Bromo-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: N-[4-Bromo-5-(trifluoromethyl)pyridin-2-yl]nitramide



N-[4-Bromo-5-(trifluoromethyl)pyridin-2-yl]nitramide was prepared according to General procedure A with 4-bromo-5-(trifluoromethyl)pyridin-2-amine (600 mg, 1.49 mmol) in conc. H_2SO_4 (2 mL) and a mixture of 65% HNO_3 (0.29 mL, 4.23 mmol) and conc. H_2SO_4 (0.26 mL).Yield 542 mg. ^1H NMR (400 MHz, DMSO-d_6) δ: 8.75 (s, 1H), 8.24 (s, 1H).

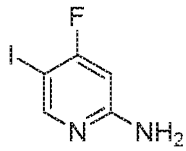
Step 2: 7-Bromo-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



7-Bromo-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one was prepared according to General procedure B using *N*-[4-bromo-5-(trifluoromethyl)pyridin-2-yl]nitramide (236 mg, 0.83 mmol), NH_4Cl (265 mg, 4.95 mmol), Zn dust (324 mg, 4.95 mmol) and triphosgene (367 mg, 1.24 mmol) in THF (9 mL), MeOH (1.7 mL) and H_2O (1.7 mL). After completion of the reaction, 1 M HCl solution was added and organic solvents were evaporated. The precipitated product was filtered off, washed with water and dried in vacuum at 40 °C yielding 60 mg of the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ: 12.81 (br s, 1H), 8.24 (s, 1H), 7.92 (s, 1H).

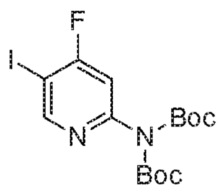
Example 43: 7-Fluoro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: 4-Fluoro-5-iodopyridin-2-amine



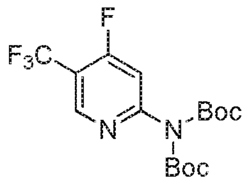
To a solution of 4-fluoropyridin-2-amine (2.5 g, 22.3 mmol) in acetonitrile (25 mL) was added TFA (0.85 mL, 11.16 mmol), NIS (5.5 g, 24.55 mmol) at 0 °C and the reaction mixture was stirred at rt for 4 hours. After completion of the reaction, the reaction mixture was diluted with EtOAc (75 mL). The organic layer was washed with water (20 mL), dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (silica gel) to get 2.2 g of 4-fluoro-5-iodopyridin-2-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.21-8.24 (d, 1H), 7.10 (s, 2H), 6.31-6.34 (d, 1H). UPLC: [M+H] = 239.1.

Step 2: DiBoc-protected 4-fluoro-5-iodopyridin-2-amine



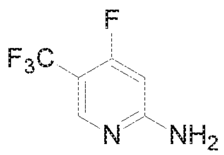
To a solution of 4-fluoro-5-iodopyridin-2-amine (2.0 g, 8.40 mmol) in THF (20 mL) was added Et_3N (3.4 mL, 25.20 mmol), di-tert-butyl dicarbonate (4.5 mL, 21.00 mmol) and the reaction mixture was stirred at 70 °C for 16 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The resulting crude material was purified by column chromatography (silica gel) to get 1.6 g of diBoc-protected 4-fluoro-5-iodopyridin-2-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.80 (d, 1H), 7.58 (d, 1H), 1.39 (s, 18H). UPLC: [M+H] = 439.0.

Step 3: DiBoc-protected 4-fluoro-5-(trifluoromethyl)pyridin-2-amine



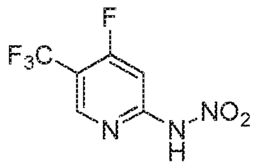
To a solution of diBoc-protected 4-fluoro-5-iodopyridin-2-amine (1.5 g, 3.42 mmol) in DMF (10 mL) was added CuI (0.98 g, 5.13 mmol), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.98 g, 5.13 mmol) and the reaction mixture was stirred at 100°C for 6 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The evaporation residue was dissolved in EtOAc (100 mL) and washed with water (25 mL), dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (silica gel) to get 800 mg of diBoc-protected 4-fluoro-5-(trifluoromethyl)pyridin-2-amine. ^1H NMR (400 MHz, DMSO-d_6) δ: 8.89 (d, 1H), 7.88 (d, 1H), 1.43 (s, 18H). LCMS: [M+H, diBoc-deprotected mass] = 108.9.

