

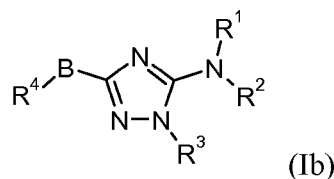
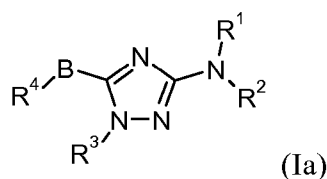


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(54) **Title:** TRIAZOLO COMPOUNDS AS PDE10 INHIBITORS

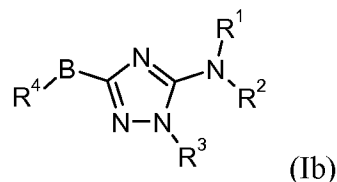
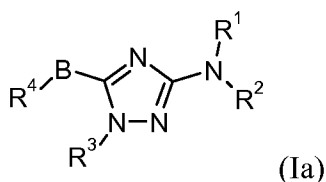


(57) **Abstract:** The present invention provides compounds of formula (Ia) and (Ib) wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as defined in the description and in the claims, as well as physiologically acceptable salts thereof. These compounds inhibit PDE10A and can be used as medicaments.

## TRIAZOLO COMPOUNDS AS PDE10 INHIBITORS

## FIELD OF INVENTION

The present invention relates to compounds of formula (Ia) and (Ib)



wherein

5 B is C<sub>1</sub>-C<sub>4</sub> -alkylene, C<sub>2</sub>-C<sub>4</sub> -alkenylene, C<sub>2</sub>-C<sub>4</sub> -alkynylene, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl,

R<sup>1</sup> and R<sup>2</sup>, are independently selected from hydrogen, C<sub>1</sub>-C<sub>7</sub>-alkyl optionally substituted by C<sub>3</sub>-C<sub>5</sub>-cycloalkyl; C<sub>1</sub>-C<sub>7</sub>-hydroxyalkyl, C<sub>1</sub>-C<sub>7</sub>-alkoxyalkyl, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl, R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom to which they are attached, form an azaspiro-cycloalkyl, a bicyclic ring or heterocycloalkyl which can be substituted by 1 to 3 substituents  
 10 independently selected from the group consisting of halogen, C<sub>1</sub>-C<sub>7</sub> -alkyl optionally substituted by C<sub>1</sub>-C<sub>7</sub> alkoxy; C<sub>1</sub>-C<sub>7</sub>-hydroxyalkyl, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> -haloalkyl, hydroxyl, -NR<sup>9</sup>R<sup>10</sup> and oxo;

R<sup>3</sup> is selected from hydrogen, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl, C<sub>1</sub>-C<sub>7</sub>-alkoxyalkyl, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, heterocycloalkyl, -(CH<sub>2</sub>)<sub>0,1,2</sub> - aryl optionally substituted by C<sub>1</sub>-C<sub>7</sub> alkoxy and C<sub>1</sub>-C<sub>7</sub>-alkyl op-  
 15 tionally substituted by C<sub>3</sub>-C<sub>5</sub>-cycloalkyl;

R<sup>4</sup> is selected from heteroaryl optionally substituted by 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>7</sub> -alkyl, C<sub>1</sub>-C<sub>7</sub> -hydroxyalkyl, C<sub>1</sub>-C<sub>7</sub> -haloalkoxy, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl, cyano, amino, nitro, -O-R<sup>6</sup>-C(O)-R<sup>7</sup>, -SO<sub>2</sub>R<sup>8</sup>, C<sub>1</sub>-C<sub>2</sub>-alkoxy optionally substituted by halogen, C<sub>1</sub>-C<sub>2</sub>-alkoxy, heterocycloalkyl,

20 R<sup>6</sup> and R<sup>8</sup> are selected from C<sub>1</sub>-C<sub>7</sub> -alkyl,

R<sup>7</sup> is selected from heterocycloalkyl,

R<sup>9</sup> and R<sup>10</sup> are independently selected from hydrogen, C<sub>1</sub>-C<sub>7</sub>-alkyl, -C(O)-O- C<sub>1</sub>-C<sub>7</sub>-alkyl.

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

#### SUMMARY OF THE INVENTION

5 Schizophrenia is a progressive and devastating neurological disease characterized by episodic positive symptoms such as delusions, hallucinations, thought disorders and psychosis and persistent negative symptoms such as flattened affect, impaired attention and social withdrawal, and cognitive impairments (Lewis DA and Lieberman JA, *Neuron*, , 28:325-33, 2000). For decades research has focused on the "dopaminergic hyperactivity" hypothesis which has led to therapeutic interventions involving blockade of the dopaminergic system (Vandenberg RJ and Aubrey KR., *Exp. Opin. Ther. Targets*, 5(4): 507-518, 2001; Nakazato A and Okuyama S, et al., *Exp. Opin. Ther. Patents*, 10(1): 75-98, 2000). This pharmacological approach, besides ameliorating positive symptoms in schizophrenic patients, poorly addresses negative and cognitive symptoms which are the best predictors of functional outcome (Sharma T., *Br.J. Psychiatry*, 15 174(suppl. 28): 44-51, 1999). In addition, current antipsychotic treatment is associated with adverse effects like weight gain, extrapyramidal symptoms or effects on glucose and lipid metabolism, related to their unspecific pharmacology.

In conclusion there is still a need for developing new antipsychotics with improved efficacy and safety profile. A complementary model of schizophrenia was proposed in the mid-20 1960' based upon the psychotomimetic action caused by the blockade of the glutamate system by compounds like phencyclidine (PCP) and related agents (ketamine) which are non-competitive NMDA receptor antagonists. Interestingly, in healthy volunteers PCP-induced psychotomimetic action incorporates positive and negative symptoms as well as cognitive dysfunction, thus closely resembling schizophrenia in patients (Javitt DC et al., *Biol. Psychiatry*, 45: 25 668-679, 1999).

Cyclic nucleotides cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are ubiquitous second messengers responsible for mediating the biological response of a variety of extracellular signals, including neurotransmitters, light and hormones. cAMP and cGMP regulate a variety of intracellular processes particularly in neurons of 30 the central nervous system by activating cAMP- and cGMP-dependent kinases which then phosphorylate proteins involved in the regulation of synaptic transmission, neuronal differentiation and survival.

A crucial mechanism for controlling intracellular cyclic nucleotide levels and therefore cyclic nucleotide signaling is via hydrolysis of the 3',5'-phosphodiester bond by phosphodiesterases. Phosphodiesterases (PDEs) are a family of widely expressed enzymes encoded by 21 dif- 35

ferent genes in humans, with each gene encoding several splice variants (Beavo, J., *Physiol. Rev.* 1995, 75, 725–748; Conti, M., Jin, S.L., *Prog. Nucleic Acid Res. Mol. Biol.* 1999, 63, 1–38; Soderling, S.H., Beavo, J.A., *Curr. Opin. Cell Biol.* 2000, 12, 174–179, Manallack, D.T. et al. *J. Med. Chem.* 2005, 48 (10), 3449-3462).

5           The PDE families differ in their substrate specificity for the cyclic nucleotides, their mechanism of regulation and their sensitivity to inhibitors. Moreover, they are differentially localized in the organism, among the cells of an organ and even within the cells. These differences lead to a differentiated involvement of the PDE families in the various physiological functions.

10           PDE10A is a dual substrate PDE encoded by a single gene as reported in 1999 by three separate research groups (Fujishige K., et al., *Eur J Biochem* (1999) 266(3):1118-1127, Soderling S.H., et al., *Proc Natl Acad Sci USA* (1999) 96(12):7071-7076, Loughney K., et al., *Gene* (1999) 234(1):109-117). PDE10A is unique from other members of the multigene family with respect to amino acid sequence (779 aa), tissue-specific pattern of expression, affinity for cAMP and cGMP and the effect on PDE activity by specific and general inhibitors.

15           PDE10A has one of the most restricted distribution of any PDE family being primarily expressed in the brain particularly in the nucleus accumbens and the caudate putamen. Additionally thalamus, olfactory bulb, hippocampus and frontal cortex show moderate levels of PDE10A expression. All these brain areas have been suggested to be involved in the pathophysiology of schizophrenia and psychosis, suggesting a central role of PDE10A in this devastating mental illness. Outside the central nervous system PDE10A transcript expression is also observed in peripheral tissues like thyroid gland, pituitary gland, insulin secreting pancreatic cells and testes (Fujishige, K. et al., *J. Biol. Chem.* 1999, 274, 18438–18445, Sweet, L. (2005) WO 2005/012485). On the other hand expression of PDE10A protein has been observed only in enteric ganglia, in testis and epididymal sperm (Coskran T.M, et al., *J. Histochem. Cytochem.* 2006, 25 54 (11), 1205-1213).

30           In the striatum both mRNA and protein are expressed only in the GABA ( - aminobutyric acid)-containing medium spiny projection neurons making it an intriguing target for the treatment of diseases of the central nervous system (Fujishige, K. et al., *Eur. J. Biochem.* 1999, 266, 1118-1127; Seeger, T.F. et al., *Brain Res.* 2003, 985, 113-126). The striatal medium spiny neurons are the principal input site and first site for information integration in the basal ganglia circuit of the mammalian brain. The basal ganglia are a series of interconnected subcortical nuclei that integrate widespread cortical input with dopaminergic signaling to plan and execute relevant motor and cognitive patterns while suppressing unwanted or irrelevant patterns (Graybiel, A.M. *Curr. Biol.* 2000, 10, R509–R511 (2000)).

Papaverine, a relatively specific PDE10A inhibitor, and PDE10A-knockout mice have been used to explore the physiology of this enzyme and the possible therapeutic utility of PDE10A inhibition. Inhibition of this enzyme pharmacologically or through gene disruption causes a reduction in activity and a reduced response to psychomotor stimulants. Inhibition also  
5 reduces the conditioned avoidance response, a behavioural response that is predictive of clinical antipsychotic activity (Siuciak, J.A.; et al., *Neuropharmacology* 2006, 51 (2), 386-396; Siuciak, J.A.; et al., *Neuropharmacology* 2006, 51 (2), 374-385).

In addition PDE10A inhibition bears the potential to improve the negative and cognitive symptoms associated to schizophrenia. Indeed papaverine have been shown to attenuate the defi-  
10 cits in the extra-dimensional shift learning induced in rats by sub-chronic treatment with PCP, an animal paradigm of NMDA receptor hypofunction (Rodefer, J.S., et al., *Eur. J. Neuroscience* 2005, 2, : 1070-1076). In addition increased social interaction in PDE10A2-deficient mice have been observed (Sano, H. *J. Neurochem.* 2008, 105, 546-556).

Diseases that can be treated with PDE10A inhibitors include, but are not limited to, dis-  
15 eases thought to be mediated in part by dysfunction of the basal ganglia, of other parts of the central nervous system and of other PDE10A expressing tissues. In particular, diseases can be treated, where inhibition of PDE10A can have therapeutic effects.

These diseases include, but are not limited to, certain psychotic disorders such as schizo-  
20 phrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder or substance-induced psychotic disorder, anxiety disorders such as panic disorder, obsessive-compulsive disorder, acute stress disorder or generalized anxiety disorder, obses- sive/compulsive disorders, drug addictions, movement disorders such as Parkinson's disease or restless leg syndrome, cognition deficiency disorders such as Alzheimer's disease or multi- infarct dementia, mood disorders such as depression or bipolar disorders, or neuropsychiatric  
25 conditions such as psychosis, attention-deficit/hyperactivity disorder (ADHD) or related attentional disorders.

The compounds of the present invention are also suitable for the treatment of diabetes and related disorders such as obesity by regulating the cAMP signaling system.

PDE10A inhibitors might also be useful in preventing neurons from undergoing apopto-  
30 sis by raising cAMP and cGMP levels and, thus, might possess anti-inflammatory properties. Neurodegenerative disorders treatable with PDE10A inhibitors include, but are not limited to, as Alzheimer's disease, Huntington's disease, Parkinson's disease, multiple sclerosis, stroke or spinal cord injury.

The growth of cancer cells is inhibited by cAMP and cGMP. Thus by raising cAMP and cGMP, PDE10A inhibitors can also be used for the treatment of different solid tumors and hematological malignancies such as renal cell carcinoma or breast cancer.

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

The terms "compound(s) of the formula (Ia) and( Ib)", "compound(s) of formula (Ia) and( Ib)", "compound(s) of this invention" or "compound(s) of the present invention" refer to any compound selected from the genus of compounds as defined by the formula (Ia) and( Ib) including stereoisomers, tautomers, solvates, and salts (e.g. pharmaceutically acceptable salts)  
10 thereof.

It must be noted that, as used in the specification and the claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise.

When indicating the number of substituents, the term "one or more" means from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to  
15 replacement of all hydrogens by substituents.

The term "optional" or "optionally" denotes that a subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

The term "substituent" denotes an atom or a group of atoms replacing a hydrogen atom  
20 on the parent molecule.

The term "halogen" refers to fluorine, chlorine, bromine and iodine, more superficially fluorine, chlorine and bromine.

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

The term "alkylene" denotes a linear saturated divalent hydrocarbon group of 1 to 7 carbon atoms or a divalent branched saturated divalent hydrocarbon group of 3 to 7 carbon atoms. Examples of alkylene groups include methylene, ethylene, propylene, 2-methylpropylene,  
30 butylene, 2-ethylbutylene, pentylene, hexylene.

The term “alkenylene” denotes a linear divalent hydrocarbon chain of 2 to 7 carbon atoms or a branched divalent hydrocarbon chain of 3 to 7 carbon atoms with at least one double bond. Exemplary alkenylene include ethenylene, 2,2-dimethylethenylene, propenylene, 2-methylpropenylene, butenylene, and pentenylene.

5           The term “alkynylene” denotes a linear divalent hydrocarbon chain of 2-6 carbon atoms or a branched divalent hydrocarbon chain of 3-6 carbon atoms with at least one triple bond. Exemplary alkynylene include ethynylene, 2,2-dimethylethynylene, propynylene, 2-methylpropynylene, butynylene, and pentynylene.

10           The term “hydroxyalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by a hydroxy group. Examples of hydroxyalkyl include hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 2-hydroxy-1-hydroxymethylethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl or 2-(hydroxymethyl)-3-hydroxypropyl.

15           The term “aromatic” denotes the conventional idea of aromaticity as defined in the literature, in particular in IUPAC - Compendium of Chemical Terminology, 2nd, A. D. McNaught & A. Wilkinson (Eds). Blackwell Scientific Publications, Oxford (1997).

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

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

30           The term “alkoxyalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by an alkoxy group. Exemplary alkoxyalkyl groups include 2-methoxyethyl, 3-methoxypropyl, 1-methyl-2-methoxyethyl, 1-(2-methoxyethyl)-3-methoxypropyl, and 1-(2-methoxyethyl)-3-methoxypropyl.

The term “haloalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkyl include monofluoro-, difluoro- or trifluoro-methyl, -ethyl or -

propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, or trifluoromethyl. The term "perhaloalkyl" denotes an alkyl group where all hydrogen atoms of the alkyl group have been replaced by the same or different halogen atoms.

5 The term "aryl" denotes a monovalent aromatic carbocyclic mono- or bicyclic ring system comprising 6 to 10 carbon ring atoms. Examples of aryl moieties include phenyl and naphthyl

The term "amino" refers to a monovalent group that has a nitrogen atom with two hydrogen atoms (represented by -NH<sub>2</sub>).

10 The term "haloalkoxy" denotes an alkoxy group wherein at least one of the hydrogen atoms of the alkoxy group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkoxyl include monofluoro-, difluoro- or trifluoro-methoxy, -ethoxy or -propoxy, for example 3,3,3-trifluoropropoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, fluoromethoxy, or trifluoromethoxy. The term "perhaloalkoxy" denotes an alkoxy group where  
15 atoms.

The term "oxo" when referring to substituents on heterocycloalkyl means that an oxygen atom is attached to the heterocycloalkyl ring. Thereby, the "oxo" may either replace two hydrogen atoms on a carbon atom, or it may simply be attached to sulfur, so that the sulfur exists in oxidized form, i.e. bearing one or two oxygens.

20 The term "heterocycloalkyl" denotes a monovalent saturated or partly unsaturated mono- or bicyclic ring system of 3 to 9 ring atoms, comprising 1, 2, or 3 ring heteroatoms selected from N, O and S, the remaining ring atoms being carbon. In particular embodiments, heterocycloalkyl is a monovalent saturated monocyclic ring system of 4 to 7 ring atoms, comprising 1, 2, or 3 ring heteroatoms selected from N, O and S, the remaining ring atoms being carbon. Examples for  
25 monocyclic saturated heterocycloalkyl are aziridinyl, oxiranyl, azetidiny, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydro-thienyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholin-4-yl, azepanyl, diazepanyl, homopiperazinyl, or oxazepanyl. Examples for bicyclic saturated heterocycloalkyl are 8-aza-bicyclo[3.2.1]octyl,  
30 quinuclidinyl, 8-oxa-3-aza-bicyclo[3.2.1]octyl, 9-aza-bicyclo[3.3.1]nonyl, 3-oxa-9-aza-bicyclo[3.3.1]nonyl, or 3-thia-9-aza-bicyclo[3.3.1]nonyl. Examples for partly unsaturated heterocycloalkyl are dihydrofuryl, imidazolinyl, dihydro-oxazolyl, tetrahydro-pyridinyl, or dihydropyranyl.



The term "heteroaryl" denotes a monovalent aromatic heterocyclic mono- or bicyclic ring system of 5 to 12 ring atoms, comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, the remaining ring atoms being carbon. Examples of heteroaryl moieties include pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, 5 pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazinyl, azepinyl, diazepinyl, isoxazolyl, benzofuranyl, isothiazolyl, benzothienyl, indolyl, isoindolyl, isobenzofuranyl, benzimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, purinyl, quinoliny, isoquinoliny, quinazoliny, or quinoxaliny.

10 The term "azaspirocycloalkyl" refers to a monovalent saturated 7- to 11-membered bicyclic moiety with the rings connected through one atom, containing one, two or three N heteroatoms, the remaining ring atoms being carbon atoms, wherein the point of attachment can be through either a carbon atom or a heteroatom.

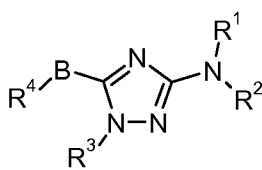
The term "bicyclic ring system" denotes two rings which are fused to each other via a 15 common single or double bond (annelated bicyclic ring system), via a sequence of three or more common atoms (bridged bicyclic ring system) or via a common single atom (spiro bicyclic ring system). Bicyclic ring systems can be saturated, partially unsaturated, unsaturated or aromatic. Bicyclic ring systems can comprise heteroatoms selected from N, O and S.

The definitions described herein apply irrespective of whether the terms in question 20 appear alone or in combination. It is contemplated that the definitions described herein may be appended to form chemically-relevant combinations, such as e.g. "heterocycloalkylaryl", "haloalkylheteroaryl", "arylalkylheterocycloalkyl", or "alkoxyalkyl". The last member of the combination is the radical which is binding to the rest of the molecule. The other members of the combination are attached to the binding radical in reversed order in respect of the literal 25 sequence, e.g. the combination arylalkylheterocycloalkyl refers to a heterocycloalkyl-radical which is substituted by an alkyl which is substituted by an aryl.

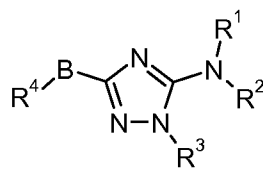
Compounds of formula (Ia) and (Ib) can form pharmaceutically acceptable salts. Examples of such pharmaceutically acceptable salts are salts of compounds of formula (Ia) and (Ib) with physiologically compatible mineral acids, such as hydrochloric acid, sulphuric acid, 30 sulphurous acid or phosphoric acid; or with organic acids, such as methanesulphonic acid, p-toluenesulphonic acid, acetic acid, lactic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The term "pharmaceutically acceptable salts" refers to such salts.

It will be appreciated that the compounds of general formula (Ia) and (Ib) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo.

The present invention relates to compounds of formula (Ia) and (Ib)



(Ia)



(Ib)

wherein

B is C<sub>1</sub>-C<sub>4</sub> -alkylene, C<sub>2</sub>-C<sub>4</sub> -alkenylene, C<sub>2</sub>-C<sub>4</sub> -alkynylene, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl,

R<sup>1</sup> and R<sup>2</sup>, are independently selected from hydrogen, C<sub>1</sub>-C<sub>7</sub>-alkyl optionally substituted by C<sub>3</sub>-C<sub>5</sub>-cycloalkyl; C<sub>1</sub>-C<sub>7</sub>-hydroxyalkyl, C<sub>1</sub>-C<sub>7</sub>-alkoxyalkyl, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl, R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom to which they are attached, form an azaspirocycloalkyl, a bicyclic ring or heterocycloalkyl which can be substituted by 1 to 3 substituents independently selected from the group consisting of halogen, C<sub>1</sub>-C<sub>7</sub> -alkyl optionally substituted by C<sub>1</sub>-C<sub>7</sub> alkoxy; C<sub>1</sub>-C<sub>7</sub>-hydroxyalkyl, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> -haloalkyl, hydroxyl, -NR<sup>9</sup>R<sup>10</sup> and oxo;

R<sup>3</sup> is selected from hydrogen, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl, C<sub>1</sub>-C<sub>7</sub>-alkoxyalkyl, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, heterocycloalkyl, -(CH<sub>2</sub>)<sub>0,1,2</sub>- aryl optionally substituted by C<sub>1</sub>-C<sub>7</sub> alkoxy and C<sub>1</sub>-C<sub>7</sub>-alkyl optionally substituted by C<sub>3</sub>-C<sub>5</sub>-cycloalkyl;

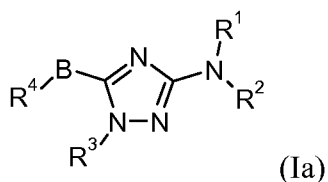
R<sup>4</sup> is selected from heteroaryl optionally substituted by 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>7</sub> -alkyl, C<sub>1</sub>-C<sub>7</sub> -hydroxyalkyl, C<sub>1</sub>-C<sub>7</sub> -haloalkoxy, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl, cyano, amino, nitro, -O-R<sup>6</sup>-C(O)-R<sup>7</sup>, -SO<sub>2</sub>R<sup>8</sup>, C<sub>1</sub>-C<sub>2</sub>-alkoxy optionally substituted by halogen, C<sub>1</sub>-C<sub>2</sub>-alkoxy and heterocycloalkyl,

R<sup>6</sup> and R<sup>8</sup> are selected from C<sub>1</sub>-C<sub>7</sub> -alkyl,

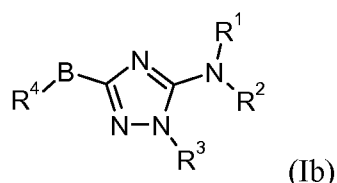
R<sup>7</sup> is selected from heterocycloalkyl,

R<sup>9</sup> and R<sup>10</sup> are independently selected from hydrogen, C<sub>1</sub>-C<sub>7</sub>-alkyl, -C(O)-O- C<sub>1</sub>-C<sub>7</sub>-alkyl.

In a particular embodiment the present invention relates to compounds of formula (Ia):



In a particular embodiment the present invention relates to compounds of formula (Ib):



In a particular embodiment the invention relates to compounds of formula (Ia) and (Ib)  
5 wherein:

B is C<sub>1</sub>-C<sub>4</sub> -alkylene, C<sub>2</sub>-C<sub>4</sub> -alkenylene, C<sub>2</sub>-C<sub>4</sub> -alkynylene.

R<sup>1</sup> and R<sup>2</sup>, are independently selected from hydrogen, C<sub>1</sub>-C<sub>7</sub>-alkyl, C<sub>1</sub>-C<sub>7</sub>-hydroxyalkyl, C<sub>1</sub>-C<sub>7</sub>-alkoxyalkyl, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, (CH<sub>2</sub>)<sub>0,1</sub>-C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom to which they are attached, form a heterocycloalkyl which can be substituted by 1  
10 to 3 substituents independently selected from the group consisting of halogen, C<sub>1</sub>-C<sub>7</sub> -alkyl, C<sub>1</sub>-C<sub>7</sub>-hydroxyalkyl, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> -haloalkyl, hydroxyl and oxo;

R<sup>3</sup> is selected from hydrogen, C<sub>1</sub>-C<sub>7</sub>-alkyl, C<sub>1</sub>-C<sub>7</sub>-alkoxyalkyl, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, (CH<sub>2</sub>)<sub>1,2</sub>- C<sub>3</sub>-C<sub>5</sub>-cycloalkyl, -(CH<sub>2</sub>)<sub>1,2</sub>- aryl optionally substituted by C<sub>1</sub>-C<sub>7</sub> alkoxy,

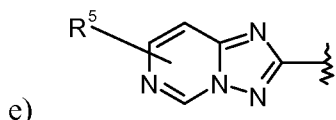
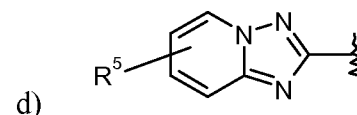
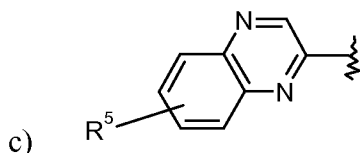
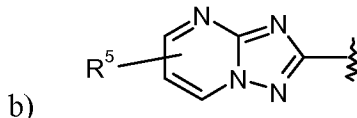
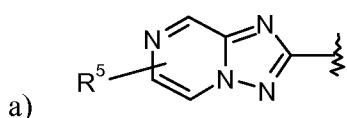
R<sup>4</sup> is selected from heteroaryl optionally substituted by 1 to 3 substituents selected from  
15 halogen, C<sub>1</sub>-C<sub>7</sub> -alkyl, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, C<sub>1</sub>-C<sub>2</sub>-alkoxy optionally substituted by halogen, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl, cyano.

In a particular embodiment the invention relates to compounds of formula (Ia) and (Ib) wherein, B is selected from the group consisting of C<sub>2</sub>-alkylene, C<sub>2</sub>-alkenylene, C<sub>2</sub>-alkynylene, preferably ethylene or ethenylene.

In a particular embodiment the invention relates to compounds of formula (Ia) and (Ib) wherein, R<sup>1</sup> and R<sup>2</sup>, together with the nitrogen atom to which they are attached, form a 4 to 7  
20 membered heterocycloalkyl, preferably azetidiny, pyrrolidinyl, piperidinyl, azepanyl.

In a particular embodiment the invention relates to compounds of formula (Ia) and (Ib) wherein R<sup>4</sup> is selected from the group consisting of:

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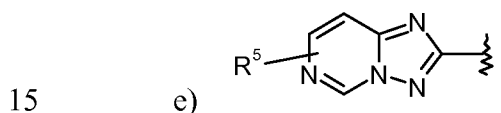
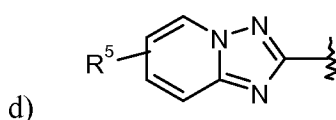
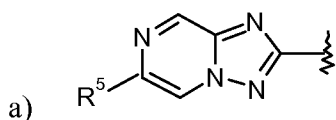
wherein R<sup>5</sup> is selected from halogen, C<sub>1</sub>-C<sub>7</sub>-alkyl, C<sub>1</sub>-C<sub>7</sub>-hydroxyalkyl, C<sub>1</sub>-C<sub>7</sub>-  
 5 haloalkoxy, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl, cyano, amino, nitro, -O-R<sup>6</sup>-C(O)-R<sup>7</sup>, -SO<sub>2</sub>R<sup>8</sup>,  
 C<sub>1</sub>-C<sub>2</sub>-alkoxy optionally substituted by halogen, C<sub>1</sub>-C<sub>2</sub>-alkoxy or heterocycloalkyl,

R<sup>6</sup> and R<sup>8</sup> are independently selected from C<sub>1</sub>-C<sub>7</sub>-alkyl,

R<sup>7</sup> is selected from heterocycloalkyl.

In a particular embodiment the invention relates to compounds of formula (Ia) and (Ib)  
 10 wherein, R<sup>5</sup> is selected from hydrogen, halogen, C<sub>1</sub>-C<sub>7</sub>-alkyl, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, C<sub>1</sub>-C<sub>7</sub>-alkoxy,  
 cyano.

In a particular embodiment the invention relates to compounds of formula (Ia) and (Ib)  
 wherein, R<sup>4</sup> is selected from the group consisting of



Particular compounds of the invention are selected from the group consisting of:

2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-  
 [1,2,4]triazolo[1,5-a]pyrazine

2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-  
 20 [1,2,4]triazolo[1,5-a]pyrazine

2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine

2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine

5 {5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-ethyl-1H-[1,2,4]triazol-3-yl}-dimethyl-amine

{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-dimethyl-amine

10 5,8-Dimethyl-2-{2-[5-pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

5,8-Dimethyl-2-[2-(5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine

2-[2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

15 2-[2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

Cyclopropyl-{5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-methyl-amine

20 Cyclopropyl-{5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-methyl-amine

5,8-Dimethyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-a]pyrazine

5,8-Dimethyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine

25 2-Methyl-3-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-quinoxaline

2-Methyl-3-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-quinoxaline

5,8-Dimethyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-a]pyrazine

5,8-Dimethyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-  
[1,2,4]triazolo[1,5-a]pyrazine

7-Chloro-2-[1-(4-methoxy-benzyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-ylethynyl]-  
[1,2,4]triazolo[1,5-a]pyridine

5 2-{2-[2-(4-Methoxy-benzyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-  
dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

2-[2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,7-dimethyl-  
[1,2,4]triazolo[1,5-a]pyrimidine

10 5,7-Dimethyl-2-{2-[5-pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-  
ethyl}-[1,2,4]triazolo[1,5-a]pyrimidine

{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-  
[1,2,4]triazol-3-yl}-ethyl-methyl-amine

5,7-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyrimidine

15 N-cyclopropyl-5-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)ethyl)-N,1-  
dimethyl-1H-1,2,4-triazol-3-amine

6-Chloro-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

20 6-Chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

6-Chloro-5-methyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-  
[1,2,4]triazolo[1,5-a]pyridine

5-Methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

25 Cyclopropyl-{5-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-vinyl]-1-methyl-  
1H-[1,2,4]triazol-3-yl}-methyl-amine

7,8-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

7,8-Dimethyl-2-(2-(1-methyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-3-methyl-quinoxaline

5 Cyclopropyl-{5-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-ethyl]-1-methyl-  
1H-[1,2,4]triazol-3-yl}-methyl-amine

6-Chloro-5,8-dimethyl-2-(2-(1-methyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)vinyl)-  
[1,2,4]triazolo[1,5-a]pyridine

6-Chloro-5,8-dimethyl-2-(2-(1-methyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

10 5,8-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

6-Chloro-5,8-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

15 2-{2-[5-(3-Fluoro-azetidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-  
[1,2,4]triazolo[1,5-a]pyrazine

5,6-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

5,6,8-Trimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyrazine

20 5,7,8-Trimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-c]pyrimidine

2-{2-[5-(3-Methoxy-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-  
dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

25 8-Chloro-5,7-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-c]pyrimidine

5,7-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-c]pyrimidine

6-Chloro-5,8-dimethyl-2-[(1S,2S)-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-  
cyclopropyl]-[1,2,4]triazolo[1,5-a]pyridine

2-((1-Ethyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethynyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

2-(2-(1-Ethyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

5 5,8-Dimethyl-2-[2-(2-methyl-5-piperidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine

5-Ethyl-8-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine

10 5,8-Dimethyl-2-{2-[2-methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

6,8-Dichloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

2-(2-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonitrile

15 8-Chloro-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-6-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

7-Methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-nitro-[1,2,4]triazolo[1,5-a]pyridine

20 2-(2-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]quinoline

5-Methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyrazine

5,8-Dimethyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-c]pyrimidine

25 {5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-diethyl-amine

Cyclopropyl-{5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-ethyl-amine



6,8-Dichloro-2-{2-[2-(4-methoxy-benzyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl]-ethyl}-5-methyl-[1,2,4]triazolo[1,5-a]pyridine

6,8-Dichloro-2-(2-(1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridine

5 6-Fluoro-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-7-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridin-5-amine

2-(2-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-5-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

10 8-Bromo-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-6-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

2-(2-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-7-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

2-(2-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine-7-carbonitrile

15 6,8-Dichloro-5-methyl-2-[2-(5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine

20 5-Methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonitrile

8-Bromo-6-chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

6-Bromo-8-chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine

25 6-Chloro-8-methanesulfonyl-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

8-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine-6-carbonitrile

8-Ethyl-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine

6-Chloro-8-methoxy-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

5 6-Chloro-8-cyclopropyl-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

5-Methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile

10 6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile

2-{6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridin-8-yl}-propan-2-ol

2-[(E)-2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-c]pyrimidine

15 6-Bromo-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine

5-Methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonitrile

20 5,6-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

6-Chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridin-8-ol

6-Ethyl-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine

25 1-{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-2-one

6-Chloro-2-{2-[5-(3,3-difluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5-methyl-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine

5,8-Dimethyl-2-{2-[2-methyl-5-(3-methyl-azetidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

2-{2-[5-(3,3-Difluoro-azetidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

5 6-Chloro-5-methyl-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine

2-{2-[5-(5-Aza-spiro[2.4]hept-5-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

10 2-{2-[5-(3,3-Difluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

2-{2-[5-((S)-3-Fluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin

6-Chloro-8-difluoromethoxy-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

15 2-{2-[5-((R)-3-Fluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

Cyclopropylmethyl-{5-[(E)-2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-methyl-amine

20 6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-8-(2,2,2-trifluoro-ethoxy)-[1,2,4]triazolo[1,5-a]pyridine

2-{2-[5-(3-Aza-bicyclo[3.2.0]hept-3-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

5,8-Dimethyl-2-{2-[2-methyl-5-((S)-2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

25 5,8-Dimethyl-2-{2-[2-methyl-5-((R)-2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

2-[(E)-2-(5-Azepan-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

7,8-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-5-(trifluoromethyl)-[1,2,4]triazolo[1,5-c]pyrimidine

1-{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-3-ol

5 6-Chloro-5-methyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine

6-Chloro-8-difluoromethoxy-5-methyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

10 ((R)-1-{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester

5,8-Dimethyl-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-[1,2,4]triazolo[1,5-a]pyrazine

5,8-Dimethyl-2-[2-(2-phenyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine

15 2-{2-[2-(2,2-Difluoro-ethyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

5,8-Dimethyl-2-{2-[2-methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-c]pyrimidine

20 5,8-Dimethyl-2-{2-[2-methyl-5-((S)-2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-c]pyrimidine

5,8-Dimethyl-2-{2-[2-methyl-5-((R)-2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-c]pyrimidine

5,8-Dimethyl-2-{2-[2-methyl-5-((R)-2-trifluoromethyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

25 5,8-Dimethyl-2-{2-[2-methyl-5-((S)-3-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

5,8-Dimethyl-2-{2-[2-methyl-5-((R)-3-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

2-[2-(2-Cyclopropylmethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

2-[2-(1-Cyclopropylmethyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (b)

5 5,8-Dimethyl-2-{2-[2-methyl-5-((R)-2-trifluoromethyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-c]pyrimidine

6-Chloro-8-(2-methoxyethoxy)-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-1,2,4-triazol-3-yl)ethyl]-[1,2,4]triazolo[1,5-a]pyridine

10 6-Chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(tetrahydro-2H-pyran-4-yloxy)-[1,2,4]triazolo[1,5-a]pyridine

4-[2-[[6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-1,2,4-triazol-3-yl)ethyl]-[1,2,4]triazolo[1,5-a]pyridin-8-yl]oxy]ethyl]morpholine

6-Chloro-5-methyl-2-(2-(3-(pyrrolidin-1-yl)-1-(tetrahydro-2H-pyran-4-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

15 2-[2-(2-Cyclopropyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

2-[2-(1-Cyclopropyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (b)

20 2-{2-[5-((R)-2-Methoxymethyl-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

2-(6-Chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridin-8-yloxy)-1-morpholinoethanone

(-)-5,8-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)propyl)-[1,2,4]triazolo[1,5-a]pyrazine

25 (R)-6-Chloro-2-(2-(3-(3-fluoropyrrolidin-1-yl)-1-methyl-1H-1,2,4-triazol-5-yl)ethyl)-5-methyl-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

6-Chloro-5-methyl-2-(2-(3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

2-{2-[5-(3-Difluoromethyl-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

6-Chloro-8-(difluoromethyl)-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine

5 6-Chloro-2-(2-(1-cyclopropyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-5-methyl-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

6-Chloro-2-(2-(1-cyclopropyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-5-methyl-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

10 7-chloro-2-((1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethynyl)quinoxaline

7-chloro-2-(2-(5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)quinoxaline

6-Chloro-3-methyl-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-quinoxaline

15 6-Chloro-2-methyl-3-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-quinoxaline

The compounds of the present invention are useful for the treatment or prophylaxis of psychotic disorders, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder, substance-induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipolar disorders, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma or breast cancer.

The compounds of the present invention are useful for the preparation of a medicament for the treatment or prophylaxis of psychotic disorders, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder, substance-induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipolar disorders, neuropsychiatric conditions, psychosis, atten-

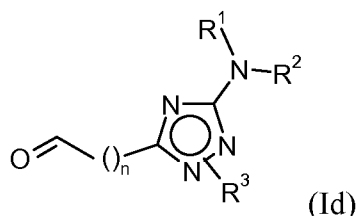
tion-deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma or breast cancer.

5 The compounds of the present invention are useful for the treatment or prophylaxis of psychotic disorders, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder, substance-induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipolar disorders, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma or breast cancer.

15 In a further embodiment the present invention relates to a method for the treatment or prophylaxis of psychotic disorders, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder, substance-induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipolar disorders, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma or breast cancer, which method comprises administering an effective amount of a compound of the present invention.

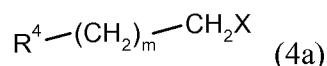
In a further embodiment the present invention relates to a process for the manufacture of compounds of the present invention, which process comprises

a) reacting a compound of formula (Id)



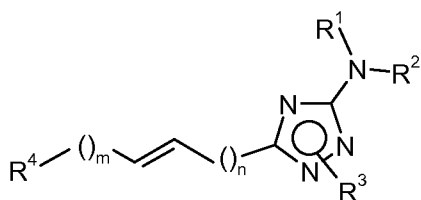
with

b) a compound of formula (4a)



5

to a compound of formula (Ie)



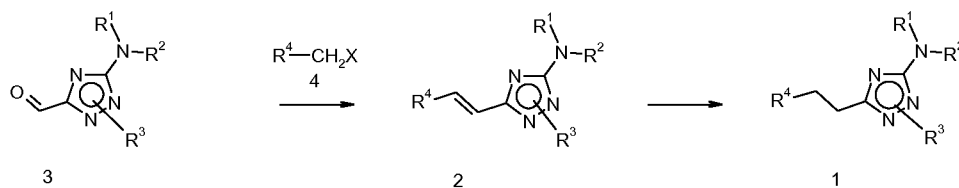
wherein n and m are 0 or 1, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and X are as defined above.

10 GENERAL PROCEDURES:

Compounds of formula **1** can be prepared from compound **2** according to scheme 1, typically by catalytic hydrogenation. Compound **2** can be prepared from building blocks **3** and **4** according to scheme 1. The conversion, commonly known as Wittig reaction, can be achieved in several ways. In one method, the halogenide **4** is activated by reaction with a suitable phosphine such as triphenylphosphine. The formed phosphonium salt is then reacted with the aldehyde **3** and a suitable base such as n-butyllithium, hexamethyldisilazane or DBU to the desired product **2**.

15

**Scheme 1**



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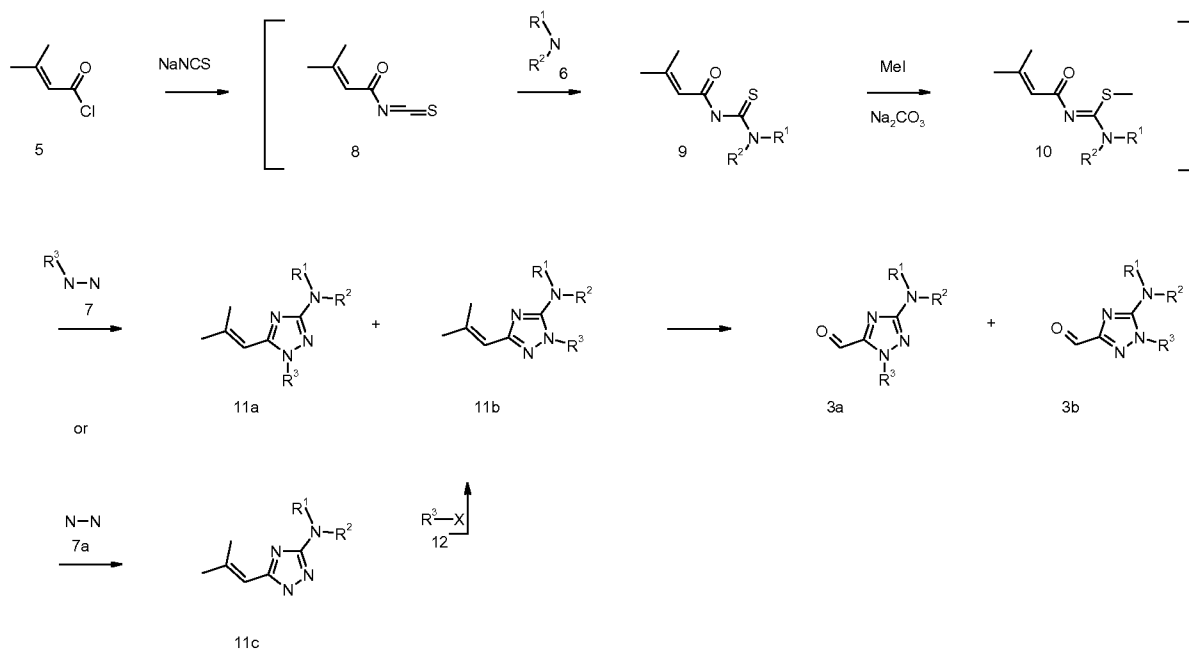
Compounds of formula **3** can be prepared according to Scheme 2: 3-Methyl-but-2-enoyl chloride is reacted with sodium isothiocyanate to form 3-methyl-but-2-enoyl isothiocyanate **8** which is then reacted with a suitable substituted amine **6** to form thiourea **9**. Compound **9** is activated with an alkylation reagent such as methyl iodide and then reacted with a suitable substituted hydrazine **7** to form triazole **11**. Triazole **11** is then oxidized with a suitable reagent such as ozone or potassium periodate/osmium tetroxide to form the desired aldehyde **3**. If isomers are formed during the formation of **11**, these can be separated by methods known in the

25



art. Alternatively, compound **10** is reacted with hydrazine to form compound **11c** which is alkylated with a suitable substituted alkylating reagent **12** to form compound **11b** which is then converted in the described way to aldehyde **3b**.

Scheme 2

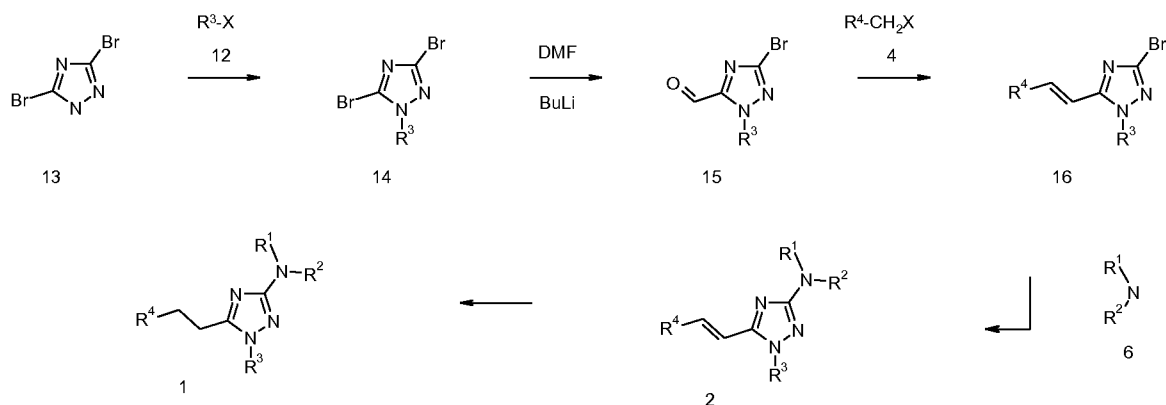


Another method for preparing compounds of formula **1** is depicted in scheme 3: 3,5-Dibromo-1H-[1,2,4]triazole **13** is alkylated with a suitable substituted alkylating reagent **12** to form **14** by methods well known in the art. For example, if X is an alkylsulfonate, iodide or bromide, **12** can be deprotonated with a suitable base such as sodium hydride and then be reacted with **13**. Compound **14** is then deprotonated with a suitable base such as n-butyllithium and reacted with dimethylformamide to yield aldehyde **15**. Aldehyde **15** is then reacted with a suitable substituted halogenide **4** in the same way as described for compound **2** (scheme 1) to form compound **16**. Compound **16** can be used in a palladium-catalyzed cross coupling reaction using a suitable substituted amine **6** and a suitable ligand, such as Xantphos, to yield the desired compound **2**.

10

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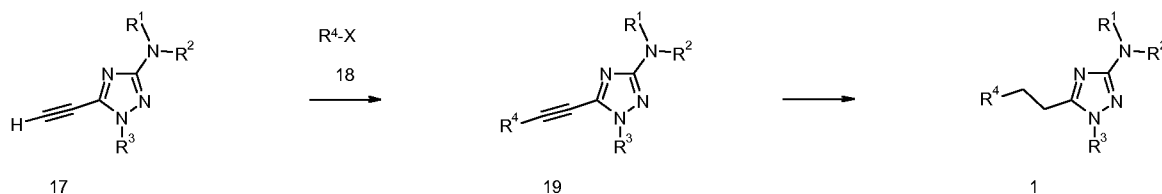
## Scheme 3



Another method for preparing compounds of formula **1** is depicted in scheme 3: A compound of formula **17** is used in a palladium-catalyzed cross coupling reaction using a suitable substituted arylhalogenide **18** and a suitable ligand, such as Xantphos, to form compound **19**. Compound **19** is then converted to compound **1** by methods well known in the art. For example, **19** can be hydrogenated with a suitable catalysts such as Palladium to yield compound **1**.

## Scheme 4

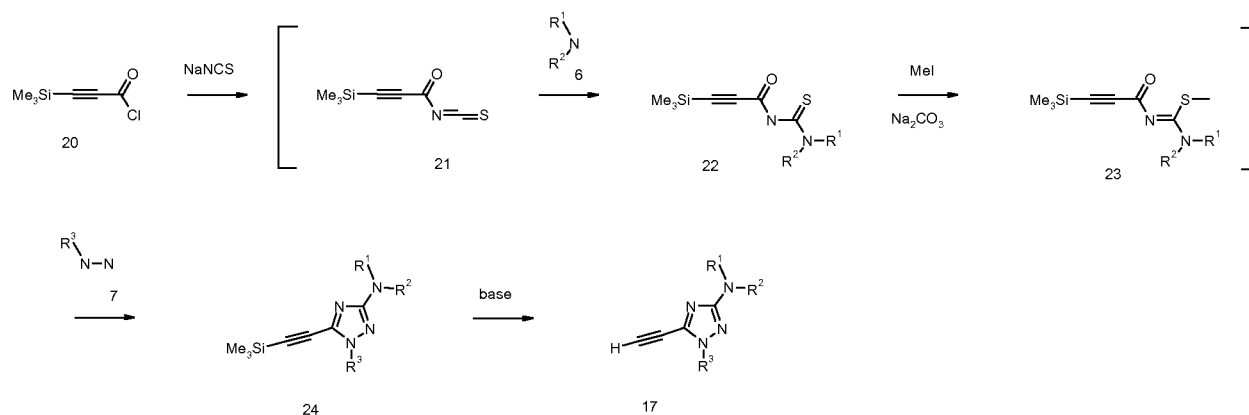
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Compounds of formula **17** can be prepared according to Scheme 5: But-2-ynoyl chloride **20** is reacted with sodium isothiocyanate to form but-2-ynoyl isothiocyanate **21** which is then reacted with a suitable substituted amine **6** to form thiourea **22**. Compound **22** is activated with an alkylation reagent such as methyl iodide and then reacted with a suitable substituted hydrazine **7** to form triazole **24**. Triazole **11** is then deprotected with a suitable base such as sodium hydroxide to form compound **17**.

