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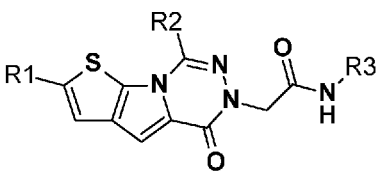
(54) Title: THIENOPYRROLOTRIAZINE COMPOUNDS, THEIR PREPARATION AND THEIR THERAPEUTIC USE



(I)

(57) Abstract: The invention relates to thienopyrrolotriazine compounds of formula (I) their preparation, and their therapeutic use.

THIENOPYRROLOTRIAZINE COMPOUNDS, THEIR PREPARATION AND THEIR THERAPEUTIC USE

Disclosed herein are thienopyrrolotriazine compounds, their preparation, their pharmaceutical composition comprising said compounds, and their therapeutic use.

The compounds according to the present disclosure are useful as inhibitors of NOD-like receptor protein 3 (NLRP3) inflammasome pathway.

The NOD-like receptor protein 3:

The NOD-like receptor (NLR) family, pyrin domain-containing protein 3 (NLRP3) or NACHT, LRR and PYD domains-containing protein 3 (NALP3), is a cytosolic sensor of diverse pathogen- and host-derived molecules. Upon activation, NLRP3 oligomerizes and recruits an adaptor protein called apoptosis-associated speck like protein (ASC). ASC then polymerizes to form a large aggregate known as ASC speck. In turn, polymerized ASC interacts with the cysteine protease caspase-1 to form a complex termed the inflammasome. This multicomplex protein forms a platform for the binding, dimerization, and activation of the caspase-1 protease. Caspase-1 then cleaves the precursor forms of the pro-inflammatory cytokines IL1β and IL18 (termed pro- IL1β and pro-IL18) and thereby activates adapted inflammatory responses. However, this pathway was shown to be associated with various inflammation associated processes and diseases, including:

- Neurodegenerative diseases such as Parkinson's Disease (PD), Multiple System Atrophy (MSA), Alzheimer's Disease (AD), Frontotemporal Dementia (FTD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS) and Brain injury (Guan Y & Han F. Front. Integr., Neurosci. 14 :37, 2020);
- Inflammatory diseases including Muckle-Wells Autoinflammatory Disorder (Agostini et al., 2004), cryopyrin-associated periodic syndrome (CAPS) (Mortimer et al., Nature Immunol. 2016, 17(10), 1176-1188); sickle cell disease; systemic lupus erythematosus (SLE); liver related diseases, viral hepatitis, non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis, and alcoholic liver disease (Petrasek et al., J. Clin. Invest. 2012, 122, 3476-89), and inflammatory arthritis related disorders, such as gout, pseudogout (chondrocalcinosis), osteoarthritis (Ridker et al., N. Engl. J. Med. 2017, 377, 1119-31), and rheumatoid arthritis (Mathews et al., Ann. Rheum. Dis. 2014, 73, 1202-10), acute or chronic arthropathy, and kidney related diseases such as hyperoxaluria (Knaufet et al., Kidney Int. 2013, 84, 895-901), lupus nephritis, hypertensive nephropathy (Krishnan et

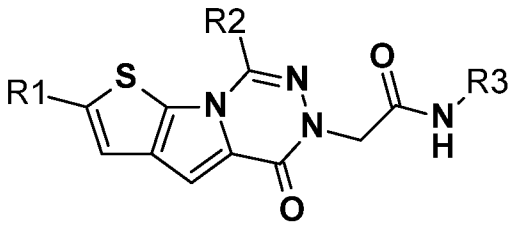
al., Br. J. Pharmacol. 2016, 173, 752-10 65), hemodialysis related inflammation and diabetic nephropathy (Shahzad et al., Kidney Int. 2015, 87, 74-84);

- Obesity & insulin resistance (Rheinheimer J. et al., Metabolism Clin & Experimental 74: 1-9, 2017); Pancreatitis (Fu Q. et al., BioMed Research International Volume 2018, Article ID 12949512018); Myocarditis (Toldo S et al, Int J Cardiol 2014);
- Eye diseases, where the NLRP3 inflammasome has been shown to contribute to diabetic retinopathy (Perrone L. et al., J. Cell. Physiol. 221: 262–272, 2009), acute glaucoma (Chi W. et al. National Academy Science 111: 11181-11186, 2014), age-related macular degeneration (Tseng W.A. et al., Investigative Ophthal & Visual Science 54: 11-120, 2013), Behcet's syndrome and dry eye disease (Zheng Q. et al., Experimental Eye Research 134: 133-140, 2015);
- Metabolic, cardiac, skin disorder & cancer, *e.g.,* diabetic cardiomyopathy (Luo B. et al., PLoS ONE 9(8): e104771, 2014); Kawasaki disease (Jia et al. Cell Death and Disease 10:778; 2019; Anzai F. et al., J. Molecular & Cell Cardiology 138: 185-196, 2020); cardiovascular metabolic disorders, atherosclerosis, type I and type II diabetes and related complications, peripheral artery disease (PAD), acute heart failure and hypertension (Ridker et al., N. Engl. J. Med. 2017, 377, 1119-31; wound healing and scar formation; inflammatory skin diseases (Sweeney et al., Br. J. Dermatol. 2015, 173, 1361), asthma, sarcoidosis, age-related macular degeneration; cancer related diseases, *e.g.,* myeloproliferative neoplasms, leukemias, myelodysplastic syndromes (MDS), myelofibrosis, lung cancer, colon cancer (Ridker et al., Lancet 2017, 390, 1833-42); and
- SARS-Cov-2: NLRP3 inflammasome is key player in antiviral responses (Zhao C. and Zhao W. 11, 211: 2020; Freeman & Swartz, Frontiers in Immunol. 11, 1518, 2020).

Inhibitors of NLRP3 are potential treatments for these conditions with unmet clinical needs.

Therefore, there is a need for inhibitors of the NLRP3 inflammasome pathway to provide new or alternative treatments.

Disclosed herein are compounds corresponding to formula (I)



(I)

in which:

R1 represents a hydrogen atom, a halogen atom, a -(C_1-C_2)-alkyl group,

R2 represents a -(C_1-C_3)alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from a hydroxy group , a -(C_1-C_3)-alkoxy group, or a -(C_3-C_4)cycloalkyl group,

R3 is selected from

- a -(C_5-C_8)bicycloalkyl group, being unsubstituted or substituted with one -(C_1-C_3)alkyl group being unsubstituted or substituted with one or two -NH(CO)Me group,
- a -(C_4-C_7)heterocycloalkyl group with nitrogen as heteroatom, being unsubstituted or substituted with one or more substituents independently selected from
  - a halogen atom,
  - an oxo group,
  - a -(C_1-C_4)-alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from a hydroxy group, a -(C_1-C_2)-alkyl group, a halogen atom, -(C_1-C_2)-alkoxy group, a nitrile group, a -C(O)O(C_1-C_3) group, or a -(C_3-C_8)-cycloalkyl group being unsubstituted or substituted by one or more halogen group,
  - a -(C_3-C_6)-cycloalkyl group, being unsubstituted or substituted by one or more (C_1-C_2) alkyl groups,
  - a –(CO)-(C_1-C_2)-alkyl group,
  - a heterocycloalkyl group, or
  - a heteroaryl group, being unsubstituted or substituted with one or more -(C_1-C_4)alkyl groups,
- a hetero(C_6-C_9)bicycloalkyl group with nitrogen as heteroatom, optionally substituted with one or more substituents independently selected from
  - a -(C_3-C_4) cycloalkyl group, or
  - a -(C_1-C_3)alkyl group,

or

- a mono- or bicycloheteroaryl group, being unsubstituted or substituted with one or more substituents independently selected from
  - a -(C_1-C_4)-alkyl group,
  - a -(C_1-C_4)-alkoxy group, or
  - a halogen atom,

or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) may comprise one or more asymmetric carbon atoms. They may thus exist in the form of enantiomers, diastereoisomers, or mixtures thereof.

The compounds of formula (I) may exist in the form of bases or addition salts with acids or bases, in particular pharmaceutically acceptable salts.

Pharmaceutically acceptable salts of the compounds of formula (I) form part of the present disclosure.

As used herein, certain terms have the following definitions:

- a halogen atom: a fluorine, a chlorine, or a bromine atom;
- a –(C_1-C_4)-alkyl group: a linear or branched saturated aliphatic group containing between 1 and 4 carbon atoms. Examples include, but are not limited to, methyl (Me), ethyl, propyl, isopropyl (iPr), butyl, isobutyl, t-butyl, etc;
- a cycloalkyl group: a cyclic alkyl group. Examples include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, etc.;
- a bicycloalkyl group: a two cyclic alkyl group, where the cycloalkyl can have a bond or a carbon atom in common. Examples include, but are not limited to bicyclo[1.1.1]pentane, etc;
- a heterocycloalkyl group: a saturated cyclic group containing between 3 and 6 carbon atoms and containing one or two heteroatoms such as nitrogen. Examples include, but are not limited to, piperidine, azepane, and pyrrolidine;
- a heterobicycloalkyl group: a saturated bicyclic group containing between 3 and 4 carbon atoms and containing one or two heteroatoms such as nitrogen or oxygen. Examples include, but are not limited to, quinuclidine, *N*-2-azabicyclo[2.2.1]heptan-6-amine, azabicyclo[2.2.1]heptane, and azaspiro[3.3]heptane;
- an alkoxy group: a radical -O-alkyl in which the alkyl group is as defined above. Examples of alkoxy group include, but are not limited to, methoxy, ethoxy, etc.;
- a nitrile group: a group including -CN;
- a hydroxy group: a group including -OH;
- an aryl group: a cyclic aromatic group comprising between 5 and 10 carbon atoms. Example of an aryl group include phenyl group, etc;
- a mono or bicycloheteroaryl group: an unsaturated cyclic group containing between 4 and

9 carbon atoms and containing 1 or 2 heteroatoms such as sulfur or nitrogen. Examples include, but are not limited to, thiazole, pyrazole, pyrimidine, indazole, benzothiazole, etc.

In an embodiment the compounds of formula (I) comprise a first group composed of the compounds in which:

R1 represents a hydrogen atom, a halogen atom chosen between bromine and chlorine atom, methyl group,

R2 represents a -(C_1-C_3)alkyl group chosen between methyl, ethyl, propyl and isopropyl group being unsubstituted or substituted with 1 substituent independently selected from a hydroxy group, a methoxy group, or a cyclopropyl group,

R3 is selected from

- a bicyclopentyl group, being substituted with one -(C_1-C_3)alkyl group being unsubstituted or substituted with one -NH(CO)Me group,
- a -(C_4-C_6)heterocycloalkyl group with nitrogen as heteroatom, being unsubstituted or substituted with one or more substituents independently selected from
    - a fluorine atom,
    - an oxo group,
    - a –(C_1-C_4)-alkyl group, being unsubstituted or substituted with 1 to 3 substituents independently selected from a hydroxy group, a methyl group, a fluorine atom, a methoxy group, a nitrile group, a -C(O)O(C_1-C_2) group, or a -(C_3-C_6)-cycloalkyl group being unsubstituted or substituted by one fluorine atom,
    - a –(C_3-C_5)-cycloalkyl group, being unsubstituted or substituted by one or more methyl groups,
    - –(CO)-methyl group,
    - a heterocyclopropyl group, or
    - an imidazole group, being unsubstituted or substituted with one methyl group,
- a hetero(C_6-C_9)bicycloalkyl group with nitrogen as heteroatom, optionally substituted with one or more substituents independently selected from
    - a -(C_3-C_4)cycloalkyl group, or
    - a methyl group,

or

- a mono, or bicycloheteroaryl group, being unsubstituted or substituted with one or two substituents independently selected from
  - a methyl group,
  - a methoxy group, or
  - a fluorine atom,

or a pharmaceutically acceptable salt thereof.

In an embodiment the compounds of formula (I) comprise a second group composed of the compounds in which

R1 represents a hydrogen atom, a halogen atom chosen between a bromine and a chlorine atom,

R2 represents -(C_1-C_3)alkyl group being unsubstituted or substituted with 1 to 3 hydroxy group, or a -(C_3-C_4)cycloalkyl group,

R3 is selected from

- a (C_5-C_8)bicycloalkyl group, being unsubstituted or substituted with one -(C_1-C_3)alkyl group being unsubstituted or substituted with one or two -NH(CO)Me groups,
- a (C_4-C_7)heterocycloalkyl group with nitrogen as heteroatom, being unsubstituted or substituted with one or more substituents independently selected from
  - a -(C_1-C_4)-alkyl group, being unsubstituted or substituted with 1 to 3 substituents independently selected from a hydroxy group, a methyl group, a fluorine atom, a methoxy group, a nitrile group, a -C(O)O(C_1-C_3) group, or a -(C_3-C_5)cycloalkyl group being unsubstituted or substituted by one or more fluorine atom,
  - a (C_3-C_6)-cycloalkyl group, being unsubstituted or substituted by one or more -(C_1-C_2)alkyl groups, or
  - a heterocycloalkyl group,
- a hetero(C_6-C_8)bicycloalkyl group with nitrogen as heteroatom, optionally substituted with one or more -(C_3-C_4)cycloalkyl groups,

or

- a mono- or bicycloheteroaryl group, being unsubstituted or substituted with one fluorine atom,

or a pharmaceutically acceptable salt thereof.

In an embodiment the compounds of formula (I) comprise a third group composed of the compounds in which **R1** represents a hydrogen atom or a pharmaceutically acceptable salt thereof.

In an embodiment the compounds of formula (I) comprise a fourth group composed of the compounds in which **R1** represents a bromine atom or a pharmaceutically acceptable salt thereof.

In an embodiment the compounds of formula (I) comprise a fifth group composed of the compounds in which **R1** represents a chlorine atom or a pharmaceutically acceptable salt thereof.

In an embodiment, the compounds of formula (I) comprise a sixth group composed of the compounds in which **R2** represents a -iPr group or a pharmaceutically acceptable salt thereof.

In an embodiment, the compounds of formula (I) comprise a seventh group composed of the compounds in which **R2** represents a -cyclopropyl group or a pharmaceutically acceptable salt thereof.

In an embodiment, the compounds of formula (I) comprise a eighth group composed of the compounds in which **R3** represents a –(C_4-C_7)heterocycloalkyl group with nitrogen as heteroatom, being unsubstituted or substituted with one or more substituents independently selected from

- a -(C_1-C_4)-alkyl group, being unsubstituted or substituted with 1 to 3 substituents independently selected from a hydroxy group, -(C_1-C_2)-alkyl group, a fluorine atom, -(C_1-C_2)-alkoxy group, a nitrile group, a -C(O)O(C_1-C_3) group, or a -(C_3-C_5)-cycloalkyl group being unsubstituted or substituted by one or more fluorine atom,
- a -(C_3-C_6)-cycloalkyl group, being unsubstituted or substituted by one or more -(C_1-C_2)alkyl group, or
- a heterocyclopropyl group.

or a pharmaceutically acceptable salt thereof.

All these sub-groups taken alone or in combination are part of the description.

Among the compounds of formula (I), mention may be made in particular of the following compounds:

1 (R)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide

2 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(thiazol-5-yl) acetamide

3 N-((R)-1-((S)-2-hydroxypropyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5] pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

4 (R)-N-(1-cyclopropylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d] [1,2,4]triazin-6(5H)-yl)acetamide

5 (R)-2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4] triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate

6 (R)-2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclopropylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate

7 2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(thiazol-5-yl)acetamide

8 (R)-2-(2-bromo-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide

9 (R)-2-(8-isopropyl-2-methyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate

10 (R)-2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclobutylpiperidin-3-yl)acetamide formate

11 (R)-N-(1-cyclobutylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d] [1,2,4]triazin-6(5H)-yl)acetamide formate

12 N-(benzo[d]thiazol-6-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

13 (R)-2-(2-chloro-8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclopropylpiperidin-3-yl)acetamide

14 (R)-N-(1-isobutylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d] [1,2,4]triazin-6(5H)-yl)acetamide

15 N-(benzo[d]thiazol-5-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

16 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(6-methoxypyridin-3-yl)acetamide

17 (R)-N-(1-(cyclopentylmethyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo [1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

18 N-((3R)-1-((2,2-difluorocyclopropyl)methyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno [3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide compound with formaldehyde

19 (R)-N-(1-(2-hydroxyethyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno [3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide compound with formaldehyde

20 (R)-N-(1-cyclobutylpiperidin-3-yl)-2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

21 (R)-2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclopropylpiperidin-3-yl)acetamide

22 2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-((R)-1-((S)-2-hydroxypropyl)piperidin-3-yl)acetamide

23 (R)-N-(1-(2-hydroxy-2-methylpropyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate

24 (R)-2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide formate

25 N-((R)-1-cyclobutylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)propanamide formate

26 N-((R)-1-cyclopropylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)propanamide formate

27 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methyl-1H-indazol-6-yl)acetamide formate

28 (R)-N-(1-(cyclopropylmethyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate

29 (R)-2-(2-chloro-8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclobutylpiperidin-3-yl)acetamide formate

30 (R)-2-(2-chloro-8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclopropylpiperidin-3-yl)acetamide formate

31 (R)-2-(2-bromo-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclobutylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate

32 (R)-N-(1-cyclobutylpiperidin-3-yl)-2-(8-(methoxymethyl)-5-oxothieno [3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

33 (R)-N-(1-cyclopropylpiperidin-3-yl)-2-(8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide 2,2,2-trifluoroacetate

34 2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(5,5-difluoro-1-methylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate

35 N-(5,5-difluoro-1-methylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

36 (R)-N-(1-(2-fluoroethyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate

37 N-(1-(tert-butyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate

38 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-(2,2,2-trifluoroethyl)piperidin-3-yl)acetamide 2,2,2-trifluoroacetate

39 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(quinuclidin-3-yl)acetamide

40 (R)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-(oxetan-3-yl)piperidin-3-yl)acetamide

41 (R)-N-(1-(3-fluoropropyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate

42 (R)-N-(1-acetylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

43 (R)-N-(1-((3,3-difluorocyclobutyl)methyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate

44 N-((R)-1-cyclopropylpiperidin-3-yl)-2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

45 (R)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-(1-methyl-1H-imidazol-2-yl)piperidin-3-yl)acetamide

46 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methyl-2-oxopiperidin-4-yl)acetamide

47 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methyl-6-oxopiperidin-3-yl)acetamide

48 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(3R)-1-isopropyl-3-piperidyl]acetamide

