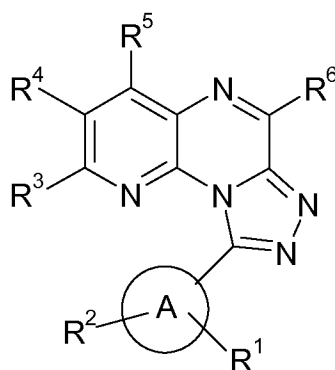


4-Methyl-2,3,5,9,9b-pentaaza-cyclopenta[a]naphthalenes

Field of the invention

- 5 The invention relates to 4-methyl-2,3,5,9,9b-pentaaza-cyclopenta[a]naphthalene derivatives of general formula (I) which are inhibitors of phosphodiesterase 2 and/or 10, useful in treating central nervous system diseases and other diseases. In addition, the invention relates to processes for preparing pharmaceutical compositions as well as processes for manufacture the compounds according to the invention.

Background of the invention

- Cognitive dysfunction plays a role in a number of central nervous system disorders, including neurological disorders, such as Alzheimer's disease (AD), Parkinson disease and dementia, but also psychiatric disorders, such as schizophrenia, depression and bipolar disorders. As world population grows older the number of patients with dementia and AD is growing. Therefore, most people are familiar with the cognitive deficits related to these neurological diseases (Massoud and Gauthier, 2010).

- 20 However, also in psychiatric disorders cognitive impairment adversely affect the progress and the treatment outcome of the disease. A most prominent example is schizophrenia. Schizophrenia has a heterogeneous symptomatic picture (American Psychiatric Association, 1994) that may be divided into three distinct disease domains: positive symptoms (psychotic episodes of hallucinations, delusions and agitation), negative symptoms (social withdrawal, anhedonia, flattened affect) and
- 25

cognitive deficits (deficits in executive function, verbal learning and memory, verbal fluency) (Thompson and Meltzer, 1993).

Whereas positive symptoms are essentially alleviated by dopamine D2 receptor antagonist and second generation antipsychotics negative symptoms and cognitive deficits are still hardly affected by current treatments. Therefore, research on cognitive deficits in schizophrenia has been intensified over the past years. A worldwide network initiative, called MATRICS, has been founded to characterise the cognitive deficits more deeply and to find novel therapies (Young et al., 2009).

However, cognitive impairment is also seen in patients with depression, bipolar disorders (Sachs et al., 2007; Pavuluri et al., 2009) and in many patients with disorders usually first diagnosed in infancy, childhood and adolescence, such as attention deficit/hyperactivity disorder (ADHD) (Jucaite et al., 2005; Turner et al., 2003).

Depression is a severe mental disorder which extremely impairs daily life. Its prevalence is about 10 % of the world population with an incidence of 2 % according to WHO. Women are more affected than men and elder people more than younger people. The disorder mostly implies a life-long treatment due to the progression of the disease and permanent total disability.

The most prominent symptoms of the disease are anhedonia, feeling of hopelessness, decreased self esteem, loss of appetite and sleep disturbances.

Suicide ideation is also a common symptom of depression and about 10% of depressed patients (Holma et al., 2010) attempt suicide. Depression is often combined with anxiety disorders. Interestingly, it is less known that depression is also regularly associated with various cognitive impairments (Gualtieri et al., 2006; Mandelli et al., 2006). Here, deficits of attentional and executive functions are mostly reported (Paelecke-Habermann et al., 2005). Cognitive deficits are even discussed to be involved in the development of the disease (Beck depression model, Beck, 2008). More recent studies indicate that the severity of the cognitive deficits may predict

non-response to certain antidepressant treatment (Dunkin et al., 2000; Gorlyn et al., 2008).

Up to now, current antidepressant therapy seems not to be sufficient regarding
5 cognitive deficits. Elder antidepressants are reported to impair memory in animal
models of learning and memory probably due to their anticholinergic component
(Kumar and Kulkarni, 1996). In contrast, SSRIs, in particular fluoxetine, are described
to impair hippocampal-independent but not hippocampal dependent learning in
different rodent models (Valluzi and Chan, 2007). At least, in clinic current therapy it
10 is not possible to fully reverse cognitive deficits. Thus, in depressive patients who
had been successfully treated cognitive performance could be improved but not
normalised (Gualtieri et al., 2006). Therefore, an antidepressant with higher efficacy
on cognitive impairment may improve disease outcome.

15 Bipolar disorders are characterized by complex symptomatology, including severe
symptoms of mood disorders but also manic episodes and cognitive deficits. The
Diagnostic and Statistical Manual, 4th edition and International Classification of
Mental Disorder recommend subgroups of bipolar disorder based on whether
depressive or manic [psychotic] symptoms and episodes are dominating and on the
20 frequency of the episodes (Gaiwani, 2009). Pharmacological agents commonly used
in the management of bipolar disorder include lithium; anticonvulsants, such as
valproate, carbamazepine and lamotrigine; and recent years have witnessed
increasing use of atypical antipsychotics (Altamura et al., 2011). As a problem of
current therapy the development of tolerance against anticonvulsant treatment and
25 30% of treatment refractory cases are described (Post and Weiss, 2010; Gaiwani,
2009).

Attention deficit hyperactivity disorder (ADHD) is a central nervous system disorder
that is mainly defined by its clinical signs. ADHD shows a heterogeneous symptom
30 pattern in humans. The most important indicators are attention deficits, impulsivity
and a hyperactivity that is primarily seen in boys. The disease starts at an early age
and symptoms are most intense during childhood. After puberty the signs of the
disease are more masked and focus on cognitive dysfunction (Jucaite et al. 2005;

Turner et al. 2003). Although modern research broadened the understanding of the pathomechanism the exact etiology of the disease remains unclear.

Interestingly, the symptoms seen in ADHD are not due to a hyperactivity but a
5 hypoactivity of the so called executive loop of the striatum (Winstanley et al., 2006; Plizska, 2005). The executive loop is responsible for the regulation of cognitive processes such as planning, working memory and attention (Benke et al., 2003; Easton et al., 2007). A dysfunction of the prefrontal cortex or other pathways within
10 the loop induces impulsivity and a loss of the ability to filter stimuli that come from the outside. The latter causes the symptoms of sustained attention and hyperactivity (Roberts and Wallis, 2000; Gonzales et al., 2000). The dopaminergic neurotransmitter system plays a central role in regulating the activity of the executive loop (Jucaite et al., 2005). This conclusion is also supported by the current treatment for ADHD that aims for an activation of the dopaminergic neurotransmitter system
15 (Jucaite et al., 2005).

Phosphodiesterases (PDE) are expressed in nearly all mammalian cells. To date eleven families of phosphodiesterases have been identified in mammals (Essayan, 2001). It is well established that PDEs are critically involved in cell signalling.
20 Specifically, PDEs are known to inactivate the cyclic nucleotides cAMP and/or cGMP (Soderling and Beavo, 2000). The cyclic nucleotides cAMP and cGMP are synthesised by the adenylyl and guanylyl cyclases and are second messengers that control many key cellular functions. The synthesis of cAMP and cGMP is regulated by different G-protein-coupled receptor types including dopamine D1 and D2
25 receptors (Mutschler, 2001).

The phosphodiesterases of the different families vary in their substrate selectivity. Thus, some families only hydrolyse cAMP others only cGMP. Some phosphodiesterases, such as phosphodiesterase 2 and 10, inactivate both cAMP and
30 cGMP (Menniti et al., 2006).

Furthermore, there is a difference in the distribution of the different phosphodiesterases within the organism and additionally, within any particular tissue

or organ. For instance, the distribution pattern of the phosphodiesterases within the brain is quite specific (Menniti et al., 2006).

Finally, phosphodiesterase families have different regulatory properties and
5 intracellular location; some are bound to cell membranes and some are dissociated in the cytoplasm, additionally, a division into various intracellular compartments has been reported (Conti and Jin, 1999).

These differences in the function and location of the different PDE enzyme families
10 suggest that the individual phosphodiesterases are selectively involved in regulating many different physiological processes. Accordingly, selective phosphodiesterase inhibitors may with fine specificity regulate different physiological and pathophysiological processes.

15 PDE2 and PDE10 hydrolyse both, cGMP and cAMP (Menniti et al., 2006; Soderling et al., 1999; Kotera et al., 1999).

They are both abundantly expressed in the brain indicating their relevance in CNS function (Bolger et al., 1994; Menniti et al., 2001).

20 PDE2 mRNA is mainly distributed in olfactory bulb, olfactory tubercle, cortex, amygdala, striatum, and hippocampus (Lakics et al., 2005; van Staveren et al., 2003). PDE10 (PDE10A) is primarily expressed in the nucleus accumbens and the caudate putamen. Areas with moderate expression are the thalamus, hippocampus,
25 frontal cortex and olfactory tubercle (Menniti et al., 2001).

Although there are certainly fine differences in the function and expression patterns of PDE2 and 10, the expression of PDE2 in the hippocampus, the cortex and in the striatum and the expression of PDE10 in striatum, hippocampus and frontal cortex
30 indicate an involvement in the mechanism of learning and memory/cognition. This is further supported by the fact that increased levels of both cGMP and cAMP are involved in the process of short and long term potentiation (LTP) forming (Blokland et al., 2006; Prickaerts et al., 2002). LTP is regarded as the electrophysiological basis

of long term memory (Baddeley, 2003). Boess et al. (2004) showed that PDE2 inhibitors amplify the generation of LTP. Additionally, it is reported that the selective PDE2 inhibitor BAY60-7550 enhances learning and memory in rats and mice in different animal models (Boess et al., 2004; Rutten et al., 2006). Similar pro-cognitive effects are described for selective PDE10 inhibitors, such as papaverine and MP-10. Rodefer et al. (2005) have found that papaverine reverses attentional set-shifting deficits induced by subchronic administration of phencyclidine, an NMDA antagonist, in rats. Grauer et al. (2009) could show a positive effect of papaverine and MP-10 on cognitive deficits in the novel object recognition and in prepulse inhibition of acoustic startle response in rats. These data support the procognitive effect of PDE2 and/or 10 and a synergistic effect of PDE2 and 10 on cognition.

Furthermore, the expression of PDE2 in the nucleus accumbens (part of the striatum), the olfactory bulb, the olfactory tubercle and the amygdala and the expression of PDE10 in the nucleus accumbens, the olfactory tubercle and the thalamus supports additional involvement of PDE2 and 10 in the pathophysiology of anxiety and depression (Modell et al., 1990). This is supported by in vivo studies. The selective PDE2 inhibitors BAY60-7550 and ND-7001 are described to be effective in animal models of anxiety and stress-induced behavior (Masood et al., 2008, 2009).

In addition to the pro-cognitive and antidepressant potential of PDE10 inhibition there is evidence for an additional antipsychotic potential of PDE10 inhibitors. In the striatum PDE10 is predominately found postsynaptic in the medium spiny neurons (Xie et al., 2006). By this location, PDE10 may have an important influence on the signal cascade induced by dopaminergic and glutamatergic input on the striatum, two neurotransmitter systems playing a predominate role in the pathomechanism of psychosis. Focusing on the dopaminergic input on the medium spiny neurons, PDE10A inhibitors by up-regulating cAMP and cGMP levels act as D1 agonists and D2 antagonists because the activation of Gs-protein coupled dopamine D1 receptor increases intracellular cAMP, whereas the activation of the Gi-protein coupled dopamine D2 receptor decreases intracellular cAMP levels through inhibition of adenylyl cyclase activity (Mutschler et al., 2001). Accordingly, PDE10 inhibitors are

reported to be active in several animal models of schizophrenia (Schmidt et al., 2008; Siuciak et al., 2006; Grauer et al., 2009).

PDE10 inhibitors have been disclosed recently in J. Med. Chem, 2011, 54, 7621-
5 7638.

For drugs with an intended action in the central nervous system (CNS), it is assumed that unbound drug in interstitial spaces in the brain is in direct contact or in equilibrium with the site of action (de Lange and Danhof, 2002).

10 It is commonly accepted that unbound or free drug is the species available for interaction with drug targets within the body, and this is referred to as the free drug hypothesis.

Because cerebrospinal fluid (CSF) is in direct contact with the brain tissue, it is
15 assumed to readily equilibrate with brain interstitial fluid concentration (Meineke et al., 2002; Shen et al., 2004) so that CSF concentration is used as a common surrogate measure for drug unbound concentration in clinical pharmacology studies (Bonati et al., 1982; Cherubin et al., 1989; Garver, 1989; Reiter and Doron, 1996; Ostermann et al., 2004). Accordingly, for compounds with an intended action in the
20 central nervous system it is important that they reach a high CSF concentration and a high CSF to plasma ratio in order to have high pharmacological activity in the CNS.

Inhibition of the hERG channel by xenobiotics and subsequent delayed cardiac repolarization is associated with an increased risk for a specific polymorphic
25 ventricular tachyarrhythmia, torsade de pointes, as established by Sanguinetti et al. (1995, Cell, Apr. 21, 81(2):299-307) and a large body of subsequent evidence. As such, low hERG channel inhibition, such as that shown by the compounds of the present invention, is highly desirable for therapeutics.

30 Several families of PDE2 inhibitors are known. Imidazotriazinones are claimed in WO 2002/068423 for the treatment of e.g. memory deficiency, cognitive disorders, dementia and Alzheimer's disease. Oxindoles are described in WO 2005/041957 for the treatment of dementia. Further inhibitors of PDE2 are known from WO

2007/121319 for the treatment of anxiety and depression, from WO 2013/034761, WO 2012/104293 and WO2013/000924 for the treatment of neurological and psychiatric disorders, from WO 2006/072615, WO 2006/072612, WO 2006/024640 and WO 2005/113517 for the treatment of arthritis, cancer, edema and septic shock,
 5 from WO 2005/063723 for the treatment of renal and liver failure, liver dysfunction, restless leg syndrome, rheumatic disorders, arthritis, rhinitis, asthma and obesity, from WO 2005/041957 for the treatment of cancer and thrombotic disorders, from WO 2006/102728 for the treatment of angina pectoris and hypertension from WO 2008/043461 for the treatment of cardiovascular disorders, erectile dysfunction,
 10 inflammation and renal failure and from WO 2005/061497 for the treatment of e.g. dementia, memory disorders, cancer and osteoporosis.

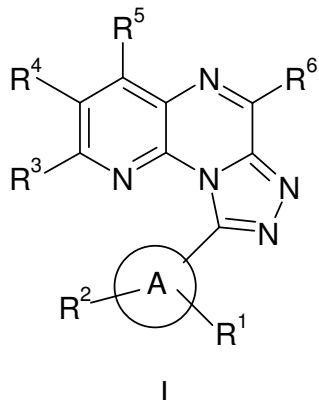
Finally, benzodiazepines are described in WO 2005/063723 for the general treatment of CNS diseases including anxiety, depression, ADHD, neurodegeneration,
 15 Alzheimer's disease and psychosis.

Aim

It has now been found that compounds of the present disclosure according to general formula I are effective inhibitors of phosphodiesterase 2 and/or 10.
 20 Besides the inhibition property toward phosphodiesterase 2 and/or 10 enzymes, the compounds of the present disclosure provide further advantageous pharmacokinetic properties. For example the compounds of the present disclosure show high concentration in cerebrospinal fluid (CSF) and have a high CSF to plasma ratio, which translates in lower efficacious doses of the compounds for disease treatment
 25 and as a consequence in further potential advantages such as minimization of side effects . Furthermore, compounds of the present disclosure show good metabolic stability and low potential of formation of biologically active metabolite and low hERG potassium channel inhibition.

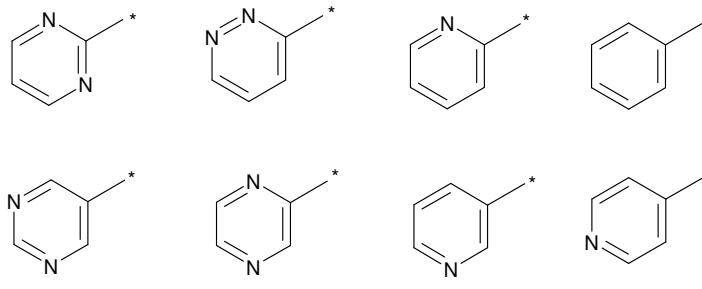
30 Accordingly, the disclosure refers to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and salts thereof as inhibitors of phosphodiesterase 2 and/or 10.

According to a first aspect, there is provided compounds of formula I



wherein

A is selected from the group A^a consisting of



wherein above mentioned phenyl-, pyridinyl-, pyrimidinyl-, pyridazinyl and pyrazinyl groups are substituted with R¹ and R²;

5

R¹ is selected from the group R^{1a} consisting of
H, halogen, NC-, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl and R⁸-(CH₂)_n-O-
with n = 0, 1, 2, 3 or 4,

wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl and R⁸-(CH₂)_n-O- groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO- and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-;

R² is selected from the group R^{2a1} consisting of
HO-, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-,
heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸-(CH₂)_n-O- with n
= 0, 1, 2, 3 or 4, and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O- with m = 0, 1 or 2 and
o = 0, 1 or 2,

10

wherein above mentioned C₁₋₆-alkyl-, and C₁₋₆-alkyl-O-groups are substituted with 1 to 5 substituents independently selected from the group consisting of HO-, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O-, and

5 wherein above mentioned C₁₋₆-alkyl- and C₁₋₆-alkyl-O-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-,

and

10 wherein above mentioned C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸-(CH₂)_n-O- and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO-, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O-,
15 and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-;

R³ is selected from the group R^{3a} consisting of H, halogen, NC-, C₁₋₄-alkyl- and C₃₋₆-cycloalkyl-, wherein the above mentioned C₁₋₄-alkyl- and C₃₋₆-cycloalkyl-groups may optionally be substituted with 1 to 9 substituents independently selected from the group consisting of halogen, NC-, HO-, C₁₋₃-alkyl- and C₁₋₃-alkyl-O-;

R⁴, R⁵ are selected independently of each other from the group R^{4a}/R^{5a} consisting of H, halogen, NC-, HO-, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O-, heterocyclyl-O-, heterocyclyl, heteroaryl, R⁷-CH₂-O- and R⁷-(CH₂)₂-O-, wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O-, heterocyclyl-O-, heterocyclyl, heteroaryl, R⁷-CH₂-O- and R⁷-(CH₂)₂-O-groups, may optionally be

substituted with 1 to 5 substituents independently selected from the group consisting of halogen, optionally with 1 to 5 halogen atoms, substituted C₁₋₂-alkyl-, and optionally with 1 to 5 halogen atoms substituted C₁₋₂-alkyl-O-;

R⁶ is selected from the group R^{6a} consisting of H, NC-, C₁₋₆-alkyl-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl- and C₃₋₈-cycloalkyl-O- wherein above mentioned C₁₋₆-alkyl- groups may optionally be substituted with 1-3 halogen atoms;

R⁷ is selected from the group R^{7a} consisting of H, carbocyclyl, heterocyclyl and heteroaryl, wherein above mentioned carbocyclyl, heterocyclyl and heteroaryl-groups may optionally be substituted with 1 to 4 substituents independently selected from the group consisting of HO-, optionally with 1 to 3 halogen atoms substituted C₁₋₄-alkyl-, optionally with 1 to 3 halogen atoms substituted C₁₋₄-alkyl-O- and halogen;

R⁸ is selected from the group R^{8a} consisting of C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl, wherein above mentioned C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO-, fluorine and optionally with 1 to 7 halogen atoms substituted C₁₋₃-alkyl-;

the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the salts thereof.

The disclosure also refers to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof as inhibitors of phosphodiesterase 2 and/or 10 and reaching high concentrations in cerebrospinal fluid (CSF) and/or having high CSF to plasma ratio.

The disclosure also refers to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof as inhibitors of phosphodiesterase 2 and/or 10 and showing good metabolic stability.

The disclosure also refers to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof as inhibitors of phosphodiesterase 2 and/or 10 with low hERG channel inhibition.

The disclosure also refers to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof as inhibitors of phosphodiesterase 2 and/or 10 with low potential of forming biologically active metabolite.

According to a second aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable tautomers thereof, stereoisomer thereof, mixtures thereof, solvate thereof, hydrate thereof or salt thereof for use as a medicament.

The disclosure also relates to pharmaceutical compositions, containing at least one compound according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof optionally together with one or more inert carriers and/or diluents.

According to a third aspect, there is provided pharmaceutical compositions containing at least one compound as defined herein or a pharmaceutically acceptable tautomers thereof, stereoisomer thereof, mixtures thereof, solvate thereof, hydrate thereof or salt thereof together with one or more pharmaceutically acceptable carrier.

The disclosure also relates to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof or pharmaceutical compositions comprising compounds according to formula I, the

tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof for the use in the prevention and/or treatment of disorders associated with PDE2 and/or 10 hyperactivity and/or cAMP and/or cGMP hypofunction.

5

The disclosure also relates to processes of manufacture of the compounds of the present disclosure.

The disclosure also relates to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the
10 hydrates thereof and the physiologically acceptable salts thereof or pharmaceutical compositions comprising compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof for the use in the prevention and/or treatment of diseases or conditions which can be influenced by inhibition of
15 PDE2 and/or 10 hyperactivity and/or cAMP and/or cGMP hypofunction, such as (1) disorders comprising the symptom of cognitive deficiency; (2) organic, including symptomatic, mental disorders, dementia; (3) mental retardation; (4) mood affective disorders; (5) neurotic, stress-related and somatoform disorders including anxiety disorders; (6) behavioural and emotional disorders with onset usually occurring in
20 childhood and adolescence, attention deficit hyperactivity syndrome (ADHD) including Autism spectrum disorders; (7) disorders of psychological development, developmental disorders of scholastic skills; (8) schizophrenia and other psychotic disorders; (9) disorders of adult personality and behaviour; (10) mental and behavioural disorders due to psychoactive substance use; (11) extrapyramidal and
25 movement disorders; (12) episodic and paroxysmal disorders, epilepsy; (13) Systemic atrophies primarily affecting the central nervous system, ataxia; (14) Behavioural syndromes associated with physiological disturbances and physical factors; (15) sexual dysfunction comprising excessive sexual drive; (16) factitious disorders.

30 In addition, the compounds of the present disclosure can be used for the treatment, amelioration and / or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory.

In addition, the compounds of the present disclosure can be used for the treatment amelioration and / or prevention of cognitive impairment being related to age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotrophic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis. In addition, the compounds of the present invention can be used for the treatment of Alzheimer's disease.

In addition compounds of the present disclosure can be used for the treatment of pain disorders, including but not limited to inflammatory, neuropathic and osteoarthritic pain.

In addition, the compounds of the present disclosure can be used for the treatment of sleep disorders, bipolar disorder, metabolic syndrome, obesity, diabetes mellitus, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

According to a fourth aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable tautomer thereof, stereoisomer thereof, mixtures thereof, solvate thereof, hydrate thereof or salt thereof or a pharmaceutical composition according to claim 22 for use in the prevention or treatment of (1) disorders comprising the symptom of cognitive deficiency; (2) organic, including symptomatic, mental disorders, dementia; (3) mental retardation; (4) mood [affective] disorders; (5) neurotic, stress-related and somatoform disorders including anxiety disorders; (6) behavioural and emotional disorders with onset usually occurring in childhood and adolescence, attention deficit hyperactivity syndrome (ADHD) and Autism spectrum disorders; (7) disorders of psychological development, developmental disorders of scholastic skills; (8) schizophrenia and other psychotic

disorders; (9) disorders of adult personality and behaviour; (10) mental and behavioural disorders due to psychoactive substance use; (11) extrapyramidal and movement disorders; (12) episodic and paroxysmal disorders, epilepsy; (13) Systemic atrophies primarily affecting the central nervous system, ataxia; (14)

5 Behavioural syndromes associated with physiological disturbances and physical factors; (15) sexual dysfunction comprising excessive sexual drive; (16) factitious disorders; (17) Treatment, amelioration and / or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory; (18) Treatment amelioration and / or prevention of cognitive impairment being related to

10 age-associated learning and memory impairments; (19) Age-associated memory losses; (20) Vascular dementia; (21) Craniocerebral trauma; (22) Stroke; (23) Dementia occurring after strokes (post stroke dementia); (24) Post-traumatic dementia; (25) General concentration impairments; (26) Concentration impairments in children with learning and memory problems; (27) Alzheimer's disease; (28) Lewy

15 body dementia; (29) Dementia with degeneration of the frontal lobes; including Pick's syndrome; (30) Parkinson's disease; (31) Progressive nuclear palsy; (32) Dementia with corticobasal degeneration; (33) Amyotrophic lateral sclerosis (ALS); (34) Huntington's disease; (35) Multiple sclerosis; (36) Thalamic degeneration; (37) Creutzfeld-Jacob dementia; (38) HIV dementia; (38) Schizophrenia with dementia or

20 Korsakoff's psychosis; (39) Sleep disorders; (40) Bipolar disorder; (41) Metabolic syndrome; (42) Obesity; (43) Diabetes mellitus; (44) Hyperglycemia; (45) Dyslipidemia; (46) Impaired glucose tolerance; (47) Disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen and (48) pain disorders.

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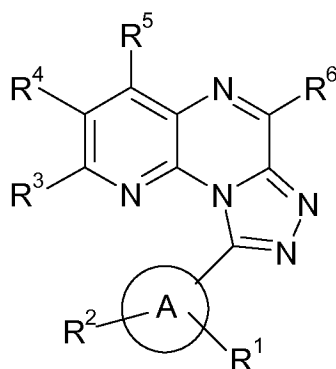
According to a fifth aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable tautomer thereof, stereoisomer thereof, mixtures thereof, solvate thereof, hydrate thereof or salt thereof or a pharmaceutical composition as defined herein for use in symptomatic treatment of Alzheimer's

30 Disease, symptomatic treatment of prodromal and/or mild-to-moderate Alzheimer's Disease and/or for the treatment of cognitive impairment associated with schizophrenia.

Other aims of the present disclosure will become apparent to the skilled man directly from the foregoing and following remarks.

Detailed description

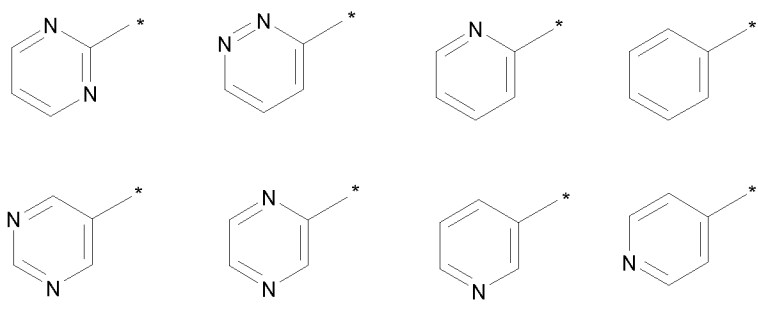
- 5 In a first aspect the present invention relates to compounds of general formula I



I

wherein

A is selected from the group A^a consisting of



wherein above mentioned phenyl-, pyridinyl-, pyrimidinyl-, pyridazinyl and pyrazinyl groups are substituted with R¹ and R²;

R¹ is selected from the group R^{1a} consisting of

H, halogen, NC-, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl and R⁸-(CH₂)_n-O- with n = 0, 1, 2, 3 or 4,

wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl and R⁸-(CH₂)_n-O- groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO- and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-;

5

R² is selected from the group R^{2a} consisting of

H, HO-, halogen, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸-(CH₂)_n-O- with n = 0, 1, 2, 3 or 4, and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O- with m = 0, 1 or 2 and o = 0, 1 or 2,

wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸-(CH₂)_n-O- and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO-, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O-, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-;

R³ is selected from the group R^{3a} consisting of

H, halogen, NC-, C₁₋₄-alkyl- and C₃₋₆-cycloalkyl-, wherein the above mentioned C₁₋₄-alkyl- and C₃₋₆-cycloalkyl-groups may optionally be substituted with 1 to 9 substituents independently selected from the group consisting of halogen, NC-, HO-, C₁₋₃-alkyl- and C₁₋₃-alkyl-O-;

R⁴, R⁵ are selected independently of each other from the group R^{4a}/R^{5a} consisting of

H, halogen, NC-, HO-, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O-, heterocyclyl-O-, heterocyclyl, heteroaryl, R⁷-CH₂-O- and R⁷-(CH₂)₂-O-,

wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O-, heterocyclyl-O-, heterocyclyl, heteroaryl, R⁷-CH₂-O- and R⁷-(CH₂)₂-O-groups, may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, optionally with 1 to 5 halogen atoms, substituted C₁₋₂-alkyl-, and optionally with 1 to 5 halogen atoms substituted C₁₋₂-alkyl-O-;

R⁶ is selected from the group R^{6a} consisting of

H, NC-, C₁₋₆-alkyl-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl- and C₃₋₈-cycloalkyl-O-

wherein above mentioned C₁₋₆-alkyl- groups may optionally be substituted with 1-3 halogen atoms;

R^7 is selected from the group R^{7a} consisting of
 H, carbocyclyl, heterocyclyl and heteroaryl,
 wherein above mentioned carbocyclyl, heterocyclyl and heteroaryl-
 groups may optionally be substituted with 1 to 4 substituents
 independently selected from the group consisting of HO-, optionally
 with 1 to 3 halogen atoms substituted C_{1-4} -alkyl-, optionally with 1 to 3
 halogen atoms substituted C_{1-4} -alkyl-O- and halogen;

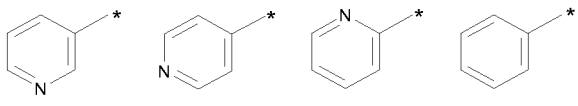
R^8 is selected from the group R^{8a} consisting of
 C_{3-6} -cycloalkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl-, phenyl and pyridyl,
 wherein above mentioned C_{3-6} -cycloalkyl, heterocyclyl, heterocyclyl-
 C_{1-3} -alkyl-, phenyl and pyridyl groups may optionally be substituted
 with 1 to 5 substituents independently selected from the group
 consisting of HO-, fluorine and optionally with 1 to 7 halogen atoms
 substituted C_{1-3} -alkyl-;

the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates
 5 thereof, the hydrates thereof and the salts thereof.

Unless otherwise stated, the groups, residues, and substituents, particularly R^1 , R^2 ,
 R^3 , $R^{4/5}$, R^6 , R^7 , R^8 and A are defined as above and hereinafter. If residues,
 substituents, or groups occur several times in a compound they may have the same
 10 or different meanings. Some preferred meanings of groups and substituents of the
 compounds according to the invention will be given hereinafter.

In a further embodiment of the present invention

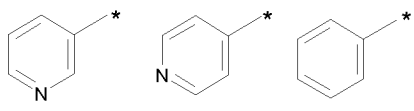
A is selected from the group A^b consisting of



wherein above mentioned phenyl- and pyridinyl- groups are
 substituted with R^1 and R^2 .

In a further embodiment of the present invention

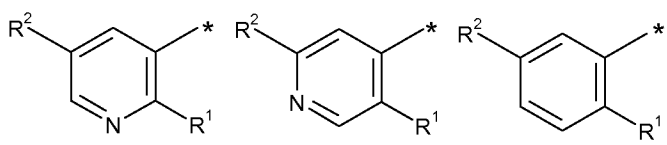
A is selected from the group A^c consisting of



wherein above mentioned phenyl- and pyridinyl- groups are substituted with R¹ and R².

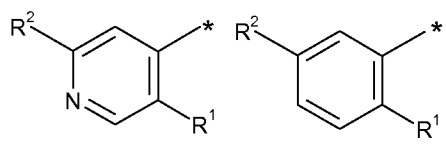
In a further embodiment of the present invention

A is selected from the group A^d consisting of



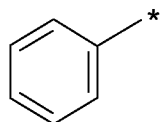
5 In a further embodiment of the present invention

A is selected from the group A^e consisting of



In a further embodiment of the present invention

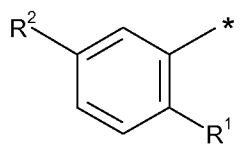
A is selected from the group A^f consisting of



wherein above mentioned phenyl-group is substituted with R¹ and R².

In a further embodiment of the present invention

A is selected from the group A^g consisting of



In a further embodiment of the present invention

R^1 is selected from the group R^{1b} consisting of
 H, halogen, C_{1-6} -alkyl- and C_{3-6} -cycloalkyl
 wherein above mentioned C_{1-6} -alkyl- and C_{3-6} -cycloalkyl-groups may
 optionally be substituted with 1 to 5 substituents independently
 selected from the group consisting of halogen, HO- and optionally
 with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-.

In a further embodiment of the present invention

R^1 is selected from the group R^{1c} consisting of
 H, H_3C- , F_3C- , F_2HC- , FH_2C- , fluorine, chlorine and bromine.

In a further embodiment of the present invention

R^1 is selected from the group R^{1c1} consisting of
 H_3C- , fluorine and chlorine.

5

In a further embodiment of the present invention

R^1 is selected from the group R^{1d} consisting of
 H, fluorine and chlorine.

In a further embodiment of the present invention

R^2 is selected from the group R^{2a1} consisting of
 HO-, C_{1-6} -alkyl-, C_{1-6} -alkyl-O-, C_{3-6} -cycloalkyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl-,
 heterocyclyl, heterocyclyl- C_{1-3} -alkyl-, phenyl, heteroaryl, $R^8-(CH_2)_n-O-$
 with $n = 0, 1, 2, 3$ or 4 , and $R^8-(CH_2)_m-(CH)(CH_3)-(CH_2)_o-O-$ with $m = 0, 1$
 or 2 and $o = 0, 1$ or 2
 wherein above mentioned C_{1-6} -alkyl- and C_{1-6} -alkyl-O-groups are
 substituted with 1 to 5 substituents independently selected from the
 group consisting of HO-, and optionally with 1 to 7 fluorine atoms
 substituted C_{1-3} -alkyl-O-,
 and
 wherein above mentioned C_{1-6} -alkyl- and C_{1-6} -alkyl-O-groups may
 optionally be substituted with 1 to 5 substituents independently
 selected from the group consisting of halogen, and optionally with 1 to

7 fluorine atoms substituted C₁₋₃-alkyl-,
 and
 wherein above mentioned C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-,
 heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸-(CH₂)_n-O-
 and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O-groups may optionally be
 substituted with 1 to 5 substituents independently selected from the
 group consisting of halogen, HO-, optionally with 1 to 7 fluorine atoms
 substituted C₁₋₃-alkyl-O-, and optionally with 1 to 7 fluorine atoms
 substituted C₁₋₃-alkyl-.

In a further embodiment of the present invention

R² is selected from the group R^{2b} consisting of

H, HO-, C₁₋₄-alkyl-, C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl, heterocyclyl,
 heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸-(CH₂)_n-O- with n = 0, 1, 2
 or 3 and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O- with m = 0 or 1 and o = 0 or 1
 wherein above mentioned C₁₋₄-alkyl-, C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl,
 heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, R⁸-(CH₂)_n-O- and and R⁸-
 (CH₂)_m-(CH)(CH₃)-(CH₂)_o-O-groups may optionally be substituted with
 1 to 3 substituents independently selected from the group consisting
 of halogen, HO-, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-
 alkyl-O-, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-
 alkyl-.

In a further embodiment of the present invention

R² is selected from the group R^{2b1} consisting of

HO-, C₁₋₄-alkyl-, C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-,
 heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸-(CH₂)_n-O-
 with n = 0, 1, 2 or 3 and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O- with m = 0 or 1
 and o = 0 or 1

wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O- groups are
 substituted with 1 to 3 substituents independently selected from the
 group consisting of HO- and optionally with 1 to 7 fluorine atoms
 substituted C₁₋₃-alkyl-O-,

and

wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O-groups may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halogen, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-,

and

wherein above mentioned C₃₋₆-cycloalkyl-, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, R⁸-(CH₂)_n-O- and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O-groups may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halogen, HO-, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O-, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-.

In a further embodiment of the present invention

R² is selected from the group R^{2c} consisting of

H, HO-, C₁₋₄-alkyl-, C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl, heterocyclyl, R⁸-(CH₂)_n-O- with n = 0, 1, 2, or 3, and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O- with m = 0 or 1 and o = 0 or 1

wherein above mentioned C₁₋₄-alkyl-, C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl, heterocyclyl, R⁸-(CH₂)_n-O- and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO-, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O-, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-.

In a further embodiment of the present invention

R² is selected from the group R^{2c1} consisting of

HO-, C₁₋₄-alkyl-, C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, R⁸-(CH₂)_n-O- with n = 0, 1, 2, or 3, and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O- with m = 0 or 1 and o = 0 or 1

wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O-groups are substituted with 1 to 5, preferably 1 to 3, substituents independently

selected from the group consisting of HO-, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O-,
 and
 wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O-groups may optionally be substituted with 1 to 5, preferably 1 to 3, substituents independently selected from the group consisting of halogen, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-,
 and
 wherein above mentioned C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, R⁸-(CH₂)_n-O- and and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O-groups may optionally be substituted with 1 to 5, preferably 1 to 3, substituents independently selected from the group consisting of halogen, HO-, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O-, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-.

In a further embodiment of the present invention

R² is selected from the group R^{2d} consisting of

H, HO-, C₁₋₄-alkyl-, C₁₋₄-alkyl-O-, a saturated 6 membered monocyclic heterocycle containing one heteroatom selected from N or O, R⁸-(CH₂)_n-O- with n = 0, 1 or 2, and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O- with m = 0 or 1 and o = 0 or 1

wherein above mentioned C₁₋₄-alkyl-, C₁₋₄-alkyl-O-, saturated 6 membered monocyclic heterocycle containing one heteroatom selected from N or O, R⁸-(CH₂)_n-O- and and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O- groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO-, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O-, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-.

In a further embodiment of the present invention

R² is selected from the group R^{2d1} consisting of

HO-, C₁₋₄-alkyl-, C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, a saturated 5 or 6 membered monocyclic heterocycle containing one heteroatom selected from N or O, R⁸-(CH₂)_n-O- with n = 0, 1 or 2, and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O- with m = 0 or 1 and o = 0 or 1

wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O-groups are substituted with 1 to 5, preferably 1 to 3, substituents independently selected from the group consisting of HO-, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O-,

and

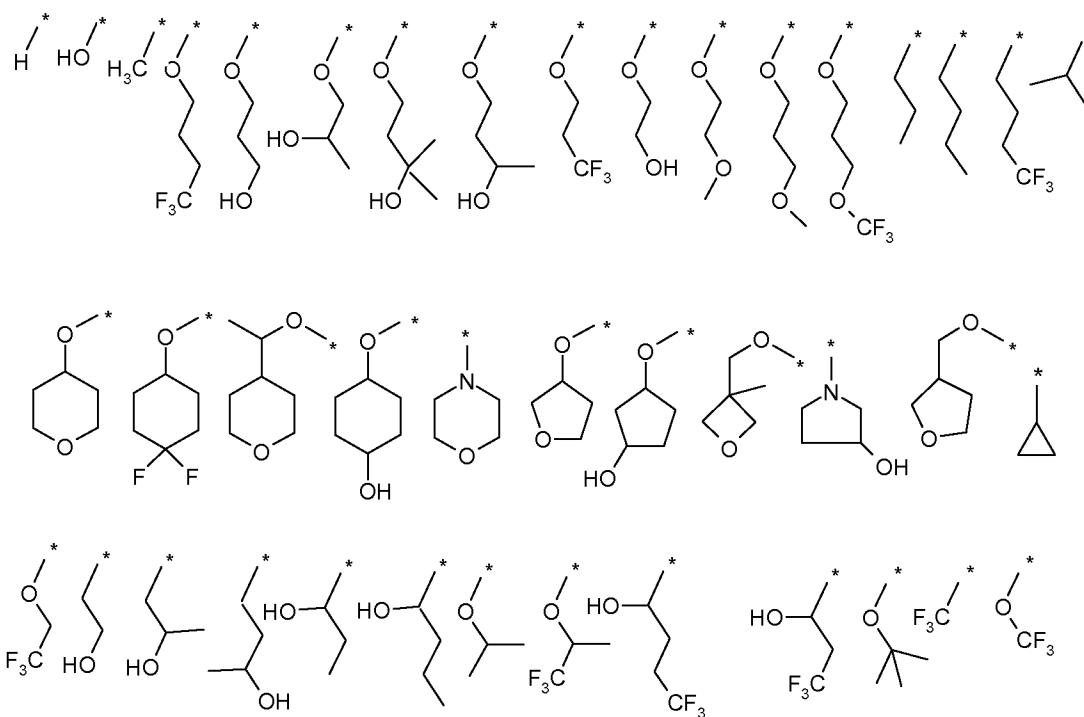
wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O-groups may optionally be substituted with 1 to 5, preferably 1 to 3, substituents independently selected from the group consisting of halogen, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-,

and

wherein above mentioned C₃₋₆-cycloalkyl-, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, saturated 5 or 6 membered monocyclic heterocycle containing one heteroatom selected from N or O, R⁸-(CH₂)_n-O- and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O- groups may optionally be substituted with 1 to 5, preferably 1 to 3, substituents independently selected from the group consisting of halogen, HO-, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O-, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-.

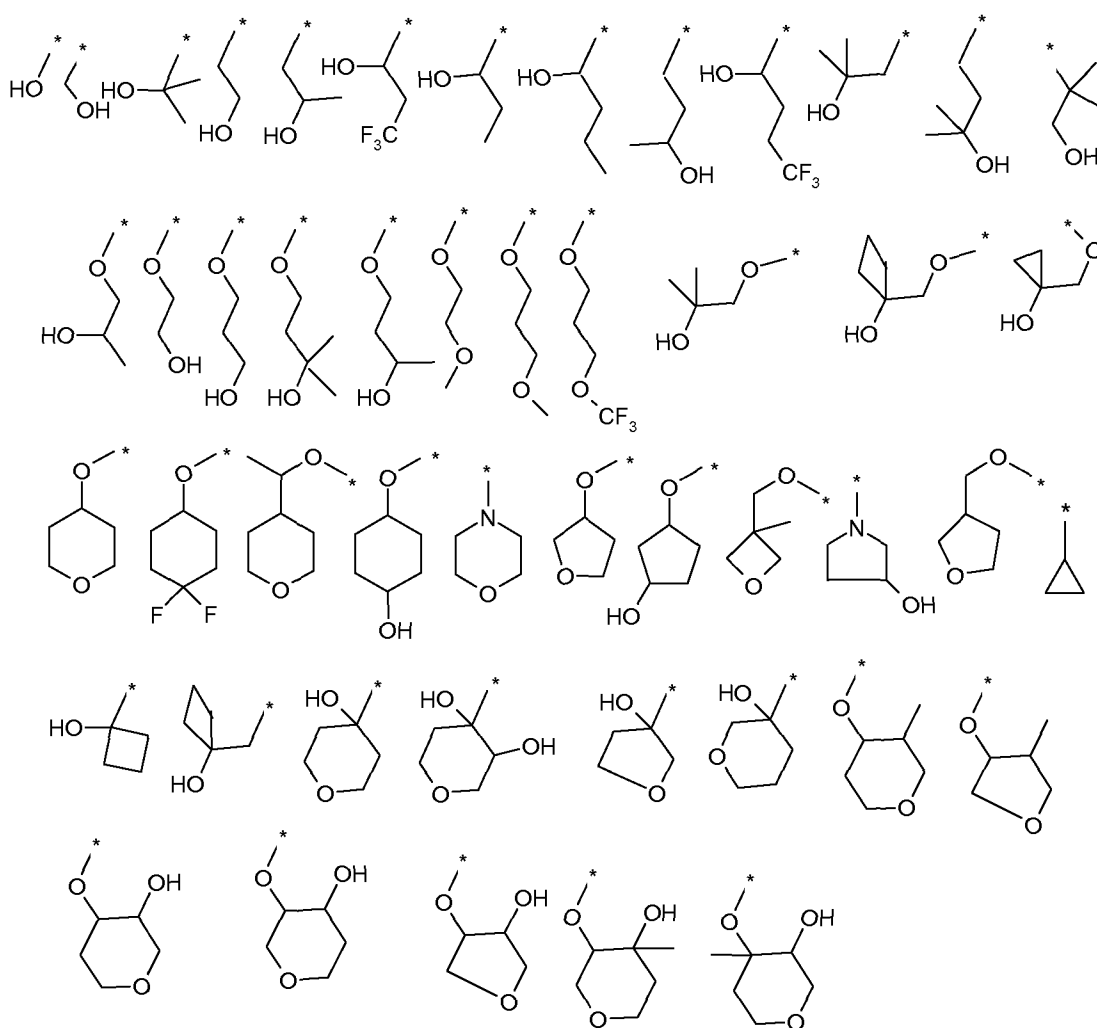
In a further embodiment of the present invention

R² is selected from the group R^{2e} consisting of



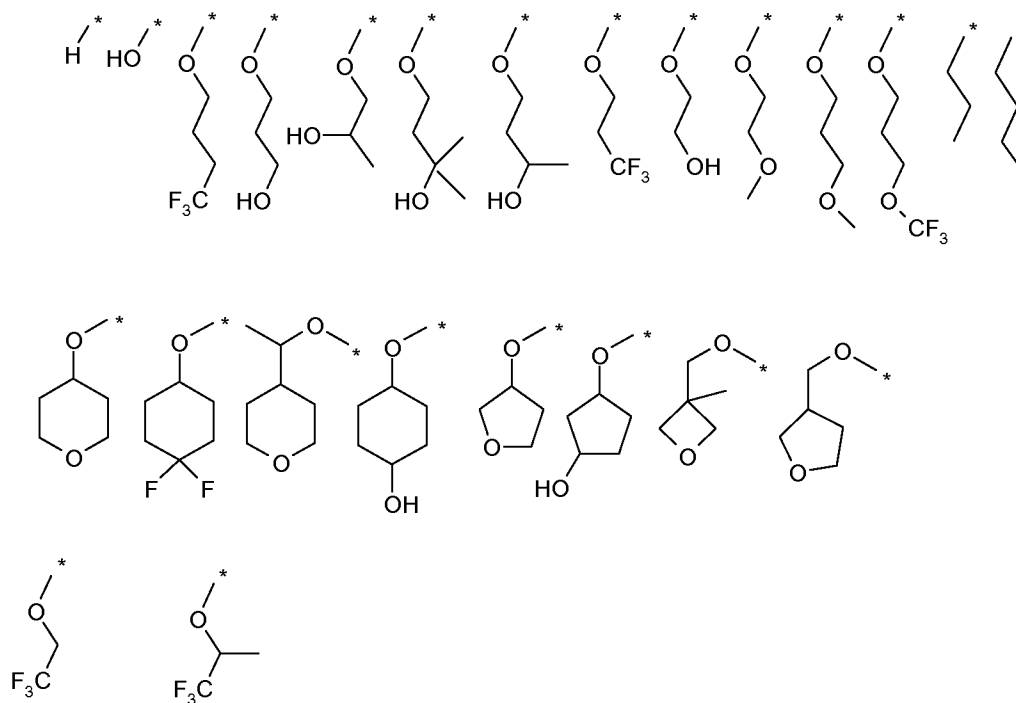
In a further embodiment of the present invention

R^2 is selected from the group R^{2e1} consisting of



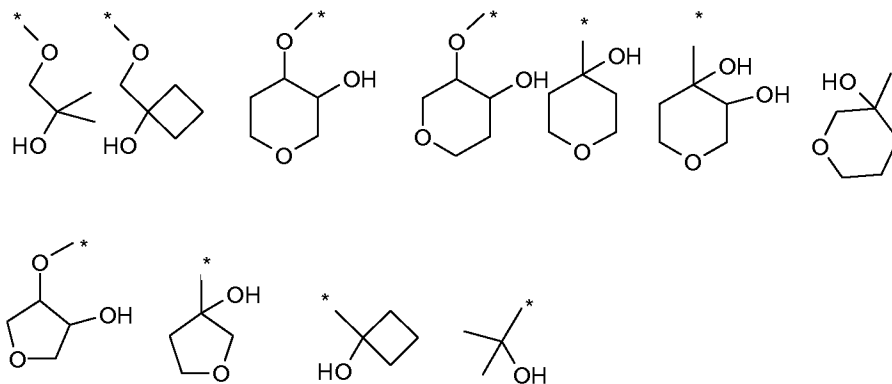
In a further embodiment of the present invention

R^2 is selected from the group R^{2f} consisting of



In a further embodiment of the present invention

R^2 is selected from the group R^{2f1} consisting of



In a further embodiment of the present invention

R^3 is selected from the group R^{3a1} consisting of

C_{3-6} -cycloalkyl-,

wherein the above mentioned C_{3-6} -cycloalkyl-group may optionally be substituted with 1 to 9 substituents independently selected from the group consisting of halogen, NC-, HO-, C_{1-3} -alkyl- and C_{1-3} -alkyl-O-.

In a further embodiment of the present invention

R^3 is selected from the group R^{3b} consisting of
H, C_{1-3} -alkyl-, cyclobutyl- and cyclopropyl-,
wherein the above mentioned C_{1-3} -alkyl-, cyclobutyl- and cyclopropyl-
groups may optionally be substituted with 1 to 7 substituents
independently selected from the group consisting of halogen, C_{1-3} -
alkyl-O-, NC- and HO-.

In a further embodiment of the present invention

R^3 is selected from the group R^{3c} consisting of
H, and H_3C - and cyclopropyl-,
wherein the above mentioned H_3C - and cyclopropyl-groups may
optionally be substituted with 1 to 3 fluorine atoms.

In a further embodiment of the present invention

R^3 is selected from the group R^{3d} consisting of
H and H_3C -,
wherein the above mentioned H_3C -group may optionally be
substituted with 1 to 3 fluorine atoms.

5

In a further embodiment of the present invention

R^3 is selected from the group R^{3e} consisting of
H.

In a further embodiment of the present invention

R^3 is selected from the group R^{3f} consisting of
 H_3C -,
wherein the above mentioned H_3C -group may optionally be
substituted with 1 to 3 fluorine atoms.

10 In a further embodiment of the present invention

R^3 is selected from the group R^{3g} consisting of
cyclopropyl-,
wherein the above mentioned cyclopropyl-group may optionally be

substituted with 1 to 7 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl-O-, NC- and HO-.

In a further embodiment of the present invention

R⁴, R⁵ are selected independently of each other from the group R^{4b}/R^{5b} consisting of

H, halogen, HO-, H₃C-, F₃C-, H₃C-O-, F₂HC-O-, FH₂C-O-, F₃C-O-, C₁₋₄-alkyl-O-, R⁷-CH₂-O- and R⁷-(CH₂)₂-O-,

wherein above mentioned C₁₋₄-alkyl-O-, R⁷-CH₂-O- and R⁷-(CH₂)₂-O- groups, may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, optionally with 1 to 5 halogen atoms substituted C₁₋₂-alkyl-, and optionally with 1 to 5 halogen atoms substituted C₁₋₂-alkyl-O-.

In a further embodiment of the present invention

R⁴, R⁵ are selected independently of each other from the group R^{4c}/R^{5c} consisting of

H, fluorine, chlorine, bromine, HO-, H₃C-, F₃C-, H₃C-O-, F₃C-O- and R⁷-CH₂-O-.

5

In a further embodiment of the present invention

R⁴, R⁵ are selected from the group R^{4d}/R^{5d} consisting of
H-.

In a further embodiment of the present invention

R⁶ is selected from the group R^{6b} consisting of

H, C₁₋₄-alkyl- and cyclopropyl-,

wherein above mentioned C₁₋₄-alkyl-group may optionally be substituted with 1-9 fluorine and/or chlorine atoms.

10 In a further embodiment of the present invention

R⁶ is selected from the group R^{6c} consisting of
H and C₁₋₂-alkyl-,

wherein above mentioned C₁₋₂-alkyl- group may optionally be substituted with 1-5 fluorine and/or chlorine atoms.