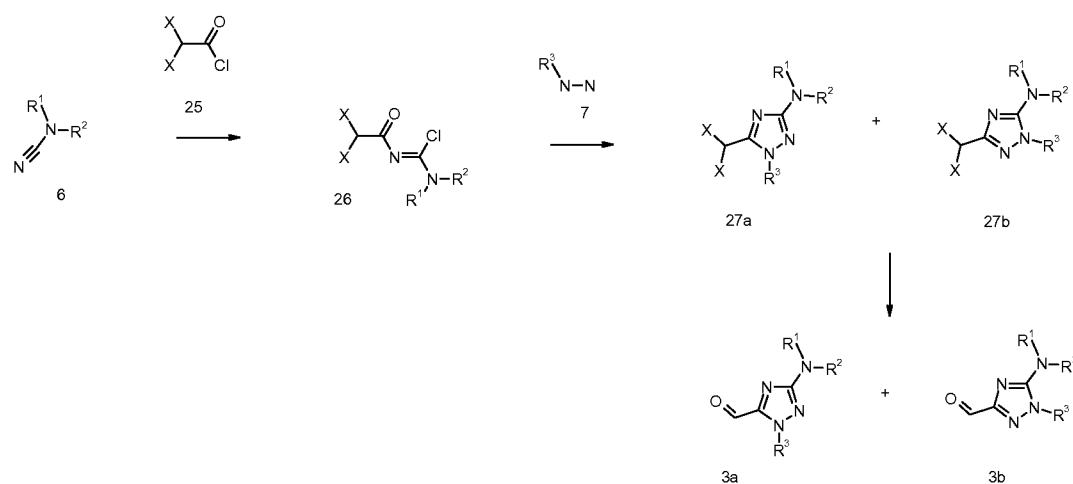
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## Scheme 5



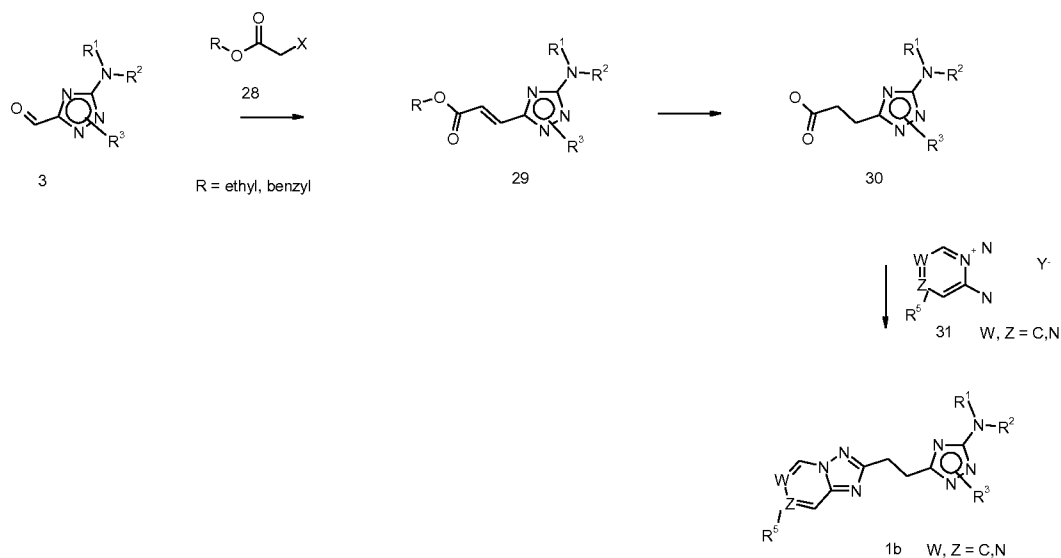
3-Methyl-but-2-enoyl chloride **5**, sodium isothiocyanate, 3,5-dibromo-1H-[1,2,4]triazole **13** and but-2-ynoyl chloride **20** are commercially available. Halogenides **4** and **18**, amines **6**, hydrazines **7** and alkylating reagents **12** are either commercially available, or can be prepared by methods well known in the art.

## Scheme 6



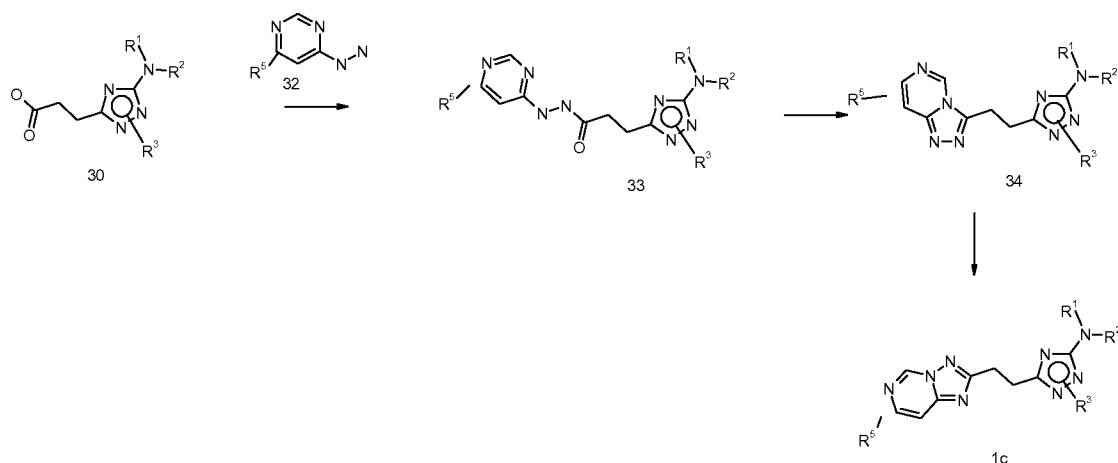
Another method for preparing compounds of formula **3** is shown in scheme 6: A compound of formula **6** is reacted with an acid chloride containing a masked aldehyde of formula **25** to obtain an intermediate of formula **26**. A suitable method is to protect the aldehyde as a geminal dihalide such as X=Cl. The molecule of formula **26** is reacted with a substituted hydrazine derivative of formula **7**, in presence of a suitable base, to give intermediates of formula **27a** or formula **27b**. Deprotection of the aldehyde by methods well known in the art gives compounds of formula **3a** or formula **3b**.

## Scheme 7



Scheme 7 shows a method for the preparation of compounds of the formula **1b**: A compound of the formula **3** is reacted with a suitable ester of formula **28** in a conversion commonly known as Wittig (using a phosphine) or Horner-Wadsworth-Emmons (using a phosphonate) reaction to give an alkene of formula **29**. Alkenes of formula **29** are then reduced and hydrolyzed to an acid of formula **30**. Acids of formula **30** are reacted with salts of formula **31** in presence of a suitable coupling agent such as O-(7-azabenzotriazol-1-yl)-N,N,N',N-tetramethyluronium hexafluorophosphate (HATU) in presence of a suitable base to give compounds of formula **1b**.

## Scheme 8



Scheme 8 shows a method for the preparation of compounds of the formula **1c**: Acids of formula **30** are reacted with compounds of formula **32** in presence of a suitable coupling agent such as O-(7-azabenzotriazol-1-yl)-N,N,N',N-tetramethyluronium hexafluorophosphate (HATU) in presence of a suitable base to give compounds of formula **33**. Compounds of formula **33** are

then cyclized in presence of a suitable dehydrating agent such as methyl N-(triethylammoniumsulfonyl)carbamate (Burgess reagent) to compounds of formula 34.

Compounds of formula 34 are then rearranged in presence of a suitable reagent, typically an acid such as hydrochloric acid or base in a reaction commonly known as Dimroth rearrangement to  
5 compounds of formula 1c.

## PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

Another embodiment provides pharmaceutical compositions or medicaments containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments.

10 In one example, compounds of formula (Ia) and (Ib) may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from  
15 about 3 to about 8. In one example, a compound of formula (Ia) and (Ib) is formulated in an acetate buffer, at pH 5. In another embodiment, the compounds of formula (Ia) and (Ib) are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good  
20 medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "effective amount" of the compound to be administered will be governed by such considerations, and is the mini-  
25 mum amount necessary to inhibit PDE10 and to control the cAMP signaling pathway. For example, such amount may be below the amount that is toxic to normal cells, or the mammal as a whole.

In one example, the pharmaceutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.01-100 mg/kg, alternatively  
30 about 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day. In another embodiment, oral unit dosage forms, such as tablets and capsules, preferably contain from about 25-100 mg of the compound of the invention.

The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcuta-  
35 neous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and,

if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, 5 suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art 10 and are described in detail in, e.g., Ansel, Howard C., et al., *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*. Philadelphia: Lippincott, Williams & Wilkins, 2004; Genaro, Alfonso R., et al. *Remington: The Science and Practice of Pharmacy*. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. *Handbook of Pharmaceutical Excipients*. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more 15 buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medica- 20 ment).

An example of a suitable oral dosage form is a tablet containing about 25 mg, 50 mg, 100 mg, 250 mg, or 500 mg of the compound of the invention compounded with about 90-30 mg anhydrous lactose, about 5-40 mg sodium croscarmellose, about 5-30 mg polyvinylpyrrolidone (PVP) K30, and about 1-10 mg magnesium stearate. The powdered ingredients are first mixed 25 together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving the compound, for example 5-400 mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such sodium chloride, if desired. The solution may be fil- 30 tered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

An embodiment, therefore, includes a pharmaceutical composition comprising a compound of Formula (Ia) and (Ib), or a stereoisomer or pharmaceutically acceptable salt thereof. In a further embodiment includes a pharmaceutical composition comprising a compound of Formula (Ia) and (Ib), or a stereoisomer or pharmaceutically acceptable salt thereof, together with a 35 pharmaceutically acceptable carrier or excipient.

The following test was carried out in order to determine the activity of the compounds of the present invention. PDE10 activity of the compounds of the present invention was determined using a Scintillation Proximity Assay (SPA)-based method similar to the one previously described (Fawcett, L. et al., ProcNatl Acad Sci USA (2000) 97(7):3702-3707).

5 The human PDE10A full length assay was performed in 96-well micro titer plates. The reaction mixture of 50  $\mu$ l contained 20 mM HEPES pH=7.5 /10 mM MgCl<sub>2</sub>/0.05 mg/ml BSA (Sigma cat. # A-7906), 50 nM cGMP (Sigma, cat. # G6129) and 50 nM [3H]-cGMP (GE Healthcare, cat. # TRK392 S.A. 13.2Ci/mmol), 3.75 ng/well PDE10A enzyme (Enzo Life Science, Lausen, Switzerland cat # SE-534) with or without a specific test compound. A range of  
10 concentrations of the potential inhibitor was used to generate data for calculating the concentration of inhibitor resulting in 50% of the effect (e.g. IC<sub>50</sub>, the concentration of the competitor inhibiting PDE10A activity by 50%). Non-specific activity was tested without the enzyme. The reaction was initiated by the addition of the substrate solution (cGMP and [3H]-cGMP) and allowed to progress for 20 minutes at room temperature. The reaction was terminated by adding 25  
15  $\mu$ l of YSi-SPA scintillation beads (GE Healthcare, cat. # RPNQ0150) in 18 mM zinc sulphate solution (stop reagent). After 1 h under shaking, the plate was centrifuged one minute at 170 g to allow beads to settle. Afterwards, radioactive counts were measured on a Perkin Elmer Top-Count Scintillation plate reader.

20 The compounds according to formula (Ia) and (Ib) have an IC<sub>50</sub> value below 10  $\mu$ M, more specifically below 5  $\mu$ M, yet more specifically below 1  $\mu$ M. The following table shows data for some examples.

<b>Example</b>	<b>IC<sub>50</sub> [nM]</b>	<b>Example</b>	<b>IC<sub>50</sub> [nM]</b>
1	11.88	71	1.01
2	5.57	72	1.22
3	205.12	73	86.93
4	10.87	74	2.16
6	334.23	75	3.78
7	17.01	76	0.44
8	1.87	77	9.99
10	1.4	78	30.63

11	42.26	79	2.22
12	263.09	80	76.34
13	27.68	81	74.41
14	5.76	82	0.48
15	104.8	83	6.84
16	61.41	84	1.45
17	6.72	85	4.22
18	2.68	86	3.44
19	476.78	87	287.66
20	5.00	88	9.78
21	91.55	89	108.21
22	20.41	90	475.46
23	103.21	91	0.88
24	23.56	92	13.94
25	42.26	93	166.38
26	62.68	94	121.96
27	0.98	95	0.23
28	2.13	96	10.65
29	55.9	97	79.33
30	57.86	98	0.51
31	4.49	99	273.37
32	7.23	100	5.5



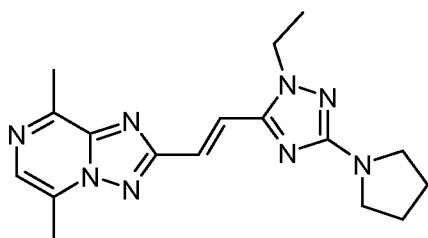
33	54.96	101	57.63
34	128.45	102	179.4
35	0.15	103	10.18
36	0.58	104	131.25
37	4.21	105	0.44
38	0.28	106	0.55
39	55.57	107	171.18
40	10.25	108	0.8
41	37.26	109	0.29
42	13.63	110	3.25
43	84.3	111	18.44
44	9.41	112	9
45	58.83	113	131.01
46	4.98	114	34.21
47	4.48	115	5.46
48	28.49	116	8.94
49	31.65	117a	1.32
50	4.9	117b	6.69
51	28.43	118	27.38
52	0.63	119	0.23
53	380.76	120	0.36
54	104.77	121	1.37

55	94.65	122	0.35
56	29.2	123a	2.03
57	251.42	123b	8.2
58	8.21	124	14.1
59	50.57	125	2.07
60	185.98	126	321.27
61	0.72	127	2.71
62	3.23	128	0.72
63	32.35	129	48.1
64	56.59	130	0.89
65	36.51	131	1.58
66	330.99	132	0.72
67	317.27	133	17.79
68	0.22	134	33.05
69	0.5	135	10.74
70	3.47	136	5.17

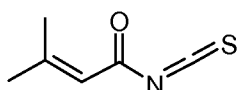
## EXAMPLES

**Example 1**

2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-  
5 [1,2,4]triazolo[1,5-a]pyrazine

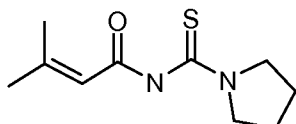


## a) 3-Methyl-but-2-enoyl isothiocyanate



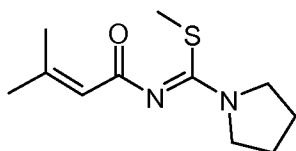
To a solution of potassium thiocyanate (10 g, 101 mmol, Eq: 1.00) and hexaethylene glycol monomethyl ether (896 mg, 830  $\mu$ l, 3.02 mmol, Eq: 0.03) in dry dichloromethane (120 ml) was added dropwise at 0 °C a solution of 3-methylbut-2-enoyl chloride (12.0 g, 11.2 ml, 101 mmol, Eq: 1.00) in dry dichloromethane (20.0 ml) over 1 hour under argon atmosphere. After the addition was completed, the mixture (now light brown & turbid) was allowed to warm to 25 °C and was stirred for additional 3 hours. The mixture was filtrated, the filtrate was evaporated the residue was distilled under reduced pressure affording 3-methyl-but-2-enoyl isothiocyanate (9.989 g / 70.2%) as a yellow liquid. GC-MS: m/e= 141 (M) / bp: 86 °C / 2mbar

## b) 3-Methyl-but-2-enoic acid (pyrrolidine-1-carbothioyl)-amide



To a solution of 3-methylbut-2-enoyl isothiocyanate (500 mg, 3.54 mmol, Eq: 1.00) in benzene (10.0 ml) was added a solution of pyrrolidine (252 mg, 293  $\mu$ l, 3.54 mmol, Eq: 1.00) in benzene (5.00 ml). The mixture was stirred for 30 minutes. The solvent was evaporated affording 3-methyl-but-2-enoic acid (pyrrolidine-1-carbothioyl)-amide (824 mg / 110%) as a light yellow solid. MS: m/e= 213.1 (M+H+)

## c) 3-Methyl-but-2-enoic acid 1-methylsulfanyl-1-pyrrolidin-1-yl-meth-(Z)-ylideneamide

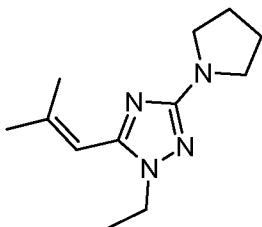


20

A mixture of 3-methyl-N-(pyrrolidine-1-carbonothioyl)but-2-enamide (230 mg, 1.08 mmol, Eq: 1.00), sodium carbonate (121 mg, 1.14 mmol, Eq: 1.05) and iodomethane (769 mg,

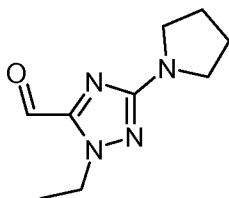
339  $\mu$ l, 5.42 mmol, Eq: 5) in tetrahydrofuran (7 ml) was stirred for 18 hours at 70 °C. The crude material was applied on silicagel and purified by flash chromatography over a 20 g silicagel column using heptane / ethyl acetate 50-100 % as eluent affording 3-methyl-but-2-enoic acid 1-methylsulfanyl-1-pyrrolidin-1-yl-meth-(Z)-ylideneamide (119 mg / 48.5%) as a light yellow liquid. MS: m/e= 227.1 (M+H<sup>+</sup>)

d) 1-Ethyl-5-(2-methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole



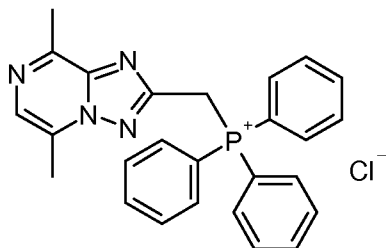
A mixture of (Z)-methyl N-3-methylbut-2-enoylpyrrolidine-1-carbimidothioate (1.19 g, 5.26 mmol, Eq: 1.00), ethylhydrazine oxalate (2.37 g, 15.8 mmol, Eq: 3) and N,N-diisopropyl ethyl amine (5.44 g, 7.15 ml, 42.1 mmol, Eq: 8) in dioxane (20 ml) was heated to 100 °C, the resulting suspension was stirred for 3 hours at 100 °C. The mixture was diluted with ethyl acetate and washed with water for 3 times. The organic layer was separated, dried over magnesium sulfate, filtrated and evaporated. The crude material was applied on silicagel and purified by flash chromatography over a 20 g silicagel column using heptane / ethyl acetate 30-70 % as eluent affording 1-ethyl-5-(2-methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (441 mg / 38.1%) as a light yellow oil. MS: m/e= 221.0 (M+H<sup>+</sup>)

e) 2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde



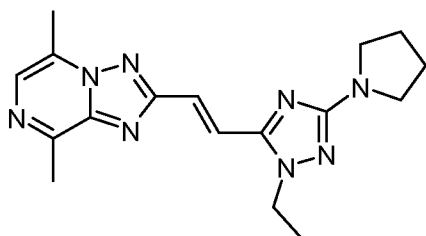
A mixture of 1-ethyl-5-(2-methylprop-1-enyl)-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole (441 mg, 2.00 mmol, Eq: 1.00), osmium(VIII) oxide (382 mg, 382  $\mu$ l, 60.1  $\mu$ mol, Eq: 0.03), sodium periodate (1.71 g, 8.01 mmol, Eq: 4) and benzyltriethylammonium chloride (182 mg, 801  $\mu$ mol, Eq: 0.4) in dioxane (21 ml) and water (6.3 ml) was stirred for 2 hours at 120 °C. The mixture was diluted with ethyl acetate and washed with 2x water and brine. The organic layer was separated, dried over magnesium sulfate, filtrated and evaporated affording 2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde (268 mg / 69.2%) as a dark green viscous oil. MS: m/e= 195.4 (M+H<sup>+</sup>)

f) (5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylmethyl)-triphenyl-phosphonium chloride



A mixture of 2-(chloromethyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (prepared as  
 5 described in WO2009/152825) (500 mg, 2.54 mmol, Eq: 1.00) and triphenylphosphine (667 mg,  
 2.54 mmol, Eq: 1.00) in acetonitrile (24.9 ml) was refluxed for 18 hours under argon  
 atmosphere. The solvent was evaporated the light pink solid was triturated with ether, the solid  
 was filtered off, washed with ether and dried in vacuo affording (5,8-dimethyl-  
 [1,2,4]triazolo[1,5-a]pyrazin-2-ylmethyl)-triphenyl-phosphonium chloride (1.292 g, 72.5%) as a  
 10 light pink solid. MS-Cl: m/e= 423 (M+H+)

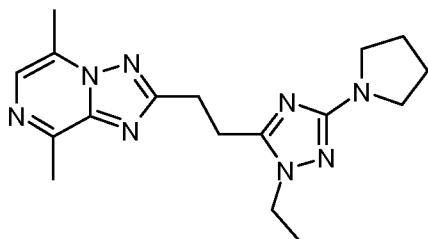
g) 2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-  
 [1,2,4]triazolo[1,5-a]pyrazine



A mixture of ((5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-  
 15 yl)methyl)triphenylphosphonium chloride (125 mg, 272  $\mu$ mol, Eq: 1.00), 1-ethyl-3-(pyrrolidin-  
 1-yl)-1H-1,2,4-triazole-5-carbaldehyde (52.9 mg, 272  $\mu$ mol, Eq: 1.00) and 1,8-  
 diazabicyclo[5.4.0]undec-7-ene (104 mg, 103  $\mu$ l, 681  $\mu$ mol, Eq: 2.5) in tetrahydrofuran (6 ml)  
 was stirred for 18 hours at 25 °C under nitrogen atmosphere. The crude material was applied on  
 silicagel and purified by flash chromatography over a 50 g silicagel column using ethyl acetate /  
 20 methanol 0-10 % as eluent affording 2-[2-(2-ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-  
 vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (37 mg / 40.1%) as a bright yellow viscous  
 oil. MS: m/e= 339.5 (M+H+)

## Example 2

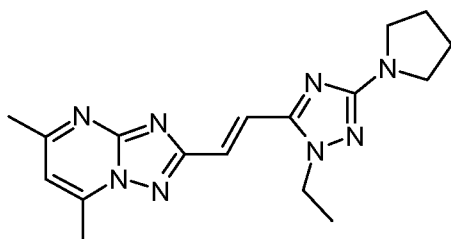
2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



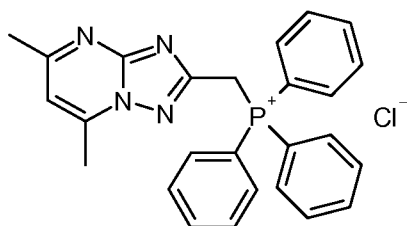
A mixture of 2-(2-(1-ethyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-  
5 [1,2,4]triazolo[1,5-a]pyrazine (33 mg, 97.5  $\mu\text{mol}$ , Eq: 1.00) and palladium on carbon 10 % (10.4 mg, 9.75  $\mu\text{mol}$ , Eq: 0.1) in methanol (30 ml) was stirred for 5 hours under hydrogen atmosphere at 25 °C. The catalyst was filtered off and the filtrate was evaporated affording 2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (32 mg / 96.4%) as a yellow oil. MS: m/e= 341.5 (M+H<sup>+</sup>)

### 10 Example 3

2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine



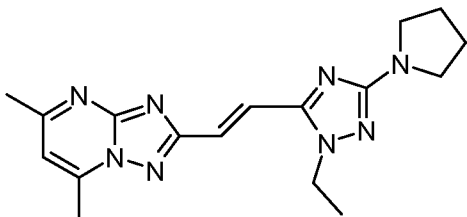
a) (5,7-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-triphenyl-phosphonium  
15 chloride



Was prepared in the same manner as described in General Procedure Example 1f) using 2-(chloromethyl)-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine (prepared as described in WO2009/152825) (120 mg, 610  $\mu\text{mol}$ , Eq: 1.00) affording (5,7-dimethyl-[1,2,4]triazolo[1,5-

a) pyrimidin-2-ylmethyl)-triphenyl-phosphonium chloride (249 mg, 88.9%) as an off-white solid. MS-Cl: m/e= 423.2 (M+H+), mp: 220.5

b) 2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine



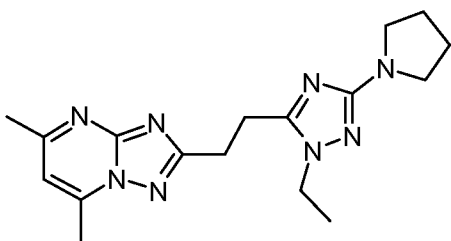
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Was prepared in the same manner as described in General Procedure Example 1g) using ((5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl)triphenylphosphonium chloride (85 mg, 185  $\mu\text{mol}$ , Eq: 1.00) and 1-ethyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole-5-carbaldehyde (36.0 mg, 185  $\mu\text{mol}$ , Eq: 1.00) as starting materials. Chromatography afforded 2-[2-(2-ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine (28 mg / 44.7%) as a bright yellow viscous oil. MS: m/e= 339.5 (M+H+)

10

#### Example 4

2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine



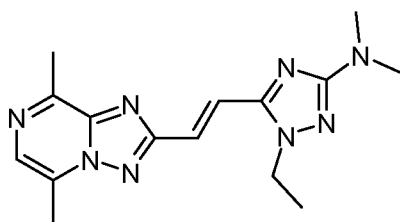
15

Was prepared in the same manner as described in General Procedure Example 2 using 2-(2-(1-ethyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine (24 mg, 70.9  $\mu\text{mol}$ , Eq: 1.00). Filtration and evaporation of the solvent afforded 2-[2-(2-ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine (10 mg / 41.4%) as a white solid. MS: m/e= 341.1 (M+H+)

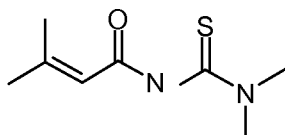
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#### Example 5

{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-vinyl]-1-ethyl-1H-[1,2,4]triazol-3-yl}-dimethyl-amine

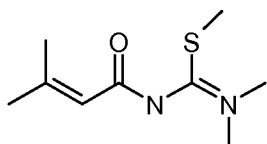


a) 1,1-Dimethyl-3-(3-methyl-but-2-enyl)-thiourea



Was prepared in the same manner as described in General Procedure Example 1b) using  
 5 3-methylbut-2-enyl isothiocyanate (2 g, 14.2 mmol, Eq: 1.00) and dimethylamine solution 2M  
 in THF (7.08 ml, 14.2 mmol, Eq: 1.00). Evaporation of the solvent afforded 1,1-dimethyl-3-(3-  
 methyl-but-2-enyl)-thiourea (2.239 g / 84.9%) as a yellow oil which was used without further  
 purification in the next step. MS: m/e= 187.4 (M+H<sup>+</sup>)

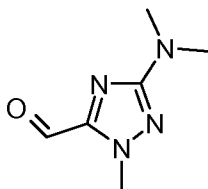
b) 1,1,2-Trimethyl-3-(3-methyl-but-2-enyl)-isothioureia



10

Was prepared in the same manner as described in General Procedure Example 1c) using  
 N-(dimethylcarbamothioyl)-3-methylbut-2-enamide (2.24 g, 12.0 mmol, Eq: 1.00) as starting  
 material. Filtration and evaporation of the solvents afforded 1,1,2-trimethyl-3-(3-methyl-but-2-  
 enyl)-isothioureia (3.17 g / 154 %) as a red oil, which was used without further purification in  
 15 the next step. MS: m/e= 201.4 (M+H<sup>+</sup>)

c) 5-Dimethylamino-2-methyl-2H-[1,2,4]triazole-3-carbaldehyde

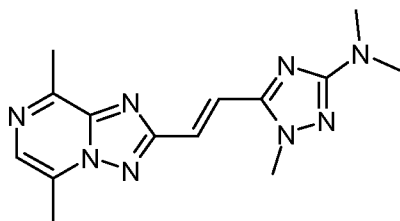


A mixture of (Z)-methyl N,N-dimethyl-N'-(3-methylbut-2-enyl)carbamimidothioate  
 (2.41 g, 12.0 mmol, Eq: 1.00) and methylhydrazine (5.54 g, 6.34 ml, 120 mmol, Eq: 10) was  
 20 heated to 100 °C for 30 minutes. The mixture was dissolved in ethyl acetate and washed with



water 3 times and once with brine. The organic layer was separated, dried over magnesium sulfate, filtrated and evaporated affording dimethyl-[1-methyl-5-(2-methyl-propenyl)-1H-[1,2,4]triazol-3-yl]-amine (824 mg / 38.0%) as a yellow liquid. A mixture of N,N,1-trimethyl-5-(2-methylprop-1-enyl)-1H-1,2,4-triazol-3-amine (824 mg, 4.57 mmol, Eq: 1.00), osmium tetroxide 4% aq. (872 mg, 872  $\mu$ l, 137  $\mu$ mol, Eq: 0.03), sodium periodate (3.91 g, 18.3 mmol, Eq: 4) and benzyltriethylammonium chloride (416 mg, 1.83 mmol, Eq: 0.4) in dioxane (42 ml) and water (13 ml) was stirred for 2 hours at 60 °C. The mixture was diluted with ethyl acetate and washed with 2x water and brine. The organic layer was separated, dried over magnesium sulfate, filtrated and evaporated affording 1.0 g dark brown oil. The crude material was applied on silicagel and purified by flash chromatography over a 50 g silicagel column using ethyl acetate / methanol 0-10 % as eluent affording 5-dimethylamino-2-methyl-2H-[1,2,4]triazole-3-carbaldehyde (127 mg / 60.0%) as a brown oil. MS: m/e= 155.3 (M+H+)

d) {5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-ethyl-1H-[1,2,4]triazol-3-yl}-dimethyl-amine

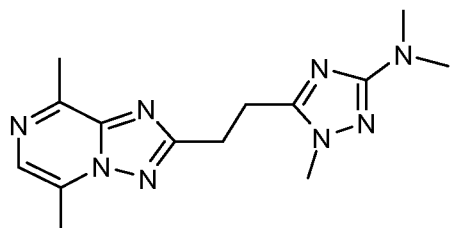


15

Was prepared in the same manner as described in General Procedure Example 1g) using ((5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)methyl)triphenylphosphonium chloride (100 mg, 218  $\mu$ mol, Eq: 1.00), 3-(dimethylamino)-1-methyl-1H-1,2,4-triazole-5-carbaldehyde (33.6 mg, 218  $\mu$ mol, Eq: 1.00) as starting materials. Chromatography afforded {5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-ethyl-1H-[1,2,4]triazol-3-yl}-dimethyl-amine (16 mg / 24.6 %) as a bright yellow viscous oil. MS: m/e= 299.4 (M+H+)

### Example 6

{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-dimethyl-amine

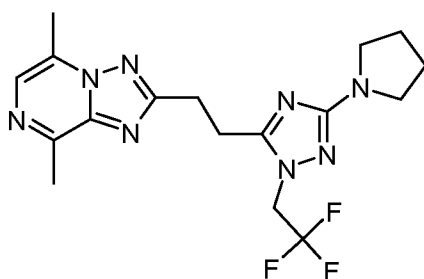


25

Was prepared in the same manner as described in General Procedure Example 2 using 5-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)vinyl)-N,N,1-trimethyl-1H-1,2,4-triazol-3-amine (16 mg, 53.6  $\mu\text{mol}$ , Eq: 1.00) as starting material. Filtration and evaporation of the solvent afforded {5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-  
 5 [1,2,4]triazol-3-yl}-dimethyl-amine (12 mg / 74.5%) as a colorless viscous oil. MS: m/e= 301.9 (M+H+)

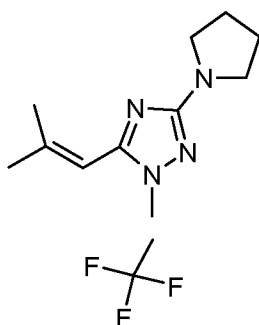
### Example 7

5,8-Dimethyl-2-{2-[5-pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine



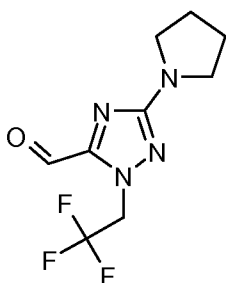
10

a) 5-(2-Methyl-propenyl)-3-pyrrolidin-1-yl-1-(2,2,2-trifluoro-ethyl)-1H-[1,2,4]triazole



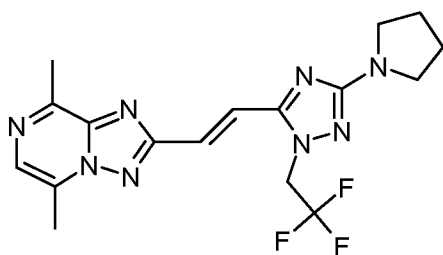
A mixture of (Z)-methyl N-3-methylbut-2-enoylpyrrolidine-1-carbimidothioate (2.515 g, 11.1 mmol, Eq: 1.00) and (2,2,2-trifluoroethyl)hydrazine (5 g, 30.7 mmol, Eq: 2.76) was stirred  
 15 for 1 hour at 100 °C. The mixture was dissolved in ethyl acetate and washed with water 3 times and once with brine. The organic layer was separated, dried over magnesium sulfate, filtrated and evaporated affording 5-(2-methyl-propenyl)-3-pyrrolidin-1-yl-1-(2,2,2-trifluoro-ethyl)-1H-[1,2,4]triazole (1.599 g / 52.5%) as an off- white waxy solid. MS: m/e= 275.4 (M+H+)

b) 5-Pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazole-3-carbaldehyde



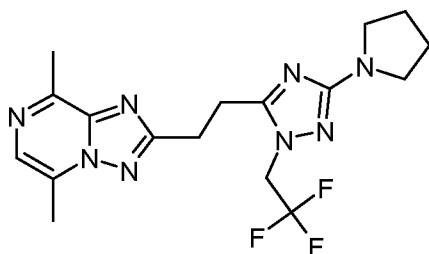
Was prepared in the same manner as described in General Procedure Example 1e) using 5-(2-methylprop-1-enyl)-3-(pyrrolidin-1-yl)-1-(2,2,2-trifluoroethyl)-1H-1,2,4-triazole (1.599 g, 5.83 mmol, Eq: 1.00) as starting material. Extraction and evaporation of the solvents afforded 5-pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazole-3-carbaldehyde (1.134 g / 78.4%) as a dark brown waxy solid. MS: m/e= 249.4 (M+H<sup>+</sup>)

c) 5,8-Dimethyl-2-{2-[5-pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-vinyl}-[1,2,4]triazolo[1,5-a]pyrazine



10 Was prepared in the same manner as described in General Procedure Example 1g) using ((5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)methyl)triphenylphosphonium chloride (85 mg, 185 μmol, Eq: 1.00), 3-(pyrrolidin-1-yl)-1-(2,2,2-trifluoroethyl)-1H-1,2,4-triazole-5-carbaldehyde (50.6 mg, 204 μmol, Eq: 1.1) as starting materials. Chromatography afforded 5,8-dimethyl-2-{2-[5-pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-vinyl}-[1,2,4]triazolo[1,5-a]pyrazine (20 mg / 27.5%) as a white viscous oil. MS: m/e= 393.5 (M+H<sup>+</sup>)

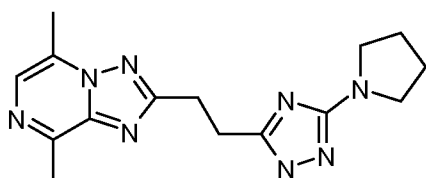
d) 5,8-Dimethyl-2-{2-[5-pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine



Was prepared in the same manner as described in General Procedure Example 2 using 5,8-dimethyl-2-(2-(3-(pyrrolidin-1-yl)-1-(2,2,2-trifluoroethyl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyrazine (20 mg, 51.0  $\mu\text{mol}$ , Eq: 1.00) as starting material. The crude material was applied on a 5 g silicagel column using ethyl acetate / methanol 0-10 % as eluent  
 5 affording 5,8-dimethyl-2-{2-[5-pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine (11 mg / 52.4%) as a white solid. MS: m/e= 395.8 (M+H+)

### Example 8

5,8-Dimethyl-2-[2-(5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine

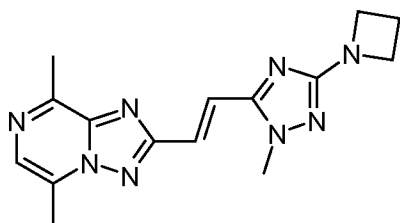


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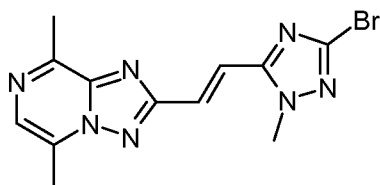
2-(2-(1-(4-methoxybenzyl)-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-5,8-dimethyl-  
 [1,2,4]triazolo[1,5-a]pyrazine (13.6 mg, 31.4  $\mu\text{mol}$ , Eq: 1.00) was stirred with trifluoroacetic  
 acide (143 mg, 96.3  $\mu\text{l}$ , 1.26 mmol, Eq: 40) and anisole (61.2 mg, 61.8  $\mu\text{l}$ , 566  $\mu\text{mol}$ , Eq: 18) in  
 Dichloromethane (400  $\mu\text{l}$ ) overnight at room-temperature. The reaction mixture was extracted  
 15 with aq. sodium borohydride sat. and dichloromethane three times, dried over magnesium  
 sulfate, filtered and evaporated to give 5,8-Dimethyl-2-[2-(5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-  
 yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine (6.6 mg, 67.2%) as off-white solid.

### Example 9

2-[2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-  
 20 [1,2,4]triazolo[1,5-a]pyrazine

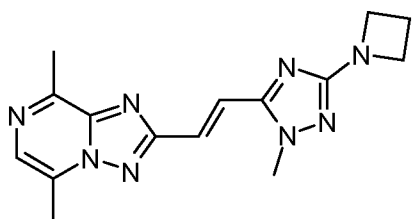


a) 2-[(E)-2-(5-Bromo-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-  
 [1,2,4]triazolo[1,5-a]pyrazine



Was prepared in the same manner as described in Example 1g) using 3-bromo-1-methyl-1H-1,2,4-triazole-5-carbaldehyde (218 mg, 1.15 mmol, Eq: 1.00) and ((5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)methyl)triphenylphosphonium chloride (527 mg, 1.15 mmol, Eq: 1.00) as starting materials. Chromatography afforded 2-[(E)-2-(5-bromo-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (258 mg / 67.3%) as a white solid. MS: m/e= 336.0/334.1 (M+H+), mp: 199.4°C

b) 2-[2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



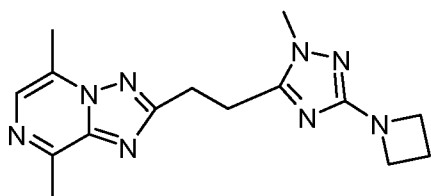
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A solution of 2-(2-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (28 mg, 83.8 μmol, Eq: 1.00) in dioxane (1 ml) was purged with argon, then sodium phenoxide (14.6 mg, 126 μmol, Eq: 1.5), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xant-phos) (3.88 mg, 6.7 μmol, Eq: 0.08), tris(dibenzylideneacetone) dipalladium chloroform complex / Pd<sub>2</sub>(dba)<sub>3</sub>CHCl<sub>3</sub> (3.47 mg, 3.35 μmol, Eq: 0.04) and azetidine (9.57 mg, 11.3 μl, 168 μmol, Eq: 2) were added. The vial was capped and irradiated at 140 °C for 30 minutes in the microwave oven. The crude material was applied on silicagel and purified by chromatography over a 5 g silicagel column using ethyl acetate / methanol 0-10 % as eluent affording 2-[2-(5-azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (4 mg / 15.4%) as a light yellow solid. MS: m/e= 311.4 (M+H+)

20

### Example 10

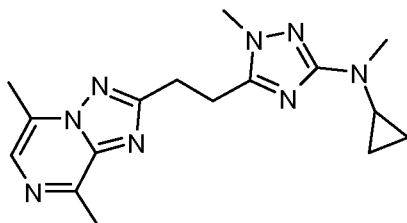
2-[2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



Was prepared in the same manner as described in General Procedure Example 2 using 2-(2-(3-(azetidin-1-yl)-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (10 mg, 32.2  $\mu\text{mol}$ , Eq: 1.00) as starting material. Filtration and evaporation afforded  
 5 2-[2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (15 mg / 149 %) as a white solid. MS:  $m/e = 313.4$  (M+H<sup>+</sup>), mp: 103-107°C

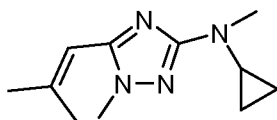
### Example 11

Cyclopropyl-{5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-methyl-amine



10

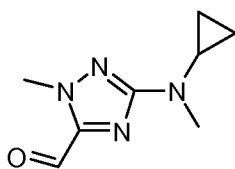
a) Cyclopropyl-methyl-[1-methyl-5-(2-methyl-propenyl)-1H-[1,2,4]triazol-3-yl]-amine



To a solution of 3-methylbut-2-enoyl isothiocyanate (500 mg, 3.54 mmol, Eq: 1.00) in Tetrahydrofuran (3.5 ml) was added a solution of N-methylcyclopropanamine (264 mg, 3.72 mmol, Eq: 1.05) in Tetrahydrofuran (3.5 ml). The mixture was stirred for 30 minutes. Sodium carbonate (394 mg, 3.72 mmol, Eq: 1.05) and iodomethane (1.01 g, 443  $\mu\text{l}$ , 7.08 mmol, Eq: 2)  
 15 was added and stirred overnight at 70°C. The solvent was evaporated. Methylhydrazine (1.63 g, 1.86 ml, 35.4 mmol, Eq: 10) was added and the mixture was stirred for 2 hours at 100°C. MS showed just product peak. The crude material was applied on silica gel and purified by column  
 20 chromatography using heptane / ethyl acetate (0-40% ethyl acetate) as eluent affording

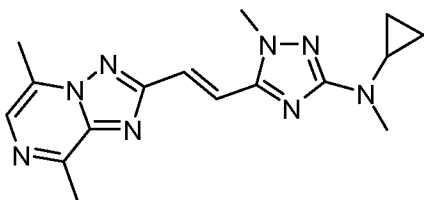
Cyclopropyl-methyl-[1-methyl-5-(2-methyl-propenyl)-1H-[1,2,4]triazol-3-yl]-amine (305 mg, 41.8%) as light yellow oil. MS:  $m/z = 207.0$  (M+H<sup>+</sup>)

b) 5-(Cyclopropyl-methyl-amino)-2-methyl-2H-[1,2,4]triazole-3-carbaldehyde



Was prepared in the same manner as described in General Procedure Example 1e) using N-cyclopropyl-N,1-dimethyl-5-(2-methylprop-1-enyl)-1H-1,2,4-triazol-3-amine (150 mg, 727  $\mu\text{mol}$ , Eq: 1.00) as starting material. Extraction and evaporation of the solvents afforded 5- (Cyclopropyl-methyl-amino)-2-methyl-2H-[1,2,4]triazole-3-carbaldehyde ( 105 mg / 80.1%) as a black semisolid.