Step 4: 4-Fluoro-5-(trifluoromethyl)pyridin-2-amine



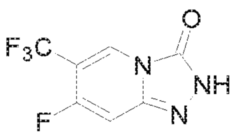
To a solution of diBoc-protected 4-fluoro-5-(trifluoromethyl)pyridin-2-amine (300 mg, 0.0789 mmol) in DCM (3 mL) was added TFA (0.9 g, 7.89 mmol) at 0 °C and the reaction mixture was stirred at rt for 12 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The crude mass was dissolved in EtOAc (10 mL), washed with $NaHCO_3$ (10%) and water, dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. The resulting crude material was triturated with n-hexane (5 mL) to get 85 mg of 4-fluoro-5-(trifluoromethyl)pyridin-2-amine. ^1H NMR (400 MHz, DMSO-d_6) δ: 8.23 (d, 1H), 7.08 (s, 2H), 6.34 (d, 1H). LCMS: [M+H] = 181.1.

Step 5: *N*-[4-Fluoro-5-(trifluoromethyl)pyridin-2-yl]nitramide



N-[4-Fluoro-5-(trifluoromethyl)pyridin-2-yl]nitramide was prepared according to General procedure A using 4-fluoro-5-(trifluoromethyl)pyridin-2-amine (100 mg, 0.56 mmol) in conc. H_2SO_4 (0.38 mL) and a mixture of 65% HNO_3 (0.066 mL, 0.96 mmol) and conc. H_2SO_4 (0.059 mL). Yield 96 mg. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.83 (d, 1H), 7.93 (d, 1H).

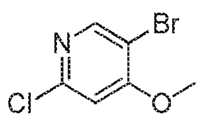
Step 6: 7-Fluoro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



7-Fluoro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one was prepared according to Example 42 Step 2 using *N*-[4-fluoro-5-(trifluoromethyl)pyridin-2-yl]nitramide (95 mg, 0.42 mmol), NH_4Cl (135 mg, 2.53 mmol), Zn dust (166 mg, 2.53 mmol) and triphosgene (188 mg, 0.63 mmol) in THF (3.7 mL), MeOH (0.75 mL) and H_2O (0.75 mL). Yield 30 mg. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 12.74 (s, 1H), 8.40 (d, 1H), 7.45 (d, 1H).

Example 44: 6-bromo-7-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

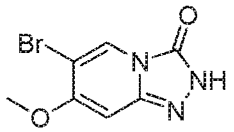
Step 1: 5-bromo-2-chloro-4-methoxypyridine



A solution of sodium methylate in methanol (0.95 ml, 0.90 mmol, 21%) was added dropwise to a flask containing 5-bromo-2,4,-dichloro-pyridine (0.75 g, 3.31 mmol) at 0 °C.

The reaction mixture was stirred at rt for 4 hours after which it was poured into ice-cold water and extracted with EtOAc. Organic phases were combined, washed with brine, dried (Na_2SO_4), filtered and evaporated to dryness yielding 0.68 g of 5-bromo-2-chloro-4-methoxypyridine. ^1H NMR (DMSO-d_6) δ: 8.43 (s, 1H), 7.32 (s, 1H), 3.99 (s, 3H).

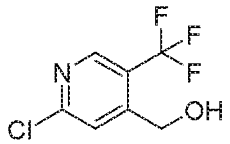
Step 2: 6-bromo-7-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



A solution of hydrogen chloride in 1,4-dioxane (4M, 0.020ml) was added to the solution of 5-bromo-2-chloro-4-methoxypyridine (0.18 g, 0.81 mmol) and methyl hydrazinecarboxylate (0.30 g, 3.34 mmol) in ethanol (5 ml). The reaction mixture was heated in microwave reactor at 160 °C for 9 hours. The mixture was cooled and evaporated to dryness. Purification of the evaporation residue by preparative reverse phase HPLC afforded 4.8 mg of 6-bromo-7-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^1H NMR (DMSO-d_6) δ: 12.24 (br s, 1H), 8.08 (s, 1H), 6.63 (s, 1H), 3.87 (s, 3H).

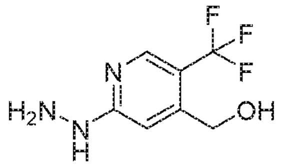
Example 45: 7-(hydroxymethyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

Step 1: (2-Chloro-5-(trifluoromethyl)pyridin-4-yl)methanol



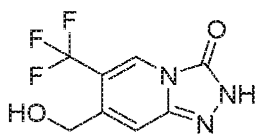
To a solution of methyl 2-chloro-5-(trifluoromethyl)isonicotinate (2.00 g, 8.35 mmol) in THF (6 ml) and MeOH (28 ml) at 0 °C was added $NaBH_4$ (0.62 g, 16.7 mmol). The resulting mixture was stirred at rt for 1 hour. H_2O was added and the organic solvents were evaporated off. The resulting mixture was extracted with EtOAc. The combined organic phases were washed with H_2O and brine, dried with Na_2SO_4, filtered and evaporated to dryness yielding 1.74 g of (2-chloro-5-(trifluoromethyl)pyridin-4-yl)methanol. ^{1}H NMR ($CDCl_3$) δ: 8.61-8.56 (m, 1H), 7.86-7.82 (m, 1H), 4.94 (s, 2H), 2.24 (br s, 1H).