In a further embodiment of the present invention

R⁶ is selected from the group R^{6d} consisting of
H, H₃C-, FH₂C-, F₂HC- and F₃C-.

In a further embodiment of the present invention

R⁶ is selected from the group R^{6e} consisting of
H₃C-, FH₂C-, F₂HC- and F₃C-.

5

In a further embodiment of the present invention

R⁶ is selected from the group R^{6f} consisting of
H₃C-.

In a further embodiment of the present invention

R⁷ is selected from the group R^{7b} consisting of
H, phenyl, heteroaryl, cycloalkyl and heterocyclyl
wherein above mentioned phenyl, heteroaryl, cycloalkyl and
heterocyclyl-groups may optionally be substituted with 1 to 4
substituents independently selected from the group consisting of
halogen, and optionally with 1 to 3 halogen atoms substituted C₁₋₃-
alkyl-O-.

10 In a further embodiment of the present invention

R⁷ is selected from the group R^{7c} consisting of
H and phenyl,
wherein above mentioned phenyl group may optionally be substituted
with 1 to 4 substituents independently selected from the group
consisting of halogen and optionally with 1 to 3 halogen atoms
substituted C₁₋₃-alkyl-O-.

In a further embodiment of the present invention

R⁷ is selected from the group R^{7d} consisting of
H-.

In a further embodiment of the present invention

R⁸ is selected from the group R^{8b} consisting of
C₃₋₆-cycloalkyl, heterocyclyl and heterocyclyl-C₁₋₃-alkyl-,
wherein above mentioned C₃₋₆-cycloalkyl, heterocyclyl and
heterocyclyl-C₁₋₃-alkyl-groups may optionally be substituted with 1 to 5
substituents independently selected from the group consisting of HO-,
fluorine and optionally with 1 to 7 halogen atoms substituted C₁₋₃-alkyl-.

In a further embodiment of the present invention

R⁸ is selected from the group R^{8c} consisting of
C₃₋₆-cycloalkyl and heterocyclyl,
wherein above mentioned C₃₋₆-cycloalkyl and heterocyclyl-groups
may optionally be substituted with 1 to 5 substituents independently
selected from the group consisting of HO-, fluorine and optionally with
1 to 7 halogen atoms substituted C₁₋₃-alkyl-.

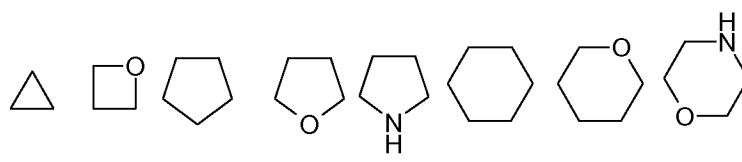
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In a further embodiment of the present invention

R⁸ is selected from the group R^{8c1} consisting of
C₃₋₆-cycloalkyl and a saturated 4 to 6 membered monocyclic heterocycle
containing one or two heteroatoms selected from N or O,
wherein above mentioned C₃₋₆-cycloalkyl and heterocyclyl-groups
may optionally be substituted with 1 to 5 substituents independently
selected from the group consisting of HO-, fluorine and optionally with
1 to 7 halogen atoms substituted C₁₋₃-alkyl-.

In a further embodiment of the present invention

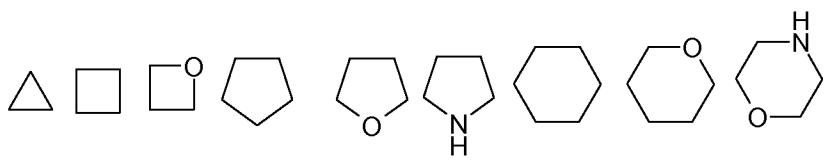
R⁸ is selected from the group R^{8d} consisting of



wherein above mentioned groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO-, fluorine and optionally with 1 to 5 halogen atoms substituted C₁₋₃-alkyl-.

In a further embodiment of the present invention

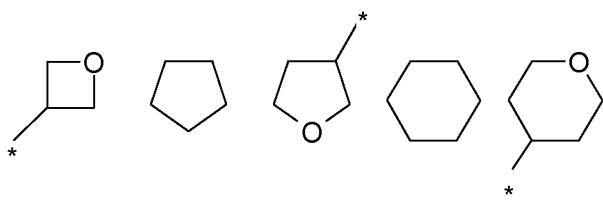
R⁸ is selected from the group R^{8d1} consisting of



wherein above mentioned groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO-, fluorine and optionally with 1 to 5 halogen atoms substituted C₁₋₃-alkyl-.

In a further embodiment of the present invention

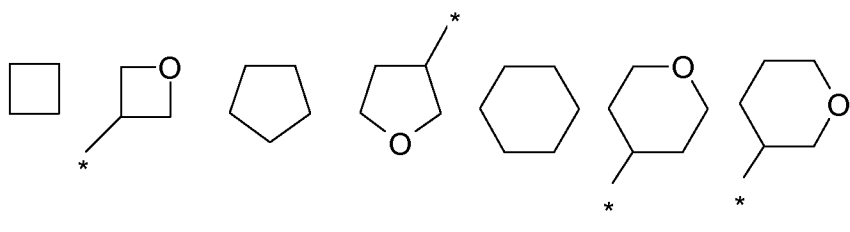
R⁸ is selected from the group R^{8e} consisting of



wherein above mentioned groups may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of HO-, fluorine and optionally with 1 to 3 halogen atoms substituted C₁₋₃-alkyl-.

In a further embodiment of the present invention

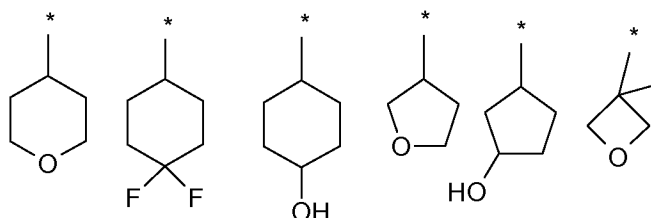
R⁸ is selected from the group R^{8e1} consisting of



wherein above mentioned groups may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of HO-, fluorine and optionally with 1 to 3 halogen atoms substituted C₁₋₃-alkyl-.

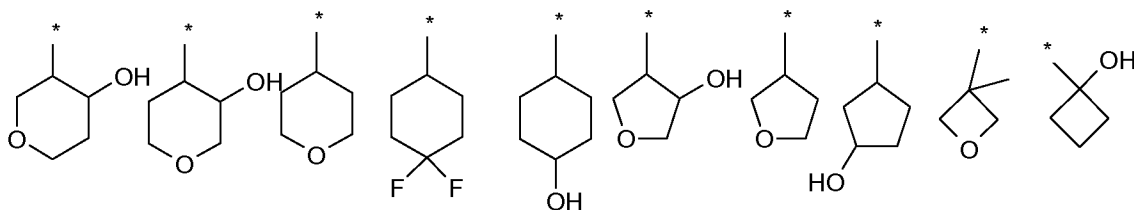
In a further embodiment of the present invention

R^8 is selected from the group R^{8f} consisting of



In a further embodiment of the present invention

R^8 is selected from the group R^{8f1} consisting of



5

Each R^{1x} , R^{2x} , R^{3x} , $R^{4x/5x}$, R^{6x} , R^{7x} , R^{8x} and A^x represents a characterized, individual embodiment for the corresponding substituent as described above. Thus given the above definitions, preferred individual embodiments of the first aspect of the invention are fully characterized by the term (R^{1x} , R^{2x} , R^{3x} , $R^{4x/5x}$, R^{6x} , R^{7x} , R^{8x} and A^x),
 10 wherein for each index x an individual figure is given that ranges from "a" to the highest letter given above. All individual embodiments described by the term in parentheses with full permutation of the indices x, referring to the definitions above, shall be comprised by the present invention.

The following Table 1 shows, exemplarily and in the order of increasing preference from the first line to the last line, such embodiments E-1 to E-37 of the invention that are considered preferred. This means that embodiment E-37, represented by the entries in the last row of Table 1, is the most preferred embodiment.

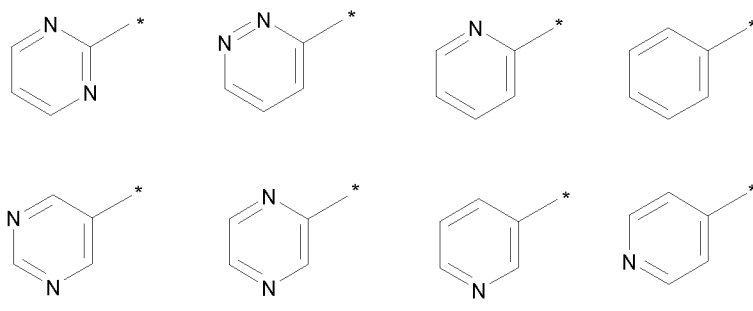
5 Table 1: Preferred embodiments E-1 to E-37 of the invention

	A^x	R^{1x}	R^{2x}	R^{3x}	R^{4x}/R^{5x}	R^{6x}	R^{7x}	R^{8x}
E-1	A^b	R^{1b}	R^{2a}	R^{3b}	R^{4b}/R^{5b}	R^{6b}	R^{7b}	R^{8a}
E-2	A^c	R^{1b}	R^{2a}	R^{3b}	R^{4b}/R^{5b}	R^{6b}	R^{7b}	R^{8a}
E-3	A^c	R^{1c}	R^{2b}	R^{3b}	R^{4b}/R^{5b}	R^{6b}	R^{7c}	R^{8b}
E-4	A^c	R^{1c}	R^{2b}	R^{3c}	R^{4c}/R^{5c}	R^{6b}	R^{7c}	R^{8c}
E-5	A^c	R^{1c}	R^{2b}	R^{3c}	R^{4c}/R^{5c}	R^{6b}	R^{7d}	R^{8c}
E-6	A^c	R^{1c}	R^{2c}	R^{3c}	R^{4c}/R^{5c}	R^{6c}	R^{7c}	R^{8c}
E-7	A^c	R^{1c}	R^{2d}	R^{3c}	R^{4c}/R^{5c}	R^{6c}	R^{7c}	R^{8d}
E-8	A^d	R^{1c}	R^{2d}	R^{3d}	R^{4d}/R^{5d}	R^{6c}	-	R^{8d}
E-9	A^e	R^{1d}	R^{2d}	R^{3d}	R^{4d}/R^{5d}	R^{6e}	-	R^{8f}
E-10	A^e	R^{1d}	R^{2e}	R^{3d}	R^{4d}/R^{5d}	R^{6f}	-	-
E-11	A^f	R^{1d}	R^{2d}	R^{3d}	R^{4d}/R^{5d}	R^{6e}	-	R^{8f}
E-12	A^f	R^{1d}	R^{2e}	R^{3d}	R^{4d}/R^{5d}	R^{6f}	-	-
E-13	A^f	R^{1d}	R^{2f}	R^{3d}	R^{4d}/R^{5d}	R^{6e}	-	-
E-14	A^f	R^{1d}	R^{2f}	R^{3d}	R^{4d}/R^{5d}	R^{6f}	-	-
E-15	A^a	R^{1a}	R^{2a}	R^{3a1}	R^{4a}/R^{5a}	R^{6a}	R^{7a}	R^{8a}
E-16	A^b	R^{1c}	R^{2c}	R^{3a1}	R^{4b}/R^{5b}	R^{6b}	R^{7b}	R^{8b}
E-17	A^d	R^{1c}	R^{2d}	R^{3a1}	R^{4c}/R^{5c}	R^{6b}	-	R^{8c}
E-18	A^e	R^{1c}	R^{2d}	R^{3a1}	R^{4d}/R^{5d}	R^{6b}	-	R^{8d}
E-19	A^g	R^{1c}	R^{2d}	R^{3a1}	R^{4d}/R^{5d}	R^{6b}	-	R^{8f}

E-20	A ^d	R ^{1c}	R ^{2d}	R ^{3g}	R ^{4d} /R ^{5d}	R ^{6b}	-	R ^{8c1}
E-21	A ^e	R ^{1c}	R ^{2d}	R ^{3g}	R ^{4d} /R ^{5d}	R ^{6b}	-	R ^{8d}
E-22	A ^g	R ^{1c}	R ^{2d}	R ^{3g}	R ^{4d} /R ^{5d}	R ^{6b}	-	R ^{8f}
E-23	A ^a	R ^{1a}	R ^{2a1}	R ^{3a}	R ^{4a} /R ^{5a}	R ^{6a}	R ^{7a}	R ^{8a}
E-24	A ^b	R ^{1b}	R ^{2b1}	R ^{3a}	R ^{4c} /R ^{5c}	R ^{6b}	R ^{7c}	R ^{8b}
E-25	A ^c	R ^{1c}	R ^{2b1}	R ^{3a}	R ^{4d} /R ^{5d}	R ^{6c}	-	R ^{8c1}
E-26	A ^d	R ^{1c}	R ^{2c1}	R ^{3b}	R ^{4d} /R ^{5d}	R ^{6c}	-	R ^{8d1}
E-27	A ^d	R ^{1c}	R ^{2d1}	R ^{3c}	R ^{4d} /R ^{5d}	R ^{6d}	-	R ^{8e1}
E-28	A ^d	R ^{1c1}	R ^{2c1}	R ^{3c}	R ^{4d} /R ^{5d}	R ^{6d}	-	R ^{8f1}
E-29	A ^e	R ^{1c}	R ^{2d1}	R ^{3b}	R ^{4d} /R ^{5d}	R ^{6c}	-	R ^{8c1}
E-30	A ^e	R ^{1c}	R ^{2d1}	R ^{3b}	R ^{4d} /R ^{5d}	R ^{6d}	-	R ^{8d1}
E-31	A ^e	R ^{1c1}	R ^{2e1}	R ^{3c}	R ^{4d} /R ^{5d}	R ^{6e}	-	-
E-32	A ^f	R ^{1c}	R ^{2d1}	R ^{3b}	R ^{4d} /R ^{5d}	R ^{6c}	-	R ^{8e1}
E-33	A ^f	R ^{1c1}	R ^{2e1}	R ^{3c}	R ^{4d} /R ^{5d}	R ^{6e}	-	-
E-34	A ^f	R ^{1c1}	R ^{2f1}	R ^{3c}	R ^{4d} /R ^{5d}	R ^{6f}	-	-
E-35	A ^g	R ^{1c}	R ^{2c1}	R ^{3b}	R ^{4d} /R ^{5d}	R ^{6c}	-	R ^{8e1}
E-36	A ^g	R ^{1c}	R ^{2d1}	R ^{3c}	R ^{4d} /R ^{5d}	R ^{6e}	-	R ^{8f1}
E-37	A ^g	R ^{1c1}	R ^{2f1}	R ^{3c}	R ^{4d} /R ^{5d}	R ^{6f}	-	-

Accordingly, for example E-15 covers compounds of formula I,
wherein

A is selected from the group A^a consisting of



wherein above mentioned phenyl-, pyridinyl-, pyrimidinyl-, pyridazinyl- and pyrazinyl- groups are substituted with R^1 and R^2 ;

R^1 is selected from the group R^{1a} consisting of
H, halogen, NC-, C_{1-6} -alkyl-, C_{1-6} -alkyl-O-, C_{3-6} -cycloalkyl and $R^8-(CH_2)_n$ -O- with $n = 0, 1, 2, 3$ or 4 ,

wherein above mentioned C_{1-6} -alkyl-, C_{1-6} -alkyl-O-, C_{3-6} -cycloalkyl and $R^8-(CH_2)_n$ -O- groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO- and optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-;

R^2 is selected from the group R^{2a} consisting of
H, HO-, halogen, C_{1-6} -alkyl-, C_{1-6} -alkyl-O-, C_{3-6} -cycloalkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl-, phenyl, heteroaryl, $R^8-(CH_2)_n$ -O- with $n = 0, 1, 2, 3$ or 4 , and $R^8-(CH_2)_m-(CH)(CH_3)-(CH_2)_o$ -O- with $m = 0, 1$ or 2 and $o = 0, 1$ or 2 ,

wherein above mentioned C_{1-6} -alkyl-, C_{1-6} -alkyl-O-, C_{3-6} -cycloalkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl-, phenyl, heteroaryl, $R^8-(CH_2)_n$ -O- and $R^8-(CH_2)_m-(CH)(CH_3)-(CH_2)_o$ -O-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO-, optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-O-, and optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-;

R^3 is selected from the group R^{3a1} consisting of
 C_{3-6} -cycloalkyl-,

wherein the above mentioned C₃₋₆-cycloalkyl-group may optionally be substituted with 1 to 9 substituents independently selected from the group consisting of halogen, NC-, HO-, C₁₋₃-alkyl- and C₁₋₃-alkyl-O-;

R⁴, R⁵ are selected independently of each other from the group R^{4a}/R^{5a} consisting of

H, halogen, NC-, HO-, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O-, heterocyclyl-O-, heterocyclyl, heteroaryl, R⁷-CH₂-O- and R⁷-(CH₂)₂-O-,

wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O-, heterocyclyl-O-, heterocyclyl, heteroaryl, R⁷-CH₂-O- and R⁷-(CH₂)₂-O-groups, may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, optionally with 1 to 5 halogen atoms, substituted C₁₋₂-alkyl-, and optionally with 1 to 5 halogen atoms substituted C₁₋₂-alkyl-O-;

R⁶ is selected from the group R^{6a} consisting of

H, NC-, C₁₋₆-alkyl-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl- and C₃₋₈-cycloalkyl-O-

wherein above mentioned C₁₋₆-alkyl- groups may optionally be substituted with 1-3 halogen atoms;

R⁷ is selected from the group R^{7a} consisting of

H, carbocyclyl, heterocyclyl and heteroaryl,

wherein above mentioned carbocyclyl, heterocyclyl and heteroaryl-groups may optionally be substituted with 1 to 4 substituents independently selected from the group consisting of HO-, optionally with 1 to 3 halogen atoms substituted C₁₋₄-alkyl-, optionally with 1 to 3 halogen atoms substituted C₁₋₄-alkyl-O- and halogen;

R⁸ is selected from the group R^{8a} consisting of

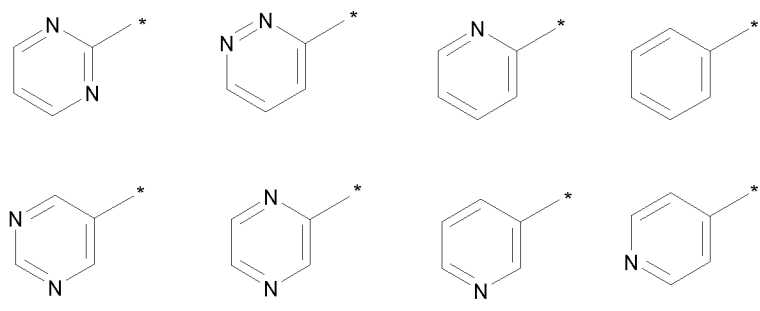
C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl,

wherein above mentioned C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO-, fluorine and optionally with 1 to 7 halogen atoms substituted C₁₋₃-alkyl-;

the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the salts thereof.

- 5 Accordingly, for example E-23 covers compounds of formula I, wherein

A is selected from the group A^a consisting of



wherein above mentioned phenyl-, pyridinyl-, pyrimidinyl-, pyridazinyl- and pyrazinyl- groups are substituted with R¹ and R²;

R¹ is selected from the group R^{1a} consisting of

H, halogen, NC-, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl and R⁸-(CH₂)_n-O- with n = 0, 1, 2, 3 or 4,

wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl and R⁸-(CH₂)_n-O- groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO- and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-;

R² is selected from the group R^{2a1} consisting of

HO-, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸-(CH₂)_n-O-

with $n = 0, 1, 2, 3$ or 4 , and $R^8-(CH_2)_m-(CH)(CH_3)-(CH_2)_o-O-$ with $m = 0, 1$ or 2 and $o = 0, 1$ or 2

wherein above mentioned C_{1-6} -alkyl- and C_{1-6} -alkyl-O-groups are substituted with 1 to 5 substituents independently selected from the group consisting of HO-, and optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-O-,

and

wherein above mentioned C_{1-6} -alkyl- and C_{1-6} -alkyl-O-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, and optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-,

and

wherein above mentioned C_{3-6} -cycloalkyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl-, heterocyclyl, heterocyclyl- C_{1-3} -alkyl-, phenyl, heteroaryl, $R^8-(CH_2)_n-O-$ and $R^8-(CH_2)_m-(CH)(CH_3)-(CH_2)_o-O-$ groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO-, optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-O-, and optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-;

R^3 is selected from the group R^{3a} consisting of

H, halogen, NC-, C_{1-4} -alkyl- and C_{3-6} -cycloalkyl-,

wherein the above mentioned C_{1-4} -alkyl- and C_{3-6} -cycloalkyl-groups may optionally be substituted with 1 to 9 substituents independently selected from the group consisting of halogen, NC-, HO-, C_{1-3} -alkyl- and C_{1-3} -alkyl-O-;

R^4, R^5 are selected independently of each other from the group R^{4a}/R^{5a} consisting of

H, halogen, NC-, HO-, C_{1-6} -alkyl-, C_{1-6} -alkyl-O-, C_{3-8} -cycloalkyl-, C_{3-8} -cycloalkyl- C_{1-3} -alkyl-, C_{3-8} -cycloalkyl-O-, heterocyclyl-O-, heterocyclyl, heteroaryl, R^7-CH_2-O- and $R^7-(CH_2)_2-O-$,

wherein above mentioned C_{1-6} -alkyl-, C_{1-6} -alkyl-O-, C_{3-8} -cycloalkyl-,

C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O-, heterocyclyl-O-, heterocyclyl, heteroaryl, R⁷-CH₂-O- and R⁷-(CH₂)₂-O-groups, may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, optionally with 1 to 5 halogen atoms, substituted C₁₋₂-alkyl-, and optionally with 1 to 5 halogen atoms substituted C₁₋₂-alkyl-O-;

R⁶ is selected from the group R^{6a} consisting of
H, NC-, C₁₋₆-alkyl-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl- and C₃₋₈-cycloalkyl-O-

wherein above mentioned C₁₋₆-alkyl- groups may optionally be substituted with 1-3 halogen atoms;

R⁷ is selected from the group R^{7a} consisting of
H, carbocyclyl, heterocyclyl and heteroaryl,
wherein above mentioned carbocyclyl, heterocyclyl and heteroaryl-groups may optionally be substituted with 1 to 4 substituents independently selected from the group consisting of HO-, optionally with 1 to 3 halogen atoms substituted C₁₋₄-alkyl-, optionally with 1 to 3 halogen atoms substituted C₁₋₄-alkyl-O- and halogen;

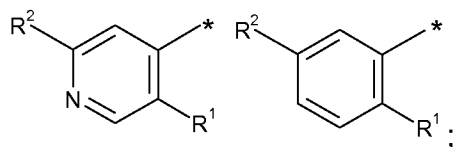
R⁸ is selected from the group R^{8a} consisting of
C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl,
wherein above mentioned C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO-, fluorine and optionally with 1 to 7 halogen atoms substituted C₁₋₃-alkyl-;

- 5 the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the salts thereof.

Accordingly, for example E-29 covers compounds of formula I,

wherein

A is selected from the group A^e consisting of



R¹ is selected from the group R^{1c} consisting of
H, H₃C-, F₃C-, F₂HC-, FH₂C-, fluorine, chlorine and bromine:

R² is selected from the group R^{2d1} consisting of
HO-, C₁₋₄-alkyl-, C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-,
a saturated 5 or 6 membered monocyclic heterocycle containing one
heteroatom selected from N or O, R⁸-(CH₂)_n-O- with n = 0, 1 or 2, and
R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O- with m = 0 or 1 and o = 0 or 1
wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O-groups are
substituted with 1 to 5, preferably 1 to 3, substituents independently
selected from the group consisting of HO-, and optionally with 1 to 7
fluorine atoms substituted C₁₋₃-alkyl-O-,
and
wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O-groups may
optionally be substituted with 1 to 5, preferably 1 to 3, substituents
independently selected from the group consisting of halogen, and
optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-,
and
wherein above mentioned C₃₋₆-cycloalkyl-, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-,
saturated 5 or 6 membered monocyclic heterocycle containing one
heteroatom selected from N or O, R⁸-(CH₂)_n-O- and and R⁸-(CH₂)_m-
(CH)(CH₃)-(CH₂)_o-O- groups may optionally be substituted with 1 to 5,
preferably 1 to 3, substituents independently selected from the group
consisting of halogen, HO-, optionally with 1 to 7 fluorine atoms
substituted C₁₋₃-alkyl-O-, and optionally with 1 to 7 fluorine atoms
substituted C₁₋₃-alkyl-;

R^3 is selected from the group R^{3b} consisting of
 H, C_{1-3} -alkyl-, cyclobutyl- and cyclopropyl-,
 wherein the above mentioned C_{1-3} -alkyl-, cyclobutyl-, and cyclopropyl-
 groups may optionally be substituted with 1 to 7 substituents
 independently selected from the group consisting of halogen, C_{1-3} -
 alkyl-O-, NC- and HO-;

R^4, R^5 are selected from the group R^{4d}/R^{5d} consisting of
 H;

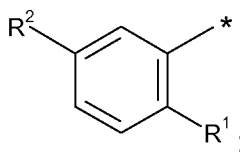
R^6 is selected from the group R^{6c} consisting of
 H and C_{1-2} -alkyl-,
 wherein above mentioned C_{1-2} -alkyl- group may optionally be
 substituted with 1-5 fluorine and/or chlorine atoms;

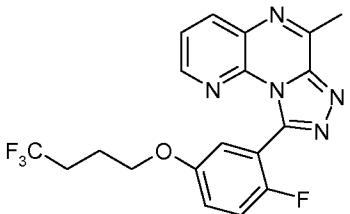
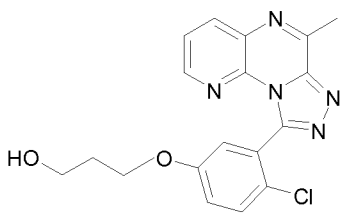
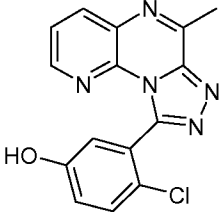
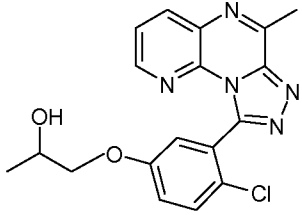
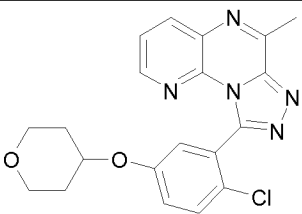
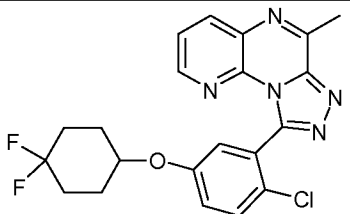
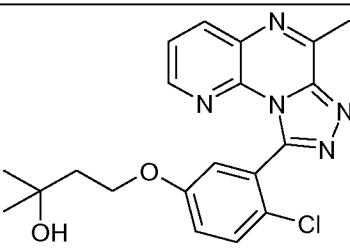
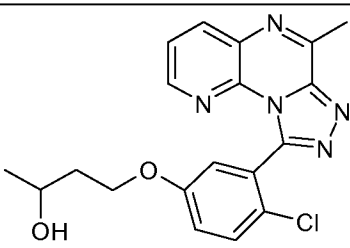
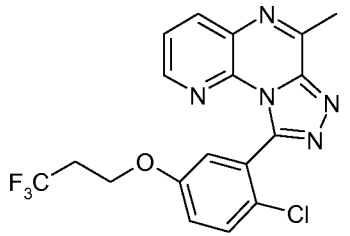
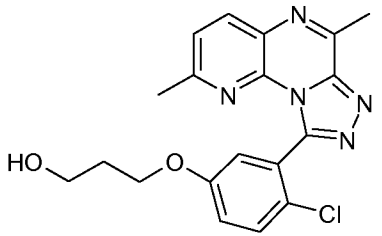
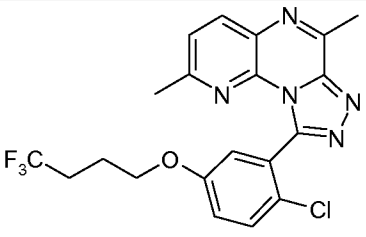
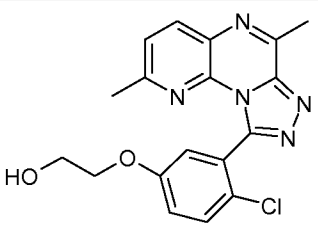
R^8 is selected from the group R^{8c1} consisting of
 C_{3-6} -cycloalkyl and a saturated 4 to 6 membered monocyclic heterocycle
 containing one or two heteroatoms selected from N or O,
 wherein above mentioned C_{3-6} -cycloalkyl and heterocyclyl-groups
 may optionally be substituted with 1 to 5 substituents independently
 selected from the group consisting of HO-, fluorine and optionally with
 1 to 7 halogen atoms substituted C_{1-3} -alkyl-;

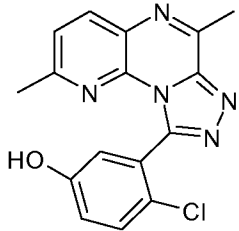
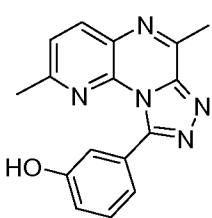
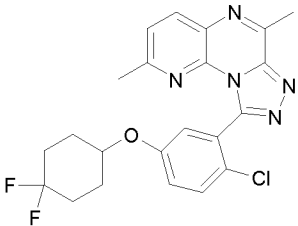
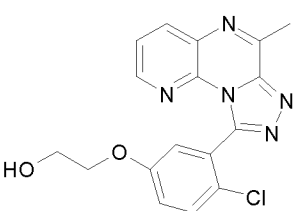
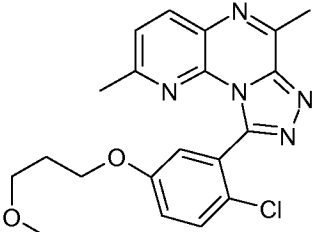
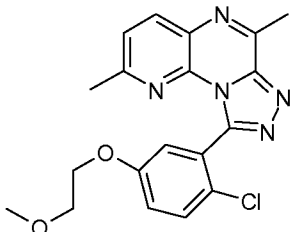
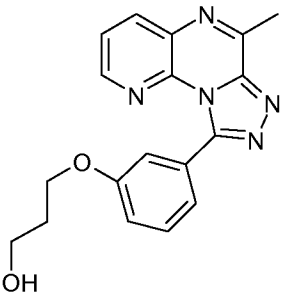
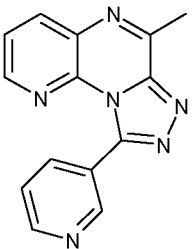
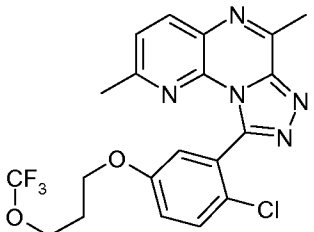
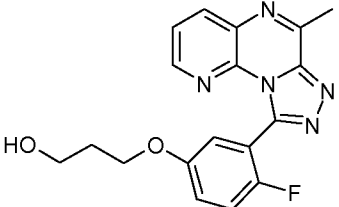
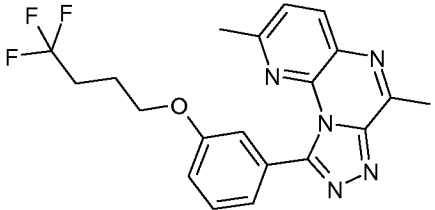
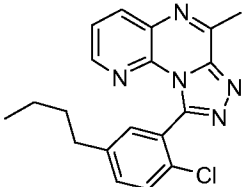
- 5 the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the salts thereof.

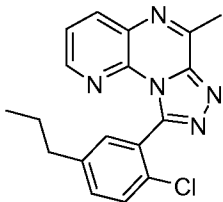
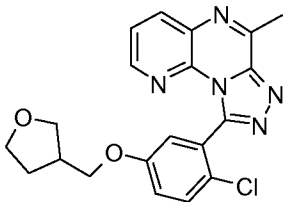
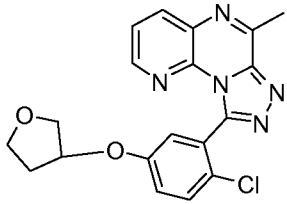
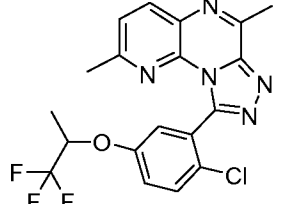
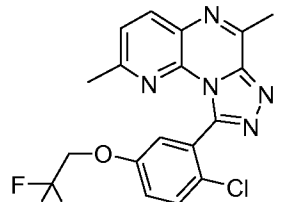
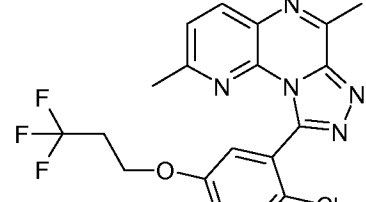
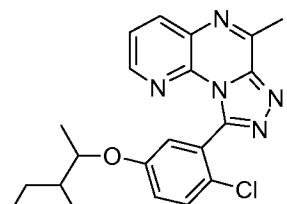
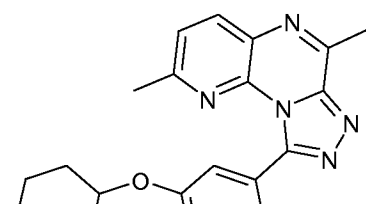
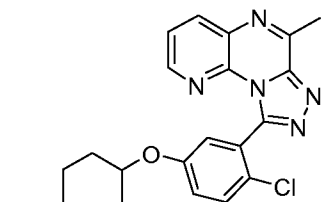
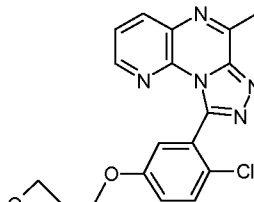
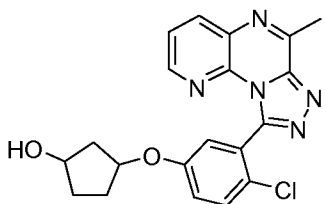
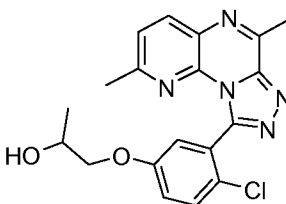
Accordingly, for example E-37 covers compounds of formula I,
 wherein

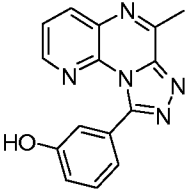
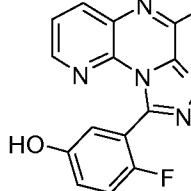
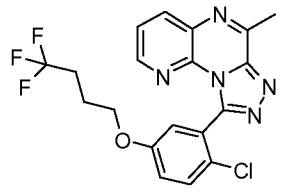
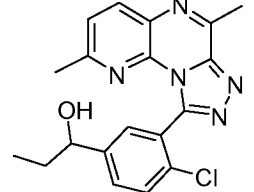
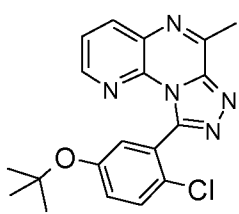
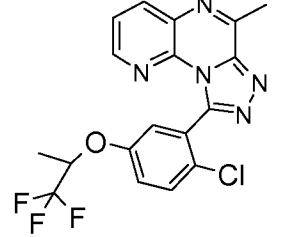
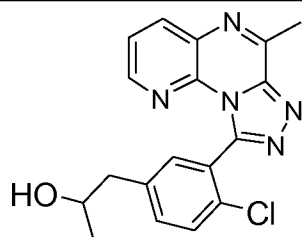
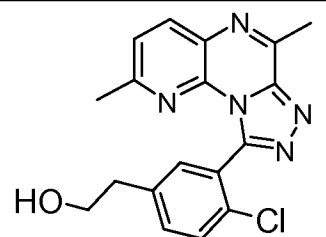
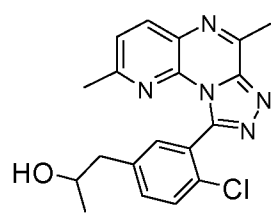
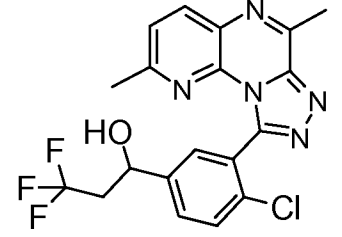
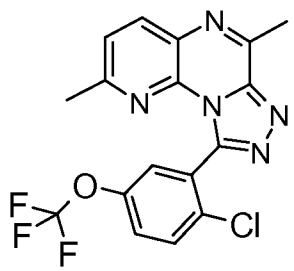
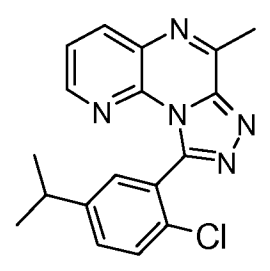
A is selected from the group A^g consisting of

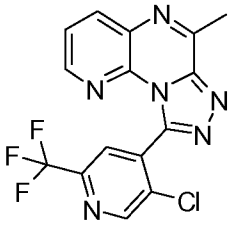
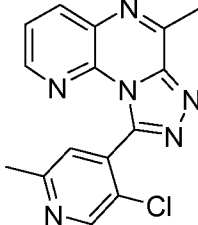
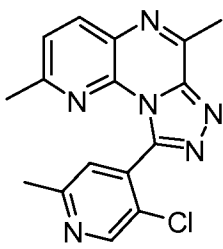
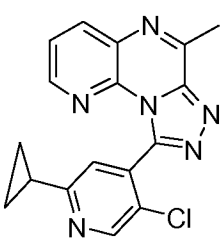
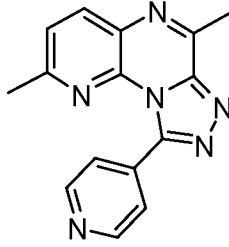
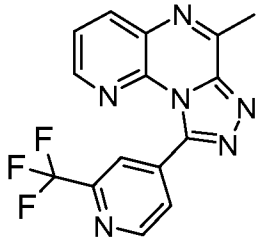
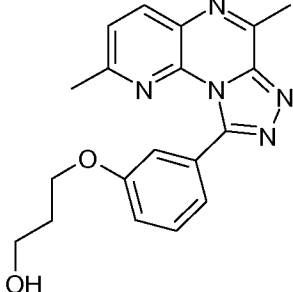
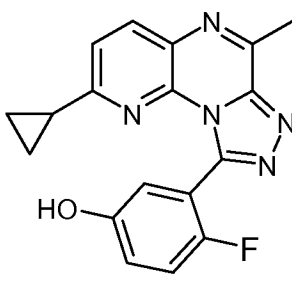
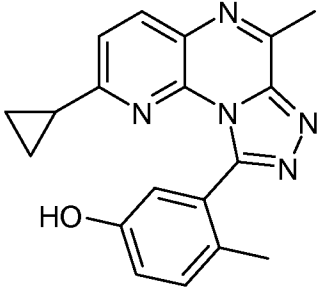
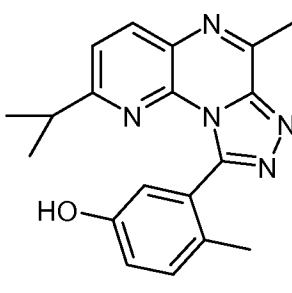


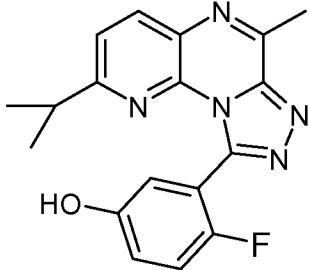
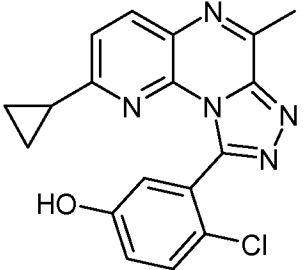
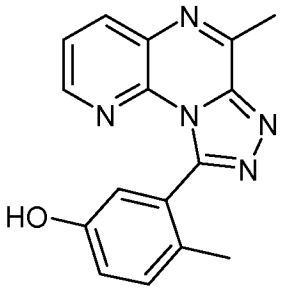
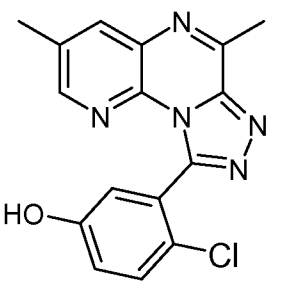
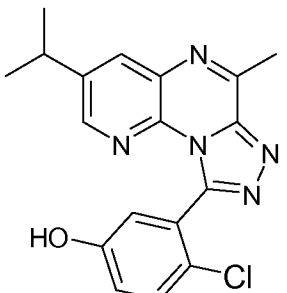
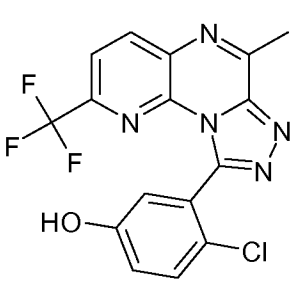
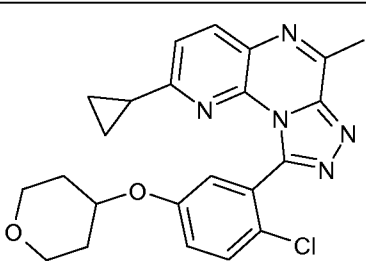
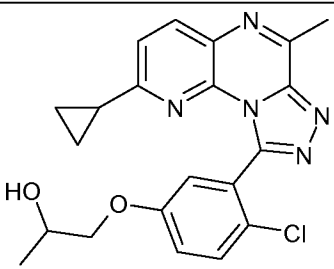
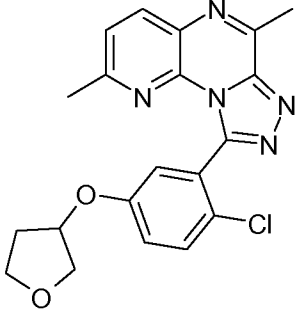
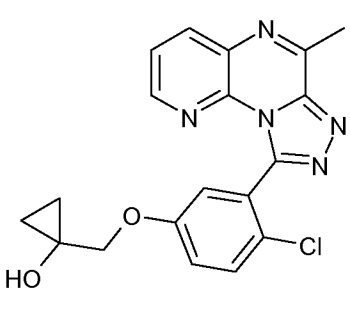
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XI		XII	

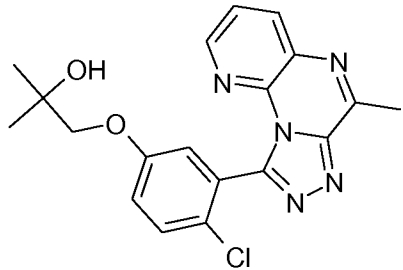
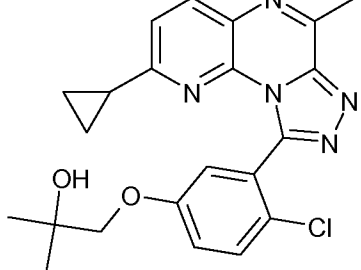
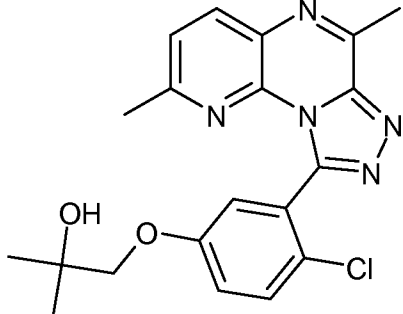
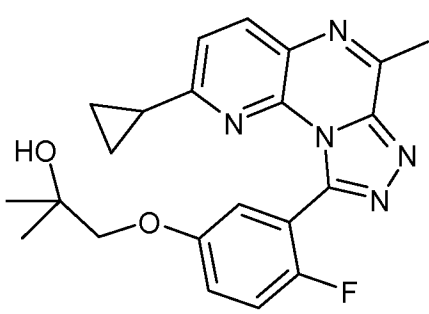
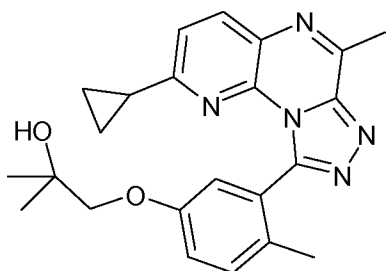
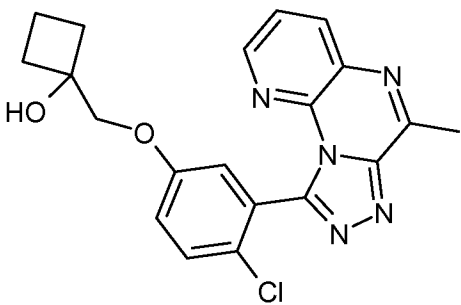
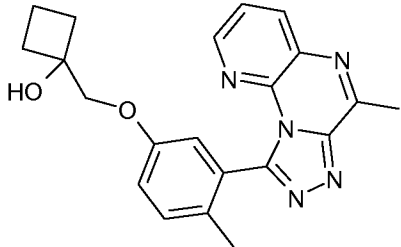
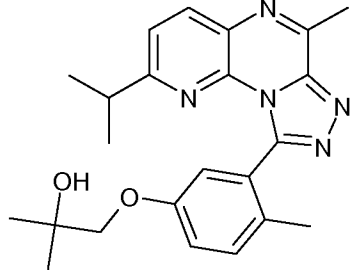
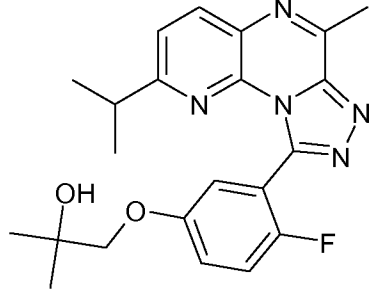
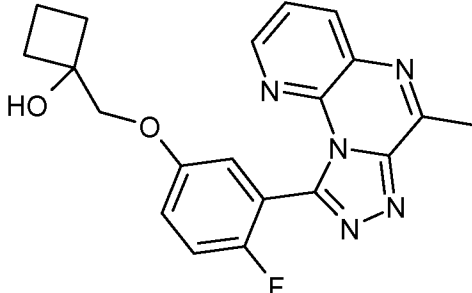
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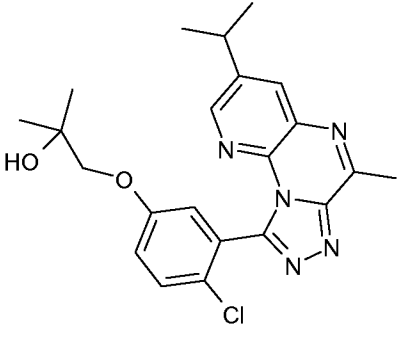
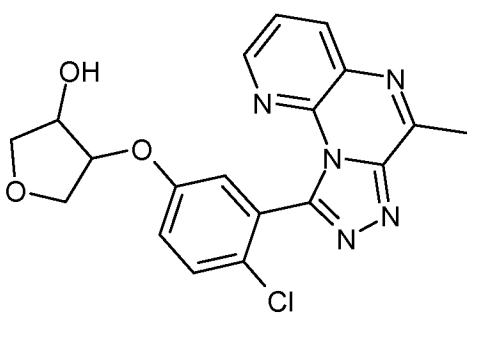
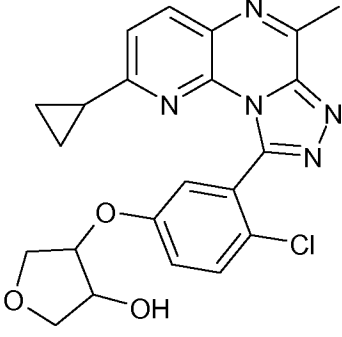
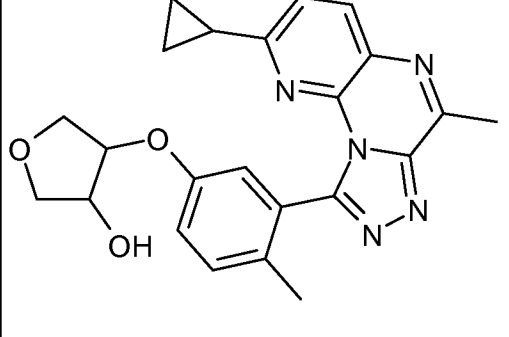
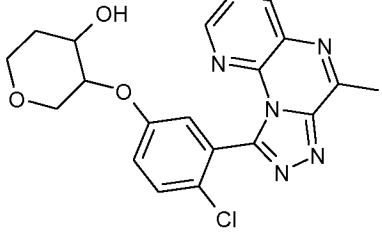
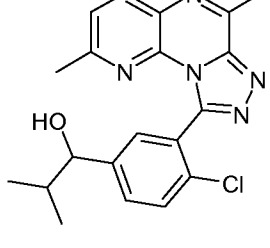
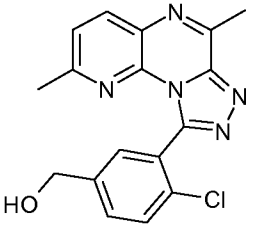
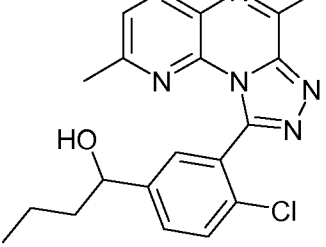
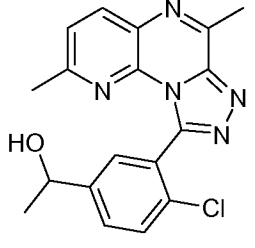
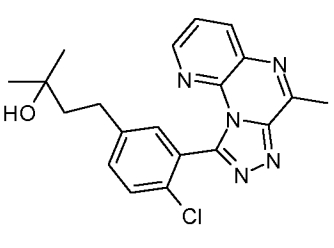
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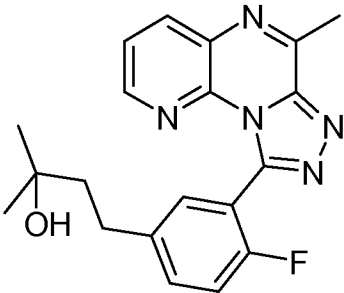
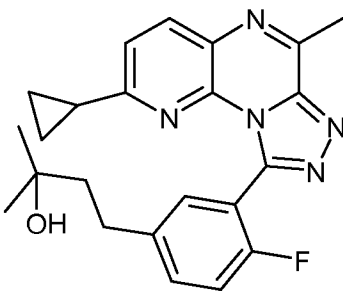
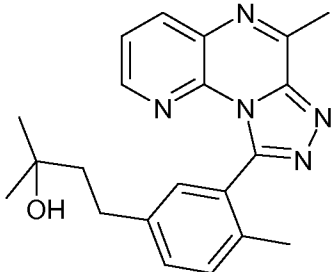
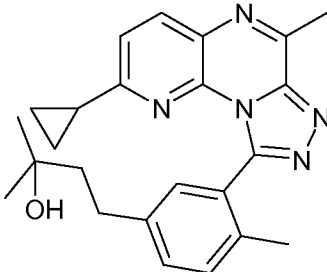
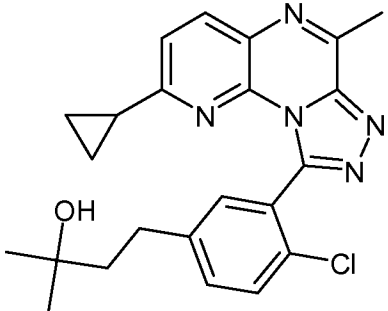
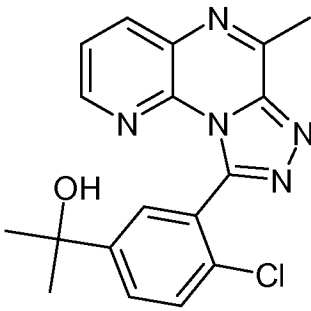
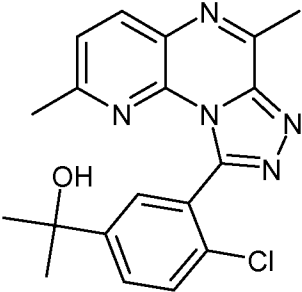
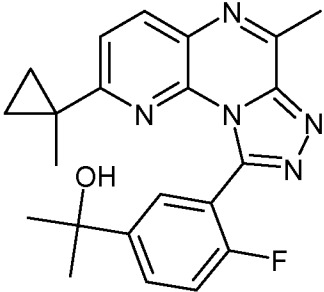
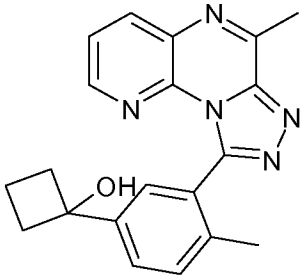
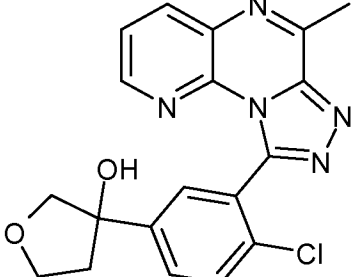
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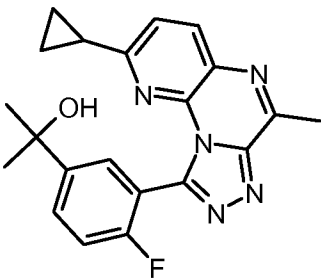
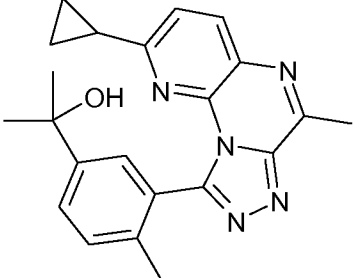
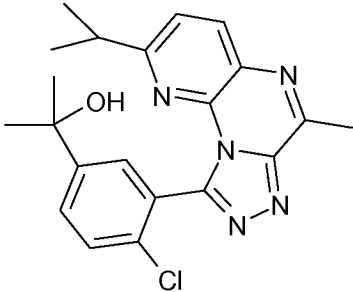
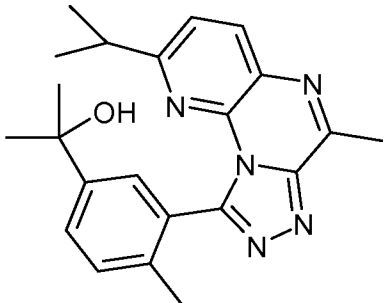
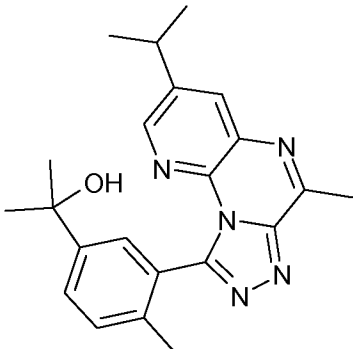
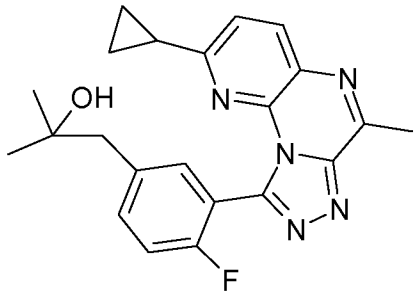
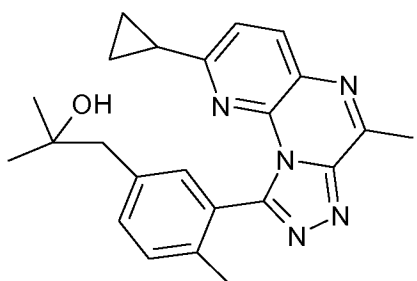
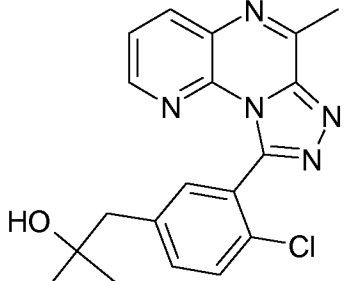
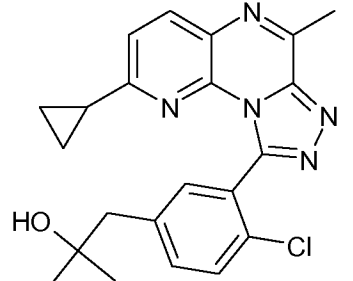
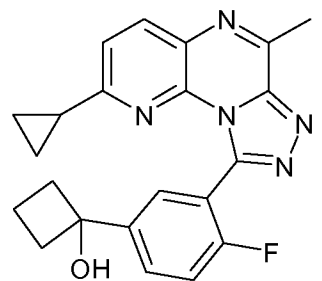
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LV		LVI	
LVII		LVIII	