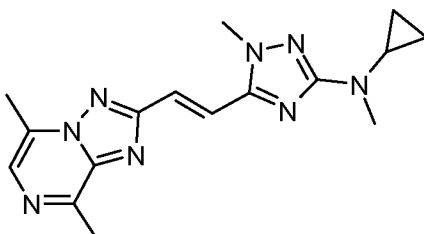
c) Cyclopropyl- {5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl} -methyl-amine



10 Was prepared in the same manner as described in General Procedure Example 1g) using ((5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)methyl)triphenylphosphonium chloride (127 mg, 277  $\mu\text{mol}$ , Eq: 1.00) and 3-(cyclopropyl(methyl)amino)-1-methyl-1H-1,2,4-triazole-5-carbaldehyde (50 mg, 277  $\mu\text{mol}$ , Eq: 1.00) as starting materials. Chromatography afforded Cyclopropyl- {5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-  
15 [1,2,4]triazol-3-yl} -methyl-amine (30 mg, 33.3%) as light yellow waxy solid. MS:  $m/z = 325.5$  (M+H<sup>+</sup>)

### Example 12

Cyclopropyl- {5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl} -methyl-amine



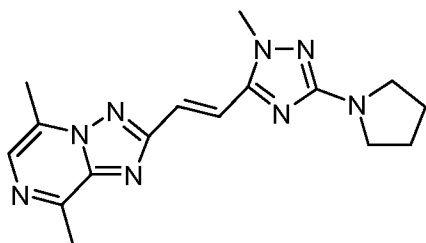
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Was prepared in the same manner as described in General Procedure Example 2 using N-cyclopropyl-5-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)vinyl)-N,1-dimethyl-1H-1,2,4-

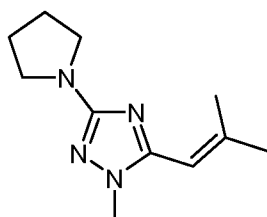
triazol-3-amine (23 mg, 70.9  $\mu\text{mol}$ , Eq: 1.00) as starting material. Filtration and evaporation of the solvent afforded Cyclopropyl- $\{5-[2-(5,8\text{-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1\text{-methyl-1H-[1,2,4]triazol-3-yl}\}$ -methyl-amine (15 mg / 64.8%) as a white waxy solid. MS:  $m/z = 327.5$  (M+H<sup>+</sup>)

### 5 Example 13

5,8-Dimethyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-a]pyrazine



a) 1-Methyl-5-(2-methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole

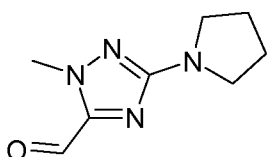


10

Was prepared in the same manner as described in General procedure 1d, using 3-Methyl-but-2-enoic acid 1-methylsulfanyl-1-pyrrolidin-1-yl-meth-(Z)-ylideneamide and methylhydrazine as starting materials. Extraction and evaporation of the solvents afforded 1-Methyl-5-(2-methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (261 mg / 106%) as yellow oil. MS:  $m/z = 207.1$  (M+H<sup>+</sup>)

15

b) 2-Methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde



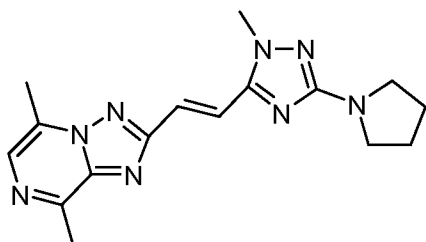
Was prepared in the same manner as described in General procedure 1e, using 1-methyl-5-(2-methylprop-1-enyl)-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole (1.346 g, 6.52 mmol, Eq: 1.00) as starting material. Extraction and evaporation of the solvents afforded 2-Methyl-5-pyrrolidin-1-

20



yl-2H-[1,2,4]triazole-3-carbaldehyde (599 mg / 50.9%) as yellow solid. MS:  $m/z = 181.4$  (M+H<sup>+</sup>), mp: 64.7 °C.

c) 5,8-Dimethyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-a]pyrazine



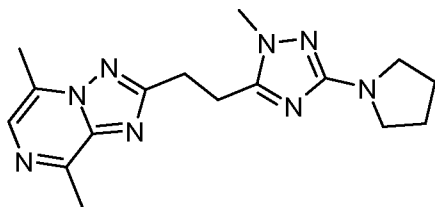
5

Was prepared in the same manner as described in General Procedure Example 1g) using 1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole-5-carbaldehyde (75 mg, 416  $\mu\text{mol}$ , Eq: 1.00) and ((5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)methyl)triphenylphosphonium chloride (191 mg, 416  $\mu\text{mol}$ , Eq: 1.00) as starting materials. Chromatography afforded Cyclopropyl-{5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-methyl-amine (71 mg, 52.6%) as light yellow solid. MS:  $m/z = 325.4$  (M+H<sup>+</sup>), mp: 196.4 °C

10

#### Example 14

5,8-Dimethyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine



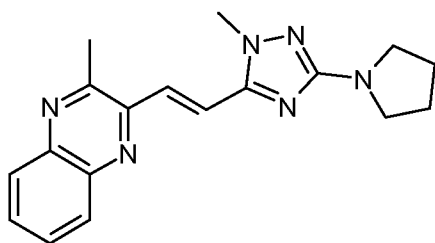
15

Was prepared in the same manner as described in General Procedure Example 2 using 5,8-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyrazine (65 mg, 200  $\mu\text{mol}$ , Eq: 1.00) as starting material. Filtration and evaporation of the solvent afforded Cyclopropyl-{5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-methyl-amine (45 mg / 68.6%) as a white solid. MS:  $m/z = 327.3$  (M+H<sup>+</sup>), mp: 126.5 °C

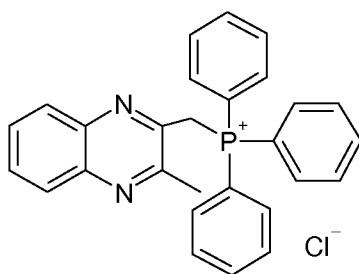
20

#### Example 15

2-Methyl-3-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-quinoxaline

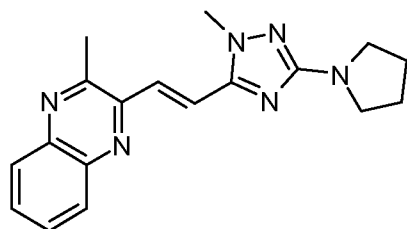


a) (3-Methyl-quinoxalin-2-ylmethyl)-triphenyl-phosphonium chloride



Was prepared in same manner as described in General Procedure Example 1f) using 2-(chloromethyl)-3-methylquinoxaline (350 mg, 1.82 mmol, Eq: 1.00) as starting material affording (3-Methyl-quinoxalin-2-ylmethyl)-triphenyl-phosphonium chloride (724 mg, 87.6%) as light brown solid. MS:  $m/z = 419.5$  (M-Cl+H<sup>+</sup>), mp: 155.4

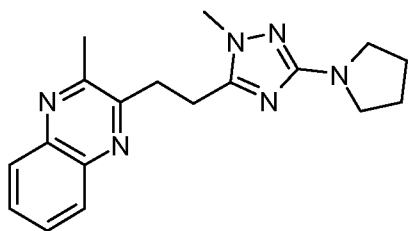
b) 2-Methyl-3-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-quinoxaline



Was prepared in the same manner as described in General Procedure Example 1g) using 1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole-5-carbaldehyde (50 mg, 277  $\mu$ mol, Eq: 1.00) and ((3-methylquinoxalin-2-yl)methyl)triphenylphosphonium chloride (126 mg, 277  $\mu$ mol, Eq: 1.00) as starting materials. Chromatography afforded 2-Methyl-3-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-quinoxaline (50 mg, 56.2%) as light yellow solid. MS:  $m/z = 321.4$  (M+H<sup>+</sup>)

### Example 16

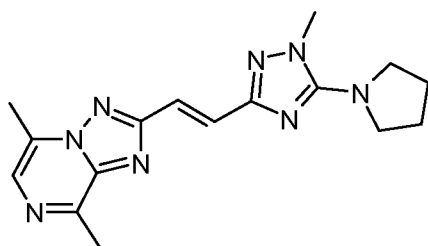
2-Methyl-3-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-quinoxaline



Was prepared in the same manner as described in General Procedure Example 2 using 2-methyl-3-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)quinoxaline (45 mg, 140  $\mu\text{mol}$ , Eq: 1.00) as starting material. Filtration and evaporation of the solvent afforded 2-Methyl-3-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-quinoxaline (15 mg / 33.1%) as a light yellow solid. MS:  $m/z = 323.4$  (M+H<sup>+</sup>)

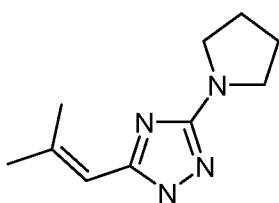
### Example 17

5,8-Dimethyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-a]pyrazine



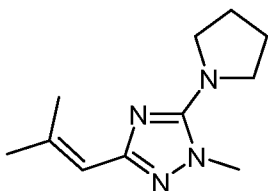
10

a) 5-(2-Methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole



Was prepared in the same manner as described in General Procedure Example 2, using (Z)-methyl N-3-methylbut-2-enoylpyrrolidine-1-carbimidothioate (3.69 g, 16.3 mmol, Eq: 1.00) and hydrazine 1M in THF (16.3 ml, 16.3 mmol, Eq: 1.00). Chromatography afforded 5-(2-Methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (695 mg, 22.2%) as white waxy solid. MS:  $m/z = 193.1$  (M+H<sup>+</sup>)

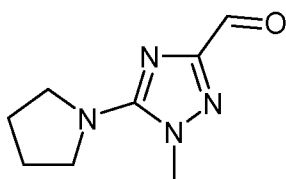
b) 1-Methyl-3-(2-methyl-propenyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazole



5-(2-methylprop-1-enyl)-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole (220 mg, 1.14 mmol, Eq: 1.00) was solved in DMF (4.5 ml) and cooled in a icebath to 0°C. sodium hydride (54.9 mg, 1.37 mmol, Eq: 1.2) was added and stirring was continued for 30min. iodomethane (325 mg, 143  $\mu$ l, 2.29 mmol, Eq: 2) was added under ice cooling. The cooling bath was removed after 15min. and stirring was continued overnight. Water was added and extracted two times with ethyl acetate, dried over magnesium sulfate, filtered and evaporated. Separation of the isomers afforded

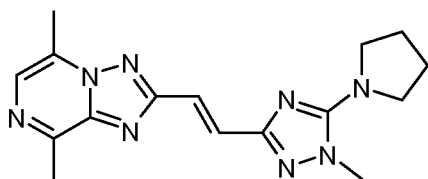
1-Methyl-3-(2-methyl-propenyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazole (51 mg, 21.6%) as light yellow solid. MS:  $m/z = 193.1$  (M+H<sup>+</sup>)

10 c) 1-Methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole-3-carbaldehyde



Was prepared in the same manner as described in General procedure 1e, using 1-methyl-3-(2-methylprop-1-enyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazole (48 mg, 233  $\mu$ mol, Eq: 1.00) as starting material. Extraction and evaporation of the solvents afforded 1-Methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole-3-carbaldehyde (47 mg / 112%) as light brown oil.

d) 5,8-Dimethyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-a]pyrazine

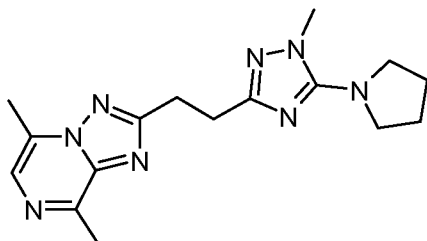


Was prepared in the same manner as described in General Procedure Example 1g) using 1-methyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazole-3-carbaldehyde (45 mg, 250  $\mu$ mol, Eq: 1.00) and ((5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)methyl)triphenylphosphonium chloride (115 mg, 250  $\mu$ mol, Eq: 1.00) as starting materials. Chromatography afforded 5,8-Dimethyl-2-[2-(1-

methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-a]pyrazine (32 mg, 39.5%) as white solid. MS:  $m/z = 325.5$  ( $M+H^+$ )

### Example 18

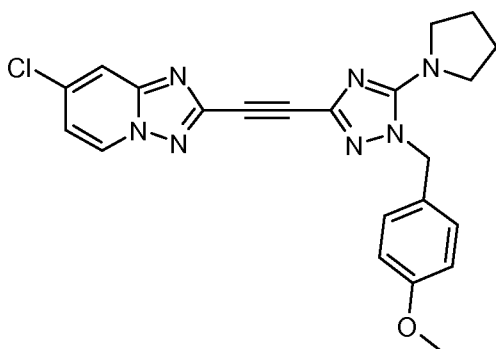
5,8-Dimethyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-  
5 [1,2,4]triazolo[1,5-a]pyrazine



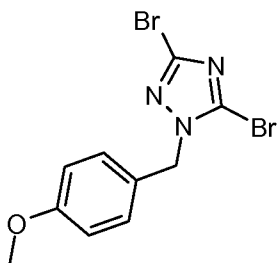
Was prepared in the same manner as described in General Procedure Example 2 using 5,8-dimethyl-2-(2-(1-methyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyrazine (25 mg, 77.1  $\mu\text{mol}$ , Eq: 1.00) as starting material. Filtration and evaporation of the solvent afforded 5,8-Dimethyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-  
10 [1,2,4]triazolo[1,5-a]pyrazine (20.1 mg / 79.9%) as a white waxy solid. MS:  $m/z = 326.4$  ( $M+H^+$ )

### Example 19

7-Chloro-2-[1-(4-methoxy-benzyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-ylethynyl]-  
15 [1,2,4]triazolo[1,5-a]pyridine

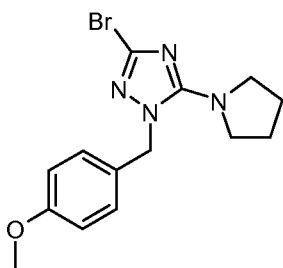


a) 3,5-Dibromo-1-(4-methoxy-benzyl)-1H-[1,2,4]triazole



3,5-dibromo-1H-1,2,4-triazole (1.5 g, 6.61 mmol, Eq: 1.00), potassium iodide (110 mg, 661  $\mu\text{mol}$ , Eq: 0.10), 4-methoxybenzyl chloride (1.14 g, 990  $\mu\text{l}$ , 7.27 mmol, Eq: 1.1) and N,N-diisopropylethylamine (1.71 g, 2.31 ml, 13.2 mmol, Eq: 2.0) was stirred in acetonitrile (23.0 ml) overnight at room temperature. The crude material was applied on silica gel and purified by column chromatography using heptane / ethyl acetate gradient as eluent to afford 3,5-dibromo-1-(4-methoxy-benzyl)-1H-[1,2,4]triazole (1.79 g / 78.0%) as a white solid. MS: m/e= 345/6/8/50/51 (M+H<sup>+</sup>), mp: 75.7°C

b) 3-Bromo-1-(4-methoxy-benzyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazole

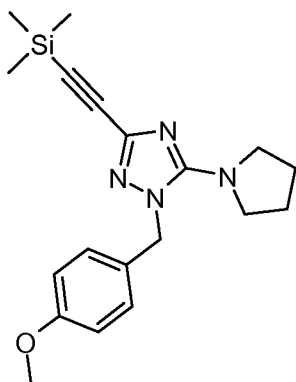


10

A mixture of 3,5-dibromo-1-(4-methoxybenzyl)-1H-1,2,4-triazole (1.268 g, 3.65 mmol, Eq: 1.00) and pyrrolidine (273 mg, 317  $\mu\text{l}$ , 3.84 mmol, Eq: 1.05) in dimethyl formamide (12 ml) was heated for 18 hours to 110 °C under argon atmosphere. The crude material was applied on silicagel and purified by flash chromatography over a 50 g silicagel column using heptane / ethyl acetate 30-50 % as eluent affording 3-bromo-1-(4-methoxy-benzyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazole (608 mg / 49.3%) as a colorless oil. MS: m/e= 338/339 (M+H<sup>+</sup>)

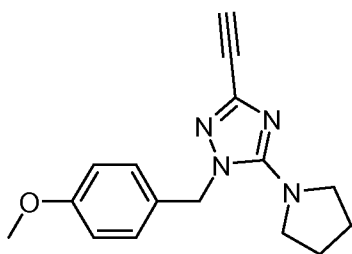
15

c) 1-(4-Methoxy-benzyl)-5-pyrrolidin-1-yl-3-trimethylsilanylethynyl-1H-[1,2,4]triazole



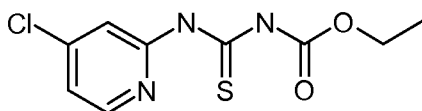
A mixture of 3-bromo-1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazole (197 mg, 584  $\mu\text{mol}$ , Eq: 1.00), ethynyltrimethylsilane (115 mg, 164  $\mu\text{l}$ , 1.17 mmol, Eq: 2) and triethylamine (88.7 mg, 122  $\mu\text{l}$ , 876  $\mu\text{mol}$ , Eq: 1.5) in tetrahydrofuran (3 ml) was purged for 5 minutes with nitrogen. Then copper (I) iodide (1.11 mg, 5.84  $\mu\text{mol}$ , Eq: 0.01), bis(triphenylphosphine) palladium(II) chloride (4.1 mg, 5.84  $\mu\text{mol}$ , Eq: 0.01) and triphenylphosphine (1.53 mg, 5.84  $\mu\text{mol}$ , Eq: 0.01) were added, the vessel was capped and heated to 75  $^{\circ}\text{C}$  for 18 hours. The crude material was applied on silicagel and purified by flash chromatography over a 20 g silicagel column using heptane / ethyl acetate 10-30 % as eluent affording 1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-3-(trimethylsilyl)ethynyl-1H-[1,2,4]triazole (95 mg / 45.9%) as an orange oil. MS:  $m/e = 355.4$  (M+H<sup>+</sup>)

d) 3-Ethynyl-1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-[1,2,4]triazole



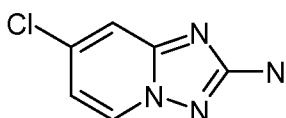
A mixture of 1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-3-((trimethylsilyl)ethynyl)-1H-1,2,4-triazole (95 mg, 268  $\mu\text{mol}$ , Eq: 1.00) and sodium hydroxide sol. 1N (0.1 ml) in methanol (3 ml) was stirred for 18 hours at 25  $^{\circ}\text{C}$ . The mixture was diluted with ethyl acetate and washed with water, the organic layer was separated, dried over magnesium sulfate, filtrated and evaporated affording 3-ethynyl-1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-[1,2,4]triazole (83 mg / 110%) as a yellow oil. MS:  $m/e = 283.4$  (M+H<sup>+</sup>)

e) 1-Ethoxycarbonyl-3-(4-chloro-pyridin-2-yl)-thiourea



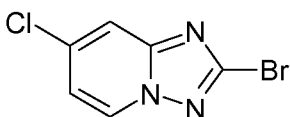
To a solution of 4-chloropyridin-2-amine (2.16 g, 16.8 mmol, Eq: 1.00) in dioxane (70 ml) was added O-ethyl carbonisothiocyanatidate (2.2 g, 1.9 ml, 16.8 mmol, Eq: 1.00) at 25 °C. The resulting mixture was stirred for 2 hours at 25 °C. The mixture was diluted with ethyl acetate and washed with water and brine, the organic layer was separated, dried over magnesium sulfate, filtrated and evaporated affording 1-ethoxycarbonyl-3-(4-chloro-pyridin-2-yl)-thiourea (4.02 g/ 92.1%) as a green waxy solid. MS: m/e= 257.9 (M-H+)

f) 7-Chloro-[1,2,4]triazolo[1,5-a]pyridin-2-ylamine



A mixture of hydroxylamine hydrochloride (5.35 g, 77.0 mmol, Eq: 5) and N-ethyl-diisopropylamine (5.97 g, 8.07 ml, 46.2 mmol, Eq: 3) in ethanol (80 ml) was stirred for a few minutes at 25 °C, then the mixture was added to 1-ethoxycarbonyl-3-(4-chloro-pyridin-2-yl)-thiourea (4.0 g, 15.4 mmol, Eq: 1.00) and the resulting mixture was refluxed for 2.5 days (over the weekend). The crude material was applied on SiO<sub>2</sub> and purified by flash chromatography over a 20 g SiO<sub>2</sub> column using ethyl acetate 100 % as eluent affording 7-chloro-[1,2,4]triazolo [1,5-a]pyridin-2-ylamine (2.03 g / 78.2%) as a white solid. MS: m/e= 169.1 (M+H<sup>+</sup>), mp: 189-190°C

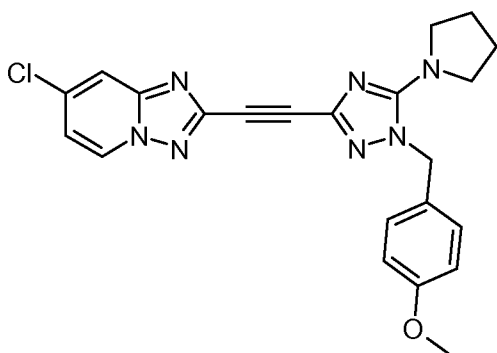
g) 2-Bromo-7-chloro-[1,2,4]triazolo[1,5-a]pyridine



A solution of copper(II) bromide (1.43 g, 6.39 mmol, Eq: 1.1) and tert-butyl nitrite (733 mg, 845 µl, 6.39 mmol, Eq: 1.1) in acetonitrile (29.4 ml) (dark green) was heated to 75 °C, then 7-chloro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (980 mg, 5.81 mmol, Eq: 1.00) was added in small portions. The resulting mixture was stirred for 2 hours at 75 °C. The mixture was diluted with dichloromethane and washed 3 times with water, the organic layers were combined, dried over magnesium sulfate filtrated and evaporated. The crude material was applied on SiO<sub>2</sub> and purified by flash chromatography over a 20 g SiO<sub>2</sub> column using heptane / ethyl acetate 10-40 % as eluent affording 2-bromo-7-chloro-[1,2,4]triazolo[1,5-a]pyridine (434 mg / 32.1%) as a white solid. MS: m/e= 230 (M+H<sup>+</sup>)

h) 7-Chloro-2-[1-(4-methoxy-benzyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-ylethynyl]-[1,2,4]triazolo[1,5-a]pyridine

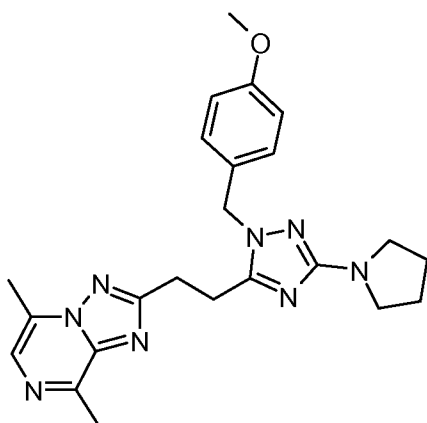


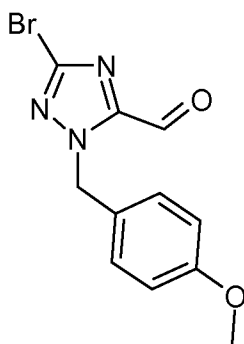


A mixture of 3-ethynyl-1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazole (75 mg, 266  $\mu\text{mol}$ , Eq: 1.00), 2-bromo-7-chloro-[1,2,4]triazolo[1,5-a]pyridine (67.9 mg, 292  $\mu\text{mol}$ , Eq: 1.1) and triethylamine (40.3 mg, 55.5  $\mu\text{l}$ , 398  $\mu\text{mol}$ , Eq: 1.5) in tetrahydrofuran (2 ml) was  
 5 purged with argon, then copper (I) iodide (1.01 mg, 5.31  $\mu\text{mol}$ , Eq: 0.02), bis(triphenylphosphine) palladium(II) chloride (3.73 mg, 5.31  $\mu\text{mol}$ , Eq: 0.02) and triphenylphosphine (1.39 mg, 5.31  $\mu\text{mol}$ , Eq: 0.02) were added, the vessel was capped and heated for 18 hours to 75 °C. Still starting material. The mixture was cooled, purged with argon and another  
 10 portion of copper (I) iodide (1.01 mg, 5.31  $\mu\text{mol}$ , Eq: 0.02), bis(triphenylphosphine) palladium(II) chloride (3.73 mg, 5.31  $\mu\text{mol}$ , Eq: 0.02) and triphenylphosphine (1.39 mg, 5.31  $\mu\text{mol}$ , Eq: 0.02) was added and the mixture was stirred again over night at 75 °C. The crude material was applied on silicagel and purified by flash chromatography over a 20 g silicagel column using ethyl acetate / methanol 0-10 % as eluent affording 7-chloro-2-[1-(4-methoxybenzyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-ylethynyl]-[1,2,4]triazolo[1,5-a]pyridine (33 mg /  
 15 26.8%) as an orange oil. MS: m/e= 434.4 (M+H+)

### Example 20

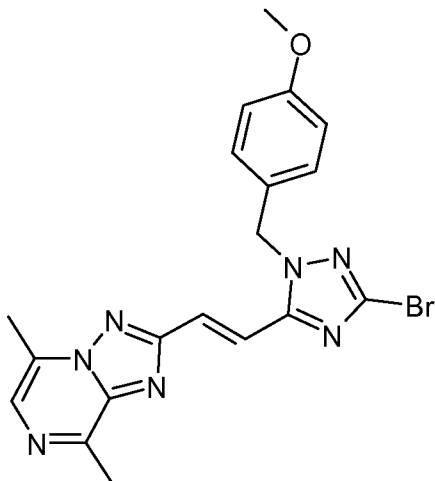
2-{2-[2-(4-Methoxy-benzyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine





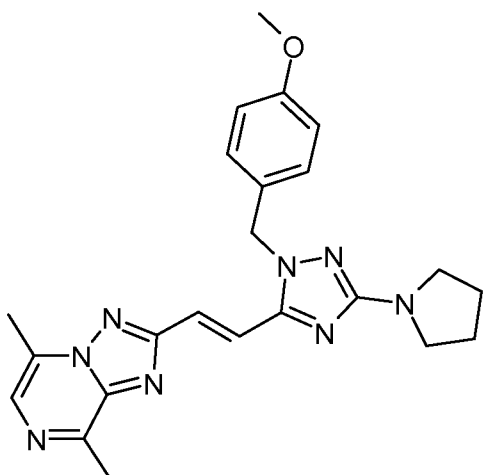
Was prepared in the same manner as described in General Procedure Example 8a) using 3,5-dibromo-1-(4-methoxybenzyl)-1H-1,2,4-triazole (150 mg, 432  $\mu\text{mol}$ , Eq: 1.00) as starting material. Extraction and evaporation of the solvents afforded 1-Methyl-5-pyrrolidin-1-yl-1H-  
5 [1,2,4]triazole-3-carbaldehyde (150 mg / 117%) as dark green oil.

b) 2-{2-[5-Bromo-2-(4-methoxy-benzyl)-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



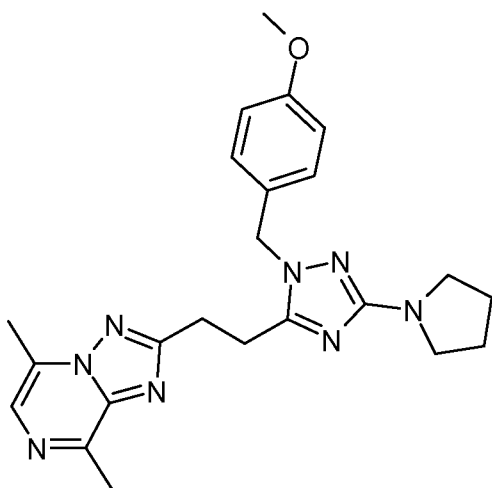
Was prepared in the same manner as described in General Procedure Example 1g) using  
10 3-bromo-1-(4-methoxybenzyl)-1H-1,2,4-triazole-5-carbaldehyde (50 mg, 169  $\mu\text{mol}$ , Eq: 1.00) and ((5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)methyl)triphenylphosphonium chloride (77.5 mg, 169  $\mu\text{mol}$ , Eq: 1.00) as starting materials. Chromatography afforded 2-{2-[5-Bromo-2-(4-methoxy-benzyl)-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (50 mg, 35.4%) as a white solid. MS:  $m/z = 442.3$  ( $M+H^+$ )

15 c) 2-{2-[2-(4-Methoxy-benzyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



Was prepared in the same manner as described in General Procedure Example 9 using 2-(2-(3-bromo-1-(4-methoxybenzyl)-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (55 mg, 125  $\mu\text{mol}$ , Eq: 1.00) and pyrrolidine (17.8 mg, 20.7  $\mu\text{l}$ , 250  $\mu\text{mol}$ , Eq: 2) as starting materials. Chromatography afforded 2-{2-[2-(4-Methoxy-benzyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (23 mg, 42.8%) as a light yellow solid. MS:  $m/z = 431.5$  (M+H<sup>+</sup>)

d) 2-{2-[2-(4-Methoxy-benzyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



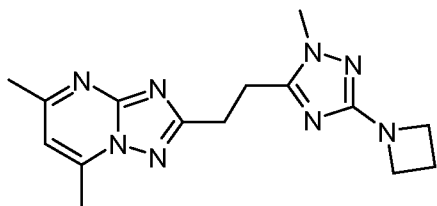
10

Was prepared in the same manner as described in General Procedure Example 2 using 2-(2-(1-(4-methoxybenzyl)-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (21 mg, 48.8  $\mu\text{mol}$ , Eq: 1.00) as starting material. Filtration and evaporation of the solvent afforded 2-{2-[2-(4-Methoxy-benzyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (17 mg / 80.6%) as a colorless oil. MS:  $m/z = 433.5$  (M+H<sup>+</sup>)

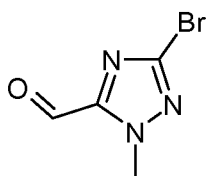
15

**Example 21**

2-[2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine



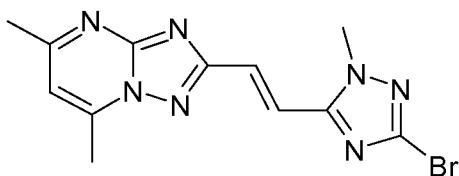
5 a) 5-Bromo-2-methyl-2H-[1,2,4]triazole-3-carbaldehyde



To a solution of 3,5-dibromo-1-methyl-1H-1,2,4-triazole (500 mg, 2.08 mmol, Eq: 1.00) in tetrahydrofuran (5 ml) was added dropwise at -45 °C under argon atmosphere n-butyllithium  
 10 1.6 M in hexane (1.56 ml, 2.49 mmol, Eq: 1.2). The resulting mixture was stirred for 30 minutes at -45°C and was then cooled to -70°C. Then dimethyl formamide (197 mg, 209 µl, 2.7 mmol, Eq: 1.3) was added dropwise. After 15 minutes the cooling bath was removed and the mixture was allowed to reach 25 °C. The mixture was stirred for additional 2 hours at 25 °C. The mixture was poured on water and extracted twice with ethyl acetate, the organic layers were combined,  
 15 washed with water and brine, dried over magnesium sulfate, filtrated and evaporated, affording 5-bromo-2-methyl-2H-[1,2,4]triazole-3-carbaldehyde (218 mg / 55.3 %) as an orange semi solid.  
 MS: m/e= 189 (M+H+)

b) 2-[2-(5-Bromo-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine

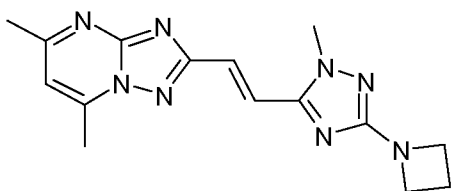
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A mixture of 3-bromo-1-methyl-1H-1,2,4-triazole-5-carbaldehyde (193 mg, 1.02 mmol, Eq: 1.00), ((5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl)triphenylphosphonium chloride (466 mg, 1.02 mmol, Eq: 1.00) and DBU (387 mg, 383  $\mu$ l, 2.54 mmol, Eq: 2.5) in tetrahydrofuran (12 ml) was stirred for 18 hours at 25 °C under argon atmosphere.

- 5 Chromatography afforded ) 2-[2-(5-bromo-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine (161 mg / 47.4%) as a white solid. MS:  $m/z = 334/336$  (M+H<sup>+</sup>), mp: 277.4°C.

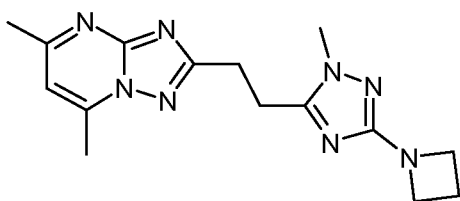
c) 2-[2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine



10

A solution of 2-(2-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine (59 mg, 177  $\mu$ mol, Eq: 1.00) in dioxane (2.11 ml) was purged with argon, then azetidine (15.1 mg, 17.8  $\mu$ l, 265  $\mu$ mol, Eq: 1.5), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (8.17 mg, 14.1  $\mu$ mol, Eq: 0.08), tris(dibenzylideneacetone)dipalladium chloroform complex (7.31 mg, 7.06  $\mu$ mol, Eq: 0.04) and sodium phenolate (20.5 mg, 177  $\mu$ mol, Eq: 1.00) were added. The vial was capped and irradiated at 140 °C for 60 minutes in the microwave oven. Chromatography afforded 2-[2-(5-azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine (15 mg / 27.4%) as a light yellow solid. MS:  $m/z = 311.4$  (M+H<sup>+</sup>).

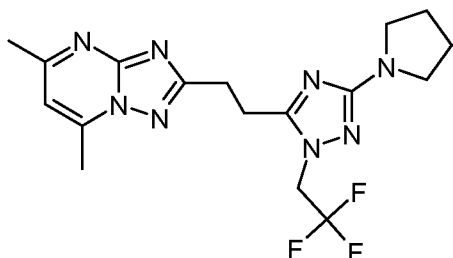
- 20 d) 2-[2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine



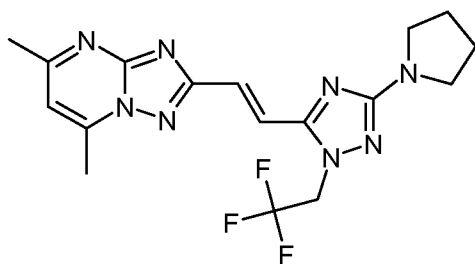
- 25 A mixture of 2-(2-(3-(azetidin-1-yl)-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine (15 mg, 48.3  $\mu$ mol, Eq: 1.00) and palladium on carbon 10 % (5.14 mg, 4.83  $\mu$ mol, Eq: 0.1) in methanol (15 ml) was stirred for 6 hours at 25 °C under hydrogen atmosphere. The catalyst was filtered off, evaporation of the solvent afforded 2-[2-(5-azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine (14.3 mg / 94.7%) as a light yellow solid. MS:  $m/z = 313.4$  (M+H<sup>+</sup>).

**Example 22**

5,7-Dimethyl-2-{2-[5-pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrimidine

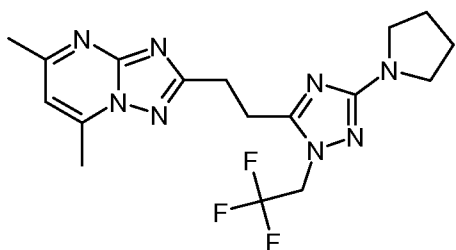


- 5 a) 5,7-Dimethyl-2-{2-[5-pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-vinyl}-[1,2,4]triazolo[1,5-a]pyrimidine



- A mixture of 3-(pyrrolidin-1-yl)-1-(2,2,2-trifluoroethyl)-1H-1,2,4-triazole-5-carbaldehyde (54 mg, 218  $\mu\text{mol}$ , Eq: 1.00), ((5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl)triphenylphosphonium chloride (99.8 mg, 218  $\mu\text{mol}$ , Eq: 1.00) and 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (82.8 mg, 544  $\mu\text{mol}$ , Eq: 2.5) in tetrahydrofuran (3.36 ml) was stirred for 18 hours at 25 °C under argon atmosphere. Chromatography afforded 5,7-dimethyl-2-{2-[5-pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-vinyl}-[1,2,4]triazolo[1,5-a]pyrimidine (20 mg / 23.4%) as a light yellow viscous oil. . MS:  $m/z = 393.4$  (M+H+).

- 15 b) 5,7-Dimethyl-2-{2-[5-pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrimidine

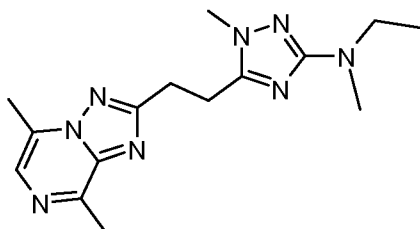


A mixture of 5,7-dimethyl-2-(2-(3-(pyrrolidin-1-yl)-1-(2,2,2-trifluoroethyl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyrimidine (19 mg, 48.4  $\mu\text{mol}$ , Eq: 1.00) and palladium

on carbon 10% (5.15 mg, 4.84  $\mu\text{mol}$ , Eq: 0.1) in methanol (15 ml) was stirred for 6 hours at 25 °C under hydrogen atmosphere. Evaporation of the solvent afforded 5,7-dimethyl-2-{2-[5-pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrimidine (19 mg / 99.5%) as a white solid. MS:  $m/z = 395.5$  (M+H<sup>+</sup>), mp: 180.2°C.

### 5 Example 23

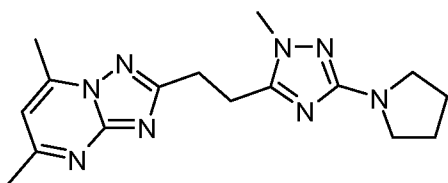
{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-ethyl-methyl-amine



A mixture of 5-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)vinyl)-N-ethyl-N,1-dimethyl-1H-1,2,4-triazol-3-amine (7 mg, 22.4  $\mu\text{mol}$ , Eq: 1.00) and palladium on carbon 10 % (4.77 mg, 4.48  $\mu\text{mol}$ , Eq: 0.2) in methanol (1 ml) was stirred for 14 hours at 25 °C under hydrogen atmosphere. TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 19:1 / UV 254 nm) showed complete reaction (spot to spot). palladium was filtered off and the filtrate was evaporated and applied on silica gel. Purification by column chromatography over 10g SiO<sub>2</sub> using ethyl acetate / methanol (0-10% MeOH) as eluent to give {5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-ethyl-methyl-amine (3.5 mg, 49.7%) as off-white solid

### Example 24

5,7-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyrimidine

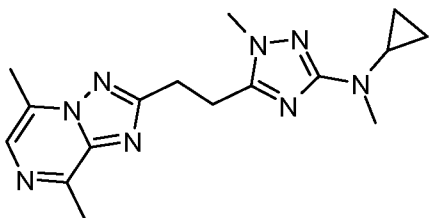


A mixture of 5,7-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyrimidine (65 mg, 200  $\mu\text{mol}$ , Eq: 1.00) and palladium on carbon 10 % (42.6 mg, 40.1  $\mu\text{mol}$ , Eq: 0.2) in methanol (10.0 ml) was stirred for 14 hours at 25 °C under hydrogen atmosphere. TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 19:1 / UV 254 nm) showed complete reaction (spot to spot). palladium was filtered off and the filtrate was evaporated and dried under

high vacuum to give 5,7-Dimethyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrimidine (34 mg, 52%) as viscous oil

### Example 25

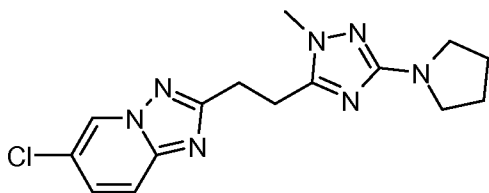
N-cyclopropyl-5-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)ethyl)-N,1-dimethyl-1H-1,2,4-triazol-3-amine



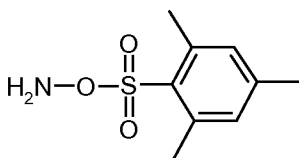
A mixture of N-cyclopropyl-5-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)vinyl)-N,1-dimethyl-1H-1,2,4-triazol-3-amine (23 mg, 70.9  $\mu\text{mol}$ , Eq: 1.00) and palladium on carbon 10 % (7.55 mg, 7.09  $\mu\text{mol}$ , Eq: 0.1) in methanol (3.5 ml) was stirred for 14 hours at 25 °C under hydrogen atmosphere. Palladium was filtered off, the crude material was applied on silica gel and purified by column chromatography using ethyl acetate / methanol (0-10% methanol) as eluent to give N-cyclopropyl-5-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)ethyl)-N,1-dimethyl-1H-1,2,4-triazol-3-amine (15 mg, 64.8%) as white waxy solid

### Example 26

6-Chloro-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine



a) O-(mesitylsulfonyl)hydroxylamine

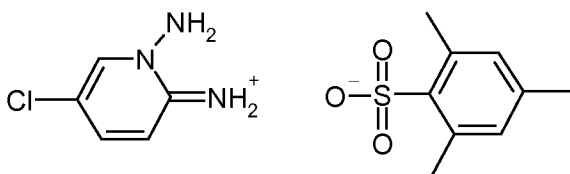


70% aq. perchloric acid (4.34 g, 2.6 ml, 43.2 mmol, Eq: 4.12) was added to ethyl N-mesitylsulfonyloxyacetimidate (2.99 g, 10.5 mmol, Eq: 1.00) in THF (4 ml) at 0 °C. The reaction



mixture was stirred for 1 h at 0 °C. The mixture was poured into water (60 ml) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml + 2 x 10 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. The solution was used without further purification in the next step.

b) 1-Amino-5-chloropyridin-2(1H)-iminium 2,4,6-trimethylbenzenesulfonate

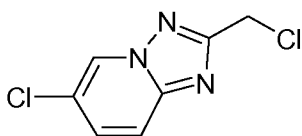


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The fresh solution of O-(mesitylsulfonyl)hydroxylamine (2.14 g, 9.96 mmol, Eq: 1.00) in CH<sub>2</sub>Cl<sub>2</sub> prepared in the previous step was added dropwise at 0 °C to a solution of 5-chloropyridin-2-amine (1.28 g, 9.96 mmol, Eq: 1.00) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml). The suspension was stirred for 20 min and then filtered. The residue was washed with DCM and dried under high vacuum to give the desired product as a white powder (2.5 g, 73%). MS m/z = 144.03 (M-MsO+H<sup>+</sup>)

10

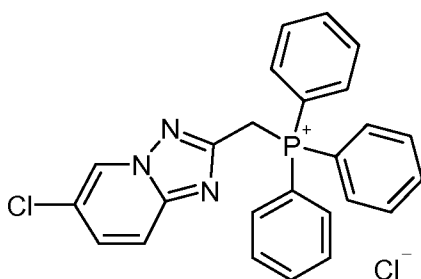
c) 6-Chloro-2-(chloromethyl)-[1,2,4]triazolo[1,5-a]pyridine



A mixture of 1-amino-5-chloropyridin-2(1H)-iminium 2,4,6-trimethylbenzenesulfonate (500 mg, 1.45 mmol, Eq: 1.00), 2-chloroacetyl chloride (172 mg, 122 µl, 1.53 mmol, Eq: 1.05) and pyridine (242 mg, 247 µl, 3.05 mmol, Eq: 2.1) in DMF (5.00 ml) was stirred at 90 °C for 2 h. The mixture was poured on 20 ml half saturated aq. NaHCO<sub>3</sub> and extracted with EtOAc. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to an oil. Purification by column chromatography (SiO<sub>2</sub>, 0 to 80% EtOAc in n-heptane) gave the desired product (68 mg, 23%) as a white solid. MS m/z = 202.1 (M+H<sup>+</sup>)

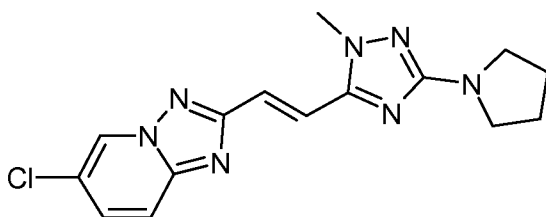
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d) ((6-Chloro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)methyl)triphenylphosphonium chloride



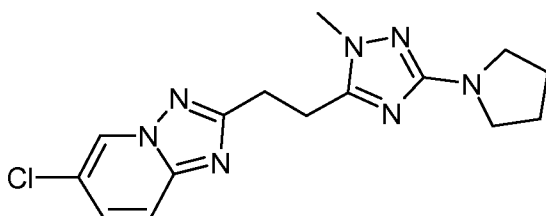
The desired product (225 mg, 75%) was obtained as a white solid in analogy to Example 1f) from 6-chloro-2-(chloromethyl)-[1,2,4]triazolo[1,5-a]pyridine (98 mg, 485  $\mu\text{mol}$ , Eq: 1.00). MS  $m/z = 428.3(\text{M}-\text{Cl}+\text{H}^+)$

5 e) 6-Chloro-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyridine



The desired product was prepared in analogy to Example 1 g) from ((6-chloro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)methyl)triphenylphosphonium chloride (170 mg, 366  $\mu\text{mol}$ , Eq: 1.00) and 1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole-5-carbaldehyde (66.0 mg, 366  $\mu\text{mol}$ , Eq: 1.00). 110 mg (91%) of the desired product were obtained as a light yellow solid. MS:  $m/z = 330.4 (\text{M}+\text{H}^+)$

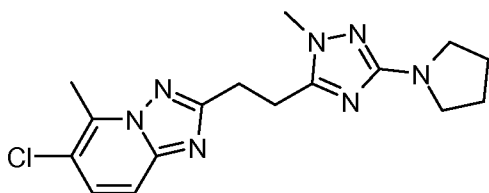
f) 6-Chloro-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine



15 A suspension of 6-chloro-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyridine (50 mg, 152  $\mu\text{mol}$ , Eq: 1.00) and 5% Pd on BaSO<sub>4</sub> (150 mg) in EtOAc (5 ml) was stirred under hydrogen (1 atm) for 2 h. The mixture was filtered over Celite and the residue purified by prep. HPLC to give the desired product (7.7 mg, 15%) as a white solid. MS:  $m/z = 331.9 (\text{M}+\text{H}^+)$

## 20 Example 27

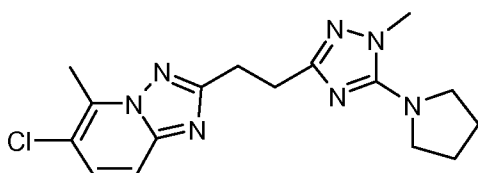
6-Chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine



The product (6.9 mg) was obtained from 5-chloro-6-methylpyridin-2-amine in analogy to Example 26 as a light yellow solid. MS:  $m/z=346.5$  (M+H<sup>+</sup>)

### Example 28

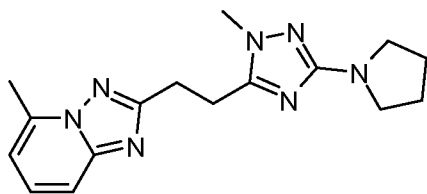
- 5 6-Chloro-5-methyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine



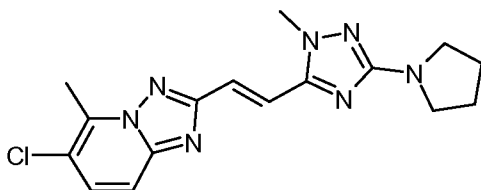
- 10 The product (7 mg) was obtained as a light yellow powder in analogy to Example 26 using 5-chloro-6-methylpyridin-2-amine (step b) and 1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole-3-carbaldehyde (step e) as starting materials. MS:  $m/z=346.5$  (M+H<sup>+</sup>)

### Example 29

- 15 a) 5-Methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine

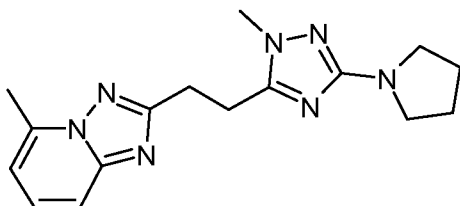


- 15 a) 6-chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyridine



The product (36 mg) was obtained as a light yellow solid from 5-chloro-6-methylpyridin-2-amine in analogy to Example 26, steps b-e. MS:  $m/z=344.3$  (M+H<sup>+</sup>)

b) 5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine



5

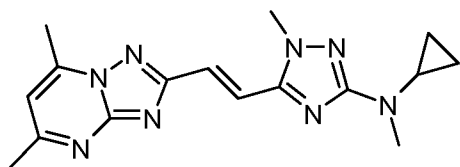
A mixture of 6-chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyridine (5 mg, 14.5  $\mu\text{mol}$ , Eq: 1.00), palladium on carbon (10.0 mg, 94.0  $\mu\text{mol}$ , Eq: 6.46) and triethylamine (0.02 ml) in ethanol (3 ml) was stirred 1 h under hydrogen (1 atm). The mixture was filtered over Celite and then concentrated to an oil. The residue was dissolved in DCM (15 ml) and Na<sub>2</sub>CO<sub>3</sub> (50 mg) was added. The mixture was stirred for 5 min and then filtered over Celite and concentrated to give the desired product (5 mg) as a colorless oil. MS:  $m/z=312.3$  (M+H<sup>+</sup>)

10

### Example 30

Cyclopropyl-5-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-methyl-amine

15



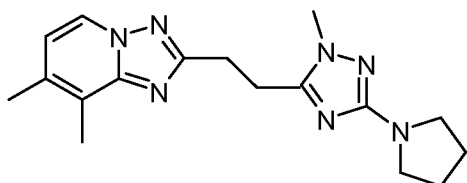
To a solution of 3-(cyclopropyl(methyl)amino)-1-methyl-1H-1,2,4-triazole-5-carbaldehyde (45 mg, 250  $\mu\text{mol}$ , Eq: 1.00) in tetrahydrofuran (2.3 ml) were added ((5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl)triphenylphosphonium chloride (115 mg, 250  $\mu\text{mol}$ , Eq: 1.00) and DBU (95.0 mg, 94.1  $\mu\text{l}$ , 624  $\mu\text{mol}$ , Eq: 2.5). The resulting mixture was stirred for 18 hours at 25 °C. TLC (Hep/EtOAc 1:1 / UV 254 nm) showed no starting material left and new product spot. MS showed product peak also. The crude material was applied on silicagel and purified by flash chromatography over a 20 g silicagel column using heptane / ethyl acetate 1:1 as eluent to give Cyclopropyl-5-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-methyl-amine (30 mg, 37%) as light yellow waxy solid

20

25

**Example 31**

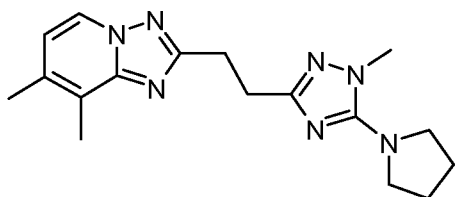
7,8-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine



- 5 The desired product (12.2 mg) was obtained as a light yellow solid in analogy to Example 29 from 5-bromo-3,4-dimethylpyridin-2-amine. MS:  $m/z = 328.5$  (M+H<sup>+</sup>)

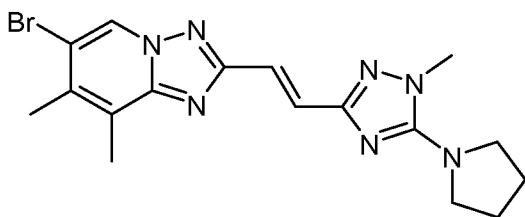
**Example 32**

7,8-Dimethyl-2-(2-(1-methyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine



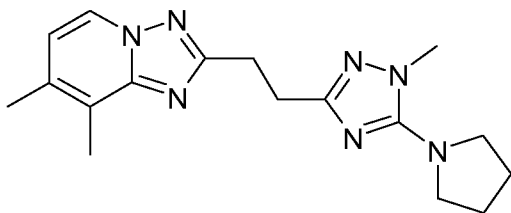
10

a) 6-bromo-7,8-dimethyl-2-(2-(1-methyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyridine



- 15 The desired product (26 mg) was obtained as a light yellow solid in analogy to Example 26 steps a-e using 5-bromo-3,4-dimethylpyridin-2-amine (step b) and 1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole-3-carbaldehyde (step e) as starting materials. MS:  $m/z = 404.4$  (M+H<sup>+</sup>)

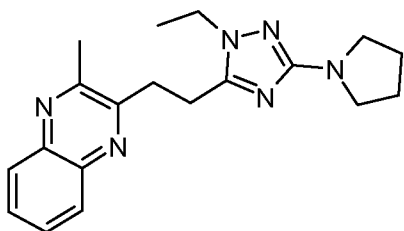
b) 7,8-Dimethyl-2-(2-(1-methyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine



The desired product (10.1 mg) was obtained in analogy to Example 29b from 6-bromo-7,8-dimethyl-2-(2-(1-methyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyridine as a light yellow solid. MS:  $m/z = 326.5$  (M+H<sup>+</sup>)

### 5 Example 33

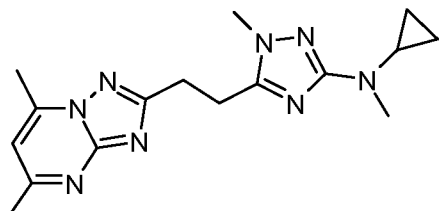
2-[2-(2-Ethyl-5-pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl]-ethyl-3-methyl-quinoxaline



2-(2-(1-ethyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-3-methylquinoxaline (10 mg, 29.9  $\mu\text{mol}$ , Eq: 1.00) was stirred in Ethyl acetate (6 ml) using 5% Pd on Ba<sub>2</sub>SO<sub>4</sub> (3 mg, 30.8  $\mu\text{mol}$ , Eq: 1.00) as catalyst in a hydrogen atmosphere. The mixture was stirred at room temperature for totally 12h. TLC showed nearly complete conversion. The crude material was applied on silica gel and purified by column chromatography using ethyl acetate / methanol (0-5% methanol) as eluent to give 2-[2-(2-Ethyl-5-pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl]-ethyl-3-methyl-quinoxaline (3.2 mg, 31.8%) as off-white semisolid

### 15 Example 34

Cyclopropyl-5-(2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-ethyl)-1-methyl-1H-[1,2,4]triazol-3-yl)-methyl-amine

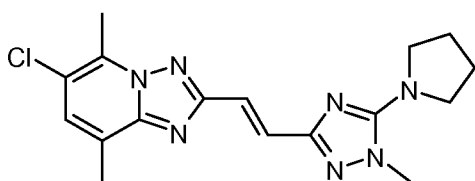


N-cyclopropyl-5-(2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)vinyl)-N,1-dimethyl-1H-1,2,4-triazol-3-amine (10 mg, 30.8  $\mu\text{mol}$ , Eq: 1.00) was stirred in Ethyl acetate (6

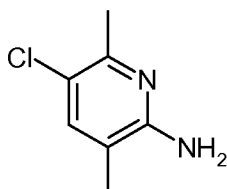
ml) using 5% Pd on Ba<sub>2</sub>SO<sub>4</sub> (3 mg, 30.8 μmol, Eq: 1.00) as catalyst in a hydrogen atmosphere. The mixture was stirred at room temperature for 4h. No reaction. Palladium on activated charcoal 10% (5 mg, 30.8 μmol, Eq: 1.00) was added an stirring was continued for 4h. TLC showed new product but still starting material left. Palladium on activated charcoal 10% (4 mg, 30.8 μmol, Eq: 1.00) was added and stirring was continued for 4h again. TLC showed nearly complete conversion. The crude material was applied on silica gel an purified by column chromatography using ethyl acetate / methanol (0-5% methanol) as eluent to give Cyclopropyl-  
 5 {5-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-methyl-amine (8.4 mg, 83.5%) as off-white semisolid.