Step 2: (2-Hydrazinyl-5-(trifluoromethyl)pyridin-4-yl)methanol

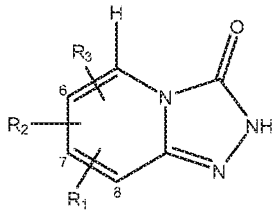


The title compound was synthesised according to general procedure C from (2-chloro-5-(trifluoromethyl)pyridin-4-yl)methanol (1.00 g, 4.73 mmol) and hydrazine hydrate (2.29 ml, 47.3 mmol) in IPA (10 ml) in a sealed tube at 110 °C with 3 hours reaction time yielding 0.75 g of (2-hydrazinyl-5-(trifluoromethyl)pyridin-4-yl)methanol. ^{1}H NMR (DMSO-d6) δ: 8.26 (br s, 1H), 8.15 (s, 1H), 7.05 (br s, 1H), 5.53 (t, 1H), 4.56-4.50 (m, 2H) 4.33 (br s, 2H).

Step 3: 7-(hydroxymethyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



The title compound was synthesised according to general procedure D from (2-hydrazinyl-5-(trifluoromethyl)pyridin-4-yl)methanol (0.73 g, 3.52 mmol) and CDI (0.69 g, 4.23 mmol) in THF (15 ml) yielding, after aqueous workup, 0.55 g of 7-(hydroxymethyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one. ^{1}H NMR (DMSO-d6) δ: 12.65 (br s, 1H), 8.18-8.13 (m, 1H), 7.34-7.27 (m, 1H), 5.74 (t, 1H), 4.50 (d, 2H).



No.	R_1	R_2	R_3	No.	R_1	R_2	R_3
1	8-F	7-H	6-Cl	24	8-H	7-Br	6-F
2	8-H	7-Cl	6-Br	25	8-H	7-CD_3	6-CF_3
3	8-H	7-Cl	6-Cl	26	8-H	7-CHF_2	6-CF_3
4	8-H	7-F	6-Br	27	8-Cl	7-H	6-Br
5	8-H	7-F	6-Cl	28	8-H	7-CH_3	6-F
6	8-H	7-Br	6-Cl	29	8-H	7-CF_3	6-CF_3
7	8-H	7-H	6-CHF_2	30	8-H	7-CH_3	6-CF_3
8	8-H	6-Cl	7-CF_3	31	8-H	7-cyclopropyl	6-Br
9	8-H	6-Br	7-CF_3	32	8-H	7-cyclopropyl	6-Cl
10	8-H	7-Br	6-Br	33	8-H	6-H	7-CHF_2
11	8-H	7- CHF_2	6-Br	34	8-H	7-Cl	6-F
12	8-H	7-Cl	6-CH_3	35	8-H	7-CF_3	6-F
13	8-H	7-CN	6-Br	36	8-H	7-I	6-CH_3
14	8-H	7-CH_3	6-CH_3	37	8-H	6-CN	7-Cl
15	8-H	7-CN	6-Cl	38	8-H	6-CN	7-CH_3
16	8-F	7-CH_3	6-Cl	39	8-H	7-CN	6-CH_3
17	8-F	7-Cl	6-Br	40	8-H	6-I	7-CH_3
18	8-H	7-F	6-CH_3	41	8-H	7-Cl	6-CF_3
19	8-H	7-Br	6-CH_3	42	8-H	7-Br	6-CF_3
20	8-H	7-CH_3	6-CHF_2	43	8-H	7-F	6-CF_3
21	8-F	7-Cl	6-Cl	44	8-H	7-OCH_3	6-Br
22	8-H	7-F	6-CHF_2	45	8-H	7-CH_2OH	6-CF_3
23	8-H	7-F	6-F				

Preparation of pharmaceutical compositions

The following formulation examples illustrate representative pharmaceutical compositions of this invention. The present invention, however, is not limited to the following pharmaceutical compositions.