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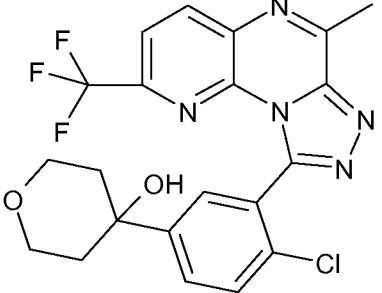
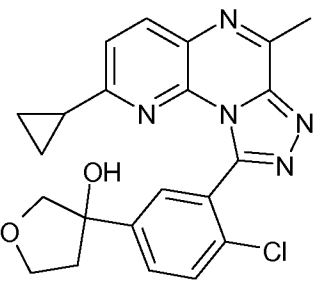
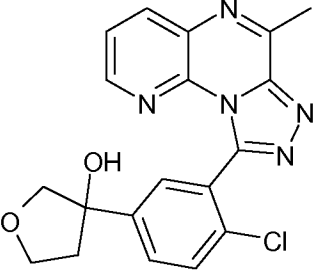
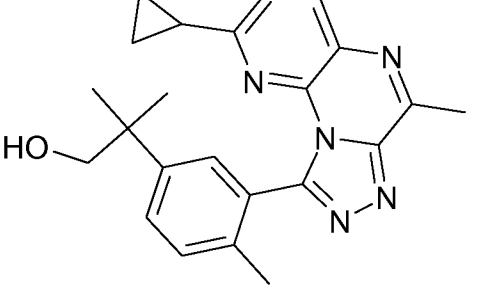
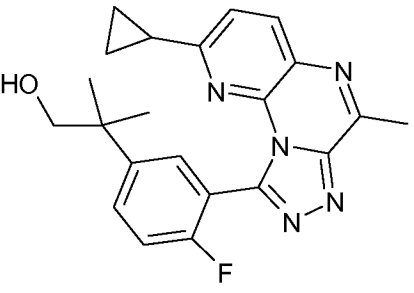
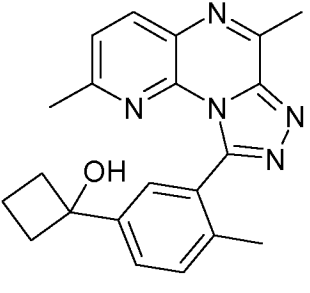
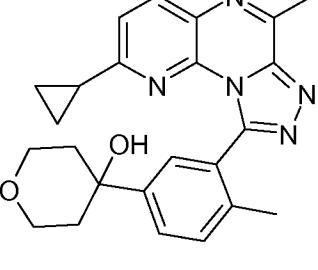
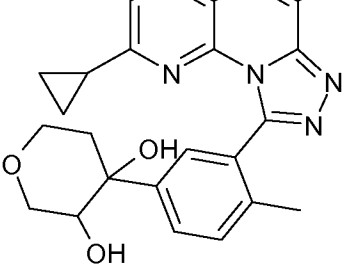
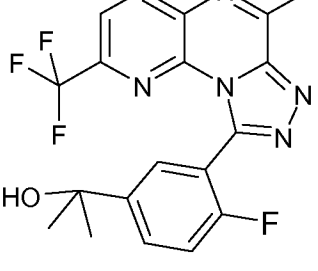
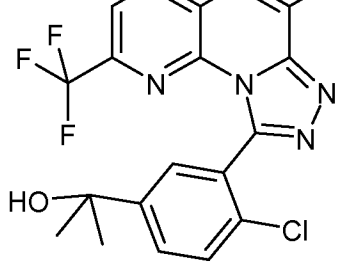
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LXXV		LXXVI	
LXXVII		LXXVIII	

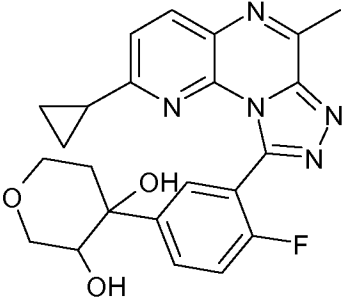
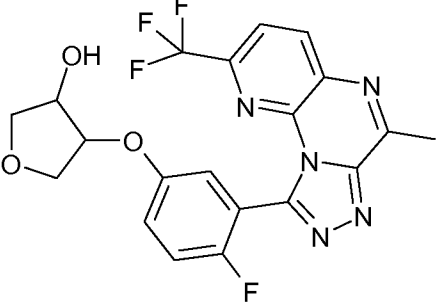
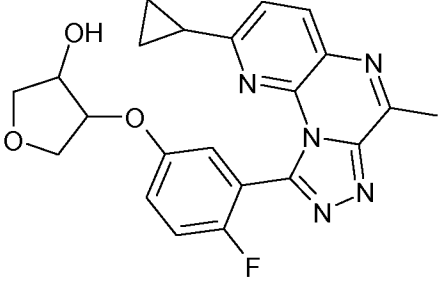
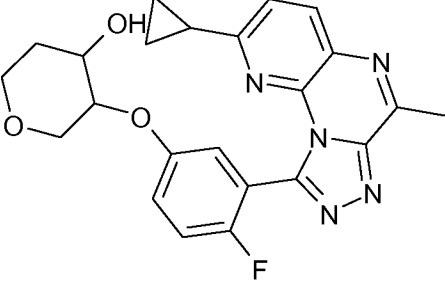
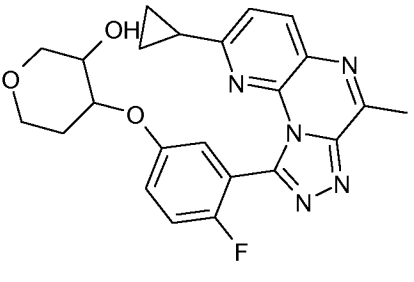
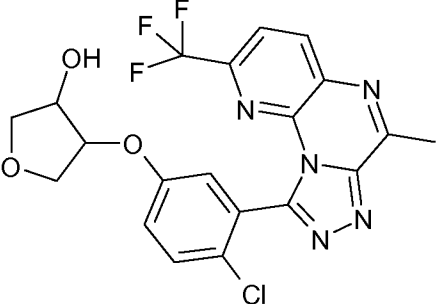
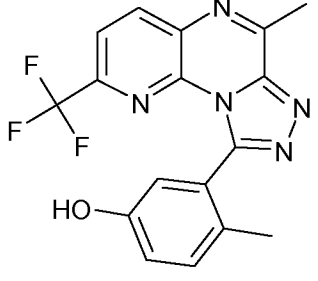
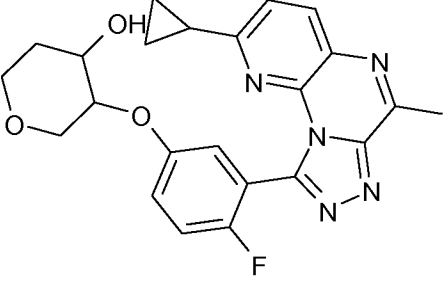
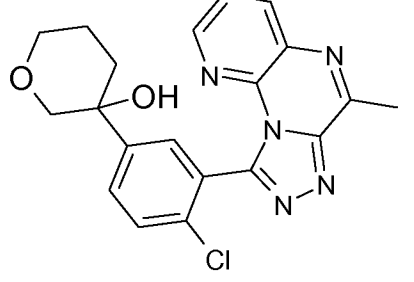
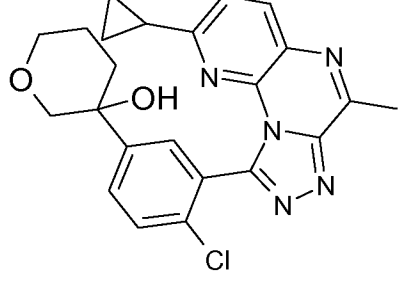
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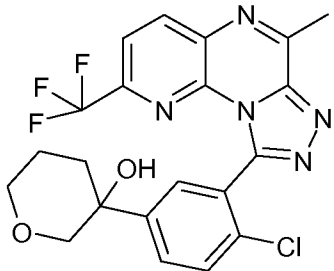
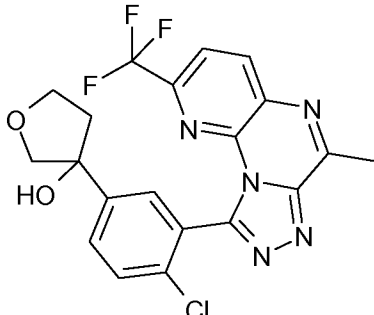
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XCVII		XCVIII	

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CI		CII	
CIII		CIV	
CV		CVI	
CVII		CVIII	

CIX		CX	
CXI		CXII	
CXIII		CXIV	
CXV		CXVI	
CXVII		CXVIII	

CXIX		CXX	
CXXI		CXXII	
CXXIII		CXXIV	
CXXV		CXXVI	
CXXVII		CXXVIII	

CXXIX		CXXX	
CXXXI		CXXXII	
CXXXIII		CXXXIV	
CXXXV		CXXXVI	
CXXXVII		CXXXVIII	

CXXXIX		CXL	
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the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the salts thereof.

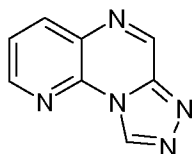
- 5 Some terms used above and hereinafter to describe the compounds according to the invention will now be defined more closely.

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As

- 10 used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to. In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example C₁₋₆-alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general, for groups comprising two or more
- 15 subgroups, the last named subgroup is the radical attachment point, for example, the substituent "aryl-C₁₋₃-alkyl-" means an aryl group which is bound to a C₁₋₃-alkyl group, the latter of which is bound to the core molecule or to the group to which the substituent is attached.

Within the present invention, the term "core molecule" is defined by the following

20 structure:



In general, the attachment site of a given residue to another group shall be variable, i.e. any capable atom, bearing hydrogens to be replaced, within this residue may be the linking spot to the group being attached, unless otherwise indicated.

- 5 In case a compound of the present invention is depicted in form of a chemical name and as a formula in case of any discrepancy the formula shall prevail.

An asterisk may be used in sub-formulas to indicate the bond which is connected to the core molecule or to the substituent to which it is bound as defined.

10

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers etc...) and racemates thereof as well as mixtures in different proportions of the separate
15 enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates including solvates of the free compounds or solvates of a salt of the compound.

20

The phrase "pharmaceutically acceptable" or "physiologically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive
25 toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

30

As used herein, "pharmaceutically acceptable salts" or "physiologically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound
is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts or physiologically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. For example, such salts

include salts from ammonia, L-arginine, betaine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine (2,2'-iminobis(ethanol)), diethylamine, 2-(diethylamino)-ethanol, 2-aminoethanol, ethylenediamine, N-ethyl-glucamine, hydrabamine, 1H-imidazole, lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-

5 morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, sodium hydroxide, triethanolamine (2,2',2''-nitrilotris(ethanol)), tromethamine, zinc hydroxide, acetic acid, 2,2-dichloro-acetic acid, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 2,5-dihydroxybenzoic acid, 4-acetamido-benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, carbonic acid,

10 cinnamic acid, citric acid, cyclamic acid, decanoic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, ethylenediaminetetraacetic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, D-glucoheptonic acid, D-gluconic acid, D-glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycine, glycolic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, DL-lactic acid, lactobionic acid, lauric acid, lysine, maleic acid, (-)-L-malic acid, malonic acid, DL-mandelic acid, methanesulfonic acid, galactaric acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, octanoic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid

15 (embonic acid), phosphoric acid, propionic acid, (-)-L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like

20 (also see Pharmaceutical salts, Berge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or

30 base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention (e.g. trifluoro acetate salts) also comprise a part of the invention.

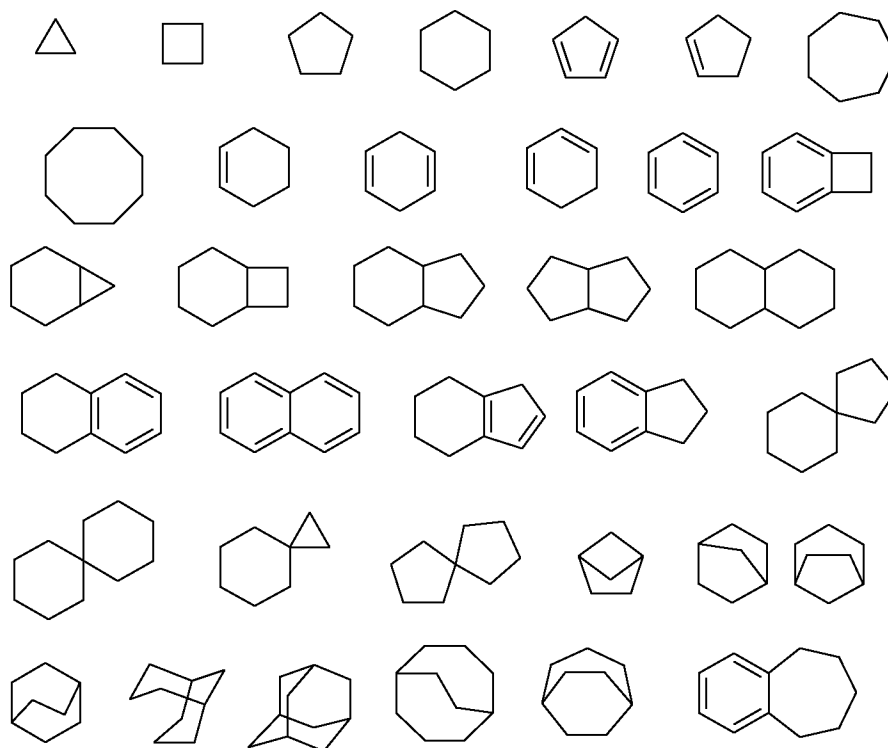
- 5 The term "substituted" as used herein means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's viable valence number is not exceeded, and that the substitution results in a stable compound.
- 10 The term "partially unsaturated" as used herein means that in the designated group or moiety 1, 2, or more, preferably 1 or 2, double bonds are present. Preferably, as used herein, the term "partially unsaturated" does not cover fully unsaturated groups or moieties.
- 15 Terms like "...optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O-." or "...optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-" in a section like "... groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO-, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O-, and optionally with 1 to 7 fluorine atoms substituted
20 C₁₋₃-alkyl-" means that the referenced group may be substituted with 1 to 5 substituents, wherein these substituents can be halogen, HO-, C₁₋₃-alkyl-O- which may be optionally fluorinated with 1 to 7 fluoro atoms, and C₁₋₃-alkyl-O- which may be optionally fluorinated with 1 to 7 fluoro atoms.
- 25 The term "halogen" generally denotes fluorine, chlorine, bromine and iodine.

- The term "C_{1-n}-alkyl", wherein n is an integer from 2 to n, either alone or in combination with another radical denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C₁₋₅-alkyl embraces
- 30 the radicals H₃C-, H₃C-CH₂-, H₃C-CH₂-CH₂-, H₃C-CH(CH₃)-, H₃C-CH₂-CH₂-CH₂-, H₃C-CH₂-CH(CH₃)-, H₃C-CH(CH₃)-CH₂-, H₃C-C(CH₃)₂-, H₃C-CH₂-CH₂-CH₂-CH₂-, H₃C-CH₂-CH₂-CH(CH₃)-, H₃C-CH₂-CH(CH₃)-CH₂-, H₃C-CH(CH₃)-CH₂-CH₂-, H₃C-

$\text{CH}_2\text{-C}(\text{CH}_3)_2\text{-}$, $\text{H}_3\text{C-C}(\text{CH}_3)_2\text{-CH}_2\text{-}$, $\text{H}_3\text{C-CH}(\text{CH}_3)\text{-CH}(\text{CH}_3)\text{-}$ and $\text{H}_3\text{C-CH}_2\text{-CH}(\text{CH}_2\text{CH}_3)\text{-}$.

The terms “carbocyclyl” and “carbocycle” as used either alone or in combination with another radical, mean, if not mentioned otherwise, a mono- bi- or tricyclic ring structure consisting of 3 to 14 carbon atoms. The terms, if not mentioned otherwise, refers to fully saturated, partially saturated and aromatic ring systems. The terms encompass fused, bridged and spirocyclic systems.

Thus, the terms include the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:

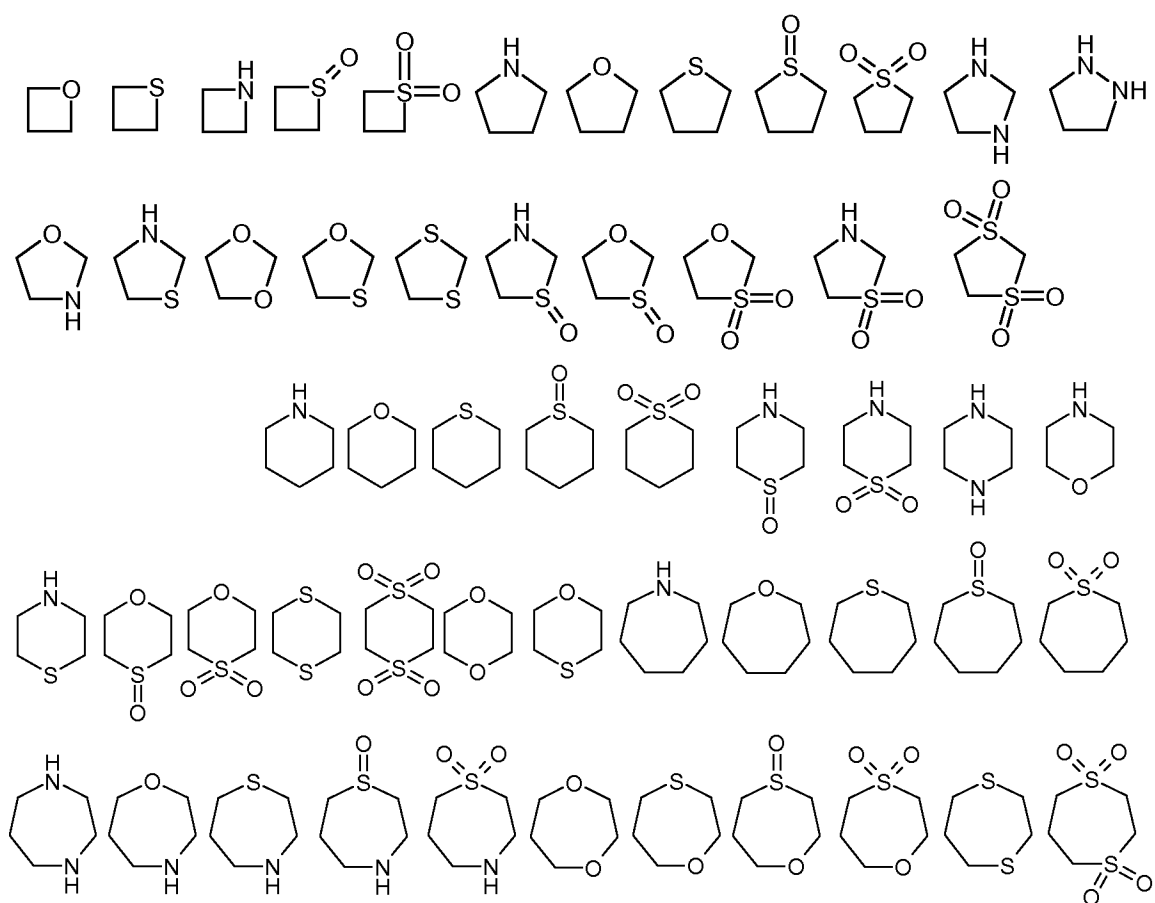


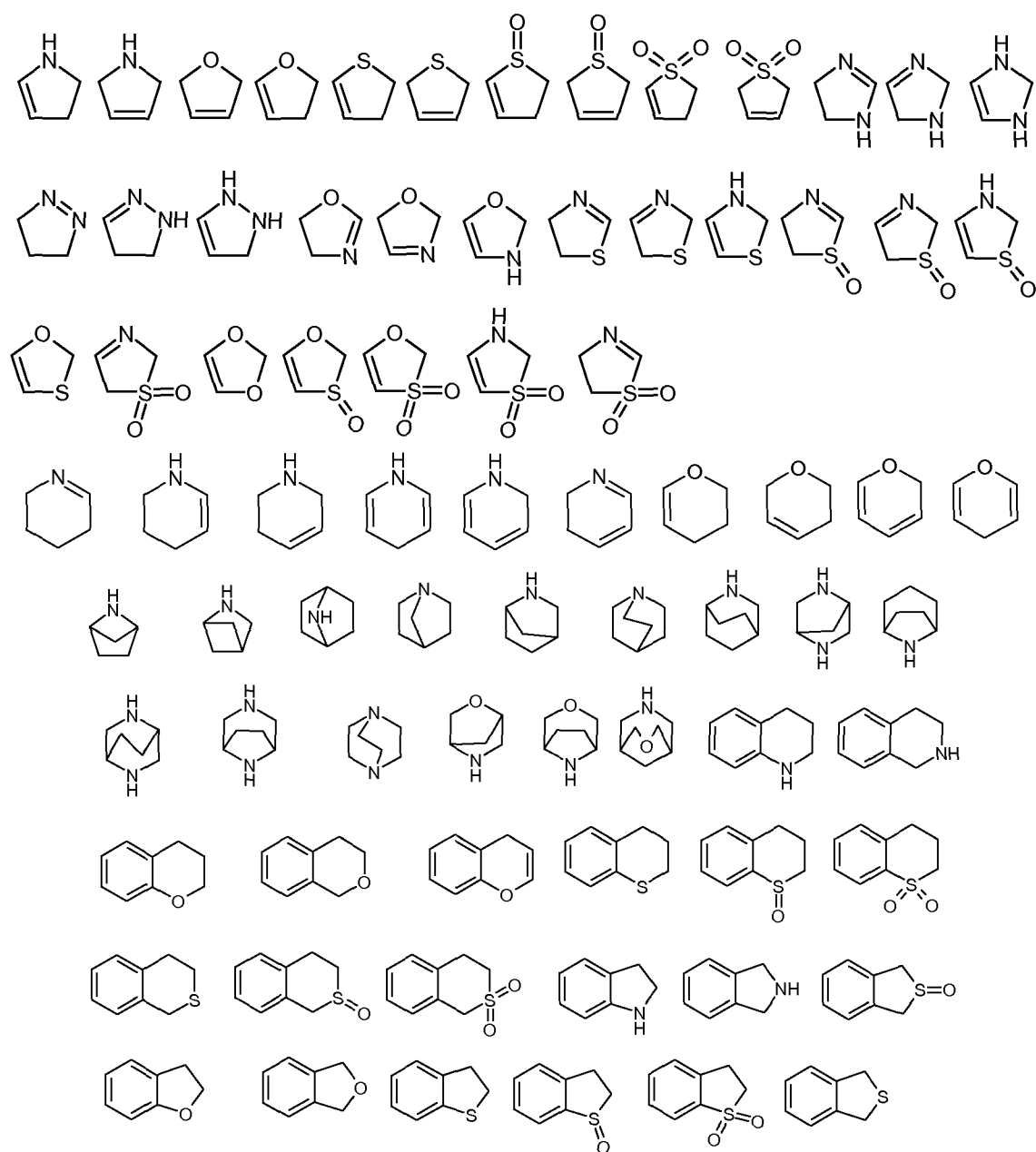
The term “ C_{3-n} -cycloalkyl”, wherein n is an integer from 4 to n, either alone or in combination with another radical denotes a cyclic, saturated, unbranched hydrocarbon radical with 3 to n C atoms. For example the term C_{3-7} -cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

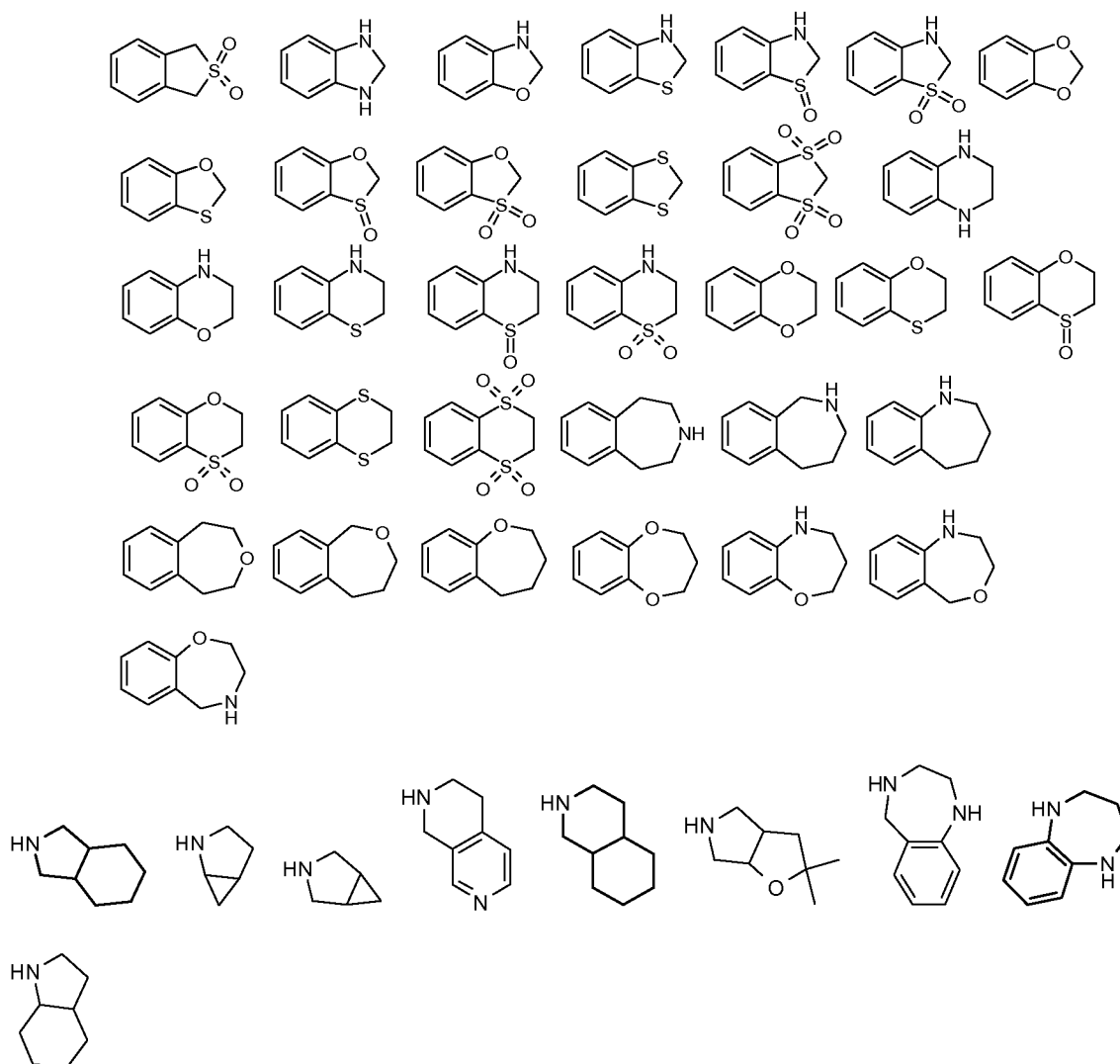
The terms “heterocyclyl” and “heterocycle” as used either alone or in combination with another radical, mean a saturated or unsaturated mono- or polycyclic ring

system containing one or more heteroatoms selected from N, O or S(O)_r, wherein r=0, 1 or 2, which may contain aromatic rings consisting of, if not mentioned otherwise, 3 to 14 ring atoms wherein none of the heteroatoms is part of an aromatic ring. The terms encompass fused, bridged and spirocyclic systems. The terms are intended to include all the possible isomeric forms.

Thus, the terms include the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:



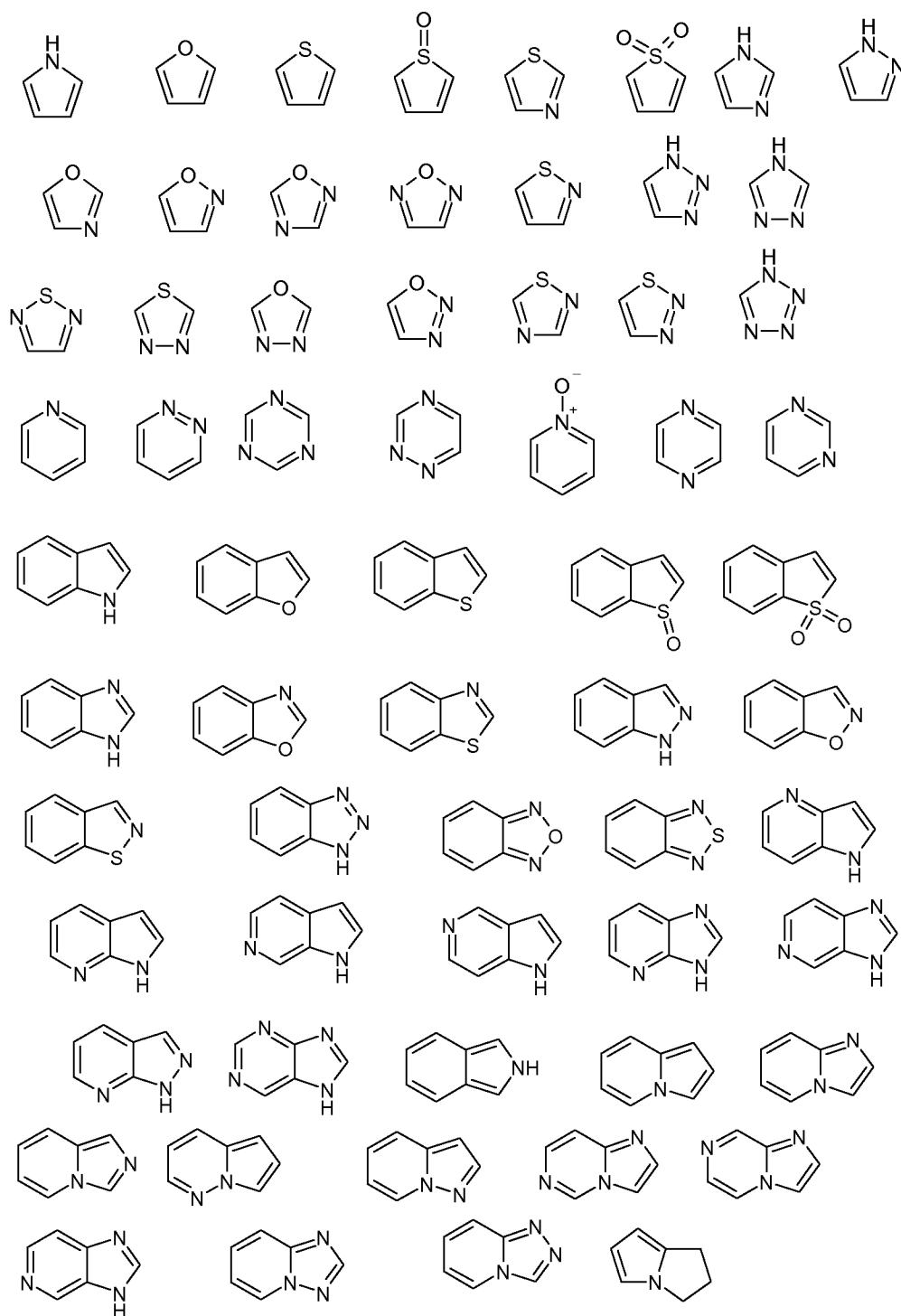


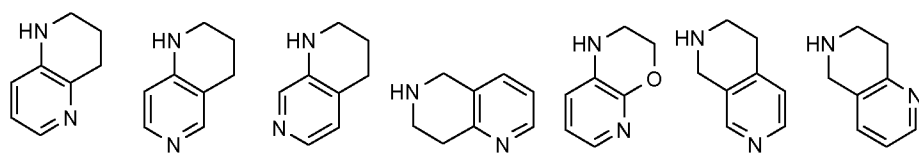


- 5 The term “aryl” as used herein, either alone or in combination with another radical,
denotes a carbocyclic aromatic monocyclic group containing 6 carbon atoms which
may be further fused to a second 5- or 6-membered carbocyclic group which may be
aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl,
indanyl, indenyl, naphthyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl and
10 dihydronaphthyl.

The term "heteroaryl" means a mono- or polycyclic-ring systems containing one or more heteroatoms selected from N, O or S(O)_r, wherein r=0, 1 or 2, consisting of 5 to 14 ring atoms wherein at least one of the heteroatoms is part of an aromatic ring. The term "heteroaryl" is intended to include all the possible isomeric forms.

Thus, the term “heteroaryl” includes the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:





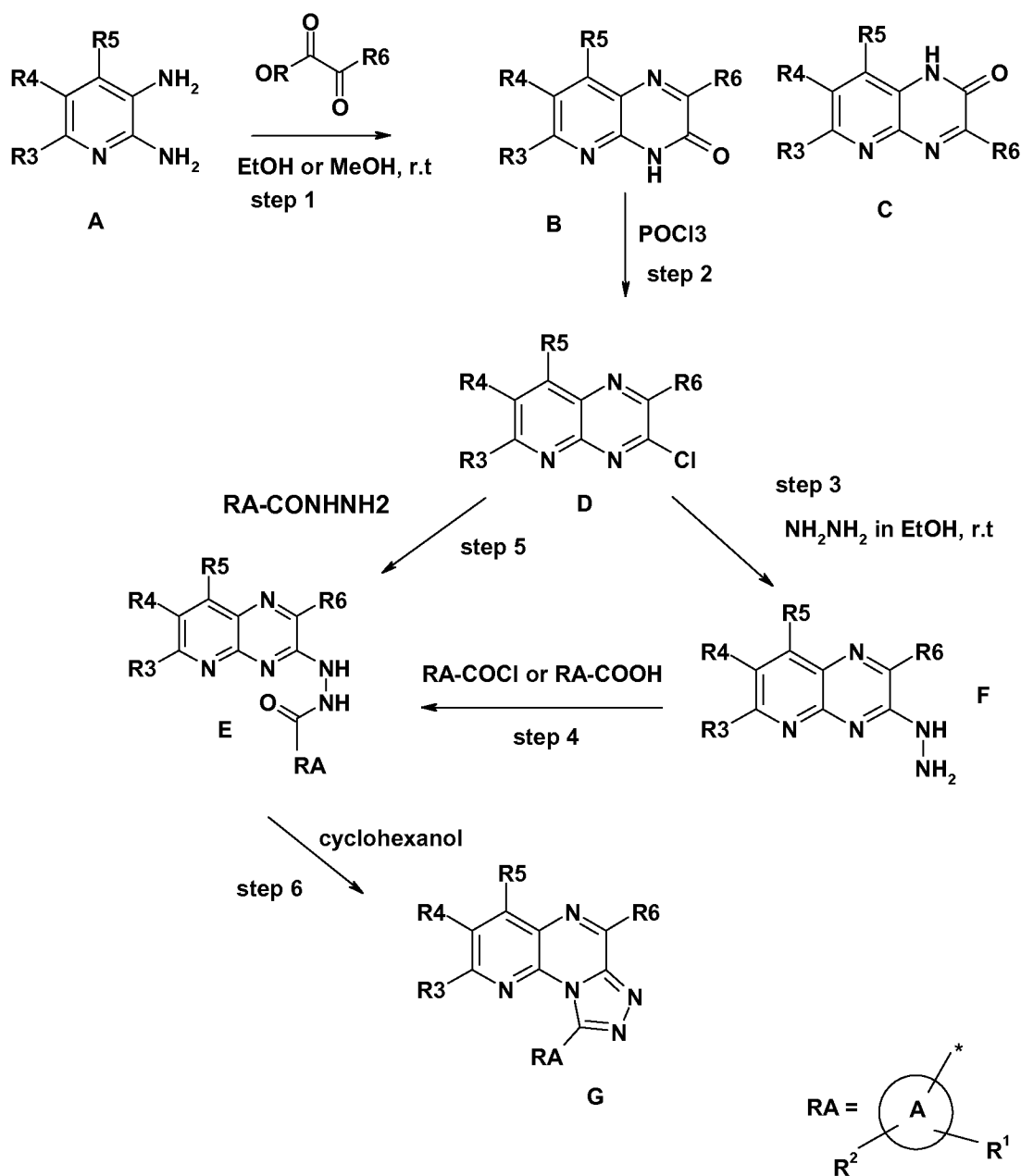
Many of the terms given above may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of
5 one another.

The compounds according to the invention may be obtained using methods of synthesis known in principle. Preferably, the compounds are obtained by the following methods according to the invention which are described in more detail
10 hereinafter.

Preparation

The following schemes illustrate generally how to manufacture the compounds of the present invention by way of example. The abbreviated substituents may be as
15 defined above if not defined otherwise within the context of the schemes :

Scheme 1:



Scheme 1: In a first step, substituted 1,2-pyridine-diamines (A), commercially available or prepared following well known reported procedures, were reacted with the appropriate 1,2 – keto ester or acid in EtOH or MeOH as solvents at room temperature, to form the corresponding pyrido[2,3-b] pyrazinone intermediates (B,C). Where required, regioisomers were separated by flash chromatography and treated with POCl3 under heating to obtain the 2-chloro-pyridopyrazines(D). Nucleophilic substitution was performed using hydrazine hydrate in appropriate solvents (e.g. EtOH) at room temperature to form the corresponding pyrido[2,3-b]-pyrazin-3-ylhydrazines derivatives (F). Reaction with appropriate acyl chlorides or

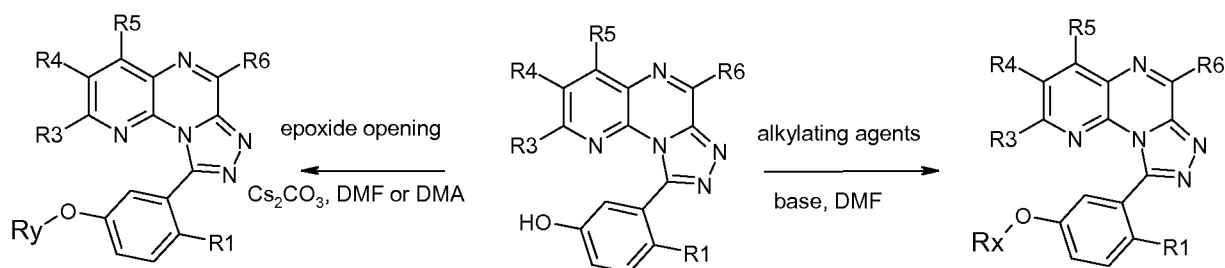
carboxylic acids in the presence of a coupling agent (e.g. HATU or TBTU) and a base (e.g. TEA or DIPEA), gave the corresponding hydrazides (E) which were submitted to in situ cyclization to triazoles core by heating in appropriate solvent (e.g. cyclohexanol) .

- 5 Alternatively, in step 5, preformed hydrazides derivative were reacted with 2-chloro-pyridopyrazines (D) in appropriate solvents (such as DMF) to gave intermediates hydrazides (E) which were then converted to compounds G as described before or heating directly the 2-chloro-pyridopyrazines (D) with the appropriate hydrazides in appropriate solvent such as cyclohexanol at high temperature.

10

Further examples of the present invention were prepared following Scheme 2:

Scheme 2:



15

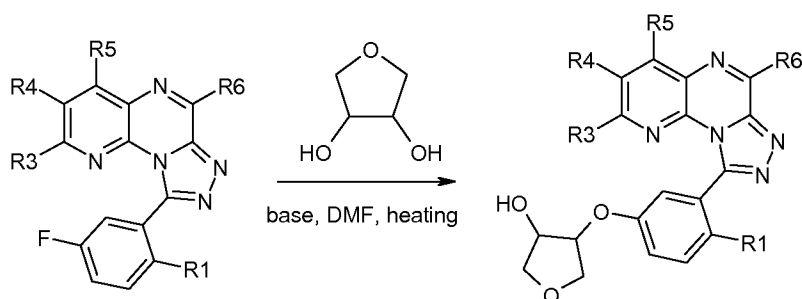
Further examples of the present invention were prepared by alkylation of the appropriate phenol derivative (obtained as described in Scheme 1) with alkylating agents (e.g. chloride, bromide or tosylates derivatives) in the presence of a suitable base (e.g. tBuOK or Cs₂CO₃) in a solvent like DMF under heating or by ring opening of the appropriate epoxides in the presence of a suitable base (e.g. Cs₂CO₃) in a solvent like DMF or DMA under conventional heating or microwave irradiation.

20

25

Rx and Ry : Examples 13, 15, 16, 17,18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 32a , 33, 34, 35, 35a, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45,46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57,58,106,107,108a, 108b, 108c, 108d, 109a, 109b, 109c, 109d, 110b,110d,111 were prepared following the above described procedures.

Scheme 3:

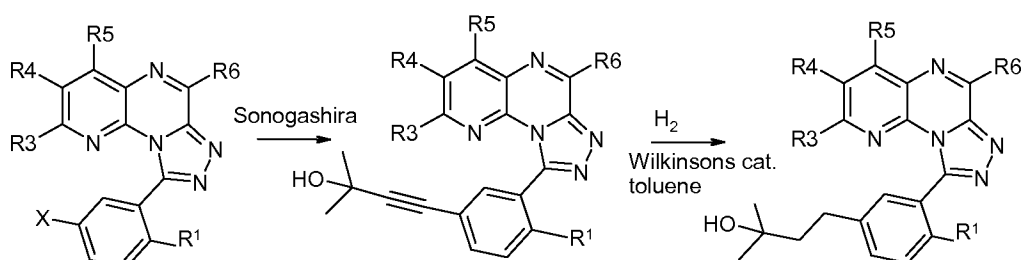


Further examples of the present invention were prepared by aromatic nucleophilic substitution, reacting the appropriate aromatic fluoro derivatives (prepared as described in Scheme 1) with primary or secondary alcohols in the presence of a

5

Examples 58a, 58b, 58c were prepared following the above described procedure.

Scheme 4:



10

Further examples of the present invention were prepared by well-known cross coupling reaction (i.e Sonogashira, see for example Organic Letters, 2007, vol. 9, p. 4057 – 4060) starting from appropriate aromatic halogen intermediates (X=Br,I). The resulting unsaturated triple bond intermediates were then converted to final

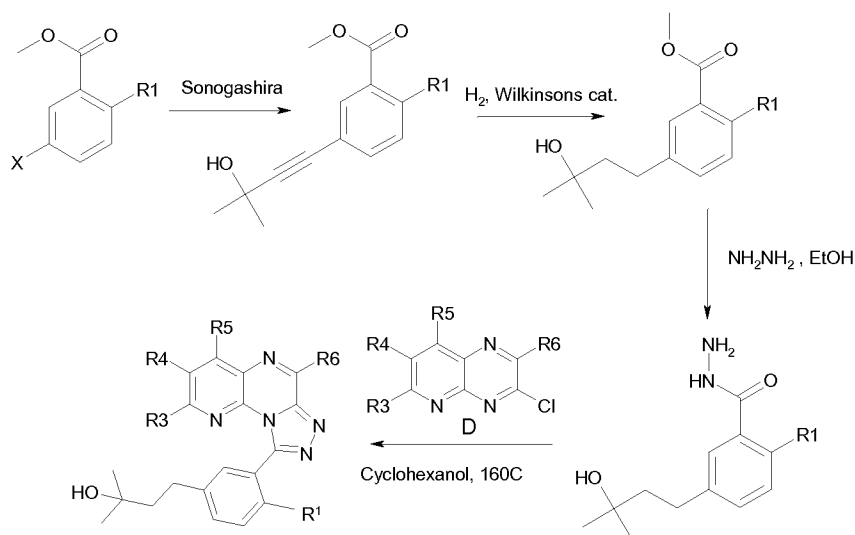
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Examples 66, 67, 68, 69 were prepared following the above described procedure.

Alternatively, the same synthetic approach was applied for the preparation of preformed hydrazides which were then reacted with intermediate D as described in

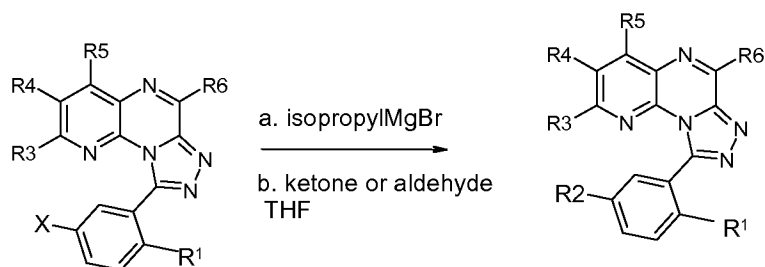
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Scheme 5



Examples 64 and 65 were prepared following the above described procedure.

5 Scheme 6:

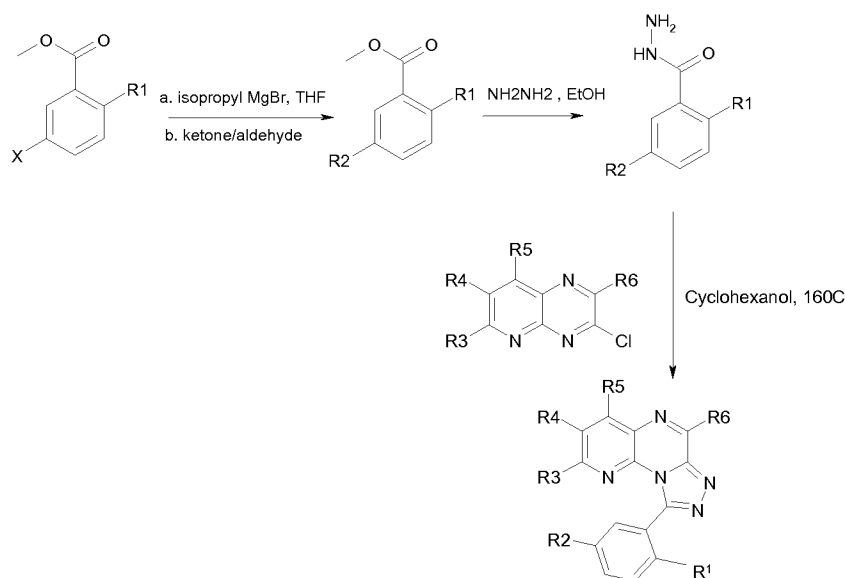


Further examples of the present invention were prepared as described in Scheme 6 :
 in a first step the appropriate aromatic alogen derivatives ($X=I$) was treated with
 isopropyl magnesium bromide in a suitable solvent (like THF) at low temperature
 followed by addition of the appropriate ketone or aldehyde derivatives.

