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(54) Benævnelse: **TETRAZOLDERIVATER SOM TRPA1-HÆMMERE**

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WO-A1-2017/060488
LAURIE B. SCHENKEL ET AL: "Optimization of a Novel Quinazolinone-Based Series of Transient Receptor Potential A1 (TRPA1) Antagonists Demonstrating Potent in Vivo Activity", JOURNAL OF MEDICINAL CHEMISTRY, vol. 59, no. 6, 24 March 2016 (2016-03-24), pages 2794 - 2809, XP055373392, ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.6b00039

DESCRIPTION

Description

FIELD OF THE INVENTION

[0001] The present disclosure provides certain tetrazole derivatives that are inhibitors of transient receptor potential ankyrin 1 (TRPA1), and are therefore useful for the treatment of diseases treatable by inhibition of TRPA1. Also provided are pharmaceutical compositions containing the same, and processes for preparing said compounds.

BACKGROUND INFORMATION

[0002] Transient receptor potential channels (TRP channels) are a group of voltage-gated ion channels located mostly on the plasma membrane of numerous mammalian cell types. There are approximately 30 structurally related TRP channels sorted into groups: TRPA, TRPC, TRPM, TRPML, TRPN, TRPP and TRPV. Transient receptor potential cation channel, subfamily A, member 1 (TRPA1), also known as transient receptor potential ankyrin 1, is the only member of the TRPA gene subfamily. Structurally, TRPA channels are characterized by multiple N-terminal ankyrin repeats (~14 in the N-terminus of human TRPA1) that gives rise to the "A" for ankyrin designation (Montell, 2005).

[0003] TRPA1 is highly expressed in the plasma membrane of sensory neurons in the dorsal root and nodose ganglia that serve both skin and lung, as well as in small intestine, colon, pancreas, skeletal muscle, heart, brain, bladder and lymphocytes (https://www.proteinatlas.org/) as well as in human lung fibroblasts.

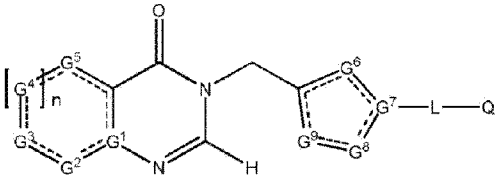
[0004] TRPA1 is best known as a sensor for environmental irritants giving rise to somatosensory modalities such as pain, cold and itch. TRPA1 is activated by a number of reactive, electrophilic stimuli (e.g. allyl isothiocyanate, reactive oxygen species), as well as non-reactive compounds (e.g. icilin), implicated in cough associated with asthma, chronic pulmonary obstructive disease (COPD), idiopathic pulmonary fibrosis (IPF) or post-viral cough or for chronic idiopathic cough as well as cough in sensitive patients. (Song and Chang, 2015; Grace and Belvisi, 2011). TRPA1 inhibitors are useful in the treatment of IPF in which cough is highly prevalent because of the link between cough and lung injury, based on studies showing cough-induced elevation of TGF-β (Xie et al., 2009; Froese et al., 2016; Tschumperlin et al., 2003; Yamamoto et al., 2002; Ahamed et al., 2008). TRPA1 antagonists inhibit calcium signaling triggered by cough triggers such as cigarette smoke extract (CSE) oxidative stress,

inflammatory mediator release and downregulated antioxidant gene expression (Lin et al., 2015; Wang et al., 2019). TRPA1 antagonists are effective in studies of atopic dermatitis (Oh et al., 2013; Wilson et al., 2013), contact dermatitis (Liu et al., 2013), psoriasis-associated itch (Wilson et al., 2013) and IL-31-dependent itch (Cevikbas et al., 2014). A human TRPA1 gain-of-function has been associated with familial episodic pain syndrome (Kremeyer et al., 2010). A TRPA1 antagonist was effective in a behavioral model of migraine-related allodynia (Edelmayer et al., 2012). TRPA1 is selectively increased in trigeminal ganglia innervating injured teeth when compared to TRPA1 expression in trigeminal ganglia innervating healthy teeth (Haas et al., 2011). Several anaesthetics are known to be TRPA1 agonists, including isoflurane (Matta et al., 2008) providing rationale for TRPA1 inhibitors for the relief of post-surgical pain. TRPA1 knockout mice and wild type mice treated with a TRPA1 antagonist showed anxiolytic- and antidepressant-like phenotypes (de Moura et al., 2014). TRPA1 inhibitors are expected to have benefit in the treatment of diabetic neuropathy based on studies showing a mechanistic link of inverse regulation between AMPK and TRPA1 (Hiyama et al., 2018; Koivisto and Pertovaara, 2013; Wang et al., 2018). TRPA1 knockout mice exhibit smaller myocardial infarct sizes compared to wild type mice (Conklin et al., 2019). TRPA1 knockout and pharmacological intervention inhibited TNBS-induced colitis in mice (Engel et al., 2011). In a mouse brain ischaemia model, TRPA1 knock-out and TRPA1 antagonists reduce myelin damage (Hamilton et al., 2016). Urate crystals and joint inflammation are reduced in TRPA1 knockout mice in a monosodium urate mouse model of gout (Moilanen et al., 2015). TRPA1 deletion in rats ameliorated joint inflammation and hyperalgesia in a rat model of acute gout flares (Trevisan et al., 2014). Activation of TRPA1 elicits an inflammatory response in osteoarthritic chondrocytes (Nummenmaa et al., 2016). TRPA1 inhibition and genetic deletion reduces inflammatory mediators in osteoarthritic mouse chondrocytes and murine cartilage (Nummenmaa et al., 2016). Finally, TRPA1 knockout mice exhibited improvements in weight bearing on the osteoarthritic limb in an MIA-evoked knee swelling model (Horvath et al., 2016). TRPA1 is differentially expressed in the bladder epithelium of rats (Du et al., 2007) and of patients with bladder outlet obstruction (Du et al., 2008). TRPA1 receptor modulation attenuates bladder overactivity in a rat model of spinal cord injury (Andrade et al., 2011) and intrathecal administration of TRPA1 antagonists attenuate cyclophosphamide-induced cystitis in rats with hyper-reflexia micturition (Chen et al., 2016).

[0005] It is therefore desirable to provide potent TRPA1 inhibitors.

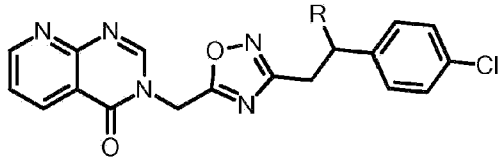
[0006] TRPA1 inhibitors of various structural classes are reviewed in S. Skerratt, Progress in Medicinal Chemistry, 2017, Volume 56, 81-115 and in D. Preti, G. Saponaro, A. Szallasi, Pharm. Pat. Anal. (2015) 4 (2), 75-94.

[0007] WO2017/060488 discloses compounds that are antagonists of TRPA1, having the generalized structural formula



[0008] The TRPA1 activity of Examples 28 and 29 bearing a tetrazolyl ring therein is not disclosed.

[0009] L. Schenkel, et al., J. Med. Chem. 2016, 59, 2794-2809 discloses quinazolinone-based TRPA1 antagonists including compounds of the generalized structural formula



of which compound 31, wherein R is OH, is disclosed as having an antagonistic TRPA1 activity of IC_{50} 58 nM in a FLIPR assay and having an intrinsic clearance in human liver microsomes of <14 µL/min/kg.

DETAILED DESCRIPTION OF THE INVENTION

[0010] The present invention discloses novel tetrazole derivatives that are inhibitors of transient receptor potential ankyrin 1 (TRPA1), possessing appropriate pharmacological and pharmacokinetic properties enabling their use as medicaments for the treatment of conditions and/or diseases treatable by inhibition of TRPA1.

[0011] The compounds of the present invention may provide several advantages, such as enhanced potency, high metabolic and/or chemical stability, high selectivity, safety and tolerability, enhanced solubility, enhanced permeability, desirable plasma protein binding, enhanced bioavailability, suitable pharmacokinetic profiles, and the possibility to form stable salts.

The compounds of the invention

[0012] The present invention provides novel tetrazole derivatives that are surprisingly potent inhibitors of TRPA1 (Assay A), further characterised by

- improved stability in human liver microsomes (Assay B)
- improved stability in human hepatocytes (Assay C)

[0013] Compounds of the present invention differ structurally from examples **28** and **29** in WO2017/060488 in their substituted bicyclic cores (pyrimido[4,5-b][1,4]oxazine-4,6-di-one, pyrimido[4,5-b][1,4]thiazine-4,6-dione or pyrido[3,2-d][1,4]pyrimidone-4,6-dione) as well as substituents adjacent to a secondary aliphatic alcohol. Compounds of the present invention

additionally differ structurally from example **31** in L. Schenkel, et al., J. Med. Chem. 2016, 59, 2794-2809, in that they bear a tetrazolyl ring. These structural differences unexpectedly lead to a favourable combination of (i) inhibition of TRPA1, (ii) stability in human liver microsomes, and (iii) stability in human hepatocytes.

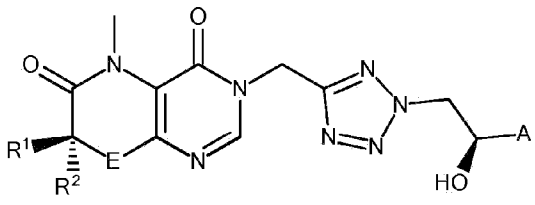
[0014] Compounds of the invention are thus superior to those disclosed in the prior art in terms of the combination of the following parameters:

- potency as inhibitors of TRPA1
- stability in human liver microsomes
- stability in human hepatocytes

[0015] Stability in human liver microsomes refers to the susceptibility of compounds to biotransformation in the context of selecting and/or designing drugs with favorable pharmacokinetic properties as a first screening step. The primary site of metabolism for many drugs is the liver. Human liver microsomes contain the cytochrome P450s (CYPs), and thus represent a model system for studying phase I drug metabolism *in vitro.* Enhanced stability in human liver microsomes is associated with several advantages, including increased bioavailability and adequate half-life, which can enable lower and less frequent dosing of patients. Thus, enhanced stability in human liver microsomes is a favorable characteristic for compounds that are to be used for drugs. Therefore, compounds of the present invention in addition to being able to inhibit TRPA1 are expected to have a favorable *in vivo* clearance and thus the desired duration of action in humans.

[0016] Stability in human hepatocytes refers to the susceptibility of compounds to biotransformation in the context of selecting and/or designing drugs with favorable pharmacokinetic properties. The primary site of metabolism for many drugs is the liver. Human hepatocytes contain the cytochrome P450s (CYPs) and other drug metabolizing enzymes, and thus represent a model system for studying drug metabolism in vitro. (Importantly, in contrast to liver microsomes assay, the hepatocytes assay covers also phase II biotransformations as well as liver-specific transporter-mediated processes, and therefore represents a more complete system for drug metabolism studies). Enhanced stability in human hepatocytes is associated with several advantages, including increased bioavailability and adequate half-life, which can enable lower and less frequent dosing of patients. Thus, enhanced stability in human hepatocytes is a favorable characteristic for compounds that are to be used for drugs.

[0017] The present invention provides novel compounds according to formula (I)



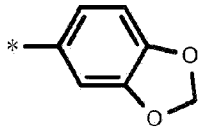
(I)

wherein

A is selected from the group consisting of phenyl, thiophenyl, benzothiophenyl or benzofuranyl, unsubstituted or substituted with one, two or three members of the group R^3 consisting of halogen, CN, C_{1-4}-alkyl, O-C_{1-4}-alkyl, C_{1-4}-fluoroalkyl, O-C_{1-4}-fluoroalkyl, C_{3-4}-cycloalkyl, O-C_{3-4}-cycloalkyl, C_{3-4}-cyclofluoroalkyl and O-C_{3-4}-cyclofluoroalkyl,

or

A is selected from the group consisting of



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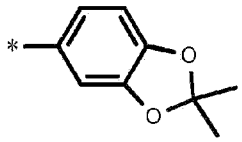

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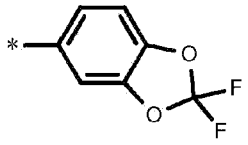


;

E is selected from the group consisting of O, S, SO, SO_2 and CH_2;

and

R^1 and R^2 are independently selected from the group consisting of H, C_{1-4}-alkyl, C_{1-4}-fluoroalkyl and halogen,

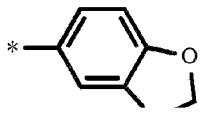
or R^1 and R^2 together with the carbon to which they are attached form a cyclopropyl or cyclobutyl ring.

[0018] Another embodiment of the present invention relates to a compound of formula (I), wherein

A is selected from the group consisting of phenyl, thiophenyl, benzothiophenyl or benzofuranyl, unsubstituted or substituted with one or two members of the group R^3 consisting of halogen, C_{1-4}-alkyl, CN, and O-C_{1-4}-alkyl,

or

A is



;

E is selected from the group consisting of O, S, and CH_2;

and

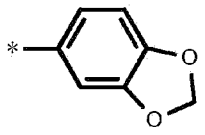
R^1 and R^2 are independently selected from the group consisting of H, C_{1-4}-alkyl, and halogen.

[0019] Another embodiment of the present invention relates to a compound of formula (I), wherein

A is selected from the group consisting of phenyl, thiophenyl, benzothiophenyl or benzofuranyl, unsubstituted or substituted with one or two members of the group R^3 selected from the group consisting of F, Cl, Br, C_{1-4}-alkyl, CN, and OCH_3,

or

A is



;

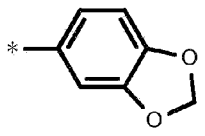
and substituents E, $R^1$and R^2 are defined as in the preceding embodiment.

[0020] Another embodiment of the present invention relates to a compound of formula (I), wherein

A is selected from the group consisting of phenyl, thiophenyl, benzothiophenyl or benzofuranyl, unsubstituted or substituted with one or two members of the group R^3 selected from the group consisting of F, Cl, Br, CH_3, CN, and OCH_3,

or

A is

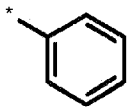
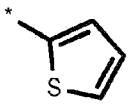
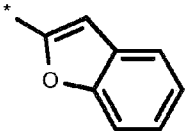
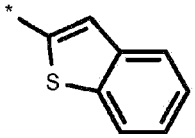
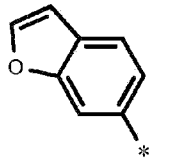


;

and substituents E, R^1 and R^2 are defined as in any of the preceding embodiments.

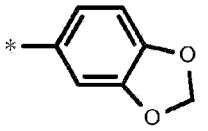
[0021] Another embodiment of the present invention relates to a compound of formula (I), wherein

A is selected from the group consisting of

 ,  ,  ,  and  ,

unsubstituted or substituted with one or two members of the group R^3,
or

A is

 ;

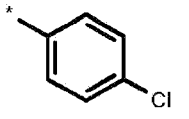
and substituents E, R^1, R^2 and R^3 are defined as in any of the preceding embodiments.

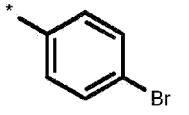
[0022] Another embodiment of the present invention relates to a compound of formula (I), wherein

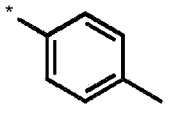
R^3 is selected from the group consisting of F, Cl, Br, CH_3, CN, and OCH_3;

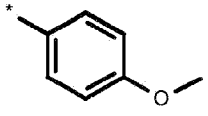
and substituents A, E, R^1, and R^2 are defined as in any of the preceding embodiments.

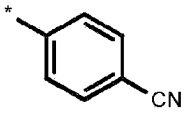
[0023] Another embodiment of the present invention relates to a compound of formula (I), wherein
A is selected from the group consisting of

 ,

 ,

 ,

 ,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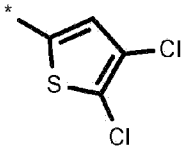
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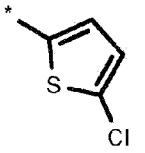
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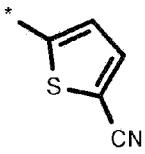
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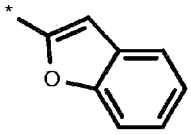
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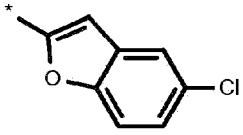
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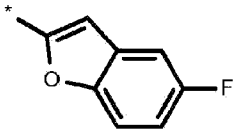
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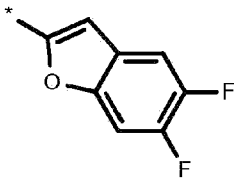
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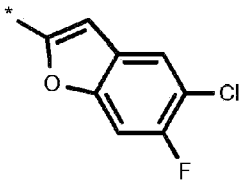
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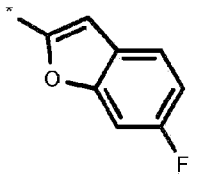
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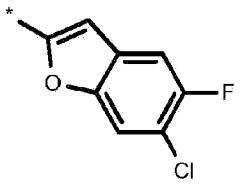
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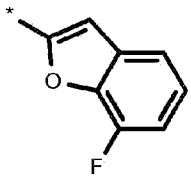
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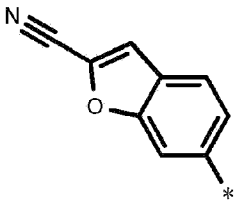
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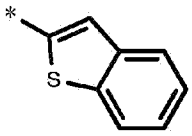
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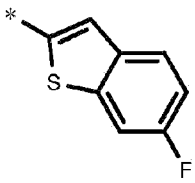
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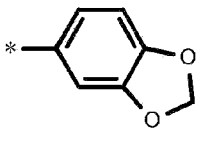

;

and substituents E, R^1, and R^2 are defined as in any of the preceding embodiments.

[0024] Another embodiment of the present invention relates to a compound of formula (I), wherein

E is selected from the group consisting of O and S;

and substituents A, R^1, R^2 and R^3 are defined as in any of the preceding embodiments.

[0025] Another embodiment of the present invention relates to a compound of formula (I), wherein

E is selected from the group consisting of O and CH_2;

and substituents A, R^1, R^2 and R^3 are defined as in any of the preceding embodiments.

[0026] Another embodiment of the present invention relates to a compound of formula (I), wherein

E is O;

and substituents A, R^1, R^2 and R^3 are defined as in any of the preceding embodiments.

[0027] Another embodiment of the present invention relates to a compound of formula (I), wherein

E is S;

and substituents A, R^1, R^2 and R^3 are defined as in any of the preceding embodiments.

[0028] Another embodiment of the present invention relates to a compound of formula (I), wherein

E is CH_2;

and substituents A, R^1, R^2 and R^3 are defined as in any of the preceding embodiments.

[0029] Another embodiment of the present invention relates to a compound of formula (I), wherein

R^1 and R^2 are independently selected from the group consisting of H, CH_3, and halogen;

and substituents A, E and R^3 are defined as in any of the preceding embodiments.

[0030] Another embodiment of the present invention relates to a compound of formula (I), wherein

R^1 and R^2 are independently selected from the group consisting of H, CH_3, and F;

and substituents A, E and R^3 are defined as in any of the preceding embodiments.

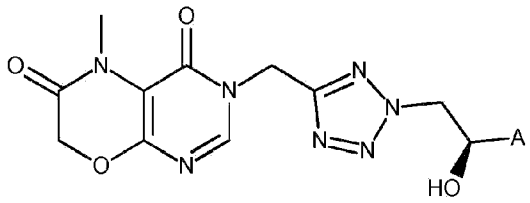
[0031] Another embodiment of the present invention relates to a compound of formula (I), wherein R^1 and R^2 are H;
and substituents A, E and R^3 are defined as in any of the preceding embodiments.

[0032] Another embodiment of the present invention relates to a compound of formula (I), wherein

one of R^1 and R^2 is H and the other of R^1 and R^2 is selected from the group consisting of CH_3, and F;

and substituents A, E and R^3 are defined as in any of the preceding embodiments.

[0033] Preferred is a compound of formula (I), selected from the group consisting of



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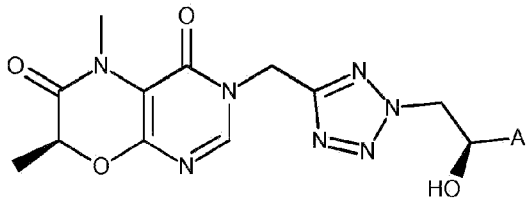

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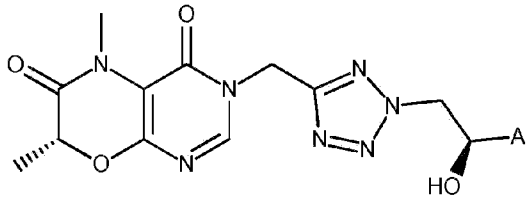

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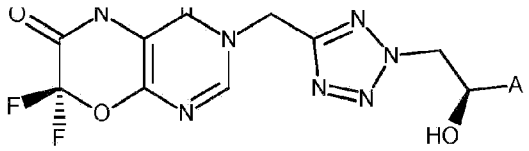

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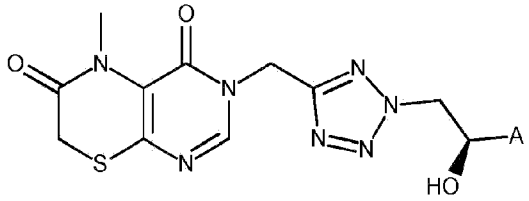

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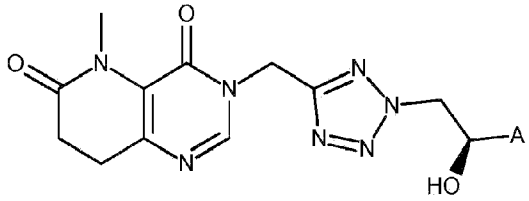
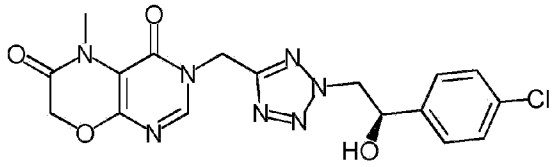


;

and substituent A is defined as in any of the preceding embodiments.