A) Solid oral dosage forms

I., Tablets

Active ingredient(s)	0.01 – 90%
Filler	1 – 99.9%
Binder	0 – 20%
Disintegrant	0 – 20%
Lubricant	0 – 10%
Other specific excipient(s)	0 – 50%

II., Orodispersible films

Active ingredient(s)	0.01 – 90%
Film forming agent	1 – 99.9%
Plasticizer	0 – 40%
Other specific excipient(s)	0 – 50%

B) Liquid oral dosage forms

III., Oral suspensions

Active ingredient(s)	0.01 – 50%
Liquid vehicle	10 – 99.9%
Wetting agent	0 – 50%
Thickener	0 – 50%
Buffering agent	quantum satis
Osmotic agent	0 – 50%
Preservatives	quantum satis

IV., Syrups

Active ingredient(s)	0.01 – 50%
Solvent	10 – 99.9%
Sugar component	1 – 20%
Flavouring agents	0 – 10%

C) Parenteral dosage forms

V., Intravenous injections

Active ingredient(s)	0.01 – 50%
Solvent	10 – 99.9%
Co-solvent	0 – 99.9%
Osmotic agent	0 – 50%
Buffering agent	quantum satis

D) Other dosage forms

VI., Suppositories

Active ingredient(s)	0.01 – 50%
Suppository base	1 – 99.9%
Surface-active agents	0 – 20%
Lubricants	0 – 20%
Preservatives	quantum satis

VII., Eye drops

Active ingredient(s)	0.01 – 50%
Water	0 – 99.9%
Solvent	0 – 99.9%
Osmotic agent	0 – 20%
Viscosity enhancer	0 – 20%
Buffering agent	quantum satis
Preservatives	quantum satis

As already mentioned hereinbefore, the compounds of formula (I) show valuable pharmacological properties, namely they exhibit DAAO inhibiting activity and possess enhanced brain permeability. Said properties are demonstrated with the pharmacological tests presented below.

BIOLOGICAL ACTIVITY

<u>Assessment of DAAO enzyme inhibition, in vitro</u>

The DAAO inhibiting activity of compounds was determined by using D-kynurenine as substrate for DAAO. DAAO transforms D-kynurenine into D-kynurenic acid and production of the latter can be detected by fluorescence spectroscopy. The changes in fluorescence were monitored in a Novostar (BMG) fluorescence plate reader (excitation/emission wavelength: 344/405 nm).

Recombinant human DAAO enzyme was supplied by Novoprotein (Summit, NJ, USA), D-kynurenine was supplied by Sigma-Aldrich.

On the day of the assay compounds were serially diluted in DMSO. First, 2 µl of diluted compounds were added to the wells of a white 96 well plate (Tomtec), then 3 µl of assay buffer (40 mM Tris, pH=8.3) was added. In the following step 85 µl of a mixture of DAAO, FAD and BSA in assay buffer was added to the wells. The final concentrations were the followings: DAAO 150 ng/100 µl, FAD 20 µM and BSA 0.08 mg/ml. Then the plate was incubated in 37 °C for 15 minutes to reach equilibrium. After this 10 µl of 10 mM D-kynurenine in assay buffer was added to the wells. The plate was incubated at 37 °C for 15 minutes again. Finally, the change in fluorescence was determined for 15 minutes at 37 °C in a Novostar plate reader. The slope of change in fluorescence was determined by the software of Novostar reader and was used for evaluation of DAAO activity.

Concentration-response relationships for compounds were determined from 5-7 concentration points prepared by threefold serial dilutions establishing IC_{50} values, concentration of compounds required to display 50% inhibition of DAAO activity in the presence of 1 mM D-kynurenine. Data are presented in Table 1

Table 1. IC_{50} values (in nM) for inhibiting the human DAAO enzyme by the test compounds.

IUPAC name	Mean IC_{50} (nM)
6-Bromo-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one	210
7-Bromo-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one	220
7-Chloro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one	221
6-Chloro-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one	281
6-Bromo-7-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one	314
7-Bromo-6-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one	367
6,7-Dichloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one	394
7-Bromo-6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one	604
7-Chloro-6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one	616
6,7-Dibromo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one	640
7-(Methyl-*d*$_3$)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one	712
7-Methyl-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one	800

Determination of drug penetration in Caco-2 assay

Penetration of test compounds through Caco-2 monolayers (Hellinger, É. et al. *Eur. J. Pharm. Sci., 41* (2010) 96) was investigated at a nominal concentration of 1 μM in both inward apical (A) to basolateral (B) and outward (B to A) directions, and apparent permeability (P_{app}) and permeability directional ratio (PDR= $P_{appB\ to\ A}/P_{appA\ to\ B}$) were calculated.

Caco-2 cells were seeded at a density of ~ 500,000 cells/1.12 cm^2 on basement membrane matrix covered Transwell^R polycarbonate filters (0.45 μm pore size; 1.12 cm^2 surface area; Costar). The cultures were grown at 37 °C in an atmosphere of 5% CO_2 and 95% relative humidity and used for permeability assays on days between 19-21.

The test compound dosing solution was added to the donor side of individual Transwells and transport buffer without test compound was added to the receiver side. The 12-well plate was placed in a shaking water bath (120-140 rpm) with saturating humidity at 37°C. The plates were incubated up to 40 minutes. The concentration of the test compound present in the donor and receiver side was analysed using HPLC-UV.

