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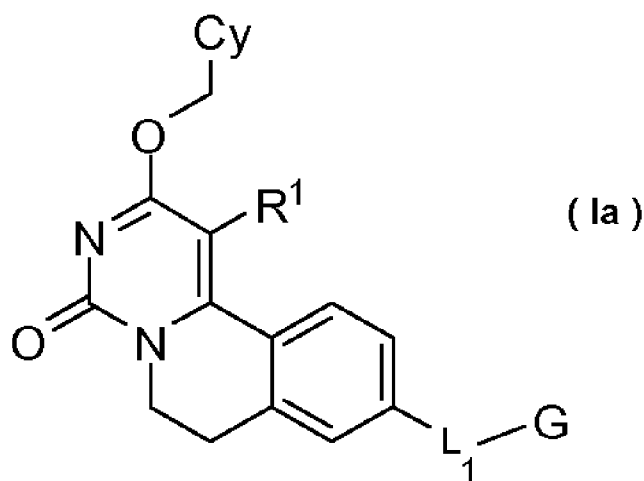
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(54) Title: NOVEL DIHYDROPYRIMIDINOISOQUINOLINONES AND PHARMACEUTICAL COMPOSITIONS THEREOF  
FOR THE TREATMENT OF INFLAMMATORY DISORDERS (GPR84 ANTAGONISTS)



(57) Abstract: A compound according to Formula (Ia), wherein Cy, L<sub>1</sub>, G, and R<sup>1</sup> are as described herein. The present invention relates to novel compounds according to Formula (I) that antagonize GPR84, a G-protein-coupled receptor that is involved in inflammatory conditions, and methods for the production of these novel compounds, pharmaceutical compositions comprising these compounds, and methods for the prevention and/or treatment of inflammatory conditions (for example inflammatory bowel diseases (IBD), rheumatoid arthritis, vasculitis), lung diseases (e.g. chronic obstructive pulmonary disease (COPD) and lung interstitial diseases (e.g. idiopathic pulmonary fibrosis (IPF))), neuroinflammatory conditions, infectious diseases, autoimmune diseases, endocrine and/or metabolic diseases, and/or diseases involving impairment of immune cell functions by administering a compound of the invention.

NOVEL DIHYDROPYRIMIDINOISOQUINOLINONES AND PHARMACEUTICAL  
COMPOSITIONS THEREOF FOR THE TREATMENT OF INFLAMMATORY DISORDERS  
(GPR84 ANTAGONISTS)

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**FIELD OF THE INVENTION**

[0001] The present invention relates to novel compounds that antagonize GPR84, a G-protein-coupled receptor that is involved in inflammatory conditions.

[0002] The present invention also provides methods for the production of these novel compounds, pharmaceutical compositions comprising these compounds, and methods for the prevention and/or treatment  
10 of inflammatory conditions (e.g. inflammatory bowel diseases (IBD), rheumatoid arthritis, vasculitis), lung diseases (e.g. chronic obstructive pulmonary disease (COPD) and lung interstitial diseases (e.g. idiopathic pulmonary fibrosis (IPF))), neuroinflammatory conditions, infectious diseases, autoimmune diseases, endocrine and/or metabolic diseases, and/or diseases involving impairment of immune cell functions by administering a compound of the invention.

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**BACKGROUND OF THE INVENTION**

[0003] GPR84 was recently isolated and characterized from human B cells (Wittenberger et al., 2001, J Mol Biol, 307, 799-813) as the result of an expressed sequence tag data mining strategy, and also using a  
20 degenerate primer reverse transcriptase-polymerase chain reaction (RT-PCR) approach aimed to identify novel chemokine receptors expressed in neutrophils (Yousefi S et al. 2001 J Leukoc Biol;69, 1045-52).

[0004] GPR84 (also known as EX33) remained an orphan GPCR until the identification of medium-chain FFAs with carbon chain lengths of 9-14 as ligands for this receptor (Wang et al. (2006) J. Biol. Chem. 281:3457-64). GPR84 was described to be activated by capric acid (C10:0), undecanoic acid (C11:0) and  
25 lauric acid (C12:0) with potencies of 5  $\mu$ M, 9  $\mu$ M and 11  $\mu$ M, respectively. Three small molecules were also described to have some GPR84 agonist activity: 3,3'-diindolylmethane (DIM) (Wang et al. (2006) J. Biol. Chem. 281:3457-64), embelin (WO 2007/027661) and 6-*n*-octylaminouracil (6-OAU) (Suzuki et al. (2013) J. Biol Chem. 288:10684-91).

[0005] GPR84 has been shown to be expressed in immune cells at least but not limited to  
30 polymorphonuclear leukocytes (PMN), neutrophils, monocytes, T cells and B cells. (Wang et al. (2006) J. Biol. Chem. 281:3457-64, Yousefi S et al. 2001 J Leukoc Biol;69, 1045-52, Venkataraman and Kuo, 2005, Immunology Letters, 101, 144-153, WO2007/027661). Higher levels of GPR84 were measured in neutrophils and eosinophils than in T-cells and B-cells. GPR84 expression was demonstrated in tissues that may play a role in the propagation of the inflammatory response such as lung, spleen, bone marrow.

[0006] For example, in a recent review, Du Bois reported the current status of therapies for lung interstitial diseases, such as idiopathic pulmonary fibrosis (IPF). There are almost 300 distinct injurious or inflammatory causes of interstitial lung disease that can result in diffuse lung scarring, and the initial stages of the IPF pathology are very likely to involve inflammation (Du Bois, 2010, Nat Rev, Drug Discovery, 9, 129), and combination therapies involving anti-inflammatory treatment could be advantageously used.

[0007] The expression of GPR84 was highly up-regulated in monocytes/macrophages upon LPS stimulation (Wang et al. (2006) J. Biol. Chem. 281:3457-64).

[0008] GPR84 knock-out (KO) mice are viable and indistinguishable from wild-type littermate controls (Venkataraman and Kuo, 2005, Immunology Letters, 101, 144-153). The proliferation of T and B cells in response to various mitogens is reported to be normal in GPR84-deficient mice (Venkataraman and Kuo, 2005, Immunology Letters, 101, 144-153). T helper 2 (Th2) differentiated T cells from GPR84 KO secreted higher levels of IL4, IL5, IL13, the 3 major Th2 cytokines, compared to wild-type littermate controls. In contrast, the production of the Th1 cytokine, INF $\gamma$ , was similar in Th1 differentiated T cells from GPR84 KO and wild-type littermate (Venkataraman and Kuo, 2005, Immunology Letters, 101, 144-153).

[0009] In addition, capric acid, undecanoic acid and lauric acid dose dependently increased the secretion of interleukin-12 p40 subunit (IL-12 p40) from RAW264.7 murine macrophage-like cells stimulated with LPS. The pro-inflammatory cytokine IL-12 plays a pivotal role in promoting cell-mediated immunity to eradicate pathogens by inducing and maintaining T helper 1 (T<sub>h</sub>1) responses and inhibiting T helper 2 (T<sub>h</sub>2) responses. Medium-chain FFAs, through their direct actions on GPR84, may affect T<sub>h</sub>1/T<sub>h</sub>2 balance.

[0010] Berry et al. identified a whole-blood 393-gene transcriptional signature for active tuberculosis (TB) (Berry et al., 2010, Nature, 466, 973-979). GPR84 was part of this whole-blood 393-gene transcriptional signature for active TB indicating a potential role for GPR84 in infectious diseases.

[0011] GPR84 expression was also described in microglia, the primary immune effector cells of the central nervous system (CNS) from myeloid-monocytic origin (Bouchard et al., 2007, Glia, 55:790-800).

As observed in peripheral immune cells, GPR84 expression in microglia was highly inducible under inflammatory conditions such as TNF $\alpha$  and IL1 treatment but also notably endotoxemia and experimental autoimmune encephalomyelitis (EAE), suggesting a role in neuro-inflammatory processes. Those results suggest that GPR84 would be up-regulated in CNS not only during endotoxemia and multiple sclerosis, but also in all neurological conditions in which TNF $\alpha$  or IL1b pro-inflammatory cytokines are produced, including brain injury, infection, Alzheimer's disease (AD), Parkinson's disease (PD).

[0012] GPR84 expression was also observed in adipocytes and shown to be enhanced by inflammatory stimuli (Nagasaki *et al.*, 2012, FEBS Letters, 586, 368-372). The results suggest that GPR84 emerges in adipocytes in response to TNF $\alpha$  from infiltrating macrophages and exacerbates the vicious cycle between

adiposity and diabetes, and therefore the inhibition of GPR84 activity might be beneficial for the treatment of endocrine and/or metabolic diseases.

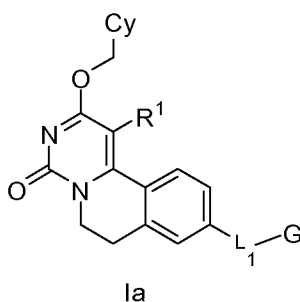
[0013] Therefore, the present invention provides novel compounds, processes for their preparation and their use in the preparation of a medicament for the treatment of inflammatory conditions (e.g. inflammatory bowel diseases (IBD), rheumatoid arthritis, vasculitis), lung diseases (e.g. chronic obstructive pulmonary disease (COPD) and lung interstitial diseases (e.g. idiopathic pulmonary fibrosis (IPF))), neuroinflammatory conditions, infectious diseases, autoimmune diseases, endocrine and/or metabolic diseases, and/or diseases involving impairment of immune cell functions.

## SUMMARY OF THE INVENTION

[0014] The present invention relates to novel dihydropyrimidinoisoquinolinone compounds that antagonize GPR84, and that are potentially useful for the treatment of inflammatory conditions (e.g. inflammatory bowel diseases (IBD), rheumatoid arthritis, vasculitis), lung diseases (e.g. chronic obstructive pulmonary disease (COPD) and lung interstitial diseases (e.g. idiopathic pulmonary fibrosis (IPF))), neuroinflammatory conditions, infectious diseases, autoimmune diseases, endocrine and/or metabolic diseases, and/or diseases involving impairment of immune cell functions.

[0015] The present invention also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds and methods for treating inflammatory conditions (e.g. inflammatory bowel diseases (IBD), rheumatoid arthritis, vasculitis), lung diseases (e.g. chronic obstructive pulmonary disease (COPD) and lung interstitial diseases (e.g. idiopathic pulmonary fibrosis (IPF))), neuroinflammatory conditions, infectious diseases, autoimmune diseases, endocrine and/or metabolic diseases, and/or diseases involving impairment of immune cell functions.

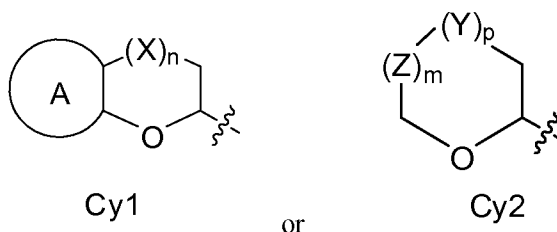
[0016] Accordingly, in a first aspect of the invention, a compound of the invention is disclosed having a Formula Ia:



wherein



Cy is



wherein

X is O or S;

5                      Y is -CH<sub>2</sub>-, or S;

Z is -CH<sub>2</sub>-;

each of the subscript n, m, or p is independently selected from 0, and 1; and A is phenyl, or 5-6-membered heteroaryl comprising one or two N-atoms; optionally substituted with one or more independently selected R<sup>5</sup> groups;

10                      any one of Cy1 and Cy2 is optionally substituted by one or more independently selected C<sub>1-4</sub> alkyl groups;

R<sup>1</sup> is H, Me, or halo;

L<sub>1</sub> is absent or is -O-, -S-, or -NR<sup>4a</sup>-;

G is

15                      R<sup>2</sup>,  
                         -W-L<sub>2</sub>-R<sup>2</sup>, or  
                         -W-L<sub>3</sub>-R<sup>3</sup>;

W is C<sub>1-4</sub> alkylene, C<sub>2-4</sub> alkenylene having one double bond, or C<sub>2-4</sub> alkynylene having one triple bond;

20                      L<sub>2</sub> is absent or is -O-;

R<sup>2</sup> is

- H,

- C<sub>1-8</sub> alkyl optionally substituted with one to three groups independently selected from
  - o OH,
  - o halo,
  - o CN,
  - o C<sub>1-6</sub> alkoxy,
  - o C<sub>3-7</sub> cycloalkyl,
  - o 4-6 membered heterocycloalkyl (comprising one to three heteroatoms independently selected from S, and O),
  - o 5-6 membered heteroaryl (comprising one to three heteroatoms independently selected from N, S, and O), and
  - o phenyl,
- C<sub>4-7</sub> cycloalkenyl comprising one double bond,
- 5-7 membered heterocycloalkenyl comprising one double bond, and one to three heteroatoms independently selected from O, and S,
- C<sub>3-7</sub> cycloalkyl (optionally substituted with one or more independently selected R<sup>6</sup> groups),
- 4-10 membered heterocycloalkyl comprising one to two heteroatoms independently selected from S, and O, (optionally substituted with one to three independently selected R<sup>6</sup> groups),
- 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O (optionally substituted with one to three independently selected R<sup>7</sup> groups), or
- C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>7</sup> groups);

L<sub>3</sub> is -NR<sup>4b</sup>-;

R<sup>3</sup> is

- C<sub>1-4</sub> alkyl substituted with C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>8</sup> groups), or 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, (optionally substituted with one or more independently selected R<sup>8</sup> groups),
- 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, (optionally substituted with one or more independently selected R<sup>8</sup> groups), or
- C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>8</sup> groups);

each R<sup>4a</sup> and R<sup>4b</sup> is independently selected from H, C<sub>1-4</sub> alkyl, and C<sub>3-7</sub> cycloalkyl;

R<sup>5</sup> is halo, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy;

R<sup>6</sup> is oxo or R<sup>7</sup>;

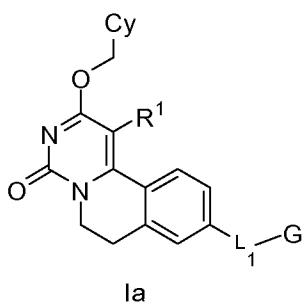
R<sup>7</sup> is

- OH,
- halo,
- 5    - -NO<sub>2</sub>,
- C<sub>1-6</sub> alkyl (optionally substituted with one to three groups independently selected from halo, and OH),
- C<sub>1-6</sub> alkoxy (optionally substituted with one to three groups independently selected from halo, and OH),
- 10    - C<sub>3-7</sub> cycloalkyl,
- -C(=O)OR<sup>9</sup>,
- -C(=O)NR<sup>10</sup>R<sup>11</sup>,
- -NHC(=O)-C<sub>1-4</sub> alkyl,
- -CN,
- 15    - phenyl,
- -O-phenyl,
- 4-7 membered heterocycloalkyl comprising one to three heteroatoms independently selected from N, O, and S, or
- 5-6 membered heteroaryl comprising one to three heteroatoms independently selected from N, O, and S; (optionally substituted with one or more independently selected C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, CN, halo, and -C(=O)OR<sup>12</sup>);
- 20

R<sup>8</sup> is C<sub>1-4</sub> alkyl, or halo; and

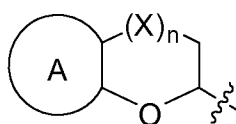
each of R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup>, is independently selected from H and C<sub>1-4</sub> alkyl.

[0017] Accordingly, in another aspect of the invention, a compound of the invention is disclosed having a Formula Ia:

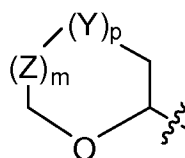


5 wherein

Cy is



or



wherein

X is is O or S;

10 Y is is -CH<sub>2</sub>-, or S;

Z is is -CH<sub>2</sub>-;

each of the subscript n, m, or p is independently selected from 0, and 1 and

A is phenyl, or 5-6-membered heteroaryl comprising one or two N-atoms; optionally substituted with one or more independently selected R<sup>5</sup> groups;

15 R<sup>1</sup> is H, Me, or halo;

L<sub>1</sub> is absent or is -O-, -S-, or -NR<sup>4a</sup>-;

G is

R<sup>2</sup>,

-W-L<sub>2</sub>-R<sup>2</sup>, or

-W-L<sub>3</sub>-R<sup>3</sup>;

W is C<sub>1-4</sub> alkylene, C<sub>2-4</sub> alkenylene having one double bond, or C<sub>2-4</sub> alkynylene having one triple bond;

L<sub>2</sub> is absent or is -O-;

5 R<sup>2</sup> is

- H,
- C<sub>1-8</sub> alkyl optionally substituted with one to three groups independently selected from
  - o OH,
  - o halo,
  - 10 o CN,
  - o C<sub>1-6</sub> alkoxy,
  - o C<sub>3-7</sub> cycloalkyl,
  - o 4-6 membered heterocycloalkyl (comprising one to three heteroatoms independently selected from S, and O),
  - 15 o 5-6 membered heteroaryl (comprising one to three heteroatoms independently selected from N, S, and O), and
  - o phenyl,
- C<sub>4-7</sub> cycloalkenyl comprising one double bond,
- 5-7 membered heterocycloalkenyl comprising one double bond, and one to three heteroatoms independently selected from O, and S,
- 20 - C<sub>3-7</sub> cycloalkyl (optionally substituted with one or more independently selected R<sup>6</sup> groups),
- 4-10 membered heterocycloalkyl comprising one to two heteroatoms independently selected from S, and O, (optionally substituted with one to three independently selected R<sup>6</sup> groups),
- 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O (optionally substituted with one to three independently selected R<sup>7</sup> groups), or
- 25 - C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>7</sup> groups);

L<sub>3</sub> is -NR<sup>4b</sup>-;

R<sup>3</sup> is

- C<sub>1-4</sub> alkyl substituted with C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>8</sup> groups), or 5-10 membered heteroaryl comprising one to three heteroatoms

independently selected from N, S, and O, (optionally substituted with one or more independently selected R<sup>8</sup> groups),

- 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, (optionally substituted with one or more independently selected R<sup>8</sup> groups), or
- 5    - C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>8</sup> groups);

each R<sup>4a</sup> and R<sup>4b</sup> is independently selected from H, C<sub>1-4</sub> alkyl, and C<sub>3-7</sub> cycloalkyl;

R<sup>5</sup> is halo, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy;

R<sup>6</sup> is oxo or R<sup>7</sup>;

R<sup>7</sup> is

- 10    - OH,
- halo,
- -NO<sub>2</sub>,
- C<sub>1-6</sub> alkyl (optionally substituted with one to three groups independently selected from halo, and OH),
- 15    - C<sub>1-6</sub> alkoxy (optionally substituted with one to three groups independently selected from halo, and OH),
- C<sub>3-7</sub> cycloalkyl,
- -C(=O)OR<sup>9</sup>,
- -C(=O)NR<sup>10</sup>R<sup>11</sup>,
- 20    - -NHC(=O)-C<sub>1-4</sub> alkyl,
- -CN,
- phenyl,
- -O-phenyl,
- 4-7 membered heterocycloalkyl comprising one to three heteroatoms independently selected
- 25    from N, O, and S, or
- 5-6 membered heteroaryl comprising one to three heteroatoms independently selected from N, O, and S; (optionally substituted with one or more independently selected C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, CN, halo, and -C(=O)OR<sup>12</sup>);

R<sup>8</sup> is C<sub>1-4</sub> alkyl, or halo; and

- 30    each of R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup>, is independently selected from H and C<sub>1-4</sub> alkyl.

[0018] In a further aspect, the present invention provides pharmaceutical compositions comprising a compound of the invention, and a pharmaceutical carrier, excipient or diluent. Moreover, a compound of the present invention useful in the pharmaceutical compositions and treatment methods disclosed herein, is pharmaceutically acceptable as prepared and used. In this aspect of the invention, the pharmaceutical composition may additionally comprise further active ingredients suitable for use in combination with a compound of the invention.

[0019] In another aspect of the invention, this invention provides novel compounds of the invention for use in therapy.

[0020] In a further aspect of the invention, this invention provides a method of treating a mammal susceptible to or afflicted with a condition from among those listed herein, and particularly, such condition as may be associated with aberrant activity of GPR84 and/or aberrant GPR84 expression and/or aberrant GPR84 distribution, for example inflammatory conditions (e.g. inflammatory bowel diseases (IBD), rheumatoid arthritis, vasculitis), lung diseases (e.g. chronic obstructive pulmonary disease (COPD) and lung interstitial diseases (e.g. idiopathic pulmonary fibrosis (IPF))), neuroinflammatory conditions, infectious diseases, autoimmune diseases, endocrine and/or metabolic diseases, and/or diseases involving impairment of immune cell functions, which method comprises administering a therapeutically effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described.

[0021] In a further aspect, the present invention provides a compound of the invention for use in the treatment or prevention of a condition selected from those listed herein, particularly such conditions as may be associated with aberrant activity of GPR84 and/or aberrant GPR84 expression and/or aberrant GPR84 distribution expression such as inflammatory conditions (e.g. inflammatory bowel diseases (IBD), rheumatoid arthritis, vasculitis), lung diseases (e.g. chronic obstructive pulmonary disease (COPD) and lung interstitial diseases (e.g. idiopathic pulmonary fibrosis (IPF))), neuroinflammatory conditions, infectious diseases, autoimmune diseases, endocrine and/or metabolic diseases, and/or diseases involving impairment of immune cell functions.

[0022] In additional aspects, this invention provides methods for synthesizing a compound of the invention, with representative synthetic protocols and pathways disclosed herein.

[0023] Accordingly, it is a principal object of this invention to provide a compound of the invention, which can modify the activity of GPR84 and thus prevent or treat any conditions that may be causally related thereto.

[0024] It is further an object of this invention to provide a compound of the invention that can treat or alleviate conditions or diseases or symptoms of same, such as inflammatory conditions (e.g. inflammatory bowel diseases (IBD), rheumatoid arthritis, vasculitis), lung diseases (e.g. chronic obstructive pulmonary disease (COPD) and lung interstitial diseases (e.g. idiopathic pulmonary fibrosis (IPF))), neuroinflammatory

conditions, infectious diseases, autoimmune diseases, endocrine and/or metabolic diseases, and/or diseases involving impairment of immune cell functions, that may be causally related to the activity and/or expression and/or distribution of GPR84.

[0025] A still further object of this invention is to provide pharmaceutical compositions that may be used in the treatment or prevention of a variety of disease states, including the diseases associated with aberrant activity of GPR84 and/or aberrant GPR84 expression and/or aberrant GPR84 distribution such as inflammatory conditions (e.g. inflammatory bowel diseases (IBD), rheumatoid arthritis, vasculitis), lung diseases (e.g. chronic obstructive pulmonary disease (COPD) and lung interstitial diseases (e.g. idiopathic pulmonary fibrosis (IPF))), neuroinflammatory conditions, infectious diseases, autoimmune diseases, endocrine and/or metabolic diseases, and/or diseases involving impairment of immune cell functions.

[0026] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

## **DETAILED DESCRIPTION OF THE INVENTION**

### **Definitions**

[0027] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

[0028] When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term 'substituted' is to be defined as set out below. It should be further understood that the terms 'groups' and 'radicals' can be considered interchangeable when used herein.

[0029] The articles 'a' and 'an' may be used herein to refer to one or to more than one (i.e. at least one) of the grammatical objects of the article. By way of example 'an analogue' means one analogue or more than one analogue.

[0030] 'Alkyl' means straight or branched aliphatic hydrocarbon having the specified number of carbon atoms. Particular alkyl groups have 1 to 6 carbon atoms or 1 to 4 carbon atoms. Branched means that one or more alkyl groups such as methyl, ethyl or propyl is attached to a linear alkyl chain. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, sec-butyl, n-pentyl, n-hexyl, and 1,2-dimethylbutyl. Particular alkyl groups have between 1 and 4 carbon atoms.



**[0031]** 'Alkylene' refers to divalent alkane radical groups having the number of carbon atoms specified, in particular 1 to 6 carbon atoms and more particularly 1 to 4 carbon atoms which can be straight-chained or branched. This term is exemplified by groups such as methylene ( $-\text{CH}_2-$ ), ethylene ( $-\text{CH}_2\text{CH}_2-$ ), the propylene isomers (e.g.,  $-\text{CH}_2\text{CH}_2\text{CH}_2-$  and  $-\text{CH}(\text{CH}_3)\text{CH}_2-$ ) and the like.

5 **[0032]** 'Alkenylene' refers to divalent alkene radical groups having the number of carbon atoms and the number of double bonds specified, in particular 2 to 6 carbon atoms and more particularly 2 to 4 carbon atoms which can be straight-chained or branched. This term is exemplified by groups such as  $-\text{CH}=\text{CH}-$ ,  $-\text{CH}_2\text{CH}=\text{CH}-$ ,  $-\text{C}(\text{CH}_3)=\text{CH}-$ ,  $-\text{C}(\text{CH}_3)=\text{CHCH}_2-$ ,  $-\text{C}(\text{CH}_3)=\text{C}(\text{CH}_3)-$ , and  $-\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}-$ .

10 **[0033]** 'Alkynylene' refers to divalent alkyne radical groups having the number of carbon atoms and the number of triple bonds specified, in particular 2 to 6 carbon atoms and more particularly 2 to 4 carbon atoms which can be straight-chained or branched. This term is exemplified by groups such as  $-\text{C}\equiv\text{C}-$ ,  $-\text{CH}_2\text{C}\equiv\text{C}-$ , and  $-\text{C}(\text{CH}_3)\text{H}-\text{C}\equiv\text{CH}-$ .

**[0034]** 'Alkoxy' refers to the group O-alkyl, where the alkyl group has the number of carbon atoms specified. In particular the term refers to the group  $-\text{O}-\text{C}_1\text{C}_6$  alkyl. Particular alkoxy groups are methoxy, 15 ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy. Particular alkoxy groups are lower alkoxy, i.e. with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

**[0035]** 'Amino' refers to the radical  $-\text{NH}_2$ .

20 **[0036]** 'Aryl' refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. In particular aryl refers to an aromatic ring structure, mono-cyclic or poly-cyclic that includes the number of ring members specified. Particular aryl groups have from 6 to 10 ring members. Where the aryl group is a monocyclic ring system it preferentially contains 6 carbon atoms. Particularly aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl.

25 **[0037]** 'Carboxy' refers to the radical  $-\text{C}(\text{O})\text{OH}$ .

**[0038]** 'Cycloalkyl' refers to cyclic non-aromatic hydrocarbyl groups having the number of carbon atoms specified. Particular cycloalkyl groups have from 3 to 7 carbon atoms. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

30 **[0039]** 'Cyano' refers to the radical  $-\text{CN}$ .

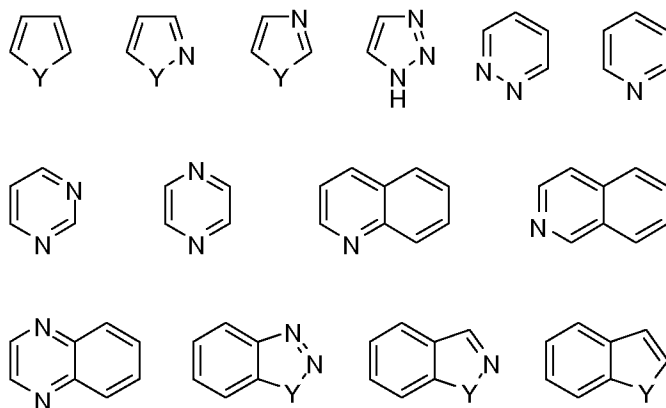
**[0040]** 'Halo' or 'halogen' refers to fluoro (F), chloro (Cl), bromo (Br) and iodo (I). Particular halo groups are either fluoro or chloro.

**[0041]** 'Hetero' when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, or sulfur

heteroatom. Hetero may be applied to any of the hydrocarbonyl groups described above such as alkyl, e.g. heteroalkyl, cycloalkyl, e.g. heterocycloalkyl, aryl, e.g. heteroaryl, and the like having from 1 to 5, and particularly from 1 to 3 heteroatoms.

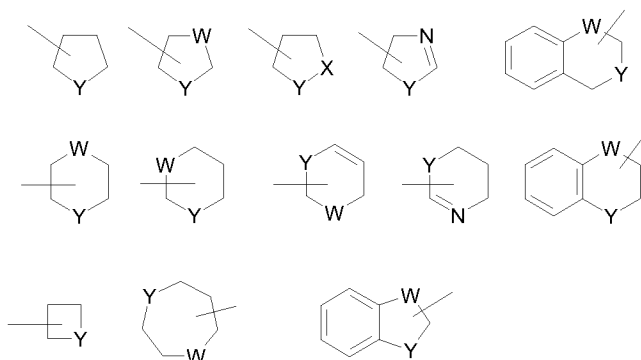
[0042] 'Heteroaryl' means an aromatic ring structure, mono-cyclic or polycyclic, that includes one or more heteroatoms and the number of ring members specified. Particular heteraryl groups have 5 to 10 ring members, or 5 to 6 ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings or, by way of a further example, two fused five membered rings. Each ring may contain up to four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five. Examples of five membered monocyclic heteroaryl groups include but are not limited to pyrrole, furan, thiophene, imidazole, furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, pyrazole, triazole and tetrazole groups. Examples of six membered monocyclic heteroaryl groups include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine. Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five membered ring include but are not limited to imidazothiazole and imidazoimidazole. Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzofuran, benzthiophene, benzimidazole, benzoxazole, isobenzoxazole, benzisoxazole, benzthiazole, benzisothiazole, isobenzofuran, indole, isoindole, isoindolone, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, pyrazolopyrimidine, triazolopyrimidine, benzodioxole and pyrazolopyridine groups. Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiochroman, chromene, isochromene, chroman, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups. Particular heteroaryl groups are those derived from thiophene, pyrrole, benzothiophene, benzofuran, indole, pyridine, quinoline, imidazole, oxazole and pyrazine.

[0043] Examples of representative heteroaryls include the following:



wherein each Y is selected from  $>C=O$ , NH, O and S.

**[0044]** As used herein, the term ‘heterocycloalkyl’ refers to a stable heterocyclic non-aromatic ring and/or rings containing one or more heteroatoms independently selected from N, O and S, fused thereto wherein the group contains the number of ring members specified. Particular heterocycloalkyl groups have 4-10 ring members or 5 to 7 ring members, or 5 to 6 ring members. The heterocycloalkyl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings or, by way of a further example, two fused five membered rings. Each ring may contain up to four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heterocycloalkyl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heterocycloalkyl ring contains at least one ring nitrogen atom. A fused heterocyclic ring system may include carbocyclic rings and need only include one heterocyclic ring. Examples of heterocyclic rings include, but are not limited to, morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydro pyranyl), imidazoline, imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. Further examples include thiomorpholine and its S-oxide and S,S-dioxide (particularly thiomorpholine). Still further examples include azetidine, piperidone, piperazone, and N-alkyl piperidines such as N-methyl piperidine. Particular examples of heterocycloalkyl groups are shown in the following illustrative examples:



wherein each W is selected from CH<sub>2</sub>, NH, O and S; and each Y is selected from NH, O, CO, SO<sub>2</sub>, and S.

**[0045]** 'Hydroxy' refers to the radical -OH.

**[0046]** 'Nitro' refers to the radical -NO<sub>2</sub>.

5 **[0047]** 'Substituted' refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s).

**[0048]** 'Thiol' refers to the group -SH.

**[0049]** 'Thioalkoxy' refers to the group -SR<sup>10</sup> where R<sup>10</sup> is an alkyl group with the number of carbon atoms specified. In particular thioalkoxy groups where R<sup>10</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl. Particular thioalkoxy groups  
 10 are thiomethoxy, thioethoxy, n-thiopropoxy, thioisopropoxy, n-thiobutoxy, tert-thiobutoxy, sec-thiobutoxy, n-thiopentoxy, n-thiohexoxy, and 1,2-dimethylthiobutoxy. Particular thioalkoxy groups are lower thioalkoxy, i.e. with between 1 and 6 carbon atoms. Further particular thioalkoxy groups have between 1 and 4 carbon atoms.

**[0050]** As used herein, the term 'substituted with one or more' refers to one to four substituents. In one  
 15 embodiment it refers to one to three substituents. In further embodiments it refers to one or two substituents. In a yet further embodiment it refers to one substituent.

**[0051]** One having ordinary skill in the art of organic synthesis will recognize that the maximum number of heteroatoms in a stable, chemically feasible heterocyclic ring, whether it is aromatic or non aromatic, is determined by the size of the ring, the degree of unsaturation and the valence of the  
 20 heteroatoms. In general, a heterocyclic ring may have one to four heteroatoms so long as the heteroaromatic ring is chemically feasible and stable.

**[0052]** 'Pharmaceutically acceptable' means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and  
 25 more particularly, in humans.

**[0053]** 'Pharmaceutically acceptable salt' refers to a salt of a compound that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular,

such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like. The term 'pharmaceutically acceptable cation' refers to an acceptable cationic counter-ion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium cations, and the like.

**[0054]** 'Pharmaceutically acceptable vehicle' refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.

**[0055]** 'Prodrugs' refers to compounds, including derivatives of the compounds of the invention, which have cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

**[0056]** 'Solvate' refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association includes hydrogen bonding. Conventional solvents include water, ethanol, acetic acid and the like. The compounds of the invention may be prepared e.g. in crystalline form and may be solvated or hydrated. Suitable solvates include pharmaceutically acceptable solvates, such as hydrates, and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. 'Solvate' encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanولات and methanولات.

[0057] 'Subject' includes humans. The terms 'human', 'patient' and 'subject' are used interchangeably herein.

[0058] 'Effective amount' means the amount of a compound of the invention that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The "effective amount" can vary depending on the compound, the disease and its severity, and the age, weight, etc., of the subject to be treated.

[0059] 'Preventing' or 'prevention' refers to a reduction in risk of acquiring or developing a disease or disorder (i.e., causing at least one of the clinical symptoms of the disease not to develop in a subject that may be exposed to a disease-causing agent, or predisposed to the disease in advance of disease onset.

[0060] The term 'prophylaxis' is related to 'prevention', and refers to a measure or procedure the purpose of which is to prevent, rather than to treat or cure a disease. Non-limiting examples of prophylactic measures may include the administration of vaccines; the administration of low molecular weight heparin to hospital patients at risk for thrombosis due, for example, to immobilization; and the administration of an anti-malarial agent such as chloroquine, in advance of a visit to a geographical region where malaria is endemic or the risk of contracting malaria is high.

[0061] 'Treating' or 'treatment' of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (i.e., arresting the disease or reducing the manifestation, extent or severity of at least one of the clinical symptoms thereof). In another embodiment 'treating' or 'treatment' refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, 'treating' or 'treatment' refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In a further embodiment, "treating" or "treatment" relates to slowing the progression of the disease.

[0062] As used herein the term 'inflammatory condition(s)' refers to the group of conditions including, rheumatoid arthritis, osteoarthritis, juvenile idiopathic arthritis, vasculitis, psoriasis, gout, allergic airway disease (e.g. asthma, rhinitis), inflammatory bowel diseases (e.g. Crohn's disease, ulcerative colitis), and endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure). Particularly the term refers to rheumatoid arthritis, allergic airway disease (e.g. asthma) and inflammatory bowel diseases.

[0063] As used herein, the term 'infectious diseases' refers to bacterial infectious diseases and includes but is not limited to conditions such as sepsis, septicemia, endotoxemia, systemic inflammatory response syndrome (SIRS), gastritis, enteritis, enterocolitis, tuberculosis, and other infections involving, for example, Yersinia, Salmonella, Chlamydia, Shigella, or enterobacteria species.

[0064] As used herein the term 'autoimmune disease(s)' refers to the group of diseases including obstructive airways disease (including conditions such as COPD (chronic obstructive pulmonary disease)),

psoriasis, asthma (e.g. intrinsic asthma, extrinsic asthma, dust asthma, infantile asthma) particularly chronic or inveterate asthma (for example late asthma and airway hyperreponsiveness), bronchitis, including bronchial asthma, systemic lupus erythematosus (SLE), multiple sclerosis, type I diabetes mellitus and complications associated therewith, atopic eczema (atopic dermatitis), contact dermatitis and further  
5 eczematous dermatitis, vasculitis, inflammatory bowel disease (e.g. Crohn's disease and ulcerative colitis), atherosclerosis and amyotrophic lateral sclerosis. Particularly the term refers to COPD, asthma, psoriasis, systemic lupus erythematosus, type I diabetes mellitus, vasculitis and inflammatory bowel disease.

**[0065]** As used herein the term 'endocrine and/or metabolic disease(s)' refers to the group of conditions involving the body's over- or under-production of certain hormones, while metabolic disorders affect the  
10 body's ability to process certain nutrients and vitamins. Endocrine disorders include hypothyroidism, congenital adrenal hyperplasia, diseases of the parathyroid gland, diabetes mellitus, diseases of the adrenal glands (including Cushing's syndrome and Addison's disease), and ovarian dysfunction (including polycystic ovary syndrome), among others. Some examples of metabolic disorders include cystic fibrosis, phenylketonuria (PKU), diabetes, hyperlipidemia, gout, and rickets.

**[0066]** As used herein, the term 'diseases involving impairment of immune cell functions' includes conditions with symptoms such as recurrent and drawn out viral and bacterial infections, and slow recovery. Other invisible symptoms may be the inability to kill off parasites, yeasts and bacterial pathogens in the  
15 intestines or throughout the body.

**[0067]** As used herein the term 'neuroinflammatory conditions' refers to diseases or disorders  
20 characterized by abrupt neurologic deficits associated with inflammation, demyelination, and axonal damage, and includes but is not limited to conditions such as Guillain-Barré syndrome (GBS), multiple sclerosis, axonal degeneration, and autoimmune encephalomyelitis.

**[0068]** 'Compound(s) of the invention', and equivalent expressions, are meant to embrace compounds of the Formula(e) as herein described, which expression includes the pharmaceutically acceptable salts, and  
25 the solvates, e.g., hydrates, and the solvates of the pharmaceutically acceptable salts where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

**[0069]** When ranges are referred to herein, for example but without limitation, C<sub>1-6</sub> alkyl, the citation of a range should be considered a representation of each member of said range.

**[0070]** Other derivatives of the compounds of this invention have activity in both their acid and acid  
30 derivative forms, but in the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well know to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by

reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the compounds of this invention are particularly useful prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters.

5 Particular such prodrugs are the C<sub>1</sub> to C<sub>8</sub> alkyl, , and substituted or unsubstituted C<sub>6-10</sub> aryl, esters of the compounds of the invention.

[0071] As used herein, the term 'isotopic variant' refers to a compound that contains unnatural proportions of isotopes at one or more of the atoms that constitute such compound. For example, an 'isotopic variant' of a compound can contain one or more non-radioactive isotopes, such as for example, 10 deuterium (<sup>2</sup>H or D), carbon-13 (<sup>13</sup>C), nitrogen-15 (<sup>15</sup>N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be <sup>2</sup>H/D, any carbon may be <sup>13</sup>C, or any nitrogen may be <sup>15</sup>N, and that the presence and placement of such atoms may be determined within the skill of the art. Likewise, the invention may include the preparation of isotopic variants with radioisotopes, in the instance for example, 15 where the resulting compounds may be used for drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. <sup>3</sup>H, and carbon-14, i.e. <sup>14</sup>C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Further, compounds may be prepared that are substituted with positron emitting isotopes, such as <sup>11</sup>C, <sup>18</sup>F, <sup>15</sup>O and <sup>13</sup>N, and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

20 [0072] All isotopic variants of the compounds provided herein, radioactive or not, are intended to be encompassed within the scope of the invention.

[0073] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed 'isomers'. Isomers that differ in the arrangement of their atoms in space are termed 'stereoisomers'.

25 [0074] Stereoisomers that are not mirror images of one another are termed 'diastereomers' and those that are non-superimposable mirror images of each other are termed 'enantiomers'. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the 30 plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a 'racemic mixture'.

[0075] 'Tautomers' refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be



in equilibrium through the movement of  $\pi$  electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro- forms of phenylnitromethane, that are likewise formed by treatment with acid or base.

5 [0076] Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[0077] The compounds of the invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)- stereoisomers or as mixtures thereof.

10 [0078] Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

[0079] It will be appreciated that compounds of the invention may be metabolized to yield biologically active metabolites.

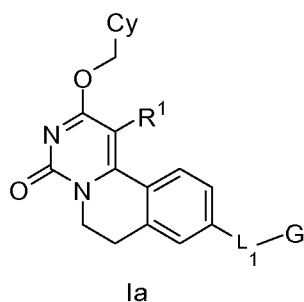
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### THE COMPOUNDS

[0080] The present invention relates to novel compounds that antagonize GPR84 and that may be useful for the treatment of inflammatory conditions (e.g. inflammatory bowel diseases (IBD), rheumatoid arthritis, 20 vasculitis), lung diseases (e.g. chronic obstructive pulmonary disease (COPD) and lung interstitial diseases (e.g. idiopathic pulmonary fibrosis (IPF))), neuroinflammatory conditions, infectious diseases, autoimmune diseases, endocrine and/or metabolic diseases, and/or diseases involving impairment of immune cell functions.

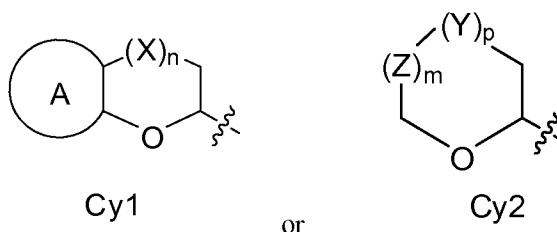
25 [0081] The present invention also provides methods for the production of the compounds of the invention, pharmaceutical compositions comprising the compounds of the invention and methods for treating inflammatory conditions (e.g. inflammatory bowel diseases (IBD), rheumatoid arthritis, vasculitis), lung diseases (e.g. chronic obstructive pulmonary disease (COPD) and lung interstitial diseases (e.g. idiopathic pulmonary fibrosis (IPF))), neuroinflammatory conditions, infectious diseases, autoimmune diseases, endocrine and/or metabolic diseases, and/or diseases involving impairment of immune cell 30 functions, by administering a compound of the invention. A compound of the invention is an inhibitor of GPR84.

[0082] Accordingly, in a first aspect of the invention, a compound of the invention is disclosed having a Formula Ia:



wherein

5 Cy is



wherein

X is O or S;

Y is -CH<sub>2</sub>-, or S;

10 Z is -CH<sub>2</sub>-;

each of the subscripts n, m, or p is independently selected from 0, and 1; and A is phenyl, or 5-6-membered heteroaryl comprising one or two N-atoms; optionally substituted with one or more independently selected R<sup>5</sup> groups;

15 any one of Cy1 and Cy2 is optionally substituted by one or more independently selected C<sub>1-4</sub> alkyl groups;

R<sup>1</sup> is H, Me, or halo;

L<sub>1</sub> is absent or is -O-, -S-, or -NR<sup>4a</sup>-;

G is

R<sup>2</sup>,

-W-L<sub>2</sub>-R<sup>2</sup>, or

-W-L<sub>3</sub>-R<sup>3</sup>;

W is C<sub>1-4</sub> alkylene, C<sub>2-4</sub> alkenylene having one double bond, or C<sub>2-4</sub> alkynylene having one triple bond;

5 L<sub>2</sub> is absent or is -O-;

R<sup>2</sup> is

- H,

- C<sub>1-8</sub> alkyl optionally substituted with one to three groups independently selected from

○ OH,

○ halo,

○ CN,

○ C<sub>1-6</sub> alkoxy,

○ C<sub>3-7</sub> cycloalkyl,

○ 4-6 membered heterocycloalkyl (comprising one to three heteroatoms independently selected from S, and O),

○ 5-6 membered heteroaryl (comprising one to three heteroatoms independently selected from N, S, and O), and

○ phenyl,

- C<sub>4-7</sub> cycloalkenyl comprising one double bond,

- 5-7 membered heterocycloalkenyl comprising one double bond, and one to three heteroatoms independently selected from O, and S,

- C<sub>3-7</sub> cycloalkyl (optionally substituted with one or more independently selected R<sup>6</sup> groups),

- 4-10 membered heterocycloalkyl comprising one to two heteroatoms independently selected from S, and O, (optionally substituted with one to three independently selected R<sup>6</sup> groups),

- 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O (optionally substituted with one to three independently selected R<sup>7</sup> groups), or

- C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>7</sup> groups);

L<sub>3</sub> is -NR<sup>4b</sup>-;

R<sup>3</sup> is

- C<sub>1-4</sub> alkyl substituted with C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>8</sup> groups), or 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, (optionally substituted with one or more independently selected R<sup>8</sup> groups),
- 5      - 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, (optionally substituted with one or more independently selected R<sup>8</sup> groups), or
- C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>8</sup> groups);

each R<sup>4a</sup> and R<sup>4b</sup> is independently selected from H, C<sub>1-4</sub> alkyl, and C<sub>3-7</sub> cycloalkyl;

R<sup>5</sup> is halo, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy;

10      R<sup>6</sup> is oxo or R<sup>7</sup>;

R<sup>7</sup> is

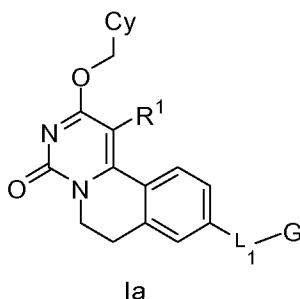
- OH,
- halo,
- -NO<sub>2</sub>,
- 15      - C<sub>1-6</sub> alkyl (optionally substituted with one to three groups independently selected from halo, and OH),
- C<sub>1-6</sub> alkoxy (optionally substituted with one to three groups independently selected from halo, and OH),
- C<sub>3-7</sub> cycloalkyl,
- 20      - -C(=O)OR<sup>9</sup>,
- -C(=O)NR<sup>10</sup>R<sup>11</sup>,
- -NHC(=O)-C<sub>1-4</sub> alkyl,
- -CN,
- phenyl,
- 25      - -O-phenyl,
- 4-7 membered heterocycloalkyl comprising one to three heteroatoms independently selected from N, O, and S, or
- 5-6 membered heteroaryl comprising one to three heteroatoms independently selected from N, O, and S; (optionally substituted with one or more independently selected C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, CN, halo, and -C(=O)OR<sup>12</sup>);
- 30

$R^8$  is  $C_{1-4}$  alkyl, or halo; and

each of  $R^9$ ,  $R^{10}$ ,  $R^{11}$  and  $R^{12}$ , is independently selected from H and  $C_{1-4}$  alkyl.

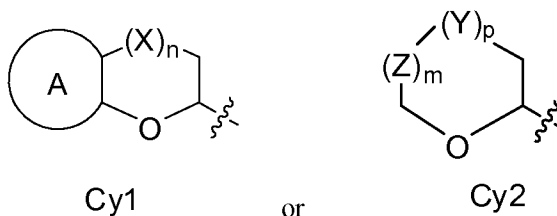
**[0083]** In one embodiment, each Cy1 or Cy2 is substituted with one or more independently selected  $C_{1-4}$  alkyl. In a particular embodiment, each Cy1 or Cy2 is substituted with one or two independently selected  $C_{1-4}$  alkyl. In a more particular embodiment, each Cy1 or Cy2 is substituted with one  $C_{1-4}$  alkyl. In a most particular embodiment, each  $C_{1-4}$  alkyl is selected from Me, Et, *i*-Pr, and *t*-Bu. In a further most particular embodiment, the  $C_{1-4}$  alkyl is *i*-Pr.

**[0084]** Accordingly, in another aspect of the invention, a compound of the invention is disclosed having a Formula Ia:



wherein

Cy is



wherein

X is O or S;

Y is  $-CH_2-$ , or S;

Z is  $-CH_2-$ ;

each of the subscripts n, m, or p is independently selected from 0, and 1 and

A is phenyl, or 5-6-membered heteroaryl comprising one or two N-atoms; optionally substituted with one or more independently selected R<sup>5</sup> groups;

R<sup>1</sup> is H, Me, or halo;

L<sub>1</sub> is absent or is -O-, -S-, or -NR<sup>4a</sup>-;

5 G is

R<sup>2</sup>,  
-W-L<sub>2</sub>-R<sup>2</sup>, or  
-W-L<sub>3</sub>-R<sup>3</sup>;

10

W is C<sub>1-4</sub> alkylene, C<sub>2-4</sub> alkenylene having one double bond, or C<sub>2-4</sub> alkynylene having one triple bond;

L<sub>2</sub> is absent or is -O-;

R<sup>2</sup> is

15

- H,
- C<sub>1-8</sub> alkyl optionally substituted with one to three groups independently selected from

20

- o OH,
- o halo,
- o CN,
- o C<sub>1-6</sub> alkoxy,
- o C<sub>3-7</sub> cycloalkyl,
- o 4-6 membered heterocycloalkyl (comprising one to three heteroatoms independently selected from S, and O),
- o 5-6 membered heteroaryl (comprising one to three heteroatoms independently selected from N, S, and O), and
- o phenyl,

25

- C<sub>4-7</sub> cycloalkenyl comprising one double bond,
- 5-7 membered heterocycloalkenyl comprising one double bond, and one to three heteroatoms independently selected from O, and S,
- C<sub>3-7</sub> cycloalkyl (optionally substituted with one or more independently selected R<sup>6</sup> groups),
- 4-10 membered heterocycloalkyl comprising one to two heteroatoms independently selected

30

from S, and O, (optionally substituted with one to three independently selected R<sup>6</sup> groups),

- 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O (optionally substituted with one to three independently selected R<sup>7</sup> groups), or
- C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>7</sup> groups);

L<sub>3</sub> is -NR<sup>4b</sup>-;

5 R<sup>3</sup> is

- C<sub>1-4</sub> alkyl substituted with C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>8</sup> groups), or 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, (optionally substituted with one or more independently selected R<sup>8</sup> groups),

- 10
- 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, (optionally substituted with one or more independently selected R<sup>8</sup> groups), or
  - C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>8</sup> groups);

Each R<sup>4a</sup> and R<sup>4b</sup> is independently selected from H, C<sub>1-4</sub> alkyl, and C<sub>3-7</sub> cycloalkyl;

R<sup>5</sup> is halo, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy;

15 R<sup>6</sup> is oxo or R<sup>7</sup>;

R<sup>7</sup> is

- OH,
- halo,
- -NO<sub>2</sub>,

- 20
- C<sub>1-6</sub> alkyl (optionally substituted with one to three groups independently selected from halo, and OH),
  - C<sub>1-6</sub> alkoxy (optionally substituted with one to three groups independently selected from halo, and OH),

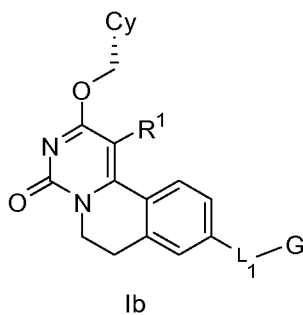
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- C<sub>3-7</sub> cycloalkyl,
  - -C(=O)OR<sup>9</sup>,
  - -C(=O)NR<sup>10</sup>R<sup>11</sup>,
  - -NHC(=O)-C<sub>1-4</sub> alkyl,
  - -CN,
  - phenyl,

- -O-phenyl,
- 4-7 membered heterocycloalkyl comprising one to three heteroatoms independently selected from N, O, and S, or
- 5-6 membered heteroaryl comprising one to three heteroatoms independently selected from N, O, and S; (optionally substituted with one or more independently selected C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, CN, halo, and -C(=O)OR<sup>12</sup>);

R<sup>8</sup> is C<sub>1-4</sub> alkyl, or halo; and

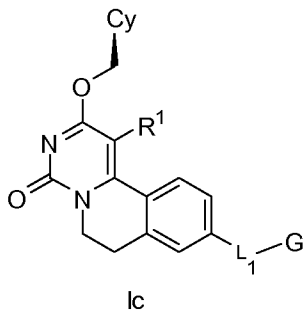
each of R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup>, is independently selected from H and C<sub>1-4</sub> alkyl.

**[0085]** In one embodiment, the compound of the invention is according to Formula Ib:



wherein Cy, R<sup>1</sup>, L<sub>1</sub> and G are as previously described.

**[0086]** In another embodiment, the compound of the invention is according to Formula Ic:



wherein Cy, R<sup>1</sup>, L<sub>1</sub> and G are as previously described.

**[0087]** In one embodiment, the compound of the invention is according to Formula Ia, Ib, or Ic, wherein Cy is Cy1, and wherein X, the subscript n, and the ring A are as described above. In a particular embodiment, the subscript n is 0, or the subscript n is 1 and X is O. In a more particular embodiment, the subscript n is 1 and X is O.

**[0088]** In another particular embodiment, the compound of the invention is according to Formula Ia, Ib, or Ic, wherein Cy is Cy1, wherein the subscript n is 0, or the subscript n is 1 and X is O, and the ring A is phenyl. In a more particular embodiment, the subscript n is 1 and X is O, and the ring A is phenyl.



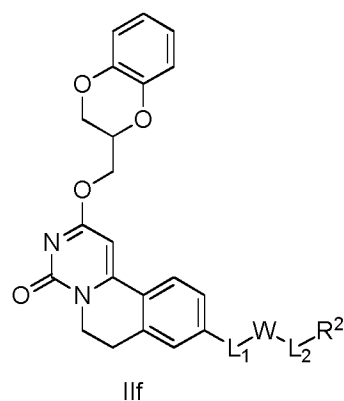
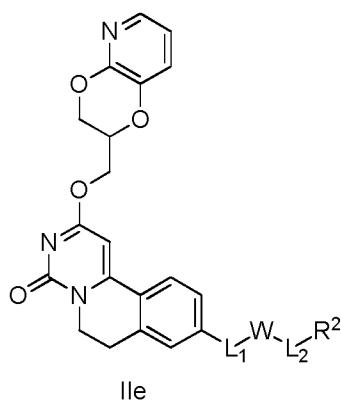
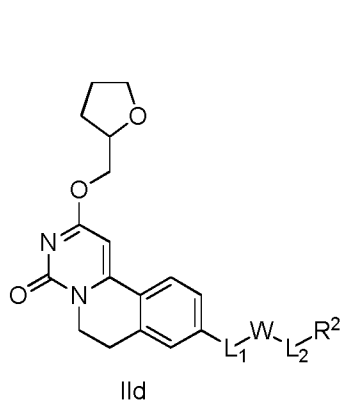
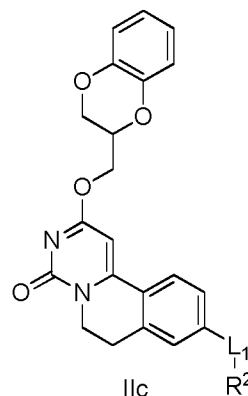
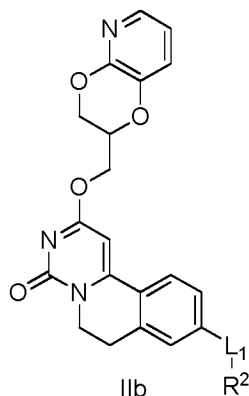
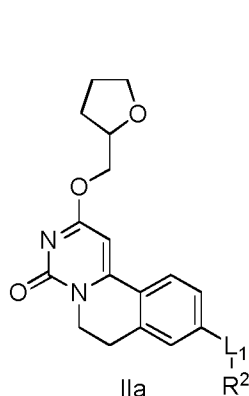
**[0089]** In yet another particular embodiment, the compound of the invention is according to Formula Ia, Ib, or Ic, wherein Cy is Cy1, wherein the subscript n is 0, or the subscript n is 1 and X is O, and the ring A is pyridinyl. In a more particular embodiment, the subscript n is 1 and X is O, and the ring A is pyridinyl.

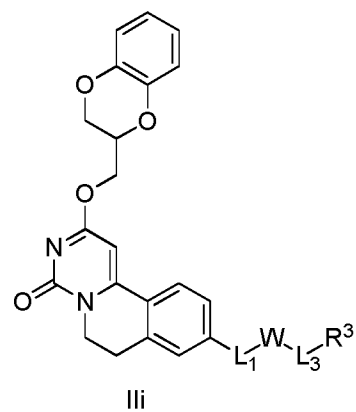
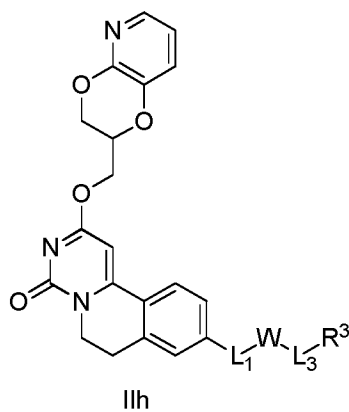
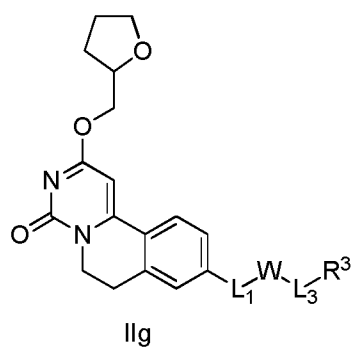
**[0090]** In one embodiment, the compound of the invention is according to Formula Ia, Ib, or Ic, wherein  
 5 Cy is Cy2, wherein Z, Y, the subscript m, and the subscript p are as described above. In a particular embodiment, the subscript m is 0, the subscript p is 1 and Y is  $-\text{CH}_2-$ . In another particular embodiment, the subscript m is 1, Z is  $-\text{CH}_2-$ , the subscript p is 1 and Y is  $-\text{CH}_2-$ . In yet another particular embodiment, the subscript m is 1, Z is  $-\text{CH}_2-$ , the subscript p is 1 and Y is S. In a further particular embodiment, the subscript m and the subscript p are both 0.

10 **[0091]** In one embodiment, the compound of the invention is according to Formula Ia, Ib, or Ic, wherein  $\text{R}^1$  is Me, F, or Cl.

**[0092]** In one embodiment, the compound of the invention is according to Formula Ia, Ib, or Ic, wherein  $\text{R}^1$  is H.

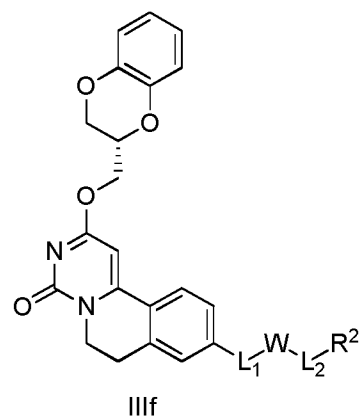
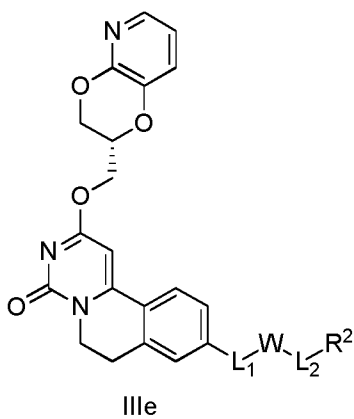
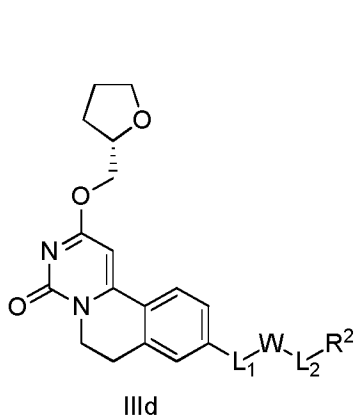
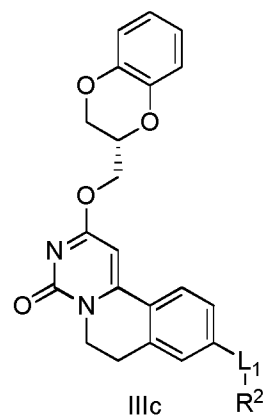
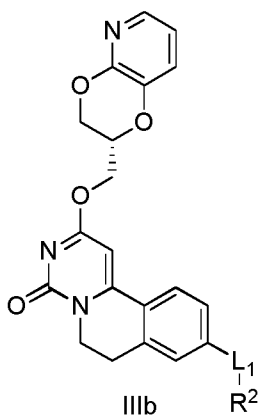
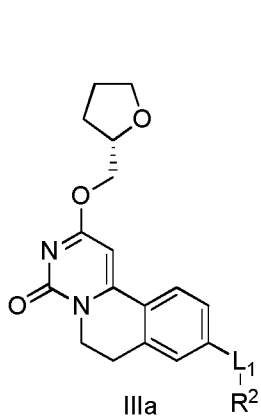
**[0093]** In one embodiment, the compound of the invention is according to any one of Formulae IIa-IIIi:

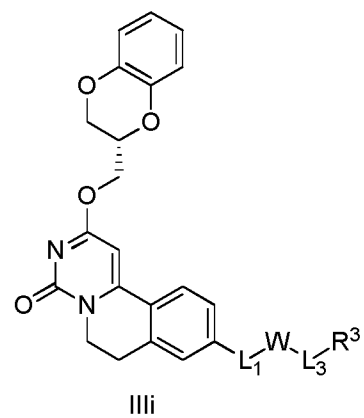
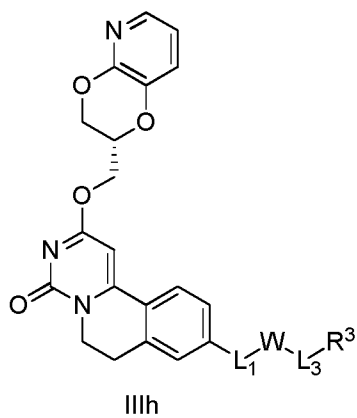
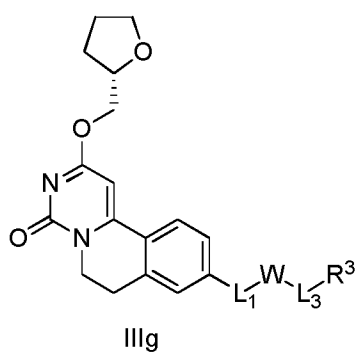




wherein  $L_1$ ,  $W$ ,  $L_2$ ,  $L_3$ ,  $R^2$  and  $R^3$  are as described previously.

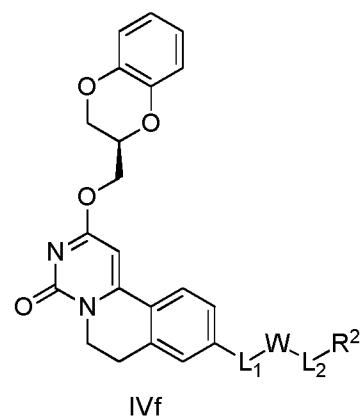
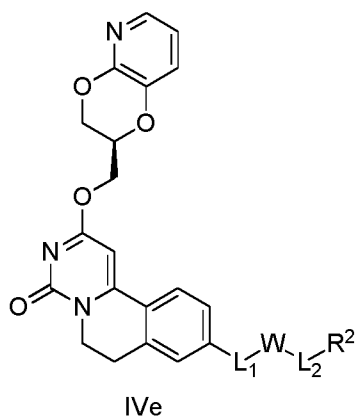
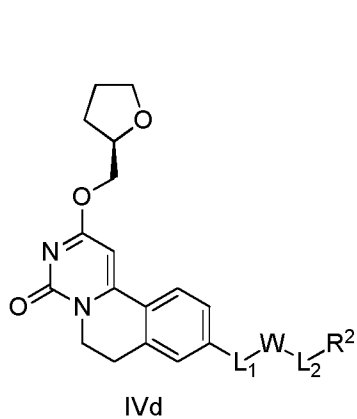
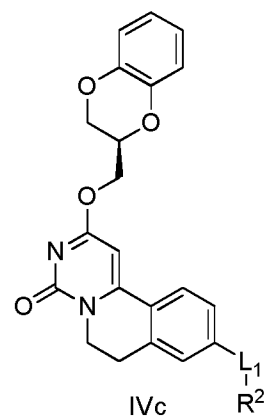
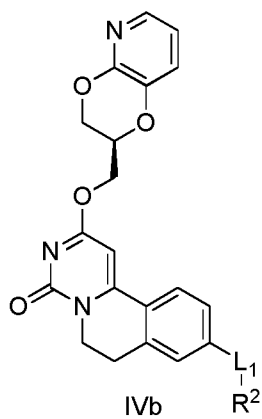
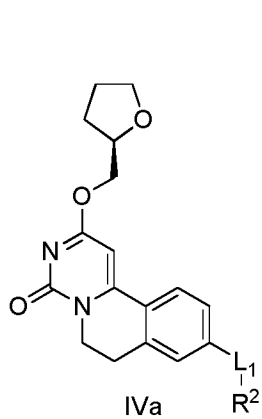
[0094] In one embodiment, the compound of the invention is according to any one of Formulae IIIa-IIIi:

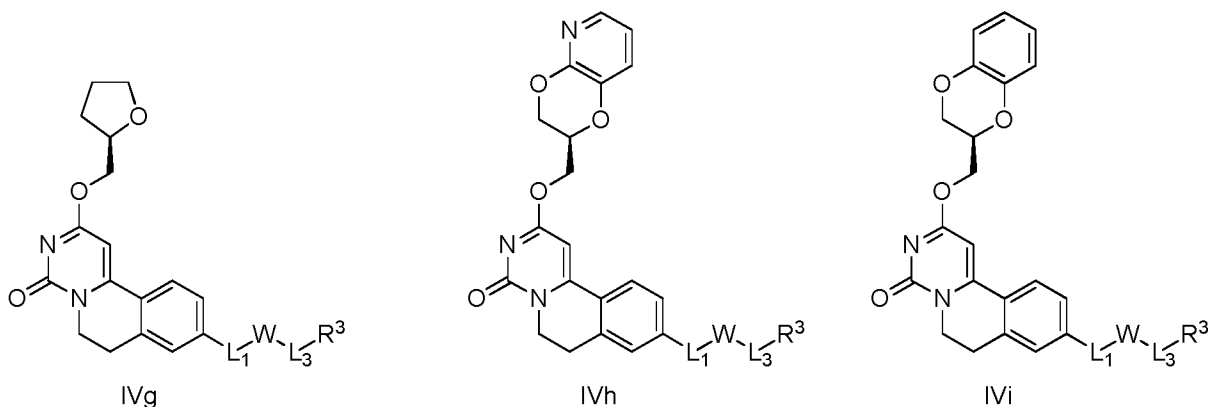




wherein  $L_1$ ,  $W$ ,  $L_2$ ,  $L_3$ ,  $R^2$  and  $R^3$  are as described previously.

**[0095]** In one embodiment, the compound of the invention is according to any one of Formulae IVa-IVi:





wherein  $L_1$ ,  $W$ ,  $L_2$ ,  $L_3$ ,  $R^2$  and  $R^3$  are as described previously.

**[0096]** In one embodiment, the compound of the invention is according to any one of Formulae Ia-IVi, wherein  $L_1$  is absent, or is  $-O-$ . In a preferred embodiment,  $L_1$  is absent.

**[0097]** In another embodiment, the compound of the invention is according to any one of Formulae Ia-IVi, wherein  $L_1$  is  $-NR^{4a}-$ , wherein  $R^{4a}$  is as described previously. In a preferred embodiment,  $R^{4a}$  is H, Me, Et, or cyclopropyl. In a more preferred embodiment,  $R^{4a}$  is H.

**[0098]** In one embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IId-IIi, IIId-IIli, or IVd-IVi, wherein  $W$  is  $C_{1-4}$  alkylene. In a preferred embodiment,  $W$  is  $-CH_2-$ ,  $-CH_2-CH_2-$ ,  $-CH_2-CH_2-CH(CH_3)-$ ,  $-CH_2-CH(-CH_2-CH_3)-$ ,  $-CH_2-C(CH_3)_2-$ , or  $-CH_2-CH_2-CH_2-$ . In a more preferred embodiment,  $W$  is  $-CH_2-$ . In another more preferred embodiment,  $W$  is  $-CH_2-CH_2-$ .