Examples 70, 71, 72, 73, 74 were prepared following the above described procedure.

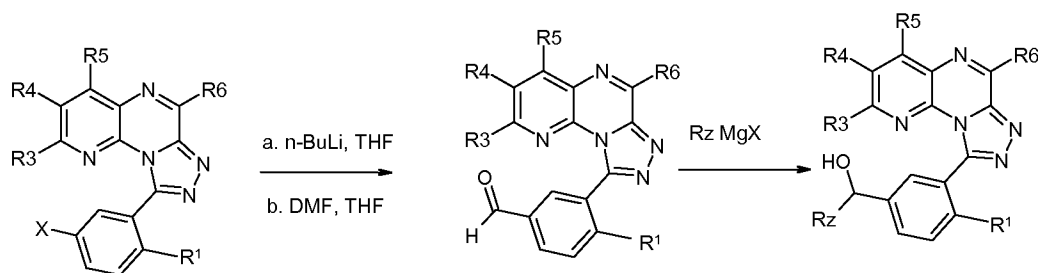
Alternatively, the same synthetic approach was applied for the preparation of
 preformed hydrazides which were then reacted with intermediate D as described in
 Scheme 1.

Scheme 7



Examples 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 96a, 96b, 96c, 97 were prepared following the above described procedure.

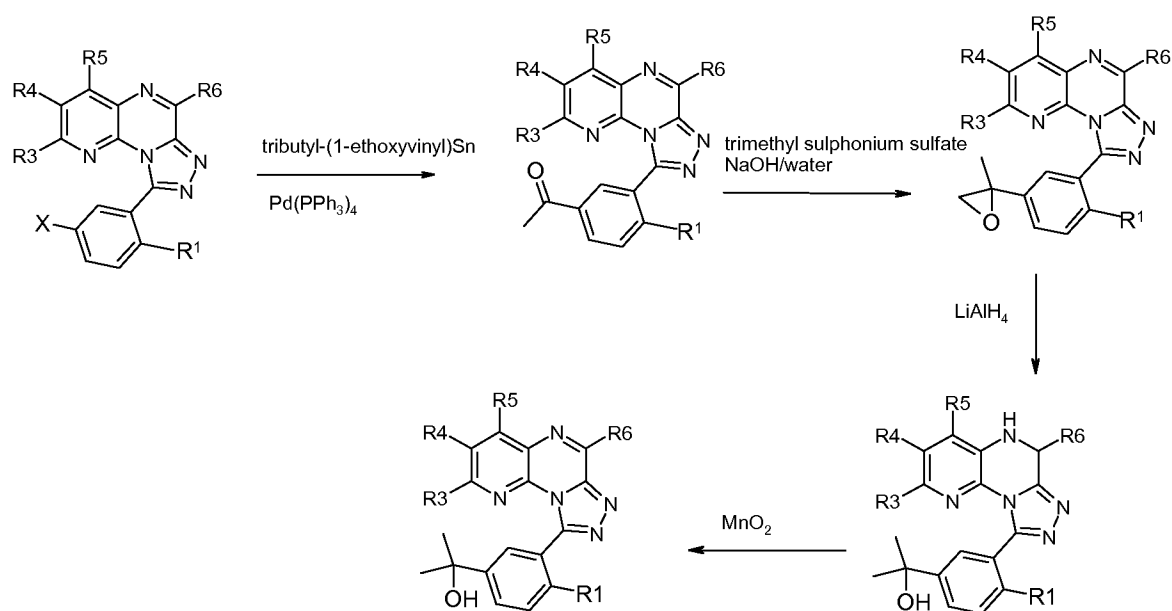
5 Scheme 8:



Further examples of the present invention were prepared as described in Scheme 8: in a first step the appropriate aromatic aldehyde is obtained by reaction of alogen derivatives ($\text{X}=\text{I}$) with n-BuLi in a suitable solvent (like THF) at low temperature followed by addition of dry DMF in THF. In a second step the suitable commercially available Grignard reagent is added at low temperature.

Rz: Examples 59,61,62,63 were prepared following the above reported procedure.

Scheme 9

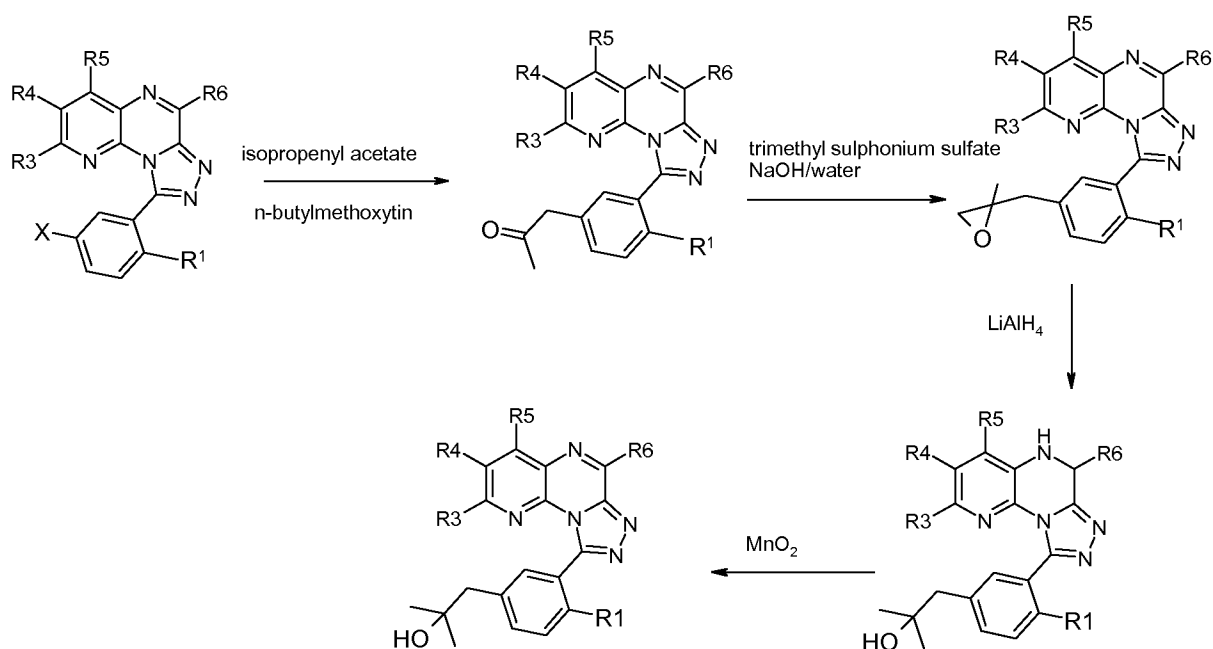
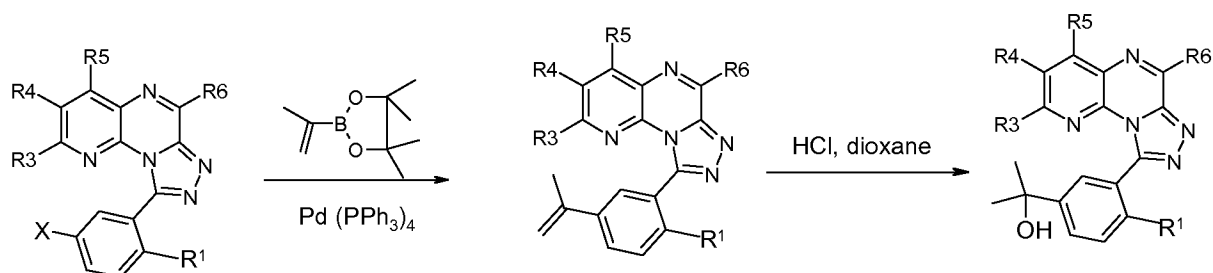


Further examples of the present invention were prepared as described in Scheme 9: in a first step the appropriate ketone is obtained by reaction of alogen derivatives ($X=\text{I},\text{Br}$) with tributyl-(1-ethoxyvinyl)-tin in the presence of $\text{Pd}(\text{PPh}_3)_4$. The epoxide obtained by reaction with appropriate trimethyl sulphonium ylide was then subjected to ring opening with hydride and subsequent oxidation with suitable agents such as manganese dioxide in appropriate solvents (DCM).

Examples 76, 77, 78, 79 were prepared following the above reported procedure.

In analogy, the omologated derivatives Examples 80, 81 were obtained performing the first step as described in Scheme 9a.

Scheme 9a

**Scheme 10**

5

Further examples of the present invention were prepared as described in Scheme 10: in a first step the appropriate double bond is installed by Suzuki coupling with suitable boronic acids or esters (such as for example 2-isopropenyl- dioxaborolane, Scheme 10). In a second step, the hydration of the double bond (HCl/dioxane) allowed to introduce hydroxylic function.

10

Example 103,103b,103c were prepared following the above described procedure.

The compounds according to the invention are advantageously also obtainable using the methods described in the examples that follow, which may also be combined for this purpose with methods known to the skilled man from the literature.

15

As already mentioned, the compounds of general formula I according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly as inhibitors of phosphodiesterase 2 and/or 10.

5 Biological Examples

In-vitro effect:

The *in-vitro* effect of the active compounds of the invention can be shown with the following biological assays.

10

a) radioactive PDE2 assay protocol:

For all experiments the Phosphodiesterase [^3H]cAMP SPA Enzyme Assay (TRKQ7090, GE Healthcare Europe GmbH) were used. The enzymatic activity of the PDE2 and the inhibitory potency of compounds was measured by the conversion of [^3H]cAMP to [^3H]AMP. [^3H]AMP associate to the scintillator soaked yttrium-silicate beads resulting in an increase in scintillation events. Compounds that inhibit the respective enzymes decrease the generation of [^3H]AMP and accordingly the number of counts detected.

15

SF9 lysate containing PDE2A is incubated at room temperature for 1 h with [^3H]cAMP and the reaction is terminated by addition of SPA beads in 18 mM zinc sulphate. The [^3H]AMP bound to SPA beads is determined after at least 3 hours of sedimentation of the beads, the signal is recorded using the TopCount with a recording time of 3 min/well.

20

PDE 2A protein is expressed upon baculovirus infection in SF9 cells. The cells have been incubated upon infection for ~3 days and protein production was confirmed by Western Blot. The cells were collected by centrifugation and the pellet frozen in liquid nitrogen before it was resuspended in PBS containing 1% Triton X-100 and protease inhibitors. After 45 min incubation on ice, the cell debris was removed by centrifugation (13.000 rpm, 30 min).

25

30

The assay conditions were as follows :

total assay volume:	40 μl
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protein amount:	5 ng
protein concentration:	500 pg/ μ l
substrate concentration:	20 nM; $\sim$ 1,08 mCi/l
incubation time:	60 min

The buffer used for above described assay buffer was:

50 mM Tris/HCl, pH 7.4
8.3 mM MgCl ₂
1.7 mM EGTA
0.1 % (w/v) BSA
0.05 % (v/v) Tween 20

5

In detail the protocol is as follows:

Into a 384 well plate (OptiPlate, white), the following components are pipetted (either manually or using automated pipetting devices):

- 10 20 μ l test-compound solution (test compound diluted in assay buffer at twofold the desired concentration)
+ 10 μ l PDE 2A preparation (enzyme diluted in assay buffer to a concentration of 0,5 ng/ μ l protein)
+ 10 μ l [³H]cAMP (diluted in assay buffer to a concentration of 80 nM cAMP)

15

Controls included into each experiment:

positive control: no inhibitor, DMSO at the concentration as used in the compound dilutions

negative control: no PDE 2 (SF9 lysate instead of SF9/PDE 2A lysate)

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Calculation of % inhibition:

The activity of the positive control (minus the negative control = background) is set to 100% and activity in the presence of compound is expressed relative to these 100%.

Calculation of IC50:

IC50 are calculated with GraphPadPrism or other suited software setting the positive control as 100 and the negative control as 0. For calculation of IC50 usually 11 dilutions of the test compound are selected.

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b) radioactive PDE10 assay protocol:

For assessing activity of compounds on PDE10 inhibition, the following modifications of the protocol described above are applied:

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protein amount: 3 ng

protein concentration: 75 pg/μl

In detail the protocol is as follows:

15 Into a 384 well plate (OptiPlate, white), the following components are pipetted (either manually or using automated pipetting devices):

20 μl test-compound solution (test compound diluted in assay buffer at twofold the desired concentration)

20 + 10 μl PDE 10A preparation (enzyme diluted in assay buffer to a concentration of 0,3 ng/μl protein)

+ 10 μl cAMP tracer (diluted in assay buffer to a concentration of 80 nM cAMP, specific activity ~4 mCi/l)

25 After addition of all 3 components the plates are shortly spun and incubated at room temperature for 60 min. The reaction is stopped by the addition of 20 μl Yttrium SPA PDE Beads containing 18 mM zinc sulphate in water

After at least 3 hours sedimentation of the beads, the signal is recorded using the TopCount with a recording time of 3 min/well.

30 PDE 10A protein is expressed upon baculovirus infection in SF9 cells. The cells have been incubated upon infection for ~3 days and protein production was confirmed by Western Blot. The cells were collected by centrifugation and the pellet frozen in liquid nitrogen before it was resuspended in PBS containing 1% Triton X-100 and protease

inhibitors. After 45 min incubation on ice, the cell debris was removed by centrifugation (13.000 rpm, 30 min).

In the following table the results of the above described experiments are listed.

- 5 Table 3: Activity of the examples (Ex) compiled in the experimental part, based on above described assays (cAMPA SPA radioactive).

Ex.	PDE2 IC ₅₀ [μM]	PDE10 IC ₅₀ [μM]	Ex.	PDE2 IC ₅₀ [μM]	PDE10 IC ₅₀ [μM]
1	0,016	0.421	25	0,055	3.26
2	0,004	0.040	26	0,116	1.38
3	0,155	0.411	27	0,004	0.97
4	0,138	0.441	28	0,009	>10
13	0,053	2.190	29	0,017	2.38
14	0,202	3.580	30	0,027	3.92
15	0,040	>10	31	0,007	1.90
16	0,058	1.876	32	0,003	1.76
17	0,098	5.72	33	0,004	2.50
18	0,071	3.01	34	0,009	1.89
19	0,146	3.01	35	0,009	1.30
20	0,028	2.76	36	0,219	0.85
21	0,070	2.82	37	0,171	3.08
22	0,115	>5	38	0,417	1.96
23	0,071	5.10	39	0,914	2.10
24	0,138	6.69	40	0,080	3.47

Another, non radioactive, in-vitro assay was performed as follows

- 10 c) Phosphodiesterase (PDE) 2A and 10 assay with fluorescent substrate

Assay principle:

The PDE reaction cleaves cAMP to AMP. The IMAP system (Molecular Device) using fluorescence polarization (FP) as detection principle was used to measure enzyme

activity. A fluorescent labeled cAMP was used as substrate for the reaction, generating a labeled AMP. The fluorescent AMP binds specifically to the large M(III)-based nano-particles which reduces the rotational speed of the substrate and thus increases its polarization.

5

Detailed method:

The inhibition of PDE 2A or 10 enzyme activity was assessed using IMAP-Phosphodiesterase-cAMP fluorescence labeled substrate (Molecular Devices, Order No. R7506), IMAP TR-FRET screening express (Molecular Devices, Order No.

10 R8160, the TR-FRET component will not be used) and PDE 2A or PDE10 protein expressed upon baculovirus infection in SF9 cells. The cells were incubated after infection for ~3 days and protein production was confirmed by Western Blot. The cells were collected by centrifugation and the pellet frozen in liquid nitrogen before it was resuspended in PBS containing 1% Triton X-100 and protease inhibitors. After
15 45 min incubation on ice, the cell debris was removed by centrifugation (13.000 rpm, 30 min). Since SF 9 cells do not express cAMP hydrolyzing enzymes to a high extent, no further purification of the protein was needed.

All reactions were performed in 384 well plates, Perkin Elmer black optiplates and IMAP reaction buffer with 0.1% Tween20 (kit component)

20

Compounds were serial diluted in DMSO. With an intermediate dilution step with reaction buffer DMSO concentration was reduced to achieve 1% DMSO in the assay reaction. Setup of the assay started with 10µl enzyme (~10ng/well, depending on prep. batch), 5 µl compound, reaction was started by addition of 5 µl labeled cAMP
25 (30 nM, final concentration), immediately mixed for 15 seconds on a Eppendorf mixmate (2000 rpm) followed by an incubation at room temperature for 90 minutes in the dark. Reaction is stopped by adding of 60 µl binding buffer for FP/cAMP (kit component). After at least 90 min of further incubation (room temperature, dark) the assay was measured at 485 nm excitation/525 nm emission in an Envision multilabel
30 reader (PerkinElmer).

Each assay plate contained wells with vehicle controls (1% DMSO) for the measurement of non-inhibited reaction (=100% control) and wells without enzyme as 0% controls.

- 5 The analysis of the data was performed by calculation of the percentage of inhibition in the presence of test compound compared to the vehicle control samples (100% control, no inhibition) and a low control (0% control, no enzyme).

IC₅₀ values are calculated with Assay Explorer or other suited software based on curve fitting of results of at least 8 different compound concentrations. The compound

- 10 concentrations may vary according to the needed range, but typically cover the range between 10μM and 0.1pM.

Table 3a: Activity of the examples (Ex) compiled in the experimental part, based on above described assays (IMAP fluorescent).

Ex.	PDE2 IC ₅₀ [μM]	PDE10 IC ₅₀ [μM]	Ex.	PDE2 IC ₅₀ [μM]	PDE10 IC ₅₀ [μM]	Ex.	PDE2 IC ₅₀ [μM]	PDE10 IC ₅₀ [μM]
1	0,041	0,355	55	0,080	5,298	96	0,043	5,945
2	0,003	0,033	55a	0,033	2,435	96a	0,199	10,000
4	0,120	0,256	56	0,002	0,061	96b	0,087	10,000
5	0,003	0,005	56a	0,008	0,061	96c	0,591	7,460
6	0,003	0,010	56b	0,001	0,066	97	0,004	2,142
7	0,003	0,016	57	0,006	0,045	97a	0,004	5,945
8	0,002	0,008	57a	0,012	0,167	97b	0,004	0,891
9	0,001	0,015	57b	0,003	0,091	98	0,139	1,560
10	0,229	0,254	58	0,143	0,663	99	0,125	1,510
11	0,059	0,123	58a	0,054	0,713	100	0,017	3,856
12	0,009	0,044	58b	0,045	0,663	101	0,047	1,125
12a	0.036	0.170	58c	0,037	0,241	102	0,103	2,265
13	0,095	6,363	59	0,008	0,936	103	0,003	1,007
15	0,112	1,118	60	0,019	0,285	103b	0,100	10,000
16	0,098	8,700	61	0,004	0,534	103c	0,622	7980

17	0,162	10,200	62	0,011	1,300	104	0,036	7,715
18	0,090	8,418	63	0,060	1,710	104a	0,040	3,229
20	0,077	8,162	64	0,045	3,870	104b	0,030	9,765
21	0,022	7,047	65	0,214	3,545	105	0,023	1,540
22	0,207	9,317	66	0,003	0,674	105a	0,104	3,630
23	0,216	9,193	67	0,175	3,905	105b	0,038	3,410
25	0,038	7,333	68	0,002	1,007	106	0,160	1,940
27	0,018	0,958	69	0,001	0,891	106a	0,429	1,410
28	0,020	0,299	70	0,163	8,620	106b	0,050	2,500
29	0,037	5,097	71	0,109	2,080	107	0,007	0,022
30	0,020	2,573	72	0,032	2,865	111	0,022	3,980
31	0,008	2,897	73	0,189	10,000	108a	0,011	0,548
32	0,026	6,703	74	0,131	2,340	108b	0,059	0,594
32a	0,006	7,390	75	0,012	2,403	108c	0,024	0,262
33	0,005	3,417	76	0,021	1,105	108d	0,046	0,630
34	0,017	2,143	77	0,004	1,400	109a	0,014	1,670
35	0,017	1,477	78	0,010	2,845	109b	0,009	1,090
35a	0,003	0,822	79	0,144	0,305	109c	0,009	1,360
40	0,077	8,707	80	0,010	5,405	109d	0,004	1,830
41	0,050	2,770	81	0,007	5,384	110b	0,388	>10
42	0,035	2,520	82	0,199	5,615	110d	0,467	7,600
43	0,057	3,015	83	0,004	8,815	111a	0,065	1,830
43a	0,109	4,510	84	0,006	0,565	111b	0,011	2,130
44	0,156	6,037	85	0,006	4,325	112	0,018	7,000
45	0,005	1,488	86	0,434	5,750	112a	0,025	2,600
46	0,050	1,035	87	0,074	2,594	112b	0,068	2,500
47	0,008	0,852	88	0,001	0,302	113	0,0002	3,190
48	0,008	1,520	89	0,018	0,187	114	0,022	10,000
49	0,033	3,760	90	0,103	0,485	114a	0,009	10,000
50	0,194	7,120	91	0,001	0,077	114b	0,011	10,000
51	0,009	2,150	92	0,002	0,553	115	0,039	10,000
52	0,011	1,195	93	0,086	6,107	115a	0,082	10,000

53	0,140	2,830	94	0,001	2,719	115b	0,045	10,000
54	0,058	0,798	95	0,005	1,369			

In-vivo effect:

5 **Animal Experiments and sample analysis (CSF):**

Test compounds were administered to animals (rat) different routes at doses of 10.0 or 5 µmol/kg, (both oral and intravenous). After compound administration, the animals were sacrificed in a CO₂ chamber and CSF samples were carefully collected by puncture of the cisterna magna. Immediately after CSF sampling, blood was taken by heart puncture and brains were dissected out. Blood was collected in EDTA-coated microvettes and plasma was prepared by centrifugation. Concentration of the test compounds in plasma, CSF or brain homogenate was determined using HPLC-MS-MS.

15 Table 4 : Plasma, brain and CSF concentration

Ex.	Time(*) (h)	conc plasma (nmol/L)	conc brain (nmol/L)	c(brain)/ c(plasma)	conc CSF (nmol/L)	c(CSF)/ c(plasma)
44	0.5	2187	670	0.31	228	0.10
34	0.5	223	146	0.7	19	0.09
18	0.5	1225	351	0.3	163	0.13
20	0.5	338	272	0.82	37	0.11
45	2	801	183	0.20	25	0.03
64	2	783	254	0.5	37	0.06
76	2	463	218	0.5	18	0.04
75	2	1130	383	0.34	31	0.03
70	2	2377	695	0.29	276	0.12
47	2	622	441	0.7	22	0.04
49	2	239	47	0.2	13	0.06

(*) Time between administration and CSF sampling

For the skilled in the art it is evident from the experimental results shown above that the compounds of the present invention are not only very potent phosphodiesterase 2 and/or 10 inhibitors but also reach high CSF concentrations and adequate CSF to plasma ratios.

Metabolic stability

The metabolic stability of the compounds according to the invention has been investigated as follows:

The metabolic degradation of the test compound was assayed at 37 °C with pooled liver microsomes from various species. The final incubation volume of 100 µl per time point contains TRIS buffer pH 7.6 at room temperature (0.1 M), magnesium chloride (5 mM), microsomal protein (1 mg/mL for human and dog, 0.5 mg/mL for other species) and the test compound at a final concentration of 1 µM. Following a short preincubation period at 37°C, the reactions were initiated by addition of betanicotinamide adenine dinucleotide phosphate, reduced form (NADPH, 1 mM), and terminated by transferring an aliquot into solvent after different time points. After centrifugation (10000 g, 5 min), an aliquot of the supernatant was assayed by LC10 MS/MS for the amount of parent compound. The half-life was determined by the slope of the semi-logarithmic plot of the concentration-time profile.

Table 4: Stability of compounds of the present invention in human liver microsomes.

Ex.	Half-life - t1/2 [min]	Ex.	Half-life - t1/2 [min]	Ex.	Half-life - t1/2 [min]
1	130	54	130	76	130
5	43	55	130	77	90
6	66	55a	130	78	79
9	41	56	120	80	83
12	63	56a	110	81	26
13	130	56b	62	82	130
17	130	57	130	83	100

18	130	57a	130	84	39
20	130	57b	93	85	130
21	130	58	130	87	130
30	130	58a	130	88	53
32	130	58b	130	89	130
32a	36	58c	130	91	28
34	130	59	49	92	23
35	130	61	65	93	130
35a	130	62	130	94	38
42	130	63	130	96	110
43	130	64	130	97	51
44	130	66	57	99	130
45	130	67	130	100	12
46	130	68	39	101	22
47	130	69	53	102	130
48	130	70	130	104	130
49	130	71	130	104a	130
50	130	72	130	104b	130
51	130	73	130		
52	130	75	130		

hERG (human Ether-à-go-go-Related Gene) -Channel Assay

hERG channel inhibition of compounds of the present invention has been

5 investigated as follows:

HEK (human embryonic kidney) 293 cells were stably transfected with hERG cDNA. Cells were superfused with a bath solution containing (mM): NaCl (137), KCl (4.0), MgCl₂ (1.0), CaCl₂ (1.8), Glucose (10), HEPES (10), pH 7.4 with NaOH. Patch
 10 pipettes were made from borosilicate glass tubing using a horizontal puller and filled with pipette solution containing (mM): K-aspartate (130), MgCl₂ (5.0), EGTA (5.0),

K2ATP (4.0), HEPES (10.0), pH 7.2 with KOH. Resistance of the microelectrodes was in the range between 2 and 5 M Ω .

Stimulation and recording:

5 Membrane currents were recorded using an EPC-10 patch clamp amplifier and PatchMaster software. hERG-mediated membrane currents were recorded at 35°C, using the whole-cell configuration of the patch-clamp technique. Transfected HEK293 cells were clamped at a holding potential of -60 mV and hERG-mediated inactivating
10 tail currents were elicited using a pulse pattern with fixed amplitudes (activation/inactivation: 40 mV for 2000 ms; recovery: 120 mV for 2 ms; ramp to 40 mV in 2 ms; inactivating tail current: 40 mV for 50 ms) repeated at 15 s intervals. During each inter-pulse interval 4 pulses scaled down by a factor of 0.2 were recorded for a P/n leak subtraction procedure. Rs compensation was employed up to
15 a level that safely allowed recording devoid of ringing.

Compound preparation and application:

The different concentrations of the test compound were applied sequentially on each
20 of the different cells investigated. A steady state level of baseline current was measured for at least 6 sweeps prior to the application of the first test compound concentration.

The test compound was dissolved in DMSO to yield a master stock solution which was diluted further in DMSO to stock solutions needed for the lower concentrations.
25 Final dilutions in extracellular buffer were prepared freshly from these stocks by a 1:1000 dilution step each before starting the experiments.

Data analysis and IC50 determination:

30 Peak current amplitudes were measured 3 ms after the ramp to +40 mV. For baseline and each concentration the peak currents of the three last sweeps before application of the next concentration were averaged. Residual currents (I/I₀) were calculated for each cell as the fraction of actual average peak current and average baseline peak current.

35 The logistic concentration-response curve of the following form was fitted to the residual current data using a genetic algorithm:

$$I/I_0 = 1 - 1/(1+(C/IC_{50})^{**p})$$

C: actual concentration of compound (in μM)

IC₅₀: half-inhibitory concentration (in μM)

p: Hill slope

5

Table 4: hERG channel inhibition of compounds of the present invention.

Ex.	hERG IC ₅₀ [μM]	Ex.	hERG IC ₅₀ [μM]
13	>10	64	>10
18	>10	66	>10
20	>10	68	8.3
21	>10	75	>10
27	>10	76	>10
28	>10	80	>10
32	>10	82	>10
32a	>10	83	>10
34	>10	84	6.3
35a	>10	85	>10
45	>10	87	>10
47	>10	88	>10
48	>10	93	>10
49	>10		
55	>10		

10

In view of their ability to inhibit the activity of phosphodiesterase 2 and/or 10 activity, their CSF values and their metabolic stability and their low inhibition of the hERG channel, the compounds of general formula I according to the invention, including the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the hydrates thereof, the solvates and the physiologically acceptable salts thereof, are suitable for the treatment and/or preventative treatment of all those diseases or conditions which

15

can be influenced by inhibition of PDE2 and/or 10 hyperactivity and/or cAMP and/or cGMP hypofunction. Therefore, compounds according to the invention, including the physiologically acceptable salts thereof, are particularly suitable for the prevention or treatment of diseases, particularly (1) disorders comprising the symptom of cognitive
5 deficiency; (2) organic, including symptomatic, mental disorders, dementia; (3) mental retardation; (4) mood [affective] disorders; (5) neurotic, stress-related and somatoform disorders including anxiety disorders; (6) behavioural and emotional disorders with onset usually occurring in childhood and adolescence, attention deficit hyperactivity syndrome (ADHD) and Autism spectrum disorders; (7) disorders of
10 psychological development, developmental disorders of scholastic skills; (8) schizophrenia and other psychotic disorders; (9) disorders of adult personality and behaviour; (10) mental and behavioural disorders due to psychoactive substance use; (11) extrapyramidal and movement disorders; (12) episodic and paroxysmal disorders, epilepsy; (13) Systemic atrophies primarily affecting the central nervous
15 system, ataxia; (14) Behavioural syndromes associated with physiological disturbances and physical factors; (15) sexual dysfunction comprising excessive sexual drive; (16) factitious disorders.

In addition, the compounds according to the invention can be used for the treatment, amelioration and / or prevention of cognitive impairment being related to perception,
20 concentration, cognition, learning or memory.

In addition, the compounds according to the invention can be used for the treatment amelioration and / or prevention of cognitive impairment being related to age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes
25 (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotrophic lateral sclerosis (ALS),
30 Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis. In

addition, the compounds of the present invention can be used for the treatment of Alzheimer's disease.

In addition compounds according to the invention can be used for the treatment of pain disorders including but not limited to inflammatory, neuropathic and osteoarthritic pain.

In addition, the compounds according to the invention can be used for the treatment of sleep disorders, bipolar disorder, metabolic syndrome, obesity, diabetes mellitus, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

10 Preferably the compounds according to the invention are suitable for the treatment of Alzheimer's Disease and for the treatment of schizophrenia.

More preferably the compounds according to the invention are suitable for symptomatic treatment of Alzheimer's Disease and for the treatment of cognitive impairment associated with schizophrenia.

15 In particular the compounds according to the invention are suitable for symptomatic treatment of prodromal and mild-to-moderate Alzheimer's Disease and for the treatment of cognitive impairment associated with schizophrenia.

In a further aspect of the present invention the present invention relates to methods for the treatment or prevention of above mentioned diseases and conditions, which method comprises the administration of an effective amount of a compound of general formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the hydrates thereof, the solvates and the physiologically acceptable salts thereof, to a human being.

25 The dose range of the compounds of general formula I applicable per day is usually from 0.1 to 1000 mg, preferably from 1 to 500 mg by oral route, in each case administered 1 to 4 times a day.

Each dosage unit may conveniently contain from 0.1 to 500 mg, preferably 1 to 100 mg.

The actual pharmaceutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case the combination
5 will be administered at dosages and in a manner which allows a pharmaceutically effective amount to be delivered based upon patient's unique condition.

Suitable preparations for administering the compounds of formula I, including the physiologically acceptable salts thereof, will be apparent to those with ordinary skill in
10 the art and include for example tablets, pills, capsules, suppositories, lozenges, troches, solutions, syrups, elixirs, sachets, injectables, inhalatives, powders, etc.. The content of the pharmaceutically active compound(s) should be in the range from 0.1 to 95 wt.-%, preferably 5.0 to 90 wt.-% of the composition as a whole.

15 Suitable tablets may be obtained, for example, by mixing one or more compounds according to formula I with known excipients, for example inert diluents, carriers, disintegrants, adjuvants, surfactants, binders and/or lubricants. The tablets may also consist of several layers.

20 For this purpose, the compounds of formula I prepared according to the invention may be formulated, optionally together with other active substances, together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, citric acid, tartaric acid, water, polyvinylpyrrolidone, water/ethanol, water/glycerol, water/sorbitol,
25 water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof.

The compounds according to the invention may also be used in conjunction with
30 other active substances, particularly for the treatment and/or prevention of the diseases and conditions mentioned above. Other active substances which are suitable for such combinations include, for example, BACE inhibitors; amyloid aggregation inhibitors (e.g. ELND-005); directly or indirectly acting neuroprotective

and/or disease-modifying substances; anti-oxidants (e.g. vitamin E or ginkgolide); anti-inflammatory substances (e.g. Cox inhibitors, NSAIDs additionally or exclusively having Abeta lowering properties); HMG-CoA reductase inhibitors (statins); acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine, tacrine, galantamine);

5 NMDA receptor antagonists (e.g. memantine); AMPA receptor agonists; AMPA receptor positive modulators, AMPAkinases, monoamine receptor reuptake inhibitors, substances modulating the concentration or release of neurotransmitters; substances inducing the secretion of growth hormone (e.g., ibutamoren mesylate and capromorelin); CB-1 receptor antagonists or inverse agonists; antibiotics (e.g.,

10 minocyclin or rifampicin); PDE2, PDE4, PDE5, PDE9, PDE10 inhibitors, GABAA receptor inverse agonists, GABAA receptor antagonists, nicotinic receptor agonists or partial agonists or positive modulators, alpha4beta2 nicotinic receptor agonists or partial agonists or positive modulators, alpha7 nicotinic receptor agonists or partial agonists or positive modulators; histamine H3 antagonists, 5 HT-4 agonists or partial

15 agonists, 5HT-6 antagonists, alpha2-adrenoreceptor antagonists, calcium antagonists, muscarinic receptor M1 agonists or partial agonists or positive modulators, muscarinic receptor M2 antagonists, muscarinic receptor M4 antagonists, metabotropic glutamate-receptor 5 positive modulators, glycine transporter 1 inhibitors, antidepressants, such as citalopram, fluoxetine, paroxetine,

20 sertraline and trazodone; anxiolytics, such as lorazepam and oxazepam; antipsychotics, such as aripiprazole, clozapine, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone, and other substances that modulate receptors or enzymes in a manner such that the efficacy and/or safety of the compounds according to the invention is increased and/or unwanted side effects are reduced.

25 The compounds according to the invention may also be used in combination with immunotherapies (e.g., active immunisation with Abeta or parts thereof or passive immunisation with humanised anti-Abeta antibodies or nanobodies) for the treatment of the above-mentioned diseases and conditions.

30 The dosage for the combination partners mentioned above is usefully 1/5 of the lowest dose normally recommended up to 1/1 of the normally recommended dose.

Therefore, in another aspect, this invention relates to the use of a compound according to the invention or a physiologically acceptable salt thereof combined with at least one of the active substances described above as a combination partner, for preparing a pharmaceutical composition which is suitable for the treatment or prevention of diseases or conditions which can be affected by inhibitors of phosphodiesterase 2 and/or 10. These are preferably pathologies related to PDE2 and/or 10 hyperactivity and/or cAMP and/or cGMP hypofunction, particularly one of the diseases or conditions listed above, most particularly prodromal and mild-to-moderate Alzheimer's Disease and cognitive impairment associated with schizophrenia.

The use of the compound according to the invention, or a physiologically acceptable salt thereof, in combination with another active substance may take place simultaneously or at staggered times, but particularly within a short space of time. If they are administered simultaneously, the two active substances are given to the patient together; while if they are used at staggered times the two active substances are given to the patient within a period of less than or equal to 12 hours, but particularly less than or equal to 6 hours.

Consequently, in another aspect, this invention relates to a pharmaceutical composition which comprises a compound according to the invention or a physiologically acceptable salt of such a compound and at least one of the active substances described above as combination partners, optionally together with one or more inert carriers and/or diluents.

The compound according to the invention, or a physiologically acceptable salt thereof, and the additional active substance to be combined therewith may both be present together in one formulation, for example a tablet or capsule, or separately in two identical or different formulations, for example as a so-called kit-of-parts.

Examples

The following examples are intended to illustrate the invention, without restricting its scope.

Chemical Manufacture**Abbreviations:**

	ACN	acetonitrile
5	APCI	Atmospheric pressure chemical ionization
	d	day
	Cy	cyclohexane
	DCM	dichloromethane
	DIPEA	diisopropylethylamine
10	DMF	dimethylformamide
	DMA	dimethylacetamide
	ESI	electrospray ionization (in MS)
	EtOAc	ethylacetate
	EtOH	ethanol
15	Ex.	example
	h	hour(s)
	HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate
	HPLC	high performance liquid chromatography
20	HPLC-MS	coupled high performance liquid chromatography-mass spectrometry
	M	molar (mol/L)
	MeOH	methanol
	min	minute(s)
	MS	mass spectrometry
25	NMP	1-methyl-2-pyrrolidinone
	rt	room temperature
	R _t	retention time (in HPLC)
	TBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
	TEA	triethylamine
30	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	TLC	thin-layer chromatography
	UPLC- MS	ultra performance liquid chromatography - mass spectrometry

Methods:**UPLC-MS methods:****Method 1**

5 Instrument: LC/MS Waters Acquity UPLC System DAD, SQD single quadrupole;
column: HSS C18 1,8 μm 2,1 x 50 mm, Temp 35°C; mobile phase: A = H₂O 90% +
10% CH₃CN + CF₃COOH 0,1%, B = CH₃CN 90% + H₂O 10%; gradient: 0.0 min 0%
B → 1.20 min 100% B → 1.45 min 100% B → 1.55 min 0% B → 1.75 min 0% B; flow
rate: 0.70 mL/min; detection: UV 254 nm; detection: SQD, single quadrupole; ion
10 source: ES+/ ES-; scan range: 90-900 amu.

Method 2

Instrument: LC/MS Waters Acquity UPLC System DAD, SQD single quadrupole;
column: BEH C18 1,7 μm 2,1 x 50 mm, Temp 35°C; mobile phase: A = H₂O 90% +
10% CH₃CN + NH₄COOH 5 mmol, B = CH₃CN 90% + H₂O 10%; gradient: 0.0 min
15 0% B → 1.20 min 100% B → 1.45 min 100% B → 1.55 min 0% B → 1.75 min 0% B;
flow rate: 0.70 mL/min; detection: UV 254 nm; detection: SQD, single quadrupole; ion
source: ES+/ ES-; scan range: 90-900 amu.

Method 3

Instrument: LC/MS Waters Acquity UPLC System DAD, ELSD detector, SQD single
20 quadrupole; column: HSS C18 1,8 μm 2,1 x 50 mm, Temp 35°C; mobile phase:
A = H₂O 90% + 10% CH₃CN + CF₃COOH 0,1%, B = CH₃CN 90% + H₂O 10%;
gradient: 0.0 min 0% B → 2.40 min 100% B → 2.70 min 100% B → 2.80 min 0% B →
3.00 min 0% B; flow rate: 0.70 mL/min; detection: UV 254 nm; detection: ELSD
detector; detection: SQD, single quadrupole; ion source: ES+/ ES-; scan range: 90-
25 900 amu.

Method 4

Instrument: LC/MS Waters Acquity UPLC System DAD, ELSD detector, SQD single
quadrupole; column: HSS C18 1,8 μm 2,1 x 50 mm, Temp 35°C; mobile phase:
A = H₂O 90% + 10% CH₃CN + NH₄COOH 5 mmol, B = CH₃CN 90% + H₂O 10%;
30 gradient: 0.0 min 0% B → 2.40 min 100% B → 2.70 min 100% B → 2.80 min 0% B →
3.00 min 0% B; flow rate: 0.70 mL/min; detection: UV 254 nm; detection: ELSD
detector; detection: SQD, single quadrupole; ion source: ES+/ ES-; scan range: 90-
900 amu.

HPLC-MS methods:**Method 5**

Instrument: LC/MS ThermoFinnigan. Hplc Surveyor DAD, MSQ Quadrupole; column:

- 5 Synergi Hydro-RP80A, 4 μ m, 4.60 x 100 mm; eluent A: 90% water + 10% ACN + ammonium formate 10 mM; eluent B = ACN 90%+10% H₂O + NH₄COOH 10 mM; gradient: A (100) for 1.5 min, then to B (100) in 10 min for 1.5 min; flow rate: 1.2 mL/min; UV Detection: 254nm; Ion source: APCI.

Method 6

- 10 Instrument: LC/MS ThermoFinnigan HPLC Surveyor DAD, LCQ Fleet Ion Trap; column:

Simmetry Shield RP8, 5 μ m, 4,6 x 150 mm; eluent A: 90% water + 10% ACN + HCOOH 0.1%; eluent B = ACN 90%+10% H₂O + HCOOH 0.1%; gradient: 0.0 min 5% B → 1.5 min 5% B → 11.5 min 95% B → 13.0 min 95% B → 13.3 min 5% B → 15.0 min 5% B; flow rate: 1.0 mL/min; UV Detection: 254 nm; Detection: Finnigan Fleet, Ion Trap; ion source: ES+; scan range: 100-900 amu.

- 15

Method 7

Instrument: LC/MS ThermoFinnigan. Hplc Surveyor DAD, MSQ Quadrupole; column:

- 20 Synergi Hydro-RP8, 4 μ m, 4.60 x 100 mm; eluent A: 90% water + 10% ACN + ammonium formate 10 mM; eluent B = ACN 90%+10% H₂O + NH₄COOH 10 mM; gradient: 0.0 min 30% B → 1.50 min 50% B → 8.50 min 100% B → 13.50 min 100% B → 14.00 min 30% B → 15.00 min 30% B; flow rate: 0.85 mL/min; UV Detection: 254 nm; Ion source: ES+.

Method 8

- 25 Instrument: LC/MS ThermoFinnigan. Hplc Surveyor DAD, MSQ Quadrupole; column: Synergi Hydro-RP100A, 2.5 μ m, 3 x 50 mm; eluent A: 90% water + 10% ACN + ammonium formate 10 mM; eluent B = ACN 90%+10% H₂O + NH₄COOH 10 mM; gradient: A (100) for 1.5 min, then to B (100) in 10 min for 1.5 min; flow rate: 0.7 mL/min; UV Detection: 254nm; Ion source: APCI.

- 30 **Method 9**

Instrument: LC/MS ThermoFinnigan. Hplc Surveyor DAD, MSQ Quadrupole; column:

Synergi Hydro-RP100A, 2.5 μ m, 3 x 50 mm; eluent A: 90% water + 10% ACN +

NH₄COOH 5 mM; eluent B = ACN 90%+10% H₂O; gradient: A (100), then to B (100) in 4min for 1.3 min; flow rate: 1.2 mL/min; UV Detection: 254nm; Ion source: APCI.

Method 13

Instrument: LC/MS ThermoFinnigan HPLC Surveyor DAD, LCQ Fleet Ion Trap;

- 5 column: Xselect CSH, 2.5 μ m, 4.6 x 50 mm; eluent A: 90% water + 10% ACN + HCOOH 0.1%; eluent B = ACN 90%+10% H₂O + HCOOH 0.1%; gradient: A (100), then to B (100) in 4min for 1.3 min; then to A(100) in 1.6min. flow rate: 1.4 mL/min; UV Detection: 254nm; Ion source: ESI.

Method 16

- 10 Instrument: LC/MS Waters Alliance 2695 HPLC System DAD, Quattro Micro Triple quadrupole; Column:Atlantis dC18 5 μ m 4,6 x 50 mm, Temp 35°C: Mobile phase:A = H₂O 90% + 10% CH₃CN + CF₃COOH 0,05%; B = CH₃CN 90% + 10% H₂O; flow rate: 1.3 mL/min; UV Detection: 254nm; Ion source: ESI.

Gradient:

- | 15 | Time in min | %A | %B |
|----|-------------|-----|-----|
| | 0.00 | 100 | 0 |
| | 0.70 | 100 | 0 |
| | 4.5 | 0 | 100 |
| | 5.80 | 0 | 100 |
| 20 | 6.00 | 100 | 0 |

Method 17

Instrument: LC/MS ThermoFinnigan HPLC Surveyor DAD, LCQ Fleet Ion Trap;

- column: Xselect CSH, 2.5 μ m, 4.6 x 50 mm; eluent A: 90% water + 10% ACN + HCOOH 0.1%; eluent B = ACN 90%+10% H₂O + HCOOH 0.1%; flow rate: 1.4 mL/min; UV Detection: 254nm; Ion source: ESI.

Gradient:

- | | Time in min: | %A | %B |
|----|--------------|-----|-----|
| | 0.00 | 100 | 0 |
| | 1.00 | 100 | 0 |
| 30 | 8.50 | 0 | 100 |
| | 10.0 | 0 | 100 |
| | 10.2 | 100 | 0 |
| | 11.0 | 100 | 0 |

GC-MS methods:**Method 10 (3A.2)**

Instrument: GC/MS Thermo Scientific TRACE GC ULTRA, DSQ II MS single
5 quadrupole; column: Agilent DB-5MS, 25m x 0.25 mm x 0.25 μ m; carrier
gas: Helium, 1 mL/min constant flow; oven program: 50°C, to 100°C in 10°C/min, to
200°C in 20°C/min, to 320°C in 30°C/min (hold 10 min); detection: DSQ II MS single
quadrupole; ion source: EI; scan range: 50- 450 amu.

10 Preparative HPLC methods :**Method 11 :**

Instrument: Waters Autopurification HPLC/MS System; column: Sunfire C18, ODB
5.0 μ m, 19x100mm. MS Zq single quadrupole; eluent A: 90% water + 0.05% TFA;
15 eluent B = ACN gradient: 0.0 min 20% B $\rightarrow$ 6.5 min 60% B $\rightarrow$ 7.0 min 95% B $\rightarrow$ 8.5
min 20% B flow rate: 40 mL/min; UV Detection: 254 nm; Ion source: ES+.

Method 12 :

Instrument: Waters Autopurification HPLC/MS System; column: Sunfire C18, ODB
5.0 μ m, 19x100mm. MS Zq single quadrupole; eluent A: 90% water + 0.05% TFA;
20 eluent B = ACN gradient: 0.0 min 50% B $\rightarrow$ 6.5 min 90% B $\rightarrow$ 7.0 min 95% B $\rightarrow$ 8.5
min 50% B flow rate: 40 mL/min; UV Detection: 254 nm; Ion source: ES+.

Method 14:

Instrument: Waters Autopurification HPLC/MS System; column: Xbridge, C18 5 μ m,
19x100mm. MS Zq single quadrupole; eluent A: 90% water + NH₄COOH 5mM,
25 eluent B = ACN gradient: 0.0 min 40% B $\rightarrow$ 6.5 min 80% B $\rightarrow$ 7.0 min 95% B $\rightarrow$ 8.0
min 95% B $\rightarrow$ 8.5 min 40% B flow rate: 40 mL/min; UV Detection: 254 nm; Ion
source: ES+.

Method 15

Instrument: Waters Autopurification HPLC/MS System; column: Xbridge, C18 5 μ m,
30 19x100mm. MS Zq single quadrupole; eluent A: 90% water + NH₄COOH 5mM,
eluent B = ACN gradient: 0.0 min 30% B $\rightarrow$ 6.5 min 80% B $\rightarrow$ 6.50 min 70% B $\rightarrow$ 8.0
min 95% B $\rightarrow$ 8.5 min 30% B flow rate: 40 mL/min; UV Detection: 254 nm; Ion
source: ES+.

Chiral HPLC methods :

Instrument: HPLC Agilent 1100 (DAD equipped; UV Detection: 230 nm); flow rate: 15 mL/min; column temperature: 25°C.

5 Method C1

column: Daicel Chiralpack AS-H; eluent: Hexane:EtOH=70:30

Method C1a

column: Daicel Chiralpack AS-H; eluent: Hexane:EtOH=80:20

Method C2

10 column: Daicel Chiralpack AD-H; eluent: Hexane:Isopropanol=70:30

Method C2a

column: Daicel Chiralpack AD-H; eluent: Hexane:Isopropanol=75:25

Method C2b

column: Daicel Chiralpack AD-H; eluent: Hexane:Isopropanol=80:20

15 Method C2c

column: Daicel Chiralpack AD-H; eluent: Hexane:Isopropanol=60:40

Method C3

column: Daicel Chiralcel OJ-H; eluent: Hexane:EtOH=80:20

20 The most suitable purification techniques applied for the purification of compounds of the present invention are direct phase silica gel flash chromatography and reverse phase chromatography or preparative HPLC.

25 General comment concerning the presentation of the structures

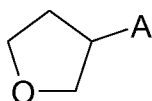
Compounds with stereogenic centre(s) : The structures depicted in the experimental section will not necessarily show all the stereochemical possibilities of the compounds but only one.

30 The structural presentation of the compounds in the experimental section will show a stereochemical bond only in case where the absolute stereochemistry is known.

The structural presentation of the compounds in the experimental section with unknown absolute stereochemistry will show a planar bond plus an additional comment that indicates if the described compound is a racemic mixture, a single stereoisomer and where applicable the relative stereochemistry.

5 Two examples are given below.

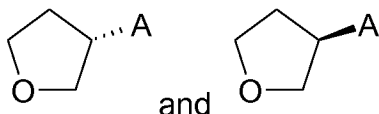
Example 1 : the presented chemical structure is depicted as:



Racemic mixture

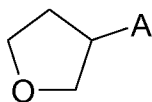
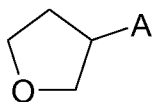
10

The added term racemic mixture points to the two stereochemical options and thus the manufactured compounds is a mixture of:



15

When racemic mixtures of above depicted structures are separated, the single stereoisomers are depicted as :



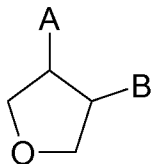
20 **Single stereoisomer a**

Single stereoisomer b

The added term 'single stereoisomer' indicates that the absolute configuration is unknown.

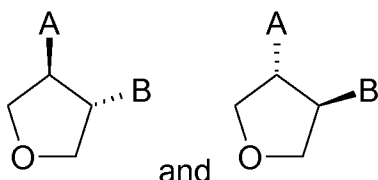
25 Single stereoisomer a is assigned to the first eluting isomer in chiral HPLC, single stereoisomer b is assigned to the second eluting isomer in chiral HPLC .

Example 2 : the presented chemical structure is depicted as:



TRANS-racemic mixture

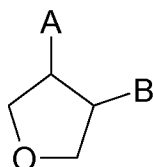
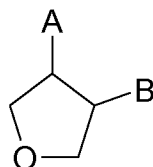
- 5 The added term 'TRANS- racemic mixture' points to the two stereochemical options and thus the manufactured compounds is a mixture of:



The same principles applies to 'CIS-racemic mixture' .

10

When racemic mixtures of above depicted structures are separated, the single stereoisomers are depicted as:



TRANS- single stereoisomer a

TRANS- single stereoisomer b

- 15 The added term 'TRANS-single stereoisomer' indicates a relative configuration known (trans) and the planar bond indicates the unknown absolute configuration.

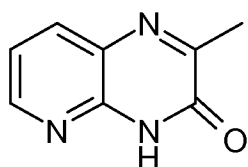
The same principles applies to 'CIS-single stereoisomer'.

Single stereoisomer a is assigned to the first eluting isomer in chiral HPLC, single stereoisomer b is assigned to the second eluting isomer in chiral HPLC .

20

Intermediates

Intermediate 1:

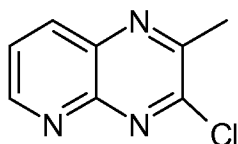


To a stirred solution of 2-oxo-propanoic acid (157 mL, 2.23 mmol) in dry MeOH (100 mL) at 0 °C, pyridine-2,3-diamine (20 g, 18 mmol) was added portionwise. The resulting solution was stirred at room temperature overnight, solvent was evaporated
5 under reduced pressure and the suspension filtered. The solid was washed with MeOH, dried to obtain 14 g of title compound.