49 N-[(3R)-1-cyclopentyl-3-piperidyl]-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide

50 N-((R)-1-cyclobutylpiperidin-3-yl)-2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

51 N-((R)-1-cyclopropylpiperidin-3-yl)-2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2d][1,2,4]triazin-6(5H)-yl)acetamide

52 (R)-N-(1-cyclopropylpiperidin-3-yl)-2-(8-(2-hydroxypropan-2-yl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

53 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(2-methylpyrazol-3-yl)acetamide

54 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(1-methylpyrazol-3-yl)acetamide

55 N-[(1-tert-butyl-5-oxo-pyrrolidin-3-yl)methyl]-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide

56 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(3-pyridyl)acetamide

57 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[rac-(3R)-1-(2,2-dimethylcyclobutyl)-3-piperidyl]acetamide

58 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(2-pyridyl)acetamide

59 2-(4-bromo-12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(1-tert-butyl-3-piperidyl)acetamide

60 N-[(3R)-1-cyclopropyl-3-piperidyl]-2-(12-ethyl-9-oxo-3-thia-1,10,11-triazatricyclo [6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide

61 N-[(3R)-1-cyclopropylazepan-3-yl]-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo [6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide

62 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(3R)-1-methylazepan-3-yl]acetamide

63 N-(1-cyclopropyl-5,5-difluoropiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo [1,2-d][1,2,4]triazin-6(5H)-yl)acetamide 2,2,2-trifluoroacetate

64 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-((3R)-1-(1-methoxypropan-2-yl)piperidin-3-yl)acetamide

65 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(2-methoxypyridin-4-yl)acetamide

66 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-pyrimidin-4-yl-acetamide

67 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(4-pyridyl)acetamide

68 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(6-methyl-3-pyridyl)acetamide

69 2-(12-ethyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(3R)-1-[(2S)-2-hydroxypropyl]-3-piperidyl]acetamide

70 N-(5-fluoropyrimidin-4-yl)-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6] dodeca-2(6),4,7,11-tetraen-10-yl)acetamide

71 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(3R)-1-(1-methylcyclopentyl)-3-piperidyl]acetamide

72 N-[(3R)-1-cyclopropylpiperidin-3-yl]-2-(9-oxo-12-propyl-3-thia-1,10,11-triazatricyclo [6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide

73 2-(12-ethyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(3R)-1-methyl-3-piperidyl]acetamide

74 N-[3-(acetamidomethyl)bicyclo[1.1.1]pentan-1-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5] pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

75 N-[(3R)-1-(cyanomethyl)piperidin-3-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d] [1,2,4]triazin-6(5H)-yl)acetamide

76 N-[(3R)-1-methylpyrrolidin-3-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4] triazin-6(5H)-yl)acetamide

77 N-[(3R)-1-(2-cyanoethyl)piperidin-3-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d] [1,2,4]triazin-6(5H)-yl)acetamide

78 N-[(3R)-1-[(2R)-2-hydroxypropyl]piperidin-3-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5] pyrrolo [1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

79 N-[(3R)-1-(1-hydroxy-2-methylpropan-2-yl)piperidin-3-yl]-2-(8-isopropyl-5-oxothieno [3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

80 ethyl 2-methyl-2-[3-[[2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetyl]amino]piperidin-1-yl]propanoate

81 N-((R)-1-cyclobutylpiperidin-3-yl)-2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

82 N-[(1R,4R)-2-methyl-2-azabicyclo[2.2.1]heptan-6-yl]-2-(8-isopropyl-5-oxothieno [3',2':4,5] pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

83 N-(2-methyl-2-azaspiro[3.3]heptan-6-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

84 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-pyrimidin-5-ylacetamide

85 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(2-oxo-4-piperidyl)acetamide

86 N-(1-cyclopropylpyrrolidin-3-yl)-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo [6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide

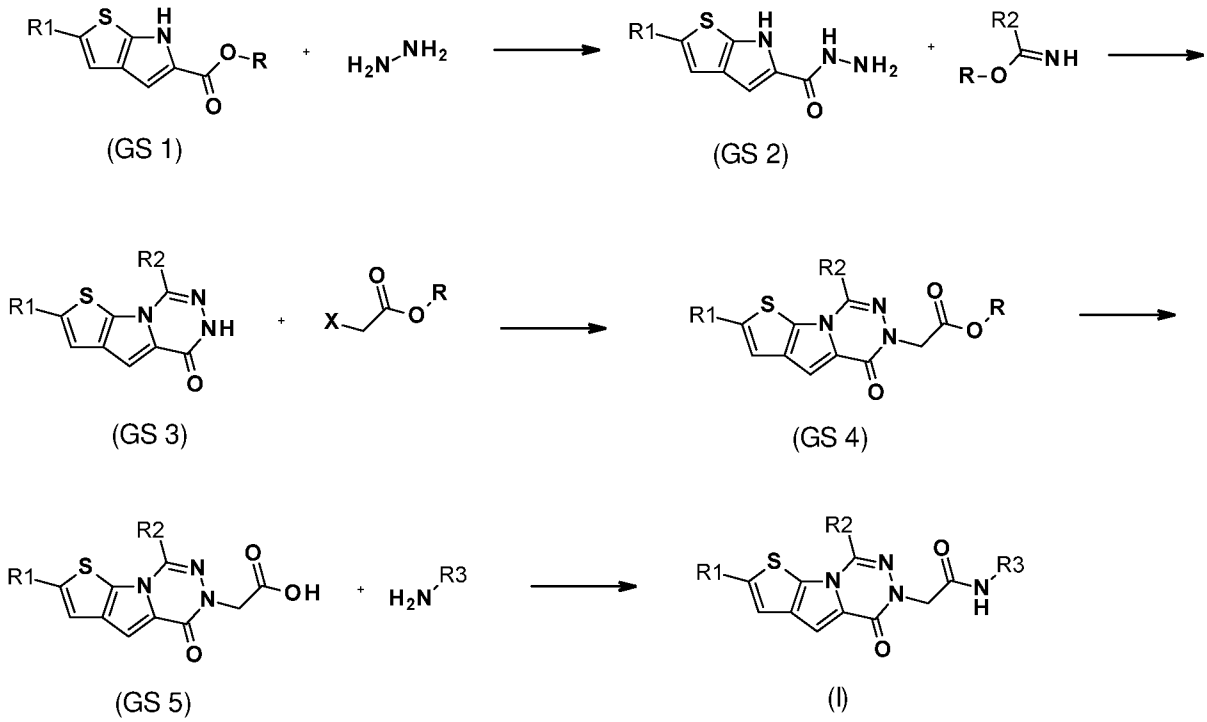
87 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[rac-(3R)-1-tert-butylpyrrolidin-3-yl]acetamide

88 N-[(1S,4R)-2-azabicyclo[2.2.1]heptan-6-yl]-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamidehydrochloride

In accordance with the present disclosure the compounds of general formula (I) can be prepared by the following process.

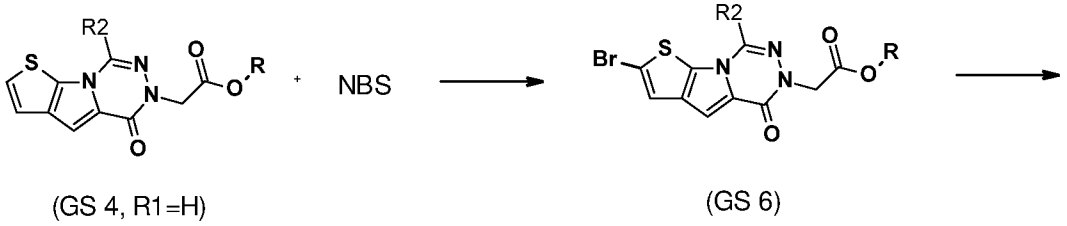
Unless otherwise mentioned, R is an alkyl group, X is a halogen atom and R_1 to R_3 are as defined previously.

REACTION SCHEME 1 (for R_1 = H, Cl, Me)

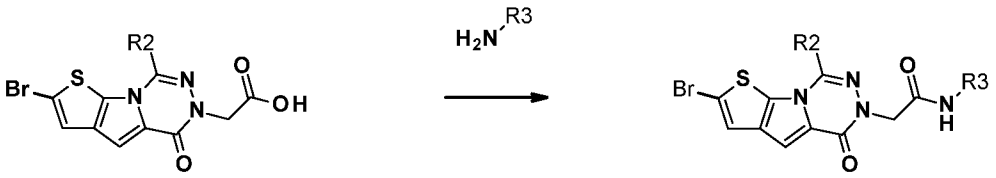


Compounds of general formula (I) can be prepared by the Reaction scheme 1 where a bicyclic thienopyrrolecarboxylic ester (GS 1) is transformed with hydrazine to provide the carboxy hydrazide analogue (GS 2). (GS 2) is then reacted with a hydrochloride salt of an imidate where R_2 is alkyl, cycloalkyl, alkoxyalkyl or hydroxyalkyl, following by addition of a base such as tBuOK to obtain after cyclization triazinone (GS 3). (GS 3) is then alkylated with alkyl haloacetate using a base like K_2CO_3 to give ester (GS 4), which is then saponified using an aqueous base to give acid (GS 5), followed by a coupling with an appropriate amine H_2N-R_3 using known standard methods like EDC/HOBT Et_3N, HATU DIPEA to provide a compound of general formula (I).

REACTION SCHEME 2 (for R_1 = Br)



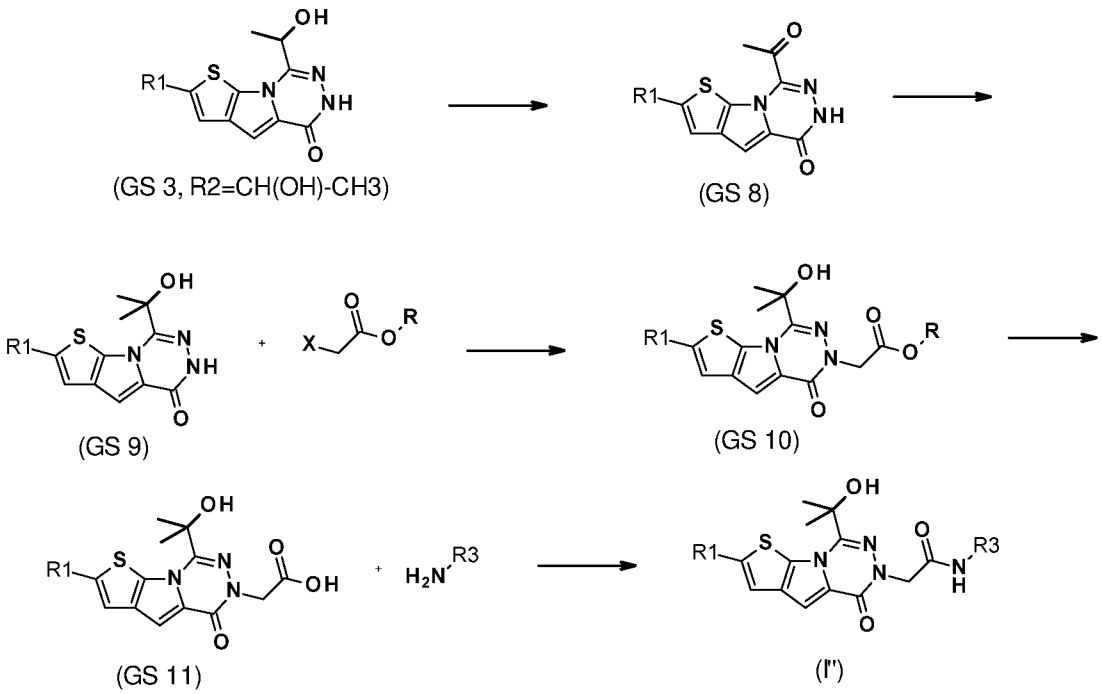
(GS 4, R1=H) (GS 6)



(GS 7) (I')

Compounds of the present disclosure with R_1=Br may be prepared by the reaction scheme 2 where the ester intermediate in which R_1=H (GS 4, R_1=H) is reacted with a brominated agent like NBS to obtain the corresponding brominated derivative (GS 6), which is then saponified using an aqueous base to obtain the carboxylic acid (GS 7), followed by a coupling with an appropriate amine H_2N-R_3 using known standard methods like EDC/HOBT Et_3N, HATU DIPEA to provide a compound of general formula (I').

REACTION SCHEME 3 (for R_2 = $C(OH)(CH_3)_2$)



(GS 3, R2=CH(OH)-CH3) (GS 8)

(GS 9) (GS 10)

(GS 11) (I'')

A modified reaction sequence of scheme 1 is applied for R_2 = $C(OH)(CH_3)_2$. Compounds of general formula (I), where R_2 is 2-hydroxypropan-2-yl, can be prepared by the reaction scheme 4 where general structure (GS 3 with R_2 = $CH(OH)$-CH_3) is oxidized with standard methods like Swern oxidation or Dess-Martin oxidation to provide a ketone (GS 8) which is engaged in a Grignard reaction using for example MeMgCl to obtain (GS 9). This intermediate is then alkylated with alkyl haloacetate using a base like K_2CO_3 to give ester (GS 10), which is then saponified to the corresponding carboxylic acid (GS 11), followed by a coupling with an appropriate amine H_2N-R_3 using known standard methods like EDC/HOBT Et_3N, HATU DIPEA to provide a compound of general formula (I'').

In the following schemes, the starting compounds and the reagents, when their preparation method is not described, are commercially available or described in the literature, or else may be prepared according to methods that are described therein or that are known to those skilled in the art.

The following abbreviations and empirical formulae are used:

ACN	acetonitrile
DAST	diethylaminosulfur trifluoride
DCM	dichloromethane
Cs_2CO_3	cesium carbonate
DIPEA	diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et_2O	diethylether
EtOAc	ethylacetate
Et_3N	triethylamine
EtOH	ethanol
FA	formic acid
HATU	hexafluorophosphate Azabenzotriazole Tetramethyl Uronium
HOBT	hydroxybenzotriazole
HCl	hydrochloric acid
IL 1b	Interleukin 1 beta
K_2CO_3	potassium carbonate
MeOH	methanol
$NaHCO_3$	sodium bicarbonate

Na_2CO_3	sodium carbonate
$Na_2S_2O_3$	sodium thiosulfate
Na_2SO_4	sodium sulfate
NaOH	sodium hydroxyde
NBS	N-bromosuccinimide
NH_4Cl	ammonium chloride
TMSO	trimethylsilyloxy
P_2O_5	phosphorous pentoxyde
tBuOK	potassium tertbutylate
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TNF-α	Tumor necrosis factor-α
rt	room temperature
Rt	Retention time
°C	degree Celsius
ml	milliliter(s)
mmol	millimole(s)
min	minute(s)
µmol	micromole(s)
µl	microliter(s)
h	hour(s)

The examples which follow describe the preparation of certain compounds in accordance with the present disclosure. These examples are not limitative, and merely illustrate the present disclosure. The numbers of the compounds exemplified match those given in the above list of compounds and the table of IC_{50} values, which illustrates the chemical structures and physical properties of some compounds according to the present disclosure.

In the tables:

NMR: the proton magnetic resonance spectra (^{1}H NMR), as described below, are recorded at 400 MHz or 500 MHz in DMSO-d_6, using the DMSO-d_6 peak as reference. The chemical shifts (δ) are expressed in parts per million (ppm). The signals observed are expressed as follows: s = singlet; d = doublet; t = triplet; m = multiplet or br s = broad singlet; br m = broad multiplet.

LCMS: the LCMS characteristics, as described below, indicates the different high-performance liquid chromatography analytical methods used.

LCMS final compounds:

Method A:

System Waters UPLC/SQD; ionization: electrospray in positive and/or negative mode (ES+/-)

Column: ACQUITY CORTECS C18+ 1.7µm 2.1x50mm; Column temperature: 40°C; Flow: 1.0 ml/min; Solvents: A = H_2O (0.1% formic acid) ; B = ACN (0.1% formic acid)

Gradient:

(min)	%A	%B
0	98	2
2.00	0	100
2.60	0	100
2.70	98	2
3.00	98	2

Method B:

System Waters UPLC/SQD2; ionization: electrospray in positive &/or negative mode (ES+/-)

Column : ACQUITY CSH C18+ 1.7µm 2.1x50mm; Column temperature: 60°C; Flow: 1.0 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)

Gradient:

(min)	%A	%B
0	97	3
2.10	0	100
2.45	0	100
2.50	97	3

Method C:

System Waters UPLC/SQD; ionization: electrospray in positive &/or negative mode (ES+/-)

Column: ACQUITY CORTECS C18+ 1.7µm 2.1x50mm; Column temperature: 40°C; Flow: 1.0 ml/min; Solvents: A = H2O (0.1% formic acid) ; B = ACN (0.1% formic acid)

Gradient:

(min)	%A	%B
0	98	2
1.00	98	2
7.50	0	100
9.20	0	100
9.30	98	2

Method D:

System Waters XeVo – Qtof; ionization: electrospray in positive and/or negative mode (ES+)

Column: ACQUITY CSH C18+ 1.7µm 2.1x100mm; Column temperature: 45°C; Flow: 0.5 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)

Gradient:

(min)	%A	%B
0	95	5
0.3	95	5
4.00	0	100
4.60	0	100
5.30	95	5

LCMS, intermediates

Methods E and F:

LC-MS: system Waters UPLC Hclass / SQD2; ionization: electrospray in positive and/or negative mode (ES+/-); Column: Cortecs uplc C18 1.6µm 2.1x50mm; Column temperature: 55°C; Flow: 0.8 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)
Gradient:

Method E (2 min):

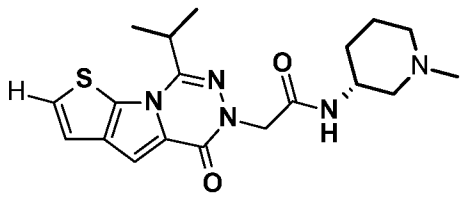
(min)	%A	%B
0	95	5
1.00	50	50
1.30	0	100
1.45	0	10
1.75	98	2
2.00	98	2

Method F (3 min):

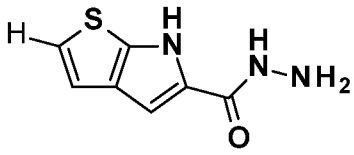
(min)	%A	%B
0	98	2
2.50	0	100
2.90	0	100
2.95	98	2
3.00	98	2

Mass spectrometry results are reported as the ratio of mass over charge.