**[0099]** In one embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IId-IIi, IIId-IIli, or IVd-IVi, wherein  $W$  is  $C_{2-4}$  alkenylene having one double bond. In a preferred embodiment,  $W$  is  $-CH=CH-$ ,  $-CH_2-CH=CH-$ , or  $-CH=CH-CH_2-$ . In a more preferred embodiment,  $W$  is  $-CH=CH-$ . In another more preferred embodiment,  $W$  is  $-CH_2-CH=CH-$ .

**[00100]** In one embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IId-IIi, IIId-IIli, or IVd-IVi, wherein  $W$  is  $C_{2-4}$  alkynylene having one triple bond. In a preferred embodiment,  $W$  is  $-C\equiv C-$ ,  $-CH_2-C\equiv C-$ , or  $-C\equiv C-CH_2-$ . In a more preferred embodiment,  $W$  is  $-C\equiv C-$ . In another more preferred embodiment,  $W$  is  $-CH_2-C\equiv C-$ .

**[00101]** In one embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IId, IIe, IIi, IIId, IIle, IIIf, IVd, IVe, or IVf, wherein  $L_2$  is absent. In another embodiment,  $L_2$  is  $-O-$ .

**[00102]** In one embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IId, IIe, IIi, IIId, IIle, IIIf, IVd, IVe, or IVf, wherein  $L_1$  is absent or is  $-O-$ ,  $W$  is  $C_{1-4}$  alkylene; and  $L_2$  and  $R^2$  are as described previously. In a preferred embodiment,  $W$  is  $-CH_2-$ ,  $-CH_2-CH_2-$ , or  $-CH_2-CH_2-CH_2-$ . In a more preferred embodiment,  $W$  is  $-CH_2-$ . In another preferred embodiment,  $W$  is  $-CH_2-CH_2-$ .

**[00103]** In another embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IId, IIe, IIIf, IIId, IIIf, IIIf, IVd, IVe, or IVf, wherein  $L_1$  is absent or is  $-O-$ , W is  $C_{2-4}$  alkenylene having one double bond; and  $L_2$  and  $R^2$  are as described previously. In a preferred embodiment, W is  $-CH=CH-$ ,  $-CH_2-CH=CH-$ , or  $-CH=CH-CH_2$ . In a more preferred embodiment, W is  $-CH=CH-$ . In another more preferred embodiment, W is  $-CH_2-CH=CH-$ .

**[00104]** In yet another embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IId, IIe, IIIf, IIId, IIIf, IIIf, IVd, IVe, or IVf, wherein  $L_1$  is absent, W is  $C_{2-4}$  alkynylene having one triple bond; and  $L_2$  and  $R^2$  are as described previously. In a preferred embodiment, W is  $-C\equiv C-$ ,  $-CH_2-C\equiv C-$ , or  $-C\equiv C-CH_2$ . In a more preferred embodiment, W is  $-C\equiv C-$ . In another more preferred embodiment, W is  $-CH_2-C\equiv C-$ .

**[00105]** In one embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IId, IIe, IIIf, IIId, IIIf, IIIf, IVd, IVe, or IVf, wherein  $L_1$  and  $L_2$  are absent, W is  $C_{1-4}$  alkylene; and  $R^2$  is as described previously. In a preferred embodiment, W is  $-CH_2-$ ,  $-CH_2-CH_2-$ , or  $-CH_2-CH_2-CH_2-$ . In a more preferred embodiment, W is  $-CH_2-$ . In another more preferred embodiment, W is  $-CH_2-CH_2-$ .

**[00106]** In another embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IId, IIe, IIIf, IIId, IIIf, IIIf, IVd, IVe, or IVf, wherein  $L_1$  and  $L_2$  are absent, W is  $C_{2-4}$  alkenylene having one double bond; and  $R^2$  is as described previously. In a preferred embodiment, W is  $-CH=CH-$ ,  $-CH_2-CH=CH-$ , or  $-CH=CH-CH_2$ . In a more preferred embodiment, W is  $-CH=CH-$ . In another more preferred embodiment, W is  $-CH_2-CH=CH-$ .

**[00107]** In yet another embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IId, IIe, IIIf, IIId, IIIf, IIIf, IVd, IVe, or IVf, wherein  $L_1$  and  $L_2$  are absent, W is  $C_{2-4}$  alkynylene having one triple bond; and  $R^2$  is as described previously. In a preferred embodiment, W is  $-C\equiv C-$ ,  $-CH_2-C\equiv C-$ , or  $-C\equiv C-CH_2$ . In a more preferred embodiment, W is  $-C\equiv C-$ . In another more preferred embodiment, W is  $-CH_2-C\equiv C-$ .

**[00108]** In yet another embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IId, IIe, IIIf, IIId, IIIf, IIIf, IVd, IVe, or IVf, wherein  $L_1$  is absent,  $L_2$  is  $-O-$ , W is  $C_{2-4}$  alkynylene having one triple bond; and  $R^2$  is as described previously. In a preferred embodiment, W is  $-C\equiv C-$ ,  $-CH_2-C\equiv C-$ , or  $-C\equiv C-CH_2$ . In a more preferred embodiment, W is  $-C\equiv C-$ . In another more preferred embodiment, W is  $-CH_2-C\equiv C-$ .

**[00109]** In yet a further embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IId, IIe, IIIf, IIId, IIIf, IIIf, IVd, IVe, or IVf, and wherein  $-L_1-W-L_2-$  is selected from  $-CH_2-CH_2-$ ,  $-O-CH_2-$ ,  $-O-CH_2-CH_2-$ ,  $-O-CH_2-CH_2-O-$ ,  $-C\equiv C-$ ,  $-C\equiv C-CH_2-$ .

[00110] In one embodiment, the compound of the invention is according to any one of Formulae Ia-IIf, IIIa-IIIg, or IVa-IVf, wherein R<sup>2</sup> is H.

[00111] In another embodiment, the compound of the invention is according to any one of Formulae Ia-IIf, IIIa-IIIg, or IVa-IVf, wherein R<sup>2</sup> is C<sub>1-8</sub> alkyl. In a preferred embodiment, R<sup>2</sup> is Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, or *t*-Bu. In a more preferred embodiment, R<sup>2</sup> is Me, Et, *i*-Pr or *t*-Bu. In a more preferred embodiment, R<sup>2</sup> is *t*-Bu.

[00112] In one embodiment, the compound of the invention is according to any one of Formulae Ia-IIf, IIIa-IIIg, or IVa-IVf, wherein R<sup>2</sup> is C<sub>1-8</sub> alkyl substituted with one to three groups selected from OH, halo, CN, C<sub>1-6</sub> alkoxy, C<sub>3-7</sub> cycloalkyl, 4-6 membered heterocycloalkyl (comprising one to three heteroatoms independently selected from S, and O), 5-6 membered heteroaryl (comprising one to three heteroatoms independently selected from N, S, and O), and phenyl. In a preferred embodiment, R<sup>2</sup> is Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, or *t*-Bu substituted with one to three groups selected from OH, halo, CN, C<sub>1-6</sub> alkoxy, C<sub>3-7</sub> cycloalkyl, 4-6 membered heterocycloalkyl (comprising one to three heteroatoms independently selected from S, and O), 5-6 membered heteroaryl (comprising one to three heteroatoms independently selected from N, S, and O), and phenyl. In another preferred embodiment, is C<sub>1-8</sub> alkyl substituted with one to three groups selected from OH, F, Cl, CN, -OMe, -OEt, *Oi*-Pr, cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrololyl, imidazolyl, triazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and phenyl. In a more preferred embodiment, R<sup>2</sup> is Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, or *t*-Bu substituted with one to three groups selected from OH, F, Cl, CN, -OMe, -OEt, -*Oi*-Pr, cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrololyl, imidazolyl, triazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and phenyl.

[00113] In another embodiment, the compound of the invention is according to any one of Formulae Ia-IIf, IIIa-IIIg, or IVa-IVf, wherein R<sup>2</sup> is C<sub>1-8</sub> alkyl substituted with one group selected from OH, halo, CN, C<sub>1-6</sub> alkoxy, C<sub>3-7</sub> cycloalkyl, 4-6 membered heterocycloalkyl (comprising one to three heteroatoms independently selected from S, and O), 5-6 membered heteroaryl (comprising one to three heteroatoms independently selected from N, S, and O), and phenyl. In a preferred embodiment, R<sup>2</sup> is Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, or *t*-Bu substituted with one group selected from OH, halo, CN, C<sub>1-6</sub> alkoxy, C<sub>3-7</sub> cycloalkyl, 4-6 membered heterocycloalkyl (comprising one to three heteroatoms independently selected from S, and O), 5-6 membered heteroaryl (comprising one to three heteroatoms independently selected from N, S, and O), and phenyl. In another preferred embodiment, R<sup>2</sup> is C<sub>1-8</sub> alkyl substituted with one group selected from OH, F, Cl, CN, -OMe, -OEt, -*Oi*-Pr, cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrololyl, imidazolyl, triazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and phenyl. In a more preferred embodiment, R<sup>2</sup> is Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, or *t*-Bu substituted with one group selected from OH, F, Cl, CN, -OMe, -OEt, -*Oi*-Pr, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,

oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrololyl, imidazolyl, triazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and phenyl. In a most preferred embodiment,  $R^2$  is  $-CH_2-OH$ ,  $-C(CH_3)_2-OH$ ,  $-CH(OH)CH_3$ ,  $-CH(OH)-C_2H_5$ ,  $-CH(OH)-C_3H_7$ ,  $-C(OH)(C_2H_5)_2$ ,  $-C(OH)H-CH(CH_3)_2$ ,  $-C(OH)H-CH_2-CH(CH_3)_2$ ,  $-C(OH)H-C(CH_3)_3$ ,  $-CH_2-CN$ ,  $-CH_2-OCH_3$ ,  $-CH_2-CH_2-OCH_3$ ,  $-CH(OCH_3)-CH_3$ ,  
 5  $-C(OCH_3)H-CH(CH_3)_2$ ,  $-CH_2-F$ ,  $-CH_2-CH_2-F$ ,  $-CH_2$ -cyclopropyl,  $-CH_2$ -cyclopentyl,  $-CH_2$ -oxetanyl,  $-CH_2$ -tetrahydrofuranyl, or  $-CH_2$ -tetrahydropyranyl.

**[00114]** In one embodiment, the compound of the invention is according to any one of Formulae Ia-IIf, IIIa-IIIIf, or IVa-IVf, wherein  $R^2$  is  $C_{4-7}$  cycloalkenyl comprising one double bond. In a preferred embodiment,  $R^2$  is cyclohexenyl.

10 **[00115]** In one embodiment, the compound of the invention is according to any one of Formulae Ia-IIf, IIIa-IIIIf, or IVa-IVf, wherein  $R^2$  is 5-7 membered heterocycloalkenyl comprising one double bond, and one to three heteroatoms independently selected from N, O, and S. In a preferred embodiment,  $R^2$  is dihydropyranyl.

**[00116]** In one embodiment, the compound of the invention is according to any one of Formulae Ia-IIf, IIIa-IIIIf, or IVa-IVf, wherein  $R^2$  is unsubstituted  $C_{3-7}$  cycloalkyl. In a preferred embodiment,  $R^2$  is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In a more preferred embodiment,  $R^2$  is cyclopropyl.

**[00117]** In another embodiment, the compound of the invention is according to any one of Formulae Ia-IIf, IIIa-IIIIf, or IVa-IVf, wherein  $R^2$  is  $C_{3-7}$  cycloalkyl substituted with one to three independently selected  $R^6$  groups. In a preferred embodiment,  $R^2$  is  $C_{3-7}$  cycloalkyl substituted with one  $R^6$  group. In a more preferred embodiment,  $R^2$  is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, each of which is substituted with one  $R^6$  group. In another more preferred embodiment,  $R^2$  is  $C_{3-7}$  cycloalkyl substituted with one  $R^6$  group, wherein  $R^6$  is oxo, or  $R^7$ , and  $R^7$  is OH, or  $C_{1-6}$  alkyl. In a most preferred embodiment,  $R^2$  is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, each of which is substituted with one  $R^6$  group, wherein  $R^6$  is oxo, or  $R^7$  and  $R^7$  is OH, or  $C_{1-6}$  alkyl. In a further most preferred embodiment,  $R^2$  is cyclopropyl,  
 20 cyclobutyl, cyclopentyl or cyclohexyl, each of which is substituted with one  $R^6$  group, wherein  $R^6$  is  $R^7$  and  $R^7$  is OH.

**[00118]** In one embodiment, the compound of the invention is according to any one of Formulae Ia-IIf, IIIa-IIIIf, or IVa-IVf, wherein  $R^2$  is 4-10 membered heterocycloalkyl comprising one to two heteroatoms independently selected from S, and O. In a preferred embodiment,  $R^2$  is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl.  
 30

**[00119]** In another embodiment, the compound of the invention is according to any one of Formulae Ia-IIf, IIIa-IIIIf, or IVa-IVf,  $R^2$  is 4-10 membered heterocycloalkyl comprising one to two heteroatoms independently selected from S, and O, substituted with one to three independently selected  $R^6$  groups. In a preferred embodiment,  $R^2$  is 4-10 membered heterocycloalkyl comprising one to two heteroatoms

independently selected from S, and O, substituted with one R<sup>6</sup> group. In a more preferred embodiment, R<sup>2</sup> is 4-10 membered heterocycloalkyl comprising one to two heteroatoms independently selected from S, and O, substituted with one R<sup>6</sup> group, wherein R<sup>6</sup> is selected from oxo, and R<sup>7</sup>, and R<sup>7</sup> is OH, or C<sub>1-6</sub> alkyl. In another more preferred embodiment, R<sup>2</sup> is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl, each of which is substituted with one R<sup>6</sup> group. In a most preferred embodiment, R<sup>2</sup> is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl, each of which is substituted with one R<sup>6</sup> group, wherein R<sup>6</sup> is selected from oxo, and R<sup>7</sup>, and R<sup>7</sup> is OH, or C<sub>1-6</sub> alkyl,

**[00120]** In one embodiment, the compound of the invention is according to any one of Formulae Ia-IIf, IIIa-IIIIf, or IVa-IVf, R<sup>2</sup> is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O. In a preferred embodiment, R<sup>2</sup> is furanyl, thienyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, triazolyl, pyridinyl, pyrazinyl, pyrimidinyl, indanyl, or indazolyl.

**[00121]** In another embodiment, the compound of the invention is according to any one of Formulae Ia-IIf, IIIa-IIIIf, or IVa-IVf, R<sup>2</sup> is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, substituted with one to three independently selected R<sup>7</sup> groups. In a preferred embodiment, R<sup>2</sup> is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, substituted with one or two independently selected R<sup>7</sup> groups. In a more preferred embodiment, R<sup>2</sup> is furanyl, thienyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, triazolyl, pyridinyl, pyrazinyl, pyrimidinyl, indanyl, or indazolyl, substituted with one or two independently selected R<sup>7</sup> groups. In another more preferred embodiment, R<sup>2</sup> is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, substituted with one or two independently selected R<sup>7</sup> groups, wherein each R<sup>7</sup> is independently selected from OH, halo, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyl substituted with one or more halo, C<sub>1-6</sub> alkoxy, -CN, C<sub>3-7</sub> cycloalkyl, 4-7 membered heterocycloalkyl comprising one to three heteroatoms independently selected from N, O, and S, and phenyl. In most preferred embodiment, R<sup>2</sup> is furanyl, thienyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, triazolyl, pyridinyl, pyrazinyl, pyrimidinyl, indanyl, or indazolyl, each of which is substituted with one or two independently selected R<sup>7</sup> groups, wherein each R<sup>7</sup> is independently selected from OH, halo, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyl substituted with one or more halo, C<sub>1-6</sub> alkoxy, -CN, C<sub>3-7</sub> cycloalkyl, 4-7 membered heterocycloalkyl comprising one to three heteroatoms independently selected from N, O, and S, and phenyl. In another most preferred embodiment, R<sup>2</sup> is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, substituted with one or two independently selected R<sup>7</sup> groups, wherein each R<sup>7</sup> is independently selected from OH, F, Cl, Me, Et, Pr, *i*-Pr, *t*-Bu, -CF<sub>3</sub>, -OMe, -OEt, *Oi*-Pr, -CN, cyclopropyl, pyrrolidinyl, morpholinyl, piperidinyl, or phenyl. In further most preferred embodiment, R<sup>2</sup> is furanyl, thienyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, triazolyl, pyridinyl, pyrazinyl, pyrimidinyl, indanyl, or indazolyl, each of which is substituted with one or two



independently selected  $R^7$  groups, wherein each  $R^7$  is independently selected from OH, F, Cl, Me, Et, Pr, *i*-Pr, *t*-Bu, -CF<sub>3</sub>, -OMe, -OEt, -O*i*-Pr, -CN, cyclopropyl, pyrrolidinyl, morpholinyl, piperidinyl, and phenyl.

**[00122]** In another embodiment, the compound of the invention is according to any one of Formulae Ia-IIf, IIIa-IIIf, or IVa-IVf,  $R^2$  is C<sub>6-10</sub> aryl. In a preferred embodiment,  $R^2$  is phenyl.

- 5 **[00123]** In another embodiment, the compound of the invention is according to any one of Formulae Ia-IIf, IIIa-IIIf, or IVa-IVf,  $R^2$  is C<sub>6-10</sub> aryl substituted with one or more independently selected  $R^7$  groups. In a preferred embodiment,  $R^2$  is C<sub>6-10</sub> aryl substituted with one or two independently selected  $R^7$  groups. In a more preferred embodiment,  $R^2$  is C<sub>6-10</sub> aryl substituted with one or two independently selected  $R^7$  groups, wherein each  $R^7$  group is selected from halo, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, or -NHC(=O)-C<sub>1-4</sub> alkyl. In another more preferred embodiment,  $R^2$  is C<sub>6-10</sub> aryl substituted with one or two independently selected  $R^7$  groups, wherein each  $R^7$  group is selected from -C(=O)NR<sup>10</sup>R<sup>11</sup>, and each R<sup>10</sup> and R<sup>11</sup> is independently selected from H and C<sub>1-4</sub> alkyl. In yet another more preferred embodiment,  $R^2$  is phenyl substituted with one or two independently selected  $R^6$  groups. In a most preferred embodiment,  $R^2$  is phenyl substituted with one or two independently selected  $R^7$  groups, wherein each  $R^7$  group is selected from halo, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, and -NHC(=O)-C<sub>1-4</sub> alkyl. In another most preferred embodiment,  $R^2$  is phenyl substituted with one or two independently selected  $R^7$  groups, wherein each  $R^7$  group is selected from -C(=O)NR<sup>10</sup>R<sup>11</sup>, and each R<sup>10</sup> and R<sup>11</sup> is independently selected from H and C<sub>1-4</sub> alkyl. In a further most preferred embodiment  $R^2$  is phenyl substituted with one or two independently selected  $R^7$  groups, wherein each  $R^7$  group is selected from F, Cl, CN, Me, -OMe, -OEt, and -NHC(=O)Me. In another further most preferred embodiment  $R^2$  is phenyl substituted with one or two independently selected  $R^7$  groups, wherein each  $R^7$  group is selected from -C(=O)NH<sub>2</sub>, and -C(=O)NHMe.

**[00124]** In another embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IIg-IIi, IIIg-IIIi, or IVg-IVi, wherein L<sub>3</sub> is -NR<sup>4b</sup>-, and L<sub>1</sub>, W and R<sup>4b</sup> are as described previously. In a preferred embodiment, R<sup>4b</sup> is H, Me, Et, or cyclopropyl. In a more preferred embodiment, R<sup>4a</sup> is H.

- 25 **[00125]** In another embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IIg-IIi, IIIg-IIIi, or IVg-IVi, wherein L<sub>1</sub>, W and L<sub>3</sub> are as described previously, and R<sup>3</sup> is C<sub>1-4</sub> alkyl substituted with C<sub>6-10</sub> aryl optionally substituted with one or more independently selected  $R^7$  groups, or 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, optionally substituted with one or more independently selected  $R^8$  groups. In a preferred embodiment, R<sup>3</sup> is Me or Et, each of which is substituted with C<sub>6-10</sub> aryl optionally substituted with one or more independently selected  $R^8$  groups), or 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, optionally substituted with one or more independently selected  $R^8$  groups. In another preferred embodiment, R<sup>3</sup> is C<sub>1-4</sub> alkyl substituted with phenyl, or pyridinyl, each of which is optionally substituted with one or more independently selected  $R^8$  groups. In a more preferred embodiment,

R<sup>3</sup> is C<sub>1-4</sub> alkyl substituted with phenyl, or pyridinyl. In a more preferred embodiment, R<sup>3</sup> is C<sub>1-4</sub> alkyl substituted with phenyl, or pyridinyl, each of which is substituted with Me, Et, F, or Cl. In a most preferred embodiment, R<sup>3</sup> is Me or Et, each of which is substituted with phenyl, or pyridinyl. In a more preferred embodiment, R<sup>3</sup> is Me or Et, each of which is substituted with phenyl, or pyridinyl, each of which is substituted with Me, Et, F, or Cl.

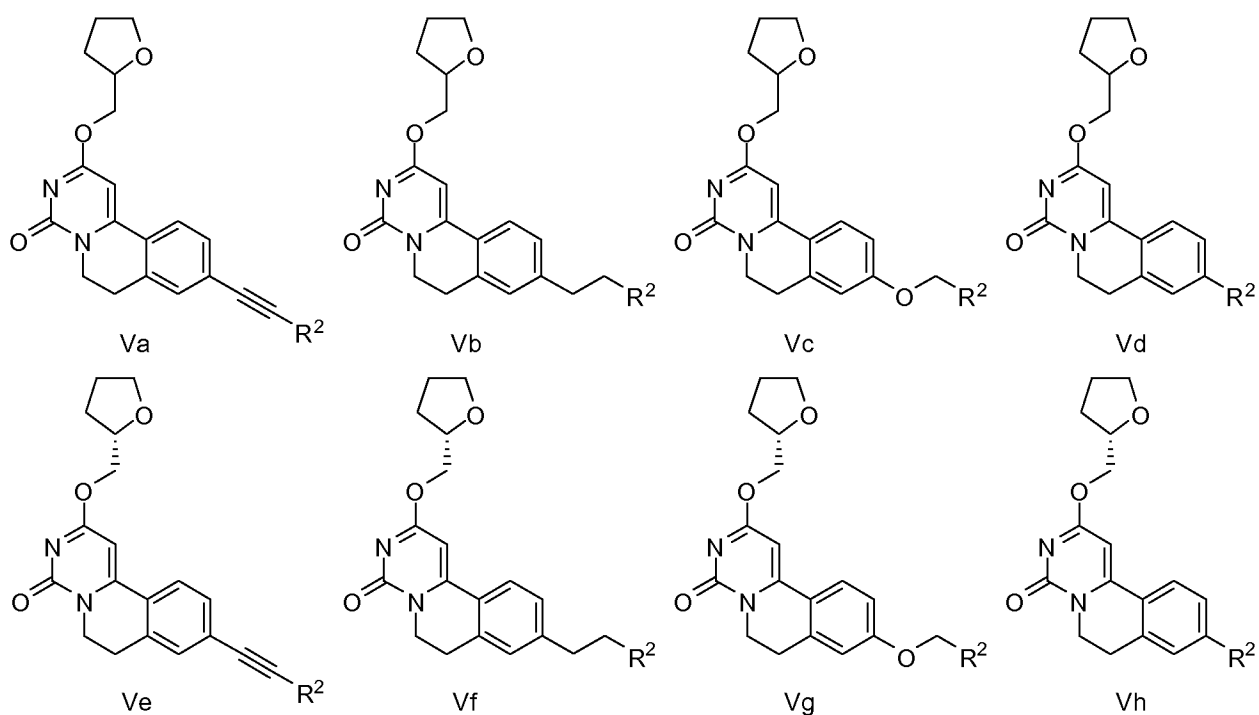
**[00126]** In one embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IIg-IIIi, IIIg,-IIIi, or IVg-IVi, wherein L<sub>1</sub>, W and L<sub>3</sub> are as described previously, and R<sup>3</sup> is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O. In a preferred embodiment, R<sup>3</sup> is pyridinyl.

**[00127]** In one embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IIg-IIIi, IIIg,-IIIi, or IVg-IVi, wherein L<sub>1</sub>, W and L<sub>3</sub> are as described previously, and R<sup>3</sup> is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, substituted with one or more independently selected R<sup>8</sup> groups, wherein each R<sup>8</sup> group is as described previously. In a preferred embodiment, R<sup>3</sup> is pyridinyl, substituted with one or more independently selected R<sup>8</sup> groups, wherein each R<sup>8</sup> group is as described previously. In another preferred embodiment, R<sup>3</sup> is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, substituted with one or more independently selected R<sup>8</sup> groups, wherein each R<sup>8</sup> group is selected from Me, Et, F, and Cl. In a more preferred embodiment, R<sup>3</sup> is pyridinyl substituted with one or more independently selected R<sup>8</sup> groups, wherein each R<sup>8</sup> group is selected from Me, Et, F, and Cl. In a most preferred embodiment, R<sup>3</sup> is pyridinyl substituted with one R<sup>8</sup> group selected from Me, Et, F, and Cl.

**[00128]** In one embodiment, the compound of the invention is according to one of Formulae I or IIg-IIIi, wherein L<sub>1</sub>, W and L<sub>3</sub> are as described previously, and R<sup>3</sup> is C<sub>6-10</sub> aryl. In a preferred embodiment, R<sup>3</sup> is phenyl.

**[00129]** In one embodiment, the compound of the invention is according to any one of Formulae Ia-Ic, IIg-IIIi, IIIg,-IIIi, or IVg-IVi, wherein L<sub>1</sub>, W and L<sub>3</sub> are as described previously, and R<sup>3</sup> is C<sub>6-10</sub> aryl substituted with one or more independently selected R<sup>8</sup> groups, wherein each R<sup>8</sup> group is as described previously. In a preferred embodiment, R<sup>3</sup> is phenyl, substituted with one or more independently selected R<sup>8</sup> groups, wherein each R<sup>8</sup> group is as described previously. In another preferred embodiment, R<sup>3</sup> is C<sub>6-10</sub> aryl substituted with one or more independently selected R<sup>8</sup> groups, wherein each R<sup>8</sup> group is selected from Me, Et, F, and Cl. In a more preferred embodiment, R<sup>3</sup> is phenyl substituted with one or more independently selected R<sup>8</sup> groups, wherein each R<sup>8</sup> group is selected from Me, Et, F, and Cl. In a most preferred embodiment, R<sup>3</sup> is phenyl substituted with one R<sup>8</sup> group selected from Me, Et, F, and Cl.

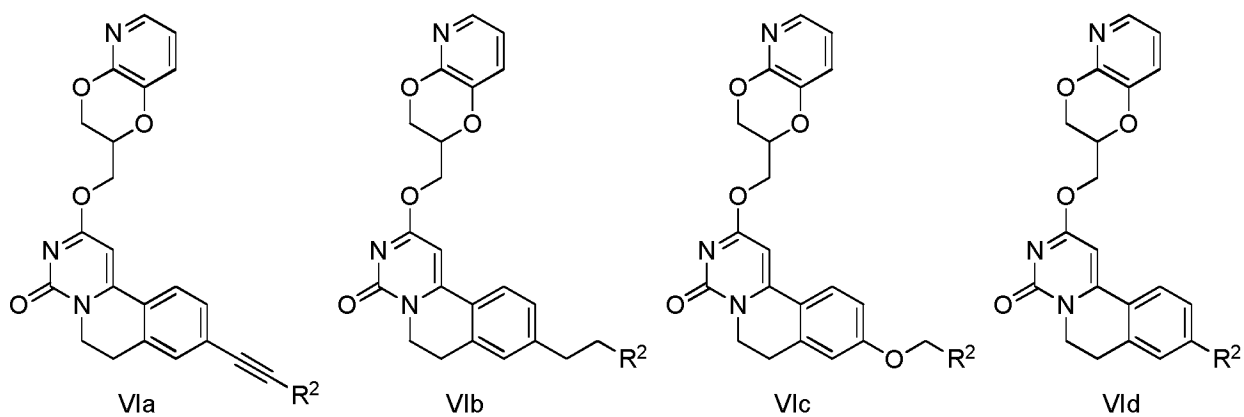
**[00130]** In one embodiment, the compound of the invention according to any one of Formulae Va-Vh:

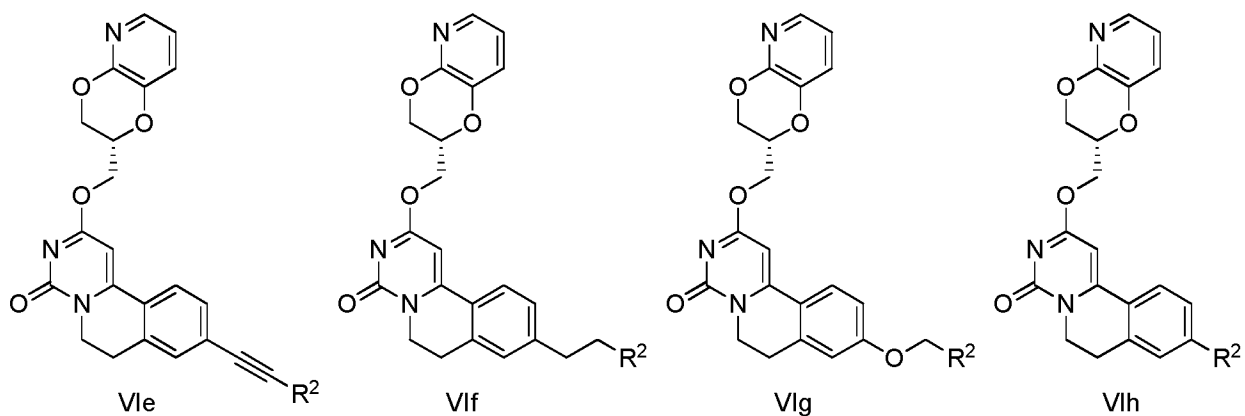


wherein  $R^2$  is as described previously.

**[00131]** In one embodiment, the compound of the invention is according to any one of Formulae VIa-

5 VIh:

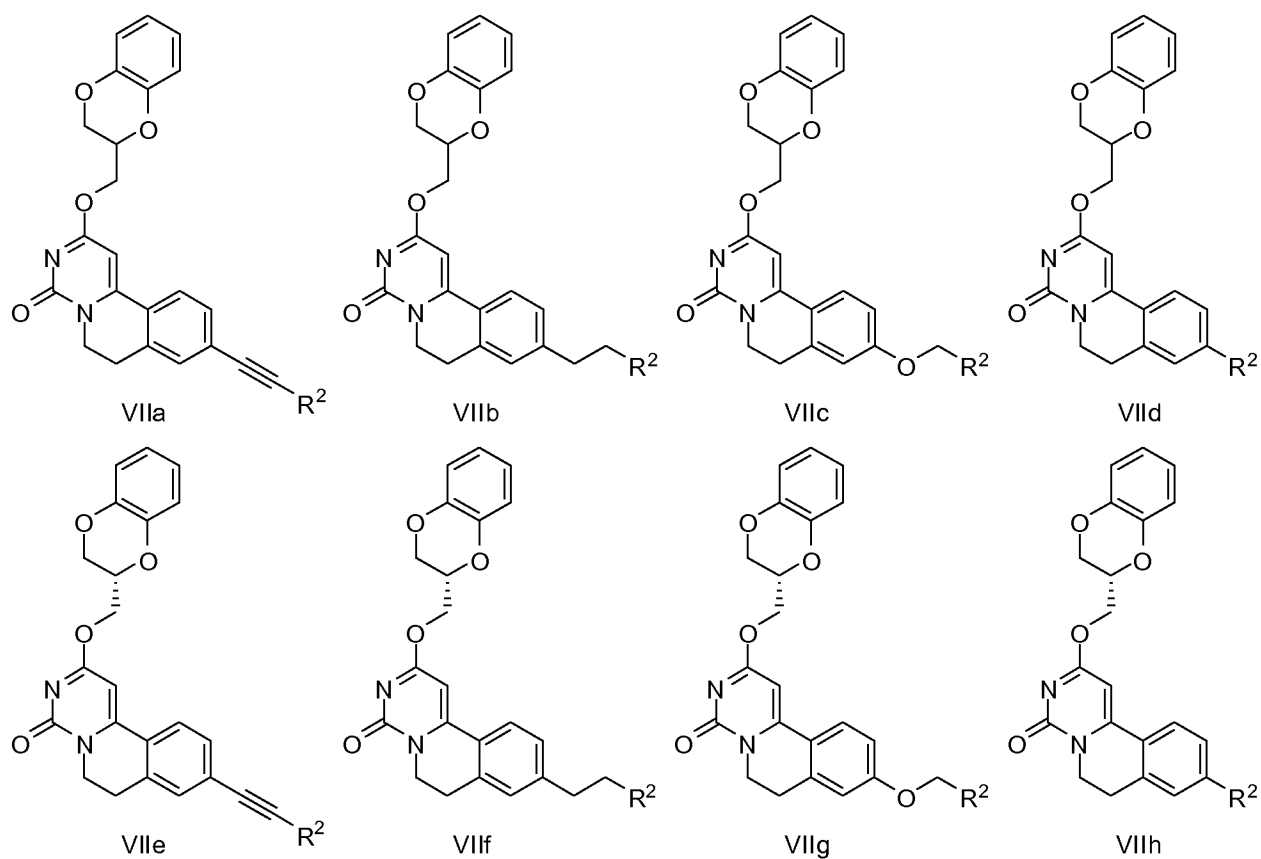




wherein  $R^2$  is as described previously.

**[00132]** In one embodiment, the compound of the invention is according to any one of Formulae VIIa-

5 VIIh:



wherein  $R^2$  is as described previously.

**[00133]** In one embodiment, the compound of the invention is according to any one of Formulae Va, Vb,

10 Ve, Vf, VIa, VIb, VIe, VI f, VIIa, VIIb, VIIe, or VII f, wherein  $R^2$  is unsubstituted  $C_{3-7}$  cycloalkyl. In a

preferred embodiment,  $R^2$  is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In a more preferred embodiment,  $R^2$  is cyclopropyl.

**[00134]** In another embodiment, the compound of the invention is according to any one of Formulae Va, Vb, Ve, Vf, VIa, VIb, VIe, VIf, VIIa, VIIb, VIIe, or VIIf, wherein  $R^2$  is  $C_{3-7}$  cycloalkyl substituted with one to three independently selected  $R^6$  groups. In a preferred embodiment,  $R^2$  is  $C_{3-7}$  cycloalkyl substituted with one  $R^6$  group. In a more preferred embodiment,  $R^2$  is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, each of which is substituted with one  $R^6$  group. In another more preferred embodiment,  $R^2$  is  $C_{3-7}$  cycloalkyl substituted with one  $R^6$  group, wherein  $R^6$  is oxo, or  $R^7$ , and  $R^7$  is OH, or  $C_{1-6}$  alkyl. In a most preferred embodiment,  $R^2$  is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, each of which is substituted with one  $R^6$  group, wherein  $R^6$  is oxo, or  $R^7$ , and  $R^7$  is OH, or  $C_{1-6}$  alkyl. In a further most preferred embodiment,  $R^2$  is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, each of which is substituted with one  $R^6$  group, wherein  $R^6$  is  $R^7$ , and  $R^7$  is OH.

**[00135]** In one embodiment, the compound of the invention is according to any one of Formulae Vc, Vd, Vg, Vh, VIc, VId, VIg, VIh, VIIf, VIId, VIIf, or VIIh, wherein  $R^2$  is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O. In a preferred embodiment,  $R^2$  is furanyl, thienyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, triazolyl, pyridinyl, pyrazinyl, pyrimidinyl, indanyl, or indazolyl.

**[00136]** In another embodiment, the compound of the invention is according to any one of Formulae Vc, Vd, Vg, Vh, VIc, VId, VIg, VIh, VIIf, VIId, VIIf, or VIIh, wherein  $R^2$  is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, substituted with one to three independently selected  $R^7$  groups. In a preferred embodiment,  $R^2$  is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, substituted with one or two independently selected  $R^7$  groups. In a more preferred embodiment,  $R^2$  is furanyl, thienyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, triazolyl, pyridinyl, pyrazinyl, pyrimidinyl, indanyl, or indazolyl, substituted with one or two independently selected  $R^7$  groups. In another more preferred embodiment,  $R^2$  is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, substituted with one or two independently selected  $R^7$  groups, wherein each  $R^7$  is independently selected from OH, halo,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl substituted with one or more halo,  $C_{1-6}$  alkoxy, -CN,  $C_{3-7}$  cycloalkyl, 4-7 membered heterocycloalkyl comprising one to three heteroatoms independently selected from N, O, and S, and phenyl. In a most preferred embodiment,  $R^2$  is furanyl, thienyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, triazolyl, pyridinyl, pyrazinyl, pyrimidinyl, indanyl, or indazolyl, each of which is substituted with one or two independently selected  $R^7$  groups, wherein each  $R^7$  is independently selected from OH, halo,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl substituted with one or more halo,  $C_{1-6}$  alkoxy, -CN,  $C_{3-7}$  cycloalkyl, 4-7 membered heterocycloalkyl comprising one to three heteroatoms independently

selected from N, O, and S, and phenyl. In another most preferred embodiment,  $R^2$  is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, substituted with one or two independently selected  $R^7$  groups, wherein each  $R^7$  is independently selected from OH, F, Cl, Me, Et, Pr, *i*-Pr, *t*-Bu, -CF<sub>3</sub>, -OMe, -OEt, *Oi*-Pr, -CN, cyclopropyl, pyrrolidinyl, morpholinyl, piperidinyl, and phenyl. In a further most preferred embodiment,  $R^2$  is furanyl, thienyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, triazolyl, pyridinyl, pyrazinyl, pyrimidinyl, indanyl, or indazolyl, each of which is substituted with one or two independently selected  $R^7$  groups, wherein each  $R^7$  is independently selected from OH, F, Cl, Me, Et, Pr, *i*-Pr, *t*-Bu, -CF<sub>3</sub>, -OMe, -OEt, -*Oi*-Pr, -CN, cyclopropyl, pyrrolidinyl, morpholinyl, piperidinyl, and phenyl.

**[00137]** In another embodiment, the compound of the invention is according to any one of Formulae Vc, Vd, Vg, Vh, VIc, VId, VIg, VIh, VIIc, VIId, VIIg, or VIIh, wherein  $R^2$  is C<sub>6-10</sub> aryl. In a preferred embodiment,  $R^2$  is phenyl.

**[00138]** In another embodiment, the compound of the invention is according to any one of Formulae Vc, Vd, Vg, Vh, VIc, VId, VIg, VIh, VIIc, VIId, VIIg, or VIIh, wherein  $R^2$  is C<sub>6-10</sub> aryl substituted with one or more independently selected  $R^7$  groups. In a preferred embodiment,  $R^2$  is C<sub>6-10</sub> aryl substituted with one or two independently selected  $R^7$  groups. In a more preferred embodiment,  $R^2$  is C<sub>6-10</sub> aryl substituted with one or two independently selected  $R^7$  groups, wherein each  $R^7$  group is selected from halo, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, and -NHC(=O)-C<sub>1-4</sub> alkyl. In another more preferred embodiment,  $R^2$  is C<sub>6-10</sub> aryl substituted with one or two independently selected  $R^7$  groups, wherein each  $R^7$  group is -C(=O)NR<sup>9</sup>R<sup>10</sup>, and each R<sup>10</sup> and R<sup>11</sup> is independently selected from H and C<sub>1-4</sub> alkyl. In another more preferred embodiment,  $R^2$  is phenyl substituted with one or two independently selected  $R^7$  groups. In a most preferred embodiment,  $R^2$  is phenyl substituted with one or two independently selected  $R^6$  groups, wherein each  $R^7$  group is selected from halo, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, and -NHC(=O)-C<sub>1-4</sub> alkyl. In another most preferred embodiment,  $R^2$  is phenyl substituted with one or two independently selected  $R^7$  groups, wherein each  $R^7$  group is -C(=O)NR<sup>10</sup>R<sup>11</sup>, and each R<sup>10</sup> and R<sup>11</sup> is independently selected from H and C<sub>1-4</sub> alkyl. In a further most preferred embodiment  $R^2$  is phenyl substituted with one or two independently selected  $R^7$  groups, wherein each  $R^7$  group is selected from F, Cl, CN, Me, -OMe, -OEt, - and -NHC(=O)Me. In a further most preferred embodiment  $R^2$  is phenyl substituted with one or two independently selected  $R^7$  groups, wherein each  $R^7$  group is selected from C(=O)NH<sub>2</sub>, and -C(=O)NHMe.

**[00139]** In one embodiment, the compound of the invention is selected from:

9-Methoxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 2-(Chroman-2-ylmethoxy)-9-methoxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-methoxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 9-Allyloxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

- 2-(2,3-Dihydro-benzofuran-2-ylmethoxy)-9-methoxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 9-Hydroxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 9-Benzyloxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 9-(Pyridin-3-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 5 [4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetonitrile,  
 9-Butoxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 9-Cyclopropylmethoxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 9-Phenethyloxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 9-(Pyridin-4-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 10 9-(Pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 9-(Pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 9-(2-Phenoxy-ethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 9-Methoxy-2-(tetrahydro-pyran-4-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 9-Methoxy-2-(tetrahydro-pyran-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 15 9-Methoxy-2-(tetrahydro-pyran-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-  
 benzonitrile,  
 4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-  
 benzonitrile,  
 20 9-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-  
 pyrimido[6,1-a]isoquinolin-4-one,  
 9-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-  
 pyrimido[6,1-a]isoquinolin-4-one,  
 3-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-  
 25 benzonitrile,  
 2-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-  
 benzonitrile,  
 9-(4-Chloro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 9-(3-Chloro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 30 9-(2-Chloro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 9-(4-Fluoro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 9-(2-Nitro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-  
 benzoic acid methyl ester,

- 3-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-benzoic acid methyl ester,
- 3-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-benzoic acid methyl ester,
- 5 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- [2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetic acid tert-butyl ester,
- 2,9-Bis-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 10 [2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetic acid,
- 9-(3-Nitro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(3-Nitro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(4-Nitro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 9-(3-Methyl-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(4-Methyl-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(4-Methoxy-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(Naphthalen-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 20 9-(Naphthalen-1-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(2-Methyl-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-[2-(2-Methoxy-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 25 9-[2-(3-Methoxy-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-[2-(4-Methoxy-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-[2-(2-Chloro-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 30 9-[2-(3-Chloro-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-[2-(4-Chloro-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,



- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-morpholin-4-yl-2-oxo-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-morpholin-4-yl-2-oxo-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 5 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-morpholin-4-yl-2-oxo-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-morpholin-4-yl-2-oxo-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 10 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide,
- 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N,N-dimethyl-acetamide,
- 9-(2,2-Dimethoxy-ethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-2-methyl-propionamide,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(1,1-dimethyl-2-morpholin-4-yl-2-oxo-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(2-Benzyloxy-ethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 20 2,9-Bis-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(6-Phenyl-pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 25 9-[6-(1-Methyl-1H-pyrazol-4-yl)-pyridin-2-ylmethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(6-Furan-3-yl-pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(6-Pyrimidin-5-yl-pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 30 9-(1-Cyclopropyl-1H-tetrazol-5-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide,

- N,N-Diethyl-2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide,
- N,N-Dimethyl-2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide,
- 5 N-Isopropyl-N-methyl-2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide,
- 2-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N-phenyl-acetamide,
- 9-(1-Propyl-1H-tetrazol-5-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 10 9-(Oxazol-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N,N-diethyl-acetamide,
- 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N-isopropyl-N-methyl-acetamide,
- 15 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N-phenyl-acetamide,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(1-propyl-1H-tetrazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 20 9-(1-Butyl-1H-tetrazol-5-ylmethoxy)-2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-morpholin-4-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- [2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetonitrile,
- 25 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 30 9-(1-Cyclopropyl-1H-tetrazol-5-ylmethoxy)-2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(1H-tetrazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

- 9-Allyloxy-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
N-Benzyl-2-[2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide,
- 5 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-pyrrolidin-1-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-piperidin-1-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(3-piperidin-1-yl-propoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 10 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(3-dimethylamino-propoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-[3-(4-methyl-piperazin-1-yl)-propoxy]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
5-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-furan-2-carboxylic acid ethyl ester,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 20 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 25 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-(5-tert-Butyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-(5-Phenyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 30 [2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetonitrile,  
[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetonitrile,

- [2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl)-acetonitrile,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-morpholin-4-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 5 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1H-tetrazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 10 9-Pyridin-3-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 3-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile,
- 9-Phenyl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-4-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 3-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile,
- 9-(2-Methoxy-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(3-Methoxy-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 20 9-(4-Methoxy-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile,
- 3-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzoic acid,
- 4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzoic acid,
- 9-(4-Dimethylamino-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 25 4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzamide,
- 2-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile,
- 9-(1-Methyl-1H-pyrazol-4-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 30 N,N-Dimethyl-3-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzamide,
- 9-(6-Methoxy-pyridin-3-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(2,6-Dimethyl-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

- 9-(3,5-Dimethyl-isoxazol-4-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-Naphthalen-2-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-Naphthalen-1-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 5 9-Pyrimidin-5-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(5-Chloro-thiophen-2-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-pyrrole-1-carboxylic acid tert-butyl ester,
- 10 Trifluoro-methanesulfonic acid 4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl ester,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-methoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-Cyclopropylethynyl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 9-(3,3-Dimethyl-but-1-ynyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(pyridin-4-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-3-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 20 2-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-methoxy-phenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 25 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1H-indazol-5-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyrimidin-5-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 3-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzamide,
- 30 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-dimethylamino-phenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-3-ylethynyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methoxy-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(4-hydroxy-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
5 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1,5-dimethyl-1H-pyrazol-3-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methyl-[1,2,4]oxadiazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-3-methyl-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
10 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-4-ylethynyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
15 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-methyl-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-methoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-Cyclopropylethynyl-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
20 9-Cyclopropylethynyl-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1-hydroxy-cyclopentylethynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
25 5-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-pent-4-ynenitrile,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3,3-dimethyl-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-methoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
30 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
5-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-pyridine-2-carboxylic acid methylamide,

- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-furan-3-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 5 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-morpholin-4-ylmethyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- [2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-ylamino]-acetonitrile,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinoline-9-carbonitrile,
- 10 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-[(oxazol-2-ylmethyl)-amino]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-methyl-[1,2,4]oxadiazol-3-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-ethyl-[1,2,4]oxadiazol-3-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(5-Cyclopropyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-isopropyl-[1,2,4]oxadiazol-3-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 20 9-(5-tert-Butyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methyl-isoxazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 25 9-(3-Chloro-2-methoxy-pyridin-4-yl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3,6-dihydro-2H-pyran-4-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 5-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-pyridine-2-carbonitrile,
- 30 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-ethoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-ethoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-morpholin-4-yl-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-methoxy-pyrimidin-5-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 5 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2,3-dimethoxy-phenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2,5-dimethoxy-phenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 10 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-3-phenyl-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 3-{3-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-prop-2-ynyloxy}-propionitrile,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methylamino-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-dimethylamino-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-[3-(Benzyl-methyl-amino)-prop-1-ynyl]-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-[3-(1,1-dioxo-thiomorpholin-4-yl)-prop-1-ynyl]-
- 20 6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- {3-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-prop-2-ynyl}-urea,
- 1-{3-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-prop-2-ynyl}-imidazolidine-2,4-dione,
- 25 9-(3-Diethylamino-prop-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(3-Amino-3-methyl-but-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(tetrahydro-pyran-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 30 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1H-pyrazol-4-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,



- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-pent-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-hex-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 5 9-(1-Amino-cyclohexylethynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-5-methyl-hex-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-ethyl-3-hydroxy-pent-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 10 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-3-phenyl-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-4-methyl-pent-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 2-[(R)-1-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-yl)methoxy]-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-[(R)-1-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-yl)methoxy]-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-[(S)-1-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-yl)methoxy]-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 20 9-(3-Butylamino-prop-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-morpholin-4-yl-ethoxymethyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 25 9-(3-Benzylamino-prop-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-phenylamino-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinoline-9-carboxylic acid (tetrahydro-pyran-4-yl)-amide,
- 30 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinoline-9-carboxylic acid (oxetan-3-ylmethyl)-amide,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyrrolidin-1-ylmethyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

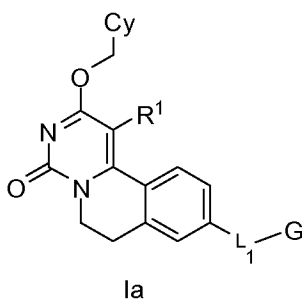
- 9-(tert-Butylamino-methyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-piperidin-1-ylmethyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 5 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methyl-oxetan-3-ylmethoxymethyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methyl-oxetan-3-ylmethoxymethyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 10 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(oxetan-3-yloxymethyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 9-Cyclopropylethynyl-2-(4-isopropyl-oxetan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
 and  
 9-Cyclopropylethynyl-2-((R)-4-isopropyl-oxetan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one.
- 15 **[00140]** In one embodiment a compound of the invention is not an isotopic variant.  
**[00141]** In one aspect a compound of the invention is present as the free base.  
**[00142]** In one aspect a compound of the invention is a pharmaceutically acceptable salt.  
**[00143]** In one aspect a compound of the invention is present as the free base or a pharmaceutically acceptable salt.
- 20 **[00144]** In one aspect a compound of the invention is a solvate.  
**[00145]** In one aspect a compound of the invention is a solvate of a pharmaceutically acceptable salt of the compound.  
**[00146]** In certain aspects, the present invention provides prodrugs and derivatives of a compound of the invention according to the formula above. Prodrugs are derivatives of a compound of the invention, which  
 25 have metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention, which are pharmaceutically active, *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.
- [00147]** Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but the acid sensitive form often offers advantages of solubility, tissue compatibility, or  
 30 delayed release in the mammalian organism (see, Bundgard, H. Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well know to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups

pendant on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Particularly useful are the C<sub>1</sub> to C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, aryl, C<sub>7</sub>-C<sub>12</sub> substituted aryl, and C<sub>7</sub>-C<sub>12</sub> arylalkyl esters of the compounds of the invention.

- 5 [00148] While specified groups for each embodiment have generally been listed above separately, a compound of the invention includes one in which several or each embodiment in the above Formula, as well as other formulae presented herein, is selected from one or more of particular members or groups designated respectively, for each variable. Therefore, this invention is intended to include all combinations of such embodiments within its scope.
- 10 [00149] While specified groups for each embodiment have generally been listed above separately, a compound of the invention may be one for which one or more variables (for example, R groups) is selected from one or more embodiments according to any of the Formula(e) listed above. Therefore, the present invention is intended to include all combinations of variables from any of the disclosed embodiments within its scope.
- 15 [00150] Alternatively, the exclusion of one or more of the specified variables from a group or an embodiment, or combinations thereof is also contemplated by the present invention.

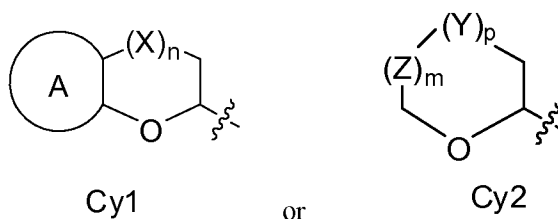
### CLAUSES

- 20 1. A compound according to Formula Ia:



wherein

Cy is



wherein

X is O or S;

Y is  $-\text{CH}_2-$ , or S;

Z is  $-\text{CH}_2-$ ;

each of the subscript n, m, or p is independently selected from 0, and 1; and A is phenyl, or 5-6-membered heteroaryl comprising one or two N-atoms; optionally substituted with one or more independently selected  $\text{R}^5$  groups;

any one of Cy1 and Cy2 is optionally substituted by one or more independently selected  $\text{C}_{1-4}$  alkyl groups;

$\text{R}^1$  is H, Me, or halo;

$\text{L}_1$  is absent or is  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}^{4a}-$ ;

G is

$\text{R}^2$ ,

$-\text{W}-\text{L}_2-\text{R}^2$ , or

$-\text{W}-\text{L}_3-\text{R}^3$ ;

W is  $\text{C}_{1-4}$  alkylene,  $\text{C}_{2-4}$  alkenylene having one double bond, or  $\text{C}_{2-4}$  alkynylene having one triple bond;

$\text{L}_2$  is absent or is  $-\text{O}-$ ;

$\text{R}^2$  is

- H,
- $\text{C}_{1-8}$  alkyl (optionally substituted with one to three groups independently selected from
  - o OH,
  - o halo,

- CN,
  - C<sub>1-6</sub> alkoxy,
  - C<sub>3-7</sub> cycloalkyl,
  - 4-6 membered heterocycloalkyl (comprising one to three heteroatoms independently selected from S, and O),
  - 5-6 membered heteroaryl (comprising one to three heteroatoms independently selected from N, S, and O), and
  - phenyl,
- C<sub>4-7</sub> cycloalkenyl comprising one double bond,
- 5-7 membered heterocycloalkenyl comprising one double bond, and one to three heteroatoms independently selected from O, and S,
- C<sub>3-7</sub> cycloalkyl (optionally substituted with one or more independently selected R<sup>6</sup> groups),
- 4-10 membered heterocycloalkyl comprising one to two heteroatoms independently selected from S, and O, (optionally substituted with one to three independently selected R<sup>6</sup> groups),
- 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O (optionally substituted with one to three independently selected R<sup>7</sup> groups), or
- C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>7</sup> groups);

L<sub>3</sub> is -NR<sup>4b</sup>-;

R<sup>3</sup> is

- C<sub>1-4</sub> alkyl substituted with C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>8</sup> groups), or 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, (optionally substituted with one or more independently selected R<sup>8</sup> groups),
- 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, (optionally substituted with one or more independently selected R<sup>8</sup> groups), or
- C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>8</sup> groups);

Each R<sup>4a</sup> and R<sup>4b</sup> is independently selected from H, C<sub>1-4</sub> alkyl, or C<sub>3-7</sub> cycloalkyl;

R<sup>5</sup> is halo, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy;

R<sup>6</sup> is oxo or R<sup>7</sup>;

R<sup>7</sup> is

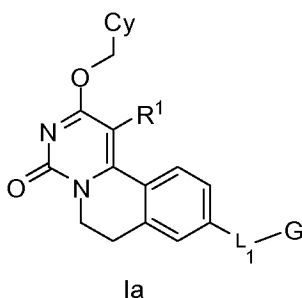
- OH,
- halo,
- -NO<sub>2</sub>,
- C<sub>1-6</sub> alkyl (optionally substituted with one to three groups independently selected from halo, and OH),
- C<sub>1-6</sub> alkoxy (optionally substituted with one to three groups independently selected from halo, and OH),
- C<sub>3-7</sub> cycloalkyl,
- -C(=O)OR<sup>9</sup>,
- -C(=O)NR<sup>10</sup>R<sup>11</sup>,
- -NHC(=O)-C<sub>1-4</sub> alkyl,
- -CN,
- phenyl,
- -O-phenyl,
- 4-7 membered heterocycloalkyl comprising one to three heteroatoms independently selected from N, O, and S, or
- 5-6 membered heteroaryl comprising one to three heteroatoms independently selected from N, O, and S; (optionally substituted with one or more independently selected C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, CN, halo, and -C(=O)OR<sup>12</sup>);

R<sup>8</sup> is C<sub>1-4</sub> alkyl, or halo; and

each of R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup>, is independently selected from H and C<sub>1-4</sub> alkyl.

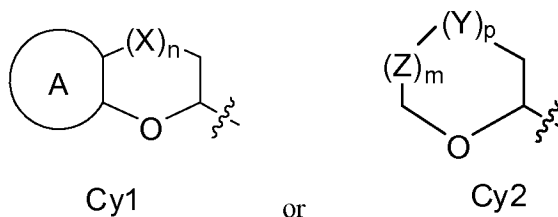
or a pharmaceutically acceptable salt, or a solvate, or a solvate of the pharmaceutically acceptable salts.

2. A compound according to Formula Ia:



wherein

Cy is



wherein

5                      X is is O or S;

Y is is -CH<sub>2</sub>-, or S;

Z is is -CH<sub>2</sub>-;

each of the subscript n, m, or p is independently selected from 0, and 1; and

10                      A is phenyl, or 5-6-membered heteroaryl comprising one or two N-atoms; optionally substituted with one or more independently selected R<sup>5</sup> groups;

R<sup>1</sup> is H, Me, or halo;

L<sub>1</sub> is absent or is -O-, -S-, or -NR<sup>4a</sup>-;

G is

15                      R<sup>2</sup>,  
                         -W-L<sub>2</sub>-R<sup>2</sup>, or  
                         -W-L<sub>3</sub>-R<sup>3</sup>;

W is C<sub>1-4</sub> alkylene, C<sub>2-4</sub> alkenylene having one double bond, or C<sub>2-4</sub> alkynylene having one triple bond;

L<sub>2</sub> is absent or is -O-;

20                      R<sup>2</sup> is

- H,
- C<sub>1-8</sub> alkyl (optionally substituted with one to three groups independently selected from
  - OH,

- halo,
  - CN,
  - C<sub>1-6</sub> alkoxy,
  - C<sub>3-7</sub> cycloalkyl,
- 5
  - 4-6 membered heterocycloalkyl (comprising one to three heteroatoms independently selected from S, and O),
  - 5-6 membered heteroaryl (comprising one to three heteroatoms independently selected from N, S, and O), and
  - phenyl,
- 10
  - C<sub>4-7</sub> cycloalkenyl comprising one double bond,
  - 5-7 membered heterocycloalkenyl comprising one double bond, and one to three heteroatoms independently selected from O, and S,
  - C<sub>3-7</sub> cycloalkyl (optionally substituted with one or more independently selected R<sup>6</sup> groups),
  - 4-10 membered heterocycloalkyl comprising one to two heteroatoms independently selected
- 15
  - from S, and O, (optionally substituted with one to three independently selected R<sup>6</sup> groups),
  - 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O (optionally substituted with one to three independently selected R<sup>7</sup> groups), or
  - C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>7</sup> groups);

L<sub>3</sub> is -NR<sup>4b</sup>-;

- 20
  - R<sup>3</sup> is
  - C<sub>1-4</sub> alkyl substituted with C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>8</sup> groups), or 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, (optionally substituted with one or more independently selected R<sup>8</sup> groups),
- 25
  - 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, (optionally substituted with one or more independently selected R<sup>8</sup> groups), or
  - C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>8</sup> groups);

Each R<sup>4a</sup> and R<sup>4b</sup> is independently selected from H, C<sub>1-4</sub> alkyl, or C<sub>3-7</sub> cycloalkyl;

R<sup>5</sup> is halo, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy;

- 30
  - R<sup>6</sup> is oxo or R<sup>7</sup>;



R<sup>7</sup> is

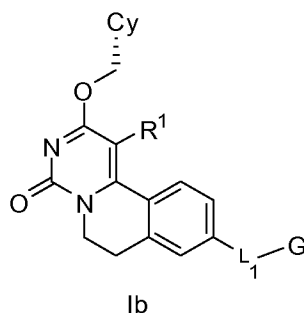
- OH,
- halo,
- -NO<sub>2</sub>,
- 5    - C<sub>1-6</sub> alkyl (optionally substituted with one to three groups independently selected from halo, and OH),
- C<sub>1-6</sub> alkoxy (optionally substituted with one to three groups independently selected from halo, and OH),
- C<sub>3-7</sub> cycloalkyl,
- 10    - -C(=O)OR<sup>9</sup>,
- -C(=O)NR<sup>10</sup>R<sup>11</sup>,
- -NHC(=O)-C<sub>1-4</sub> alkyl,
- -CN,
- phenyl,
- 15    - -O-phenyl,
- 4-7 membered heterocycloalkyl comprising one to three heteroatoms independently selected from N, O, and S, or
- 5-6 membered heteroaryl comprising one to three heteroatoms independently selected from N, O, and S; (optionally substituted with one or more independently selected C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy,
- 20    CN, halo, and -C(=O)OR<sup>12</sup>);

R<sup>8</sup> is C<sub>1-4</sub> alkyl, or halo; and

each of R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup>, is independently selected from H and C<sub>1-4</sub> alkyl.

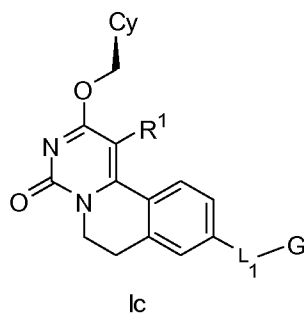
or a pharmaceutically acceptable salt, or a solvate, or a solvate of the pharmaceutically acceptable salts.

3. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein the compound is according to Formula Ib:



wherein Cy, R<sup>1</sup>, L<sub>1</sub> and G are as previously described.

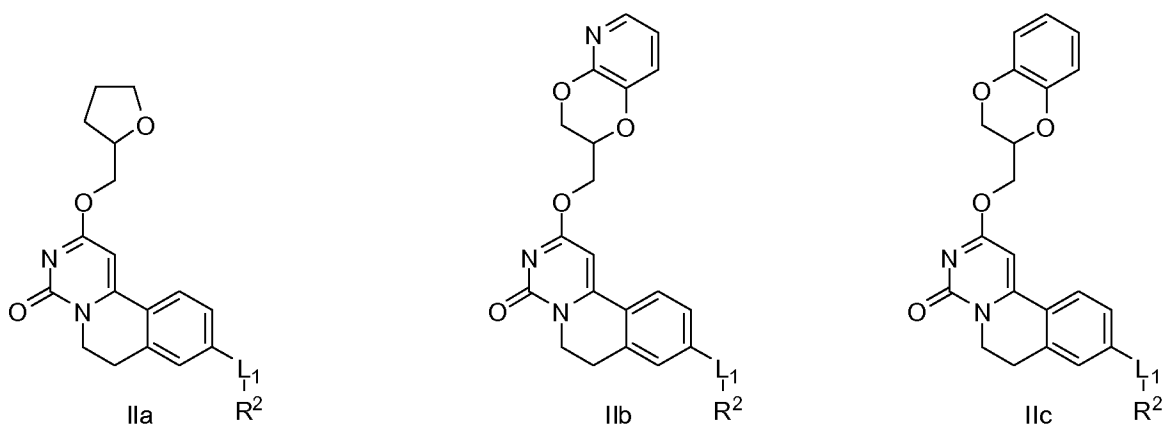
4. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein the compound is according to Formula Ic:



wherein Cy, R<sup>1</sup>, L<sub>1</sub> and G are as previously described.

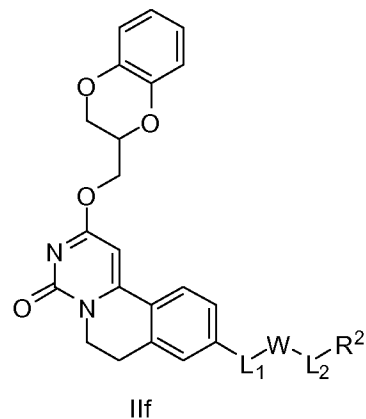
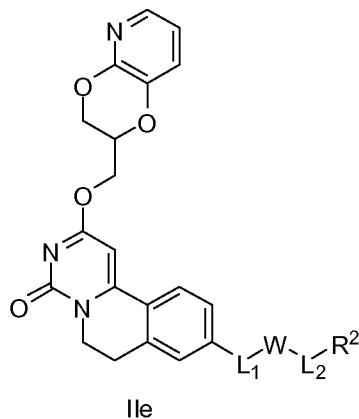
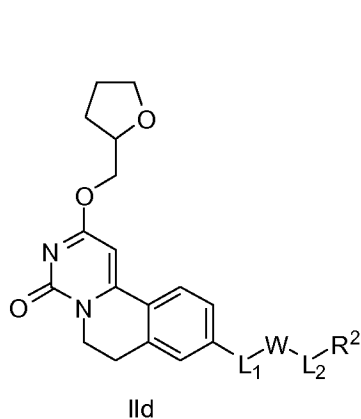
5. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-4, wherein Cy is Cy1.
6. A compound or pharmaceutically acceptable salt thereof, according to clause 5, wherein the subscript n is 0.
7. A compound or pharmaceutically acceptable salt thereof, according to clause 5, wherein the subscript n is 1 and X is O.
8. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 5-6, wherein the ring A is phenyl.
9. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 5-6, wherein the ring A is pyridinyl.
10. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-4, wherein Cy is Cy2.
11. A compound or pharmaceutically acceptable salt thereof, according to clause 10, wherein the subscript m is 0, the subscript p is 1 and Y is -CH<sub>2</sub>-.

12. A compound or pharmaceutically acceptable salt thereof, according to clause 10, wherein, the subscript m is 1, Z is -CH<sub>2</sub>-, the subscript p is 1 and Y is -CH<sub>2</sub>-.
13. A compound or pharmaceutically acceptable salt thereof, according to clause 10, wherein the subscript m is 1, Z is -CH<sub>2</sub>-, the subscript p is 1 and Y is S.
- 5 14. A compound or pharmaceutically acceptable salt thereof, according to clause 10, wherein the subscript m and p are both 0.
15. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-14, wherein R<sup>1</sup> is Me, F, or Cl.
- 10 16. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-4, or 10, wherein R<sup>1</sup> is H.
17. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein the compound is according to any one of Formulae IIa-IIc:



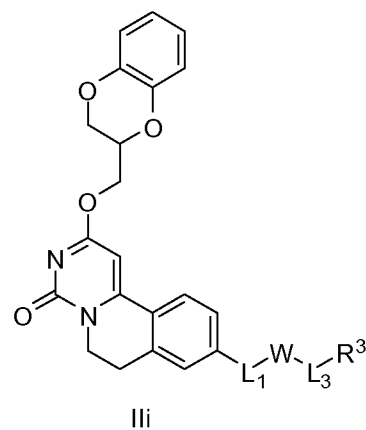
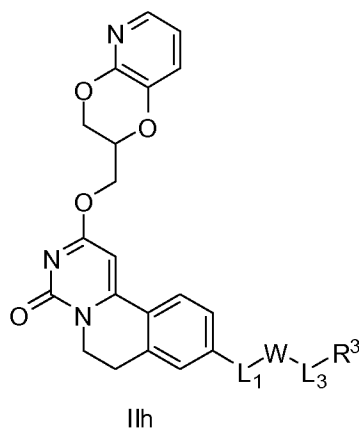
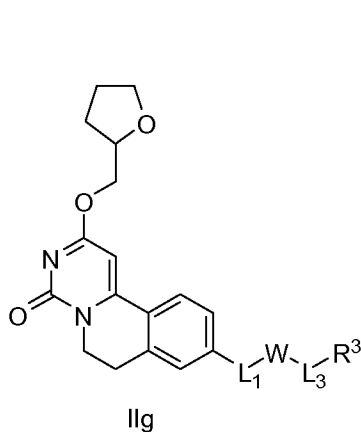
wherein L<sub>1</sub>, and R<sup>2</sup> are as described in clause 1 or 2.

- 15 18. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein the compound is according to any one of Formulae IIId-IIIf:



wherein  $L_1$ ,  $W$ ,  $L_2$ , and  $R^2$  are as described in clause 1 or 2.

19. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein the compound is according to any one of Formulae IIg-III:



wherein  $L_1$ ,  $W$ ,  $L_3$ , and  $R^3$  are as described in clause 1 or 2.

20. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-19, wherein  $L_1$  is absent.
21. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-19, wherein  $L_1$  is  $-O-$ .
22. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-19, wherein  $L_1$  is  $-NR^{4a}-$ , and  $R^{4a}$  is H, Me, Et, or cyclopropyl.
23. A compound or pharmaceutically acceptable salt thereof, according to clause 22 wherein  $R^{4a}$  is H.