HPLC-MS (Method 6): $R_t = 5$ min

MS: $m/z = 162$ ($M+H$)⁺

10 Intermediate 2:

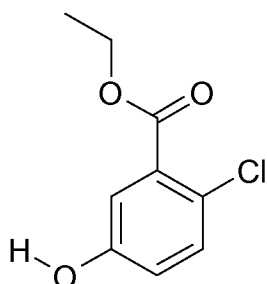


A mixture of Intermediate 1 (1 g) and phosphorus oxychloride (15 mL) was heated to 90 °C for 2.5 h. After cooling, the reaction mixture was carefully poured on ice, then neutralized with a saturated solution of Na₂CO₃ and diluted with DCM. Phases were
15 separated, organics washed with a saturated solution of NaCl, dried over sodium sulphate and evaporated to obtain 0.95 g of the title compound.

HPLC-MS (Method 8): $R_t = 4.54$ min

MS: $m/z = 180$ ($M+H$)⁺

20 Intermediate 3:



To a mixture of commercially available 2-chloro-5-hydroxybenzoic acid (4 g, 23.18mmol) in dry EtOH (90 mL), concentrated sulphuric acid (1 mL, 17.62mmol) was added. The mixture was stirred under reflux overnight, then solvent evaporated under reduced pressure and the residue dissolved with DCM. A saturated solution of

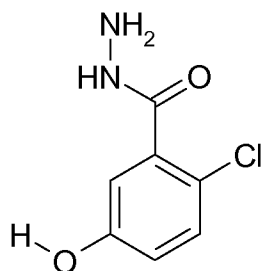
5 NaHCO₃ was added, phases were separated, organics dried over sodium sulphate , filtered and evaporated to obtain 5 g of the corresponding 2-chloro-5-hydroxybenzoic acid ethyl ester.

HPLC-MS (Method 2): R_t = 1.0 min

MS: m/z = 201.6 (M+H)⁺

10

Intermediate 4:



Intermediate 3 (5 g, 23.62 mmol) was dissolved in EtOH (100 mL) and hydrazine hydrate (13.0 mL, 262.12 mmol) was added. Mixture was stirred under reflux for 24 h,

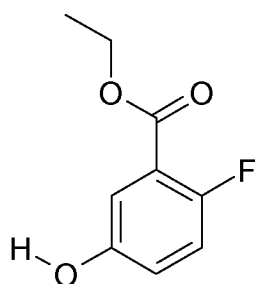
15 solvent evaporated and the crude treated with 20 mL of water. The white solid formed was filtered and washed with water and dried for 3 h at 60°C over P₂O₅ to obtain 3.0 g of title compound.

HPLC-MS (Method 2): R_t = 0.53 min

MS: m/z = 180 (M+H)⁺

20

Intermediate 5:



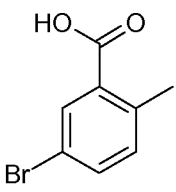
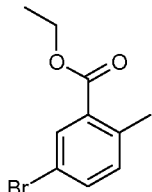
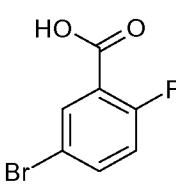
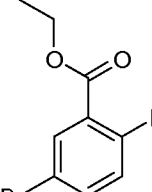
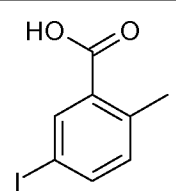
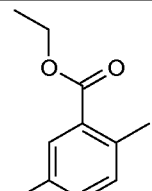
Intermediate 5 was prepared as described for Intermediate 3 starting from commercially available 2-fluoro-5-hydroxy-benzoic acid (1 g, 6.41 mmol) to obtain 1.17 g of the title compound.

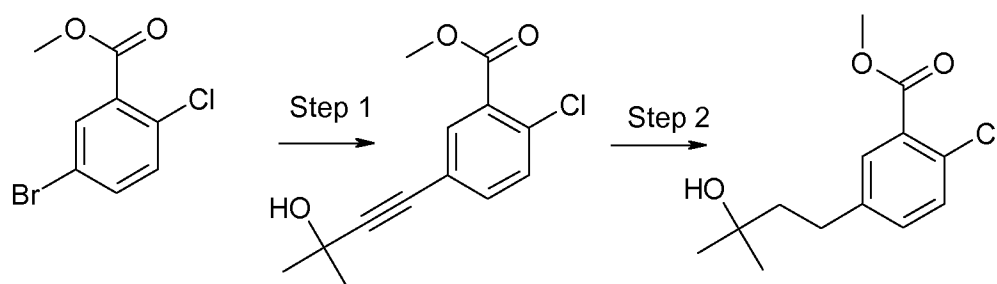
HPLC-MS (Method 2): $R_t = 0.94$ min

5 MS : $m/z = 185.16$ ($M+H$)⁺

The following Ester Intermediates were prepared in analogy to Intermediate 3 starting from commercially available benzoic acids.

Starting benzoic acid	Ester Intermediate		MS m/z	R_t (min)	Method
	5a		180 [M] ⁺	9.73	10
	5b		203 [M+H] ⁺	1.2	2
	5c		263 [M] ⁺	9.90	10
	5d		310 [M] ⁺	10.47	10
	5e		294 [M] ⁺	9.52	10

	5f		242 [M] ⁺	9.42	10
	5g		246 [M] ⁺	8.84	10
	5h		290 [M] ⁺	10.15	10

Intermediate 5iStep 1:

- 5 Step 1 was performed in analogy to what reported in literature reference: Li, Yuanzhen et al. Organic Letters, 2007, vol. 9, # 20 p. 4057 – 4060, starting from Ester Intermediate 5c.

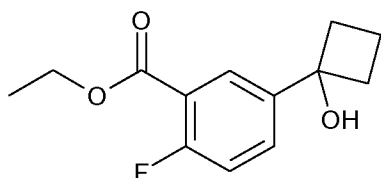
Step 2:

Intermediate obtained from Step 1 (0.5 g), was dissolved in toluene (10 mL).

- 10 Wilkinson's catalyst $\text{RhCl}(\text{TPP})_3$ (0.1g) was added and the reaction mixture stirred at 60°C under hydrogen atmosphere for 18h. The reaction mixture was filtered on a celite pad and the solvent was removed under vacuum to obtain the desired product (0.4 g).

GC-MS (Method 10) $R_t = 11,55$ min

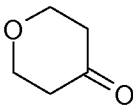
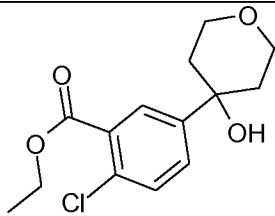
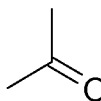
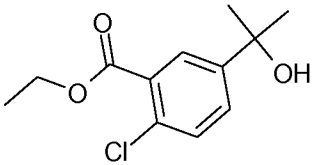
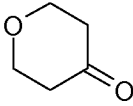
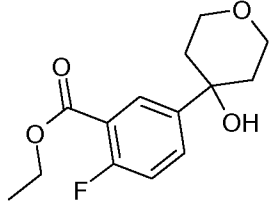
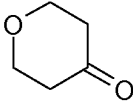
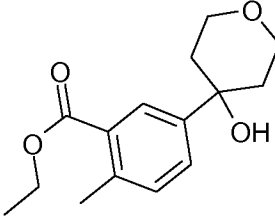
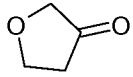
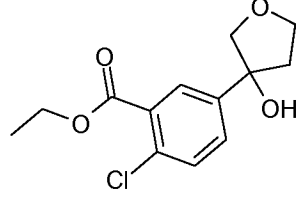
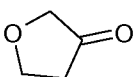
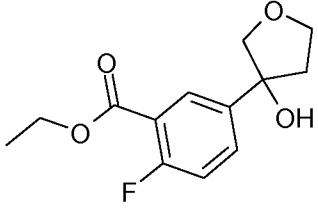
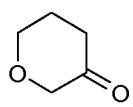
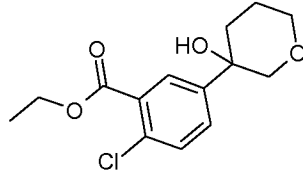
- 15 MS : $m/z = 256$ [M]⁺

Intermediate 5j

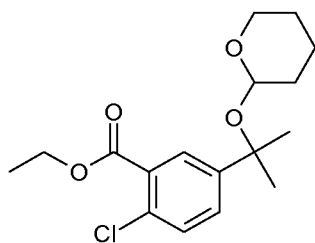
- Under nitrogen atmosphere, starting Ester Intermediate 5e (5.0 g, 15.3 mmol) was dissolved in THF (40 mL), the reaction mixture was cooled to -50°C and stirred for 10 minutes. Isopropyl-magnesium-chloride (11 mL of a 2M solution in THF) was added dropwise and the reaction mixture was stirred at -50°C for 2h. The reaction mixture was cooled to -78°C and a solution of cyclobutanone (2.15 g, 30.6 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred at -78°C for 1h, then warmed to room temperature and stirred for 18h. The solvent was removed under vacuum, dichloromethane was added and the reaction mixture was washed with a saturated solution of NaHCO₃, The organic phase was concentrated under vacuum and the crude product obtained was purified by flash chromatography (eluent from 90:10 to 80:20 Cy/EtOAc) to obtain the desired product (3.0 g).
- GC-MS (Method 10): R_t = 10.91 min
MS : m/z = 210 (M-28)⁺

- The following Ester Intermediates were prepared in analogy to Intermediate 5j and purified applying the most suitable purification technique, starting from the corresponding Starting Esters Intermediates and commercially available ketones.

Starting Ester intermediate	Starting ketone	Ester intermediate Structure		MS m/z	R _t (min)	Method
5d		5k		255 [M+H] ⁺	4.23	16

5d		5l		284[M] ⁺	12.58	10
5d		5m		243 [M+H] ⁺	1.04	2
5e		5n		268[M] ⁺	11.97	10
5h		5na		264[M] ⁺	12.18	10
5d		5q		253 [M+H] ⁺	2.84	13
5e		5r		237 [M-17] ⁺	2.68	13
5d		5s		284[M] ⁺	12.42	10

Intermediate 5o

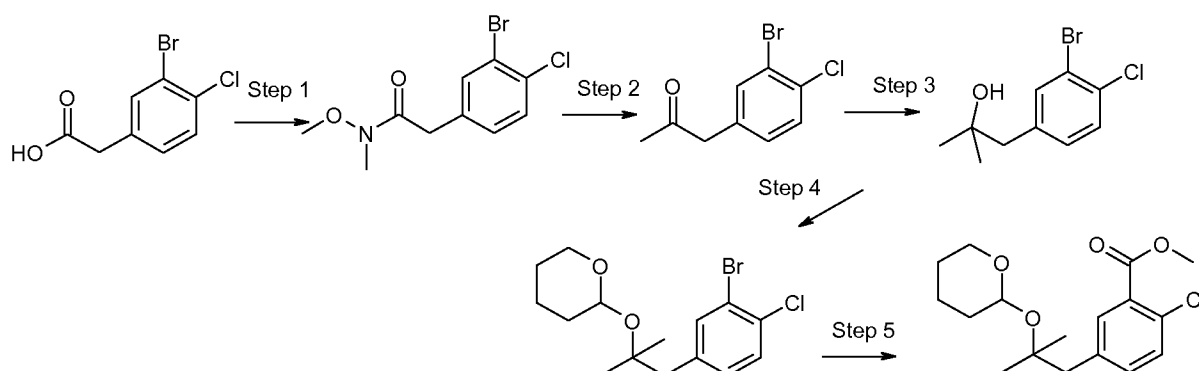


To a solution of Ester Intermediate 5m (0.37 g, 1.52 mmol) in dichloromethane (9 mL), pyridinium-para-toluenesulfonate (0.06 mg, 0.23 mmol) and 3,4-dihydro-2H-pyran (0.2 mL, 2.29 mmol) were added and the reaction mixture was stirred at room temperature for 4h. The reaction mixture was washed with water and the organic phase was concentrated under vacuum. Crude was purified by flash chromatography (eluent from 100:0 to 80:20 Cy/EtOAc) to obtain the desired product (0.4 g).

GC-MS (Method 10): $R_t = 12.52$ min

MS : $m/z = 326$ (M)⁺

Intermediate 5p



Step 1:

Step 1 was performed in analogy to what reported in the literature reference: Duong, Hung A.; et al. *Angewandte Chemie, International Edition*, 2011, vol.50, p. 463 – 466, starting from commercially available (3-bromo-4-chloro-phenyl)-acetic acid.

Step 2:

Under nitrogen atmosphere, a solution of Intermediate from Step 1 (0.24 g) in THF (10 mL) was stirred at -60°C, methylmagnesium bromide was added dropwise and the reaction mixture was stirred at -78 °C to r.t. for 2 h. The reaction mixture was quenched with saturated ammonium chloride water solution and extracted with ethyl acetate twice, dried over sodium sulfate and concentrated under vacuum to get the crude product as colour-less oil.

Step 3:

Step 3 was performed in analogy to Step 2 starting from Intermediate obtained in Step 2.

Step 4:

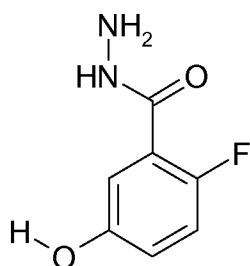
- 5 Step 4 was performed in analogy to preparation of Intermediate 5o, starting from Intermediate obtained in Step 3.

Step 5:

- To a solution of the Intermediate obtained from Step 4 (15 g) in MeOH (150 mL), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)] (3.088g) and
 10 triethylamine (22 g, 21.4 mL) were added and the reaction mixture was stirred at 80°C under CO atmosphere for 36 h.

The solvent was removed under vacuum and the crude product obtained was purified by flash chromatography to get the desired product.

15 Intermediate 6:



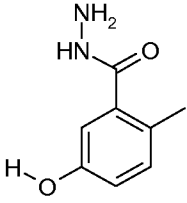
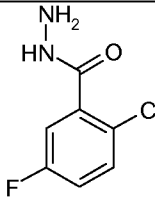
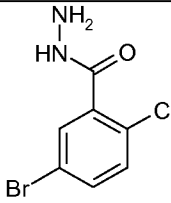
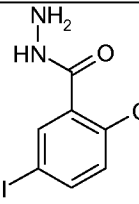
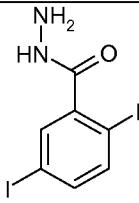
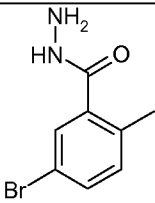
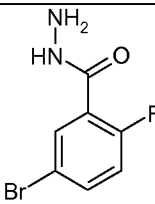
Intermediate 6 (4,4 g) was prepared as described for Intermediate 4 and purified applying the most suitable purification technique, starting from Intermediate 5 (5.84 g, 0.03 mmol).

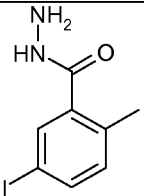
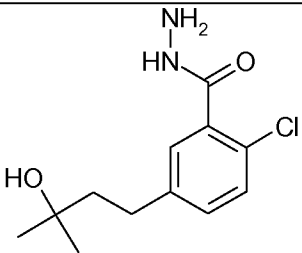
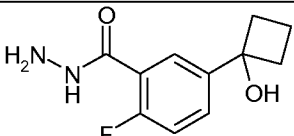
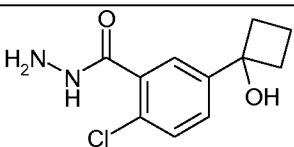
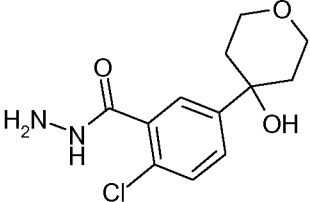
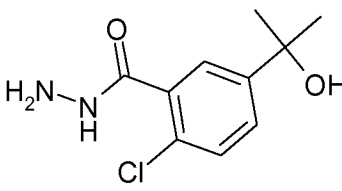
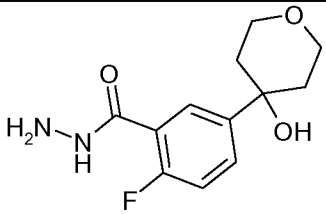
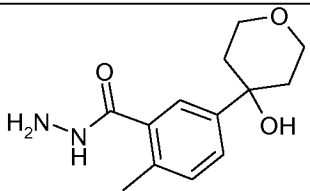
- 20 HPLC-MS (Method 2): $R_t = 0.42$ min

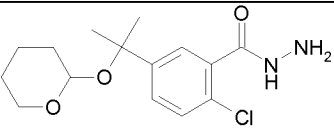
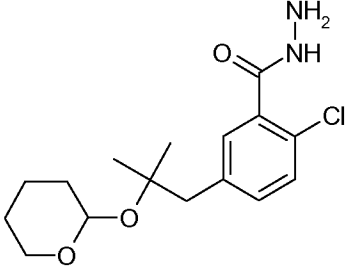
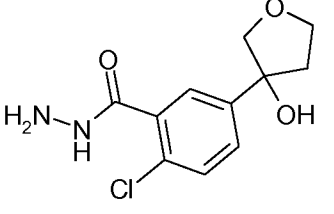
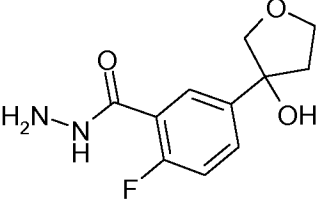
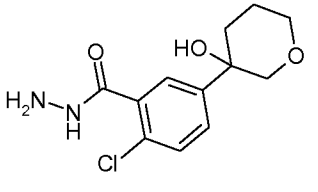
MS: $m/z = 171.2$ ($M+H$)⁺

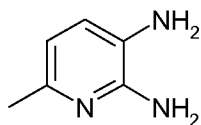
- The following Hydrazide Intermediates were prepared in analogy to Intermediate 4 and purified applying the most suitable purification technique, starting from the
 25 corresponding Ester Intermediates.

Starting Ester	Hydrazide Intermediate Structure	MS m/z	R_t (min)	Method
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intermediate					
5a	6a		167 [M+H] ⁺	0.47	17
5b	6b		188 [M] ⁺	9.47	10
5c	6c		249 [M+H] ⁺	1.98	13
5d	6d		296 [M] ⁺	11.78	10
5e	6e		281[M+H] ⁺	1.83	9
5f	6f		229[M+H] ⁺	1.80	9
5g	6g		233[M+H] ⁺	1.55	9

5h	6h		277 [M+H] ⁺	1.94	9
5i	6i		256 [M+H] ⁺	0.68	2
5j	6j		225 [M+H] ⁺	0.56	2
5k	6k		241 [M+H] ⁺	0.59	2
5l	6l		271 [M+H] ⁺	0.57	2
5m	6m		228 [M] ⁺	11.79	10
5n	6n		255 [M+H] ⁺	0.43	2
5na	6na		251 [M+H] ⁺	0.57	2

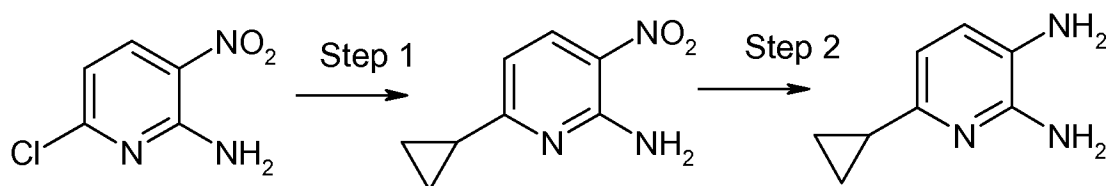
5o	6o		313[M+H] ⁺	0.85	2
5p	6p		327[M+H] ⁺	0.90	2
5q	6q		257 [M+H] ⁺	0.49	13
5r	6r		241[M+H] ⁺	0.44	2
5s	6s		271[M+H] ⁺	0.58	2

Intermediate 7:

- 5 Commercially available 2-amino-6-methyl-3-nitropyridine (12 g, 78.36 mmol) was dissolved in a mixture of dry THF/MeOH (1:1, 60 mL) and hydrogenated in the presence of Pd/C (10%, 1.2 g) under 5 bar hydrogen atmosphere for 5 h. Catalyst was filtered, solvent evaporated under reduced pressure to obtain 7 g of the title compound.
- 10 HPLC-MS (Method 2): R_t = 0.77 min

MS : $m/z = 154(M+H)^+$

Intermediate 7a



5 Step 1:

2-Amino-6-chloro-3-nitro-pyridine (20 g, 115 mmol), cyclopropylboronic acid (12.8 g, 150 mmol), tricyclohexylphosphine (3.2 g, 11.5 mmol), 2,6-ditert-butyl-4-methylphenol (5.08 g, 23 mmol), palladium acetate (1.3 g, 5.7 mmol) and tri-potassium-phosphate (73 g, 346 mmol) were suspended in toluene (40 mL) and
10 water (2 mL). The reaction mixture was stirred at reflux for 18h, diluted with ethyl acetate and washed with water. The organic phase was separated, concentrated under vacuum and dried over sodium sulfate. The crude product obtained was purified by flash chromatography (eluent from 90:10 to 45:55 Cy/EtOAc) to obtain the desired product (10.6 g).

15 GC-MS (Method 10): $R_t = 10.54$ min

MS : $m/z = 179 (M)^+$

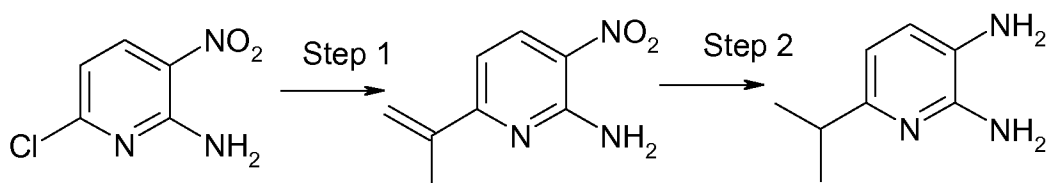
Step 2:

To a solution of Intermediate from Step 1 (6 g, 19 mmol) in absolute EtOH (120 mL), zinc (13.7 g, 209 mmol) and ammonium chloride (30.8 g, 573 mmol) were added and
20 the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was filtered on a celite pad, the solvent was removed under vacuum and the crude product obtained was purified by flash chromatography (eluent 90:10 dichloromethane/MeOH) to obtain the desired product (2.4 g).

HPLC-MS (Method 9): $R_t = 1.42$ min

25 MS : $m/z = 150 (M+H)^+$

Intermediate 7b

Step 1:

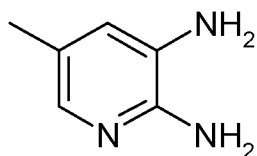
Step 1 was performed in analogy to what described in Step 1 in the preparation of Intermediate 7a, starting from commercially available 2-isopropenyl-4,4,5,5-

Step 2:

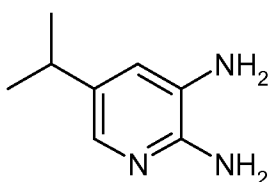
Intermediate from Step 1 (5 g, 26.5 mmol) was dissolved in 20 mL of methanol, Pd/C (0.25 g) was added and the reaction mixture was stirred under hydrogen atmosphere (4 bar) for 2h at room temperature. The reaction mixture was filtered on a celite pad and the solvent was removed under vacuum to give the desired product (3 g).

GC-MS (Method 10): $R_t = 8.91$ min

MS : $m/z = 151$ (M)⁺

Intermediate 7c:

Intermediate 7c (3.99 g) was prepared in analogy to Intermediate 7 and purified applying the most suitable purification technique, starting from commercially available 2-amino-3-nitro-5-picoline (5.0 g, 32.65 mmol).

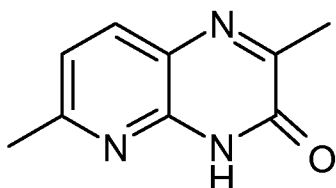
Intermediate 7d

Intermediate 7d (4 g) was prepared in analogy to Intermediate 7b and purified applying the most suitable purification technique, starting from commercially available 2-amino-5-chloro-3-nitro-pyridine (5 g, 26.5 mmol).

HPLC-MS (Method 2): $R_t = 0.6$ min

MS: $m/z = 152 (M+H)^+$

Intermediate 8:



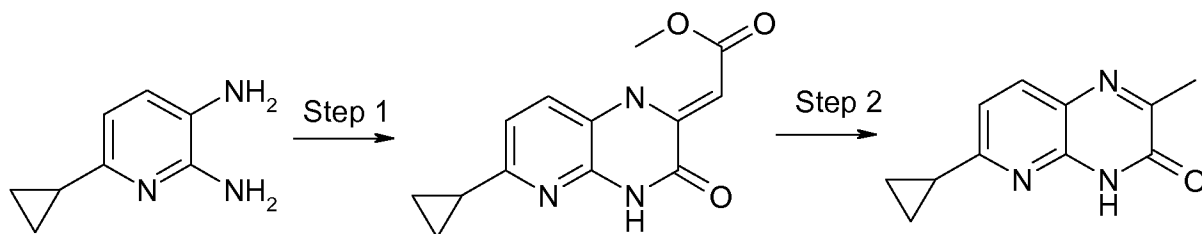
- 5 To stirred solution of 2-oxo-propanoic acid (40.8 mL, 587 mmol) in dry MeOH (130 mL) at 0 °C, 6-methyl-pyridine-2,3-diamine (Intermediate 7, 6.8 g, 55.2 mmol) dissolved in dry MeOH (40mL) was added dropwise. The solution was stirred at room temperature overnight then solvent was evaporated under reduced pressure and the resulting suspension filtered. The solid was washed with MeOH, dried to obtain 1.35

10 g of title compound.

HPLC-MS (Method 9): $R_t = 1.31$ min

MS: $m/z = 176 (M+H)^+$

Intermediate 8a



15

Step 1:

- Intermediate 7a (2.4 g, 15.2 mmol) was dissolved in absolute EtOH and stirred at 0°C, Dimethylacetylenedicarboxylate (2.4 g, 16.8 mmol) was added dropwise and the reaction mixture was allowed to react room temperature for 18h. The solid formed was filtered, washed with EtOH, Ethyl Ether and dried in vacuum to give the desired product (3 g).

20 HPLC-MS (Method 13): $R_t = 3.16$ min

MS : $m/z = 260 (M+H)^+$

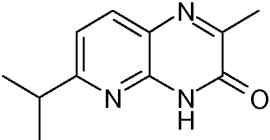
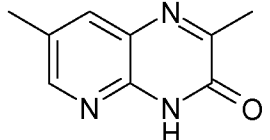
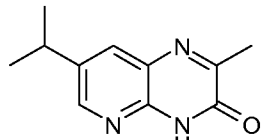
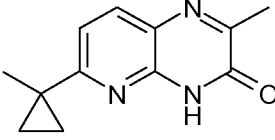
25 Step 2:

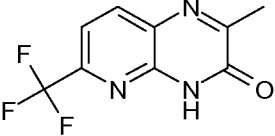
Intermediate obtained from Step 1 (3 g 0.01 mol) was dissolved in a sodium hydroxide water solution (1.36 g , 0.03 mol in 50 mL) and the reaction mixture was reflux for 2h. pH was adjusted to 2-3 and the reaction mixture was extracted with ethyl acetate. The organic phase was dried over sodium sulfate, concentrated under vacuum. The crude product obtained was purified by flash chromatography (eluent from 80:20 to 20:80 Cy/EtOAc) to obtained the desired product (2.0 g).

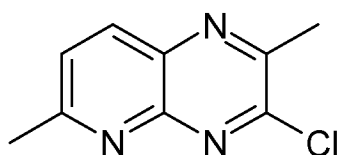
HPLC-MS (Method 13): $R_t = 2.46$ min

MS : $m/z = 202$ (M+H)⁺

- 10 The following Amide Intermediates were prepared in analogy to Amide Intermediate 8a and purified applying the most suitable purification technique, starting from the corresponding Di-amine Intermediates.

Starting Di-amine Intermediate	Amide Intermediate Structure		MS m/z	R_t (min)	Method
7b	8b		204 [M+H] ⁺	2.48	13
7c	8c		176 [M+H] ⁺	1.88	13
7d	8d		204[M+H] ⁺	0.78	2
6-(1-Methyl-cyclopropyl)-pyridine-2,3-diamine (commercially available)	8e		216 [M+H] ⁺	4.96	17

6-trifluoromethyl-pyridine-2,3-diamine (commercially available)	8f		229 [M] ⁺	9.42	10
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Intermediate 9:

5

A mixture of Amide intermediate 8 (1.35 g, 7.71 mmol) and phosphorus oxychloride (16 mL) was heated to 90 °C for 3h. After cooling, solvent was reduced under reduced pressure, the reaction mixture was carefully poured on ice and neutralized with a saturated solution of Na₂CO₃. DCM was added, phases were separated, organics washed with a saturated solution of NaCl, dried over sodium sulphate and evaporated to obtain 1.39 g of the title compound.

10

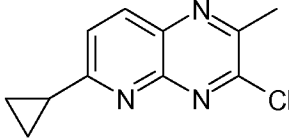
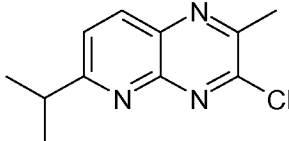
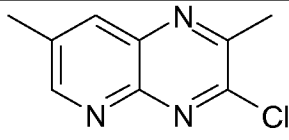
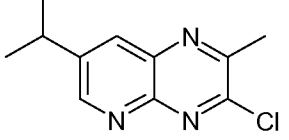
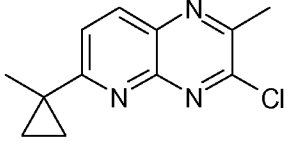
HPLC-MS (Method 8): R_t = 0.84min

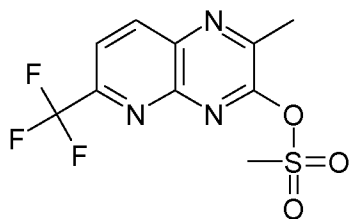
MS : m/z = 194.6 (M+H)⁺

15

The following Chloride Intermediates were prepared in analogy to Chloride Intermediate 9 and purified applying the most suitable purification technique, starting from the corresponding Amide Intermediates. Heating temperature reported in Table.

Starting Amide Intermediate	Chloride Intermediate Structure	Heating Temperature	MS m/z	R _t (min)	Method
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8a	9a		55°C	220 [M+H] ⁺	1.01	2
8b	9b		80°C	222 [M+H] ⁺	3.18	13
8c	9c		90°C	194 [M+H] ⁺	2.52	13
8d	9d		55°C	222 [M+H] ⁺	3.19	13
8e	9e		80°C	234 [M+H] ⁺	1.15	2

Intermediate 9f

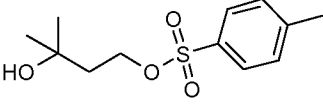
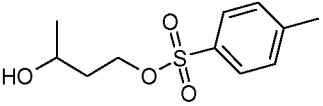
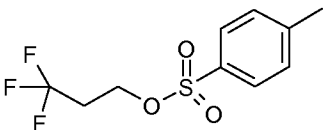
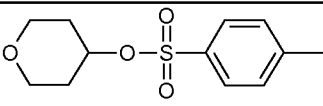
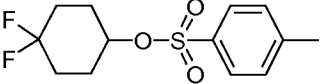
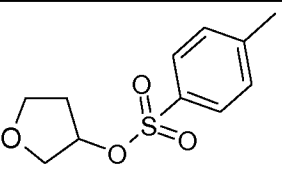
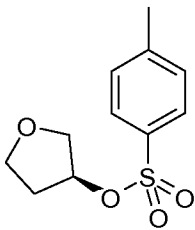
Intermediate 8f (1.35 g, 5.9 mmol) and N,N-diisopropylethylamine (2.28 g, 3 mmol) were dissolved in DMF (10 mL). The reaction mixture was cooled to 0°C and methanesulfonylchloride (0.74 g, 6.48 mmol) was added dropwise. The reaction mixture was allowed to reach room temperature and stirred for 4h. Ammonium chloride saturated water solution was added and the reaction mixture was extracted with dichloromethane. The organic phase was washed with citric acid (10% water solution), dried over sodium sulfate and concentrated under vacuum, to give the desired product (1.5 g).

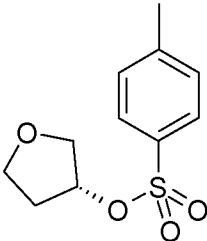
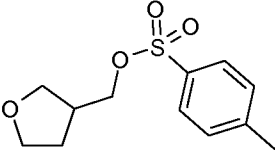
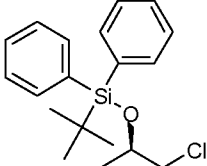
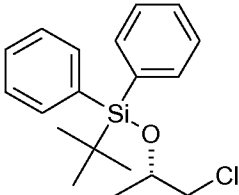
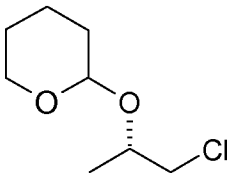
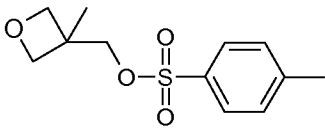
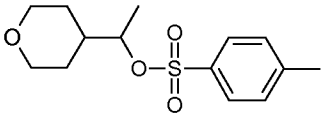
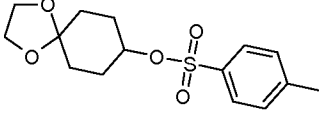
HPLC-MS (Method 13): $R_t = 3.09$ min

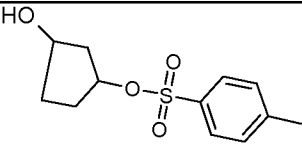
MS : $m/z = 308$ (M+H)⁺

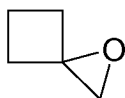
The following Intermediates were prepared based on well known reported

5 procedures starting from commercially available starting materials.

Intermediate		Structure	Reference
10	<u>Toluene-4-sulfonic acid</u> <u>3-hydroxy-3-methyl-</u> <u>butyl ester</u>		Bioorganic & Medicinal Chemistry Letters (2007), 17(22), 6164-6168
11	<u>Toluene-4-sulfonic acid</u> <u>3-hydroxy-butyl ester</u>		Bioorganic & Medicinal Chemistry, 18(4), 1665-1675; 2010
12	<u>Toluene-4-sulfonic acid</u> <u>3,3,3-trifluoro-propyl</u> <u>ester</u>		US 2009-564132
13	<u>Toluene-4-sulfonic acid</u> <u>tetrahydropyran-4-yl</u> <u>ester</u>		WO 2011-20767
14	<u>Toluene-4-sulfonic acid</u> <u>4,4-difluoro-cyclohexyl</u> <u>ester</u>		WO 2008-119663
15	<u>Toluene-4-sulfonic acid</u> <u>tetrahydro-furan-3-yl</u> <u>ester</u>		WO 2010- 023594
16	<u>Toluene-4-sulfonic acid</u> <u>(S)-(tetrahydro-furan-3-</u> <u>yl) ester</u>		WO 2011-061590

17	<u>Toluene-4-sulfonic acid</u> <u>(R)-(tetrahydro-furan-3-</u> <u>yl) ester</u>		WO 2010-102512
18	<u>Toluene-4-sulfonic acid</u> <u>tetrahydro-furan-3-</u> <u>ylmethyl ester</u>		WO 2011-084402
19	<u>tert-Butyl-(R)-2-chloro-</u> <u>1-methyl-ethoxy)-</u> <u>diphenyl-silane</u>		Tetrahedron Letters (1982), 23(25), 2543- 6.
20	<u>tert-Butyl-(S)-2-chloro-</u> <u>1-methyl-ethoxy)-</u> <u>diphenyl-silane</u>		Tetrahedron Letters (1982), 23(25), 2543- 6.
21	<u>2-((S)-2-Chloro-1-</u> <u>methyl-ethoxy)-te</u> <u>tetrahydro-pyran</u>		Tetrahedron Letters (1982), 23(25), 2543- 6.
26	<u>Toluene-4-sulfonic acid</u> <u>3-methyl-oxetan-3-</u> <u>ylmethyl ester</u>		Synthetic Communications (2011), 41(17), 2539- 2543
27	<u>Toluene-4-sulfonic acid</u> <u>1-(tetrahydro-pyran-4-</u> <u>yl)-ethyl ester</u>		Journal of Organometallic Chemistry (1978), 150(2), 179-85
28	<u>Toluene-4-sulfonic acid</u> <u>1,4-dioxa-</u> <u>spiro[4.5]dec-8-yl ester</u>		WO 2010-006086

29	<u>Toluene-4-sulfonic acid</u> <u>3-hydroxy-cyclopentyl</u> <u>ester</u>		US 2007-0049537
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Intermediate 29a

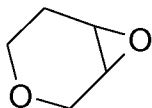
Literature Reference: Journal of Organic Chemistry USSR (English Translation),
 5 1989 , vol. 25, # 6.1 p. 1019-1025).

Epoxide Intermediate 29a (4 g) was prepared in analogy to what described in
 WO2010/47956 A1, starting from methylene cyclobutane (5 g, 73 mmol).

GC-MS (Method 10) $R_t = 2.70$ min

$[M]^+ = 83$

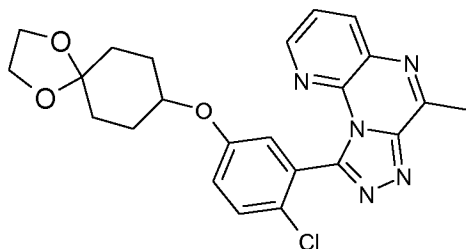
10

Intermediate 29b

Epoxide Intermediate 29b (1 g) was prepared in analogy to what described in
 WO2013/55577 A1 starting from 3,6-Dihydro-2H-pyran (2 g, 23.78 mmol).

15 GC-MS (Method 10) $R_t = 8.10$ min

$[M]^+ = 99$

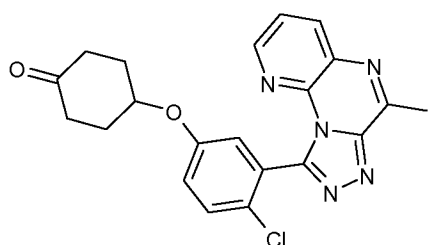
Intermediate 29c:

20 To a solution of Example 1 (0.2 g, 0.67 mmol) in dry DMF (3 mL), cesium carbonate (0.63 g, 1.92 mmol) and Intermediate 28 (0.41 g, 1.28 mmol) were added. Mixture was heated at 80°C for 1 h, then solvent evaporated under reduced pressure and the

residue dissolved in DCM and washed with a saturated solution of NaCl. Phases were separated, organics dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.21 g of the title compound.

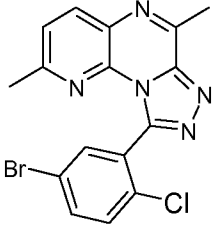
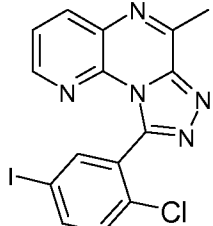
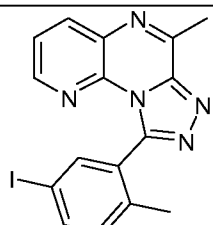
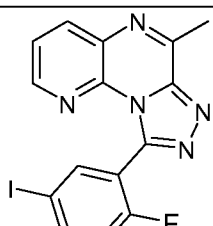
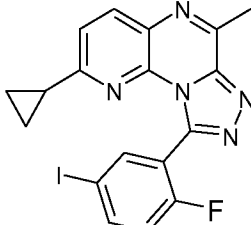
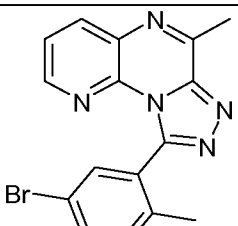
- 5 HPLC-MS (Method 2): $R_t = 1.12$ min
MS: $m/z = 452$ ($M+H$)⁺

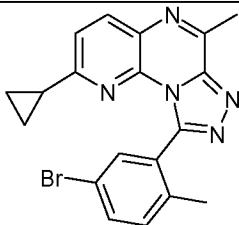
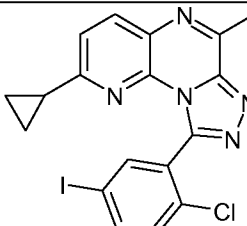
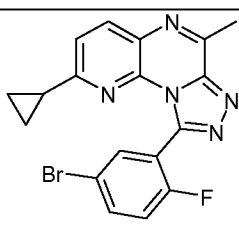
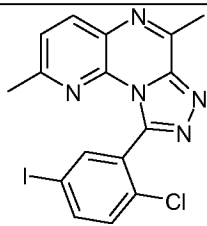
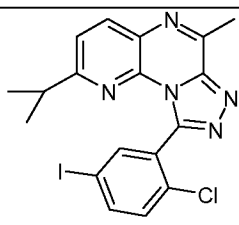
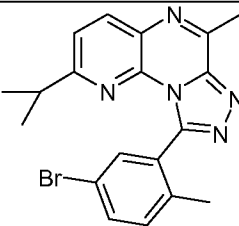
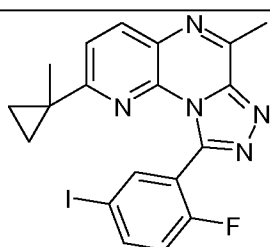
Intermediate 30:

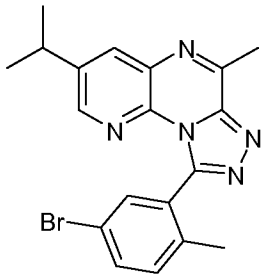
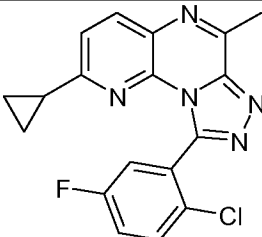
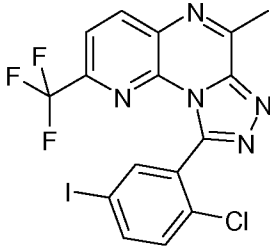
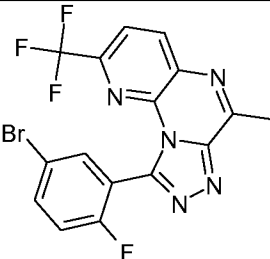


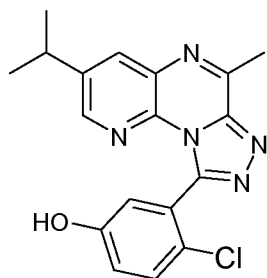
- 10 To a solution of Intermediate 29c (0.21 g, 0.46 mmol) in acetone (10 mL), a 4M solution of HCl (1 mL) was added and mixture stirred at room temperature for 2 h. Solvent was evaporated under reduced pressure, the residue treated with DCM, washed with a saturated solution of NaHCO₃. Phases were separated, organics dried over sodium sulphate and evaporated. The residue was purified by flash
- 15 chromatography (eluent from 90:10 to 50:50 Cy/EtOAc) to obtain 0.18 g of the title compound.
- HPLC-MS (Method 2): $R_t = 1.09$ min
MS: $m/z = 410$ ($M+H$)⁺
- 20 The following intermediates were prepared in analogy to Example 1 and purified applying the most suitable purification technique, starting from the corresponding Chloride and Idrazide intermediates:

Chloride Inter- mediate	Hydrazide	Intermediate Structure	MS m/z	R_t (min)	Method
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9	6c	30a		388 [M+H] ⁺	3.58	13
2	6d	30b		422 [M+H] ⁺	1.07	2
2	6h	30c		402 [M+H] ⁺	3.00	9
2	6e	30d		406 [M+H] ⁺	3.02	9
9a	6e	30e		446 [M+H] ⁺	3.78	13
2	6f	30f		354 [M+H] ⁺	3.35	13

9a	6f	30g		394 [M+H] ⁺	3.69	13
9a	6d	30h		462 [M+H] ⁺	3.81	13
9a	6g	30i		398 [M+H] ⁺	3.72	13
9	6d	30j		436 [M+H] ⁺	3.64	13
9b	6d	30k		464 [M+H] ⁺	3.99	13
9b	6f	30l		396 [M+H] ⁺	3.85	13
9e	6e	30m		460 [M+H] ⁺	1.29	2

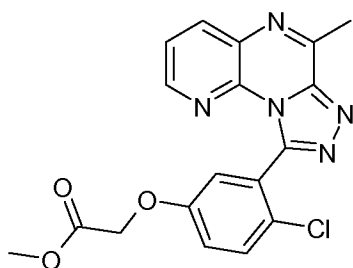
9d	6f	30n		397 [M+H] ⁺	1.27	2
9a	6b	30o		354 [M+H] ⁺	3.53	13
9f	6d	30r		490 [M+H] ⁺	1.25	2
9f	6g	30s		427 [M+H] ⁺	1.15	2

Intermediate 30p

Intermediate 30p (0.26 g) was prepared in analogy to Example 1 and purified
 5 applying the most suitable purification technique, starting from Chloride Intermediate
 9d (0.25 g, 1.01 mmol) and Hydrazide Intermediate 4 (0.19 g, 1.01 mmol) .
 HPLC-MS (Method 2): R_t = 1.01 min

MS: $m/z = 354 (M+H)^+$

Intermediate 31

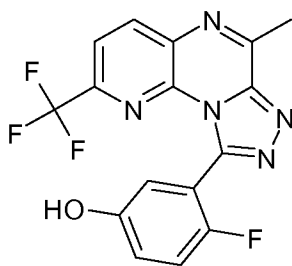


- 5 To a solution of Example 1 (0.4 g, 1.3 mmol) in dry DMF (4 mL), cesium carbonate (0.85 g, 2.62 mmol) and methylbromoacetate (0.152 mL, 1.56 mmol) were added. Mixture was stirred at room temperature overnight, solvent evaporated and the residue treated with EtOAc. A saturated solution of NH_4Cl was added, phases were separated and evaporated. The crude was purified by flash chromatography (eluent
- 10 from 50:50 to 0:100 Cy/EtOAc) to obtain 0.29 g of the title compound.

HPLC-MS (Method 13): $R_t = 3.06$ min

MS: $m/z = 384 (M+H)^+$

Intermediate 32



15

Intermediate 32 (0.5 g) was prepared in analogy to Example 1 and purified applying the most suitable purification technique, starting from Intermediate 9f (0.9 g, 2.52 mmol) and Hydrazide Intermediate 6 (0.47 g, 2.77 mmol).

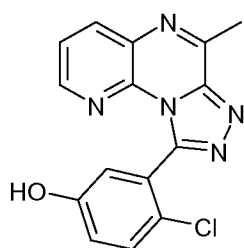
HPLC-MS (Method 13) $R_t = 3.11$ min

20

MS : $m/z = 380 (M+H)^+$

Exemplary embodiments:

Example 1:



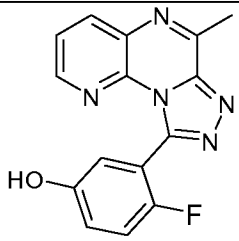
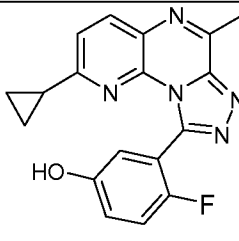
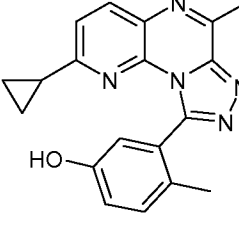
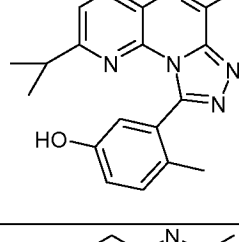
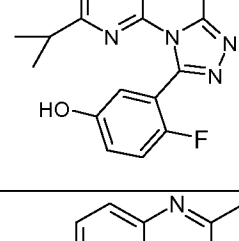
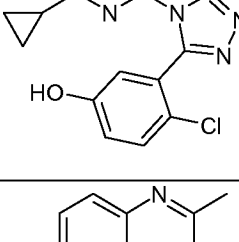
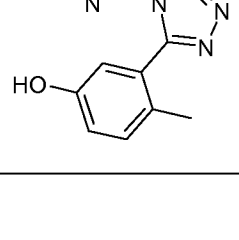
Intermediate 2 (0.60 g, 3.34 mmol) and Intermediate 4 (0.62 g, 3.34 mmol) were suspended in cyclohexanol (5 mL) and heated under reflux for 2 h. The resulting solution was cooled and solvent evaporated under reduced pressure and the residue purified by flash chromatography (eluent 95:5 DCM/EtOH) to obtain 0.95 g of the title compound.

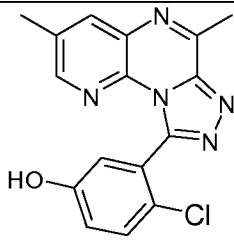
HPLC-MS (Method 9): $R_t = 2.17$ min

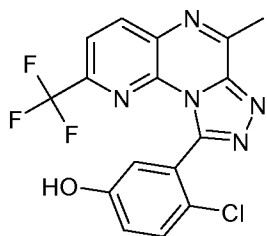
MS : $m/z = 312$ ($M+H$)⁺

- 10 The following Examples were prepared in analogy to Example 1 and purified applying the most suitable purification technique, starting from the corresponding Chloride Intermediates and Hydrazide Intermediates:

Starting Chloride Intermediate	Starting Hydrazide Intermediate	Ex.	Structure	MS m/z [$M+H$] ⁺	R_t (min)	Method
9	4	2		326	0.93	2
9	3-hydroxy-benzhydrazide (commercially available)	3		292	2.62	13

2	6	4		296	0.79	13
9a	6	5		336	2.97	13
9a	6a	6		226	2.93	13
9b	6a	7		334	3,16	13
9b	6	8		338	3,14	13
9a	4	9		352	2,59	9
2	6a	10		292	2.03	13

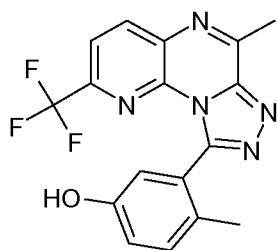
9c	4	11		326	2.96	13
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Example 12

Example 12 (0.04 g) was prepared in analogy to Example 1 and purified applying the most suitable purification technique, starting from Intermediate 9f (0.3 g, 0.68 mmol) and Hydrazide Intermediate 4 (0.27, 0.68 mmol).

HPLC-MS (Method 13) $R_t = 3.11$ min

MS : $m/z = 380$ (M+H)⁺

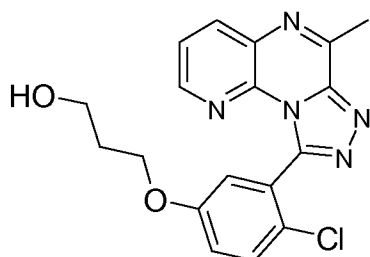
Example 12a

Example 12a (0.15 g) was prepared in analogy to Example 12 and purified applying the most suitable purification technique, starting from the Hydrazide Intermediate 6a (0.23 g, 1.45 mmol).

HPLC-MS (Method) $R_t = 3.00$ min

MS : $m/z = 360$ (M+H)⁺

Example 13:



To a solution of Example 1 (0.1 g, 0.24 mmol) in dry ACN (3 mL), cesium carbonate (0.2 g) and commercially available 3-chloro-1-propanol (0.04 mL) were added.

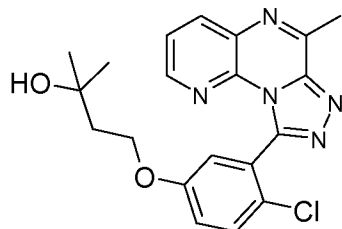
Mixture was heated at 80°C for 1 h, then solvent evaporated under reduced pressure and the residue dissolved in DCM and washed with a saturated solution of NaCl.