[0034] Particularly preferred is the compound according to formula (I) selected from the group consisting of



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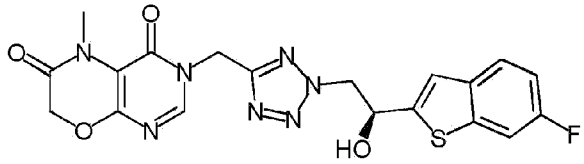

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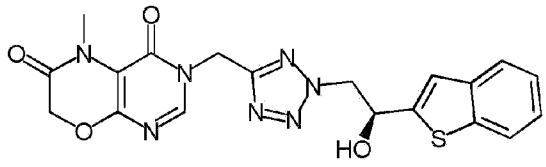

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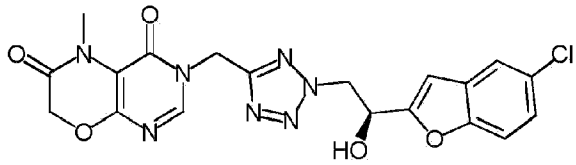

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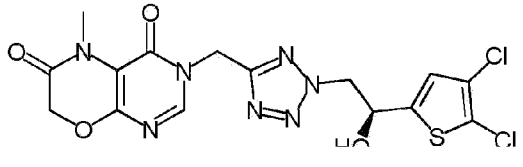

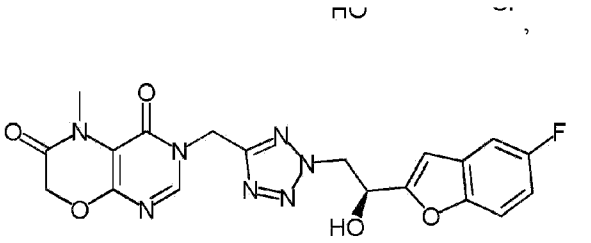

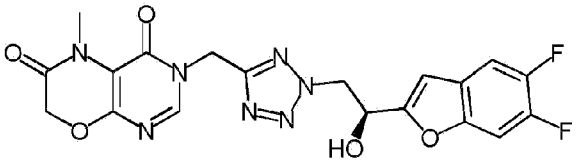

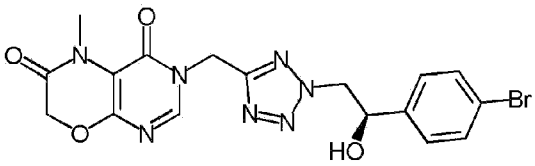

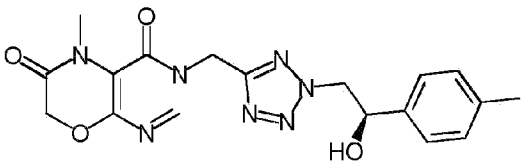

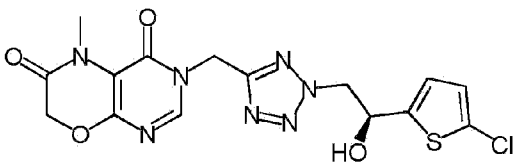

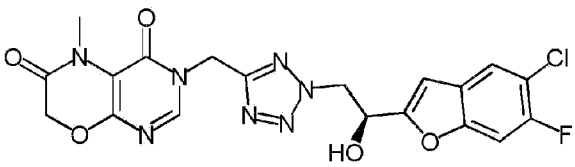

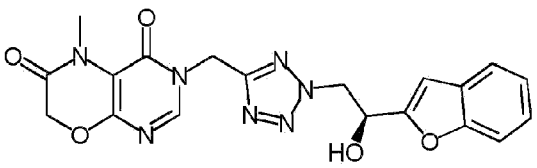

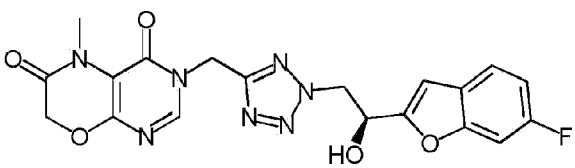

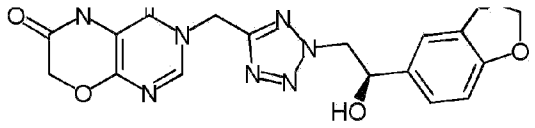

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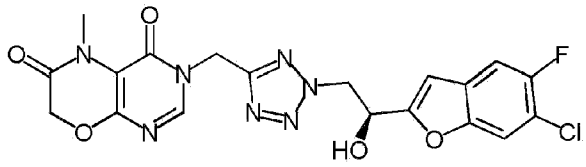

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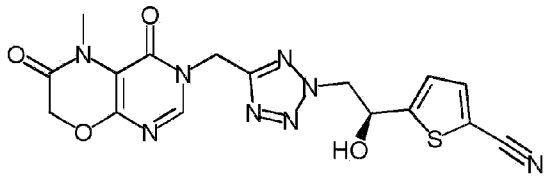

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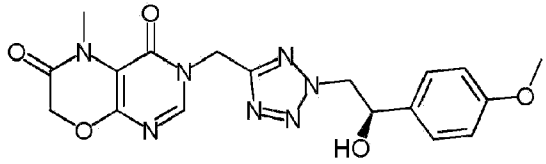

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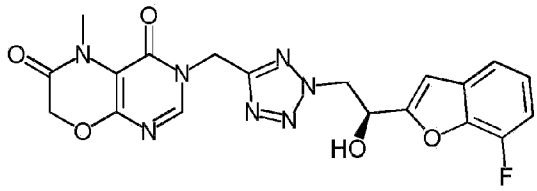

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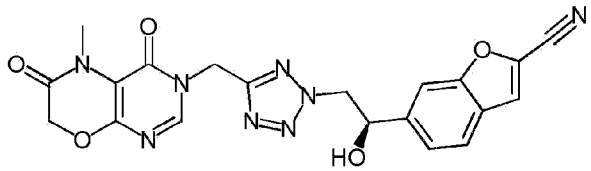

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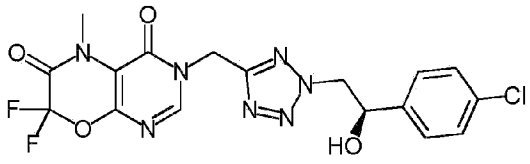

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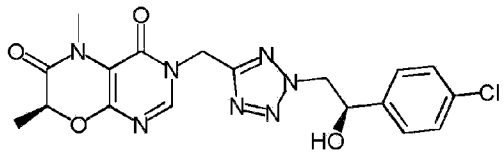

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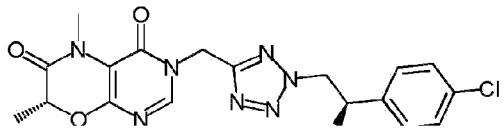

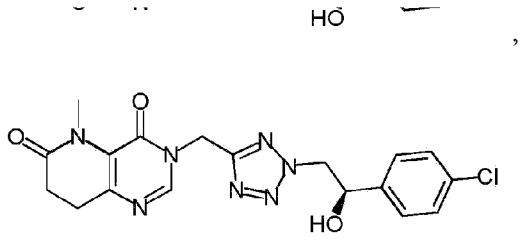

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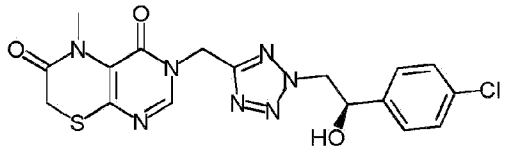


USED TERMS AND DEFINITIONS

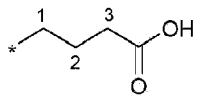
[0035] Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

[0036] In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C_{1-6}-alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general in groups like HO, H_2N, (O)S, $(O)_2S$, NC (cyano), HOOC, F_3C or the like, the skilled artisan can see the radical attachment point(s) to the molecule from the free valences of the group itself. For combined groups comprising two or more subgroups, the last named subgroup is the radical attachment point, for example, the substituent "aryl-C_{1-3}-alkyl" means an aryl group which is bound to a C_{1-3}-alkyl-group, the latter of which is bound to the core or to the group to which the substituent is attached.

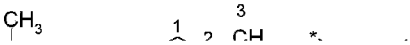
[0037] In case a compound of the present invention is depicted in form of a chemical name and as a formula in case of any discrepancy the formula shall prevail. An asterisk may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

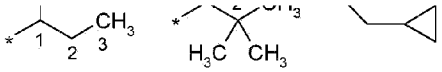
[0038] The numeration of the atoms of a substituent starts with the atom that is closest to the core or to the group to which the substituent is attached.

[0039] For example, the term "3-carboxypropyl-group" represents the following substituent:



wherein the carboxy group is attached to the third carbon atom of the propyl group. The terms "1-methylpropyl-", "2,2-dimethylpropyl-" or "cyclopropylmethyl-" group represent the following groups:



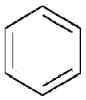


[0040] The asterisk may be used in sub-formulas to indicate the bond that is connected to the core molecule as defined.

[0041] The term "C_{1-n}-alkyl", wherein n is an integer selected from 2, 3, 4 or 5, 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 C_{1-5}-alkyl embraces the radicals H_3C-, H_3C-CH_2-, H_3C-CH_2-CH_2-, H_3C-$CH(CH_3)$-, H_3C-CH_2-CH_2-CH_2-, H_3C-CH_2-$CH(CH_3)$-, H_3C-$CH(CH_3)$-CH_2-, H_3C-$C(CH_3)_2$-, H_3C-CH_2-CH_2-CH_2-CH_2-, H_3C-CH_2-CH_2-$CH(CH_3)$-, H_3C-CH_2-$CH(CH_3)$-CH_2-, H_3C-$CH(CH_3)$-CH_2-CH_2-, H_3C-CH_2-$C(CH_3)_2$-, H_3C-$C(CH_3)_2$-CH_2-, H_3C-$CH(CH_3)$-$CH(CH_3)$- and H_3C-CH_2-$CH(CH_2CH_3)$-.

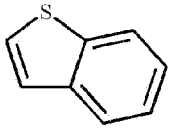
[0042] The term "fluoro" added to an "alkyl", "alkylene" or "cycloalkyl" group (saturated or unsaturated) means such a alkyl or cycloalkyl group wherein one or more hydrogen atoms are replaced by a fluorine atom. Examples include, but are not limited to: H_2FC-, HF_2C- and F_3C-.

[0043] The term phenyl refers to the radical of the following ring

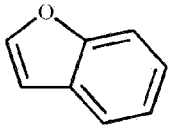


[0044] The term thiophenyl refers to the radical of the following ring

[0045] The term benzothiophenyl refers to the radical of the following ring

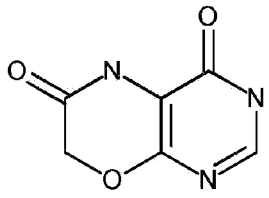


[0046] The term benzofuranyl refers to the radical of the following ring

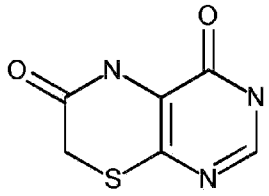


[0047] The term tetrazolyl refers to the radical of the following ring

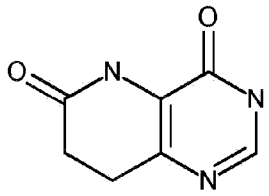
[0048] The term pyrimido[4,5-b][1,4]oxazine-4,6-dione refers to the radical of the following bicyclic core



[0049] The term pyrimido[4,5-b][1,4]thiazine-4,6-dione refers to the radical of the following bicyclic core



[0050] The term pyrido[3,2-d][1,4]pyrimidone-4,6-dione refers to the radical of the following bicyclic core



[0051] 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 normal valence is not exceeded, and that the substitution results in a stable compound.

[0052] 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 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.

[0053] In general, substantially pure stereoisomers can be obtained according to synthetic principles known to a person skilled in the field, e.g. by separation of corresponding mixtures, by using stereochemically pure starting materials and/or by stereoselective synthesis. It is known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, e.g. starting from optically active starting materials and/or by using chiral reagents.

[0054] Enantiomerically pure compounds of this invention or intermediates may be prepared via asymmetric synthesis, for example by preparation and subsequent separation of appropriate diastereomeric compounds or intermediates which can be separated by known methods (e.g. by chromatographic separation or crystallization) and/or by using chiral reagents, such as chiral starting materials, chiral catalysts or chiral auxiliaries.

[0055] Further, it is known to the person skilled in the art how to prepare enantiomerically pure compounds from the corresponding racemic mixtures, such as by chromatographic separation of the corresponding racemic mixtures on chiral stationary phases; or by resolution of a racemic mixture using an appropriate resolving agent, e.g. by means of diastereomeric salt formation of the racemic compound with optically active acids or bases, subsequent resolution of the salts and release of the desired compound from the salt; or by derivatization of the corresponding racemic compounds with optically active chiral auxiliary reagents, subsequent diastereomer separation and removal of the chiral auxiliary group; or by kinetic resolution of a racemate (e.g. by enzymatic resolution); by enantioselective crystallization from a conglomerate of enantiomorphous crystals under suitable conditions; or by (fractional) crystallization from a suitable solvent in the presence of an optically active chiral auxiliary.

[0056] The phrase "pharmaceutically 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 without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

[0057] As used herein, "pharmaceutically acceptable salt" refers to derivatives of the disclosed compounds wherein the parent compound forms a salt or a complex with an acid or a base. Examples of acids forming a pharmaceutically acceptable salt with a parent compound containing a basic moiety include mineral or organic acids such as benzenesulfonic acid, benzoic acid, citric acid, ethanesulfonic acid, fumaric acid, gentisic acid, hydrobromic acid, hydrochloric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, 4-methyl-benzenesulfonic acid, phosphoric acid, salicylic acid, succinic acid, sulfuric acid and tartaric acid.

[0058] Examples for cations and bases forming a pharmaceutically acceptable salt with a parent compound containing an acidic moiety include Na^+, K^+, Ca^{2+}, Mg^{2+}, NE_4^+, L-arginine, 2,2'-iminobisethanol, L-lysine, N-methyl-D-glucamine or tris(hydroxymethyl)-aminomethane. The pharmaceutically acceptable salts of the present invention can be synthesized from the

parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or 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.

[0059] 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. trifluoroacetate salts,) also comprise a part of the present invention.

BIOLOGICAL ASSAYS

Evaluation of TRPA1 activity

Assay A: TRPA1 assay

[0060] The activity of the compounds of the invention may be demonstrated using the following in vitro TRPA1 cell assay:

Method:

[0061] A human HEK293 cell line over-expressing the human TRPA1 ion channel (Perkin Elmer, Product No. AX-004-PCL) is used as a test system for compound efficacy and potency. Compound activity is determined by measuring the effect of compounds on intracellular calcium concentration induced by AITC (Allylisothiocyanat) agonism in a FLIPRtetra system (Molecular Devices).

Cell culture:

[0062] The cells are obtained as frozen cells in cryo-vials and stored until use at -150°C.

[0063] Cells are grown in culture medium (MEM/EBSS medium with 10% FCS and 0.4mg/ML Geneticin). It is important that density does not exceed 90% confluence. For sub-culturing cells are detached from flasks by Versene. At the day before the assay, cells are detached, washed twice with medium (MEM/EBSS medium with 10% FCS) and 20000 cells in 20µl/well are seeded to Poly D-Lysin biocoated 384-well plates (black, clear bottom, Cat.356697) from Corning. Plates are incubated for 24 hours at 37°C/5% CO_2 before use in the assay.

Compound preparation

[0064] The test compounds are dissolved in 100 % DMSO at a concentration of 10 mM and in a first step diluted in DMSO to a concentration of 5 mM, followed by serial dilution steps in 100% DMSO. Dilution factor and number of dilution steps may vary according to needs. Typically 8 different concentrations by 1:5 dilutions are prepared, further intermediate dilutions (1:20) of the substances are carried out with HBSS/HEPES buffer (1xHEPES,Cat.14065 from Gibco, 20mM HEPES, Cat. 83264 from SIGMA, 0.1% BSA Cat.11926 from Invitrogen, pH 7.4

FLIPR assay:

[0065] At the assay day cells are washed 3x with assay puffer, 20 µL buffer remaining in the wells after washing. 10 µL Ca6 kit (Cat.R8191 MolecularDevices) loading buffer in HBSS/HEPES is added to the cells and the plates are incubated with lid for 120 minutes at 37°/5% CO2. 10 µL of compound or controls in HBSS/HEPES buffer/5% DMSO from the intermediate dilution plate are carefully added to the wells. Luminescence (indicating the calcium influx or release) is read on the FLIPRtetra device for 10 minutes to monitor the compound induced effects (e.g. agonism). Finally 10 µL of the agonist AITC 50µM dissolved in HBSS/HEPES buffer/0.05% DMSO (final concentration 10 µM) is added to the wells followed by an additional read on the FLIPRtetra device for 10 minutes. The area under the signal curve (AUC) after AITC addition is used for IC50 / % inhibition calculations

Data evaluation and calculation:

[0066] Each assay microtiter plate contains wells with vehicle (1% DMSO) controls instead of compound as controls for AITC induced luminescence (100 %CTL; high controls) and wells with vehicle controls without AITC as controls for non-specific changes in luminescence (0 %CTL; low controls).

[0067] The analysis of the data is performed by the calculation of the area under signal curve of the individual wells. Based on this values the % value for the measurement of each substance concentration is calculated (AUC(sample) - AUC(low))*100/(AUC(high) - AUC(low)) using MegaLab software (in house development). The IC50 values are calculated from the % control values using MegaLab software. Calculation: [y=(a-d)/(1+(x/c)^b)+d], a = low value, d = high value; x = cone M; c=IC50 M; b = hill; y = % ctrl

Table 1: Biological data for compounds of the invention as obtained in Assay A

Example	hTRPA1 IC_{50} [nM]
1	53
2	15
3	23

Example	hTRPA1 IC_{50} [nM]
4	32
5	39
6	45
7	60
8	62
9	73
10	80
11	81
12	115
13	145
14	191
15	227
16	237
17	248
18	153
19	214
20	140
21	155
22	74
23	52
24	100

Table 2: Biological data for prior art compounds (examples **28** and **29** in WO2017/060488) as obtained in Assay A.

Example in WO2017/060488	hTRPAI IC_{50} [nM]
28	366
29	1120

Table 3: Biological data for prior art compounds (example **31** in L. Schenkel, *et al.,* J. Med. Chem. 2016, 59, 2794-2809) as obtained in Assay A.

Example in Med. Chem. 2016, 59, 2794-2809	hTRPAI IC_{50} [nM]
31	52

Evaluation of Microsomal Clearance

Assay B: Microsomal clearance:

[0068] The metabolic degradation of the test compound is assayed at 37°C with pooled liver microsomes. The final incubation volume of 100 µl per time point contains TRIS buffer pH 7.6 at RT (0.1 M), magnesium chloride (5 mM), microsomal protein (1 mg/ml) and the test compound at a final concentration of 1 µM.

[0069] Following a short preincubation period at 37°C, the reactions are initiated by addition of beta-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH, 1 mM) and terminated by transferring an aliquot into solvent after different time points (0, 5, 15, 30, 60 min). Additionally, the NADPH-independent degradation is monitored in incubations without NADPH, terminated at the last time point. The [%] remaining test compound after NADPH independent incubation is reflected by the parameter c(control) (metabolic stability). The quenched incubations are pelleted by centrifugation (10000 g, 5 min).

[0070] An aliquot of the supernatant is assayed by LC-MS/MS for the amount of parent compound. The half-life (t1/2 INVITRO) is determined by the slope of the semilogarithmic plot of the concentration-time profile.

[0071] The intrinsic clearance (CL_INTRINSIC) is calculated by considering the amount of protein in the incubation:

Qh [%] = CL [ml/min/kg] / hepatic blood flow [ml/min/kg])

Hepatocellularity, human: 120x10e6 cells / g liver
Liver factor, human: 25.7 g / kg bodyweight
Blood flow, human: 21 ml/(min x kg)

Table 4: Biological data for compounds of the invention as obtained in Assay B

Example	human LM [%Qh]
1	<23
2	<23
3	<23
4	<23
5	<23
6	<23
7	<23
8	<23
9	<23
10	<23
11	34
12	<23

Example	human LM [%Qh]
13	<23
14	<23
15	26
16	<23
17	<23
18	<23
19	<23
20	<23
21	<23
22	35
23	25
24	<23

Table 5: Biological data for prior art compounds (examples **28** and **29** in WO2017/060488) as obtained in Assay B.

Example in WO2017/060488	human LM [%Qh]
28	62
29	<23

Table 6: Biological data for prior art compounds (example **31** in L. Schenkel, *et al.,* J. Med. Chem. 2016, 59, 2794-2809) as obtained in Assay B.

Example in Med. Chem. 2016, 59, 2794-2809	human LM [%Qh]
31	<23

Evaluation of Hepatocyte Clearance

Assay C: Hepatocyte clearance

[0072] The metabolic degradation of the test compound is assayed in a hepatocyte suspension. Hepatocytes (cryopreserved) are incubated in Dulbecco's modified eagle medium (supplemented with 3.5µg glucagon/500mL, 2.5mg insulin/500mL and 3.75mg/500mL hydrocortison) containing 5% or 50% species serum.

[0073] Following a 30 min preincubation in an incubator (37°C, 10% CO2) 5 µl of test compound solution (80 µM; from 2mM in DMSO stock solution diluted 1:25 with medium) are added into 395 µl hepatocyte suspension (cell density in the range 0.25-5 Mio cells/mL depending on the species, typically 1 Mio cells/mL; final concentration of test compound 1µM,

final DMSO concentration 0.05%).

[0074] The cells are incubated for six hours (incubator, orbital shaker) and samples (25µl) are taken at 0, 0.5, 1, 2, 4 and 6 hours. Samples are transferred into acetonitrile and pelleted by centrifugation (5 min). The supernatant is transferred to a new 96-deepwell plate, evaporated under nitrogen and resuspended.

Decline of parent compound is analyzed by HPLC-MS/MS

[0075] CLint is calculated as follows CL_INTRINSIC = Dose / AUC = (C0/CD) / (AUD + clast/k) x 1000/60. C0: initial concentration in the incubation [µM], CD: cell density of vital cells [10e6cells/mL], AUD: area under the data [µM x h], clast: concentration of last data point [µM], k: slope of the regression line for parent decline [h-1].

[0076] The calculated in vitro hepatic intrinsic clearance can be scaled up to the intrinsic in vivo hepatic Clearance and used to predict hepatic in vivo blood clearance (CL) by the use of a liver model (well stirred model).

$$Qh\ [\%] = CL\ [ml/min/kg] / hepatic\ blood\ flow\ [ml/min/kg])$$

Hepatocellularity, human: 120x10e6 cells / g liver
Liver factor, human: 25.7 g / kg bodyweight
Blood flow, human: 21 ml/(min x kg)

Table 7: Biological data for compounds of the invention as obtained in Assay C

Example	human Hepatocytes [%Qh]
1	7
2	16
3	18
4	31
5	29
6	13
7	21
8	11
9	5
10	<4
11	29
12	8
13	10
14	5
15	29

Example	human Hepatocytes [%Qh]
16	<4
17	13
18	8
19	19
20	<4
21	6
22	12
23	36
24	16

Table 8: Biological data for prior art compounds (examples **28** and **29** in WO2017/060488) as obtained in Assay C.

Example in WO2017/060488	human Hepatocytes [%Qh]
28	49
29	22

Table 9: Biological data for prior art compounds (example **31** in L. Schenkel, *et al.,* J. Med. Chem. 2016, 59, 2794-2809) as obtained in Assay C.

Example in Med. Chem. 2016, 59, 2794-2809	human Hepatocytes [%Qh]
31	73

Evaluation of permeability

[0077] Caco-2 cells (1 - 2 x 105 cells/1 cm2 area) are seeded on filter inserts (Costar transwell polycarbonate or PET filters, 0.4 µm pore size) and cultured (DMEM) for 10 to 25 days. Compounds are dissolved in appropriate solvent (like DMSO, 1-20 mM stock solutions). Stock solutions are diluted with HTP-4 buffer (128.13 mM NaCl, 5.36 mM KCl, 1 mM MgSO4, 1.8 mM CaCl2, 4.17 mM NaHCO3, 1.19 mM Na2HPO4 x 7H2O, 0.41 mM NaH2PO4xH2O, 15 mM HEPES, 20 mM glucose, 0.25% BSA, pH 7.2) to prepare the transport solutions (0.1 - 300 µM compound, final DMSO <= 0.5 %). The transport solution (TL) is applied to the apical or basolateral donor side for measuring A-B or B-A permeability (3 filter replicates), respectively. Samples are collected at the start and end of experiment from the donor and at various time intervals for up to 2 hours also from the receiver side for concentration measurement by HPLC-MS/MS or scintillation counting. Sampled receiver volumes are replaced with fresh receiver solution.

Evaluation of plasma protein binding

[0078] This equilibrium dialysis (ED) technique is used to determine the approximate in vitro fractional binding of test compounds to plasma proteins. Dianorm Teflon dialysis cells (micro 0.2) are used. Each cell consists of a donor and an acceptor chamber, separated by an ultrathin semipermeable membrane with a 5 kDa molecular weight cutoff. Stock solutions for each test compound are prepared in DMSO at 1 mM and diluted to a final concentration of 1.0 µM. The subsequent dialysis solutions are prepared in pooled human or rat plasma (with NaEDTA) from male and female donors. Aliquots of 200 µL dialysis buffer (100 mM potassium phosphate, pH 7.4) are dispensed into the buffer chamber. Aliquots of 200 µL test compound dialysis solution are dispensed into the plasma chambers. Incubation is carried out for 2 hours under rotation at 37°C.

[0079] At the end of the dialysis period, the dialysate is transferred into reaction tubes. The tubes for the buffer fraction contain 0.2 mL ACN/water (80/20). Aliquots of 25 µL of the plasma dialysate are transferred into deep well plates and mixed with 25 µL ACN/water (80/20), 25 µL buffer, 25 µL calibration solution and 25 µL Internal Standard solution. Protein precipitation is done by adding 200 µL ACN. Aliquots of 50 µL of the buffer dialysate are transferred into deep well plates and mixed with 25 µL blank plasma, 25 µL

[0080] Internal Standard solution and 200 µL ACN. Samples are measured on HPLC-MS/MS-Systems and evaluated with Analyst-Software. Percent bound is calculated with the formula: %bound = (plasma concentration - buffer concentration/ plasma 30 concentration) X 100.

Evaluation of solubility

[0081] Saturated solutions are prepared in well plates (format depends on robot) by adding an appropriate volume of selected aqueous media (typically in the range of 0.25 - 1.5 ml) into each well which contains a known quantity of solid drug substance (typically in the range 0.5 - 5.0 mg). The wells are shaken or stirred for a predefined time period (typically in a range of 2 - 24 h) and than filtered using appropriate filter membranes (typically PTFE-filters with 0.45 µm pore size). Filter absorption is avoided by discarding the first few drops of filtrate. The amount of dissolved drug substance is determined by UV spectroscopy. In addition the pH of the aqueous saturated solution is measured using a glass-electrode pH meter.

Evaluation of pharmacokinetic characteristics in rodents

[0082] The test compound is administered either intravenously to fed rats or orally to fasted rats. Blood samples are taken at several time points post application of the test compound, anticoagulated and centrifuged.