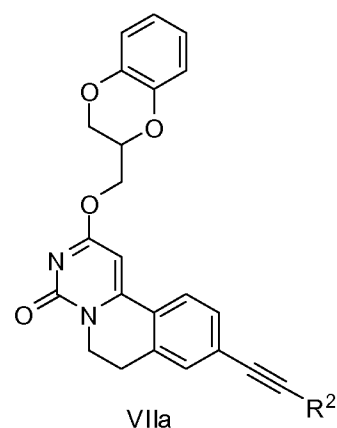
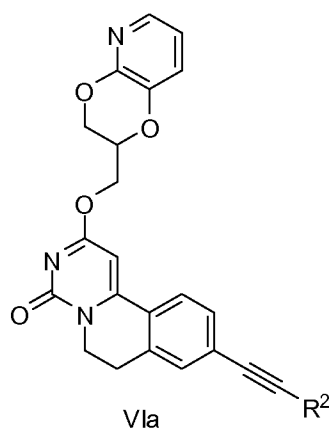
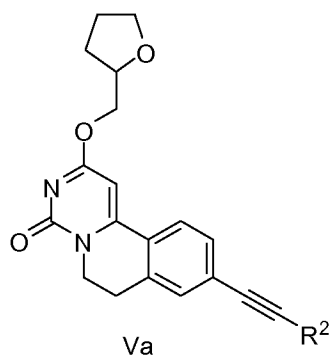
24. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-16, or 18-23 wherein W is C<sub>1-4</sub> alkylene.
25. A compound or pharmaceutically acceptable salt thereof, according to clause 24, wherein W is -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-CH(CH<sub>3</sub>)-, -CH<sub>2</sub>-CH(-CH<sub>2</sub>-CH<sub>3</sub>)-, -CH<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>-, or -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-.
- 5 26. A compound or pharmaceutically acceptable salt thereof, according to clause 25, wherein W is -CH<sub>2</sub>-CH<sub>2</sub>-.
27. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-16, or 18-23, wherein W is C<sub>2-4</sub> alkenylene having one double bond.
28. A compound or pharmaceutically acceptable salt thereof, according to clause 27, wherein W is -CH=CH-, -CH<sub>2</sub>-CH=CH-, or -CH=CH-CH<sub>2</sub>-.
- 10 29. A compound or pharmaceutically acceptable salt thereof, according to clause 28, wherein W is -CH=CH-.
30. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-16, or 18-23, wherein W is C<sub>2-4</sub> alkynylene having one triple bond.
- 15 31. A compound or pharmaceutically acceptable salt thereof, according to clause 30, wherein W is -C≡C-, -CH<sub>2</sub>-C≡C-, or -C≡C-CH<sub>2</sub>-.
32. A compound or pharmaceutically acceptable salt thereof, according to clause 31, wherein W is -C≡C-.
33. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-16, 18, or 20-32, wherein L<sub>2</sub> is -O-.
- 20 34. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-16, 18, or 20-32, wherein L<sub>2</sub> is absent.
35. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-16 or 18, wherein L<sub>1</sub> and L<sub>2</sub> are absent, and W is -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, or -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-.
- 25 36. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-16 or 18, wherein L<sub>1</sub> and L<sub>2</sub> are absent, and W is -CH=CH-, -CH<sub>2</sub>-CH=CH-, or -CH=CH-CH<sub>2</sub>-.
37. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-16 or 18, wherein L<sub>1</sub> and L<sub>2</sub> are absent, and W is -C≡C-, -CH<sub>2</sub>-C≡C-, or -C≡C-CH<sub>2</sub>-.
38. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-18, or 20-30 37, wherein R<sup>2</sup> is H.
39. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-18, or 20-37, wherein R<sup>2</sup> is C<sub>1-8</sub> alkyl.
40. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-18, or 20-37, wherein R<sup>2</sup> is C<sub>1-8</sub> alkyl substituted with one group selected from OH, halo, CN, C<sub>1-6</sub> alkoxy, C<sub>3-7</sub>

cycloalkyl, 4-6 membered heterocycloalkyl (comprising one to three heteroatoms independently selected from S, and O), 5-6 membered heteroaryl (comprising one to three heteroatoms independently selected from N, S, and O), and phenyl.

41. A compound or pharmaceutically acceptable salt thereof, according to clause 39 or 40, wherein R<sup>2</sup> is Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, or *t*-Bu.
42. A compound or pharmaceutically acceptable salt thereof, according to clause 40, wherein R<sup>2</sup> is C<sub>1-8</sub> alkyl substituted with one group selected from OH, F, Cl, CN, -OMe, -OEt, -Oi-Pr, cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrololyl, imidazolyl, triazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and phenyl.
43. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-18, or 20-37, wherein R<sup>2</sup> is C<sub>4-7</sub> cycloalkenyl comprising one double bond.
44. A compound or pharmaceutically acceptable salt thereof, according to clause 43, wherein R<sup>2</sup> is cyclohexenyl.
45. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-18, or 20-37, wherein R<sup>2</sup> is 5-7 membered heterocycloalkenyl comprising one double bond, and one to three heteroatoms independently selected from N, O, and S.
46. A compound or pharmaceutically acceptable salt thereof, according to clause 45, wherein R<sup>2</sup> is dihydropyranyl.
47. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-18, or 20-37, wherein R<sup>2</sup> is C<sub>3-7</sub> cycloalkyl.
48. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-18, or 20-37, wherein R<sup>2</sup> is C<sub>3-7</sub> cycloalkyl substituted with one R<sup>6</sup> group.
49. A compound or pharmaceutically acceptable salt thereof, according to clause 48, wherein R<sup>6</sup> is oxo, or R<sup>7</sup>, and R<sup>7</sup> is OH, or C<sub>1-6</sub> alkyl.
50. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48 or 49, wherein R<sup>2</sup> is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.
51. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-18, or 20-37, wherein R<sup>2</sup> is 4-10 membered heterocycloalkyl comprising one to two heteroatoms independently selected from S, and O.
52. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-18, or 20-37, wherein R<sup>2</sup> is 4-10 membered heterocycloalkyl comprising one to two heteroatoms independently selected from S, and O, substituted with one R<sup>6</sup> group.
53. A compound or pharmaceutically acceptable salt thereof, according to clause 52, wherein R<sup>6</sup> is oxo, or R<sup>7</sup>, and R<sup>7</sup> is OH, or C<sub>1-6</sub> alkyl.

54. A compound or pharmaceutically acceptable salt thereof, according to clause 50, 51 or 52, wherein R<sup>2</sup> is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl.
55. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-18, or 20-37, wherein R<sup>2</sup> is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O.
56. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-18, or 20-37, wherein R<sup>2</sup> is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, substituted with one or two independently selected R<sup>7</sup> groups.
57. A compound or pharmaceutically acceptable salt thereof, according to clause 56, wherein each R<sup>7</sup> is independently selected from OH, halo, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyl substituted with one or more halo, C<sub>1-6</sub> alkoxy, -CN, C<sub>3-7</sub> cycloalkyl, 4-7 membered heterocycloalkyl comprising one to three heteroatoms independently selected from N, O, and S, and phenyl.
58. A compound or pharmaceutically acceptable salt thereof, according to clause 55, 56 or 57, wherein R<sup>2</sup> is furanyl, thienyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, triazolyl, pyridinyl, pyrazinyl, pyrimidinyl, indanyl, or indazolyl.
59. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-18, or 20-37, wherein R<sup>2</sup> is C<sub>6-10</sub> aryl.
60. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-18, or 20-37, wherein R<sup>2</sup> is C<sub>6-10</sub> aryl, substituted with one or two independently selected R<sup>7</sup> groups.
61. A compound or pharmaceutically acceptable salt thereof, according to clause 60, wherein R<sup>7</sup> is selected from halo, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, -NHC(=O)-C<sub>1-4</sub> alkyl, and -C(=O)NR<sup>10</sup>R<sup>11</sup>, wherein each R<sup>10</sup> and R<sup>11</sup> is independently selected from H and C<sub>1-4</sub> alkyl.
62. A compound or pharmaceutically acceptable salt thereof, according to clause 59, 60 or 61, wherein R<sup>2</sup> is phenyl.
63. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-16, or 19-32, wherein L<sub>3</sub> is -NR<sup>4b</sup>-, and R<sup>4b</sup> is H, Me, Et, or cyclopropyl.
64. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-16, 19-32, or 63, wherein R<sup>3</sup> is C<sub>1-4</sub> alkyl substituted with phenyl, or pyridyl.
65. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-16, 19-32, or 63, wherein R<sup>3</sup> is C<sub>1-4</sub> alkyl substituted with phenyl, or pyridyl, each of which is substituted with Me, Et, F, or Cl.
66. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-16, 19-32, or 63, wherein R<sup>3</sup> is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O.

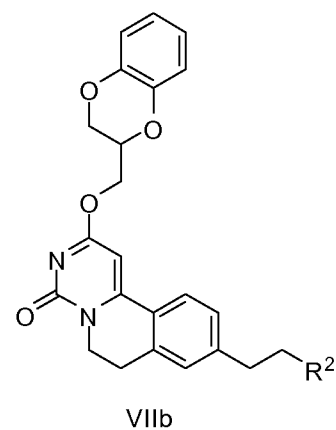
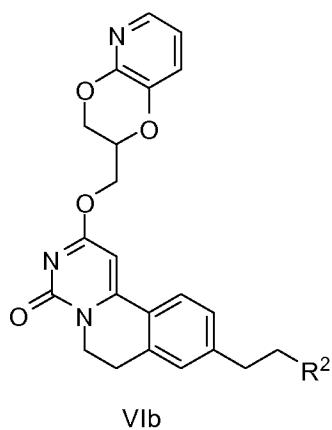
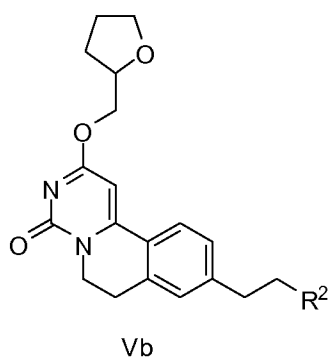
67. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-16, 19-32, or 63, wherein  $R^3$  is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, substituted with one or more independently selected  $R^8$  groups.
68. A compound or pharmaceutically acceptable salt thereof, according to clause 67 wherein  $R^8$  is selected from Me, Et, F, and Cl.
69. A compound or pharmaceutically acceptable salt thereof, according to clause 66, 67, or 68 wherein  $R^3$  is pyridyl.
70. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-16, 19-32, or 63, wherein  $R^3$  is  $C_{6-10}$  aryl.
71. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-16, 19-32, or 63, wherein  $R^3$  is  $C_{6-10}$  aryl, substituted with one or more independently selected  $R^8$  groups.
72. A compound or pharmaceutically acceptable salt thereof, according to clause 71, wherein  $R^8$  is selected from Me, Et, F, and Cl.
73. A compound or pharmaceutically acceptable salt thereof, according to clause 70, 71, or 72, wherein  $R^3$  is phenyl.
74. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein the compound is according to Formulae Va, VIa, or VIIa:



wherein  $R^2$  is as described in clause 1 or 2.

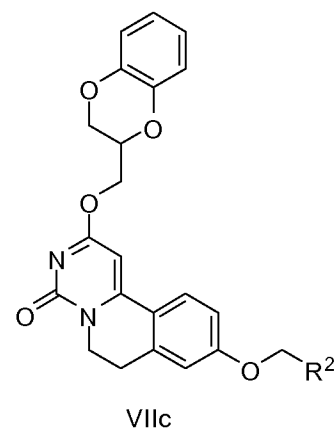
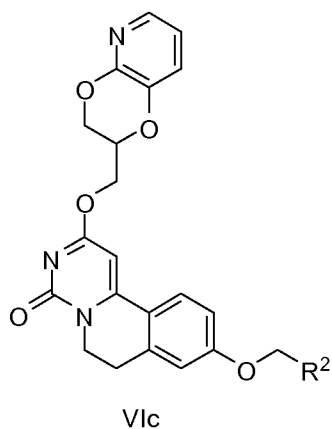
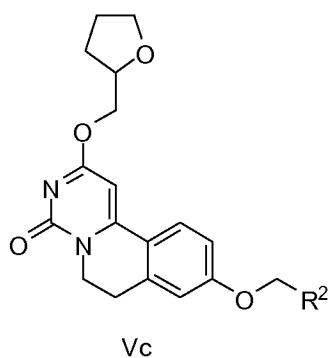
75. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein the compound is according to Formulae Vb, VIb, or VIIb:





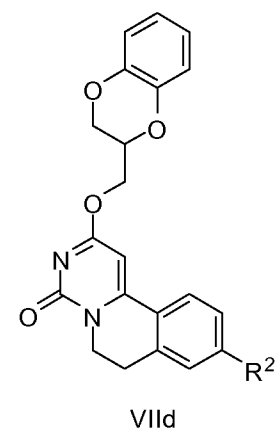
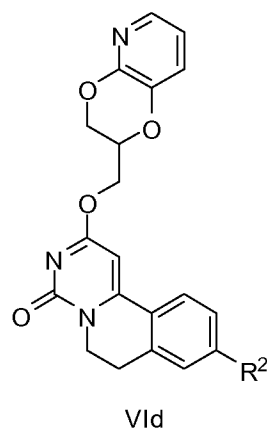
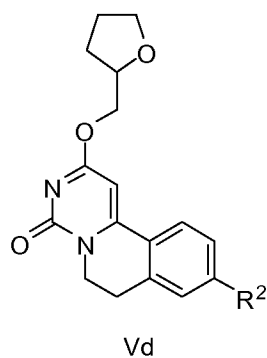
wherein R<sup>2</sup> is as described in clause 1 or 2.

76. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein the compound is according to Formulae Vc, VIc, or VIIc:



wherein R<sup>2</sup> is as described in clause 1 or 2.

77. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein the compound is according to Formulae Vd, VIId, or VIIId:



wherein  $R^2$  is as described in clause 1 or 2.

78. A compound or pharmaceutically acceptable salt thereof, according to clause 74 or 75, wherein  $R^2$  is  $C_{3-7}$  cycloalkyl.
79. A compound or pharmaceutically acceptable salt thereof, according to clause 74 or 75, wherein  $R^2$  is  $C_{3-7}$  cycloalkyl substituted with one  $R^6$  group.
80. A compound or pharmaceutically acceptable salt thereof, according to clause 79, wherein  $R^6$  is oxo, or  $R^7$ , and  $R^7$  is OH, or  $C_{1-6}$  alkyl.
81. A compound or pharmaceutically acceptable salt thereof, according to clause 78, 79 or 80, wherein  $R^2$  is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.
82. A compound or pharmaceutically acceptable salt thereof, according to clause 76 or 77, wherein  $R^2$  is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O.
83. A compound or pharmaceutically acceptable salt thereof, according to clause 76 or 77, wherein  $R^2$  is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, substituted with one or two independently selected  $R^7$  groups.
84. A compound or pharmaceutically acceptable salt thereof, according to clause 83, wherein  $R^7$  is selected from OH, halo,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl substituted with one or more halo,  $C_{1-6}$  alkoxy, -CN,  $C_{3-7}$  cycloalkyl, 4-7 membered heterocycloalkyl comprising one to three heteroatoms independently selected from N, O, and S, and phenyl.
85. A compound or pharmaceutically acceptable salt thereof, according to clause 82, 83 or 84, wherein  $R^2$  is furanyl, thienyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, triazolyl, pyridinyl, pyrazinyl, pyrimidinyl, indanyl, or indazolyl.
86. A compound or pharmaceutically acceptable salt thereof, according to clause 76 or 77, wherein  $R^2$  is  $C_{6-10}$  aryl.
87. A compound or pharmaceutically acceptable salt thereof, according to clause 76 or 77, wherein  $R^2$  is  $C_{6-10}$  aryl substituted with one or two independently selected  $R^7$  groups.
88. A compound or pharmaceutically acceptable salt thereof, according to clause 87, wherein  $R^7$  is selected from halo, CN,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, -NHC(=O)- $C_{1-4}$  alkyl, and -C(=O)NR<sup>10</sup>R<sup>11</sup>, and each  $R^{10}$  and  $R^{11}$  is independently selected from H and  $C_{1-4}$  alkyl.
89. A compound or pharmaceutically acceptable salt thereof, according to clause 86, 87 or 88, wherein  $R^2$  is phenyl.

### PHARMACEUTICAL COMPOSITIONS

[00151] When employed as a pharmaceutical, a compound of the invention is typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, a compound of the invention is administered in a pharmaceutically effective amount. The amount of a compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[00152] The pharmaceutical compositions of the invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intra-articular, intravenous, intramuscular, intranasal and inhalation. Depending on the intended route of delivery, a compound of this invention is preferably formulated as either injectable or oral compositions or as salves, as lotions or as patches all for transdermal administration.

[00153] The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient, vehicle or carrier. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, a compound of the invention is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

[00154] Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00155] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As before, the active compound in such compositions is

typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

[00156] Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s), generally in an amount ranging from about 0.01 to about 20% by weight, preferably from about 0.1 to about 20% by weight, preferably from about 0.1 to about 10% by weight, and more preferably from about 0.5 to about 15% by weight. When formulated as a ointment, the active ingredients will typically be combined with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration of stability of the active ingredients or the formulation. All such known transdermal formulations and ingredients are included within the scope of this invention.

[00157] A compound of the invention can also be administered by a transdermal device. Accordingly, transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.

[00158] The above-described components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of Remington's Pharmaceutical Sciences, 17th edition, 1985, Mack Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

[00159] A compound of the invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in Remington's Pharmaceutical Sciences.

[00160] The following formulation examples illustrate representative pharmaceutical compositions that may be prepared in accordance with this invention. The present invention, however, is not limited to the following pharmaceutical compositions.

#### **Formulation 1 - Tablets**

[00161] A compound of the invention may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate may be added as a lubricant. The mixture may be formed into 240-270 mg tablets (80-90 mg of active amide compound per tablet) in a tablet press.

#### **Formulation 2 - Capsules**

[00162] A compound of the invention may be admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture may be filled into 250 mg capsules (125 mg of active amide compound per capsule).

**Formulation 3 - Liquid**

[00163] A compound of the invention (125 mg), may be admixed with sucrose (1.75 g) and xanthan gum (4 mg) and the resultant mixture may be blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color may be diluted with water and added with stirring. Sufficient water may then be added with stirring. Sufficient water may be then added to produce a total volume of 5 mL.

**Formulation 4 - Tablets**

[00164] A compound of the invention may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate may be added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active amide compound) in a tablet press.

**Formulation 5 - Injection**

[00165] A compound of the invention may be dissolved or suspended in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/mL.

**Formulation 6 - Topical**

[00166] Stearyl alcohol (250 g) and a white petrolatum (250 g) may be melted at about 75°C and then a mixture of a compound of the invention (50 g) methylparaben (0.25 g), propylparaben (0.15 g), sodium lauryl sulfate (10 g), and propylene glycol (120 g) dissolved in water (about 370 g) may be added and the resulting mixture may be stirred until it congeals.

**METHODS OF TREATMENT**

[00167] A compound of the invention may be used as a therapeutic agent for the treatment of conditions in mammals that are causally related or attributable to aberrant activity of GPR84 and/or aberrant GPR84 expression and/or aberrant GPR84 distribution.

[00168] Accordingly, a compound and pharmaceutical compositions of the invention find use as therapeutics for the prophylaxis and/or treatment of inflammatory conditions (e.g. inflammatory bowel diseases (IBD), rheumatoid arthritis, vasculitis), lung diseases (e.g. chronic obstructive pulmonary disease (COPD) and lung interstitial diseases (e.g. idiopathic pulmonary fibrosis (IPF))), neuroinflammatory conditions, infectious diseases, autoimmune diseases, endocrine and/or metabolic diseases, and/or diseases involving impairment of immune cell functions, in mammals including humans.

[00169] Accordingly, in one aspect, the present invention provides the compound of the invention, or a pharmaceutical composition comprising the compound of the invention for use as a medicament.

[00170] In another aspect, the present invention provides the compound of the invention, or a pharmaceutical composition comprising the compound of the invention for use in the manufacture of a medicament.

[00171] In yet another aspect, the present invention provides a method of treating a mammal having, or at risk of having a disease disclosed herein. In a particular aspect, the present invention provides a method of treating a mammal having, or at risk of having inflammatory conditions (e.g. inflammatory bowel diseases (IBD), rheumatoid arthritis, vasculitis), lung diseases (e.g. chronic obstructive pulmonary disease (COPD) and lung interstitial diseases (e.g. idiopathic pulmonary fibrosis (IPF))), neuroinflammatory conditions, infectious diseases, autoimmune diseases, endocrine and/or metabolic diseases, and/or diseases involving impairment of immune cell functions, in mammals including humans, said method comprising administering an effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described.

[00172] In one aspect, the present invention provides the compound of the invention, or a pharmaceutical composition comprising the compound of the invention for use in the prophylaxis and/or treatment of inflammatory conditions. In a specific embodiment, the inflammatory condition is selected from inflammatory bowel disease (IBD), rheumatoid arthritis, vasculitis, chronic obstructive pulmonary disease (COPD), and idiopathic pulmonary fibrosis (IPF).

[00173] In another aspect, the present invention provides the compound of the invention, or a pharmaceutical composition comprising the compound of the invention for use in the manufacture of a medicament for the prophylaxis and/or treatment of inflammatory conditions. In a specific embodiment, the inflammatory condition is selected from inflammatory bowel disease (IBD), rheumatoid arthritis, vasculitis, chronic obstructive pulmonary disease (COPD), and idiopathic pulmonary fibrosis (IPF).

[00174] In another aspect, the present invention provides a method of treating a mammal having, or at risk of having a disease selected from inflammatory conditions (for example inflammatory bowel diseases (IBD), rheumatoid arthritis, vasculitis), lung diseases (e.g. chronic obstructive pulmonary disease (COPD) and lung interstitial diseases (e.g. idiopathic pulmonary fibrosis (IPF))), neuroinflammatory conditions, infectious diseases, autoimmune diseases, endocrine and/or metabolic diseases, and/or diseases involving impairment of immune cell functions, which method comprises administering an effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described.

[00175] In additional method of treatment aspects, this invention provides methods of treatment and/or prophylaxis of a mammal susceptible to or afflicted with inflammatory conditions, which method comprises administering an effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described. In a specific embodiment, the inflammatory condition is selected from

inflammatory bowel disease (IBD), rheumatoid arthritis, vasculitis, chronic obstructive pulmonary disease (COPD), and idiopathic pulmonary fibrosis (IPF).

**[00176]** In one aspect, the present invention provides a compound of the invention, or a pharmaceutical composition comprising the compound of the invention for use in the prophylaxis and/or treatment of neuroinflammatory conditions, Guillain-Barré syndrome (GBS), multiple sclerosis, axonal degeneration, autoimmune encephalomyelitis.

**[00177]** In another aspect, the present invention provides a compound of the invention, or a pharmaceutical composition comprising the compound of the invention for use in the manufacture of a medicament for the prophylaxis and/or treatment of neuroinflammatory conditions, Guillain-Barré syndrome (GBS), multiple sclerosis, axonal degeneration, autoimmune encephalomyelitis.

**[00178]** In additional method of treatment aspects, this invention provides methods of treatment and/or prophylaxis of a mammal susceptible to or afflicted with neuroinflammatory conditions, Guillain-Barré syndrome (GBS), multiple sclerosis, axonal degeneration, autoimmune encephalomyelitis, which method comprises administering an effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described.

**[00179]** In one aspect, the present invention provides a compound of the invention, or a pharmaceutical composition comprising the compound of the invention for use in the prophylaxis and/or treatment of infectious disease(s). In a specific embodiment, the infectious disease(s) is selected from sepsis, septicemia, endotoxemia, systemic inflammatory response syndrome (SIRS), gastritis, enteritis, enterocolitis, tuberculosis, and other infections involving, for example, Yersinia, Salmonella, Chlamydia, Shigella, enterobacteria species.

**[00180]** In another aspect, the present invention provides a compound of the invention, or a pharmaceutical composition comprising the compound of the invention for use in the manufacture of a medicament for the prophylaxis and/or treatment of infectious disease(s). In a specific embodiment, the infectious disease(s) is selected from sepsis, septicemia, endotoxemia, systemic inflammatory response syndrome (SIRS), gastritis, enteritis, enterocolitis, tuberculosis, and other infections involving, for example, Yersinia, Salmonella, Chlamydia, Shigella, enterobacteria species.

**[00181]** In additional method of treatment aspects, this invention provides methods of treatment and/or prophylaxis of a mammal susceptible to or afflicted with infectious disease(s), which method comprises administering an effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described. In a specific embodiment, the infectious disease is selected from sepsis, septicemia, endotoxemia, systemic inflammatory response syndrome (SIRS), gastritis, enteritis, enterocolitis, tuberculosis, and other infections involving, for example, Yersinia, Salmonella, Chlamydia, Shigella, enterobacteria species.

[00182] In one aspect, the present invention provides the compound of the invention, or a pharmaceutical composition comprising the compound of the invention for use in the prophylaxis and/or treatment of autoimmune diseases, and/or diseases involving impairment of immune cell functions. In a specific embodiment, the autoimmune diseases and/or diseases involving impairment of immune cell functions is selected from COPD, asthma, psoriasis, systemic lupus erythematosus, type I diabetes mellitus, vasculitis and inflammatory bowel disease.

[00183] In another aspect, the present invention provides the compound of the invention, or a pharmaceutical composition comprising the compound of the invention for use in the manufacture of a medicament for the prophylaxis and/or treatment of autoimmune diseases and/or diseases involving impairment of immune cell functions. In a specific embodiment, the autoimmune diseases, and/or diseases involving impairment of immune cell functions is selected from COPD, asthma, psoriasis, systemic lupus erythematosus, type I diabetes mellitus, vasculitis and inflammatory bowel disease.

[00184] In additional method of treatment aspects, this invention provides methods of treatment and/or prophylaxis of a mammal susceptible to or afflicted with autoimmune diseases and/or diseases involving impairment of immune cell functions, which method comprises administering an effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described. In a specific embodiment, the autoimmune diseases and/or diseases involving impairment of immune cell functions is selected from COPD, asthma, psoriasis, systemic lupus erythematosus, type I diabetes mellitus, vasculitis and inflammatory bowel disease.

[00185] In one aspect, the present invention provides the compound of the invention, or a pharmaceutical composition comprising the compound of the invention for use in the prophylaxis and/or treatment of endocrine and/or metabolic diseases. In a specific embodiment, the endocrine and/or metabolic diseases is selected from hypothyroidism, congenital adrenal hyperplasia, diseases of the parathyroid gland, diabetes mellitus, diseases of the adrenal glands (including Cushing's syndrome and Addison's disease), ovarian dysfunction (including polycystic ovary syndrome), cystic fibrosis, phenylketonuria (PKU), diabetes, hyperlipidemia, gout, and rickets.

[00186] In another aspect, the present invention provides the compound of the invention, or a pharmaceutical composition comprising the compound of the invention for use in the manufacture of a medicament for the prophylaxis and/or treatment of endocrine and/or metabolic diseases. In a specific embodiment, the endocrine and/or metabolic diseases is selected from hypothyroidism, congenital adrenal hyperplasia, diseases of the parathyroid gland, diabetes mellitus, diseases of the adrenal glands (including Cushing's syndrome and Addison's disease), ovarian dysfunction (including polycystic ovary syndrome), cystic fibrosis, phenylketonuria (PKU), diabetes, hyperlipidemia, gout, and rickets.



[00187] In additional method of treatment aspects, this invention provides methods of treatment and/or prophylaxis of a mammal susceptible to or afflicted with endocrine and/or metabolic diseases, which method comprises administering an effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described. In a specific embodiment, the endocrine and/or metabolic diseases is selected from hypothyroidism, congenital adrenal hyperplasia, diseases of the parathyroid gland, diabetes mellitus, diseases of the adrenal glands (including Cushing's syndrome and Addison's disease), ovarian dysfunction (including polycystic ovary syndrome), cystic fibrosis, phenylketonuria (PKU), diabetes, hyperlipidemia, gout, and rickets.

[00188] As a further aspect of the invention there is provided a compound of the invention for use as a medicament especially in the treatment or prevention of the aforementioned conditions and diseases. Also provided herein is the use of the compound in the manufacture of a medicament for the treatment or prevention of one of the aforementioned conditions and diseases.

[00189] A particular regimen of the present method comprises the administration to a subject in suffering from an inflammatory condition, of an effective amount of a compound of the invention for a period of time sufficient to reduce the level of inflammation in the subject, and preferably terminate, the processes responsible for said inflammation. A special embodiment of the method comprises administering of an effective amount of a compound of the invention to a subject suffering from or susceptible to the development of inflammatory condition, for a period of time sufficient to reduce or prevent, respectively, inflammation of said patient, and preferably terminate, the processes responsible for said inflammation.

[00190] Injection dose levels range from about 0.1 mg/kg/h to at least 10 mg/kg/h, all for from about 1 to about 120 h and especially 24 to 96 h. A preloading bolus of from about 0.1 mg/kg to about 10 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 2 g/day for a 40 to 80 kg human patient.

[00191] Transdermal doses are generally selected to provide similar or lower blood levels than are achieved using injection doses.

[00192] When used to prevent the onset of a condition, a compound of the invention will be administered to a patient at risk for developing the condition, typically on the advice and under the supervision of a physician, at the dosage levels described above. Patients at risk for developing a particular condition generally include those that have a family history of the condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition.

[00193] A compound of the invention can be administered as the sole active agent or it can be administered in combination with other therapeutic agents, including other compounds that demonstrate the same or a similar therapeutic activity, and that are determined to be safe and efficacious for such combined

administration. In a specific embodiment, co-administration of two (or more) agents allows for significantly lower doses of each to be used, thereby reducing the side effects seen.

**[00194]** In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of an inflammatory condition; particular agents include, but are not limited to, immunoregulatory agents e.g. azathioprine, corticosteroids (e.g. prednisolone or dexamethasone), cyclophosphamide, cyclosporin A, tacrolimus, Mycophenolate Mofetil, muromonab-CD3 (OKT3, e.g. Orthocolone®), ATG, aspirin, acetaminophen, ibuprofen, naproxen, and piroxicam.

**[00195]** In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of arthritis (e.g. rheumatoid arthritis); particular agents include but are not limited to analgesics, non-steroidal anti-inflammatory drugs (NSAIDS), steroids, synthetic DMARDS (for example but without limitation methotrexate, leflunomide, sulfasalazine, auranofin, sodium aurothiomalate, penicillamine, chloroquine, hydroxychloroquine, azathioprine, and cyclosporin), and biological DMARDS (for example but without limitation Infliximab, Etanercept, Adalimumab, Rituximab, Golimumab, Certolizumab pegol, Tocilizumab, Interleukin 1 blockers and Abatacept).

**[00196]** In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of autoimmune diseases; particular agents include but are not limited to: glucocorticoids, cytostatic agents (e.g. purine analogs), alkylating agents, (e.g. nitrogen mustards (cyclophosphamide), nitrosoureas, platinum compounds, and others), antimetabolites (e.g. methotrexate, azathioprine and mercaptopurine), cytotoxic antibiotics (e.g. dactinomycin anthracyclines, mitomycin C, bleomycin, and mithramycin), antibodies (e.g., anti-CD20, anti-CD25 or anti-CD3 (OTK3) monoclonal antibodies, Atgam® and Thymoglobuline®), cyclosporin, tacrolimus, rapamycin (sirolimus), interferons (e.g. IFN-β), TNF binding proteins (e.g. infliximab (Remicade™), etanercept (Enbrel™), or adalimumab (Humira™)), mycophenolate, Fingolimod, and Myriocin.

**[00197]** In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of infectious diseases; particular agents include but are not limited to antibiotics. In a particular embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of infections of any organ of the human body; particular agents include but are not limited to: aminoglycosides, ansamycins, carbacephem, carbapenems, cephalosporins, glycopeptides, lincosamides, macrolides, monobactams, nitrofurans, penicillins, polypeptides, quinolones, sulfonamides, tetracyclins, anti-mycobacterial agents, as well as chloramphenicol, fosfomycin, linezolid, metronidazole, mupirocin, rifamycin, thiamphenicol and tinidazole.

**[00198]** In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of vasculitis, particular agents include but are not limited to

steroids (for example prednisone, prednisolone), cyclophosphamide and eventually antibiotics in case of cutaneous infections (for example cephalexin)

**[00199]** In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of IPF, particular agents include but are not limited to pirfenidone and bosentan.

**[00200]** In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of asthma and/or rhinitis and/or COPD; particular agents include but are not limited to: beta<sub>2</sub>-adrenoceptor agonists (e.g. salbutamol, levalbuterol, terbutaline and bitolterol), epinephrine (inhaled or tablets), anticholinergics (e.g. ipratropium bromide), glucocorticoids (oral or inhaled) Long-acting β<sub>2</sub>-agonists (e.g. salmeterol, formoterol, bambuterol, and sustained-release oral albuterol), combinations of inhaled steroids and long-acting bronchodilators (e.g. fluticasone/salmeterol, budesonide/formoterol), leukotriene antagonists and synthesis inhibitors (e.g. montelukast, zafirlukast and zileuton), inhibitors of mediator release (e.g. cromoglycate and ketotifen), phosphodiesterase-4 inhibitors (e.g. Roflumilast), biological regulators of IgE response (e.g. omalizumab), antihistamines (e.g. ceterizine, cinnarizine, fexofenadine), and vasoconstrictors (e.g. oxymethazoline, xylomethazoline, nafazoline and tramazoline).

**[00201]** Additionally, a compound of the invention may be administered in combination with emergency therapies for asthma and/or COPD, such therapies include oxygen or heliox administration, nebulized salbutamol or terbutaline (optionally combined with an anticholinergic (e.g. ipratropium), systemic steroids (oral or intravenous, e.g. prednisone, prednisolone, methylprednisolone, dexamethasone, or hydrocortisone), intravenous salbutamol, non-specific beta-agonists, injected or inhaled (e.g. epinephrine, isoetharine, isoproterenol, metaproterenol), anticholinergics (IV or nebulized, e.g. glycopyrrolate, atropine, ipratropium), methylxanthines (theophylline, aminophylline, bamiphylline), inhalation anesthetics that have a bronchodilatory effect (e.g. isoflurane, halothane, enflurane), ketamine, and intravenous magnesium sulfate.

**[00202]** In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of inflammatory bowel disease (IBD); particular agents include but are not limited to: glucocorticoids (e.g. prednisone, budesonide) synthetic disease modifying, immunomodulatory agents (e.g. methotrexate, leflunomide, sulfasalazine, mesalazine, azathioprine, 6-mercaptopurine and ciclosporin) and biological disease modifying, immunomodulatory agents (infliximab, adalimumab, rituximab, and abatacept).

**[00203]** By co-administration is included any means of delivering two or more therapeutic- agents to the patient as part of the same treatment regime, as will be apparent to the skilled person. Whilst the two or more agents may be administered simultaneously in a single formulation this is not essential. The agents may be administered in different formulations and at different times.

## **GENERAL SYNTHETIC PROCEDURES**

### **General**

5   **[00204]**   A compound of the invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art  
10 by routine optimization procedures.

**[00205]**   Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction  
15 and removal, are described in T. W. Greene and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, Wiley-Blackwell; 4th Revised edition edition (2006), and references cited therein.

**[00206]**   The following methods are presented with details as to the preparation of representative 6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one compounds that have been listed hereinabove. A compound of the invention may be prepared from known or commercially available starting materials and reagents by one  
20 skilled in the art of organic synthesis.

**[00207]**   All reagents were of commercial grade and were used as received without further purification, unless otherwise stated. Commercially available anhydrous solvents were used for reactions conducted under inert atmosphere. Reagent grade solvents were used in all other cases, unless otherwise specified. Column chromatography was performed on silica standard (30-70  $\mu$ m). Thin layer chromatography was  
25 carried out using pre-coated silica gel 60 F-254 plates (thickness 0.25 mm).  $^1\text{H}$  NMR spectra were recorded on a Bruker Advance 400 NMR spectrometer (400 MHz) or a Bruker Advance 300 NMR spectrometer (300 MHz). Chemical shifts ( $\delta$ ) for  $^1\text{H}$  NMR spectra are reported in parts per million (ppm) relative to tetramethylsilane ( $\delta$  0.00) or the appropriate residual solvent peak as internal reference. Multiplicities are given as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), multiplet (m) and broad (br).  
30 Electrospray MS spectra were obtained either on a Waters platform LC/MS spectrometer or on an Agilent 1100 Series LC/MSD. Analytic LCMS: Columns used, Waters Acquity UPLC BEH C18 1.7 $\mu$ m, 2.1mm ID x 50mm L or Waters Acquity UPLC BEH C18 1.7 $\mu$ m, 2.1mm ID x 30mm L or Waters XBridge C18 3.5 $\mu$ m, 2.1mm ID x 50mm L. All the methods are using MeCN/H<sub>2</sub>O gradients. MeCN and H<sub>2</sub>O contain either 0.1% Formic Acid or NH<sub>3</sub> (10mM). Preparative LCMS: Column used, Waters XBridge Prep C18

5  $\mu$ m ODB 30mm ID x 100mm L. All the methods are using either MeOH/H<sub>2</sub>O or MeCN/H<sub>2</sub>O gradients. MeOH, MeCN and H<sub>2</sub>O contain either 0.1% Formic Acid or 0.1% Diethylamine. Analytic chiral LC: Column used, Chiralpak IA 5  $\mu$ m 250 x 4.6 mm. Microwave heating was performed with a Biotage Initiator.

5 [00208] **Table I:** List of abbreviations used in the experimental section:

$\mu$ L	microliter
AcOH	Acetic acid
Aq.	aqueous
ATP	Adenosine 5'-Triphosphate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	tert-Butyloxy-carbonyl
Boc <sub>2</sub> O	Di- <i>tert</i> -butyl dicarbonate
br s	broad singlet
Calcd	calculated
Cat.	Catalytic amount
D	doublet
Dd	Doublet of doublet
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIPEA	N,N-diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide

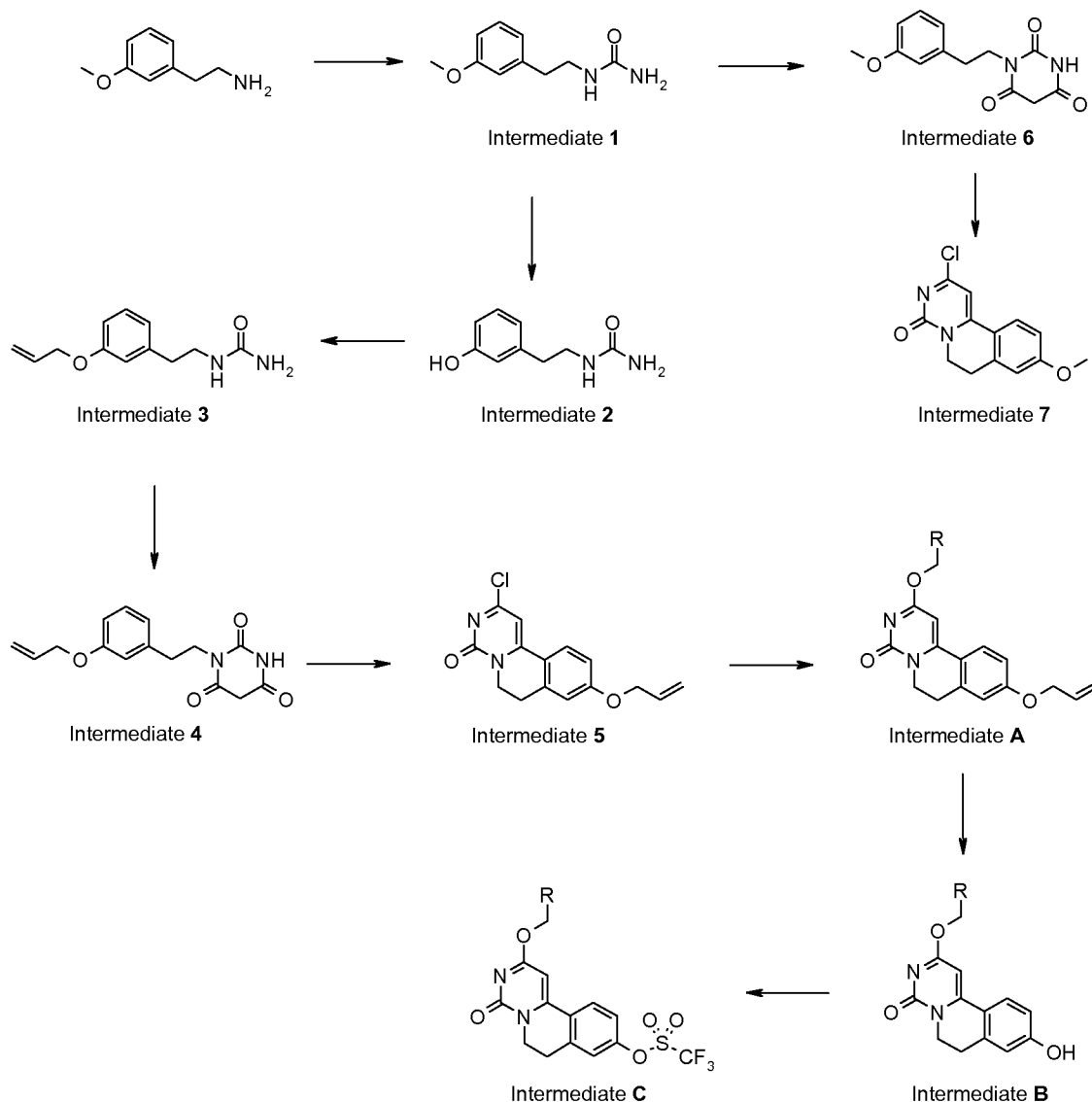
DPBS	Dulbecco's Phosphate-Buffered Saline
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
EtOAc	Ethyl acetate
Et <sub>2</sub> O	Diethyl ether
eq.	equivalent
g	gram
GTP $\gamma$ S	guanosine 5'-O-[gamma-thio]triphosphate
h	hour
H	Heptane
HPLC	High-performance liquid chromatography
<i>i</i> PrOH	isopropanol
<i>i</i> Pr <sub>2</sub> O	Diisopropyl ether
KHMDS	Potassium hexamethyldisilazane
LCMS	Liquid Chromatography- Mass Spectrometry
L	Liter
M	multiplet
MeOH	Methanol
MeCN	Acetonitrile
MeI	Methyl iodide
MEK	Methyl ethyl ketone

Mg	milligram
Min	minute
mL	milliliter
Mmol	millimole
MS	mass spectrometry
MW	Molecular weight
MW (obs)	Molecular weight observed
MW (calc)	Molecular weight calculated
NADP	Nicotinamide adenine dinucleotide phosphate
NEAA	Non-Essential Amino Acid
NMP	<i>N</i> -Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
obsd	observed
Pd(OAc) <sub>2</sub>	Palladium(II) acetate
Pd(PPh <sub>3</sub> ) <sub>4</sub>	Tetrakis(triphenylphosphine)palladium(0)
Pd/C	Palladium on Carbon 10%

ppm	part-per-million
q	quadruplet
rpm	revolutions per minute
RT	Room temperature
Rt	retention time
RuPhos	2-Dicyclohexylphosphino-2',6'-di- <i>i</i> -propoxy-1,1'-biphenyl
s	singlet
SM	Starting material
spA	Scintillation proximity assay
SPE	Solid phase extraction
STAB	sodiumtriacetoxyborohydride
t	triplet
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography

## General Synthetic Method

[00209] Intermediates to prepare the compounds according to the invention can be produced according to the following schemes.



**Intermediate 1:** [2-(3-methoxy-phenyl)-ethyl]-urea

[00210] A solution of 3-methoxyphenethylamine (100 g, 661.3 mmol, 1 eq.), urea (157.3 g, 2619.0 mmol, 4 eq.), AcOH (36 mL) and aq. HCl (12 mL) in H<sub>2</sub>O (800 mL) was heated under reflux for 5 days. The reaction mixture was cooled to room temperature, the solid was filtered off, washed with water and dried to afford intermediate 1.

(<sup>1</sup>H, CDCl<sub>3</sub>) δ (ppm): 7.24 (1H, t), 6.82-6.77 (3H, m), 5.10 (1H, br s), 4.52 (2H, br), 3.81 (1H, s), 3.42 (2H, br t), 2.80 (2H, t).

**Intermediate 2:** [2-(3-hydroxy-phenyl)-ethyl]-urea

**[00211]** A solution of intermediate **1** (72 g, 370.7 mmol) in concentrated HBr (500 mL) was heated under reflux overnight. The reaction mixture was basified with the addition of NaHCO<sub>3</sub> and extracted with EtOAc.

5 The organic layer was dried over MgSO<sub>4</sub> and concentrated under vacuum to afford intermediate **2**.

(<sup>1</sup>H, MeOD-*d*4) δ (ppm): 7.15 (1H, t), 6.76-6.68 (3H, m), 3.40-3.36 (2H, t), 2.77-2.74 (2H, t).

**Intermediate 3:** [2-(3-allyloxy-phenyl)-ethyl]-urea

**[00212]** To a solution of intermediate **2** (45 g, 249.7 mmol, 1 eq.) and K<sub>2</sub>CO<sub>3</sub> (103.5 g, 749.1 mmol, 3 eq.) in dry DMF (300 mL) under nitrogen, was added allylbromide (50.5 mL, 499.4 mmol, 2 eq.). The reaction mixture was stirred for 2.5 days, then DMF was evaporated to dryness. The residue was dissolved in EtOAc, washed with a saturated solution of Na<sub>2</sub>CO<sub>3</sub>, brine, dried over MgSO<sub>4</sub> and concentrated under vacuum to afford intermediate **3**.

(<sup>1</sup>H, MeOD-*d*4) δ (ppm): 7.24 (1H, t), 6.87-6.81 (3H, m), 6.16-6.06 (1H, m), 5.45 (1H, dd), 5.29 (1H, dd),  
15 4.59-4.57 (2H, m), 3.38 (2H, t), 2.80 (2H, t)

**Intermediate 4:** 1-[2-(3-allyloxy-phenyl)-ethyl]-pyrimidine-2,4,6-trione

**[00213]** Sodium (20.06 g, 872 mmol, 1 eq.) was dissolved in EtOH (1.4 L). Diethyl malonate (132.4 mL, 872 mmol, 1 eq.) was added and the reaction mixture was heated under reflux for 1h. Intermediate **3** (96 g, 436 mmol, 0.5 eq.) in EtOH (300 mL) was added and the reaction mixture was heated under reflux for 12 h. The reaction was cooled to room temperature, 1N aq. HCl was added and the precipitate was filtered off, washed with water and dried to afford intermediate **4**.

(<sup>1</sup>H, CDCl<sub>3</sub>) δ (ppm): 8.40 (1H, br s), 7.25 (1H, t), 6.88-6.82 (3H, m), 6.14-6.04 (1H, m), 5.45 (1H, dd), 5.32 (1H, dd), 4.58-4.56 (2H, m), 4.13 (2H, t), 3.64 (2H, s), 2.92 (2H, t)

25 MW (calcd): 288.3; MW (obsd): 289.3 (M + 1)

**Intermediate 5:** 9-allyloxy-2-chloro-6,7-dihydro-pyrimido[6,1-*a*]isoquinolin-4-one

**[00214]** A solution of intermediate **4** (20 g, 69.4 mmol, 1 eq.) in POCl<sub>3</sub> (150 mL) was stirred at 50°C for 3 days. POCl<sub>3</sub> was evaporated under vacuum and the residue was dissolved in DCM and quenched with a saturated solution of NaHCO<sub>3</sub>. The organic layer was washed with water, dried over MgSO<sub>4</sub> and concentrated to afford intermediate **5**.

(<sup>1</sup>H, CDCl<sub>3</sub>) δ (ppm): 7.71 (2H, d), 6.97 (1H, dd), 6.86 (1H, d), 6.71 (1H, s), 6.13-6.04 (1H, m), 5.47 (1H, dd), 5.36 (1H, dd), 4.67-4.65 (2H, m), 4.27 (2H, t), 3.05 (2H, t)

MW (calcd): 288.7; MW (obsd): 289.3 (M+1)



**[00215]** Sodium (2.96 g, 128.7 mmol, 2.5 eq.) was dissolved in EtOH (200 mL), diethyl malonate (11.73 mL, 77.2 mmol, 1.5 eq.) was added and the reaction was heated under reflux for 1h. Intermediate **1** (10 g, 51.5 mmol, 1 eq.) was then added and the reaction mixture was heated under reflux for 48 h. The reaction was cooled to RT, conc. HCl was added and the mixture was concentrated to dryness. The residue was dissolved in brine and extracted with AcOEt. The organic layer was dried over MgSO<sub>4</sub> and concentrated to afford intermediate **6**.

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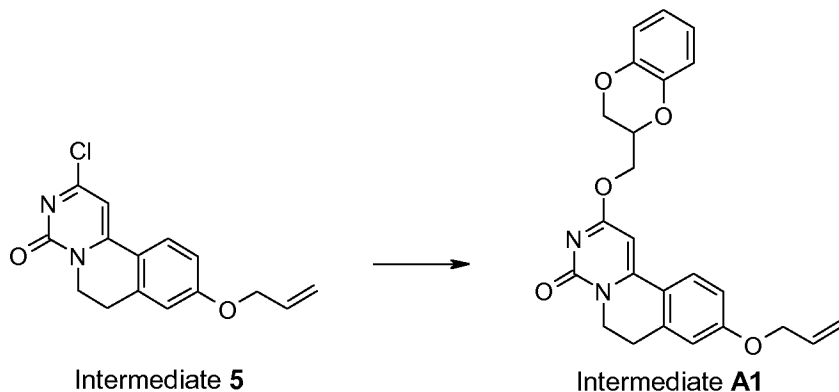
**[00216]** A round bottom flask was charged with intermediate **6** (6.21 g, 23.67 mmol, 1 eq.) and POCl<sub>3</sub> (71 mL) and heated at 80°C for 1.5 days. The volatiles were then removed under vacuum, the residue was dissolved in H<sub>2</sub>O and the pH was adjusted to pH 7 with solid NaHCO<sub>3</sub>. The mixture was extracted with DCM, which was washed with H<sub>2</sub>O, brine and dried over MgSO<sub>4</sub>. Upon filtration, volatiles were removed under vacuum, and the residue was purified by flash chromatography on silica gel eluting with 5% iPrOH/DCM to give intermediate **7**.

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**Illustrative synthesis of general method A:**

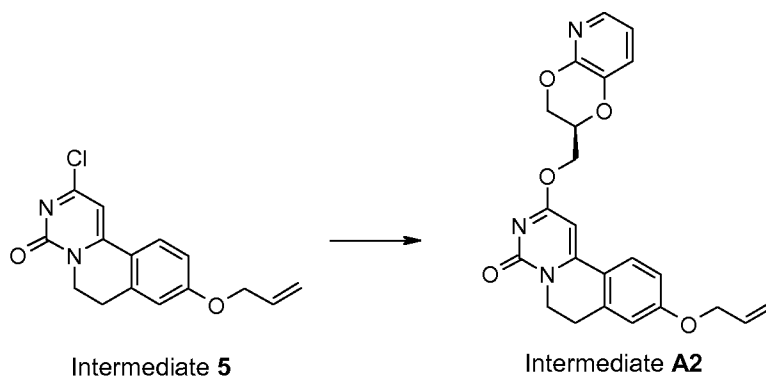
**Intermediate A1:** 9-allyloxy-2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



- 5 **[00218]** To a solution of (2,3-dihydro-benzo[1,4]dioxin-2-yl)-methanol (8.63 g, 51.9 mmol, 1.5 eq.) and *t*BuOK (7.76 g, 69.2 mmol, 2eq.) in dry DCM (150 mL) was added intermediate 5 (10 g, 34.6 mmol, 1 eq.) at 0°C. The reaction mixture was stirred at room temperature for 1h, then the organic layer was washed with water, dried over MgSO<sub>4</sub> and evaporated to dryness. The crude product was purified by flash chromatography on silica gel eluting with 5% MeOH/DCM to afford intermediate A1.
- 10 (<sup>1</sup>H, CDCl<sub>3</sub>) δ (ppm): 7.68 (1H, d), 6.98-6.84 (6H, m), 6.31 (1H, s), 6.13-6.06 (1H, m), 5.50-5.34 (2H, m), 4.17-4.59 (5H, m), 4.41-4.13 (4H, m), 3.02 (2H, t)
- MW (calcd): 418.5; MW (obsd): 419 (M+1)

**Intermediate A2:** 9-allyloxy-2-[(R)-1-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-yl)methoxy]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

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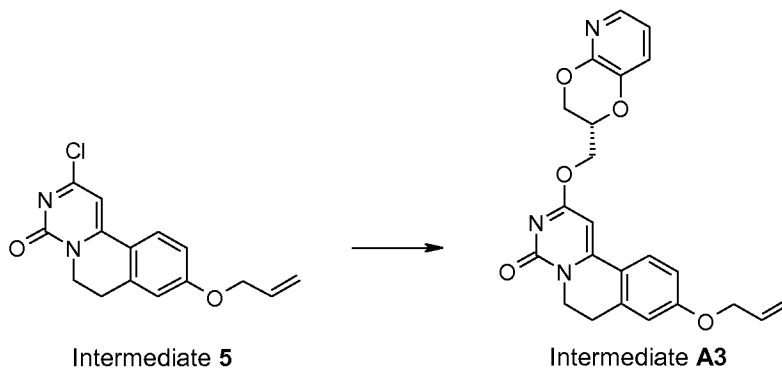
**[00219]** Intermediate A2 is prepared using general method A with intermediate 5 and (S)-1-(2,3-dihydro-1,4]dioxino[2,3-b]pyridin-2-yl)-methanol.

$^1\text{H}$ ,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.87 (1H, dd), 7.69 (1H, d), 7.30-7.28 (1H, m), 6.97-6.93 (2H, m), 6.85-6.84 (1H, m), 6.30 (1H, s), 6.14-6.04 (1H, m), 5.47 (1H, dd), 5.38 (1H, dd), 4.73-4.72 (2H, m), 4.66-4.58 (4H, m), 4.40-4.34 (1H, m), 4.25 (2H, t), 3.00 (2H, t)

MW (calcd): 419.4; MW (obsd): 420 (M+1)

5

**Intermediate A3:** 9-allyloxy-2-[(S)-1-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-yl)methoxy]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

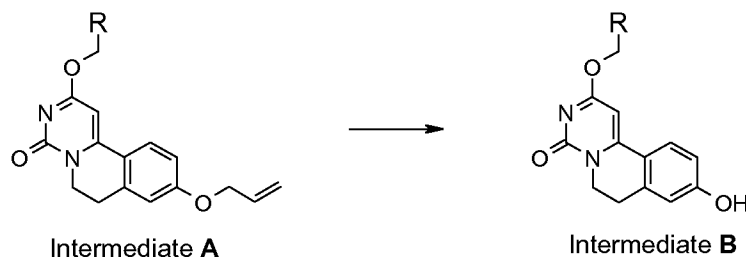


**[00220]** Intermediate A3 is prepared using general method A with intermediate 5 and (R)-1-(2,3-dihydro-1,4]dioxino[2,3-b]pyridin-2-yl)-methanol.

**[00221]** (S)-1-(2,3-Dihydro-1,4]dioxino[2,3-b]pyridin-2-yl)-methanol and (R)-1-(2,3-dihydro-1,4]dioxino[2,3-b]pyridin-2-yl)-methanol can be prepared according to following publication [Bolchi *et al.*, Tetrahedron: Asymmetry 16(20), (2005) 3380–3384]

$^1\text{H}$ ,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.87 (1H, dd), 7.67 (1H, d), 7.28-7.26 (1H, m), 6.97-6.91 (2H, m), 6.85-6.82 (1H, m), 6.30 (1H, s), 6.14-6.04 (1H, m), 5.47 (1H, dd), 5.37 (1H, dd), 4.73-4.71 (2H, m), 4.66-4.57 (4H, m), 4.39-4.33 (1H, m), 4.26 (2H, t), 3.01 (2H, t)

#### General method B for intermediates B:

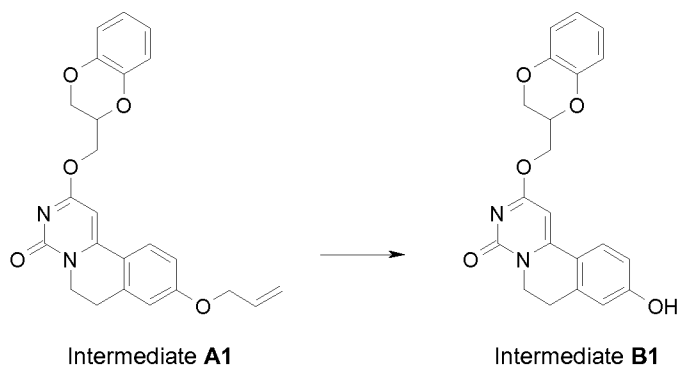


**[00222]** To a suspension of intermediate A (1 eq.) in a mixture of DCM/MeOH (1/1) is added  $\text{K}_2\text{CO}_3$  (2 eq.) and  $\text{Pd}(\text{PPh}_3)_4$  (0.05 eq.). The reaction mixture is degassed before stirring at room temperature. After full completion, water is added to the reaction mixture and the aqueous layer is separated. The pH of the aqueous

solution is adjusted to pH 1 with 2M aq. HCl. The precipitate is filtered off, washed with water and dried to afford intermediate **B**.

**Illustrative synthesis of general method B:**

- 5 **Intermediate B1:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-hydroxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

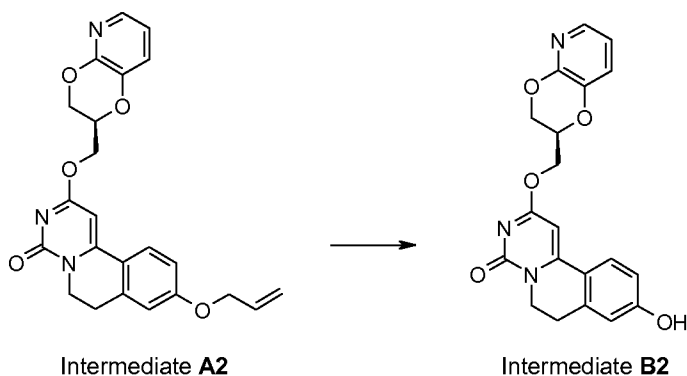


- 10 **[00223]** To a suspension of intermediate **A1** (1.04 g, 2.49 mmol, 1 eq.) in a mixture of DCM/MeOH (1/1, 60 mL) was added  $K_2CO_3$  (0.75 g, 5.47 mmol, 2.2 eq.) and  $Pd(PPh_3)_4$  (144 mg, 0.12 mmol, 0.05 eq.). The reaction mixture was stirred at room temperature for 2 h. The reaction was evaporated to dryness and the residue was purified by flash chromatography on silica gel eluting with 5% MeOH/DCM to afford intermediate **B1**.

( $^1H$ , DMSO- $d_6$ )  $\delta$  7.84 ppm (1 H, d), 6.83 - 6.94 (4 H, m), 6.71 - 6.80 (2 H, m), 6.50 (1 H, s), 4.38 - 4.62 (4 H, m), 4.07 - 4.16 (1 H, m), 4.00 (2 H, t), 2.91 (2 H, t)

- 15 MW (calcd): 378.4; MW (obsd): 379.1 (M+1)

**Intermediate B2:** 2-[(R)-1-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-yl)methoxy]-9-hydroxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

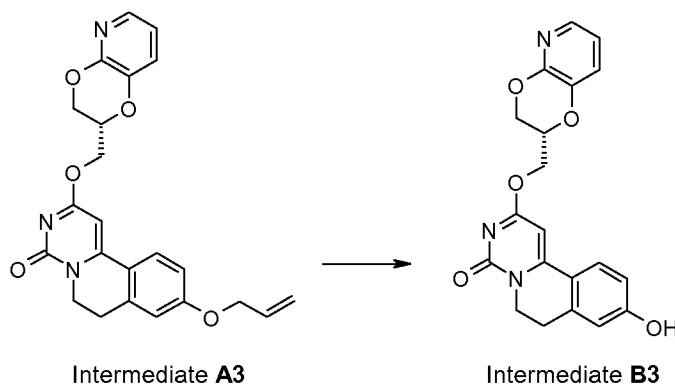


- 20 **[00224]** Intermediate **B2** was prepared using general method **B** starting from intermediate **A2**.

(<sup>1</sup>H, DMSO-*d*<sub>6</sub>) δ ppm 7.75 - 7.90 (2 H, m), 7.37 (1 H, dd), 6.93 - 7.03 (2 H, m), 6.72 - 6.83 (2 H, m), 4.41 - 4.68 (4 H, m), 4.24 - 4.37 (1 H, m), 4.01 (2 H, t), 2.87 - 2.98 (2 H, m)

MW (calcd): 379.4; MW (obsd): 380.1 (M+1)

- 5 **Intermediate B3:** 2-[(S)-1-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-yl)methoxy]-9-hydroxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



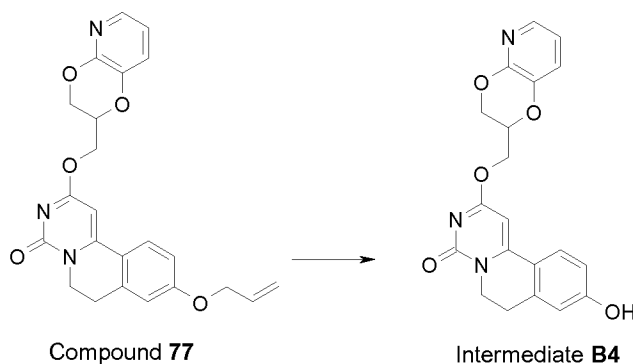
[00225] Intermediate **B3** was prepared using general method **B** starting from intermediate **A3**.

(<sup>1</sup>H, DMSO-*d*<sub>6</sub>) δ ppm 7.84 (1 H, d), 7.77 (1 H, dd), 7.36 (1 H, dd), 6.97 (1 H, dd), 6.73 - 6.81 (2 H, m), 6.49 (1 H, s), 4.47 - 4.67 (4 H, m), 4.26 - 4.35 (1 H, m), 3.97 - 4.03 (2 H, m), 2.88 - 2.95 (2 H, m)

10

MW (calcd): 379.4; MW (obsd): 380.3 (M+1)

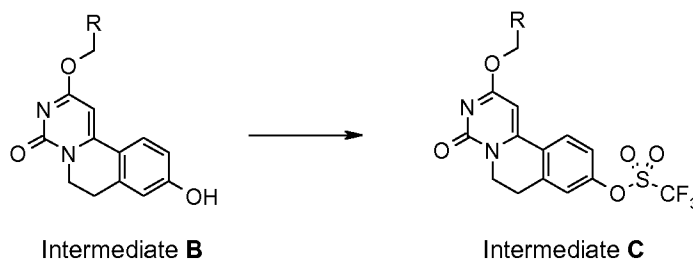
**Intermediate B4:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-hydroxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



15

[00226] Intermediate **B4** was prepared using general method **B** starting from compound **77**.

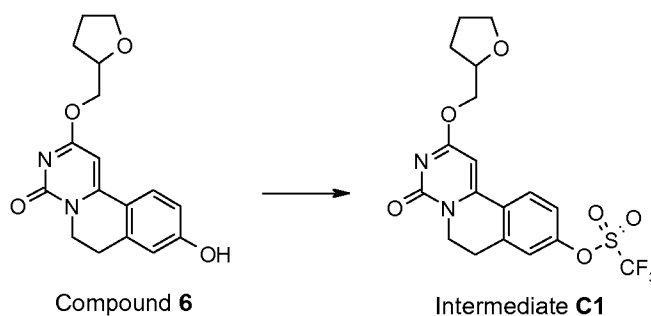
(<sup>1</sup>H, DMSO-*d*<sub>6</sub>) δ ppm 7.84 (1 H, d), 7.77 (1 H, dd), 7.33 - 7.38 (1 H, m), 6.94 - 6.99 (1 H, m), 6.71 - 6.80 (2 H, m), 6.49 (1 H, s), 4.46 - 4.67 (4 H, m), 4.26 - 4.34 (1 H, m), 4.00 (2 H, s), 2.87 - 2.95 (2 H, m)

**General method C for intermediate C:**

**[00227]** A solution of intermediate **B** (1 eq.), N-phenyl-bis(trifluoromethanesulfonimide) (1.2 eq.) and Et<sub>3</sub>N (1.3 eq.) in DCM under nitrogen is stirred at room temperature until full completion. The reaction mixture is concentrated and the crude is purified by crystallization from *i*PrOH to afford intermediate **C**.

**Illustrative synthesis of general method C:**

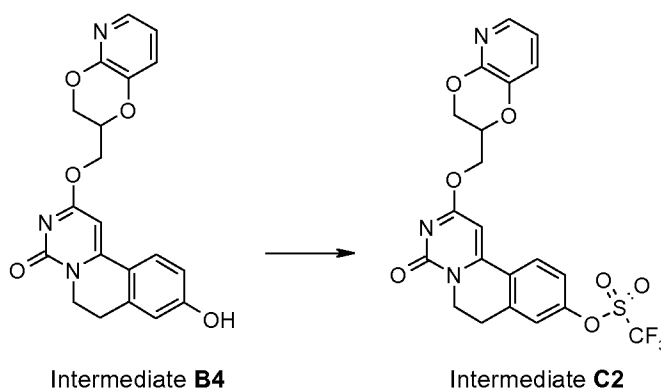
**Intermediate C1:** methanesulfonic acid 4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl ester



**[00228]** A solution of compound **6** (117 mg, 0.37 mmol, 1 eq.), N-phenyl-bis(trifluoromethanesulfonimide) (146 mg, 0.41 mmol, 1.1 eq.) and Et<sub>3</sub>N (0.093 mL, 0.67 mmol, 1.8 eq.) in DCM (4 mL) under a nitrogen atmosphere is stirred at room temperature for 2h. The reaction mixture is concentrated under vacuum and the residue is purified by flash chromatography on silica gel eluting with 4% MeOH/DCM to afford intermediate **C1**.

(<sup>1</sup>H, CDCl<sub>3</sub>) δ ppm 7.76 - 7.82 (1 H, m), 7.28 - 7.36 (1 H, m), 7.26 (1 H, s), 6.38 (1 H, s), 4.53 - 4.63 (1 H, m), 4.25 (4 H, d), 3.80 - 3.99 (2 H, m), 3.04 - 3.12 (2 H, m), 1.87 - 2.14 (2 H, m), 1.61 - 1.71 (2 H, m)

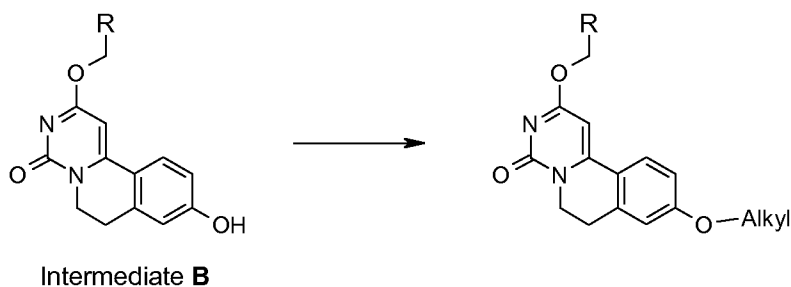
**Intermediate C2:** methanesulfonic acid 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl ester



**[00229]** A solution of intermediate **B4** (150 mg, 0.40 mmol, 1 eq.), N-phenyl-bis(trifluoromethanesulfonimide) (155 mg, 0.43 mmol, 1.1 eq.) and Et<sub>3</sub>N (0.1 mL, 0.71 mmol, 1.8 eq.) in DCM (5 mL) under a nitrogen atmosphere is stirred at room temperature overnight. The reaction mixture is concentrated under vacuum and the residue is purified by flash chromatography on silica gel eluting with 4% MeOH/DCM to afford intermediate **C2**.