Example 1 ; (*R*)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide



Int 1: 6H-thieno[2,3-b]pyrrole-5-carbohydrazide

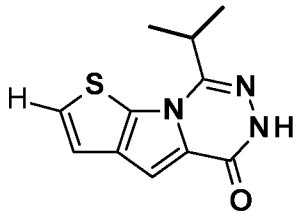


To a solution of methyl 6*H*-thieno[2,3-*b*]pyrrole-5-carboxylate (15.45 mmol, 2,8 g) in 15 ml of MeOH, hydrazine solution (50-60% in water) (61.13 mmol, 6ml) is added, and this mixture is heated at reflux overnight. After cooling down the solution, the precipitate formed is filtered off,

washed with Et_2O and dried under vacuum. The title compound is obtained as a white solid (2.56 g, 91% yield).

LCMS (method E): Rt = 0.61 min; MS m/z $[M+H]^+$ 182

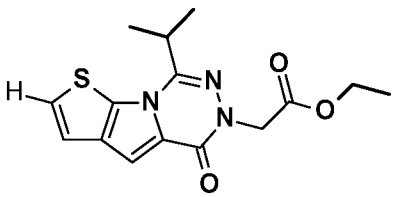
Int 2: 8-isopropylthieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one



Under nitrogen, to a solution of 6H-thieno[2,3-b]pyrrole-5-carbohydrazide (1,55 g, 8,55 mmol) in 20 ml of DMF is added methyl 2-methylpropanimidoate hydrochloride (1,46 g, 10,26 mmol). This mixture is stirred at rt for 30 min. Then, solid tBuOK (2.15g, 18.82 mmol) is added and the resulting mixture is stirred in a preheated oil bath at 90°C for 1 h. After cooling down to 0°C, 70 ml of water is added, and the mixture is acidified with HCl (1M) to pH 5. The precipitate formed is filtered off, washed with water and EtOAc/CH_2Cl_2 (9/1). The solid obtained is washed with pentane and dried under vacuum to give the title compound as a beige solid (1.0 g, 50% yield).

LCMS (method E): Rt = 1.21 min; MS m/z $[M+H]^+$ 234

Int 3: Ethyl 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate

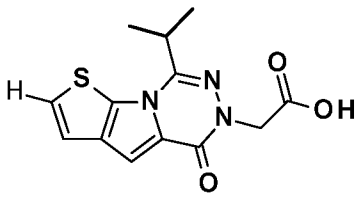


Under nitrogen, to a solution of 8-isopropylthieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one (717 mg, 3,07 mmol) in 10 ml of DMF is added K_2CO_3 (637 mg, 4,61 mmol), followed by a dropwise addition of ethyl iodoacetate (557 µl, 4,61 mmol). The resulting mixture is stirred at rt for 1h. Then, the mixture is diluted with a saturated aqueous solution of NH_4Cl and extracted twice with EtOAc. The combined organic layers are dried over Na_2SO_4, filtered off and concentrated under reduced pressure. The residue is purified by flash chromatography on

silica gel using cyclohexane/EtOAc (from 0% to 50%) to give the title compound as a white solid (620 mg, 63% yield).

LCMS (method E): Rt = 1.46 min; MS m/z $[M+H]^+$ 320

Int 4: 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid

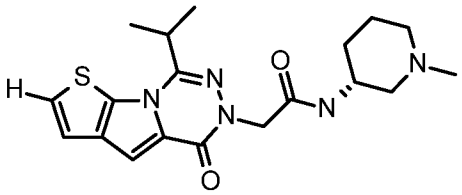


To a solution of ethyl 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate (620 mg, 1,94 mmol) in 20 ml of dioxane is added a solution of NaOH (1M) (2,91 ml, 2,91 mmol). The resulting solution is stirred at rt overnight.

The mixture is acidified with HCl (1M). The precipitate formed is filtered off, washed with water and pentane. After drying overnight under vacuum in presence of P_2O_5, the title compound is obtained as a white solid (433 mg, 77% yield).

LCMS (method E): Rt = 1.22 min; MS m/z $[M+H]^+$ 292

Ex 1: (*R*)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide



Under nitrogen, to a suspension of (3*R*)-1-methylpiperidin-3-amine dihydrochloride (22 mg, 113 µmol) and 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid (30 mg, 103 µmol) in 2 ml of DMF is added DIPEA (54 µl, 0,31 mmol), followed by HATU (51 mg, 134 µmol). The resulting mixture is stirred at rt for 20h. The crude mixture is purified by reverse phase chromatography Waters SunFire PrepC18 OBD 30 x 100 mm column, water containing 0.1% HCO_2H with a gradient of acetonitrile 10 to 80% in 18 min. After evaporation under reduced pressure and drying overnight, the title compound is obtained as a yellow solid (24 mg, 60% yield).

1H NMR (400 MHz, DMSO-d6) δ ppm 1.24 (m, 1 H), 1.35 (d, J=6.8 Hz, 6 H), 1.48 (qd, J=10.2, 3.9 Hz, 1 H), 1.62 - 1.72 (m, 2 H), 1.92 (m, 1 H), 2.02 (m, 1 H), 2,21 (s, 3H), 2.57 (m, 1 H), 2.71 (m, 1 H), 3.37 (m, 1 H), 3.77 (m, 1 H), 4.55 (s, 2 H), 7.32 (d, J=5.5 Hz, 1 H), 7.36 (s, 1 H), 7.58 (d, J=5.5 Hz, 1 H), 7.92 (d, J=7.8 Hz, 1 H), 8.14 (s, 1 H)

LCMS $[M+H]^+$ = 388; Rt = 0.65; Method A

The following examples were synthesized analogous to the previous procedure, using the appropriate amines:

Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method
2	2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(thiazol-5-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.36 (d, J=6.5 Hz, 6 H), 3.39 (sept, J=6,5 Hz, 1 H), 4.85 (s, 2 H), 7.33 (d, J=5.5 Hz, 1 H), 7.41 (s, 1 H), 7.60 (d, J=5.5 Hz, 1 H), 7.64 (d, J=0.8 Hz, 1 H), 8.60 (br s, 1 H), 11.54 (br s, 1 H)	1.06	374	A
3	N-((R)-1-((S)-2-hydroxypropyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.0 (d, *J*=6.1 Hz, 3 H), 1.35 (d, J=6.8 Hz, 6 H), 1.64 (m, 1 H), 1.71 - 1.85 (m, 2 H), 2.96 - 3.20 (m, 2 H) 3.35 (m, 1 H), 3.87 - 4.08 (m, 2 H), 4.56 (s, 2 H), 4.97 (br s, 1 H), 7.32 (d, J=5.5 Hz, 1 H), 7.37 (s, 1 H), 7.59 (d, J=5.5 Hz, 1 H), 8.04 (br d, J=6.4 Hz, 1 H)	0.69	432	A
4	(R)-N-(1-cyclopropylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 0.74 - 0.99 (m, 4 H), 1.36 (d, J=6.7 Hz, 6 H), 1.46 (m, 1 H), 1.64 (m, 1 H), 1.75 - 2.00 (m, 2 H), 2.89 (m, 2 H), 3.04 (m, 1 H), 3.37 (sept, *J*=6.7 Hz, 1 H), 3.45 (m, 2 H), 3.94 (m, 1 H), 4.58 (s, 2 H), 7.32 (d, J=5.4 Hz, 1 H), 7.38 (s, 1 H), 7.59 (d, J=5.4 Hz, 1 H), 8.29 (br d, *J*=6.7 Hz, 1 H), 9.06 (br s, 1 H)	0.65	414	A
11	(R)-N-(1-cyclobutylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate	1H NMR (400 MHz, DMSO-d6) δ ppm 1.23 (br d, J=9 Hz, 1 H), 1.35 (d, J=7 Hz, 6 H), 1.40 - 2.00 (m, 12 H), 2.60 - 2.71 (m, 2 H), 3.21 - 3.37 (m, 1 H), 3.62 - 3.76 (m, 1 H), 4.55 (d, J=3 Hz, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=6 Hz, 1 H), 7.83 (br d, J=8 Hz, 1 H)	0.70	428	A
12	N-(benzo[d]thiazol-6-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.37 (d, J=7 Hz, 6 H), 3.36 - 3.47 (m, 1 H), 4.84 (s, 2 H), 7.33 (d, J=5 Hz, 1 H), 7.41 (s, 1 H), 7.56 - 7.65 (m, 2 H), 8.03 (d, J=9 Hz, 1 H), 8.49 (d, J=2 Hz, 1 H), 9.27 (s, 1 H), 10.44 (s, 1 H)	1.21	424	A
14	(R)-N-(1-isobutylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 0.77 (d, J=6 Hz, 6 H), 1.10 - 1.55 (m, 8 H), 1.59 - 2.12 (m, 7 H), 2.65 (br d, J=12 Hz, 2 H), 3.35 - 3.43 (m, 1 H), 3.69 - 3.79 (m, 1 H), 4.47 - 4.64 (m, 2 H), 7.29 - 7.40 (m, 2 H), 7.58 (d, J=5 Hz, 1 H), 7.73 (br d, J=8 Hz, 1 H)	0.74	430	A

Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method
15	N-(benzo[d]thiazol-5-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.38 (d, J=7 Hz, 6 H), 3.37 - 3.47 (m, 1 H), 4.85 (s, 2 H), 7.33 (d, J=5 Hz, 1 H), 7.41 (s, 1 H), 7.56 - 7.67 (m, 2 H), 8.09 (d, J=9 Hz, 1 H), 8.40 - 8.47 (m, 1 H), 9.37 (s, 1 H), 10.44 (s, 1 H)	1.28	424	A
16	2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(6-methoxypyridin-3-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.37 (d, J=7 Hz, 6 H), 3.34 - 3.44 (m, 1 H), 3.82 (s, 3 H), 4.78 (s, 2 H), 6.81 (d, J=9 Hz, 1 H), 7.33 (d, J=6 Hz, 1 H), 7.40 (s, 1 H), 7.60 (d, J=5 Hz, 1 H), 7.86 (dd, J=9, 3 Hz, 1 H), 8.34 (d, J=3 Hz, 1 H), 10.15 (s, 1 H)	1.16	398	A
17	(R)-N-(1-(cyclopentylmethyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.09 (br dd, J=13, 7 Hz, 2 H), 1.27 - 1.52 (m, 12 H), 1.55 - 1.76 (m, 4 H), 1.98 - 2.09 (m, 2 H), 2.13 - 2.22 (m, 1 H), 2.29 - 2.48 (m, 2 H), 2.66 - 2.86 (m, 2 H), 3.27 - 3.38 (m, 1 H), 3.81 (br s, 1 H), 4.49 - 4.62 (m, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.38 (s, 1 H), 7.59 (d, J=5 Hz, 1 H), 7.79 (br s, 1 H)	0.82	456	A
18	N-((3R)-1-((2,2-difluorocyclopropyl)methyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide compound with formaldehyde	1H NMR (400 MHz, DMSO-d6) δ ppm 1.08 - 1.30 (m, 2 H), 1.35 (d, J=7 Hz, 6 H), 1.42 - 1.59 (m, 2 H), 1.62 - 1.81 (m, 3 H), 1.86 - 2.07 (m, 2 H), 2.27 - 2.39 (m, 1 H), 2.53 - 2.69 (m, 2 H), 2.76 (br dd, J=16, 11 Hz, 1 H), 3.37 - 3.46 (m, 1 H), 3.76 (br d, J=9 Hz, 1 H), 4.50 - 4.57 (m, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=5 Hz, 1 H), 7.87 (br d, J=8 Hz, 1 H)	0.70	464	A
19	(R)-N-(1-(2-hydroxyethyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide compound with formaldehyde	1H NMR (400 MHz, DMSO-d6) δ ppm 1.19 - 1.31 (m, 1 H), 1.35 (d, J=7 Hz, 6 H), 1.41 - 1.52 (m, 1 H), 1.61 - 1.70 (m, 2 H), 1.99 (br t, J=10 Hz, 1 H), 2.04 - 2.14 (m, 1 H), 2.38 - 2.45 (m, 2 H), 2.62 - 2.69 (m, 1 H), 2.73 - 2.80 (m, 1 H), 3.35 (br dd, J=13, 7 Hz, 1 H), 3.48 (br t, J=6 Hz, 2 H), 3.72 - 3.83 (m, 1 H), 4.55 (d, J=2 Hz, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=5 Hz, 1 H), 7.88 (d, J=8 Hz, 1 H)	0.61	418	A
23	(R)-N-(1-(2-hydroxy-2-methylpropyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate	1H NMR (400 MHz, DMSO-d6) δ ppm 0.98 (s, 6 H), 1.22 (br d, J=9 Hz, 1 H), 1.35 (br d, J=7 Hz, 6 H), 1.46 (br d, J=9 Hz, 1 H), 1.62 (br d, J=9 Hz, 2 H), 2.06 - 2.21 (m, 4 H), 2.60 - 2.82 (m, 2 H), 3.39 - 3.51 (m, 1 H), 3.75 (br s, 1 H), 4.48 - 4.60 (m, 2 H), 7.29 - 7.39 (m, 2 H), 7.58 (d, J=5 Hz, 1 H), 7.73 (br d, J=8 Hz, 1 H)	0.65	446	A
25	N-((R)-1-cyclobutylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)propanamide formate	1H NMR (400 MHz, DMSO-d6) δ ppm 1.14 - 1.29 (m, 1 H), 1.33 - 1.38 (m, 6 H), 1.41 - 1.78 (m, 12 H), 1.91 (dt, J=6, 3 Hz, 2 H), 2.54 - 2.61 (m, 1 H), 2.63 - 2.72 (m, 2 H), 3.33 - 3.39 (m, 1 H), 3.69 - 3.81 (m, 1 H), 5.32 (dd, J=7, 5 Hz, 1 H), 7.32 (d, J=5 Hz, 1 H), 7.37 (s, 1 H), 7.40 - 7.54 (m, 1 H), 7.58 (dd, J=5, 1 Hz, 1 H)	0.75	442	A

Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method
26	N-((R)-1-cyclopropylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)propanamide formate	1H NMR (400 MHz, DMSO-d6) δ ppm 0.14 - 0.26 (m, 2 H), 0.30 - 0.40 (m, 2 H), 1.15 - 1.27 (m, 1 H), 1.28 - 1.42 (m, 7 H), 1.42 - 1.67 (m, 6 H), 1.90 - 2.15 (m, 2 H), 2.69 - 2.87 (m, 2 H), 3.33 - 3.39 (m, 1 H), 3.61 - 3.73 (m, 1 H), 5.30 (q, J=7 Hz, 1 H), 7.32 (d, J=5 Hz, 1 H), 7.37 (d, J=1 Hz, 1 H), 7.39 - 7.52 (m, 1 H), 7.58 (d, J=5 Hz, 1 H)	0.72	428	A
27	2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methyl-1H-indazol-6-yl)acetamide formate	1H NMR (400 MHz, DMSO-d6) δ ppm 1.38 (d, J=7 Hz, 6 H), 3.38 - 3.50 (m, 1 H), 3.94 (s, 3 H), 4.85 (s, 2 H), 7.13 (dd, J=9, 2 Hz, 1 H), 7.34 (d, J=5 Hz, 1 H), 7.42 (s, 1 H), 7.61 (d, J=6 Hz, 1 H), 7.70 (d, J=9 Hz, 1 H), 7.95 (s, 1 H), 8.08 (s, 1 H), 10.39 (s, 1 H)	1.23	421	A
28	(R)-N-(1-(cyclopropylmethyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate	1H NMR (400 MHz, DMSO-d6) δ ppm 0.08 - 0.19 (m, 2 H), 0.48 (dd, J=8, 2 Hz, 2 H), 0.85 (br d, J=5 Hz, 1 H), 1.35 (d, J=7 Hz, 7 H), 1.54 (br d, J=11 Hz, 1 H), 1.69 - 1.77 (m, 2 H), 2.05 - 2.30 (m, 2 H), 2.38 - 2.44 (m, 2 H), 2.86 - 3.06 (m, 2 H), 3.26 - 3.40 (m, 1 H), 3.75 - 3.93 (m, 1 H), 4.52 - 4.58 (m, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=6 Hz, 1 H), 7.95 (br d, J=8 Hz, 1 H)	0.70	428	A
35	N-(5,5-difluoro-1-methylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.35 (d, J=7 Hz, 6 H), 1.63 - 1.88 (m, 1 H), 1.95 (t, J=10 Hz, 1 H), 2.09 - 2.39 (m, 5 H), 2.70 - 3.00 (m, 2 H), 3.34 - 3.42 (m, 1 H), 3.91 - 4.06 (m, 1 H), 4.56 (s, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.38 (s, 1 H), 7.58 (d, J=6 Hz, 1 H), 7.99 (d, J=8 Hz, 1 H)	0.74	424	A
36	(R)-N-(1-(2-fluoroethyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate	1H NMR (400 MHz, DMSO-d6) δ ppm 1.18 - 1.51 (m, 8 H), 1.62 - 1.73 (m, 2 H), 1.90 - 2.08 (m, 2 H), 2.58 (t, J=5 Hz, 2 H), 2.63 - 2.73 (m, 2 H), 2.80 (dd, J=10, 3 Hz, 1 H), 3.70 - 3.79 (m, 1 H), 4.41 - 4.65 (m, 4 H), 7.32 (d, J=5 Hz, 1 H), 7.37 (s, 1 H), 7.59 (d, J=5 Hz, 1 H), 7.86 (d, J=8 Hz, 1 H)	0.63	420	A
37	N-(1-(tert-butyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate	1H NMR (400 MHz, DMSO-d6) δ ppm 0.98 (s, 9 H), 1.35 (d, J=7 Hz, 8 H), 1.67 (br d, J=10 Hz, 2 H), 1.97 - 2.25 (m, 2 H), 2.73 - 2.93 (m, 2 H), 3.46 - 3.56 (m, 1 H), 3.66 - 3.79 (m, 1 H), 4.48 - 4.63 (m, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.38 (s, 1 H), 7.58 (d, J=6 Hz, 1 H), 7.77 (br d, J=8 Hz, 1 H)	0.67	430	A
38	2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-(2,2,2-trifluoroethyl)piperidin-3-yl)acetamide 2,2,2-trifluoroacetate	1H NMR (400 MHz, DMSO-d6) δ ppm 1.16 - 1.30 (m, 1 H), 1.35 (d, J=7 Hz, 6 H), 1.39 - 1.53 (m, 1 H), 1.61 - 1.74 (m, 2 H), 2.18 (t, J=10 Hz, 1 H), 2.25 - 2.36 (m, 1 H), 2.70 - 2.80 (m, 1 H), 2.87 - 2.98 (m, 1 H), 3.12 - 3.26 (m, 2 H), 3.32 - 3.41 (m, 1 H), 3.72 (br d, J=9 Hz, 1 H), 4.49 - 4.64 (m, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=5 Hz, 1 H), 7.85 (br d, J=8 Hz, 1 H)	1.25	456	A

Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method
39	2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(quinuclidin-3-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.35 (d, J=7 Hz, 6 H), 1.68 - 1.93 (m, 3 H), 2.01 - 2.12 (m, 2 H), 2.97 (br dd, J=13, 4 Hz, 1 H), 3.14 - 3.26 (m, 4 H), 3.36 - 3.45 (m, 1 H), 3.52 - 3.67 (m, 1 H), 4.13 (br d, J=5 Hz, 1 H), 4.57 - 4.67 (m, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.38 (s, 1 H), 7.59 (d, J=5 Hz, 1 H), 8.41 (d, J=6 Hz, 1 H)	0.62	400	A
40	(R)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-(oxetan-3-yl)piperidin-3-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.22(m, 1 H), 1.34 (d, J=7 Hz, 6 H), 1.48 (m, 1 H), 1.63 - 1.77 (m, 3 H), 1.83 (t, J=10 Hz, 1 H), 2.41 - 2.47 (m, 1 H), 2.52 - 2.59 (m, 1 H), 3.38 (m, 2 H), 3.76 (m, 1 H), 4.38 (dt, J=9, 6 Hz, 2 H), 4.50 (td, J=6, 1 Hz, 2 H), 4.55 (d, J=2 Hz, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.37 (s, 1 H), 7.59 (d, J=5 Hz, 1 H), 7.92 (d, J=8 Hz, 1 H)	1,02	N/A	B
41	(R)-N-(1-(3-fluoropropyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate	1H NMR (400 MHz, DMSO-d6) δ ppm 1.20 - 1.50 (m, 8 H), 1.62 - 1.99 (m, 6 H), 2.32 - 2.44 (m, 2 H), 2.53 - 2.62 (m, 1 H), 2.66 - 2.73 (m, 1 H), 3.39 - 3.48 (m, 1 H), 3.70 - 3.78 (m, 1 H), 4.36 - 4.60 (m, 4 H), 7.32 (d, J=5 Hz, 1 H), 7.38 (s, 1 H), 7.59 (d, J=5 Hz, 1 H), 7.84 (d, J=8 Hz, 1 H)	0.65	434	A
42	(R)-N-(1-acetylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) Mixture of Isomers majo 60% : δ ppm 1.25 (m, 1 H), 1.35 (m, 6 H), 1.39 - 1.58 (m, 2 H), 1.62 - 1.86 (m, 2 H), 1.92 - 1.98 (m, 3 H), 2.47 (m, 1 H), 3.16 (m, 1 H), 3.38 (m, 1 H), 3.53 - 3.70 (m, 2 H), 4.49 - 4.66 (m, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.37 (s, 1 H), 7.59 (d, J=5 Hz, 1 H), 8.13 (d, J=7 Hz, 1 H)	1.38	N/A	B
43	(R)-N-(1-((3,3-difluorocyclobutyl)methyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate	1H NMR (400 MHz, DMSO-d6) δ ppm 1.18 - 1.31 (m, 1 H), 1.35 (d, J=7 Hz, 6 H), 1.45 (br dd, J=10, 3 Hz, 1 H), 1.61 - 1.71 (m, 2 H), 1.89 - 2.07 (m, 2 H), 2.13 - 2.38 (m, 3 H), 2.39 - 2.46 (m, 2 H), 2.52 - 2.73 (m, 4 H), 3.33 - 3.45 (m, 1 H), 3.70 - 3.78 (m, 1 H), 4.45 - 4.64 (m, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=5 Hz, 1 H), 7.81 (br d, J=8 Hz, 1 H)	0.72	478	A
45	(R)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-(1-methyl-1H-imidazol-2-yl)piperidin-3-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.31 (d, J=8 Hz, 3 H), 1.34 (d, J=8 Hz, 3 H), 1.45 (m, 1 H), 1.61 (m, 1 H), 1.70 - 1.83 (m, 2 H), 2.62 - 2.76 (m, 2 H), 3.02(m, 1 H), 3.12 (dd, J=12, 3 Hz, 1 H), 3.36 (m, 1 H), 3.40 (s, 3 H), 3.88 (m, 1 H), 4.58 (q, J=15 Hz, 2 H), 6.41 (d, J=1 Hz, 1 H), 6.80 (d, J=1 Hz, 1 H), 7.32 (d, J=5 Hz, 1 H), 7.38 (s, 1 H), 7.59 (d, J=5 Hz, 1 H), 8.20 (d, J=8 Hz, 1 H)	1,08	454	B
46	2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methyl-2-oxopiperidin-4-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.36 (d, J=7 Hz, 6 H), 1.69 - 1.79 (m, 1 H), 1.89 - 1.97 (m, 1 H), 2.16 (dd, J=17, 8 Hz, 1 H), 2.44 - 2.47 (m, 1 H), 2.81 (s, 3 H), 3.22 - 3.30 (m, 2 H), 3.36 - 3.46 (m, 1 H), 4.00 - 4.09 (m, 1 H), 4.57 (s, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.38 (s, 1 H), 7.59 (d, J=6 Hz, 1 H), 8.15 (d, J=7 Hz, 1 H)	0.91	402	A

Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method
47	2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methyl-6-oxopiperidin-3-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.35 (d, J=7 Hz, 6 H), 1.74 - 1.91 (m, 2 H), 2.21 - 2.42 (m, 2 H), 2.79 (s, 3 H), 3.10 (dd, J=12, 7 Hz, 1 H), 3.34 - 3.46 (m, 2 H), 4.04 - 4.13 (m, 1 H), 4.53 - 4.64 (m, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=6 Hz, 1 H), 8.25 (d, J=7 Hz, 1 H)	0.89	402	A
48	2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(3R)-1-isopropyl-3-piperidyl]acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.11 (br d, J=5 Hz, 6 H), 1.35 (d, J=7 Hz, 7 H), 1.60 (br d, J=10 Hz, 1 H), 1.81 (br s, 2 H), 2.47 - 2.58 (m, 2 H), 2.98 - 3.17 (m, 2 H), 3.24 - 3.30 (m, 1 H), 3.37 - 3.42 (m, 1 H), 3.91 (br s, 1 H), 4.52 - 4.63 (m, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.38 (s, 1 H), 7.59 (d, J=5 Hz, 1 H), 8.05 (br s, 1 H)	0.66	416	A
49	N-[(3R)-1-cyclopentyl-3-piperidyl]-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.35 (d, J=7 Hz, 14 H), 1.71 - 1.80 (m, 2 H), 1.84 (br s, 2 H), 2.18 - 2.44 (m, 2 H), 3.01 (br d, J=13 Hz, 3 H), 3.34 - 3.46 (m, 1 H), 3.84 (br s, 1 H), 4.52 - 4.62 (m, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.38 (s, 1 H), 7.59 (d, J=6 Hz, 1 H), 7.98 (br s, 1 H)	0.71	442	A
53	2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(2-methylpyrazol-3-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.37 (d, J=7 Hz, 6 H), 3.33 - 3.44 (m, 1 H), 3.67 (s, 3 H), 4.82 (s, 2 H), 6.15 (d, J=2 Hz, 1 H), 7.31 - 7.35 (m, 2 H), 7.36 - 7.43 (m, 1 H), 7.59 (d, J=5 Hz, 1 H), 10.12 (s, 1 H)	0.99-1.02	371	A
54	2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(1-methylpyrazol-3-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.36 (d, J=7 Hz, 6 H), 3.33 - 3.43 (m, 1 H), 3.74 (s, 3 H), 4.73 (s, 2 H), 6.39 (d, J=2 Hz, 1 H), 7.32 (d, J=5 Hz, 1 H), 7.38 (s, 1 H), 7.54 (d, J=2 Hz, 1 H), 7.59 (d, J=6 Hz, 1 H), 10.60 (s, 1 H)	1.02	371	A
55	N-[(1-tert-butyl-5-oxo-pyrrolidin-3-yl)methyl]-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide	1H NMR (500 MHz, DMSO-d6) δ ppm 1.29 (s, 9 H), 1.35 (dd, J=7, 2 Hz, 6 H), 1.90 - 2.02 (m, 1 H), 2.25 - 2.35 (m, 2 H), 3.03 - 3.15 (m, 3 H), 3.34 - 3.40 (m, 1 H), 3.45 (dd, J=10, 7 Hz, 1 H), 4.55 (s, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=6 Hz, 1 H), 8.09 (br t, J=6 Hz, 1 H)	1.09	444	A
56	2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(3-pyridyl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.37 (d, J=7 Hz, 6 H), 3.34 - 3.44 (m, 1 H), 4.82 (s, 2 H), 7.30 - 7.38 (m, 2 H), 7.40 (s, 1 H), 7.60 (d, J=5 Hz, 1 H), 8.01 (d, J=9 Hz, 1 H), 8.29 (br d, J=4 Hz, 1 H), 8.73 (br s, 1 H), 10.37 (s, 1 H)	0.79	368	A
57	2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[rac-(3R)-1-(2,2-dimethylcyclobutyl)-3-piperidyl]acetamide	1H NMR (500 MHz, DMSO-d6) δ ppm 0.85 - 0.98 (m, 2 H), 1.03 (br d, J=10 Hz, 3 H), 1.23 - 1.41 (m, 9 H), 1.43 - 1.87 (m, 6 H), 2.41 - 2.70 (m, 6 H), 3.33 - 3.41 (m, 1 H), 3.76 (br s, 1 H), 4.49 - 4.61 (m, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.38 (d, J=3 Hz, 1 H), 7.59 (d, J=6 Hz, 1 H)	0.75	456	A

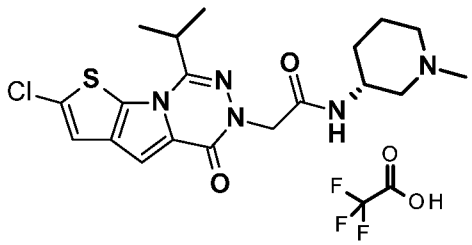
Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method
58	2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(2-pyridyl)acetamide	1H NMR (500 MHz, DMSO-d6) δ ppm 1.36 (d, J=7 Hz, 6 H), 3.36 - 3.42 (m, 1 H), 4.86 (s, 2 H), 7.12 (ddd, J=7, 5, 1 Hz, 1 H), 7.33 (d, J=6 Hz, 1 H), 7.39 (s, 1 H), 7.60 (d, J=6 Hz, 1 H), 7.75 - 7.87 (m, 1 H), 8.00 (br d, J=8 Hz, 1 H), 8.29 - 8.42 (m, 1 H), 10.75 (s, 1 H)	1.10	368	A
61	N-[(3R)-1-cyclopropylazepan-3-yl]-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo [6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide	1H NMR (500 MHz, DMSO-d6) δ ppm -0.05 - 0.05 (m, 2 H), 0.13 (dd, J=6, 1 Hz, 2 H), 1.15 (d, J=7 Hz, 6 H), 1.18 - 1.53 (m, 6 H), 1.66 - 1.71 (m, 1 H), 2.38 - 2.51 (m, 3 H), 2.64 (dd, J=13, 4 Hz, 1 H), 3.17 (spt, J=7 Hz, 1 H), 3.57 - 3.64 (m, 1 H), 4.28 - 4.39 (m, 2 H), 7.12 (d, J=6 Hz, 1 H), 7.18 (s, 1 H), 7.38 (d, J=5 Hz, 1 H), 7.44 (br d, J=8 Hz, 1 H)	0.64	428	A
62	2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo [6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(3R)-1-methylazepan-3-yl]acetamide	1H NMR (500 MHz, DMSO-d6) δ ppm 1.35 (d, J=7 Hz, 6 H), 1.42 - 1.64 (m, 5 H), 1.69 - 1.75 (m, 1 H), 2.27 (s, 3 H), 2.43 (dd, J=13, 8 Hz, 1 H), 2.50 - 2.53 (m, 2 H), 2.63 (dd, J=13, 4 Hz, 1 H), 3.30 - 3.41 (m, 1 H), 3.84 - 3.91 (m, 1 H), 4.53 - 4.58 (m, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=5 Hz, 1 H), 7.85 (br d, J=8 Hz, 1 H)	0.64	402	A
63	N-(1-cyclopropyl-5,5-difluoropiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide 2,2,2-trifluoroacetate	1H NMR (400 MHz, DMSO-d6) δ ppm 0.25 - 0.36 (m, 2 H), 0.39 - 0.48 (m, 2 H), 1.35 (d, J=7 Hz, 6 H), 1.73 - 1.89 (m, 2 H), 2.14 - 2.27 (m, 2 H), 2.52 - 2.68 (m, 1 H), 2.89 - 3.03 (m, 2 H), 3.33 - 3.42 (m, 1 H), 3.89 (br s, 1 H), 4.56 (s, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.38 (s, 1 H), 7.59 (d, J=6 Hz, 1 H), 7.93 (d, J=8 Hz, 1 H)	1.26	450	A
64	2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-((3R)-1-(1-methoxypropan-2-yl)piperidin-3-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 0.90 (d, J=7 Hz, 3 H), 1.22 (m, 1 H), 1.36 (d, J=7 Hz, 6 H), 1.42 (m, 1 H), 1.58 - 1.72 (m, 2 H), 2.05 - 2.29 (m, 2 H), 2.61 (m, 1 H), 2.69 - 2.79 (m, 2 H), 3.13 - 3.22 (m, 4 H), 3.34 - 3.41 (m, 2 H), 3.69 (m, 1 H), 4.48 - 4.62 (m, 2 H), 7.33 (d, J=5 Hz, 1 H), 7.38 (s, 1 H), 7.59 (d, J=6 Hz, 1 H), 7.78 (dd, J=8, 3 Hz, 1 H)	1.07	446	B
65	2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(2-methoxypyridin-4-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.36 (d, J=7 Hz, 6 H), 3.33 - 3.41 (m, 1 H), 3.82 (s, 3 H), 4.81 (s, 2 H), 7.05 - 7.13 (m, 2 H), 7.33 (d, J=6 Hz, 1 H), 7.40 (s, 1 H), 7.60 (d, J=5 Hz, 1 H), 8.05 (d, J=6 Hz, 1 H), 10.57 (s, 1 H)	1.07	398	A
66	2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo [6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-pyrimidin-4-yl-acetamide	1H NMR (500 MHz, DMSO-d6) δ ppm 1.36 (d, J=7 Hz, 6 H), 3.35 - 3.43 (m, 1 H), 4.90 (s, 2 H), 7.33 (d, J=6 Hz, 1 H), 7.40 (s, 1 H), 7.60 (d, J=5 Hz, 1 H), 7.99 (dd, J=6, 1 Hz, 1 H), 8.66 (d, J=6 Hz, 1 H), 8.91 (d, J=1 Hz, 1 H), 11.22 (br s, 1 H)	1.03	369	A
67	2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo [6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(4-pyridyl)acetamide	1H NMR (500 MHz, DMSO-d6) δ ppm 1.36 (d, J=7 Hz, 2 H), 3.35 - 3.44 (m, 1 H), 4.84 (s, 2 H), 7.33 (d, J=5 Hz, 1 H), 7.41 (s, 1 H), 7.57 - 7.61 (m, 3 H), 8.46 (d, J=6 Hz, 2 H), 10.66 (s, 1 H)	0.67	368	A

Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method
68	2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo [6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(6-methyl-3-pyridyl)acetamide	1H NMR (500 MHz, DMSO-d6) δ ppm 1.36 (d, J=7 Hz, 6 H), 2.45 (s, 3 H), 3.37 - 3.42 (m, 1 H), 4.81 (s, 2 H), 7.30 - 7.35 (m, 2 H), 7.40 (s, 1 H), 7.60 (d, J=5 Hz, 1 H), 7.95 (dd, J=8, 2 Hz, 1 H), 8.66 - 8.68 (m, 1 H), 10.38 (br s, 1 H)	0.72	382	A
70	N-(5-fluoropyrimidin-4-yl)-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo [6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.37 (d, J=7 Hz, 6 H), 3.45 - 3.61 (m, 1 H), 4.99 (s, 2 H), 7.33 (d, J=5 Hz, 1 H), 7.42 (s, 1 H), 7.60 (d, J=5 Hz, 1 H), 8.82 (dd, J=7, 3 Hz, 2 H), 11.08 (s, 1 H)	1.02	387	A
71	2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(3R)-1-(1-methylcyclopentyl)-3-piperidyl]acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 0.85 (s, 3 H), 1.21 - 1.34 (m, 3 H), 1.37 (dd, J=7, 1 Hz, 6 H), 1.39 - 1.55 (m, 7 H), 1.55 - 1.69 (m, 2 H), 2.13 (t, J=9 Hz, 1 H), 2.26 (t, J=10 Hz, 1 H), 2.58 (m, 1 H), 2.72(m, 1 H), 3.45 (m hidden, 1 H), 3.75 (m, 1 H), 4.46 - 4.66 (m, 2 H), 7.33 (d, J=6 Hz, 1 H), 7.40 (s, 1 H), 7.60 (d, J=6 Hz, 1 H), 7.62 (br d, J=8 Hz, 1 H)	0.73	456	A
74	N-[3-(acetamidomethyl) bicyclo[1.1.1]pentan-1-yl]-2-(8-isopropyl-5-oxothieno [3',2':4,5] pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.35 (d, J=7 Hz, 6 H), 1.80 (s, 3 H), 1.84 (s, 6 H), 3.11 - 3.26 (m, 2 H), 3.35 (m, 1 H), 4.48 (s, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.36 (s, 1 H), 7.58 (d, J=6 Hz, 1 H), 7.72 (t, J=6 Hz, 1 H), 8.48 (s, 1 H)	0.98	428	A
75	N-[(3R)-1-(cyanomethyl)piperidin-3-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.13 - 1.30 (m, 1 H), 1.35 (d, J=7 Hz, 6 H), 1.50 (m, 1 H), 1.65 - 1.79 (m, 2 H), 2.04 (br t, J=10 Hz, 1 H), 2.14 (t, J=11 Hz, 1 H), 2.62 (m, 1 H), 2.75 (m, 1 H), 3.38 (m, 1 H), 3.73 (d, J=4 Hz, 2 H), 3.81 (m, 1 H), 4.55 (d, J=2 Hz, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=5 Hz, 1 H), 7.94 (d, J=8 Hz, 1 H)	1.06	413	A
76	N-[(3R)-1-methylpyrrolidin-3-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.35 (d, J=7 Hz, 6 H), 1.69 (m, 1 H), 2.03 - 2.30 (m, 1 H), 2.43 (s, 3 H), 2.56 - 2.65 (m, 2 H), 2.82 - 2.91 (m, 2 H), 3.26 - 3.31 (m hidden, 1 H), 4.25 (m, 1 H), 4.55 (d, J=3 Hz, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=6 Hz, 1 H), 8.29 (br d, J=7 Hz, 1 H)	0.60	374	A
77	N-[(3R)-1-(2-cyanoethyl)piperidin-3-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.23 (m, 1 H), 1.35 (d, J=7 Hz, 6 H), 1.49 (m, 1 H), 1.59 - 1.79 (m, 2 H), 1.82 - 2.09 (m, 2 H), 2.31 - 2.90 (m partially hidden, 6 H), 3.35 - 3.49 (m partially hidden, 1 H), 3.76 (br s, 1 H), 4.48 - 4.61 (m, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=6 Hz, 1 H), 7.86 (br s, 1 H)	0.64	427	A