Phases were separated, organics dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (eluent from 100:0 to 94:6 DCM/EtOH) to obtain 0.02 g of the title compound.

HPLC-MS (Method 8) R_t = 5.23 min

MS : m/z = 370 (M+H)⁺

Example 14:

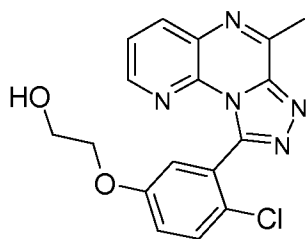


To a solution of Example 1 (0.05 g, 0.16 mmol) in dry DMF (3 mL), Intermediate 10 (0.05 g, 0.018 mmol) and cesium carbonate (0.08 g, 0.24 mmol) were added and mixture heated at 100 °C for 2h. Solvent was evaporated, the residue was dissolved with DCM, washed with a saturated solution of NaCl. Phases were separated, organics dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (eluent from 70:30 to 20:80 Cy/EtOAc) to obtain 0.025 g of the title compound.

HPLC-MS (Method 9): R_t = 2.57 min

MS : m/z = 398 (M+H)⁺

Example 15:

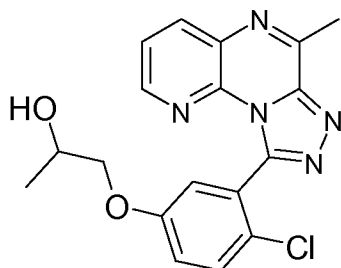


To a solution of Example 1 (0.08 g, 0.16 mmol) in dry ACN (3 mL), commercially available 2-bromo-ethanol (0.65g, 0.52mmol) and cesium carbonate (0.5 g, 1.54 mmol) were added and mixture heated at 80 °C for 48 h. Solvent was evaporated, the residue was dissolved with DCM, washed with 1N solution of NaOH and then with a saturated solution of NaCl. Phases were separated, organics dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (eluent from 100:0 to 97:3 DCM/EtOH) to obtain 0.04 g of the title compound.

HPLC-MS (Method 6): R_t = 8.75 min

MS: m/z = 356 ($M+H$)⁺

Example 16:

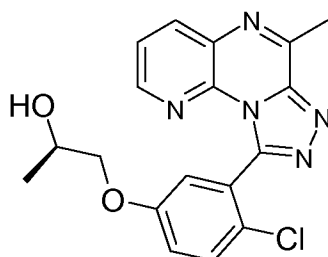


To a solution of Example 1 (0.05 g, 0.16 mmol) in dry DMF (3 mL), commercially available 1-bromo-2-propanol (0.09 g, 0.64 mmol) and potassium tert-butoxide (0.1 g, 0.96 mmol) were added and mixture heated at 130°C for 8h. Solvent was evaporated, the residue was dissolved with DCM, washed with 1N solution of NaOH and then with a saturated solution of NaCl. Phases were separated, organics dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (eluent from 100:0 to 97:3 DCM/EtOH) to obtain 0.05 g of the title compound.

HPLC-MS (Method 9): R_t = 2.23 min

MS: m/z = 370 ($M+H$)⁺

Example 17:

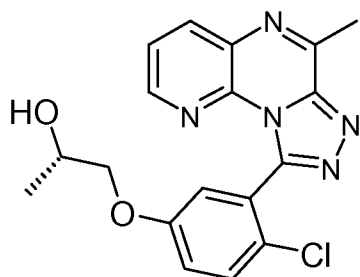


To a solution of Example 1 (0.085 g, 0.27 mmol) in dry DMF (3 mL), commercially available (R)-1-chloro-2-propanol (0.052 g, 0.55 mmol) and potassium tert-butoxide (0.093 g, 0.82 mmol) were added and mixture heated at 130 °C for 48h. Solvent was evaporated, the residue was dissolved with DCM, washed with 1N solution of NaOH and then with a saturated solution of NaCl. Phases were separated, organics dried over sodium sulphate and evaporated . The residue was purified by flash chromatography (eluent from 100:0 to 97:3 DCM/EtOH) to obtain 0.0085 g of the title compound.

10 HPLC-MS (Method 9): R_t = 2.22 min

MS : m/z = 370 ($M+H$)⁺

Example 18:

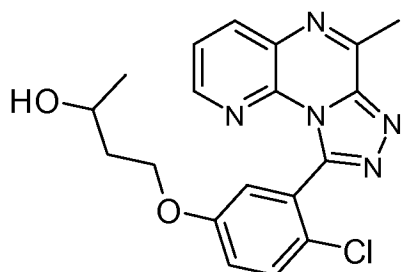


15 Example 18 was prepared as described for Example 17 starting from Example 1 (0.085 g, 0.27 mmol) and commercially available (S)-1-chloro-2-propanol. The residue was purified by flash chromatography (eluent from 100:0 to 90:10 DCM/MeOH) to obtain 0.045 g of the title compound.

HPLC-MS (Method 9): R_t = 2.19 min

20 MS: m/z = 370 ($M+H$)⁺

Example 19:

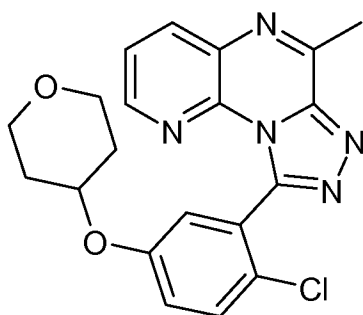


To a solution of Example 1 (0.115 g, 0.37 mmol) in dry DMF (3 mL), cesium carbonate (0.36 g, 1.11 mmol) and Intermediate 11 (0.09 g, 0.37 mmol) were added and mixture heated at 100°C for 4h. Solvent was evaporated, the residue was
5 dissolved with DCM, washed with a saturated solution of NaCl. Phases were separated, organics dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (eluent from 100:0 to 80:20 DCM/EtOH) to obtain 0.025 g of the title compound.

HPLC-MS (Method 9): R_t = 2.4 min

10 MS : m/z = 384 (M+H)⁺

Example 20:



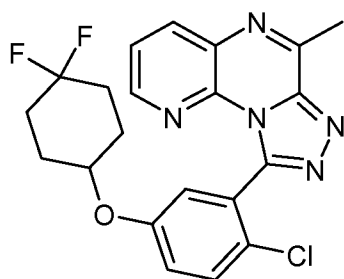
Example 20 was prepared as described for Example 19 , starting from Example 1
15 (0.08 g, 0.26 mmol) and Intermediate 13 (0.2 g, 0.78 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.032 g of the title compound.

HPLC-MS (Method 9): R_t = 2.65 min

MS : m/z = 396 (M+H)⁺

20

Example 21:

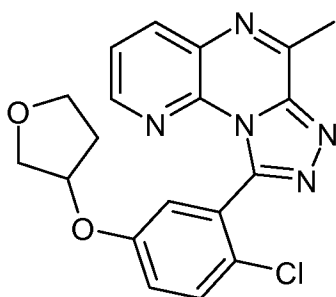


Example 21 was prepared as described for Example 20, starting from Example 1 (0.065g, 0.21mmol) and Intermediate 14 (0.12 g, 0.42 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.035 g of the title compound.

HPLC-MS (Method 9): $R_t = 3.32$ min

MS: $m/z = 430$ ($M+H$)⁺

Example 22:

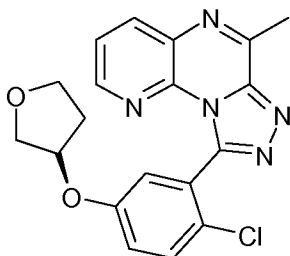


Example 22 was prepared as described for Example 20, starting from Example 1 (0.1 g, 0.32 mmol) and Intermediate 15 (0.093 g, 0.38 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.032 g of the title compound.

HPLC-MS (Method 13): $R_t = 3.03$ min

MS: $m/z = 382$ ($M+H$)⁺

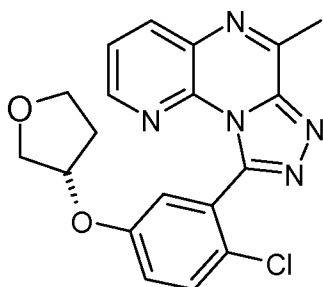
Example 23:



Example 23 was prepared as described for Example 20, starting from Example 1 (0.1 g, 0.32 mmol) and Intermediate 17 (0.093 g, 0.38 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.02 g of the title compound.

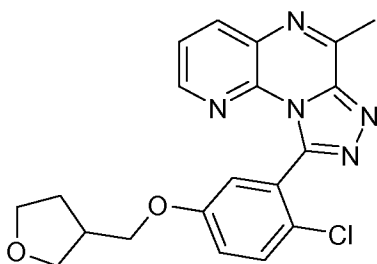
- 5 HPLC-MS (Method13): $R_t = 3.07$ min
MS : $m/z = 382$ (M+H)⁺

Example 24:

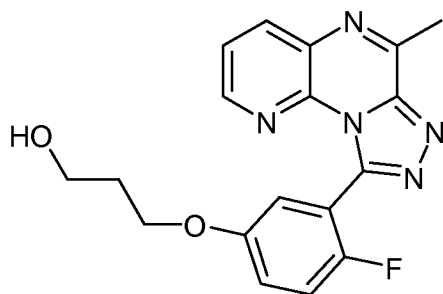


- 10 Example 24 was prepared as described for Example 20, starting from Example 1 (0.1 g, 0.32 mmol) and Intermediate 16 (0.093 g, 0.38 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.03 g of the title compound.
- HPLC-MS (Method 13): $R_t = 3.05$ min
- 15 MS : $m/z = 382$ (M+H)⁺

Example 25:



- 20 Example 25 was prepared as described for Example 20, starting from Example 1 (0.1 g, 0.32 mmol) and Intermediate 18 (0.097 g, 0.38 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.03 g of the title compound.
- HPLC-MS (Method 13): $R_t = 3.18$ min
- MS : $m/z = 396$ (M+H)⁺

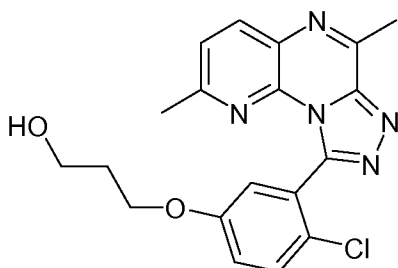
Example 26:

Example 26 was prepared as described for Example 20, starting from Example 4
(0.08 g, 0.27 mmol) and commercially available 3-chloro-1-propanol (0.052 g, 0.54
5 mmol). The crude was purified by flash chromatography (eluent from 100:0 to 97:3
DCM/EtOH) to obtain 0.052 g of the title compound.

HPLC-MS (Method 13): R_t = 2.71 min

MS: m/z = 354 ($M+H$)⁺

10

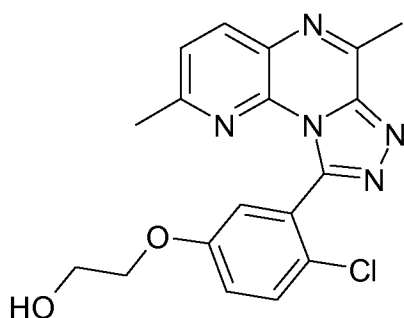
Example 27:

Example 27 was prepared as described for Example 20, starting from Example 2
(0.133 g, 80% content, 0.32 mmol) and commercially available 3-chloro-1-propanol
15 (0.046 g, 0.49 mmol). The crude was purified by prep-HPLC (Method 11). Fractions
containing the pure compound were combined and evaporated to reduced volume,
diluted with DCM and treated with a saturated solution of sodium carbonate. Phases
were separated, dried over sodium sulphate and evaporated under reduced pressure
to obtain 0.039 g of the title compound.

20 HPLC-MS (Method 9): R_t = 2.46 min

MS: m/z = 384 ($M+H$)⁺

Example 28:

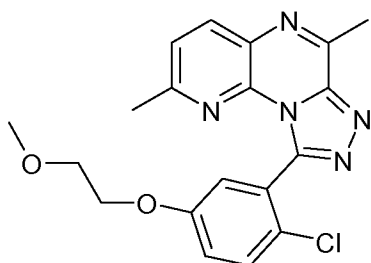


Example 28 was prepared as described for Example 20, starting from Example 2 (0.133 g, 80% content, 0.32 mmol) and commercially available 2-bromo-ethanol (0.061 g, 0.49 mmol). The crude was purified by prep-HPLC (Method 12). Fractions containing the pure compound are combined and evaporated to reduced volume, diluted with DCM and treated with a saturated solution of sodium carbonate. Phases were separated, dried over sodium sulphate and evaporated under reduced pressure to obtain 0.025 g of the title compound.

HPLC-MS (Method 9): R_t = 2.35 min

MS : m/z = 370($M+H$)⁺

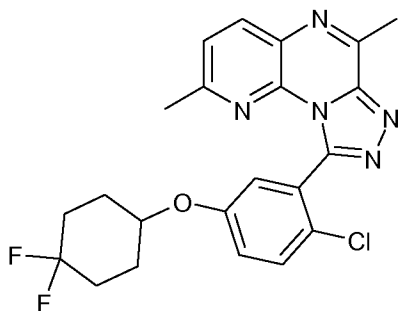
Example 29:



To a solution of Example 2 (0.07 g, 0.20 mmol) and commercially available 2-bromo-methylether (0.057 g, 0.41 mmol) in dry DMF (3 mL), cesium carbonate (0.199 g, 0.61 mmol) was added and the mixture heated at 100°C for 1 h. Solvent was evaporated under reduced pressure, the residue dissolved with DCM and treated with water. Phases were separated, dried over sodium sulphate and the crude purified by flash chromatography (eluent from 80:20 to 40:60 hexane/EtOAc) to obtain 0.023 g of the title compound.

HPLC-MS (Method 9): R_t = 2.82 min

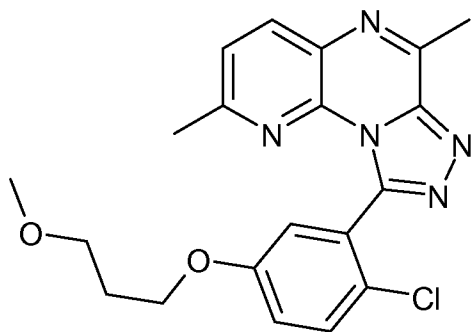
MS: m/z = 384 ($M+H$)⁺

Example 30:

To a solution of Example 2 (0.07 g, 0.20 mmol) and Intermediate 14 (0.12 g, 0.41 mmol) in dry DMF (3mL), cesium carbonate (0.2 g, 0.61 mmol) was added and the mixture heated at 90°C for 2 h. Solvent was evaporated under reduced pressure, the residue dissolved with DCM and treated with water. Phases were separated, dried over sodium sulphate and the crude purified by flash chromatography (eluent from 80:20 to 40:60 hexane/EtOAc) and then further purified by prep-HPLC (Method 14). Fractions containing the pure compound were combined and evaporated to reduced volume, diluted with DCM. Phases were separated, dried over sodium sulphate and evaporated under reduced pressure to obtain 0.047 g of the title compound.

HPLC-MS (Method 9): $R_t = 3.56$ min

MS: $m/z = 444$ ($M+H$)⁺

Example 31:

Example 31 was prepared as described for Example 30 starting from Example 2 (0.07 g, 0.20 mmol) and commercially available 1-bromo-3-methoxy-propane (0.063 g, 0.41 mmol). After heating for 3h at 100°C in dry DMF (3 mL), solvent was evaporated under reduced pressure, the residue dissolved with DCM and treated with water. Phases were separated, dried over sodium sulphate and the crude

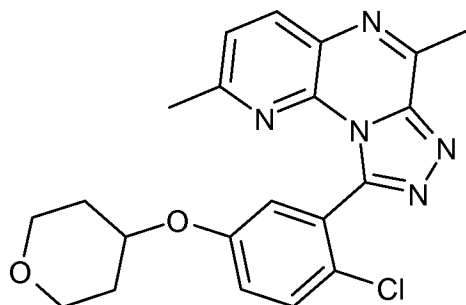
purified by flash chromatography (eluent from 88:12 to 0:100 Cy/EtOAc) to obtain 0.043 g of the title compound.

HPLC-MS (Method 13): R_t = 3.55 min

MS: m/z = 398 ($M+H$)⁺

5

Example 32:



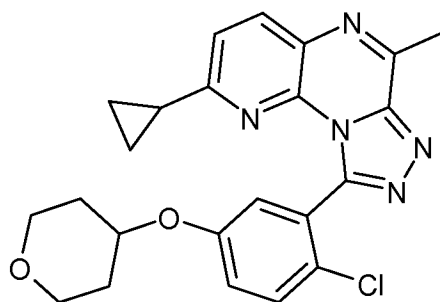
Example 32 was prepared as described for Example 31 starting from Example 2 (0.09 g, 0.26 mmol) and Intermediate 13 (0.20 g, 0.78 mmol). Solvent was

10 evaporated under reduced pressure, the residue dissolved with DCM and washed with 1N solution of NaOH. Phases were separated, dried over sodium sulphate and the crude purified by flash chromatography (eluent from 88:12 to 0:100 Cy/EtOAc) to obtain 0.037 g of the title compound.

HPLC-MS (Method 9): R_t = 2.95 min

15 MS: m/z = 410 ($M+H$)⁺

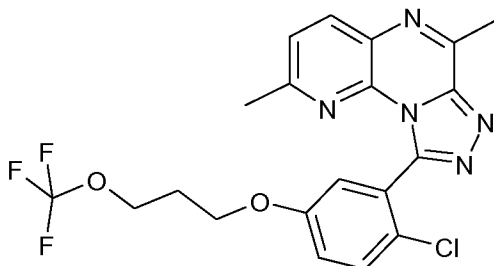
Example 32a



20 Example 32a (0.06 g) was prepared in analogy to Example 32 and purified applying the most suitable purification technique, starting from Example 9 (0.08 g, 0.23 mmol).

HPLC-MS (Method 16): R_t = 4.51 min

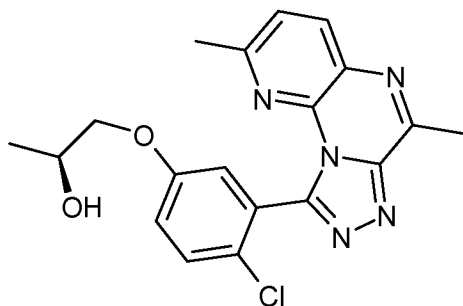
MS: m/z = 436 ($M+H$)⁺

Example 33:

Example 33 was prepared as described for Example 31 starting from Example 2 (0.07 g, 0.20 mmol) and commercially available 1-bromo-3-trifluoro-methoxypropane (0.084 g, 0.41 mmol). Solvent was evaporated under reduced pressure, the residue dissolved with DCM and washed with water. Phases were separated, dried over sodium sulphate and the crude purified by flash chromatography (eluent from 88:12 to 0:100 Cy/EtOAc) and then further purified by prep-HPLC (Method 14). Fractions containing the pure compound were combined and evaporated to reduced volume, diluted with DCM. Phases were separated, dried over sodium sulphate and evaporated under reduced pressure to obtain 0.047 g of the title compound. chromatography (eluent from 88:12 to 0:100 Cy/EtOAc) to obtain 0.037 g of the title compound.

HPLC-MS (Method 13): $R_t = 1.06$ min

MS: $m/z = 452$ ($M+H$)⁺

Example 34:

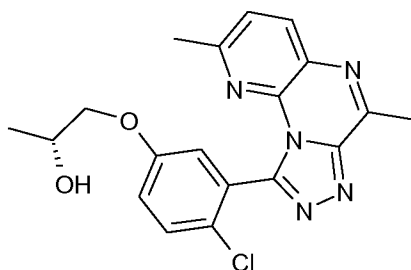
To a solution of Example 2 (0.082 g, 0.25 mmol) in dry DMF (3mL), potassium tert-butoxide (0.084 g, 0.65 mmol) and Intermediate 20 (0.176 g, 0.50 mmol) were added. The resulting solution was heated at 120°C for 5 h. The mixture was left at room temperature for 24 h. Solvent was evaporated under reduced pressure, the residue

dissolved in DCM and treated with a 1N solution of NaOH. Phases were separated, dried over sodium sulphate and the crude purified by flash chromatography (eluent from 20:80 to 0:100 ACN/H₂O) to obtain 0.033 g of the title compound.

HPLC-MS (Method 9): R_t = 2.98 min

5 MS: m/z = 384 (M+H)⁺

Example 35:

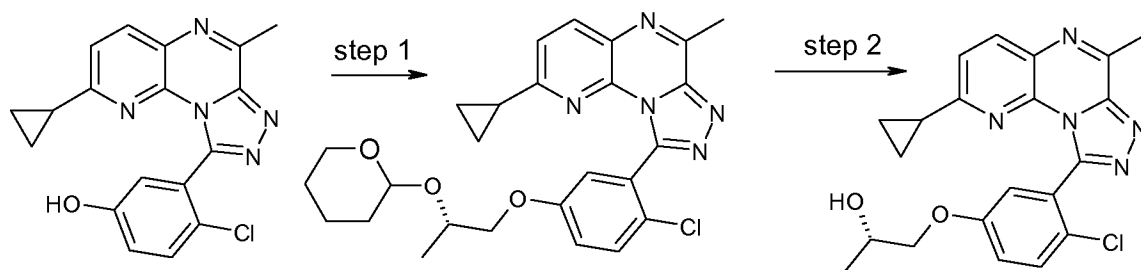


To a solution of Example 2 (0.095 g, 0.29 mmol) in dry DMF (3 mL), potassium tert-butoxide (0.074 g, 0.22 mmol) and Intermediate 19 (0.204 g, 0.58 mmol) were added. The resulting solution was heated at 120 °C for 5h. Solvent was evaporated under reduced pressure, the residue dissolved in DCM and treated with a 1N solution of NaOH. Phases were separated, dried over sodium sulphate and the crude purified by flash chromatography (eluent from 80:20 to 0:100 Cy/EtOAc) to obtain 0.023 g of the title compound.

HPLC-MS (Method 13): R_t = 2.98 min

MS: m/z = 384 (M+H)⁺

Example 35a



Example 35a

To a suspension of Intermediate 9a (0.08 g, 0.23 mmol) in dry DMF (4 mL), t-BuOK (0.076 g, 0.68 mmol) and Intermediate 21 (0.09 g, 0.45 mmol) were added and the

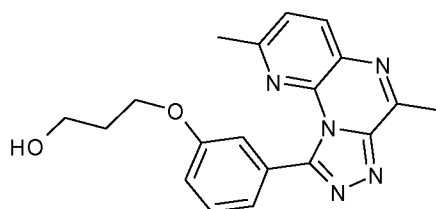
reaction mixture was heated at 90 °C for 5h. Dry DMF was then added and mixture heated at 110 °C overnight. Solvent was evaporated under reduced pressure, the residue dissolved in DCM and treated with a 1N solution of NaOH. Phases were separated, dried over sodium sulphate and the crude purified by flash chromatography (eluent from 80:20 to 0:100 Cy/EtOAc) to obtain 0.055 g of the protected intermediate 1-{2-chloro-5-[(S)-2-(tetrahydro-pyran-2-yloxy)-propoxy]-phenyl}-8-cyclopropyl-4-methyl-2,3,5,9,9b-pentaaza-cyclopenta[a]naphthalene.

The compound (0.055 g, 0.11 mmol) was then dissolved in dry MeOH (1 mL) and p-toluenesulfonic acid monohydrate (0.012 g, 0.06 mmol) was added. Mixture was stirred at room temperature for 1 h, solvent evaporated under reduced pressure and the residue purified by reverse phase flash chromatography (eluent ACN/H₂O from 10:100 to 100:0) and then by silica flash chromatography (eluent DCM/EtOH 90:10) to obtain 0.03 g of the title compound.

HPLC-MS (Method 9): R_t = 2.69 min

MS: m/z = 384 (M+H)⁺

Example 36:

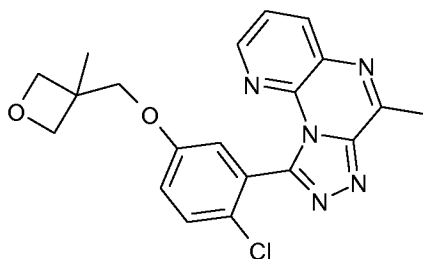


To a solution of Example 3 (0.07 g, 0.24 mmol) in dry DMF (3 mL), cesium carbonate (0.23g, 0.71 mmol) and commercially available 3-chloro-1-propanol (0.024g, 0.26 mmol) were added and the mixture heated at 100 °C for 3 h. Solvent was evaporated under reduced pressure, the residue dissolved with DCM and washed with 1N solution of NaOH. Phases were separated, dried over sodium sulphate and the crude purified by prep-HPLC (Method 11). Fractions containing the pure compound were combined and evaporated to reduced volume, diluted with DCM and washed with a saturated solution of sodium carbonate. Phases were separated, dried over sodium sulphate and evaporated under reduced pressure to obtain 0.02 g of the title compound.

HPLC-MS (Method 13): R_t = 2.71 min

MS: $m/z = 350 (M+H)^+$

Example 37:

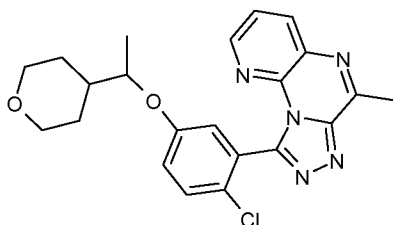


- 5 Example 37 was prepared as described for Example 32 starting from Example 1 (0.07 g, 0.22 mmol) and Intermediate 26 (0.22 g, 0.67 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.046 g of the title compound.

HPLC-MS (Method 13): $R_t = 3.15$ min

- 10 MS: $m/z = 396 (M+H)^+$

Example 38



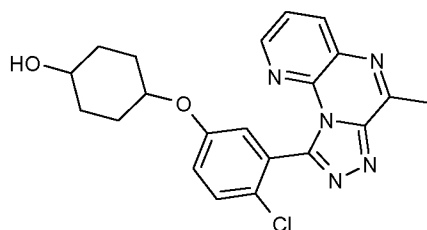
- 15 Example 38 was prepared as described for Example 32 starting from Example 1 (0.07 g, 0.22 mmol) and Intermediate 27 (0.127 g, 0.44 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.045 g of the title compound.

HPLC-MS (Method 13): $R_t = 3.45$ min

MS: $m/z = 424 (M+H)^+$

20

Example 39



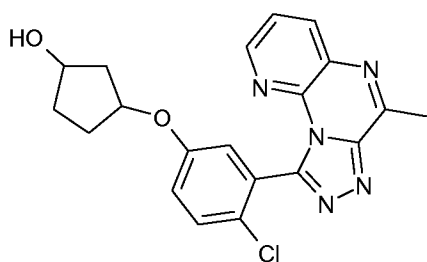
To a solution of Intermediate 30 (0.18 g, 0.44 mmol) in absolute EtOH (10 mL) sodiumborohydride (0.008 g, 0.22 mmol) was added and the mixture stirred at room temperature for 30 min. Solvent was evaporated under reduced pressure, the residue
5 treated with DCM and washed with a saturated solution of sodiumcarbonate. Phases were separated, dried over sodium sulphate and evaporated under reduced pressure to obtain 0.047 g of the title compound.

HPLC-MS (Method 13): $R_t = 2.96$ min

MS: $m/z = 410$ (M+H)⁺

10

Example 40



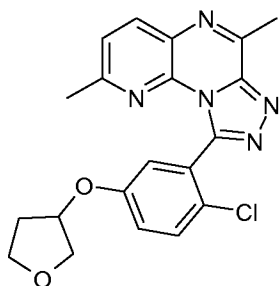
Example 40 was prepared as described Example 14, starting from Example 1 (0.075 g, 0.24 mmol) and Intermediate 31 (0.12 g, 0.48 mmol). Crude was purified by flash
15 chromatography (eluent from 100:0 to 95:5 DCM/EtOH) to obtain 0.046 g of the title compound.

HPLC-MS (Method 13): $R_t = 2.87$ min

MS: $m/z = 396$ (M+H)⁺

20

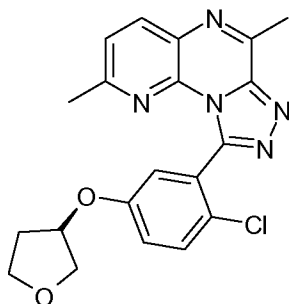
Example 41



Example 41 (0.05 g) was prepared as described for Example 22 and purified applying the most suitable purification technique, starting from Example 2 (0.1 g, 0.3 mmol).

- 5 HPLC-MS (Method 13): $R_t = 3.21$ min
MS: $m/z = 396$ ($M+H$)⁺

Example 42:



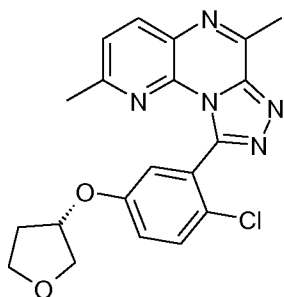
- 10 Example 42 (0.06 g) was prepared as described for Example 23 and purified applying the most suitable purification technique, starting from Example 2 (0.09 g, 0.28 mmol).

(HPLC-MS (Method 13): $R_t = 3.21$ min

MS: $m/z = 396$ ($M+H$)⁺

15

Example 43:

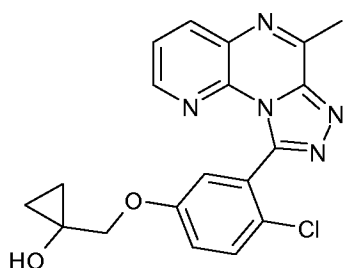


Example 43 (0.03 g) was prepared as described for Example 24 and purified applying the most suitable purification technique, starting from Example 2 (0.09 g, 0.28 mmol).

HPLC-MS (Method 13): R_t = 3.21 min

5 MS: m/z = 396 ($M+H$)⁺

Example 43a:

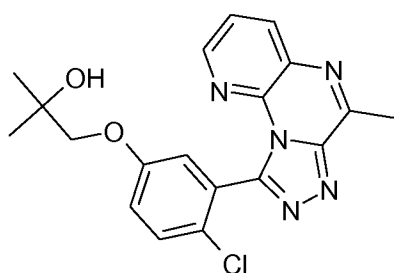


To a solution of ethylmagnesium bromide (0.7 mL of a 3M solution in diethyl ether) in dry DCM (2 mL) at -75°C, titanium(IV) isopropoxide (0.2 mL, 0.7 mmol) was added. Mixture was stirred for 10 min, then a solution of Intermediate 31 (0.28 g, 0.73 mmol) in dry DCM (8 mL) was added dropwise. Mixture was allowed to reach room temperature and stirred at room temperature overnight. Mixture was diluted with EtOAc, hydrochloric acid (1N solution) was added and phases separated. Organics were dried over sodium sulphate and evaporated under reduced pressure and the crude purified by silica flash chromatography (eluent AcOEt/EtOH 90:10) followed by a reverse phase chromatography to obtain 0.006 g of the title compound.

HPLC-MS (Method 13): R_t = 2.93 min

MS: m/z = 382 ($M+H$)⁺

Example 44:



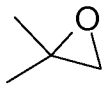
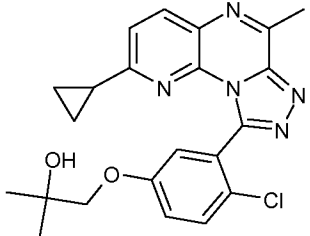
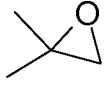
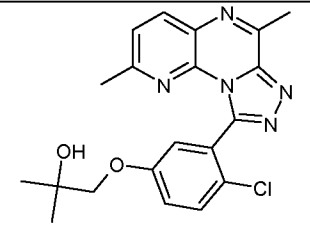
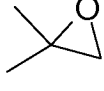
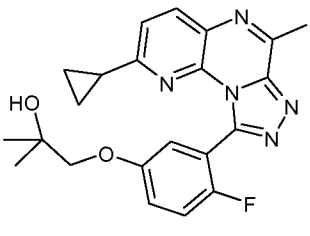
Example 1 (0.07 mg, 0.2 mmol) was dissolved in DMF (3 mL), isobutylene oxide (0.03 mg, 0.43 mmol) and cesium carbonate (208 mg, 0.64 mmol) were added and

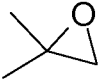
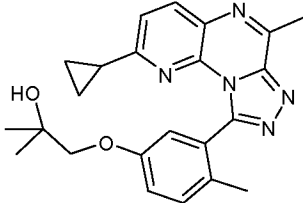
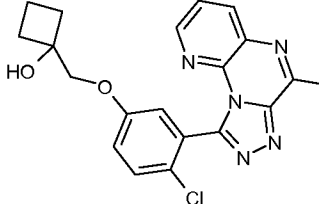
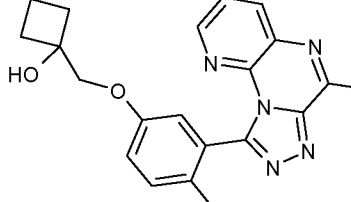
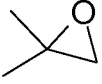
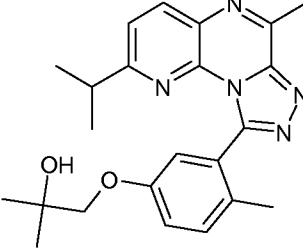
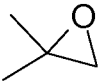
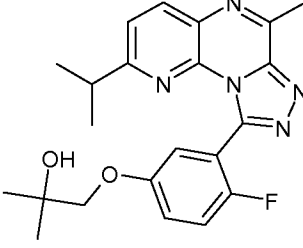
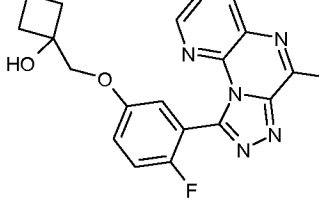
the reaction mixture was warmed to 100 °C for 2h. The solvent was removed, dichloromethane was added and the organic phase was washed with a 1M NaOH water solution, dried over sodium sulfate, concentrated under vacuum. The crude product obtained was purified by reverse phase chromatography to give the desired compound (29 mg).

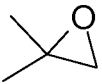
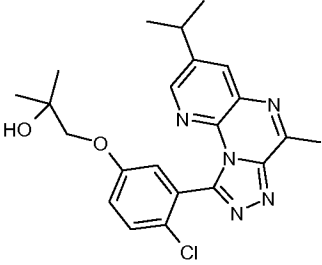
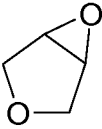
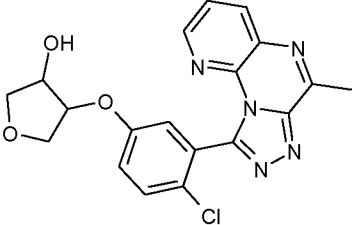
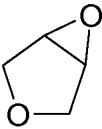
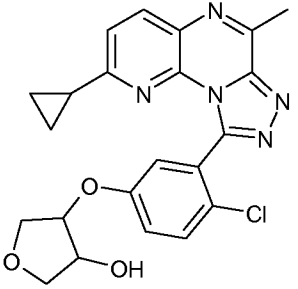
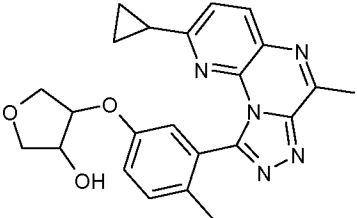
HPLC-MS (Method 13): R_t = 2.93 min

MS: m/z = 386 ($M+H$)⁺

The following Examples were prepared in analogy to Example 44 and purified applying the most suitable purification technique, starting from the corresponding Starting Example and the suitable epoxides.

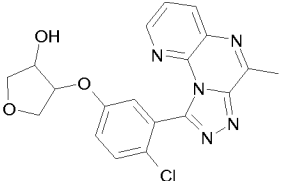
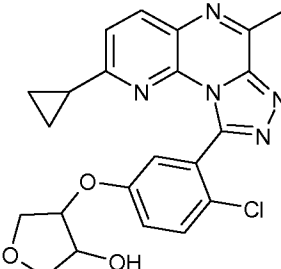
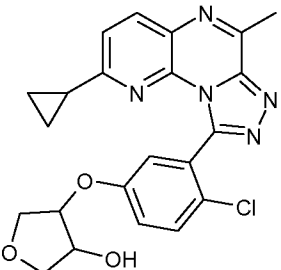
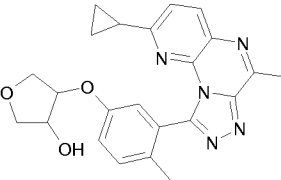
Starting Example or Starting Intermediate	Starting Epoxide	Ex. #	Structure	MS m/z [$M+H$] ⁺	R_t (min)	Method
9		45		424	2,88	9
2		46		398	3,01	9
5		47		408	3.19	13

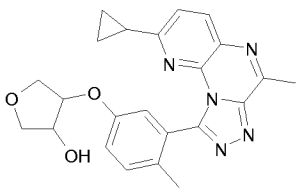
6		48		404	3.19	13
1	29a	49		396	3,04	13
10	29a	50		376	2.88	13
7		51		406	3,32	13
8		52		410	3,32	13
4	29a	53		380	2,89	13

30p		54		426	3,56	13
1		55 TRANS- racemic mixture		398	2,74	13
9		56 TRANS- racemic mixture		438	3.10	13
6		57 TRANS- racemic mixture		418	2.94	13

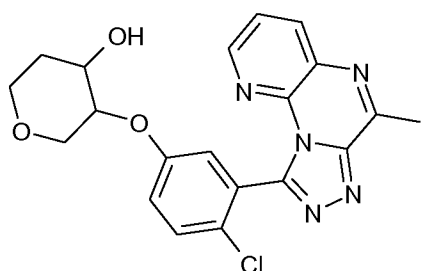
The following examples were obtained as single stereoisomers by chiral HPLC separation of the corresponding racemic mixture.

Starting Racemic Mixture	Ex. #	Structure	MS m/z [M+H] ⁺	R _t (min) [LC-MS Method]	R _t (min) [Chiral HPLC Method]
--------------------------------	-------	-----------	---------------------------------	---	---

55	55a		398	2,63 [13]	8.23 [C1]
56	56a		438	3,03 [13]	12.13 [C2]
56	56b		438	3,03 [13]	16.56 [C2]
57	57a		418	2.18 [13]	17.66 [C2]

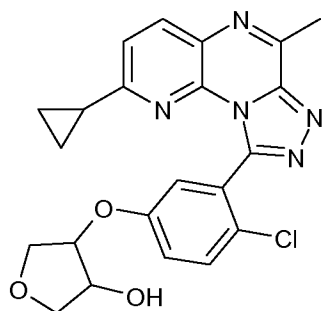
mixture	stereoisomer a				
57 TRANS- racemic mixture	57b TRANS- single stereoisomer b		418	2,81 [13]	19.81 [C2]

Example 58 (TRANS- single stereoisomer a):



- 5 Example 58 (0.01 g) was prepared in analogy to example 44 starting from Example 1 (0.2 g, 0.61 mmol) and epoxide intermediate 29 (0.07 g, 0.73 mmol) after chiral HPLC separation HPLC-MS (Method 13): $R_t = 2.63$ min
 MS: $m/z = 412$ ($M+H$)⁺
 Chiral HPLC (Method C2): $R_t = 16.84$ min

Example 58a (CIS- racemic mixture):

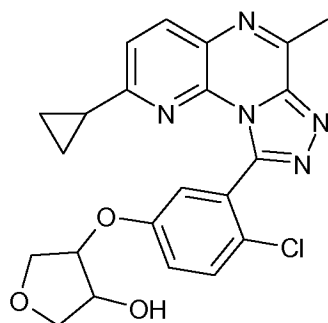


To a solution of Intermediate 30o (0.13 g, 0.37 mmol) in dry DMF (3 mL), potassium tert.butoxide (0.083 g, 0.73 mmol) and commercially available 1,4-anhydroerythritol (0.06 mL, 0.73 mmol) were added and mixture heated at 90 C for 6 h. Solvent was
5 evaporated, DCM and water added. Organics were separated, washed with a saturated solution of ammonium chloride, evaporated. The crude was purified by flash chromatography (eluent Cy/EtOAc 90:10 to 0:100) to give the desired compound (0.055 g).

HPLC-MS (Method 13): R_t = 2.94 min

10 MS: m/z = 438 ($M+H$)⁺

Example 58b (CIS- single stereoisomer a):



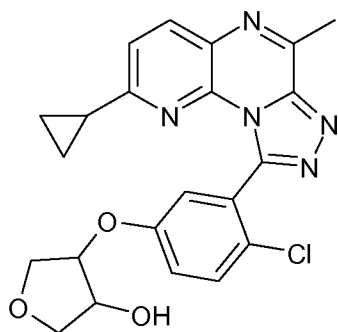
Example 58b was obtained by chiral HPLC separation of Example 58.

15 HPLC-MS (Method 13): R_t = 2.95 min

MS : m/z = 438 ($M+H$)⁺

Chiral HPLC (Method C1): R_t = 7.65 min

Example 58c (CIS- single stereoisomer b):



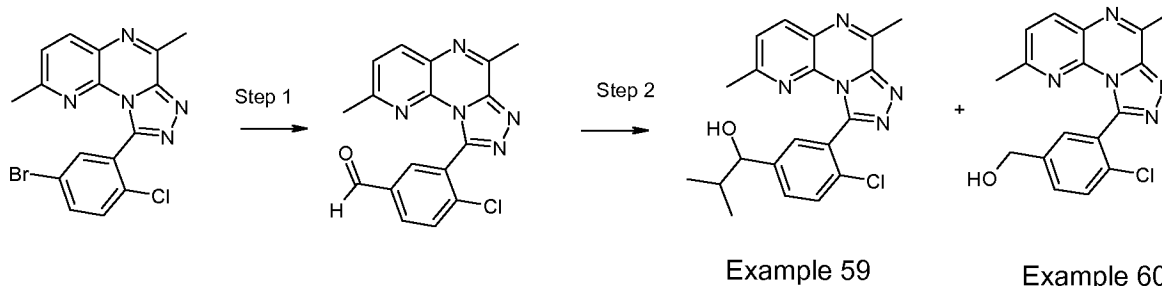
Further elution from the chiral column in the purification of Example 58 gave Example 58c

HPLC-MS (Method 13): $R_t = 2.95$ min

5 MS : $m/z = 438$ (M+H)⁺

Chiral HPLC (Method C1): $R_t = 9.54$ min

Example 59 and Example 60:



10

Step 1:

Scaffold Intermediate 30a (1.4 g, 3.5 mmol) was suspended in THF (40 mL) and stirred at -78°C under nitrogen atmosphere. N-Butyllithium (3 mL of a 2.5M solution in hexane) was added dropwise and the reaction mixture was stirred at -78°C for 0.5h. A solution of N,N-dimethylformamide (1.43 mL, 17.6 mmol) in THF (15 mL) was added dropwise and the reaction mixture was stirred at -78°C for 30 minutes.

15

Ammonium chloride saturated water solution (20 mL) was added and the reaction mixture was allowed to reach room temperature. The reaction mixture was diluted with ethyl acetate and washed with water. The organic phase was washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude product obtained was purified by flash chromatography (eluent from 100:0 to 80:20 Cy/EtOAc) to obtain the title compound (0.3 g).

20

Step 2:

Intermediate obtained from Step 1 (0.07 g, 0.21 mmol) was suspended in THF (2 mL) and stirred at 0 °C. A 2M solution of isopropylmagnesium chloride in THF (0.1 mL) was added and the reaction mixture was allowed to reach room temperature in 2h. Ammonium chloride saturated water solution (20 mL) was added and the reaction mixture was allowed to reach room temperature. The reaction mixture was diluted with ethyl acetate and washed with water. The organic phase was washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude product obtained was purified by flash chromatography (eluent 50:50 Cy/EtOAc) to obtain Example 60 (0.02 g).

10 HPLC-MS (Method 9): R_t = 2.85 min

MS : m/z = 382 (M+H)⁺

Further elution from the column (eluent from 50:50 to 0:100 Cy/EtOAc) gave

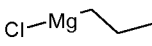
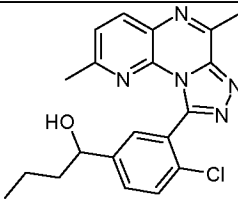
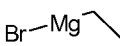
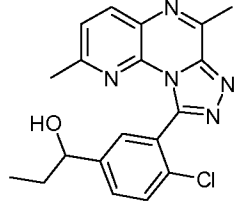
Example 60 (0.03 g)

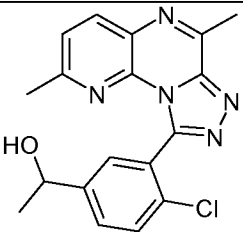
HPLC-MS (Method 9): R_t = 2.28 min

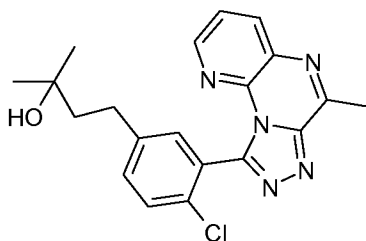
15 MS : m/z = 340 (M+H)⁺

The following examples were prepared in analogy to Example 59 and purified applying the most suitable purification technique, starting from Scaffold Intermediate 30a and the corresponding commercially available Grignard reagents.

20

Grignard reagent	Ex. #	Structure	MS m/z (M+H) ⁺	R_t (min)	Method
	61		382	2,89	9
	62		368	3,12	13

—Mg·Cl	63		354	2,93	13
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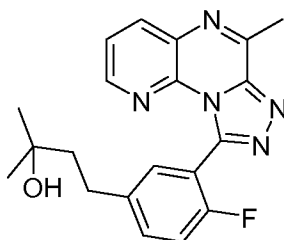
Example 64:

- 5 Example 64 (0.03 g) was prepared in analogy to Example 1 and purified applying the most suitable purification technique, starting from Intermediate 2 (0.1 g, 0.55 mmol) and Hydrazide Intermediate 6i (0.15 g, 0.55 mmol).

HPLC-MS (Method 9): $R_t = 2.52$ min

MS: $m/z = 382$ ($M+H$)⁺

10

Example 65:

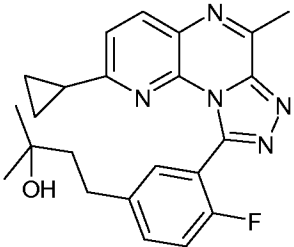
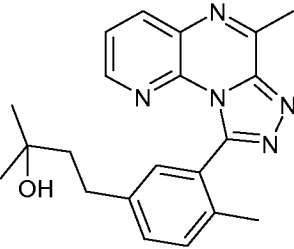
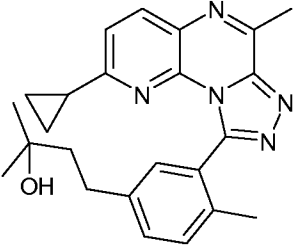
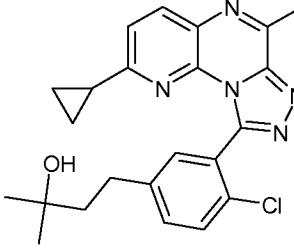
Example 65 (0.03 mg) was prepared in analogy to the preparation of Intermediate 5i and purified applying the most suitable purification technique, starting from Scaffold

- 15 Intermediate 30d (0.1 g, 0.25 mmol).

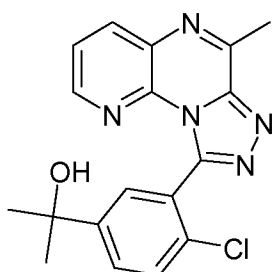
HPLC-MS (Method 9): $R_t = 2.45$ min

MS : $m/z = 366$ ($M+H$)⁺

The following examples were prepared in analogy to Example 65 and purified applying the most suitable purification technique, starting from the corresponding Scaffold Intermediates.

Starting Intermediate	Ex. #	Structure	MS m/z (M+H) ⁺	R _t (min)	Method
30e	66		406	3.29	13
30f	67		362	3,83	16
30g	68		402	3,22	13
30h	69		422	3,33	13

Example 70:



Example 70 (0.03 g) was prepared in analogy to the preparation of Intermediate 5j and purified applying the most suitable purification technique, starting from Scaffold Intermediate 30b (0.16 g, 0.38 mmol) and acetone (0.07 mg, 1.13 mmol).

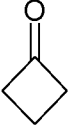
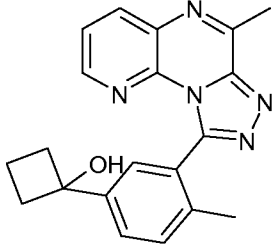
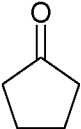
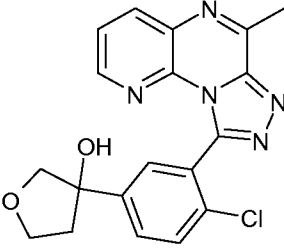
5 HPLC-MS (Method 13): $R_t = 2.67$ min

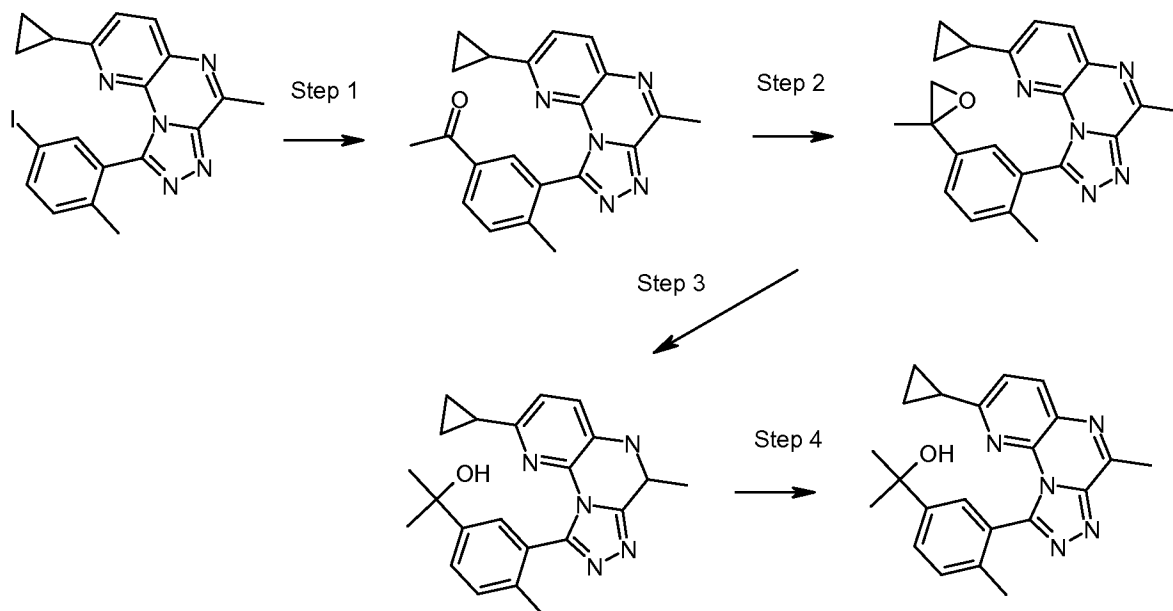
MS: $m/z = 354$ (M+H)⁺

The following examples were prepared in analogy to Example 70 and purified applying the most suitable purification technique, starting from the corresponding

10 Scaffold Intermediates and commercially available ketons.

Starting Intermediate	Ketone	Ex. #	Structure	MS m/z (M+H) ⁺	R_t (min)	Method
30j		71		368	2,95	13
30m		72		392	3,32	13

30c		73		346	2,77	13
30b		74		382	2,61	13

Example 75:5 **Step 1:**

Under N₂ atmosphere, to a solution of Scaffold Intermediate 30g (1.0 g, 2.54 mmol) in toluene (35 mL), tributyl-(1-ethoxyvinyl)-tin (1.3 mL, 3.04 mmol) and Pd tetrakis(triphenylphosphine) (580 mg, 0.51 mmol). The solution was stirred at 105°C for 18h. The reaction mixture was cooled at room temperature, concentrated in vacuo and the crude product obtained was dissolved in THF. A 2N water solution of HCl 2N (5ml) was added and the reaction mixture was stirred for 30 mins. After dilution with

10

ethyl acetate, phases were separated and organic layer was dried over sodium sulfate and concentrated. The crude product obtained was purified by flash chromatography (eluent from 90:10 to 75:25 Cy/EtOAc) to obtain the desired compound (0.8 g).