Permeability screening was performed under iso-pH condition (pH 7.4_A-7.4_B).

The apparent permeability (P_{app}) of the compounds across the cell monolayers is calculated using the following equation:

$$P_{app} = \left[\frac{Vr}{C_0}\right] \times \left[\frac{1}{A}\right] \times \left(\frac{dC}{dt}\right)$$

Where P_{app} = apparent permeability in cm/sec, Vr is the volume of medium in the receiver chamber, A to B Vr = 1.5 mL, B to A Vr = 0.5 mL; C_0 is the initial concentration of the test drug in the donor chamber, A = 1.12 cm^2 is the surface area of cell monolayer, dC/dt is the linear slope of the drug concentration in the receiver chamber with time.

Flux through the monolayer was linear with time (dC/dt is constant).

The permeability directional ratio (PDR) for B to A (basolateral to apical) and A to B (apical to basolateral) transport is defined by the following equation:

$$PDR = \frac{P_{app_{B\to A}}}{P_{app_{A\to B}}}$$

Where $P_{app\ B\ to\ A}$ and $P_{app\ A\ to\ B}$ represent the apparent permeability of test compound from the basal to apical, and apical to basal side of the cellular monolayer, respectively. Data are presented in Table 2.

Characterization of the pharmacokinetic profile in rat plasma and brain samples

Pharmacokinetics of compounds was studied in adult Crl:WI(Han) rats (250-300 g) purchased from Charles River Laboratories. The test items were suspended in 5% Tween80 in water and dosed orally by gavage at 10 mg/kg (dose volume 2.5 ml/kg). Blood samples of 0.5-1 ml (to yield at least 150 µl of plasma) were collected at time points 1, 2 and 4 hours by cardiac puncture under carbon dioxide anesthesia into pre-cooled K_2EDTA polypropylene tubes and kept cooled until the separation of plasma by centrifugation. Brain tissue samples were collected after the collection of blood and flushed with ice cold saline. The tissue samples were thereafter frozen on dry ice and stored at -80 °C.

Liquid chromatography-tandem mass spectrometric (UHPLC-MS/MS) methods were used for the determination of the compounds in rat plasma and brain tissue. The tissue samples were weighed, homogenized with cold phosphate buffer pH 7.2 (1:4, w/w), and the homogenates were stored at -70 °C prior to analysis. The stock solutions of compounds were prepared in acetonitrile and diluted with distilled water:acetonitrile mixture (50:50) to obtain the series of concentrations as working standards. The calibration standards were prepared by spiking the working standards into blank plasma or tissue homogenates (1:9 v/v). Low, medium and high quality control samples were prepared in the same fashion. The calibration standards and the quality controls were stored at -70 °C prior to analysis. Thawed plasma and tissue homogenate samples, calibration standards, quality controls and analyte-free blank samples were extracted by pipetting 50 µl of sample and 2.5 ml of mixture of ethylacetate:hexane (50:50, v/v) in glass vials, followed by vortexing for 3 minutes and centrifugation for 7 minutes (4400 rpm, 10 °C). After evaporation and reconstitution of the organic extract with mobile phase, the samples were analysed using reversed-phase chromatography followed by mass spectrometry with electrospray ionization and selected ion monitoring.

The results of the characterization of the pharmacokinetic profile in rat plasma and brain samples are shown in Table 2. The results show that the compounds of formula (I) possess enhanced brain permeability.

Table 2. In vitro penetration properties and rat pharmacokinetic data after single oral dosing with 10 mg/kg of the compound.

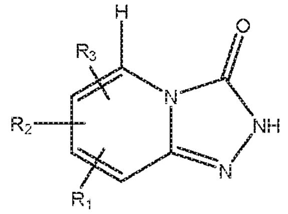
Compound	Penetration[a] $Papp_{in}$/PDR[b] (10^{-6} cm/s)	C_{max} (ng/mL; plasma)	C_{max} (ng/g; brain)	AUC_{last} (ng/mL*h; plasma)	AUC_{last} (ng/g*h; brain)	Brain/ plasma (AUC_{last} ratio)
Example 2	94/0.76	2070	1270	3940	2410	0.61
Example 4	92/0.79	7140	4340	8380	5140	0.61
Example 30	83/0.68	4550	5160	9480	10800	1.1
Example 41	53/0.70	2890	1370	4780	2490	0.52

[a]Penetration of test compounds through Caco-2 cell monolayers

[b] Permeability Directional Ratio (PDR=$Papp_{out}$/$Papp_{in}$)

CLAIMS

1. A compound of formula (I),



(I)

wherein

R_1 and R_2 are independently H, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxy or cyano;

R_3 is fluoro, chloro, bromo, C_{1-6}alkyl, difluoromethyl or trifluoromethyl;

or a pharmaceutically acceptable ester, salt, hydrate or solvate thereof;

with the provisos that

a) when R_3 is chloro, bromo or C_{1-6}alkyl, R_1 and R_2 are not simultaneously H;

b) the compound is not 6-bromo-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-chloro-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 7-bromo-8-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 7-bromo-8-iodo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-bromo-7-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6,8-dichloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one or 6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.