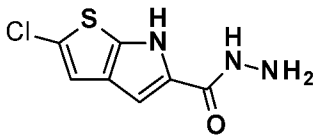
Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method
78	N-[(3R)-1-[(2R)-2-hydroxypropyl]piperidin-3-yl]-2-(8-isopropyl-5-oxothieno [3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.01 (d, J=6 Hz, 3 H), 1.28 (m, 1 H), 1.35 (d, J=7 Hz, 6 H), 1.57 (m, 1 H), 1.63 - 1.75 (m, 2 H), 2.08 - 3.01 (m partially hidden, 7 H), 3.40 (m, 1 H), 3.74 - 3.92 (m, 2 H), 4.46 - 4.65 (m, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.37 (s, 1 H), 7.59 (d, J=6 Hz, 1 H), 7.96 (br d, J=8 Hz, 1 H)	0.60	432	A
79	N-[(3R)-1-(1-hydroxy-2-methylpropan-2-yl)piperidin-3-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 0.92 (s, 6 H), 1.24 (m, 1 H), 1.35 (d, J=7 Hz, 6 H), 1.45 (m, 1 H), 1.65 (d, J=9 Hz, 2 H), 2.17 (br dd, J=11, 9 Hz, 1 H), 2.26 - 2.34 (m, 1 H), 2.71 (m, 1 H), 2.85 (m, 1 H), 3.31 - 3.42 (m partially hidden, 3 H), 3.71 - 3.78 (m, 2 H), 4.47 - 4.63 (m, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=6 Hz, 1 H), 7.83 (d, J=8 Hz, 1 H)	2.55	446	C
80	ethyl-2-methyl-2-[3-[[2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetyl]amino] piperidin-1-yl]propanoate	1H NMR (400 MHz, DMSO-d6) δ ppm 1.13 - 1.20 (m, 9 H), 1.25 (m, 1 H), 1.35 (d, J=7 Hz, 6 H), 1.43 (m, 1 H), 1.55 - 1.76 (m, 2 H), 2.02 (t, J=10 Hz, 1 H), 2.15 (t, J=10 Hz, 1 H), 2.67 (m, 1 H), 2.79(m, 1 H), 3.36 (spt, J=6 Hz, 1 H), 3.67 (m, 1 H), 4.03 (q, J=7 Hz, 2 H), 4.48 - 4.61 (m, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=5 Hz, 1 H), 7.74 (br d, J=8 Hz, 1 H)	0.84	488	A
82	N-[(1R,4R)-2-methyl-2-azabicyclo[2.2.1]heptan-6-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5] pyrrolo[1,2-d][1,2,4] triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 0.81 (m, 1 H), 1.27 (d, J=10 Hz, 1 H), 1.36 (d, J=7 Hz, 6 H), 1.57 (m, 1 H), 1.88 (m, 1 H), 2.19 (m, 1 H), 2.22 (s, 3 H), 2.30 - 2.37 (m, 2 H), 2.69 (d, J=9 Hz, 1 H), 2.89 (br s, 1 H), 3.94 (m, 1 H), 4.53 - 4.68 (m, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.38 (s, 1 H), 7.58 (d, J=5 Hz, 1 H), 7.72 (br d, J=8 Hz, 1 H)	0.62	400	A
83	N-(2-methyl-2-azaspiro[3.3]heptan-6-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.34 (d, J=7 Hz, 6 H), 1.96 - 2.07 (m, 2 H), 2.17 - 2.30 (m, 3 H), 2.31 - 2.38 (m, 2 H), 3.13 - 3.22 (m, 2 H), 3.28 (br s, 2 H), 3.37(m, 1 H), 4.07 (m, 1 H), 4.49 (s, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.36 (s, 1 H), 7.58 (d, J=5 Hz, 1 H), 8.14 (d, J=8 Hz, 1 H)	0.63	400	A
84	2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-pyrimidin-5-ylacetamide	1H NMR (500 MHz, DMSO-d6) δ ppm 1.37 (d, J=7 Hz, 6 H), 3.40 (spt, J=7 Hz, 1 H), 4.85 (s, 2 H), 7.33 (d, J=5 Hz, 1 H), 7.41 (s, 1 H), 7.60 (d, J=5 Hz, 1 H), 8.90 (s, 1 H), 8.99 (s, 2 H), 10.63 (br s, 1 H)	0.97	369	A
85	2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(2-oxo-4-piperidyl) acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.35 (dd, J=7, 2 Hz, 6 H), 1.70 - 1.88 (m, 2 H), 2.03 - 2.27 (m, 2 H), 3.02 - 3.13 (m, 1 H), 3.24 - 3.32 (m, 1 H), 3.55 - 3.61 (m, 1 H), 3.89 - 4.05 (m, 1 H), 4.58 (s, 2 H), 7.32 (dd, J=5, 1 Hz, 1 H), 7.37 (d, J=3 Hz, 1 H), 7.58 (d, J=5 Hz, 1 H), 8.06 (br t, J=6 Hz, 1 H), 8.18 (d, J=7 Hz, 1 H)	2.86-2.91	388	C

Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method
86	N-(1-cyclopropylpyrrolidin-3-yl)-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 0.59 - 1.06 (m, 4 H), 1.35 (d, J=7 Hz, 6 H), 1.72 - 2.27 (m, 2 H), 2.75 - 3.76 (m, 5 H), 4.25 - 4.48 (m, 1 H), 4.59 (s, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.38 (s, 1 H), 7.59 (d, J=5 Hz, 1 H), 8.39 (br s, 1 H), 9.65 (br s, 1 H)	0.63	400	A
87	2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[rac-(3R)-1-tert-butylpyrrolidin-3-yl]acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.09 (s, 9 H), 1.35 (d, J=7 Hz, 6 H), 1.57 - 1.73 (m, 1 H), 1.98 - 2.14 (m, 1 H), 2.52 - 2.62 (m, 1 H), 2.71 - 2.83 (m, 1 H), 2.84 - 2.95 (m, 1 H), 3.04 (br dd, J=10, 7 Hz, 1 H), 3.30 - 3.43 (m, 1 H), 4.15 - 4.28 (m, 1 H), 4.50 - 4.60 (m, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=6 Hz, 1 H), 8.24 (br d, J=7 Hz, 1 H)	0.66	416	A

Example 5 ; (R)-2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate



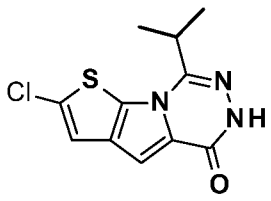
Int 5: 2-chloro-6H-thieno[2,3-b]pyrrole-5-carbohydrazide



To a solution of methyl 2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylate (1.5 g, 6.96 mmol) in 10 ml of MeOH, hydrazine (1.31 ml, 20.87 mmol) is added, and this mixture is heated at reflux overnight. After cooling down the solution, the precipitate formed is filtered off, washed with ether and dried under vacuum. The title compound is obtained as a beige solid (1.39 g, 92% yield).

LCMS (method F): Rt = 1.14 min; MS m/z $[M+H]^+$ 216/218

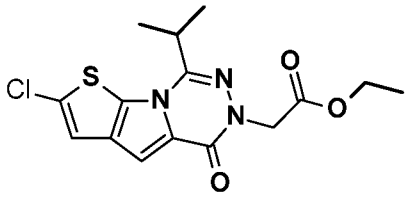
Int 6: 2-chloro-8-isopropylthieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one



Under nitrogen, to a solution of 2-chloro-6H-thieno[2,3-b]pyrrole-5-carbohydrazide (1.39 g, 6.45 mmol) in 20 ml of DMF is added methyl 2-methylpropanimidoate hydrochloride (1.10 g, 7.73 mmol). This mixture is stirred at rt for 30 min. Then solid tBuOK (2.15g, 18.82 mmol) is added and the resulting mixture is stirred in a preheated oil bath at 90°C for 24 h. After cooling down to 0°C, the solution is acidified to pH 5 with a saturated NH_4Cl aqueous solution. The precipitate formed is filtered off and purified by flash chromatography on silica gel using Cyclohexane/EtOAc (from 10% to 50%) to give the title compound (750 mg, 43% yield) as a brown solid.

LCMS (method F): Rt = 1.82 min; MS m/z $[M+H]^+$ 268/270

Int 7: ethyl 2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate

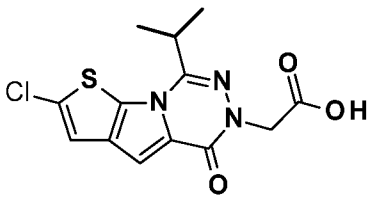


Under nitrogen, to a solution of, 2-chloro-8-isopropylthieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one (750 mg, 2.80 mmol) in 20ml of DMF is added K_2CO_3 (581 mg, 4.20 mmol), followed by a dropwise addition of ethyl iodoacetate (508 µl, 4.20 mmol). The mixture is stirred at rt for 12h.

The reaction mixture is diluted with water then extracted twice with EtOAc. The combined organic layers are washed with water, then with brine, dried over Na_2SO_4, filtered off and concentrated under reduced pressure. The residue is purified by Flash chromatography on silica gel using Cyclohexane/EtOAc (from 10% to 30%) to give the title compound as a white solid (800 mg, 80% yield).

LCMS (method F): Rt = 2.18 min; MS m/z $[M+H]^+$ 354/356

Int 8: 2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid

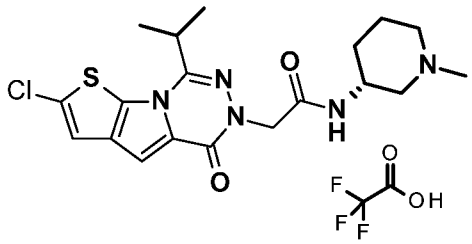


To a solution of ethyl 2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate (808 mg, 2.28 mmol) in 20ml of dioxane is added a solution of NaOH (1M) (6.85 ml, 6.85 mmol). The resulting solution is stirred at rt overnight.

The mixture is acidified with HCl (1M). The precipitate formed is filtered off, washed with water and pentane. After drying overnight under vacuum in presence of P_2O_5, the title compound is obtained as a white solid (613 mg, 82% yield).

LCMS (method F): Rt = 1.84 min; MS m/z $[M+H]^+$ 326/328

Ex 5: (*R*)-2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate



Under nitrogen, to a suspension of (3*R*)-1-methylpiperidin-3-amine dihydrochloride (73 mg, 368 µmol) and 2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid (100 mg, 307 µmol) in 2 ml of DMF is added DIPEA (268 µl, 1.53 mmol) followed by HATU (175 mg, 460 µmol). The resulting mixture is stirred at rt for 12h. Some drops of TFA are added and the resulting solution is purified by reverse layer chromatography Waters SunFire PrepC18 OBD 30 x 100 mm column, water containing 0.1% TFA with a gradient of acetonitrile 20 to 80% in 18 min.

After evaporation under reduced pressure and drying overnight, the title compound is obtained as a solid (116 mg, 71% yield).

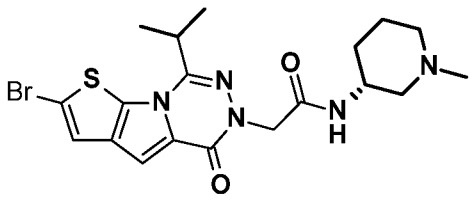
1H NMR (400 MHz, DMSO-d6) δ ppm 1.24 - 1.50 (m, 7 H), 1.67 (m, 1 H), 1.79 - 1.95 (m, 2 H), 2.64 (m, 1 H), 2.73 - 2.89 (m, 1 H), 3.22 (sept, J=6.6 Hz, 1H), 3.32 - 3.46 (m, 4 H), 3.94 (m, 1 H), 4.57 (s, 2 H), 7.34 (s, 1 H), 7.50 (s, 1 H), 8.26 (d, J=7.5 Hz, 1 H), 9.54 (br s, 1 H)

LCMS $[M+H]^+$ = 422; Rt =0.76; Method A

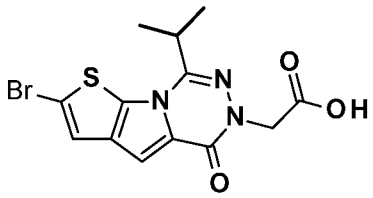
The following examples were synthesized analogous to the previous procedure, using the appropriate amines:

Ex N°	Name	NMR	LCMS Rt(min)	LCMS [M+H]+	LCMS Analytical method
6	(R)-2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclopropylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate	1H NMR (400 MHz, DMSO-d6) δ ppm 0.76 - 1.01 (m, 4 H), 1.34 (d, J=6.7, 6 H), 1.45 (m, 1 H), 1.65 (m, 1 H), 1.75 - 1.99 (m, 2 H), 2.89 (m, 2 H), 3.05 (m, 1 H), 3.23 (sept, *J*=6.7, 1 H), 3.46 (m, 2 H), 3.92 (m, 1 H), 4.58 (s, 2 H), 7.35 (s, 1 H), 7.50 (s, 1 H), 8.30 (br d, J=7.3 Hz, 1 H), 9.02 (br s, 1 H)	0.80	448	A
7	2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(thiazol-5-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.34 (d, J=6.5 Hz, 6 H), 3.24 (sept, J=6,5 Hz, 1 H), 4.85 (s, 2 H), 7.38 (s, 1 H), 7,51 (s, 1 H), 7.64 (d, J=0.8 Hz, 1 H), 8.60 (br s, 1 H), 11.55 (s, 1 H)	1.27	408	A
10	(R)-2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclobutylpiperidin-3-yl)acetamide formate	1H NMR (500 MHz, DMSO-d6) δ ppm 1.17 - 1.26 (m, 1 H), 1.33 (d, J=7 Hz, 6 H), 1.38 - 1.46 (m, 1 H), 1.54 - 1.77 (m, 8 H), 1.92 (br d, J=6 Hz, 2 H), 2.60 - 2.68 (m, 3 H), 3.19 - 3.25 (m, 1 H), 3.67 - 3.74 (m, 1 H), 4.53 - 4.58 (m, 2 H), 7.34 (s, 1 H), 7.49 (s, 1 H), 7.82 (br d, J=8 Hz, 1 H)	0.83	462	A
34	2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(5,5-difluoro-1-methylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate	1H NMR (400 MHz, DMSO-d6) δ ppm 1.34 (d, J=7 Hz, 6 H), 1.81 - 2.08 (m, 2 H), 2.28 - 2.43 (m, 4 H), 2.59 - 2.80 (m, 3 H), 3.19 - 3.33 (m, 1 H), 4.12 (br s, 1 H), 4.59 (s, 2 H), 7.35 (s, 1 H), 7.50 (s, 1 H), 8.32 (br d, J=3 Hz, 1 H)	0.89	458	A

Example 8 ; (*R*)-2-(2-bromo-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide



Int 9: 2-(2-bromo-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid

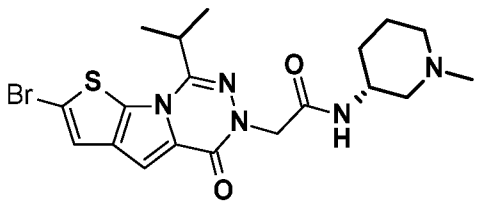


Under nitrogen, to a solution of ethyl 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate (260 mg, 814 µmol) in 10 ml of $CHCl_3$ is added 1 ml of acetic acid and NBS (159 mg, 896 µmol). The mixture is stirred at rt overnight. A solution of $Na_2S_2O_3$ (1M) is added and the mixture is extracted with DCM. The organic layer is dried over Na_2SO_4, filtered and concentrated under reduced pressure.

The residue obtained is dissolved in 10 ml of THF and 1 ml of MeOH, and 0.5 ml of a solution of NaOH (1N) is added. The solution is stirred at rt 1h, then the mixture is acidified with a solution of HCl (1N) followed by extraction with EtOAc, dried over Na_2SO_4 then filtered off and concentrated. The corresponding acid is obtained as a white solid (270 mg, 89% yield).

LCMS (method E): Rt = 1.43 min; MS m/z $[M+H]^+$ 370/372

Ex 8: (*R*)-2-(2-bromo-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide



Under nitrogen, to a suspension of (3*R*)-1-methylpiperidin-3-amine dihydrochloride (74 mg, 375 µmol) and 2-(2-bromo-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid (126 mg, 340 µmol) in 2 ml of DMF is added DIPEA (180 µl, 1,03 mmol) followed by HATU (168 mg, 442 µmol). The mixture is stirred at rt for 12h. The crude mixture is purified

by reverse layer chromatography Waters SunFire PrepC18 OBD 30 x 100 mm column, water containing 0.1% HCO_2H with a gradient of acetonitrile 10 to 80% in 18 min. After evaporation under reduced pressure and drying overnight, the title compound is obtained as a solid (51 mg, 32% yield).