(<sup>1</sup>H, CDCl<sub>3</sub>) δ ppm 7.76 - 7.85 (2 H, m), 7.23 - 7.33 (2 H, m), 7.20 (1 H, dd), 6.86 (1 H, dd), 6.35 (1 H, s), 4.66 (2 H, d), 4.48 - 4.60 (2 H, m), 4.30 (1 H, dd), 4.18 - 4.25 (2 H, m), 3.07 (2 H, t)

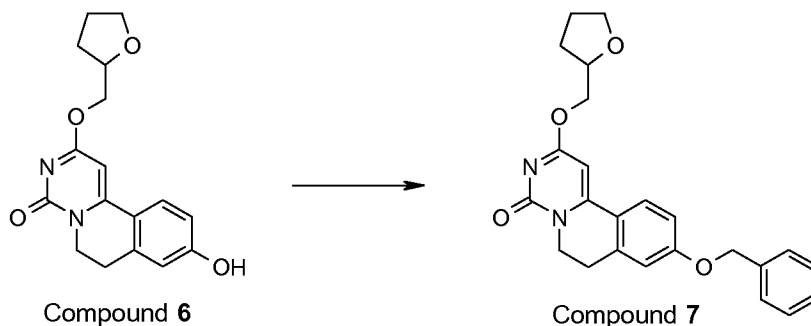
#### 10 General method D:



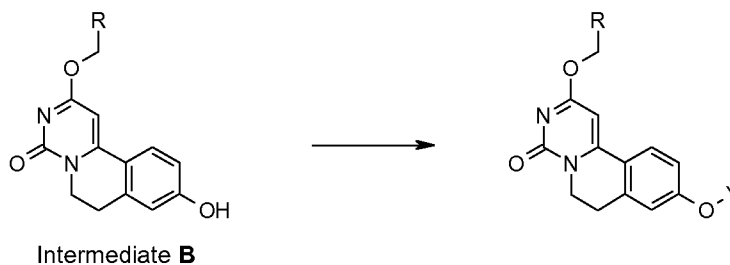
**[00230]** A vial is charged with intermediate **B** (1 eq.), tBuOK (2.4 eq.), the appropriate alkylating agent (2.7 eq.) in dry DCM. After 16h, the mixture is partitioned between DCM and H<sub>2</sub>O. The organic phase is collected and washed with H<sub>2</sub>O, brine and dried over MgSO<sub>4</sub>. After evaporation, the crude product is purified by flash chromatography on silica gel to give clean product.

**Illustrative synthesis of general method D:**

**Compound 7: 9-benzyloxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one**



- 5 **[00231]** A vial was charged with compound 6 (9.1 mg, 0.029 mmol, 1 eq.), *t*BuOK (7.7 mg, 0.007 mmol, 2.4 eq.), benzyl bromide (0.0095 mL, 0.008 mmol, 2.7 eq.) and dry DCM (0.5 mL). After 16h, the mixture was partitioned between DCM and H<sub>2</sub>O. The organic phase was collected and washed with H<sub>2</sub>O, brine and dried over MgSO<sub>4</sub>. After evaporation, the crude product was purified by flash chromatography eluting with EtOAc/DCM/*i*PrOH (10/10/1) to give compound 7.
- 10 (<sup>1</sup>H, CDCl<sub>3</sub>) δ ppm 7.63 (1 H, d), 7.33 - 7.48 (5 H, m), 6.91 - 7.01 (1 H, m), 6.82 - 6.89 (1 H, m), 6.29 (1 H, s), 5.14 (2 H, s), 4.51 - 4.61 (1 H, m), 4.15 - 4.33 (4 H, m), 3.90 - 3.98 (1 H, m), 3.79 - 3.89 (1 H, m), 2.97 (2 H, t), 2.01 - 2.11 (1 H, m), 1.86 - 2.00 (2 H, m), 1.58 - 1.73 (1 H, m).

**General method E:**

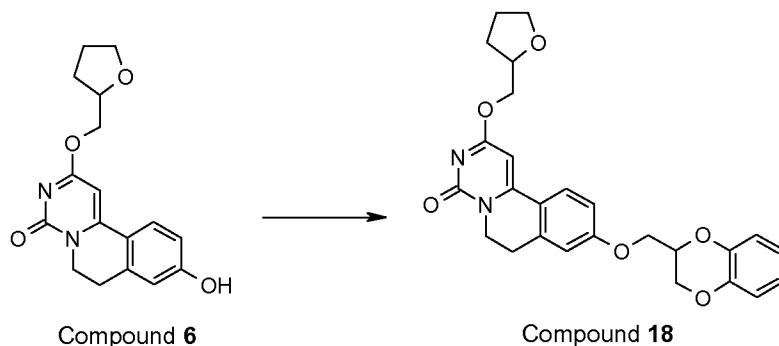
15

- [00232]** A solution of intermediate **B** (1 eq.), the appropriate alkylating agent (1.5 eq.), K<sub>2</sub>CO<sub>3</sub> (2 eq.), KI or NaI (1 eq.) in MEK is heated at 80°C. When the reaction has reached completion, the volatiles are evaporated to dryness and the product is then obtained after purification by either flash chromatography on silica gel, preparative TLC or preparative HPLC-MS.
- 20

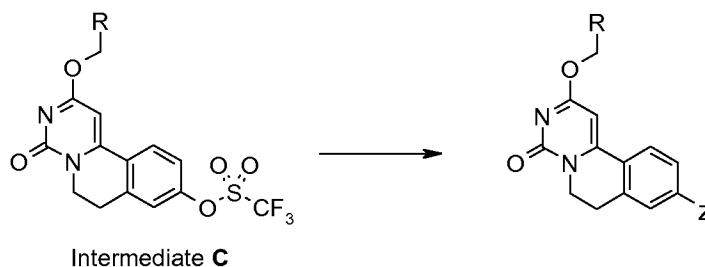


**Illustrative synthesis of general method E:**

**Compound 18:** 9-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



- 5 **[00233]** A solution of compound **6** (122 mg, 0.39 mmol, 1 eq.), 2-bromomethyl-2,3-dihydro-benzo[1,4]dioxine (409 mg, 1.79 mmol, 4.6 eq.),  $K_2CO_3$  (520 mg, 3.76 mmol, 9.7 eq.), NaI (157 mg, 1.05 mmol, 2.7 eq.) in MEK (3.5 mL) was heated at 80°C for 16 h. The reaction was evaporated to dryness and the residue was purified by flash chromatography on silica gel, eluting with 4% MeOH/DCM to give compound **18**.
- 10 ( $^1H$ ,  $CDCl_3$ )  $\delta$  ppm 7.64 (1 H, d), 6.85 - 6.96 (5 H, m), 6.83 (1 H, d), 6.29 (1 H, s), 4.51 - 4.65 (2 H, m), 4.36 - 4.44 (1 H, m), 4.16 - 4.35 (7 H, m), 3.89 - 3.99 (1 H, m), 3.79 - 3.88 (1 H, m), 2.97 (2 H, t), 2.00 - 2.13 (1 H, m), 1.85 - 2.00 (2 H, m), 1.58 - 1.72 (1 H, m).

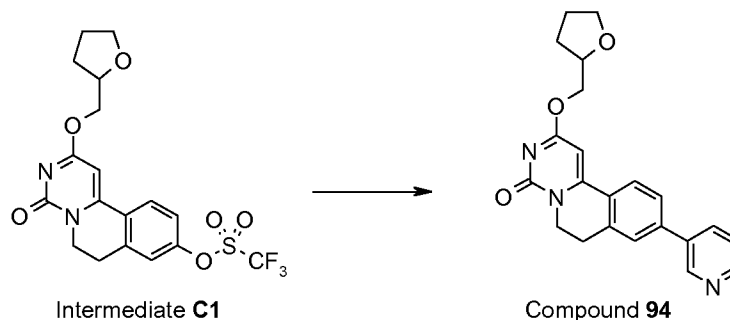
**General method F:**

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- [00234]** A vial is charged with intermediate **C** (1 eq.), the appropriate boronic acid, boronic ester or potassium trifluoroborate (3 eq.),  $Cs_2CO_3$  (3.5 eq.), (DPPF) $PdCl_2$ .DCM (0.05 eq.), in 1,4-dioxane/ $H_2O$  (10/1, v/v), and the mixture is degassed with  $N_2$ . The vial is sealed and heated at 80°C. When the reaction has
- 20 reached full completion, the vial is cooled to room temperature and the reaction is either worked up or volatiles are evaporated under vacuum. The product is then obtained after purification by either flash chromatography on silica gel, preparative TLC or preparative HPLC-MS.

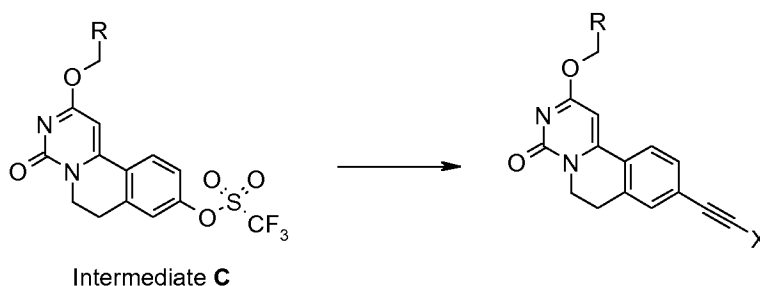
**Illustrative synthesis of general method F:**

**Compound 94:** 9-pyridin-3-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



- 5 **[00235]** A vial was charged with intermediate **C1** (56 mg, 0.13 mmol, 1 eq.), pyridine-3-boronic acid (65 mg, 0.53 mmol, 4.2 eq.),  $\text{Cs}_2\text{CO}_3$  (143 mg, 0.44 mmol, 3.5 eq.),  $(\text{DPPF})\text{PdCl}_2 \cdot \text{DCM}$  (5 mg, 0.0063 mmol, 0.05 eq.), in 1,4-dioxane (2 mL) and  $\text{H}_2\text{O}$  (0.2 mL), and the mixture was degassed with  $\text{N}_2$ . The vial was sealed and heated at  $80^\circ\text{C}$ . After 2h, the vial was cooled to room temperature and volatiles were evaporated under vacuum. The residue was then purified by preparative HPLC-MS to afford compound **94**.
- 10 ( $^1\text{H}$ ,  $\text{CDCl}_3$ )  $\delta$  ppm 8.89 (1 H, d), 8.66 (1 H, d), 7.88 - 7.96 (1 H, m), 7.77 - 7.84 (1 H, m), 7.58 - 7.64 (1 H, m), 7.49 - 7.54 (1 H, m), 7.39 - 7.45 (1 H, m), 6.44 (1 H, s), 4.53 - 4.63 (1 H, m), 4.23 - 4.34 (4 H, m), 3.94 (1 H, dt), 3.81 - 3.89 (1 H, m), 3.10 (2 H, t), 2.02 - 2.13 (1 H, m), 1.89 - 2.01 (2 H, m), 1.61 - 1.72 (1 H, m).  
MW (calcd): 375.4; MW (obsd): 376.3 (M+1)

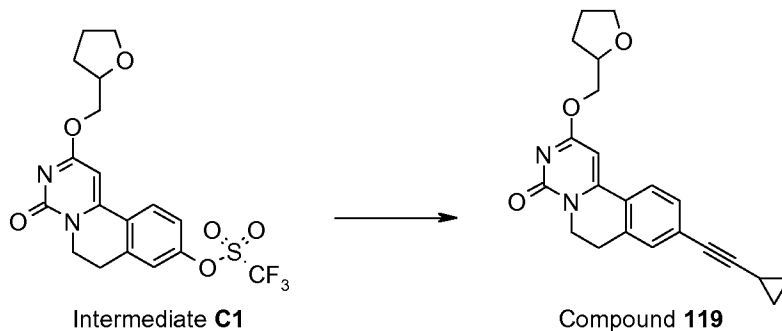
15 **General method G:**



- [00236]** Intermediate **C** (1 eq.) is dissolved in DMF, the appropriate alkyne (3 eq.) is added followed by TEA or  $i\text{Pr}_2\text{NH}$  (3.5 eq.), and the mixture is degassed.  $\text{Pd}(\text{PPh}_3)_3\text{Cl}_2$  (0.05 eq.) is added with  $\text{CuI}$  (0.2 eq.) and the reaction mixture is heated at  $80^\circ\text{C}$ . When the reaction is gone to completion, it is cooled to room temperature and either worked up or volatiles are evaporated to dryness. The product is then obtained after purification by either flash chromatography on silica gel, preparative TLC or preparative HPLC-MS.
- 20

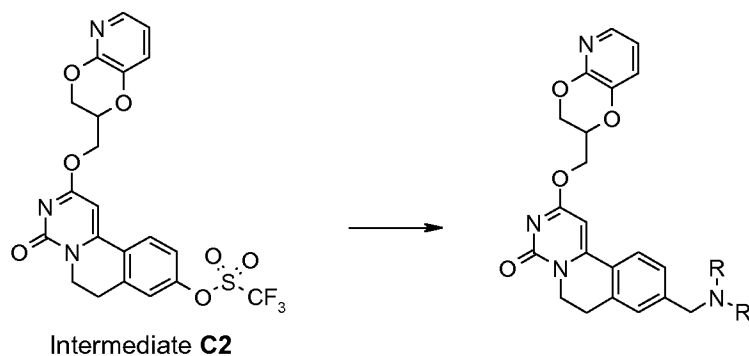
**Illustrative synthesis of general method G:**

**Compound 119:** 9-cyclopropylethynyl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



- 5 **[00237]** Intermediate **C1** (40 mg, 0.089 mmol, 1 eq.) was dissolved in DMF (2 mL), ethynyl-cyclopropane (18 mg, 0.27 mmol, 3 eq.) was added followed by TEA (0.044 mL, 0.31 mmol, 3 eq.). The mixture was degassed and Pd(PPh<sub>3</sub>)<sub>3</sub>Cl<sub>2</sub> (3 mg, 0.0045 mmol, 0.05 eq.) was added with CuI (3.3 mg, 0.018 mmol, 0.2 eq.). The reaction mixture was heated at 80°C for 2 days. The reaction was cooled to room temperature and evaporated to dryness. The crude product was then purified by preparative HPLC-MS to give compound **119**.
- 10 (<sup>1</sup>H, CDCl<sub>3</sub>) δ ppm 7.57 (1 H, d), 7.32 (1 H, dd), 7.27 (1 H, s), 6.33 (1 H, s), 4.48 - 4.59 (1 H, m), 4.09 - 4.31 (4 H, m), 3.87 - 3.96 (1 H, m), 3.78 - 3.86 (1 H, m), 2.95 (2 H, t), 1.84 - 2.11 (3 H, m), 1.57 - 1.70 (1 H, m), 1.39 - 1.53 (1 H, m), 0.77 - 0.96 (4 H, m).
- MW (calcd): 362.4; MW (obsd): 363.4 (M+1)

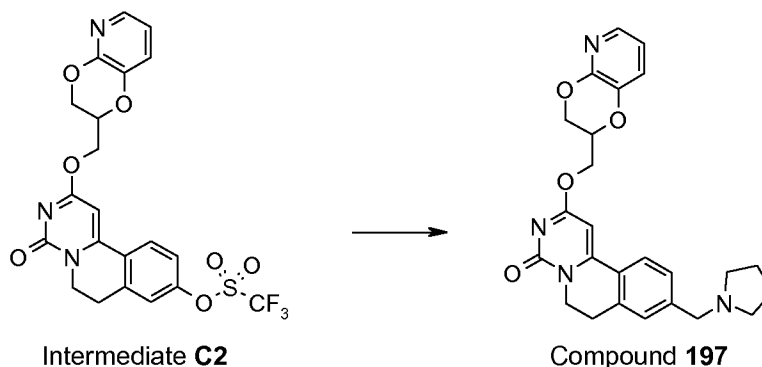
15 **General method H:**



- [00238]** A vial is charged with intermediate **C2** (1 eq.), the corresponding potassium trifluoroborate (1 eq.), Cs<sub>2</sub>CO<sub>3</sub> (3 eq.), Pd(OAc)<sub>2</sub> (0.03 eq.) and XPhos (0.06 eq.) in a mixture of THF/H<sub>2</sub>O (10/1, v/v), then the mixture is degassed with N<sub>2</sub>. The vial is sealed and heated at 80°C for 16h. The vial is then cooled to room temperature, the reaction is quenched with brine, extracted with EtOAc and dried over MgSO<sub>4</sub>. After evaporation to dryness, clean product is obtained by preparative HPLC-MS.
- 20

**Illustrative synthesis of general method H**

**Compound 197:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyrrolidin-1-ylmethyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



**[00239]** A vial was charged with intermediate **C2** (80 mg, 0.157 mmol, 1 eq.), potassium [(pyrrolidin-1-yl)methyl]trifluoroborate (30 mg, 0.157 mmol, 1 eq.), Cs<sub>2</sub>CO<sub>3</sub> (153 mg, 0.471 mmol, 3 eq.), Pd(OAc)<sub>2</sub> (1 mg, 0.0047 mmol, 0.03 eq.) and XPhos (5 mg, 0.0094 mmol, 0.06 eq.) in a mixture of THF/H<sub>2</sub>O (3 mL, 10/1, v/v), then the mixture was degassed with N<sub>2</sub>. The vial was sealed and heated at 80°C for 16h. The vial was then cooled to room temperature, the reaction was quenched with brine, extracted with EtOAc and dried over MgSO<sub>4</sub>. After evaporation to dryness, compound **197** was obtained by preparative HPLC-MS.

(<sup>1</sup>H, CDCl<sub>3</sub>) δ ppm 7.84 (1 H, dd), 7.66 (1 H, d), 7.35 (1 H, m), 7.31 (1 H, s), 7.23 (1 H, dd), 6.89 (1 H, dd), 6.35 (1 H, s), 4.68 (2 H, d), 4.52 - 4.61 (2 H, m), 4.33 (1 H, dd), 4.18 - 4.25 (2 H, m), 3.66 (2 H, s), 3.01 (2 H, t), 2.49 - 2.57 (4 H, m), 1.81 (4 H, m).

MW (calcd): 446.1; MW (obsd): 447.1 (M+1)

**Compounds of the invention**

**Compound 1:** 9-methoxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00240]** This compound is prepared via general method A using intermediate 7 and (tetrahydro-furan-2-yl)-methanol.

**Compound 2:** 2-(chroman-2-ylmethoxy)-9-methoxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00241]** This compound is prepared via general method A using intermediate 7 and chroman-2-yl-methanol.

**Compound 3:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-methoxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00242] This compound is prepared via general method A using intermediate 7 and (2,3-dihydro-benzo[1,4]dioxin-2-yl)-methanol.

**Compound 4:** 9-allyloxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

5 [00243] This compound is prepared via general method A using intermediate 5 and (tetrahydro-furan-2-yl)-methanol.

**Compound 5:** 2-(2,3-dihydro-benzofuran-2-ylmethoxy)-9-methoxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

10 [00244] This compound is prepared via general method A using intermediate 7 and (2,3-dihydro-benzofuran-2-yl)-methanol.

**Compound 6:** 9-hydroxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

15 [00245] This compound is prepared via general method B using compound 4.

**Compound 7:** 9-benzyloxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00246] Synthesis fully described above.

**Compound 8:** 9-(pyridin-3-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

20 [00247] This compound is prepared via general method D using compound 6 and 3-bromomethyl-pyridine.

**Compound 9:** [4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]oxy]-acetonitrile

25 [00248] This compound is prepared via general method D using compound 6 and bromo-acetonitrile.

**Compound 10:** 9-butoxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00249] This compound is prepared via general method D using compound 6 and 1-bromo-butane.

**Compound 11:** 9-cyclopropylmethoxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

30 [00250] This compound is prepared via general method D using compound 6 and bromomethyl-cyclopropane.

**Compound 12:** 9-phenethyloxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00251] This compound is prepared via general method **D** using compound **6** and (2-bromo-ethyl)-benzene.

5

**Compound 13:** 9-(pyridin-4-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00252] This compound is prepared via general method **D** using compound **6** and 4-chloromethyl-pyridine hydrochloride.

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**Compound 14:** 9-(pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00253] This compound is prepared via general method **D** using compound **6** and 2-chloromethyl-pyridine hydrochloride.

15

**Compound 15:** 9-(2-phenoxy-ethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00254] This compound is prepared via general method **D** using compound **6** and (2-bromo-ethoxy)-benzene.

20

**Compound 16:** 9-methoxy-2-(tetrahydro-pyran-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00255] This compound is prepared via general method **A** using intermediate **7** and (tetrahydro-pyran-2-yl)-methanol.

**Compound 17:** 4-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-benzonitrile

[00256] This compound is prepared via general method **E** using compound **6** and 4-bromomethyl-benzonitrile.

**Compound 18:** 9-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00257] Synthesis fully described above.

**Compound 19:** 3-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-benzonitrile

35

[00258] This compound is prepared via general method E using compound 6 and 3-bromomethyl-benzonitrile.

**Compound 20:** 2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-benzonitrile

[00259] This compound is prepared via general method E using compound 6 and 2-bromomethyl-benzonitrile.

**Compound 21:** 9-(4-chloro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00260] This compound is prepared via general method E using compound 6 and 1-chloro-4-chloromethyl-benzene.

**Compound 22:** 9-(3-chloro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00261] This compound is prepared via general method E using compound 6 and 1-bromomethyl-3-chloro-benzene.

**Compound 23:** 9-(2-chloro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00262] This compound is prepared via general method E using compound 6 and 1-bromomethyl-2-chloro-benzene.

**Compound 24:** 9-(4-fluoro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00263] This compound is prepared via general method E using compound 6 and 1-chloromethyl-4-fluoro-benzene.

**Compound 25:** 9-(2-nitro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00264] This compound is prepared via general method E using compound 6 and 1-chloromethyl-2-nitro-benzene.

**Compound 26:** 4-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-benzoic acid methyl ester

**[00265]** This compound is prepared via general method **E** using compound **6** and 4-bromomethyl-benzoic acid methyl ester.

**Compound 27:** 3-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-benzoic acid methyl ester

**[00266]** This compound is prepared via general method **E** using compound **6** and 3-bromomethyl-benzoic acid methyl ester.

**Compound 28:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00267]** This compound is prepared via general method **E** using intermediate **B1** and 2-chloromethyl-pyridine.

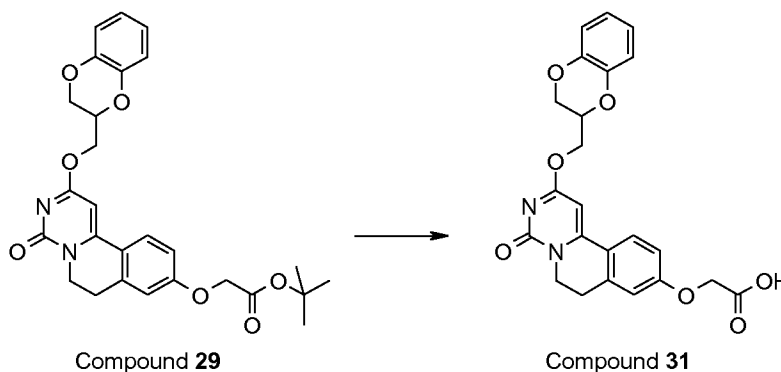
**Compound 29:** [2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetic acid tert-butyl ester

**[00268]** This compound is prepared via general method **E** using intermediate **B1** and bromo-acetic acid tert-butyl ester.

**Compound 30:** 2,9-bis-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00269]** This compound is prepared via general method **E** using intermediate **B1** and 2-bromomethyl-2,3-dihydro-benzo[1,4]dioxine.

**Compound 31:** [2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetic acid





**[00270]** Compound **29** (33 mg, 0.06 mmol, 1 eq.) was dissolved in dioxane (0.4 mL), conc. HCl (51 µL, 10 eq.) was added and the reaction was stirred until full completion. The white precipitate was filtered and dried to obtain compound **31**.

5    **Compound 32:**    9-(3-nitro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00271]** This compound is prepared via general method **E** using compound **6** and 1-bromomethyl-3-nitro-benzene.

10    **Compound 33:**    9-(4-nitro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00272]** This compound is prepared via general method **E** using compound **6** and 1-chloromethyl-4-nitro-benzene.

15    **Compound 34:**    9-(3-methyl-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00273]** This compound is prepared via general method **E** using compound **6** and 1-bromomethyl-3-methyl-benzene.

20    **Compound 35:**    9-(4-methyl-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00274]** This compound is prepared via general method **E** using compound **6** and 1-bromomethyl-4-methyl-benzene.

25    **Compound 36:**    9-(2-methoxy-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00275]** This compound is prepared via general method **E** using compound **6** and 1-chloromethyl-4-methoxy-benzene.

30    **Compound 37:**    9-(naphthalen-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00276]** This compound is prepared via general method **E** using compound **6** and 2-chloromethyl-naphthalene.

**Compound 38:** 9-(naphthalen-1-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00277] This compound is prepared via general method E using compound 6 and 1-chloromethyl-naphthalene.

5

**Compound 39:** 9-(2-methyl-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00278] This compound is prepared via general method E using compound 6 and 1-chloromethyl-2-methyl-benzene.

10

**Compound 40:** 9-[2-(2-methoxy-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00279] This compound is prepared via general method E using compound 6 and 1-(2-bromo-ethoxy)-2-methoxy-benzene.

15

**Compound 41:** 9-[2-(3-methoxy-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00280] This compound is prepared via general method E using compound 6 and 1-(2-bromo-ethoxy)-3-methoxy-benzene.

20

**Compound 42:** 9-[2-(4-methoxy-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00281] This compound is prepared via general method E using compound 6 and 1-(2-bromo-ethoxy)-4-methoxy-benzene.

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**Compound 43:** 9-[2-(2-chloro-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00282] This compound is prepared via general method E using compound 6 and 1-(2-bromo-ethoxy)-2-chloro-benzene.

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**Compound 44:** 9-[2-(3-chloro-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00283] This compound is prepared via general method E using compound 6 and 1-(2-bromo-ethoxy)-3-chloro-benzene.

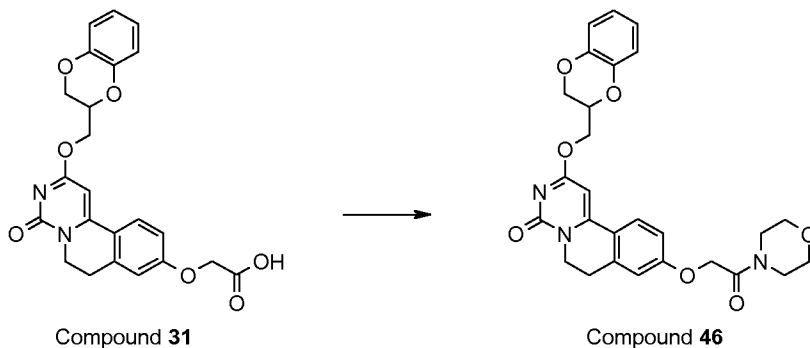
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**Compound 45:** 9-[2-(4-chloro-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00284]** This compound is prepared via general method E using compound 6 and 1-(2-bromo-ethoxy)-4-chloro-benzene.

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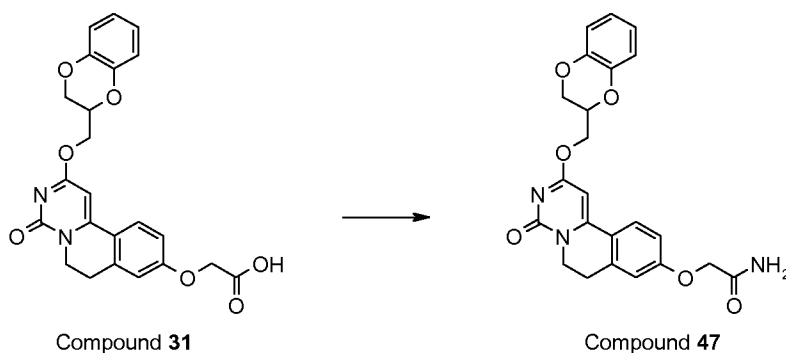
**Compound 46:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-morpholin-4-yl-2-oxo-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



**[00285]** A vial was charged with compound 31 (50 mg, 0.11 mmol, 1 eq.), morpholine (12  $\mu$ L, 0.14 mmol, 1.2 eq.), EDC (33 mg, 0.17 mmol, 1.5 eq.) and DMAP (28 mg, 0.23 mmol, 2 eq.) in DMF (1 mL). The vial was sealed and the reaction was stirred for 16h. The reaction was evaporated to dryness then the residue was dissolved in DCM and washed with a saturated solution of  $\text{NaHCO}_3$ . After evaporation of the organic phase under vacuum, the crude product was purified by flash chromatography on silica gel eluting with 5% MeOH/DCM to give compound 46.

15

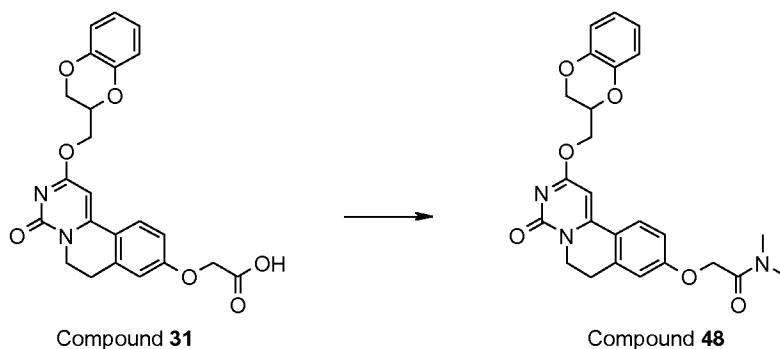
**Compound 47:** 2-[2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide



**[00286]** Compound 31 (50 mg, 0.11 mmol, 1 eq.), isobutyl chloroformate (16.5  $\mu$ L, 0.13 mmol, 1.1 eq.) and NMM (15  $\mu$ L, 0.14 mmol, 1.2 eq.) were dissolved in DCM (1 mL) at 0°C. After 5 min, 20% aq.  $\text{NH}_3$  (50  $\mu$ L, 0.57 mmol, 5 eq.) was added and the reaction was stirred for 16h. The reaction was evaporated to

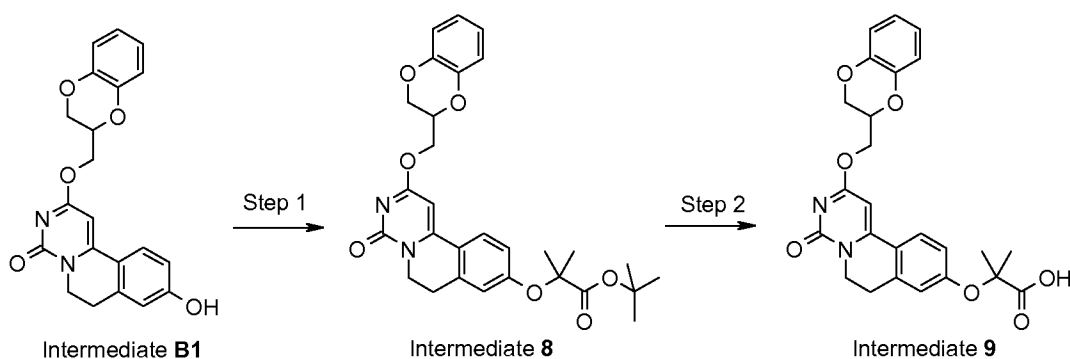
dryness, the residue was dissolved in DCM and washed with aq. HCl (1 N). The DCM layer was dried over MgSO<sub>4</sub>, and evaporated to dryness to recover compound **47**.

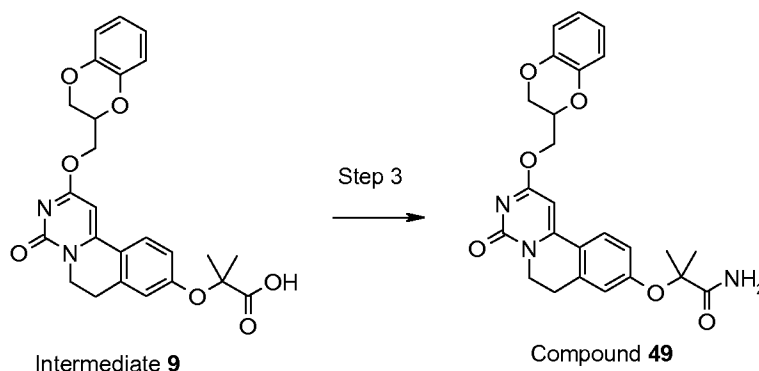
**Compound 48:** 2-[2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N,N-dimethyl-acetamide



**[00287]** A vial was charged with compound **31** (50 mg, 0.11 mmol, 1 eq.), dimethylamine hydrochloride (11 mg, 0.14 mmol, 1.2 eq.), EDC (33 mg, 0.17 mmol, 1.5 eq.), DIEA (57  $\mu$ L, 0.34 mmol, 3 eq.) and DMAP (28 mg, 0.23 mmol, 2 eq.) in DMF (1 mL). The vial was sealed and the reaction was stirred for 16h. The reaction was evaporated to dryness then the residue was dissolved in DCM and washed with a saturated solution of NaHCO<sub>3</sub>. After evaporation of the organic phase under vacuum, the crude product was purified by flash chromatography on silica gel eluting with 5% MeOH/DCM to give compound **48**.

**Compound 49:** 2-[2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-2-methyl-propionamide





*Step 1: 2-[2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-2-methyl-propionic acid tert-butyl ester (intermediate **8**)*

**[00288]** Intermediate **8** is prepared via general method **F** using intermediate **B1** and 2-bromo-2-methyl-propionic acid tert-butyl ester.

$^1\text{H}$ ,  $\text{CDCl}_3$ )  $\delta$  ppm 7.54 (1 H, d), 6.67 - 6.89 (4 H, m), 6.64 (1 H, d), 6.16 - 6.26 (2 H, m), 4.57 (2 H, dd), 4.43 - 4.51 (2 H, m), 4.27 (2 H, dd), 4.00 - 4.15 (3 H, m), 1.56 (6 H, s), 1.37 (9 H, s)

*Step 2: 2-[2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-2-methyl-propionic acid (intermediate **9**)*

**[00289]** Intermediate **8** (203 mg, 0.39 mmol, 1 eq.) was dissolved in dioxane (6 mL), TFA (300  $\mu\text{L}$ , 3.9 mmol, 10 eq.) was added and the reaction was heated at 85°C. After full completion, the reaction was evaporated to dryness, the residue was then purified on SPX cartridge to give intermediate **9**.

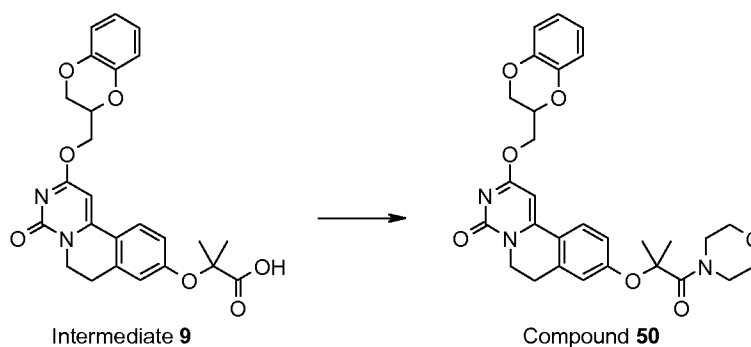
$^1\text{H}$ ,  $\text{CDCl}_3$ )  $\delta$  ppm 7.43 - 7.77 (2 H, m), 6.84 (4 H, d), 6.50 (2 H, br. s.), 4.47 - 4.78 (1 H, m), 4.03 - 4.38 (3 H, m), 3.64 - 3.90 (4 H, m), 2.86 - 3.14 (2 H, m), 1.70 (6 H, br. s.)

MW (calcd): 464.5; MW (obsd): 465.8 (M + 1)

*Step 3: 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-2-methyl-propionamide (compound **49**)*

**[00290]** Intermediate **9** (28 mg, 0.06 mmol, 1 eq.), isobutyl chloroformate (8.7  $\mu\text{L}$ , 0.7 mmol, 1.1 eq.) and NMM (8  $\mu\text{L}$ , 0.7 mmol, 1.2 eq.) were dissolved in DCM (1 mL) at 0°C. After 5 min, 20% aq.  $\text{NH}_3$  (26  $\mu\text{L}$ , 0.30 mmol, 5 eq.) was added and the reaction was stirred for 16h. The reaction was evaporated to dryness, the residue was purified by flash chromatography on silica gel eluting with 5% MeOH/DCM to recover compound **49**.

**Compound 50:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(1,1-dimethyl-2-morpholin-4-yl-2-oxo-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



**[00291]** A vial was charged with intermediate **9** (28 mg, 0.06 mmol, 1 eq.), morpholine (7  $\mu$ L, 0.08 mmol, 1.3 eq.), EDC (17 mg, 0.09 mmol, 1.5 eq.) and DMAP (15 mg, 0.12 mmol, 2 eq.) in DMF (1 mL). The vial was sealed and the reaction was stirred for 16h. The reaction was evaporated to dryness then the crude product was purified by flash chromatography on silica gel eluting with 5% MeOH/DCM to give compound **50**.

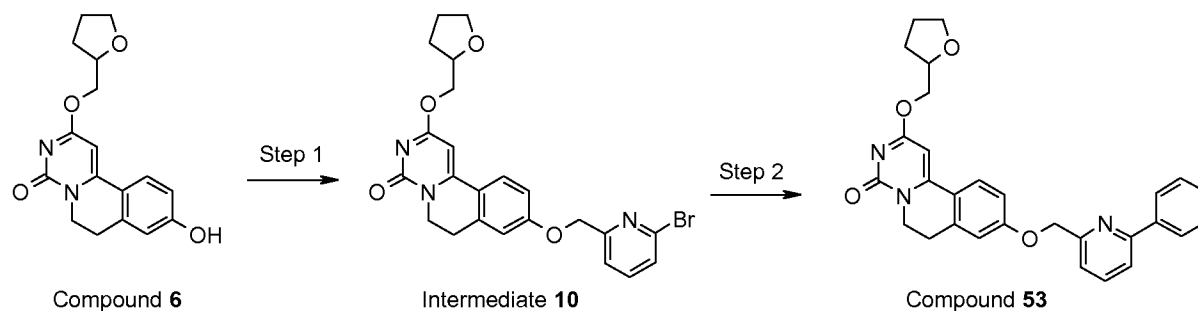
**Compound 51:** 9-(2-benzyloxy-ethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00292]** This compound is prepared via general method **E** using compound **6** and (2-bromoethoxymethyl)-benzene.

**Compound 52:** 2,9-bis-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00293]** This compound is prepared via general method **E** using compound **6** and 2-bromomethyl-tetrahydro-furan.

**Compound 53:** 9-(6-phenyl-pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



Step 1: 9-(6-bromo-pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one (intermediate 10)

[00294] Intermediate 10 is prepared via general method E using compound 6 and 2-bromo-6-bromomethyl-pyridine.

5 (<sup>1</sup>H, CDCl<sub>3</sub>) δ ppm 7.49 - 7.60 (2 H, m), 7.39 (2 H, s), 6.83 - 6.93 (1 H, m), 6.76 - 6.83 (1 H, m), 6.21 (1 H, s), 5.15 (2 H, s), 4.38 - 4.55 (1 H, m), 4.04 - 4.29 (4 H, m), 3.68 - 3.94 (2 H, m), 2.82 - 2.99 (2 H, m), 1.74 - 2.08 (3 H, m), 1.46 - 1.67 (1 H, m)

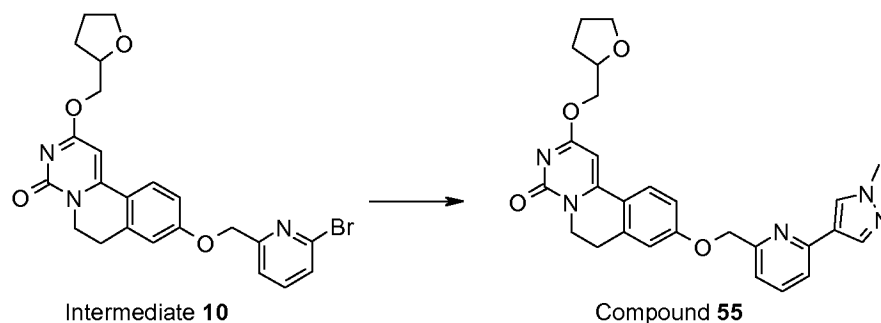
Step 2: 9-(6-phenyl-pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one (compound 53)

[00295] This compound is prepared via general method F using intermediate 10 and phenylboronic acid.

Compound 54: 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

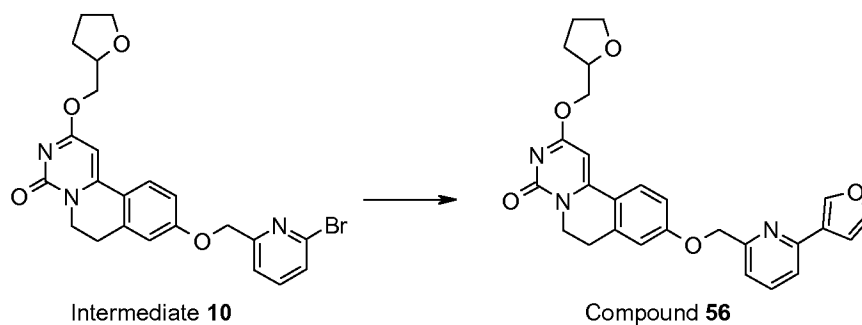
15 [00296] This compound is prepared via general method E using intermediate B1 and 2-bromomethyl-tetrahydro-furan.

Compound 55: 9-[6-(1-methyl-1H-pyrazol-4-yl)-pyridin-2-ylmethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



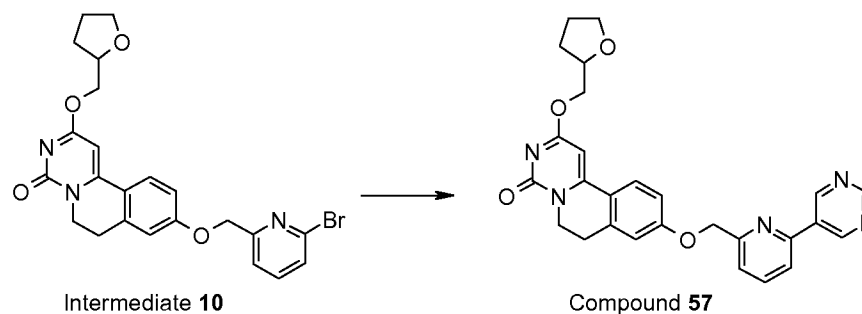
20 [00297] This compound is prepared via general method F using intermediate 10 and 1-methyl-1H-pyrazole-4-boronic acid pinacol ester.

**Compound 56:** 9-(6-furan-3-yl-pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



[00298] This compound is prepared via general method **F** using intermediate **10** and furan-3-boronic acid.

**Compound 57:** 9-(6-pyrimidin-5-yl-pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



[00299] This compound is prepared via general method **F** using intermediate **10** and 5-pyrimidinylboronic acid.

**Compound 58:** 9-(1-cyclopropyl-1H-tetrazol-5-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00300] This compound is prepared via general method **E** using compound **6** and 5-chloromethyl-1-cyclopropyl-1H-tetrazole.

**Compound 59:** 2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide

[00301] This compound is prepared via general method **E** using compound **6** and 2-bromo-acetamide.

**Compound 60:** N,N-diethyl-2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide



**[00302]** This compound is prepared via general method **E** using compound **6** and 2-chloro-N,N-diethyl-acetamide.

**Compound 61:** N,N-dimethyl-2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide

**[00303]** This compound is prepared via general method **E** using compound **6** and 2-chloro-N,N-dimethyl-acetamide.

**Compound 62:** N-isopropyl-N-methyl-2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide

**[00304]** This compound is prepared via general method **E** using compound **6** and 2-bromo-N-isopropyl-N-methyl-acetamide.

**Compound 63:** 2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N-phenyl-acetamide

**[00305]** This compound is prepared via general method **E** using compound **6** and 2-chloro-N-phenyl-acetamide.

**Compound 64:** 9-(1-propyl-1H-tetrazol-5-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00306]** This compound is prepared via general method **E** using compound **6** and 5-chloromethyl-1-propyl-1H-tetrazole.

**Compound 65:** 9-(oxazol-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00307]** This compound is prepared via general method **E** using compound **6** and 2-chloromethyl-oxazole.

**Compound 66:** 2-[2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N,N-diethyl-acetamide

**[00308]** This compound is prepared via general method **E** using intermediate **B1** and 2-chloro-N,N-diethyl-acetamide.

**Compound 67:** 2-[2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N-isopropyl-N-methyl-acetamide

[00309] This compound is prepared via general method E using intermediate B1 and 2-bromo-N-isopropyl-N-methyl-acetamide.

**Compound 68:** 2-[2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl-oxy]-N-phenyl-acetamide

[00310] This compound is prepared via general method E using intermediate B1 and 2-chloro-N-phenyl-acetamide.

**Compound 69:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(1-propyl-1H-tetrazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00311] This compound is prepared via general method E using intermediate B1 and 5-chloromethyl-1-propyl-1H-tetrazole.

**Compound 70:** 9-(1-butyl-1H-tetrazol-5-ylmethoxy)-2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00312] This compound is prepared via general method E using intermediate B1 and 5-chloromethyl-1-butyl-1H-tetrazole.

**Compound 71:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-morpholin-4-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00313] This compound is prepared via general method E using intermediate B1 and 4-(2-chloro-ethyl)-morpholine hydrochloride.

**Compound 72:** [2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl-oxy]-acetonitrile

[00314] This compound is prepared via general method E using intermediate B1 and bromo-acetonitrile.

**Compound 73:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00315] This compound is prepared via general method E using intermediate B1 and 2-chloromethyl-oxazole.

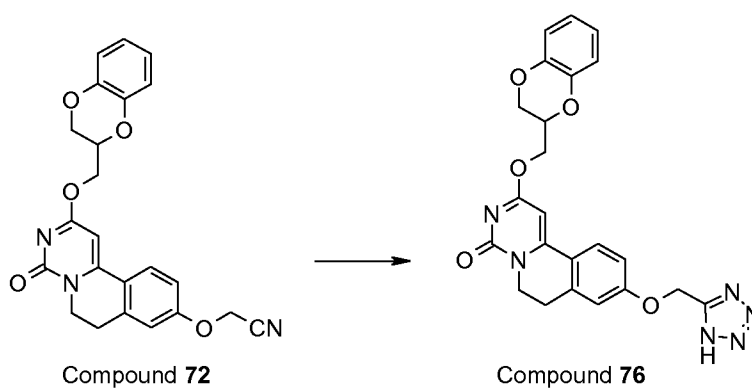
**Compound 74:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00316]** This compound is prepared via general method **E** using intermediate **B1** and 2-chloro-1-pyrrolidin-1-yl-ethanone.

**Compound 75:** 9-(1-cyclopropyl-1H-tetrazol-5-ylmethoxy)-2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00317]** This compound is prepared via general method **E** using intermediate **B1** and 5-chloromethyl-1-cyclopropyl-1H-tetrazole.

**Compound 76:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(1H-tetrazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



**[00318]** Compound **72** (100 mg, 0.24 mmol, 1 eq.) and  $\text{Bu}_3\text{SnN}_3$  (131  $\mu\text{L}$ , 0.48 mmol, 2 eq.) were mixed in dioxane (5 mL) and the reaction was heated to 95°C for 16h. The mixture was evaporated to dryness and the residue was purified by preparative HPLC to obtain compound **76**.

**Compound 77:** 9-allyloxy-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00319]** This compound is prepared via general method **A** using intermediate **5** and (2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-yl)-methanol.

**Compound 78:** N-benzyl-2-[2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide

**[00320]** This compound is prepared via general method **E** using intermediate **B1** and N-benzyl-2-chloro-acetamide.

**Compound 79:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-pyrrolidin-1-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00321] This compound is prepared via general method E using intermediate B1 and 1-(2-chloro-ethyl)-pyrrolidine hydrochloride.

**Compound 80:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-piperidin-1-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00322] This compound is prepared via general method E using intermediate B1 and 1-(2-chloro-ethyl)-piperidine hydrochloride.

**Compound 81:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(3-piperidin-1-yl-propoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00323] This compound is prepared via general method E using intermediate B1 and 1-(3-chloro-propyl)-piperidine hydrochloride.

**Compound 82:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(3-dimethylamino-propoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00324] This compound is prepared via general method E using intermediate B1 and (3-chloro-propyl)-dimethyl-amine hydrochloride.

**Compound 83:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00325] This compound is prepared via general method E using intermediate B1 and 2-(2-chloro-ethyl)-1-methyl-pyrrolidine hydrochloride.

**Compound 84:** 2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-[3-(4-methyl-piperazin-1-yl)-propoxy]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00326] This compound is prepared via general method E using intermediate B1 and 1-(3-chloro-propyl)-4-methyl-piperazine hydrochloride.

**Compound 85:** 5-[2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-ylloxymethyl]-furan-2-carboxylic acid ethyl ester

[00327] This compound is prepared via general method E using intermediate B1 and 5-chloromethyl-furan-2-carboxylic acid ethyl ester hydrochloride.

**Compound 86:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00328] This compound is prepared via general method E using intermediate B4 and 2-chloromethyl-oxazole.

**Compound 87:** 9-(5-tert-butyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00329] This compound is prepared via general method E using compound 6 and 5-tert-butyl-3-chloromethyl-[1,2,4]oxadiazole.

**Compound 88:** 9-(5-phenyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00330] This compound is prepared via general method E using compound 6 and 3-chloromethyl-5-phenyl-[1,2,4]oxadiazole.

**Compound 89:** [2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetonitrile

[00331] This compound is prepared via general method E using intermediate B4 and bromo-acetonitrile.

**Compound 90:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-morpholin-4-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00332] This compound is prepared via general method E using intermediate B4 and 4-(2-chloro-ethyl)-morpholine.

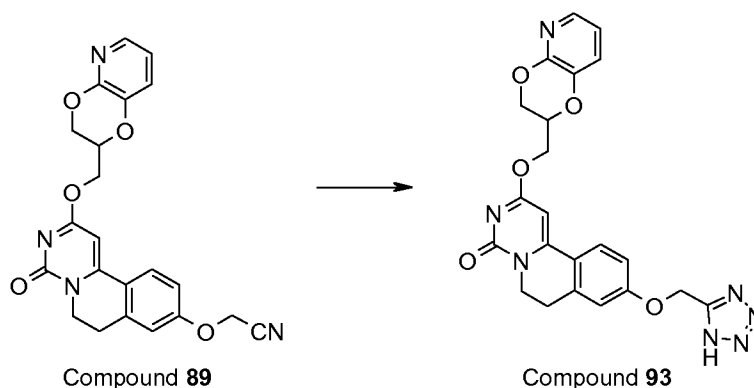
**Compound 91:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00333] This compound is prepared via general method E using intermediate B4 and 2-chloromethyl-pyridine hydrochloride.

**Compound 92:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00334] This compound is prepared via general method E using intermediate B4 and 2-(2-chloro-ethyl)-1-methyl-pyrrolidine hydrochloride.

**Compound 93:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1H-tetrazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



**[00335]** Compound **89** (90 mg, 0.22 mmol, 1 eq.) and  $\text{Bu}_3\text{SnN}_3$  (118  $\mu\text{L}$ , 0.43 mmol, 2 eq.) were mixed in dioxane (3 mL) and the reaction was heated to 95°C for 16h. The mixture was evaporated to dryness and the residue was purified by preparative HPLC to obtain compound **93**.

**Compound 94:** 9-Pyridin-3-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00336]** Synthesis fully described above.

**Compound 95:** 3-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile

**[00337]** This compound is prepared via general method **F** using intermediate **C1** and 3-cyanophenylboronic acid.

**Compound 96:** 9-phenyl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00338]** This compound is prepared via general method **F** using intermediate **C1** and phenylboronic acid.

**Compound 97:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-4-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00339]** This compound is prepared via general method **F** using intermediate **C2** and pyridine-4-boronic acid.

**Compound 98:** 3-[2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile

**[00340]** This compound is prepared via general method **F** using intermediate **C2** and 3-cyanophenylboronic acid.

**Compound 99:** 9-(2-methoxy-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00341] This compound is prepared via general method F using intermediate C1 and 2-methoxyphenylboronic acid.

**Compound 100:** 9-(3-methoxy-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00342] This compound is prepared via general method F using intermediate C1 and 3-methoxyphenylboronic acid.

**Compound 101:** 9-(4-methoxy-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00343] This compound is prepared via general method F using intermediate C1 and 4-methoxyphenylboronic acid.

**Compound 102:** 4-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile

[00344] This compound is prepared via general method F using intermediate C1 and 4-cyanophenylboronic acid.

**Compound 103:** 3-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzoic acid

[00345] This compound is prepared via general method F using intermediate C1 and 3-carboxyphenylboronic acid.

**Compound 104:** 4-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzoic acid

[00346] This compound is prepared via general method F using intermediate C1 and 4-carboxyphenylboronic acid.

**Compound 105:** 9-(4-dimethylamino-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00347] This compound is prepared via general method F using intermediate C1 and 4-(N,N-dimethylamino)phenylboronic acid.

**Compound 106:** 4-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzamide

[00348] This compound is prepared via general method F using intermediate C1 and benzamide-4-boronic acid.

**Compound 107:** 2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile

[00349] This compound is prepared via general method F using intermediate C1 and 2-cyanophenylboronic acid.

**Compound 108:** 9-(1-methyl-1H-pyrazol-4-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00350] This compound is prepared via general method F using intermediate C1 and 1-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole.

**Compound 109:** N,N-dimethyl-3-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzamide

[00351] This compound is prepared via general method F using intermediate C1 and 3-(dimethylcarbamoyl)phenylboronic acid.

**Compound 110:** 9-(6-methoxy-pyridin-3-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00352] This compound is prepared via general method F using intermediate C1 and 2-methoxy-5-pyridineboronic acid.

**Compound 111:** 9-(2,6-dimethyl-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00353] This compound is prepared via general method F using intermediate C1 and 2,6-dimethylphenylboronic acid.

**Compound 112:** 9-(3,5-dimethyl-isoxazol-4-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00354] This compound is prepared via general method F using intermediate C1 and 3,5-dimethylisoxazole-4-boronic acid.



**Compound 113:** 9-naphthalen-2-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00355] This compound is prepared via general method F using intermediate C1 and 2-naphthaleneboronic acid.

**Compound 114:** 9-naphthalen-1-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00356] This compound is prepared via general method F using intermediate C1 and 1-naphthaleneboronic acid.

**Compound 115:** 9-pyrimidin-5-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00357] This compound is prepared via general method F using intermediate C1 and 5-pyrimidinylboronic acid.

**Compound 116:** 9-(5-chloro-thiophen-2-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00358] This compound is prepared via general method F using intermediate C1 and 5-chlorothiophene-2-boronic acid.

**Compound 117:** 2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-pyrrole-1-carboxylic acid tert-butyl ester

[00359] This compound is prepared via general method F using intermediate C1 and 1-tert-butoxycarbonyl-2-pyrrolylboronic acid.

**Compound 118:** 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-methoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00360] This compound is prepared via general method F using intermediate C2 and 2-methoxy-5-pyridineboronic acid.

**Compound 119:** 9-cyclopropylethynyl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00361] Synthesis fully described above.

**Compound 120:** 9-(3,3-dimethyl-but-1-ynyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00362] This compound is prepared via general method G using intermediate C1 and 3,3-dimethyl-but-1-yne.

**Compound 121:** 9-(4-methoxy-phenylethynyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00363] This compound is prepared via general method G using intermediate C1 and 1-ethynyl-4-methoxy-benzene.

**Compound 122:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(pyridin-4-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00364] This compound is prepared via general method E using intermediate B4 and 4-chloromethyl-pyridine hydrochloride.

**Compound 123:** 9-quinoxalin-6-ylethynyl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00365] This compound is prepared via general method G using intermediate C1 and 6-ethynyl-quinoxaline.

**Compound 124:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-3-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00366] This compound is prepared via general method F using intermediate C2 and pyridine-3-boronic acid.

**Compound 125:** 2-[2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile

[00367] This compound is prepared via general method F using intermediate C2 and 2-cyanophenylboronic acid.

**Compound 126:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-methoxy-phenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00368] This compound is prepared via general method F using intermediate C2 and 2-methoxyphenylboronic acid.

**Compound 127:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1H-indazol-5-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00369]** This compound is prepared via general method **F** using intermediate **C2** and 1H-indazole-5-boronic acid.

5

**Compound 128:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyrimidin-5-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00370]** This compound is prepared via general method **F** using intermediate **C2** and 5-pyrimidinylboronic acid.

10

**Compound 129:** 3-[2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzamide

**[00371]** This compound is prepared via general method **F** using intermediate **C2** and 3-carbamoylphenylboronic acid.

15

**Compound 130:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-dimethylamino-phenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00372]** This compound is prepared via general method **F** using intermediate **C2** and 2-(dimethylamine)phenylboronic acid.

20

**Compound 131:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-3-ylethynyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00373]** This compound is prepared via general method **G** using intermediate **C2** and 3-ethynyl-pyridine.

25

**Compound 132:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methoxy-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00374]** This compound is prepared via general method **G** using intermediate **C2** and 3-methoxy-propyne.

30

**Compound 133:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(4-hydroxy-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00375]** This compound is prepared via general method **G** using intermediate **C2** and but-3-yn-1-ol.

**Compound 134:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1,5-dimethyl-1H-pyrazol-3-methoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00376] This compound is prepared via general method E using intermediate B4 and 3-chloromethyl-1,5-dimethyl-1H-pyrazole.

**Compound 135:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methyl-[1,2,4]oxadiazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00377] This compound is prepared via general method E using intermediate B4 and 5-chloromethyl-3-methyl-[1,2,4]oxadiazole.

**Compound 136:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-3-methyl-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00378] This compound is prepared via general method G using intermediate C2 and 2-methyl-but-3-yn-2-ol.

**Compound 137:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-4-ylethynyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00379] This compound is prepared via general method G using intermediate C2 and 4-ethynyl-pyridine.

**Compound 138:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00380] This compound is prepared via general method G using intermediate C2 and prop-2-yn-1-ol.

**Compound 139:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-methyl-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00381] This compound is prepared via general method F using intermediate C2 and 6-methylpyridin-3-ylboronic acid.

**Compound 140:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-methoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00382] This compound is prepared via general method F using intermediate C2 and 3-methoxy-5-pyridineboronic acid pinacol ester.

**Compound 141:** 9-cyclopropylethynyl-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00383] This compound is prepared via general method G using intermediate C2 and ethynyl-cyclopropane.

**Compound 142:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1-hydroxy-cyclopentylethynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00384] This compound is prepared via general method G using intermediate C2 and 1-ethynyl-cyclopentanol.

**Compound 143:** 5-[2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-pyrimido[6,1-a]isoquinolin-9-yl]-pent-4-ynenitrile

[00385] This compound is prepared via general method G using intermediate C2 and pent-4-ynenitrile.

**Compound 144:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3,3-dimethyl-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00386] This compound is prepared via general method G using intermediate C2 and 3,3-dimethyl-but-1-yne.

**Compound 145:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-methoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00387] This compound is prepared via general method F using intermediate C2 and 2-methoxy-3-pyridinyl boronic acid.

**Compound 146:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00388] This compound is prepared via general method F using intermediate C2.

**Compound 147:** 5-[2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-pyridine-2-carboxylic acid methylamide

[00389] This compound is prepared via general method F using intermediate C2 and 2-(N-methylaminocarbonyl) pyridine-5-boronic acid pinacol ester.

**Compound 148:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-furan-3-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00390] This compound is prepared via general method F using intermediate C2 and furan-3-boronic acid.

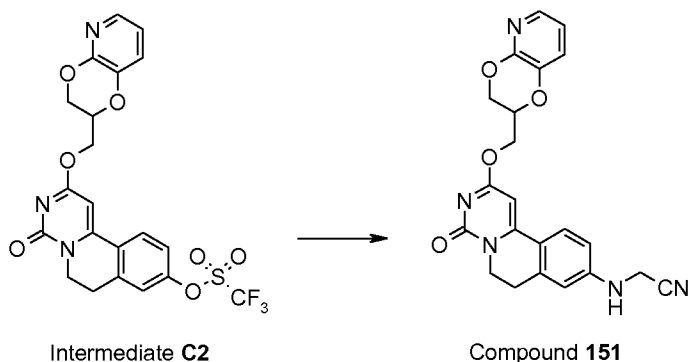
**Compound 149:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00391]** This compound is prepared via general method **F** using intermediate **C2** and 1-methylpyrazole-4-boronic acid pinacol ester.

**Compound 150:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-morpholin-4-ylmethyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

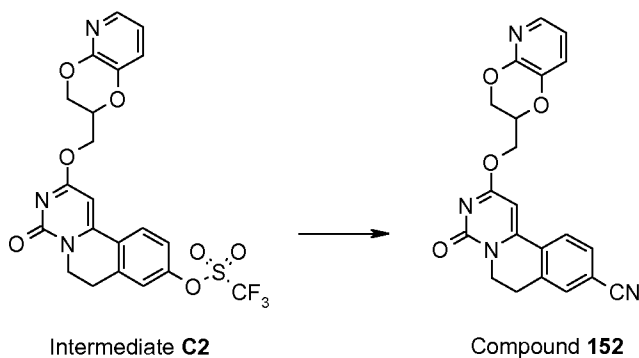
**[00392]** This compound is prepared via general method **F** using intermediate **C2** and potassium (morpholin-4-yl) methyltrifluoroborate.

**Compound 151:** [2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-ylamino]-acetonitrile



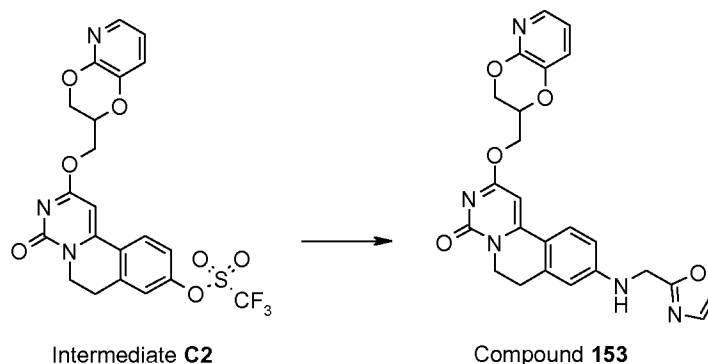
**[00393]** A vial was charged with intermediate **C2** (56 mg, 0.109 mmol, 1 eq.), cyanomethyl-ammonium chloride (68 mg, 0.73 mmol, 7 eq.),  $\text{Cs}_2\text{CO}_3$  (75 mg, 0.229 mmol, 2.1 eq.),  $\text{Pd}(\text{OAc})_2$  (6 mg, 0.028 mmol, 0.26 eq.) and XPhos (13 mg, 0.029 mmol, 0.27 eq.) in dry toluene (3 mL), the vial was sealed and degazed. The reaction was heated at 100°C for 16h, then the mixture was filtered through Celite and evaporated to dryness. The residue was then purified by preparative HPLC to give compound **151**.

**Compound 152:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinoline-9-carbonitrile



**[00394]** A vial was charged with intermediate **C2** (56 mg, 0.109 mmol, 1 eq.), cyanomethyl-ammonium chloride (68 mg, 0.73 mmol, 7 eq.), Cs<sub>2</sub>CO<sub>3</sub> (75 mg, 0.229 mmol, 2.1 eq.), Pd(OAc)<sub>2</sub> (6 mg, 0.028 mmol, 0.26 eq.) and XPhos (13 mg, 0.029 mmol, 0.27 eq.) in dry toluene (3 mL), the vial was sealed and degazed. The reaction was heated at 100°C for 16h, then the mixture was filtered through Celite and evaporated to dryness. The residue was then purified by preparative HPLC to give compound **152**.

**Compound 153:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-[(oxazol-2-ylmethyl)-amino]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



**[00395]** A vial was charged with intermediate **C2** (50 mg, 0.099 mmol, 1 eq.), oxazol-2-ylmethyl-ammonium chloride (45 mg, 0.33 mmol, 3.3 eq.), Cs<sub>2</sub>CO<sub>3</sub> (68 mg, 0.208 mmol, 2.1 eq.), Pd(OAc)<sub>2</sub> (5.5 mg, 0.025 mmol, 0.26 eq.) and XPhos (13 mg, 0.027 mmol, 0.27 eq.) in dry toluene (3 mL), the vial was sealed and degazed. The reaction was heated at 100°C for 16h, then the mixture was filtered through Celite and evaporated to dryness. The residue was then purified by preparative HPLC to give compound **153**.

**Compound 154:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-methyl-[1,2,4]oxadiazol-3-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00396]** This compound is prepared via general method **E** using intermediate **B4** and 3-chloromethyl-5-methyl-[1,2,4]oxadiazole.

**Compound 155:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-ethyl-[1,2,4]oxadiazol-3-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00397]** This compound is prepared via general method **E** using intermediate **B4** and 3-chloromethyl-5-ethyl-[1,2,4]oxadiazole.

**Compound 156:** 9-(5-cyclopropyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00398]** This compound is prepared via general method **E** using intermediate **B4** and 3-chloromethyl-5-cyclopropyl-[1,2,4]oxadiazole.

**Compound 157:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-isopropyl-[1,2,4]oxadiazol-3-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00399]** This compound is prepared via general method **E** using intermediate **B4** and 3-chloromethyl-5-isopropyl-[1,2,4]oxadiazole.

**Compound 158:** 9-(5-tert-Butyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00400]** This compound is prepared via general method **E** using intermediate **B4** and 5-tert-butyl-3-chloromethyl-[1,2,4]oxadiazole.

**Compound 159:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methyl-isoxazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00401]** This compound is prepared via general method **E** using intermediate **B4** and 5-chloromethyl-3-methyl-isoxazole.

**Compound 160:** 9-(3-chloro-2-methoxy-pyridin-4-yl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00402]** This compound is prepared via general method **F** using intermediate **C2** and 3-chloro-2-methoxypyridine-4-boronic acid.

**Compound 161:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3,6-dihydro-2H-pyran-4-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00403]** This compound is prepared via general method **F** using intermediate **C2** and 3,6-dihydro-2H-pyran-4-boronic acid.

**Compound 162:** 5-[2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-pyrimido[6,1-a]isoquinolin-9-yl]-pyridine-2-carbonitrile

**[00404]** This compound is prepared via general method **F** using intermediate **C2** and 2-cyanopyridine-5-boronic acid.

**Compound 163:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-ethoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



[00405] This compound is prepared via general method F using intermediate C2 and 2-ethoxypyridine-3-boronic acid.

**Compound 164:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-ethoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00406] This compound is prepared via general method F using intermediate C2 and 6-ethoxypyridine-3-boronic acid.

**Compound 165:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-morpholin-4-yl-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00407] This compound is prepared via general method F using intermediate C2 and 2-morpholino-5-pyridineboronic acid.

**Compound 166:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-methoxy-pyrimidin-5-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00408] This compound is prepared via general method F using intermediate C2 and 2-methoxypyrimidine-5-boronic acid.

**Compound 167:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2,3-dimethoxy-phenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00409] This compound is prepared via general method F using intermediate C2 and 2,3-dimethoxyphenylboronic acid.

**Compound 168:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2,5-dimethoxy-phenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00410] This compound is prepared via general method F using intermediate C2 and 2,5-dimethoxyphenylboronic acid.

**Compound 169:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-3-phenyl-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00411] This compound is prepared via general method G using intermediate C2 and 1-phenyl-prop-2-yn-1-ol.

**Compound 170:** 3-{3-[2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-prop-2-ynyloxy}-propionitrile

[00412] This compound is prepared via general method **G** using intermediate **C2** and 3-prop-2-ynyloxy-propionitrile.

**Compound 171:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methylamino-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00413] This compound is prepared via general method **G** using intermediate **C2** and methyl-prop-2-ynyl-amine.

**Compound 172:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-dimethylamino-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00414] This compound is prepared via general method **G** using intermediate **C2** and dimethyl-prop-2-ynyl-amine.