2. A compound according to claim 1, wherein

R_1 and R_2 are independently H, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxy or cyano;

R_3 is fluoro, chloro, bromo, C_{1-6}alkyl, difluoromethyl or trifluoromethyl;

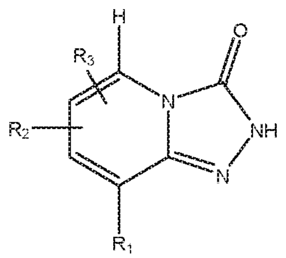
with the provisos that

a) when R_3 is fluoro, chloro, bromo, C_{1-6}alkyl or trifluoromethyl, R_1 and R_2 are not simultaneously H;

b) the compound is not 8-bromo-7-iodo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-chloro-7-iodo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-bromo-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-bromo-8-methyl-[1,2,4]triazolo[4,3-

a]pyridin-3(2H)-one, 6-chloro-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-chloro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-bromo-6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-bromo-7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 6-bromo-8-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 7-bromo-8-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 7-bromo-8-iodo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one, 8-bromo-7-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one or 6,8-dichloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.

3. A compound according any one of claims 1 or 2, wherein the compound is a compound of formula (III),



(III)

wherein

R_1 and R_2 are independently H, halogen, $C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkyl, hydroxy$C_{1\text{-}6}$alkyl, $C_{3\text{-}5}$cycloalkyl, $C_{3\text{-}5}$cycloalkyl$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy or cyano;
R_3 is fluoro, chloro, bromo, $C_{1\text{-}6}$alkyl, difluoromethyl or trifluoromethyl.

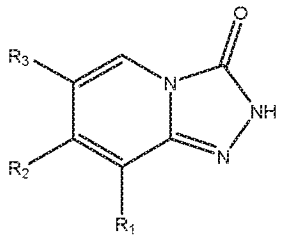
4. A compound according any one of claims 1 or 2, wherein
R_1 and R_2 are independently H, halogen, methyl, trifluoromethyl, hydroxymethyl, cyclopropyl, methoxy or cyano;
R_3 is fluoro, chloro, bromo, methyl, difluoromethyl or trifluoromethyl.

5. A compound according to any one of claims 1 or 2, wherein
R_1 and R_2 are independently H, halogen, halo$C_{1\text{-}6}$alkyl, hydroxy$C_{1\text{-}6}$alkyl or cyano;
R_3 is fluoro, chloro, bromo, $C_{1\text{-}6}$alkyl or trifluoromethyl.

6. A compound according to claim 5, wherein
R_1 and R_2 are independently H, halogen, halo$C_{1\text{-}6}$alkyl or hydroxy$C_{1\text{-}6}$alkyl;
R_3 is fluoro, chloro, bromo, $C_{1\text{-}6}$alkyl or trifluoromethyl.

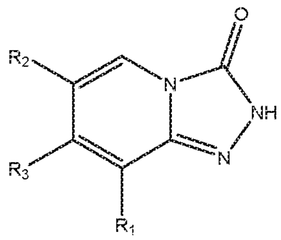
7. A compound according to claim 6, wherein
R_1 and R_2 are independently H, halogen or haloC_{1-6}alkyl;
R_3 is chloro, bromo or C_{1-6}alkyl.

8. A compound according to any one of claims 1 or 2, wherein the compound is a compound of formula (IV),



(IV)

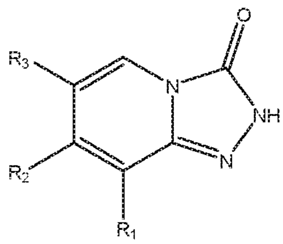
wherein
R_1 is H or halogen;
R_2 is H, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl or cyano;
R_3 is fluoro, chloro, bromo, C_{1-6}alkyl, difluoromethyl or trifluoromethyl;
or a compound of formula (V),



(V)

wherein
R_1 is H;
R_2 is halogen or cyano;
R_3 is chloro or C_{1-6}alkyl.

9. A compound according to claim 8, wherein the compound is a compound of formula (IV),



(IV)

wherein

R_1 is H or halogen;

R_2 is H, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl or hydroxyC_{1-6}alkyl;

R_3 is fluoro, chloro, bromo, C_{1-6}alkyl, difluoromethyl or trifluoromethyl.