[0083] The concentration of analytes - the administered compound and/or metabolites - are quantified in the plasma samples. PK parameters are calculated using non compartment

methods. AUC and Cmax are normalized to a dose of 1 µmol/kg.

Evaluation of Metabolism in human hepatocytes *in vitro*

[0084] The metabolic pathway of a test compound is investigated using primary human hepatocytes in suspension. After recovery from cryopreservation, human hepatocytes are incubated in Dulbecco's modified eagle medium containing 5% human serum and supplemented with 3.5 µg glucagon/500ml, 2.5mg insulin/500ml and 3.75mg/500ml hydrocortisone.

[0085] Following a 30 min preincubation in a cell culture incubator (37°C, 10% CO_2), test compound solution is spiked into the hepatocyte suspension to obtain a final cell density of $1.0*10^6$ to $4.0*10^6$ cells/ml (depending on the metabolic turnover rate of the compound observed with primary human hepatocytes), a final test compound concentration of 10 µM, and a final DMSO concentration of 0.05%.

[0086] The cells are incubated for six hours in a cell culture incubator on a horizontal shaker, and samples are removed from the incubation after 0, 0.5, 1, 2, 4 or 6 hours, depending on the metabolic turnover rate. Samples are quenched with acetonitrile and pelleted by centrifugation. The supernatant is transferred to a 96-deepwell plate, evaporated under nitrogen and resuspended prior to bioanalysis by liquid chromatography-high resolution mass spectrometry for identification of putative metabolites.

[0087] The structures are assigned tentatively based on Fourier-Transform-MS^n data. Metabolites are reported as percentage of the parent in human hepatocyte incubation with a threshold of ≥ 4%.

METHOD OF TREATMENT

[0088] The present invention is directed to compounds of general formula 1 which are useful in the prevention and/or treatment of a disease and/or condition associated with or modulated by TRPA1 activity, including but not limited to the treatment and/or prevention of fibrotic disease, inflammatory and immunoregulatory disorders, respiratory or gastrointestinal diseases or complaints, ophthalmic diseases, inflammatory diseases of the joints and inflammatory diseases of the nasopharynx, eyes, and skin and pain and neurological disorders. Said disorders, diseases and complaints include cough, idiopathic pulmonary fibrosis, other pulmonary interstitial diseases and other fibrotic, asthma or allergic diseases, eosinophilic diseases, chronic obstructive pulmonary disease, as well as inflammatory and immunoregulatory disorders, such as rheumatoid arthritis and atherosclerosis, as well as pain and neurological disorders, such as acute pain, surgical pain, chronic pain and depression and bladder disorders.

[0089] The compounds of general formula 1 are useful for the prevention and/or treatment of:

1. (1) Cough such as chronic idiopathic cough or chronic refractory cough, cough associated with asthma, COPD, lung cancer, post-viral infection and idiopathic pulmonary fibrosis and other pulmonary interstitial diseases.
2. (2) Pulmonary fibrotic diseases such as pneumonitis or interstitial pneumonitis associated with collagenosis, e.g. lupus erythematodes, systemic scleroderma, rheumatoid arthritis, polymyositis and dermatomysitis, idiopathic interstitial pneumonias, such as pulmonary lung fibrosis (IPF), non-specific interstitial pneumonia, respiratory bronchiolitis associated interstitial lung disease, desquamative interstitial pneumonia, cryptogenic orgainizing pneumonia, acute interstitial pneumonia and lymphocytic interstitial pneumonia, lymangioleiomyomatosis, pulmonary alveolar proteinosis, Langerhan's cell histiocytosis, pleural parenchymal fibroelastosis, interstitial lung diseases of known cause, such as interstitial pneumonitis as a result of occupational exposures such as asbestosis, silicosis, miners lung (coal dust), farmers lung (hay and mould), Pidgeon fanciers lung (birds) or other occupational airbourne triggers such as metal dust or mycobacteria, or as a result of treatment such as radiation, methotrexate, amiodarone, nitrofurantoin or chemotherapeutics, or for granulomatous disease, such as granulomatosis with polyangitis, Churg-Strauss syndrome, sarcoidosis, hypersensitivity pneumonitis, or interstitial pneumonitis caused by different origins, e.g. aspiration, inhalation of toxic gases, vapors, bronchitis or pneumonitis or interstitial pneumonitis caused by heart failure, X-rays, radiation, chemotherapy, M. boeck or sarcoidosis, granulomatosis, cystic fibrosis or mucoviscidosis, or alpha-1-antitrypsin deficiency.
3. (3) Other fibrotic diseases such as hepatic bridging fibrosis, liver cirrhosis, non-alcoholic steatohepatitis (NASH), atrial fibrosis, endomyocardial fibrosis, old myocardial infarction, glial scar, arterial stiffness, arthrofibrosis, Dupuytren's contracture, keloid, scleroderma/systemic sclerosis, mediastinal fibrosis, myelofibrosis, Peyronie's disease, nephrogenic systemic fibrosis, retroperitoneal fibrosis, adhesive capsulitis.
4. (4) Inflammatory, auto-immune or allergic diseases and conditions such as allergic or non-allergic rhinitis or sinusitis, chronic sinusitis or rhinitis, nasal polyposis, chronic rhinosinusitis, acute rhinosinusitis, asthma, pediatric asthma, allergic bronchitis, alveolitis, hyperreactive airways, allergic conjunctivitis, bronchiectasis, adult respiratory distress syndrome, bronchial and pulmonary edema, bronchitis or pneumonitis, eosinophilic cellulites (e.g., Well's syndrome), eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic eosinophilic pneumonia), eosinophilic fasciitis (e. g., Shulman's syndrome), delayed-type hypersensitivity, non-allergic asthma; exercise induced bronchoconstriction; chronic obstructive pulmonary disease (COPD), acute bronchitis, chronic bronchitis, cough, pulmonary emphysema; systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporin), eosinophiliamyalgia syndrome due to the ingestion of contaminated tryptophane, insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, Graves' disease, Sjogren's syndrome psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, immune thrombocytopenia (adult ITP, neonatal thrombocytopenia,

pediatric ITP), immune hemolytic anemia (auto-immune and drug induced), Evans syndrome (platelet and red cell immune cytopaenias), Rh disease of the newborn, Goodpasture's syndrome (anti-GBM disease), Celiac, autoimmune cardio-myopathy juvenile onset diabetes; glomerulonephritis, autoimmune thyroiditis, Behcet's disease; graft rejection (e.g., in transplantation), including allograft rejection or graftversus-host disease; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such as an dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e. g., necrotizing, cutaneous, and hypersensitivity vasculitis); erythema nodosum; eosinophilic myositis, eosinophilic fasciitis, cancers with leukocyte infiltration of the skin or organs; ophthalmic diseases such as age related macular degeneration, diabetic retinopathy and diabetic macular edema, keratitis, eosinophilic keratitis, keratoconjunctivitis, vernal keratoconjunctivitis, scarring, anterior segment scarring, blepharitis, blepharoconjunctivitis, bullous disorders, cicatricial pemphigoid, conjunctival melanoma, papillary conjunctivitis, dry eye, episcleritis, glaucoma, gliosis, Granuloma annulare, Graves' ophthalmopathy, intraocular melanoma, Pinguecula, proliferative vitreoretinopathy, pterygia, scleritis, uveitis, acute gout flares, gout or osteoarthritis.

5. (5) Pain such as chronic idiopathic pain syndrome, neuropathic pain, dysesthesia, allodynia, migraine, dental pain and post-surgical pain.
6. (6) Depression, anxiousness, diabetic neuropathy and bladder disorders such as bladder outlet obstruction, overactive bladder, cystitis; myocardial reperfusion injury or brain ischaemia injury.

[0090] Accordingly, the present invention relates to a compound of general formula 1 for use as a medicament.

[0091] Furthermore, the present invention relates to the use of a compound of general formula 1 for the treatment and/or prevention of a disease and/or condition associated with or modulated by TRPA1 activity.

[0092] Furthermore, the present invention relates to the use of a compound of general formula 1 for the treatment and/or prevention of fibrotic disease, inflammatory and immunoregulatory disorders, respiratory or gastrointestinal diseases or complaints, ophthalmic diseases, inflammatory diseases of the joints and inflammatory diseases of the nasopharynx, eyes, and skin, pain and neurological disorders. Said disorders, diseases and complaints include cough, idiopathic pulmonary fibrosis, other pulmonary interstitial diseases and other fibrotic, asthma or allergic diseases, eosinophilic diseases, chronic obstructive pulmonary disease, as well as inflammatory and immunoregulatory disorders , such as rheumatoid arthritis and atherosclerosis, as well as pain and neurological disorders, such as acute pain, surgical pain, chronic pain and depression and bladder disorders.

[0093] Furthermore, the present invention relates to the use of a compound of general formula 1 for the treatment and/or prevention of:

1. (1) Cough such as chronic idiopathic cough or chronic refractory cough, cough associated with asthma, COPD, lung cancer, post-viral infection and idiopathic pulmonary fibrosis and other pulmonary interstitial diseases.
2. (2) Pulmonary fibrotic diseases such as pneumonitis or interstitial pneumonitis associated with collagenosis, e.g. lupus erythematodes, systemic scleroderma, rheumatoid arthritis, polymyositis and dermatomysitis, idiopathic interstitial pneumonias, such as pulmonary lung fibrosis (IPF), non-specific interstitial pneumonia, respiratory bronchiolitis associated interstitial lung disease, desquamative interstitial pneumonia, cryptogenic orgainizing pneumonia, acute interstitial pneumonia and lymphocytic interstitial pneumonia, lymangioleiomyomatosis, pulmonary alveolar proteinosis, Langerhan's cell histiocytosis, pleural parenchymal fibroelastosis, interstitial lung diseases of known cause, such as interstitial pneumonitis as a result of occupational exposures such as asbestosis, silicosis, miners lung (coal dust), farmers lung (hay and mould), Pidgeon fanciers lung (birds) or other occupational airbourne triggers such as metal dust or mycobacteria, or as a result of treatment such as radiation, methotrexate, amiodarone, nitrofurantoin or chemotherapeutics, or for granulomatous disease, such as granulomatosis with polyangitis, Churg-Strauss syndrome, sarcoidosis, hypersensitivity pneumonitis, or interstitial pneumonitis caused by different origins, e.g. aspiration, inhalation of toxic gases, vapors, bronchitis or pneumonitis or interstitial pneumonitis caused by heart failure, X-rays, radiation, chemotherapy, M. boeck or sarcoidosis, granulomatosis, cystic fibrosis or mucoviscidosis, or alpha-1-antitrypsin deficiency.
3. (3) Other fibrotic diseases such as hepatic bridging fibrosis, liver cirrhosis, non-alcoholic steatohepatitis (NASH), atrial fibrosis, endomyocardial fibrosis, old myocardial infarction, glial scar, arterial stiffness, arthrofibrosis, Dupuytren's contracture, keloid, scleroderma/systemic sclerosis, mediastinal fibrosis, myelofibrosis, Peyronie's disease, nephrogenic systemic fibrosis, retroperitoneal fibrosis, adhesive capsulitis.
4. (4) Inflammatory, auto-immune or allergic diseases and conditions such as allergic or non-allergic rhinitis or sinusitis, chronic sinusitis or rhinitis, nasal polyposis, chronic rhinosinusitis, acute rhinosinusitis, asthma, pediatric asthma, allergic bronchitis, alveolitis, hyperreactive airways, allergic conjunctivitis, bronchiectasis, adult respiratory distress syndrome, bronchial and pulmonary edema, bronchitis or pneumonitis, eosinophilic cellulites (e.g., Well's syndrome), eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic eosinophilic pneumonia), eosinophilic fasciitis (e. g., Shulman's syndrome), delayed-type hypersensitivity, non-allergic asthma; exercise induced bronchoconstriction; chronic obstructive pulmonary disease (COPD), acute bronchitis, chronic bronchitis, cough, pulmonary emphysema; systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporin), eosinophiliamyalgia syndrome due to the ingestion of contaminated tryptophane, insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, Graves' disease, Sjogren's syndrome psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, immune thrombocytopenia (adult ITP, neonatal thrombocytopenia,

pediatric ITP), immune hemolytic anemia (auto-immune and drug induced), Evans syndrome (platelet and red cell immune cytopaenias), Rh disease of the newborn, Goodpasture's syndrome (anti-GBM disease), Celiac, autoimmune cardio-myopathy juvenile onset diabetes; glomerulonephritis, autoimmune thyroiditis, Behcet's disease; graft rejection (e.g., in transplantation), including allograft rejection or graftversus-host disease; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such as an dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e. g., necrotizing, cutaneous, and hypersensitivity vasculitis); erythema nodosum; eosinophilic myositis, eosinophilic fasciitis, cancers with leukocyte infiltration of the skin or organs; ophthalmic diseases such as age related macular degeneration, diabetic retinopathy and diabetic macular edema, keratitis, eosinophilic keratitis, keratoconjunctivitis, vernal keratoconjunctivitis, scarring, anterior segment scarring, blepharitis, blepharoconjunctivitis, bullous disorders, cicatricial pemphigoid, conjunctival melanoma, papillary conjunctivitis, dry eye, episcleritis, glaucoma, gliosis, Granuloma annulare, Graves' ophthalmopathy, intraocular melanoma, Pinguecula, proliferative vitreoretinopathy, pterygia, scleritis, uveitis, acute gout flares, gout or osteoarthritis.

5. (5) Pain such as chronic idiopathic pain syndrome, neuropathic pain, dysesthesia, allodynia, migraine, dental pain and post-surgical pain.
6. (6) Depression, anxiousness, diabetic neuropathy and bladder disorders such as bladder outlet obstruction, overactive bladder, cystitis; myocardial reperfusion injury or brain ischaemia injury.

[0094] In a further aspect the present invention relates to a compound of general formula 1 for use in the treatment and/or prevention of above mentioned diseases and conditions.

[0095] In a further aspect the present invention relates to the use of a compound of general formula 1 for the preparation of a medicament for the treatment and/or prevention of above mentioned diseases and conditions.

COMBINATION THERAPY

[0096] The compounds of the invention may further be combined with one or more, preferably one additional therapeutic agent. According to one embodiment the additional therapeutic agent is selected from the group of therapeutic agents useful in the treatment of diseases or conditions described hereinbefore, in particular associated with fibrotic diseases, inflammatory and immunoregulatory disorders, respiratory or gastrointestinal diseases or complaints, inflammatory diseases of the joints or of the nasopharynx, eyes, and skin or conditions such as for example cough, idiopathic pulmonary fibrosis, other pulmonary interstitial diseases, asthma or allergic diseases, eosinophilic diseases, chronic obstructive pulmonary disease, atopic

dermatitis as well as autoimmune pathologies, such as rheumatoid arthritis and atherosclerosis, or therapeutic agents useful for the treatment of ophthalmic diseases, pain and depression.

[0097] Additional therapeutic agents that are suitable for such combinations include in particular those, which, for example, potentiate the therapeutic effect of one or more active substances with respect to one of the indications mentioned and/or allow the dosage of one or more active substances to be reduced.

[0098] Therefore, a compound of the invention may be combined with one or more additional therapeutic agents selected from the group consisting of antifibrotic agents, anti-tussive agents, anti-inflammatory agents, anti-atopic dermatitis agents, analgesics, anti-convulsants, anxiolytics, sedatives, skeletal muscle relaxants or anti-depressants.

[0099] Antifibrotic agents are for example nintedanib, pirfenidone, phosphodiesterase-IV (PDE4) inhibitors such as roflumilast, autotaxin inhibitors such as GLPG-1690 or BBT-877; connective tissue growth factor (CTGF) blocking antibodies such as Pamrevlumab; B-cell activating factor receptor (BAFF-R) blocking antibodies such as Lanalumab; alpha-V/beta-6 blocking inhibitors such as BG-00011/STX-100, recombinant pentraxin-2 (PTX-2) such as PRM-151; c-Jun N-terminal kinase (JNK) inhibitors such as CC-90001; galectin-3 inhibitors such as TD-139; G-protein coupled receptor 84 (GPR84) inhibitors such as GLPG-1205; G-protein coupled receptor 84/ G-protein coupled receptor 40 dual inhibitors such as PBI-4050; Rho Associated Coiled-Coil Containing Protein Kinase 2 (ROCK2) inhibitors such as KD-025; heat shock protein 47 (HSP47) small interfering RNA such as BMS-986263/ND-L02-s0201; Wnt pathway inhibitor such as SM-04646; LD4 / PDE3/4 inhibitors such as Tipelukast; recombinant immuno-modulatory domains of histidyl tRNA synthetase (HARS) such as ATYR-1923; prostaglandin synthase inhibitors such as ZL-2102 / SAR-191801; 15-hydroxy-eicosapentaenoic acid (15-HEPE e.g. DS-102); Lysyl Oxidase Like 2 (LOXL2) inhibitors such as PAT-1251, PXS-5382/PXS-5338; phosphoinositide 3-kinases (PI3K)/ mammalian target of rapamycin (mTOR) dual inhibitors such as HEC-68498; calpain inhibitors such as BLD-2660; mitogen-activated protein kinase kinase kinase (MAP3K19) inhibitors such as MG-S-2525; chitinase inhibitors such as OATD-01; mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2) inhibitors such as MMI-0100; transforming growth factor beta 1 (TGF-beta1) small interfering RNA such as TRK250BNC-1021; or lysophosphatidic acid receptor antagonists such as BMS-986278.

[0100] Anti-tussive agents are, for example, purinoceptor 3 (P2X3) receptor antagonists such as gefapixant, S-600918, BAY-1817080, or BLU-5937; neurokinin 1 (NK-1) receptor antagonist such as Orvepitant, Aprepitant; nicotinic acetylcholine receptor alpha 7 subunit stimulator such as ATA-101/bradanicline; codeine, gabapentin, pregablin, or azithromycin. Anti-inflammatory agents are, for example, corticosteroids such as prednisolone or dexamethasone; cyclo-oxygenase-2 (COX2) inhibitors such as celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib or lumiracoxib; prostaglandin E2 antagonists; leukotriene B4 antagonists; leukotriene D4 antagonists such as monteleukast; 5-lipoxygenase inhibitors; or other nonsteroidal anti-

inflammatory agents (NSAIDs) such as aspirin, diclofenac, diflunisal, etodolac, ibuprofen or indomethacin.

[0101] Anti-atopic dermatitis agents are, for example, cyclosporin, methotrexate, mycophenolate mofetil, azathioprine, phosphodiesterase inhibitors (e.g. apremilast, crisaborole), Janus Associated Kinase (JAK) inhibitors (e.g. tofacitinib), neutralizing antibodies against IL-4/IL-13 (e.g. dupilamab), IL-13 (e.g. lebrikizumab, tralokinumab) and IL-31 (nemolizumab). Analgesics are, for example, of the opioid type, such as morphine, oxymorphine, levopanol, oxycodon, propoxyphene, nalmefene, fentanyl, hydrocondon, hydromorphone, meripidine, methadone, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine, pentazocine; or of the non-opioid type, such as acetophenamine.

[0102] Anti-depressants are, for example, tricyclic anti-depressants such as amitriptyline, clomipramine, despramine, doxepin, desipramine, imipramine, nortriptyline; selective serotonin reuptake inhibitor anti-depressants (SSRIs) such as fluoxetine, paroxetine, sertraline, citalopram, escitalopram; norepinephrine reuptake inhibitor anti-depressants (SNRIs) such as maprotiline, lofepramine, mirtazapine, oxaprotiline, fezolamine, tomoxetine, mianserin, buproprion, hydroxybuproprion, nomifensine, viloxazine; dual serotonin-norepinephrine reuptake inhibitor anti-depressants (SNRIs) such as duloxetine, venlafaxine, desvenlafaxine, levomilnacipran; atypical antidepressants such as trazodone, mirtazapine, vortioxetine, vilazodone, bupropion; or monoamine oxidase inhibitor anti-depressantss (MAOIs) such as tranylcypromine, phenelzine, or isocarboxazid.

[0103] Anxiolytics are, for example, benzodiazepines such as alprazolam, bromazepam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam, triazolam, or tofisopam; or they are nonbenzodiazepine hypnoticssuch as eszopiclone, zaleplon, zolpidem, or zopiclone; or they are carbamates e.g. meprobamate, carisoprodol, tybamate, or lorbamate; or they are antihistamines such as hydroxyzine, chlorpheniramine or diphenhydramine.

[0104] Sedatives are, for example, barbiturate sedatives, such as amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, secobarbital, talbutal, theamylal, or thiopental; or they are non-barbiturate sedatives such as glutethimide, meprobamate, methaqualone or dichloalphenazone.

[0105] Skeletal muscle relaxants are, for example, baclofen, meprobamate, carisoprodol, cyclobenzaprine, metaxalone, methocarbamol, tizanidine, chlorzoxazone or orphenadrine. Other suitable combination partners are inhibitors of Acetylcholinesterase inhibitors such as donepezil; 5-HT-3 anatgonists such as ondansetron; metabotropic glutamate receptor antagonists; antiarrhythmics such as mexiletine or phenytoin; or NMDA receptor antagonists. Further suitable combination partners are incontinence medications, for example, anticholinergics such as oxybutynin, tolterodine, darifenacin, fesoterodine, solifenacin or trospium; or they are bladder muscle relaxants such as mirabegron; or they are alpha blockers such as tamsulosin, alfuzosin, silodosin, doxazosin or terazosin.

[0106] The dosage for the combination partners mentioned above is usually 1/5 of the lowest dose normally recommended up to 1/1 of the normally recommended dose.

[0107] Therefore, in another aspect, this invention relates to the use of a compound according to the invention in combination with one or more additional therapeutic agents described hereinbefore and hereinafter for the treatment of diseases or conditions which may be affected or which are mediated by TRPA1, in particular diseases or conditions as described hereinbefore and hereinafter.

[0108] In a further aspect this invention relates to a method for treating a disease or condition which can be influenced by the inhibition of TRPA1 in a patient that includes the step of administering to the patient in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in combination with a therapeutically effective amount of one or more additional therapeutic agents.

[0109] In a further aspect this invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in combination with one or more additional therapeutic agents for the treatment of diseases or conditions which can be influenced by the inhibition of TRPA1 in a patient in need thereof.

[0110] In yet another aspect the present invention relates to a method for the treatment of a disease or condition mediated by TRPA1 activity in a patient that includes the step of administering to the patient, preferably a human, in need of such treatment a therapeutically effective amount of a compound of the present invention in combination with a therapeutically effective amount of one or more additional therapeutic agents described in hereinbefore and hereinafter.

[0111] The use of the compound according to the invention in combination with the additional therapeutic agent may take place simultaneously or at staggered times.

[0112] The compound according to the invention and the one or more additional therapeutic agents 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. Consequently, in another aspect, this invention relates to a pharmaceutical composition that comprises a compound according to the invention and one or more additional therapeutic agents described hereinbefore and hereinafter, optionally together with one or more inert carriers and/or diluents.

[0113] In yet another aspect the present invention relates to the use of a compound according to the invention in a cough-measuring device.

[0114] Other features and advantages of the present invention will become apparent from the following more detailed examples which illustrate, by way of example, the principles of the

invention.

PREPARATION

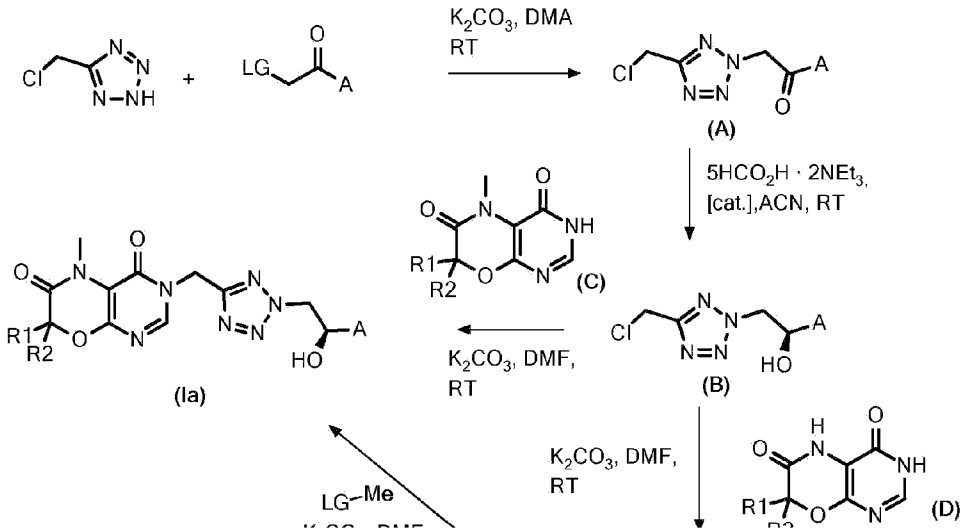
[0115] The compounds according to the present invention and their intermediates may be obtained using methods of synthesis which are known to the one skilled in the art and described in the literature of organic synthesis. Preferably, the compounds are obtained in analogous fashion to the methods of preparation explained more fully hereinafter, in particular as described in the experimental section. In some cases, the order in carrying out the reaction steps may be varied. Variants of the reaction methods that are known to the one skilled in the art but not described in detail here may also be used.