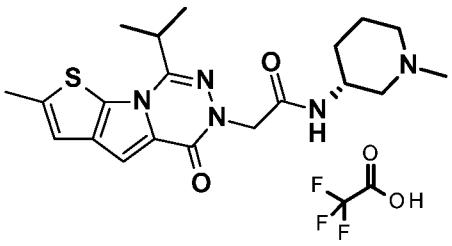
1H NMR (500 MHz, DMSO-d6) δ ppm 1.33 (d, J=6.8 Hz, 6 H), 1.39 (m, 1 H), 1.66 (m, 1 H), 1.85 (m, 1 H), 1.91 (m, 1 H), 2.63 (m, 1 H), 2.78 - 2.89 (m, 4 H), 3.23 (sept, J=6.8 Hz, 1 H), 3.41 (m, 2 H), 3.94 (m, 1 H), 4.57 (s, 2 H), 7.33 (s, 1 H), 7.58 (s, 1 H), 8.25 (d, J=7.6 Hz, 1 H), 9.45 (br s, 1 H)

LCMS $[M+H]^+$ = 466/468; Rt =0.76; Method A

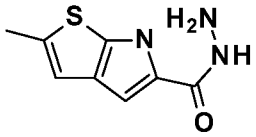
The following examples were synthesized analogous to the previous procedure, using the appropriate amines

Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method
31	(R)-2-(2-bromo-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclobutylpiperidin-3-yl) acetamide 2,2,2-trifluoroacetate	1H NMR (400 MHz, DMSO-d6) δ ppm 1.33 (d, J=7 Hz, 6 H), 1.43 (br dd, J=13, 4 Hz, 1 H), 1.59 - 1.81 (m, 3 H), 1.83 - 1.98 (m, 2 H), 2.08 - 2.22 (m, 4 H), 2.39 - 2.46 (m, 1 H), 2.57 - 2.70 (m, 1 H), 3.19 - 3.34 (m, 3 H), 3.68 (q, J=8 Hz, 1 H), 3.84 - 4.01 (m, 1 H), 4.52 - 4.65 (m, 2 H), 7.34 (s, 1 H), 7.59 (s, 1 H), 8.28 (d, J=8 Hz, 1 H), 9.49 (br d, J=7 Hz, 1 H)	2.86	506	A
59	2-(4-bromo-12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(1-tert-butyl-3-piperidyl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.06 (s, 9 H), 1.20 - 1.38 (m, 7 H), 1.43 - 1.54 (m, 1 H), 1.67 - 1.77 (m, 2 H), 2.15 (br t, J=10 Hz, 1 H), 2.24 - 2.38 (m, 1 H), 2.88 - 3.02 (m, 2 H), 3.22 (spt, J=7 Hz, 1 H), 3.71 - 3.88 (m, 1 H), 4.50 - 4.61 (m, 2 H), 7.33 (s, 1 H), 7.58 (s, 1 H), 7.90 (br d, J=8 Hz, 1 H)	0.80	508	A

Example 9 ; (*R*)-2-(8-isopropyl-2-methyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate

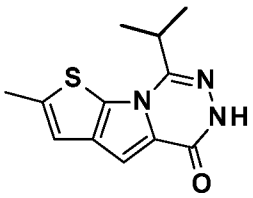


Int 10: 2-methyl-6H-thieno[2,3-b]pyrrole-5-carbohydrazide



Similarly to 6H-thieno[2,3-b]pyrrole-5-carbohydrazide synthesis, starting from Ethyl 2-methyl-6H-thieno[2,3-b]pyrrole-5-carboxylate (300 mg, 1.43 mmol) and hydrazine (0.270 ml, 4.3 mmol), 150 mg (53% yield) of the title compound is obtained as a solid.
LCMS (method E): Rt = 0.96 min; MS m/z $[M+H]^+$ 196

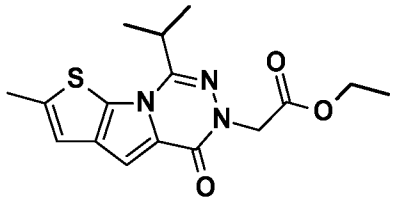
Int 11: 8-isopropyl-2-methylthieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one



Under nitrogen, to a solution of 2-methyl-6H-thieno[2,3-b]pyrrole-5-carbohydrazide (100 mg, 512 µmol) in 5 ml of DMF is added methyl 2-methylpropanimidoate hydrochloride (87 mg, 615 µmol).

This mixture is stirred at rt for 30 min. Then solid tBuOK (115 mg, 1,02 mmol) is added and the resulting mixture is stirred in a preheated oil bath at 100°C for 1 h. After cooling to 0°C, the mixture is acidified with (1N) HCl to pH 5. The precipitate formed is filtered off, washed with water and dried under vacuum to give the title compound as a violet solid. (110 mg, 86% yield).
LCMS (method E): Rt = 1.33 min; MS m/z $[M+H]^+$ 248

Int 12: ethyl 2-(8-isopropyl-2-methyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate

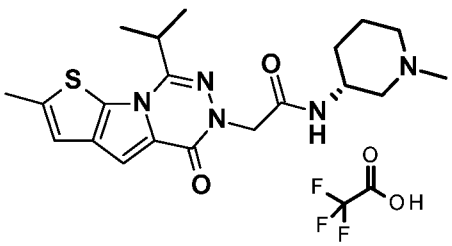


Under nitrogen, to a solution of 8-isopropyl-2-methylthieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one (110 mg, 445 µmol) in 5 ml of DMF is added K_2CO_3 (92 mg, 667 µmol), followed by a dropwise addition of ethyl iodoacetate (81 µl, 667 µmol). The resulting mixture is stirred at rt for 12h.

The reaction mixture is diluted with a saturated aqueous solution of NH_4Cl, then extracted twice with EtOAc. The combined organic layers are washed with water, then with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue is purified by Flash chromatography on silica gel using Cyclohexane/EtOAc (from 10% to 100%) to give the title compound as a white solid (71 mg, 48% yield)

LCMS (method E): Rt = 1.57 min; MS m/z $[M+H]^+$ 334

Ex 9: (*R*)-2-(8-isopropyl-2-methyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate



To a solution of ethyl 2-(8-isopropyl-2-methyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate (71 mg, 213 µmol) in 2 ml of dioxane and 5 ml H2O is added solid NaOH (26 mg, 639 µmol).The solution is stirred at rt overnight.

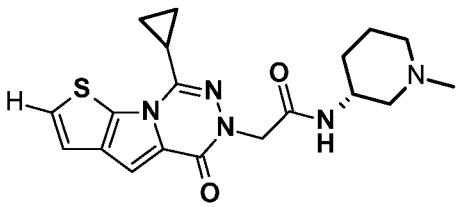
The mixture is acidified with HCl (1N), then extracted with EtOAc. The organic layer is dried over Na_2SO_4, filtered and concentrated under vacuum. Under nitrogen, the residue is solubilized in 5 ml DMF, then (3*R*)-1-methylpiperidin-3-amine dihydrochloride (50 mg, 256 µmol), DIPEA (149 µl, 852 µmol) and HATU (1221 mg, 319 µmol) are added to the solution. The mixture is stirred at rt for 12h. The resulting solution is purified by reverse layer chromatography Waters SunFire PrepC18 OBD 30 x 100 mm column, water containing 0.1% TFA with a gradient of acetonitrile 20 to 80% in 18 min.

After evaporation under reduced pressure and drying overnight, the title compound is obtained as a yellow solid (35 mg, 32% yield).

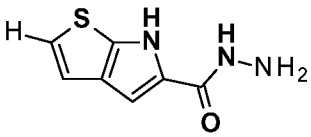
1H NMR (400 MHz, DMSO-d6) δ ppm 1.34 (d, J=7 Hz, 7 H), 1.66 (br d, J=14 Hz, 1 H), 1.80 - 1.94 (m, 2 H), 2.58 (d, J=1 Hz, 3 H), 2.63 (br d, J=10 Hz, 1 H), 2.77 - 2.85 (m, 4 H), 3.26 - 3.36 (m, 3 H), 3.89 - 3.99 (m, 1 H), 4.56 (s, 2 H), 7.03 (d, J=1 Hz, 1 H), 7.26 (s, 1 H), 8.24 (d, J=8 Hz, 1 H)

LCMS $[M+H]^+$ = 402; Rt =0.71; Method A

Example 24 ; (*R*)-2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide



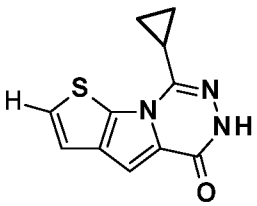
Int 1: 6H-thieno[2,3-b]pyrrole-5-carbohydrazide



To a solution of methyl 6*H*-Thieno[2,3-*b*]pyrrole-5-carboxylate (4 g, 22.07 mmol) in 100 ml of EtOH is added hydrazine solution (35% in water) (24.7 ml, 176.59 mmol) and this mixture is heated at reflux overnight. After cooling down the solution, the precipitate formed is filtered off, washed with ether and dried under vacuum. The title compound is obtained as a white solid (3.4 g, 85% yield).

LCMS (method F): Rt = 1.15 min; MS m/z $[M+H]^+$ 181.2

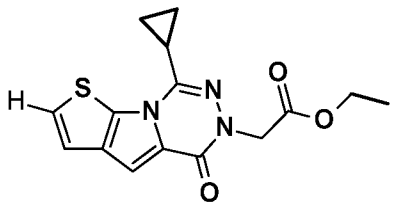
Int 13: 8-cylopropylthieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one



Under nitrogen, to a solution of 6H-thien[2,3-b]pyrrole-5-carbohydrazide (1g, 5.52 mmol) in 40 ml of DMF is added methyl cyclopropanecarboximidate hydrochloride (945 mg, 6.62 mmol) and the mixture is stirred at rt for 1 h.

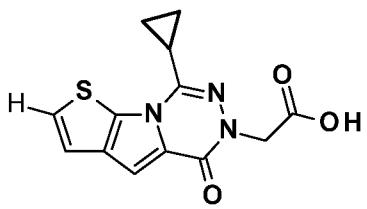
Then, solid tBuOK (1.26 g, 11.04 mmol) is added and the resulting mixture is stirred in a preheated Dry-syn (90°C) for 1h. The mixture is cooled to RT, diluted with EtOAc and washed with 10% $NaHCO_3$ aq solution. The organic layer is dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the title product (490mg, 38% yield).
LCMS (method F): Rt = 1.41 min; MS m/z $[M+H]^+$ 232.2

Int 14: Ethyl 2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate



Under nitrogen, to a solution of 8-cylopropylthieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one (490 mg, 2.12 mmol) in 5 ml of DMF is added Cs_2CO_3 (828 mg, 2.54 mmol), followed by a dropwise addition of ethyl iodoacetate (557 µl, 4,61 mmol). The resulting mixture is stirred at rt for 20 h. Then, the mixture is diluted with water and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel using cyclohexane/EtOAc (from 5% to 40%) to give the title compound as a white solid (500 mg, 77% yield).
LCMS (method F): Rt = 1.79 min; MS m/z $[M+H]^+$ 318.4

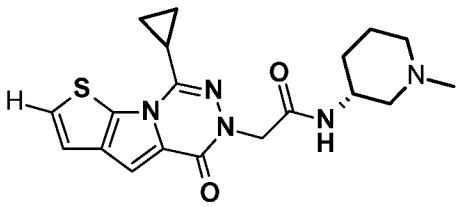
Int 15: 2-(-8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid



To a solution of ethyl 2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate (650 mg, 2,14 mmol) in 15 ml of dioxane/MeOH (1/1) is added a solution of (1M) NaOH (6.43 ml 6.43 mmol). The resulting solution is stirred 20 h at rt. The mixture is acidified with HCl (1M) and extracted with DCM. The organic layer is washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the title compound as a white solid (500 mg, 80% yield).

LCMS (method F): Rt = 1.47 min; MS m/z $[M+H]^+$ 290.0

Ex 24: (*R*)-2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide



Under nitrogen, to a suspension of (*R*)-1-methylpiperidin-3-amine hydrochloride (38 mg 331 µmol) and 2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid (80 mg, 277 µmol) in 5 ml of DMF is added DIPEA (241 µl,1.38 mmol), followed by HATU (126 mg, 331 µmol). The resulting mixture is stirred at rt for 20 h. EtOAc is added to the mixture and the solution is washed twice with water, then with an aqueous solution of HCl (1M), and twice with brine. The organic layer is dried over Na_2SO_4, filtered off and concentrated under reduced pressure. The residue is purified by reverse layer chromatography using Gilson GX271 system, CSH 50x250mm, 5µm column (Waters™), water/formic acid (0.1% v/v) with a gradient of ACN/FA (0.1% v/v) 18 to 50% in 25 min, to provide the title compound as a white solid (6 mg, 5.2% yield).

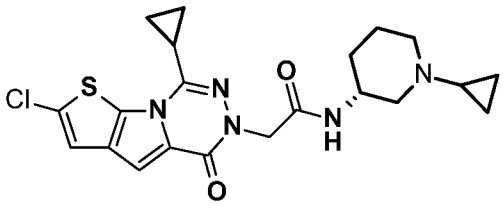
1H NMR (400 MHz, DMSO-d6) δ ppm 0.99 - 1.06 (m, 2 H), 1.10 - 1.25 (m, 3 H), 1.46 (br d, J=7 Hz, 1 H), 1.65 (br d, J=9 Hz, 2 H), 1.83 (br t, J=10 Hz, 1 H), 1.95 (br t, J=10 Hz, 1 H), 2.16 (s, 3 H), 2.30 - 2.42 (m, 1 H), 2.50 (d, J=2 Hz, 1 H), 2.62 - 2.72 (m, 1 H), 3.70 - 3.78 (m, 1 H), 4.46 - 4.54 (m, 2 H), 7.29 - 7.34 (m, 2 H), 7.57 (d, J=6 Hz, 1 H), 7.86 (br d, J=8 Hz, 1 H)

LCMS $[M+H]^+$ = 386; Rt = 0.56 ; Method A

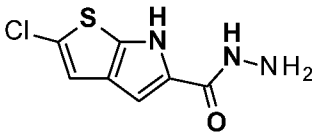
The following examples were synthesized analogous to the previous procedure, using the appropriate amines:

Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method
20	(R)-N-(1-cyclobutylpiperidin-3-yl)-2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 0.92 - 1.27 (m, 5 H), 1.04 - 1.04 (m, 1 H), 1.35 - 1.81 (m, 9 H), 1.86 - 2.02 (m, 2 H), 2.30 - 2.39 (m, 1 H), 2.57 - 2.67 (m, 2 H), 3.61 - 3.77 (m, 1 H), 4.50 (s, 2 H), 7.30 - 7.34 (m, 2 H), 7.57 (d, J=5 Hz, 1 H), 7.75 (d, J=8 Hz, 1 H)	0.62	426	A
21	(R)-2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclopropylpiperidin-3-yl)acetamide	1H NMR (500 MHz, DMSO-d6) δ ppm 0.22 - 0.31 (m, 2 H), 0.39 (br d, J=6 Hz, 2 H), 1.00 - 1.05 (m, 2 H), 1.11 - 1.26 (m, 3 H), 1.35 - 1.43 (m, 1 H), 1.58 - 1.70 (m, 3 H), 2.04 (br s, 1 H), 2.17 (br s, 1 H), 2.31 - 2.38 (m, 1 H), 2.71 (br s, 1 H), 2.85 (br d, J=9 Hz, 1 H), 3.62 - 3.69 (m, 1 H), 4.50 (s, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.34 (s, 1 H), 7.58 (d, J=5 Hz, 1 H), 7.78 (br d, J=8 Hz, 1 H)	0.60	412	A
22	2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-((R)-1-((S)-2-hydroxypropyl)piperidin-3-yl)acetamide	1H NMR (500 MHz, DMSO-d6) δ ppm 0.98 - 1.06 (m, 5 H), 1.11 - 1.18 (m, 2 H), 1.21 - 1.30 (m, 1 H), 1.44 - 1.52 (m, 1 H), 1.65 (br d, J=9 Hz, 2 H), 1.99 - 2.15 (m, 2 H), 2.17 - 2.29 (m, 2 H), 2.31 - 2.40 (m, 1 H), 2.63 - 2.66 (m, 1 H), 2.71 (br d, J=9 Hz, 1 H), 3.70 - 3.81 (m, 2 H), 4.47 - 4.55 (m, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.34 (s, 1 H), 7.58 (d, J=5 Hz, 1 H), 7.84 (d, J=8 Hz, 1 H)	0.57	429	A

Example 13 ; (*R*)-2-(2-chloro-8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclopropylpiperidin-3-yl)acetamide



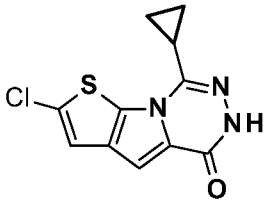
Int 5: 2-Chloro-6H-thieno[2,3-b]pyrrole-5-carbohydrazide



To a solution of methyl 2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylate (3.0 g, 13.91 mmol) in 60 ml of EtOH is added a solution of hydrazine hydrate (35% in water) (7.78 ml, 55.65 mmol) and the mixture is heated at reflux overnight. After cooling down the solution, the precipitate formed is filtered off, washed with ether and dried under vacuum. The title compound is obtained as a yellow solid (3g, 100% yield).

LCMS (method F): Rt = 1.15 min; MS m/z $[M+H]^+$ 216.0

Int 16: 2-Chloro-8-cylopropylthieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one

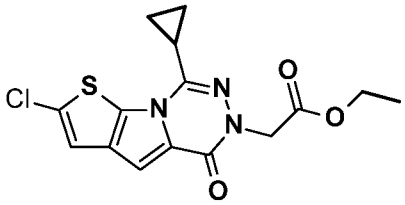


Under nitrogen, to a solution of 2-chloro-6H-thieno[2,3-b]pyrrole-5-carbohydrazide (500 mg, 2.32 mmol) in 10 ml of DMF is added methyl cyclopropanecarboximidate hydrochloride (1.10 g, 7.73 mmol). This mixture is stirred at rt for 1 h.

Then solid tBuOK (531 mg 4.64 mmol) is added and the resulting mixture is stirred in a preheated Dry-syn at 90°C for 18 h. After cooling to 0°C, the solution is acidified to pH 5 with a solution of (1M) HCl and the precipitate formed is filtered off, rinsed with water then DCM, and dried under reduced pressure in the presence of P_2O_5 to give the title compound as a brown solid. (250 mg, 40% yield).

LCMS (method F): Rt = 1.70 min; MS m/z $[M+H]^+$ 266.0

Int 17: Ethyl 2-(2-Chloro-8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate

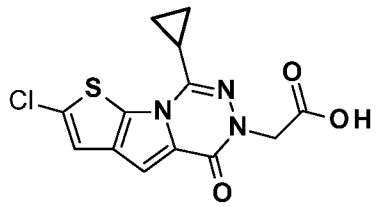


Under nitrogen, to a solution of 2-Chloro-8-cylopropylthieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one (650 mg, 2.45 mmol) in 15 ml of DMF is added K_2CO_3 (406 mg, 2.94 mmol) followed by a dropwise addition of ethyl iodoacetate (641 mg, 2.94 mmol). The mixture

is stirred at rt for 20h. The reaction mixture is diluted with water and extracted twice with EtOAc. The organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

The residue is purified by Flash chromatography on silica gel using Cyclohexane/EtOAc (from 5% to 50%) to give the title compound as a light yellow solid (250 mg, 29% yield).
LCMS (method F): Rt = 2.04 min; MS m/z $[M+H]^+$ 352.1

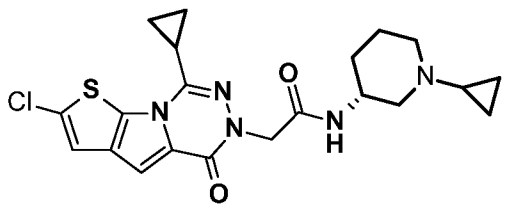
Int 18: 2-(2-Chloro-8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid



To a solution of Ethyl 2-(2-Chloro-8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate (220 mg, 0.625 mmol) in 10 ml of dioxane/MeOH (1/1) is added a solution of (1M) NaOH (1.88 ml, 1.88 mmol) and the resulting solution is stirred 20 h at rt. The mixture is acidified with (1M) HCl and extracted with CH_2Cl_2. The organic layer is washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the title compound as a white solid (202 mg, 74% yield).