10. A compound according to claim 9, wherein

R_1 is H;

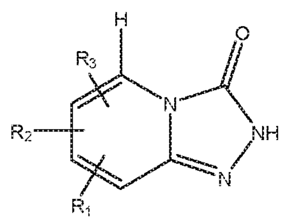
R_2 is halogen or C_{1-6}alkyl;

R_3 is fluoro, chloro, bromo or trifluoromethyl.

11. A compound according to claim 1, selected from the group of:

6-Bromo-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one;
7-Bromo-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one;
7-Chloro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one;
6-Chloro-7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one;
6-Bromo-7-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one;
7-Bromo-6-chloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one;
6,7-Dichloro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one;
7-Bromo-6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one;
7-Chloro-6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one;
6,7-Dibromo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one;
7-(Methyl-d3)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one;
7-Methyl-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one;
or a pharmaceutically acceptable ester, salt, hydrate or solvate thereof.

12. A compound of formula (II),



(II)

wherein

R_1 and R_2 are independently H, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxy or cyano;

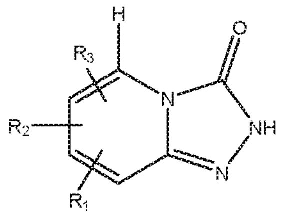
R_3 is fluoro, chloro, bromo, C_{1-6}alkyl, difluoromethyl, trifluoromethyl or cyano;

or a pharmaceutically acceptable ester, salt, hydrate or solvate thereof; for use in the treatment or prevention of a disease associated with D-amino acid oxidase.

13. A compound according to claim 12, wherein the disease is schizophrenia, schizophreniform disorder, schizoaffective disorder or another psychotic disorders, a cognitive disorder, an anxiety disorder, a mood disorder, posttraumatic stress disorder, an eating disorder, addiction, a sleep disorder, a disorder usually first diagnosed in infancy, childhood or adolescence, pain, a neurodegenerative disorder, a motor defective syndrome or another movement disorder.

14. A compound according to claim 13, wherein the disease is schizophrenia, schizophreniform disorder, schizoaffective disorder, a cognitive disorder or pain.

15. Use of a compound of formula (II),



(II)

wherein

R_1 and R_2 are independently H, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxy or cyano;

R_3 is fluoro, chloro, bromo, C_{1-6}alkyl, difluoromethyl, trifluoromethyl or cyano;

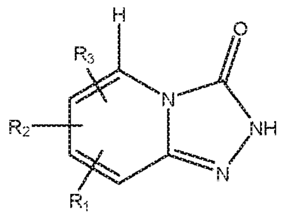
or a pharmaceutically acceptable ester, salt, hydrate or solvate thereof; for the manufacture of a medicament for the treatment or prevention of a disease associated with D-amino acid oxidase.

16. Use according to claim 15, wherein the disease is schizophrenia, schizophreniform disorder, schizoaffective disorder or another psychotic disorder, a cognitive disorder, an anxiety disorder, a mood disorder, posttraumatic stress disorder, an eating disorder, addiction, a sleep disorder, a disorder usually first diagnosed in infancy, childhood or adolescence, pain, a

neurodegenerative disorder, a motor defective syndrome or another movement disorder.

17. Use according to claim 16, wherein the disease is schizophrenia, schizophreniform disorder, schizoaffective disorder, a cognitive disorder or pain.

18. A method for the treatment or prevention of a disease associated with D-amino acid oxidase comprising administering to a mammal in need of such treatment or prevention an effective amount of at least one compound of formula (II),



(II)

wherein

R_1 and R_2 are independently H, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxy or cyano;

R_3 is fluoro, chloro, bromo, C_{1-6}alkyl, difluoromethyl, trifluoromethyl or cyano;

or a pharmaceutically acceptable ester, salt, hydrate or solvate thereof.

19. A method according to claim 18, wherein the disease is schizophrenia, schizophreniform disorder, schizoaffective disorder or another psychotic disorder, a cognitive disorder, an anxiety disorder, a mood disorder, posttraumatic stress disorder, an eating disorder, addiction, a sleep disorder, a disorder usually first diagnosed in infancy, childhood or adolescence, pain, a neurodegenerative disorder, a motor defective syndrome or another movement disorder.

20. A method according to claim 19, wherein the disease is schizophrenia, schizophreniform disorder, schizoaffective disorder, a cognitive disorder or pain.

21. A pharmaceutical composition comprising as active ingredient at least one compound according to any one of claims 1 to 11 and at least one pharmaceutically acceptable excipient.

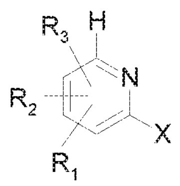
22. A pharmaceutical composition according to claim 21, wherein the composition further comprises one or more other active ingredients.