### 10 Example 35

6-Chloro-5,8-dimethyl-2-(2-(1-methyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyridine



a) 5-Chloro-3,6-dimethylpyridin-2-amine

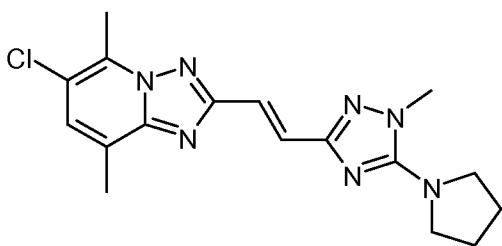


15

NCS (3.28 g, 24.6 mmol, Eq: 1.00) was added at 15 °C in one portion to a solution of 3,6-dimethylpyridin-2-amine (3 g, 24.6 mmol, Eq: 1.00) in ethyl acetate (130 mL). The temperature was maintained between 20-24 °C for 1 h. The red mixture was stirred overnight. The mixture was filtered. The filtrate was washed with 40% aq. sodium bisulfite solution (100  
 20 ml) and brine.

The aqueous phase was extracted with EtOAc (2x100 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and then concentrated to an oil. The residue was purified by column chromatography (70g SiO<sub>2</sub>, 0 to 50% EtOAc/n-heptane) to afford 5-chloro-3,6-dimethylpyridin-2-amine (1.16 g, 30.2 %) as a light yellow-brown product. MS: m/z = 157.1 (M+H<sup>+</sup>)

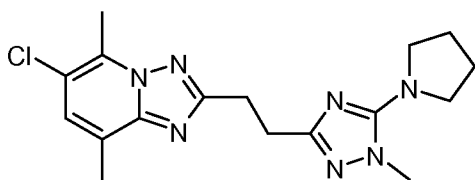
25 b) 6-chloro-5,8-dimethyl-2-(2-(1-methyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyridine



Using 5-chloro-3,6-dimethylpyridin-2-amine as starting material, the product (87mg) was obtained in analogy to Example 26, steps b-e as a light yellow solid. MS:  $m/z = 358.5$  ( $M+H^+$ )

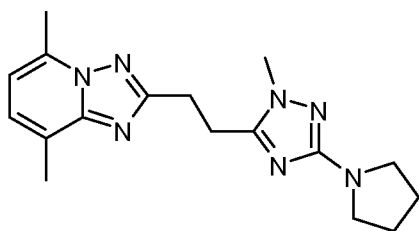
### Example 36

- 5 6-Chloro-5,8-dimethyl-2-(2-(1-methyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine



### Example 37

- 10 5,8-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine

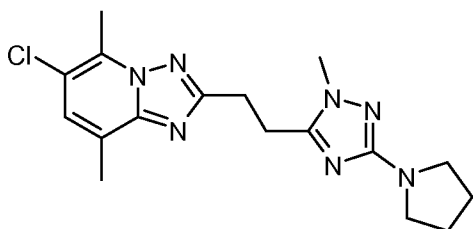


The product (35 mg, 91.1%) was obtained as a white solid in analogy to Example 29b from (E)-6-chloro-5,8-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyridine. MS:  $m/z = 326.5$  ( $M+H^+$ )

- 15 **Example 38**

6-Chloro-5,8-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine

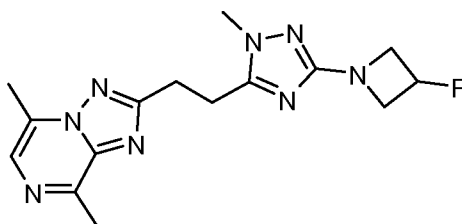




Ethyl acetate was added to (E)-6-chloro-5,8-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyridine (15 mg). Palladium (5 wt. %) on barium sulfate (20 mg) was added. The mixture was stirred for 5 h under a hydrogen atmosphere and then filtered over Celite. The mixture was concentrated and purified by preparative HPLC to give the desired product (10.2 mg, 67.8%) as a light yellow powder. MS:  $m/z = 360.5$  (M+H<sup>+</sup>)

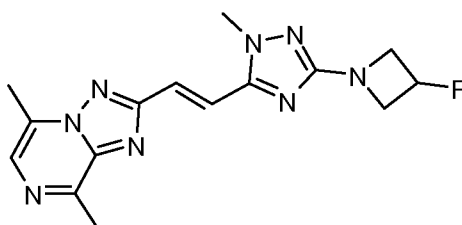
### Example 39

2-{2-[5-(3-Fluoro-azetidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



10

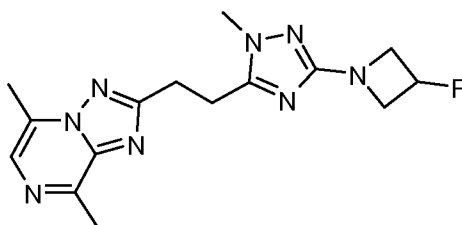
a) 2-{(E)-2-[5-(3-Fluoro-azetidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



Was prepared in the same manner as described in Example 87a) using 3-fluoroazetidine hydrochloride (26.7 mg, 239  $\mu\text{mol}$ , Eq: 2) instead of pyrrolidin-2-one affording 2-{(E)-2-[5-(3-Fluoro-azetidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (12.3 mg, 31.3%) as off-white solid. MS:  $m/z = 329.4$  (M+H<sup>+</sup>)

b) 2-{2-[5-(3-Fluoro-azetidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

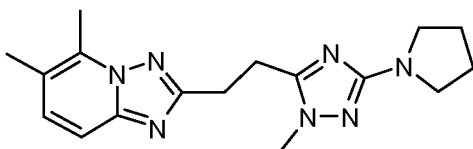
-73-



Was prepared in the same manner as described in Example 87 b) from (E)-2-(2-(3-(3-fluoroazetidin-1-yl)-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (10 mg, 30.5  $\mu\text{mol}$ , Eq: 1.00) affording 2-{2-[5-(3-Fluoro-azetidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (10.1 mg, 100%) as off-white waxy solid. MS:  $m/z = 331.4$  ( $M+H^+$ )

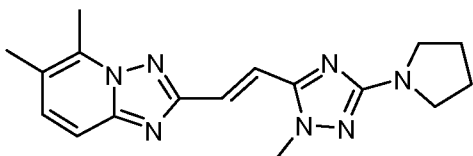
### Example 40

5,6-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine



10

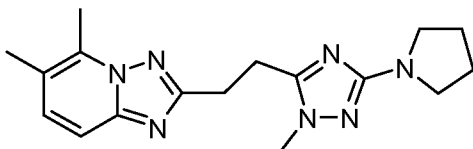
a) (E)-5,6-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyridine



The product (55 mg) was obtained in analogy to Example 26 (steps a-e) from 5,6-dimethylpyridin-2-amine as a yellow solid. MS:  $m/z = 324.19$  ( $M+H^+$ )

15

b) 5,6-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine



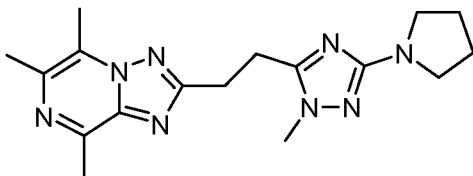
(E)-5,6-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyridine (45 mg) and Pd/C (5 mg) were stirred in acetic acid (0.7 ml) under

20

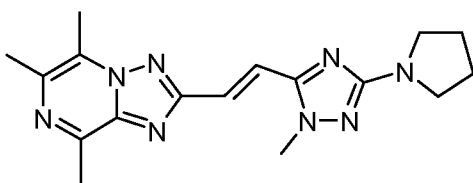
hydrogen for 1 h. The mixture was filtered and concentrated to give the product (45 mg, 99.4%) as a light yellow solid. MS:  $m/z = 326.2$  (M+H<sup>+</sup>)

### Example 41

5 5,6,8-Trimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyrazine

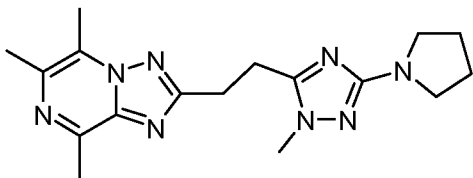


a) (E)-5,6,8-Trimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-  
[1,2,4]triazolo[1,5-a]pyrazine



10 The product (55 mg) was obtained in analogy to Example 26 (steps a-e) from 3,5,6-trimethylpyrazin-2-amine as a yellow solid. MS:  $m/z = 339.20$  (M+H<sup>+</sup>)

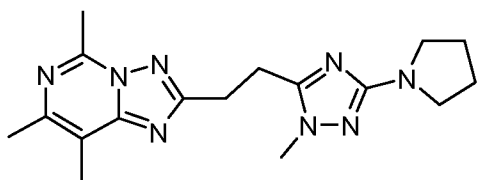
b) 5,6,8-Trimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyrazine



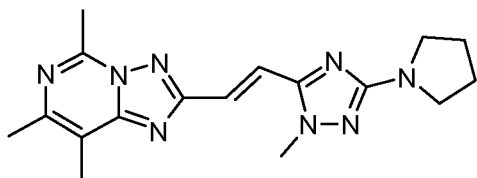
15 (E)-5,6,8-Trimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-  
[1,2,4]triazolo[1,5-a]pyrazine (45 mg, 99.4%) and Pd/C (5 mg) were stirred in acetic acid (0.7 ml) under hydrogen for 1 h. The mixture was filtered and concentrated to give the product (25 mg) as a light brown solid. MS:  $m/z = 341.2$  (M+H<sup>+</sup>)

### Example 42

20 5,7,8-Trimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-c]pyrimidine

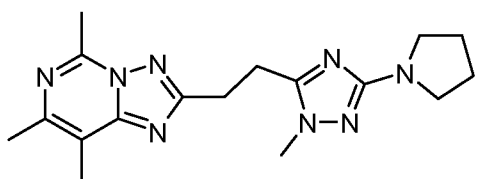


a) (E)-5,7,8-Trimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-c]pyrimidine



5 The product (35 mg) was obtained in analogy to Example 26 (steps a-e) from 2,5,6-trimethylpyrimidin-4-amine as a yellow solid. MS:  $m/z = 339.5$  (M+H<sup>+</sup>)

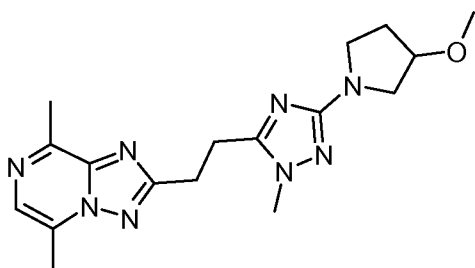
b) 5,7,8-Trimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine



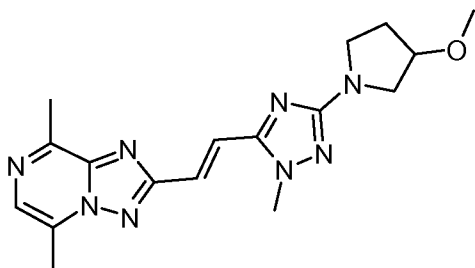
10 (E)-5,7,8-Trimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-c]pyrimidine (32 mg) and Pd/C (10 mg) were stirred in ethanol (0.4 ml) under hydrogen for 1 h. The mixture was filtered and concentrated to give the product (20 mg, 62.5%) as a white waxy solid. MS:  $m/z = 341.4$  (M+H<sup>+</sup>)

### Example 43

15 2-{2-[5-(3-Methoxy-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

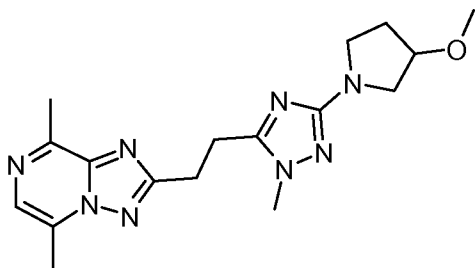


a) 2-{(E)-2-[5-(3-Fluoro-azetid-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



Was prepared in the same manner as described in Example 87a) using 3-methoxypyrrolidine (24.2 mg, 239  $\mu\text{mol}$ , Eq: 2) instead of pyrrolidin-2-one affording 2-{(E)-2-[5-(3-Fluoro-azetid-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (15.4 mg, 36.3%) as yellow oil. MS:  $m/z = 355.4$  ( $M+H^+$ )

b) 2-{2-[5-(3-Methoxy-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



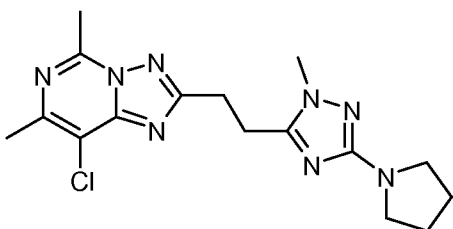
10

Was prepared in the same manner as described in Example 87 b) from (E)-2-(2-(3-(3-methoxypyrrolidin-1-yl)-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (13.5 mg, 38.1  $\mu\text{mol}$ , Eq: 1.00) affording 2-{2-[5-(3-Methoxy-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (4.7 mg, 34.6%) as off-white semisolid. MS:  $m/z = 357.5$  ( $M+H^+$ )

15

#### Example 44

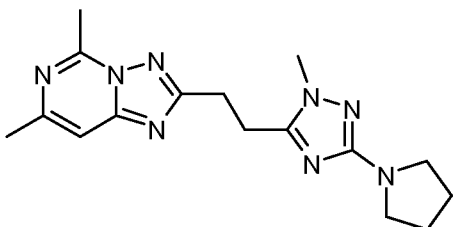
8-Chloro-5,7-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine



The product (6.6 mg) was obtained as a light yellow solid in analogy to Example 26 from 5-chloro-2,6-dimethylpyrimidin-4-amine. MS:  $m/z = 361.5$  (M+H<sup>+</sup>)

#### Example 45

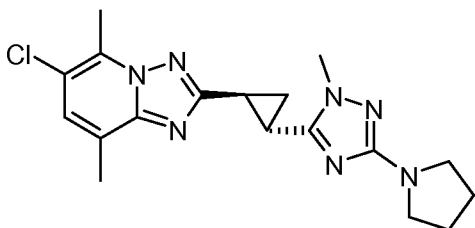
- 5 5,7-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine



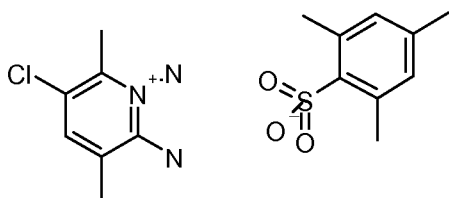
- 10 The product (7.1 mg, 31.2%) was obtained as a white solid in analogy to Example 29b from 8-chloro-5,7-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine. MS:  $m/z = 327.2$  (M+H<sup>+</sup>)

#### Example 46

- 6-Chloro-5,8-dimethyl-2-[(1S,2S)-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-cyclopropyl]-[1,2,4]triazolo[1,5-a]pyridine

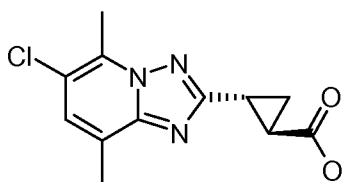


- 15 a) 1-Amino-5-chloro-3,6-dimethylpyridin-2(1H)-iminium 2,4,6-trimethylbenzenesulfonate



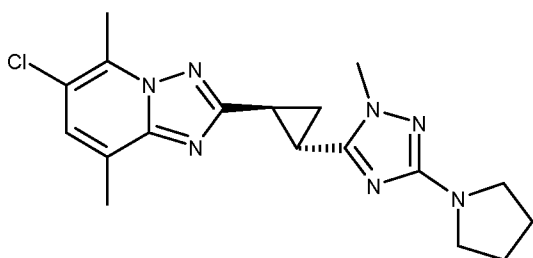
The product (1.5 g, 54.5%) was obtained as a white solid from 5-chloro-3,6-dimethylpyridin-2-amine in analogy to Example 26b. MS:  $m/z = 169.2$  (M<sup>+</sup>),  $m/z = 199.3$  (M<sup>-</sup>)

5 b) 2-(6-Chloro-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxylic acid



1-Amino-5-chloro-3,6-dimethylpyridin-2(1H)-iminium 2,4,6-trimethylbenzenesulfonate (100 mg, 269  $\mu\text{mol}$ , Eq: 1.00) was added to a solution of ethyl 2-formylcyclopropanecarboxylate (38.2 mg, 269  $\mu\text{mol}$ , Eq: 1.00) in methanol (2 ml). 2 N KOH aq (200  $\mu\text{l}$ , 400  $\mu\text{mol}$ , Eq: 1.49) was added and the yellow mixture was stirred for 1 h at room temperature under air. 1 N LiOH aq (4 mL, 4 mmol, Eq: 14.9) and tetrahydrofuran (8 ml) were added and the mixture was stirred for 30 min at room temperature. Volatile organic solvents were evaporated, water (10 ml) was added and the mixture was washed with diethyl ether (10 ml). The aqueous phase was acidified with 2 N HCl aq and then extracted with ethyl acetate (3 x 10 ml). The combined organic layers were dried over sodium sulfate and then concentrated to give the desired product (70 mg, 98%) as a white solid. MS:  $m/z = 266.1$  (M+H<sup>+</sup>)

c) 6-Chloro-5,8-dimethyl-2-[(1S,2S)-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-cyclopropyl]-[1,2,4]triazolo[1,5-a]pyridine

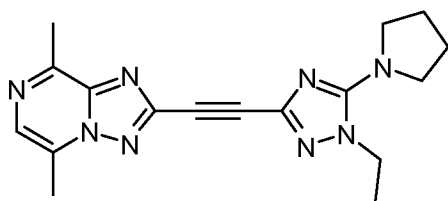


20 Oxalyl chloride (290 mg, 200  $\mu\text{L}$ , 2.28 mmol, Eq: 8.67) was added to 2-(6-chloro-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxylic acid (70 mg, 263  $\mu\text{mol}$ , Eq: 1.00) in dichloromethane (2 ml), 0.002 ml dimethylformamide was added and the mixture stirred

for 30 min. The mixture was concentrated to an oil. The residue was dissolved in acetone (2 mL) and potassium thiocyanate (30.7 mg, 316  $\mu\text{mol}$ , Eq: 1.2) was added. The white suspension was stirred for 30 min and then filtered. The filtrate was concentrated to an oil. The residue was dissolved in toluene (2 mL). Pyrrolidine (22.5 mg, 316  $\mu\text{mol}$ , Eq: 1.2) was added and the mixture  
5 was stirred for 1 h. The mixture was concentrated to an oil. The residue was dissolved in tetrahydrofuran, cesium carbonate (172 mg, 527  $\mu\text{mol}$ , Eq: 2) and iodomethane (187 mg, 1.32 mmol, Eq: 5) were added, the mixture was stirred for 5 h at room temperature. The mixture was filtered and concentrated to an oil. The residue was dissolved in methylhydrazine (2 mL) and heated to 100 °C for 1 h. Water (10 ml) was added and the mixture was extracted with dichloromethane (3  
10 x 10 ml). The organic layer was dried over sodium sulfate and then purified by column chromatography to give the desired product (9.8 mg, 10%) as a colorless oil. MS:  $m/z = 372.5$  (M+H+)

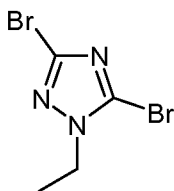
### Example 47

2-((1-Ethyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethynyl)-5,8-dimethyl-  
[1,2,4]triazolo[1,5-a]pyrazine



15

a) 3,5-Dibromo-1-ethyl-1H-[1,2,4]triazole

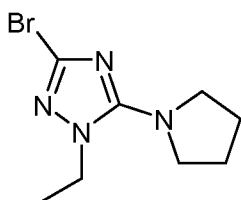


3,5-Dibromo-1H-1,2,4-triazole (2.5 g, 11.0 mmol, Eq: 1.00) was dissolved in dimethylformamide (31.8 ml) and sodium hydride (529 mg, 60% dispersion in mineral oil, 13.2 mmol, Eq: 1.2) was added slowly. Ethyl methanesulfonate (2.74 g, 2.27 ml, 22.0 mmol, Eq: 2) was added to the reaction and the mixture was heated in a microwave oven for 60 minutes at 100 °C. The mixture was diluted with water and extracted 3x with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and the solvent was evaporated to give 3,5-dibromo-1-ethyl-1H-  
20 [1,2,4]triazole (2.54 g, 90.4%) as a white powder. MS:  $m/z = 255.9$  (M+H+)

b) 3-Bromo-1-ethyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole

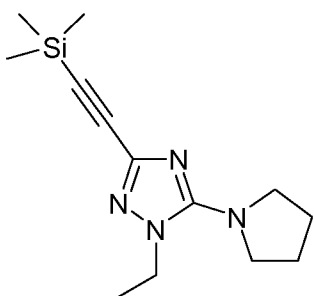
25





A mixture of 3,5-dibromo-1-ethyl-1H-1,2,4-triazole (462 mg, 1.81 mmol, Eq: 1.00) and pyrrolidine (135 mg, 157  $\mu$ l, 1.9 mmol, Eq: 1.05) in dimethylformamide (4 ml) was heated for 40 minutes at 110 °C in a microwave oven. Evaporation of the solvent afforded 578 mg of an orange oil. The crude material was applied on silica gel and purified by flash chromatography over a 20 g silica gel column using dichloromethane / methanol 0-10 % as eluent to give 3-bromo-1-ethyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole (240 mg, 54%) as an orange oil. MS: m/z= 245/247 (M+H<sup>+</sup>)

c) 1-Ethyl-5-pyrrolidin-1-yl-3-trimethylsilanylethynyl-1H-[1,2,4]triazole

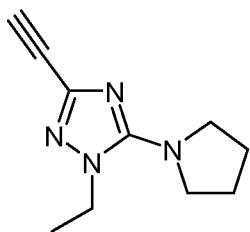


10

A mixture of 3-bromo-1-ethyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazole (240 mg, 979  $\mu$ mol, Eq: 1.00), ethynyltrimethylsilane (192 mg, 275  $\mu$ l, 1.96 mmol, Eq: 2) and triethylamine (149 mg, 205  $\mu$ l, 1.47 mmol, Eq: 1.5) in tetrahydrofuran (3.65 ml) was purged for 5 minutes with nitrogen. Then copper (I) iodide (1.86 mg, 9.79  $\mu$ mol, Eq: 0.01), bis(triphenylphosphine)palladium(II) chloride (6.87 mg, 9.79  $\mu$ mol, Eq: 0.01) and triphenylphosphine (2.57 mg, 9.79  $\mu$ mol, Eq: 0.01) were added, the vessel was capped and heated to 120 °C for 1 day. Once more copper (I) iodide (1.86 mg, 9.79  $\mu$ mol, Eq: 0.01), triphenylphosphine (2.57 mg, 9.79  $\mu$ mol, Eq: 0.01), bis(triphenylphosphine)palladium(II) chloride (6.87 mg, 9.79  $\mu$ mol, Eq: 0.01) and ethynyltrimethylsilane (192 mg, 275  $\mu$ l, 1.96 mmol, Eq: 2) were added, the vial was purged with argon, capped again and stirred for one more day at 120 °C. The crude material was applied on silica gel and purified by flash chromatography over a 20 g silica gel column using heptane / ethyl acetate 10-30 % as eluent affording 1-ethyl-5-pyrrolidin-1-yl-3-trimethylsilanylethynyl-1H-[1,2,4]triazole (122 mg, 47.5%) as an orange oil. MS: m/z= 263.4 (M+H<sup>+</sup>)

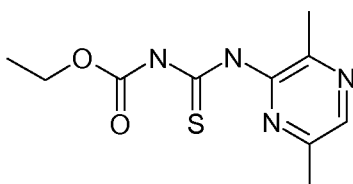
20

d) 1-Ethyl-3-ethynyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole



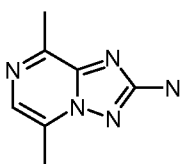
A mixture of 1-ethyl-5-(pyrrolidin-1-yl)-3-((trimethylsilyl)ethynyl)-1H-1,2,4-triazole (122 mg, 465  $\mu\text{mol}$ , Eq: 1.00) in methanol (3 ml) and 1N NaOH aq. (0.1 ml) was stirred for 18 hours at 25 °C under argon atmosphere. The mixture was diluted with ethyl acetate and washed with water. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated affording 1-ethyl-3-ethynyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole (79 mg, 89.3%) as an orange oil. MS:  $m/z = 191.2$  (M+H<sup>+</sup>)

e) Ethyl-N-[(3,6-dimethylpyrazin-2-yl)carbamothioyl]carbamate



To a solution of 3, 6-dimethyl-pyrazin-2-ylamine (5 g, 40.65 mmol) in dioxane (150ml) was added ethoxycarbonyl isothiocyanate (4.75 ml, 40.65 mmol) at 25 °C, and the reaction mixture was stirred for 18 hours at 25 °C. Volatiles were removed in vacuo. The resultant residue was dissolved in ethyl acetate, washed with water twice, and brine, dried over anhydrous sodium sulfate, filtered, and evaporated affording ethyl-N-[(3,6-dimethylpyrazin-2-yl)carbamothioyl]carbamate (10 g, 96.73%) as a light yellow solid. MS:  $m/z = 255$  (M+H<sup>+</sup>)

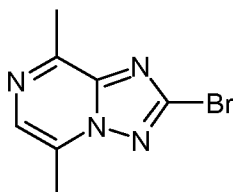
f) 5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamine



A mixture of hydroxylamine hydrochloride (13.68 g, 196.85 mmol) and N,N-diisopropylethylamine (20.6 ml, 118.11 mmol) in ethanol (200 ml) was stirred for 10 minutes at 25 °C. To this mixture was then added ethyl-N-[(3,6-dimethylpyrazin-2-yl)carbamothioyl]carbamate (10 g, 39.37 mmol), and the resultant mixture was heated under reflux for 16 hours. The resultant mixture was diluted with water (100 ml), stirred for 10 min, and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated. The crude material thus obtained was

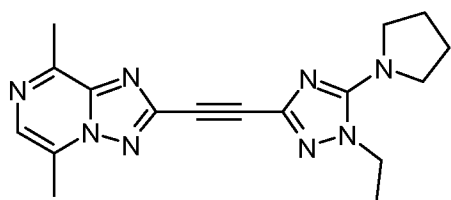
trituated with hexane affording 5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamine (2.4 g, 71.87%) as a white solid. MS:  $m/z = 164$  (M+H<sup>+</sup>)

g) 2-Bromo-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



5 A mixture of 5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-ylamine (2.4 g, 14.71 mmol), sodium nitrite (10.15 g, 147.08 mmol) and benzyltriethylammonium bromide (8 g, 29.42 mmol) in bromoform (76.2 ml, 872.17 mmol) was stirred at 25 °C for 30 minutes. To this mixture was then added dichloroacetic acid (2.43 ml, 29.42 mmol) and the reaction mixture was stirred at 25 °C for further 20 hours. (The reaction flask was wrapped in aluminum foil to protect the mixture  
10 from light). Water (100 ml) was added to the reaction mixture, which was then stirred for 30 minutes at 25° C, and finally extracted 4 times with dichloromethane. The combined organic layers were washed twice with water and brine, dried over anhydrous sodium sulfate, filtered and evaporated. The crude material thus obtained was purified by silica gel column chromatography using hexane / ethyl acetate 20 % as eluent affording 2-bromo-5, 8-dimethyl-[1,2,4]triazolo[1,5-  
15 a]pyrazine (4.8 g, 74.72%) as an off white solid. MS:  $m/z = 227$  (M+H<sup>+</sup>)

h) 2-((1-Ethyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethynyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

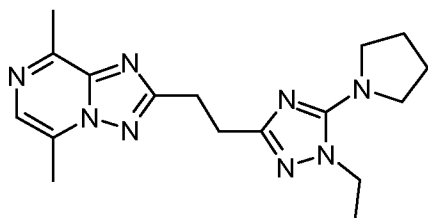


A mixture of 1-ethyl-3-ethynyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazole (79 mg, 415 μmol, Eq: 1.00), 2-bromo-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (104 mg, 457 μmol, Eq: 1.1) and triethylamine (63.0 mg, 86.8 μl, 623 μmol, Eq: 1.5) in dioxane (2.11 ml) was purged with argon, then copper (I) iodide (1.58 mg, 8.31 μmol, Eq: 0.02), bis(triphenylphosphine)palladium(II) chloride (5.83 mg, 8.31 μmol, Eq: 0.02) and triphenylphosphine (2.18 mg, 8.31 μmol, Eq: 0.02) were added, the vessel was capped and heated for 18 hours to 110 °C. The crude material was  
25 applied on silica gel and purified by flash chromatography over a 20 g silica gel column using ethyl acetate 100 % as eluent affording 2-((1-ethyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-

yl)ethynyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (52 mg, 37.2%) as an orange oil. MS:  $m/z = 337.4$  (M+H<sup>+</sup>)

### Example 48

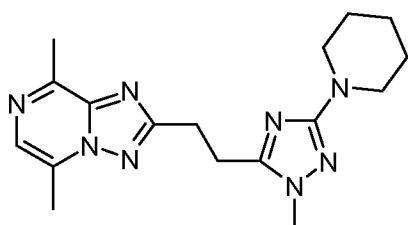
2-(2-(1-Ethyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-5,8-dimethyl-  
5 [1,2,4]triazolo[1,5-a]pyrazine



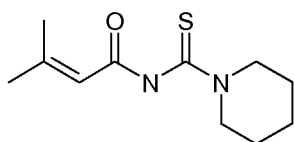
A mixture of 2-((1-ethyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethynyl)-5,8-dimethyl-  
[1,2,4]triazolo[1,5-a]pyrazine (43 mg, 128  $\mu\text{mol}$ , Eq: 1.00) and palladium on carbon 10 % (13.6  
mg, 12.8  $\mu\text{mol}$ , Eq: 0.1) in methanol (10 ml) was stirred for 20 hours at 25 °C under hydrogen  
10 atmosphere. The catalyst was filtered off, the filtrate was evaporated affording 2-(2-(1-ethyl-5-  
(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (42  
mg, 96.5%) as a light yellow oil. MS:  $m/z = 341.5$  (M+H<sup>+</sup>)

### Example 49

5,8-Dimethyl-2-[2-(2-methyl-5-piperidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-  
15 [1,2,4]triazolo[1,5-a]pyrazine



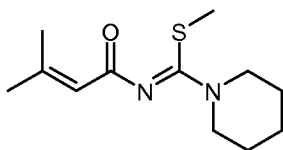
a) 3-Methyl-but-2-enoic acid (piperidine-1-carbothioyl)-amide



To a solution of 3-methylbut-2-enoyl isothiocyanate (2 g, 14.2 mmol, Eq: 1.00) in ben-  
20 zene (40.0 ml) was added a solution of piperidine (1.21 g, 1.4 ml, 14.2 mmol, Eq: 1.00) in ben-  
zene (20.0 ml). The mixture was stirred for 2 hours. The mixture was evaporated affording 3-

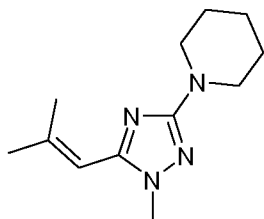
methyl-but-2-enoic acid (piperidine-1-carbothiyl)-amide (3.32 g, 104%) as a yellow oil. MS:  $m/z = 227.2$  (M+H<sup>+</sup>)

b) 3-Methyl-but-2-enoic acid 1-methylsulfanyl-1-piperidin-1-yl-meth-(Z)-ylideneamide



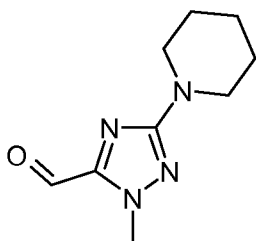
5 A mixture of 3-methyl-N-(piperidine-1-carbonothioyl)but-2-enamide (3.21 g, 14.2 mmol, Eq: 1.00), sodium carbonate (1.58 g, 14.9 mmol, Eq: 1.05) and iodomethane (10.1 g, 4.43 ml, 70.9 mmol, Eq: 5) in tetrahydrofuran (100 ml) was stirred for 2.5 days under reflux. The mixture was evaporated, 30 ml of ethyl acetate was added and the mixture was filtrated, the filtrate was evaporated affording 3-methyl-but-2-enoic acid 1-methylsulfanyl-1-piperidin-1-yl-meth-(Z)-ylideneamide (5.137 g, 151%) as an orange-brown semi-solid. MS:  $m/z = 241.2$  (M+H<sup>+</sup>)

c) 1-[1-Methyl-5-(2-methyl-propenyl)-1H-[1,2,4]triazol-3-yl]-piperidine



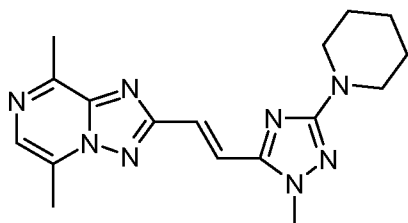
A mixture of (Z)-methyl N-3-methylbut-2-enoylpiperidine-1-carbimidothioate (3.2 g, 9.32 mmol, Eq: 1.00) and methylhydrazine (4.9 g, 5.6 ml, 106 mmol, Eq: 11.4) was heated for 15 1.5 hours at 100 °C. The mixture was diluted with ethyl acetate and washed 3 times with water. The organic layer was separated, dried over magnesium sulfate, filtrated and evaporated to give 1.135 g of a yellow oil. The crude material was applied on silica gel and purified by flash chromatography over a 50 g silica gel column using heptane / ethyl acetate 10-50 % as eluent affording 1-[1-methyl-5-(2-methyl-propenyl)-1H-[1,2,4]triazol-3-yl]-piperidine (376 mg, 18.3%) as a 20 light yellow oil. MS:  $m/z = 221.2$  (M+H<sup>+</sup>)

d) 2-Methyl-5-piperidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde



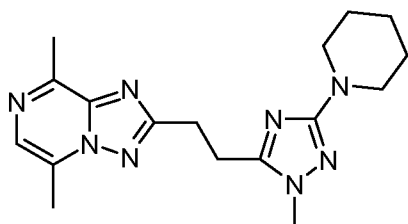
A mixture of 1-(1-methyl-5-(2-methylprop-1-enyl)-1H-1,2,4-triazol-3-yl)piperidine (376 mg, 1.71 mmol, Eq: 1.00), sodium periodate (1.46 g, 6.83 mmol, Eq: 4), osmium tetroxide 4% aq. (325 mg, 325  $\mu$ l, 51.2  $\mu$ mol, Eq: 0.03) and benzyltriethylammonium chloride (155 mg, 683  $\mu$ mol, Eq: 0.4) in dioxane (17.9 ml) and water (4.12 ml) was stirred for 1.5 hours at 70 °C. The mixture was diluted with ethyl acetate and washed 2x with water and brine. The organic layer was separated, dried over magnesium sulfate, filtrated and evaporated affording 2-methyl-5-piperidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde (331 mg, 99.9%) as a brown waxy solid. MS: m/z= 195.4 (M+H+)

e) 5,8-Dimethyl-2-[(E)-2-(2-methyl-5-piperidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-a]pyrazine



A mixture of 1-methyl-3-(piperidin-1-yl)-1H-1,2,4-triazole-5-carbaldehyde (60 mg, 309  $\mu$ mol, Eq: 1.00), ((5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)methyl)triphenylphosphonium chloride (142 mg, 309  $\mu$ mol, Eq: 1.00) and DBU (51.7 mg, 51.2  $\mu$ l, 340  $\mu$ mol, Eq: 1.1) in tetrahydrofuran (15 ml) was stirred for 18 hours at 25 °C under argon. The crude material was applied on silica gel and purified by flash chromatography over a 20 g silica gel column using ethyl acetate / methanol 0-7 % as eluent affording 5,8-dimethyl-2-[(E)-2-(2-methyl-5-piperidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-a]pyrazine (56 mg, 53.6%) as a yellow solid. MS: m/z= 339.5 (M+H+), MP: 186-188 °C

f) 5,8-Dimethyl-2-[2-(2-methyl-5-piperidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine

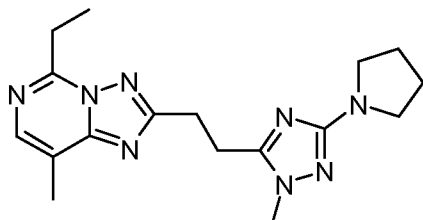


A mixture of (E)-5,8-dimethyl-2-(2-(1-methyl-3-(piperidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyrazine (52 mg, 154  $\mu$ mol, Eq: 1.00) and palladium on carbon 10 % (16.4 mg, 15.4  $\mu$ mol, Eq: 0.1) in methanol (20 ml) was stirred for 24 hours at 25 °C under a hydrogen atmosphere. The catalyst was filtered off, the filtrate was evaporated affording 5,8-

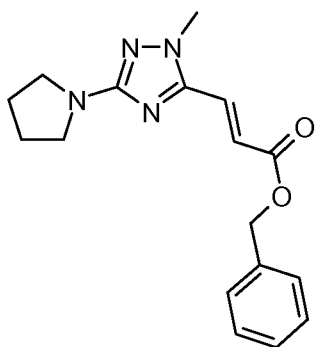
dimethyl-2-[2-(2-methyl-5-piperidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine (30 mg, 57.4%) as a yellow oil. MS:  $m/z = 341.5$  ( $M+H^+$ )

### Example 50

5-Ethyl-8-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
5 [1,2,4]triazolo[1,5-c]pyrimidine

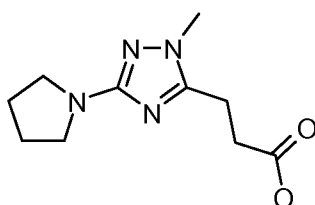


a) (E)-Benzyl 3-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)acrylate



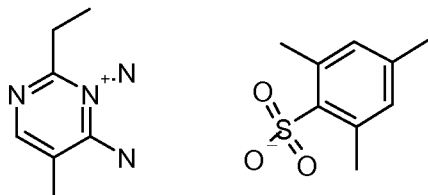
DBU (3.79 g, 3.75 ml, 24.9 mmol, Eq: 1.2) was added to 2-methyl-5-pyrrolidin-1-yl-2H-  
10 [1,2,4]triazole-3-carbaldehyde (3.74 g, 20.8 mmol, Eq: 1.00), benzyl 2-(dimethoxyphosphoryl)  
acetate (6.43 g, 24.9 mmol, Eq: 1.2) and lithium chloride (2.64 g, 62.3 mmol, Eq: 3) in acetonitrile (100 ml). The mixture was stirred for 1 h at room temperature. Half saturated sodium chloride solution (20 ml) was added and the mixture was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate. The product (3.8 g, 58.8%) was obtained as  
15 a yellow solid after column chromatography ( $\text{SiO}_2$ , ethyl acetate/n-heptane). MS:  $m/z = 313.3$  ( $M+H^+$ ).

b) 3-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)propanoic acid



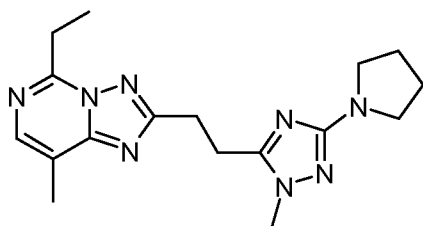
(E)-Benzyl 3-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)acrylate was stirred with palladium on carbon (10 wt%, 140 mg) in dioxane (60 ml) under hydrogen for 2 h. Additional palladium on carbon (10 wt%, 250 mg) was added and the mixture was stirred overnight under hydrogen. The mixture was filtered over Celite and concentrated to give the product (1.95 g, 96.7%) as a white solid. MS:  $m/z = 225.2$  (M+H+).

c) 3-Amino-2-ethyl-5-methylpyrimidin-4(3H)-iminium 2,4,6-trimethylbenzenesulfonate



The product (410 mg, 72.5%) was obtained as a white solid in analogy to Example 26b from 2-ethyl-5-methylpyrimidin-4-amine. MS:  $m/z = 153.2$  (M+),  $m/z = 199.3$  (M-).

10 d) 5-Ethyl-8-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine

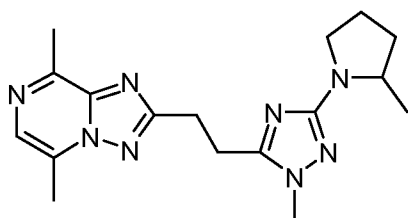


HATU (40.5 mg, 106  $\mu\text{mol}$ , Eq: 1.5) and N,N-diisopropylethylamine (27.5 mg, 37.2  $\mu\text{L}$ , 213  $\mu\text{mol}$ , Eq: 3) were added to 3-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)propanoic acid in dimethylformamide (1 ml). The mixture was stirred for 10 min at room temperature. 3-Amino-2-ethyl-5-methylpyrimidin-4(3H)-iminium 2,4,6-trimethylbenzenesulfonate was added, and the mixture was stirred at 100 °C for 1 h. The product (2.7 mg, 100%) was obtained as a white solid after purification by preparative HPLC.

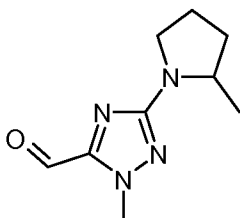
### Example 51

20 5,8-Dimethyl-2-{2-[2-methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine



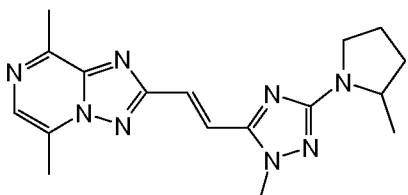


a) 2-Methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazole-3-carbaldehyde



Was prepared in the same manner as described in Example 49 a-d) using 2-  
 5 methylpyrrolidine instead of piperidine, affording 2-methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-  
 [1,2,4]triazole-3-carbaldehyde (449 mg, 74.9%) as a dark green waxy solid. MS:  $m/z = 195.4$   
 (M+H<sup>+</sup>)

b) 5,8-Dimethyl-2-{(E)-2-[2-methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-  
 vinyl}-[1,2,4]triazolo[1,5-a]pyrazine



10

Was prepared in the same manner as described in Example 49 e) using 2-methyl-5-(2-  
 methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazole-3-carbaldehyde (60 mg, 309  $\mu\text{mol}$ , Eq: 1.00) as alde-  
 hyde, affording 5,8-dimethyl-2-{(E)-2-[2-methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-  
 3-yl]-vinyl}-[1,2,4]triazolo[1,5-a]pyrazine (58 mg, 55.5%) as a yellow viscous oil. MS:  $m/z =$   
 15 339.5 (M+H<sup>+</sup>)

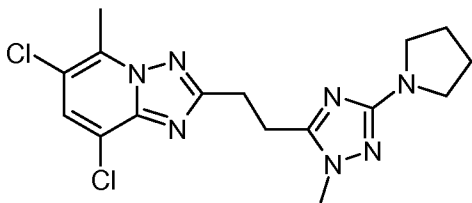
c) 5,8-Dimethyl-2-{2-[2-methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-  
 ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

A mixture of (E)-5,8-dimethyl-2-(2-(1-methyl-3-(2-methylpyrrolidin-1-yl)-1H-1,2,4-  
 triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyrazine (50 mg, 148  $\mu\text{mol}$ , Eq: 1.00) and palladium on  
 20 carbon 10 % (31.4 mg, 29.5  $\mu\text{mol}$ , Eq: 0.2) in methanol (20 ml) was stirred for 5 hours at 25 °C  
 under hydrogen atmosphere. The catalyst was filtered off, the filtrate was evaporated affording

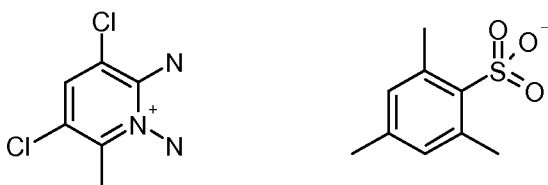
5,8-dimethyl-2-{2-[2-methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine (49 mg, 97.4%) as a colorless viscous oil. MS:  $m/z = 341.5$

### Example 52

6,8-Dichloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

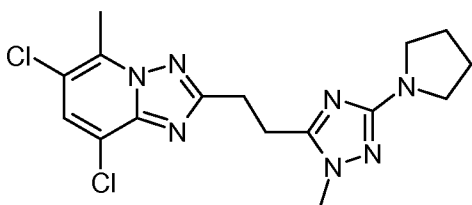


a) 1,2-Diamino-3,5-dichloro-6-methylpyridinium 2,4,6-trimethylbenzenesulfonate



The product (2.2 g, 99.3%) was obtained as a white solid in analogy to Example 26b from 3,5-dichloro-6-methylpyridin-2-amine. MS:  $m/z = 192.1$  (M<sup>+</sup>),  $m/z = 199.2$  (M<sup>-</sup>).