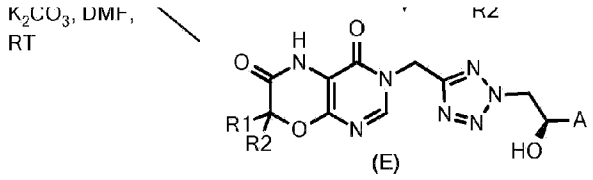
[0116] The general processes for preparing the compounds according to the invention will become apparent to the one skilled in the art studying the following schemes. Any functional groups in the starting materials or intermediates may be protected using conventional protecting groups. These protecting groups may be cleaved again at a suitable stage within the reaction sequence using methods familiar to the one skilled in the art.

[0117] The compounds according to the invention are prepared by the methods of synthesis described hereinafter in which the substituents of the general formulae have the meanings given herein before. These methods are intended as an illustration of the invention without restricting its subject matter and the scope of the compounds claimed to these examples. Where the preparation of starting compounds is not described, they are commercially obtainable or may be prepared analogously to known compounds or methods described herein. Substances described in the literature are prepared according to the published methods of synthesis. Abbreviations are as defined in the Examples section.

[0118] Compounds of formula (I) with E=O, denoted by (Ia), may be prepared as shown in Scheme 1 below.

Scheme 1:

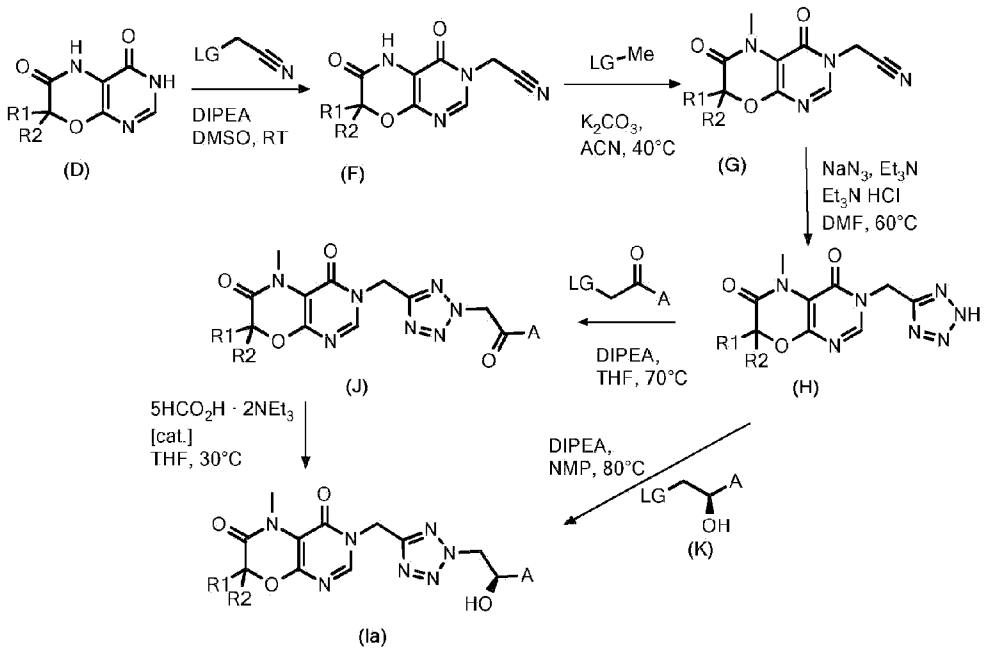




[0119] In scheme 1, chloromethyltetrazole is *N*-alkylated with an appropriate ethanone derivative carrying a leaving group "LG" (e.g. Cl or Br) alpha to the carbonyl group in the presence of a base (e.g. K_2CO_3) to yield a mixture of two regioisomers. The undesired regioisomer (not shown) can be removed by chromatography using an appropriate gradient. The resulting ketone (A) can be reduced in an enantioselective fashion by using appropriate catalytic systems using a transition metal complex (of e.g. Ru or Ir) in combination with a chiral ligand (e.g. ([(1*S*,2*S*)-2-amino-1,2-diphenylethyl](4-toluenesulfonyl)amido) and a hydrogen source such as formic acid triethylamine complex. In presence of a base, the resulting alcohol (B) can either be used to alkylate (C) directly affording compounds of general formula (Ia), or to alkylate (D) to yield intermediate (E), which upon methylation with a methylating reagent (e.g. methyl iodide) in the presence of a base also yields compounds of general formula (Ia).

[0120] Compounds of formula (I) with E=O, denoted by (Ia), may also be prepared as shown in Scheme 2 below.

Scheme 2:

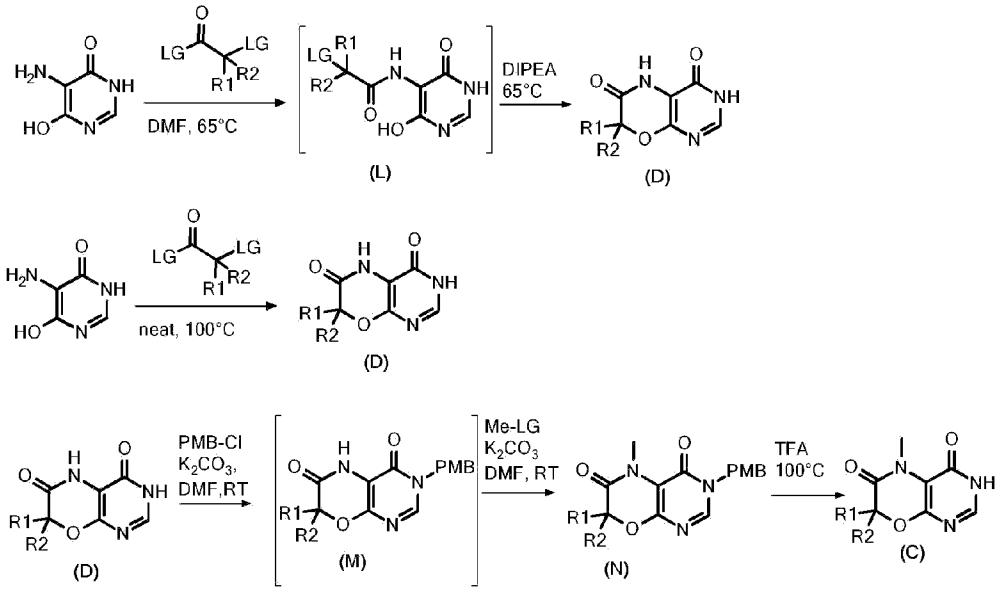


[0121] In scheme 2, compound (G) can be prepared by alkylation of (D) with an acetonitrile derivative carrying a leaving group "LG" (e.g. Cl or Br) in presence of a mild base such as DIPEA, followed by methylation of intermediate (F) with a methylation reagent (e.g. MeI) in presence of a base (e.g. K_2CO_3). Formation of the tetrazole (H) can be accomplished by typical reaction conditions for tetrazole formation (e.g. using NaN_3 in the presence of TEA/TEA

hydrochloride in DMF). Alkylation of the tetrazole (H) with an appropriate ethanone derivative carrying a leaving group "LG" (e.g. Cl or Br) alpha to the carbonyl group is run in presence of a base such as K_2CO_3 to yield a mixture of two regioisomers. The undesired regioisomer (not shown) can be removed by chromatography using an appropriate gradient. Finally, the keto group of (J) can be reduced in an enantioselective fashion by using appropriate catalytic systems using a transition metal complex (of e.g. Ru or Ir) in combination with a chiral ligand (e.g. ([(1*S*,2*S*)-2-amino-1,2-diphenylethyl](4-toluenesulfonyl)amido) and a hydrogen source such as formic acid triethylamine complex to provide final compounds (Ia). Alternatively, final compounds (Ia) can be prepared by alkylation of intermediate (H) with an appropriate ethanol derivative (K) carrying a leaving group "LG" (e.g. Cl or Br) alpha to the hydroxy group, in the presence of a base such as DIPEA and subsequent isolation of the desired regioisomer.

[0122] Intermediates (C) and (D) of schemes 1 and 2 may be prepared as shown in scheme 3

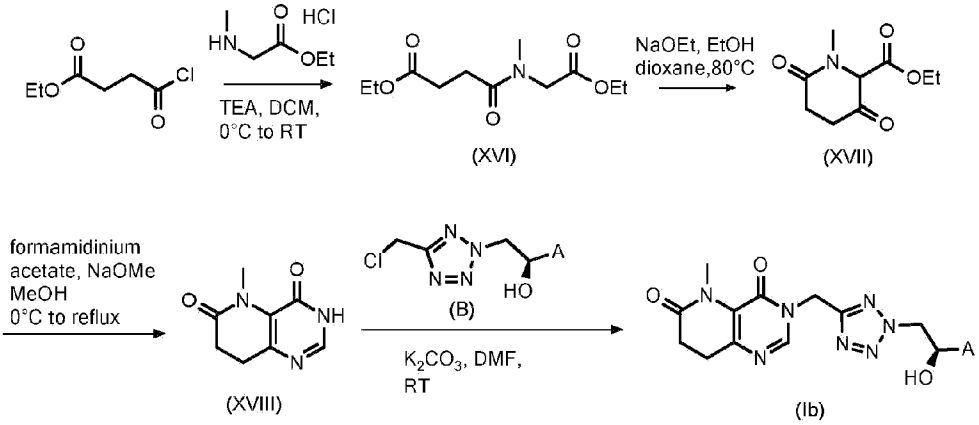
Scheme 3



[0123] In scheme 3, intermediates (C) and (D) can be synthesized starting from 5-aminopyrimidine-4,6-diol. Amidation of 5-aminopyrimidine-4,6-diol with an activated carboxylic acid with a leaving group (LG) in alpha position (e.g. chloro-acetylchloride) yields (L), which can be further progressed to intermediate (D) in presence of a base (e.g. DIPEA). Alternatively, intermediate (D) can be synthesized from 5-aminopyrimidine-4,6-diol via reaction with a carboxylic acid or carboxylic acid derivative carrying a leaving group (LG) in alpha position under neat conditions. N-Alkylation of the pyrimidone (D) with a protecting group such as para-methoxybenzyl can be achieved by treating (D) with an appropriate reagent carrying a leaving group (e.g. para-methoxybenzyl chloride, PMB-C1) in presence of a base (e.g. K_2CO_3). This allows subsequent methylation (e.g. with MeI) of (M) in presence of a base (e.g. K_2CO_3) to give (N). Finally, cleavage of the protecting group of (N) under suitable conditions (e.g. for PMB: trifluoroacetic acid, 100°C) gives intermediate (C).

[0124] Compounds of formula (I) with E=CH_2, denoted by (Ib), may be prepared as shown in Scheme 4 below.

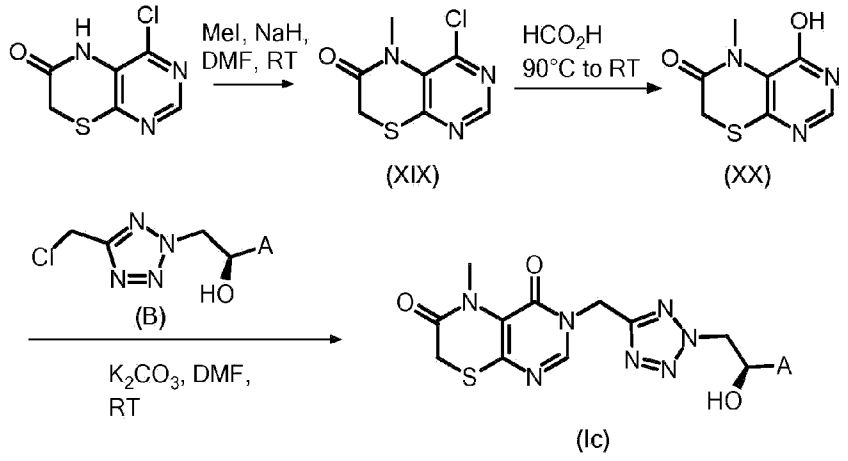
Scheme 4



[0125] In scheme 4, amide coupling of sarcosine ethyl ester hydrochloride and ethyl succinyl chloride in presence of a base provides intermediate (XVI), which can be further reacted to intermediate (XVII) in a Claisen condensation in the presence of a base (e.g. NaOEt). Subsequent condensation with a formamidinium salt (e.g. formamidinium acetate) yields intermediate (XVIII), which can be alkylated with alcohol (B) in presence of a base (e.g. K_2CO_3) to provide (Ib).

[0126] Compounds of formula (I) with E=S, SO and SO_2 exemplified by (Ic), may be prepared as shown in Scheme 5 below.

Scheme 5:



[0127] In scheme 5, intermediate (XIX) can be synthesized by methylation of 4-chloro-5H,6H,7H-pyrimido[4,5-b][1,4]thiazin-6-one with a methylation reagent (e.g. MeI) in presence of a base (e.g. NaH). Subsequent hydrolysis of (XIX) in presence of an acid (e.g. formic acid) yields intermediate (XX) which can be N-alkylated with alcohol (B) in presence of a base (e.g.

K_2CO_3) to provide (Ic).

EXAMPLES

PREPARATION

[0128] The compounds according to the invention and their intermediates may be obtained using methods of synthesis which are known to the one skilled in the art and described in the literature of organic synthesis for example using methods described in "Comprehensive Organic Transformations", 2nd Edition, Richard C. Larock, John Wiley & Sons, 2010, and "March's Advanced Organic Chemistry", 7th Edition, Michael B. Smith, John Wiley & Sons, 2013. Preferably the compounds are obtained analogously to the methods of preparation explained more fully hereinafter, in particular as described in the experimental section. In some cases the sequence adopted in carrying out the reaction schemes may be varied. Variants of these reactions that are known to the skilled artisan but are not described in detail herein may also be used. The general processes for preparing the compounds according to the invention will become apparent to the skilled man on studying the schemes that follow. Starting compounds are commercially available or may be prepared by methods that are described in the literature or herein, or may be prepared in an analogous or similar manner. Before the reaction is carried out, any corresponding functional groups in the starting compounds may be protected using conventional protecting groups. These protecting groups may be cleaved again at a suitable stage within the reaction sequence using methods familiar to the skilled man and described in the literature for example in "Protecting Groups", 3rd Edition, Philip J. Kocienski, Thieme, 2005, and "Protective Groups in Organic Synthesis", 4th Edition, Peter G. M. Wuts, Theodora W. Greene, John Wiley & Sons, 2006. The terms "ambient temperature" and "room temperature" are used interchangeably and designate a temperature of about 20 °C, e.g. between 19 and 24 °C.

Abbreviations:

[0129]

ACN	acetonitrile
Aq.	Aqueous
°C	Degree celsius
CyH/CH	cyclohexane
cone.	Concentrated
DCM	dichloro methane
DIPEA	*N*,*N*-diisopropylethylamine

DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
ESI-MS	Electrospray ionisation mass spectrometry
EtOAc	ethyl acetate
EtOH	ethanol
ex	example
eq	equivalent
FA	formic acid
h	hour
HCl	Hydrochloric acid
HPLC	High performance liquid chromatography
K_2CO_3	potassium carbonate
L	liter
$LiOH*H_2O$	Lithium hydroxide monohydrate
M	molar
MeOH	methanol
$MgSO_4$	magnesium sulphate
min	minute
mL	milliliter
MTBE	*tert*-butylmethylether
NH_3	ammonia
PMB	Para-methoxy benzyl
Prep.	preparative
RP	Reversed phase
RT	room temperature (about 20°C)
sat.	saturated
TBTU	Benzotriazolyl tetramethyluronium tetrafluoroborate
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran

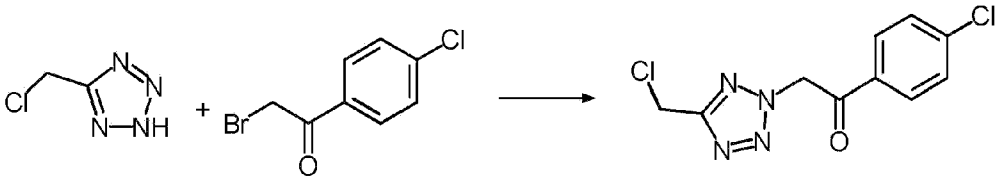
Preparation of Intermediates

Intermediates I

Intermediate I.1 (general procedure)

2-[5-(chloromethyl)-2H-1,2,3,4-tetrazol-2-yl]-1-(4-chlorophenyl)ethan-1-one

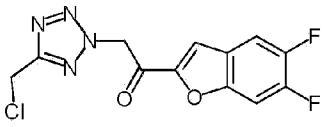
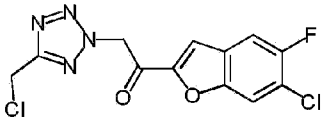
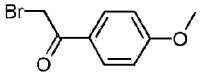
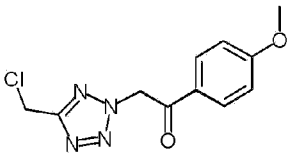
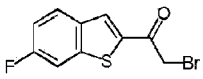
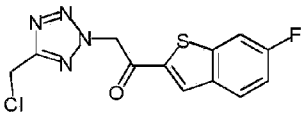
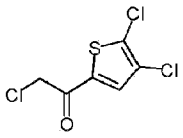
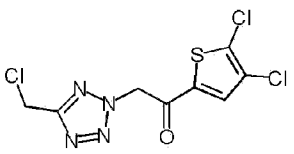
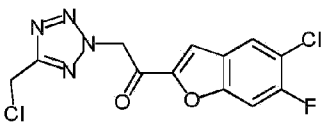
[0130]

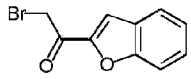
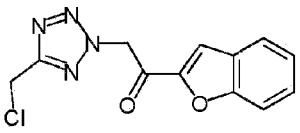
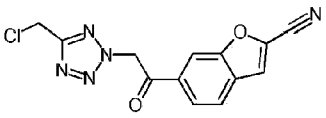
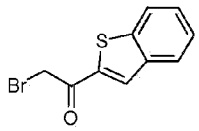
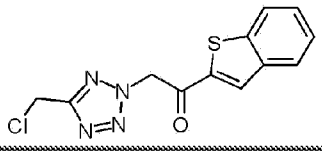
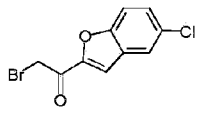
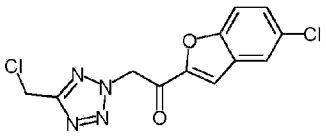
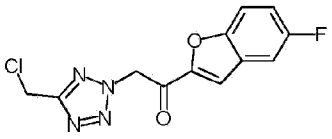
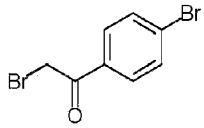
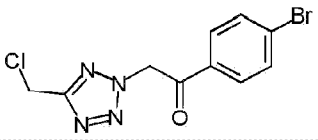
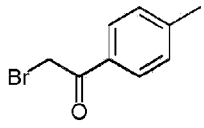
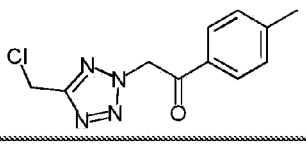
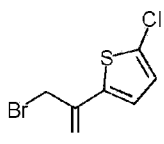
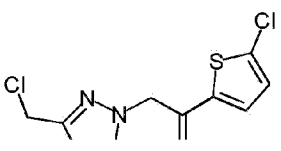


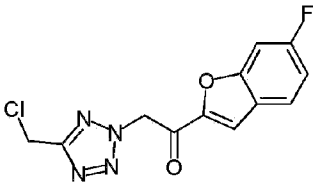
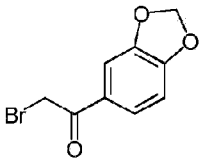
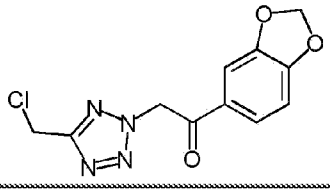
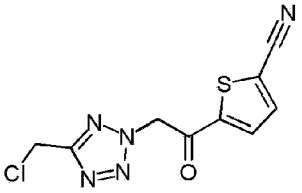
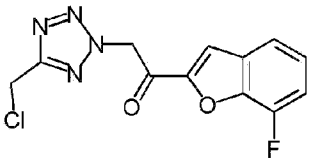
[0131] To 1.00 g (8.44 mmol) 5-(chloromethyl)-2H-1,2,3,4-tetrazole and 2.17 g (9.28 mmol) 4-chlorophenacyl bromide in 15 mL DMA are added 1.63 g (11.8 mmol) K_2CO_3 under stirring at RT. The reaction mixture is stirred at RT for 30 min and subsequently filtered. The filtrate is diluted with water and sat. aq. NaCl-solution and is extracted with EtOAc three times. The combined organic phases are washed with water, dried over Na_2SO_4, filtered over activated charcoal and the solvent is removed under reduced pressure. The residue is purified by column chromatography (silica gel; CH/EtOAc, 80/20 to 50/50 gradient) to provide the product.

$C_{10}H_8Cl_2N_4O$	(M = 271.1 g/mol)
ESI-MS:	271 $[M+H]^+$
R_t (HPLC):	1.01 min (method B)

[0132] The following compounds are prepared using procedures analogous to those described for intermediate I.1 using appropriate starting materials. As is appreciated by those skilled in the art, these analogous examples may involve variations in general reaction conditions.

Int.	Starting materials	Structure	ESI-MS	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm or HPLC retention time [min] (method)	Reaction Conditions (deviation from general procedure)
I.2	IV. 1		--	5.03 (s, 2H), 6.59 (s, 2H), 8.08 (m, 2H), 8.18 (m, 1H),	Stirred for 1h
I.3	IV.2		--	5.10 (s, 2H), 6.59 (s, 2H), 8.04 (m, 1H), 8.17 (m, 1H) 8.25 (m, 1H)	Stirred for 1h
I.4			267 $[M+H]^+$	0.75 (C)	*see below table
I.5			311 $[M+H]^+$	1.23 (B)	2.0 eq of base
I.6			311 $[M+H]^+$	1.31 (B)	
I.7	IV. 3		--	5.10 (s, 2H), 6.59 (s, 2H), 8.09 (m, 1H), 8.15 (m, 1H), 8.27 (m, 2H)	Stirred for 1h
					2 eq base,

Int.	Starting materials	Structure	ESI-MS	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm or HPLC retention time [min] (method)	Reaction Conditions (deviation from general procedure)
I.8			277 $[M+H]^+$	1.26 (B)	starting materials 1:1 Stirred for 15min
I.9	IV.4		--	5.11 (s, 2H), 6.79 m, 2H), 8.08 (m, 2H), 8.27 (m, 1H), 8.54 (m, 1H)	Stirred for 2h
I.10			293 $[M+H]^+$	1.12 (B)	Starting materials 1:1
I.11			311 $[M+H]^+$	1.08 (H)	Starting materials 1:1
I.12	IV.5		295 $[M+H]^+$	1.02 (B)	Starting materials 1:1
I.13			315/317 $[M+H]^+$	1.00 (H)	Stirred for 1h;
I.14			251 $[M+H]^+$	0.95 (H)	
I.15			277 $[M+H]^+$	1.01 (H)	

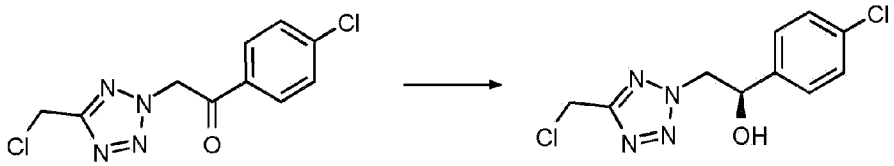
Int.	Starting materials	Structure	ESI-MS	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm or HPLC retention time [min] (method)	Reaction Conditions (deviation from general procedure)
					
I.16	IV.6		295 $[M+H]^+$	1.02 (B)	Starting materials 1:1
I.17			281 $[M+H]^+$	0.89 (H)	
I.18	IV. 7		268 $[M+H]^+$	0.47 (G)	ACN, stirred for 1.5h, purified by prep. HPLC
I.19	IV. 8		295 $[M+H]^+$	0.56 (A)	ACN, stirred for 10 min
*p-methoxyphenacyl bromide (1.04 eq.) is slowly added to a stirred solution of chloromethyltetrazol and K_2CO_3 (1.4 eq) in DMA at 18°C; mixture is stirred at RT for 1.5 h; purification via reversed phase HPLC (ACN/H_2O gradient, 0.1% TFA).					