23. A pharmaceutical composition according to claim 22, wherein the other active ingredient(s) are selected from antidepressants, antipsychotics, anxiolytics, anticonvulsants, mood stabilizers, $5HT_{1B}$ ligands, mGluR2 agonists, alpha 7 nicotinic agonists, chemokine receptor CCR1 inhibitors, delta opioid agonists and compounds used in the treatment of Alzheimer's disease, Parkinson's disease, migraine, stroke, neuropathic pain or nociceptive pain.

24. Process for preparing the compounds of formula (I) according to claim 1 characterized by

Route A

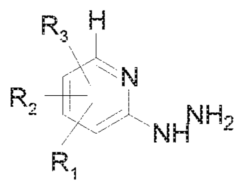
step 1) reacting a 2-halopyridine of formula (VI)



(VI)

- wherein X is F, Cl, Br, I, and R_1, R_2 and R_3 are described above for compound of formula (I) with hydrazine hydrate, then

step 2) the so obtained 2-hydrazinopyridine (VII) is reacted

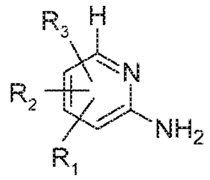


(VII)

with carbonyl diimidazole to obtain derivative of formula (I)

Route B

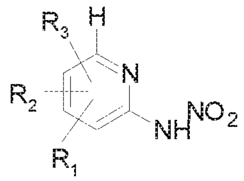
step 1) reacting a 2-aminopyridine of formula (VIII)



(VIII)

- wherein R_1, R_2 and R_3 are described above for compound of formula (I) with nitric acid in the presence of sulphuric acid, then

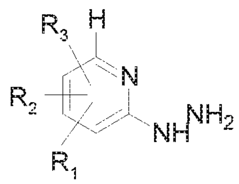
step 2) the so obtained N-nitro-pyridine-2-amine (IX) is reacted



(IX)

- wherein R_1, R_2 and R_3 are described above for compound of formula (I) with zinc/ammonium chloride, then

step 3) the so obtained 2-hydrazinopyridine (VII) is reacted

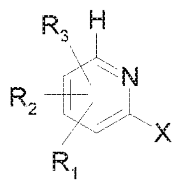


(VII)

- wherein R_1, R_2 and R_3 are described above for compound of formula (I) with triphosgene to obtain derivative of formula (I).

Route C

step 1) reacting a 2-halopyridine of formula (VI)

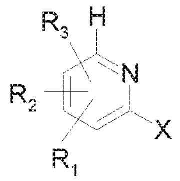


(VI)

- wherein X is Cl, Br, I, and R_1, R_2 and R_3 are described above for compound of formula (I) with methyl hydrazinocarboxylate to obtain derivative of formula (I).

Route D

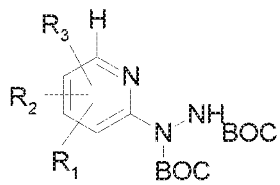
step 1) reacting a 2-halopyridine of formula (VI)



(VI)

- wherein X is Cl, Br, I, and R_1, R_2 and R_3 are described above for compound of formula (I) with tris(dibenzylideneacetone)dipalladium(0) in the presence of 1,1′-bis(diphenylphosphino)ferrocene and cesium carbonate then

step 2) the so obtained di-tert-butyl 1-(pyridin-2-yl)hydrazine-1,2-dicarboxylate (X) is reacted



(X)

- wherein R_1, R_2 and R_3 are described above for compound of formula (I) with HCl/dioxane to obtain 2-hydrazinopyridine of formula(VII). This compound is reacted further as described in Route A above, starting from Route A / step 2.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/056660

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61P25/00 A61K31/44
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

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 practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 106 749 045 A (UNIV SHANGHAI JIAOTONG) 31 May 2017 (2017-05-31) cited in the application paragraphs [0002], [0003]; claims; examples -----	1-24
A	WO 2013/004995 A1 (TAKEDA PHARMACEUTICAL [JP]; COCKCROFT XIAO-LING FAN [GB]; FARNABY WILL) 10 January 2013 (2013-01-10) cited in the application page 1, line 4 - page 1, line 7; claims; examples -----	1-24

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 October 2018	12/11/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schmid, Arnold

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/004996 A1 (TAKEDA PHARMACEUTICAL [JP]; FARNABY WILLIAM [GB]; FIELDHOUSE CHARLOTTE) 10 January 2013 (2013-01-10) cited in the application page 1, line 4 - page 1, line 7; claims; tables -----	1-24
A	WO 2010/005528 A2 (IRONWOOD PHARMACEUTICALS INC [US]; LUDRIGAN REGINA [US]; JEFFREY JOHN) 14 January 2010 (2010-01-14) cited in the application page 1, line 10 - page 1, line 15; claims; examples -----	1-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2018/056660

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