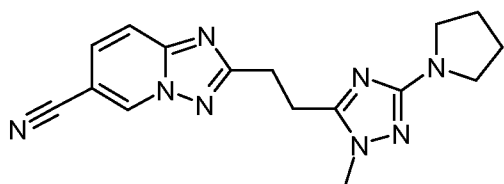
b) 6,8-Dichloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine



The product (22 mg, 95%) was obtained as a light yellow oil in analogy to Example 50d from 1,2-diamino-3,5-dichloro-6-methylpyridinium 2,4,6-trimethylbenzenesulfonate. MS:  $m/z = 380.5$  (M+H<sup>+</sup>)

### Example 53

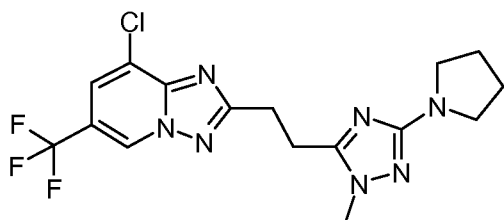
2-(2-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonitrile



The desired product (6.1 mg, 18.9%) was obtained in analogy to Example 52 from 6-aminonicotinonitrile. MS:  $m/z = 323.1$  ( $M+H^+$ )

#### Example 54

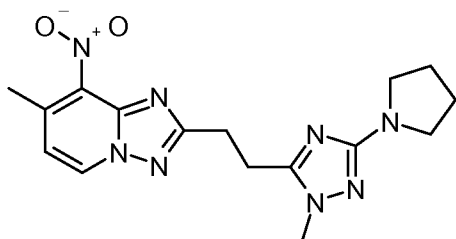
- 5 8-Chloro-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-6-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine



The desired product (4 mg, 10%) was obtained in analogy to Example 52 from 3-chloro-5-(trifluoromethyl)pyridin-2-amine. MS:  $m/z = 400.1$  ( $M+H^+$ )

- 10 **Example 55**

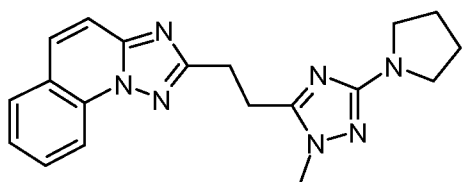
7-Methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-nitro-[1,2,4]triazolo[1,5-a]pyridine



- 15 The desired product (1.8 mg, 5%) was obtained in analogy to Example 52 from 4-methyl-3-nitropyridin-2-amine. MS:  $m/z = 357.2$  ( $M+H^+$ )

#### Example 56

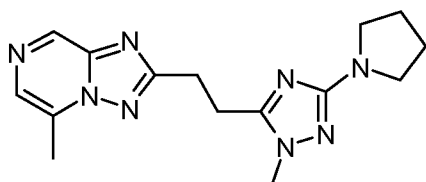
2-(2-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]quinoline



The desired product (2.2 mg, 6%) was obtained in analogy to Example 52 from quinolin-2-amine. MS:  $m/z = 348.2$  (M+H<sup>+</sup>)

### Example 57

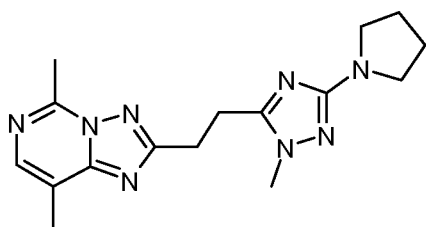
- 5 5-Methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyrazine



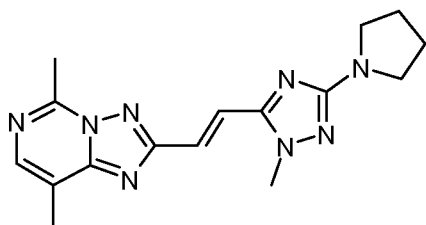
The desired product (1.9 mg, 3.5%) was obtained in analogy to example 52 from 6-methylpyrazin-2-amine. MS:  $m/z = 313.2$  (M+H<sup>+</sup>)

- 10 **Example 58**

5,8-Dimethyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-c]pyrimidine



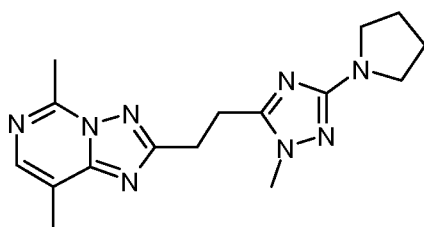
- a) 5,8-Dimethyl-2-[(E)-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-c]pyrimidine
- 15



Was prepared in the same manner as described in Example 81a) using 1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole-5-carbaldehyde (30 mg, 166  $\mu\text{mol}$ , Eq: 1.00) and ((5,8-dimethyl-[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)methyl)triphenylphosphonium chloride (76.4 mg, 166  $\mu\text{mol}$ , Eq: 1.00) (prepared as described in WO2011150156, pp123-125, Expl. 24g) affording

5 5,8-dimethyl-2-[(E)-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-c]pyrimidine (27 mg, 50.0%) as light yellow amorphous. MS:  $m/z = 325.6$  ( $M+H^+$ )

b) 5,8-Dimethyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-c]pyrimidine



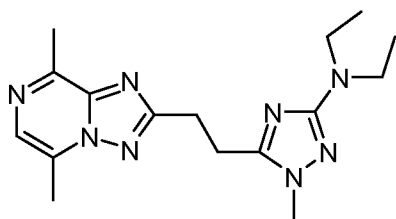
10

Was prepared in the same manner as described in Example 87 b) from (E)-5,8-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-c]pyrimidine (23 mg, 70.9  $\mu\text{mol}$ , Eq: 1.00) affording 5,8-dimethyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-c]pyrimidine (16 mg, 69.1%) as light yellow waxy

15 solid. MS:  $m/z = 327.5$  ( $M+H^+$ )

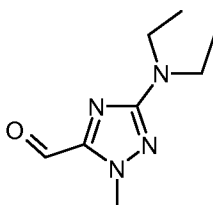
### Example 59

{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-diethyl-amine



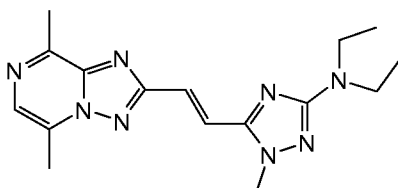
20

a) 5-Diethylamino-2-methyl-2H-[1,2,4]triazole-3-carbaldehyde



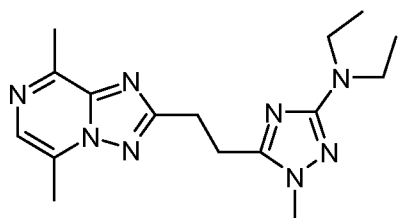
Was prepared in the same manner as described in Example 49 a-d) using diethylamine instead of piperidine, affording 5-diethylamino-2-methyl-2H-[1,2,4]triazole-3-carbaldehyde (792 mg, 79.3 %) as a brown liquid. MS:  $m/z = 183.2$  (M+H<sup>+</sup>)

b) {5-[(E)-2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-diethyl-amine



Was prepared in the same manner as described in Example 49 e) using 3-(diethylamino)-1-methyl-1H-1,2,4-triazole-5-carbaldehyde (60 mg, 329  $\mu\text{mol}$ , Eq: 1.00) as aldehyde affording {5-[(E)-2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-diethyl-amine (73 mg, 67.9%) as a yellow solid. MS:  $m/z = 327.5$  (M+H<sup>+</sup>), MP: 162.5 °C

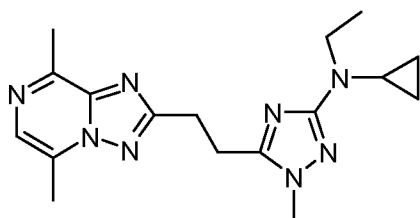
c) {5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-diethyl-amine



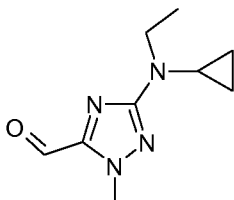
A mixture of (E)-5-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)vinyl)-N,N-diethyl-1-methyl-1H-1,2,4-triazol-3-amine (62 mg, 190  $\mu\text{mol}$ , Eq: 1.00) and palladium on carbon 10 % (10.1 mg, 9.5  $\mu\text{mol}$ , Eq: 0.05) in methanol (15 ml) was stirred for 5 hours at 25 °C under hydrogen atmosphere. The catalyst was filtered off, the filtrate was evaporated affording {5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-diethyl-amine (62 mg, 99.4%) as a light yellow viscous oil. MS:  $m/z = 329.5$  (M+H<sup>+</sup>)

## 20 Example 60

Cyclopropyl-{5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-ethyl-amine

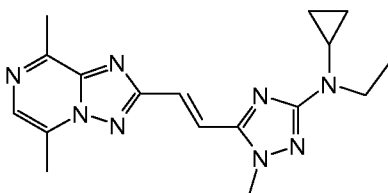


a) 5-(Cyclopropyl-ethyl-amino)-2-methyl-2H-[1,2,4]triazole-3-carbaldehyde



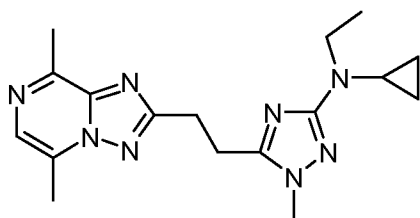
Was prepared in the same manner as described in Example 49 a-d) using N-ethylcyclopropan-amine hydrochloride (861 mg, 7.08 mmol, Eq: 1.00) instead of piperidine and N,N-diisopropyl ethyl-amine (915 mg, 1.2 ml, 7.08 mmol, Eq: 1.00) as base, affording 5-(cyclopropyl-ethyl-amino)-2-methyl-2H-[1,2,4]triazole-3-carbaldehyde (222 mg, 66.4%) as a black waxy solid. MS:  $m/z = 195.2$  (M+H<sup>+</sup>)

b) Cyclopropyl-{5-[(E)-2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-ethyl-amine



Was prepared in the same manner as described in Example 49 e) using 3-(cyclopropyl(ethyl)amino)-1-methyl-1H-1,2,4-triazole-5-carbaldehyde (60 mg, 309  $\mu\text{mol}$ , Eq: 1.00) as aldehyde affording cyclopropyl-{5-[(E)-2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-ethyl-amine (80 mg, 76.5%) as a yellow viscous oil. MS:  $m/z = 339.5$  (M+H<sup>+</sup>)

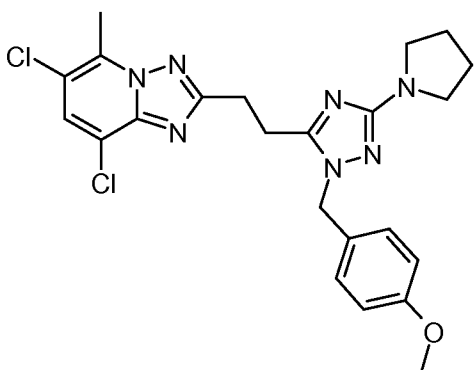
c) Cyclopropyl-{5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-ethyl-amine



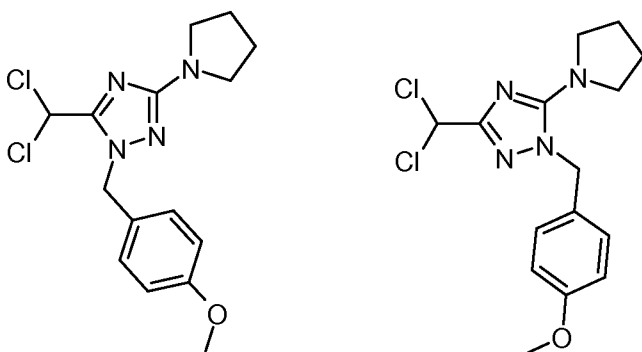
A mixture of (E)-N-cyclopropyl-5-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)vinyl)-N-ethyl-1-methyl-1H-1,2,4-triazol-3-amine (75mg, 222  $\mu\text{mol}$ , Eq: 1.00) and palladium on carbon 10 % (11.8 mg, 11.1  $\mu\text{mol}$ , Eq: 0.05) in methanol (15 ml) was stirred for 5 hours at 25  $^{\circ}\text{C}$  under hydrogen atmosphere. The catalyst was filtered off, the filtrate was evaporated affording cyclopropyl-{5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-ethyl-amine (65 mg, 86.2%) as a light yellow viscous oil. MS:  $m/z=341.5$  (M+H<sup>+</sup>)

### Example 61

10 6,8-Dichloro-2-{2-[2-(4-methoxy-benzyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl]-ethyl}-5-methyl-[1,2,4]triazolo[1,5-a]pyridine



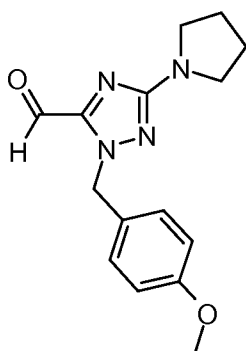
a) 5-(Dichloromethyl)-1-(4-methoxybenzyl)-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole and 3-(dichloromethyl)-1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazole





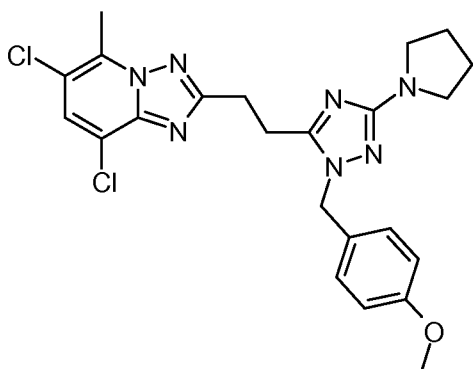
2,2-Dichloroacetyl chloride (662 mg, 433  $\mu$ L, 4.49 mmol, Eq: 0.9) was added dropwise below 0 °C to pyrrolidine-1-carbonitrile (0.48 g, 505  $\mu$ L, 4.99 mmol, Eq: 1.00). The mixture was stirred for 15 min at room temperature. Dichloromethane (7.5 mL) was added, followed by N,N-diisopropylethylamine (1.87 g, 2.53 mL, 14.5 mmol, Eq: 2.9) and (4-methoxybenzyl) hydrazine dihydrochloride (1.01 g, 4.49 mmol, Eq: 0.9) at 0 °C. The mixture was stirred for 1 h at room temperature and then heated for 2 h under reflux. The reaction mixture was concentrated and then partitioned between aqueous ammonium chloride and ethyl acetate. The combined organic layers were dried over sodium sulfate and then concentrated to an oil. The product (1.6 g, 93%, mixture of isomers) was obtained as a light yellow solid after filtration over silica (eluted with ethyl acetate). MS:  $m/z = 341.4$  (M+H<sup>+</sup>)

b) 1-(4-Methoxybenzyl)-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole-5-carbaldehyde



The mixture of 5-(dichloromethyl)-1-(4-methoxybenzyl)-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole and 3-(dichloromethyl)-1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazole from the previous step (299 mg, 0.876 mmol, Eq: 1) was suspended in ethanol (5 ml) and water (5 ml). Sodium acetate (180 mg, 2.2 mmol, Eq: 5) was added. The reaction mixture was heated for 16 h at 60 °C. The mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate. The product (74 mg, 29%) was obtained as a yellow solid by column chromatography (SiO<sub>2</sub>, ethyl acetate / n-heptane). MS:  $m/z = 287.3$  (M+H<sup>+</sup>)

c) 6,8-Dichloro-2-{2-[2-(4-methoxy-benzyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl]-ethyl}-5-methyl-[1,2,4]triazolo[1,5-a]pyridine

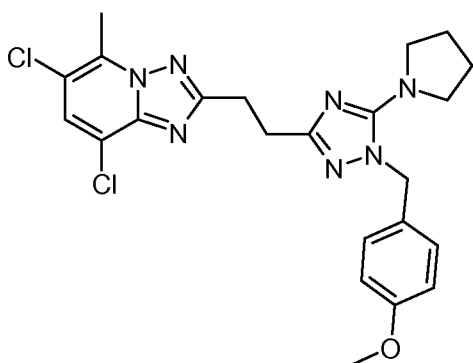


The product (40 mg, 22%) was obtained as a light yellow oil in analogy to Example 50 using 1-(4-methoxybenzyl)-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole-5-carbaldehyde and 1,2-diamino-3,5-dichloro-6-methylpyridinium 2,4,6-trimethylbenzenesulfonate as starting materials.

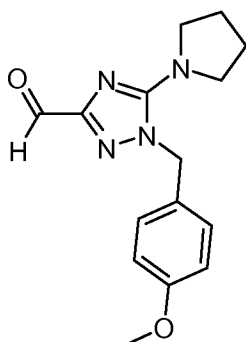
5 MS:  $m/z = 486.2$  (M+H<sup>+</sup>)

### Example 62

6,8-Dichloro-2-(2-(1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridine

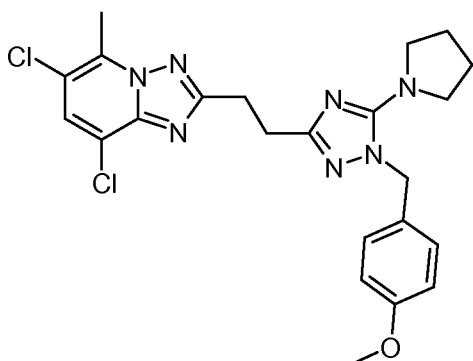


10 a) 1-(4-Methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazole-3-carbaldehyde



The product (117 mg, 46%) was obtained as a light yellow oil in the chromatographic separation from Example 61b. MS:  $m/z = 287.15$  (M+H<sup>+</sup>)

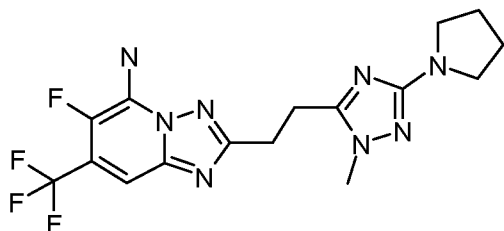
b) 6,8-Dichloro-2-(2-(1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridine



The product (65 mg, 39%) was obtained in analogy to Example 61 from 1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazole-3-carbaldehyde. MS:  $m/z = 486.2$  (M+H<sup>+</sup>)

### Example 63

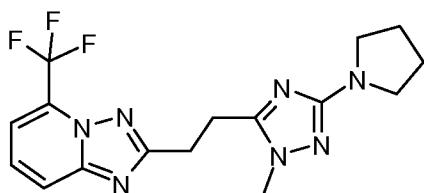
6-Fluoro-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-7-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridin-5-amine



10 The desired product (9 mg, 12%) was obtained in analogy to Example 52 from 3-fluoro-4-(trifluoromethyl)pyridine-2,6-diamine. MS:  $m/z = 399.4$  (M+H<sup>+</sup>)

### Example 64

2-(2-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-5-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

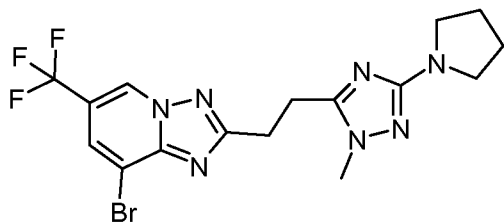


15

The desired product (4 mg, 8%) was obtained in analogy to Example 52 from 6-(trifluoromethyl)pyridin-2-amine. MS:  $m/z = 366.3$  (M+H<sup>+</sup>)

**Example 65**

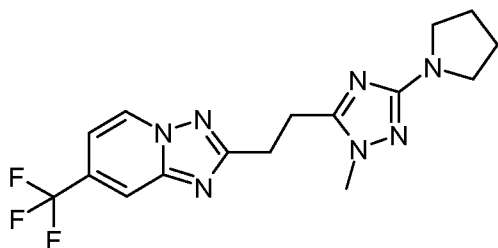
8-Bromo-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-6-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine



- 5 The desired product (31 mg, 38%) was obtained in analogy to Example 52 from 3-bromo-5-(trifluoromethyl)pyridin-2-amine. MS:  $m/z = 445.3$  (M+H<sup>+</sup>)

**Example 66**

2-(2-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-7-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

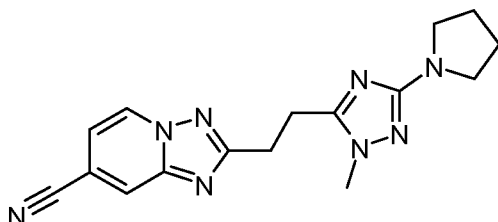


10

The desired product (13 mg, 19%) was obtained in analogy to Example 52 from 4-(trifluoromethyl)pyridin-2-amine. MS:  $m/z = 366.3$  (M+H<sup>+</sup>)

**Example 67**

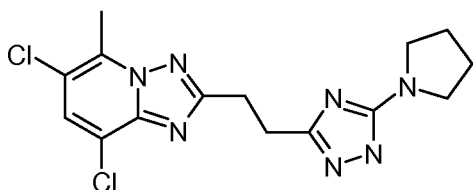
- 15 2-(2-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine-7-carbonitrile



The desired product (9 mg, 15%) was obtained in analogy to Example 52 from 2-aminoisonicotinonitrile. MS:  $m/z = 323.3$  (M+H<sup>+</sup>)

**Example 68**

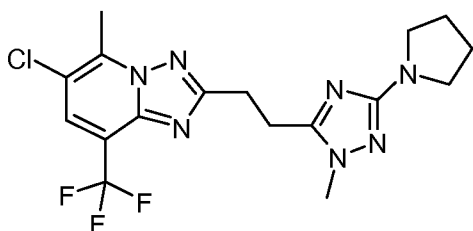
6,8-Dichloro-5-methyl-2-[2-(5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine



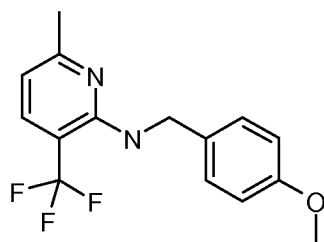
- 5 6,8-Dichloro-2-(2-(1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridine (17 mg, 35.0  $\mu\text{mol}$ , Eq: 1.00) in trifluoroacetic acid (539  $\mu\text{l}$ ) was heated 3 h under reflux. The product (12.8 mg, 100%) was obtained as a white solid by preparative HPLC. MS:  $m/z = 366.2$  (M+H<sup>+</sup>)

**Example 69**

- 10 6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine



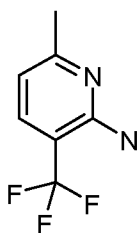
a) N-(4-Methoxybenzyl)-6-methyl-3-(trifluoromethyl)pyridin-2-amine



- 15 2-Chloro-6-methyl-3-(trifluoromethyl)pyridine (200 mg, 1.02 mmol, Eq: 1.00), (4-methoxyphenyl)methylamine (168 mg, 159  $\mu\text{L}$ , 1.23 mmol, Eq: 1.2) and potassium carbonate (212 mg, 1.53 mmol, Eq: 1.5) were combined in dimethylformamide (1.2 mL) to give a light yellow suspension. The mixture was stirred at 120 °C for 2 h. Additional potassium carbonate (141 mg, 1.02 mmol, Eq: 1) and (4-methoxyphenyl)methanamine (140 mg, 133  $\mu\text{L}$ , 1.02 mmol, Eq: 1)
- 20 were added and the mixture was stirred at 120 °C for 7 h. Saturated aqueous sodium chloride so-

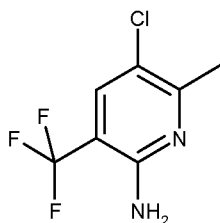
lution was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to an oil. The product (100 mg, 33%) was obtained as a colorless oil by column chromatography (SiO<sub>2</sub>, ethyl acetate/n-heptane). MS: m/z = 297.3 (M+H<sup>+</sup>)

5            b) 6-Methyl-3-(trifluoromethyl)pyridin-2-amine



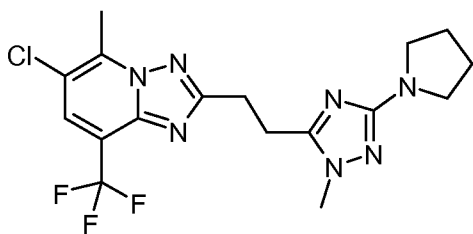
N-(4-Methoxybenzyl)-6-methyl-3-(trifluoromethyl)pyridin-2-amine (100 mg, 338 μmol, Eq: 1.00) in trifluoroacetic acid (2 ml) was heated under reflux for 30 min. The mixture was concentrated. The crude product (120 mg, pink solid) was used in the next step without further purification. MS: m/z = 218.2 (M+H<sup>+</sup>)

10            c) 5-Chloro-6-methyl-3-(trifluoromethyl)pyridin-2-amine



6-Methyl-3-(trifluoromethyl)pyridin-2-amine (59 mg, 335 μmol, Eq: 1.00) was suspended in 37% HCl aq (4.13 ml) and 35% hydrogen peroxide aq (488 mg, 440 μl, 5.02 mmol, Eq: 15) was added dropwise. The mixture was stirred for 20 min. Water (50 ml) was added. The mixture was alkalinized by addition of sodium bicarbonate and extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated to an oil. The product (70 mg, 99.2%) was obtained as a light yellow solid by column chromatography (SiO<sub>2</sub>, ethyl acetate/n-heptane). MS: m/z = 211.2 (M+H<sup>+</sup>)

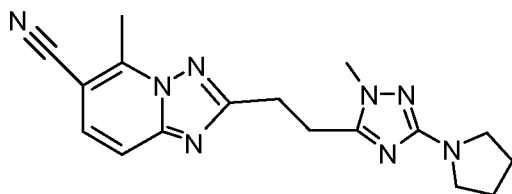
20            d) 6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine



The desired product (52 mg) was obtained as a white solid in analogy to Example 52 from 5-chloro-6-methyl-3-(trifluoromethyl)pyridin-2-amine. MS:  $m/z = 414.3$  ( $M+H^+$ )

### Example 70

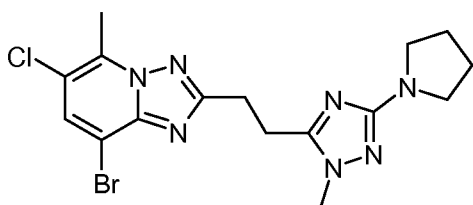
- 5 5-Methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonitrile



The desired product (25 mg) was obtained as a white powder in analogy to example 52 from 6-amino-2-methylnicotinonitrile. MS:  $m/z = 349.7$  ( $M+H^+$ )

- 10 **Example 71**

8-Bromo-6-chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)ethyl]-[1,2,4]triazolo[1,5-a]pyridine

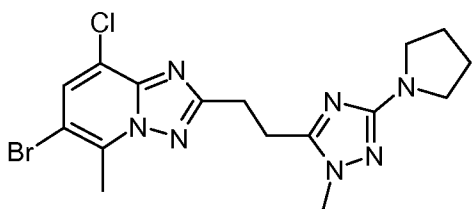


- 15 The desired product (92 mg) was obtained as a white solid in analogy to example 52 from 3-bromo-5-chloro-6-methylpyridin-2-amine. MS:  $m/z = 426.3$  ( $M+H^+$ )

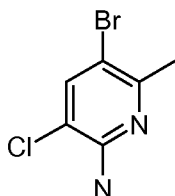
### Example 72

6-Bromo-8-chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine

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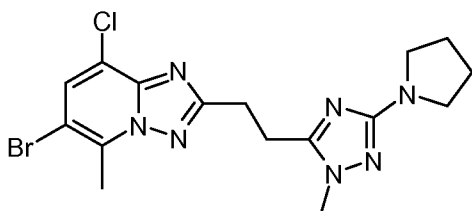


a) 5-Bromo-3-chloro-6-methylpyridin-2-amine



The product (947 mg, 80%) was obtained as an orange solid in analogy to Example 69c  
5 from 5-bromo-6-methylpyridin-2-amine. MS:  $m/z = 221.2$  (M+H<sup>+</sup>)

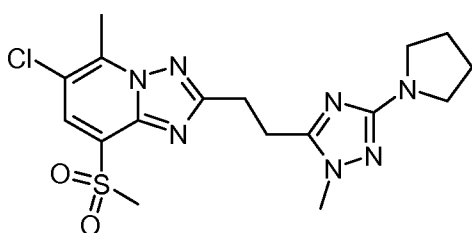
b) 6-Bromo-8-chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine



The desired product (123 mg) was obtained as a white solid in analogy to Example 52  
10 from 5-bromo-3-chloro-6-methylpyridin-2-amine. MS:  $m/z = 426.1$  (M+H<sup>+</sup>)

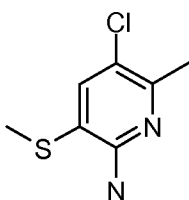
### Example 73

6-Chloro-8-methanesulfonyl-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine



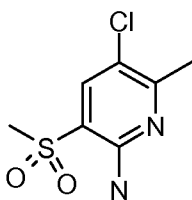
15 a) 5-Chloro-6-methyl-3-methylsulfanyl-pyridin-2-ylamine





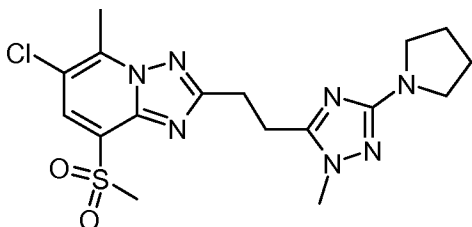
3-Bromo-5-chloro-6-methylpyridin-2-amine (300 mg, 1.35 mmol, Eq: 1.00) was dissolved in tetrahydrofuran (5ml). 1.6M n-BuLi in hexanes (3.39 ml, 5.42 mmol, Eq: 4) was added at -78 °C. The mixture was stirred for 10 min. 1,2-Dimethyldisulfane (510 mg, 481  $\mu$ l, 5.42 mmol, Eq: 4) was added and mixture allowed to warm to room temperature. The mixture was stirred for 30 min. Water was added and the mixture was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated to an oil. The product (158 mg, 61.8%) was obtained as a light yellow solid by chromatography (SiO<sub>2</sub>, ethyl acetate/n-heptane). MS: m/z = 230.1 (M+acetonitrile+H<sup>+</sup>)

10 b) 5-Chloro-6-methyl-3-(methylsulfonyl)pyridin-2-amine



5-Chloro-6-methyl-3-methylsulfonyl-pyridin-2-ylamine (160mg, 848  $\mu$ mol, Eq: 1.00) and oxone (1.56 g, 2.54 mmol, Eq: 3) were combined in methanol (15 ml) to give an off-white suspension. The mixture was cooled to 0 °C, and water (30 ml) was added dropwise, followed by 39% hydrogen sulfite (1.5 ml) and saturated sodium bicarbonate solution (6 ml). The mixture was stirred for 10 min and then extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to an oil. The product (88 mg, 47%) was obtained as a white solid by chromatography (SiO<sub>2</sub>, ethyl acetate/n-heptane). MS: m/z = 221.2 (M+H<sup>+</sup>)

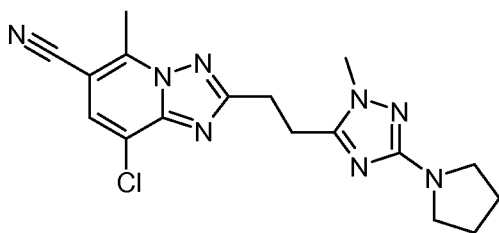
20 c) 6-Chloro-8-methanesulfonyl-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine



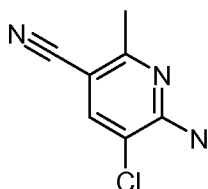
The desired product (24 mg) was obtained as an off-white solid in analogy to Example 52 from 5-chloro-6-methyl-3-(methylsulfonyl)pyridin-2-amine. MS: m/z = 424.4 (M+H<sup>+</sup>)

**Example 74**

8-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2*H*-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-*a*]pyridine-6-carbonitrile



5 a) 6-Amino-5-chloro-2-methylnicotinonitrile



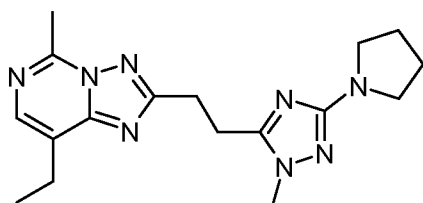
The product (53 mg, 31%) was obtained as a white powder in analogy to Example 69c from 6-amino-2-methylnicotinonitrile. MS:  $m/z = 209.2$  ( $M + \text{acetonitrile} + H^+$ )

10 b) 8-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2*H*-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-*a*]pyridine-6-carbonitrile

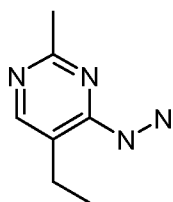
The desired product (27 mg) was obtained as a white powder in analogy to Example 52 from 6-amino-5-chloro-2-methylnicotinonitrile. MS:  $m/z = 370.7$  ( $M + H^+$ )

**Example 75**

15 8-Ethyl-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1*H*-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-*c*]pyrimidine

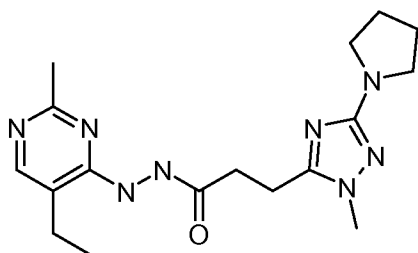


a) 5-Ethyl-4-hydrazinyl-2-methylpyrimidine



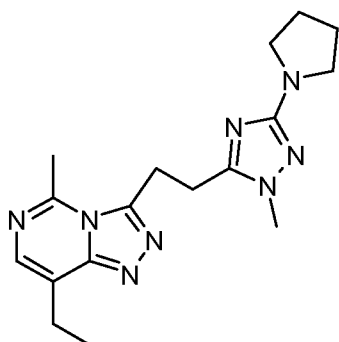
Hydrazine monohydrate (0.398 mL, 5.24 mmol) was added to 4-chloro-5-ethyl-2-methylpyrimidine (216 mg, 1.31 mmol). The reaction mixture was stirred in a sealed tube at room temperature overnight. Remaining hydrazine was evaporated. Purification by column chromatography (SiO<sub>2</sub>, methanol/ammonia/dichloromethane) to afforded the desired product (136 mg, 68.2%) as an amorphous off-white solid. MS: m/z = 153.11 (M+H<sup>+</sup>)

b) N<sup>1</sup>-(5-Ethyl-2-methylpyrimidin-4-yl)-3-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)propanehydrazide



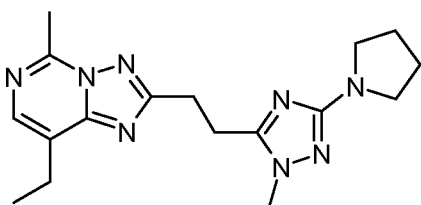
3-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)propanoic acid (140 mg, 0.624 mmol), HATU (712 mg, 1.87 mmol) and N,N-diisopropylethylamine (600 μl, 3.53 mmol) were dissolved in dimethylformamide (18 mL). The mixture was stirred for 20 minutes. 5-Ethyl-4-hydrazinyl-2-methylpyrimidine (99 mg, 0.655 mmol) was added and the reaction mixture was allowed to stir at room temperature overnight. The mixture was concentrated to an oil. Preparative HPLC afforded the desired product (71 mg, 31%) as a yellow gum. MS: m/z = 359.23 (M+H<sup>+</sup>)

c) 8-Ethyl-5-methyl-3-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[4,3-c]pyrimidine



N'-(5-Ethyl-2-methylpyrimidin-4-yl)-3-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)propanehydrazide (56.6mg, 158  $\mu$ mol) in tetrahydrofuran (4 ml) was added to Burgess reagent (155 mg, 632  $\mu$ mol). The mixture was heated in a sealed tube at 80 °C for 1 h. Saturated sodium bicarbonate solution was added and extracted with dichloromethane. The organic layers were  
5 dried over sodium sulfate and concentrated to an oil to afford the desired product (69 mg) as a yellow solid which was used without further purification in the next step. MS:  $m/z = 341.2$  (M+H<sup>+</sup>)

d) 8-Ethyl-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine

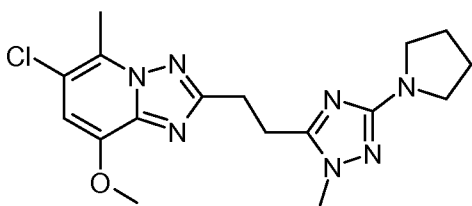


10

1.25 N HCl in methanol (57.3  $\mu$ l, 71.7  $\mu$ mol) was added to a solution of 8-ethyl-5-methyl-3-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[4,3-c]pyrimidine (24.4 mg, 71.7  $\mu$ mol) in methanol (2 mL). The reaction mixture was stirred at room temperature for 2 h. Additional 1.25 N HCl in methanol (57.3  $\mu$ l, 71.7  $\mu$ mol) was added and the  
15 mixture was stirred for 15 min. The solvent was evaporated. The crude product was purified with preparative HPLC to afford the desired product (20 mg, 82%) as a white solid. MS:  $m/z = 341.2$  (M+H<sup>+</sup>)

### Example 76

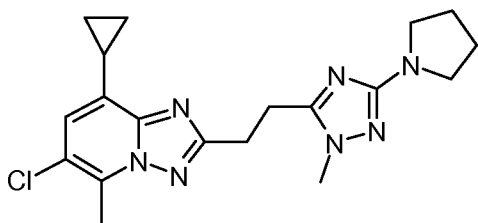
6-Chloro-8-methoxy-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine  
20



The desired product (13 mg) was obtained as a white solid from 3-methoxy-6-methylpyridin-2-amine in analogy to Example 72. MS:  $m/z = 376.4$  (M+H<sup>+</sup>)

### Example 77

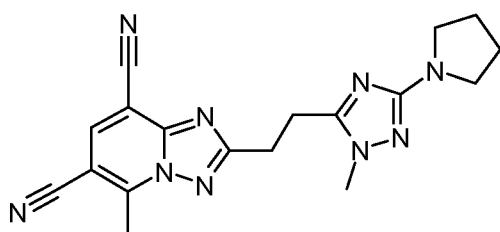
6-Chloro-8-cyclopropyl-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2*H*-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-*a*]pyridine



A mixture of 8-bromo-6-chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2*H*-  
 5 [1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-*a*]pyridine (30 mg, 70.6  $\mu\text{mol}$ , Eq: 1), cyclopropyl-  
 boronic acid (9.1 mg, 106  $\mu\text{mol}$ , Eq: 1.5) and cesium carbonate (46.0 mg, 141  $\mu\text{mol}$ , Eq: 2) in  
 dioxane (0.75 mL) and water (0.075 ml) was stirred for 4 min. Dichloro1,1'-  
 bis(diphenylphosphino)ferrocene palladium(II) (11.6 mg, 14.2  $\mu\text{mol}$ , 0.2 Eq) was added, and the  
 mixture was heated at 100 °C for 30 min in a microwave oven. The mixture was separated by  
 10 preparative HPLC to give the desired product (6.2 mg, 22%) as a white solid. MS:  $m/z = 386.4$   
 (M+H<sup>+</sup>)

### Example 78

5-Methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2*H*-[1,2,4]triazol-3-yl)-ethyl]-  
 [1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile

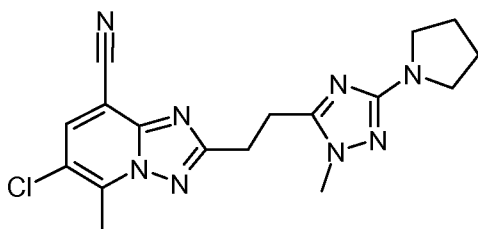


15

A mixture of 8-bromo-6-chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2*H*-  
 [1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-*a*]pyridine (40mg, 94.2  $\mu\text{mol}$ , Eq: 1.00), dicy-  
 anozinc (11.1 mg, 94.2  $\mu\text{mol}$ , Eq: 1) and tetrakis(triphenylphosphine)palladium (10.9 mg, 9.42  
 $\mu\text{mol}$ , Eq: 0.1) in dimethylformamide (0.9 mL) was heated for 15 min at 170 °C in a microwave  
 20 oven. Separation of the mixture by preparative HPLC afforded the product (9.9 mg, 29%) as a  
 yellow solid. MS:  $m/z = 362.4$  (M+H<sup>+</sup>)

### Example 79

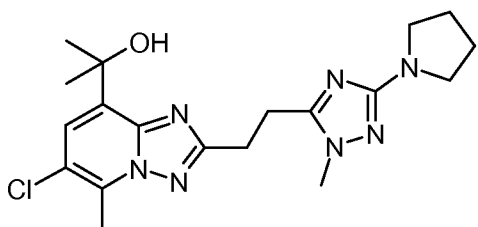
6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2*H*-[1,2,4]triazol-3-yl)-ethyl]-  
 [1,2,4]triazolo[1,5-*a*]pyridine-8-carbonitrile



The product (2.3 mg, 6.6%) was obtained in the preparative HPLC separation of Example 78. MS:  $m/z = 371.3$  (M+H<sup>+</sup>)

### Example 80

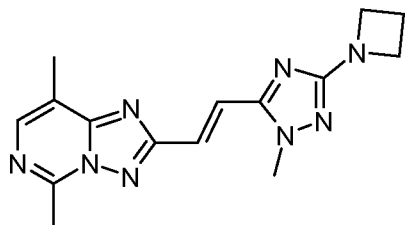
- 5 2-{6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-*a*]pyridin-8-yl}-propan-2-ol



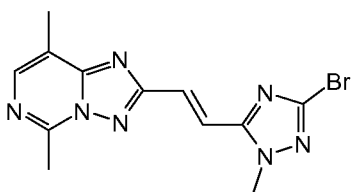
- A 1.6M solution of n-BuLi in hexanes (38.3  $\mu$ L, 61.2  $\mu$ mol, Eq: 1.3) was added at -68 °C to a solution of 8-bromo-6-chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-*a*]pyridine (20 mg, 47.1  $\mu$ mol, Eq: 1.00) in tetrahydrofuran (1 mL). This solution was stirred 5 min at -68 °C, then propan-2-one (2.73 mg, 1 mL, 47.1  $\mu$ mol, Eq: 1.00) was added and the cooling bath was removed. The mixture was stirred at room temperature for 10 min. Separation of the mixture by preparative HPLC afforded the desired product (1.7 mg, 8.9%) as a colorless oil. MS:  $m/z = 404.2$  (M+H<sup>+</sup>)
- 10

### 15 Example 81

- 2-[(E)-2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-*c*]pyrimidine

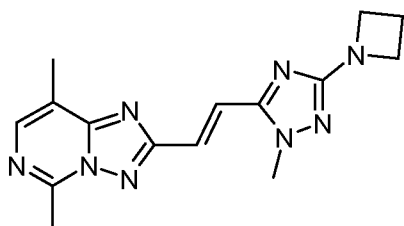


- a) 2-[(E)-2-(5-Bromo-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-*c*]pyrimidine
- 20



To a solution of 3-bromo-1-methyl-1H-1,2,4-triazole-5-carbaldehyde (120 mg, 632  $\mu\text{mol}$ , Eq: 1.00) in tetrahydrofuran (25 ml) were added ((5,8-dimethyl-[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)methyl)triphenylphosphonium chloride (290 mg, 632  $\mu\text{mol}$ , Eq: 1.00) (prepared as described in WO2011150156, pp123-125, Expl. 24g) and DBU (106 mg, 105  $\mu\text{l}$ , 695  $\mu\text{mol}$ , Eq: 1.1). The resulting solution was stirred for 18 hours at 25 °C. The crude material was applied on silica gel and purified by flash chromatography over a 20 g silica gel column using ethyl acetate / methanol 0-10 % as eluent affording 2-[(E)-2-(5-bromo-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-c]pyrimidine (154 mg, 73%) as a white solid. MS:  $m/z=$  336.6/35/37 (M+H+)

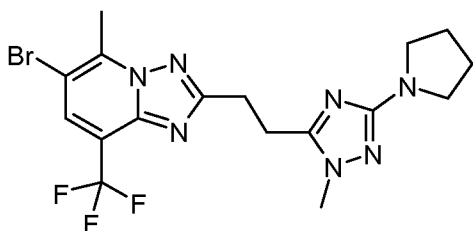
b) 2-[(E)-2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-c]pyrimidine



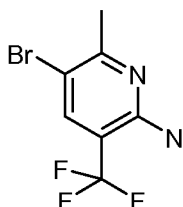
A solution of (E)-2-(2-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-c]pyrimidine (150 mg, 449  $\mu\text{mol}$ , Eq: 1.00) in dioxane (210.4 ml) was purged with argon, then sodium phenolate (78.2 mg, 673  $\mu\text{mol}$ , Eq: 1.5), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xant-phos) (20.8 mg, 35.9  $\mu\text{mol}$ , Eq: 0.08), tris(dibenzylideneacetone)-dipalladium chloroform complex /  $\text{Pd}_2(\text{dba})_3\text{CHCl}_3$  (18.6 mg, 18.0  $\mu\text{mol}$ , Eq: 0.04) and azetidine (76.9 mg, 90.5  $\mu\text{l}$ , 1.35 mmol, Eq: 3) were added. The vial was capped and irradiated at 140 °C for 40 minutes in a microwave oven. The crude material was applied on silica gel and purified by flash chromatography over a 20 g silica gel column using ethyl acetate / methanol 0-10 % as eluent affording 2-[(E)-2-(5-azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-c]pyrimidine (89 mg, 63.9%) as light yellow solid. MS:  $m/z=$  311.5 (M+H+), MP: 210.4 °C

## 25 Example 82

6-Bromo-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine

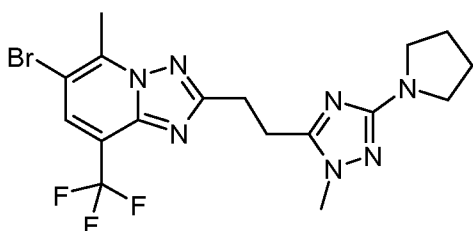


a) 5-Bromo-6-methyl-3-trifluoromethyl-pyridin-2-ylamine



Bromine (1.7 g, 548  $\mu$ l, 10.6 mmol, Eq: 5) was added to 6-methyl-3-  
 5 (trifluoromethyl)pyridin-2-amine (375 mg, 2.13 mmol, Eq: 1) in trifluoroacetic acid (7 ml). The  
 mixture was stirred for 30 min and then concentrated to an oil. Water (30 ml) and dichloro-  
 methane (10 ml) were added. The mixture was alkalinized by addition of sodium bicarbonate and  
 extracted with dichloromethane. The combined organic layers were dried over sodium sulfate  
 and concentrated to an oil. The crude product was purified by chromatography ( $\text{SiO}_2$ , ethyl ac-  
 10 tate/n-heptane) to give the desired product (450 mg, 82.9%) as a yellow solid. MS:  $m/z = 255.1$   
 ( $M+H^+$ )

b) 6-Bromo-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2*H*-[1,2,4]triazol-3-yl)-ethyl]-8-  
 trifluoromethyl-[1,2,4]triazolo[1,5-*a*]pyridine