Intermediates II

Intermediate II, 1 (general procedure)

(1R)-2-[5-(chloromethyl)-2H-1,2,3,4-tetrazol-2-yl]-1-(4-chlorophenyl)ethan-1-ol

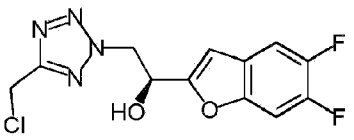
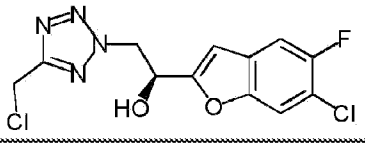
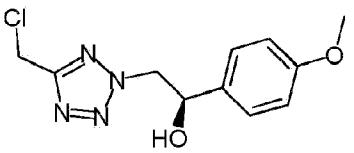
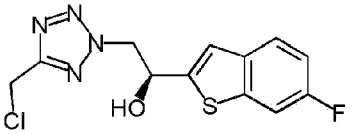
[0133]

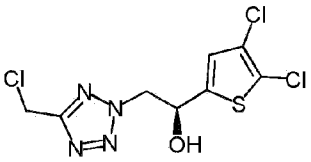
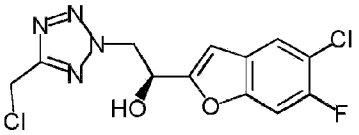
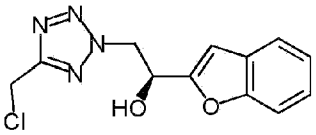
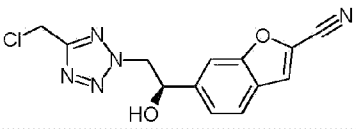
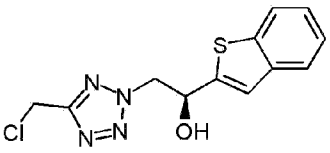
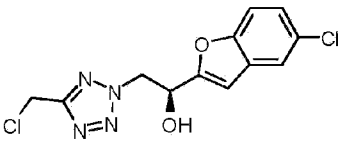
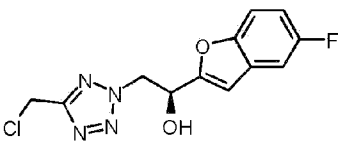
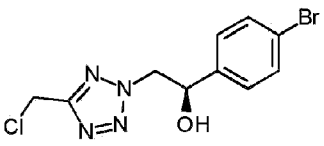
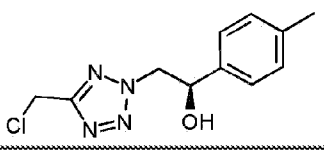


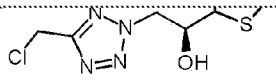
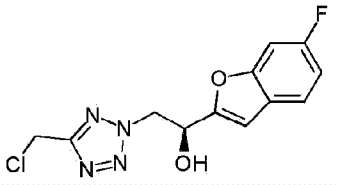
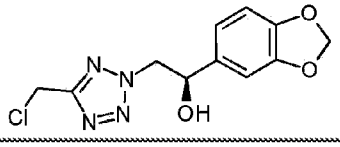
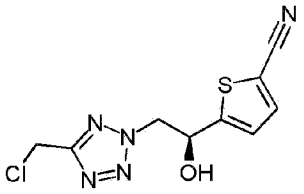
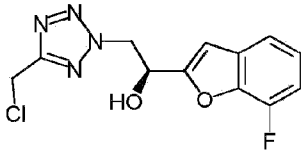
1.30 g (4.80 mmol) 1-(4-chlorophenyl)-2-[5-(chloromethyl)-2H-1,2,3,4-tetrazol-2-yl]ethan-1-one (I.1) is dissolved in 20 mL ACN under inert atmosphere. 12 mg (0.02 mmol) Chloro([(1S,2S)-2-amino-1,2-diphenylethyl](4-toluenesulfonyl)amido)(mesitylene)ruthenium (II) (CAS 174813-81-1) are added followed by dropwise addition of 0.72 mL (1.73 mmol) formic acid triethylamine complex (5:2). After stirring at RT for 3 h, the solvent is removed in under reduced pressure. To the remaining crude mixture is added water and this mixture is extracted with EtOAc. The organic layers are combined, dried over Na_2SO_4, filtered, treated with activated charcoal, filtered, and the solvent is removed under reduced pressure to provide intermediate II. 1.

$C_{10}H_{10}Cl_2N_4O$	(M = 273.1 g/mol)
ESI-MS:	273 $[M+H]^+$
R_t (HPLC):	0.96 min (method B)

[0134] The following compounds are prepared using procedures analogous to those described for intermediate II. 1 using appropriate starting materials. As is appreciated by those skilled in the art, these analogous examples may involve variations in general reaction conditions.

Int.	Starting materials	Structure	ESI-MS	HPLC retention time [min] (method)
II.2	I.2		359 $[M+HCO_2]^-$	3.05 (N)
II.3	I.3		375 $[M+HCO_2]^-$	3.47 (O)
II.4	I.4		269 $[M+H]^+$	0.45 (G)
II.5	I.5		313 $[M+H]^+$	1.17 (B)

Int.	Starting materials	Structure	ESI-MS	HPLC retention time [min] (method)
II.6	I.6		313 $[M+H]^+$	1.26 (B)
II.7	I.7		375 $[M+HCO_2]^-$	4.21 (O)
II.8	I.8		279 $[M+H]^+$	1.14 (B)
II.9	I.9		348 $[M+HCO_2]^-$	2.56 (N)
II.10	I.10		295 $[M+H]^+$	1.10 (B)
II.11	I.11		313 $[M+H]^+$	1.03 (B)
II.12	I.12		297 $[M+H]^+$	0.97 (B)
II.13	I.13		317/319 $[M+H]^+$	1.14 (B)
II.14	I.14		253 $[M+H]^+$	0.48 (A)
II.15	I.15		279 $[M+H]^+$	0.97 (H)

Int.	Starting materials	Structure	ESI-MS	HPLC retention time [min] (method)
				
II.16	I.16		297 $[M+H]^+$	0.97 (B)
II.17	I.17		283 $[M+H]^+$	0.43 (A)
II.18	I.18		270 $[M+H]^+$	0.41 (A)
II.19	I.19		297 $[M+H]^+$	0.52 (A)

Intermediate III

Intermediate III. 1 (general procedure)

1-(5,6-difluoro-1-benzofuran-2-yl)ethan-1-one

[0135]

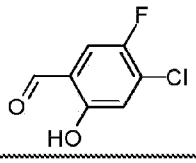
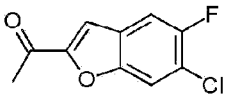
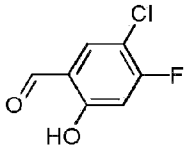
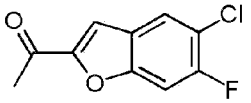
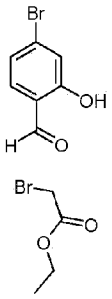
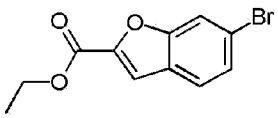
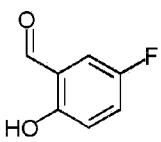
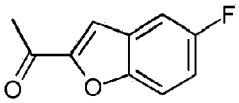
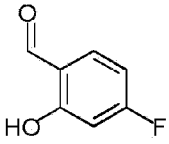
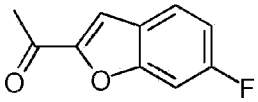
5.00 g (31.6 mmol) 4,5-difluoro-2-hydroxybenzaldehyde in 50 mL acetone is treated with 6.99 g (50.6 mmol) potassium carbonate under argon at 0°C. After additional stirring for 10 min at 0°C, 3.78 mL (47.4 mmol) chloroacetone are added dropwise and the reaction mixture is stirred at 70°C for 3 h. The reaction mixture is cooled to RT and concentrated. The crude is

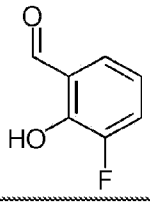
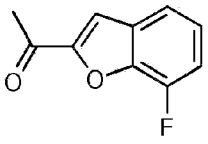
extracted with EtOAc/water and the organic phase is concentrated under reduced pressure to provide intermediate III.1.

$C_{10}H_6F_2O_2$	(M = 196.2 g/mol)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.56 (s, 3H), 7.89 (m, 1H), 7.92 (m, 1H), 8.01 (m, 1H)

[0136] The following compounds are prepared using procedures analogous to those described for intermediate III.1 using appropriate starting materials. As is appreciated by those skilled in the art, these analogous examples may involve variations in general reaction conditions.

Int.	Starting materials	Structure	ESI-MS	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm or HPLC retention time [min] (method)	Reaction conditions (deviation from general procedure)
III.2			--	2.57 (s, 3H), 7.90 (m, 2H), 8.16 (dd, *J*=6.0, 1.0 Hz, 1H)	
III.3			--	2.56 (s, 3H), 7.88 (d, *J*= 1.0 Hz, 1H), 8.01 (dd, *J*= 9.4, 1.0 Hz, 1H), 8.12 (d, *J*= 7.6 Hz, 1H)	Heated to 90°C for 1h
III.4			--	1.34 (t, *J*=7.1 Hz, 3H), 4.37 (q, *J*= 7.1 Hz, 2H), 7.55 (m, 1H), 7.77 (m, 2H), 8.10 (m, 1H)	DMF, 1.0 eq bromo acetic acid ethyl ester, stirred at 90°C overnight
III. 5			179 $[M+H]^+$	0.95 (B)	1.1 eq chloroacetone;
III.6			179 $[M+H]^+$	0.95 (B)	1.1 eq chloroacetone;

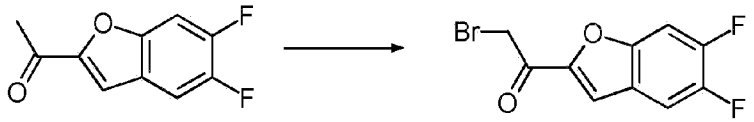
Int.	Starting materials	Structure	ESI-MS	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm or HPLC retention time [min] (method)	Reaction conditions (deviation from general procedure)
III.7			179 $[M+H]^+$	0.50 (A)	Stirred at 90°C for 1h

Intermediate IV

Intermediate IV.1(generalprocedure)

2-bromo-1-(5,6-difluoro-1-benzofuran-2-yl)ethan-1-one

[0137]



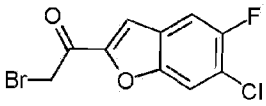
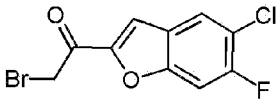
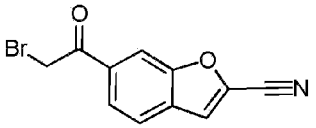
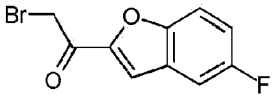
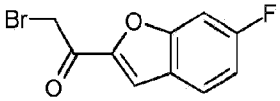
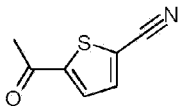
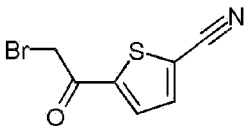
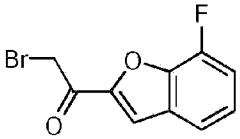
500 mg (2.55 mmol) 1-(5,6-difluoro-1-benzofuran-2-yl)ethan-1-one (III.1) in 6 mL THF is treated dropwise with 1.23 g (2.55 mmol) tetrabutylammonium tribromide in 300 µL MeOH and 3 mL THF. The reaction mixture is stirred at RT for 2 h. The reaction mixture is concentrated under reduced pressure and the residue is extracted with EtOAc/water. The organic phase is concentrated under reduced pressure and the crude material is purified by column chromatography (silica gel; Hexanes/EtOAc, 9/1 to 7/3 gradient).

$C_{10}H_5BrF_2O_2$	(M = 275.0 g/mol)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 4.83 (s, 2H), 7.98-8.12 (m, 3H)

[0138] The following compounds are prepared using procedures analogous to those described for intermediate IV. 1 using appropriate starting materials. As is appreciated by those skilled in the art, these analogous examples may involve variations in general reaction conditions

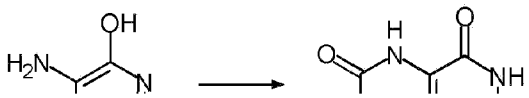
Int.	Starting materials	Structure	ESI-MS	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm or

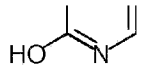
				HPLC retention time [min] (method)
IV.2	III.2		--	4.84 (s, 2H), 7.97 (d, *J*= 8.9 Hz, 1H), 8.08 (d, *J*= 1.0Hz, 1H), 8.20 (dd, *J*= 6.0, 0.9 Hz, 1H)
IV.3	III.3		--	4.83 (s, 2H), 8.03-8.21 (m, 3H)
IV.4	XV		--	5.05 (s, 2H), 7.96-8.10 (m, 2H), 8.17-8.27 (m, 1H), 8.34-8.53 (m, 1H)
IV.5	III. 5		257/259 $[M+H]^+$	1.03 (B)
IV.6	III. 6		--	4.80 (s, 2H), 7.31 (ddd, *J*=9.7, 8.8, 2.3 Hz, 1H), 7.73 (m, 1H), 7.93 (m, 1H), 8.10 (d, *J*=0.9Hz, 1H)
IV.7 **			228/230 $[M-H]^-$	0.75 (I)
IV.8	III. 7		257/259 $[M+H]^+$	0.58 (A)
**: The reaction is performed with bromine (13.6 eq) at RT for 2 h in dioxane/diethyl ether and quenched with sodium thiosulfate solution.				

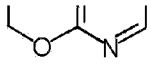
Intermediate V

3H,4H,5H,6H,7H-pyrimido[4,5-b][1,4]oxazine-4,6-dione

[0139]







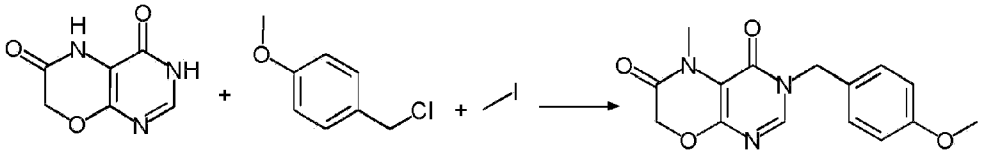
[0140] To 10.0 g (127.10 mmol) 5-aminopyrimidine-4,6-diol in 300 mL DMF is slowly added 7.5 mL (94.41 mmol) chloroacetyl chloride under stirring at 65°C. After stirring at 65°C for 1.5 h, 36.1 mL (129.94 mmol) DIPEA are slowly added to the reaction mixture and stirring at 65°C is continued for 45 min. The reaction mixture is concentrated under reduced pressure, treated with water, and the precipitated product is filtered, washed with small amounts of EtOH, and dried.

$C_6H_5N_3O_3$	(M = 167.1 g/mol)
ESI-MS:	168 $[M+H]^+$
R_t (HPLC):	0.20 min (method M)

Intermediate VI

3-[(4-methoxyphenyl)methyl]-5-methyl-3H,4H,5H,6H,7H-pyrimido[4,5-b][1,4]oxazine-4,6-dione

[0141]



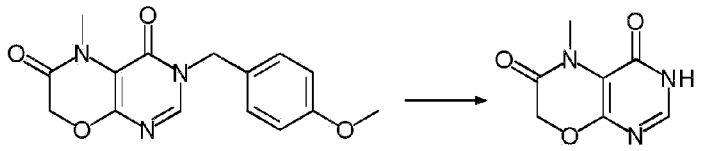
680 mg (4.07 mmol) 3H,4H,5H,6H,7H-pyrimido[4,5-b][1,4]oxazine-4,6-dione (intermediate V) in 15 mL DMF is treated with 843 mg (6.10 mmol) potassium carbonate and is stirred at RT for 15 min. 0.58 mL (4.27 mmol) 1-(chloromethyl)-4-methoxybenzene is added and the reaction mixture is stirred for 20 h. 843 mg (6.10 mmol) potassium carbonate and 0.30 ml (4.88 mmol) methyl iodide are added and the reaction mixture is stirred at RT for 20 h. 0.26 ml (4.07 mmol) methyl iodide is added and the reaction mixture is stirred at RT for 20 h, filtered, concentrated under reduced pressure, and purified by reversed phase HPLC (ACN/H_2O gradient, 0.1% TFA).

$C_{15}H_{15}N_3O_4$	(M = 301.3 g/mol)
ESI-MS:	302 $[M+H]^+$
R_t (HPLC):	0.95 min (method B)

Intermediate VII

5-methyl-3H,4H,5H,6H,7H-pyrimido[4,5-b][1,4]oxazine-4,6-dione

[0142]



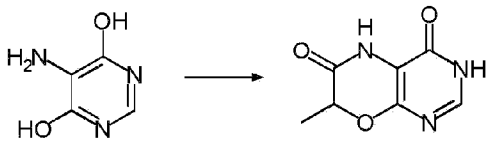
5.30 g (14.07 mmol) 3-[(4-methoxyphenyl)methyl]-5-methyl-3H,4H,5H,6H,7H-pyrimido[4,5-b][1,4]oxazine-4,6-dione (intermediate VI) is treated with 16 ml TFA and stirred at 100°C for 1.5 h. Afterwards, the reaction mixture is stirred in the microwave at 120°C for 15 min, poured onto iced water and filtered. The filtrate is lyophilized and directly used without further purification.

$C_7H_7N_3O_3$	(M = 181.2 g/mol)
ESI-MS:	182 $[M+H]^+$
R_t (HPLC):	0.37 min (method B)

Intermediate VIII

7-methyl-3H,4H,5H,6H,7H-pyrimido[4,5-b][1,4]oxazine-4,6-dione

[0143]



[0144] A mixture of 200 mg (1.57 mmol) 5-aminopyrimidine-4,6-diol and 1.44 g (9.44 mmol) 2-bromopropionic acid is stirred under neat conditions at 100°C for 22.5 h. The reaction mixture is diluted with DCM, filtered, and the concentrated filtrate is purified by column chromatography (silica gel; DCM/MeOH, 1/0 to 7/3 gradient).

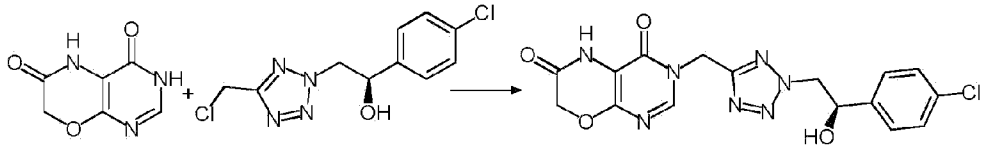
$C_7H_7N_3O_3$	(M = 181.2 g/mol)
ESI-MS:	182 $[M+H]^+$
R_t (HPLC):	0.23 min (method E)

Intermediate IX

Intermediate IX.1 (general procedure)

3-({2-[(2R)-2-(4-chlorophenyl)-2-hydroxyethyl]-2H-1,2,3,4-tetrazol-5-yl}methyl)-3H,4H,5H,6H,7H-pyrimido[4,5-b][1,4]oxazine-4,6-dione

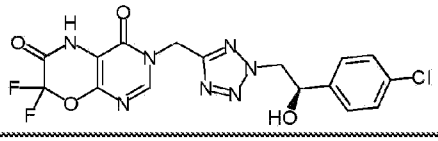
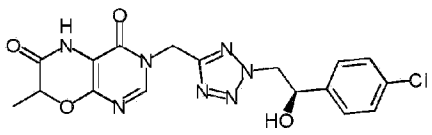
[0145]



[0146] To 61 mg (0.37 mmol) 3H,4H,5H,6H,7H-pyrimido[4,5-b][1,4]oxazine-4,6-dione (V) in 3 mL DMF is added 76 mg (0.55 mmol) potassium carbonate and 100 mg (0.37 mmol) (1*R*)-2-[5-(chloromethyl)-2H-1,2,3,4-tetrazol-2-yl]-1-(4-chlorophenyl)ethan-1-ol (II.1) and the mixture is stirred at RT overnight. The reaction mixture is quenched with Water/ACN/TFA, filtered and purified by reversed phase HPLC (ACN/H_2O gradient, 0.1% TFA) to yield the desired product.

$C_{16}H_{14}ClN_7O_4$	(M = 403.8 g/mol)
ESI-MS:	404 $[M+H]^+$
R_t (HPLC):	0.77 min (method H)

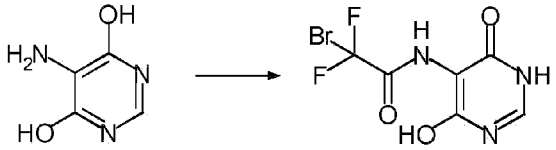
[0147] The following compounds are prepared using procedures analogous to those described for intermediate IX.1 using appropriate starting materials. As is appreciated by those skilled in the art, these analogous examples may involve variations in general reaction conditions.

Int.	Starting materials	Structure	ESI-MS	HPLC retention time [min] (method)
IX.2	XI		440 $[M+H]^+$	0.49 (A)
IX.3	VIII		418 $[M+H]^+$	0.46 (A)

Intermediate X

2-bromo-2,2-difluoro-N-(4-hydroxy-6-oxo-1,6-dihydropyrimidin-5-yl)acetamide

[0148]



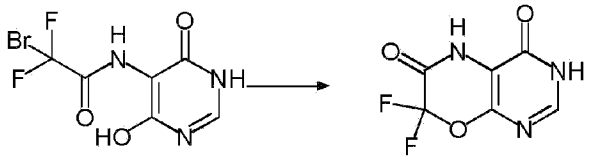
200 mg (1.57 mmol) 5-aminopyrimidine-4,6-diol is treated with 456 mg (2.36 mmol) bromodifluoroacetylchloride and is stirred under neat conditions at 90°C for 3.5 h. The reaction mixture is triturated with diethylether and filtered to yield intermediate X.

$C_6H_4BrF_2N_3O_3$	(M = 284.0 g/mol)
ESI-MS:	284/286 $[M+H]^+$
R_t (HPLC):	0.10 min (method E)

Intermediate XI

7,7-difluoro-3H,4H,5H,6H,7H-pyrimido[4,5-b][1,4]oxazine-4,6-dione

[0149]



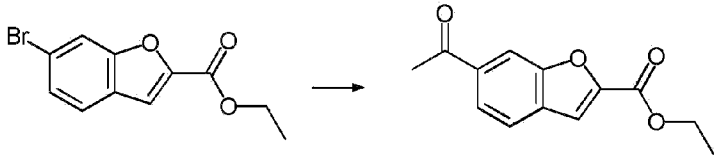
30 mg (0.11 mmol) 2-bromo-2,2-difluoro-N-(4-hydroxy-6-oxo-1,6-dihydropyrimidin-5-yl)acetamide (X) in 2.5 ml DMF is treated with 16 mg (0.37 mmol) sodium hydride and is stirred 18 h at 50°C. The reaction mixture is is purified by reversed phase HPLC (ACN/H_2O gradient, 0.1% TFA) to yield the desired product.

$C_6H_3F_2N_3O_3$	(M = 203.1 g/mol)
ESI-MS:	204 $[M+H]^+$
R_t (HPLC):	0.23 min (method A)

Intermediate XII

Ethyl 6-acetyl-1-benzofuran-2-carboxylate

[0150]



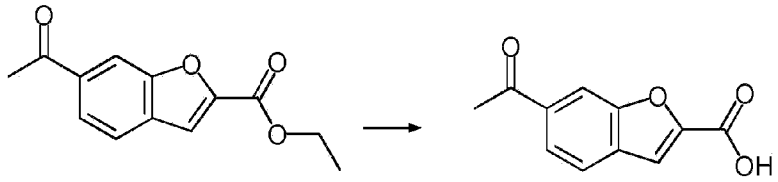
[0151] To 1.00 g (3.72 mmol) ethyl 6-bromo-1-benzofuran-2-carboxylate (IΠ.4) in 12.5 mL DMF is added 616 mg (4.46 mmol) potassium carbonate. The mixture is purged with argon and 92 mg (0.22 mmol) 1,3-Bis(diphenylphosphino)propane, 250 mg (0.11 mmol) palladium(II) acetate and 670 mg (9.29 mmol) ethyl vinyl ether are added. The reaction mixture is stirred at 80°C for 18 h, then cooled to RT and the pH is adjusted to pH=1 by addition of 1M aq. HCl. The crude product was extracted with EtOAc, concentrated under reduced pressure, and purified by column chromatography (silica gel; Hexane/EtOAc 7/3).