5 HPLC-MS (Method 13): $R_t = 3.09$ min

MS : $m/z = 358(M+H)^+$

Step 2:

To a solution of the intermediate from Step 1 (0.8 g, 2.2 mmol) in DCM (20 mL) 50% NaOH/H₂O solution (0.8 mL) was added and the reaction mixture was stirred for 10
10 minutes. Trimethylsulfonium methyl sulfate (0.4 g, 2.8 mmol) was added and the reaction mixture was refluxed for 2h. The reaction mixture was diluted with DCM and washed with water. The organic layer was separated, dried over sodium sulfate and concentrated. The crude product obtained was purified by flash chromatography (eluent 85:15 Cy/EtOAc) to obtain the desired compound (0.5 g).

15 HPLC-MS (Method 13): $R_t = 3.33$ min

MS : $m/z = 372(M+H)^+$

Step 3:

To a solution of lithiumaluminiumhydride (0.15 mL of a 2M solution in THF) in 15 mL of THF stirred at 0°C, the intermediate from step 2 (0.4 g, 0.4 mmol) was added
20 slowly. The reaction mixture was stirred for 1h and allowed to reach room temperature. Water (2 mL) and NaOH (1mL of a 2M water solution) were added and the reaction mixture was diluted with ethyl acetate. Organic phase was separated, dried over sodium sulfate and concentrated to give the desired product (0.28 g).

HPLC-MS (Method 13): $R_t = 3.0$ min

25 MS : $m/z = 376(M+H)^+$

Step 4:

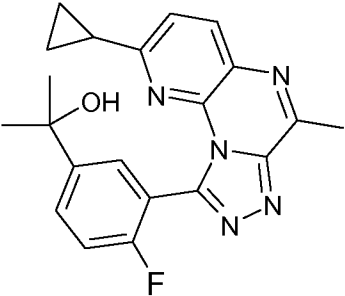
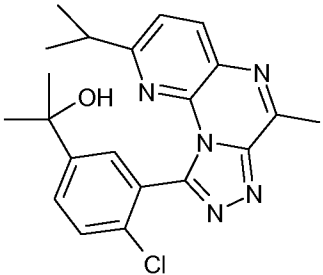
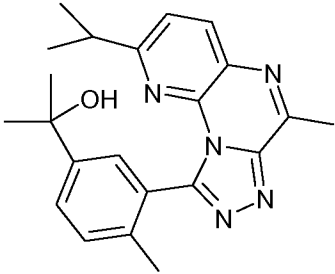
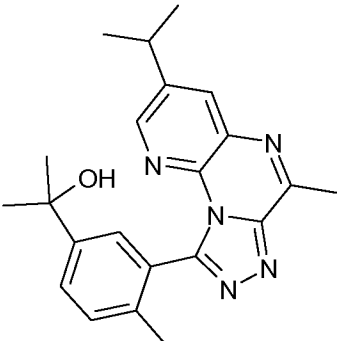
Intermediate from step 3 (0.17 g, 0.38 mmol) was dissolved in DCM (10 mL), manganese dioxide (0.38 g, 3.38 mmol) was added and the suspension was stirred for 1h at room temperature. The reaction mixture was filtered on a celite pad and the
30 solvent was evaporated. The crude product obtained was purified by flash chromatography (eluent 90:10 DCM/MeOH) to obtain the desired compound (0.14 g).

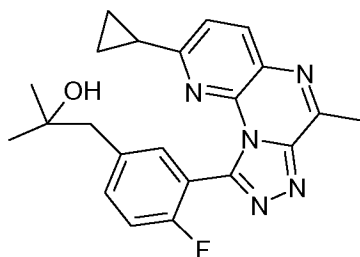
HPLC-MS (Method 13): $R_t = 3.04$ min

MS : m/z = 374 (M+H)⁺

The following examples were prepared in analogy to Example 75 and purified applying the most suitable purification technique, starting from the corresponding

5 Intermediates.

Starting Intermediate	Ex.	Structure	MS m/z (M+H) ⁺	R _t (min)	Method
30e	76		378	3.12	13
30k	77		396	3.37	13
30l	78		376	3,3	13
30n	79		376	3,31	13

Example 80:

- 5 Example 80 (0.02 g) was prepared in step 2, step 3 and step 4 step in analogy to Example 75 and purified applying the most suitable purification technique, starting from the Intermediate obtained in step 1.

Step 1 was performed as follow:

- Scaffold Intermediate 30i (1.35 g, 3.39 mmol) tri-n-butylmethoxytin (1.51 mL, 5.08
 10 mmol), isopropenyl acetate (5.6 mL, 51 mmol), tri-o-tolylphosphine (0.07 g, 0.25 mmol) and palladium acetate (0.03 g) were suspended in toluene (30 mL) under nitrogen atmosphere and stirred for 2h at room temperature, then at 110°C for 20 minutes. Water (10 mL) and a bicarbonate saturated water solution (3 mL) were added, toluene was removed under vacuum and DCM was added. The organic
 15 phase was separated, and concentrated. The crude product obtained was purified by flash chromatography (eluent from 30:70 to 0:100 cyclohexane/AcOEt) to obtain the desired compound (0.5 g).

Step 2, Step 3 and Step 4 were performed in analogy to Example 75.

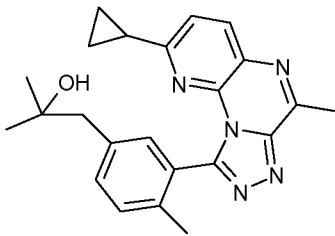
HPLC-MS (Method 16): $R_t = 3.13$ min

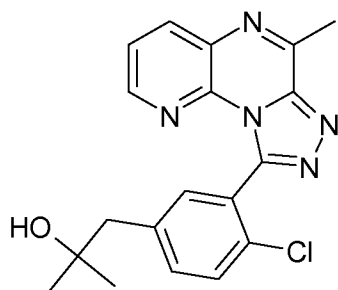
- 20 MS: $m/z = 392$ (M+H)⁺

The following example was prepared in analogy to Example 80 and purified applying the most suitable purification technique, starting from the corresponding Scaffold Intermediates.

25

Intermediate	Ex. #	Structure	MS m/z (M+H) ⁺	R_t (min)	Method
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30g	81		388	5.75	17
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Example 82:

Example 82 (0.09 g) was prepared in analogy to Example 1 starting from Chloride

5 Intermediate 2 (0.1 g, 0.61 mmol) and Hydrazide Intermediate 6p (0.2 g, 0.61 mmol).

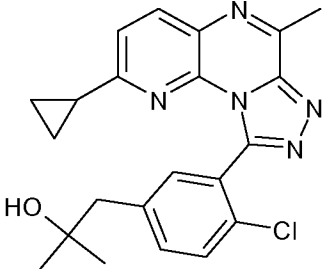
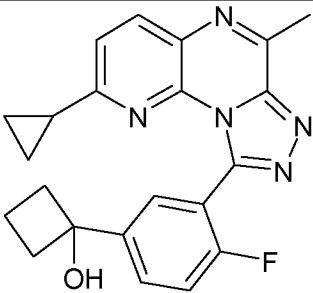
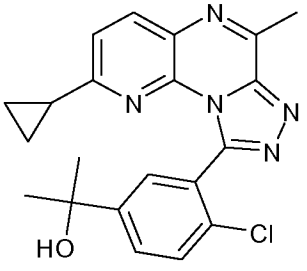
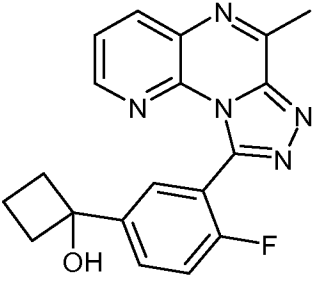
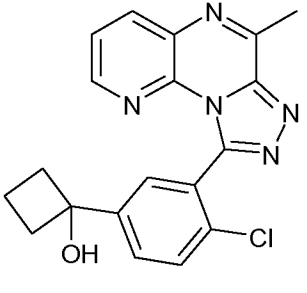
(HPLC-MS (Method 13): R_t 2.80 =min

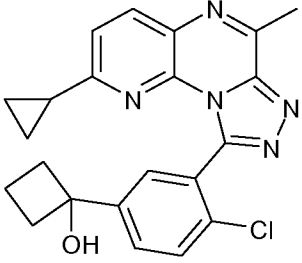
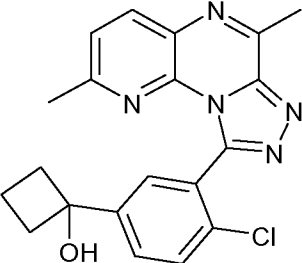
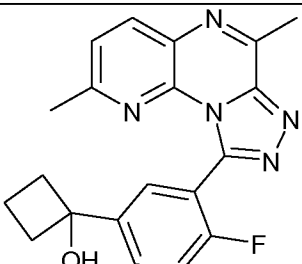
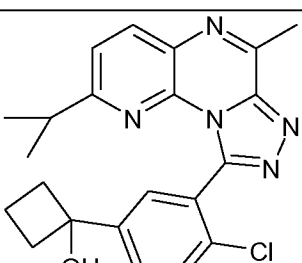
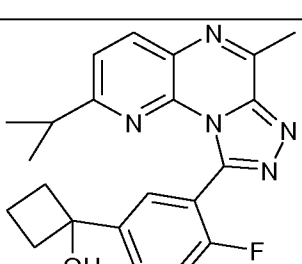
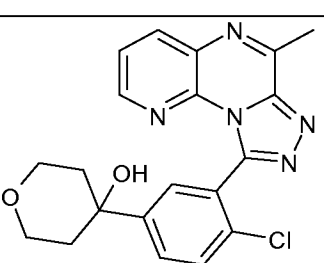
MS : m/z = 368 ($M+H$)⁺

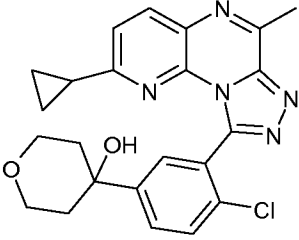
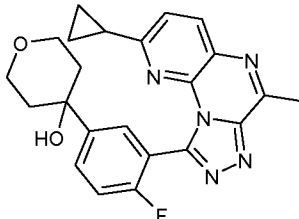
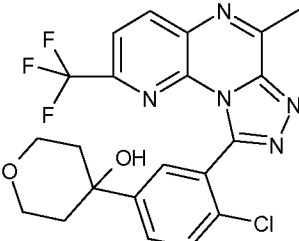
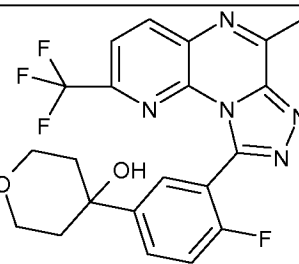
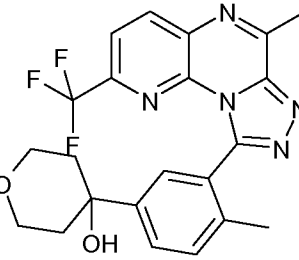
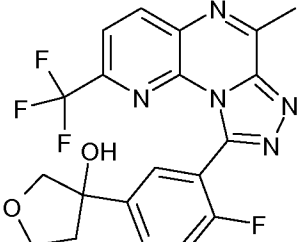
The following examples were prepared in analogy to Example 82 and purified

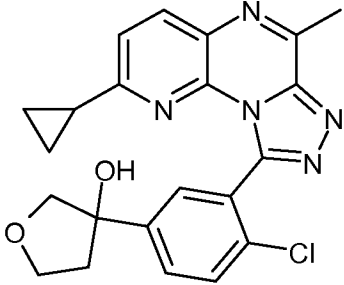
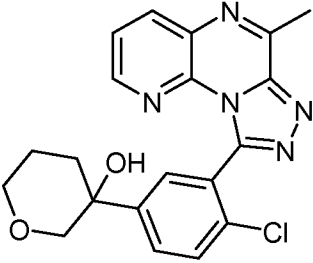
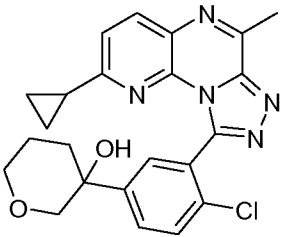
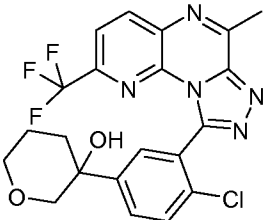
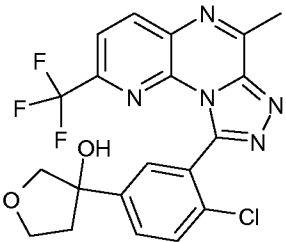
10 applying the most suitable purification technique, starting from the corresponding Chloride and Hydrazide Intermediates.

Starting Chloride Intermediate	Starting Hydrazide Intermediate	Ex. #	Structure	MS m/z ($M+H$) ⁺	R_t (min)	Method

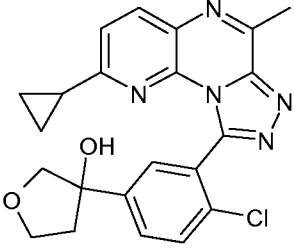
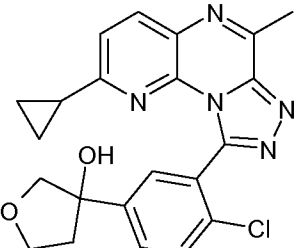
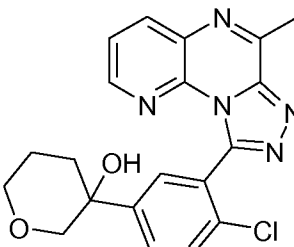
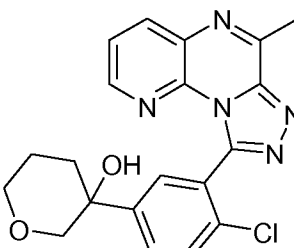
9a	6p	83		408	3,24	13
9a	6j	84		390	3,18	13
9a	6o	85		394	3,22	13
2	6j	86		350	2,76	13
2	6k	87		366	2,93	13

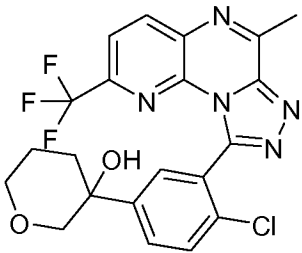
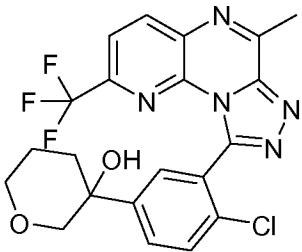
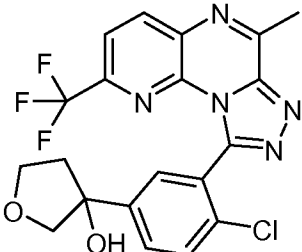
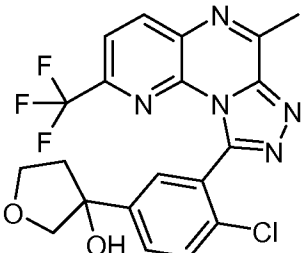
9a	6k	88		406	3,33	13
9	6k	89		380	3,05	13
9	6j	90		364	2,91	13
9b	6k	91		408	3.45	13
9b	6j	92		392	3.34	13
2	6l	93		396	2,96	13

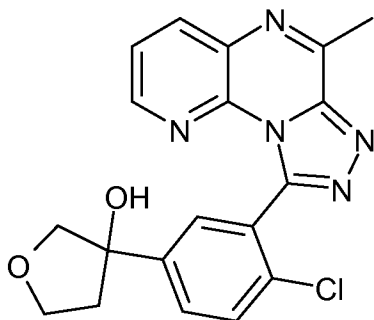
9a	6l	94		436	3,08	13
9a	6n	95		420	2,9	13
9f	6l	96		464	3,04	13
9f	6n	96a		448	2,98	13
9f	6na	96b		444	2,94	13
9f	6r	96c		434	2,91	13

9a	6q	97		422	2.90	13
2	6s	112		396	2.67	13
9a	6s	113		436	3.10	13
9f	6s	114		464	3.21	13
9f	6r	115		450	3.90	13

The following examples were obtained as single stereoisomers by chiral HPLC separation of the corresponding racemic mixture.

Starting Racemic Mixture	Ex. #	Structure	MS m/z [M+H] ⁺	R _t (min) [LC-MS Method]	R _t (min) [Chiral HPLC Method]
97 Racemic mixture	97a Single stereoisomer b		422	2.,89 [13]	15.75 [C2a]
97 Racemic mixture	97b Single stereoisomer a		422	2.89 [13]	13.32 [C2a]
112 Racemic mixture	112a Single stereoisomer a		<u>396</u>	2.85 [13]	<u>14.5</u> [C2a]
112 Racemic mixture	112b Single stereoisomer b		<u>396</u>	2.85 [13]	<u>15.6</u> [C2a]

114 Racemic mixture	114a Single stereoisomer a		<u>464</u>	<u>3.21 [13]</u>	<u>13.8[C2]</u>
114 Racemic mixture	114b Single stereoisomer b		<u>464</u>	<u>3.21 [13]</u>	<u>16.76[C2]</u>
115 Racemic mixture	115a Single stereoisomer a		<u>450</u>	<u>3.05 [13]</u>	<u>28.0[C2b]</u>
115 Racemic mixture	115b Single stereoisomer b		<u>450</u>	<u>3.05 [13]</u>	<u>31.2[C2b]</u>

Example 98 (Single stereoisomer a):

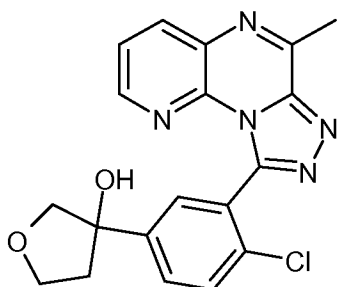
Example 98 (0.026 g) was prepared in analogy to Example 1 starting from Chloride
5 Intermediate 2 (0.3 g, 1.45 mmol) and Hydrazide Intermediate 6q (0.4 g, 1.56 mmol)
after semipreparative chiral purification.

HPLC-MS (Method 13): $R_t = 2.56$ min

MS: $m/z = 382$ ($M+H$)⁺

Chiral HPLC (Method C1a): $R_t = 9.55$ min

10

Example 99 (Single stereoisomer b):

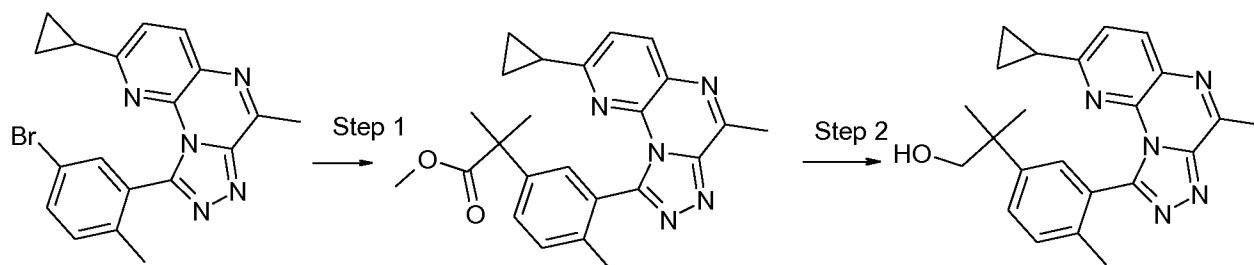
Example 99 (0.028 g) was obtained via further elution from the column in the
semipreparative chiral chromatographic purification of Example 98.

15 HPLC-MS (Method 13): $R_t = 2.52$ min

MS: $m/z = 382$ ($M+H$)⁺

Chiral HPLC (Method C1a): $R_t = 11.03$ min

Example 100:

**Step 1:**

Scaffold Intermediate 30g (0.5 g, 1.27 mmol), 1-methoxy-2-methyl-1-(trimethylsiloxy)propene (1.9 g, 11.4 mmol), bis(dibenzylideneacetone)palladium(0) (0.14 g, 0.25 mmol) and zinc fluoride (0.19 g, 1.9 mmol) were suspended in DMF (25 mL) and stirred under nitrogen atmosphere for 10 minutes. Tri-tert-butyl-phosphine (0.06 mL, 0.25 mmol) was added and the reaction mixture was stirred at 115 °C for 18h. The reaction mixture was concentrated, an ammonium chloride water saturated solution was added and the reaction mixture was extracted with DCM. The organic phase was separated, dried over sodium sulfate and concentrated. The crude product obtained was purified by flash chromatography (eluent from 100:0 to 50:50 cyclohexane/AcOEt) to obtain the desired compound (0.4 g).

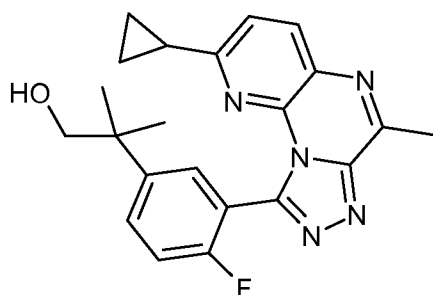
Step 2:

The intermediate obtained in Step 1 (0.4 g, 0.07 mmol) was dissolved in THF (6 mL) and stirred under nitrogen atmosphere at 0 °C for 5 minutes. Lithiumaluminium hydride (0.5 mL of a 2M solution in THF) was added. The reaction mixture was stirred at 0 °C for 10 minutes then allowed to reach room temperature and stirred for 0.5h. The solvent was removed, the crude product was dissolved in DCM and the reaction mixture was washed with water (4 mL), bicarbonate saturated water solution (2 mL) and brine (2 mL). The organic phase was separated, dried over sodium sulfate and manganese dioxide (0.15 g, 1.73 mmol) was added. The reaction mixture was stirred for 0.5 h, filtered on a celite pad and concentrated. The crude product obtained was purified by flash chromatography (eluent from 100:0 to 95:5 DCM/MeOH) to obtain the desired compound (0.1 g).

(HPLC-MS (Method 13): R_t = 3.29 min

MS: m/z = 388 ($M+H$)⁺

Example 101:

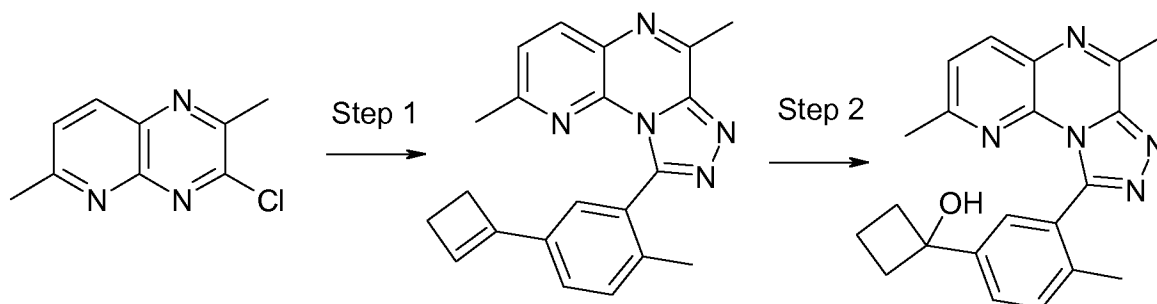


Example 101 (0.05 g) was prepared in analogy to Example 100 and purified applying the most suitable purification technique, starting from Scaffold Intermediate 30i (0.36 g, 0.9 mmol).

5 HPLC-MS (Method): $R_t = 3.3$ min

MS : $m/z = 392$ ($M+H$)⁺

Example 102:



10 **Step 1:**

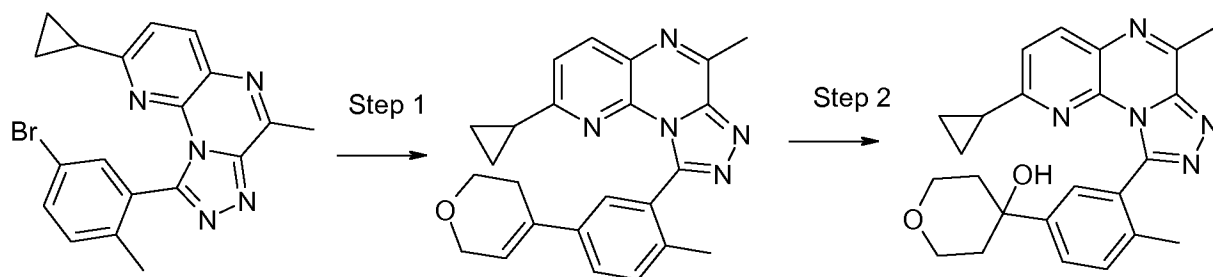
Step 1 was performed in analogy to preparation of Example 1 starting from Chloride Intermediate 9 (0.3 g, 1.39 mmol) and Hydrazide Intermediate 6o (0.47 g, 1.39 mmol).

Step 2:

15 Intermediate from step 1 (0.09 g, 0.26 mmol) and hydrochloric acid (10 mL of a 37% water solution) were dissolved in 10 mL of 1,4-dioxane. The reaction mixture was stirred at room temperature for 20 minutes. A bicarbonate saturated water solution was added, THF was removed in vacuum and the reaction mixture was extracted with DCM. The organic phase was separated, dried over sodium sulfate and
20 concentrated. The crude product obtained was purified by flash chromatography (eluent from 100:0 to 90:10 DCM/MeOH) to obtain the title compound (0.03 g).

HPLC-MS (Method 13): $R_t = 2.95$ min

MS: $m/z = 360$ ($M+H$)⁺

Example 103:5 **Step 1:**

Under nitrogen atmosphere, Scaffold Intermediate 30g (0.3 g, 0.61 mmol), potassium carbonate (0.34 g, 2.4 mmol) and [1,1'Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.05 g) were suspended in toluene (150 mL) and stirred at room temperature for 10 minutes. 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (0.17 g, 0.79 mmol) was added and the reaction mixture was stirred at 100°C for 4h. Water (30 mL) was added and the reaction mixture was extracted with AcOEt. The organic phase was separated and concentrated. The crude product obtained was purified by flash chromatography (eluent from 100:0 to 90:10 DCM/MeOH) to obtain the title compound (0.02 g).

15 **Step 2:**

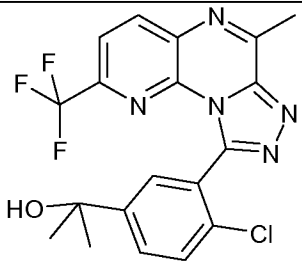
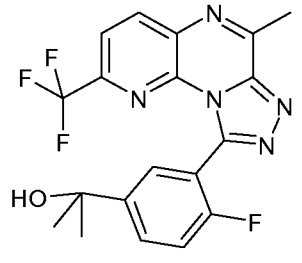
Step 2 was performed in analogy to Step 2 in the preparation of Example 102. 0.02 g of the desired product were obtained after purification by flash chromatography (eluent from 100:0 to 90:10 DCM/MeOH).

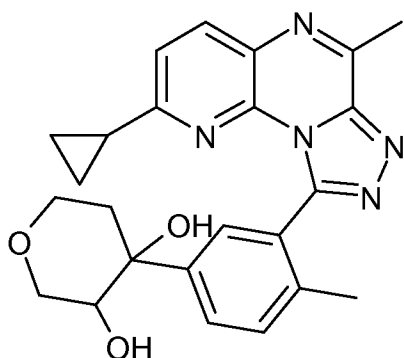
(HPLC-MS (Method 13): $R_t = 2.88$ min

20 MS : $m/z = 416$ (M+H)⁺

The following examples were prepared in analogy to Example 103 and purified applying the most suitable purification technique, starting from the corresponding Scaffold Intermediate and the boronic ester 2-Isopropenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane.

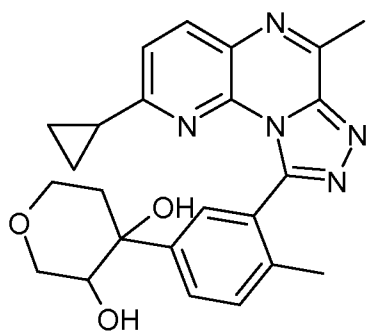
Starting Intermediate	Ex. #	Structure	MS m/z (M+H) ⁺	R_t (min)	Method
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30r	103b		422	3,25	13
30s	103c		406	3.17	13

Example 104 (CIS-racemic mixture):

- 5 Intermediate obtained from Step 1 in preparation of Example 103 (50 mg, 0.13 mmol) was dissolved in DCM (5 mL). Osmium tetroxide (0.1 mL, 0.01 mmol) and 4-methylmorpholine-4-oxide (0.07g, 0.63 mmol) were added and the reaction mixture was stirred at room temperature for 5 h. The solvent was removed and the crude product obtained was purified by flash chromatography (eluent from 100:0 to 80:20
- 10 DCM/MeOH) to obtain the title compound (0.03 g).
HPLC-MS (Method 13): $R_t = 2.73$ min
MS: $m/z = 432$ ($M+H$)⁺

Example 104a (CIS-single stereoisomer a):



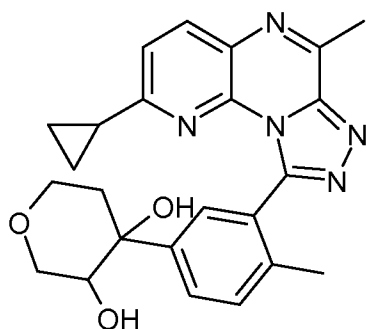
Example 104a was obtained via Chiral HPLC purification of Example 104.

HPLC-MS (Method 13): $R_t = 2.65$ min

MS: $m/z = 432$ ($M+H$)⁺

- 5 Chiral HPLC (Method C2b): $R_t = 18.70$ min

Example 104b (CIS-single stereoisomer b):



Further elution from the chiral column gave Example 104b.

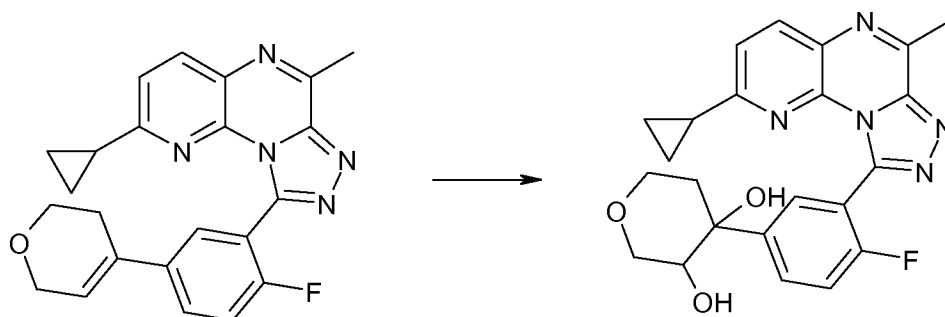
- 10 HPLC-MS (Method 13): $R_t = 2.65$ min

MS: $m/z = 432$ ($M+H$)⁺

Chiral HPLC (Method C2b): $R_t = 21.04$ min

Example 105 (CIS-racemic mixture):

15

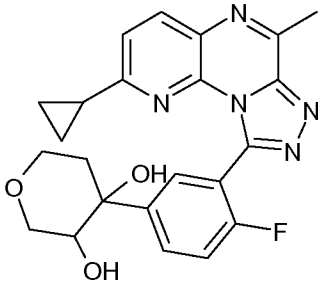
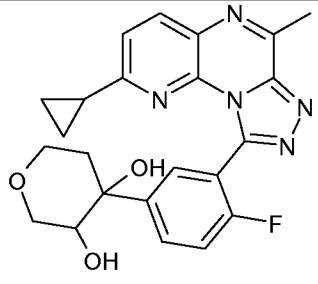


Example 105 (0.03 g) was prepared in analogy to Example 104, starting from 8-Cyclopropyl-1-[5-(3,6-dihydro-2H-pyran-4-yl)-2-fluoro-phenyl]-4-methyl-2,3,5,9,9b-pentaaza-cyclopenta[a]naphthalene (0.05g, 0.12 mmol) which was obtained as by-product in the preparation of Example 95 and isolated from the same flash chromatography purification.

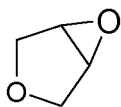
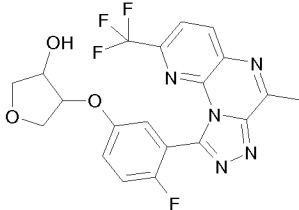
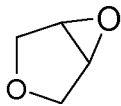
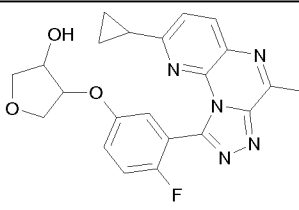
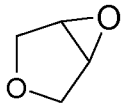
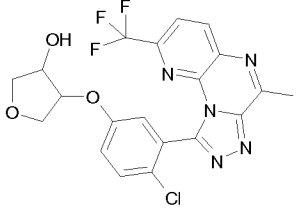
HPLC-MS (Method 13): $R_t = 2.68$ min

MS: $m/z = 436$ ($M+H$)⁺

- 10 The following examples were obtained as single stereoisomers by chiral HPLC separation of the corresponding racemic mixture.

Starting Racemic Mixture	Ex. #	Structure	MS m/z [$M+H$] ⁺	R_t (min) [LC-MS Method]	R_t (min) [Chiral HPLC Method]
105 CIS- Racemic mixture	105a CIS- Single stereoisomer a		436	2,69 [13]	15.05 [C2b]
97 CIS- Racemic mixture	105b CIS- Single stereoisomer b		436	2.68 [13]	18.47 [C2b]

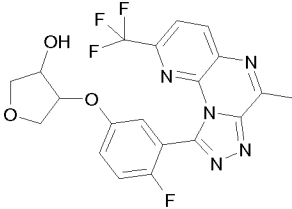
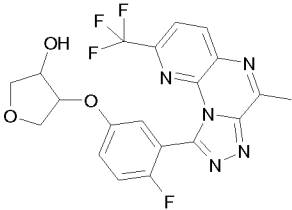
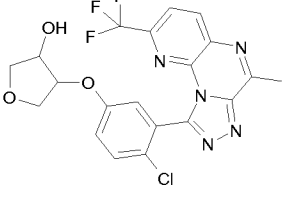
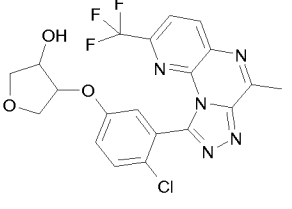
- 15 The following Examples were prepared in analogy to Example 44 and purified applying the most suitable purification technique, starting from the corresponding Starting Example and the corresponding epoxides.

Starting Example or Starting Intermediate	Starting Epoxide	Ex. #	Structure	MS m/z (M+H)+	R _t (min)	Method
Intermediate 32		106 TRANS- Racemic mixture		450	2,97	13
5		107 TRANS- Racemic mixture		422	3,88	16
12		111 TRANS- Racemic mixture		466	3.09	13

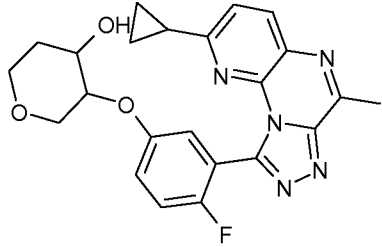
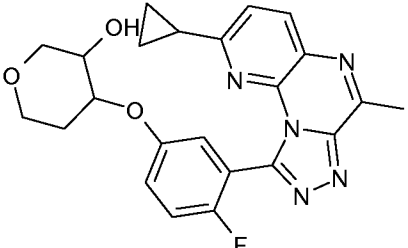
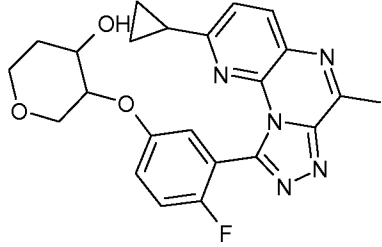
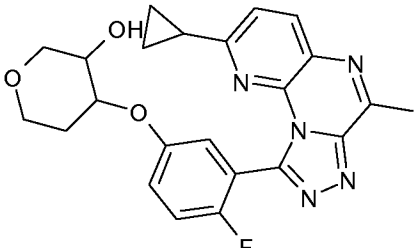
The following examples were obtained as single stereoisomers by chiral HPLC separation of the corresponding racemic mixture.

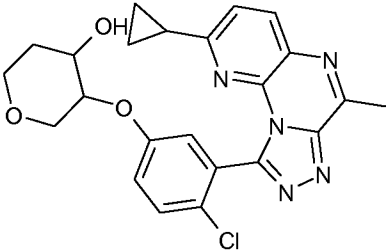
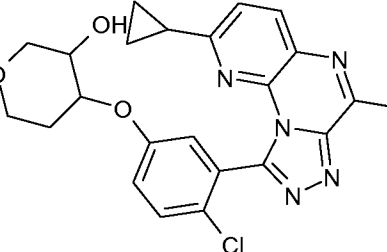
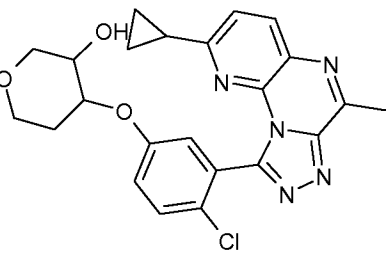
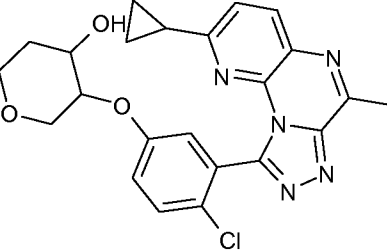
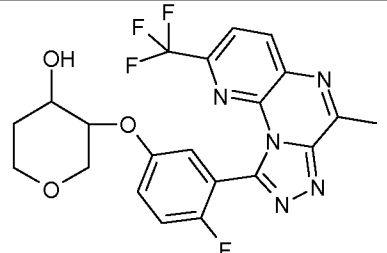
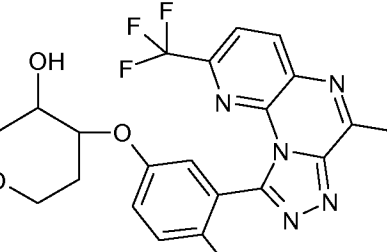
5

Starting Racemic Mixture	Ex. #	Structure	MS m/z [M+H] ⁺	R _t (min) [LC-MS Method]	R _t (min) [Chiral HPLC Method]
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106 TRANS- Racemic mixture	106a TRANS- single stereoisomer a		450	2,95 [13]	7.77 [C2c]
106 TRANS- Racemic mixture	106b TRANS- single stereoisomer b		450	2,98 [13]	11.58 [C2c]
111 TRANS- Racemic mixture	111a TRANS- single stereoisomer a		466	3.10 [13]	13.65 [C2]
111 TRANS- Racemic mixture	111b TRANS- single stereoisomer b		466	3.10 [13]	16.14 [C2]

The following examples were obtained as single stereoisomers by chiral HPLC separation of the corresponding TRANS regioisomeric racemic mixtures. TRANS regioisomeric racemic mixtures were obtained in analogy to preparation of Example 44, starting from epoxide Intermediate 29 and the corresponding Starting Examples or Starting Intermediates.

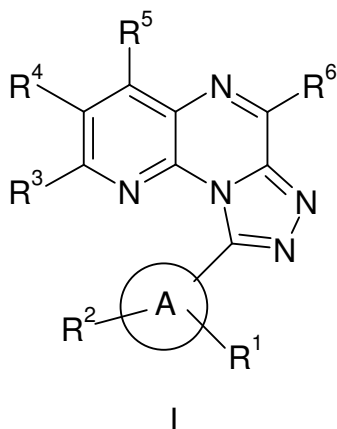
Starting Example or Starting Intermediate	Ex. #	Structure	MS m/z [M+H] ⁺	R _t (min) [LC-MS Method]	R _t (min) [Chiral HPLC Method]
5	108a TRANS- single stereoiso mer b		436	2,91 [13]	31.54 [C3]
5	108c TRANS- single stereoiso mer b		436	2,91 [13]	44.59 [C2c]
5	108b TRANS- single stereoiso mer a		436	2,92 [13]	27.61 [C3]
5	108d TRANS- single stereoiso mer a		436	2,91 [13]	22.06 [C2c]

9	109a TRANS- single stereoisomer a		452	3,03 [13]	23.62 [C2]
9	109c TRANS- single stereoisomer a		452	3,03 [13]	40.91 [C2]
9	109b TRANS- single stereoisomer b		452	3,03 [13]	89.29 [C2]
9	109d TRANS- single stereoisomer b		452	3,03 [13]	25.61 [C2]
Intermediate 32	110b TRANS- single stereoisomer b		464	3.00 [13]	21.99 [C2]
Intermediate 32	110d TRANS- single stereoisomer b		464	3.02 [13]	62.95 [C2]

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Claims

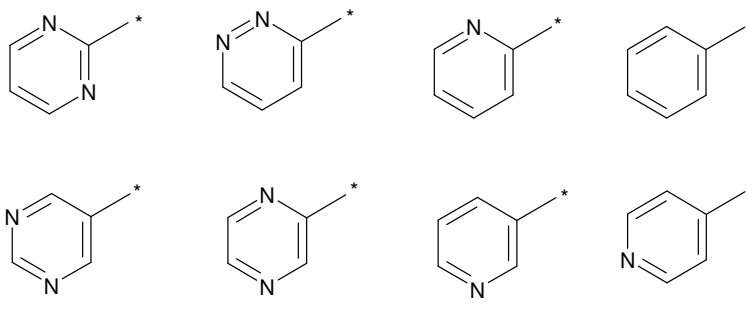
1. Compounds of formula I



5

wherein

A is selected from the group A^a consisting of



wherein above mentioned phenyl-, pyridinyl-, pyrimidinyl-, pyridazinyl and pyrazinyl groups are substituted with R¹ and R²;

R¹ is selected from the group R^{1a} consisting of

H, halogen, NC-, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl and R⁸-(CH₂)_n-O- with n = 0, 1, 2, 3 or 4,

wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl and R⁸-(CH₂)_n-O- groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO- and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-;

R² is selected from the group R^{2a1} consisting of

HO-, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl,

C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸-(CH₂)_n-O- with n = 0, 1, 2, 3 or 4, and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O- with m = 0, 1 or 2 and o = 0, 1 or 2,

wherein above mentioned C₁₋₆-alkyl-, and C₁₋₆-alkyl-O-groups are substituted with 1 to 5 substituents independently selected from the group consisting of HO-, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O-, and

wherein above mentioned C₁₋₆-alkyl- and C₁₋₆-alkyl-O-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-,

and

wherein above mentioned C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸-(CH₂)_n-O- and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO-, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O-, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-;

R³ is selected from the group R^{3a} consisting of

H, halogen, NC-, C₁₋₄-alkyl- and C₃₋₆-cycloalkyl-,

wherein the above mentioned C₁₋₄-alkyl- and C₃₋₆-cycloalkyl-groups may optionally be substituted with 1 to 9 substituents independently selected from the group consisting of halogen, NC-, HO-, C₁₋₃-alkyl- and C₁₋₃-alkyl-O-;

R⁴, R⁵ are selected independently of each other from the group R^{4a}/R^{5a} consisting of

H, halogen, NC-, HO-, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₈-cycloalkyl-, C₃₋₈-

cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O-, heterocyclyl-O-, heterocyclyl, heteroaryl, R⁷-CH₂-O- and R⁷-(CH₂)₂-O-,

wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O-, heterocyclyl-O-, heterocyclyl, heteroaryl, R⁷-CH₂-O- and R⁷-(CH₂)₂-O-groups, may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, optionally with 1 to 5 halogen atoms, substituted C₁₋₂-alkyl-, and optionally with 1 to 5 halogen atoms substituted C₁₋₂-alkyl-O-;

R⁶ is selected from the group R^{6a} consisting of
H, NC-, C₁₋₆-alkyl-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl- and C₃₋₈-

cycloalkyl-O-

wherein above mentioned C₁₋₆-alkyl- groups may optionally be substituted with 1-3 halogen atoms;

R⁷ is selected from the group R^{7a} consisting of
H, carbocyclyl, heterocyclyl and heteroaryl,
wherein above mentioned carbocyclyl, heterocyclyl and heteroaryl-
groups may optionally be substituted with 1 to 4 substituents
independently selected from the group consisting of HO-, optionally
with 1 to 3 halogen atoms substituted C₁₋₄-alkyl-, optionally with 1 to 3
halogen atoms substituted C₁₋₄-alkyl-O- and halogen;

R⁸ is selected from the group R^{8a} consisting of
C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl,
wherein above mentioned C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-
C₁₋₃-alkyl-, phenyl and pyridyl groups may optionally be substituted
with 1 to 5 substituents independently selected from the group
consisting of HO-, fluorine and optionally with 1 to 7 halogen atoms
substituted C₁₋₃-alkyl-;

the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates
5 thereof, the hydrates thereof and the salts thereof.

2. A compound according to claim 1, wherein

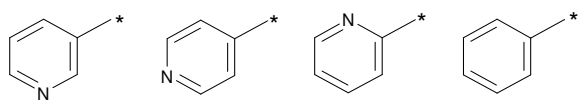
R^3 is selected from the group R^{3a1} consisting of

C_{3-6} -cycloalkyl-,

wherein the above mentioned C_{3-6} -cycloalkyl-group may optionally be substituted with 1 to 9 substituents independently selected from the group consisting of halogen, NC-, HO-, C_{1-3} -alkyl- and C_{1-3} -alkyl-O-.

3. A compound according to any one or more of claims 1 to 2, wherein

A is selected from the group A^b consisting of



wherein above mentioned phenyl- and pyridinyl- groups are substituted with R^1 and R^2 .

4. A compound according to any one or more of claims 1 to 3, wherein

R^1 is selected from the group R^{1b} consisting of

H, halogen, C_{1-6} -alkyl- and C_{3-6} -cycloalkyl

wherein above mentioned C_{1-6} -alkyl- and C_{3-6} -cycloalkyl-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO- and optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-.

5. A compound according to any one or more of claims 1 to 4, wherein

R^2 is selected from the group R^{2b1} consisting of

HO-, C_{1-4} -alkyl-, C_{1-4} -alkyl-O-, C_{3-6} -cycloalkyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl-, heterocyclyl, heterocyclyl- C_{1-3} -alkyl-, phenyl, heteroaryl, $R^8-(CH_2)_n-O-$ with $n = 0, 1, 2$ or 3 and $R^8-(CH_2)_m-(CH)(CH_3)-(CH_2)_o-O-$ with $m = 0$ or 1 and $o = 0$ or 1

wherein above mentioned C_{1-4} -alkyl- and C_{1-4} -alkyl-O- groups are substituted with 1 to 3 substituents independently selected from the group consisting of HO- and optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-O-,

and

wherein above mentioned C_{1-4} -alkyl- and C_{1-4} -alkyl-O-groups may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halogen, and optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-,

and

wherein above mentioned C_{3-6} -cycloalkyl-, C_{3-6} -cycloalkyl- C_{1-3} -alkyl-,

heterocyclyl, heterocyclyl- C_{1-3} -alkyl-, $R^8-(CH_2)_n-O-$ and $R^8-(CH_2)_m-(CH)(CH_3)-(CH_2)_6-O-$ groups may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halogen, $HO-$, optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl- $O-$, and optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-.

6. A compound according to any one or more of claims 1 and 3 to 5, wherein

R^3 is selected from the group R^{3b} consisting of
 H, C_{1-3} -alkyl-, cyclobutyl- and cyclopropyl-,
 wherein the above mentioned C_{1-3} -alkyl-, cyclobutyl- and cyclopropyl-
 groups may optionally be substituted with 1 to 7 substituents
 independently selected from the group consisting of halogen, C_{1-3} -
 alkyl-O-, NC- and HO-.

7. A compound according to any one or more of claims 1 to 6, wherein

R^4 , R^5 are selected independently of each other from the group R^{4b}/R^{5b} consisting
 of

H, halogen, HO-, H_3C -, F_3C -, H_3C -O-, F_2HC -O-, FH_2C -O-, F_3C -O-, C_{1-4} -
 alkyl-O-, R^7 -CH₂-O- and R^7 -(CH₂)₂-O-,
 wherein above mentioned C_{1-4} -alkyl-O-, R^7 -CH₂-O- and R^7 -(CH₂)₂-O-
 groups, may optionally be substituted with 1 to 5 substituents
 independently selected from the group consisting of halogen,
 optionally with 1 to 5 halogen atoms substituted C_{1-2} -alkyl-, and
 optionally with 1 to 5 halogen atoms substituted C_{1-2} -alkyl-O-.

8. A compound according to any one or more of claims 1 to 7, wherein

R^6 is selected from the group R^{6b} consisting of

H, C_{1-4} -alkyl- and cyclopropyl-,
 wherein above mentioned C_{1-4} -alkyl-group may optionally be
 substituted with 1-9 fluorine and/or chlorine atoms.

9. A compound according to any one or more of claims 1 to 8 wherein

R^7 is selected from the group R^{7b} consisting of

H, phenyl, heteroaryl, cycloalkyl and heterocyclyl

wherein above mentioned phenyl, heteroaryl, cycloalkyl and heterocyclyl-groups may optionally be substituted with 1 to 4 substituents independently selected from the group consisting of halogen, and optionally with 1 to 3 halogen atoms substituted C_{1-3} -alkyl-O-.

10. A compound according to any one or more of claims 1 to 9, wherein

R^8 is selected from the group R^{8b} consisting of

C_{3-6} -cycloalkyl, heterocyclyl and heterocyclyl- C_{1-3} -alkyl-,

wherein above mentioned C₃₋₆-cycloalkyl, heterocyclyl and heterocyclyl-C₁₋₃-alkyl-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO-, fluorine and optionally with 1 to 7 halogen atoms substituted C₁₋₃-alkyl-.