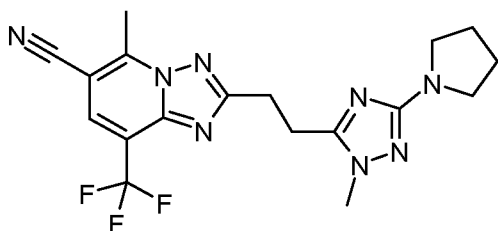
15 The product (190 mg) was obtained as a white solid in analogy to Example 52 from 5-  
 bromo-6-methyl-3-trifluoromethyl-pyridin-2-ylamine. MS:  $m/z = 458.4$  ( $M+H^+$ )

### Example 83

5-Methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1*H*-1,2,4-triazol-5-yl)ethyl)-8-  
 (trifluoromethyl)-[1,2,4]triazolo[1,5-*a*]pyridine-6-carbonitrile



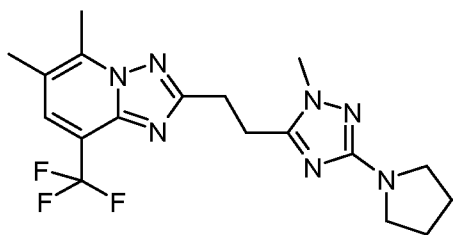
-112-



The product (6 mg, 18%) was obtained as a light yellow solid in analogy to Example 78 from 6-bromo-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine. MS:  $m/z = 405.4$  (M+H<sup>+</sup>)

### 5 Example 84

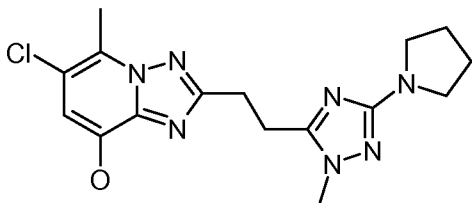
5,6-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine



1 M dimethylzinc in heptane (70  $\mu$ L, 70  $\mu$ mol, Eq: 1.00) was added to 6-bromo-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine (30 mg, 65.5  $\mu$ mol, Eq: 1.00) and 1,3-bis(diphenylphosphino)propane-nickel(II) chloride (13 mg, 24.0  $\mu$ mol, Eq: 0.366) in dioxane (1 ml). The mixture was heated to 100  $^{\circ}$ C for 1 h in a microwave oven. Purification by preparative HPLC gave the desired product (16 mg, 61.7%) as a white solid. MS:  $m/z = 394.4$  (M+H<sup>+</sup>)

### 15 Example 85

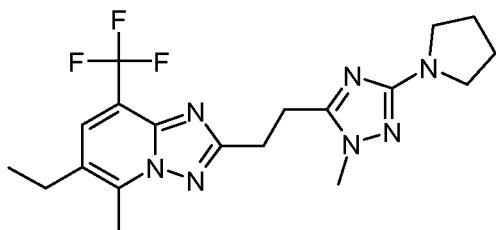
6-Chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridin-8-ol



The product (6.3 mg) was obtained as a white solid in analogy to Example 72 from 2-amino-6-methylpyridin-3-ol. MS:  $m/z = 362.3$  (M+H<sup>+</sup>)

**Example 86**

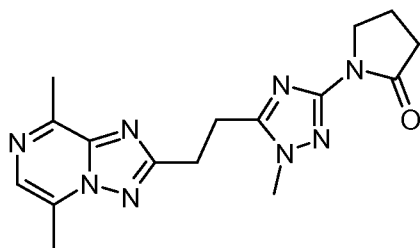
6-Ethyl-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine



- 5 The product (18 mg, 40%) was obtained as a white powder in analogy to Example 84 using diethylzinc instead of dimethylzinc as starting material. MS:  $m/z = 408.2$  (M+H<sup>+</sup>)

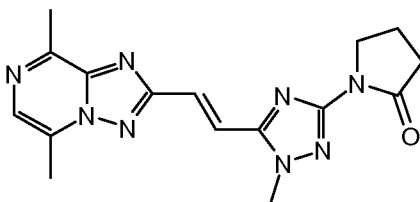
**Example 87**

1-{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-2-one



10

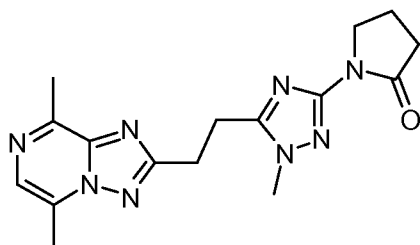
a) 1-{5-[(E)-2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-2-one



- 15 An argon-purged mixture of (E)-2-(2-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (case 30922, Expl. 9a) p31) (56 mg, 168  $\mu\text{mol}$ , Eq: 1.00), pyrrolidin-2-one (28.6 mg, 25.7  $\mu\text{l}$ , 336  $\mu\text{mol}$ , Eq: 2), cesium carbonate (76.4 mg, 235  $\mu\text{mol}$ , Eq: 1.4), tris(dibenzylideneacetone)-dipalladium(0) / Pd<sub>2</sub>(dba)<sub>3</sub> (3.07 mg, 3.35  $\mu\text{mol}$ , Eq: 0.02) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xant-phos) (3.88 mg, 6.7  $\mu\text{mol}$ , Eq: 0.04) in dioxane (3 ml) was heated in a closed vessel for 1.5 hours at 140 °C under argon atmosphere. Up to 4 additional portions of Pd<sub>2</sub>(dba)<sub>3</sub> and 4,5-bis(diphenylphosphino)-9,9-
- 20

dimethylxanthene (xant-phos) are added and heating continued for another 1.5 hours until HPLC shows complete conversion of the Aryl bromide. The crude material was applied on silica gel and purified by flash chromatography over a 20 g silica gel column using ethyl acetate / methanol 5-10 % as eluent affording 1-{5-[(E)-2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-2-one (27 mg, 47,6%) as an off-white solid. MS: m/z= 339.6 (M+H+), MP: 242.5 °C

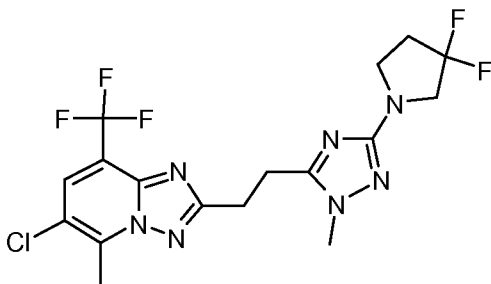
b) 1-{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-2-one



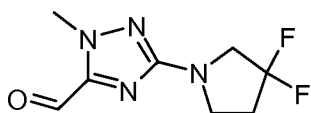
10 A mixture of (E)-1-(5-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)vinyl)-1-methyl-1H-1,2,4-triazol-3-yl)pyrrolidin-2-one (24 mg, 70.9  $\mu$ mol, Eq: 1.00) and palladium on carbon 10% (7.5 mg, 7.1  $\mu$ mol, Eq: 0.1) in methanol (15 ml) was stirred for 5 hours at 25 °C under hydrogen atmosphere. Additional catalyst (0.1 eq) was added and hydrogenation continued for another 6 hours until HPLC shows complete conversion. The catalyst was filtered off, the filtrate was evaporated affording 1-{5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-2-one (24 mg, 99.4%) as a colorless oil. MS: m/z= 341.6 (M+H+)

### Example 88

20 6-Chloro-2-{2-[5-(3,3-difluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5-methyl-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine



a) 3-(3,3-Difluoropyrrolidin-1-yl)-1-methyl-1H-1,2,4-triazole-5-carbaldehyde



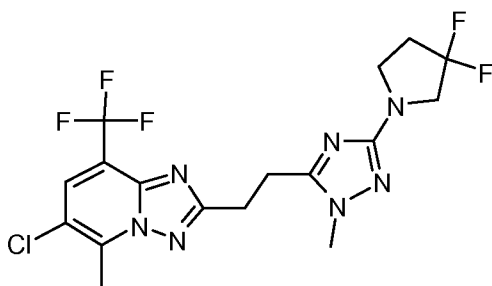
N,N-Diisopropylethylamine (900 mg, 1.22 ml, 6.97 mmol, Eq: 2.00) was added to 3,3-difluoropyrrolidine hydrochloride (500 mg, 3.5 mmol, Eq: 1.00) in diethyl ether (10 ml). A solution of cyanic bromide (369 mg, 3.5 mmol, Eq: 1.00) in diethyl ether (2 mL) was added at 0 °C.

5 The mixture was stirred over night at room temperature, filtered and concentrated on a rotatory evaporator at 40 °C, keeping the pressure above 100 mbar (product is volatile). 2,2-Dichloroacetyl chloride (510 mg, 0.336 ml, 3.5 mmol, Eq: 1.00) was added to the crude intermediate at 0 °C. The mixture was stirred for 15 min. Dichloromethane (6 ml) was added, followed by N,N-diisopropylethylamine (452 mg, 0.61 ml, 3.5 mmol, Eq: 1.00). tert-Butyl 1-

10 methylhydrazinecarboxylate (555 mg, 0.62 ml, 3.8 mmol, Eq: 1.09) was added dropwise at 0 °C. The reaction mixture was stirred for 1 h at room temperature. Trifluoroacetic acid (4 g, 2.7 ml, 35 mmol, Eq: 10) was added. The reaction mixture was heated under reflux for 1.5 h and then concentrated to an oil. The mixture was partitioned between a saturated sodium bicarbonate solution and ethyl acetate. The combined organic layers were washed with a saturated ammonium

15 chloride solution and then dried over sodium sulfate and concentrated to an oil. Ethanol (12 ml) and water (24 ml) were added, followed by sodium acetate (717 mg, 8.75 mmol, Eq: 2.5). The reaction mixture was heated to 60 °C for 1 h. The mixture was extracted with ethyl acetate. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to give the desired product (699 mg, 92%) as a white powder. MS: m/z = 217.3 (M+H<sup>+</sup>)

20 b) 6-Chloro-2-{2-[5-(3,3-difluoropyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5-methyl-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine

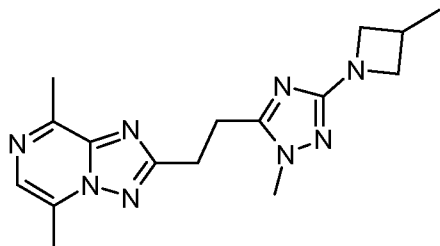


The product (16 mg) was obtained as a light yellow solid in analogy to Example 50 from 3-(3,3-difluoropyrrolidin-1-yl)-1-methyl-1H-1,2,4-triazole-5-carbaldehyde and 5-chloro-6-

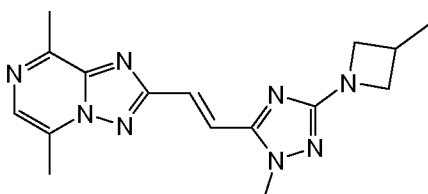
25 methyl-3-(trifluoromethyl)pyridin-2-amine. MS: m/z = 450.4 (M+H<sup>+</sup>)

### Example 89

5,8-Dimethyl-2-{2-[2-methyl-5-(3-methyl-azetidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

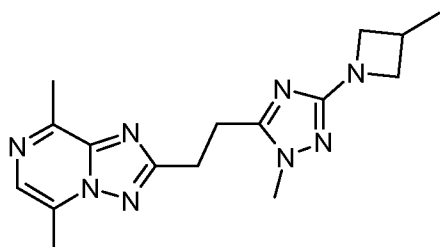


a) 5,8-Dimethyl-2-{(E)-2-[2-methyl-5-(3-methyl-azetidin-1-yl)-2H-[1,2,4]triazol-3-yl]-vinyl}-[1,2,4]triazolo[1,5-a]pyrazine



Was prepared in the same manner as described in Example 87a) using 3-methylazetidine benzenesulfonate (206 mg, 898  $\mu\text{mol}$ , Eq: 2) instead of pyrrolidin-2-one affording 5,8-dimethyl-2-{(E)-2-[2-methyl-5-(3-methyl-azetidin-1-yl)-2H-[1,2,4]triazol-3-yl]-vinyl}-[1,2,4]triazolo[1,5-a]pyrazine (51 mg, 35.0%) as a bright yellow viscous oil. MS:  $m/z= 325.6$  (M+H+)

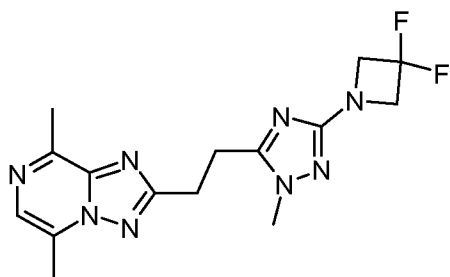
b) 5,8-Dimethyl-2-{2-[2-methyl-5-(3-methyl-azetidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine



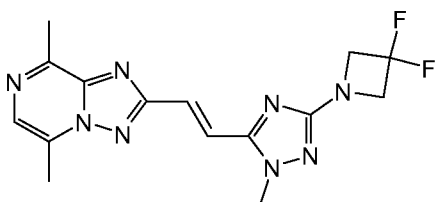
Was prepared in the same manner as described in Example 87 b) from (E)-5,8-dimethyl-2-(2-(1-methyl-3-(3-methylazetidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyrazine (50 mg, 154  $\mu\text{mol}$ , Eq: 1.00) affording 5,8-dimethyl-2-{2-[2-methyl-5-(3-methyl-azetidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine (45 mg, 89.4%) as a colorless oil. MS:  $m/z= 327.5$  (M+H+)

### Example 90

2-{2-[5-(3,3-Difluoro-azetid-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

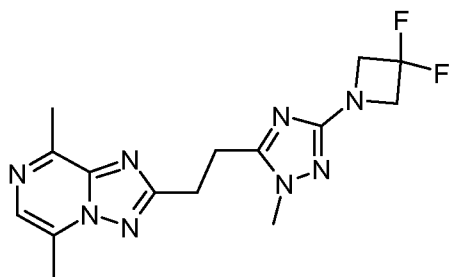


5 a) 2-{(E)-2-[5-(3,3-Difluoro-azetid-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



10 Was prepared in the same manner as described in Example 87a) using 3,3-difluoroazetidine hydrochloride (87.2 mg, 673  $\mu\text{mol}$ , Eq: 1.5) instead of pyrrolidin-2-one affording 2-{(E)-2-[5-(3,3-difluoro-azetid-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (57 mg, 36.7%) as a light yellow oil. MS:  $m/z = 347.5$  (M+H<sup>+</sup>)

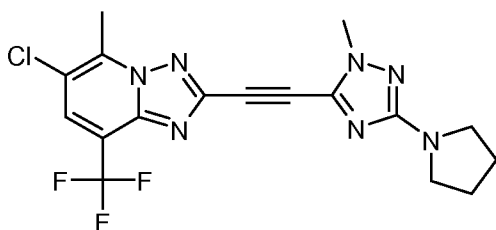
b) 2-{2-[5-(3,3-Difluoro-azetid-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



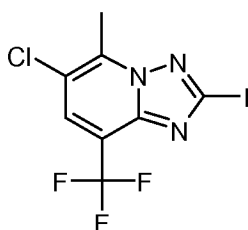
15 Was prepared in the same manner as described in Example 87 b) from (E)-2-(2-(3-(3,3-difluoroazetid-1-yl)-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (54 mg, 156  $\mu\text{mol}$ , Eq: 1.00) affording 2-{2-[5-(3,3-difluoro-azetid-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (51 mg, 93.9%) as an off-white solid. MS:  $m/z = 349.5$  (M+H<sup>+</sup>), MP: 141.3  $^{\circ}\text{C}$

**Example 91**

6-Chloro-5-methyl-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine

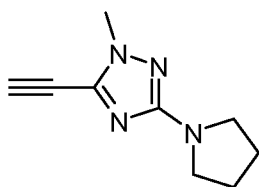


5 a) 6-Chloro-2-iodo-5-methyl-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine



Ethoxycarbonyl isothiocyanate (111 mg, 0.1 ml, 0.852 mmol, Eq:1.50) was added to 6-methyl-3-(trifluoromethyl)pyridin-2-amine (100 mg, 0.568 mmol, Eq: 1.00) in dioxane (10 ml). The mixture was heated to 60 °C for 1 h. The mixture was filtered. The residue was suspended in ethanol (10 ml), hydroxylamine hydrochloride (197 mg, 2.84 mmol, Eq: 5) and N,N-diisopropylethylamine (220 mg, 0.3 ml, 1.7 mmol, Eq: 3) were added. The mixture was heated under reflux overnight and then concentrated to an oil. Water (15 ml) was added and the mixture was filtered. The residue was washed with water and ether, and then dissolved in acetonitrile (10 ml). Isopentyl nitrite (111 mg, 127  $\mu$ l, 628  $\mu$ mol, Eq: 1.1) and copper(I)iodide (160 mg, 838  $\mu$ mol, Eq: 1.5) were added. The mixture was stirred at 80 °C for 1 h. The mixture was filtered over SiO<sub>2</sub> concentrated, suspended in ethyl acetate and filtered again over SiO<sub>2</sub> and concentrated to give the product (120 mg, 58%) as a light yellow powder. MS: m/z = 362.2 (M+H<sup>+</sup>)

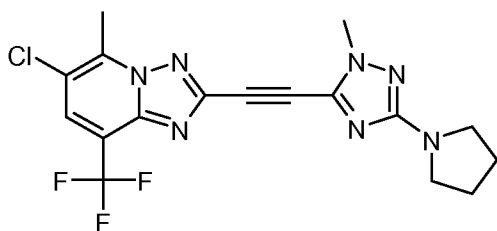
b) 5-Ethynyl-1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole



20 To a stirred mixture of 1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole-5-carbaldehyde (2.06 g, 11.4 mmol) and potassium carbonate (3.16 g, 22.9 mmol) at room temperature in metha-

nol (75 ml) under an argon atmosphere was added drop wise a solution of dimethyl 1-diazo-2-oxopropylphosphonate (2.64 g, 2.1 ml, 13.7 mmol) in methanol (15 ml). Stirring at room temperature was then continued for 3 h. The mixture was diluted with diethyl ether and washed with 10 % NaHCO<sub>3</sub> solution. The aqueous phase was extracted with diethyl ether. The combined organic layers were washed with H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The crude product was purified by silica gel chromatography using a CH<sub>2</sub>Cl<sub>2</sub>/MeOH gradient as eluent, providing the title compound (725 mg, 36%) as off-white solid. MS: m/z = 177.2 (M+H<sup>+</sup>)

c) 6-Chloro-5-methyl-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine



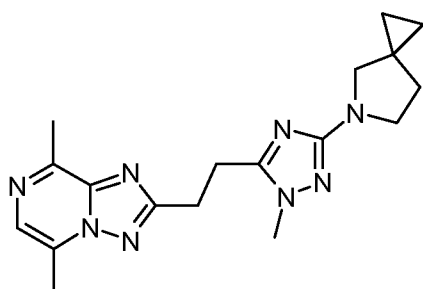
10

6-Chloro-2-iodo-5-methyl-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine (13 mg, 36.0 μmol, Eq: 1.00), 5-ethynyl-1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole (8 mg, 45.4 μmol, Eq: 1.26), triethylamine (7.26 mg, 10 μl, 71.7 μmol, Eq: 2.00), and bis(triphenylphosphine)palladium (II) chloride (5 mg, 7.12 μmol, Eq: 0.198) were added to dimethylformamide (1 ml). Copper(I)iodide (1 mg, 5.25 μmol, Eq: 0.146) was added and the mixture was stirred for 2 h at 80 °C. The crude material was purified by preparative TLC (silica gel, ethyl acetate/n-heptane) to give the product (6.8 mg, 46%) as a white powder. MS: m/z = 410.4 (M+H<sup>+</sup>)

15

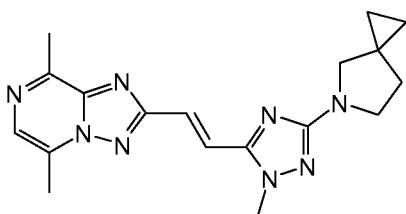
### Example 92

20 2-{2-[5-(5-Aza-spiro[2.4]hept-5-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



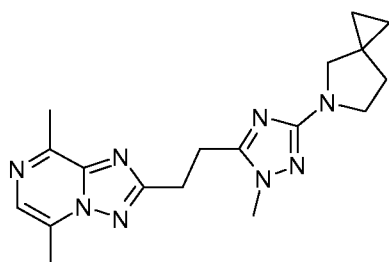
a) 2-{(E)-2-[5-(5-Aza-spiro[2.4]hept-5-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine





Was prepared in the same manner as described in Example 87a) using 5-azaspiro[2.4]heptane hydrochloride (120 mg, 898  $\mu\text{mol}$ , Eq: 2) instead of pyrrolidin-2-one affording 2-((E)-2-((5-(5-aza-spiro[2.4]hept-5-yl)-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (33 mg, 21%) as yellow amorphous solid. MS:  $m/z=351.6$  (M+H<sup>+</sup>)

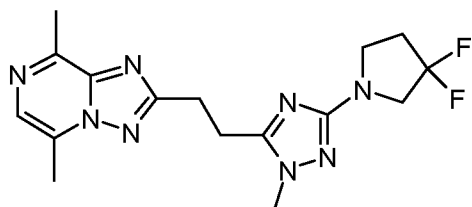
b) 2-((2-((5-(5-Aza-spiro[2.4]hept-5-yl)-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



10 Was prepared in the same manner as described in Example 87 b) from (E)-5,8-dimethyl-2-((1-methyl-3-((5-azaspiro[2.4]heptan-5-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyrazine (31 mg, 88.5  $\mu\text{mol}$ , Eq: 1.00) affording 2-((2-((5-(5-aza-spiro[2.4]hept-5-yl)-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (32 mg, 103%) as a colorless oil. MS:  $m/z=353.6$  (M+H<sup>+</sup>)

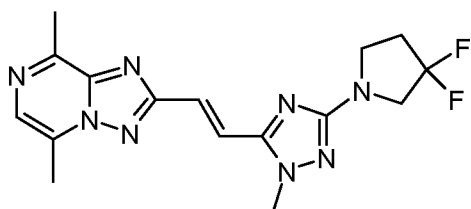
15 **Example 93**

2-((2-((5-(3,3-Difluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



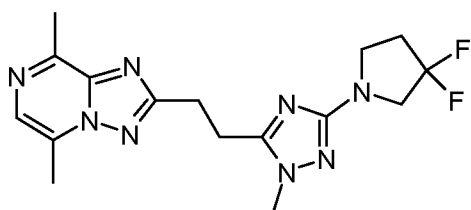
a) 2-((E)-2-((5-(3,3-Difluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

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Was prepared in the same manner as described in Example 49 e) using 3-(3,3-difluoropyrrolidin-1-yl)-1-methyl-1H-1,2,4-triazole-5-carbaldehyde (94.2 mg, 436  $\mu\text{mol}$ , Eq: 1.00) as aldehyde affording 2-((E)-2-(5-(3,3-difluoropyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl)-5,8-dimethyl-1,2,4-triazolo[1,5-a]pyrazine (80 mg, 50.9%) as a light yellow solid. MS:  $m/z = 361.5$  ( $M+H^+$ ), MP: 207.5  $^{\circ}\text{C}$

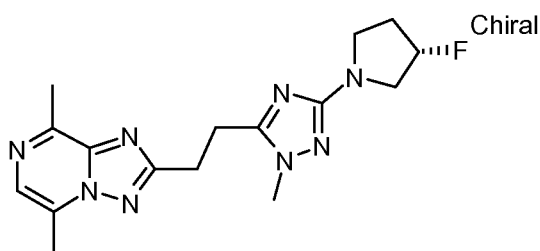
b) 2-((E)-2-(5-(3,3-Difluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl)-5,8-dimethyl-1,2,4-triazolo[1,5-a]pyrazine



Was prepared in the same manner as described in Example 87 b) using (E)-2-(2-(3-(3,3-difluoropyrrolidin-1-yl)-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-1,2,4-triazolo[1,5-a]pyrazine (71 mg, 197  $\mu\text{mol}$ , Eq: 1.00) affording 2-((E)-2-(5-(3,3-difluoropyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl)-5,8-dimethyl-1,2,4-triazolo[1,5-a]pyrazine (39 mg, 54.6%) as a white solid. MS:  $m/z = 363.6$  ( $M+H^+$ )

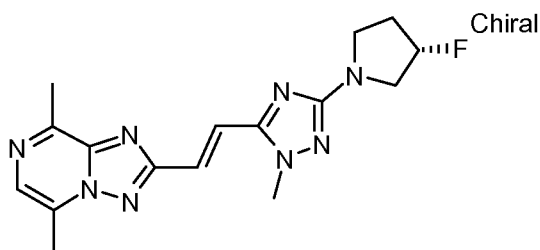
#### Example 94

2-((E)-2-(5-((S)-3-Fluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl)-5,8-dimethyl-1,2,4-triazolo[1,5-a]pyrazine



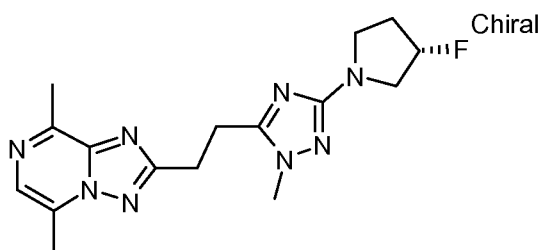
a) 2-((E)-2-(5-((S)-3-Fluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl)-5,8-dimethyl-1,2,4-triazolo[1,5-a]pyrazine

-122-



Was prepared in the same manner as described in Example 87a) using (S)-3-fluoropyrrolidine hydrochloride (113 mg, 898  $\mu\text{mol}$ , Eq: 2) instead of pyrrolidin-2-one affording 2-((E)-2-[5-((S)-3-fluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (54 mg, 35.1%) as a light yellow solid. MS:  $m/z = 343.5$  (M+H<sup>+</sup>)

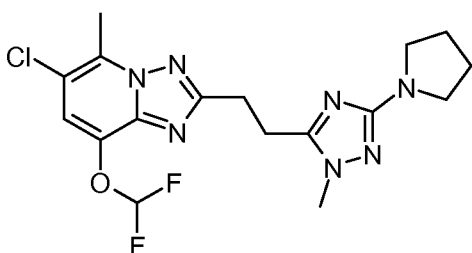
b) 2-((S)-2-[5-((S)-3-Fluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



Was prepared in the same manner as described in Example 87 b) using (S,E)-2-((S)-2-(3-(3-fluoropyrrolidin-1-yl)-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (48 mg, 140  $\mu\text{mol}$ , Eq: 1.00) affording 2-((S)-2-[5-((S)-3-fluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (56 mg, 116%) as a colorless oil. MS:  $m/z = 345.6$  (M+H<sup>+</sup>)

### Example 95

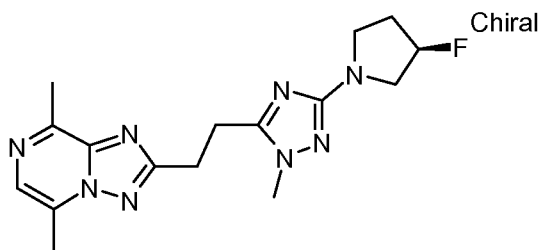
6-Chloro-8-difluoromethoxy-5-methyl-2-((S)-2-[5-((S)-3-fluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl)-[1,2,4]triazolo[1,5-a]pyridine



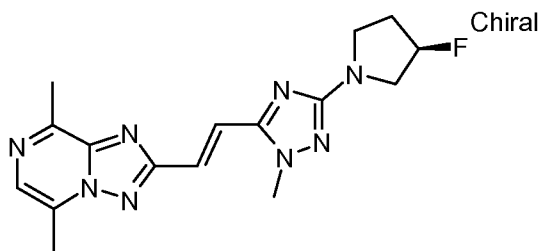
The product (37 mg) was obtained as a light brown solid from 3-(difluoromethoxy)-6-methylpyridin-2-amine in analogy to Example 72. MS:  $m/z = 412.4$  (M+H<sup>+</sup>)

**Example 96**

2-{2-[5-((R)-3-Fluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

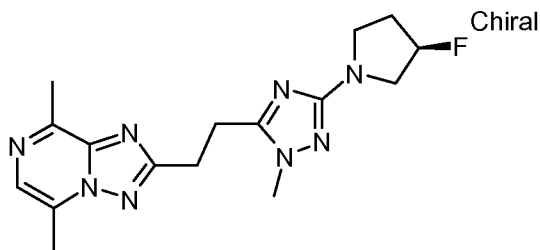


- 5 a) 2-{(E)-2-[5-((R)-3-Fluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



- 10 Was prepared in the same manner as described in Example 87a) using (R)-3-fluoropyrrolidine hydrochloride (113 mg, 898  $\mu\text{mol}$ , Eq: 2) instead of pyrrolidin-2-one affording 2-{(E)-2-[5-((R)-3-fluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (36 mg, 23.4%) as a light yellow solid. MS:  $m/z = 343.5$  (M+H<sup>+</sup>)

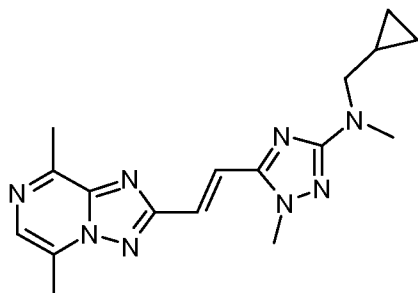
b) 2-{2-[5-((R)-3-Fluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



- 15 Was prepared in the same manner as described in Example 87 b) using (R,E)-2-(2-(3-(3-fluoropyrrolidin-1-yl)-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (37 mg, 108  $\mu\text{mol}$ , Eq: 1.00) affording 2-{2-[5-((R)-3-fluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (16 mg, 43%) as a white solid. MS:  $m/z = 345.5$  (M+H<sup>+</sup>)

**Example 97**

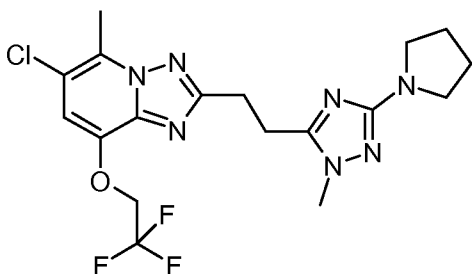
Cyclopropylmethyl- {5-[(E)-2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-methyl-amine



- 5 Was prepared in the same manner as described in Example 87a) using 1-cyclopropyl-N-methylmethanamine hydrochloride (109 mg, 898  $\mu\text{mol}$ , Eq: 2) instead of pyrrolidin-2-one affording cyclopropylmethyl- {5-[(E)-2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-methyl-amine (5 mg, 3.29%) as a yellow viscous oil. MS:  $m/z=339.5$  (M+H<sup>+</sup>)

10 **Example 98**

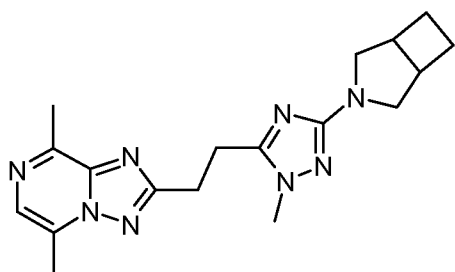
6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-8-(2,2,2-trifluoro-ethoxy)-[1,2,4]triazolo[1,5-a]pyridine



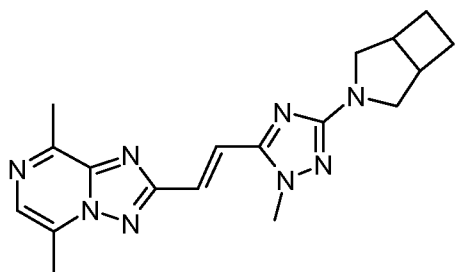
- 15 The product (27 mg) was obtained as a light yellow foam from 6-methyl-3-(2,2,2-trifluoroethoxy)-2-pyridinamine in analogy to Example 72. MS:  $m/z = 444.1$  (M+H<sup>+</sup>)

**Example 99**

2-{2-[5-(3-Aza-bicyclo[3.2.0]hept-3-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

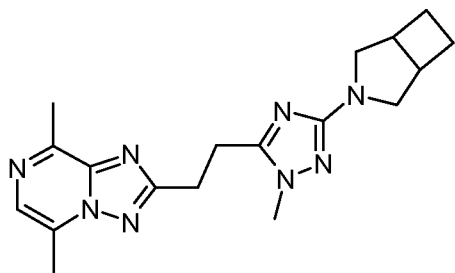


a) 2-((E)-2-(5-(3-Aza-bicyclo[3.2.0]hept-3-yl)-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl)-5,8-dimethyl-1,2,4-triazolo[1,5-a]pyrazine



5 Was prepared in the same manner as described in Example 87a) using 3-aza-bicyclo[3.2.0]-heptane hydrochloride (158 mg, 898  $\mu\text{mol}$ , Eq: 2) instead of pyrrolidin-2-one affording 2-((E)-2-(5-(3-aza-bicyclo[3.2.0]hept-3-yl)-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl)-5,8-dimethyl-1,2,4-triazolo[1,5-a]pyrazine (29 mg, 18.4%) as a yellow oil. MS:  $m/z = 351.5$  ( $M+H^+$ )

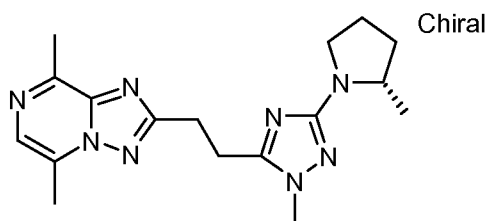
10 b) 2-((E)-2-(5-(3-Aza-bicyclo[3.2.0]hept-3-yl)-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl)-5,8-dimethyl-1,2,4-triazolo[1,5-a]pyrazine



15 Was prepared in the same manner as described in Example 87 b) using (E)-2-(2-(3-(3-azabicyclo[3.2.0]heptan-3-yl)-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-1,2,4-triazolo[1,5-a]pyrazine (20 mg, 57.1  $\mu\text{mol}$ , Eq: 1.00) affording 2-((E)-2-(5-(3-aza-bicyclo[3.2.0]hept-3-yl)-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl)-5,8-dimethyl-1,2,4-triazolo[1,5-a]pyrazine (21 mg, 104%) as a colorless oil. MS:  $m/z = 353.6$  ( $M+H^+$ )

### Example 100

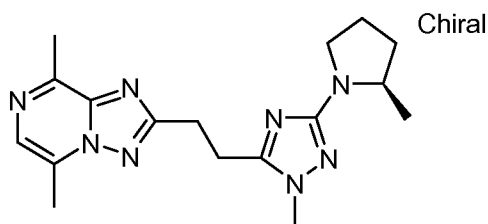
5,8-Dimethyl-2-{2-[2-methyl-5-((S)-2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine



Chiral HPLC-separation of racemic 5,8-dimethyl-2-(2-(1-methyl-3-(2-methylpyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyrazine (169 mg, 496  $\mu$ mol, Eq: 1.00) (Example 83c) : First Peak A+, afforded 5,8-dimethyl-2-{2-[2-methyl-5-((S)-2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine (67 mg, 39.6%) as a light yellow oil. MS:  $m/z$ = 341.5 (M+H<sup>+</sup>)

### Example 101

10 5,8-Dimethyl-2-{2-[2-methyl-5-((R)-2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

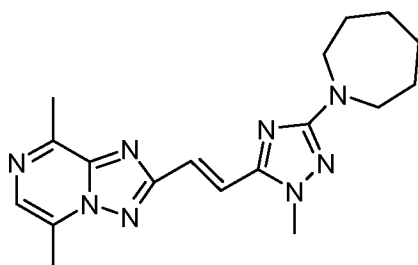


Chiral HPLC-separation of racemic 5,8-dimethyl-2-(2-(1-methyl-3-(2-methylpyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyrazine (169 mg, 496  $\mu$ mol, Eq: 1.00) (Example 83c) : Second Peak B-, afforded 5,8-dimethyl-2-{2-[2-methyl-5-((R)-2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine (66mg, 39.1%) as a light yellow oil. MS:  $m/z$ = 341.5 (M+H<sup>+</sup>)

### Example 102

20 2-[(E)-2-(5-Azepan-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

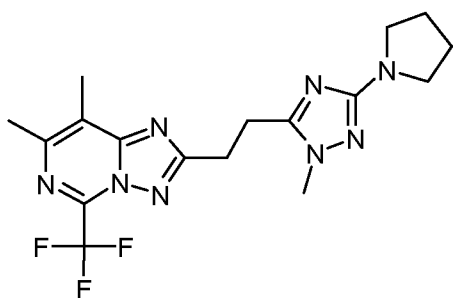
-127-



Was prepared in the same manner as described in Example 87a) using azepane (89.0 mg, 101  $\mu$ l, 898  $\mu$ mol, Eq: 2.00) instead of pyrrolidin-2-one affording 2-[(E)-2-(5,8-dimethyl-1,2,4-triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-1,2,4-triazol-3-yl-azepane (10.8mg, 6.83%) as a yellow waxy solid. MS:  $m/z$  = 353.5 (M+H<sup>+</sup>)

### Example 103

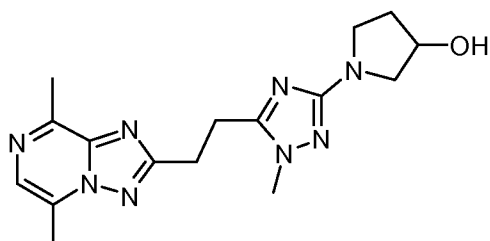
7,8-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-5-(trifluoromethyl)-[1,2,4]triazolo[1,5-c]pyrimidine



10 The product (12 mg) was obtained as a white powder in analogy to Example 75 from 4-chloro-5,6-dimethyl-2-trifluoromethyl-1,3-pyrimidine. MS:  $m/z$  = 395.6 (M+H<sup>+</sup>)

### Example 104

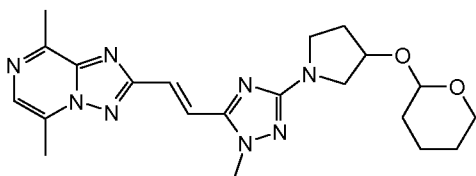
1-{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-3-ol



15

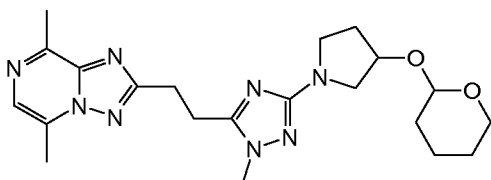
a) 5,8-Dimethyl-2-((E)-2-{2-methyl-5-[3-(tetrahydro-pyran-2-yloxy)-pyrrolidin-1-yl]-2H-[1,2,4]triazol-3-yl}-vinyl)-[1,2,4]triazolo[1,5-a]pyrazine





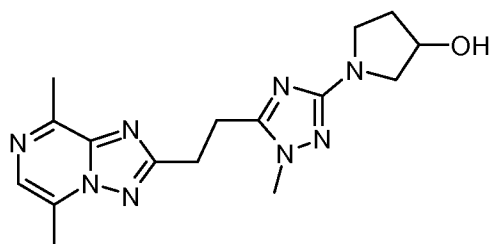
Was prepared in the same manner as described in Example 87a) using 3-(tetrahydro-2H-pyran-2-yloxy)pyrrolidine (154 mg, 898  $\mu\text{mol}$ , Eq: 2) instead of pyrrolidin-2-one affording 5,8-dimethyl-2-((E)-2-{2-methyl-5-[3-(tetrahydro-pyran-2-yloxy)-pyrrolidin-1-yl]-2H-[1,2,4]triazol-3-yl}-vinyl)-[1,2,4]triazolo[1,5-a]pyrazine (37 mg, 19.4%) as a yellow oil. MS:  $m/z=425.6$  (M+H<sup>+</sup>)

b) 5,8-Dimethyl-2-(2-{2-methyl-5-[3-(tetrahydro-pyran-2-yloxy)-pyrrolidin-1-yl]-2H-[1,2,4]triazol-3-yl}-ethyl)-[1,2,4]triazolo[1,5-a]pyrazine



10 Was prepared in the same manner as described in Example 87 b) using (E)-5,8-dimethyl-2-(2-(1-methyl-3-(3-(tetrahydro-2H-pyran-2-yloxy)pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyrazine (37 mg, 87.2  $\mu\text{mol}$ , Eq: 1.00) affording 5,8-dimethyl-2-(2-{2-methyl-5-[3-(tetrahydro-pyran-2-yloxy)-pyrrolidin-1-yl]-2H-[1,2,4]triazol-3-yl}-ethyl)-[1,2,4]triazolo[1,5-a]pyrazine (30mg, 80.7%) as a light yellow viscous oil. MS:  $m/z=427.6$   
15 (M+H<sup>+</sup>)

c) 1-{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-3-ol

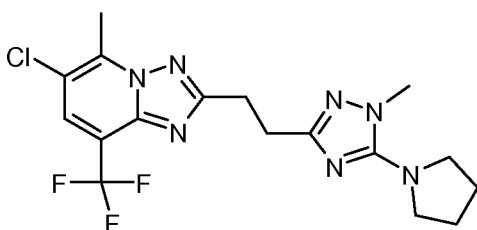


To a solution of 5,8-dimethyl-2-(2-(1-methyl-3-(3-(tetrahydro-2H-pyran-2-yloxy)pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyrazine (30 mg, 70.3  $\mu\text{mol}$ , Eq: 1.00) in methanol (3 ml) was added p-toluenesulfonic acid monohydrate (669  $\mu\text{g}$ , 3.52  $\mu\text{mol}$ , Eq: 0.05), the resulting mixture was stirred for 2 hours at 25 °C under nitrogen atmosphere --> nearly no reaction, another portion of p-toluenesulfonic acid monohydrate (13.4 mg, 70.3

μmol, Eq: 1.00) was added, stirring at 25 °C was continued overnight. The solvent was evaporated. The residue was diluted with ethyl acetate and washed with sat. sodium hydrogen carbonate. The organic layer was separated, dried over magnesium sulfate, filtrated and evaporated. Purification by HPLC separation afforded 1- $\{5-[2-(5,8\text{-dimethyl-[1,2,4]triazolo[1,5-}a\text{]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}\}$ -pyrrolidin-3-ol (2.05 mg, 8.51%) as a light yellow viscous oil. MS:  $m/z = 323.5$  (M+H<sup>+</sup>)

### Example 105

6-Chloro-5-methyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-8-trifluoromethyl-[1,2,4]triazolo[1,5-*a*]pyridine

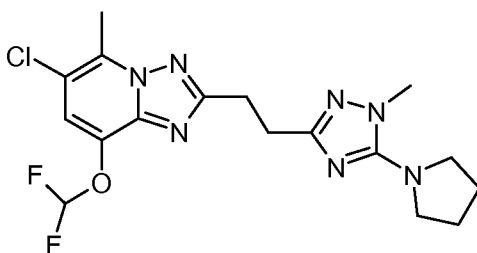


10

The product (5 mg) was obtained as a white solid in analogy to Example 69 using 1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole-3-carbaldehyde as starting material. MS:  $m/z = 414.3$  (M+H<sup>+</sup>)

### Example 106

15 6-Chloro-8-difluoromethoxy-5-methyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-*a*]pyridine

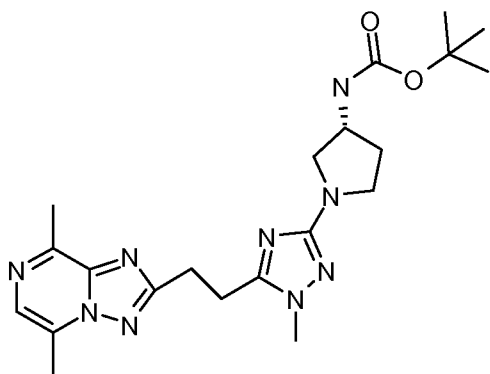


20

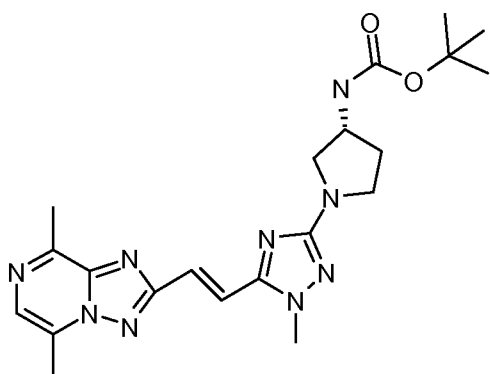
The product (20 mg) was obtained as a light yellow solid in analogy to Example 95 using 1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole-3-carbaldehyde as starting material. MS:  $m/z = 412.3$  (M+H<sup>+</sup>)

### Example 107

((R)-1- $\{5-[2-(5,8\text{-Dimethyl-[1,2,4]triazolo[1,5-}a\text{]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}\}$ -pyrrolidin-3-yl)-carbamic acid tert-butyl ester

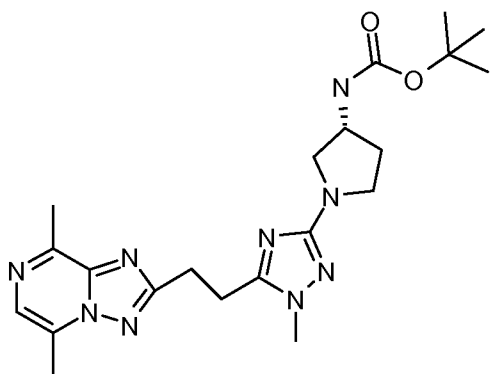


a) ((R)-1-{5-[(E)-2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester



5 Was prepared in the same manner as described in Example 87a) using (R)-tert-butyl pyrrolidin-3-ylcarbamate (125 mg, 673  $\mu\text{mol}$ , Eq: 1.50) instead of pyrrolidin-2-one affording ((R)-1-{5-[(E)-2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester (43.7 mg, 20.6%) as a yellow solid. MS:  $m/z = 440.6$  ( $M+H^+$ )

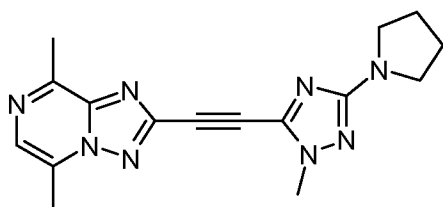
10 b) ((R)-1-{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester



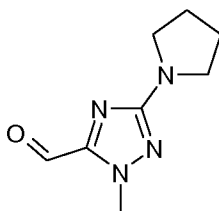
Was prepared in the same manner as described in Example 87 b) using (R,E)-tert-butyl 1-(5-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)vinyl)-1-methyl-1H-1,2,4-triazol-3-yl)pyrrolidin-3-ylcarbamate (38.68 mg, 88.0  $\mu\text{mol}$ , Eq: 1.00) affording ((R)-1-{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester (31 mg, 79.8%) as an orange solid. MS:  $m/z= 442.5$  (M+H+)

### Example 108

5,8-Dimethyl-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-[1,2,4]triazolo[1,5-a]pyrazine

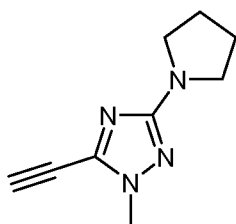


10 a) 2-Methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde



Was prepared in the same manner as described in Example 49 a)-d) using pyrrolidine instead of piperidine, affording 2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde (599 mg, 50.9%) as a yellow solid. MS:  $m/z= 181.4$  (M+H+), MP: 64.7  $^{\circ}\text{C}$

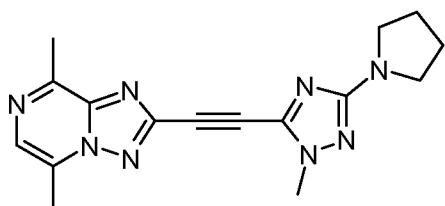
15 b) 5-Ethynyl-1-methyl-3-pyrrolidin-1-yl-1H-[1,2,4]triazole