$C_{13}H_{12}O_4$	(M = 232.2 g/mol)
ESI-MS:	233 $[M+H]^+$
R_t (HPLC):	1.38 min (method Q)

Intermediate XIII

6-acetyl-1-benzofuran-2-carboxylic acid

[0152]



[0153] To 6.60 g (28.4 mmol) ethyl 6-acetyl-1-benzofuran-2-carboxylate (XII) in 66 mL THF and 33 mL water is added 3.3 mL ethanol and 1.43 g (34.1 mmol) LiOH monohydrate. The reaction mixture is stirred at RT for 1 h and concentrated to dryness under reduced pressure to provide the intermediate.

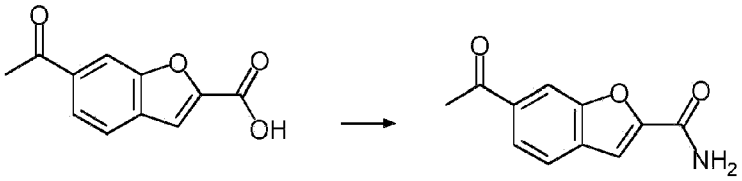
$C_{11}H_8O_4$	(M = 204.2 g/mol)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.67 (s, 3H), 7.73 (m, 1H), 7.99 - 7.85 (m, 2H), 8.32 (m, 1H), 13.30- 14.50 (br s, 1H)

Intermediate XIV

6-acetyl-1-benzofuran-2-carboxamide

[0154]



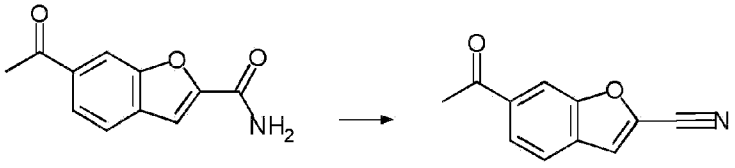
[0155] To 1.00 g (4.90 mmol) 6-acetyl-1-benzofuran-2-carboxylic acid (XIII) in 10 mL DCM is added 932 mg (7.34 mmol) oxalyl chloride and 1 drop of DMF at 0°C. The reaction mixture is stirred for 2 h at RT and concentrated to dryness. The residue is dissolved in 10 mL THF, cooled to 0°C and 15 mL 25% aqueous ammonia is added. The reaction mixture is stirred at RT for 16 h and concentrated to dryness under reduced pressure to provide the intermediate.

$C_{11}H_9NO_3$	(M = 203.2 g/mol)
ESI-MS:	204 $[M+H]^+$
R_t (HPLC):	0.96 min (method Q)

Intermediate XV

6-acetyl-1 -benzofuran-2-carbonitrile

[0156]



[0157] To 0.90 g (4.43 mmol) 6-acetyl-1-benzofuran-2-carboxamide (XIV) and 1.4 mL (9.88 mmol) TEA in 12 mL THF are added 1.1 mL (7.77 mmol) TFAA dropwise under stirring at 0 °C.

The reaction mixture is stirred at 0°C for 1h, quenched with water and extracted with EtOAc three times. The combined organic layers are washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the intermediate.

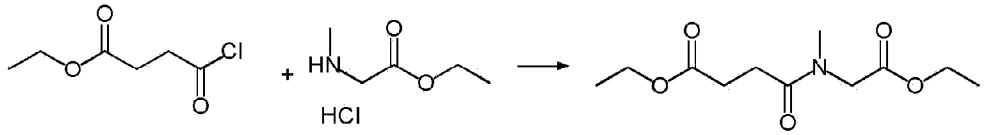
$C_{11}H_7NO_2$	(M = 185.2 g/mol)

[0158] ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 2.68 (s, 3H), 7.92-8.05 (m, 2H), 8.21 (m, 1H), 8.37 (m, 1H).

Intermediate XVI

ethyl 3-[(2-ethoxy-2-oxoethyl)(methyl)carbamoyl]propanoate

[0159]



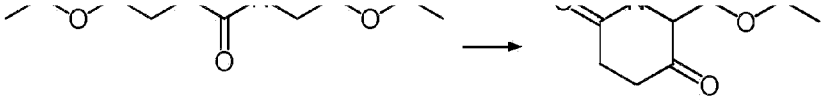
[0160] To 1.50 g sarcosine ethyl ester hydrochloride (9.77 mmol, CAS: 52605-49-9) in 30 mL DCM are added TEA (3.40 mL, 24.4 mmol) followed by ethyl succinyl chloride (1.53 mL, 10.74 mmol, CAS: 14794-31-3) at 0°C under stirring. The mixture is slowly warmed to RT, stirred at RT for 3 h, and subsequently washed with water three times. The organic layer is concentrated under reduced pressure and purified by column chromatography (silica gel; CyH/EtOAc, gradient).

$C_{11}H_{19}NO_5$	(M = 245.27 g/mol)
ESI-MS:	246 $[M+H]^+$
R_t (HPLC):	1.05 min (method M)

Intermediate XVII

ethyl 1-methyl-3,6-dioxopiperidine-2-carboxylate

[0161]



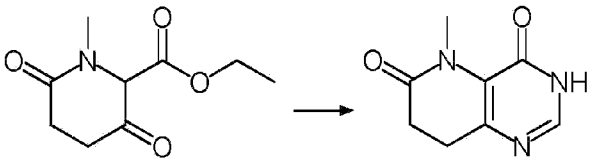
[0162] To 0.40 g (1.63 mmol) ethyl 3-[(2-ethoxy-2-oxoethyl)(methyl)carbamoyl]propanoate (XVI) in 4.0 mL abs. dioxane are slowly added 56 mg (2.45 mmol) sodium under stirring at RT, followed by slow addition of 0.2 mL abs. EtOH. The reaction mixture is stirred at 80°C for 12 h, cooled to RT, and the pH is adjusted to pH=7 by addition of aq. HCl (4N). The reaction mixture is diluted with water and extracted with EtOAc three times. The combined organic layers are dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the intermediate.

$C_9H_{13}NO_4$	(M = 199.20 g/mol)
ESI-MS:	200 $[M+H]^+$
R_t (HPLC):	0.75 min (method H)

Intermediate XVIII

1-methyl-1,2,3,4,7,8-hexahydro-1,7-naphthyridine-2,8-dione

[0163]



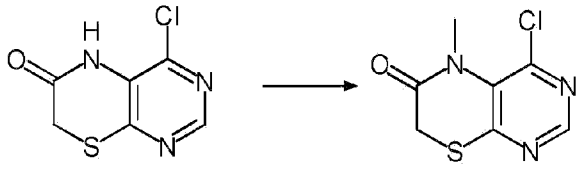
[0164] To a stirred mixture of 0.13 g (0.52 mmol) ethyl 1-methyl-3,6-dioxopiperidine-2-carboxylate (XVII) and 0.27 g formamidine acetate (2.61 mmol) in 5.0 mL abs. MeOH are slowly added 0.60 mL of a solution of sodium methylate in MeOH (25% wt) at 0°C. Subsequently, the reaction mixture is refluxed for 4 h, cooled to 0°C, neutralized with acetic acid and concentrated under reduced pressure. Purification by reversed phase HPLC (ACN/H_2O gradient, 0.1% TFA) yields the desired product.

$C_8H_9N_3O_2$	(M = 179.18 g/mol)
ESI-MS:	180 $[M+H]^+$
R_t (HPLC):	0.08 min (method J)

Intermediate XIX

4-chloro-5-methyl-5H,6H,7H-pyrimido[4,5-b][1,4]thiazin-6-one

[0165]



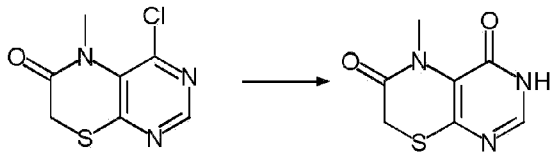
[0166] To 0.50 g (2.48 mmol) 4-chloro-5H,6H,7H-pyrimido[4,5-b][1,4]thiazin-6-one (CAS:20015-70-7) in 3.0 mL DMF under argon are added 0.12 g (2.73 mmol) sodium hydride and stirred at RT for 20 min. Methyl iodide (0.17 mL, 2.73 mmol) is added and the reaction mixture is stirred at RT overnight. The reaction mixture is diluted with brine and extracted with EtOAc. The organic layer is dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the intermediate.

$C_7H_6ClN_3OS$	(M = 215.66 g/mol)
ESI-MS:	215 $[M+H]^+$
R_t (HPLC):	0.80 min (method B)

Intermediate XX

5-methyl-3H,4H,5H,6H,7H-pyrimido[4,5-b][1,4]thiazine-4,6-dione

[0167]



0.34 g (1.58 mmol) 4-chloro-5-methyl-SH,6H,7H-pyrimido[4,5-b][1,4]thiazin-6-one (XIX) are stirred in 4.0 mL formic acid at 90°C for 3 h and at RT overnight. The reaction mixture is subsequently concentrated under reduced pressure and refluxed in EtOH for 30 min under stirring. After slow cool down to RT, the product is filtered off, washed with EtOH and dried under reduced pressure.

$C_7H_7N_3O_2S$	(M = 197.22 g/mol)
ESI-MS:	198 $[M+H]^+$

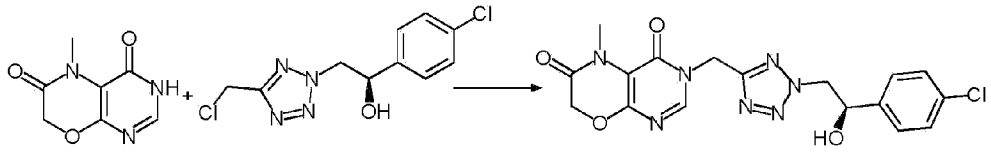
R_t (HPLC):	0.53 min (method B)

Preparation of Final Compounds

Example 1 (general procedure A)

3-({2-[(2R)-2-(4-chlorophenyl)-2-hydroxyethyl]-2H-1,2,3,4-tetrazol-5-yl}methyl)-5-methyl-3H,4H,5H,6H,7H-pyrimido[4,5-b][1,4]oxazine-4,6-dione

[0168]

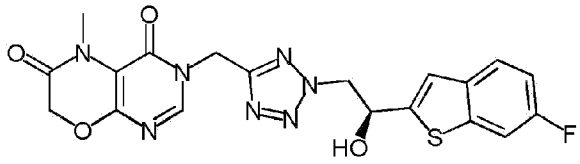
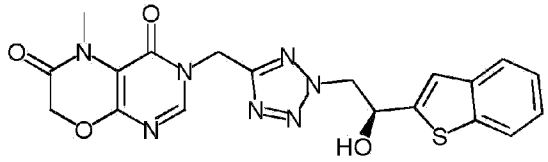
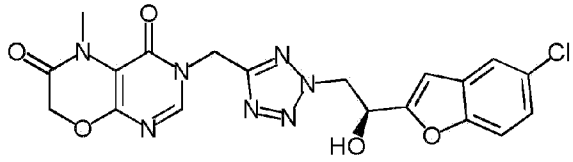
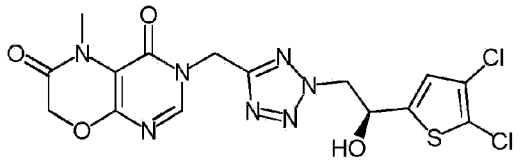
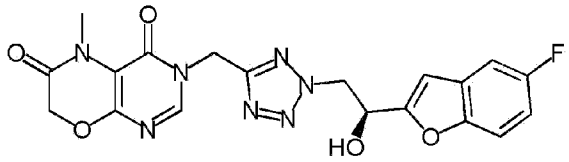
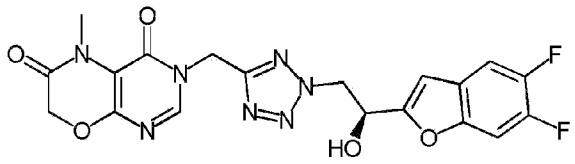
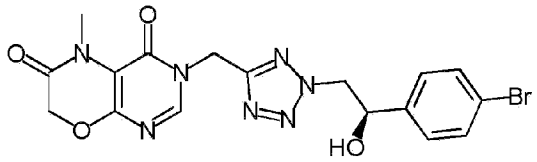
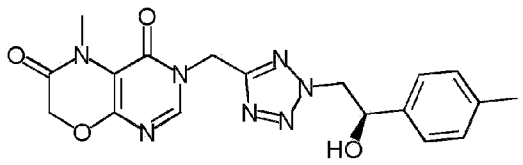
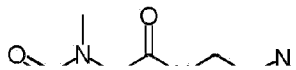


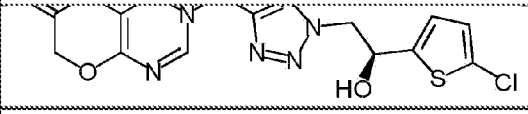
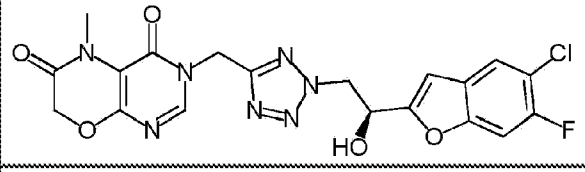
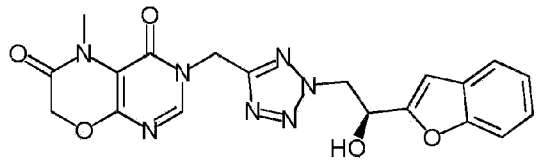
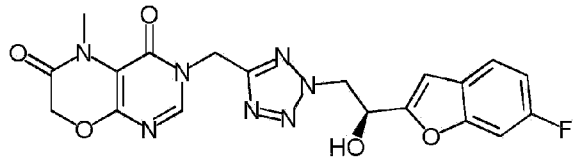
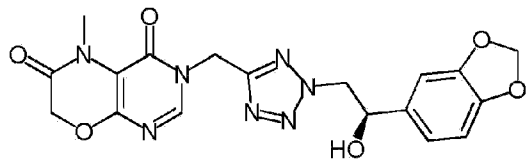
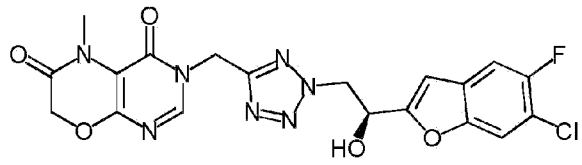
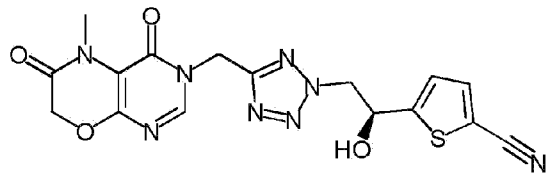
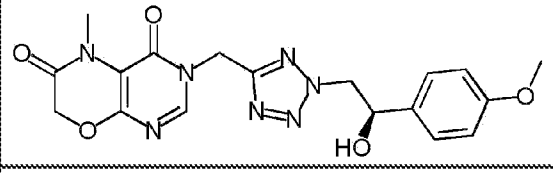
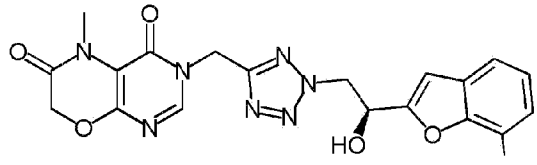
[0169] To 210 mg (0.77 mmol) (1R)-2-[5-(chloromethyl)-2H-1,2,3,4-tetrazol-2-yl]-1-(4-chlorophenyl)ethan-1-ol (II.1) in 7 mL DMF are added 159 mg (1.15 mmol) K_2CO_3 and 185 mg (0.77 mmol) 5-methyl-3H,4H,5H,6H,7H-pyrimido[4,5-b][1,4]oxazine-4,6-dione (VII) and the mixture is stirred at RT overnight. The mixture is purified by reversed phase HPLC (ACN/H_2O gradient, 0.1% TFA) to yield the desired product.

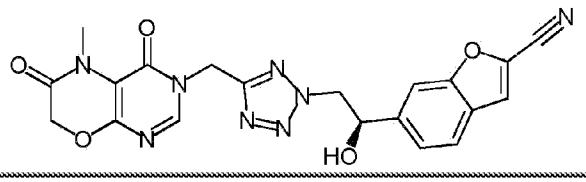
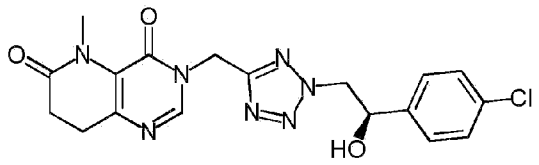
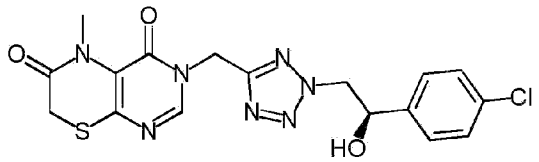
$C_{17}H_{16}ClN_7O_4$	(M = 417.8 g/mol)
ESI-MS:	418 $[M+H]^+$
R_t (HPLC):	0.81 min (method H)

^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm: 3.33 (s, 3 H), 4.74 - 4.84 (m, 4 H), 5.10 - 5.16 (m, 1 H), 5.45 (s, 2 H), 5.92 (d, *J*= 4.8 Hz, 1 H), 7.36 - 7.43 (m, 4 H), 8.46 (s, 1 H)

[0170] The following compounds are prepared using procedures analogous to those described for example 1, general procedure A, using appropriate starting materials. As is appreciated by those skilled in the art, these analogous examples may involve variations in general reaction conditions.

Ex.	Starting materials	Structure	Reaction conditions
2	II.5 + VII		3 eq. Base Solvent: DMA, 18h at RT
3	II.10 + VII		3.25 eq. Base Solvent: DMF, 3h at 50°C, 20h at RT
4	II.11 + VII		3 eq. Base Solvent: DMA, 18 h at RT
5	II.6 + VII		3 eq.base Solvent: DMF, RT overnight
6	II.12 + VII		3 eq. Base Solvent: DMA, 18h at RT
7	II.2 + VII		3.25 eq. Base Solvent: DMF, 5h at 50°C
8	II.13 + VII		3 eq. Base Solvent: DMF, 20h at RT
9	II.14 + VII		3 eq. Base Solvent: DMF, 3h at RT
10	II.15 + VII		3 eq. Base Solvent: DMA, 18h at RT

Ex.	Starting materials	Structure	Reaction conditions
			
11	II.7 + VII		3 eq. Base Solvent: DMA, overnight at RT
12	II.8 + VII		3 eq. Base Solvent: DMA, 18h at RT
13	II.16 + VII		1.5 eq. base Solvent: DMF, overnight at RT
14	II.17 + VII		1.5 eq. base Solvent: DMF, overnight at RT
15	II.3 + VII		3 eq. base Solvent: DMA, overnight at RT
16	II.18 + VII		1.5 eq. base Solvent: DMF, overnight at RT
17	II.4 + VII		1.5 eq. base Solvent: DMF, overnight at RT
18	II.19 + VII		3 eq. Base Solvent: DMA, 16.5h at RT

Ex.	Starting materials	Structure	Reaction conditions
		F	
19	II.9 + VII		1.5 eq. base Solvent: DMF, overnight at RT
20	II.1 + XVIII		1.5 eq. base Solvent: DMF, overnight at RT
21	II.1 + XX		3.25 eq base, solvent: DMF at 50°C for 3h

[0171] Analytical data for the compounds described in the table above:

Ex.	ESI-MS	HPLC retention time [min] (method)	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
2	458 $[M+H]^+$	0.62 (D)	3.31 (s, 3 H), 4.78 (s, 2 H), 4.88 - 5.02 (m, 2 H), 5.43-5.49 (m, 3H), 6.33 - 6.63 (br s, 1H), 7.22 (m, 1 H), 7.31 (s, 1 H), 7.78 (dd, *J*=8.7, 5.3 Hz, 1 H), 7.85 (dd, *J*=9.1, 2.5 Hz, 1 H), 8.46 (s, 1 H)
3	440 $[M+H]^+$	0.64 (I)	3.32 (s, 3 H), 4.78 (s, 2 H), 4.87 - 5.04 (m, 2 H), 5.45-5.51 (m, 3H), 7.30 - 7.37 (2 H), 7.32 (s, 1 H), 7.76 (m, 1 H), 7.93 (m, 1 H), 8.47 (s, 1 H)
4	458 $[M+H]^+$	0.70 (I)	3.30 (s, 3 H), 4.78 (s, 2 H), 4.97 - 5.10 (m, 2 H), 5.29 (m, 1 H), 5.44 (s, 2 H), 6.3 (br s, 1H), 6.84 (s, 1 H) 7.32 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.60 (d, *J*= 8.8 Hz, 1 H), 7.68 (d, *J*=2.2 Hz, 1 H), 8.43 (s, 1 H)
5	458 $[M+H]^+$	1.14 (B)	3.32 (s, 3 H), 4.79 (s, 2 H), 4.81 - 4.99 (m, 2 H), 5.32 (m, 1 H), 5.46 (s, 2 H), 6.59 (d, *J*=5.3 Hz, 1H), 7.10 (d, *J*=1.0 Hz, 1 H), 8.46 (s, 1H)
6	442	0.81 (J)	3.30 (s, 3 H), 4.78 (s, 2 H), 4.96 - 5.10

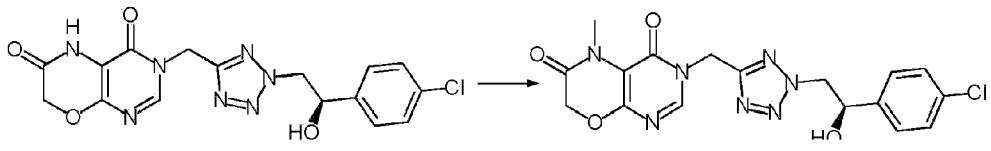
Ex.	ESI-MS	HPLC retention time [min] (method)	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
	$[M+H]^+$		(m, 2 H), 5.28 (m, 1 H), 5.44 (s, 2 H), 6.85 (s, 1 H), 7.13 (td, *J*=9.2, 2.7 Hz, 1 H), 7.41 (dd, *J*=8.9, 2.7 Hz, 1 H), 7.59 (dd, *J*=8.9, 4.2 Hz, 1 H), 8.43 (s, 1 H)
7	460 $[M+H]^+$	0.65 (I)	3.30 (s, 3 H), 4.78 (s, 2 H), 4.96 - 5.08 (m, 2 H), 5.27 (m, 1 H), 5.43 (s, 2 H), 6.85 (s, 1 H), 7.65 (dd, *J*=10.5, 8.1 Hz, 1 H), 7.81 (m, 1 H), 8.41 (s, 1 H)
8	462 $[M+H]^+$	1.04 (B)	3.33 (s, 3 H), 4.73 - 4.84 (m, 4 H), 5.11 (m, 1 H), 5.45 (s, 2 H), 5.9 (br s, 1H) 7.31-7.36 (m, 2H), 7.50-7.55 (m, 2 H), 8.46 (s, 1 H)
9	398 $[M+H]^+$	0.55 (D)	2.28 (s, 3 H), 3.33 (s, 3 H), 4.74 (d, *J*=6.6 Hz, 2 H), 4.79 (s, 2 H), 5.07 (t, *J*=6.5 Hz, 1 H), 5.45 (s, 2 H), 7.14 (d, *J*=8.0 Hz, 2 H), 7.26 (d, *J*=8.0 Hz, 2 H), 8.46 (s, 1 H)
10	424 $[M+H]^+$	0.56 (D)	3.32 (s, 3 H), 4.78 (s, 2 H), 4.79 - 4.93 (m, 2 H), 5.30 (m, 1 H), 5.46 (s, 2 H), 6.87 (dd, *J*=3.8 Hz, 0.8 Hz, 1 H), 6.97 (d, *J*=3.8 Hz, 1 H), 8.46 (s, 1 H)
11	476 $[M+H]^+$	0.65 (D)	3.30 (s, 3 H), 4.78 (s, 2 H), 4.97 - 5.09 (m, 2 H), 5.28 (m, 1 H), 5.43 (s, 2 H), 6.84 (m, 1 H), 7.80 (dd, *J*= 9.4 Hz, 0.7 Hz, 1 H), 7.83 (d, *J*= 7.5 Hz, 1 H), 8.41 (s, 1 H)
12	424 $[M+H]^+$	0.56 (D)	3.33 (s, 3 H), 4.78 (s, 2 H), 4.97 - 5.09 (m, 2 H), 5.28 (m, 1 H), 5.45 (s, 2 H), 6.84 (m, 1 H), 7.23 (m, 1 H), 7.30 (m, 1 H), 7.56 (m, 1 H), 7.60 (m, 1 H), 8.44 (s, 1 H)
13	442 $[M+H]^+$	0.79 (J)	3.29-3.31 (br m, solvent), 4.78 (s, 2 H), 4.95 - 5.09 (m, 2 H), 5.26 (m, 1 H), 5.44 (s, 2 H), 6.26 (d, *J*=5.7 Hz, 1H), 6.85 (s, 1 H), 7.12 (m, 1 H), 7.52 (dd, *J*=9.4, 1.9 Hz, 1 H), 7.61 (dd, *J*=8.6, 5.6 Hz, 1 H), 8.43 (s, 1 H)
14	428 $[M+H]^+$	0.69 (J)	3.32 (s, 3 H), 4.68 - 4.78 (m, 2 H), 4.79 (s, 2 H), 5.03 (m, 1 H), 5.45 (s, 2 H), 5.76 (d, *J*=5 Hz, 1H), 5.99 (s, 2 H), 6.75 - 6.90 (m, 2 H), 6.98 (s, 1 H), 8.46 (s, 1 H)
15	476 $[M+H]^+$	0.69 (F)	3.30 (s, 3 H), 4.78 (s, 2 H), 4.94 - 5.10 (m, 2 H), 5.28 (m, 1 H), 5.43 (s, 2 H), 6.35 (br s, 1H), 6.87 (m, 1 H), 7.64 (d,