**Compound 173:** 9-[3-(benzyl-methyl-amino)-prop-1-ynyl]-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00415] This compound is prepared via general method **G** using intermediate **C2** and benzyl-methyl-prop-2-ynyl-amine.

**Compound 174:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-[3-(1,1-dioxo-thiomorpholin-4-yl)-prop-1-ynyl]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00416] This compound is prepared via general method **G** using intermediate **C2** and 4-prop-2-ynyl-thiomorpholine 1,1-dioxide.

**Compound 175:** {3-[2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-H-pyrimido[6,1-a]isoquinolin-9-yl]-prop-2-ynyl}-urea

[00417] This compound is prepared via general method **G** using intermediate **C2** and prop-2-ynyl-urea.

**Compound 176:** 1-{3-[2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-prop-2-ynyl}-imidazolidine-2,4-dione

[00418] This compound is prepared via general method **G** using intermediate **C2** and 1-prop-2-ynyl-imidazolidine-2,4-dione.

**Compound 177:** 9-(3-diethylamino-prop-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00419] This compound is prepared via general method **G** using intermediate **C2** and diethyl-prop-2-ynyl-amine.

**Compound 178:** 9-(3-amino-3-methyl-but-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00420] This compound is prepared via general method **G** using intermediate **C2** and 1,1-dimethyl-prop-2-ynylamine.

**Compound 179:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(tetrahydro-pyran-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00421] This compound is prepared via general method **D** using intermediate **B4** and 2-(chloromethyl)tetrahydro-2H-pyran.

**Compound 180:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1H-pyrazol-4-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00422] This compound is prepared via general method **F** using intermediate **C2** and pyrazole-4-boronic acid.

**Compound 181:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00423] This compound is prepared via general method **G** using intermediate **C2** and but-3-yn-2-ol.

[00424] **Compound 182:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-pent-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00425] This compound is prepared via general method **G** using intermediate **C2** and pent-1-yn-3-ol.

**Compound 183:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-hex-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00426] This compound is prepared via general method **G** using intermediate **C2** and hex-1-yn-3-ol.

**Compound 184:** 9-(1-amino-cyclohexylethynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00427] This compound is prepared via general method **G** using intermediate **C2** and 1-ethynyl-cyclohexylamine.

**Compound 185:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-5-methyl-hex-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00428] This compound is prepared via general method **G** using intermediate **C2** and 5-methyl-hex-1-yn-3-ol.

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**Compound 186:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-ethyl-3-hydroxy-pent-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00429] This compound is prepared via general method **G** using intermediate **C2** and 3-ethyl-pent-1-yn-3-ol.

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**Compound 187:** 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-3-phenyl-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00430] This compound is prepared via general method **G** using intermediate **C2** and 2-phenyl-but-3-yn-2-ol.

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**Compound 188:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-4-methyl-pent-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00431] This compound is prepared via general method **G** using intermediate **C2** and 4-methyl-pent-1-yn-3-ol.

20

**Compound 189:** 2-[(*R*)-1-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-yl)methoxy]-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00432] This compound is prepared via general method **E** using intermediate **B2** and 2-chloromethyl-oxazole.

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**Compound 190:** 2-[(*S*)-1-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00433] This compound is prepared via general method **E** using intermediate **B3** and 2-chloromethyl-oxazole.

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**Compound 191:** 9-(3-butylamino-prop-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

[00434] This compound is prepared via general method **G** using intermediate **C2** and butyl-prop-2-ynyl-amine.

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**Compound 192:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-morpholin-4-yl-ethoxy methyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00435]** This compound is prepared via general method **F** using intermediate **C2** and potassium [2-(morpholin-4-yl)ethoxy]methyltrifluoroborate.

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**Compound 193:** 9-(3-benzylamino-prop-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00436]** This compound is prepared via general method **G** using intermediate **C2** and benzyl-prop-2-ynyl-amine.

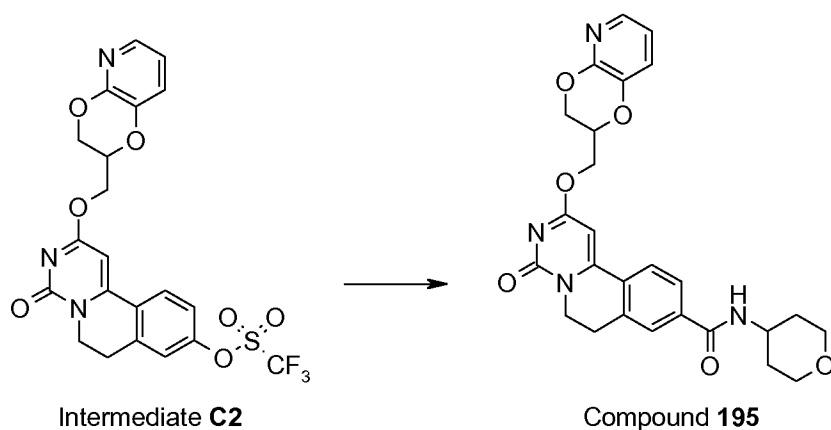
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**Compound 194:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-phenylamino-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00437]** This compound is prepared via general method **G** using intermediate **C2** and phenyl-prop-2-ynyl-amine.

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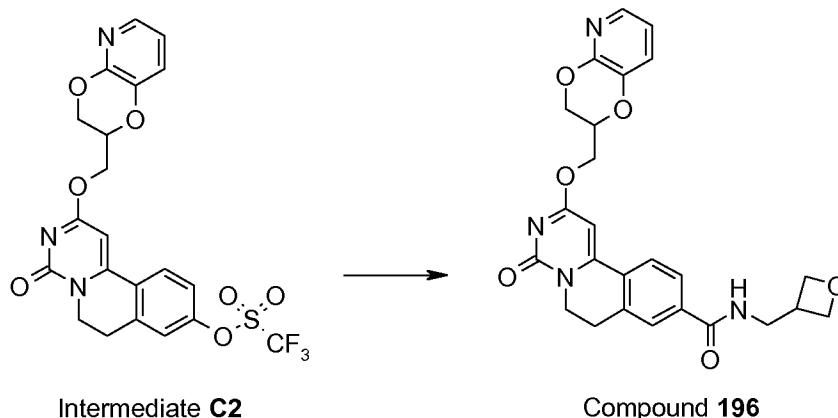
**Compound 195:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido [6,1-a]isoquinoline-9-carboxylic acid (tetrahydro-pyran-4-yl)-amide



**[00438]** A vial was charged with intermediate **C2** (100 mg, 0.196 mmol, 1 eq.), 4-aminotetrahydropyran (40  $\mu$ L, 0.391 mmol, 2 eq.),  $K_2CO_3$  (81 mg, 0.587 mmol, 3 eq.), trans-di- $\mu$ -acetatobis[2-(di-*o*-tolylphosphino)benzyl] dipalladium (II) (0.46 mg, 0.489  $\mu$ mol, 0.0025 eq.), hexacarbonyl molybdenum (53 mg, 0.196 mmol, 1 eq.), XPhos (0.67 mg, 0.00147 mmol, 0.0075 eq.), DMAP (48 mg, 0.391 mmol, 2 eq.) in dry dioxane (2 mL) and the vial was sealed. The reaction was then irradiated in a microwave at 160°C for 20 min. The reaction mixture was directly purified on a preparative TLC to obtain product **195**.

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**Compound 196:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinoline-9-carboxylic acid (oxetan-3-ylmethyl)-amide



**[00439]** A vial was charged with intermediate **C2** (100 mg, 0.196 mmol, 1 eq.), oxetan-3-ylmethanamine (40 mg, 0.46 mmol, 2.35 eq.), K<sub>2</sub>CO<sub>3</sub> (81 mg, 0.587 mmol, 3 eq.), trans-di-μ-acetatobis[2-(di-  
 5 otolylphosphino)benzyl] dipalladium (II) (0.46 mg, 0.489 μmol, 0.0025 eq.), hexacarbonyl molybdenum (53 mg, 0.196 mmol, 1 eq.), XPhos (0.67 mg, 0.00147 mmol, 0.0075 eq.), DMAP (48 mg, 0.391 mmol, 2 eq.) in dry dioxane (2 mL) and the vial was sealed. The reaction was then irradiated in a microwave at 160°C for 20 min. The reaction mixture was directly purified on a preparative TLC to obtain compound **196**.

**Compound 197:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyrrolidin-1-ylmethyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00440]** Synthesis fully described above.

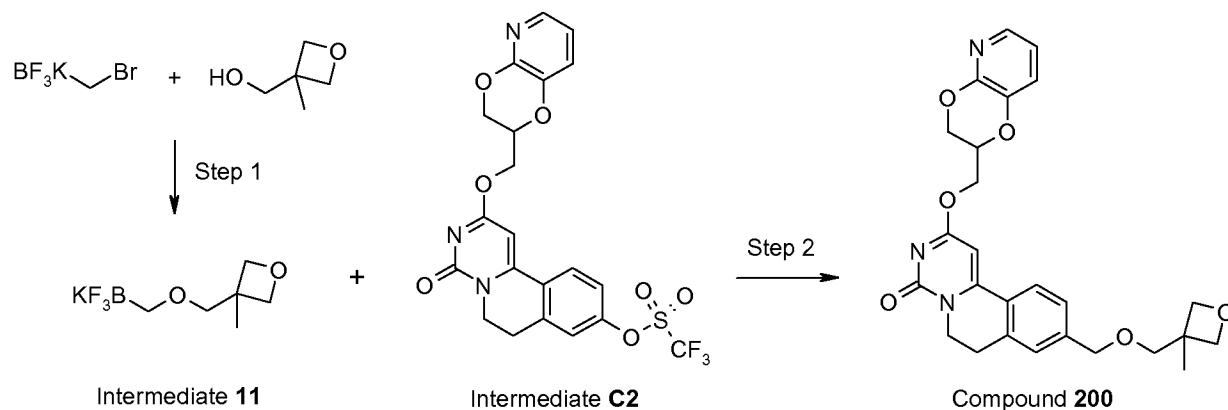
**Compound 198:** 9-(tert-butylamino-methyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00441]** This compound is prepared via general method **H** using intermediate **C2** and potassium (tert-butylaminomethyl) trifluoroborate.

**Compound 199:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-piperidin-1-ylmethyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one

**[00442]** This compound is prepared via general method **H** using intermediate **C2** and potassium trifluoro[(piperidin-1-yl)methyl]borate.

**Compound 200:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methyl-oxetan-3-ylmethoxymethyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



*Step 1: potassium (3-methyl-3-methoxy-oxetane-methyl)trifluoroborate (intermediate 11)*

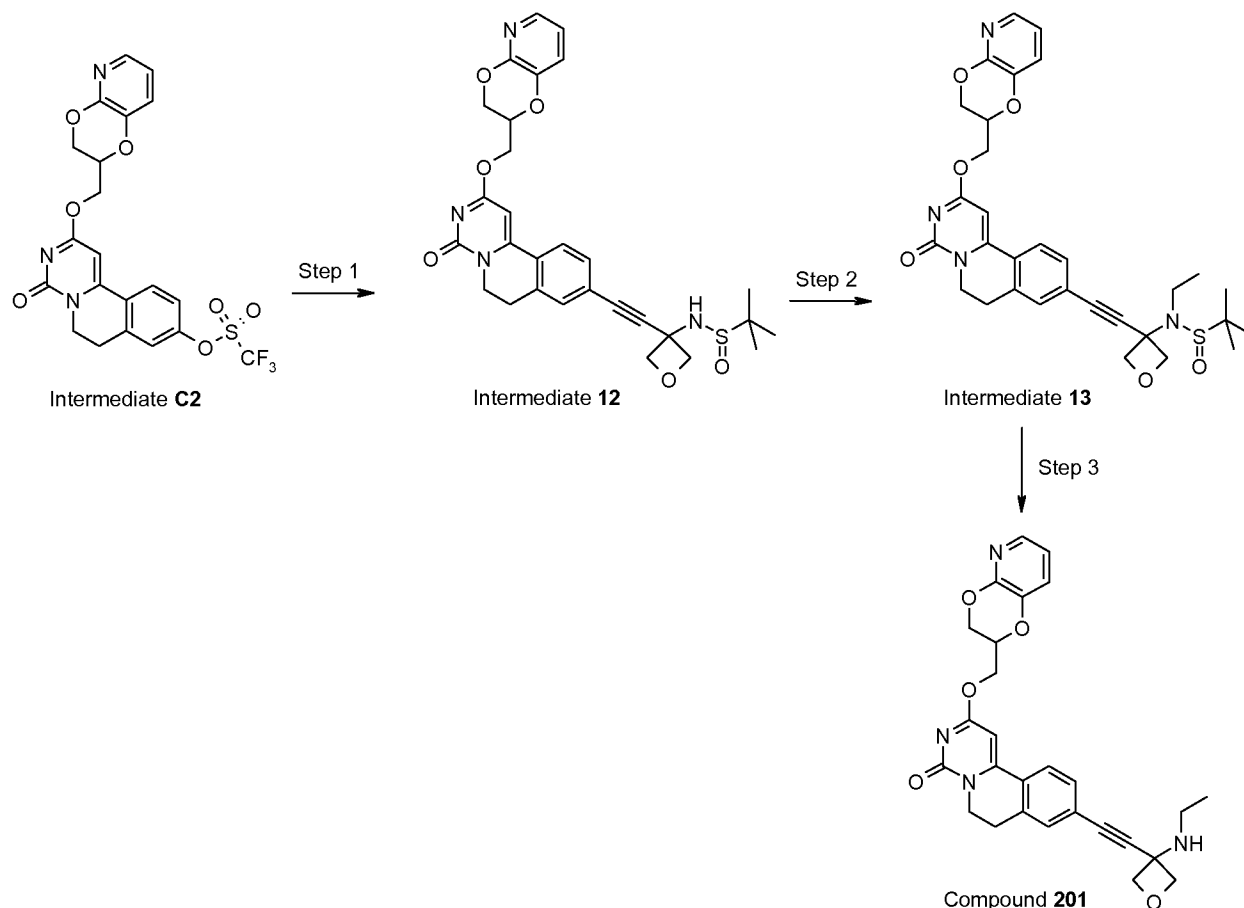
- 5 **[00443]** 3-Methyl-3-oxetanemethanol (305 mg, 2.99 mmol, 2 eq.) was added to a solution of NaH (120 mg, 2.99 mmol, 2 eq., 60% in mineral oil) in THF (5 mL) at 0°C. The reaction was warmed to room temperature for 30 min then cooled again at 0°C. Bromo methyltrifluoroborate (300 mg, 1.49 mmol, 1 eq.) was added to the reaction in one portion and the mixture was stirred at room temperature for 1 day (monitoring by <sup>19</sup>F-NMR). The reaction was quenched with a solution of KHF<sub>2</sub> (3 mL, 1.5 M, 3 eq.) and the mixture was evaporated to dryness. The residue was suspended in acetone, the inorganics were filtered off and the filtrate was evaporated to dryness. The residue was suspended in a minimum amount of acetone (1.5 mL), and Et<sub>2</sub>O (6 mL) was added. Intermediate 11 was obtained by filtration.

(<sup>1</sup>H, DMSO-*d*<sub>6</sub>) δ ppm 4.34 (2 H, d), 4.14 (2 H, d), 3.26 (2 H, s), 2.59 - 2.52 (2 H, m), 1.19 (3 H, s)

- 15 *Step 2: 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methyl-oxetan-3-ylmethoxymethyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one (compound 200)*

**[00444]** This compound is prepared via general method F using intermediates C2 and 11.

**Compound 201:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-ethylamino-oxetan-3-ylethynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



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*Step 1: 2-methyl-propane-2-sulfinic acid {3-[2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-ylethynyl]-oxetan-3-yl}-amide (intermediate 12)*

**[00445]** Intermediate **12** is prepared via general method **G** using intermediate **C2** and 2-methyl-propane-2-sulfinic acid (3-ethynyl-oxetan-3-yl)-amide.

10  $(^1\text{H}, \text{CDCl}_3)$   $\delta$  ppm 7.84 - 7.82 (1 H, m), 7.70 - 7.85 (1 H, d), 7.50 - 7.45 (1 H, d), 7.44 (1 H, s), 7.27 - 7.23 (2 H, m), 6.92 - 6.87 (1 H, m), 5.50 - 5.00 (2 H, m), 4.85 - 4.80 (2 H, m), 4.70 - 4.67 (2 H, d), 4.60 - 4.52 (1 H, m), 4.38 - 4.30 (1 H, m), 4.25 - 4.20 (2 H, t), 4.18 - 4.10 (1 H, q), 3.08 - 3.00 (2 H, t), 4.34 (2 H, d), 4.14 (2 H, d), 3.26 (2 H, s), 2.59 - 2.52 (2 H, m), 1.19 (3 H, s)

MW (calcd): 562.6; MW (obsd): 563.3 (M+1)

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*Step 2: 2-methyl-propane-2-sulfinic acid {3-[2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-ylethynyl]-oxetan-3-yl}-ethyl-amide (intermediate 13)*



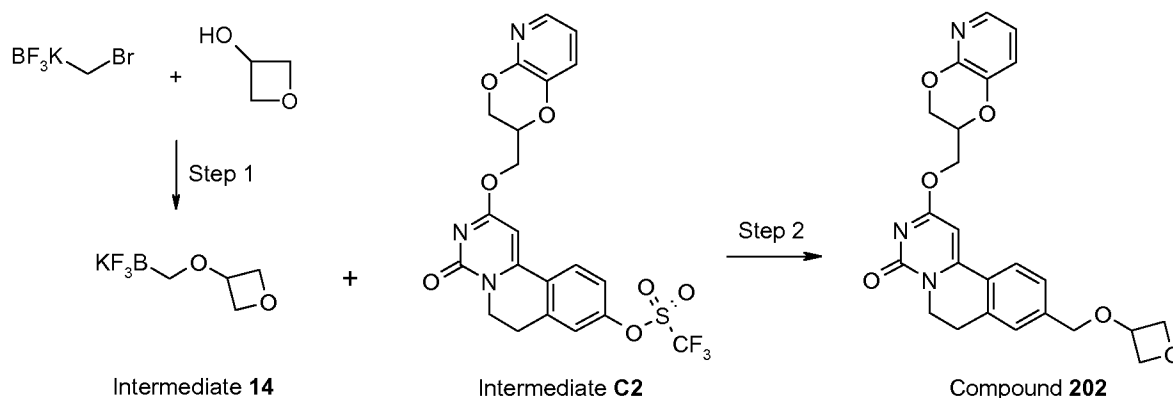
**[00446]** Intermediate **12** (107 mg, 0.190 mmol, 1 eq.) was dissolved in a mixture of THF/DMF (3mL/5mL) at 0°C and NaH (60% in mineral oil, 18 mg, 0.456 mmol, 2.4 eq.) was added. After stirring at room temperature for 2h, iodoethane (76 µL, 0.951 mmol, 5 eq.) was added and the reaction was stirred for 1h at room temperature. The reaction was then quenched with brine and extracted with EtOAc, and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. Crude intermediate **13** was used in the next step without further purification.

MW 590.7 (calcd); MW (obsd): 591.3 (M+1)

*Step 3: 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-ethylamino-oxetan-3-ylethynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one (compound 201)*

**[00447]** HCl (1M in Et<sub>2</sub>O, 0.25 mL, 0.25 mmol 2.5 eq.) was added dropwise at 0°C to a solution of intermediate **13** (60 mg, 0.102 mmol, 1 eq.) in a mixture of THF/*i*Pr<sub>2</sub>O (4 mL, 3/1). After 10 min, the precipitate was filtered off and washed with *i*Pr<sub>2</sub>O and Et<sub>2</sub>O. The solids were purified by preparative HPLC to give compound **201**.

**Compound 202:** 2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(oxetan-3-yloxymethyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



*Step 1: potassium 3-oxy-oxetanemethyltrifluoroborate (intermediate 14)*

**[00448]** Oxetan-3-ol (152 mg, 1.49 mmol, 2 eq.) was added to a solution of NaH (60 mg, 1.49 mmol, 2 eq., 60% in mineral oil) in THF (4 mL) at 0°C. The reaction was warmed to room temperature for 30 min then cooled again at 0°C. Bromo methyltrifluoroborate (150 mg, 0.75 mmol, 1 eq.) was added to the reaction in one portion and the mixture was stirred at room temperature for 1 day (monitoring by <sup>19</sup>F-NMR). The reaction was quenched with a solution of KHF<sub>2</sub> (1.5 mL, 1.5 M, 3 eq.) and the mixture was evaporated to dryness. The residue was suspended in acetone, the inorganics were filtered off and the filtrate was

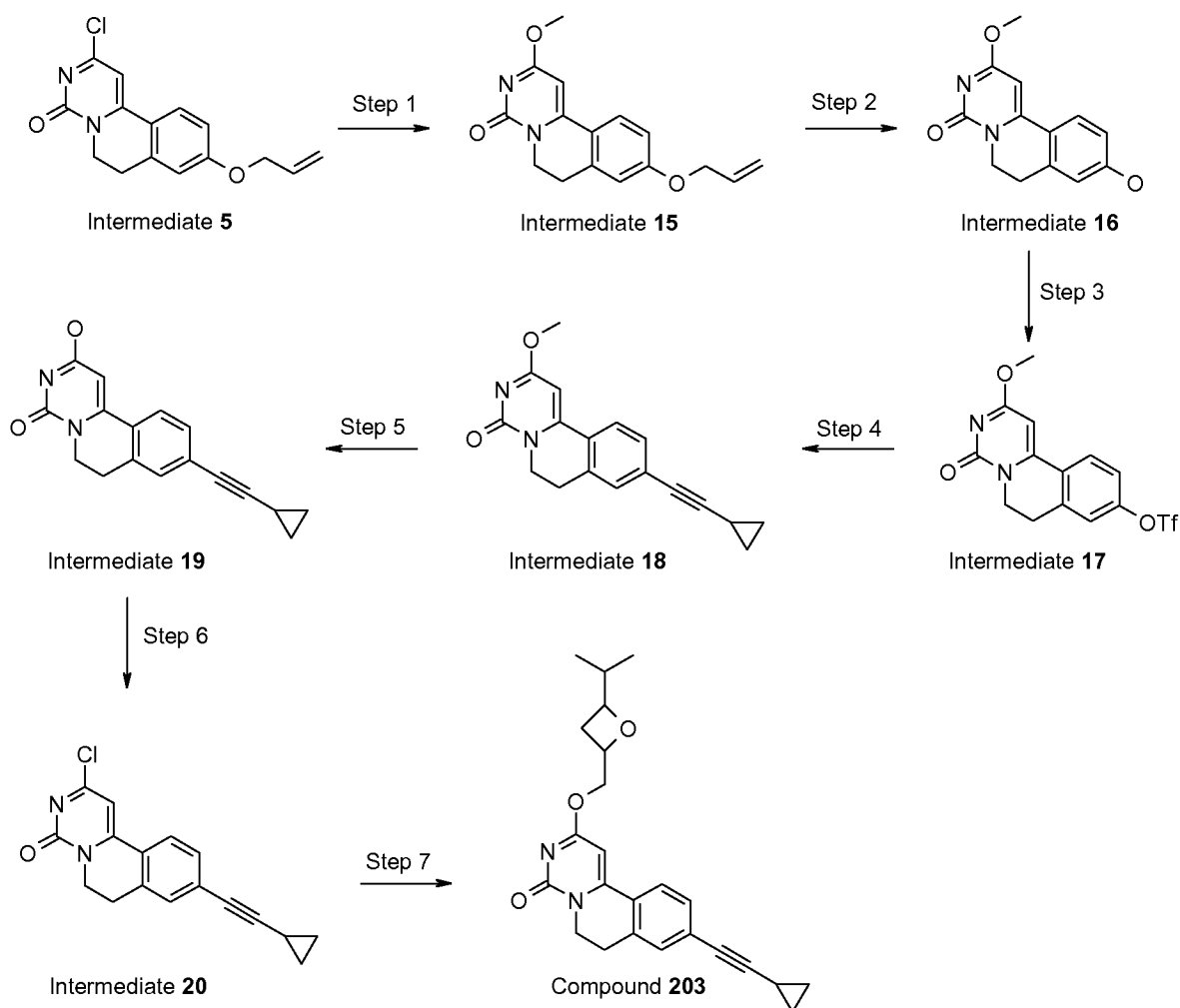
evaporated to dryness. The residue was suspended in a minimum amount of acetone (1.5 mL), and Et<sub>2</sub>O (6 mL) was added. Intermediate **14** was obtained by filtration.

(<sup>1</sup>H, DMSO-*d*<sub>6</sub>) δ ppm 4.56 (2 H, s), 4.32 (3 H, d), 2.40 (2 H, d)

5 *Step 2: 2-(2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridin-2-ylmethoxy)-9-(oxetan-3-yloxymethyl)-6,7-dihydro-pyrimido[6,1-*a*]isoquinolin-4-one (compound 202)*

[00449] This compound is prepared via general method **F** using intermediates **C2** and **14**.

10 **Compound 203:** 9-cyclopropylethynyl-2-(4-isopropyl-oxetan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-*a*]isoquinolin-4-one



*Step 1: 9-allyloxy-2-methoxy-6,7-dihydro-pyrimido[6,1-*a*]isoquinolin-4-one (intermediate 15)*

[00450] Intermediate **5** (5 g, 17.32 mmol, 1 eq.) was suspended in dry MeOH (75 mL) and *t*BuOK (1.943 g, 17.32 mmol, 1 eq.) was added, the reaction was stirred at room temperature for 2.5 days. The yellow precipitate was filtered off to give intermediate **15**.

(<sup>1</sup>H, CDCl<sub>3</sub>) δ ppm 7.70 - 7.61 (1 H, d), 6.95 - 6.89 (1 H, m), 6.80 (1 H, s), 6.19 (1 H, s), 6.12 - 5.95 (1 H, m),  
5 5.50 - 5.40 (1 H, d), 5.38 - 5.25 (1 H, m), 4.61 (2 H, d), 4.24 - 4.18 (2 H, m), 3.99 (3 H, s), 3.00 - 2.92 (2 H, m)

MW (calcd): 284.3; MW (obsd): 285.2 (M+1)

*Step 2: 9-hydroxy-2-methoxy-6,7-dihydro-pyrimido[6,1-*a*]isoquinolin-4-one (intermediate 16)*

10 [00451] Intermediate **15** (4.86 g, 17.09 mmol, 1 eq.) was dissolved in a mixture of THF (60 mL) and MeOH (40 mL), the reaction was degased then 1,3-dimethylbarbituric acid (4 g, 25.6 mmol, 1.5 eq.) was added followed by Pd(PPh<sub>3</sub>)<sub>4</sub> (0.988 g, 0.855 mmol, 0.05 eq.). After 1.5h of stirring, the precipitate was filtered off and washed with THF to afford intermediate **16**.

MW (calcd): 244.3; MW (obsd): 245.2 (M+1)

15 *Step 3: trifluoro-methanesulfonic acid 2-methoxy-4-oxo-6,7-dihydro-4H-pyrimido[6,1-*a*]isoquinolin-9-yl ester (intermediate 17)*

[00452] Intermediate **16** (3.11 g, 12.73 mmol, 1 eq.) and N-phenyl-bis(trifluoromethanesulfinimide) (4.87 g, 43.62 mmol, 1.07 eq.) were suspended in dry DCM (200 mL), TEA (3.55 mL, 25.5 mmol, 2 eq.) was then  
20 added and the reaction was stirred for 16h. The reaction mixture was directly loaded onto a silica gel column chromatography eluting with 2% MeOH/DCM to give product **17**.

(<sup>1</sup>H, CDCl<sub>3</sub>) δ ppm 7.85 - 7.80 (1 H, d), 7.44 - 7.40 (1 H, d), 7.29 (1 H, m), 6.29 (1 H, s), 4.27 - 4.23 (2 H, m),  
4.01 (3 H, s), 3.10 - 3.04 (2 H, m)

MW (calcd): 376.3; MW (obsd): 377.0 (M+1)

25 *Step 4: 9-cyclopropylethynyl-2-methoxy-6,7-dihydro-pyrimido[6,1-*a*]isoquinolin-4-one (intermediate 18)*

[00453] Intermediate **18** was prepared via general method **G** using intermediate and ethynyl-cyclopropane.

(<sup>1</sup>H, CDCl<sub>3</sub>) δ ppm 7.63 - 7.58 (1 H, d), 7.58 - 7.34 (1 H, d), 7.33 (1 H, m), 6.25 (1 H, s), 4.23 - 4.16 (2 H, m),  
3.99 (3 H, s), 3.00 - 2.93 (2 H, m), 1.53 - 1.46 (1 H, m); 0.95 - 0.82 (4 H, m)

30 MW (calcd): 292.3; MW (obsd): 293.2 (M+1)

*Step 5: 9-cyclopropylethynyl-2-hydroxy-6,7-dihydro-pyrimido[6,1-*a*]isoquinolin-4-one (intermediate 19)*

[00454] Intermediate **18** (2.25 g, 7.70 mmol, 1 eq.) was dissolved in THF (90 mL) and H<sub>2</sub>O (90 mL), and TFA (2.3 μL, 0.031 mmol, 0.004 eq.) was added, the reaction was then heated to 50°C for 2.5 days. The

mixture was cooled to room temperature and the precipitate was filtered off, washed with H<sub>2</sub>O to afford intermediate **19**.

(<sup>1</sup>H, CDCl<sub>3</sub>) δ ppm 8.64 (1 H, br. s), 7.62 - 7.56 (1 H, d), 7.38 - 7.32 (1 H, d), 7.28 - 7.26 (1 H, m), 6.12 (1 H, s), 4.10 - 4.03 (2 H, m), 3.00 - 2.95 (2 H, m), 1.51 - 1.43 (1 H, m), 0.95 - 0.80 (4 H, m)

5 MW (calcd): 278.3; MW (obsd): 279.2 (M+1)

*Step 6: 2-chloro-9-cyclopropylethynyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one (intermediate **20**)*

**[00455]** Intermediate **19** (0.5 g, 1.8 mmol, 1 eq.) was dissolved in POCl<sub>3</sub> (8.35 mL) and the reaction was heated to 50°C for 3.5 h then for 2.5 days at room temperature. The reaction mixture was then evaporated to dryness, the residue was dissolved in a mixture of DCM (5 mL) and a saturated solution of NaHCO<sub>3</sub> (5 mL), and the mixture was stirred for 1h. The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to dryness to give intermediate **20**.

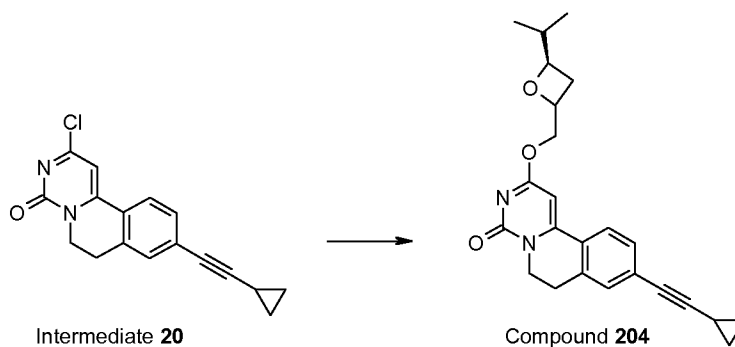
(<sup>1</sup>H, CDCl<sub>3</sub>) δ ppm 7.66 - 7.62 (1 H, d), 7.40 - 7.36 (1 H, d), 7.32 (1 H, m), 6.74 (1 H, s), 4.24 - 4.18 (2 H, m), 3.04 - 2.98 (2 H, m), 1.52 - 1.44 (1 H, m), 0.97 - 0.83 (4 H, m)

15 MW (calcd): 296.8; MW (obsd): 297.1 (M+1)

*Step 7: 9-cyclopropylethynyl-2-(4-isopropyl-oxetan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one (compound **203**)*

**[00456]** This compound is prepared via general method **A** using intermediate **20** and (4-isopropyl-oxetan-2-yl)-methanol.

**Compound 204:** 9-cyclopropylethynyl-2-((R)-4-isopropyl-oxetan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one



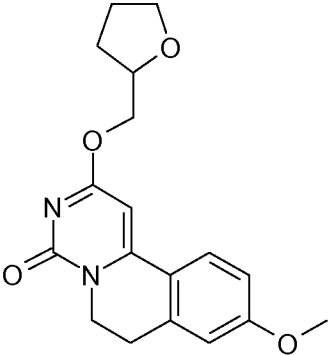
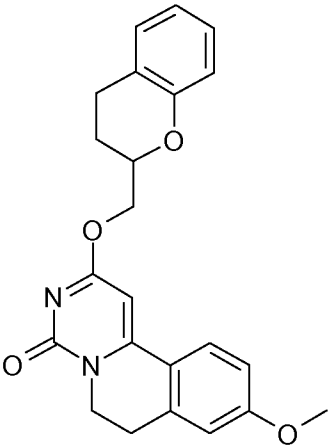
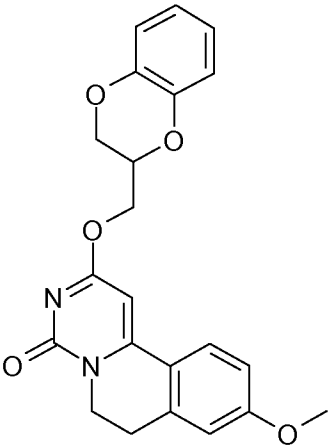
**[00457]** This compound is prepared via general method **A** using intermediate **20** and ((S)-4-isopropyl-oxetan-2-yl)-methanol.

[00458] Table II: Mass spectral data of the Compounds of the Invention

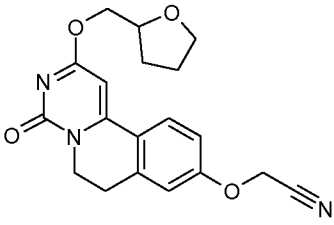
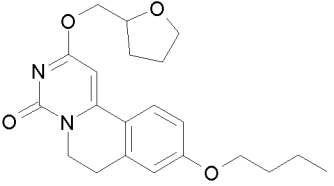
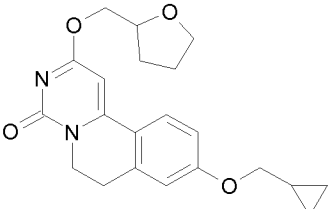
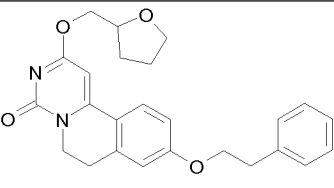
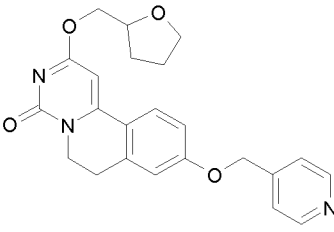
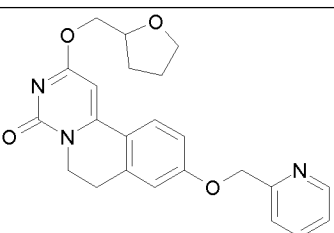
MW: Molecular weight

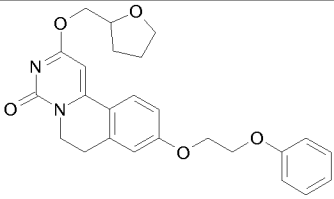
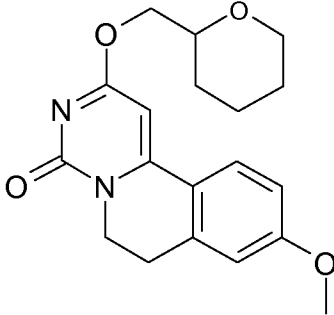
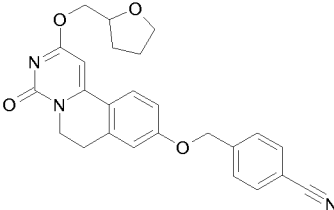
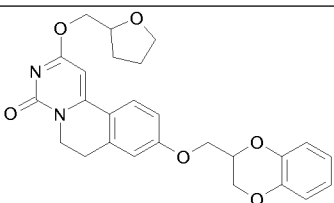
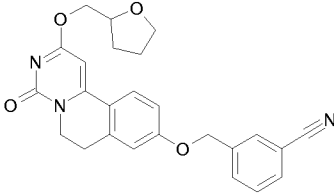
calc: calculated

obs: observed

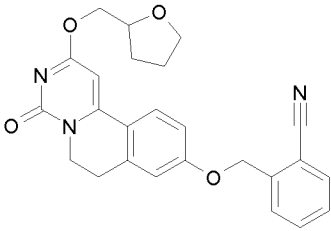
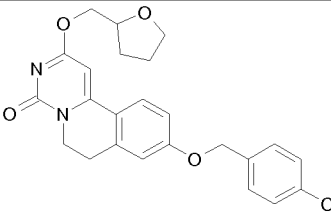
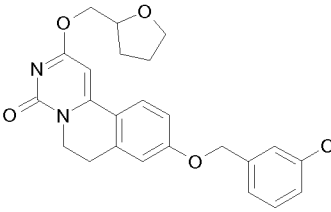
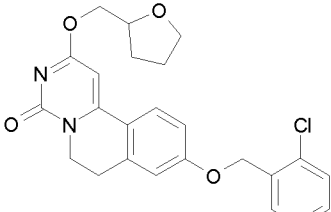
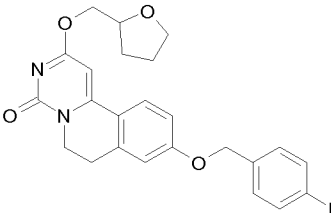
Cpd #	Structures	Name	MW (calc)	MW (obsd)
1		9-Methoxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	328	329
2		2-(Chroman-2-ylmethoxy)-9-methoxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	390	391.3
3		2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-methoxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	392	393.2

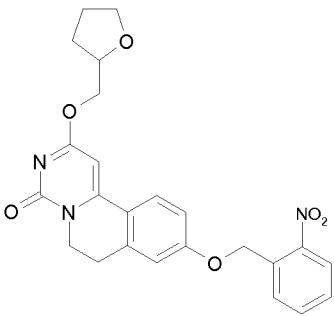
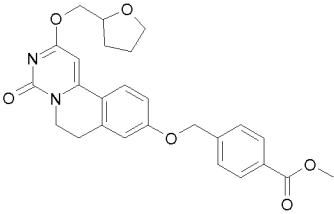
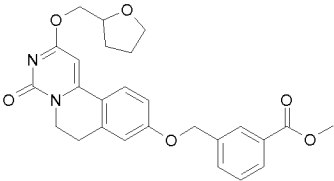
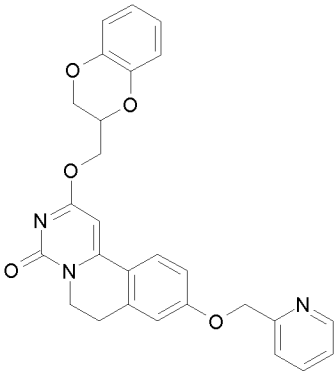
Cpd #	Structures	Name	MW (calc)	MW (obsd)
4		9-Allyloxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	354	-
5		2-(2,3-Dihydro-benzofuran-2-ylmethoxy)-9-methoxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	376	377.3
6		9-Hydroxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	314	-
7		9-Benzyloxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	298	-
8		9-(Pyridin-3-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	405	-

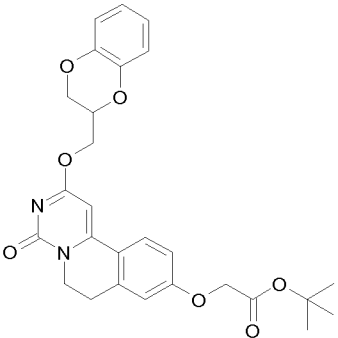
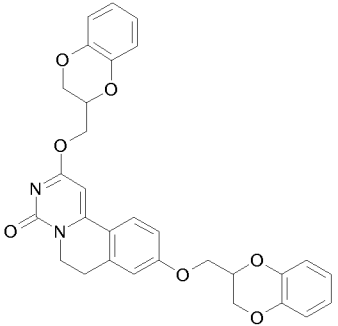
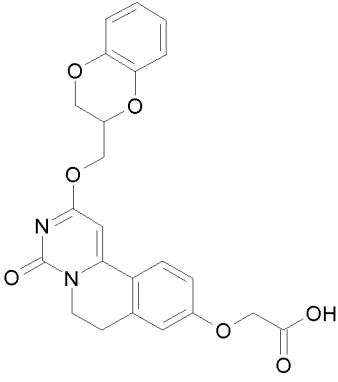
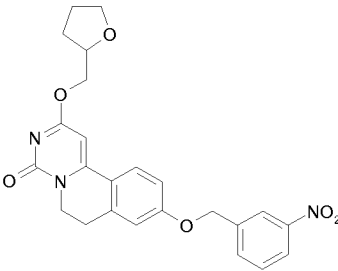
Cpd #	Structures	Name	MW (calc)	MW (obsd)
9		[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetonitrile	353	-
10		9-Butoxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	370	-
11		9-Cyclopropylmethoxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	368	-
12		9-Phenethyloxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	418	-
13		9-(Pyridin-4-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	405	-
14		9-(Pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	405	406.3

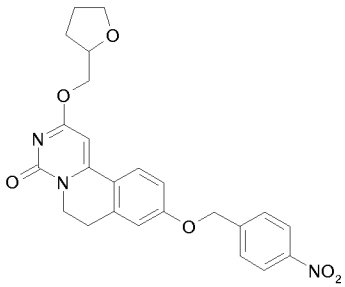
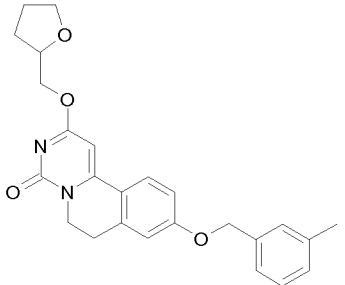
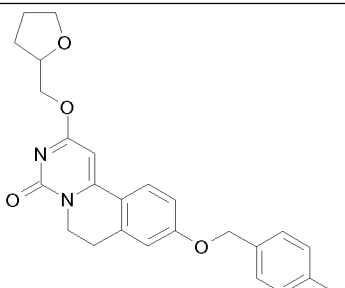
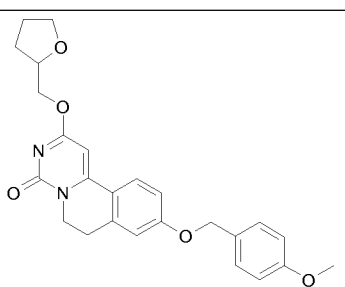
Cpd #	Structures	Name	MW (calc)	MW (obsd)
15		9-(2-Phenoxy-ethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	434	-
16		9-Methoxy-2-(tetrahydro-pyran-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	342	343.1
17		4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-ylloxymethyl]-benzonitrile	429	-
18		9-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	463	-
19		3-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-ylloxymethyl]-benzonitrile	429	430.2



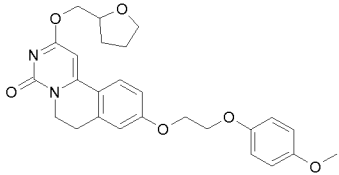
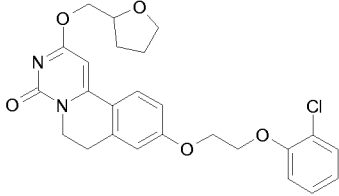
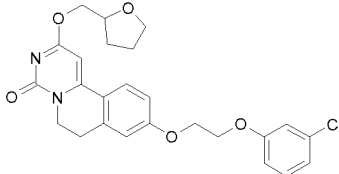
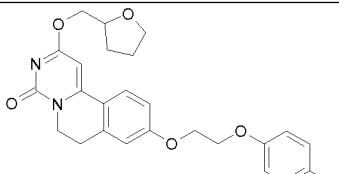
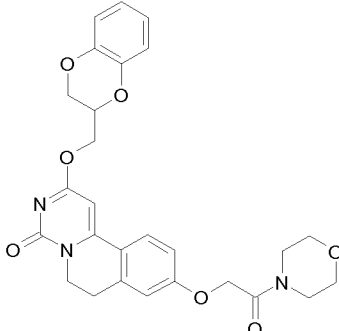
Cpd #	Structures	Name	MW (calc)	MW (obsd)
20		2-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-ylloxymethyl]-benzonitrile	429	430.3
21		9-(4-Chloro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	439	439.2
22		9-(3-Chloro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	439	439.2
23		9-(2-Chloro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	439	439.2
24		9-(4-Fluoro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	422	423.3

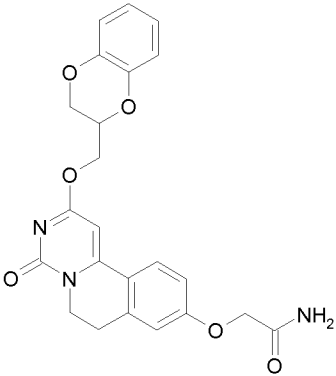
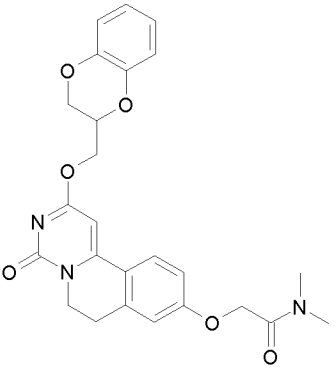
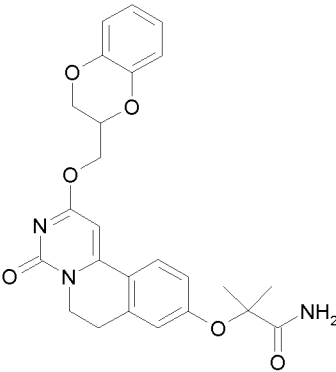
Cpd #	Structures	Name	MW (calc)	MW (obsd)
25		9-(2-Nitro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	449	450.2
26		4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-ylloxymethyl]-benzoic acid methyl ester	463	463.3
27		3-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-ylloxymethyl]-benzoic acid methyl ester	463	463.2
28		2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	470	470.0

Cpd #	Structures	Name	MW (calc)	MW (obsd)
29		[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl oxy]-acetic acid tert-butyl ester	493	-
30		2,9-Bis-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	527	-
31		[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl oxy]-acetic acid	436	437.1
32		9-(3-Nitro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	449	450.1

Cpd #	Structures	Name	MW (calc)	MW (obsd)
33		9-(4-Nitro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	449	450.1
34		9-(3-Methyl-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	418	419.1
35		9-(4-Methyl-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	418	419.1
36		9-(4-Methoxy-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	434	435.2

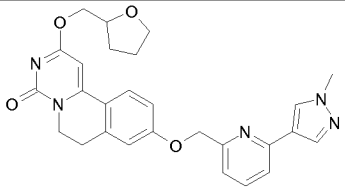
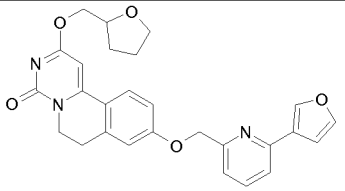
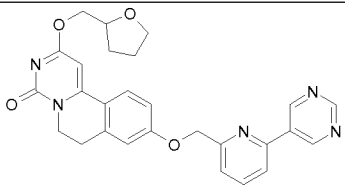
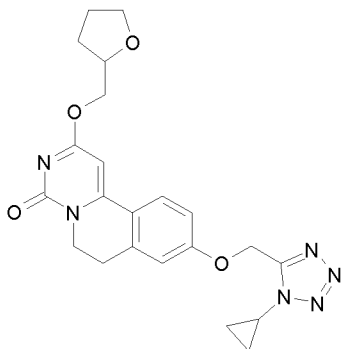
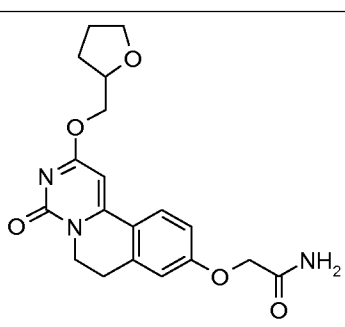
Cpd #	Structures	Name	MW (calc)	MW (obsd)
37		9-(Naphthalen-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	455	455.2
38		9-(Naphthalen-1-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	455	455.1
39		9-(2-Methyl-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	434	435.2
40		9-[2-(2-Methoxy-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	465	464.9
41		9-[2-(3-Methoxy-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	465	-

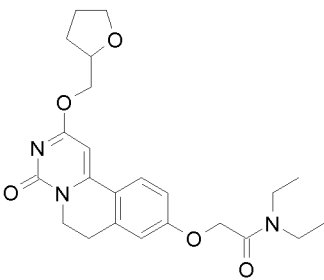
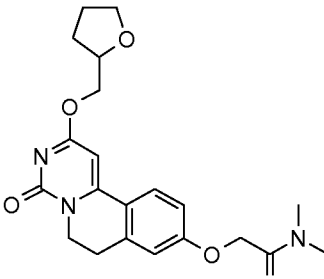
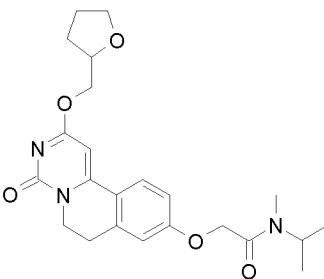
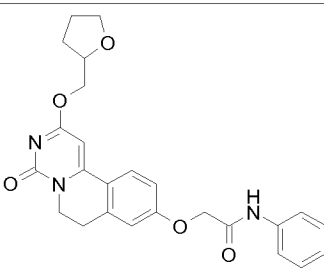
Cpd #	Structures	Name	MW (calc)	MW (obsd)
42		9-[2-(4-Methoxy-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	465	465.3
43		9-[2-(2-Chloro-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	469	469.2
44		9-[2-(3-Chloro-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	469	469.2
45		9-[2-(4-Chloro-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	469	469.2
46		2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-morpholin-4-yl-2-oxo-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	506	506.0

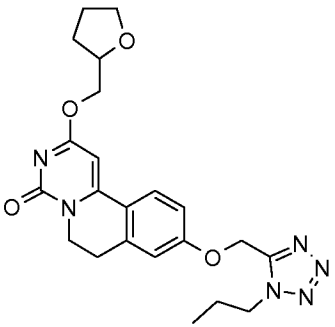
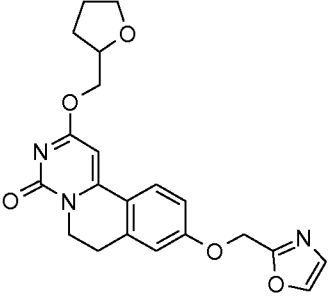
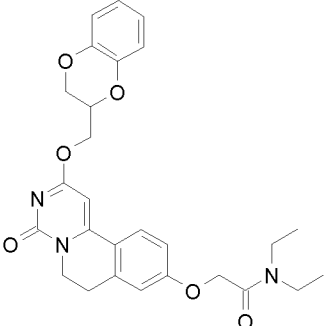
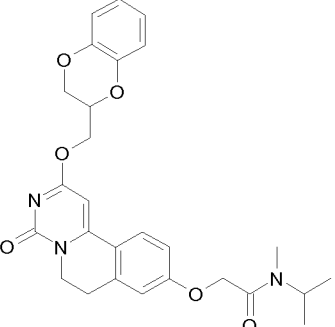
Cpd #	Structures	Name	MW (calc)	MW (obsd)
47		2-[2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide	435	435.9
48		2-[2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N,N-dimethyl-acetamide	463	464.0
49		2-[2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-2-methyl-propionamide	463	-

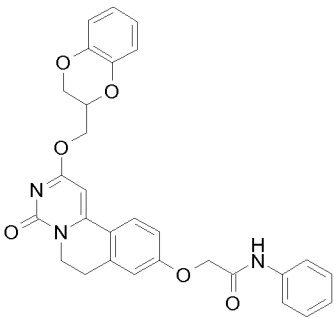
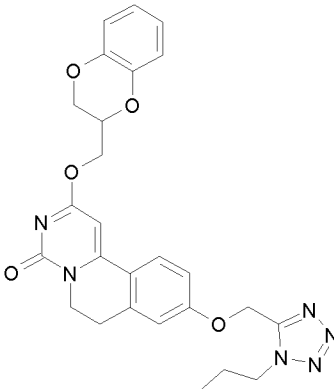
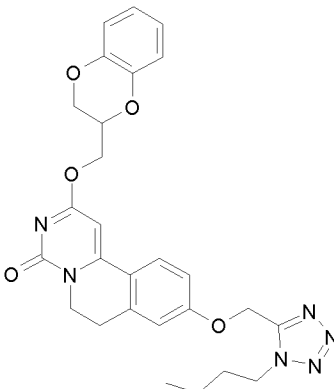
Cpd #	Structures	Name	MW (calc)	MW (obsd)
50		2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(1,1-dimethyl-2-morpholin-4-yl-2-oxo-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	534	-
51		9-(2-Benzyloxy-ethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	449	449.1
52		2,9-Bis-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	398	399.1
53		9-(6-Phenyl-pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	482	482.1
54		2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	463	463.0



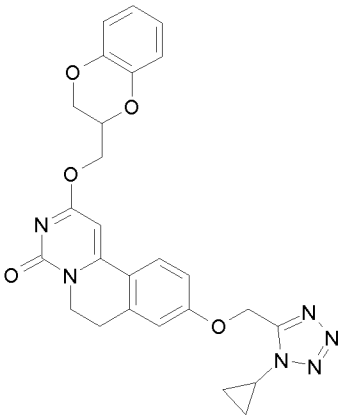
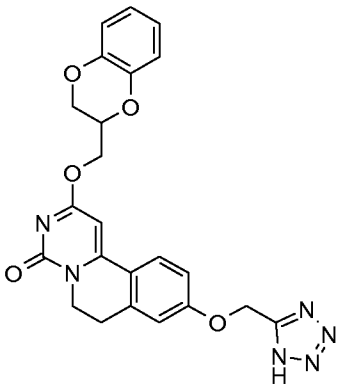
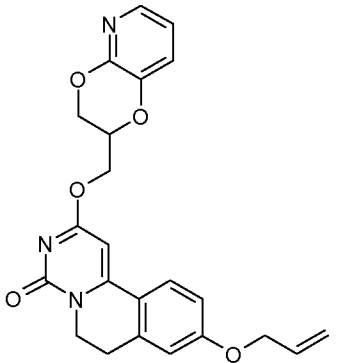
Cpd #	Structures	Name	MW (calc)	MW (obsd)
55		9-[6-(1-Methyl-1H-pyrazol-4-yl)-pyridin-2-ylmethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	486	486.1
56		9-(6-Furan-3-yl-pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	472	472.1
57		9-(6-Pyrimidin-5-yl-pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	484	484.1
58		9-(1-Cyclopropyl-1H-tetrazol-5-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	436	437.1
59		2-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl-oxy]-acetamide	371	372.1

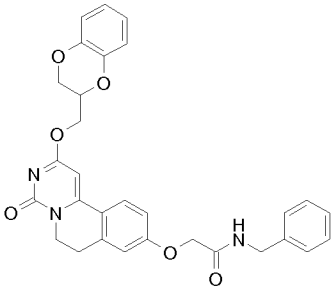
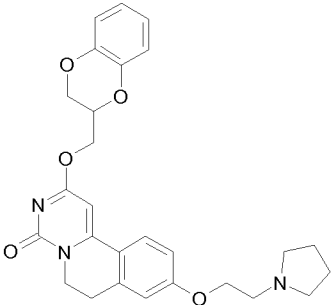
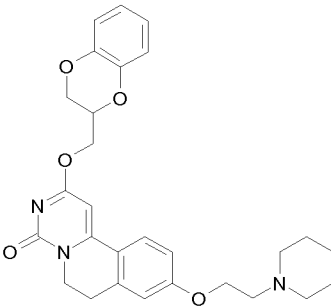
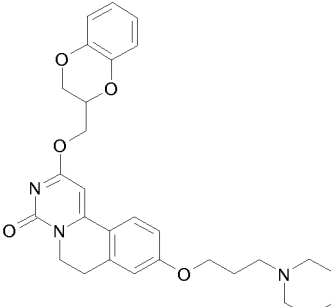
Cpd #	Structures	Name	MW (calc)	MW (obsd)
60		N,N-Diethyl-2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide	428	428.1
61		N,N-Dimethyl-2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide	399	400.0
62		N-Isopropyl-N-methyl-2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide	428	428.1
63		2-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N-phenyl-acetamide	447	448.0

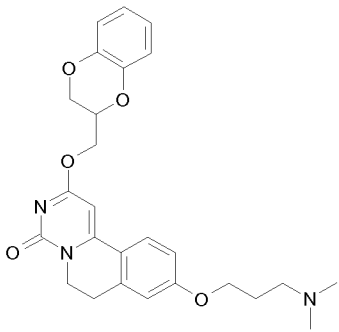
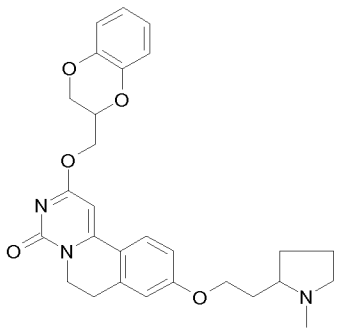
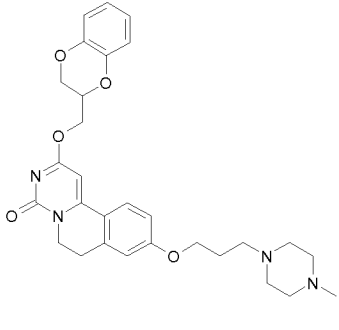
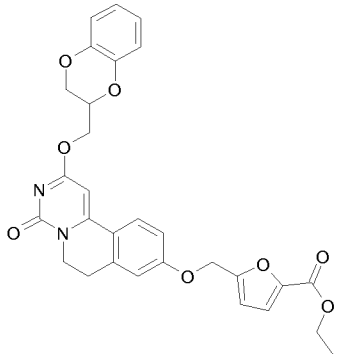
Cpd #	Structures	Name	MW (calc)	MW (obsd)
64		9-(1-Propyl-1H-tetrazol-5-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	438	439.1
65		9-(Oxazol-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	395	396.0
66		2-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N,N-diethyl-acetamide	492	492.0
67		2-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N-isopropyl-N-methyl-acetamide	492	492.0

Cpd #	Structures	Name	MW (calc)	MW (obsd)
68		2-[2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl-oxy]-N-phenyl-acetamide	512	512.0
69		2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-9-(1-propyl-1H-tetrazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	503	503.0
70		9-(1-Butyl-1H-tetrazol-5-ylmethoxy)-2-(2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	517	517.0

Cpd #	Structures	Name	MW (calc)	MW (obsd)
71		2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-9-(2-morpholin-4-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	492	492.0
72		[2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]oxy-acetonitrile	417	418.0
73		2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	459	460.0
74		2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-9-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	490	490.0

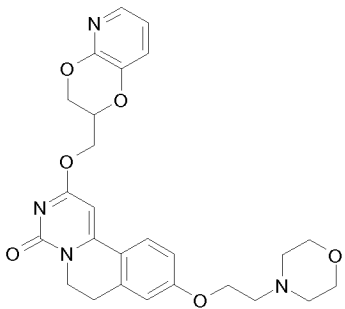
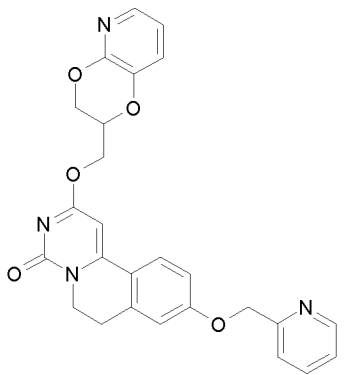
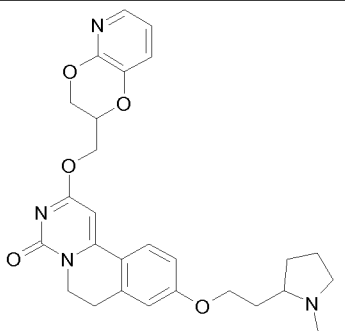
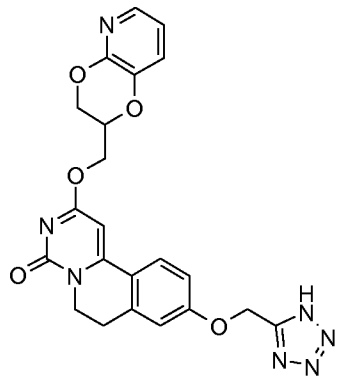
Cpd #	Structures	Name	MW (calc)	MW (obsd)
75		9-(1-Cyclopropyl-1H-tetrazol-5-ylmethoxy)-2-(2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	501	501.1
76		2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-9-(1H-tetrazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	460	461.0
77		9-Allyloxy-2-(2,3-dihydro[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	419	420.0

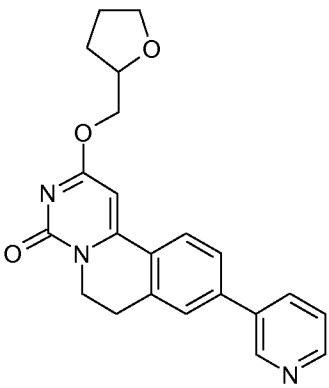
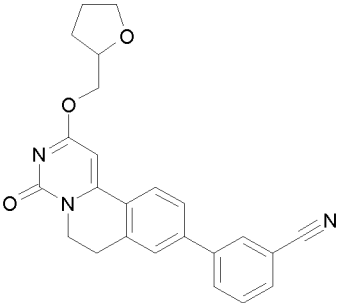
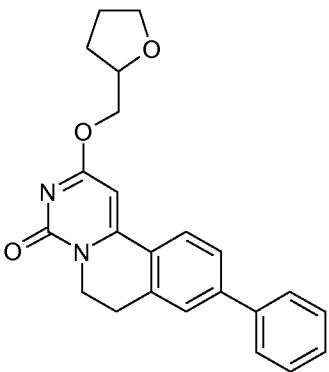
Cpd #	Structures	Name	MW (calc)	MW (obsd)
78		N-Benzyl-2-[2-(2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl-oxy]-acetamide	526	526.0
79		2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-9-(2-pyrrolidin-1-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	476	476.1
80		2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-9-(2-piperidin-1-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	490	490.1
81		2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-9-(3-piperidin-1-yl-propoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	504	504.1

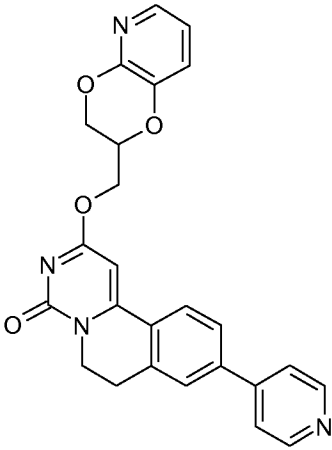
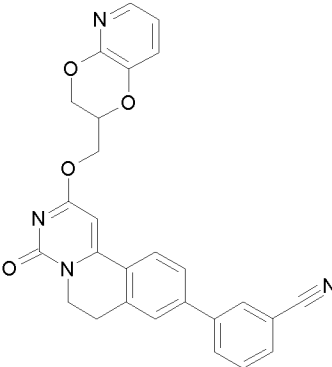
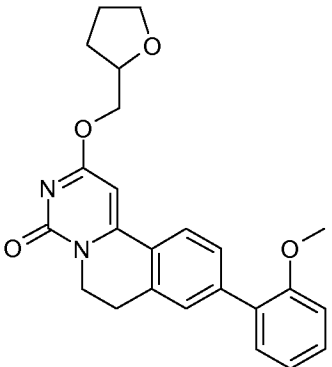
Cpd #	Structures	Name	MW (calc)	MW (obsd)
82		2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-9-(3-dimethylamino-propoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	464	464.1
83		2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-9-[2-(1-methyl-pyrrolidin-2-yl)ethoxy]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	490	490.1
84		2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-9-[3-(4-methyl-piperazin-1-yl)propoxy]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	519	519.1
85		5-[2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-ylloxymethyl]-furan-2-carboxylic acid ethyl ester	531	531.3

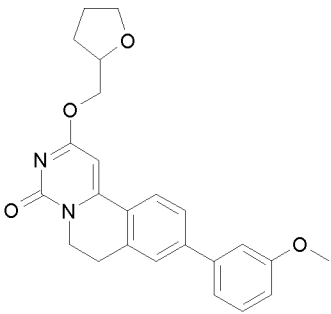
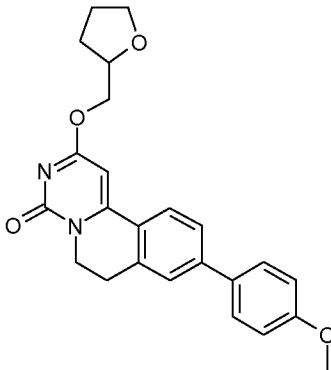
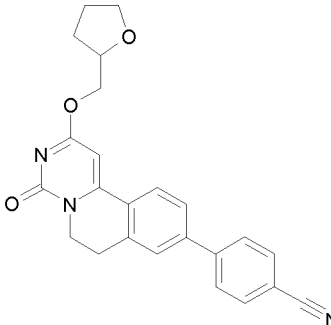
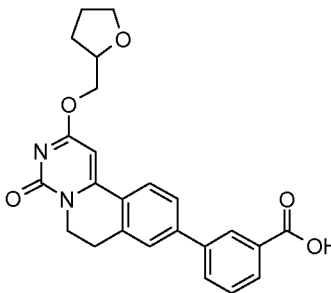


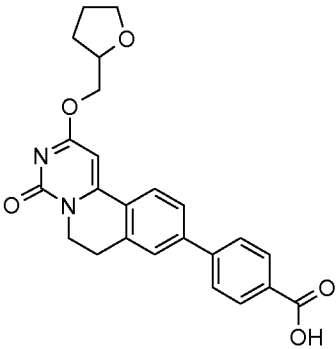
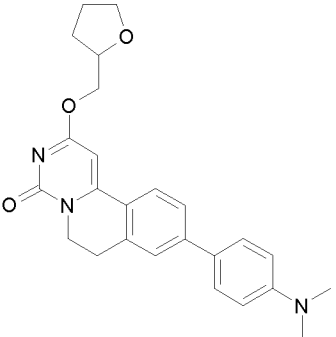
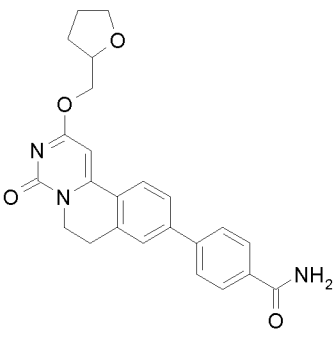
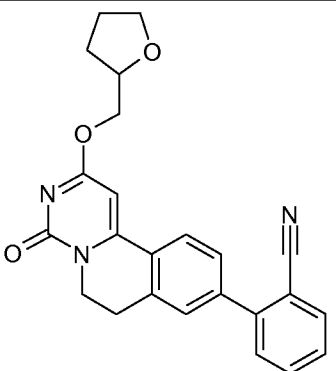
Cpd #	Structures	Name	MW (calc)	MW (obsd)
86		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	460	461.3
87		9-(5-tert-Butyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	453	453.4
88		9-(5-Phenyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	473	473.4
89		[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]acetonitrile	418	419.3