LCMS (method F): Rt = 1.72 min; MS m/z $[M+H]^+$ 324.0

Ex 13: (*R*)-2-(2-chloro-8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclopropylpiperidin-3-yl)acetamide



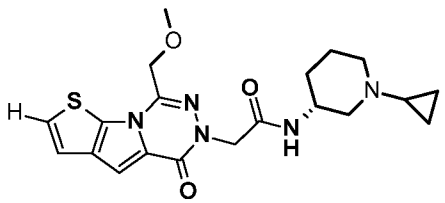
Under nitrogen, to a suspension of (*R*)-1-cyclopropylpiperidin-3-amine hydrochloride (33 mg 185 µmol) and 2-(2 chloro-8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid (50 mg, 154 µmol) in 3 ml de DMF is added DIPEA (134 µl, 772 µmol), followed by HATU (71 mg, 185 µmol). The resulting mixture is stirred at rt for 20 h.

The reaction mixture is diluted with water and extracted twice with EtOAc. The organic extracts are washed with a solution of (1M) HCl, then with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

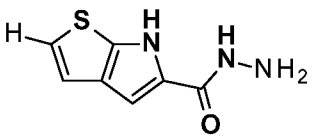
The residue is purified by reverse layer chromatography using Gilson GX271 system, CSH 50x250mm, 5µm column (Waters™), water/formic acid (0.1% v/v) with a gradient of ACN/FA (0.1% v/v) 18 to 50% in 25 min, to provide the title compound as a white solid (30 mg, 44% yield).

1H NMR (400 MHz, DMSO-d6) δ ppm 0.21 - 0.32 (m, 2 H), 0.35 - 0.42 (m, 2 H), 0.98 - 1.05 (m, 2 H), 1.11 - 1.27 (m, 3 H), 1.33 - 1.44 (m, 1 H), 1.56 - 1.70 (m, 3 H), 2.02 (br t, J=10 Hz, 1 H), 2.15 (br t, J=10 Hz, 1 H), 2.24 - 2.39 (m, 1 H), 2.67 - 2.74 (m, 1 H), 2.84 (br dd, J=10, 3 Hz, 1 H), 3.60 - 3.69 (m, 1 H), 4.50 (s, 2 H), 7.31 (s, 1 H), 7.49 (s, 1 H), 7.78 (br d, J=8 Hz, 1 H)
LCMS $[M+H]^+$ = 446 ; Rt = 0.73 ; Method A

Example 33 ; (*R*)-N-(1-cyclopropylpiperidin-3-yl)-2-(8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

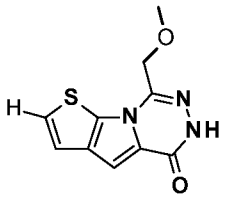


Int 1: 6H-thieno[2,3-b]pyrrole-5-carbohydrazide



To a solution of methyl 6*H*-Thieno[2,3-*b*]pyrrole-5-carboxylate (4 g, 22.07 mmol) in 100 ml of EtOH is added hydrazine solution (35% in water) (24.7 ml, 176.59 mmol) and this mixture is heated at reflux overnight. After cooling down the solution, the precipitate formed is filtered off, washed with ether and dried under vacuum. The title compound is obtained as a white solid (3.4 g, 85% yield).
LCMS (method F): Rt = 1.15 min; MS m/z $[M+H]^+$ 181.2

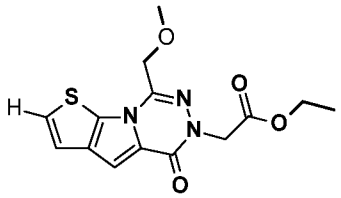
Int 19: 8-(methoxymethyl)thieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one



Under nitrogen, to a solution of 6H-thieno[2,3-b]pyrrole-5-carbohydrazide (500 mg, 2.76 mmol) in 20 ml of DMF is added ethyl 2-methoxyethanimidoate hydrochloride (524 mg, 3.31 mmol). This mixture is stirred at rt for 30 min. Then solid tBuOK (632 mg 5.52 mmol) is added and the resulting mixture is stirred in a preheated Dry-syn at 90°C for 1h. After cooling to 0°C, water is added, and the mixture is acidified with HCl (1M) to pH 5. The precipitate formed is filtered off, washed with water and dried under reduced pressure in the presence of P_2O_5 to provide the title product as a soft yellow solid (303 mg, 46% yield).

LCMS (method F): Rt = 1.27 min; MS m/z $[M+H]^+$ 236.0

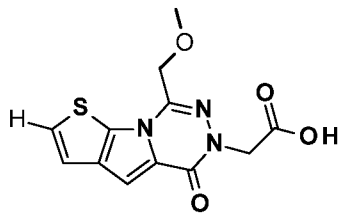
Int 20: Ethyl 2-(8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate



Under nitrogen, to a solution of 8-(methoxymethyl)thieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one (300 mg, 1.28 mmol) in 10ml of DMF is added K_2CO_3 (267 mg, 1.91 mmol), followed by a dropwise addition of ethyl iodoacetate (238 µl, 1.91 mmol). The mixture is stirred at RT for 20h. The reaction mixture is diluted with water then extracted twice with EtOAc. The combined organic layers are washed with water, then with brine, dried over Na_2SO_4, filtered off and concentrated under reduced pressure to give 450 mg of an oil which is directly engaged in the next step.

LCMS (method F): Rt = 1.64 min; MS m/z $[M+H]^+$ 322.3

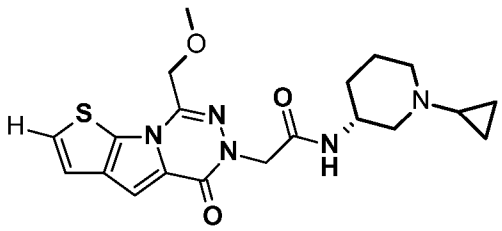
Int 21: 2-(8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid



To a solution of ethyl 2-(8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate (450 mg, 1.40 mmol) in 20ml of dioxane and 20ml of MeOH is added a solution of NaOH (1M) (4.2 ml, 4.2 mmol). The resulting solution is stirred at rt overnight. The mixture is acidified with HCl (1M). The precipitate formed is filtered off, washed with water and pentane. After drying overnight under vacuum in presence of P_2O_5, the title compound is obtained as a white solid (270 mg, 65% yield).

LCMS (method F): Rt = 1.33 min; MS m/z $[M+H]^+$ 294.0

Ex 33: (*R*)-N-(1-cyclopropylpiperidin-3-yl)-2-(8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo [1,2-d][1,2,4]triazin-6(5H)-yl)acetamide



Under nitrogen, to a suspension of (*R*)-1-cyclopropylpiperidin-3-amine hydrochloride (65 mg 368 µmol) and 2-(8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid (90 mg, 307 µmol) in 5 ml of DMF is added DIPEA (268 µl, 1,53 mmol) followed by HATU (140 mg, 368 µmol). The resulting mixture is stirred at rt for 12h. Some drops of TFA are added and the residue is purified by reverse layer chromatography using Gilson GX271 system, CSH 50x250mm, 5µm column (Waters™), water/formic acid (0.1% v/v) with a gradient of ACN/FA (0.1% v/v) 18 to 50% in 25 min, to provide after lyophilization the title compound as a white powder (20 mg, 12% yield).

1H NMR (400 MHz, DMSO-d6) δ ppm 0.69 - 0.97 (m, 4 H), 1.35 - 2.04 (m, 4 H), 2.82 - 3.15 (m, 3 H), 3.44 (s, 5 H), 3.81 - 4.01 (m, 1 H), 4.53 - 4.75 (m, 4 H), 7.27 (d, J=6 Hz, 1 H), 7.39 (s, 1 H), 7.56 (d, J=6 Hz, 1 H), 8.36 (br d, J=4 Hz, 1 H)

LCMS $[M+H]^+$ = 416; Rt = 0.52 ; Method A

The following examples was synthesized analogous to the previous procedure, using the appropriate amine

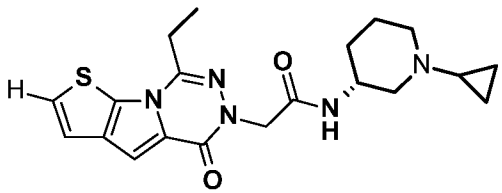
Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method

32	(R)-N-(1-cyclobutylpiperidin-3-yl)-2-(8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 0.96 - 2.36 (m, 13 H), 2.73 - 3.05 (m, 2 H), 3.44 (s, 3 H), 3.74 - 3.89 (m, 1 H), 4.59 (s, 2 H), 4.66 (s, 2 H), 7.27 (d, J=6 Hz, 1 H), 7.38 (s, 1 H), 7.56 (d, J=6 Hz, 1 H), 7.90 - 8.11 (m, 1 H)	0.55	430	A

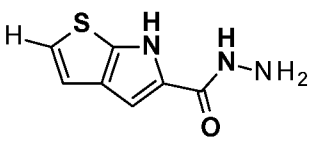
Starting from 2-Chloro-6H-thieno[2,3-b]pyrrole-5-carbohydrazide, following examples were synthesized analogous to the previous procedure:

Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method
29	(R)-2-(2-chloro-8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclobutylpiperidin-3-yl)acetamide formate	1H NMR (400 MHz, DMSO-d6) δ ppm 1.14 - 1.26 (m, 1 H), 1.36 - 1.46 (m, 1 H), 1.52 - 1.81 (m, 7 H), 1.86 - 1.98 (m, 2 H), 2.54 - 2.69 (m, 4 H), 3.44 (s, 3 H), 3.63 - 3.75 (m, 1 H), 4.56 (s, 2 H), 4.65 (s, 2 H), 7.35 (s, 1 H), 7.43 (s, 1 H), 7.90 (d, J=8 Hz, 1 H)	0.69	464	A
30	(R)-2-(2-chloro-8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclopropylpiperidin-3-yl)acetamide formate	1H NMR (400 MHz, DMSO-d6) δ ppm 0.27 (br s, 2 H), 0.39 (br d, J=6 Hz, 2 H), 1.13 - 1.47 (m, 2 H), 1.60 (br s, 3 H), 1.96 - 2.22 (m, 2 H), 2.63 - 2.94 (m, 2 H), 3.44 (s, 3 H), 3.56 - 3.72 (m, 1 H), 4.56 (s, 2 H), 4.65 (s, 2 H), 7.35 (s, 1 H), 7.43 (s, 1 H), 7.89 (br d, J=7 Hz, 1 H)	0.67	450	A

Example 60 ; (*R*)-N-(1-cyclopropylpiperidin-3-yl)-2-(8-(ethyl)-5-oxothieno[3',2':4,5] pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide



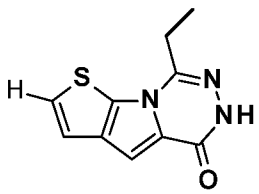
Int 1: 6H-thieno[2,3-b]pyrrole-5-carbohydrazide



To a solution of methyl 6*H*-thieno[2,3-*b*]pyrrole-5-carboxylate (4 g, 22.07 mmol) in 100 ml of EtOH is added hydrazine solution (35% in water) (24.7 ml, 176.59 mmol) and this mixture is heated at reflux overnight. After cooling down the solution, the precipitate formed is filtered off, washed with ether, and dried under vacuum. The title compound is obtained as a white solid (3.4 g, 85% yield).

LCMS (method F): Rt = 1.15 min; MS m/z $[M+H]^+$ 181.2

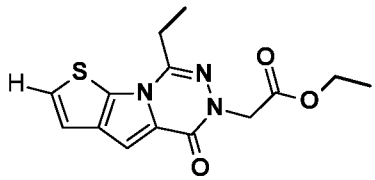
Int 22: 8-(ethyl)thieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one



Under nitrogen, to a solution of 6H-thieno[2,3-b]pyrrole-5-carbohydrazide (1.0 g, 6.53 mmol) in 15 ml of DMF is added ethyl propanecarboximidate hydrochloride (1.08 g, 7.83 mmol). This mixture is stirred at rt for 1 h. Then solid tBuOK (1.50 g, 13.05 mmol) is added and the resulting mixture is stirred in a preheated Dry-syn at 90°C for 1h30. After cooling to 0°C, water is added, and the mixture is acidified with HCl (1M) to pH 5. The precipitate formed is filtered off, washed with water and dried under reduced pressure in the presence of P_2O_5 to provide the title product as a soft yellow solid (1.2 g, 84% yield).

LCMS (method F): Rt = 1.38 min; MS m/z $[M+H]^+$ 220.1

Int 23: Ethyl 2-(8-(ethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate

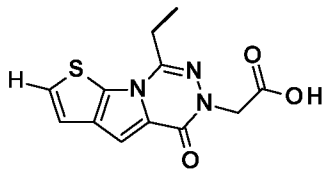


Under nitrogen, to a solution of 8-(ethyl)thieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one (1.2 g, 5.5 mmol) in 15 ml of DMF is added Cs_2CO_3 (7.1 g, 22 mmol), followed by a dropwise addition of ethyl iodoacetate (780 µl, 6.6 mmol). The mixture is stirred at RT for 20h.

The reaction mixture is diluted with water then extracted twice with EtOAc. The combined organic layers are washed with water, then with brine, dried over Na_2SO_4, filtered off and concentrated under reduced pressure to give 900 mg of an oil which is used without further purification in the next step.

LCMS (method F): Rt = 1.78 min; MS m/z $[M+H]^+$ 306.2

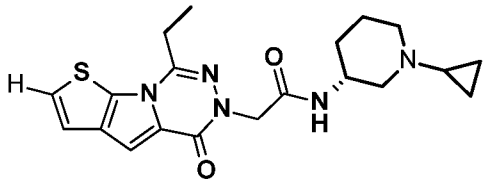
Int 24: 2-(8-(ethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid



To a solution of ethyl 2-(8-(ethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate (900 mg, 2.95 mmol) in 6 ml of THF is added a solution of NaOH (1M) (3 ml, 3 mmol). The resulting solution is stirred at rt overnight. The mixture is acidified with HCl (1M). The organic layer is extracted with DCM, concentrated under reduced pressure and the residue is triturated with Et_2O, then filtered. After drying overnight under vacuum in presence of P_2O_5 the title compound is obtained as a yellow solid (830 mg, 100% yield).

LCMS (method F): Rt = 1.42 min; MS m/z $[M+H]^+$ 278.0

Ex 60: (*R*)-N-(1-cyclopropylpiperidin-3-yl)-2-(8-(ethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide



Under nitrogen, to a suspension of (*R*)-1-cyclopropylpiperidin-3-amine hydrochloride (46 mg, 216 µmol) and 2-(8-(ethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid (50 mg, 180 µmol) in 5 ml of ACN is added DIPEA (157 µl, 0.900 mmol) followed by HATU (82 mg, 216 µmol). The resulting mixture is stirred at rt for 1h30. After evaporation under reduced pressure, the residue is purified by reverse layer chromatography using Gilson GX271 system, CSH 50x250mm, 5µm column (Waters™), water/formic acid (0.1% v/v) with a gradient of ACN/FA (0.1% v/v) 14 to 45% in 20 min, to provide after lyophilization the title compound as a white powder (10 mg, 14% yield).

1H NMR (400 MHz, DMSO-d6) δ ppm 0.20 - 0.29 (m, 2 H), 0.34 - 0.42 (m, 2 H), 1.19 - 1.43 (m, 5 H), 1.55 - 1.71 (m, 3 H), 2.04 (br t, J=10 Hz, 1 H), 2.11 - 2.21 (m, 1 H), 2.61 - 2.73 (m, 1 H), 2.84 (br d, J=7 Hz, 1 H), 3.05 (q, J=7 Hz, 2 H), 3.65 (br d, J=9 Hz, 1 H), 4.54 (s, 2 H), 7.31 (d, J=5 Hz, 1 H), 7.34 (s, 1 H), 7.57 (d, J=5 Hz, 1 H), 7.81 (br d, J=8 Hz, 1 H)

LCMS $[M+H]^+$ = 400 ; Rt = 0.57 ; Method A

The following examples were synthesized analogous to the previous procedure, using the appropriate amines

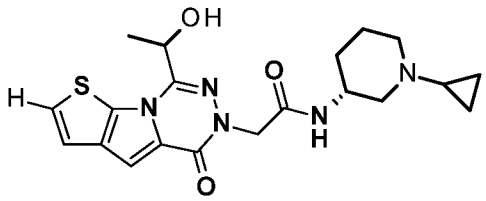
Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method

73	2-(12-ethyl-9-oxo-3-thia-1,10,11-triazatricyclo [6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(3R)-1-methyl-3-piperidyl]acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.19 - 1.35 (m, 4 H), 1.42 - 1.55 (m, 1 H), 1.68 (br d, J=9 Hz, 2 H), 1.92 (br d, J=7 Hz, 1 H), 2.04 (br s, 1 H), 2.22 (s, 3 H), 2.54 - 2.63 (m, 1 H), 2.67 - 2.75 (m, 1 H), 3.04 (q, J=7 Hz, 2 H), 3.77 (br d, J=8 Hz, 1 H), 4.55 (s, 2 H), 7.31 (d, J=5 Hz, 1 H), 7.34 (s, 1 H), 7.57 (d, J=5 Hz, 1 H), 7.95 (br d, J=8 Hz, 1 H)	0.54	374	A
69	2-(12-ethyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(3R)-1-[(2S)-2-hydroxypropyl]-3-piperidyl]acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.10 (br d, J=6 Hz, 3 H), 1.32 (t, J=7 Hz, 3 H), 1.37 - 1.47 (m, 1 H), 1.68 - 1.93 (m, 3 H), 2.63 - 2.71 (m, 1 H), 2.80 (br s, 1 H), 2.94 - 3.15 (m, 4 H), 3.49 (br s, 2 H), 3.90 - 4.31 (m, 2 H), 4.57 (s, 2 H), 5.40 (br s, 1 H), 7.32 (d, J=5 Hz, 1 H), 7.35 (s, 1 H), 7.58 (d, J=5 Hz, 1 H), 8.21 (br d, J=7 Hz, 1 H)	0.55	418	A

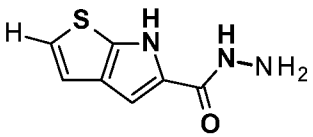
The following example was synthesized analogous to the previous procedure, using the appropriate imidate:

Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method
72	N-[(3R)-1-cyclopropylpiperidin-3-yl]-2-(9-oxo-12-propyl-3-thia-1,10,11-triazatricyclo [6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 0.25 (d, J = 1.1 Hz, 2H), 0.38 (d, J = 5.8 Hz, 2H), 1.06 (t, J = 6.8 Hz, 3H), 1.23 (brs, 1H), 1.30 - 1.46 (m, 1H), 1.59 (d, J = 2.6 Hz, 3H), 1.79 (d, J = 7.0 Hz, 2H), 1.97 - 2.06 (m, 1H), 2.11 - 2.20 (m, 1H), 2.69 (ddd, J = 2.2, 4.8, 7.9 Hz, 1H), 2.72 (d, J = 9.0 Hz, 1H), 2.96 (t, J = 7.0 Hz, 2H), 3.63 - 3.65 (m, 1H), 4.54 (brs, 2H), 7.31 - 7.35 (m, 2H), 7.57 (d, J = 4.9 Hz, 1H), 7.86 (d, J = 7.4 Hz, 1H).	0.66	414	A

Example 44 and 51 ; N-((*R*)-1-cyclopropylpiperidin-3-yl)-2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide



Int 1: 6H-thieno[2,3-b]pyrrole-5-carbohydrazide

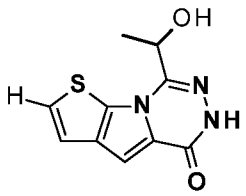


To a solution of methyl 6*H*-Thieno[2,3-*b*]pyrrole-5-carboxylate (4 g, 22.07 mmol) in 100 ml of EtOH is added hydrazine solution (35% in water) (24.7 ml, 176.59 mmol) and this solution is heated at reflux overnight. After cooling down the solution, the precipitate formed is filtered off,

washed with ether and dried under vacuum. The title compound is obtained as a white solid (3.4 g, 85% yield).