Ex.	ESI-MS	HPLC retention time [min] (method)	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
			J=9.3 Hz, 1 H), 7.92 (dd, *J*=6.0, 0.7 Hz, 1 H), 8.41 (s, 1 H)
16	415 $[M+H]^+$	0.66 (J)	3.32 (s, 3 H), 4.79 (s, 2 H), 4.84 - 5.05 (m, 2 H), 5.44-5.50 (m, 3 H), 6.70 (d, *J*=5.3 Hz, 1H), 7.19 (dd, *J*=3.9, 0.6 Hz, 1 H) 7.84 (d, *J*=3.9 Hz, 1 H), 8.46 (s, 1 H)
17	414 $[M+H]^+$	0.70 (J)	3.33 (s, 3 H), 3.74 (s, 3 H), 4.68 - 4.78 (m, 2 H), 4.79 (s, 2 H), 5.02 - 5.10 (m, 1 H), 5.45 (s, 2 H), 5.72 (d, *J*=4.8 Hz, 1H), 6.86 - 6.92 (m, 2 H), 7.27 - 7.33 (m, 2 H), 8.46 (s, 1 H)
18	442 $[M+H]^+$	0.43 (A)	3.30 (s, 3 H), 4.78 (s, 2 H), 4.99 - 5.12 (m, 2 H), 5.32 (m, 1 H), 5.44 (s, 2 H), 6.95 (m, 1 H), 7.17 - 7.27 (m, 2 H), 7.39 - 7.48 (m, 1 H), 8.43 (s, 1 H)
19	449 $[M+H]^+$	0.80 (H)	3.32 (s, 3 H), 4.79 (s, 2 H), 4.83 - 4.93 (m, 2 H), 5.30 (m, 1 H), 5.44 (s, 2 H), 7.46 (dd, *J*=8.2, 1.1 Hz, 1 H) 7.74 (s, 1 H) 7.79 (d, *J*=8.2 Hz, 1 H), 8.10 (d, *J*= 0.9 Hz, 1 H), 8.44 (s, 1H)
20	416 $[M+H]^+$	0.76 (J)	2.94 (s, 3 H), 3.18 (t, *J*= 3.2 Hz, 2H), 4.42 (t, *J*= 3.2 Hz, 2H), 4.74 - 4.83 (m, 2 H), 5.12 (m, 1 H), 5.42 (s, 2 H), 5.92 (d, *J*=4.9 Hz, 1H), 7.35-7.43 (m, 4 H), 8.59 (s, 1 H)
21	434 $[M+H]^+$	0.61 (P)	3.20 (s, 3 H), 3.64 (s, 2H), 4.74 - 4.83 (m, 2 H), 5.12 (m, 1 H), 5.45 (s, 2 H), 5.92 (d, *J*=4.8 Hz, 1H), 7.36 - 7.36-7.43 (m, 4 H), 8.48 (s, 1 H)

Example 1 (general procedure B)

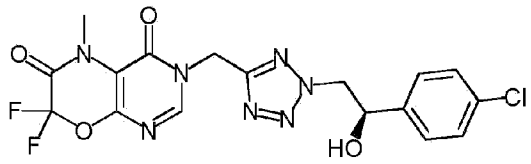
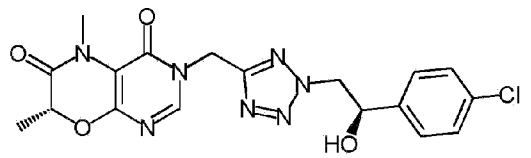
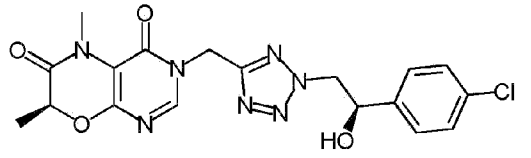
3-({2-[(2R)-2-(4-chlorophenyl)-2-hydroxyethyl]-2H-1,2,3,4-tetrazol-5-yl}methyl)-5-methyl-3H,4H,5H,6H,7H-pyrimido[4,5-b][1,4]oxazine-4,6-dione

[0172]



[0173] To 0.74 g (1.83 mmol) 3-({2-[(2R)-2-(4-chlorophenyl)-2-hydroxyethyl]-2H-1,2,3,4-tetrazol-5-yl}methyl)-3H,4H,5H,6H,7H-pyrimido[4,5-b][1,4]oxazine-4,6-dione (IX.1) in 15 ml DMF is added 0.43 g (3.12 mmol) potassium carbonate and 0.17 ml (2.75 mmol) methyl iodide. The reaction mixture is stirred at RT overnight, filtered, and the filtrate is concentrated under reduced pressure. The residue is diluted with water and extracted with EtOAc twice. The combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to provide example 1.

[0174] The following compounds are prepared using procedures analogous to those described for example 1, general procedure B, using appropriate starting materials. As is appreciated by those skilled in the art, these analogous examples may involve variations in general reaction conditions.

Ex.	Starting materials	Structure	Reaction conditions
22	IX.2		3 eq. Base 3 eq. MeI, at RT for 3.5 h; RP HPLC
23*	IX.3	 (*R*,*R*)	3 eq. base, 6 eq MeI, at RT for 3 h; RP HPLC + Chiral SFC
24	IX.3	 (*S*,*R*)	3 eq. base, 6 eq MeI, at RT for 3 h; RP HPLC + Chiral SFC
*The absolute configuration of the stereo centers of example 23 was assigned via X-Ray.			

[0175] Analytical data for the compounds described in the table above:

Ex.	ESI-MS	HPLC retention time [min] (method)	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
22	454 $[M+H]^+$	0.53 (A)	3.52 (s, 3 H), 4.73 - 4.85 (m, 2 H), 5.12 (m, 1 H), 5.49 (s, 2 H), 5.9 (br s, 1H), 7.34-7.41 (m, 4 H), 8.67 (s, 1 H)

23	432 $[M+H]^+$	2.32 (L)	1.46 (d, *J*=6.8 Hz, 3 H), 3.32 (s, 3 H), 4.72 - 4.84 (m, 2 H), 4.88 (q, *J*=6.8 Hz, 1 H), 5.13 (m, 1 H), 5.39 - 5.51 (m, 2 H), 5.92 (d, *J*=4.9 Hz, 1 H), 7.3 5-7.42 (m, 4 H), 8.46 (s, 1 H)
24	432 $[M+H]^+$	2.53 (L)	1.46 (d, *J*=6.8 Hz, 3 H), 3.32 (s, 3 H), 4.72 - 4.84 (m, 2 H), 4.88 (q, *J*=6.8 Hz, 1 H), 5.13 (m, 1 H), 5.39 - 5.51 (m, 2 H), 5.92 (d, *J*=4.9 Hz, 1 H), 7.35-7.42 (m, 4 H), 8.46 (s, 1 H)

Analytical HPLC methods

Method A

[0176]

time (min)	Vol% water (incl. 0.1% TFA)	Vol% ACN	Flow [mL/min]
0.00	99	1	1.6
0.02	99	1	1.6
1.00	0	100	1.6
1.10	0	100	1.6
Analytical column: XBridge BEH C18_2.1 × 30 mm, 1.7 µm; column temperature: 60°C			

Method B

[0177]

time (min)	Vol% water (incl. 0.1% TFA)	Vol% ACN	Flow [mL/min]
0.00	97	3	2.2
0.20	97	3	2.2
1.20	0	100	2.2
1.25	0	100	3.0
1.40	0	100	3.0
Analytical column: Stable Bond (Agilent) 1.8 µm; 3.0 × 30 mm; column temperature: 60°C			

Method C

[0178]

time (min)	Vol.% water (incl. 0.1 % TFA)	Vol. % ACN	Flow [mL/min]
0.00	95	5	1.5
1.30	0	100	1.5
1.50	0	100	1.5
Analytical column: Sunfire C18 (Waters) 2.5 µm; 3.0 × 30 mm; column temperature: 60 °C			

Method D

[0179]

time (min)	Vol.% water (incl. 0.1 % NH_4OH)	Vol. % ACN	Flow [mL/min]
0.00	95	5	1.5
1.30	0	100	1.5
1.50	0	100	1.5
1.60	95	5	1.5
Analytical column: XBridge C18_3.0 × 30 mm_2.5 µm (Waters); column temperature: 60 °C			

Method E

[0180]

time (min)	Vol% water (incl. 0.1% TFA)	Vol. % ACN	Flow [mL/min]
0.0	99.0	1.0	1.5
0.02	99.0	1.0	1.5
1.0	0.0	100.0	1.5
1.1	0.0	100.0	1.5
Analytical column: XSelectHSS PFP (Waters) _2.1 × 30 mm_1.8 µm; column temperature: 60 °C			

Method F

[0181]

time (min)	Vol.% water (incl. 0.1 % TFA)	Vol. % ACN	Flow [mL/min]
0.00	95	5	1.5
1.30	0	100	1.5
1.50	0	100	1.5
1.60	95	5	1.5
Analytical column: Sunfire (Waters) C18_3.0 × 30 mm_2.5 µm; column temperature: 60 °C			

Method G

[0182]

time (min)	Vol.% water (incl. 0.1 % TFA)	Vol. % ACN	Flow [mL/min]
0.00	99	1	1.6
0.02	99	1	1.6
1.0	0	100	1.6
1.1	0	100	1.6
Analytical column: Zorbax StableBond C18 (Agilent) 1.8 µm; 2.1 × 30 mm; column temperature: 60 °C			

Method H

[0183]

time (min)	Vol% water (incl. 0.1% TFA)	Vol% ACN	Flow [mL/min]
0.00	97	3	2.2
0.20	97	3	2.2
1.20	0	100	2.2
1.25	0	100	3.0
1.40	0	100	3.0
Analytical column: Sunfire (Waters) 2.5 µm; 3.0 × 30 mm; column temperature: 60°C			

Method I

[0184]

time (min)	Vol% water (incl. 0.1% TFA)	Vol% ACN 0.08%TFA	Flow [mL/min]
0.00	95	5	1.5
1.30	0	100	1.5
1.50	0	100	1.5
1.60	95	5	1.5
Analytical column: Sunfire (Waters); C18_3.0 × 30 mm_2.5 µm; column temperature: 60°C			

Method J

[0185]

time (min)	Vol.% water (incl. 0.1 % NH_4OH)	Vol% ACN	Flow [mL/min]
0.00	97	3	2.2
0.20	97	3	2.2
1.20	0	100	2.2
1.25	0	100	3.0
1.40	0	100	3.0
Analytical column: Xbridge (Waters); C18_3.0 × 30 mm_2.5 µm; column temperature: 60°C			

Method K

[0186]

time (min)	Vol% water (incl. 0.1% FA)	Vol% ACN	Flow [mL/min]
0.00	97	3	2.2
0.20	97	3	2.2
1.20	0	100	2.2
1.25	0	100	3.0
1.40	0	100	3.0

time (min)	Vol% water (incl. 0.1% FA)	Vol% ACN	Flow [mL/min]
Analytical column: Sunfire (Waters); C18_3.0 × 30 mm_2.5 µm; column temperature: 60°C Analytical column: Sunfire (Waters); C18_3.0 × 30 mm_2.5 µm; column temperature: 60°C			

Method L

[0187]

time (min)	Vol% $scCO_2$	Vol% MeOH 20mM NH_3	Flow [mL/min]
0.00	70	30	4.0
10.00	70	30	4.0
Analytical column: Chiral Art Cellulose (YMC); SJ_4.6 × 250 mm_5µm; column temperature: 40°C; back pressure: 2175.0 psi			

Method M

[0188]

time (min)	Vol.% water (incl. 0.1 % TFA)	Vol. % ACN	Flow [mL/min]
0.00	97	3	2.2
0.2	97	3	2.2
1.0	50	50	2.2
1.25	0	100	3.0
1.9	0	100	3.0
Analytical column: Zorbax StableBond (Agilent) C18_3.0 × 30 mm_1.8µm; column temperature: 60 °C			

Method N

[0189]

time (min)	Vol.% water (incl. 0.1 % FA)	Vol% ACN (incl. 0,1% FA)	Flow [mL/min]
0.00	70	30	1.0

time (min)	Vol.% water (incl. 0.1 % FA)	Vol% ACN (incl. 0,1% FA)	Flow [mL/min]
3.35	30	70	1.0
3.75	30	70	1.0
3.90	5	95	1.0
4.75	5	95	1.0
5	70	30	1.0
6	70	30	1.0
Analytical column: Kinetex XB ; C18_4.6 × 50 mm_2.6µm; column temperature: 25°C			

Method O

[0190]

time (min)	Vol.% water (incl. 0.1 % FA)	Vol% ACN (incl. 0,1% FA)	Flow [mL/min]
0.00	60	40	0.5
6.00	40	60	0.5
6.8	40	60	0.5
7.00	10	90	0.5
8.10	10	90	0.5
8.50	60	40	0.5
10	60	40	0.5
Analytical column: Acquity UPLC BEH ; C8_2.1 × 150 mm_1.7µm; column temperature: 55°C			

Method P

[0191]

time (min)	Vol.% water (incl. 0.1 % NH_4OH)	Vol.% ACN	Flow [mL/min]
0.0	95	5	1.5
1.3	0	100	1.5
1.5	0	100	1.5
1.6	95	5	1.5

Analytical column: Xbridge (Waters); C18_3.0 × 30 mm_2.5 µm; column temperature: 60°C

Method Q

[0192]

time (min)	Vol.% water	Vol% ACN	Flow [mL/min]
0.0	80	20	0.5
0.1	80	20	0.5
1.1	0	100	0.5
2.5	80	20	0.5
3.0	80	20	0.5
Analytical column: Acquity UPLC BEH ; C18_2.1 × 100 mm_1.7µm; column temperature: 40°C			

REFERENCES CITED IN THE DESCRIPTION

Cited references

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Patent documents cited in the description

- WO2017060488A [0007] [0013] [0067] [0071] [0076]

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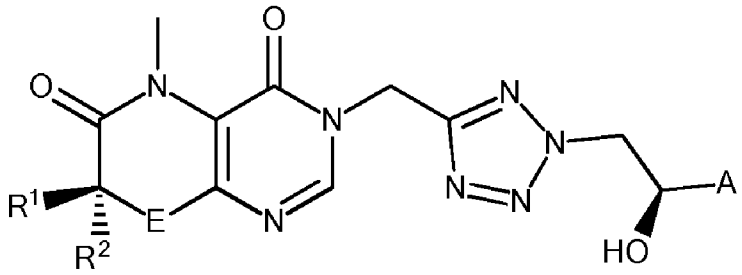
- CHEMICAL ABSTRACTS, 52605-49-9 [0160]
- CHEMICAL ABSTRACTS, 14794-31-3 [0160]

P A T E N T K R A V

1. Forbindelse ifølge formel (I)



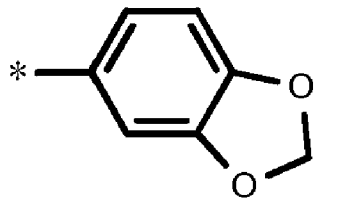
(I)

hvor

A er valgt fra gruppen bestående af phenyl, thiophenyl, benzothiophenyl eller benzofuranyl, usubstitueret eller substitueret med et, to eller tre medlemmer af gruppen R^3 bestående af halogen, CN, C_{1-4}-alkyl, O-C_{1-4}-alkyl, C_{1-4}-fluoroalkyl, O-C_{1-4}-fluoroalkyl, C_{3-4}-cycloalkyl, O-C_{3-4}-cycloalkyl, C_{3-4}-cyclofluoroalkyl og O-C_{3-4}-cyclofluoroalkyl,

eller

A er vlagt fra gruppen bestående af



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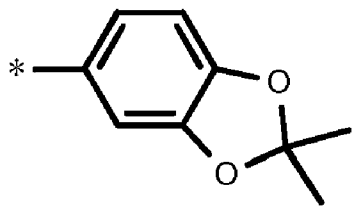

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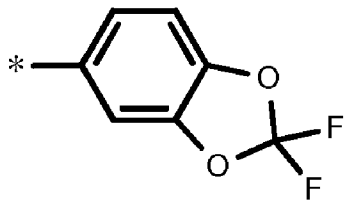


;

E er valgt fra gruppen bestående af O, S, SO, SO_2 og CH_2;

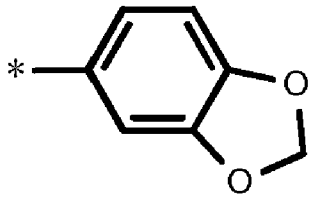
og

R^1 og R^2 er uafhængigt valgt fra gruppen bestående af H, C_{1-4}-alkyl, C_{1-4}-fluoroalkyl og halogen, eller R^1 og R^2 danner sammen med det kulstof, de er bundet til, en cyclopropyl- eller cyclobutylring.

2. Forbindelse af formel (I) ifølge krav 1, hvor hvor A er valgt fra gruppen bestående af phenyl, thiophenyl, benzothiophenyl eller benzofuranyl, usubstitueret eller substitueret med et eller to medlemmer af gruppen R^3 bestående af F, Cl, Br, CH_3, CN og OCH_3,

eller

A er



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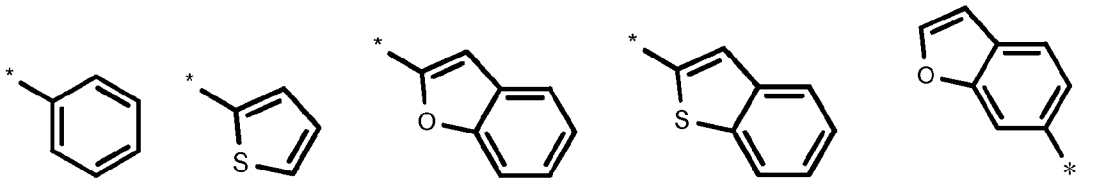
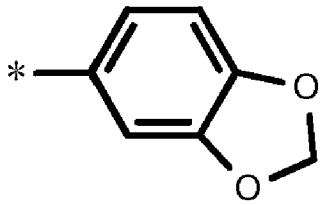
3. Forbindelse af formel (I) ifølge krav 1, hvor A er valgt fra gruppen bestående af



usubstitueret eller substitueret med et eller to medlemmer af gruppen R^3,

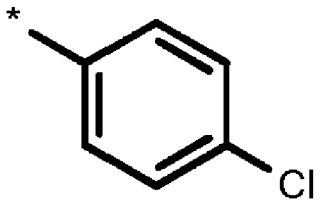
eller

A er



4. Forbindelse af formel (I) ifølge et hvilket som helst af kravene 1 til 3, hvor R^3 er valgt fra gruppen bestående af F, Cl, Br, CH_3, CN og OCH_3.

5. Forbindelse af formal (I) ifølge krav 1, hvor A er valgt fra gruppen bestående af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Cl

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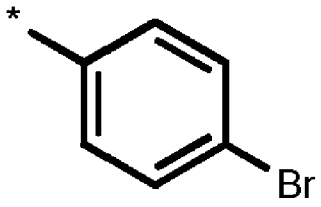
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Br

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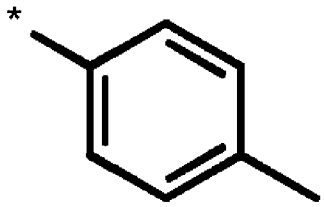
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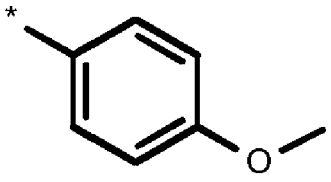
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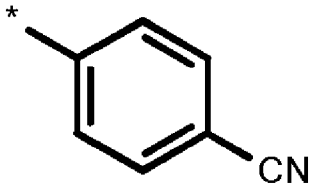
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CN

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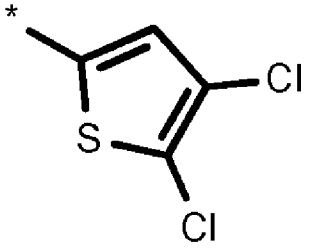
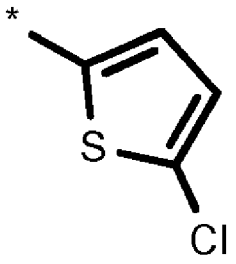

*
Cl
S
Cl

,



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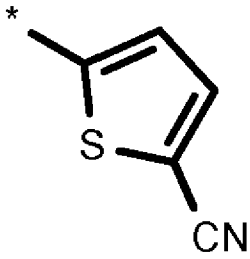

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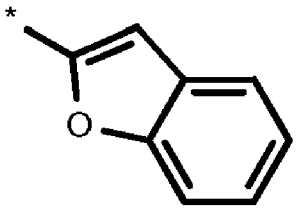

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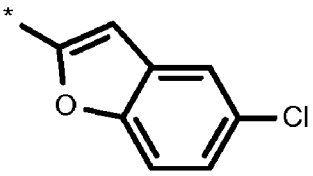

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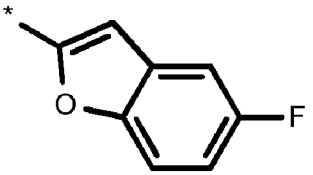

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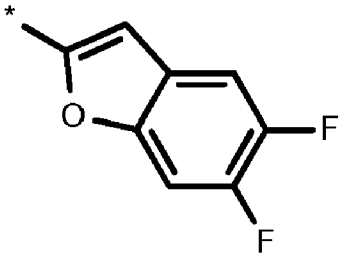

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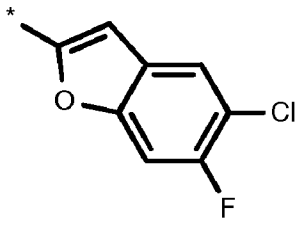

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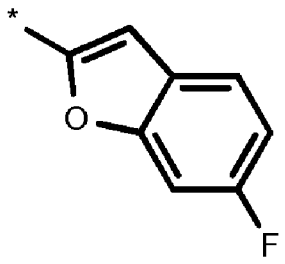

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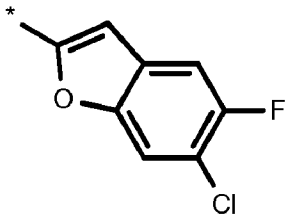

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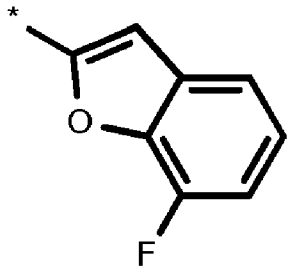

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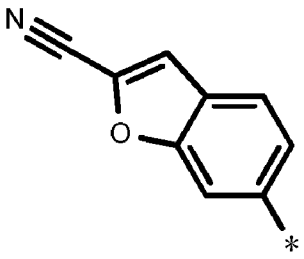

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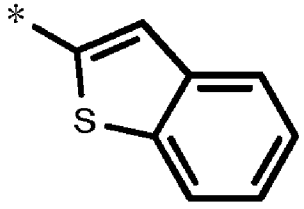

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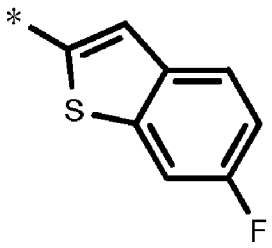

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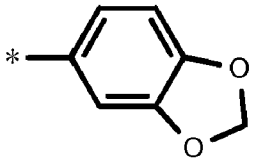
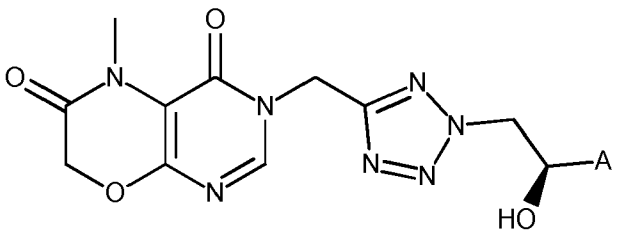


6. Forbindelse af formel (I) ifølge et hvilket som helst af kravene 1 til 5, hvor E er O.

7. Forbindelse ifølge formel (I) ifølge et hvilket som helst af kravene 1 til 6, hvor R^1 og R^2 uafhængigt er valgt fra gruppen bestående af H, CH_3 og F.