To a stirred mixture of 1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole-5-carbaldehyde (1.57 g, 8.71 mmol, Eq: 1.00) and potassium carbonate (2.41 g, 17.4 mmol, Eq: 2) at 25  $^{\circ}\text{C}$  in methanol (60 ml) under an argon atmosphere was added dropwise a solution of dimethyl 1-diazo-2-oxopropylphosphonate (2.01 g, 1.57 ml, 10.5 mmol, Eq: 1.2) in methanol (12 ml). The mixture was stirred at 25  $^{\circ}\text{C}$  for 3h. The crude material was applied on silica gel and purified by

flash chromatography over a 50 g silica gel column using dichloromethane / methanol 0-10 % as eluent affording 5-ethynyl-1-methyl-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (785 mg, 51.1%) as an orange solid. MS:  $m/z = 149.2$  (M+H<sup>+</sup>)

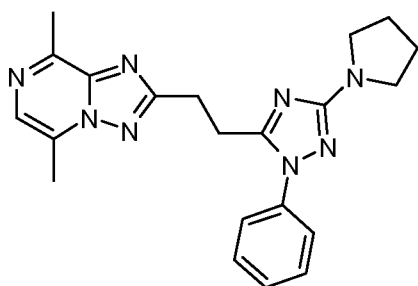
- c) 5,8-Dimethyl-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-  
5 [1,2,4]triazolo[1,5-a]pyrazine



- Was prepared in the same manner as described in Example 75e) using 5-ethynyl-1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazole (62.1 mg, 352  $\mu\text{mol}$ , Eq: 1.00) instead of 1-ethyl-3-ethynyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazole affording 5,8-dimethyl-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-[1,2,4]triazolo[1,5-a]pyrazine (33mg, 29.1%) as a light brown solid. MS:  $m/z = 323.5$  (M+H<sup>+</sup>)

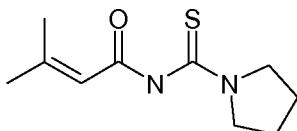
### Example 109

- 5,8-Dimethyl-2-[2-(2-phenyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-  
15 [1,2,4]triazolo[1,5-a]pyrazine



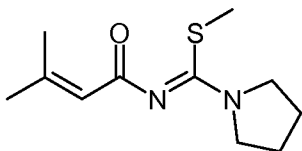
15

- a) 3-Methyl-but-2-enoic acid (pyrrolidine-1-carbothioyl)-amide



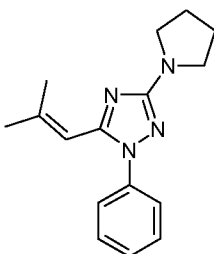
- Was prepared in the same manner as described in Example 49 a) using pyrrolidine instead of piperidine affording 3-methyl-but-2-enoic acid (pyrrolidine-1-carbothioyl)-amide  
20 (11.55g, 110%) as a yellow oil. MS:  $m/z = 213.1$  (M+H<sup>+</sup>)

## b) 3-Methyl-but-2-enoic acid 1-methylsulfanyl-1-pyrrolidin-1-yl-meth-(Z)-ylideneamide



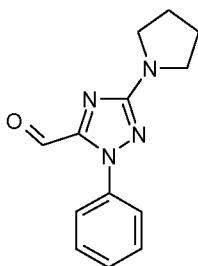
Was prepared in the same manner as described in Example 49 b) using 3-methyl-N-(pyrrolidine-1-carbonothioyl)but-2-enamide (10.5 g, 49.5 mmol, Eq: 1.00) affording 3-methyl-but-2-enoic acid 1-methylsulfanyl-1-pyrrolidin-1-yl-meth-(Z)-ylideneamide (10.94g, 97.8%) as a yellow oil. MS:  $m/z = 227.4$  (M+H<sup>+</sup>)

## c) 5-(2-Methyl-propenyl)-1-phenyl-3-pyrrolidin-1-yl-1H-[1,2,4]triazole



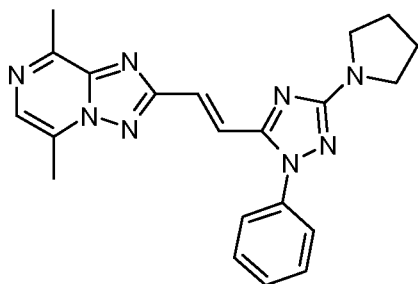
A mixture of 3-methyl-but-2-enoic acid 1-methylsulfanyl-1-pyrrolidin-1-yl-meth-(Z)-ylideneamide (130 mg, 0.575 mmol) and phenyl hydrazine (0.6 ml, 5.75 mmol) was stirred for 3 hours at 100 °C. The mixture was cooled, diluted with ethyl acetate and washed twice with water. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude material was purified by silica gel column chromatography using 50% ethyl acetate in hexane affording 5-(2-methyl-propenyl)-1-phenyl-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (60 mg, 38.87%) as colorless liquid. MS:  $m/z = 268.8$  (M+H<sup>+</sup>)

## d) 2-Phenyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde



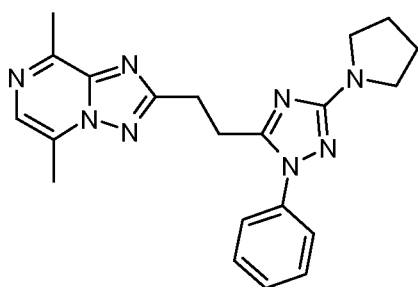
Was prepared in the same manner as described in Example 49 d) using 5-(2-methyl-propenyl)-1-phenyl-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (200 mg, 0.746 mmol) affording 2-phenyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde (220 mg, crude) as yellow liquid which was used without further purification.

e) 5,8-Dimethyl-2-[(E)-2-(2-phenyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-a]pyrazine



Was prepared in the same manner as described in Example 49 e) using 2-phenyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde (220 mg, 0.909 mmol) as aldehyde, affording 5,8-dimethyl-2-[(E)-2-(2-phenyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-a]pyrazine (150 mg, 42% with TPPO) as a white solid. MS:  $m/z = 387$  (M+H<sup>+</sup>)

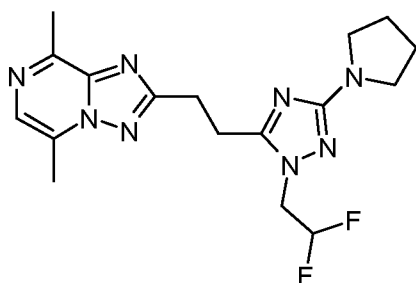
f) 5,8-Dimethyl-2-[2-(2-phenyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine



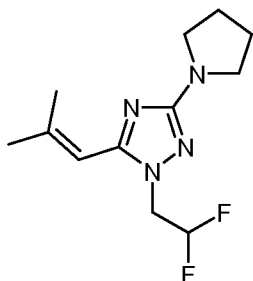
Was prepared in the same manner as described in Example 87 b) using (5,8-dimethyl-2-[(E)-2-(2-phenyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-a]pyrazine (150 mg, 0.389 mmol) affording 5,8-dimethyl-2-[2-(2-phenyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine (85 mg, 56.31% ) as a white solid. MS:  $m/z = 388.8$  (M+H<sup>+</sup>)

### Example 110

2-{2-[2-(2,2-Difluoro-ethyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

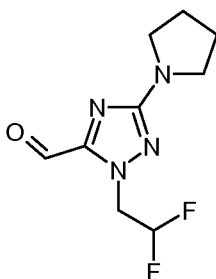


a) 1-(2, 2-Difluoro-ethyl)-5-(2-methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole



Was prepared in the same manner as described in Example 109c) using (2,2-difluoroethyl) hydrazine, hydrochloride (673 mg, 3.98 mmol) and diisopropylethylamine (1.84 ml, 10.619 mmol) as base affording 1-(2, 2-difluoro-ethyl)-5-(2-methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (150 mg, 44%) as a colorless liquid. MS:  $m/z = 256.8$  (M+H<sup>+</sup>)

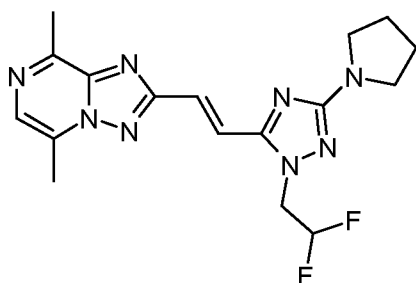
b) 2-(2, 2-Difluoro-ethyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde



Was prepared in the same manner as described in Example 49 d) using 1-(2, 2-difluoroethyl)-5-(2-methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (300 mg, 1.17 mmol) affording 2-(2, 2-difluoro-ethyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde (350 mg, crude) as a yellow solid which was used without further purification.

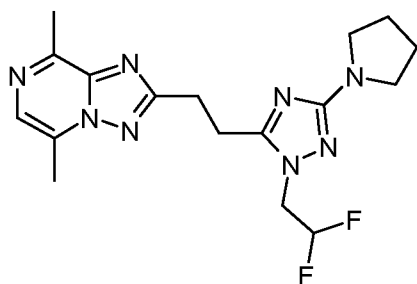
c) 2-((E)-2-[2-(2,2-Difluoro-ethyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl]-vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine





Was prepared in the same manner as described in Example 49 e) using 2-(2, 2-difluoro-ethyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde (350 mg, 1.52 mmol) as aldehyde affording 2-((E)-2-((2,2-difluoro-ethyl)-5-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl)-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (130 mg, 23%) as a yellow solid. MS:  $m/z = 375$  (M+H<sup>+</sup>)

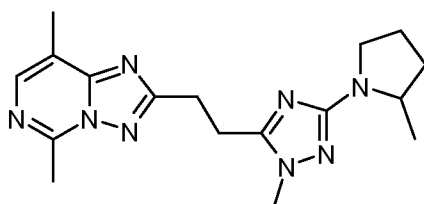
d) 2-((2-((2,2-Difluoro-ethyl)-5-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl)-ethyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



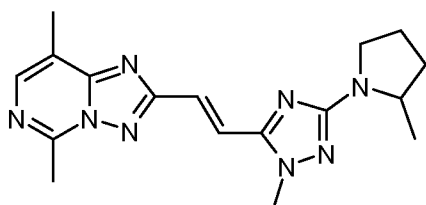
Was prepared in the same manner as described in Example 87 b) using 2-((E)-2-((2,2-difluoro-ethyl)-5-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl)-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (130 mg, 0.348 mmol) affording 2-((2-((2,2-difluoro-ethyl)-5-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl)-ethyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (35 mg, 27%) as a white solid. MS:  $m/z = 349$  (M+H<sup>+</sup>)

### Example 111

15 5,8-Dimethyl-2-((E)-2-((2-methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl)-ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine

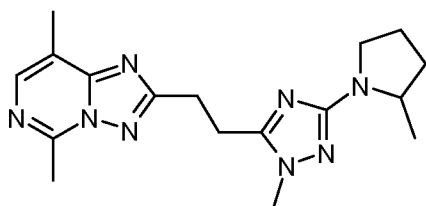


a) 5,8-Dimethyl-2-((E)-2-((2-methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl)-vinyl)-[1,2,4]triazolo[1,5-c]pyrimidine



Was prepared in the same manner as described in Example 49e) using ((5,8-dimethyl-[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)methyl)triphenylphosphonium chloride (350 mg, 763  $\mu\text{mol}$ , Eq: 1.00) and 1-methyl-3-(2-methylpyrrolidin-1-yl)-1H-1,2,4-triazole-5-carbaldehyde (148 mg, 763  $\mu\text{mol}$ , Eq: 1.00) affording 5,8-dimethyl-2-((E)-2-[2-methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-vinyl)-[1,2,4]triazolo[1,5-c]pyrimidine (190 mg, 73.6%) as a bright yellow solid. MS:  $m/z = 339.5$  ( $M+H^+$ )

b) 5,8-Dimethyl-2-{2-[2-methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-c]pyrimidine



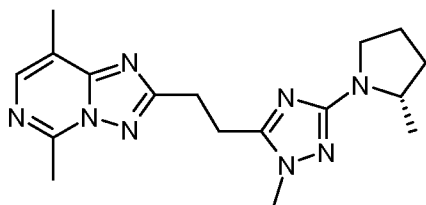
10

Was prepared in the same manner as described in Example 87 b) using (E)-5,8-dimethyl-2-(2-(1-methyl-3-(2-methylpyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-c]pyrimidine (190 mg, 561  $\mu\text{mol}$ , Eq: 1.00) affording 5,8-dimethyl-2-{2-[2-methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-c]pyrimidine (197 mg, 103%) as a light yellow oil. MS:  $m/z = 341.5$  ( $M+H^+$ )

15

### Example 112

5,8-Dimethyl-2-{2-[2-methyl-5-((S)-2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-c]pyrimidine



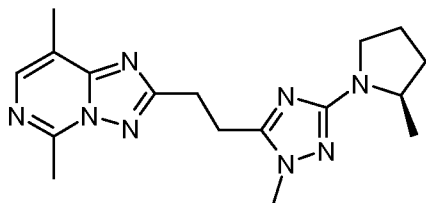
20

Chiral HPLC-separation of racemic 5,8-dimethyl-2-(2-(1-methyl-3-(2-methylpyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine (190 mg, 558  $\mu\text{mol}$ , Eq: 1.00) (Example 181b): First peak A+, afforded 5,8-dimethyl-2-{2-[2-methyl-5-((S)-2-methyl-

pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-c]pyrimidine (76.8 mg, 40.4%) as a colorless viscous oil. MS:  $m/z = 341.5$  (M+H<sup>+</sup>)

### Example 113

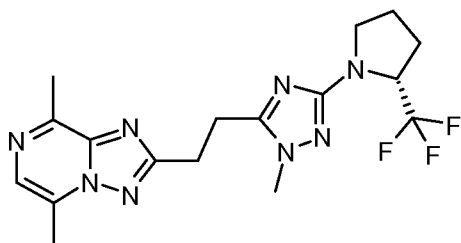
5,8-Dimethyl-2-{2-[2-methyl-5-((R)-2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-c]pyrimidine



Chiral HPLC-separation of racemic 5,8-dimethyl-2-(2-(1-methyl-3-(2-methylpyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine (190 mg, 558  $\mu$ mol, Eq: 1.00) (Example 181b): Second peak B-, afforded 5,8-dimethyl-2-{2-[2-methyl-5-((R)-2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-c]pyrimidine (32.9 mg, 38.4%) as a colorless viscous oil. MS:  $m/z = 341.5$  (M+H<sup>+</sup>)

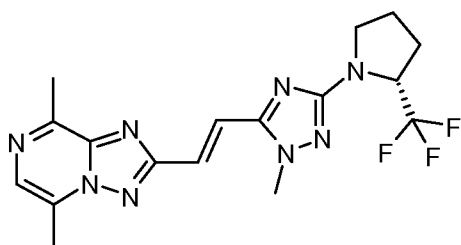
### Example 114

5,8-Dimethyl-2-{2-[2-methyl-5-((R)-2-trifluoromethyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine



15

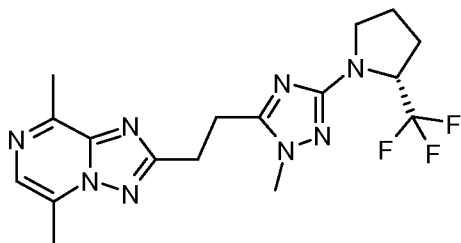
a) {5-[(E)-2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-carbamic acid tert-butyl ester



-139-

Was prepared in the same manner as described in Example 87a) using (R)-2-(trifluoromethyl)-pyrrolidine (83.3 mg, 598  $\mu\text{mol}$ , Eq: 2) instead of pyrrolidin-2-one affording {5-[(E)-2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-carbamic acid tert-butyl ester (20 mg, 17.0%) as an off-white solid. MS:  $m/z=393.5$  ( $M+H^+$ )

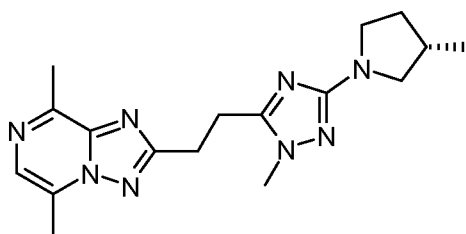
- 5 b) 5,8-Dimethyl-2-{2-[2-methyl-5-((R)-2-trifluoromethyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine



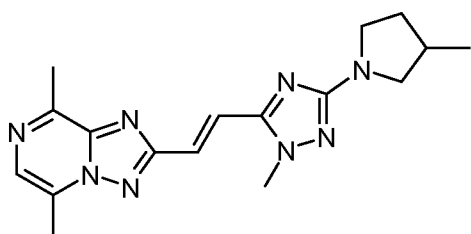
- 10 Was prepared in the same manner as described in Example 87 b) using (R,E)-5,8-dimethyl-2-(2-(1-methyl-3-(2-(trifluoromethyl)pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-a]pyrazine (20 mg, 51.0  $\mu\text{mol}$ , Eq: 1.00) affording 5,8-dimethyl-2-{2-[2-methyl-5-((R)-2-trifluoromethyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine (18 mg, 89.5%) as a light yellow viscous oil. MS:  $m/z=395.5$  ( $M+H^+$ )

### Example 115

- 15 5,8-Dimethyl-2-{2-[2-methyl-5-((S)-3-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

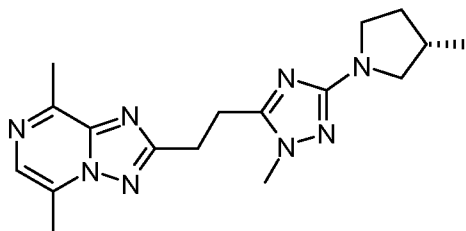


- a) 5,8-Dimethyl-2-{(E)-2-[2-methyl-5-(3-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-vinyl}-[1,2,4]triazolo[1,5-a]pyrazine



Was prepared in the same manner as described in Example 87a) using 3-methylpyrrolidine hydrochloride (83 mg, 683  $\mu\text{mol}$ , Eq: 2.28) instead of pyrrolidin-2-one 5,8-Dimethyl-2- $\{(E)\text{-}2\text{-}[2\text{-methyl-}5\text{-}(3\text{-methyl-pyrrolidin-1-yl})\text{-}2\text{H-}[1,2,4]\text{triazol-3-yl}]\text{-vinyl}\}$ -[1,2,4]triazolo[1,5-a]pyrazine (65 mg, 64.2%) as an orange solid. MS:  $m/z = 339.2$  ( $M+H^+$ )

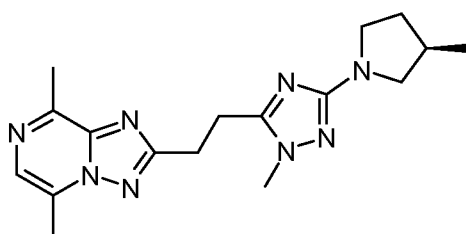
- 5            b) 5,8-Dimethyl-2- $\{2\text{-}[2\text{-methyl-}5\text{-}((S)\text{-}3\text{-methyl-pyrrolidin-1-yl})\text{-}2\text{H-}[1,2,4]\text{triazol-3-yl}]\text{-ethyl}\}$ -[1,2,4]triazolo[1,5-a]pyrazine



- 10            Was prepared in the same manner as described in Example 87 b) from (E)-5,8-dimethyl-2- $\{(2\text{-}(1\text{-methyl-}3\text{-}(3\text{-methylpyrrolidin-1-yl})\text{-}1\text{H-}1,2,4\text{-triazol-5-yl})\text{vinyl})\}$ -[1,2,4]triazolo[1,5-a]pyrazine (60 mg, 177  $\mu\text{mol}$ , Eq: 1.00) after chiral preparative HPLC separation affording 5,8-Dimethyl-2- $\{2\text{-}[2\text{-methyl-}5\text{-}((S)\text{-}3\text{-methyl-pyrrolidin-1-yl})\text{-}2\text{H-}[1,2,4]\text{triazol-3-yl}]\text{-ethyl}\}$ -[1,2,4]triazolo[1,5-a]pyrazine (5mg, 8.28%) as off-white solid. MS:  $m/z = 341.5$  ( $M+H^+$ )

### Example 116

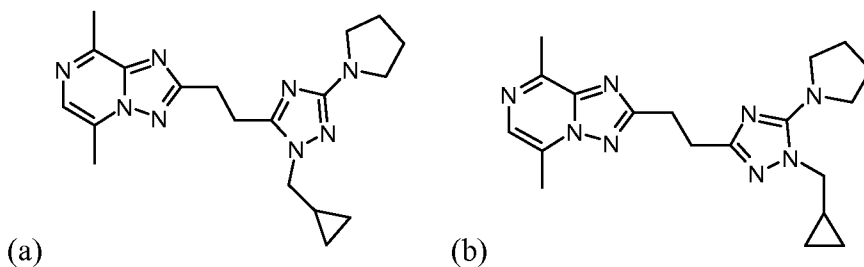
- 15            5,8-Dimethyl-2- $\{2\text{-}[2\text{-methyl-}5\text{-}((R)\text{-}3\text{-methyl-pyrrolidin-1-yl})\text{-}2\text{H-}[1,2,4]\text{triazol-3-yl}]\text{-ethyl}\}$ -[1,2,4]triazolo[1,5-a]pyrazine



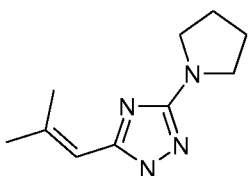
- 20            Was prepared in the same manner as described in Example 115 b) after chiral preparative HPLC separation affording 5,8-Dimethyl-2- $\{2\text{-}[2\text{-methyl-}5\text{-}((R)\text{-}3\text{-methyl-pyrrolidin-1-yl})\text{-}2\text{H-}[1,2,4]\text{triazol-3-yl}]\text{-ethyl}\}$ -[1,2,4]triazolo[1,5-a]pyrazine (7.5 mg, 12.4%) as off-white solid. MS:  $m/z = 341.5$  ( $M+H^+$ )

### Example 117

2-[2-(2-Cyclopropylmethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine and 2-[2-(1-Cyclopropylmethyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (b)

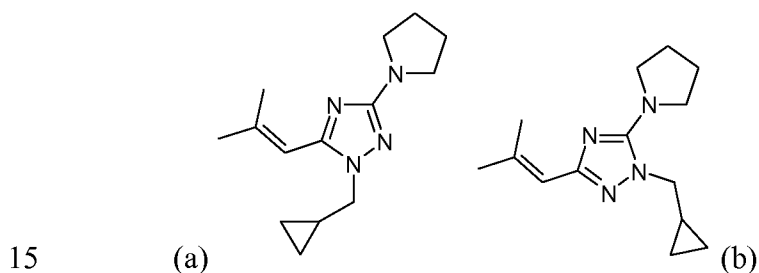


5 a) 5-(2-Methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole



A mixture of 3-methyl-but-2-enoic acid 1-methylsulfonyl-1-pyrrolidin-1-yl-meth-(Z)-ylidene amide (1.2 g, 5.3 mmol) and hydrazine solution was stirred for 2 hours at 100 °C in a sealed tube. The mixture was cooled and concentrated. The crude material was purified by combiflash column chromatography using 50% ethyl acetate in hexane to give 5-(2-methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (300 mg, 29.39%) as a white solid. MS: m/z= 193 (M+H+)

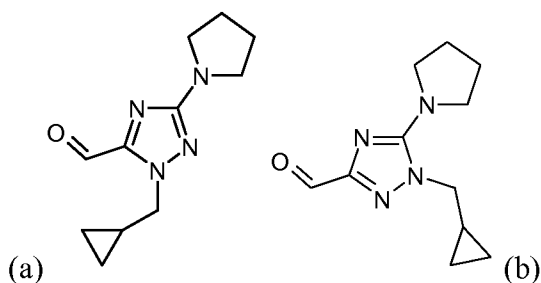
b) 1-Cyclopropylmethyl-5-(2-methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (a) with 1-Cyclopropylmethyl-3-(2-methyl-propenyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazole (b)



A solution of 5-(2-methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (300 mg, 1.56 mmol) in dimethyl formamide (10 ml) was cooled to 0 °C. Sodium hydride (60% in oil, 0.112 g, 4.68 mmol) was added slowly at 0 °C. After that bromomethyl-cyclopropane (0.3 ml, 3.12 mmol) was added drop wise at 0 °C. The mixture was allowed to warm to 25 °C and stirred for 4 hours at 25 °C. The reaction mass was diluted with water (50 ml) and extracted 3 times with ethyl acetate. The organic layer was washed with water 3 times, brine and dried over sodium sul-

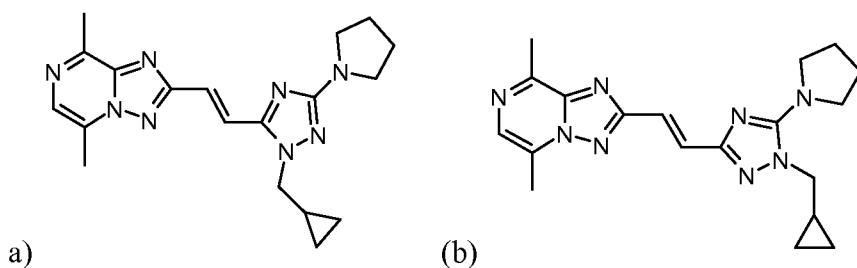
fate, filtered and evaporated. The crude material was purified by silica gel column chromatography using 20% ethyl acetate in hexane to give a mixture of 1-cyclopropylmethyl-5-(2-methylpropenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (a) and 1-cyclopropylmethyl-3-(2-methylpropenyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazole (b) (200 mg, 52%) as a white solid. MS: m/z= 247.6 (M+H<sup>+</sup>)

c) 2-Cyclopropylmethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde (a) with 1-Cyclopropylmethyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole-3-carbaldehyde (b)



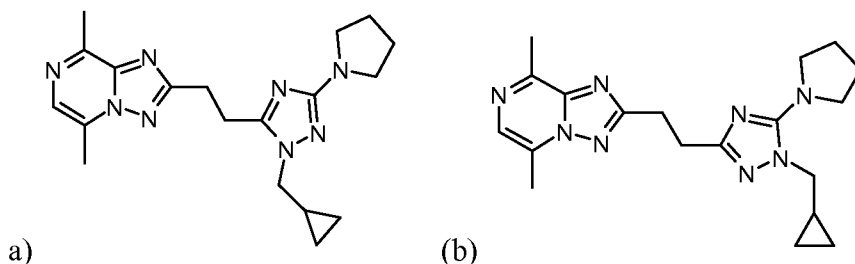
Was prepared in the same manner as described in Example 49 d) using a mixture of 1-cyclopropylmethyl-5-(2-methylpropenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole and 1-cyclopropylmethyl-3-(2-methylpropenyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazole (200 mg, 0.813 mmol) affording a mixture of 2-cyclopropylmethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde (a) with 1-cyclopropylmethyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole-3-carbaldehyde (b) (200 mg, crude) which were used without further purification.

d) 2-[(E)-2-(2-Cyclopropylmethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (a) with 2-[(E)-2-(1-Cyclopropylmethyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (b)



Was prepared in the same manner as described in Example 49 e) using a mixture of 2-cyclopropylmethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde with 1-cyclopropylmethyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole-3-carbaldehyde (220mg, 1.0 mmol) as aldehydes affording a mixture of 2-[(E)-2-(2-cyclopropylmethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (a) with 2-[(E)-2-(1-cyclopropylmethyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (b) (110 mg, 30%) as a yellow solid. MS: m/z= 365 (M+H<sup>+</sup>)

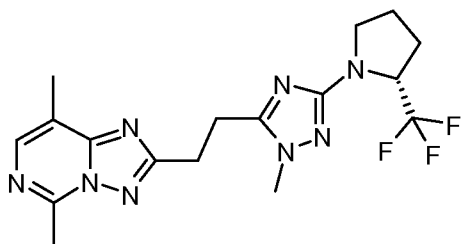
e) 2-[2-(2-Cyclopropylmethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (a) with 2-[2-(1-Cyclopropylmethyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (b)



5 Was prepared in the same manner as described in Example 87 b) using a mixture of 2-[(E)-2-(2-cyclopropylmethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine and 2-[(E)-2-(1-cyclopropylmethyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (110 mg, 0.302 mmol) affording a mixture of 2-[2-(2-cyclopropylmethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (a) and 2-[2-(1-Cyclopropylmethyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (b). Separation of the two isomers via preparative HPLC afforded 2-[2-(2-cyclopropylmethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (a) (20 mg, 18%) as a white solid. MS:  $m/z = 367$  (M+H<sup>+</sup>) and 2-[2-(1-cyclopropylmethyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (b) (18 mg, 16%) as a white solid. MS:  $m/z = 367$  (M+H<sup>+</sup>)

### Example 118

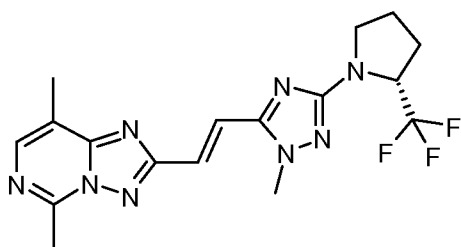
5,8-Dimethyl-2-{2-[2-methyl-5-((R)-2-trifluoromethyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-c]pyrimidine



20

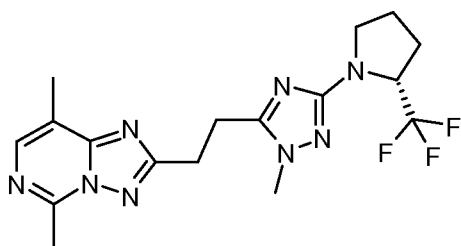
a) 5,8-Dimethyl-2-{(E)-2-[2-methyl-5-((R)-2-trifluoromethyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-vinyl}-[1,2,4]triazolo[1,5-c]pyrimidine





Was prepared in the same manner as described in Example 87a) using (E)-2-(2-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-c]pyrimidine (100 mg, 299  $\mu\text{mol}$ , Eq: 1.00) instead of 2-[(E)-2-(5-Bromo-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine and (R)-2-(trifluoromethyl)-pyrrolidine (83.3 mg, 598  $\mu\text{mol}$ , Eq: 2) instead of pyrrolidin-2-one affording 5,8-dimethyl-2-((E)-2-[2-methyl-5-((R)-2-trifluoromethyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-vinyl)-[1,2,4]triazolo[1,5-c]pyrimidine (17 mg, 14.5%) as a light yellow solid. MS:  $m/z = 393.4$  ( $M+H^+$ )

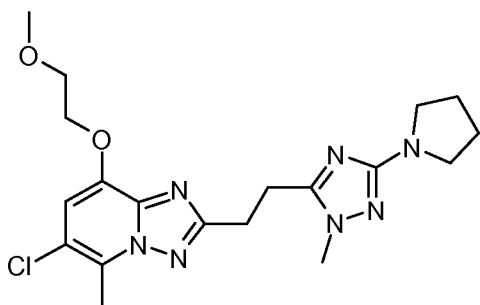
b) 5,8-Dimethyl-2-((E)-2-[2-methyl-5-((R)-2-trifluoromethyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine



Was prepared in the same manner as described in Example 87 b) using (R,E)-5,8-dimethyl-2-(2-(1-methyl-3-(2-(trifluoromethyl)pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)vinyl)-[1,2,4]triazolo[1,5-c]pyrimidine (14 mg, 35.7  $\mu\text{mol}$ , Eq: 1.00) affording 5,8-dimethyl-2-((E)-2-[2-methyl-5-((R)-2-trifluoromethyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine (14 mg, 98.6%) as a colorless viscous oil. MS:  $m/z = 395.5$  ( $M+H^+$ )

### Example 119

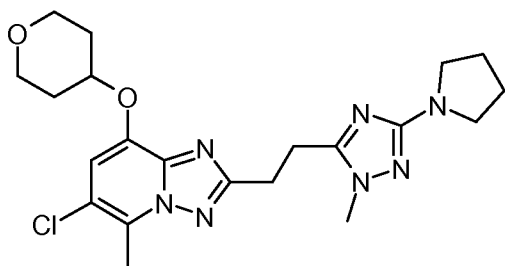
6-Chloro-8-(2-methoxyethoxy)-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl)-1,2,4-triazol-3-yl]ethyl-[1,2,4]triazolo[1,5-a]pyridine



1-Bromo-2-methoxyethane (10.7 mg, 7.26  $\mu$ l, 77.3  $\mu$ mol, Eq: 1.2) was added to 6-chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridin-8-ol (23.3 mg, 64.4  $\mu$ mol, Eq: 1.00) and  $K_2CO_3$  (26.7 mg, 193  $\mu$ mol, Eq: 3) in dimethylformamide (1 ml). The mixture was stirred at 50  $^{\circ}C$  for 2 h. The crude material was purified by preparative HPLC to give the desired product (7 mg, 25%) as a white powder. MS:  $m/z$  = 420.6 (M+H<sup>+</sup>)

### Example 120

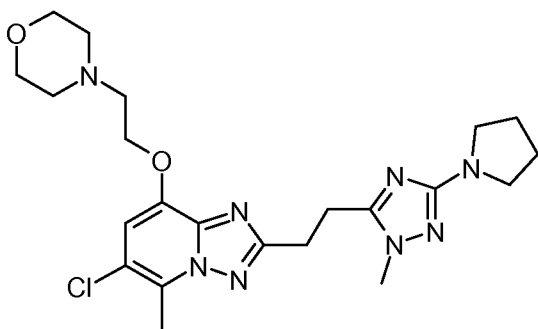
6-Chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(tetrahydro-2H-pyran-4-yloxy)-[1,2,4]triazolo[1,5-a]pyridine



The product (3 mg, 10%) was obtained as a white powder in analogy to Example 119 from 4-bromotetrahydro-2H-pyran. MS:  $m/z$  = 446.6 (M+H<sup>+</sup>)

### Example 121

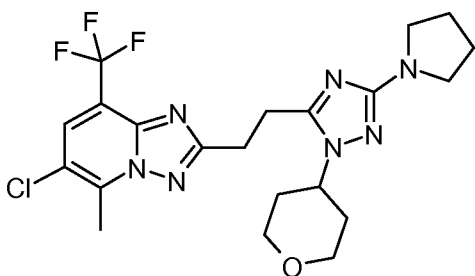
4-[2-[[6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl)-1,2,4-triazol-3-yl)ethyl]-[1,2,4]triazolo[1,5-a]pyridin-8-yl]oxy]ethyl]morpholine



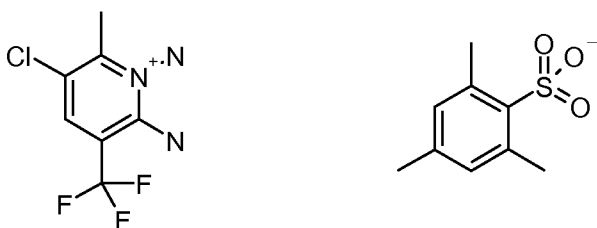
The product (5 mg, 16%) was obtained as a white powder in analogy to Example 119 from 4-(2-bromoethyl)morpholine hydrobromide. MS:  $m/z = 475.7$  (M+H<sup>+</sup>)

### Example 122

- 5      6-Chloro-5-methyl-2-(2-(3-(pyrrolidin-1-yl)-1-(tetrahydro-2H-pyran-4-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine



- a) 5-Chloro-6-methyl-3-(trifluoromethyl)pyridin-1-ium-1,2-diamine; 2,4,6-trimethylbenzenesulfonate

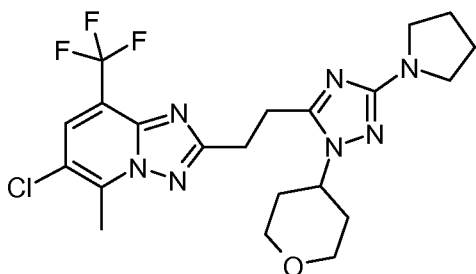


10

The salt (2 g, 68%) was prepared as a white solid in analogy to Example 26b from 6-methyl-3-(trifluoromethyl)pyridin-2-amine. MS:  $m/z = 226.2$  (M<sup>+</sup>) and 199.2 (M<sup>-</sup>)

- b) 6-Chloro-5-methyl-2-(2-(3-(pyrrolidin-1-yl)-1-(tetrahydro-2H-pyran-4-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

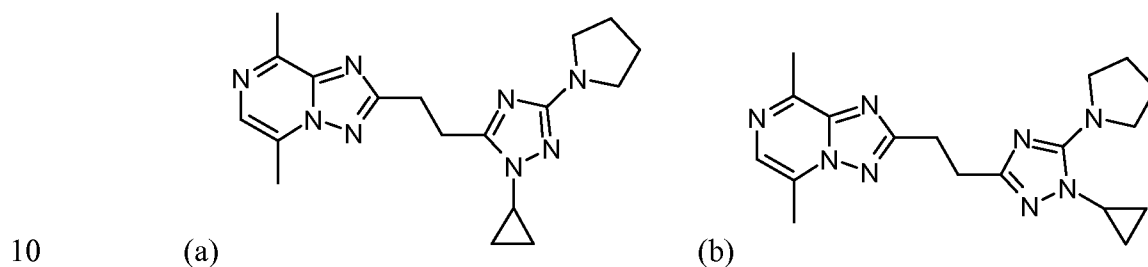
-147-



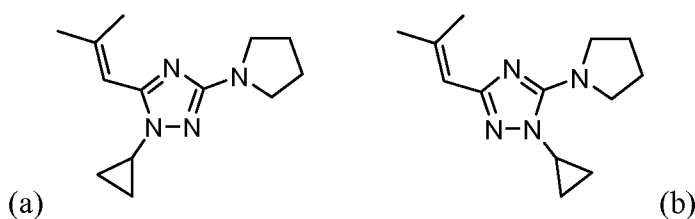
The product (14 mg) was prepared as a white solid in analogy to Example 61 using (tetrahydro-2H-pyran-4-yl)hydrazine hydrochloride and 5-chloro-6-methyl-3-(trifluoromethyl)pyridin-1-ium-1,2-diamine; 2,4,6-trimethylbenzenesulfonate as starting materials. MS:  $m/z = 484.2$  (M+H<sup>+</sup>)

### Example 123

2-[2-(2-Cyclopropyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (a) and 2-[2-(1-Cyclopropyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (b)



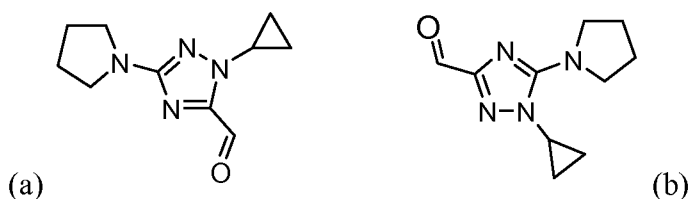
a) 1-Cyclopropyl-5-(2-methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (a) with 1-Cyclopropyl-3-(2-methyl-propenyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazole (b)



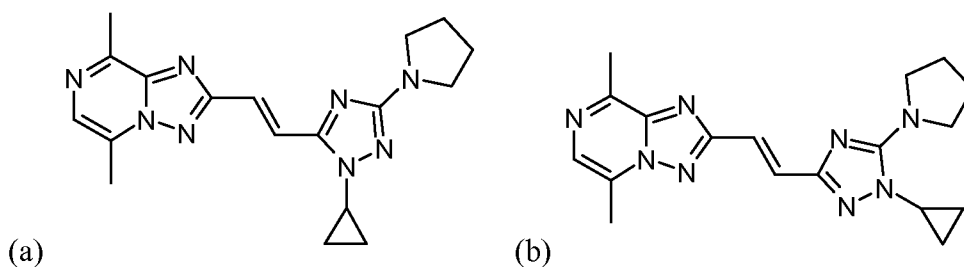
2,2'-Bipyridine (203 mg, 1.30 mmol), copper acetate (236 mg, 1.30 mmol) and sodium carbonate (276 mg, 2.60 mmol) were added to a solution of 5-(2-ethyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (250 mg, 1.30 mmol) and cyclopropyl boronic acid (203 mg, 1.30 mmol) in DCE (10 ml). The reaction mixture was heated at 70° C for 16 hours. After cooling, the mixture was diluted with dichloromethane and washed with a saturated aq. solution of ammonium chloride. The separated organic extracts were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>, filtration and concentration under reduced pressure. The crude material was purified by silica gel column

chromatography using 20% ethyl acetate in hexane affording 1-cyclopropyl-5-(2-methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (a) with 1-cyclopropyl-3-(2-methyl-propenyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazole (b) (200 mg, 66%) as a white solid. MS:  $m/z = 232.8$  (M+H+)

- b) 2-Cyclopropyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde (a) with 1-Cyclopropyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole-3-carbaldehyde (b)



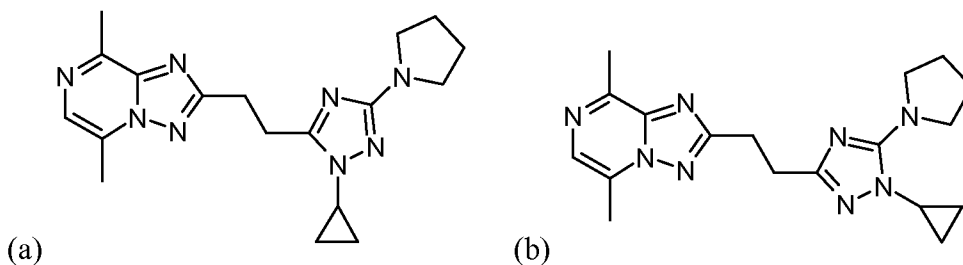
- Was prepared in the same manner as described in Example 49 d) using a mixture of 1-cyclopropyl-5-(2-methyl-propenyl)-3-pyrrolidin-1-yl-1H-[1,2,4]triazole with 1-cyclopropyl-3-(2-methyl-propenyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazole (200 mg, 0.862 mmol) affording a mixture of 2-cyclopropyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde (a) with 1-cyclopropyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole-3-carbaldehyde (b) (220 mg, crude) as a yellow solid which was used without further purification. c) 2-[(E)-2-(2-Cyclopropyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (a) with 2-[(E)-2-(1-Cyclopropyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (b)



- Was prepared in the same manner as described in Example 49 e) using a mixture of 2-cyclopropyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazole-3-carbaldehyde with 1-cyclopropyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazole-3-carbaldehyde (220 mg, 1.068 mmol) as aldehydes affording a mixture of 2-[(E)-2-(2-cyclopropyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (a) with 2-[(E)-2-(1-cyclopropyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (b) (60 mg, 16%) as a yellow solid. MS:  $m/z = 351$  (M+H+)

- d) 2-[2-(2-Cyclopropyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (a) and 2-[2-(1-Cyclopropyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (b)

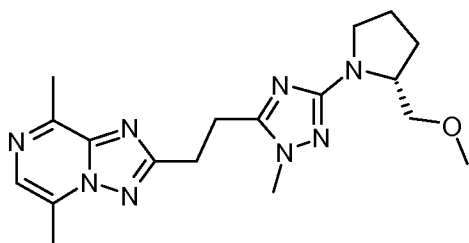
-149-



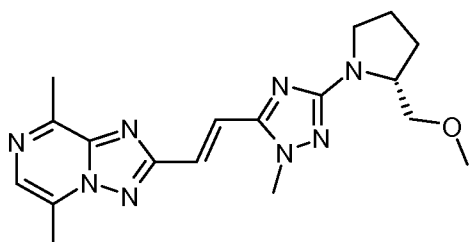
Was prepared in the same manner as described in Example 87 b) using a mixture of 2-  
 [(E)-2-(2-cyclopropyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-  
 [1,2,4]triazolo[1,5-a]pyrazine with 2-[(E)-2-(1-cyclopropyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-  
 3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (110 mg, 0.314 mmol) affording a mix-  
 5 ture of 2-[2-(2-cyclopropyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-  
 [1,2,4]triazolo[1,5-a]pyrazine (a) and 2-[2-(1-cyclopropyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-  
 yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (b). Separation of the two isomers via pre-  
 parative HPLC afforded 2-[2-(2-cyclopropyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-  
 10 dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (a) (15 mg, 13.5%) as a white solid. MS:  $m/z = 353$   
 (M+H<sup>+</sup>) and 2-[2-(1-cyclopropyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-  
 [1,2,4]triazolo[1,5-a]pyrazine (b) (18 mg, 16.2%) as a white solid. MS:  $m/z = 353$  (M+H<sup>+</sup>)

### Example 124

2-{2-[5-((R)-2-Methoxymethyl-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-  
 15 5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



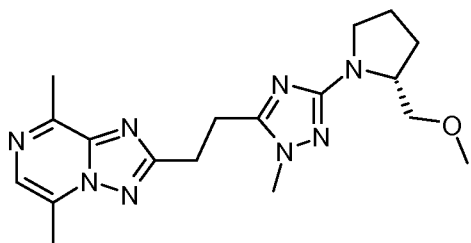
a) 2-{(E)-2-[5-((R)-2-Methoxymethyl-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-  
 vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



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Was prepared in the same manner as described in Example 87a) using (R)-2-(methoxymethyl)-pyrrolidine (68.9 mg, 598  $\mu\text{mol}$ , Eq: 2) instead of pyrrolidin-2-one affording 2-{(E)-2-[5-((R)-2-methoxy-methyl-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (21 mg, 19 %) as a yellow solid. MS:  $m/z = 369.5$  (M+H+)

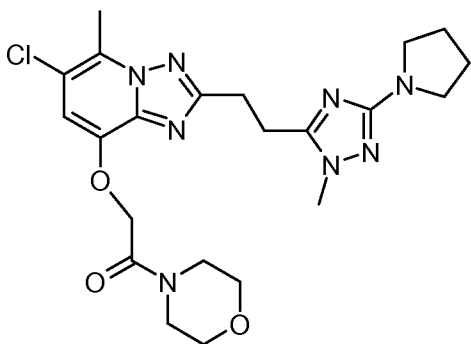
b) 2-{2-[5-((R)-2-Methoxymethyl-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



Was prepared in the same manner as described in Example 87 b) using (R,E)-2-(2-(3-(2-(methoxymethyl)pyrrolidin-1-yl)-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (20 mg, 54.3  $\mu\text{mol}$ , Eq: 1.00) affording 2-{2-[5-((R)-2-methoxymethyl-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (15.9 mg, 79%) as a colorless oil. MS:  $m/z = 371.5$  (M+H+)

### Example 125

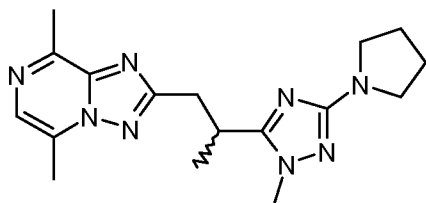
2-(6-Chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridin-8-yloxy)-1-morpholinoethanone



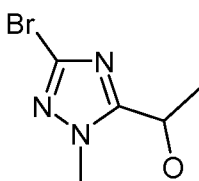
The product (12.6 mg, 51.8%) was obtained as an off white solid in analogy to Example 119 from 2-chloro-1-morpholinoethanone. MS:  $m/z = 489.6$  (M+H+)

20 **Example 126**

(-)-5,8-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)propyl)-[1,2,4]triazolo[1,5-a]pyrazine



a) 1-(5-Bromo-2-methyl-2H-[1,2,4]triazol-3-yl)-ethanol

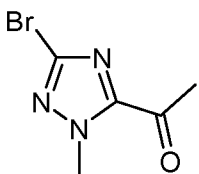


5

To a solution of 3,5-dibromo-1-methyl-1H-1,2,4-triazole (2.634 g, 10.9 mmol, Eq: 1.00) in tetrahydrofuran (184 ml) was added dropwise at -78 °C under argon atmosphere n-butyllithium 1.6 M in hexanes (6.83 ml, 10.9 mmol, Eq: 1.00). The resulting mixture was stirred for 20 minutes at -75 °C then a solution of acetaldehyde (1.2 g, 1.54 ml, 27.3 mmol, Eq: 2.5) in tetrahydrofuran (36.9 ml) was added slowly and stirring at -75 °C was continued for further 1.5 hours. The mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution and was warmed to 25 °C. The mixture was diluted with ethyl acetate and washed 2 times with water. The organic layer was separated, dried over magnesium sulfate, filtrated and evaporated affording 1-(5-bromo-2-methyl-2H-[1,2,4]triazol-3-yl)-ethanol (1.639 g, 72.7%) as a light yellow oil. MS: m/z= 206/209 (M+H<sup>+</sup>)

15

b) 1-(5-Bromo-2-methyl-2H-[1,2,4]triazol-3-yl)-ethanone



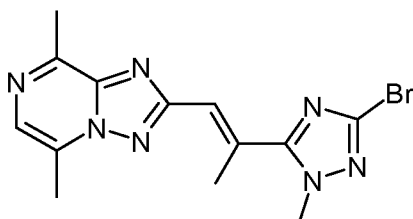
A solution of 1-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)ethanol (1.639 g, 7.95 mmol, Eq: 1.00) and pyridine (944 mg, 965 μl, 11.9 mmol, Eq: 1.5) in dichloromethane (237 ml) was cooled to 0 °C then Dess-Martin periodinane (15% in dichloromethane, 24.7 g, 8.75 mmol, Eq: 1.1) was added. The resulting mixture was stirred for 4 hours at 0 °C under nitrogen atmosphere. The mixture was diluted with dichloromethane and washed with sat. sodium hydrogen carbonate. The organic layer was separated, dried over magnesium sulfate, filtrated and evaporated. The crude material was applied on silica gel and purified by flash chromatography over a 20 g silica

20



gel column using dichloromethane / methanol 0-3 % & 5% NH<sub>3</sub> as eluent affording 1-(5-bromo-2-methyl-2H-[1,2,4]triazol-3-yl)-ethanone (948 mg, 58.4%) as a white solid. MS: m/z= 203 (EI)

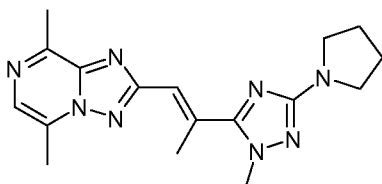
c) 2-[(E)-2-(5-Bromo-2-methyl-2H-[1,2,4]triazol-3-yl)-propenyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



5

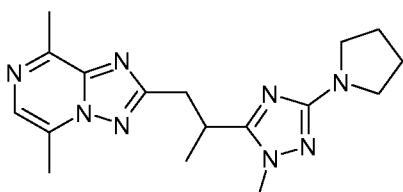
Was prepared in the same manner as described in Example 49 e) using 1-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)ethanone (667 mg, 3.27 mmol, Eq: 1) instead of aldehyde affording 2-[2-(5-bromo-2-methyl-2H-[1,2,4]triazol-3-yl)-propyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (488 mg, 39.4%) as a white solid. MS: m/z= 350.3 (M+H<sup>+</sup>)

10 d) 5,8-Dimethyl-2-[(E)-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-propenyl]-[1,2,4]triazolo[1,5-a]pyrazine



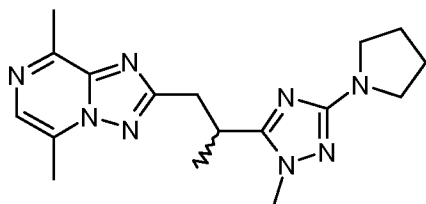
15 Was prepared in the same manner as described in Example 87a) using (E)-2-(2-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)prop-1-enyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (448 mg, 1.29 mmol, Eq: 1.00) instead of 2-[(E)-2-(5-bromo-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine and pyrrolidine (183 mg, 213 μl, 2.57 mmol, Eq: 2) instead of pyrrolidin-2-one affording 5,8-dimethyl-2-[(E)-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-propenyl]-[1,2,4]triazolo[1,5-a]pyrazine (109 mg, 41.1%) as a white solid. MS: m/z= 339.5 (M+H<sup>+</sup>)

20 e) 5,8-Dimethyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-propyl]-[1,2,4]triazolo[1,5-a]pyrazine



Was prepared in the same manner as described in Example 87 b) using (E)-5,8-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)prop-1-enyl)-[1,2,4]triazolo[1,5-a]pyrazine (173 mg, 511  $\mu$ mol, Eq: 1.00) affording 5,8-dimethyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-propyl]-[1,2,4]triazolo[1,5-a]pyrazine (170 mg, 97.7%) as a light brown solid. MS:  $m/z$ = 341.5 (M+H<sup>+</sup>)

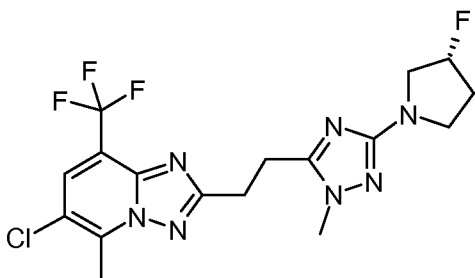
f) (-)-5,8-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)propyl)-[1,2,4]triazolo[1,5-a]pyrazine



Chiral HPLC-separation of racemic 5,8-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)propyl)-[1,2,4]triazolo[1,5-a]pyrazine (170 mg, 499  $\mu$ mol, Eq: 1.00) afforded (-)-5,8-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)propyl)-[1,2,4]triazolo[1,5-a]pyrazine (63 mg, 37.1%), as the second elution enantiomer with negative rotation as a white solid. MS:  $m/z$ = 341.5 (M+H<sup>+</sup>).