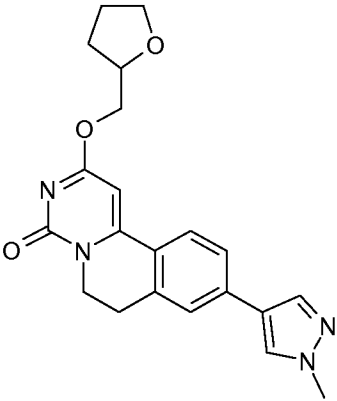
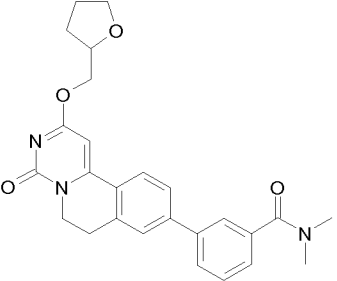
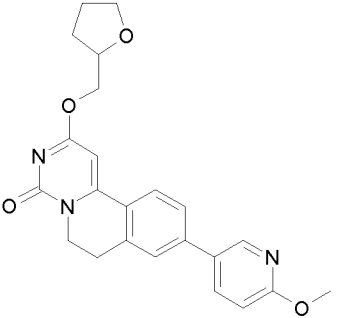
Cpd #	Structures	Name	MW (calc)	MW (obsd)
90		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-morpholin-4-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	493	493.2
91		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	470	471.3
92		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	491	491.3
93		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1H-tetrazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	461	462.3

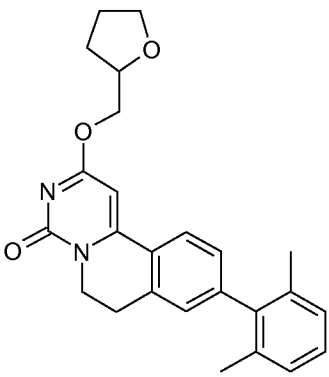
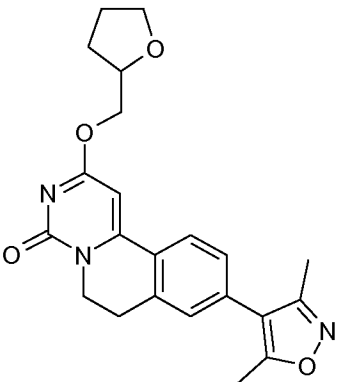
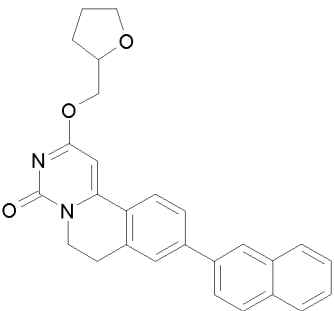
Cpd #	Structures	Name	MW (calc)	MW (obsd)
94		9-Pyridin-3-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	375	376.3
95		3-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile	399	400.3
96		9-Phenyl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	374	375.3

Cpd #	Structures	Name	MW (calc)	MW (obsd)
97		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-4-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	440	441.4
98		3-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile	464	465.4
99		9-(2-Methoxy-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	404	405.4

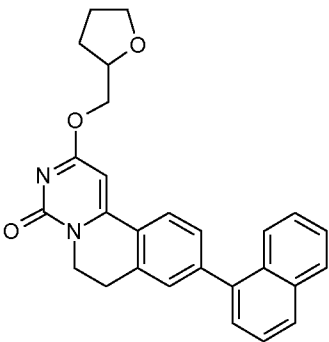
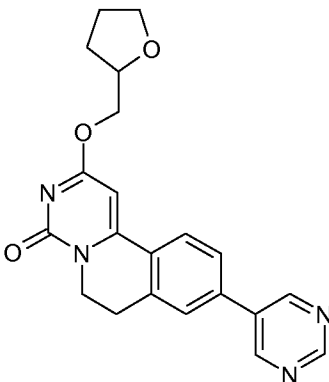
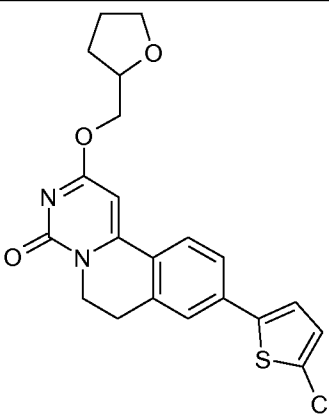
Cpd #	Structures	Name	MW (calc)	MW (obsd)
100		9-(3-Methoxy-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	404	405.4
101		9-(4-Methoxy-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	404	405.4
102		4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile	399	400.4
103		3-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzoic acid	418	419.4

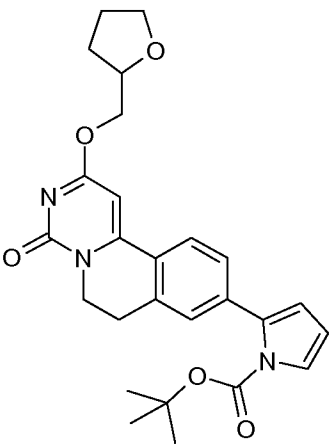
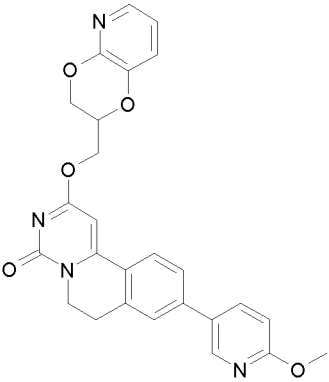
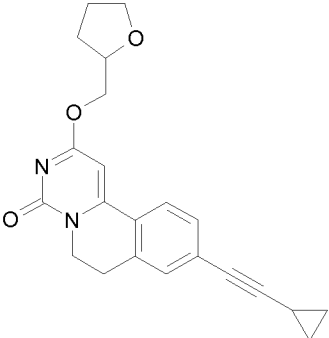
Cpd #	Structures	Name	MW (calc)	MW (obsd)
104		4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzoic acid	418	419.4
105		9-(4-Dimethylamino-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	418	418.5
106		4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzamide	417	418.5
107		2-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile	399	400.5

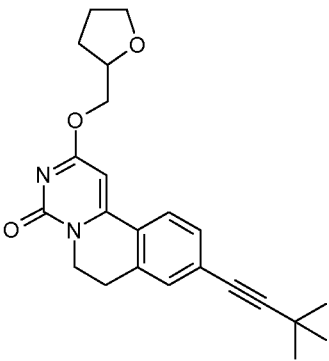
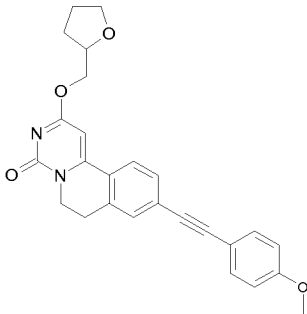
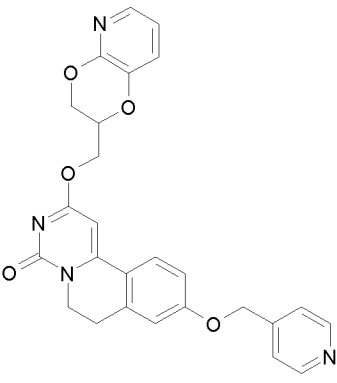
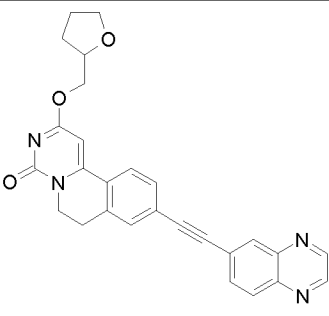
Cpd #	Structures	Name	MW (calc)	MW (obsd)
108		9-(1-Methyl-1H-pyrazol-4-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	378	379.4
109		N,N-Dimethyl-3-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzamide	446	446.5
110		9-(6-Methoxy-pyridin-3-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	405	406.5

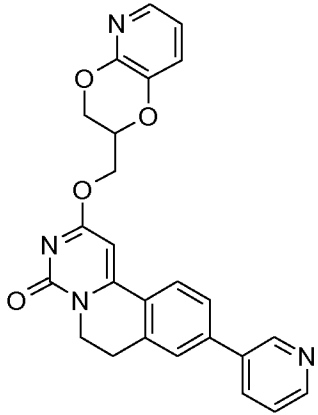
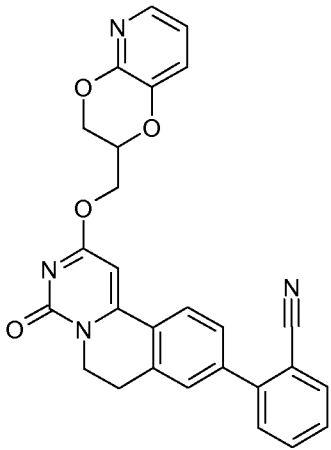
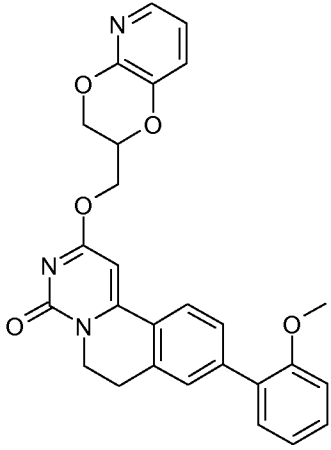
Cpd #	Structures	Name	MW (calc)	MW (obsd)
111		9-(2,6-Dimethyl-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	402	403.4
112		9-(3,5-Dimethyl-isoxazol-4-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	393	394.5
113		9-Naphthalen-2-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	425	425.5

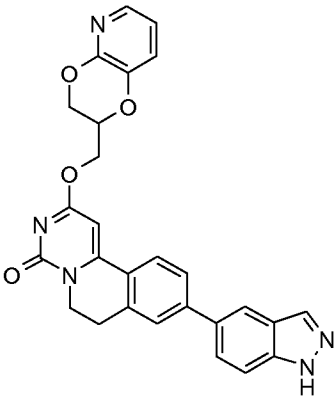
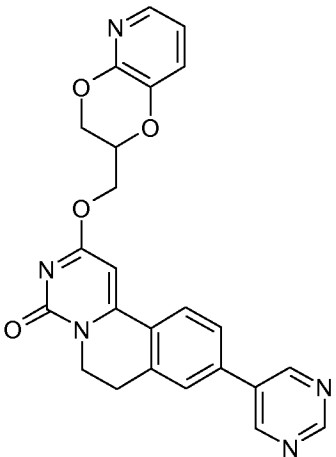
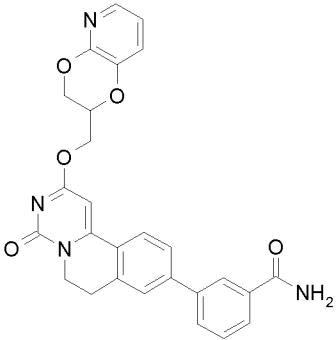


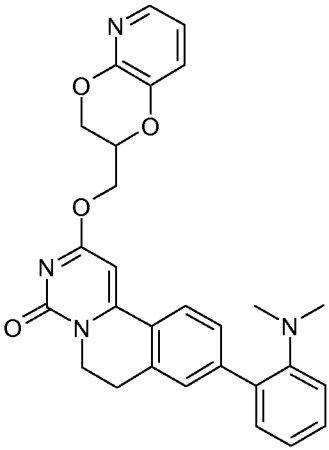
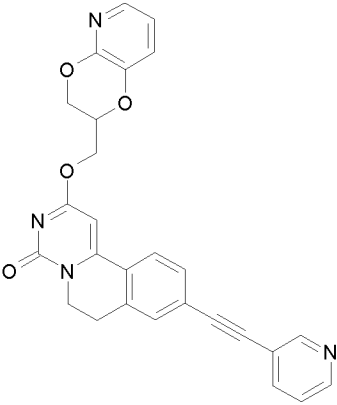
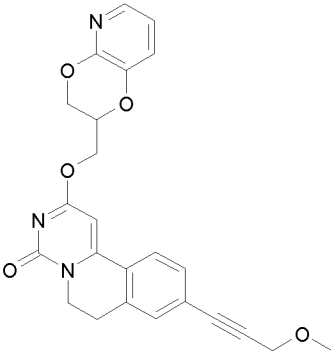
Cpd #	Structures	Name	MW (calc)	MW (obsd)
114		9-Naphthalen-1-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	425	425.5
115		9-Pyrimidin-5-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	376	377.4
116		9-(5-Chloro-thiophen-2-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	415	415.4

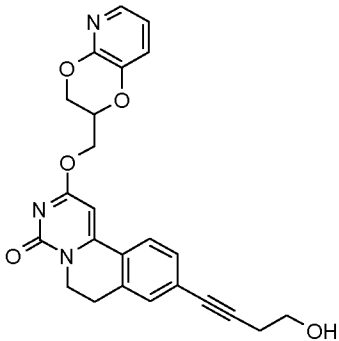
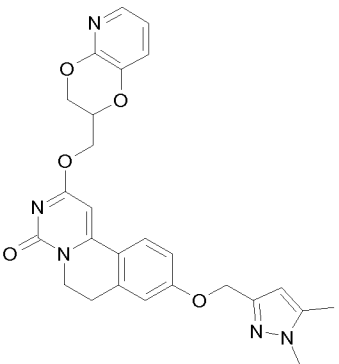
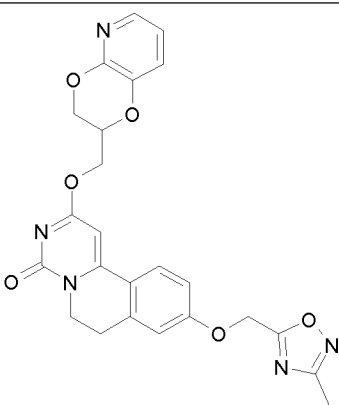
Cpd #	Structures	Name	MW (calc)	MW (obsd)
117		2-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-pyrrole-1-carboxylic acid tert-butyl ester	464	464.5
118		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-methoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	470	471.5
119		9-Cyclopropylethynyl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	362	363.4

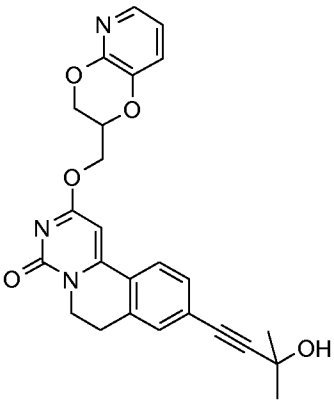
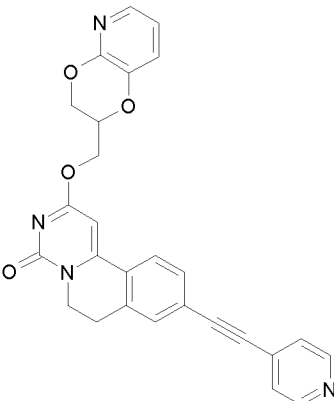
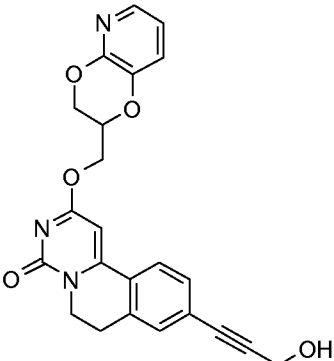
Cpd #	Structures	Name	MW (calc)	MW (obsd)
120		9-(3,3-Dimethyl-but-1-ynyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	378	379.5
121		9-(4-Methoxy-phenylethynyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	428	429.5
122		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(pyridin-4-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	470	471.4
123		9-Quinoxalin-6-ylethynyl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	450	451.5

Cpd #	Structures	Name	MW (calc)	MW (obsd)
124		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-3-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	440	441.4
125		2-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile	464	465.4
126		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-methoxyphenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	470	470.4

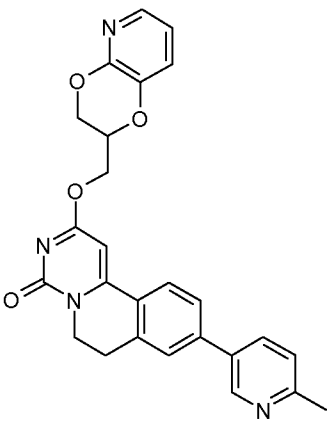
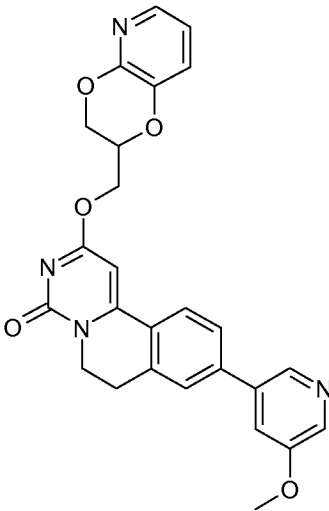
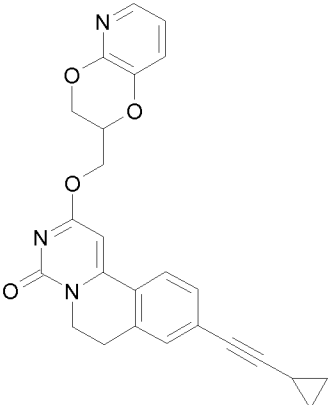
Cpd #	Structures	Name	MW (calc)	MW (obsd)
127		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1H-indazol-5-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	480	480.4
128		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyrimidin-5-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	441	442.4
129		3-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzamide	483	483.4

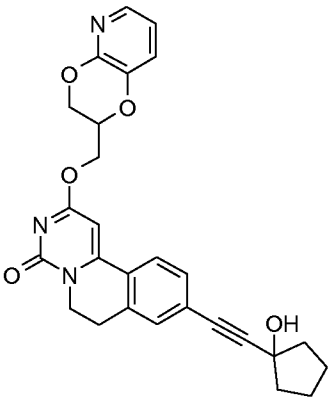
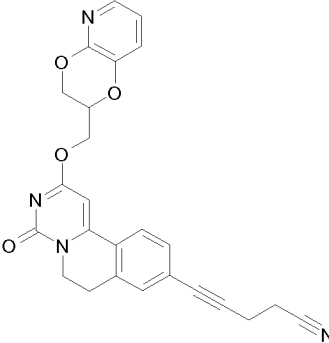
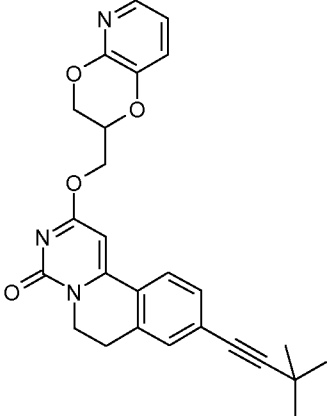
Cpd #	Structures	Name	MW (calc)	MW (obsd)
130		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-dimethylamino-phenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	483	483.4
131		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-3-ylethynyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	464	465.4
132		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methoxy-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	431	-

Cpd #	Structures	Name	MW (calc)	MW (obsd)
133		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(4-hydroxy-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	431	432.4
134		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1,5-dimethyl-1H-pyrazol-3-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	488	488.4
135		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methyl-[1,2,4]oxadiazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	475	476.4

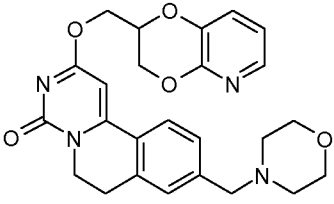
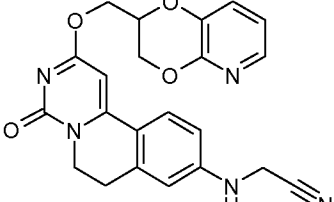
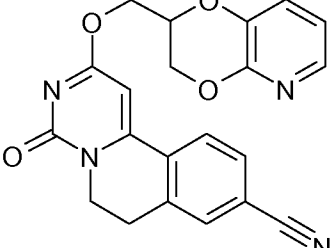
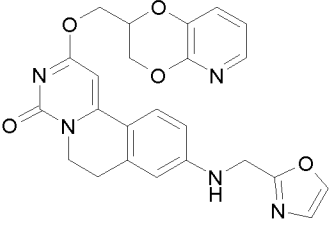
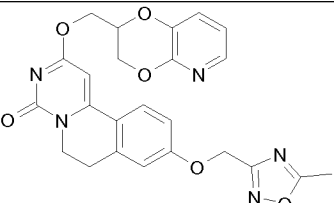
Cpd #	Structures	Name	MW (calc)	MW (obsd)
136		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-3-methyl-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	445	446.4
137		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-4-ylethynyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	464	465.4
138		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	417	418.4

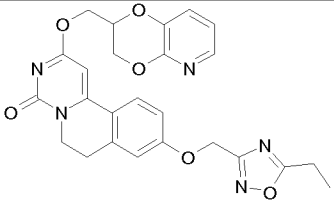
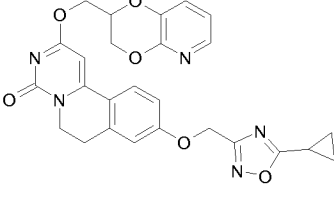
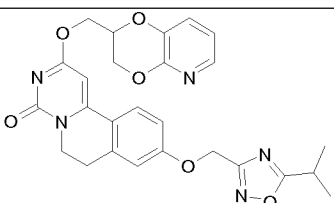
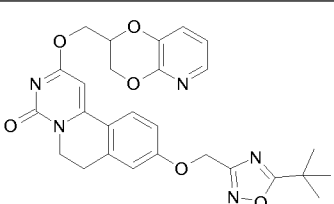
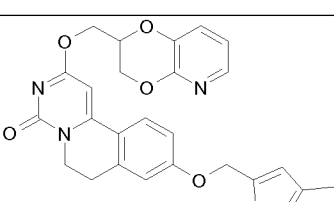
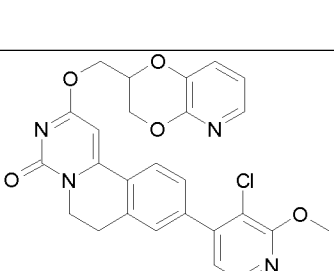


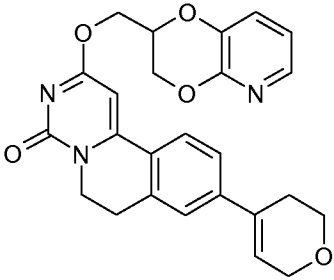
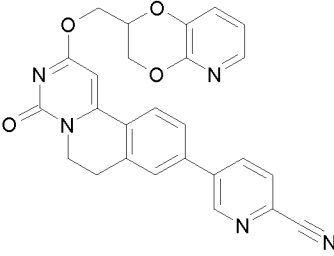
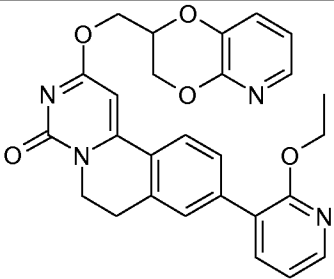
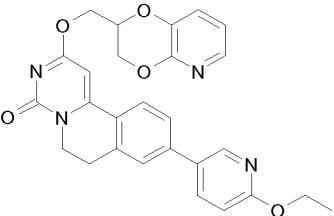
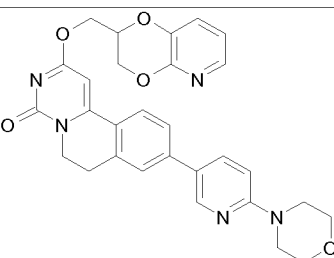
Cpd #	Structures	Name	MW (calc)	MW (obsd)
139		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-methylpyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	454	455.4
140		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-methoxy-6-methylpyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	470	471.4
141		9-Cyclopropylethynyl-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	427	428.4

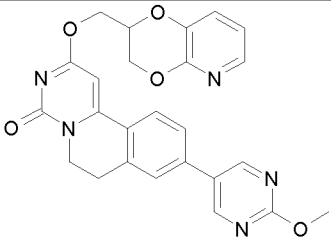
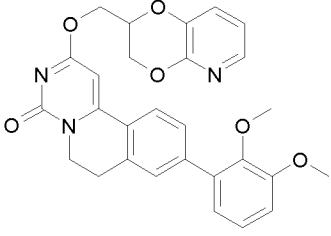
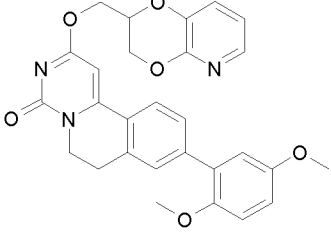
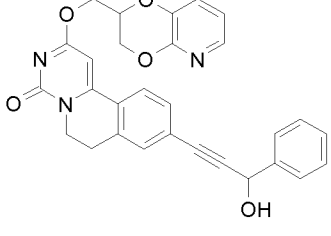
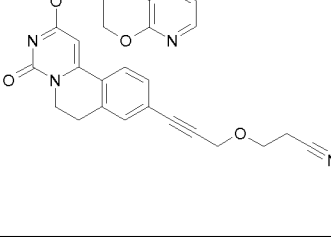
Cpd #	Structures	Name	MW (calc)	MW (obsd)
142		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1-hydroxycyclopentylethynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	472	472.4
143		5-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-pent-4-ynenitrile	440	441.4
144		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3,3-dimethylbut-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	444	444.4

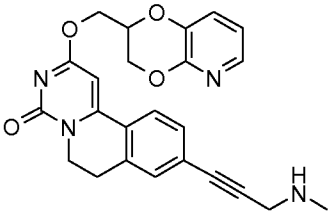
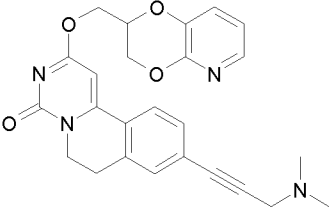
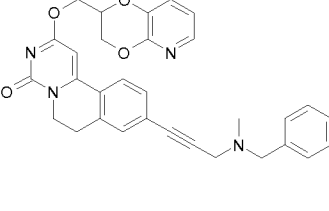
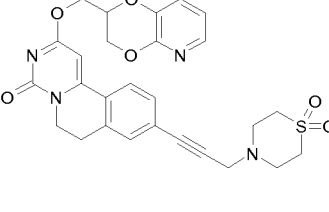
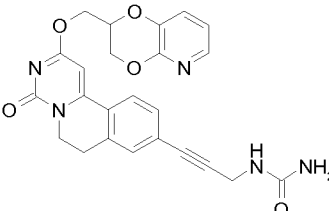
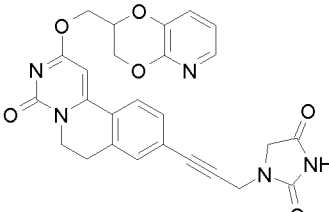
Cpd #	Structures	Name	MW (calc)	MW (obsd)
145		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-methoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	470	-
146		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	363	-
147		5-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-pyridine-2-carboxylic acid methylamide	498	498.4
148		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-furan-3-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	429	430.4
149		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	443	444.4

Cpd #	Structures	Name	MW (calc)	MW (obsd)
150		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-morpholin-4-ylmethyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	463	463.4
151		[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-ylamino]-acetonitrile	417	418.4
152		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinoline-9-carbonitrile	388	389.3
153		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-[(oxazol-2-ylmethyl)-amino]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	459	460.4
154		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-methyl-[1,2,4]oxadiazol-3-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	475	476.4

Cpd #	Structures	Name	MW (calc)	MW (obsd)
155		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-ethyl-[1,2,4]oxadiazol-3-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	489	490.4
156		9-(5-Cyclopropyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	502	502.4
157		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-isopropyl-[1,2,4]oxadiazol-3-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	504	504.4
158		9-(5-tert-Butyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	518	518.4
159		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methyl-isoxazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	474	475.3
160		9-(3-Chloro-2-methoxy-pyridin-4-yl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	505	505.4

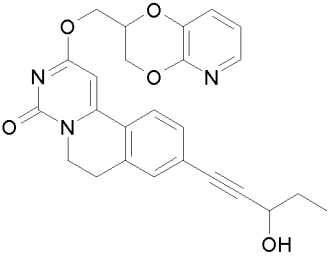
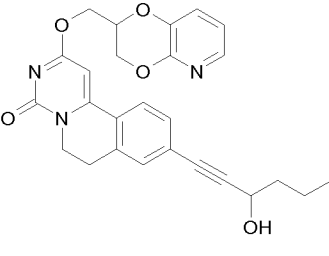
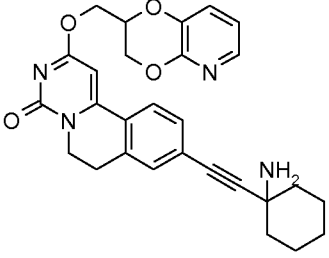
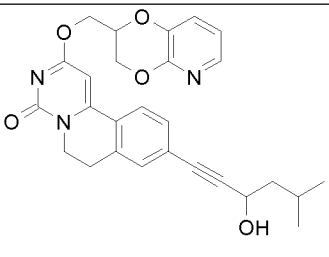
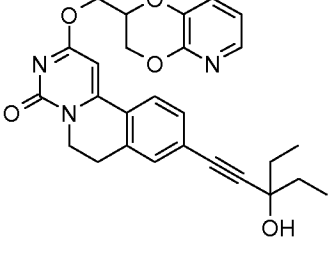
Cpd #	Structures	Name	MW (calc)	MW (obsd)
161		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3,6-dihydro-2H-pyran-4-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	445	446.4
162		5-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-pyridine-2-carbonitrile	465	466.4
163		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-ethoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	485	485.4
164		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-ethoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	485	485.4
165		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-morpholin-4-yl-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	526	526.5

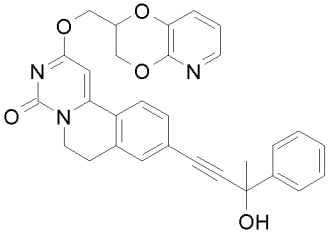
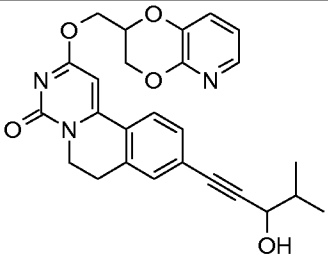
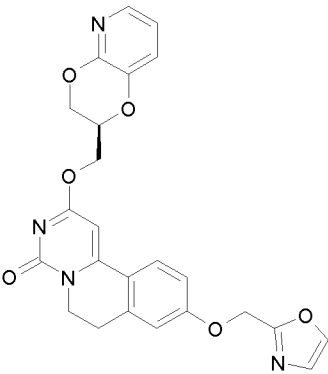
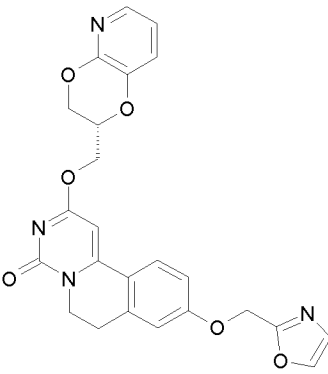
Cpd #	Structures	Name	MW (calc)	MW (obsd)
166		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-methoxypyrimidin-5-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	471	472.4
167		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2,3-dimethoxyphenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	500	500.4
168		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2,5-dimethoxyphenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	500	500.4
169		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-3-phenyl-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	494	494.4
170		3-{3-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-prop-2-ynyloxy}-propionitrile	470	471.4

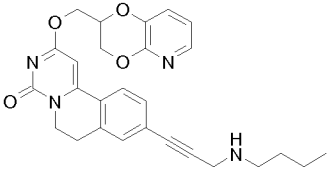
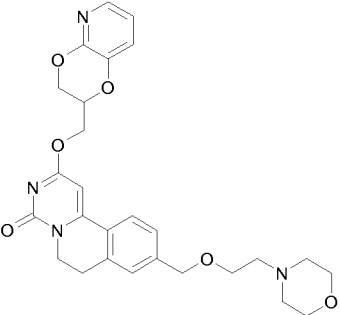
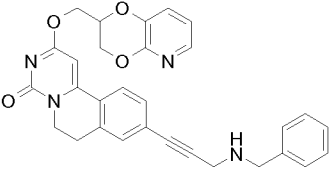
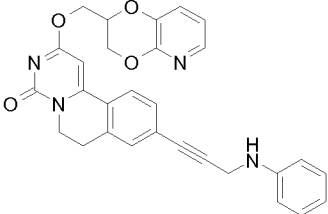
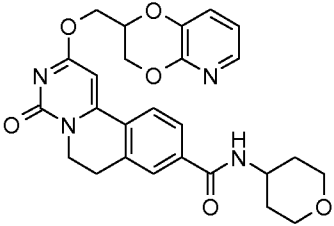
Cpd #	Structures	Name	MW (calc)	MW (obsd)
171		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methylamino-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	430	431.4
172		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-dimethylamino-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	444	445.4
173		9-[3-(Benzyl-methyl-amino)-prop-1-ynyl]-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	521	521.4
174		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-[3-(1,1-dioxo-thiomorpholin-4-yl)-prop-1-ynyl]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	535	535.4
175		{3-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-prop-2-ynyl}-urea	459	460.4
176		1-{3-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-prop-2-ynyl}-imidazolidine-2,4-dione	499	500.4

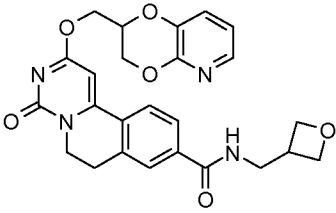
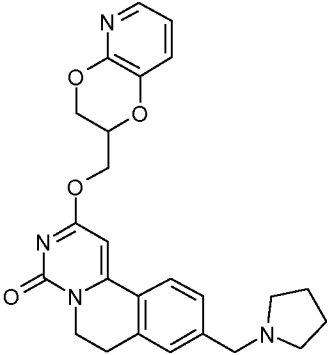
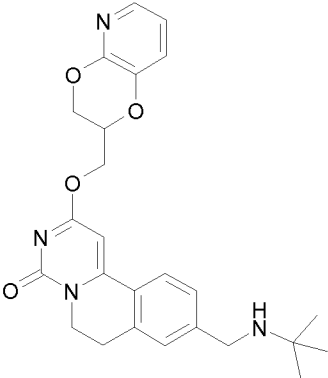
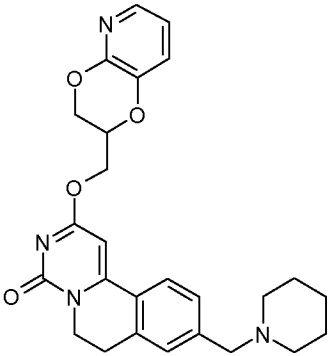


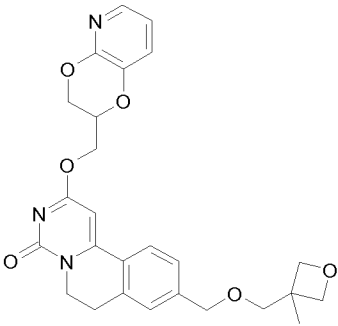
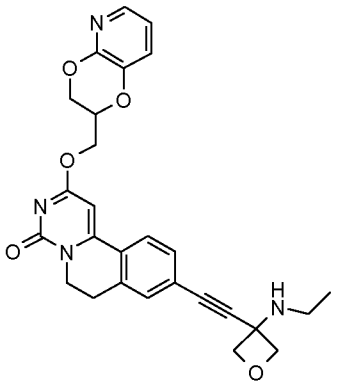
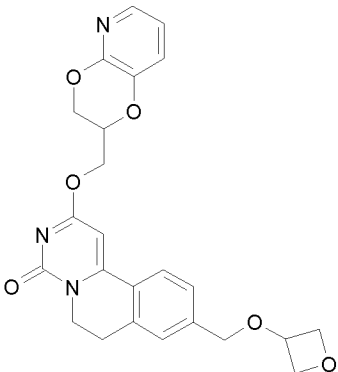
Cpd #	Structures	Name	MW (calc)	MW (obsd)
177		9-(3-Diethylamino-prop-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	473	473.4
178		9-(3-Amino-3-methyl-but-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	444	445.4
179		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(tetrahydro-pyran-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	478	478.4
180		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1H-pyrazol-4-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	429	430.3
181		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	431	432.2

Cpd #	Structures	Name	MW (calc)	MW (obsd)
182		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-pent-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	445	446.2
183		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-hex-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	460	460.2
184		9-(1-Amino-cyclohexylethynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	485	485.2
185		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-5-methyl-hex-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	474	474.2
186		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-ethyl-3-hydroxy-pent-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	474	474.2

Cpd #	Structures	Name	MW (calc)	MW (obsd)
187		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-3-phenyl-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	508	508.2
188		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-4-methyl-pent-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	460	460.2
189		2-[(R)-1-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-yl)methoxy]-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	460	461.2
190		2-[(S)-1-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-yl)methoxy]-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	460	461.4

Cpd #	Structures	Name	MW (calc)	MW (obsd)
191		9-(3-Butylamino-prop-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	473	473.2
192		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-morpholin-4-yl-ethoxymethyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	507	507.2
193		9-(3-Benzylamino-prop-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	507	507.2
194		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-phenylamino-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	493	493.2
195		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinoline-9-carboxylic acid (tetrahydro-pyran-4-yl)-amide	491	491.2

Cpd #	Structures	Name	MW (calc)	MW (obsd)
196		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinoline-9-carboxylic acid (oxetan-3-ylmethyl)-amide	476	477.0
197		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyrrolidin-1-ylmethyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	447	447.1
198		9-(tert-Butylamino-methyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	449	449.2
199		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-piperidin-1-ylmethyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	461	461.2

Cpd #	Structures	Name	MW (calc)	MW (obsd)
200		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methyloxetan-3-ylmethoxymethyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	478	478.4
201		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-ethylaminoxetan-3-ylethynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	486	487.3
202		2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(oxetan-3-ylloxymethyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	449	450.4

Cpd #	Structures	Name	MW (calc)	MW (obsd)
203		9-Cyclopropylethynyl-2-(4-isopropyl-oxetan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	390	391.2
204		9-Cyclopropylethynyl-2-((R)-4-isopropyl-oxetan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one	390	391.2

[00459] Table III: NMR Data of the Compounds of the Invention

Cpd#	NMR data ( $\delta$ )
1	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.60 (1 H, d), 6.87 (1 H, dd), 6.76 (1 H, d), 6.25 (1 H, s), 4.47 - 4.57 (1 H, m), 4.13 - 4.29 (4 H, m), 3.87 - 3.94 (1 H, m), 3.77 - 3.86 (4 H, m), 2.95 (2 H, t), 1.98 - 2.08 (1 H, m), 1.83 - 1.98 (2 H, m), 1.57 - 1.68 (1 H, m).
2	( $^1\text{H}$ , $\text{MeOD}-d_4$ ) $\delta$ ppm 8.03 - 8.09 (1 H, m), 7.27 (2 H, s), 7.13 - 7.21 (2 H, m), 7.01 - 7.08 (1 H, m), 6.96 - 7.01 (1 H, m), 6.76 (1 H, s), 4.72 - 4.83 (2 H, m), 4.60 (2 H, m), 4.34 - 4.40 (2 H, m), 4.09 - 4.13 (3 H, m), 3.23 - 3.29 (3 H, m), 3.08 - 3.15 (1 H, m), 3.03 - 3.07 (1 H, m)
3	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.66 (1 H, d), 6.78 - 6.95 (6 H, m), 6.28 (1 H, s), 4.64 - 4.72 (2 H, m), 4.53 - 4.61 (1 H, m), 4.36 (1 H, dd), 4.19 - 4.25 (2 H, m), 4.11 - 4.19 (1 H, m), 3.88 (3 H, s), 3.00 (1 H, t)
4	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.62 (1 H, d), 6.91 (1 H, dd), 6.80 (1 H, d), 6.28 (1 H, s), 5.97 - 6.13 (1 H, m), 5.39 - 5.48 (1 H, m), 5.31 - 5.37 (1 H, m), 4.52 - 4.63 (3 H, m), 4.15 - 4.32 (4 H, m), 3.89 - 3.97 (1 H, m), 3.79 - 3.88 (1 H, m), 2.97 (2 H, t), 2.00 - 2.11 (1 H, m), 1.87 - 2.00 (2 H, m), 1.59 - 1.72 (1 H, m).

Cpd#	NMR data ( $\delta$ )
5	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.64 (1 H, d), 7.17 - 7.22 (1 H, m), 7.10 - 7.16 (1 H, m), 6.81 - 6.93 (3 H, m), 6.77 - 6.81 (1 H, m), 6.30 (1 H, s), 5.10 - 5.20 (1 H, m), 4.76 (1 H, dd), 4.51 (1 H, dd), 4.19 - 4.25 (2 H, m), 3.88 (3 H, s), 3.36 (1 H, dd), 2.95 - 3.08 (3 H, m).
6	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.45 (1 H, d), 6.88 - 6.92 (1 H, m), 6.76 (1 H, d), 6.04 (1 H, s), 4.53 (1 H, dd), 4.05 - 4.41 (4 H, m), 3.87 - 4.02 (2 H, m), 2.89 (2 H, t), 1.90 - 2.15 (3 H, m), 1.59 - 1.73 (1 H, m).
7	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.63 (1 H, d), 7.33 - 7.48 (5 H, m), 6.91 - 7.01 (1 H, m), 6.82 - 6.89 (1 H, m), 6.29 (1 H, s), 5.14 (2 H, s), 4.51 - 4.61 (1 H, m), 4.15 - 4.33 (4 H, m), 3.90 - 3.98 (1 H, m), 3.79 - 3.89 (1 H, m), 2.97 (2 H, t), 2.01 - 2.11 (1 H, m), 1.86 - 2.00 (2 H, m), 1.58 - 1.73 (1 H, m).
8	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.73 (1 H, br. s.), 8.64 (1 H, m), 7.84 (1 H, d), 7.65 (1 H, d), 7.38 - 7.45 (1 H, m), 6.95 - 7.02 (1 H, m), 6.83 - 6.93 (1 H, m), 6.30 (1 H, s), 5.17 (2 H, s), 4.52 - 4.60 (1 H, m), 4.18 - 4.32 (4 H, m), 3.93 (1 H, m), 3.80 - 3.88 (1 H, m), 2.99 (2 H, t), 2.02 - 2.10 (1 H, m), 1.87 - 2.01 (2 H, m), 1.60 - 1.71 (1 H, m).
9	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.70 (1 H, d), 7.00 (1 H, dd), 6.91 (1 H, d), 6.32 (1 H, s), 4.86 (2 H, s), 4.51 - 4.60 (1 H, m), 4.12 - 4.33 (4 H, m), 3.82 - 3.99 (2 H, m), 3.03 (2 H, t), 2.03 - 2.14 (1 H, m), 1.86 - 2.02 (2 H, m), 1.59 - 1.73 (1 H, m).
10	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.62 (1 H, d), 6.82 - 6.96 (1 H, m), 6.73 - 6.81 (1 H, m), 6.28 (1 H, s), 4.50 - 4.63 (1 H, m), 4.25 - 4.33 (2 H, m), 4.15 - 4.24 (2 H, m), 4.02 (1 H, t), 3.79 - 3.98 (3 H, m), 2.95 (2 H, t), 2.00 - 2.13 (1 H, m), 1.88 - 1.99 (2 H, m), 1.74 - 1.86 (1 H, m), 1.56 - 1.72 (3 H, m), 1.44 - 1.56 (1 H, m), 0.99 (3 H, t)
11	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.62 (1 H, d), 6.85 - 6.94 (1 H, m), 6.73 - 6.82 (1 H, m), 6.28 (1 H, s), 4.50 - 4.61 (1 H, m), 4.23 - 4.34 (2 H, m), 4.15 - 4.24 (2 H, m), 3.78 - 3.98 (3 H, m), 2.86 - 3.03 (2 H, m), 1.94 (3 H, d), 1.62 (1 H, d), 1.28 (1 H, d), 0.64 - 0.74 (2 H, m), 0.31 - 0.43 (1 H, m)
12	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.61 (1 H, d), 7.24 - 7.38 (5 H, m), 6.88 (1 H, dd), 6.77 (1 H, d), 6.28 (1 H, s), 4.51 - 4.60 (1 H, m), 4.15 - 4.32 (6 H, m), 3.78 - 3.97 (2 H, m), 3.13 (2 H, t), 2.91 - 2.99 (2 H, m), 2.01 - 2.11 (1 H, m), 1.85 - 2.00 (2 H, m), 1.61 - 1.70 (1 H, m).
13	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.67 (2 H, d), 7.65 (1 H, d), 7.42 (2 H, d), 6.96 (1 H, dd), 6.86 (1 H, d), 6.30 (1 H, s), 5.19 (2 H, s), 4.55 (1 H, s), 4.17 - 4.32 (4 H, m), 3.93 (1 H, m), 3.80 - 3.89 (1 H, m), 2.98 (2 H, t), 2.01 - 2.12 (1 H, m), 1.88 - 2.00 (2 H, m), 1.60 - 1.71 (1 H, m).



Cpd#	NMR data ( $\delta$ )
14	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.62 (1 H, d), 7.70 - 7.81 (1 H, m), 7.58 - 7.67 (1 H, m), 7.45 - 7.55 (1 H, m), 7.23 - 7.31 (1 H, m), 6.94 - 7.05 (1 H, m), 6.83 - 6.92 (1 H, m), 6.28 (1 H, s), 5.27 (2 H, s), 4.50 - 4.61 (1 H, m), 4.15 - 4.34 (4 H, m), 3.77 - 4.00 (2 H, m), 2.90 - 3.03 (2 H, m), 1.78 - 2.13 (3 H, m), 1.56 - 1.74 (1 H, m).
15	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.64 (1 H, d), 7.32 (2 H, t), 6.90 - 7.06 (4 H, m), 6.85 (1 H, br. s.), 6.30 (1 H, s), 4.52 - 4.61 (1 H, m), 4.33 - 4.43 (4 H, m), 4.15 - 4.33 (4 H, m), 3.94 (1 H, q), 3.85 (1 H, q), 2.94 - 3.02 (2 H, m), 1.88 - 2.11 (3 H, m), 1.60 - 1.72 (1 H, m).
16	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.63 (1 H, d), 6.86 - 6.93 (1 H, m), 6.75 - 6.81 (1 H, m), 6.31 (1 H, s), 4.50 (1 H, dd), 4.28 (1 H, dd), 4.15 - 4.23 (2 H, m), 4.02 - 4.10 (1 H, m), 3.87 (3 H, s), 3.66 - 3.75 (1 H, m), 3.44 - 3.54 (1 H, m), 2.97 (2 H, t), 1.84 - 1.95 (1 H, m), 1.31 - 1.67 (5 H, m).
17	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.69 - 7.74 (2 H, m), 7.65 (1 H, d), 7.56 (2 H, d), 6.95 (1 H, dd), 6.85 (1 H, d), 6.30 (1 H, s), 5.20 (2 H, s), 4.53 - 4.61 (1 H, m), 4.18 - 4.32 (4 H, m), 3.94 (1 H, dt), 3.80 - 3.88 (1 H, m), 2.98 (2 H, t), 2.01 - 2.12 (1 H, m), 1.88 - 2.00 (2 H, m), 1.63 - 1.71 (1 H, m).
18	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.64 (1 H, d), 6.85 - 6.96 (5 H, m), 6.83 (1 H, d), 6.29 (1 H, s), 4.51 - 4.65 (2 H, m), 4.36 - 4.44 (1 H, m), 4.16 - 4.35 (7 H, m), 3.89 - 3.99 (1 H, m), 3.79 - 3.88 (1 H, m), 2.97 (2 H, t), 2.00 - 2.13 (1 H, m), 1.85 - 2.00 (2 H, m), 1.58 - 1.72 (1 H, m).
19	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.72 - 7.79 (1 H, m), 7.62 - 7.70 (3 H, m), 7.46 - 7.59 (1 H, m), 6.85 - 7.03 (2 H, m), 6.31 (1 H, s), 5.15 - 5.34 (2 H, m), 4.52 - 4.63 (1 H, m), 4.18 - 4.35 (4 H, m), 3.89 - 3.99 (1 H, m), 3.81 - 3.89 (1 H, m), 2.95 - 3.04 (2 H, m), 2.01 - 2.15 (1 H, m), 1.86 - 2.00 (2 H, m), 1.64 - 1.75 (1 H, m).
20	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.75 (1 H, d), 7.68 (3 H, d), 7.44 - 7.55 (1 H, m), 6.97 - 7.06 (1 H, m), 6.91 (1 H, s), 6.23 - 6.38 (1 H, m), 5.33 (2 H, s), 4.16 - 4.38 (3 H, m), 3.90 - 4.00 (1 H, m), 3.77 - 3.90 (1 H, m), 2.94 - 3.08 (2 H, m), 2.01 - 2.11 (1 H, m), 1.86 - 2.01 (1 H, m), 1.46 - 1.73 (4 H, m).
21	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.64 (1 H, d), 7.35 - 7.42 (4 H, m), 6.95 (1 H, d), 6.85 (1 H, d), 6.30 (1 H, s), 5.10 (2 H, s), 4.52 - 4.62 (1 H, m), 4.17 - 4.33 (4 H, m), 3.90 - 3.98 (1 H, m), 3.81 - 3.89 (1 H, m), 2.98 (2 H, t), 2.01 - 2.11 (1 H, m), 1.88 - 2.00 (2 H, m), 1.63 - 1.71 (1 H, m).
22	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.66 (1 H, d), 7.44 (1 H, s), 7.28 - 7.38 (3 H, m), 6.93 - 6.99 (1 H, m), 6.86 (1 H, d), 6.31 (1 H, s), 5.11 (2 H, s), 4.52 - 4.62 (1 H, m), 4.18 - 4.34 (4 H, m), 3.90 - 3.99 (1 H, m), 3.80 - 3.89 (1 H, m), 2.99 (2 H, t), 2.02 - 2.13 (1 H, m), 1.88 - 2.01 (2 H, m), 1.61 - 1.70 (1 H, m).

Cpd#	NMR data ( $\delta$ )
23	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.65 (1 H, d), 7.51 - 7.55 (1 H, m), 7.41 - 7.46 (1 H, m), 7.29 - 7.34 (2 H, m), 6.95 - 7.01 (1 H, m), 6.88 (1 H, d), 6.30 (1 H, s), 5.24 (2 H, s), 4.52 - 4.61 (1 H, m), 4.16 - 4.32 (4 H, m), 3.94 (1 H, m), 3.80 - 3.88 (1 H, m), 2.99 (2 H, t), 2.02 - 2.11 (1 H, m), 1.87 - 2.01 (2 H, m), 1.58 - 1.69 (1 H, m).
24	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.64 (1 H, d), 7.38 - 7.44 (2 H, m), 7.07 - 7.14 (2 H, m), 6.96 (1 H, dd), 6.85 (1 H, d), 6.30 (1 H, s), 5.09 (2 H, s), 4.52 - 4.61 (1 H, m), 4.16 - 4.32 (4 H, m), 3.89 - 3.97 (1 H, m), 3.81 - 3.88 (1 H, m), 2.98 (2 H, t), 2.01 - 2.11 (1 H, m), 1.87 - 2.01 (2 H, m), 1.60 - 1.65 (1 H, m).
25	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.21 (1 H, dd), 7.86 (1 H, d), 7.72 (1 H, td), 7.66 (1 H, d), 7.51 - 7.57 (1 H, m), 7.00 (1 H, dd), 6.90 (1 H, d), 6.30 (1 H, s), 5.56 (2 H, s), 4.50 - 4.59 (1 H, m), 4.17 - 4.33 (4 H, m), 3.90 - 3.98 (1 H, m), 3.79 - 3.89 (1 H, m), 3.00 (2 H, t), 2.01 - 2.12 (1 H, m), 1.86 - 2.01 (2 H, m), 1.60 - 1.75 (1 H, m).
26	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.06 - 8.13 (2 H, m), 7.64 (1 H, d), 7.47 - 7.53 (2 H, m), 6.96 (1 H, dd), 6.86 (1 H, d), 6.29 (1 H, s), 5.20 (2 H, s), 4.52 - 4.60 (1 H, m), 4.18 - 4.33 (4 H, m), 3.91 - 3.96 (4 H, m), 3.81 - 3.89 (1 H, m), 2.98 (2 H, t), 2.03 - 2.12 (1 H, m), 1.88 - 2.01 (2 H, m), 1.63 - 1.73 (1 H, m).
27	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.12 (1 H, br. s), 8.04 (1 H, d), 7.64 (2 H, d), 7.50 (1 H, t), 6.97 (1 H, dd), 6.87 (1 H, d), 6.30 (1 H, s), 5.18 (2 H, s), 4.53 - 4.61 (1 H, m), 4.17 - 4.32 (4 H, m), 3.90 - 3.98 (4 H, m), 3.81 - 3.88 (1 H, m), 2.98 (2 H, t), 2.02 - 2.11 (1 H, m), 1.88 - 2.01 (2 H, m), 1.67 - 1.73 (1 H, m).
28	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.57 - 8.67 (1 H, m), 7.75 (1 H, td), 7.66 (1 H, d), 7.48 - 7.54 (1 H, m), 7.24 - 7.30 (1 H, m), 7.00 (1 H, dd), 6.83 - 6.96 (5 H, m), 6.28 (1 H, s), 5.28 (2 H, s), 4.63 - 4.72 (2 H, m), 4.52 - 4.60 (1 H, m), 4.31 - 4.41 (1 H, m), 4.18 - 4.25 (2 H, m), 4.11 - 4.18 (1 H, m), 2.94 - 3.03 (2 H, m).
29	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.66 (1 H, d), 6.82 - 6.94 (5 H, m), 6.76 - 6.80 (1 H, m), 6.27 (1 H, s), 4.62 - 4.70 (2 H, m), 4.58 (2 H, s), 4.52 - 4.57 (1 H, m), 4.32 - 4.38 (1 H, m), 4.17 - 4.23 (2 H, m), 4.10 - 4.17 (1 H, m), 2.93 - 3.02 (2 H, m), 1.50 (9 H, s).
30	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.67 (1 H, d), 6.81 - 6.99 (10 H, m), 6.29 (1 H, s), 4.67 (2 H, m), 4.54 - 4.65 (2 H, m), 4.29 - 4.43 (3 H, m), 4.11 - 4.28 (5 H, m), 2.99 (2 H, t).
31	( $^1\text{H}$ , $\text{DMSO}-d_6$ ) $\delta$ ppm: 7.96 (1 H, d), 6.80 - 6.99 (6 H, m), 6.60 (1 H, s), 4.80 (2 H, s), 4.46 - 4.62 (3 H, m), 4.37 - 4.45 (1 H, m), 4.08 - 4.17 (1 H, m), 4.02 (2 H, t), 2.97 (2 H, t).
32	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.37 (1H, s), 8.27 (1H, d), 7.82-6.81 (1H, d), 7.70 (1H, d), 7.65 (1H, t), 7.01 (1H, dd), 6.92 (1H, d), 6.34 (1H, s), 5.27 (2H, s), 4.63-4.57 (1H, m), 4.33-4.20 (4H, m), 3.97 (1H, q), 3.88 (1H,q), 3.03 (2H, t), 2.14-1.94 (3H, m), 1.72-1.65 (1H, m).

Cpd#	NMR data ( $\delta$ )
33	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.32 (2H, dt), 7.69 (1H, d), 7.65 (2H, d), 7.0 (1H, dd), 6.90 (1H, d), 6.33 (1H, s), 6.28 (2H, s), 4.61-4.59 (1H, m), 4.32-4.18 (4H, m), 3.97 (1H, q), 3.88 (1H, q), 3.02 (2H, t), 2.12-1.92 (3H, m), 1.71-1.66 (1H, m).
34	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.67 (1H, d), 7.35-7.25 (3H, m), 7.21 (1H, d), 7.0 (1H, dd), 6.90 (1H, d), 6.32 (1H, s), 5.13 (2H, s), 4.60 (1H, m), 4.34-4.30 (2H, m), 4.26-4.22 (2H, m), 3.97 (1H, q), 3.88 (1H, q), 3.01 (2H, t), 2.42 (3H, s), 2.12-1.92 (3H, m), 1.72-1.63 (1H, m).
35	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.66 (1H, d), 7.30 (4H, dd), 6.99 (1H, dd), 6.89 (1H, d), 6.32 (1H, s), 5.12 (2H, s), 4.60 (1H, dt), 4.34-4.28 (2H, m), 4.26-4.21 (2H, m), 3.97 (1H, q), 3.88 (1H, q), 3.00 (2H, t), 2.41 (3H, s), 2.12-2.05 (1H, m), 2.03-1.92 (2H, m), 1.73-1.63 (1H, m).
36	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.65 (1H, d), 7.45 (1H, dd), 7.36 (1H, dt), 7.04-6.99 (2H, m), 6.97 (1H, d), 6.91 (1H, d), 6.31 (1H, s), 5.21 (2H, s), 4.58 (1H, dt), 4.33-4.28 (2H, m), 4.27-4.18 (2H), 3.99-3.93 (1H, m), 3.91 (3H, s), 3.90-3.84 (1H, q), 3.00 (2H, t), 2.13-2.05 (1H, m), 2.02-1.91 (2H, m), 1.71-1.64 (1H, m).
37	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.94-7.88 (4H, m), 7.67 (1H, d), 7.58-7.53 (3H, m), 7.05 (1H, dd), 6.94 (1H, d), 6.32 (1H, s), 5.34 (2H, s), 4.59 (1H, dt), 4.34-4.27 (2H, m), 4.29-4.18 (2H, m), 3.97 (1H, q), 3.87 (1H, q), 3.01 (2H, t), 2.14-1.92 (3H, m), 1.72-1.65 (1H, m).
38	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.07-8.05 (1H, m), 7.97-7.92 (2H, m), 7.69 (1H, d), 7.64-7.51 (4H, m), 7.09 (1H, dd), 6.98 (1H, d), 6.34 (1H, s), 5.60 (2H, s), 4.63-4.47 (1H, m), 4.34-4.29 (2H, m), 4.28-4.21 (2H, m), 3.97 (2H, q), 3.88 (2H, q), 3.02 (2H, t), 2.14-1.92 (3H, m), 1.74-1.65 (1H, m).
39	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.68 (1H, d), 7.42 (1H, d), 7.35-7.31 (1H, m), 7.29-7.25 (2H, m), 7.02 (1H, dd), 6.91 (1H, d), 6.33 (1H, s), 5.14 (2H, s), 4.60 (1H, dt), 4.35-4.29 (2H, m), 4.28-4.21 (2H, m), 4.0-3.94 (1H, m), 3.90-9.85 (1H, m), 3.02 (2H, t), 2.42 (3H, s), 2.14-1.92 (3H, m), 1.74-1.67 (1H, m).
40	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.63 (1 H, d), 6.88 - 7.01 (5 H, m), 6.85 (1 H, d), 6.29 (1 H, s), 4.48 - 4.61 (1 H, m), 4.37 - 4.45 (4 H, m), 4.16 - 4.31 (4 H, m), 3.89 - 3.97 (1 H, m), 3.79 - 3.88 (4 H, m), 2.97 (2 H, t), 2.00 - 2.09 (1 H, m), 1.88 - 1.99 (2 H, m), 1.59 - 1.71 (1 H, m).
41	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.59 - 7.67 (1 H, m), 7.16 - 7.23 (1 H, m), 6.94 (1 H, dd), 6.83 (1 H, d), 6.49 - 6.58 (3 H, m), 6.28 (1 H, s), 4.50 - 4.59 (1 H, m), 4.31 - 4.40 (4 H, m), 4.15 - 4.29 (4 H, m), 3.75 - 3.96 (5 H, m), 2.96 (2 H, t), 2.00 - 2.10 (1 H, m), 1.87 - 2.00 (2 H, m), 1.59 - 1.69 (1 H, m).

Cpd#	NMR data ( $\delta$ )
42	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.63 (1 H, d), 6.80 - 7.00 (6 H, m), 6.29 (1 H, s), 4.50 - 4.60 (1 H, m), 4.16 - 4.44 (8 H, m), 3.89 - 3.97 (1 H, m), 3.80 - 3.89 (1 H, m), 3.73 - 3.79 (3 H, m), 2.97 (2 H, t), 2.00 - 2.11 (1 H, m), 1.84 - 1.99 (2 H, m), 1.58 - 1.71 (1 H, m).
43	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.63 (1 H, d), 7.37 (1 H, dd), 7.20 - 7.26 (1 H, m), 6.91 - 7.03 (3 H, m), 6.88 (1 H, d), 6.29 (1 H, s), 4.50 - 4.60 (1 H, m), 4.37 - 4.48 (4 H, m), 4.16 - 4.32 (4 H, m), 3.89 - 3.97 (1 H, m), 3.79 - 3.88 (1 H, m), 2.97 (2 H, t), 2.00 - 2.11 (1 H, m), 1.88 - 1.99 (2 H, m), 1.59 - 1.70 (1 H, m).
44	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.61 - 7.68 (1 H, m), 7.17 - 7.26 (1 H, m), 6.90 - 7.01 (3 H, m), 6.79 - 6.88 (2 H, m), 6.29 (1 H, s), 4.51 - 4.62 (1 H, m), 4.16 - 4.42 (8 H, m), 3.89 - 3.98 (1 H, m), 3.79 - 3.88 (1 H, m), 2.98 (2 H, t), 2.01 - 2.12 (1 H, m), 1.88 - 2.00 (2 H, m), 1.57 - 1.70 (1 H, m).
45	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.64 (1 H, d), 7.23 - 7.28 (2 H, m), 6.94 (1 H, dd), 6.85 - 6.91 (2 H, m), 6.83 (1 H, d), 6.29 (1 H, s), 4.51 - 4.60 (1 H, m), 4.16 - 4.40 (8 H, m), 3.89 - 3.97 (1 H, m), 3.80 - 3.88 (1 H, m), 2.97 (2 H, t), 2.01 - 2.10 (1 H, m), 1.86 - 1.99 (2 H, m), 1.59 - 1.70 (1 H, m).
46	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.65 (1 H, d), 6.79 - 6.98 (6 H, m), 6.26 (1 H, s), 4.77 (2 H, s), 4.64 (2 H, m), 4.51 - 4.58 (1 H, m), 4.30 - 4.38 (1 H, m), 4.16 - 4.23 (2 H, m), 4.08 - 4.16 (1 H, m), 3.53 - 3.73 (8 H, m), 2.97 (2 H, t).
47	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.68 (1 H, d), 6.79 - 6.97 (6 H, m), 6.57 (1 H, br. s.), 6.32 (1 H, br. s.), 6.28 (1 H, s), 4.61 - 4.67 (2 H, m), 4.53 - 4.58 (3 H, m), 4.34 (1 H, dd), 4.07 - 4.24 (3 H, m), 2.99 (2 H, t).
48	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.65 (1 H, d), 6.82 - 6.97 (6 H, m), 6.27 (1 H, s), 4.78 (2 H, s), 4.66 (2 H, dd), 4.52 - 4.60 (1 H, m), 4.32 - 4.38 (1 H, m), 4.17 - 4.23 (2 H, m), 4.10 - 4.17 (1 H, m), 3.10 (3 H, s), 2.96 - 3.02 (5 H, m).
49	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.62 (1 H, d), 6.78 - 6.97 (6 H, m), 6.43 (1 H, br. s), 6.28 (1 H, s), 5.73 (1 H, br. s), 4.60 - 4.72 (2 H, m), 4.52 - 4.60 (1 H, m), 4.31 - 4.39 (1 H, m), 4.09 - 4.23 (3 H, m), 2.96 (2 H, t), 1.62 (6 H, s).
50	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.61 (1 H, d), 6.80 - 6.97 (5 H, m), 6.72 - 6.79 (1 H, m), 6.27 (1 H, s), 4.64 - 4.69 (2 H, m), 4.52 - 4.60 (1 H, m), 4.32 - 4.38 (1 H, m), 4.17 - 4.23 (2 H, m), 4.14 (1 H, dd), 3.74 - 3.83 (2 H, m), 3.55 - 3.70 (6 H, m), 2.95 (2 H, t), 1.69 (6 H, s).
51	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.62 (1 H, d), 7.28 - 7.38 (5 H, m), 6.91 (1 H, dd), 6.81 (1 H, d), 6.28 (1 H, s), 4.62 - 4.67 (2 H, m), 4.52 - 4.60 (1 H, m), 4.14 - 4.32 (6 H, m), 3.75 - 3.98 (4 H, m), 2.92 - 2.99 (2 H, m), 1.88 - 2.12 (3 H, m), 1.59 - 1.71 (1 H, m).

Cpd#	NMR data ( $\delta$ )
52	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.61 (1 H, d), 6.92 (1 H, dd), 6.81 (1 H, d), 6.28 (1 H, s), 4.49 - 4.60 (1 H, m), 4.14 - 4.34 (5 H, m), 4.00 - 4.07 (2 H, m), 3.78 - 3.99 (4 H, m), 2.92 - 3.00 (2 H, m), 1.85 - 2.18 (6 H, m), 1.53 - 1.84 (2 H, m).
53	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.96 - 8.04 (2 H, m), 7.74 - 7.82 (1 H, m), 7.58 - 7.70 (2 H, m), 7.38 - 7.52 (4 H, m), 7.00 (1 H, dd), 6.91 (1 H, d), 6.27 (1 H, s), 5.33 (2 H, s), 4.49 - 4.60 (1 H, m), 4.14 - 4.32 (4 H, m), 3.76 - 3.97 (2 H, m), 2.95 (2 H, t), 1.84 - 2.10 (3 H, m), 1.57 - 1.70 (1 H, m).
54	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.65 (1 H, d), 6.74 - 7.01 (6 H, m), 6.28 (1 H, s), 4.48 - 4.73 (3 H, m), 4.25 - 4.40 (2 H, m), 4.21 (3 H, s), 4.01 - 4.06 (2 H, m), 3.80 - 4.00 (2 H, m), 2.98 (2 H, t), 1.90 - 2.26 (3 H, m), 1.67 - 1.88 (1 H, m)
55	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.95 (2 H, d), 7.53 - 7.75 (1 H, m), 7.34 - 7.45 (1 H, m), 7.22 - 7.30 (1 H, m), 6.93 - 7.05 (1 H, m), 6.89 (1 H, d), 6.27 (1 H, s), 5.25 (2 H, s), 4.54 (1 H, m), 4.22 - 4.31 (2 H, m), 4.12 - 4.22 (2 H, m), 3.96 (3 H, s), 3.90 (2 H, s), 2.95 (2 H, t), 1.87 - 2.12 (2 H, m), 1.54 - 1.76 (2 H, m)
56	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.04 (1 H, s), 7.67 - 7.76 (1 H, m), 7.63 (1 H, d), 7.51 (1 H, t), 7.40 (1 H, d), 7.33 (1 H, d), 7.00 (1 H, dd), 6.88 - 6.93 (2 H, br s), 6.28 (1 H, s), 5.28 (2 H, s), 4.48 - 4.60 (1 H, m), 4.14 - 4.33 (4 H, m), 4.02 (1 H, quin), 3.77 - 3.97 (2 H, m), 2.96 (2 H, t), 1.98 - 2.12 (1 H, m), 1.84 - 1.98 (2 H, m), 1.56 - 1.71 (1 H, m).
57	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 9.36 (2 H, s), 9.28 (1 H, s), 7.85 - 7.94 (1 H, m), 7.74 (1 H, d), 7.65 (1 H, d), 7.57 (1 H, d), 7.02 (1 H, dd), 6.92 (1 H, d), 6.29 (1 H, s), 5.35 (2 H, s), 4.49 - 4.61 (1 H, m), 4.14 - 4.33 (4 H, m), 3.77 - 3.99 (2 H, m), 2.98 (2 H, t), 1.85 - 2.12 (3 H, m), 1.57 - 1.72 (1 H, m).
58	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.64 (1 H, d), 7.02 (1 H, dd), 6.94 (1 H, d), 6.27 (1 H, s), 5.50 (2 H, s), 4.47 - 4.56 (1 H, m), 4.20 - 4.28 (2 H, m), 4.11 - 4.19 (2 H, m), 3.86 - 3.94 (1 H, m), 3.77 - 3.85 (1 H, m), 3.69 - 3.77 (1 H, m), 2.97 (2 H, t), 1.84 - 2.09 (3 H, m), 1.57 - 1.68 (1 H, m), 1.33 - 1.42 (2 H, m), 1.21 - 1.32 (2 H, m).
59	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.65 (1 H, d), 6.92 (1 H, dd), 6.82 (1 H, d), 6.58 (1 H, br. s), 6.29 (1 H, s), 6.20 (1 H, br. s), 4.48 - 4.59 (3 H, m), 4.12 - 4.29 (4 H, m), 3.87 - 3.95 (1 H, m), 3.79 - 3.86 (1 H, m), 2.98 (2 H, t), 2.00 - 2.10 (1 H, m), 1.85 - 2.00 (2 H, m), 1.58 - 1.69 (1 H, m).
60	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.58 (1 H, d), 6.85 - 6.93 (1 H, m), 6.75 - 6.83 (1 H, m), 6.23 (1 H, s), 4.72 (2 H, s), 4.45 - 4.56 (1 H, m), 4.19 - 4.27 (2 H, m), 4.09 - 4.17 (2 H, m), 3.84 - 3.92 (1 H, m), 3.74 - 3.83 (1 H, m), 3.27 - 3.44 (4 H, m), 2.92 (2 H, t), 1.96 - 2.06 (1 H, m), 1.82 - 1.95 (2 H, m), 1.54 - 1.67 (1 H, m), 1.20 (3 H, t), 1.10 (3 H, t).