11. A compound according to any one or more of claims 1 to 10, wherein

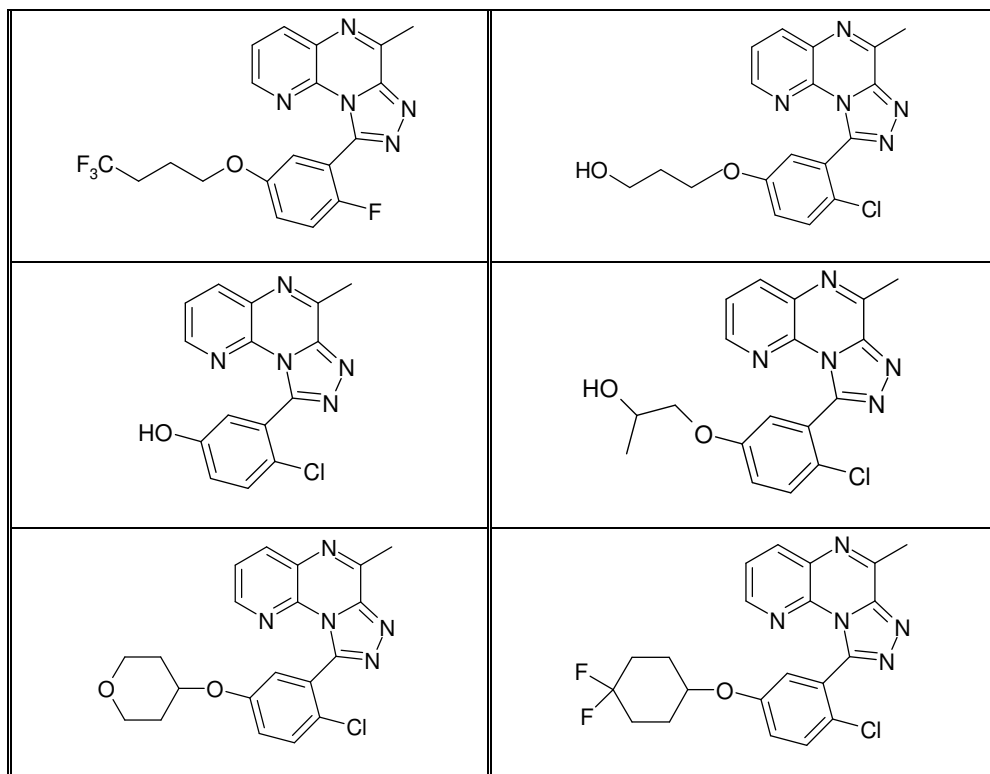
R⁸ is selected from the group R^{8c1} consisting of

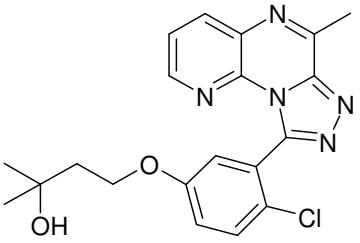
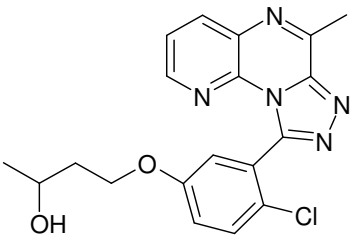
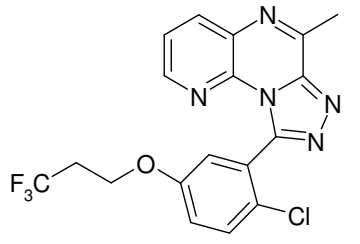
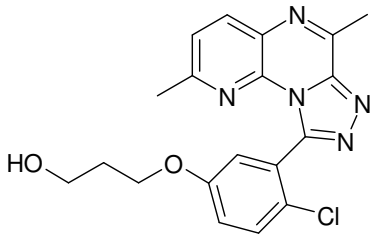
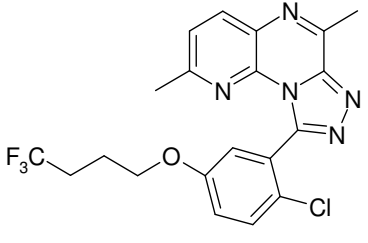
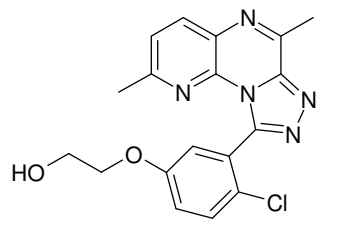
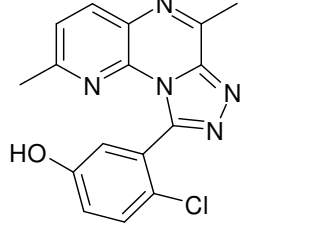
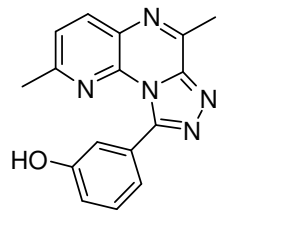
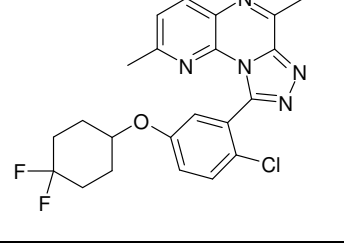
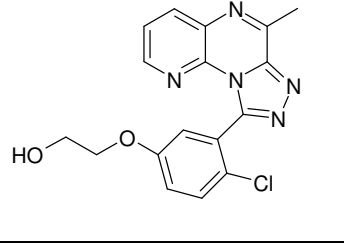
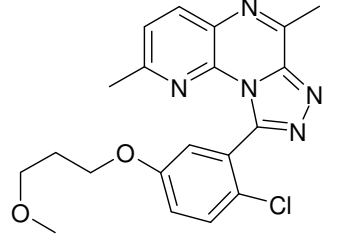
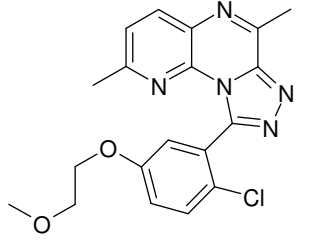
C₃₋₆-cycloalkyl and a saturated 4 to 6 membered monocyclic heterocycle containing one or two heteroatoms selected from N or O,

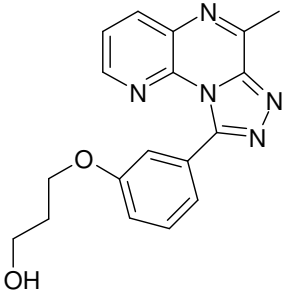
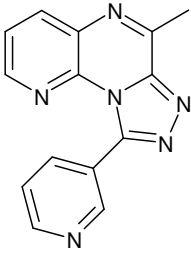
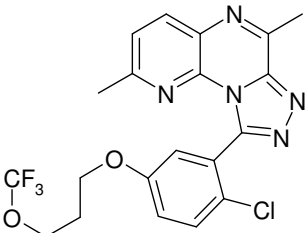
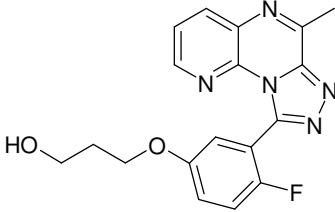
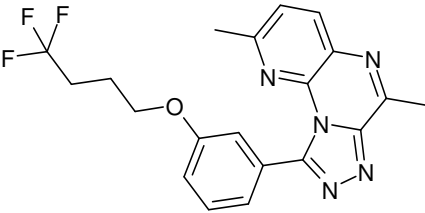
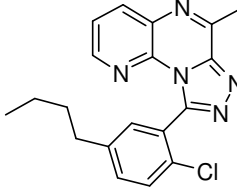
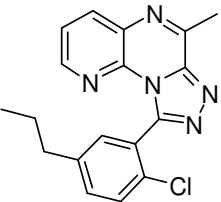
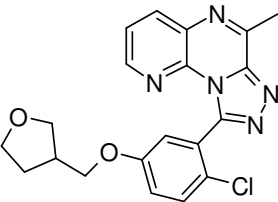
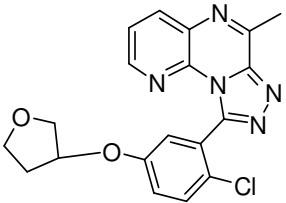
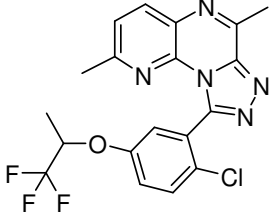
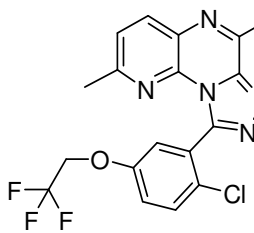
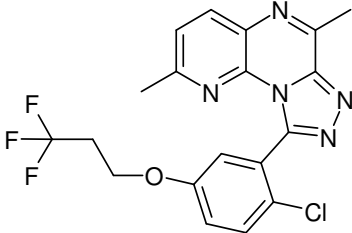
wherein above mentioned C₃₋₆-cycloalkyl and heterocyclyl-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO-, fluorine and optionally with 1 to 7 halogen atoms substituted C₁₋₃-alkyl-.

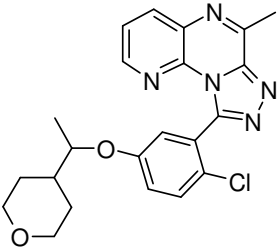
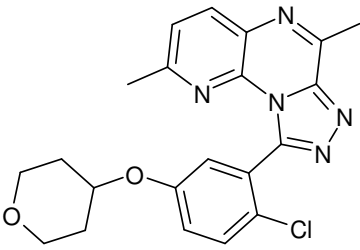
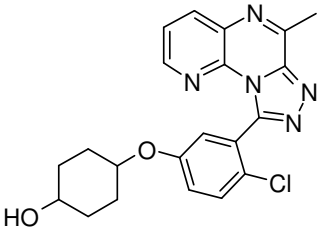
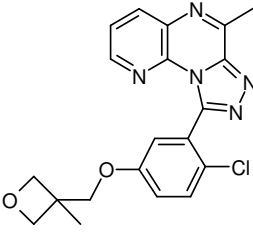
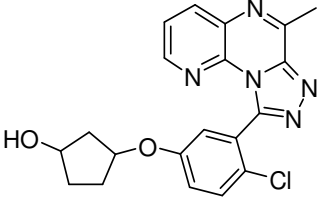
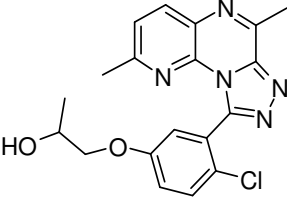
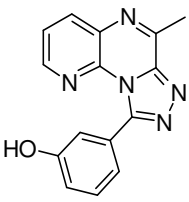
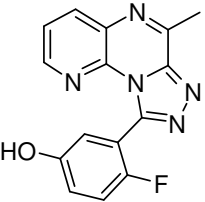
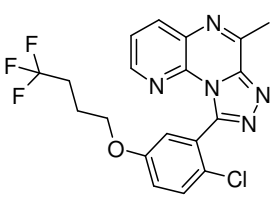
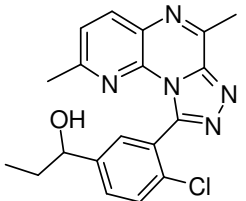
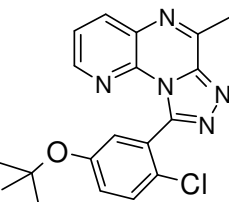
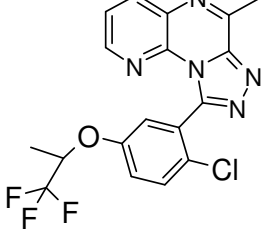
12. A compound according to any one or more of claims 1 to 11 selected from the group

5 consisting of

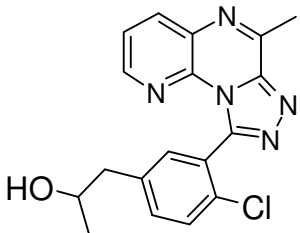
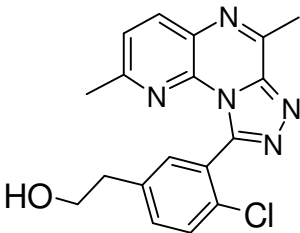
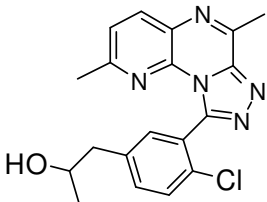
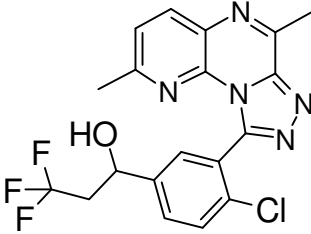
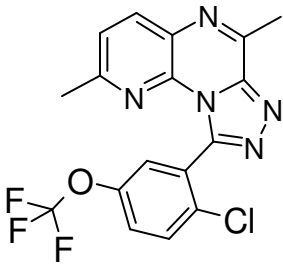
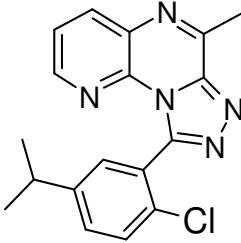
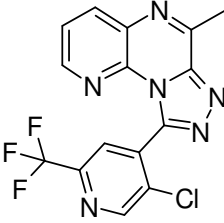
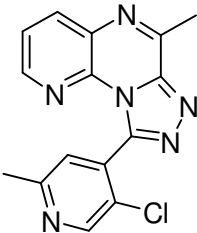
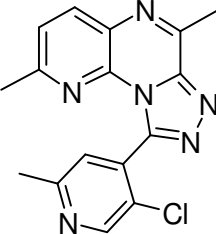
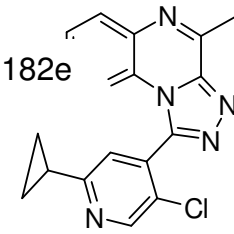
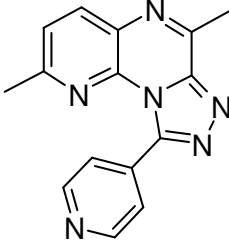
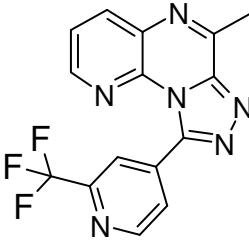


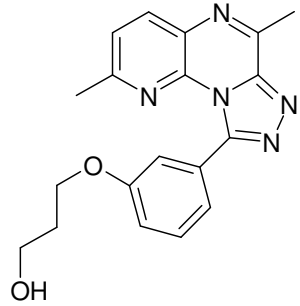
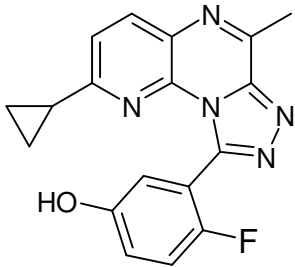
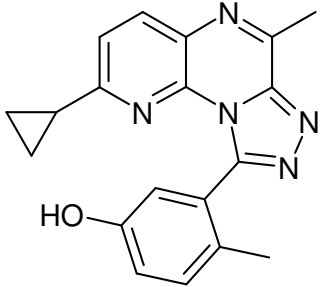
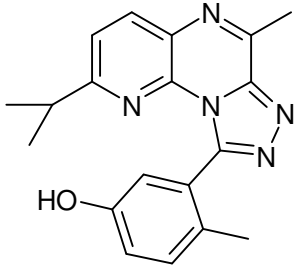
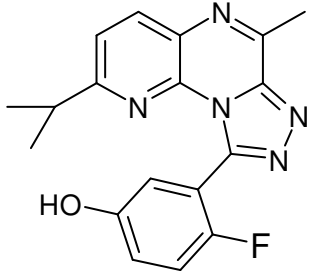
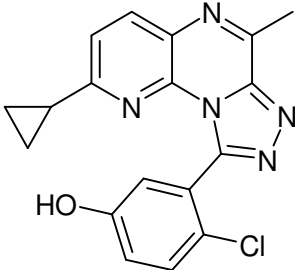
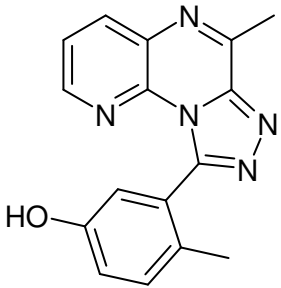
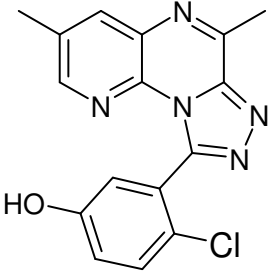
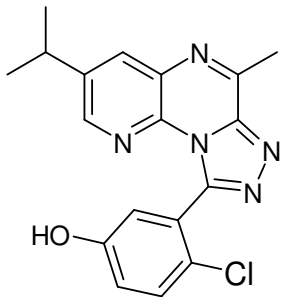
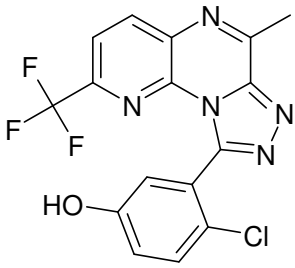
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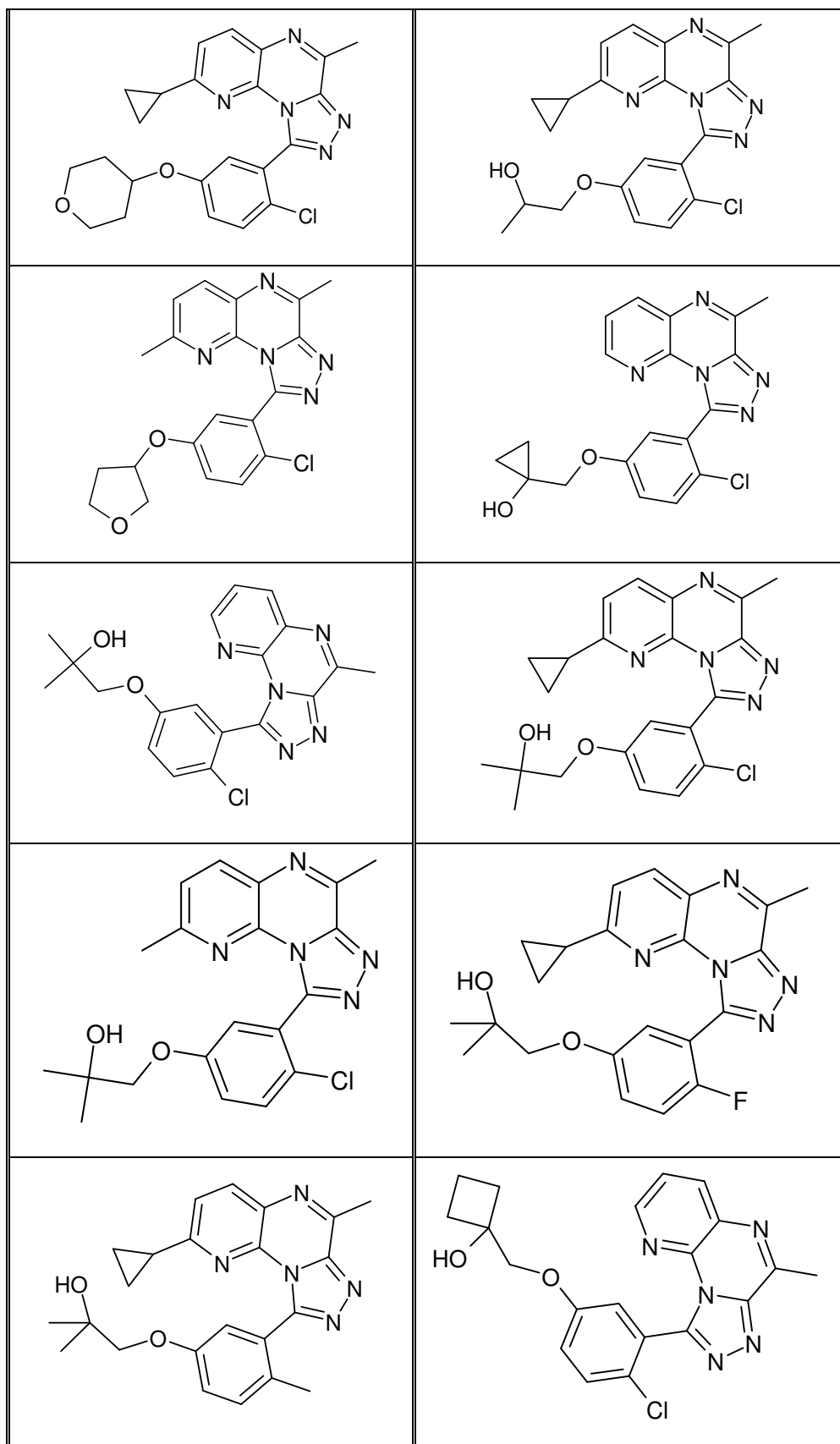
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 <chem>CC1=NC2=CC=CC=C2N1c3cc(Cl)ccc3OCC2OCC2</chem>	 <chem>CC1=NC2=CC=CC=C2N1c3cc(Cl)ccc3OC(C)(F)(F)F</chem>
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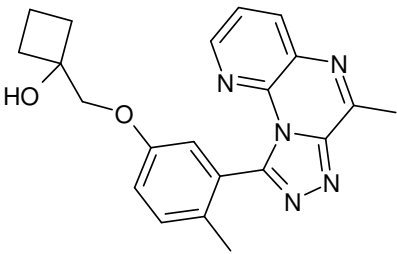
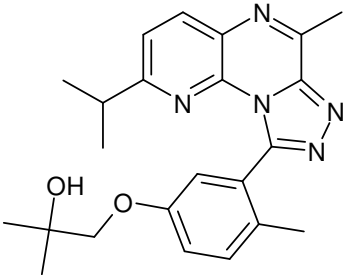
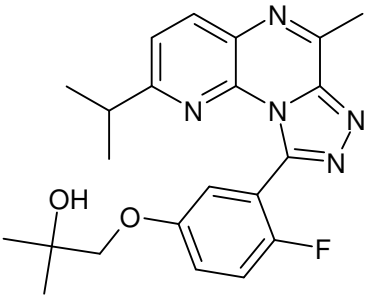
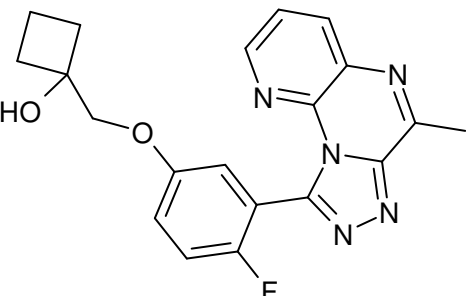
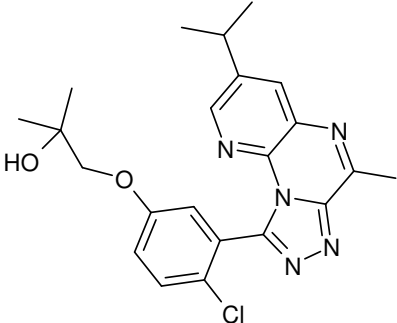
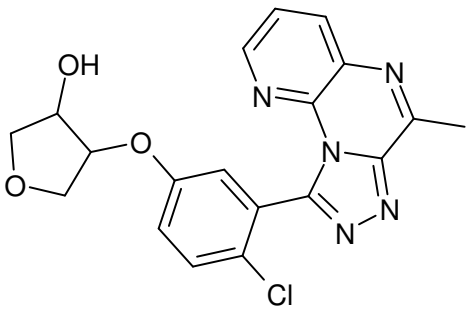
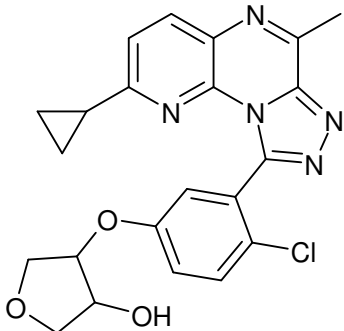
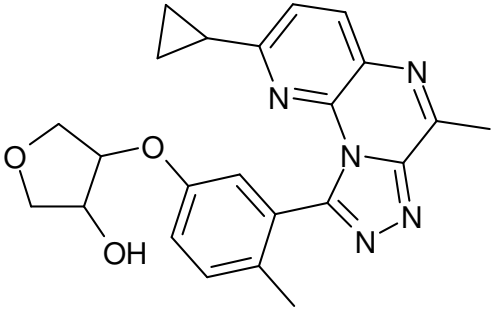
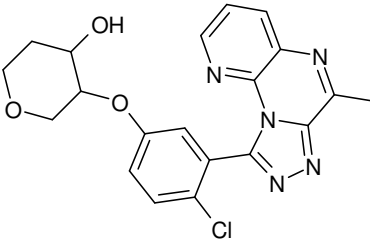
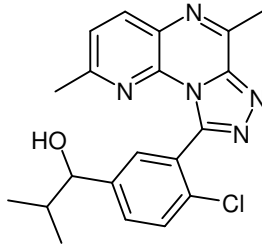
	
	
	
	
	
	

182d

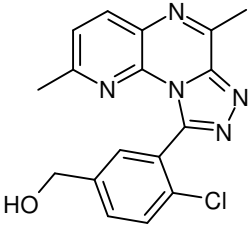
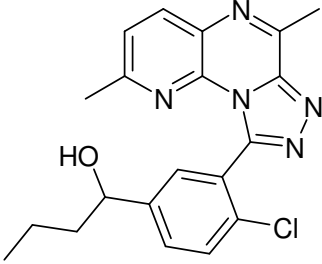
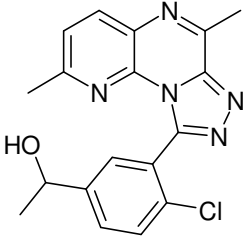
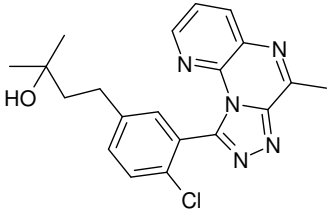
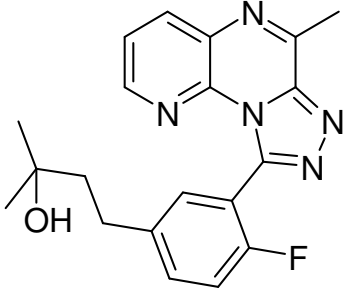
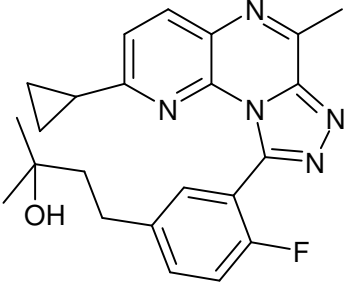
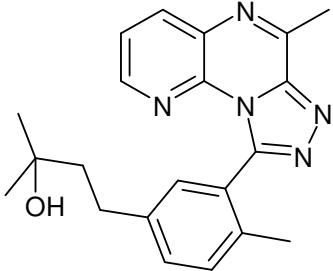
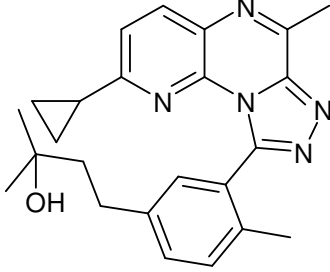
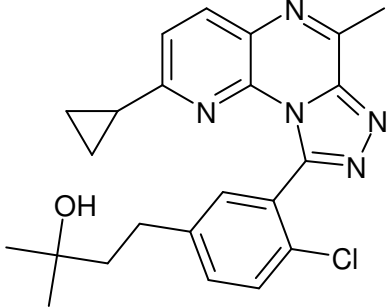
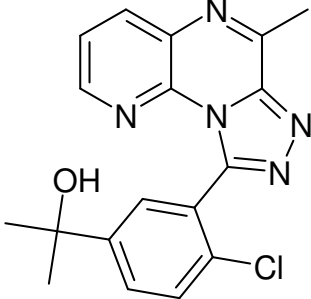
	
	
	
	
	
	

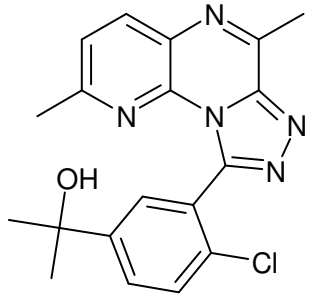
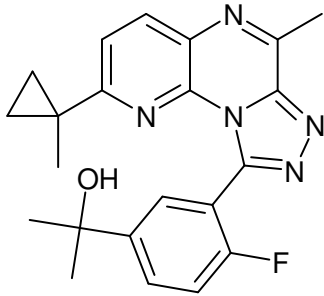
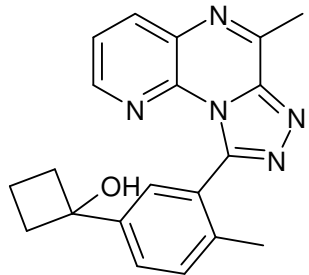
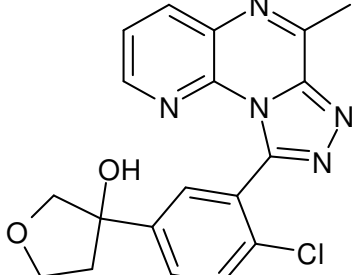
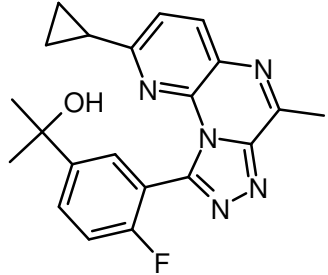
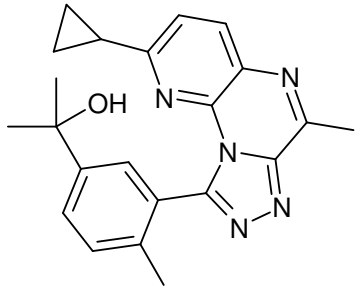
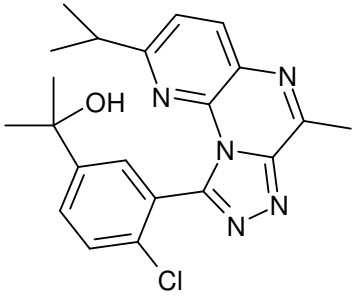
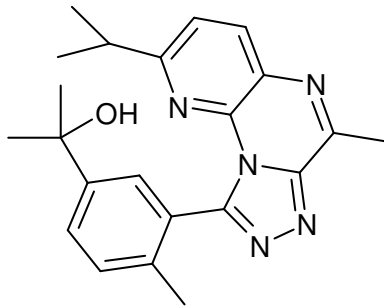
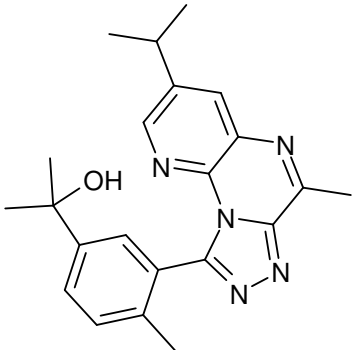
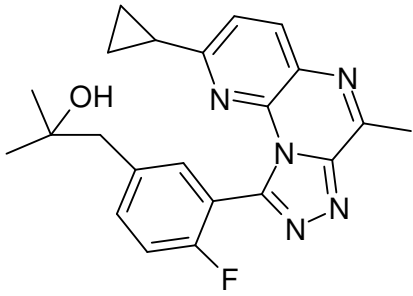
	
	
	
	
	

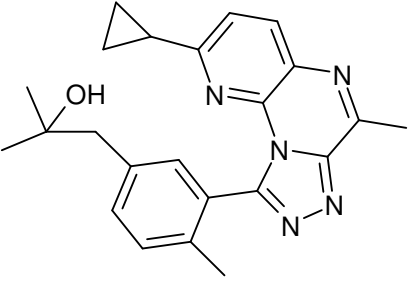
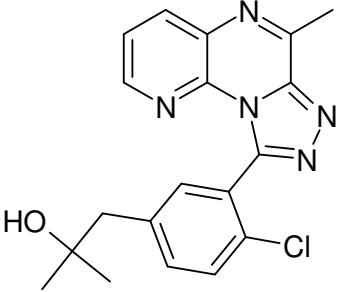
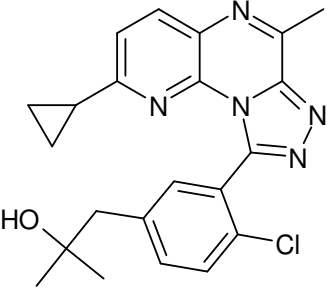
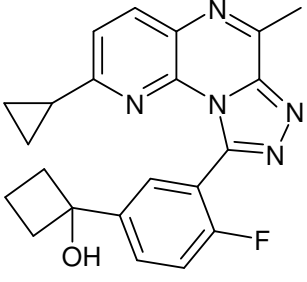
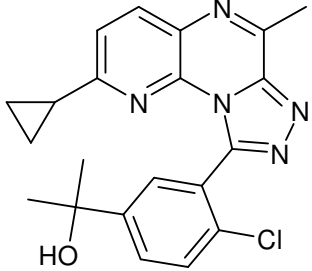
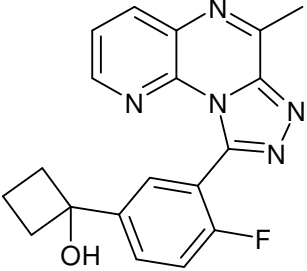
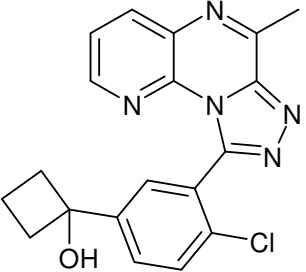
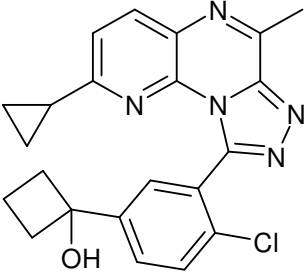
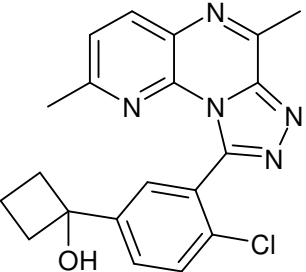
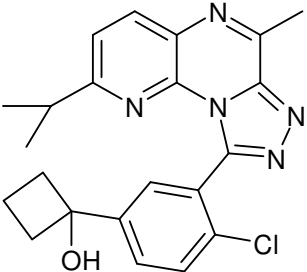


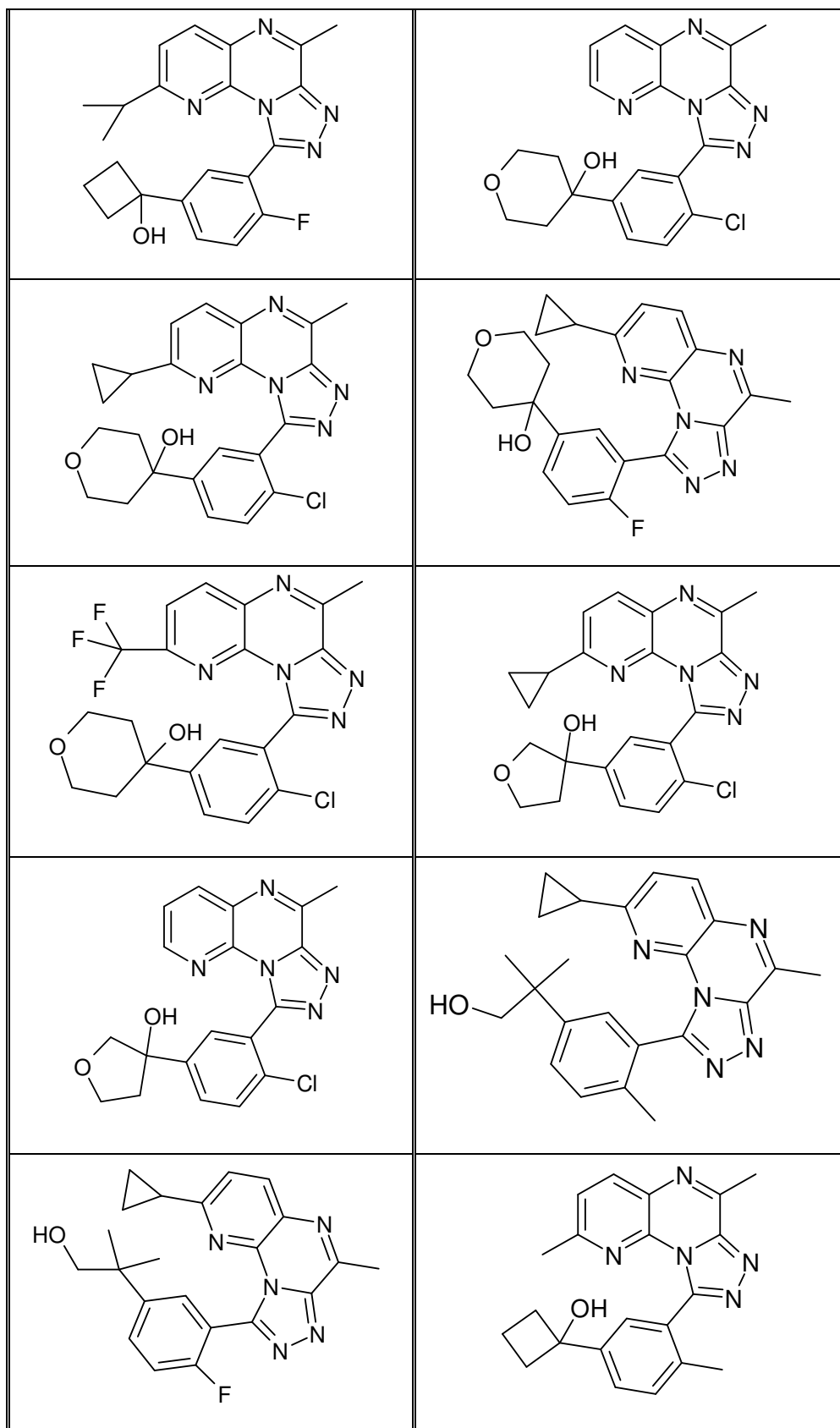
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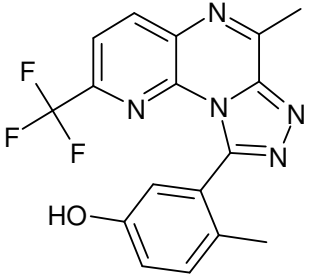
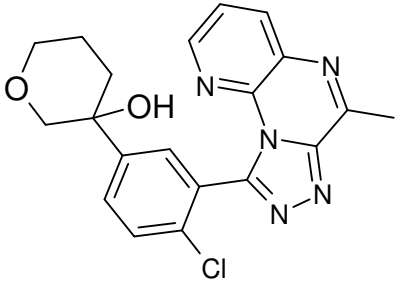
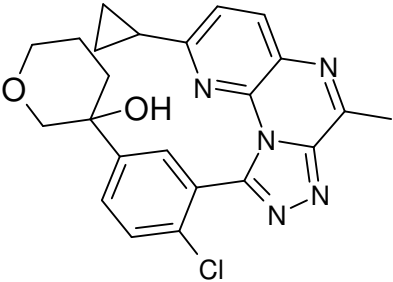
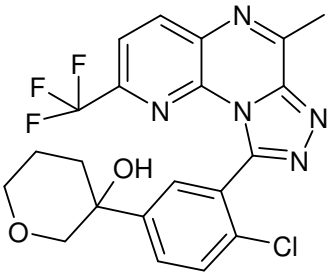
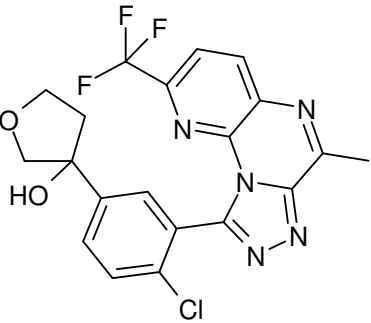
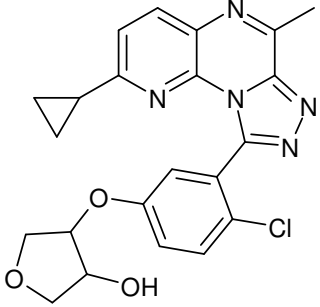
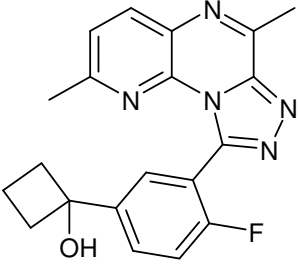
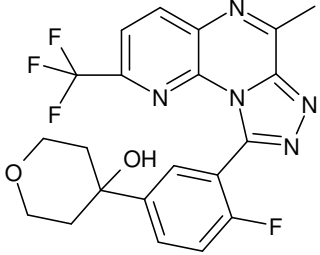
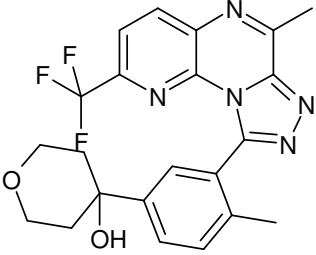
	
	
	
	
	

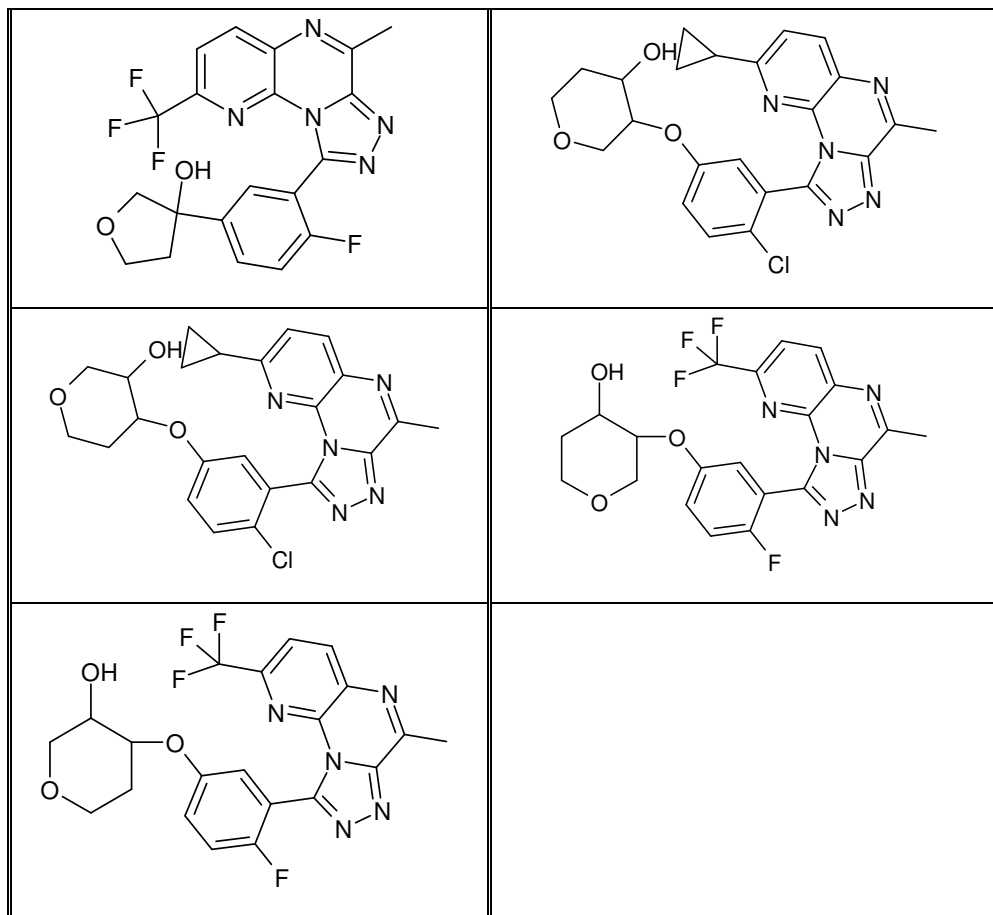
	
	
	
	
	

182k



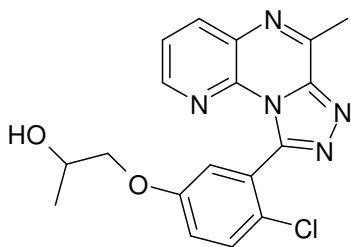
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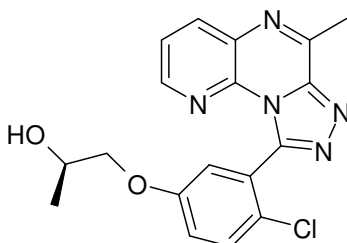
the tautomers thereof, the stereoisomers thereof, the solvates thereof, the hydrates thereof and the salts thereof.

- 5 13. A compound according to any one or more of claims 1 to 12 of the formula



the tautomers thereof, the stereoisomers thereof, the solvates thereof, the hydrates thereof and the salts thereof.

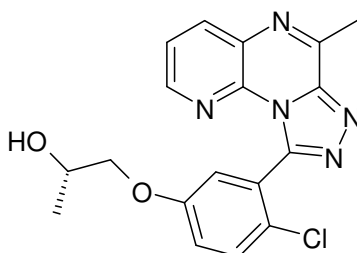
14. A compound according to any one or more of claims 1 to 12 of the formula



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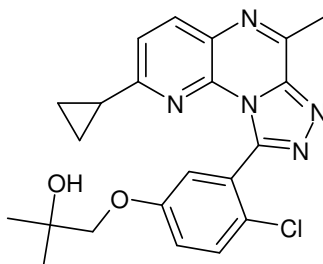
the tautomers thereof, the solvates thereof, the hydrates thereof and the salts thereof.

15. A compound according to any one or more of claims 1 to 12 of the formula



10 the tautomers thereof, the solvates thereof, the hydrates thereof and the salts thereof.

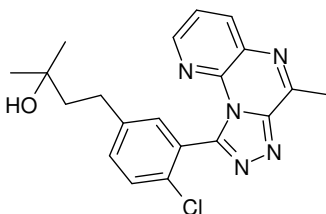
16. A compound according to any one or more of claims 1 to 12 of the formula



the tautomers thereof, the solvates thereof, the hydrates thereof and the salts thereof.

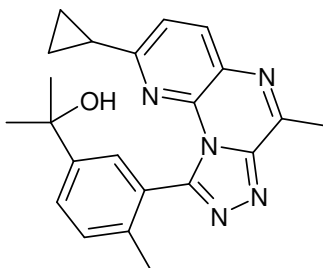
15

17. A compound according to any one or more of claims 1 to 12 of the formula



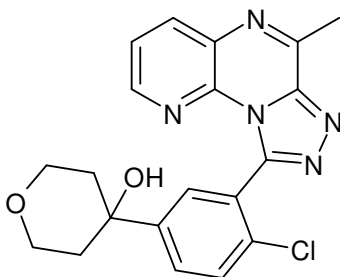
the tautomers thereof, the solvates thereof, the hydrates thereof and the salts thereof.

18. A compound according to any one or more of claims 1 to 12 of the formula



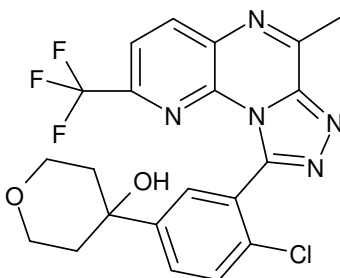
the tautomers thereof, the solvates thereof, the hydrates thereof and the salts thereof.

5 19. A compound according to any one or more of claims 1 to 12 of the formula



the tautomers thereof, the solvates thereof, the hydrates thereof and the salts thereof.

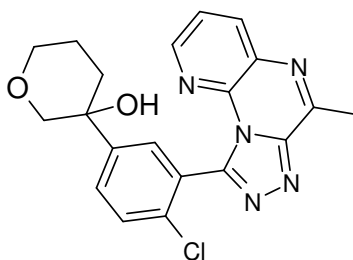
20. A compound according to any one or more of claims 1 to 12 of the formula



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the tautomers thereof, the solvates thereof, the hydrates thereof and the salts thereof.

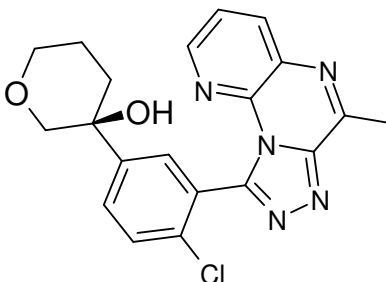
21. A compound according to any one or more of claims 1 to 12 of the formula



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the tautomers thereof, the stereoisomers thereof, the solvates thereof, the hydrates thereof and the salts thereof.

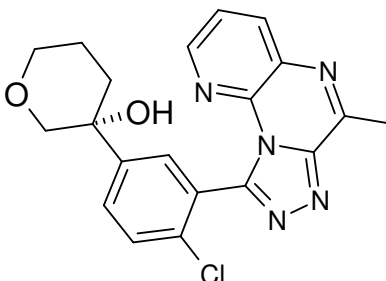
22. A compound according to any one or more of claims 1 to 12 of the formula



5

the tautomers thereof, the solvates thereof, the hydrates thereof and the salts thereof.

23. A compound according to any one or more of claims 1 to 12 of the formula



10 the tautomers thereof, the solvates thereof, the hydrates thereof and the salts thereof.

24. A compound according to any one or more of claims 1 to 23, or a pharmaceutically acceptable tautomers thereof, stereoisomer thereof, mixtures thereof, solvate thereof, hydrate thereof or salt thereof for use as a medicament.

15

25. Pharmaceutical compositions containing at least one compound according to any one or more of the claims 1 to 23 or a pharmaceutically acceptable tautomers thereof, stereoisomer thereof, mixtures thereof, solvate thereof, hydrate thereof or salt thereof together with one or more pharmaceutically acceptable carrier.

20

26. A compound according to any one or more of claims 1 to 23, or a pharmaceutically acceptable tautomer thereof, stereoisomer thereof, mixtures thereof, solvate thereof, hydrate thereof or salt thereof or a pharmaceutical composition according to claim 25 for use in the prevention or treatment of (1) disorders comprising the symptom of cognitive

deficiency; (2) organic, including symptomatic, mental disorders, dementia; (3) mental retardation; (4) mood [affective] disorders; (5) neurotic, stress-related and somatoform disorders including anxiety disorders; (6) behavioural and emotional disorders with onset usually occurring in childhood and adolescence, attention deficit hyperactivity syndrome (ADHD) and Autism spectrum disorders; (7) disorders of psychological development, developmental disorders of scholastic skills; (8)

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schizophrenia and other psychotic disorders; (9) disorders of adult personality and behaviour; (10) mental and behavioural disorders due to psychoactive substance use; (11) extrapyramidal and movement disorders; (12) episodic and paroxysmal disorders, epilepsy; (13) Systemic atrophies primarily affecting the central nervous system, ataxia; 5 (14) Behavioural syndromes associated with physiological disturbances and physical factors; (15) sexual dysfunction comprising excessive sexual drive; (16) factitious disorders; (17) Treatment, amelioration and / or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory; (18) Treatment amelioration and / or prevention of cognitive impairment being related to age- 10 associated learning and memory impairments; (19) Age-associated memory losses; (20) Vascular dementia; (21) Craniocerebral trauma; (22) Stroke; (23) Dementia occurring after strokes (post stroke dementia); (24) Post-traumatic dementia; (25) General concentration impairments; (26) Concentration impairments in children with learning and memory problems; (27) Alzheimer's disease; (28) Lewy body dementia; 15 (29) Dementia with degeneration of the frontal lobes; including Pick's syndrome; (30) Parkinson's disease; (31) Progressive nuclear palsy; (32) Dementia with corticobasal degeneration; (33) Amyotrophic lateral sclerosis (ALS); (34) Huntington's disease; (35) Multiple sclerosis; (36) Thalamic degeneration; (37) Creutzfeld-Jacob dementia; (38) HIV dementia; (38) Schizophrenia with dementia or Korsakoff's psychosis; (39) Sleep 20 disorders; (40) Bipolar disorder; (41) Metabolic syndrome; (42) Obesity; (43) Diabetis mellitus; (44) Hyperglycemia; (45) Dyslipidemia; (46) Impaired glucose tolerance; (47) Disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen and (48) pain disorders.

27. A compound according to any one or more of claims 1 to 23, or a pharmaceutically 25 acceptable tautomer thereof, stereoisomer thereof, mixtures thereof, solvate thereof, hydrate thereof or salt thereof or a pharmaceutical composition according to claim 25 for use in symptomatic treatment of Alzheimer's Disease, symptomatic treatment of prodromal and/or mild-to-moderate Alzheimer's Disease and/or for the treatment of cognitive impairment associated with schizophrenia.