### Example 127

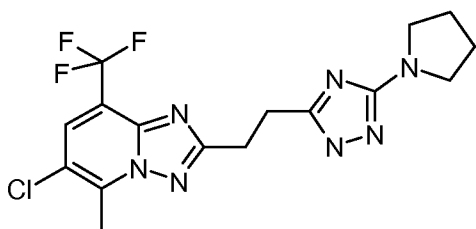
(R)-6-Chloro-2-(2-(3-(3-fluoropyrrolidin-1-yl)-1-methyl-1H-1,2,4-triazol-5-yl)ethyl)-5-methyl-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine



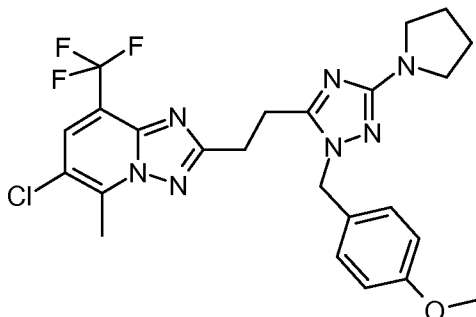
The product (28 mg) was obtained as a white solid in analogy to Example 88 from (R)-3-fluoropyrrolidine hydrochloride. MS:  $m/z$  = 432.2 (M+H<sup>+</sup>).

### Example 128

6-Chloro-5-methyl-2-(2-(3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

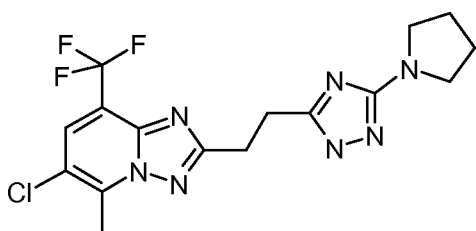


a) 6-Chloro-2-(2-(1-(4-methoxybenzyl)-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-5-methyl-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine



5 The product (450 mg) was obtained as a light brown oil in analogy to Example 61 from 5-chloro-6-methyl-3-(trifluoromethyl)pyridin-1-ium-1,2-diamine; 2,4,6-trimethylbenzenesulfonate. MS:  $m/z = 520.3$  (M+H<sup>+</sup>)

b) 6-Chloro-5-methyl-2-(2-(3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine



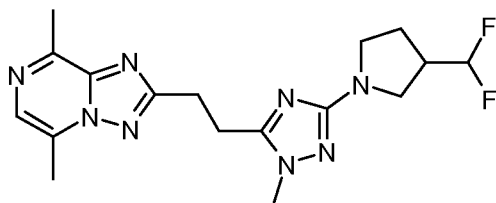
10

Trifluoroacetic acid (9.87 g, 6.67 ml, 86.5 mmol, Eq: 100) was added to 6-chloro-2-(2-(1-(4-methoxybenzyl)-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-5-methyl-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine (450 mg, 865  $\mu$ mol, Eq: 1.00). The mixture was heated under reflux for 4 h and then concentrated to an oil. Water (15 ml) was added and the mixture was alkalinized by addition of sodium bicarbonate. The mixture was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated to an oil. The crude product was purified by chromatography (SiO<sub>2</sub>, methanol / ethyl acetate) to afford the product (140 mg, 40.5%) as an off white solid. MS:  $m/z = 400.2$  (M+H<sup>+</sup>)

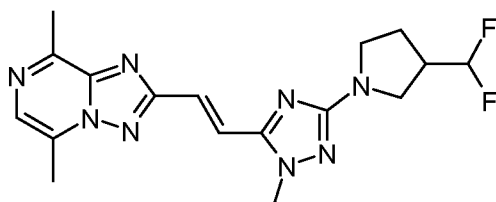
15

### Example 129

2-{2-[5-(3-Difluoromethyl-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

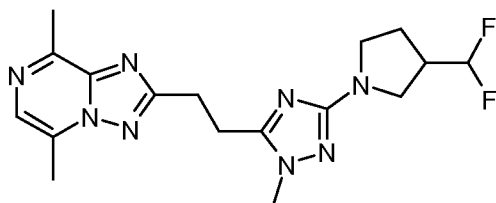


5 a) 2-{(E)-2-[5-(3-Difluoromethyl-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



10 Was prepared in the same manner as described in Example 87a) using 3-(difluoromethyl)-pyrrolidine hydrochloride (94.3 mg, 598  $\mu\text{mol}$ , Eq: 2) instead of pyrrolidin-2-one affording 2-{(E)-2-[5-(3-difluoromethyl-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-vinyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (74 mg, 66.1%) as a light yellow solid. MS:  $m/z = 375.5$  ( $M+H^+$ )

b) 2-{2-[5-(3-Difluoromethyl-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

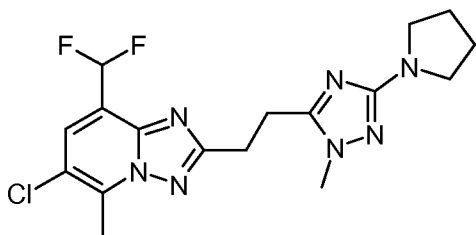


15 Was prepared in the same manner as described in Example 87 b) using (E)-2-(2-(3-(3-(difluoro- methyl)pyrrolidin-1-yl)-1-methyl-1H-1,2,4-triazol-5-yl)vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (74 mg, 198  $\mu\text{mol}$ , Eq: 1.00) affording 2-{2-[5-(3-Difluoromethyl-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (66 mg, 88.7%) as a light yellow solid. MS:  $m/z = 349.5$  ( $M+H^+$ )

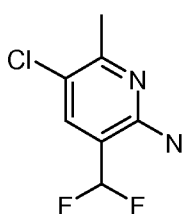
20

**Example 130**

6-Chloro-8-(difluoromethyl)-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine



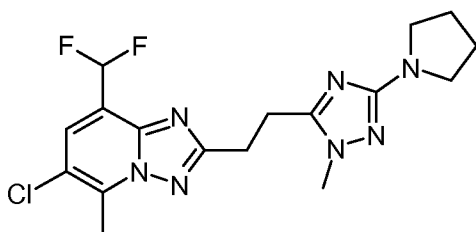
a) 5-Chloro-3-(difluoromethyl)-6-methylpyridin-2-amine



5

Diethylaminosulfur trifluoride (DAST, 355 mg, 291  $\mu$ l, 2.2 mmol, Eq: 3) was added to 2-amino-6-methylnicotinaldehyde (100 mg, 734  $\mu$ mol, Eq: 1.00) in dichloromethane (5 ml) at 0 °C. The mixture was stirred overnight at room temperature. The mixture was washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and then concentrated to an oil. Acetonitrile (5 ml) was added, followed by N-chlorosuccinimide (196 mg, 1.47 mmol, Eq: 2). The mixture was stirred overnight at room temperature and then concentrated to an oil. The mixture was purified by column chromatography (SiO<sub>2</sub>, MeOH/25% NH<sub>4</sub>OH aq / dichloromethane) to give the desired product (30 mg, 21%) as a white solid. MS: m/z = 193.3 (M+H<sup>+</sup>)

15 b) 6-Chloro-8-(difluoromethyl)-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine

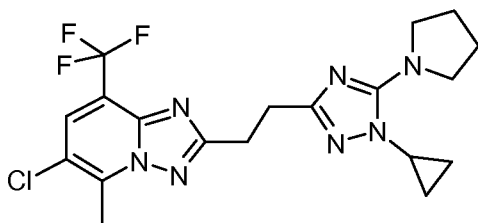


The product (4 mg) was obtained as a light yellow oil in analogy to Example 52 from 5-chloro-3-(difluoromethyl)-6-methylpyridin-2-amine. MS: m/z = 396.6 (M+H<sup>+</sup>)

20

**Example 131**

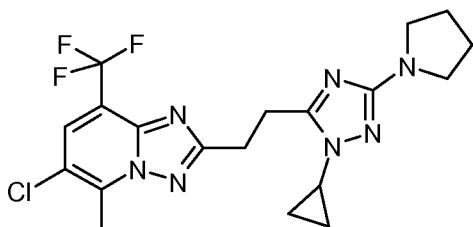
6-Chloro-2-(2-(1-cyclopropyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-5-methyl-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine



A mixture of 6-chloro-5-methyl-2-(2-(3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine (30 mg, 75.0  $\mu\text{mol}$ , Eq: 1.00), cyclopropylboronic acid (19.3 mg, 225  $\mu\text{mol}$ , Eq: 3), copper (II) acetate (27.3 mg, 150  $\mu\text{mol}$ , Eq: 2), molecular sieves, pyridine (47.5 mg, 48.6  $\mu\text{l}$ , 600  $\mu\text{mol}$ , Eq: 8), triethylamine (38.0 mg, 52.3  $\mu\text{l}$ , 375  $\mu\text{mol}$ , Eq: 5) in tetrahydrofuran (4 ml) was heated under air in a sealed tube for 2 h at 100  $^{\circ}\text{C}$ . The mixture was filtered and concentrated to an oil. Water was added and extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and then concentrated. The mixture was separated by preparative HPLC to give the product (4.8 mg, 14.5%) as a colorless oil. MS:  $m/z = 440.2$  (M+H<sup>+</sup>)

### Example 132

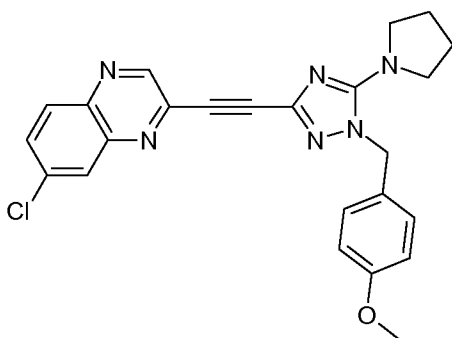
6-Chloro-2-(2-(1-cyclopropyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-5-methyl-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine



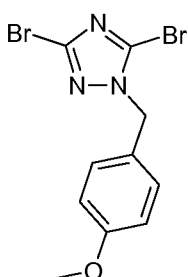
The desired product (5.1 mg, 15.5%) was obtained as a white solid in the chromatographic separation of Example 131. MS:  $m/z = 440.2$  (M+H<sup>+</sup>)

### Example 133

7-chloro-2-((1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethynyl)quinoxaline

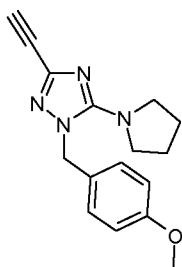


a) 2-((E)-2-[5-(3-Fluoro-azetidino-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-vinyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine



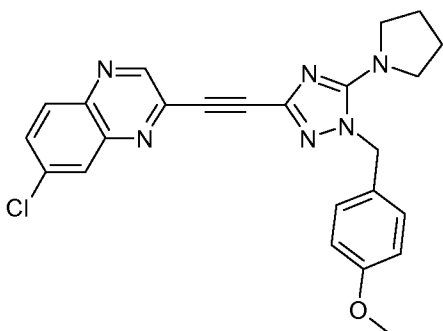
- 5 3,5-dibromo-1H-1,2,4-triazole (1.5 g, 6.61 mmol, Eq: 1.00), potassium iodide (110 mg, 661  $\mu\text{mol}$ , Eq: 0.10), 4-methoxybenzyl chloride (1.14 g, 990  $\mu\text{l}$ , 7.27 mmol, Eq: 1.1) and N,N-diisopropylethylamine (1.71 g, 2.31 ml, 13.2 mmol, Eq: 2.0) was stirred in acetonitrile (23.0 ml) overnight at room temperature. The crude material was applied on silica gel and purified by column to give 3,5-Dibromo-1-(4-methoxy-benzyl)-1H-[1,2,4]triazole (1.79g, 78%) as white solid.
- 10 MS:  $m/z = 348.1$  ( $M+H^+$ )

b) 3-Ethynyl-1-(4-methoxybenzyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazole



- 15 Was prepared in the same manner as described in Example 47 (b-d) from 1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-3-((trimethylsilyl)ethynyl)-1H-1,2,4-triazole (153 mg, 432  $\mu\text{mol}$ , Eq: 1.00) affording 3-Ethynyl-1-(4-methoxy-benzyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazole (118 mg, 96.8%) as light brown solid. MS:  $m/z = 283.4$  ( $M+H^+$ )

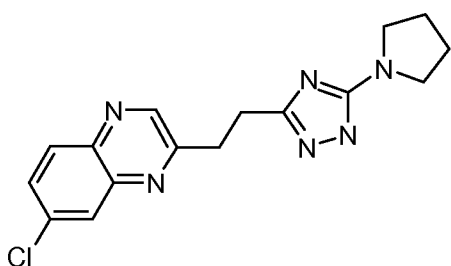
c) 7-chloro-2-((1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethynyl)quinoxaline



A mixture of 3-ethynyl-1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazole (115  
 5 mg, 407  $\mu\text{mol}$ , Eq: 1.00), 2,7-dichloroquinoxaline (89.2 mg, 448  $\mu\text{mol}$ , Eq: 1.1) and triethylamine (61.8 mg, 85.2  $\mu\text{l}$ , 611  $\mu\text{mol}$ , Eq: 1.5) in tetrahydrofuran (3 ml) was purged with argon, then copper (I) iodide (3.1 mg, 16.3  $\mu\text{mol}$ , Eq: 0.04), bis(triphenylphosphine)palladium(II) chloride (11.4 mg, 16.3  $\mu\text{mol}$ , Eq: 0.04) and triphenylphosphine (4.27 mg, 16.3  $\mu\text{mol}$ , Eq: 0.04) were added, the vessel was capped and heated for 18 hours to 75 °C. The crude material was applied  
 10 on silica gel and purified by flash chromatography to give 7-Chloro-2-[1-(4-methoxy-benzyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-ylethynyl]-quinoxaline (89 mg, 49.1%) as yellow solid. MS:  $m/z = 445.4$  ( $M+H^+$ )

### Example 134

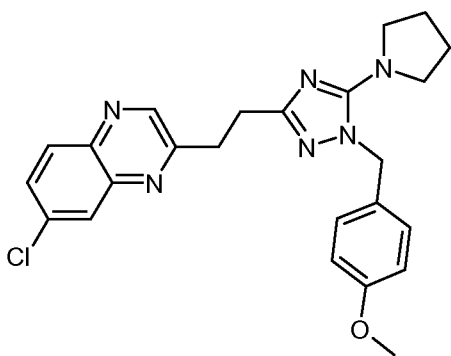
7-chloro-2-(2-(5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)quinoxaline



15

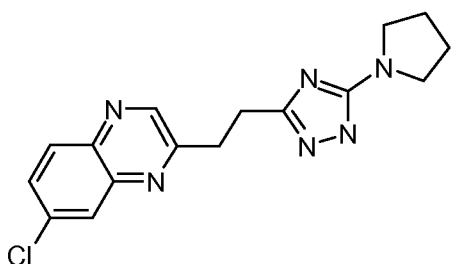
a) 7-Chloro-2-{2-[1-(4-methoxy-benzyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl]-ethyl}-quinoxaline





7-chloro-2-((1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethynyl)quinoxaline (33 mg, 74.2  $\mu\text{mol}$ , Eq: 1.00) was stirred in ethyl acetate (12 ml) with palladium, 5 wt % on barium sulfate, reduced (33.0 mg, 310  $\mu\text{mol}$ , Eq: 4.18) under a hydrogen atmosphere for 2.5 h. Then 3 drops of acetic acid were added and stirring was continued for 1.5 h. The crude material was applied on silica gel and purified by column chromatography to give 7-chloro-2-{2-[1-(4-methoxy-benzyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl]-ethyl}-quinoxaline (17 mg, 51.1%) as light red oil. MS:  $m/z= 449.4 (M+H^+)$

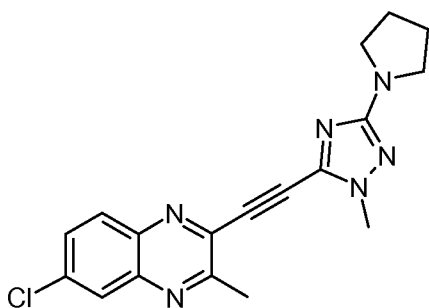
b) 7-Chloro-2-[2-(5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-quinoxaline



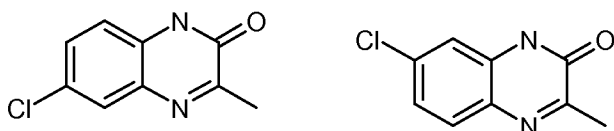
7-chloro-2-(2-(1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)quinoxaline (17 mg, 37.9  $\mu\text{mol}$ , Eq: 1.00) was stirred in trifluoroacetic acid (173 mg, 117  $\mu\text{l}$ , 1.51 mmol, Eq: 40) with anisole (81.9 mg, 82.7  $\mu\text{l}$ , 757  $\mu\text{mol}$ , Eq: 20) at 120°C overnight. The mixture was made basic by addition of sodium hydroxide 2N aq. and extracted three times with 1,2-dichloromethane, dried over magnesium sulfate, filtered and evaporated. The crude material was applied on silica gel and purified by column chromatography to give 7-Chloro-2-[2-(5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-quinoxaline (2.2 mg, 17.7%) as off-white solid. MS:  $m/z= 329.12 (M+H^+)$

### Example 135

6-Chloro-3-methyl-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-quinoxaline

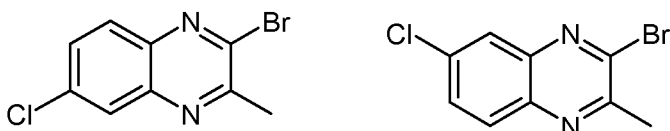


a) 6-Chloro-3-methyl-1H-quinoxalin-2-one with 7-Chloro-3-methyl-1H-quinoxalin-2-one



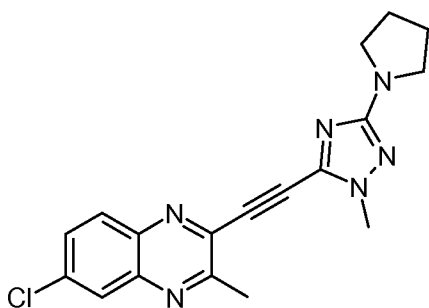
4-chlorobenzene-1,2-diamine (5 g, 35.1 mmol, Eq: 1.00) was stirred in water (50 ml) at room temperature. 2-Oxopropanoic acid (3.09 g, 2.44 ml, 35.1 mmol, Eq: 1.00) in water (20 ml) was added drop wise. The dark mixture was stirred at room temperature for 30 min. The precipitate was filtered off and washed with water and dried under high vacuum to give 6-chloro-3-methyl-1H-quinoxalin-2-one with 7-chloro-3-methyl-1H-quinoxalin-2-one (5.06g, 37.1%) as brown solid. MS:  $m/z = 195.03$  ( $M+H^+$ )

10 b) 3-Bromo-6-chloro-2-methyl-quinoxaline with 2-bromo-6-chloro-3-methyl-quinoxaline



6-Chloro-3-methylquinoxalin-2(1H)-one compound with 7-chloro-3-methylquinoxalin-2(1H)-one (300 mg, 771  $\mu\text{mol}$ , Eq: 1.00) was stirred neat in phosphoryl tribromide (1.6 g, 5.58 mmol, Eq: 7.24). N,N-Dimethylformamide (1 drop) (771  $\mu\text{mol}$ , Eq: 1.00) was added and the mixture was stirred at 105 °C for 1.5 h. The mixture was added to ice water and neutralized with aqueous 25% ammonium hydroxide. The precipitated solid was filtered and dried under high vacuum followed by preparative HPLC to give 3-Bromo-6-chloro-2-methyl-quinoxaline with 2-bromo-6-chloro-3-methyl-quinoxaline (40 mg, 10.1 %) as a light brown solid. MS:  $m/z = 195.03$  ( $M+H^+$ )

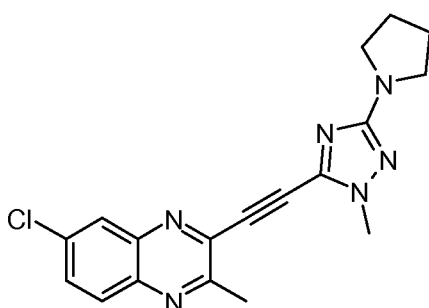
20 c) 6-Chloro-3-methyl-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-quinoxaline



To a stirred solution of 2-bromo-6-chloro-3-methylquinoxaline with 3-bromo-6-chloro-2-methylquinoxaline (250 mg, 485  $\mu\text{mol}$ , Eq: 1.00) and 5-Ethynyl-1-methyl-3-pyrrolidin-1-yl-1H-[1,2,4]triazole (94.1 mg, 534  $\mu\text{mol}$ , Eq: 1.1) at room temperature in N,N-dimethylformamide (7.5 ml) under an argon atmosphere were added triethylamine (98.2 mg, 135  $\mu\text{l}$ , 971  $\mu\text{mol}$ , Eq: 2), copper (I) iodide (4.62 mg, 24.3  $\mu\text{mol}$ , Eq: 0.05) and bis(triphenylphosphine)palladium (II) chloride (17.0 mg, 24.3  $\mu\text{mol}$ , Eq: 0.05). The mixture was purged with argon before it was stirred over weekend at room temperature (dark sol.). The mixture was stirred over an additional night at 80 °C. The crude material was applied on silica gel and purified by column chromatography. After separation of the isomers by preparative HPLC gave 6-chloro-3-methyl-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-quinoxaline (9.3 mg, 5.4%) as a yellow solid. MS:  $m/z = 353.5$  ( $M+H^+$ )

### Example 136

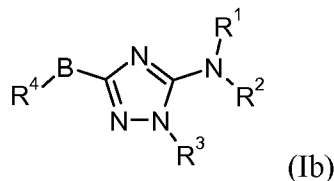
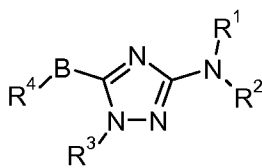
6-Chloro-2-methyl-3-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-quinoxaline



Was prepared in the same manner as described in Example 135 c) after chiral preparative HPLC separation affording 6-Chloro-2-methyl-3-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-quinoxaline (5.3 mg, 3.1%) as yellow solid. MS:  $m/z = 353.5$  ( $M+H^+$ )

### Claims

1. A compound of formula (Ia) or (Ib)



wherein

5 B is C<sub>1</sub>-C<sub>4</sub> -alkylene, C<sub>2</sub>-C<sub>4</sub> -alkenylene, C<sub>2</sub>-C<sub>4</sub> -alkynylene, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl,

R<sup>1</sup> and R<sup>2</sup>, are independently selected from hydrogen, C<sub>1</sub>-C<sub>7</sub>-alkyl optionally substituted by C<sub>3</sub>-C<sub>5</sub>-cycloalkyl; C<sub>1</sub>-C<sub>7</sub>-hydroxyalkyl, C<sub>1</sub>-C<sub>7</sub>-alkoxyalkyl, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl, R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom to which they are attached, form an azaspirocycloalkyl, a bicyclic ring or heterocycloalkyl which can be substituted by 1 to 3 substituents independently selected from the group consisting of halogen, C<sub>1</sub>-C<sub>7</sub> -alkyl, C<sub>1</sub>-C<sub>7</sub> alkoxyalkyl; C<sub>1</sub>-C<sub>7</sub>-hydroxyalkyl, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> -haloalkyl, hydroxyl, -NR<sup>9</sup>R<sup>10</sup> and oxo;

10

R<sup>3</sup> is selected from hydrogen, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl, C<sub>1</sub>-C<sub>7</sub>-alkoxyalkyl, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, heterocycloalkyl, -(CH<sub>2</sub>)<sub>0,1,2</sub>- aryl optionally substituted by C<sub>1</sub>-C<sub>7</sub> alkoxy and C<sub>1</sub>-C<sub>7</sub>-alkyl optionally substituted by C<sub>3</sub>-C<sub>5</sub>-cycloalkyl;

15 R<sup>4</sup> is selected from heteroaryl optionally substituted by 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>7</sub> -alkyl, C<sub>1</sub>-C<sub>7</sub> -hydroxyalkyl, C<sub>1</sub>-C<sub>7</sub> -haloalkoxy, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl, cyano, amino, nitro, -O-R<sup>6</sup>-C(O)-R<sup>7</sup>, -SO<sub>2</sub>R<sup>8</sup>, C<sub>1</sub>-C<sub>2</sub>-alkoxy optionally substituted by C<sub>1</sub>-C<sub>2</sub>-alkoxy, heterocycloalkyl,

R<sup>6</sup> and R<sup>8</sup> are selected from C<sub>1</sub>-C<sub>7</sub> -alkyl,

20 R<sup>7</sup> is selected from heterocycloalkyl,

R<sup>9</sup> and R<sup>10</sup> are independently selected from hydrogen, C<sub>1</sub>-C<sub>7</sub>-alkyl, -C(O)-O- C<sub>1</sub>-C<sub>7</sub>-alkyl.

2. The compound of claim 1, wherein

B is C<sub>1</sub>-C<sub>4</sub> -alkylene, C<sub>2</sub>-C<sub>4</sub> -alkenylene, C<sub>2</sub>-C<sub>4</sub> -alkynylene.

25 R<sup>1</sup> and R<sup>2</sup>, are independently selected from hydrogen, C<sub>1</sub>-C<sub>7</sub>-alkyl, C<sub>1</sub>-C<sub>7</sub>-hydroxyalkyl, C<sub>1</sub>-C<sub>7</sub>-alkoxyalkyl, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, (CH<sub>2</sub>)<sub>0,1</sub>-C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom to which they are attached, form a heterocycloalkyl which can be substituted by 1

to 3 substituents independently selected from the group consisting of halogen, C<sub>1</sub>-C<sub>7</sub> -alkyl, C<sub>1</sub>-C<sub>7</sub>-hydroxyalkyl, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> -haloalkyl, hydroxyl and oxo;

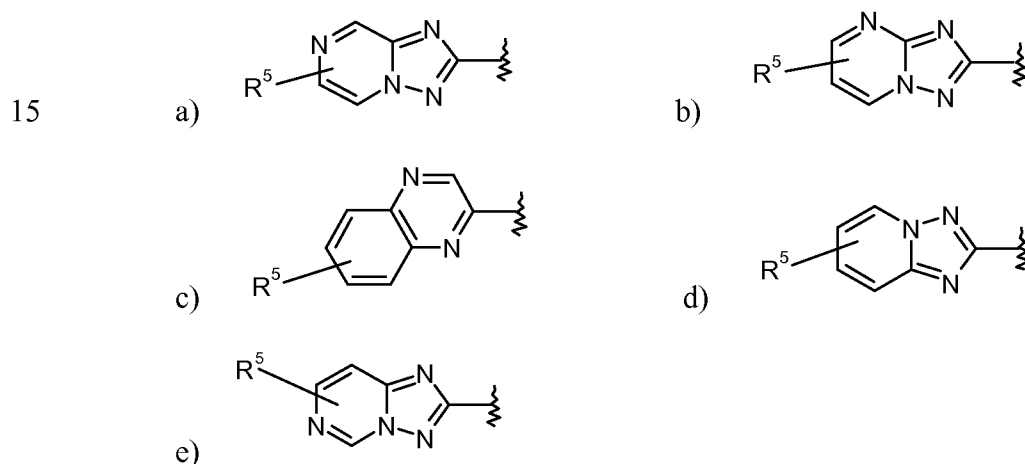
R<sup>3</sup> is selected from hydrogen, C<sub>1</sub>-C<sub>7</sub>-alkyl, C<sub>1</sub>-C<sub>7</sub>-alkoxyalkyl, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, (CH<sub>2</sub>)<sub>1,2</sub>- C<sub>3</sub>-C<sub>5</sub>-cycloalkyl, -(CH<sub>2</sub>)<sub>1,2</sub>- aryl optionally substituted by C<sub>1</sub>-C<sub>7</sub> alkoxy,

- 5 R<sup>4</sup> is selected from heteroaryl optionally substituted by 1 to 3 substituents selected from halogen, C<sub>1</sub>-C<sub>7</sub> -alkyl, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, C<sub>1</sub>-C<sub>2</sub>-alkoxy optionally substituted by halogen, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl, cyano.

3. The compound of claim 1 or 2, wherein B is selected from the group consisting of C<sub>2</sub>-alkylene, C<sub>2</sub>-alkenylene, C<sub>2</sub>-alkynylene, preferably ethylene or ethenylene.

- 10 4. The compound of claims 1 to 3, wherein R<sup>1</sup> and R<sup>2</sup>, together with the nitrogen atom to which they are attached, form a 4 to 7 membered heterocycloalkyl, preferably azetidiny, pyrrolidinyl, piperidinyl, azepanyl.

5. The compound of claims 1 to 4, wherein R<sup>4</sup> is selected from the group consisting of:



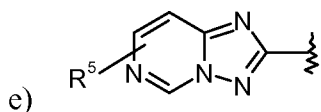
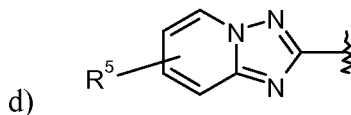
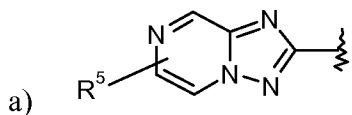
wherein R<sup>5</sup> is selected from halogen, C<sub>1</sub>-C<sub>7</sub> -alkyl, C<sub>1</sub>-C<sub>7</sub> -hydroxyalkyl, C<sub>1</sub>-C<sub>7</sub> -haloalkoxy, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, C<sub>3</sub>-C<sub>5</sub>-cycloalkyl, cyano, amino, nitro, -O-R<sup>6</sup>-C(O)-R<sup>7</sup>, -SO<sub>2</sub>R<sup>8</sup>,  
20 C<sub>1</sub>-C<sub>2</sub>-alkoxy optionally substituted by halogen, C<sub>1</sub>-C<sub>2</sub>-alkoxy or heterocycloalkyl,

R<sup>6</sup> and R<sup>8</sup> are independently selected from C<sub>1</sub>-C<sub>7</sub> -alkyl,

R<sup>7</sup> is selected from heterocycloalkyl.

6. The compound of claim 5, wherein wherein R<sup>5</sup> is selected from hydrogen, halogen, C<sub>1</sub>-C<sub>7</sub> -alkyl, C<sub>1</sub>-C<sub>7</sub>-haloalkyl, C<sub>1</sub>-C<sub>7</sub> -alkoxy, cyano.

7. The compound of claim 5 or 6, wherein R<sup>4</sup> is selected from the group consisting of:



5 8. The compound of claims 1 to 7 selected from the group consisting of:

2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

10 2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine

2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine

15 {5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-ethyl-1H-[1,2,4]triazol-3-yl}-dimethyl-amine

{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-dimethyl-amine

5,8-Dimethyl-2-{2-[5-pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

20 5,8-Dimethyl-2-[2-(5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine

2-[2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

25 2-[2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

Cyclopropyl- {5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-methyl-amine

Cyclopropyl- {5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-methyl-amine

5 5,8-Dimethyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-a]pyrazine

5,8-Dimethyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine

2-Methyl-3-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-vinyl]-quinoxaline

10 2-Methyl-3-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-quinoxaline

5,8-Dimethyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-vinyl]-[1,2,4]triazolo[1,5-a]pyrazine

5,8-Dimethyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine

15 7-Chloro-2-[1-(4-methoxy-benzyl)-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-ylethynyl]-[1,2,4]triazolo[1,5-a]pyridine

2-{2-[2-(4-Methoxy-benzyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

20 2-[2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-ethyl]-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine

5,7-Dimethyl-2-{2-[5-pyrrolidin-1-yl-2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrimidine

{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-ethyl-methyl-amine

25 5,7-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyrimidine

N-cyclopropyl-5-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)ethyl)-N,1-dimethyl-1H-1,2,4-triazol-3-amine

6-Chloro-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

6-Chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

5 6-Chloro-5-methyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-  
[1,2,4]triazolo[1,5-a]pyridine

5-Methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

10 Cyclopropyl-{5-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-vinyl]-1-methyl-  
1H-[1,2,4]triazol-3-yl}-methyl-amine

7,8-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

7,8-Dimethyl-2-(2-(1-methyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

15 2-[2-(2-Ethyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-3-methyl-quinoxaline

Cyclopropyl-{5-[2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-ethyl]-1-methyl-  
1H-[1,2,4]triazol-3-yl}-methyl-amine

6-Chloro-5,8-dimethyl-2-(2-(1-methyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)vinyl)-  
[1,2,4]triazolo[1,5-a]pyridine

20 6-Chloro-5,8-dimethyl-2-(2-(1-methyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

5,8-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

25 6-Chloro-5,8-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine

2-{2-[5-(3-Fluoro-azetidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-  
[1,2,4]triazolo[1,5-a]pyrazine

5,6-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-  
[1,2,4]triazolo[1,5-a]pyridine



5,6,8-Trimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyrazine

5,7,8-Trimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine

5 2-{2-[5-(3-Methoxy-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

8-Chloro-5,7-dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine

10 5,7-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine

6-Chloro-5,8-dimethyl-2-[(1S,2S)-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-cyclopropyl]-[1,2,4]triazolo[1,5-a]pyridine

2-((1-Ethyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethynyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

15 2-(2-(1-Ethyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

5,8-Dimethyl-2-[2-(2-methyl-5-piperidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine

20 5-Ethyl-8-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine

5,8-Dimethyl-2-{2-[2-methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

6,8-Dichloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

25 2-(2-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonitrile

8-Chloro-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-6-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

7-Methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-nitro-[1,2,4]triazolo[1,5-a]pyridine

2-(2-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]quinoline

5 5-Methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyrazine

5,8-Dimethyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-c]pyrimidine

10 {5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-diethyl-amine

Cyclopropyl-{5-[2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-ethyl-amine

6,8-Dichloro-2-{2-[2-(4-methoxy-benzyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl]-ethyl}-5-methyl-[1,2,4]triazolo[1,5-a]pyridine

15 6,8-Dichloro-2-(2-(1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridine

6-Fluoro-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-7-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridin-5-amine

20 2-(2-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-5-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

8-Bromo-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-6-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

2-(2-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-7-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

25 2-(2-(1-Methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine-7-carbonitrile

6,8-Dichloro-5-methyl-2-[2-(5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine

5-Methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonitrile

5 8-Bromo-6-chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

6-Bromo-8-chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine

10 6-Chloro-8-methanesulfonyl-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

8-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine-6-carbonitrile

8-Ethyl-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-c]pyrimidine

15 6-Chloro-8-methoxy-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

6-Chloro-8-cyclopropyl-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

20 5-Methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile

6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile

2-{6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridin-8-yl}-propan-2-ol

25 2-[(E)-2-(5-Azetidin-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-c]pyrimidine

6-Bromo-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine

5-Methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonitrile

5,6-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

5 6-Chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridin-8-ol

6-Ethyl-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine

10 1-{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-2-one

6-Chloro-2-{2-[5-(3,3-difluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5-methyl-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine

5,8-Dimethyl-2-{2-[2-methyl-5-(3-methyl-azetidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

15 2-{2-[5-(3,3-Difluoro-azetidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

6-Chloro-5-methyl-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine

20 2-{2-[5-(5-Aza-spiro[2.4]hept-5-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

2-{2-[5-(3,3-Difluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

2-{2-[5-((S)-3-Fluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin

25 6-Chloro-8-difluoromethoxy-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

2-{2-[5-((R)-3-Fluoro-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

Cyclopropylmethyl- {5-[(E)-2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-vinyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-methyl-amine

6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-8-(2,2,2-trifluoro-ethoxy)-[1,2,4]triazolo[1,5-a]pyridine

5 2-{2-[5-(3-Aza-bicyclo[3.2.0]hept-3-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

5,8-Dimethyl-2-{2-[2-methyl-5-((S)-2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

10 5,8-Dimethyl-2-{2-[2-methyl-5-((R)-2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

2-[(E)-2-(5-Azepan-1-yl-2-methyl-2H-[1,2,4]triazol-3-yl)-vinyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

7,8-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-5-(trifluoromethyl)-[1,2,4]triazolo[1,5-c]pyrimidine

15 1-{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-3-ol

6-Chloro-5-methyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-8-trifluoromethyl-[1,2,4]triazolo[1,5-a]pyridine

20 6-Chloro-8-difluoromethoxy-5-methyl-2-[2-(1-methyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyridine

((R)-1-{5-[2-(5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl]-1-methyl-1H-[1,2,4]triazol-3-yl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester

5,8-Dimethyl-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-[1,2,4]triazolo[1,5-a]pyrazine

25 5,8-Dimethyl-2-[2-(2-phenyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl)-ethyl]-[1,2,4]triazolo[1,5-a]pyrazine

2-{2-[2-(2,2-Difluoro-ethyl)-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

5,8-Dimethyl-2-{2-[2-methyl-5-(2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-c]pyrimidine

5,8-Dimethyl-2-{2-[2-methyl-5-((S)-2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-c]pyrimidine

5 5,8-Dimethyl-2-{2-[2-methyl-5-((R)-2-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-c]pyrimidine

5,8-Dimethyl-2-{2-[2-methyl-5-((R)-2-trifluoromethyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

10 5,8-Dimethyl-2-{2-[2-methyl-5-((S)-3-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

5,8-Dimethyl-2-{2-[2-methyl-5-((R)-3-methyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-a]pyrazine

2-[2-(2-Cyclopropylmethyl-5-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

15 2-[2-(1-Cyclopropylmethyl-5-pyrrolidin-1-yl)-1H-[1,2,4]triazol-3-yl]-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (b)

5,8-Dimethyl-2-{2-[2-methyl-5-((R)-2-trifluoromethyl-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl}-[1,2,4]triazolo[1,5-c]pyrimidine

20 6-Chloro-8-(2-methoxyethoxy)-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl)-1,2,4-triazol-3-yl]ethyl]-[1,2,4]triazolo[1,5-a]pyridine

6-Chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(tetrahydro-2H-pyran-4-yloxy)-[1,2,4]triazolo[1,5-a]pyridine

4-[2-[[6-Chloro-5-methyl-2-[2-(2-methyl-5-pyrrolidin-1-yl)-1,2,4-triazol-3-yl]ethyl]-[1,2,4]triazolo[1,5-a]pyridin-8-yl]oxy]ethyl]morpholine

25 6-Chloro-5-methyl-2-(2-(3-(pyrrolidin-1-yl)-1-(tetrahydro-2H-pyran-4-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

2-[2-(2-Cyclopropyl-5-pyrrolidin-1-yl)-2H-[1,2,4]triazol-3-yl]-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

2-[2-(1-Cyclopropyl-5-pyrrolidin-1-yl-1H-[1,2,4]triazol-3-yl)-ethyl]-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine (b)

2-{2-[5-((R)-2-Methoxymethyl-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

5 2-(6-Chloro-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridin-8-yloxy)-1-morpholinoethanone

(-)-5,8-Dimethyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)propyl)-[1,2,4]triazolo[1,5-a]pyrazine

10 (R)-6-Chloro-2-(2-(3-(3-fluoropyrrolidin-1-yl)-1-methyl-1H-1,2,4-triazol-5-yl)ethyl)-5-methyl-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

6-Chloro-5-methyl-2-(2-(3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

2-{2-[5-(3-Difluoromethyl-pyrrolidin-1-yl)-2-methyl-2H-[1,2,4]triazol-3-yl]-ethyl}-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazine

15 6-Chloro-8-(difluoromethyl)-5-methyl-2-(2-(1-methyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-[1,2,4]triazolo[1,5-a]pyridine

6-Chloro-2-(2-(1-cyclopropyl-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)-5-methyl-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

20 6-Chloro-2-(2-(1-cyclopropyl-3-(pyrrolidin-1-yl)-1H-1,2,4-triazol-5-yl)ethyl)-5-methyl-8-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine

7-chloro-2-((1-(4-methoxybenzyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethynyl)quinoxaline

7-chloro-2-(2-(5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl)ethyl)quinoxaline

25 6-Chloro-3-methyl-2-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-quinoxaline

6-Chloro-2-methyl-3-(2-methyl-5-pyrrolidin-1-yl-2H-[1,2,4]triazol-3-ylethynyl)-quinoxaline

9        The use of a compound of claims 1 - 8 for the treatment or prophylaxis of psychotic disorders, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder, substance-induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipolar disorders, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma or breast cancer.

10.      The use of a compound of claims 1 - 8 for the preparation of a medicament for the treatment or prophylaxis of psychotic disorders, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder, substance-induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipolar disorders, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma or breast cancer.

11.      A compound of claims 1 - 8 for the treatment or prophylaxis of psychotic disorders, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder, substance-induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipolar disorders, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma or breast cancer.

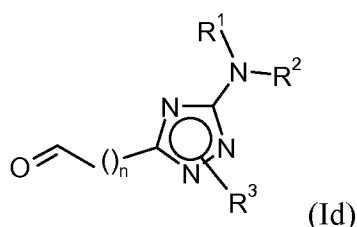
12.      A method for the treatment or prophylaxis of psychotic disorders, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder, substance-induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disorder,



ders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipolar disorders, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease,  
 5 multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma or breast cancer, which method comprises administering an effective amount of a compound as defined in claims 1 - 8.

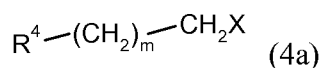
13. A process for the manufacture of compounds of formula I as defined in claims 1 - 8, which process comprises

10 c) reacting a compound of formula (Id)



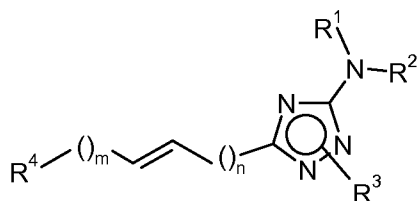
with

15 d) a compound of formula (4a)



to a compound of formula (Ie)

20



wherein n and m are 0 or 1, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and X are as defined in the previous claims.

14. The process of claim 13, wherein n = 0 and m = 0.

25 15. The invention as hereinbefore described.

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/060838

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D403/06 C07D471/04 C07D487/04 A61K31/4192 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 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.
X	C. A. LIPINSKI: "Bioisosteric Design of Conformationally Restricted Pyridyltriazole Histamine H2-Receptor Antagonists", J. MED. CHEM., vol. 26, no. 1, 1983, pages 1-6, XP002680050, table II; compounds 4, 5, 6 -----	1,3
X	WO 2012/054366 A2 (MERCK SHARP & DOHME [US]; SHIPPS GERALD W JR [US]; SAUVAGNAT BERENEGER) 26 April 2012 (2012-04-26) claims 1-21 -----	1-15
X	WO 2009/152825 A1 (LUNDBECK & CO AS H [DK]; RITZEN ANDREAS [DK]; KEHLER JAN [DK]; LANGGAA) 23 December 2009 (2009-12-23) claims 1-30 -----	1-15
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance	"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	
"E" earlier application or patent but published on or after the international filing date	"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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"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search  18 June 2013	Date of mailing of the international search report  22/07/2013	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Herz, Claus	

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Information on patent family members

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