8. Forbindelse af formel (I) ifølge et hvilket som helst af kravene 1 til 6, hvor R^1 og R^2 er H.

9. Forbindelse af formel (I) ifølge er hvilket som helst af kravene 1 til 5, valgt fra gruppen bestående af



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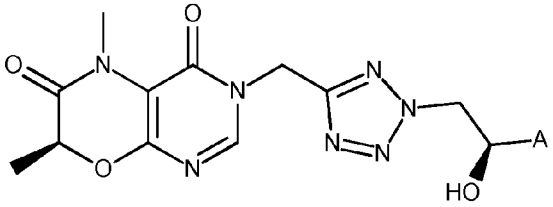

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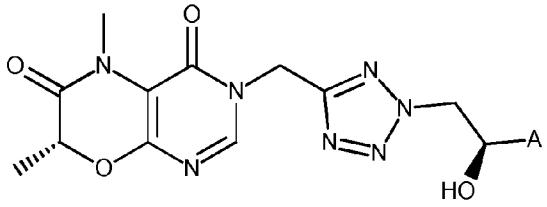

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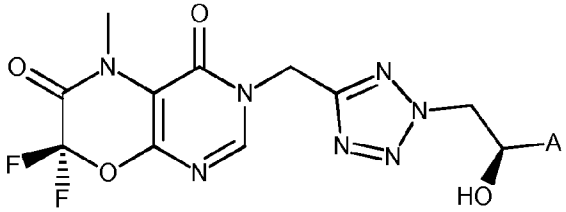

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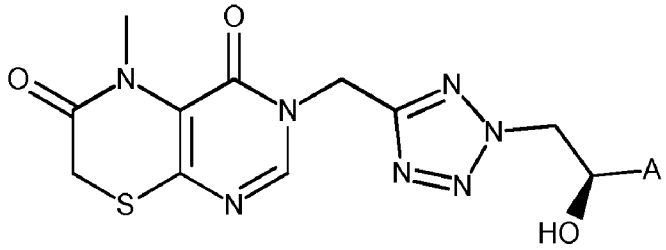

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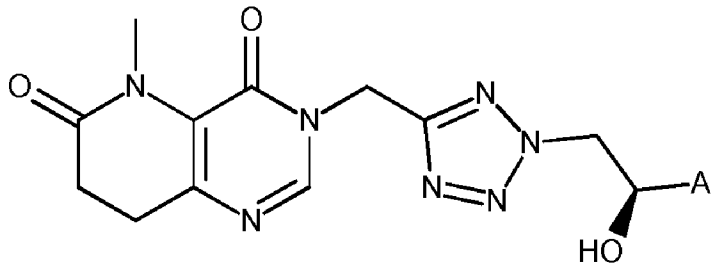
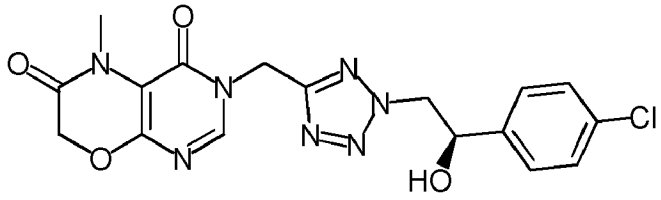


10. Forbindelse af formel (I) ifølge krav 1, valgt fra gruppen bestående af



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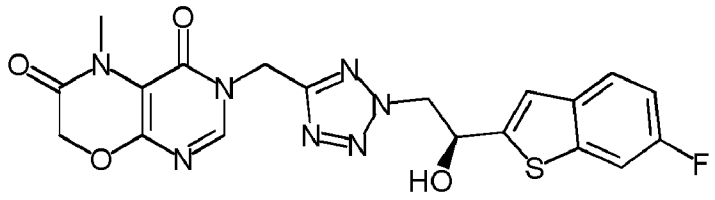

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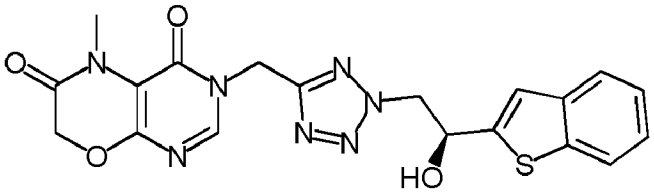

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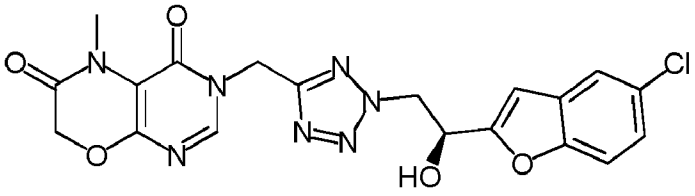

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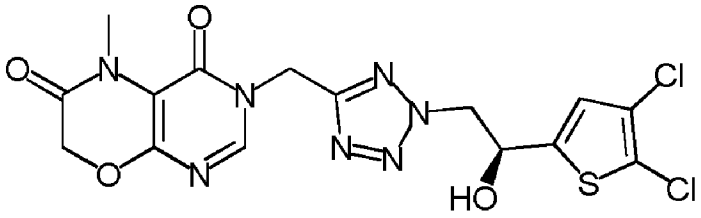

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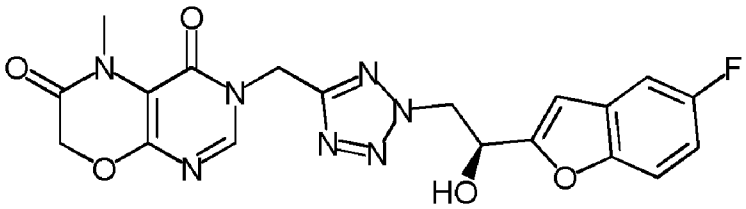

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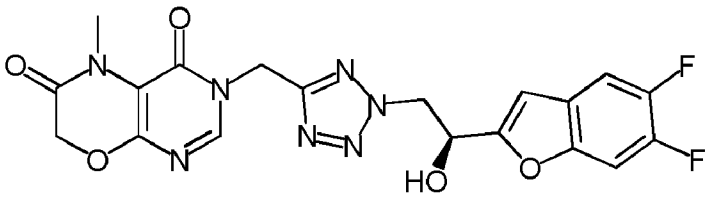

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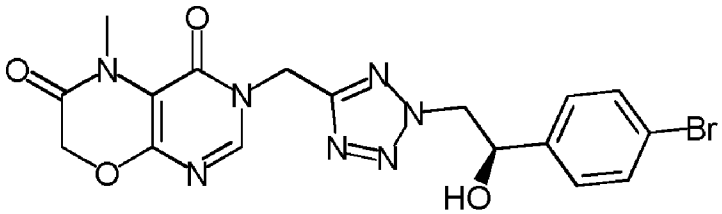

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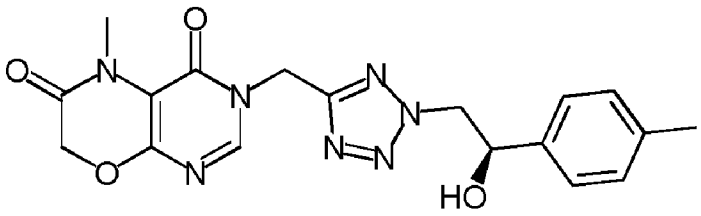

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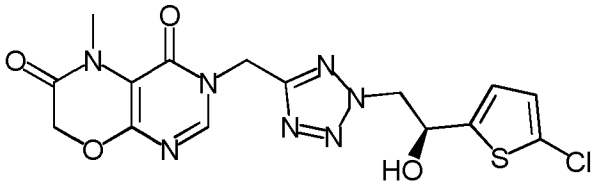

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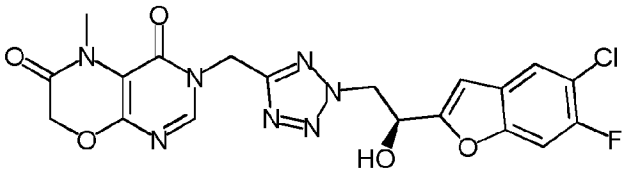

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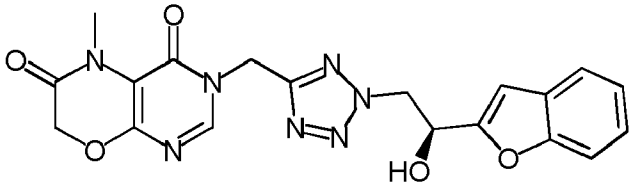

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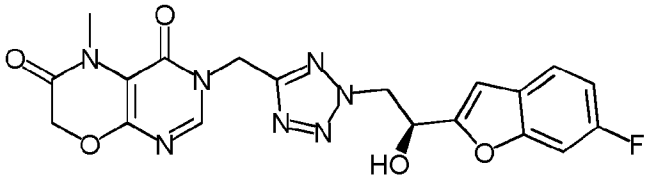

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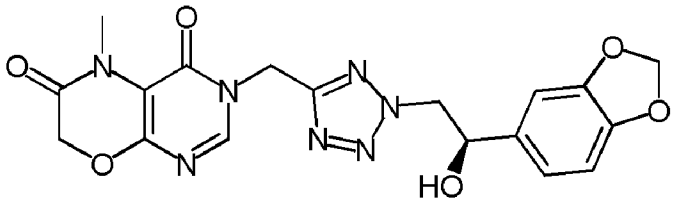

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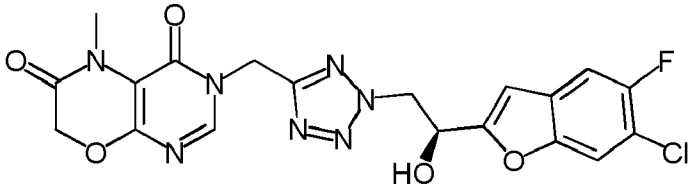

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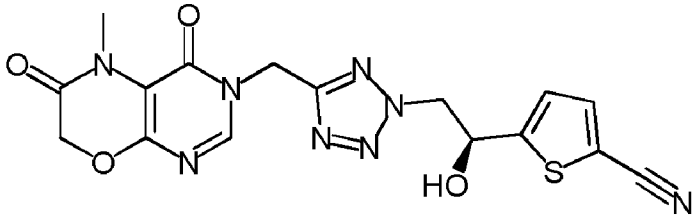

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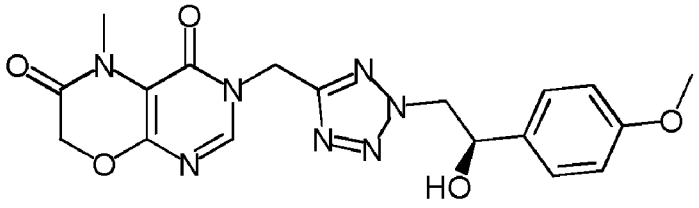

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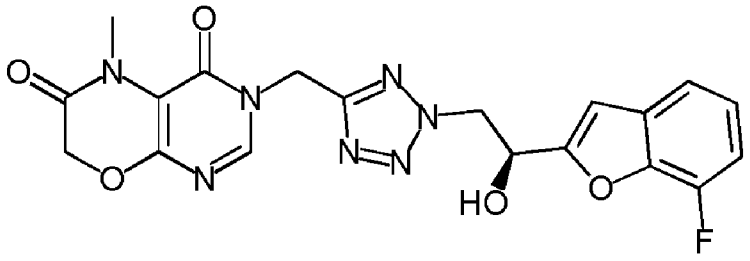

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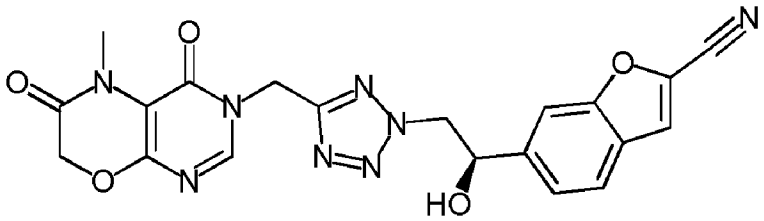

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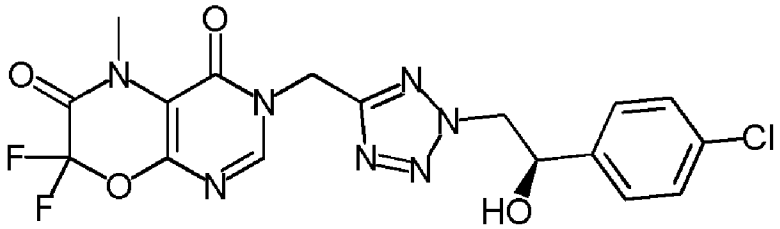

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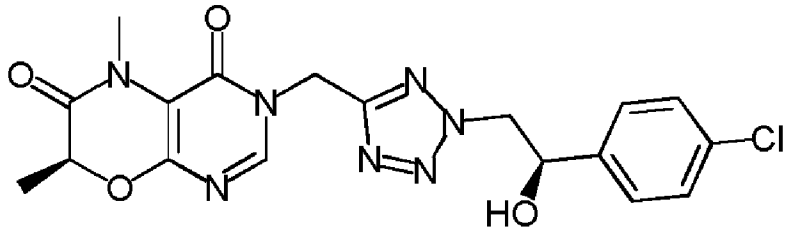

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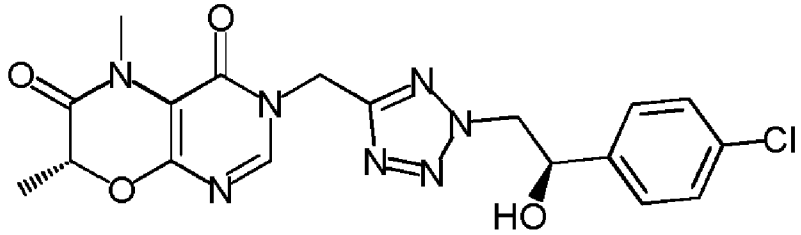

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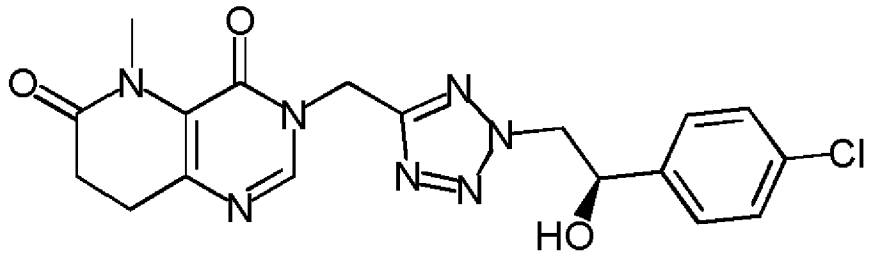

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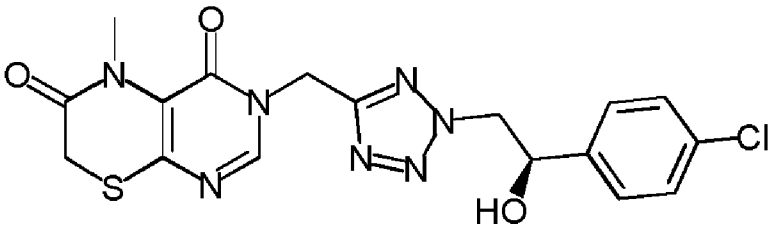
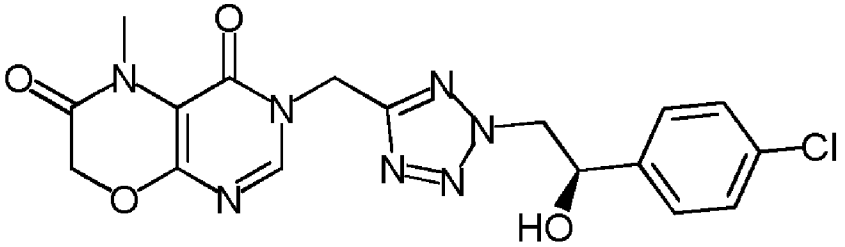
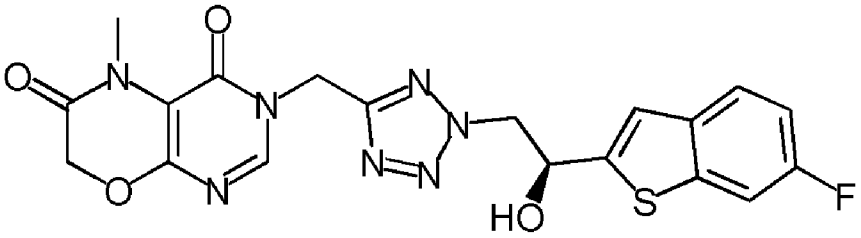


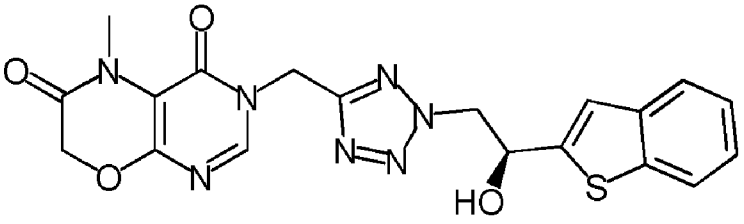
11. Forbindelse af formel (I) ifølge krav 1, som har strukturen



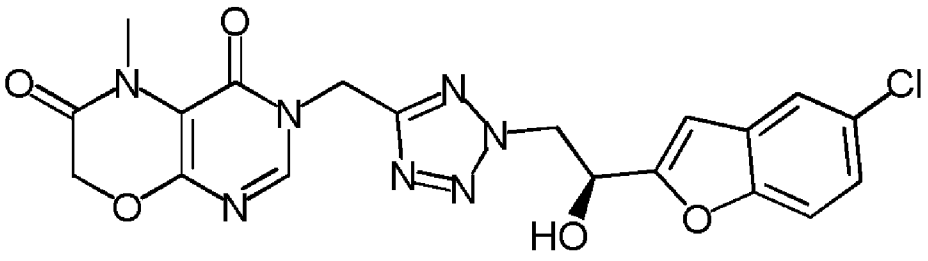
12. Forbindelse af formel (I) ifølge krav 1, som har strukturen



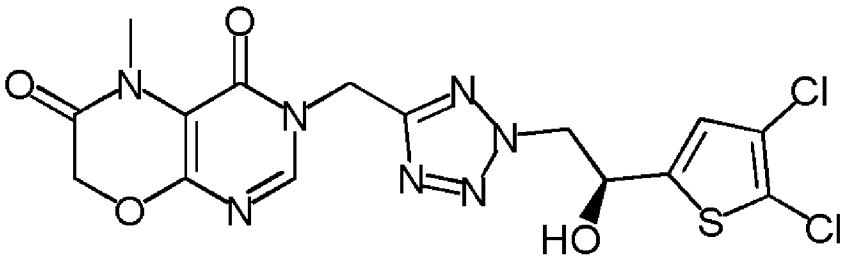
13. Forbindelse af formel (I) ifølge krav 1, som har strukturen



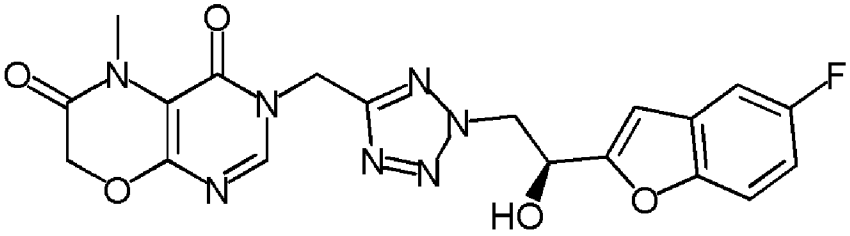
14. Forbindelse af formel (I) ifølge krav 1, som har strukturen



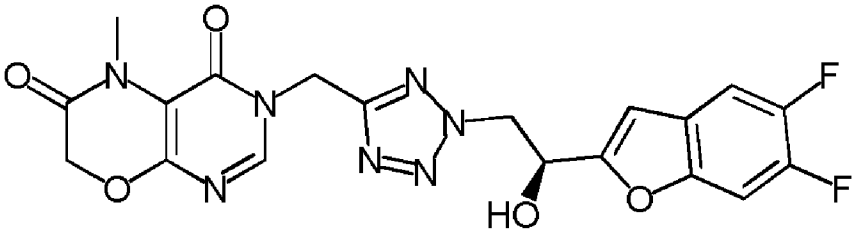
15. Forbindelse af formel (I) ifølge krav 1, som har strukturen



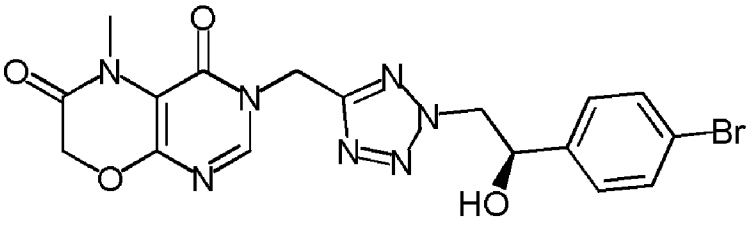
16. Forbindelse af formel (I) ifølge krav 1, som har strukturen



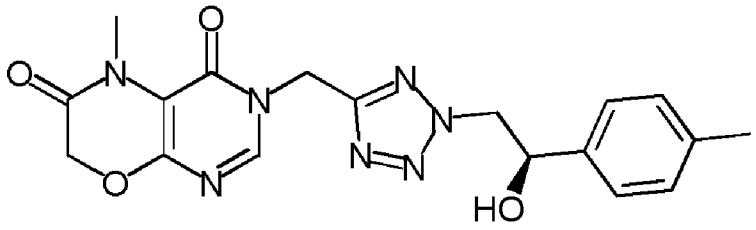
17. Forbindelse af formel (I) ifølge krav 1, som har strukturen



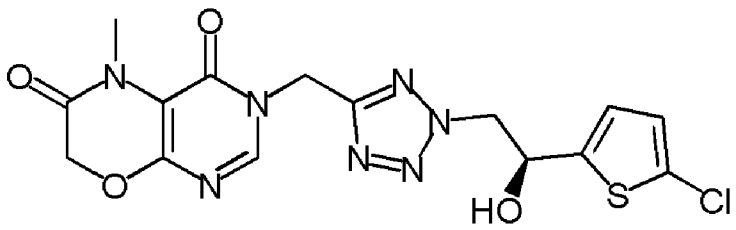
18. Forbindelse af formel (I) ifølge krav 1, som har strukturen



19. Forbindelse af formel (I) ifølge krav 1, som har strukturen



20. Forbindelse af formel (I) ifølge krav 1, som har strukturen



21. Salt, især et farmaceutisk acceptabelt salt, af en forbindelse ifølge et hvilket som helst af kravene 1 til 20.

22. Farmaceutisk sammensætning der omfatter mindst én forbindelse af formel I ifølge et hvilket som helst af kravene 1 til 20 eller et farmaceutisk acceptabelt salt heraf og en eller flere farmaceutisk acceptable hjælpestoffer.

23. Forbindelse af formel (I) ifølge ét eller flere af kravene 1 til 20, eller et farmaceutisk acceptabelt salt heraf, til anvendelse som et lægemiddel.

24. Forbindelse ifølge et hvilket som helst af kravene 1 til 20, eller et farmaceutisk acceptabelt salt heraf, til anvendelse i behandling eller forebyggelse af inflammatoriske luftvejssygdomme eller fibrotiske sygdomme eller hoste.

25. Forbindelse ifølge et hvilket som helst af kravene 1 til 20, eller et farmaceutisk acceptabelt salt heraf, til anvendelse i behandling eller forebyggelse af idiopatisk lungesygdom (IPF) eller hoste.