Cpd#	NMR data ( $\delta$ )
61	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.59 (1 H, d), 6.90 (1 H, dd), 6.80 (1 H, d), 6.25 (1 H, s), 4.75 (2 H, s), 4.47 – 4.56 (1 H, m), 4.19 - 4.29 (2 H, m), 4.10 - 4.19 (2 H, m), 3.85 - 3.93 (1 H, m), 3.76 - 3.84 (1 H, m), 3.07 (3 H, s), 2.97 (3 H, s), 2.94 (2 H, t), 1.97 - 2.09 (1 H, m), 1.84 - 1.96 (2 H, m), 1.55 - 1.69 (1 H, m).
62	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.57 (1 H, d), 6.84 - 6.94 (1 H, m), 6.75 - 6.82 (1 H, m), 6.23 (1 H, s), 4.68 - 4.82 (2.5 H, m), 4.43 - 4.55 (1 H, m), 4.17 - 4.27 (2 H, m), 4.00 - 4.17 (2.5, m), 3.84 - 3.92 (1 H, m), 3.73 - 3.83 (1 H, m), 2.88 - 2.97 (2 H, m), 2.75 - 2.87 (3 H, m), 1.95 - 2.07 (1 H, m), 1.79 - 1.95 (2 H, m), 1.51 - 1.70 (1 H, m), 1.19 (3 H, d), 1.07 (3 H, d).
63	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.27 (1 H, br. s), 7.66 - 7.71 (1 H, m), 7.58 – 7.62 (2 H, m), 7.34 – 7.39 (2 H, m), 7.14 - 7.21 (1 H, m), 7.00 (1 H, dd), 6.90 (1 H, d), 6.31 (1 H, s), 4.69 (2 H, s), 4.51 - 4.59 (1 H, m), 4.15 - 4.31 (4 H, m), 3.89 - 3.96 (1 H, m), 3.81 - 3.88 (1 H, m), 3.00 (2 H, t), 1.99 - 2.12 (1 H, m), 1.85 - 1.99 (2 H, m), 1.59 - 1.70 (1 H, m).
64	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.64 (1 H, d), 7.00 (1 H, dd), 6.92 (1 H, d), 6.27 (1 H, s), 5.47 (2 H, s), 4.48 - 4.58 (1 H, m), 4.41 (2 H, t), 4.11 - 4.29 (4 H, m), 3.87 - 3.95 (1 H, m), 3.78 - 3.86 (1 H, m), 2.98 (2 H, t), 1.83 - 2.10 (5 H, m), 1.56 - 1.68 (1 H, m), 0.99 (3 H, t).
65	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.70 (1 H, d), 7.61 (1 H, d), 7.15 (1 H, d), 6.99 (1 H, dd), 6.90 (1 H, d), 6.26 (1 H, s), 5.20 (2 H, s), 4.47 - 4.56 (1 H, m), 4.20 - 4.29 (2 H, m), 4.11 - 4.20 (2 H, m), 3.86 - 3.94 (1 H, m), 3.77 - 3.86 (1 H, m), 2.95 (2 H, t), 1.98 - 2.08 (1 H, m), 1.85 - 1.97 (2 H, m), 1.56 - 1.68 (1 H, m).
66	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.64 (1 H, d), 6.77 - 6.99 (6 H, m), 6.25 (1 H, s), 4.76 (2 H, s), 4.61 - 4.66 (2 H, m), 4.51 - 4.58 (1 H, m), 4.34 (1 H, dd), 4.16 - 4.21 (2 H, m), 4.13 (1 H, dd), 3.32 - 3.44 (4 H, m), 2.96 (2 H, t), 1.24 (3 H, t), 1.14 (3 H, t).
67	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.63 (1 H, d), 6.76 - 6.98 (6 H, m), 6.25 (1 H, s), 4.76 - 4.85 (1.5 H, m), 4.74 (1 H, s), 4.64 (2 H, dd), 4.54 (1 H, m), 4.33 (1 H, dd), 4.09 - 4.21 (3.5 H, m), 2.96 (2 H, t), 2.79 - 2.89 (3 H, m), 1.23 (3 H, d), 1.11 (3 H, d).
68	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.23 (1 H, br. s), 7.72 (1 H, d), 7.57 - 7.64 (2 H, m), 7.33 - 7.42 (2 H, m), 7.14 - 7.22 (1 H, m), 6.98 - 7.07 (1 H, m), 6.82 - 6.96 (5 H, m), 6.31 (1 H, s), 4.69 (2 H, s), 4.66 (2 H, t), 4.53 - 4.60 (1 H, m), 4.35 (1 H, dd), 4.19 - 4.25 (2 H, m), 4.14 (1 H, dd), 3.02 (2 H, t).
69	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.67 (1 H, d), 7.02 (1 H, dd), 6.78 - 6.97 (5 H, m), 6.27 (1 H, s), 5.48 (2 H, s), 4.64 (2 H, t), 4.54 (1 H, m), 4.42 (2 H, t), 4.34 (1 H, dd), 4.15 - 4.20 (2 H, m), 4.12 (1 H, dd), 2.99 (2 H, t), 2.00 (2 H, sxt), 0.98 (3 H, t).

Cpd#	NMR data ( $\delta$ )
70	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.68 (1 H, d), 7.02 (1 H, dd), 6.79 - 6.96 (5 H, m), 6.28 (1 H, s), 5.48 (2 H, s), 4.65 (2 H, t), 4.55 (1 H, m), 4.45 (2 H, t), 4.34 (1 H, dd), 4.16 - 4.21 (2 H, m), 4.13 (1 H, dd), 3.00 (2 H, t), 1.89 - 1.99 (2 H, m), 1.39 (2 H, m), 0.96 (3 H, t).
71	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.64 (1 H, d), 6.77 - 6.95 (6 H, m), 6.26 (1 H, s), 4.61 - 4.68 (2 H, m), 4.54 (1 H, m), 4.34 (1 H, dd), 4.09 - 4.22 (5 H, m), 3.70 - 3.76 (4 H, m), 2.96 (2 H, t), 2.82 (2 H, t), 2.54 - 2.60 (4 H, m).
72	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.74 (1 H, d), 7.01 (1 H, dd), 6.81 - 6.96 (5 H, m), 6.32 (1 H, s), 4.86 (2 H, s), 4.68 (2 H, t), 4.54 - 4.61 (1 H, m), 4.36 (1 H, dd), 4.20 - 4.26 (2 H, m), 4.15 (1 H, dd), 3.04 (2 H, t).
73	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.70 (1 H, d), 7.64 (1 H, d), 7.14 - 7.18 (1 H, m), 7.00 (1 H, dd), 6.78 - 6.93 (5 H, m), 6.25 (1 H, s), 5.21 (2 H, s), 4.63 (2 H, m), 4.49 - 4.57 (1 H, m), 4.32 (1 H, dd), 4.15 - 4.20 (2 H, m), 4.11 (1 H, dd), 2.96 (2 H, t).
74	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.63 (1 H, d), 6.75 - 6.97 (6 H, m), 6.25 (1 H, s), 4.69 (2 H, s), 4.63 (2 H, dd), 4.49 - 4.57 (1 H, m), 4.33 (1 H, dd), 4.17 (2 H, t), 4.12 (1 H, dd), 3.50 (4 H, q), 2.96 (2 H, t), 1.99 (2 H, q), 1.86 (2 H, q).
75	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.69 (1 H, d), 7.04 (1 H, dd), 6.96 (1 H, d), 6.81 - 6.94 (4 H, m), 6.28 (1 H, s), 5.52 (2 H, s), 4.66 (2 H, t), 4.52 - 4.59 (1 H, m), 4.35 (1 H, dd), 4.19 (2 H, t), 4.14 (1 H, dd), 3.74 (1 H, m), 3.00 (2 H, t), 1.37 - 1.45 (2 H, m), 1.25 - 1.32 (2 H, m).
76	( $^1\text{H}$ , $\text{DMSO}-d_6$ ) $\delta$ ppm: 8.01 (1 H, d), 7.12 (1 H, d), 7.09 (1 H, dd), 6.82 - 6.93 (4 H, m), 6.63 (1 H, s), 5.60 (2 H, s), 4.46 - 4.63 (3 H, m), 4.42 (1 H, dd), 4.13 (1 H, dd), 4.03 (2 H, t), 3.00 (2 H, t).
77	( $^1\text{H}$ , $\text{DMSO}-d_6$ ) $\delta$ ppm: 7.95 (1 H, d), 7.75 - 7.81 (1 H, m), 7.36 (1 H, dd), 6.87 - 7.06 (3 H, m), 6.57 (1 H, s), 5.96 - 6.14 (1 H, m), 5.42 (1 H, dd), 5.29 (1 H, dd), 4.45 - 4.70 (6 H, m), 4.31 (1 H, dd), 4.02 (2 H, t), 2.97 (2 H, t).
78	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.67 (1 H, d), 7.27 - 7.37 (5 H, m), 6.79 - 6.96 (7 H, m), 6.28 (1 H, s), 4.65 (2 H, t), 4.61 (2 H, s), 4.52 - 4.59 (3 H, m), 4.34 (1 H, dd), 4.18 (2 H, t), 4.13 (1 H, dd), 2.97 (2 H, t).
79	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.64 (1 H, d), 6.82 - 6.94 (5 H, m), 6.78 - 6.82 (1 H, m), 6.26 (1 H, s), 4.65 (2 H, dd), 4.55 (1 H, m), 4.34 (1 H, dd), 4.10 - 4.23 (5 H, m), 2.97 (2 H, t), 2.93 (2 H, t), 2.61 - 2.67 (4 H, m), 1.78 - 1.85 (4 H, m).
80	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.62 (1 H, d), 6.80 - 6.92 (5 H, m), 6.78 (1 H, d), 6.24 (1 H, s), 4.63 (2 H, dd), 4.53 (1 H, dt), 4.33 (1 H, dd), 4.08 - 4.21 (5 H, m), 2.95 (2 H, t), 2.77 (2 H, t), 2.42 - 2.54 (4 H, m), 1.59 (4 H, quin), 1.38 - 1.48 (2 H, m).

Cpd#	NMR data ( $\delta$ )
81	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.62 (1 H, d), 6.80 - 6.95 (5 H, m), 6.78 (1 H, d), 6.25 (1 H, s), 4.62 - 4.67 (2 H, m), 4.50 - 4.58 (1 H, m), 4.34 (1 H, dd), 4.19 (2 H, t), 4.12 (1 H, dd), 4.07 (2 H, t), 2.96 (2 H, t), 2.46 (2 H, t), 2.33 - 2.43 (4 H, br m), 1.99 (2 H, quin), 1.58 (4 H, quin), 1.44 (2 H, m).
82	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.64 (1 H, d), 6.82 - 6.94 (5 H, m), 6.80 (1 H, d), 6.27 (1 H, s), 4.66 (2 H, dd), 4.56 (1 H, m), 4.35 (1 H, dd), 4.18 - 4.23 (2 H, m), 4.14 (1 H, dd), 4.09 (2 H, t), 2.97 (2 H, t), 2.48 (2 H, t), 2.28 (6 H, s), 1.99 (2 H, quin).
83	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.64 (1 H, m), 6.71 - 6.95 (6 H, m), 6.22 - 6.31 (1 H, m), 4.66 (2 H, dd), 4.56 (1 H, m), 4.35 (1 H, dd), 4.03 - 4.24 (4 H, m), 2.93 - 3.16 (2 H, m), 2.52 - 2.80 (2 H, m), 1.51 - 2.44 (11 H, m).
84	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.63 (1 H, d), 6.81 - 6.94 (5 H, m), 6.78 (1 H, d), 6.26 (1 H, s), 4.65 (2 H, dd), 4.54 (1 H, m), 4.34 (1 H, dd), 4.19 (2 H, t), 4.13 (1 H, dd), 4.07 (2 H, t), 2.96 (2 H, t), 2.34 - 2.59 (10 H, m), 2.28 (3 H, s), 1.99 (2 H, quin).
85	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.65 (1 H, d), 7.13 - 7.19 (1 H, m), 6.93 - 6.98 (1 H, m), 6.81 - 6.93 (5 H, m), 6.53 - 6.58 (1 H, m), 6.27 (1 H, s), 5.12 (2 H, s), 4.65 (2 H, dd), 4.55 (1 H, m), 4.36 (1 H, q), 4.31 - 4.36 (2 H, m), 4.16 - 4.23 (2 H, m), 4.13 (1 H, dd), 2.98 (2 H, t), 1.37 (3 H, t).
86	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.82 (1 H, dd), 7.71 (1 H, s), 7.66 (1 H, d), 7.22 (1 H, dd), 7.17 (1 H, s), 7.01 (1 H, dd), 6.93 (1 H, d), 6.88 (1 H, dd), 6.26 (1 H, s), 5.22 (2 H, s), 4.66 (2 H, d), 4.50 - 4.59 (2 H, m), 4.31 (1 H, m), 4.19 (2 H, t), 2.98 (2 H, t).
87	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.61 (1 H, d), 6.98 (1 H, dd), 6.89 (1 H, d), 6.25 (1 H, s), 5.18 (2 H, s), 4.45 - 4.55 (1 H, m), 4.11 - 4.27 (4 H, m), 3.84 - 3.92 (1 H, m), 3.75 - 3.83 (1 H, m), 2.95 (2 H, t), 1.96 - 2.08 (1 H, m), 1.82 - 1.96 (2 H, m), 1.55 - 1.67 (1 H, m), 1.42 (9 H, s).
88	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.12 - 8.18 (2 H, m), 7.58 - 7.67 (2 H, m), 7.49 - 7.57 (2 H, m), 7.04 (1 H, dd), 6.95 (1 H, d), 6.28 (1 H, s), 5.31 (2 H, s), 4.50 - 4.57 (1 H, m), 4.23 - 4.30 (2 H, m), 4.14 - 4.23 (2 H, m), 3.91 (1 H, m), 3.78 - 3.86 (1 H, m), 2.98 (2 H, t), 1.99 - 2.10 (1 H, m), 1.84 - 1.98 (2 H, m), 1.58 - 1.69 (1 H, m).
89	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.85 (1 H, dd), 7.74 (1 H, d), 7.25 (1 H, dd), 7.01 (1 H, dd), 6.88 - 6.93 (2 H, m), 6.30 (1 H, s), 4.87 (2 H, s), 4.70 (2 H, d), 4.53 - 4.62 (2 H, m), 4.30 - 4.38 (1 H, m), 4.21 - 4.27 (2 H, m), 3.04 (2 H, t).
90	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.84 (1 H, dd), 7.65 (1 H, d), 7.24 (1 H, dd), 6.86 - 6.94 (2 H, m), 6.81 (1 H, d), 6.27 (1 H, s), 4.65 - 4.71 (2 H, m), 4.52 - 4.61 (2 H, m), 4.29 - 4.36 (1 H, m), 4.17 - 4.25 (4 H, m), 3.74 - 3.80 (4 H, m), 2.98 (2 H, t), 2.88 (2 H, t), 2.58 - 2.69 (4 H, m).



Cpd#	NMR data ( $\delta$ )
91	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.62 (1 H, d), 7.83 (1 H, dd), 7.74 (1 H, td), 7.62 - 7.68 (1 H, m), 7.49 (1 H, d), 7.19 - 7.31 (2 H, m), 6.99 (1 H, dd), 6.84 - 6.92 (2 H, m), 6.26 (1 H, s), 5.26 (2 H, s), 4.64 - 4.70 (2 H, m), 4.49 - 4.61 (2 H, m), 4.27 - 4.37 (1 H, m), 4.20 (2 H, t), 2.97 (2 H, t).
92	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.83 (1 H, dd), 7.61 - 7.68 (1 H, m), 7.23 (1 H, dd), 6.84 - 6.92 (2 H, m), 6.74 - 6.81 (1 H, m), 6.22 - 6.30 (1 H, m), 4.73 - 4.82 (1 H, m), 4.67 (2 H, d), 4.50 - 4.61 (2 H, m), 4.28 - 4.37 (1 H, m), 4.20 (2 H, t), 2.92 - 3.38 (6 H, m), 2.71 - 2.78 (3 H, m), 2.39 - 2.52 (1 H, m), 1.87 - 2.28 (5 H, m).
93	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.78 (1 H, d), 7.57 (1 H, d), 7.19 (1 H, d), 6.98 (1 H, d), 6.92 (1 H, br. s.), 6.85 (1 H, dd), 6.21 (1 H, s), 5.39 (2 H, br. s.), 4.59 (2 H, d), 4.49 (2 H, m), 4.21 - 4.31 (1 H, m), 4.11 (2 H, t), 2.92 (2 H, m).
94	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.89 (1 H, d), 8.66 (1 H, d), 7.88 - 7.96 (1 H, m), 7.77 - 7.84 (1 H, m), 7.58 - 7.64 (1 H, m), 7.49 - 7.54 (1 H, m), 7.39 - 7.45 (1 H, m), 6.44 (1 H, s), 4.53 - 4.63 (1 H, m), 4.23 - 4.34 (4 H, m), 3.94 (1 H, dt), 3.81 - 3.89 (1 H, m), 3.10 (2 H, t), 2.02 - 2.13 (1 H, m), 1.89 - 2.01 (2 H, m), 1.61 - 1.72 (1 H, m).
95	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.74 - 7.95 (3 H, m), 7.44 - 7.73 (4 H, m), 6.42 (1 H, br. s.), 4.55 (1 H, d), 4.17 - 4.35 (4 H, m), 3.76 - 3.98 (2 H, m), 3.01 - 3.15 (2 H, m), 2.01 - 2.12 (1 H, m), 1.94 (2 H, m), 1.57 - 1.72 (1 H, m).
96	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.75 (1 H, d), 7.56 - 7.65 (3 H, m), 7.44 - 7.53 (3 H, m), 7.37 - 7.44 (1 H, m), 6.41 (1 H, s), 4.53 - 4.61 (1 H, m), 4.20 - 4.33 (4 H, m), 3.89 - 3.97 (1 H, m), 3.81 - 3.88 (1 H, m), 3.07 (2 H, t), 2.01 - 2.11 (1 H, m), 1.87 - 2.00 (2 H, m), 1.60 - 1.71 (1 H, m).
97	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.94 (2H, br. s), 7.78 - 7.88 (2 H, m), 7.54 - 7.70 (4 H, m), 7.23 (1 H, dd), 6.88 (1 H, dd), 6.42 (1 H, s), 4.69 (2 H, d), 4.51 - 4.61 (2 H, m), 4.33 (1 H, dd), 4.26 (2 H, t), 3.12 (2 H, t).
98	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.88 - 7.91 (1 H, m), 7.81 - 7.87 (3 H, m), 7.70 (1 H, dt), 7.57 - 7.63 (2 H, m), 7.52 (1 H, d), 7.24 (1 H, dd), 6.86 - 6.91 (1 H, m), 6.42 (1 H, s), 4.70 (2 H, d), 4.53 - 4.62 (2 H, m), 4.33 (1 H, dd), 4.24 - 4.29 (2 H, m), 3.11 (2 H, t).
99	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.72 (1 H, d), 7.55 (1 H, d), 7.46 (1 H, br. s.), 7.29 - 7.41 (2 H, m), 6.97 - 7.10 (2 H, m), 6.42 (1 H, br. s.), 4.57 (1 H, m), 4.19 - 4.34 (4 H, m), 3.94 (1 H, m), 3.84 (4 H, m), 3.00 - 3.10 (2 H, m), 2.02 - 2.12 (1 H, m), 1.89 - 2.01 (2 H, m), 1.61 - 1.72 (1 H, m).

Cpd#	NMR data ( $\delta$ )
100	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.74 (1 H, d), 7.58 (1 H, dd), 7.49 (1 H, br. s), 7.35 - 7.41 (1 H, m), 7.19 (1 H, d), 7.11 - 7.14 (1 H, m), 6.94 (1 H, dd), 6.40 (1 H, s), 4.51 - 4.60 (1 H, m), 4.20 - 4.33 (4 H, m), 3.89 - 3.97 (1 H, m), 3.79 - 3.88 (4 H, m), 3.06 (2 H, t), 2.01 - 2.11 (1 H, m), 1.87 - 2.00 (2 H, m), 1.60 - 1.70 (1 H, m).
101	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.73 (1 H, d), 7.54 - 7.60 (3 H, m), 7.47 (1 H, br. s), 7.01 (2 H, d), 6.41 (1 H, s), 4.53 - 4.61 (1 H, m), 4.20 - 4.33 (4 H, m), 3.90 - 3.98 (1 H, m), 3.81 - 3.89 (4 H, m), 3.06 (2 H, t), 2.01 - 2.12 (1 H, m), 1.88 - 2.01 (2 H, m), 1.61 - 1.71 (1 H, m).
102	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.76 - 7.85 (3 H, m), 7.71 - 7.76 (2 H, m), 7.62 (1 H, dd), 7.54 (1 H, s), 6.45 (1 H, s), 4.55 - 4.63 (1 H, m), 4.24 - 4.35 (4 H, m), 3.91 - 3.99 (1 H, m), 3.82 - 3.90 (1 H, m), 3.11 (2 H, t), 2.04 - 2.14 (1 H, m), 1.89 - 2.02 (2 H, m), 1.62 - 1.73 (1 H, m).
103	( $^1\text{H}$ , $\text{DMSO}-d_6$ ) $\delta$ ppm: 8.27 (1 H, s), 8.13 (1 H, d), 8.00 (2 H, t), 7.79 (1 H, s), 7.74 (1 H, dd), 7.64 (1 H, t), 6.69 (1 H, s), 4.27 - 4.32 (1 H, m), 4.13 - 4.26 (2 H, m), 4.07 (2 H, t), 3.76 - 3.83 (1 H, m), 3.65 - 3.71 (1 H, m), 3.11 (2 H, t), 1.77 - 2.04 (3 H, m), 1.60 - 1.70 (1 H, m).
104	( $^1\text{H}$ , $\text{DMSO}-d_6$ ) $\delta$ ppm: 8.11 (1 H, d), 8.00 (2 H, d), 7.80 (3 H, d), 7.75 (1 H, dd), 6.69 (1 H, s), 4.27 - 4.32 (1 H, m), 4.13 - 4.26 (2 H, m), 4.07 (2 H, m), 3.76 - 3.83 (1 H, m), 3.64 - 3.71 (1 H, m), 3.09 (2 H, t), 1.79 - 2.04 (3 H, m), 1.60 - 1.71 (1 H, m).
105	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.70 (1 H, d), 7.52 - 7.59 (3 H, m), 7.46 (1 H, d), 6.78 - 6.82 (2 H, m), 6.39 (1 H, s), 4.53 - 4.61 (1 H, m), 4.20 - 4.34 (4 H, m), 3.90 - 3.98 (1 H, m), 3.81 - 3.88 (1 H, m), 3.01 - 3.08 (8 H, m), 2.01 - 2.12 (1 H, m), 1.89 - 2.01 (2 H, m), 1.61 - 1.72 (1 H, m).
106	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.94 (2 H, d), 7.80 (1 H, d), 7.72 (2 H, d), 7.64 (1 H, dd), 7.56 (1 H, s), 6.44 (1 H, s), 6.18 (1H, br. s), 5.71 (1H, br. s), 4.54 - 4.63 (1 H, m), 4.22 - 4.35 (4 H, m), 3.91 - 3.99 (1 H, m), 3.81 - 3.90 (1 H, m), 3.10 (2 H, t), 1.89 - 2.12 (3 H, m), 1.64 - 1.72 (1 H, m).
107	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.78 - 7.86 (2 H, m), 7.66 - 7.75 (1 H, m), 7.47 - 7.62 (4 H, m), 6.45 (1 H, s), 4.53 - 4.63 (1 H, m), 4.20 - 4.37 (4 H, m), 3.81 - 4.00 (2 H, m), 3.06 - 3.16 (2 H, m), 1.96 (3 H, m), 1.61 - 1.75 (1 H, m).
108	( $^1\text{H}$ , $\text{MeOD}-d_4$ ) $\delta$ ppm 8.02 (1 H, s), 7.87 (1 H, s), 7.75 (1 H, d), 7.46 - 7.54 (2 H, m), 6.43 - 6.49 (1 H, m), 4.28 - 4.38 (1 H, m), 4.17 - 4.27 (2 H, m), 4.09 (2 H, t), 3.85 - 3.95 (4 H, m), 3.75 - 3.84 (1 H, m), 2.96 - 3.03 (2 H, m), 1.85 - 2.14 (3 H, m), 1.63 - 1.77 (1 H, m).

Cpd#	NMR data ( $\delta$ )
109	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.75 (1 H, d), 7.55 - 7.68 (3 H, m), 7.38 - 7.54 (3 H, m), 6.40 (1 H, s), 4.49 - 4.60 (1 H, m), 4.15 - 4.34 (4 H, m), 3.77 - 3.96 (2 H, m), 2.94 - 3.20 (7 H, m), 1.83 - 2.13 (4 H, m), 1.58 - 1.72 (1 H, m).
110	$^1\text{H}$ NMR ( $\text{MeOD-}d_4$ ) $\delta$ ppm 8.45 - 8.51 (1 H, m), 7.93 - 8.06 (2 H, m), 7.61 - 7.69 (2 H, m), 6.91 (1 H, d), 6.63 (1 H, s), 4.37 - 4.46 (1 H, m), 4.23 - 4.35 (2 H, m), 4.15 - 4.24 (2 H, m), 3.76 - 4.01 (5 H, m), 3.13 (2 H, t), 1.84 - 2.17 (3 H, m), 1.67 - 1.84 (1 H, m)
111	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.76 (1 H, d), 7.07 - 7.23 (5 H, m), 6.43 (1 H, s), 4.58 (1 H, m), 4.30 (4 H, s), 3.80 - 3.99 (2 H, m), 3.00 - 3.10 (2 H, m), 1.86 - 2.15 (9 H, m), 1.60 - 1.73 (1 H, m).
112	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.77 (1 H, d), 7.27 - 7.31 (1 H, m), 7.18 - 7.22 (1 H, m), 6.42 (1 H, s), 4.55 - 4.63 (1 H, m), 4.20 - 4.35 (4 H, m), 3.81 - 3.99 (2 H, m), 3.07 (2 H, t), 2.46 (3 H, s), 2.32 (3 H, s), 1.89 - 2.14 (3 H, m), 1.60 - 1.74 (1 H, m).
113	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.43 - 8.14 (10 H, m), 6.44 (1 H, s), 4.52 - 4.68 (1 H, m), 4.18 - 4.38 (4 H, m), 3.79 - 4.03 (2 H, m), 3.03 - 3.18 (2 H, m), 1.84 - 2.20 (3 H, m), 1.59 - 1.78 (1 H, m).
114	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.76 - 7.96 (4 H, m), 7.37 - 7.58 (6 H, m), 6.46 (1 H, s), 4.54 - 4.65 (1 H, m), 4.30 (4 H, s), 3.80 - 4.00 (2 H, m), 3.08 (2 H, t), 1.83 - 2.15 (3 H, m), 1.59 - 1.75 (1 H, m).
115	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 9.27 (1 H, s), 9.00 (2 H, s), 7.84 (1 H, s), 7.59 - 7.65 (1 H, m), 7.51 - 7.55 (1 H, m), 6.45 (1 H, s), 4.54 - 4.63 (1 H, m), 4.21 - 4.34 (4 H, m), 3.80 - 3.98 (2 H, m), 3.08 - 3.17 (2 H, m), 1.85 - 2.13 (3 H, m), 1.61 - 1.72 (1 H, m).
116	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.70 (1 H, d), 7.52 (1 H, d), 7.42 (1 H, s), 7.20 (1 H, d), 6.95 (1 H, d), 6.39 (1 H, s), 4.52 - 4.63 (1 H, m), 4.19 - 4.35 (4 H, m), 3.79 - 4.00 (2 H, m), 3.05 (2 H, m), 1.90 - 2.12 (3 H, m), 1.60 - 1.72 (1 H, m).
117	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.66 (1 H, d), 7.33 - 7.39 (2 H, m), 7.27 - 7.30 (1 H, m), 6.39 (1 H, s), 6.22 - 6.29 (2 H, m), 4.50 - 4.61 (1 H, m), 4.16 - 4.34 (4 H, m), 3.77 - 3.97 (2 H, m), 3.01 (2 H, t), 1.91 (3 H, s), 1.58 - 1.73 (1 H, m), 1.42 (9 H, s).
118	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 8.45 (1 H, d), 7.76 - 7.88 (3 H, m), 7.53 - 7.60 (1 H, m), 7.44 - 7.49 (1 H, m), 7.22 - 7.27 (1 H, m), 6.83 - 6.94 (2 H, m), 6.40 (1 H, s), 4.70 (2 H, d), 4.53 - 4.64 (2 H, m), 4.31 - 4.39 (1 H, m), 4.23 - 4.31 (2 H, m), 4.01 (3 H, s), 3.07 - 3.14 (2 H, m).

Cpd#	NMR data ( $\delta$ )
119	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.57 (1 H, d), 7.32 (1 H, dd), 7.27 (1 H, s), 6.33 (1 H, s), 4.48 - 4.59 (1 H, m), 4.09 - 4.31 (4 H, m), 3.87 - 3.96 (1 H, m), 3.78 - 3.86 (1 H, m), 2.95 (2 H, t), 1.84 - 2.11 (3 H, m), 1.57 - 1.70 (1 H, m), 1.39 - 1.53 (1 H, m), 0.77 - 0.96 (4 H, m).
120	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.59 (1 H, d), 7.32 - 7.39 (1 H, m), 7.30 (1 H, s), 6.34 (1 H, s), 4.54 (1 H, m), 4.12 - 4.33 (4 H, m), 3.77 - 3.96 (2 H, m), 2.95 (2 H, t), 1.84 - 2.13 (3 H, m), 1.57 - 1.72 (1 H, m), 1.32 (9 H, s).
121	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.64 (1 H, d), 7.48 (3 H, d), 7.42 (1 H, s), 6.89 (2 H, d), 6.37 (1 H, s), 4.54 (1 H, s), 4.27 (4 H, s), 3.87 - 3.97 (1 H, m), 3.83 (3 H, s), 2.94 - 3.05 (2 H, m), 1.82 - 2.12 (4 H, m), 1.57 - 1.72 (1 H, m)
122	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 8.65 (2 H, d), 7.84 (1 H, dd), 7.68 (1 H, d), 7.36 (2 H, d), 7.24 (1 H, dd), 6.96 (1 H, dd), 6.84 - 6.92 (2 H, m), 6.27 (1 H, s), 5.17 (2 H, s), 4.67 (2 H, d), 4.50 - 4.61 (2 H, m), 4.28 - 4.37 (1 H, m), 4.16 - 4.25 (2 H, m), 2.99 (2 H, t).
123	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 8.88 (2 H, d), 8.28 - 8.34 (1 H, m), 8.12 (1 H, d), 7.90 (1 H, d), 7.72 (1 H, s), 7.55 (2 H, s), 6.42 (1 H, s), 4.58 (1 H, d), 4.30 (4 H, s), 3.79 - 4.00 (2 H, m), 3.01 - 3.11 (2 H, m), 1.88 - 2.14 (2 H, m), 1.63 - 1.75 (2 H, m)
124	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.93 (1H, s), 8.70(1H, br.s), 7.96(1H, dd), 7.88-7.86 (2H, m), 7.65 (1H, d), 7.57(1H, s), 7.48-7.45 (1H, m), 7.28 (1H, dd), 6.93 (1H, dd), 6.45 (1H,s), 4.75-4.73 (2H, m), 4.65-4.58 (2H, m), 4.38 (1H, dd), 4.31 (2H, t), 3.15 (2H, t).
125	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.90-7.88 (2H, d), 7.74(1H, dt), 7.65-7.54 (4H, m), 7.31-7.28 (1H, m), 6.94 (1H, dd), 6.47(1H, s), 4.74 (2H, d), 4.66-4.58 (2H, m), 4.39 (1H, dd), 4.32 (2H, t), 3.53 (1H, s), 3.16 (2H, t).
126	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.87 (1H, dd), 7.77 (1H, d), 7.59 (1H, dd), 7.51 (1H, dd), 7.41 (1H, dt), 7.35 (1H, dd), 7.27 (1H, dd), 7.09 (1H, dd), 7.05 (1H, d), 6.92 (1H, dd), 6.42 (1H, s), 7.73-7.72 (2H, m), 4.64-4.57 (2H, m), 4.37 (1H, dd), 4.29 (2H, t), 3.87 (3H, s), 3.09 (2H, t).
127	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.98 (1H, m), 7.83 (1H, t), 7.67 (1H, dd), 7.62 (1H, d), 7.54-7.44 (3H, m), 7.40 (1H, m), 7.08 (1H, s), 7.06 (1H, dd), 6.72 (1H, dd), 6.23 (1H, s), 4.54-4.52 (2H, m), 4.45-4.35 (2H, m), 4.16 (1H, dd), 4.11 (2H, t), 2.93 (2H, t).
128	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 9.30 (1H, s), 9.03 (2H, s), 7.93-7.90 (1H, m), 7.88 (1H, dd), 7.66 (1H, dd), 7.58 (1H, m), 7.28 (1H, dd), 6.93 (1H, dd), 6.46 (1H, s), 4.75-4.74 (2H, m), 4.66-4.57 (2H, m), 4.38 (1H, dd), 4.32 (2H, t), 3.17 (2H, t).

Cpd#	NMR data ( $\delta$ )
129	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.09 (1H, s), 7.79-7.70 (3H, m), 7.60-7.35 (4H, m), 7.19 (1H, d), 6.84 (1H, dd), 6.37 (1H, s), 4.61-4.59 (2H, m), 4.51-4.48 (2H, m), 4.27 (1H, dd), 4.16 (2H, t), 3.02 (2H, t).
130	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.87 (1H, dd), 7.77 (1H, d), 7.68 (1H, dd), 7.56 (1H, dd), 7.35 (1H, dt), 7.27 (1H, dd), 7.26 (1H, t), 7.10 (1H, d), 7.07 (1H, dt), 6.92 (1H, dd), 6.43 (1H, s), 7.74-7.73 (2H, m), 4.65-4.57 (2H, m), 4.37 (1H, dd), 4.30 (2H, t), 3.09 (2H, t), 2.60 (6H, s).
131	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.61-8.41 (2H, m), 7.63-7.61 (1H, m), 7.52 (1H, d), 7.50-7.42 (1H, m), 7.36-7.32 (1H, dd), 7.12 (1H, m), 7.05 (1H, s), 7.03 (1H, dd), 6.68 (1H, dd), 6.17 (1H, s), 4.49-4.48 (2H, m), 4.41-4.32 (2H, m), 4.12 (1H, dd), 4.03 (2H, t), 2.83 (2H, t).
132	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.87 (1H, dd), 7.70 (1H, d), 7.48 (1H, dd), 7.42 (1H, s), 7.26 (1H, dd), 6.92 (1H, dd), 6.38 (1H, s), 4.73-4.71 (2H, m), 4.63-4.56 (2H, m), 4.37 (3H, s), 4.24 (2H, t), 3.49 (3H, s), 3.03 (2H, t).
133	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.86 (1H, dd), 7.66 (1H, d), 7.42 (1H, dd), 7.37 (1H, br.s), 7.26 (1H, dd), 6.91 (1H, dd), 6.36 (1H, s), 4.71-4.69 (2H, m), 4.62-4.55 (2H, m), 4.35 (1H, dd), 4.22 (2H, t), 3.88 (2H, t), 3.00 (2H, t), 2.75 (2H, t), 2.19 (1H, br.s).
134	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.17 (1 H, br. s), 7.84 (1 H, dd), 7.64 (1 H, d), 7.25 (1 H, dd), 7.00 (1 H, dd), 6.94 - 6.84 (1 H, m), 6.22 - 6.29 (1 H, m), 6.09 - 6.14 (1 H, m), 5.07 (2 H, br. s), 4.63 - 4.70 (1 H, m), 4.50 - 4.60 (2 H, m), 4.32 (1 H, dd), 4.19 (2 H, t), 3.78 (3 H, s), 3.48 (1 H, s), 2.91 - 3.02 (2 H, m), 2.27 (3 H, s)
135	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.84 (1 H, dd), 7.71 (1 H, d), 7.25 (1 H, dd), 7.01 (1 H, dd), 6.93 - 6.89 (2 H, m), 6.29 (1 H, s), 5.36 (2 H, s), 4.70 (2 H, s), 4.0 - 4.54 (2 H, m), 4.32 (1 H, dd), 4.21 (2 H, t), 3.03 (2 H, t), 2.46 (3 H, s)
136	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.82 (1 H, dd), 7.63 (1 H, d), 7.39 (1 H, d), 7.31 - 7.36 (1 H, m), 7.22 (1 H, dd), 6.84 - 6.92 (1 H, m), 6.33 (1 H, br. s), 4.63 - 4.70 (2 H, m), 4.49 - 4.58 (1 H, m), 4.26 - 4.37 (1 H, m), 4.14 - 4.23 (2 H, m), 3.43 - 3.49 (1 H, m), 2.91 - 3.02 (1 H, m), 2.61 - 2.67 (1 H, m), 1.62 (6 H, s)
137	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.65 (1 H, br. s), 7.86 (1 H, dd), 7.75 (1 H, d), 7.57 (1 H, d), 7.51 (1 H, br. s), 7.38-7.44 (2 H, m), 7.25 (2 H, dd), 6.91 (1 H, dd), 6.39 (1 H, s), 4.71 (2 H, d), 4.52 - 4.65 (2 H, m), 4.35 (1 H, dd), 4.25 (2 H, t), 3.00 - 3.11 (2 H, m)
138	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.83 (1 H, dd), 7.63 (1 H, d), 7.37 - 7.43 (1 H, m), 7.35 (1 H, s), 7.23 (1 H, dd), 6.90 (1 H, dd), 6.33 (1 H, s), 4.65 - 4.70 (2 H, m), 4.50 - 4.61 (4 H, m), 4.32 (1 H, dd), 4.19 (2 H, t), 2.97 (2 H, t).

Cpd#	NMR data ( $\delta$ )
139	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 8.83 (1 H, d), 7.93 (1 H, s), 7.83 (2 H, m), 7.63 (1 H, m), 7.54 (1 H, s), 7.35 (1 H, d), 7.27 (1 H, s), 6.92 (1 H, dd), 6.43 (1 H, s), 4.71 (2 H, d), 4.54 - 4.64 (2 H, m), 4.36 (1 H, dd), 4.28 (2 H, t), 3.12 (2 H, t), 2.67 (3 H, s).
140	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 8.36 (2 H, br. d), 7.83 (2 H, m), 7.57 - 7.63 (1 H, m), 7.53 (1 H, s), 7.39 (1 H, s), 7.24 (1 H, dd), 6.85 - 6.92 (1 H, m), 6.41 (1 H, s), 4.67 - 4.74 (2 H, m), 4.51 - 4.63 (2 H, m), 4.26 (3 H, m), 3.94 (3 H, s), 3.07 - 3.16 (2 H, m).
141	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.87 (1H, dd), 7.64 (1H, d), 7.38 (1H, dd), 7.33 (1H, br.s), 7.27 (1H, dd), 6.93 (1H, dd), 6.36 (1H, s), 4.71-4.70 (2H, m), 4.63-4.56 (2H, m), 4.35 (1H, dd), 4.23 (2H, t), 3.00 (2H, t), 1.54-1.47 (1H, m), 0.98-0.85 (4H, m).
142	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.87 (1H, dd), 7.68 (1H, d), 7.44 (1H, dd), 7.39 (1H, m), 7.27 (1H, dd), 6.92 (1H, dd), 6.37 (1H, s), 4.72-4.71 (2H, m), 4.63-4.56 (2H, m), 4.36 (1H, dd), 4.24 (2H, t), 3.02 (2H, t), 2.15-2.08 (5H, m), 1.96-1.79 (4H, m).
143	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.86 (1H, dd), 7.68 (1H, d), 7.44 (1H, dd), 7.39 (1H, br.s), 7.26 (1H, dd), 6.91 (1H, dd), 6.37 (1H, s), 4.72-4.70 (2H, m), 4.63-4.55 (2H, m), 4.35 (1H, dd), 4.23 (2H, t), 4.02 (2H, t), 2.85 (2H, t), 2.71 (2H, t).
144	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.86(1H, dd), 7.65 (1H, d), 7.40 (1H, dd), 7.35(1H, m), 7.26 (1H, dd), 6.91 (1H, dd), 6.36 (1H, s), 4.71-4.70 (2H, m), 4.62-4.55 (2H, m), 4.35 (1H, dd), 4.22 (2H, t), 3.00 (2H, t), 1.35 (9H, s).
145	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.15(1H, dd), 7.77 (1H, d), 7.70 (1H, d), 7.56 (1H, dd), 7.53-7.51 (1H, m), 7.45 (1H, s), 7.18 (1H, d), 6.95 (1H, dd), 6.83 (1H, dd), 6.33 (1H,s), 4.64-4.63 (2H, m), 4.55-4.48 (2H, m), 4.27 (1H, dd), 4.19 (2H, t), 3.93 (3H, s), 3.01 (2H, t).
146	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.78 (1H, dt), 7.66 (1H, d), 7.45-7.30 (2H, m), 7.25 (1H, d), 7.19 (1H, dd), 6.84 (1H, dd), 6.30 (1H, s), 4.64-4.62 (2H, m), 4.55-4.47 (2H, m), 4.27 (1H, dd), 4.16 (2H, t), 2.96 (2H, t).
147	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.83 (1H, d), 8.34 (1H, dd), 8.10 (1H, dd), 8.06 (1H, d), 7.090-7.86 (2H, m), 6.67 (1H, dd), 7.60 (1H, d), 7.27 (1H, dd), 6.93 (1H, dd), 6.45 (1H, s), 4.74-4.73 (2H, m), 4.65-4.57 (2H, m), 4.37 (1H, dd), 3.31 (2H,t), 3.16 (2H, t), 3.10 (3H, d).
148	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.88-7.87 (2H, m), 7.75 (1H, d), 7.56 (1H, t), 7.53 (1H, dd), 7.45 (H, br.s), 7.28 (1H, dd), 6.99 (1H, dd), 6.77 (1H, m), 6.39 (1H, s), 4.73-4.72 (2H, m), 4.64-4.58 (2H,m), 4.37 (1H, dd), 4.27 (2H, t), 3.08 (2H, t).
149	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.86 (1H, dd), 7.85 (1H, s), 7.74-7.72 (2H, m), 7.50 (1H, dd), 7.42 (1H, d), 7.26 (1H, dd), 6.92 (1H, dd), 6.37 (1H, s), 4.72-4.71 (2H, m), 4.63-4.56 (2H, m), 4.36 (1H, dd), 4.26 (2H, t), 4.00 (3H, s), 3.06 (2H, t).

Cpd#	NMR data ( $\delta$ )
150	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.81 - 7.89 (1 H, m), 7.64 - 7.72 (1 H, m), 7.29 - 7.42 (1 H, m), 7.24 (1 H, dd), 6.90 (1 H, dd), 6.35 (1 H, s), 4.70 (1 H, d), 4.50 - 4.63 (1 H, m), 4.28 - 4.40 (1 H, m), 4.22 (1 H, t), 3.74 (4 H, br. s), 3.55 (1 H, br. s), 3.03 (1 H, t), 2.48 (4 H, br. s)
151	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.80 - 7.89 (1 H, m), 7.53 (1 H, d), 7.22 - 7.25 (1 H, m), 6.90 (1 H, dd), 6.63 (1 H, dd), 6.52 (1 H, d), 6.20 (1 H, s), 4.64 - 4.74 (3 H, m), 4.49 - 4.61 (3 H, m), 4.29 - 4.38 (1 H, m), 4.14 - 4.25 (3 H, m), 2.91 (2 H, t)
152	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.80 - 7.88 (2 H, m), 7.63 - 7.73 (2 H, m), 7.24 (1 H, dd), 6.91 (1 H, dd), 6.41 (1 H, s), 4.71 (2 H, d), 4.51 - 4.64 (2 H, m), 4.29 - 4.39 (1 H, m), 4.20 - 4.29 (2 H, m), 3.04 - 3.14 (2 H, m)
153	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.85 (1 H, dd), 7.66 (1 H, s), 7.55 (1 H, d), 7.22 - 7.26 (1 H, m), 7.12 (1 H, s), 6.89 (1 H, dd), 6.67 (1 H, dd), 6.54 (1 H, d), 6.20 (1 H, s), 4.65 - 4.71 (2 H, m), 4.50 - 4.61 (4 H, m), 4.28 - 4.40 (1 H, m), 4.20 (2 H, t), 2.94 (2 H, t)
154	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.80 - 7.87 (1 H, m), 7.67 (1 H, d), 7.24 (1 H, dd), 7.02 (1 H, dd), 6.83 - 6.95 (2 H, m), 6.27 (1 H, s), 5.23 (2 H, br. s), 4.68 (2 H, d), 4.50 - 4.61 (2 H, m), 4.27 - 4.38 (1 H, m), 4.21 (2 H, t), 2.99 (2 H, t), 2.59 - 2.68 (3 H, m)
155	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.84 (1 H, dd), 7.67 (1 H, d), 7.24 (1 H, dd), 7.03 (1 H, dd), 6.85 - 6.96 (2 H, m), 6.27 (1 H, s), 5.23 (2 H, s), 4.68 (2 H, m), 4.50 - 4.61 (2 H, m), 4.32 (1 H, dd), 4.21 (2 H, t), 2.89 - 3.05 (4 H, m), 1.40 (3 H, t)
156	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.79 - 7.87 (1 H, m), 7.65 (1 H, d), 7.24 (1 H, dd), 7.01 (1 H, dd), 6.82 - 6.95 (2 H, m), 6.27 (1 H, s), 5.18 (2 H, s), 4.64 - 4.72 (2 H, m), 4.49 - 4.61 (2 H, m), 4.28 - 4.38 (1 H, m), 4.21 (2 H, t), 2.99 (2 H, t), 2.15 - 2.30 (1 H, m), 1.16 - 1.31 (4 H, m)
157	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.77 - 7.87 (1 H, m), 7.68 (1 H, d), 7.23 (1 H, dd), 7.02 (1 H, dd), 6.92 - 6.95 (1 H, m), 6.86 - 6.91 (1 H, m), 6.26 (1 H, s), 5.23 (2 H, s), 4.63 - 4.72 (2 H, m), 4.50 - 4.61 (2 H, m), 4.32 (1 H, dd), 4.21 (2 H, t), 3.25 (1 H, spt), 2.99 (2 H, t), 1.43 (6 H, d)
158	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.79 - 7.87 (1 H, m), 7.67 (1 H, d), 7.24 (1 H, dd), 7.03 (1 H, dd), 6.94 (1 H, d), 6.89 (1 H, dd), 6.27 (1 H, s), 5.22 (2 H, s), 4.64 - 4.71 (2 H, m), 4.47 - 4.60 (2 H, m), 4.32 (1 H, dd), 4.20 (2 H, t), 3.00 (2 H, t), 1.44 (9 H, s)
159	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.84 (1 H, dd), 7.68 (1 H, d), 7.24 (1 H, dd), 6.96 (1 H, dd), 6.82 - 6.92 (2 H, m), 6.27 (1 H, s), 6.20 (1 H, s), 5.19 (2 H, s), 4.64 - 4.73 (2 H, m), 4.48 - 4.62 (2 H, m), 4.33 (1 H, dd), 4.19 (1 H, t), 3.00 (2 H, t), 2.31 (3 H, s)

Cpd#	NMR data ( $\delta$ )
160	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.09 (1 H, d), 7.75 - 7.88 (2 H, m), 7.45 - 7.53 (1 H, m), 7.40 (1 H, br. s), 7.20 - 7.26 (1 H, m), 6.84 - 6.93 (2 H, m), 6.42 (1 H, s), 4.71 (2 H, m), 4.50 - 4.65 (2 H, m), 4.31 - 4.37 (1 H, m), 4.28 (2 H, t), 4.08 (3 H, s), 3.10 (2 H, t)
161	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.78 - 7.88 (1 H, m), 7.68 (1 H, d), 7.38 - 7.46 (1 H, m), 7.32 (1 H, br. s), 7.24 (1 H, dd), 6.89 (1 H, dd), 6.35 (1 H, s), 6.29 (1 H, br. s.), 4.69 (2 H, m), 4.50 - 4.63 (2 H, m), 4.29 - 4.40 (3 H, m), 4.23 (2 H, t), 3.95 (2 H, t), 3.04 (2 H, m), 2.54 (2 H, m)
162	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 9.01 (1H, d), 8.09 (1H, dd), 7.92 (1H, dd), 7.88-7.85 (2H, m), 7.67 (1H, dd), 7.60 (1H, d), 7.27 (1h, dd), 6.93 (1h, dd), 6.47 (1H, s), 4.74-4.73 (2H, m), 4.65-4.57 (2H, m), 3.37 (1H, dd), 3.34 (2H,t), 3.17 (2H, t).
163	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.22 (1H, dd), 7.87 (1H, dd), 7.80 (1H, d), 7.67 (2H, dt), 7.57 (1H, d), 7.27 (1H, dd), 7.02 (1H, dd), 6.93 (1H, dd), 6.44 (1H, s), 4.74-4.73 (2H, m), 4.65-4.57 (2H, m), 4.49 (2H, q), 4.37 (1H, dd), 3.30 (2H, t), 3.11 (2H, t), 1.42(3H, t).
164	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.45 (1H, d), 7.88-7.81 (3H, m), 7.58(1H, dd), 7.50 (1H, dd), 7.28 (1H, dd), 6.93 (1H, dd), 6.86 (1H, d), 6.42(1H, s), 4.74-4.73 (2H, m), 4.65-4.57 (2H, m), 4.45 (2H, q), 4.37 (1H, dd), 3.30 (2H, t), 3.12 (2H, t), 1.46 (3H, t).
165	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.50 (1 H, d), 7.84 (1 H, dd), 7.74 - 7.80 (2 H, m), 7.55 (1 H, dd), 7.46 (1 H, d), 7.24 (1 H, dd), 6.89 (1 H, dd), 6.73 (1 H, d), 6.38 (1 H, s), 4.70 (2 H, d), 4.52 - 4.63 (2 H, m), 4.34 (1 H, dd), 4.26 (2 H, t), 3.80 - 3.89 (4 H, m), 3.54 - 3.64 (4 H, m), 3.08 (2 H, t)
166	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.77 (2 H, s), 7.84 (2 H, m), 7.52 - 7.60 (1 H, m), 7.48 (1 H, s), 7.20 - 7.26 (1 H, m), 6.88 (1 H, dd), 6.41 (1 H, s), 4.66 - 4.74 (2 H, m), 4.51 - 4.63 (2 H, m), 4.34 (1 H, dd), 4.27 (2 H, t), 4.05 - 4.12 (3 H, m), 3.11 (2 H, t)
167	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.84 (1 H, dd), 7.76 (1 H, d), 7.59 (1 H, dd), 7.47 - 7.52 (1 H, m), 7.25 (1 H, dd), 7.10 - 7.18 (1 H, m), 6.96 (2 H, m), 6.90 (1 H, dd), 6.41 (1 H, s), 4.71 (2 H, d), 4.51 - 4.64 (2 H, m), 4.30 - 4.39 (1 H, m), 4.26 (2 H, t), 3.93 (3 H, s), 3.64 (3 H, s), 3.07 (2 H, t)
168	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.84 (1 H, dd), 7.75 (1 H, d), 7.56 (1 H, dd), 7.45 - 7.51 (1 H, m), 7.25 (1 H, dd), 6.85 - 6.99 (4 H, m), 6.39 (1 H, s), 4.68-4.72 (2 H, m), 4.51 - 4.63 (2 H, m), 4.30 - 4.39 (1 H, m), 4.21 - 4.29 (2 H, m), 3.82 (3 H, s), 3.79 (3 H, s), 3.07 (2 H, t)
169	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.02 (2 H, d), 7.80 - 7.87 (1 H, m), 7.77 (1 H, t), 7.47 - 7.70 (5 H, m), 7.20 - 7.26 (1 H, m), 6.89 (1 H, dd), 6.40 (1 H, s), 4.65 - 4.73 (2 H, m), 4.51 - 4.62 (2 H, m), 4.33 (1 H, dd), 4.18 - 4.28 (2 H, m), 4.01 (2 H, m), 3.02 - 3.12 (2 H, m)



Cpd#	NMR data ( $\delta$ )
170	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.76 - 7.93 (1 H, m), 7.68 (1 H, d), 7.46 (1 H, dd), 7.40 (1 H, s), 7.24 (1 H, d), 6.90 (1 H, br. s.), 6.36 (1 H, s), 4.69 (2 H, d), 4.51 - 4.62 (2 H, m), 4.47 (2 H, s), 4.28 - 4.38 (1 H, m), 4.21 (2 H, t), 3.83 (2 H, t), 3.01 (2 H, t), 2.64 - 2.73 (2 H, m)
171	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 8.43 (1 H, br. s), 7.85 (1 H, dd), 7.66 (1 H, d), 7.43 (2 H, dd), 7.19 - 7.26 (1 H, m), 6.84 - 6.94 (1 H, m), 6.35 (1 H, br. s), 4.70 (2 H, d), 4.50 - 4.63 (2 H, m), 4.29 - 4.38 (1 H, m), 4.15 - 4.27 (2 H, m), 3.65 - 3.71 (1 H, m), 2.97 - 3.04 (3 H, m), 2.62 (1 H, s), 2.58 (2 H, s)
172	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.78 - 7.89 (1 H, m), 7.66 (1 H, d), 7.44 (1 H, d), 7.39 (1 H, s), 7.23 (1 H, dd), 6.84 - 6.93 (1 H, m), 6.35 (1 H, s), 4.68 (2 H, m), 4.50 - 4.62 (2 H, m), 4.28 - 4.37 (1 H, m), 4.19 (2 H, t), 3.64 (2 H, s), 3.00 (2 H, t), 2.50 (6 H, br. s)
173	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.78 - 7.86 (1 H, m), 7.65 - 7.73 (1 H, m), 7.48 (1 H, dd), 7.31 - 7.45 (5 H, m), 7.24 (1 H, dd), 6.89 (1 H, dd), 6.38 (1 H, s), 4.66 (2 H, m), 4.53 (2 H, dd), 4.31 (1 H, dd), 4.21 (2 H, t), 3.94 (2 H, s), 3.77 (2 H, s), 3.02 (2 H, t), 2.60 (3 H, s)
174	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.78 - 7.90 (1 H, m), 7.66 (1 H, d), 7.42 (1 H, dd), 7.37 (1 H, br. s), 7.23 (1 H, dd), 6.83 - 6.94 (1 H, m), 6.36 (1 H, s), 4.64 - 4.71 (2 H, m), 4.48 - 4.61 (2 H, m), 4.28 - 4.37 (1 H, m), 4.20 (2 H, t), 3.69 (2 H, s), 3.47 (2 H, s), 3.15 (6 H, s), 3.01 (2 H, t)
175	( $^1\text{H}$ , $\text{MeOD}-d_4$ ) $\delta$ ppm: 8.20 (1 H, br. s), 8.07 (1 H, d), 7.79 - 7.85 (1 H, m), 7.74 - 7.78 (2 H, m), 7.63 - 7.71 (1 H, m), 7.51 - 7.60 (1 H, m), 7.39 - 7.47 (1 H, m), 7.28 - 7.37 (1 H, m), 7.18 (1 H, d), 7.10 - 7.14 (2 H, m), 7.03 (1 H, dd), 6.81 (1 H, s), 6.65 - 6.73 (1 H, m), 6.11 - 6.20 (1 H, m), 5.03 - 5.12 (2 H, m), 4.91 - 5.03 (2 H, m), 4.70 - 4.80 (1 H, m), 4.59 (4 H, s), 4.41 - 4.47 (2 H, m), 4.26 - 4.38 (2 H, m), 4.06 - 4.19 (1 H, m), 3.89 - 3.95 (2 H, m), 3.76 - 3.81 (1 H, m), 3.34 - 3.46 (2 H, m), 3.11 - 3.17 (1 H, m), 2.70 - 2.84 (2 H, m)
176	( $^1\text{H}$ , $\text{MeOD}-d_4$ ) $\delta$ ppm: 7.00 - 7.08 (1 H, m), 6.88 - 6.97 (1 H, m), 6.61 - 6.72 (2 H, m), 6.49 (1 H, dd), 6.16 (1 H, dd), 5.65 (1 H, s), 3.89 - 3.95 (2 H, m), 3.76 - 3.86 (2 H, m), 3.69 (2 H, s), 3.53 - 3.63 (1 H, m), 3.38 - 3.48 (2 H, m), 3.27 - 3.34 (1 H, m), 2.63 (1 H, dt), 2.23 - 2.28 (2 H, m)
177	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.78 - 7.85 (1 H, m), 7.63 (1 H, d), 7.38 - 7.43 (1 H, m), 7.31 - 7.36 (1 H, m), 7.21 (1 H, dd), 6.86 (1 H, dd), 6.33 (1 H, s), 4.67 (2 H, d), 4.49 - 4.61 (2 H, m), 4.27 - 4.37 (1 H, m), 4.19 (2 H, t), 3.62 - 3.69 (2 H, m), 2.97 (2 H, t), 2.62 (4 H, q), 1.11 (6 H, t)

Cpd#	NMR data ( $\delta$ )
178	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.83 (1 H, br. s.), 7.51 - 7.66 (1 H, m), 7.36 (2 H, br. s), 7.18 - 7.25 (1 H, m), 6.89 (1 H, br. s.), 6.44 - 6.69 (1 H, m), 6.32 (1 H, s), 5.26 - 5.33 (1 H, m), 4.71-4.63 (2 H, m), 4.47 - 4.60 (2 H, m), 4.25 - 4.39 (1 H, m), 4.07 - 4.22 (2 H, m), 2.89 - 2.99 (2 H, m), 1.67 (6 H, br. s)
179	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.81 - 7.88 (1 H, m), 7.68 - 7.74 (1 H, m), 7.65 (1 H, d), 7.49 - 7.57 (1 H, m), 7.25 (1 H, dd), 6.86 - 6.97 (2 H, m), 6.80 - 6.85 (1 H, m), 6.26 (1 H, s), 5.31 (2 H, s), 4.63 - 4.71 (2 H, m), 4.52 - 4.62 (2 H, m), 4.28 - 4.38 (1 H, m), 4.16 - 4.25 (3 H, m), 4.00 - 4.12 (2 H, m), 3.91 - 3.99 (1 H, m), 3.68 - 3.79 (1 H, m), 3.46 - 3.58 (1 H, m), 2.98 (2 H, t)
180	$^1\text{H}$ , $\text{MeOD-}d_4$ ) $\delta$ ppm: 8.51 (1 H, br. s.), 8.45 - 8.53 (1 H, m), 8.39 - 8.45 (1 H, m), 8.20 - 8.26 (1 H, m), 8.12 - 8.17 (1 H, m), 8.01 (4 H, s), 7.92 - 7.99 (1 H, m), 7.81 - 7.87 (1 H, m), 7.72 - 7.80 (1 H, m), 7.54 - 7.65 (2 H, m), 7.46 - 7.53 (1 H, m), 7.36 (4 H, s), 7.06 - 7.12 (1 H, m), 6.96 (1 H, dd), 6.89 - 7.00 (1 H, m), 6.44 (1 H, s), 6.38 - 6.50 (1 H, m), 5.23 - 5.41 (3 H, m), 4.98 - 5.09 (1 H, m), 4.85 - 4.95 (1 H, m), 4.73 (2 H, m), 4.62 (2 H, d), 4.33 - 4.44 (1 H, m), 4.26 (2 H, br. s.), 4.07 (1 H, br. s.), 3.96 (25 H, br. s.), 3.70 - 3.81 (2 H, m), 3.42 (1 H, br. s.), 3.10 (1 H, br. s.), 2.71 (2 H, s), 2.63 - 2.77 (1 H, m), 2.07 (1 H, br. s.), 2.06 (6 H, s)
181	( $^1\text{H}$ $\text{DMSO-}d_6$ ) $\delta$ ppm 8.02 (1 H, d), 7.77 (1 H, d), 7.47 (1 H, s), 7.32 - 7.45 (2 H, m), 6.92 - 7.04 (1 H, m), 6.73 (1 H, s), 5.56 (1 H, d), 4.45 - 4.70 (5 H, m), 4.25 - 4.37 (1 H, m), 4.03 (2 H, t), 3.00 (2 H, t), 1.40 (3 H, m).
182	( $^1\text{H}$ $\text{DMSO-}d_6$ ) $\delta$ ppm 8.02 (1 H, d), 7.77 (1 H, d), 7.47 (1 H, s), 7.32 - 7.45 (2 H, m), 6.92 - 7.04 (1 H, m), 6.73 (1 H, s), 5.54 (1 H, d), 4.45 - 4.70 (4 H, m), 4.35 - 4.43 (1 H, m), 4.25 - 4.34 (1 H, m), 4.03 (2 H, t), 3.01 (2 H, t), 1.60 - 1.75 (2 H, m), 1.00 (3 H, m).
183	( $^1\text{H}$ $\text{DMSO-}d_6$ ) $\delta$ ppm 8.02 (1 H, d), 7.77 (1 H, d), 7.47 (1 H, s), 7.32 - 7.45 (2 H, m), 6.92 - 7.04 (1 H, m), 6.73 (1 H, s), 5.54 (1 H, d), 4.41 - 4.70 (5 H, m), 4.25 - 4.35 (1 H, m), 4.02 (2 H, t), 3.01 (2 H, t), 1.55 - 1.72 (2 H, m), 1.38 - 1.53 (2 H, m), 0.92 (3 H, m).
184	( $^1\text{H}$ $\text{DMSO-}d_6$ ) $\delta$ ppm 8.02 (1 H, d), 7.77 (1 H, d), 7.47 (1 H, s), 7.32 - 7.45 (2 H, m), 6.92 - 7.04 (1 H, m), 6.73 (1 H, s), 4.48 - 4.70 (4 H, m), 4.25 - 4.35 (1 H, m), 4.02 (2 H, t), 3.01 (2 H, t), 2.05 - 2.42 (2 H, br. s ), 1.75 - 1.90 (2 H, m), 1.30 - 1.70 (7 H, m), 1.10 - 1.28 (1 H, m).
185	( $^1\text{H}$ $\text{DMSO-}d_6$ ) $\delta$ ppm 8.02 (1 H, d), 7.77 (1 H, d), 7.47 (1 H, s), 7.32 - 7.45 (2 H, m), 6.92 - 7.04 (1 H, m), 6.73 (1 H, s), 5.54 (1 H, d), 4.45 - 4.70 (5 H, m), 4.25 - 4.35 (1 H, m), 4.02 (2 H, t), 3.01 (2 H, t), 1.75 - 1.80 (1 H, m), 1.45 - 1.65 (2 H, m), 0.92 (6 H, m).

Cpd#	NMR data ( $\delta$ )
186	( $^1\text{H}$ DMSO- $d_6$ ) $\delta$ ppm 8.02 (1 H, d), 7.77 (1 H, d), 7.47 (1 H, s), 7.32 - 7.45 (2 H, m), 6.92 - 7.04 (1 H, m), 6.73 (1 H, s), 5.28 (1 H, s), 4.45 - 4.70 (4 H, m), 4.25 - 4.35 (1 H, m), 4.02 (2 H, t), 3.01 (2 H, t), 1.55 - 1.75 (4 H, m), 1.00 (6 H, m).
187	( $^1\text{H}$ DMSO- $d_6$ ) $\delta$ ppm 8.03 (1 H, d), 7.77 (1 H, m), 7.65 (2 H, m), 7.52 (1 H, s), 7.43 - 7.47 (1 H, m), 7.34 - 7.41 (3 H, m), 7.25 - 7.32 (1 H, m), 6.94 - 7.01 (1 H, m), 6.74 (1 H, s), 6.32 (1 H, s), 4.48 - 4.70 (4 H, m), 4.25 - 4.35 (1 H, m), 4.02 (2 H, t), 3.01 (2 H, t), 1.72 (6 H, m).
188	( $^1\text{H}$ DMSO- $d_6$ ) $\delta$ ppm 8.02 (1 H, d), 7.77 (1 H, d), 7.47 (1 H, s), 7.32 - 7.45 (2 H, m), 6.92 - 7.04 (1 H, m), 6.73 (1 H, s), 5.56 (1 H, d), 4.45 - 4.70 (5 H, m), 4.25 - 4.37 (1 H, m), 4.03 (2 H, t), 3.00 (2 H, t), 1.75 - 1.92 (1 H, m), 0.95 - 1.05 (6 H, m).
189	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.84 (1 H, dd), 7.72 (1 H, d), 7.67 (1 H, d), 7.24 (1 H, dd), 7.18 (1 H, d), 7.03 (1 H, dd), 6.94 (1 H, d), 6.89 (1 H, dd), 6.26 (1 H, s), 5.23 (2 H, s), 4.66 - 4.70 (2 H, m), 4.52 - 4.61 (2 H, m), 4.32 (1 H, dd), 4.17 - 4.24 (2 H, m), 2.99 (2 H, t).
190	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm: 7.85 (1H, dd), 7.74 (1H, d), 7.69 (1H, d), 7.25 (1H, dd), 7.20-7.19 (1H, m), 7.04 (1H, dd), 6.96 (1H, d), 6.90 (1H, dd), 6.28 (1H, s), 5.25 (2H, s), 4.70-4.69 (2H, m), 4.61-4.54 (2H, m), 4.34 (1H, dd), 4.22 (2H, t), 3.01 (2H, t).
191	( $^1\text{H}$ DMSO- $d_6$ ) $\delta$ ppm 8.00 (1 H, d), 7.77 (1 H, m), 7.32 - 7.55 (3 H, m), 6.92 - 7.04 (1 H, m), 6.72 (1 H, s), 4.45 - 4.72 (4 H, m), 4.25 - 4.40 (1 H, m), 4.02 (2 H, m), 3.57 (2 H, s), 3.00 (2 H, m), 2.50 - 2.70 (2 H, m), 1.85 - 2.10 (1 H, br. s), 1.15 - 1.53 (4 H, m), 0.88 (3 H, m).
192	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.83 (1 H, dd), 7.69 (1 H, d), 7.33 - 7.37 (1 H, m), 7.29 (1 H, br. s), 7.22 (1 H, dd), 6.89 (1 H, dd), 6.35 (1 H, s), 4.66 - 4.70 (2 H, m), 4.50 - 4.62 (5 H, m), 4.32 (1 H, dd), 4.18 - 4.24 (2 H, m), 3.73 (4 H, t), 3.65 (2 H, t), 3.02 (2 H, t), 2.66 (2 H, t), 2.49 - 2.58 (3 H, m).
193	( $^1\text{H}$ DMSO- $d_6$ ) $\delta$ ppm 8.01 (1 H, d), 7.77 (1 H, m), 7.18 - 7.51 (9 H, m), 6.97 (1 H, m), 6.72 (1 H, s), 4.45 - 4.70 (4 H, m), 4.25 - 4.35 (1 H, m), 4.05 (2 H, m), 3.81 (2 H, s), 3.56 (2 H, s), 2.92 - 3.10 (2 H, m).
194	( $^1\text{H}$ DMSO- $d_6$ ) $\delta$ ppm 7.98 (1 H, d), 7.77 (1 H, m), 7.42 (1 H, s), 7.35 (2 H, m), 7.10 - 7.20 (2 H, m), 6.90 - 7.02 (1 H, m), 6.65 - 6.75 (3 H, m), 6.55 - 6.65 (1 H, m), 6.11 (1 H, s), 4.45 - 4.70 (4 H, m), 4.25 - 4.35 (1 H, m), 4.15 (2 H, d), 4.00 (2 H, m), 3.00 (2 H, t).

Cpd#	NMR data ( $\delta$ )
195	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.85 (1 H, d), 7.70 - 7.82 (3 H, m), 7.20 - 7.25 (1 H, m), 6.85 - 6.92 (1 H, m), 6.41 (1 H, s), 6.11 (1 H, d), 4.70 (2 H, d), 4.50 - 4.62 (2 H, m), 4.31 - 4.40 (1 H, m), 4.15 - 4.30 (3 H, m), 4.00 (2 H, m), 3.45 - 3.62 (2 H, m), 3.05 (2 H, m), 1.95 - 2.10 (2 H, m), 1.55 - 1.65 (2 H, m).
196	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.70 - 7.90 (4 H, m), 7.22 (1 H, m), 6.90 (1 H, m), 6.45 (1 H, m), 6.41 (1 H, s), 4.82 - 4.95 (2 H, m), 4.70 (2 H, m), 4.45 - 4.62 (4 H, m), 4.28 - 4.40 (1 H, m), 4.15 - 4.30 (2 H, m), 3.78 (2 H, m), 3.25 - 3.40 (1 H, m), 3.02 - 3.15 (2 H, m).
197	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.84 (1 H, dd), 7.66 (1 H, d), 7.35 (1 H, m), 7.31 (1 H, s), 7.23 (1 H, dd), 6.89 (1 H, dd), 6.35 (1 H, s), 4.68 (2 H, d), 4.52 - 4.61 (2 H, m), 4.33 (1 H, dd), 4.18 - 4.25 (2 H, m), 3.66 (2 H, s), 3.01 (2 H, t), 2.49 - 2.57 (4 H, m), 1.81 (4 H, m).
198	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.84 (1 H, dd), 7.66 (1 H, d), 7.33 - 7.41 (2 H, m), 7.24 (1 H, dd), 6.89 (1 H, dd), 6.34 (1 H, s), 4.69 (2 H, d), 4.52 - 4.62 (2 H, m), 4.33 (1 H, dd), 4.20 (2 H, t), 3.81 (2 H, s), 2.98 - 3.04 (2 H, m), 1.20 (9 H, s).
199	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.85 (1 H, dd), 7.68 (1 H, d), 7.32 - 7.42 (2 H, m), 7.25 (1 H, dd), 6.90 (1 H, dd), 6.35 (1 H, s), 4.70 (2 H, d), 4.53 - 4.63 (2 H, m), 4.34 (1 H, dd), 4.19 - 4.26 (2 H, t), 3.60 (2 H, s), 2.99 - 3.06 (2 H, t), 2.44 - 2.55 (4 H, m), 1.66 (4 H, m), 1.49 (2 H, m).
200	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.84 (1 H, m), 7.71 (1 H, d), 7.36 (1 H, d), 7.30 (1 H, s), 7.24 (1 H, m), 6.89 (1 H, dd), 6.36 (1 H, s), 4.69 (2 H, d), 4.51 - 4.65 (6 H, m), 4.40 (2 H, d), 4.32 (1 H, dd), 4.23 (2 H, t), 3.59 (2 H, s), 3.00 - 3.07 (2 H, m), 1.36 (3 H, s).
201	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.85 (1 H, m), 7.67 (1 H, d), 7.38 - 7.47 (2 H, m), 7.21 - 7.25 (1 H, m), 6.89 (1 H, m), 6.36 (1 H, s), 4.89 (2 H, d), 4.69 (2 H, m), 4.52 - 4.64 (4 H, m), 4.30 - 4.37 (1 H, m), 4.19 - 4.25 (2 H, m), 3.00 (2 H, m), 2.75 - 2.83 (2 H, m), 1.17 - 1.26 (3 H, m).
202	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.84 (1 H, dd), 7.71 (1 H, d), 7.29 - 7.39 (2 H, m), 7.24 (1 H, dd), 6.89 (1 H, dd), 6.36 (1 H, s), 4.74 - 4.83 (2 H, m), 4.63 - 4.72 (5 H, m), 4.51 - 4.62 (2 H, m), 4.49 (2 H, s), 4.32 (1 H, dd), 4.18 - 4.26 (2 H, m), 3.03 (2 H, t).
203	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.60 (1 H, d), 7.35 (1 H, d), 7.30 (1 H, s), 6.35 (1 H, s), 4.78 - 4.90 (1 H, m), 4.60 (2 H, m), 4.40 - 4.28 (1 H, m), 4.25 - 4.15 (2 H, m), 3.00 - 2.85 (2 H, m), 2.50 - 2.35 (2 H, m), 2.00 - 1.85 (1 H, m), 1.50 - 1.38 (1 H, m), 1.00 - 0.80 (10 H, m)

Cpd#	NMR data ( $\delta$ )
204	( $^1\text{H}$ , $\text{CDCl}_3$ ) $\delta$ ppm 7.65 (1 H, d), 7.38 (1 H, d), 7.30 (1 H, s), 6.33 (1 H, s), 5.05 - 4.90 (1 H, m), 4.60 - 4.40 (2 H, m), 4.40 - 4.25 (1 H, m), 4.25 - 4.15 (2 H, m), 3.05 - 2.90 (2 H, m), 2.60 - 2.55 (1 H, m), 2.22 - 2.10 (1 H, m), 1.95 - 1.75 (1 H, m), 1.55 - 1.40 (1 H, m), 1.00 - 0.80 (10 H, m)

### Biological Examples

#### 1. *In vitro* assays

##### 1.1. *Cell based assay: GTP- $\gamma$ S binding assay.*

- 5 [00460] The following assay can be used for determination of GPR84 activation. The [ $^{35}\text{S}$ ]GTP $\gamma$ S binding assay measures the level of G protein activation following agonist occupation of a GPCR, by determining the binding of the non-hydrolysable analog [ $^{35}\text{S}$ ]GTP $\gamma$ S to G $\alpha$  subunits.

##### 1.1.1 HEPES buffer assay

- 10 [00461] The assay is performed in a 96 well plate where the following reagents are added. First 50  $\mu\text{L}$  compound is added into the assay plate, followed by addition of 20  $\mu\text{L}$  3,3' di indolylmethane at  $\text{EC}_{80}$  concentration (concentration which gives 80% of the activity of GPR84). In a last step, 30  $\mu\text{L}$  of a mixture consisting of membranes-GTP $\gamma$ S-SpA beads is added [mixture consists of 20  $\mu\text{g}$ /well membranes derived from stable cell line over expressing GPR84 (membranes are pre-incubated with 0.1  $\mu\text{M}$  GDP for 15 min at 4°C), 0.1 nM [ $^{35}\text{S}$ ]GTP $\gamma$ S (Perkin Elmer, NEG030) and 0.5 mg/well PVT-WGA SpA beads (Perkin Elmer, RPNQ0001)]. All components are diluted in assay buffer containing 20mM HEPES pH 7.4; 5mM  $\text{MgCl}_2$ ; 250mM NaCl; 0.05% BSA; 75ug/mL saponin. Reactions are incubated for 90 min at room temperature followed by centrifugation at 2000 rpm during 15 min. Plates are read on a Topcount reader (Perkin Elmer) immediately after centrifugation (readout time, 1 min/well).

- 20 [00462] **TABLE IV: GPR84 assay GTP $\gamma$ S  $\text{IC}_{50}$  of selected Compounds of the invention.**

N/A: not active

\* > 1000 nM

\*\* > 500 -1000 nM

- 25 \*\*\* > 100-500 nM

\*\*\*\* 0.01- 100 nM

Cpd#	GPR84
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2	*

Cpd#	GPR84
3	****
4	*

Cpd#	GPR84
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Cpd#	GPR84
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Cpd#	GPR84
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### 1.1.2 Tris buffer assay

**[00463]** Alternatively, the assay is performed in a 96 well plate where the following reagents are added.

- 5 First 50  $\mu$ L compound is added into the assay plate, followed by addition of 20  $\mu$ L 3,3' di indolylmethane at  $EC_{80}$  concentration (concentration which gives 80% of the activity of GPR84). In a last step, 30  $\mu$ L of a mixture consisting of membranes-GTP $\gamma$ S-SpA beads is added [mixture consists of 20  $\mu$ g/well membranes derived from stable cell line over expressing GPR84 (membranes are pre-incubated with 0.1  $\mu$ M GDP for 15 min at 4°C), 0.1 nM [ $^{35}$ S]GTP $\gamma$ S (Perkin Elmer, NEG030) and 0.5 mg/well PVT-WGA SpA beads (Perkin
- 10 Elmer, RPNQ0001)]. All components are diluted in assay buffer containing 20mM Tris pH 7.5; 5mM MgCl<sub>2</sub>; 250mM NaCl; 0.05% BSA; 75ug/mL saponin. Reactions are incubated for 90 min at room temperature

followed by centrifugation at 2000 rpm during 15 min. Plates are read on a Topcount reader (Perkin Elmer) immediately after centrifugation (readout time, 1 min/well).

**[00464] TABLE V: Alternative GPR84 assay GTP $\gamma$ S IC<sub>50</sub> of selected Compounds of the invention.**

5

N/A: not active  
 \* > 1000 nM  
 \*\* > 500-1000 nM  
 \*\*\* > 100-500 nM  
 \*\*\*\* 0.01- 100 nM

10

Cpd#	GPR84-2
34	***
38	**
109	*
110	***
111	*
112	***
113	****
114	**
115	*
116	**
117	*
118	****
119	***
120	**
122	****
124	****
125	***

Cpd#	GPR84-2
126	***
127	****
128	****
129	****
130	***
131	***
132	***
133	****
134	****
135	****
137	****
138	****
139	****
142	****
143	****
144	****

## 2. Cellular assays

### 15 2.1. Human neutrophil migration assay

**[00465]** We have established that GPR84 agonists (MCFA such as sodiumdecanoate, 3,3' di indolylmethane and Embelin induce neutrophil chemotaxis and that GPR84 antagonists could block GPR84 agonist-induced chemotaxis but not IL8-induced chemotaxis, indicating that G Protein-Coupled Receptor 84 (GPR84) is an essential player in the process of neutrophil recruitment.

20 **[00466]** The effect of agonists or antagonists for GPR84 can therefore be assayed in a neutrophil migration test. In the neutrophil migration assay, neutrophils, freshly isolated from buffy coats from human volunteers, are treated with a compound for 30 min. Subsequently, the neutrophils are transferred to the upper wells of a



Corning HTS transwell 96 permeable support system, of which the lower wells are filled with a embelin solution at EC<sub>80</sub> (concentration which gives 80% of the activity of GPR84). After 1 h of incubation, migration of the neutrophils towards embelin in the lower compartment can be quantified by measuring the ATP-content of the lower wells using the ATPlite luminescence ATP detection assay system (Perkin Elmer, Cat. N°.: 436110).

#### 2.1.1 Isolation of neutrophils from human buffy coat

[00467] A human buffy coat is diluted with an equal volume of ice cold DPBS. 20 mL of the diluted buffy coat is gently mixed with 4 mL of ACD buffer (140 mM citric acid, 200 mM sodium citrate and 220 mM dextrose). Then, 12 mL of the 6% dextran/0.9% NaCl solution (15 g dextran T2000 and 2.25 g NaCl dissolved in 250 mL H<sub>2</sub>O) is added to the mixture and the samples are inverted gently up to 20 times. The total volume was transferred to a new recipient and incubated at room temperature for 1 h for complete separation of the two phases to occur. The yellowish supernatant is then transferred to a clean centrifugation tube and centrifuged for 12 min at 1300 rpm and 4°C. After centrifugation, the supernatant is discarded and the remaining cell pellet is rapidly resuspended in 12 mL of ice-cold H<sub>2</sub>O for red blood cell lysis to occur. After 20 seconds, 4 mL of ice-cold 0.6 M KCl is added. Samples are mixed carefully and centrifuged for 6 min at 1300 rpm, 4°C. The supernatant is discarded and the red blood cell lysis procedure is repeated one more time. Subsequently, the cell pellet is resuspended in 4 mL of DPBS and layered over 5 mL of Lymphoprep (Nycomed Pharma, Cat. N°.: 1114545) in a 15 mL centrifuge tube. After centrifugation for 12 min at 1300 rpm, 4°C, the supernatant is removed and the cell pellet, containing the neutrophils, is resuspended in 25 mL chemotaxis buffer (RPMI 1640 medium, supplemented with 10 mM HEPES; freshly made for each experiment)

#### 2.1.2 Migration assay

[00468] A cell suspension of 8.9x10<sup>6</sup> cells per milliliter is prepared. 20 µL of compound solution in chemotaxis buffer is added to 180 µL cell suspension. The mixture is incubated at 37°C for 30 min with intermediate resuspension of the cells after 15 min. Following this, 70 µL cell suspension is transferred to the upper compartment of a Corning HTS transwell 96 permeable support system with 5.0 µm pore size polycarbonate membrane (Corning, Cat.N°.: 3387). The receiver well of the transwell system is then filled with 200 µL chemotaxis buffer containing compound and chemotactic agent (embelin). After incubation at 37°C in 5% CO<sub>2</sub> for 1 h, the upper plate of the transwell system is removed and the cell suspension in the receiver plate is transferred to a 96-well V-bottom plate. 50 µL of DPBS is added to the receiver plate to prevent remaining cells from drying out. The V-bottom plate is centrifuged for 6 min at 1500 rpm. The supernatant is removed and the cells are resuspended in 50 µL DPBS. The cells are then transferred back to the receiver plate of the transwell system. After this, 100 µL ATPlite solution (Perkin Elmer, Cat. N°:

436110) was added to the cells. The plate is incubated for 10 min in the dark, while shaking. 170  $\mu$ L of cell lysate is then transferred to a white 96-well plate and luminescence is measured. The detected luminescent signal is considered as linearly related to the number of cells having migrated from the upper well to the receiver well.

5

**[00469] TABLE VI: human neutrophil migration IC<sub>50</sub> of selected Compounds of the invention.**

10

\* > 1000 nM  
 \*\* > 500-1000 nM  
 \*\*\* > 100-500 nM  
 \*\*\*\* 0.01-100 nM

Cpd#	Neutrophils
15	****
18	****
32	****
46	****
57	***
74	****
76	****
86	****
89	****
91	****
93	***
118	****
122	****
125	****
131	****
132	****
134	****

Cpd#	Neutrophils
15	****
136	****
137	****
139	****
142	****
180	****
181	****
182	****
183	****
188	****
189	****
190	****
192	****
193	****
199	****
200	****
202	****

## 2.2. Rat neutrophil migration assay

15 **[00470]** We have established that GPR84 agonists (MCFA such as sodiumdecanoate, 3,3' di indolylmethane and Embelin induce neutrophil chemotaxis and that GPR84 antagonists could block GPR84 agonist-induced chemotaxis but not IL8-induced chemotaxis, indicating that G Protein-Coupled Receptor 84 (GPR84) is an essential player in the process of neutrophil recruitment.

20 **[00471]** The effect of agonists or antagonists for GPR84 can therefore be assayed in a neutrophil migration test. In the rat neutrophil migration assay, neutrophils, freshly isolated from rat after intraperitoneal injection of glycogen (0.1 %, w/v), are treated with a compound for 30 min. Subsequently, the neutrophils are transferred to the upper wells of a Corning HTS transwell 96 permeable support system, of which the lower

wells are filled with a embelin solution at  $EC_{80}$  (concentration which give 80% of the activity of the GPR84). After 1 h of incubation, migration of the neutrophils towards embelin in the lower compartment can be quantified by measuring the ATP-content of the lower wells using the Cell Titer Glow Substrate assay system (Promega, Cat.N°.: G755B).

5

#### 2.2.1. *Isolation of neutrophils from rats*

[00472] 24 h after intraperitoneal injection of glycogen (0.1 %, w/v), cells are harvested by peritoneal lavage with 25mL HBSS then centrifuged for 12 min at 1300 rpm and 4°C. After centrifugation, the supernatant is discarded and the remaining cell pellet is rapidly resuspended in 12 mL of ice-cold H<sub>2</sub>O for red blood cell lysis to occur. After 20 seconds, 4 mL of ice-cold 0.6 M KCl is added. Samples are mixed carefully and centrifuged for 6 min at 1300 rpm, 4°C. The supernatant is discarded and the cell pellet is resuspended in 4 mL of DPBS and layered over 5 mL of Lymphoprep (Axis Shield, Cat. N°.: 1114544) in a 15 mL centrifuge tube. After centrifugation for 30 min at 1500 rpm, 4°C, the supernatant is removed and the cell pellet, containing the neutrophils, is resuspended in 5 mL chemotaxis buffer (RPMI 1640 medium, supplemented with 10 mM HEPES; freshly made for each experiment).

10

#### 2.2.2. *Migration assay*

[00473] A cell suspension of  $8.9 \times 10^6$  cells per milliliter is prepared. 10  $\mu$ L of compound solution in chemotaxis buffer is added to 90  $\mu$ L cell suspension. The mixture is incubated at 37°C for 30 min with intermediate resuspension of the cells after 15 min. Following this, 75  $\mu$ L cell suspension is transferred to the upper compartment of a Corning HTS transwell 96 permeable support system with 5.0  $\mu$ m pore size polycarbonate membrane (Corning, Cat.N°.: 3387). The receiver well of the transwell system is then filled with 200  $\mu$ L chemotaxis buffer containing compound and chemotactic agent (embelin). After incubation at 37°C in 5% CO<sub>2</sub> for 1 h, the upper plate of the transwell system is removed and 70  $\mu$ L Cell Titer Glow Substrate (Promega, Cat.N°.: G755B) are added in the receiver plate. The receiver plate is incubated for 10 min in the dark, while shaking. 180  $\mu$ L of cell lysate is then transferred to a white 96-well plate and luminescence is measured. The detected luminescent signal is considered as linearly related to the number of cells having migrated from the upper well to the receiver well.

20

25

### 3. ADME, PK and Safety Models

30

#### 3.1 *Aqueous Solubility*

[00474] Starting from a 10mM stock in DMSO, a serial dilution of the compound is prepared in DMSO. The dilution series is transferred to a 96 NUNC Maxisorb plate F-bottom and 0.1M phosphate buffer pH 7.4 or 0.1M citrate buffer pH3.0 at room temperature is added.

[00475] The final concentrations range from 18.75 to 300  $\mu\text{M}$  in 5 equal dilution steps. The final DMSO concentration does not exceed 3%.

[00476] 200 $\mu\text{M}$  Pyrene is added to the corner points of each 96 well plate and serves as a reference point for calibration of Z-axis on the microscope.

5 [00477] The assay plates are sealed and incubated for 1 h at 37°C while shaking at 230rpm. The plates are then scanned under a white light microscope, yielding individual pictures of the precipitate per concentration. The precipitate is analyzed and converted into a number by a custom-developed software tool. The first concentration at which the compound appears completely dissolved is the concentration reported, however the true concentration lies somewhere between this concentration and one dilution step higher.

10 [00478] Solubility values are reported in  $\mu\text{M}$  and in  $\mu\text{g/mL}$ .

### 3.2. *Thermodynamic solubility*

[00479] Two individual solutions of 2 mg/mL of compound are prepared in a 0.1 M phosphate buffer pH 7.4 or a 0.1 M citrate buffer pH 3.0 at room temperature in a 2mL glass vial.

15 [00480] After addition of a magnetic stir, the samples are stirred at room temperature for 24 h.

[00481] After 24 h, the vials are centrifuged 10 min at 1400 rpm. The supernatant of the sample is then transferred to a MultiscreenR Solubility Plate (Millipore, MSSLBPC50) and filtered (10-12" Hg) with the aid of a vacuum manifold into a clean Greiner polypropylene V-bottom 96 well plate. Per sample, two dilutions (factor 10 and 100) are made in DMSO. Other dilutions can be made if the acquired peak area is not within the standard curve.

20 [00482] A 10mM DMSO stock, made from dry matter, is used to make a 200 $\mu\text{g/mL}$  working stock. The standard curve for the compound is prepared in DMSO starting from the 200 $\mu\text{g/mL}$  working stock. Eight concentrations and two quality control samples (QC) are made in 2mL tubes. The first 3 concentrations (50, 35 and 15 $\mu\text{g/mL}$ ) and the first QC sample (20 $\mu\text{g/mL}$ ) are made starting with the 200 $\mu\text{g/mL}$  working stock. 25 The 4<sup>th</sup> concentration (5 $\mu\text{g/mL}$ ) is made with the 50 $\mu\text{g/mL}$  solution and the 5<sup>th</sup> concentration (1 $\mu\text{g/mL}$ ) with the 15 $\mu\text{g/mL}$ . The last three concentrations (0.2, 0.1 and 0.05 $\mu\text{g/mL}$ ) are made with the 1 $\mu\text{g/mL}$  solution. The second QC sample (0.5 $\mu\text{g/mL}$ ) is made with the first QC sample.

[00483] Of every step of the dilution series, quality control and sample dilutions, a volume is transferred to a 96-well Deepwell plate. The samples are injected on a LC-MS/MS system (API2000 from Applied Biosystems).

30 [00484] The samples are analyzed on LC-MS/MS with a flow rate of 0.5mL/min. Solvent A is 0.1% Formic Acid in water and solvent B is 0.1% Formic Acid in methanol. The sample is run under positive ion spray on a Pursuit 5 C18 2.0mm column (Varian). The solvent gradient has a total run time of 1.4 min and ranges from 10% B to 100% B.

[00485] The thermodynamic solubility samples are analyzed with the aid of QuanLynx software. For the standard curve a linear or quadratic curve can be used in the analysis. Samples of the standard curve that have more than 15% deviation are excluded; the lowest concentrations of the curve may vary up to 20%. Peak areas of the samples are plotted against the standard curve to obtain the solubility of the compound.

5 [00486] Solubility values are reported in  $\mu\text{M}$  or  $\mu\text{g/mL}$ .

### 3.3 *Microsomal stability*

[00487] A 10 mM stock solution of compound in DMSO is 1,668 fold diluted in a 105 mM phosphate buffer pH 7.4. Of this compound dilution, 50  $\mu\text{L}$  is transferred in two 96 assay plates: one for time point 0 min (T0 plate) and one for time point 30 min (T30 plate) and pre-warmed at 37°C.

[00488] In the time zero reference sample (T0 plate), 100  $\mu\text{L}$  MeOH (1:1) is added to the wells. In each assay plate (T0 and T30 min), 50  $\mu\text{L}$  of microsomal mix is then added.

[00489] Final reaction concentrations are: 3  $\mu\text{M}$  compound, 0.5 mg/mL microsomes, 0.4 U/mL GDPDH, 3.3 mM  $\text{MgCl}_2$ , 3.3 mM glucose-6-phosphate and 1.3 mM  $\text{NADP}^+$ .

15 [00490] The T30 plate is incubated at 37°C, 300 rpm and after 30 min of incubation the reaction is stopped with MeOH (1:1). The samples are mixed, centrifuged and the supernatant is harvested for analysis on LC-MS/MS (API2000 from Applied Biosystems).

[00491] The samples are analyzed on LC-MS/MS with a flow rate of 0.5 mL/min. Solvent A is 0.1% Formic Acid in water and solvent B is 0.1% Formic Acid in methanol. The sample is run under positive ion spray on a Pursuit 5 C18 2.0mm column (Varian). The solvent gradient has a total run time of 1.4 min and ranges from 10% B to 100% B. Peak area from the parent compound at time 0 is considered to be 100% remaining. The percentage remaining after 30 min incubation is calculated from time 0. The solubility of the compound in the final test concentration in buffer is inspected by microscope and results are also reported.

### 25 3.4 *Hepatocyte stability.*

[00492] Test compounds (1  $\mu\text{M}$  initial concentration,  $n=2$ ) are incubated in Williams' Medium E, containing 4 mM L-glutamine and 2 mM magnesium sulphate, with pooled cryopreserved hepatocytes (Celsis International) in suspension at cell densities of 0.25-0.5 million viable cells/mL. The incubations are performed at 37°C in a shaking water bath with 100  $\mu\text{L}$  samples taken from the incubation at 0, 10, 20, 45 and 90 min, and reactions terminated by addition of 100  $\mu\text{L}$  of acetonitrile containing carbamazepine as analytical internal standard. Samples are centrifuged and the supernatant fractions analysed by LC-MS/MS. The instrument responses (*i.e.* peak heights) are referenced to the zero time-point samples (as 100%) in order to determine the percentage of compound remaining. Ln plots of the % remaining for each compound are used to determine the half-life for the hepatocyte incubations. Half-life values are calculated from the

relationship:  $T_{1/2}$  (min) =  $-0.693/\lambda$ , where  $\lambda$  is the slope of the Ln concentration vs time curve. Standard compounds testosterone, midazolam, and 4-methylumbelliferone are included in the assay design.

### 3.5 Plasma Protein Binding (Equilibrium Dialysis)

5 [00493] A 10mM stock solution of the compound in DMSO is diluted with a factor 10 in DMSO. This solution is further diluted in freshly thawed human, rat, mouse or dog plasma (BioReclamation INC) with a final concentration of 5 $\mu$ M and final DMSO concentration of 0.5%.

[00494] A Pierce Red Device plate with inserts (ThermoScientific) is prepared and filled with 450 $\mu$ L PBS in the buffer chamber and 300 $\mu$ L of the spiked plasma in the plasma chamber. The plate is incubated for 4 h  
10 at 37°C while shaking at 100rpm. After incubation, 120 $\mu$ L of both chambers is transferred to 480 $\mu$ L methanol in a 96-well round bottom, PP deep-well plates (Nunc) and sealed with an aluminum foil lid. The samples are mixed and immediately centrifuged 30 min at 1400 rcf at 4°C and the supernatant is transferred to a 96 v-bottom PP plate (Greiner, 651201) for analysis on LC-MS/MS (API2000 from Applied Biosystems).

15 [00495] The samples are analyzed on LC-MS/MS with a flow rate of 0.5mL/min. Solvent A is 0.1% Formic Acid in water and solvent B is 0.1% Formic Acid in methanol. The sample is run under positive ion spray on a Pursuit 5 C18 2.0mm column (Varian). The solvent gradient has a total run time of 1.4 min and ranges from 10% B to 100% B.

[00496] Peak area from the compound in the buffer chamber and the plasma chamber are considered to be  
20 100% compound. The percentage bound to plasma is derived from these results and is reported as percentage bound to plasma.

[00497] The solubility of the compound in the final test concentration in PBS is inspected by microscope to indicate whether precipitation is observed or not.

### 3.6 Caco2 Permeability

25 [00498] Bi-directional Caco-2 assays are performed as described below. Caco-2 cells are obtained from European Collection of Cell Cultures (ECACC, cat 86010202) and used after a 21 day cell culture in 24-well Transwell plates (Corning, cell growth area: 0.33 cm<sup>2</sup>, Membrane pore size: 0.4  $\mu$ M, membrane diameter: 6.5 mm)..

30 [00499]  $2 \times 10^5$  cells/well are seeded in plating medium consisting of DMEM + GlutaMAX™-I + 1% NEAA + 10% FBS (FetalClone II) + 1% Pen/Strep. The medium is changed every 2 – 3 days.

[00500] Test and reference compounds (propranolol and rhodamine123 or vinblastine, all purchased from Sigma) are prepared in Hanks' Balanced Salt Solution containing 25 mM HEPES (pH7.4) and added to either the apical (125 $\mu$ L) or basolateral (600 $\mu$ L) chambers of the Transwell plate assembly at a concentration of 10  
35  $\mu$ M with a final DMSO concentration of 0.25%.

[00501] 50µM Lucifer Yellow (Sigma) is added to the donor buffer in all wells to assess integrity of the cell layers by monitoring Lucifer Yellow permeation. As Lucifer Yellow (LY) cannot freely permeate lipophilic barriers, a high degree of LY transport indicates poor integrity of the cell layer.

[00502] After a 1 h incubation at 37°C while shaking at an orbital shaker at 150rpm, 70 µL aliquots are taken from both apical (A) and basal (B) chambers and added to 100µL 50:50 acetonitrile:water solution containing analytical internal standard (0.5µM carbamazepine) in a 96 well plate.

[00503] Lucifer yellow is measured with a Spectramax Gemini XS (Ex 426nm and Em 538nm) in a clean 96 well plate containing 150µL of liquid from basolateral and apical side.

[00504] Concentrations of compound in the samples are measured by high performance liquid-chromatography/mass spectroscopy (LC-MS/MS).

[00505] Apparent permeability ( $P_{app}$ ) values are calculated from the relationship:

$$P_{app} = [\text{compound}]_{\text{acceptor final}} \times V_{\text{acceptor}} / ([\text{compound}]_{\text{donor initial}} \times V_{\text{donor}}) / T_{\text{inc}} \times V_{\text{donor}} / \text{surface area} \times 60 \times 10^{-6} \text{ cm/s}$$

V = chamber volume

$T_{\text{inc}}$  = incubation time.

Surface area = 0.33cm<sup>2</sup>

[00506] The Efflux ratios, as an indication of active efflux from the apical cell surface, are calculated using the ratio of  $P_{app} B>A / P_{app} A>B$ .

[00507] The following assay acceptance criteria are used:

Propranolol:  $P_{app} (A>B)$  value  $\geq 20(\times 10^{-6} \text{ cm/s})$

Rhodamine 123 or Vinblastine:  $P_{app} (A>B)$  value  $< 5 (\times 10^{-6} \text{ cm/s})$  with Efflux ratio  $\geq 5$ .

Lucifer yellow permeability:  $\leq 100 \text{ nm/s}$

### 3.7 Liability for QT prolongation

[00508] Potential for QT prolongation is assessed in the hERG manual patch clamp assay.

#### 3.7.1 Conventional whole-cell patch-clamp

[00509] Whole-cell patch-clamp recordings are performed using an EPC10 amplifier controlled by Pulse v8.77 software (HEKA). Series resistance is typically less than 10 MΩ and compensated by greater than 60%, recordings are not leak subtracted. Electrodes are manufactured from GC150TF pipette glass (Harvard).

[00510] The external bathing solution contains: 135 mM NaCl, 5 mM KCl, 1.8 mM CaCl<sub>2</sub>, 5 mM Glucose, 10 mM HEPES, pH 7.4.

[00511] The internal patch pipette solution contains: 100mM Kgluconate, 20 mM KCl, 1mM CaCl<sub>2</sub>, 1 mM MgCl<sub>2</sub>, 5mM Na<sub>2</sub>ATP, 2mM Glutathione, 11 mM EGTA, 10 mM HEPES, pH 7.2.

[00512] Drugs are perfused using a Biologic MEV-9/EVH-9 rapid perfusion system.

[00513] All recordings are performed on HEK293 cells stably expressing hERG channels. Cells are cultured on 12 mm round coverslips (German glass, Bellco) anchored in the recording chamber using two platinum rods (Goodfellow). hERG currents are evoked using an activating pulse to +40 mV for 1000 ms followed by a tail current pulse to -50 mV for 2000 ms, holding potential is -80 mV. Pulses are applied every 20s and all experiments are performed at room temperature.

### 3.7.2 Data Analysis

[00514] IC<sub>50</sub> values are calculated for each compound tested. The fold difference between the IC<sub>50</sub> in the manual hERG patch clamp and the unbound IC<sub>50</sub> in the whole blood assay is calculated.

[00515] For the concentration response curves, peak tail current amplitude is measured during the voltage step to -50 mV. Curve-fitting of concentration-response data is performed using the equation:

$$y = a + [(b - a) / (1 + 10^{-(\log c - x) d})]$$

[00516] where a is minimum response, b is maximum response and d is Hill slope, this equation can be used to calculate both IC<sub>50</sub> (where y = 50 and c is the IC<sub>50</sub> value) and IC<sub>20</sub> (where y = 20 and c is the IC<sub>20</sub> value). GraphPad® Prism® (Graphpad® Software Inc.) software is used for all curve fitting. A difference of 100 fold or greater indicates a low potential for QT prolongation.

## 3.8 Pharmacokinetic study

### 3.8.1 Single dose pharmacokinetic study in rats

[00517] Compounds are formulated in PEG200/physiological saline mixtures for the intravenous route and in PEG400/0.5% methylcellulose (10/90 v/v) for the oral route. Test compounds are orally dosed as a single esophageal gavage at 5-10 mg/kg and intravenously dosed as a bolus via the caudal vein at 1 mg/kg to male Sprague-Dawley rats. Each group consists of 3 rats. Blood samples are collected either via the jugular vein using cannulated rats or at the retro-orbital sinus with lithium heparin as anti-coagulant at the time points in the following range: 0.05 to 8 h (intravenous route), and 0.25 to 6 or 24 h (oral route). Whole blood samples are centrifuged at 5000 rpm for 10 min and the resulting plasma samples are stored at -20°C pending analysis.

### 3.8.2 Multiple dose pharmacokinetic study in rats

[00518] Compounds are formulated in PEG400/0.5% methylcellulose (10/90 v/v) for the oral route. Test compounds are orally dosed as an esophageal daily gavage at 30 or 300 mg/kg to male Sprague-Dawley rats for 14 days. Each group consists of 3 rats. Blood samples are collected via the tail vein with lithium heparin as anti-coagulant at the following time points on day 1, 7 and 14: 0.25, 1, 4, 8 and 24 h. In addition, on day 2



blood samples are taken at 0.25, 1 and 4 h and at day 4 and 11 at 0.25 h. Whole blood samples are centrifuged at 5000 rpm for 10 min and the resulting plasma samples are stored at -20°C pending analysis.

### 3.8.3 *Quantification of compound levels in plasma*

5 [00519] Plasma concentrations of each test compound are determined by an LC-MS/MS method in which the mass spectrometer is operated in positive or negative electrospray mode.

### 3.8.4 *Determination of pharmacokinetic parameters*

[00520] Pharmacokinetic parameters are calculated using Winnonlin® (Pharsight®, US).

10

## 3.9 *7-Day rat toxicity study*

[00521] A 7-day oral toxicity study with test compounds is performed in Sprague-Dawley male rats to assess their toxic potential and toxicokinetics, at daily doses of 100, 300 and 1000 mg/kg/day, by gavage, at the constant dosage-volume of 10 mL/kg/day.

15 [00522] The test compounds are formulated in PEG400/0.5% methylcellulose (10/90, v/v). Each group includes 6 principal male rats as well as 3 satellite animals for toxicokinetics. A fourth group is given PEG400/0.5% methylcellulose (10/90, v/v) only, at the same frequency, dosage volume and by the same route of administration, and acts as the vehicle control group.

[00523] The goal of the study is to determine the lowest dose that results in no adverse events being  
20 identified (no observable adverse effect level - NOAEL).

## 3.10 *Cytochrome P450 inhibition*

[00524] Reversible CYP inhibition and time-dependent CYP3A4 inhibition is determined in human liver microsomes and specific probe substrates.

25

### 3.10.1 *P450 inhibition in human liver microsomes, reversible inhibition*

[00525] The inhibitory potential of a test compound is assessed for human cytochrome P450 isoenzymes CYP1A2, 2C8, 2C9, 2C19, 2D6 and 3A4.

[00526] A 10 mM stock solution of the test compound is prepared in DMSO, serially diluted in Tris buffer  
30 (100 mM pH 7.4) and added to hepatic microsomes (Xenotech LLC) and NADPH at 37°C in a shaking water bath. Seven different test compounds concentrations (0.05 to 100 µM), 1% DMSO and 1 mM NADPH are obtained to react.

[00527] After 15 or 30 min reactions are terminated by addition of 100 µL of acetonitrile containing carbamazepine as analytical internal standard. Samples are centrifuged and the supernatant fractions  
35 analysed by LC-MS/MS. For each isoform, the instrument responses (peak heights) are referenced to those

for DMSO controls (considered as 100%) in order to determine the percentage reduction in probe metabolism, using midazolam and testosterone as probe substrate. Percentage inhibition of probe metabolism and Log [test compound concentration] are plotted using Graphpad Prism software. The sigmoidal dose response model is fitted to the data in order to determine the IC<sub>50</sub>.

5 [00528] Inhibition of CYP3A4 using nifedipine and atorvastatin as probe substrate is carried out as follows.

[00529] A 1.67 mM stock solution of test compound is prepared in methanol, serially diluted 1:3 in 50 mM potassium phosphate buffer pH7.4 and added to human hepatic microsomes (BD Gentest) and probe substrate. Seven different test compounds concentrations (0.045 - 33.3 µM), 2% methanol, 0.1 mg/mL  
10 microsomes, 10 µM atorvastatin or 5 µM nifedipine. After pre-warming 5 min at 37°C, the reaction was started by adding cofactor mix (7.65 mg/mL glucose-6-phosphate, 1.7 mg/mL NADP, 6U/mL of glucose-6-phosphate dehydrogenase).

[00530] After 5 min (nifedipine) or 10 min (atorvastatin) at 37°C, the reaction (50 µL) is terminated with 150 µL acetonitrile:methanol (2:1) solution with internal standard (Warfarin). Samples are centrifuged and  
15 the supernatant fractions analyzed by LC-MS/MS. The instrument responses (ratio of test compound/internal standard peak areas) are referenced to those for solvent controls (assumed as 100%) in order to determine the percentage reduction in probe metabolism. Percent of control activity vs concentration plots are generated and fitted using GraphPad Prism software to generate IC<sub>50</sub>.

### 20 3.10.2 CYP3A4 inhibition in human liver microsomes, time-dependent

[00531] The time-dependent inhibitory potential of a test compound is assessed for human cytochrome P450 isoenzyme 3A4. The compound is pre-incubated with the human liver microsomes before addition of the probe substrates. The result is compared to the condition where the compound is not pre-incubated with the human liver microsomes to see if there was a shift in IC<sub>50</sub>, indicating time-dependent inhibition.

25 [00532] A 10 mM stock solution of test compound is prepared in DMSO and diluted 1:20 with Tris buffer (100 mM pH 7.4) and further serially diluted in Tris buffer/5% DMSO,

[00533] The cofactor, NADPH, and each test compound dilution is mixed in two separate plates for 0 and 30 min pre-incubation. Human hepatic microsomes (Xenotech LLC) are added only to the “30 min pre-incubation” plate and both plates are then incubated for 30 min at 37°C in a shaking water bath. Following  
30 the pre-incubation, microsomes are added to the “0 min” plate and appropriate probe substrates (in 0.5% DMSO) are added to both plates. Plates are then returned to the water bath for a further incubation.

[00534] In total, six different test compound concentrations (1.6 to 50 µM) are assessed. Reactions are terminated with 100 µL of acetonitrile containing carbamazepine as analytical internal standard. Samples are centrifuged and the supernatant fractions analysed by LC- MS/MS. For each isoform, the instrument  
35 responses (peak height ratio with internal standard) are referenced to those for DMSO controls (considered as

100%) in order to determine the percentage reduction in probe metabolism. Percentage inhibition of probe metabolism and Log [Test Compound concentration] are plotted using Graphpad Prism software. The sigmoidal dose response model is fitted to the data in order to determine the IC<sub>50</sub>.

#### 4. *In-vivo* studies

[00535] The *in-vivo* activity of the compounds of the invention may be demonstrated in the following *in vivo* efficacy inflammation models.

##### 4.1 *Inflammatory bowel disease (mice).*

[00536] The mouse chronic DSS-induced inflammatory bowel disease model (IBD) is a well validated disease model for inflammatory bowel disease (Wirtz S. *et al.*, 2007 Nature Protocols 2, 541-546; Sina *et al.*, 2009 J. Immunol. 183 7514-7522).

[00537] To induce a chronic colitis, female BALB/c mice are fed with 4% dextran sodium sulfate (DSS) dissolved in drinking water for 4 days, followed by 3 days of regular drinking water. This cycle is repeated three times. This protocol allows inducing a strong colitis while avoiding high mortality rates. Animals are divided into several groups:

- a. intact water; vehicle alone, n=10),
- b. diseased (DSS; vehicle alone, n=10),
- c. sulfasalazine used as reference (DSS; 20 mg/kg/day, *p.o.*, n=10) and
- d. the tested compound (DSS; 1, 3, 10, 30 mg/kg/day, *p.o.*, n=10).

[00538] Clinical parameters are measured every other day. The disease activity index (DAI) is a composite measure combining of the individual scores for weight loss, stool consistency and rectal bleeding. Mice are sacrificed at day 20 of the experiment according to the protocol introduced by Sina *et al.* (2009). At sacrifice time, the complete colon is removed and rinsed with sterile PBS. Segments of the distal colon are dissected for histological analysis, gene expression and protein level measurement.

##### 4.2 *Collagen-induced arthritis (mice).*

[00539] The mouse collagen-induced arthritis (CIA) is the gold standard rheumatoid arthritis model (Brand, *et al.*, 2007 Nature Protocols 2, 1269- 1275, Lin *et al.*, 2007 Br J Pharmacol 1, 829-831). DBA1//J male mice are injected with a collagen II solution (Completed Freund's adjuvant). Immune reaction is boosted by a second injection (incomplete Freund's adjuvant) 21 days later. At day 31, arthritis is scored according to the method of Khachigian *et al.* (Khachigian *et al.*, 2006 Nature Protocols 1, 2512-2516) and animals are randomized to reach an average clinical score of 2 per group. Animals are divided into several groups: intact (no treatment, n=5), diseased (vehicle alone, n=10), Enbrel® as reference (10 mg/kg, 3x week.,

*i.p.*, n=10), and the tested compound (3, 10 or 30 mg/kg/day, *p.o.*, n=10). Therapeutic dosing lasted from day 31 to day 46 and the arthritis is scored every day. Mice are sacrificed at day 46, X-ray photos are taken of the hind paws of each individual animal and the severity of bone erosion is ranked with the radiological Larsen's score (Salvemini *et al.*, 2001 Arthritis Rheum 44, 2909-2921).

5

#### 4.3 Tobacco smoke model (mice)

[00540] Daily exposures of female inbred C57BL/6J mice to tobacco smoke (TS) for 11 consecutive days result in pulmonary inflammation, as indicated by an increase in the total number of cells recovered in the bronchoalveolar lavage (BAL), when compared with a similarly treated air-exposed group, 24 h after the final exposure. The exposure period to TS is increased initially from 25 min at the start of the study (day 1) to a maximum of 45 min on day 3 until day 11. Animals are divided into several groups: intact (no treatment, n=5), diseased (vehicle alone, n=10), Roflumilast as reference (5 mg/kg/day *p.o.*, n=10), and the tested compounds (10 or 30 mg/kg/bid, *p.o.*, n=10). At the end of 11 days, the numbers of macrophages, epithelial cells, neutrophils and lymphocytes are counted in the BAL. BAL is further analysed for gene expression and protein level. Lung tissue is dissected for histological analysis, gene expression and protein level measurement.

[00541] It will be appreciated by those skilled in the art that the foregoing descriptions are exemplary and explanatory in nature, and intended to illustrate the invention and its preferred embodiments. Through routine experimentation, an artisan will recognise apparent modifications and variations that may be made without departing from the spirit of the invention. All such modifications coming within the scope of the appended claims are intended to be included therein. Thus, the invention is intended to be defined not by the above description, but by the following claims and their equivalents.

[00542] All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

[00543] It should be understood that factors such as the differential cell penetration capacity of the various compounds can contribute to discrepancies between the activity of the compounds in the *in vitro* biochemical and cellular assays.

[00544] At least some of the chemical names of compound of the invention as given and set forth in this application, may have been generated on an automated basis by use of a commercially available chemical naming software program, and have not been independently verified. Representative programs performing this function include the Lexichem naming tool sold by Open Eye Software, Inc. and the Autonom Software tool sold by MDL, Inc. In the instance where the indicated chemical name and the depicted structure differ, the depicted structure will control.

**[00545]** Chemical structures shown herein were prepared using either ChemDraw® or ISIS® /DRAW. Any open valency appearing on a carbon, oxygen or nitrogen atom in the structures herein indicates the presence of a hydrogen atom. Where a chiral center exists in a structure but no specific stereochemistry is shown for the chiral center, both enantiomers associated with the chiral structure are encompassed by the structure.

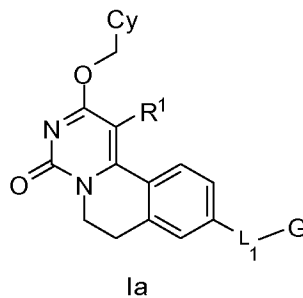
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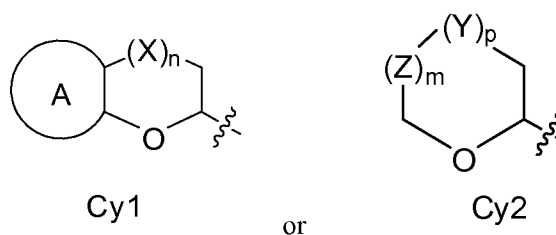
**WHAT IS CLAIMED:**

1. A compound according to Formula Ia:



wherein

- 5 Cy is



wherein

X is O or S;

Y is -CH<sub>2</sub>-, or S;

- 10 Z is -CH<sub>2</sub>-;

each of the subscript n, m, or p is independently selected from 0, and 1; and A is phenyl, or 5-6-membered heteroaryl comprising one or two N-atoms; optionally substituted with one or more independently selected R<sup>5</sup> groups;

- 15 any one of Cy1 and Cy2 is optionally substituted by one or more independently selected C<sub>1-4</sub> alkyl groups;

R<sup>1</sup> is H, Me, or halo;

L<sub>1</sub> is absent or is -O-, -S-, or -NR<sup>4a</sup>-;

G is

R<sup>2</sup>,

-W-L<sub>2</sub>-R<sup>2</sup>, or

-W-L<sub>3</sub>-R<sup>3</sup>

W is C<sub>1-4</sub> alkylene, C<sub>2-4</sub> alkenylene having one double bond, or C<sub>2-4</sub> alkynylene having one triple bond;

5 L<sub>2</sub> is absent or is -O-;

R<sup>2</sup> is

- H,

- C<sub>1-8</sub> alkyl optionally substituted with one to three groups independently selected from

o OH,

10 o halo,

o CN,

o C<sub>1-6</sub> alkoxy,

o C<sub>3-7</sub> cycloalkyl,

15 o 4-6 membered heterocycloalkyl (comprising one to three heteroatoms independently selected from S, and O),

o 5-6 membered heteroaryl (comprising one to three heteroatoms independently selected from N, S, and O), and

o phenyl,

- C<sub>4-7</sub> cycloalkenyl comprising one double bond,

20 - 5-7 membered heterocycloalkenyl comprising one double bond, and one to three heteroatoms independently selected from O, and S,

- C<sub>3-7</sub> cycloalkyl (optionally substituted with one or more independently selected R<sup>6</sup> groups),

- 4-10 membered heterocycloalkyl comprising one to two heteroatoms independently selected from S, and O, (optionally substituted with one to three independently selected R<sup>6</sup> groups),

25 - 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O (optionally substituted with one to three independently selected R<sup>7</sup> groups), or

- C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>7</sup> groups);

L<sub>3</sub> is -NR<sup>4b</sup>-;

R<sup>3</sup> is

30 - C<sub>1-4</sub> alkyl substituted with C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>8</sup> groups), or 5-10 membered heteroaryl (optionally substituted with one or more



independently selected R<sup>8</sup> groups) comprising one to three heteroatoms independently selected from N, S, and O ,

- 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, (optionally substituted with one or more independently selected R<sup>8</sup> groups), or
- C<sub>6-10</sub> aryl (optionally substituted with one or more independently selected R<sup>8</sup> groups);

Each R<sup>4a</sup> and R<sup>4b</sup> is independently selected from H, C<sub>1-4</sub> alkyl, and C<sub>3-7</sub> cycloalkyl;

R<sup>5</sup> is halo, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy;

R<sup>6</sup> is oxo or R<sup>7</sup>;

R<sup>7</sup> is

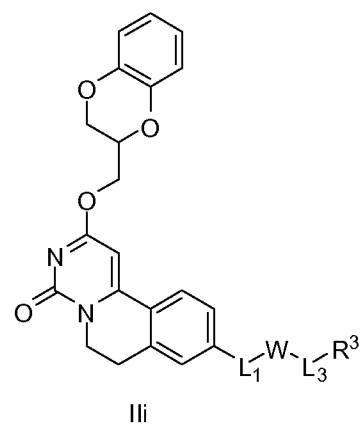
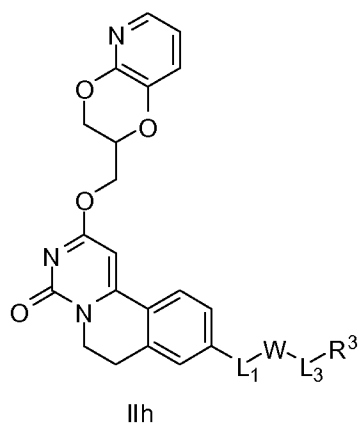
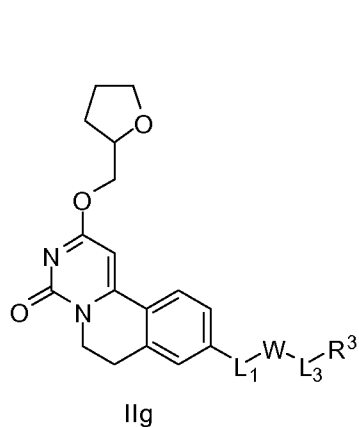
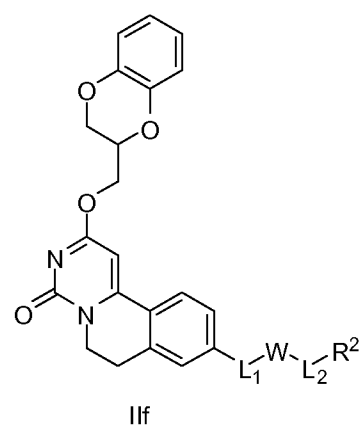
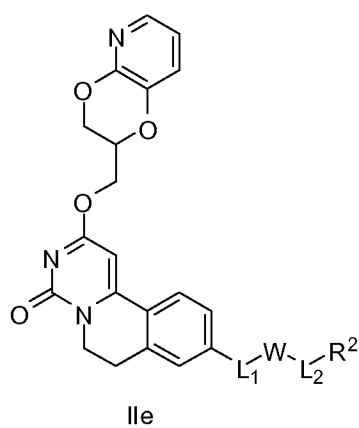
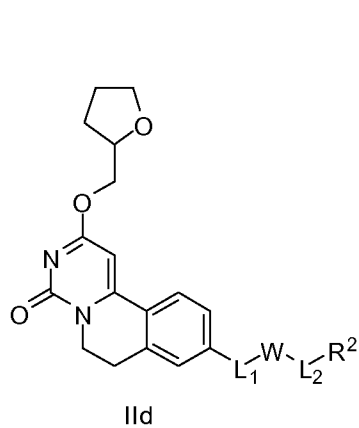
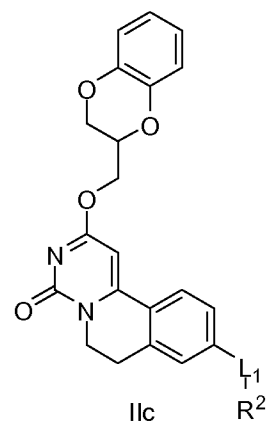
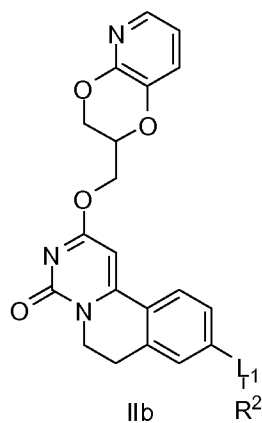
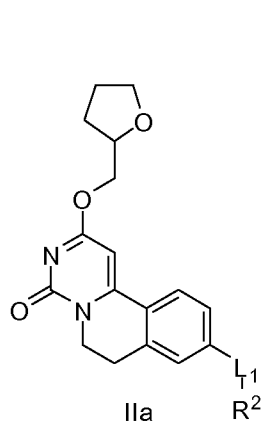
- OH,
- halo,
- -NO<sub>2</sub>,
- C<sub>1-6</sub> alkyl (optionally substituted with one to three groups independently selected from halo, and OH),
- C<sub>1-6</sub> alkoxy (optionally substituted with one to three groups independently selected from halo, and OH),
- C<sub>3-7</sub> cycloalkyl,
- -C(=O)OR<sup>9</sup>,
- -C(=O)NR<sup>10</sup>R<sup>11</sup>,
- -NHC(=O)-C<sub>1-4</sub> alkyl,
- -CN,
- phenyl,
- -O-phenyl,
- 4-7 membered heterocycloalkyl comprising one to three heteroatoms independently selected from N, O, and S, or
- 5-6 membered heteroaryl comprising one to three heteroatoms independently selected from N, O, and S; (optionally substituted with one or more independently selected C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, CN, halo, and -C(=O)OR<sup>12</sup>);

R<sup>8</sup> is C<sub>1-4</sub> alkyl, or halo;

each of R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup>, is independently selected from H and C<sub>1-4</sub> alkyl, or

a pharmaceutically acceptable salt, or a solvate, or a solvate of the pharmaceutically acceptable salts.

2. A compound or pharmaceutically acceptable salt thereof, according to claim 1, wherein  $R^1$  is H.
3. A compound or pharmaceutically acceptable salt thereof, according to claim 1, wherein the compound is according to Formula IIa-IIIi:



wherein  $L_1$ , W,  $L_2$ ,  $R^2$ ,  $L_3$  and  $R^3$  are as described in claim 1.

4. A compound or pharmaceutically acceptable salt thereof, according to claim 3, wherein the compound is according to Formula IIa-IIf, and wherein  $L_1$  is absent.
5. A compound or pharmaceutically acceptable salt thereof, according to claim 3, wherein the compound is according to Formula IIc-IIf, and wherein  $L_1$  is absent, or is  $-O-$ ; W is  $C_{1-4}$  alkylene, or  $C_{2-4}$  alkenylene having one double bond.
6. A compound or pharmaceutically acceptable salt thereof, according to claim 3, wherein the compound is according to Formula IIc-IIf, and wherein  $L_1$  is absent; W is  $C_{2-4}$  alkynylene having one triple bond.
7. A compound or pharmaceutically acceptable salt thereof, according to claims 5 or 6, wherein the compound is according to Formula IIc-IIf, and wherein  $L_2$  is absent or is  $-O-$ .
8. A compound or pharmaceutically acceptable salt thereof, according to claim 4, wherein the compound is according to Formula IIc-IIf, and wherein  $-L_1-W-L_2-$  is selected from  $-CH_2-CH_2-$ ,  $-O-CH_2-$ ,  $-O-CH_2-CH_2-$ ,  $-O-CH_2-CH_2-O-$ ,  $-C\equiv C-$ , and  $-C\equiv C-CH_2-$ .
9. A compound or pharmaceutically acceptable salt thereof, according to any one of claims 2 or 3-8, wherein  $R^2$  is 5-10 membered heteroaryl comprising one to three heteroatoms independently selected from N, S, and O, or  $C_{6-10}$  aryl each of which is optionally substituted with one to three independently selected  $R^7$  groups.
10. A compound or pharmaceutically acceptable salt thereof, according to claim 9, wherein each  $R^7$  group is independently selected from halo, CN,  $C_{1-6}$  alkyl,  $-CF_3$ ,  $-NH_2$  (optionally substituted with one or two independently selected  $C_{1-4}$  alkyl, and  $-C(=O)-C_{1-4}$  alkyl),  $-C(=O)NH_2$  (optionally substituted with one or two independently selected  $C_{1-4}$  alkyl),  $C_{3-7}$  cycloalkyl and 4-7 membered heterocycloalkyl comprising one to three heteroatoms independently selected from N, O, and S).
11. A compound or pharmaceutically acceptable salt thereof, according to any one of claims 3-8 wherein  $R^2$  is  $C_{1-6}$  alkyl optionally substituted with one to three groups independently selected from OH, halo, CN, phenyl,  $C_{1-6}$  alkoxy, and  $C_{3-7}$  cycloalkyl.
12. A compound or pharmaceutically acceptable salt thereof, according to any one of claims 3-8, wherein  $R^2$  is  $C_{3-7}$  cycloalkyl.
13. A compound or pharmaceutically acceptable salt thereof, according to any one of claims 3-8, wherein  $R^2$  is 4-10 membered heterocycloalkyl comprising one to three heteroatoms independently selected from N, S, and O; optionally substituted with one to three independently selected  $R^6$  groups.
14. A compound or pharmaceutically acceptable salt thereof, according to claim 13, wherein each  $R^6$  group is independently selected from oxo and  $R^7$ ; wherein  $R^7$  is OH, or  $C_{1-6}$  alkyl.
15. A compound or pharmaceutically acceptable salt thereof, according to claim 1, wherein the compound is selected from:

9-Methoxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

2-(Chroman-2-ylmethoxy)-9-methoxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-methoxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-Allyloxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-benzofuran-2-ylmethoxy)-9-methoxy-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
5 9-Hydroxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-Benzylloxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-(Pyridin-3-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-  
10 acetonitrile,  
9-Butoxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-Cyclopropylmethoxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-Phenethyloxy-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
15 9-(Pyridin-4-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-(Pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-(Pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
20 9-(2-Phenoxy-ethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-Methoxy-2-(tetrahydro-pyran-4-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-Methoxy-2-(tetrahydro-pyran-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
25 9-Methoxy-2-(tetrahydro-pyran-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-benzonitrile,  
4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-benzonitrile,  
30 9-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
3-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-benzonitrile,  
35

2-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-  
yloxymethyl]-benzonitrile,  
9-(4-Chloro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-  
one,  
5 9-(3-Chloro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-  
one,  
9-(2-Chloro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-  
one,  
9-(4-Fluoro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-  
10 one,  
9-(2-Nitro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-  
one,  
4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-  
yloxymethyl]-benzoic acid methyl ester,  
15 3-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-  
yloxymethyl]-benzoic acid methyl ester,  
3-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-  
yloxymethyl]-benzoic acid methyl ester,  
2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-  
20 a]isoquinolin-4-one,  
[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-  
yloxy]-acetic acid tert-butyl ester,  
2,9-Bis-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-  
25 yloxy]-acetic acid,  
9-(3-Nitro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-  
one,  
9-(3-Nitro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-  
one,  
30 9-(4-Nitro-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-  
one,  
9-(3-Methyl-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-  
one,  
9-(4-Methyl-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-  
35 one,

- 9-(4-Methoxy-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(Naphthalen-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 5 9-(Naphthalen-1-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(2-Methyl-benzyloxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 10 9-[2-(2-Methoxy-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-[2-(3-Methoxy-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-[2-(4-Methoxy-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 9-[2-(2-Chloro-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-[2-(3-Chloro-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-[2-(4-Chloro-phenoxy)-ethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 20 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-morpholin-4-yl-2-oxo-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-morpholin-4-yl-2-oxo-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 25 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-morpholin-4-yl-2-oxo-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-morpholin-4-yl-2-oxo-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 30 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide,
- 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N,N-dimethyl-acetamide,
- 9-(2,2-Dimethoxy-ethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

- 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-2-methyl-propionamide,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(1,1-dimethyl-2-morpholin-4-yl-2-oxo-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 5 9-(2-Benzylloxy-ethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2,9-Bis-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(6-Phenyl-pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 10 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-[6-(1-Methyl-1H-pyrazol-4-yl)-pyridin-2-ylmethoxy]-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(6-Furan-3-yl-pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 9-(6-Pyrimidin-5-yl-pyridin-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(1-Cyclopropyl-1H-tetrazol-5-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 20 2-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide,
- N,N-Diethyl-2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide,
- N,N-Dimethyl-2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide,
- 25 N-Isopropyl-N-methyl-2-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide,
- 2-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N-phenyl-acetamide,
- 30 9-(1-Propyl-1H-tetrazol-5-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(Oxazol-2-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N,N-diethyl-acetamide,
- 35

- 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N-isopropyl-N-methyl-acetamide,
- 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-N-phenyl-acetamide,
- 5 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(1-propyl-1H-tetrazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(1-Butyl-1H-tetrazol-5-ylmethoxy)-2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 10 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-morpholin-4-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- [2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetonitrile,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(1-Cyclopropyl-1H-tetrazol-5-ylmethoxy)-2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(1H-tetrazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 20 9-Allyloxy-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- N-Benzyl-2-[2-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetamide,
- 25 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-pyrrolidin-1-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(2-piperidin-1-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(3-piperidin-1-yl-propoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 30 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-(3-dimethylamino-propoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,



- 2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-9-[3-(4-methyl-piperazin-1-yl)-propoxy]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 5 5-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxymethyl]-furan-2-carboxylic acid ethyl ester,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 10 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(5-tert-Butyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 9-(5-Phenyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- [2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetonitrile,
- [2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetonitrile,
- 20 [2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yloxy]-acetonitrile,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-morpholin-4-yl-ethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 25 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1H-tetrazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 30 9-Pyridin-3-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 3-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile,
- 9-Phenyl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-4-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
3-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile,  
5 9-(2-Methoxy-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-(3-Methoxy-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-(4-Methoxy-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
10 4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile,  
3-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzoic acid,  
15 4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzoic acid,  
9-(4-Dimethylamino-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
4-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzamide,  
20 2-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile,  
9-(1-Methyl-1H-pyrazol-4-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
25 N,N-Dimethyl-3-[4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzamide,  
9-(6-Methoxy-pyridin-3-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-(2,6-Dimethyl-phenyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
30 9-(3,5-Dimethyl-isoxazol-4-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-Naphthalen-2-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-Naphthalen-1-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
35 9-Pyrimidin-5-yl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

- 9-(5-Chloro-thiophen-2-yl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-[4-Oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-pyrrole-1-carboxylic acid tert-butyl ester,
- 5 Trifluoro-methanesulfonic acid 4-oxo-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl ester,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-methoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-Cyclopropylethynyl-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 10 9-(3,3-Dimethyl-but-1-ynyl)-2-(tetrahydro-furan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(pyridin-4-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-3-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzonitrile,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-methoxy-phenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 20 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1H-indazol-5-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyrimidin-5-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 25 3-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-benzamide,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-dimethylamino-phenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-3-ylethynyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 30 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methoxy-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(4-hydroxy-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1,5-dimethyl-1H-pyrazol-3-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methyl-[1,2,4]oxadiazol-5-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 5 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-3-methyl-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyridin-4-ylethynyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 10 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-methyl-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-methoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 9-Cyclopropylethynyl-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-Cyclopropylethynyl-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1-hydroxy-cyclopentylethynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 20 5-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-pent-4-yne nitrile,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3,3-dimethyl-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 25 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-methoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 5-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-pyridine-2-carboxylic acid methylamide,
- 30 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-furan-3-yl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-morpholin-4-ylmethyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-ylamino]-acetonitrile,  
5 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinoline-9-carbonitrile,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-[(oxazol-2-ylmethyl)-amino]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-methyl-[1,2,4]oxadiazol-3-ylmethoxy)-  
10 6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-ethyl-[1,2,4]oxadiazol-3-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-(5-Cyclopropyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
15 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(5-isopropyl-[1,2,4]oxadiazol-3-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-(5-tert-Butyl-[1,2,4]oxadiazol-3-ylmethoxy)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methyl-isoxazol-5-ylmethoxy)-6,7-  
20 dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
9-(3-Chloro-2-methoxy-pyridin-4-yl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3,6-dihydro-2H-pyran-4-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
25 5-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-pyridine-2-carbonitrile,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-ethoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-ethoxy-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
30 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(6-morpholin-4-yl-pyridin-3-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,  
2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-methoxy-pyrimidin-5-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2,3-dimethoxy-phenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2,5-dimethoxy-phenyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 5 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-3-phenyl-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 3-{3-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-prop-2-ynyloxy}-propionitrile,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methylamino-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 10 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-dimethylamino-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-[3-(Benzyl-methyl-amino)-prop-1-ynyl]-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-[3-(1,1-dioxo-thiomorpholin-4-yl)-prop-1-ynyl]-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- {3-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-prop-2-ynyl}-urea,
- 1-{3-[2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-9-yl]-prop-2-ynyl}-imidazolidine-2,4-dione,
- 20 9-(3-Diethylamino-prop-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(3-Amino-3-methyl-but-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 25 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(tetrahydro-pyran-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(1H-pyrazol-4-yl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 30 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-pent-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-hex-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

- 9-(1-Amino-cyclohexylethynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-5-methyl-hex-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 5 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-ethyl-3-hydroxy-pent-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-3-phenyl-but-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 10 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-hydroxy-4-methyl-pent-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-[(R)-1-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-yl)methoxy]-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-[(R)-1-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-yl)methoxy]-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 15 2-[(S)-1-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-yl)methoxy]-9-(oxazol-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 9-(3-Butylamino-prop-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(2-morpholin-4-yl-ethoxymethyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 20 9-(3-Benzylamino-prop-1-ynyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-phenylamino-prop-1-ynyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 25 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinoline-9-carboxylic acid (tetrahydro-pyran-4-yl)-amide,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-4-oxo-6,7-dihydro-4H-pyrimido[6,1-a]isoquinoline-9-carboxylic acid (oxetan-3-ylmethyl)-amide,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-pyrrolidin-1-ylmethyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 30 9-(tert-Butylamino-methyl)-2-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,
- 2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-piperidin-1-ylmethyl-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methyl-oxetan-3-ylmethoxymethyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(3-methyl-oxetan-3-ylmethoxymethyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

2-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-2-ylmethoxy)-9-(oxetan-3-yloxymethyl)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one,

9-Cyclopropylethynyl-2-(4-isopropyl-oxetan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one, and

9-Cyclopropylethynyl-2-((R)-4-isopropyl-oxetan-2-ylmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one.

16. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof, according to any of claims 1-15, and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition according to claim 16 comprising a further therapeutic agent.

18. A compound, or pharmaceutically acceptable salt thereof, according to any of claims 1-15, or the pharmaceutical composition according to claim 16 or 17, for use as a medicament.

19. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-15, or the pharmaceutical composition according to claim 16 or 17, for use in the treatment and/or prophylaxis of inflammatory conditions.

20. A method for the treatment or prophylaxis of inflammatory conditions, comprising administering a prophylactically or therapeutically effective amount of a compound according to any one of claims 1-15, or a composition of claim 16 or 17.

21. The method according to claim 20, wherein a compound, or pharmaceutically acceptable salt thereof, according to claim 1-15 is administered in combination with a further therapeutic agent.

22. The use according to claim 19, or the method according to claim 20, wherein the inflammatory condition is rheumatoid arthritis, chronic obstructive pulmonary disease, asthma, idiopathic pulmonary fibrosis, psoriasis, Crohn's disease, and/or ulcerative colitis.



## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2013/076818

A. CLASSIFICATION OF SUBJECT MATTER  
INV. C07D471/04 C07D519/00 A61K31/4375 A61P29/00  
ADD.

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

## B. FIELDS SEARCHED

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

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/027661 A2 (ARENA PHARM INC [US]; HAKAK YARON [US]; UNETT DAVID J [US]; GATLIN JOE) 8 March 2007 (2007-03-08) claims; examples 10-13; table 1 -----	1-22
A	JP 2011 088847 A (TAKEDA CHEMICAL INDUSTRIES LTD) 6 May 2011 (2011-05-06) claims; examples; table 1 -----	1-22
A	DE 28 01 289 A1 (HOECHST AG [DE]) 3 May 1979 (1979-05-03) page 16, column 3; claims; examples -----	1-22
X,P	WO 2013/092791 A1 (GALAPAGOS NV [BE]) 27 June 2013 (2013-06-27) the whole document -----	1-22



Further documents are listed in the continuation of Box C.



See patent family annex.

## \* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search

22 January 2014

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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