LCMS (method F): Rt = 1.15 min; MS m/z $[M+H]^+$ 181.2

Int 25: 8-(1-hydroxyethyl)-thieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one

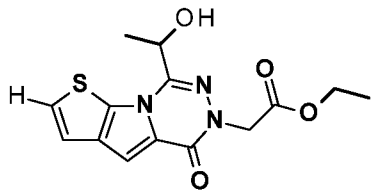


Under nitrogen, to a solution of 6H-thieno[2,3-b]pyrrole-5-carbohydrazide (2,5g, 13,80 mmol) in 50 ml of DMF is added ethyl 2-hydroxypropanimidoate hydrochloride (2,74 g, 16,97 mmol). This mixture is stirred at rt for 1h30. Then, solid tBuOK (3.16g, 27.59 mmol) is added and the resulting mixture is stirred in a preheated Dry-syn at 90°C for 1h30.

After cooling to 0°C, the mixture is acidified with HCl (1M). The precipitate formed is filtered off, washed with water and dried under reduced pressure in the presence of P_2O_5 to provide the title compound as a soft yellow solid (800 mg, 25% yield).

LCMS (method F): Rt = 1.25 min; MS m/z $[M+H]^+$ 236.1

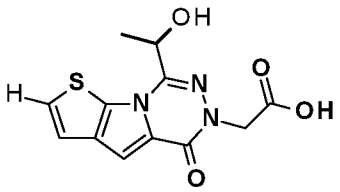
Int 26: Ethyl 2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate



To a solution of 8-(1-hydroxyethyl)thieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one (350 mg, 1,49 mmol) in 6 ml of DMF is added Cs_2CO_3 (581 mg, 1,79 mmol), followed by a dropwise addition of ethyl iodoacetate (222 µl, 1.79 mmol). The resulting mixture is stirred at rt for 20h. Then, the mixture is diluted with water and extracted twice with EtOAc. The combined organic layers are dried over Na_2SO_4, filtered off and concentrated under reduced pressure to give the title compound as a light marron powder (400 mg, 83% yield).

LCMS (method F): Rt = 1.54 min; MS m/z $[M+H]^+$ 322.1

Int 27: 2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid

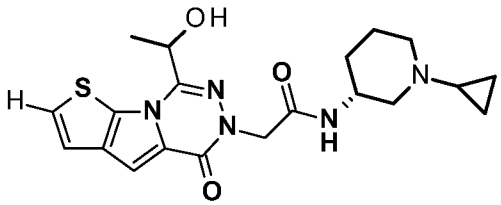


To a solution of ethyl 2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetate (250 mg, 778 µmol) in 10 ml of THF and 3 ml of MeOH is added a solution of NaOH (1M) (3.89 ml 3.89 mmol). The resulting solution is stirred at rt overnight. The mixture is acidified with (1M) HCl and extracted with CH_2Cl_2. The organic layer is washed with brine, dried over Na_2SO_4, filtered and evaporated to provide the title compound as a brown oil (230 mg, 100% yield).

LCMS (method F): Rt = 1.20 min; MS m/z $[M+H]^+$ 294.1

Ex 44: N-((*R*)-1-cyclopropylpiperidin-3-yl)-2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5] pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide (Dia 1)

Ex 51: N-((*R*)-1-cyclopropylpiperidin-3-yl)-2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5] pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide (Dia 2)



Under nitrogen, to a suspension of (*R*)-1-cyclopropylpiperidin-3-amine hydrochloride (60 mg, 341 µmol) and 2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid (100 mg, 341 µmol) in 5 ml de DMF is added DIPEA (298 µl, 1,70 mmol) followed by HATU (1565 mg, 409 µmol). The resulting mixture is stirred at rt for 20 h. After evaporation under reduced pressure, the residue is purified by reverse layer chromatography using Gilson GX271 system, CSH 50x250mm, 5µm column (Waters™), water/formic acid (0.1% v/v) with a gradient of ACN/FA (0.1% v/v) 18 to 50% in 25 min, to provide the two diastereoisomers: Dia 1 as a yellow powder (15 mg, 10% yield) and Dia 2 as an orange powder (12 mg, 8% yield).

1st diastereoisomer (Dia 1):

1H NMR (400 MHz, DMSO-d6) δ ppm 0.71 - 0.96 (m, 4 H), 1.38 - 1.71 (m, 5 H), 1.75 - 2.02 (m, 2 H), 2.84 - 3.14 (m, 3 H), 3.37 - 3.54 (m, 2 H), 3.88 (br s, 1 H), 4.94 - 5.01 (m, 1 H), 5.16 - 5.30 (m, 2 H), 6.01 (br s, 1 H), 7.07 - 7.13 (m, 2 H), 7.19 (d, J=5 Hz, 1 H), 8.58 (br s, 1 H)

LCMS $[M+H]^+$ = 416; Rt = 0.46 ; Method A

2nd diastereoisomer (Dia 2):

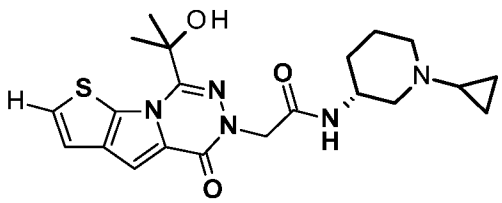
1H NMR (400 MHz, DMSO-d6) δ ppm 0.71 - 0.95 (m, 4 H), 1.53 (d, J=7 Hz, 5 H), 1.75 - 2.01 (m, 2 H), 2.81 - 2.99 (m, 2 H), 3.01 - 3.16 (m, 1 H), 3.37 - 3.56 (m, 2 H), 3.88 (br s, 1 H), 4.94 - 5.01 (m, 1 H), 5.16 - 5.30 (m, 2 H), 6.01 (br s, 1 H), 7.07 - 7.13 (m, 2 H), 7.19 (d, J=5 Hz, 1 H), 8.58 (br s, 1 H)

LCMS $[M+H]^+$ = 416; Rt = 0.49 ; Method A

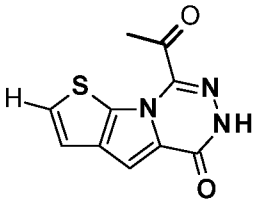
The following examples were synthesized analogous to the previous procedure, using the appropriate amine:

Ex N°	Name	NMR	LCMS Rt (min)	LCMS [M+H]+	LCMS Analytical method
50 Dia1	N-((R)-1-cyclobutylpiperidin-3-yl)-2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.38 - 1.48 (m, 1 H), 1.52 (d, J=6 Hz, 3 H), 1.61 - 1.81 (m, 3 H), 1.84 - 1.98 (m, 2 H), 2.07 - 2.24 (m, 4 H), 2.44 - 2.50 (m, 1 H), 2.60 - 2.73 (m, 1 H), 3.31 - 3.36 (m, 2 H), 3.61 - 3.74 (m, 1 H), 3.85 - 4.01 (m, 1 H), 4.52 - 4.71 (m, 2 H), 4.95 - 5.04 (m, 1 H), 6.21 (br d, J=4 Hz, 1 H), 7.25 (d, J=6 Hz, 1 H), 7.38 (s, 1 H), 7.53 (d, J=6 Hz, 1 H), 8.33 (br d, J=7 Hz, 1 H)	0.48	430	A
81 Dia2	N-((R)-1-cyclobutylpiperidin-3-yl)-2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide	1H NMR (400 MHz, DMSO-d6) δ ppm 1.43 - 1.57 (m, 4 H), 1.59 - 1.80 (m, 3 H), 1.83 - 2.02 (m, 2 H), 2.03 - 2.22 (m, 4 H), 2.53 - 2.59 (m, 1 H), 2.62 - 2.74 (m, 1 H), 3.19 - 3.30 (m, 2 H), 3.68 (br d, J=8 Hz, 1 H), 3.90 (br s, 1 H), 4.88 - 5.08 (m, 1 H), 5.21 (s, 2 H), 6.00 (br d, J=5 Hz, 1 H), 7.07 - 7.14 (m, 2 H), 7.19 (d, J=5 Hz, 1 H), 8.55 (br d, J=7 Hz, 1 H)	0.51	430	A

Example 52; N-((*R*)-1-cyclopropylpiperidin-3-yl)-2-(8-(2-hydroxypropan-2-yl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide



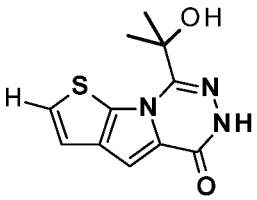
Int 28: 8-acetylthieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one



To a solution of 8-(1-hydroxyethyl)-thieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one (int 28) (400 mg, 1,70 mmol) in 15 ml of DMF is added Dess-Martin periodinane (1,14 g, 2,55 mmol) and the mixture is stirred at rt for 30 min. Then, an aqueous saturated solution of $NaHCO_3$ is added and the precipitate formed is filtered off, rinsed with DCM to provide the title compound as a marron solid (395 mg, 100% yield).

LCMS (method F): Rt = 1.36 min; MS m/z $[M+H]^+$ 234

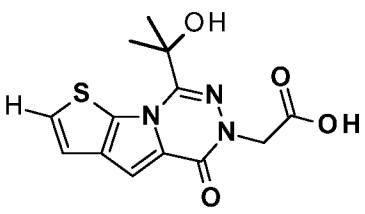
Int 29: 8-(2-hydroxypropan-2-yl)thieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one



Under nitrogen, a solution (0.6M in THF) of lanthanum(III) chloride bis(lithium chloride) complex (11,43 ml, 6,86 mmol) is added to a solution of 8-acetylthieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one (400 mg, 1,71 mmol) in 8 ml of anhydrous THF. The temperature is decreased to 0°C, then a solution (3M in THF) of methylmagnesium chloride is added dropwise with a control of the temperature between 5 and 8°C. After total addition, the mixture is stirred 1h at RT. Then, an aqueous solution of NH_4Cl (10%) is added, plus acidification with HCl (1M) and the resulting mixture is extracted with DCM (3 x). The combined organic layers are dried over Na_2SO_4, filtered off and concentrated under reduced pressure to give the title compound as a brown solid (220 mg, 51% yield).

LCMS (method F): Rt = 1.42 min; MS m/z $[M+H]^+$ 250.1

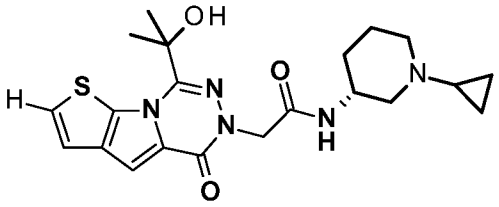
Int 30 : 2-(8-(2-hydroxypropan-2-yl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid



To a solution of 8-(2-hydroxypropan-2-yl)thieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-5(6H)-one (220 mg, 0.882 mmol) in 10 ml of DMF is added Cs_2CO_3 (345 mg, 1.06 mmol), followed by a dropwise addition of ethyl iodoacetate (128 µl, 1.06 mmol). The resulting mixture is stirred at rt for 20h and 3h at 60°C. After cooling to rt, the mixture is diluted with water and extracted twice with EtOAc. The combined organic layers are dried over Na_2SO_4, filtered off and concentrated under reduced pressure to give the title compound as a light marron wax (290 mg, purity 64%), used without further purification in the next step.

LCMS (method F): Rt = 1.32 min; MS m/z $[M+H]^+$ 308

Ex 52: N-((*R*)-1-cyclopropylpiperidin-3-yl)-2-(8-(2-hydroxypropan-2-yl)-5-oxothieno[3',2':4,5]pyrrolo [1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

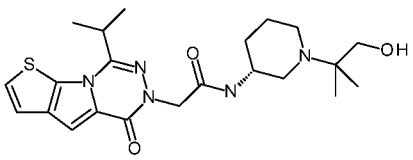


Under nitrogen, to a suspension of (*R*)-1-cyclopropylpiperidin-3-amine hydrochloride (44 mg, 246 µmol) and 2-(8-(2-hydroxypropan-2-yl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetic acid (63 mg, 205 µmol) in 2 ml de DMF is added DIPEA (179 µl, 1,02 mmol) followed by HATU (94 mg, 246 µmol). The resulting mixture is stirred at rt for 20 h. After evaporation under reduced pressure, the residue is purified by reverse layer chromatography using Gilson GX271 system, CSH 50x250mm, 5µm column (Waters™), water/formic acid (0.1% v/v) with a gradient of ACN/FA (0.1% v/v) 2 to 30% in 40 min, to provide after lyophilization the title compound as a white powder (3 mg, 3.5% yield).

1H NMR (500 MHz, DMSO-d6) δ ppm 0.15 - 0.48 (m, 4 H), 1.20 - 1.43 (m, 3 H), 1.58 (d, J=11 Hz, 9 H), 1.95 - 2.89 (m, 3 H), 3.58 - 3.73 (m, 1 H), 4.54 (s, 2 H), 6.33 (s, 1 H), 7.22 (d, J=6 Hz, 1 H), 7.39 (s, 1 H), 7.45 (d, J=6 Hz, 1 H), 7.79 - 8.06 (m, 1 H)

LCMS $[M+H]^+$ = 430 ; Rt = 1.98-2.00 ; Method C

Example 79; N-[(3R)-1-(1-hydroxy-2-methylpropan-2-yl)piperidin-3-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide



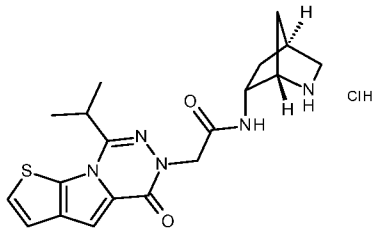
At 0°C, to a solution of ethyl-2-methyl-2-[3-[[2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetyl]amino]piperidin-1-yl]propanoate – (Example 80,130 mg, 0,27 mmol) in 20 ml of THF is added dropwise a (2M in THF) solution of LAH (0,2 ml, 0,4 mmol) and the resulting mixture is stirred at RT for 2 hours. The reaction mixture is quenched at 0°C by addition of a saturated aqueous solution of NH_4Cl. After addition of EtOAc, the organic layer is washed with NaCl (3 times), dried over $MgSO_4$, filtered and concentrated under reduced pressure.

The residue is purified by reverse phase chromatography Waters SunFire PrepC18 OBD 30 x 100 mm column, water containing 0.1% HCO_2H with a gradient of acetonitrile 10 to 60% in 15 min.

After concentration under vacuum and drying overnight, the title compound is obtained as a white solid (95 mg, 80% yield)

1H NMR (400 MHz, DMSO-d6) δ ppm 0.92 (s, 6 H), 1.24 (m, 1 H), 1.35 (d, J=7 Hz, 6 H), 1.45 (m, 1 H), 1.65 (d, J=9 Hz, 2 H), 2.17 (br dd, J=11, 9 Hz, 1 H), 2.26 - 2.34 (m, 1 H), 2.71 (m, 1 H), 2.85 (m, 1 H), 3.31 - 3.42 (m partially hidden, 3 H), 3.71 - 3.78 (m, 2 H), 4.47 - 4.63 (m, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.37 (s, 1 H), 7.58 (d, J=6 Hz, 1 H), 7.83 (d, J=8 Hz, 1 H)
LCMS $[M+H]^+$ = 446 ; Rt = 2.55 ; Method A

Example 88 ; N-[(1S,4R)-2-azabicyclo[2.2.1]heptan-6-yl]-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide hydrochloride



A solution of tert-butyl (1R,4R)-6-[[2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetyl]amino]-2-azabicyclo[2.2.1]heptane-2-carboxylate obtained following process as described in example 1 and using appropriate amine (1,1-Dimethylethyl 6-amino-2-azabicyclo[2.2.1]heptane-2-carboxylate) (676 mg, 1,39mmol) in 10 ml of DCM is treated with hydrochloric acid 4M in dioxane (1,5 ml, 6 mmol) and stirred at rt overnight. The reaction mixture is concentrated under reduced pressure. The precipitate formed is filtered off to give 830 mg of the title as a brown solid.

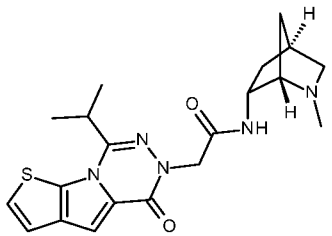
200 mg of this solid is purified by reverse phase chromatography Waters SunFire PrepC18 OBD 30 x 100 mm column, water containing 0.1% HCO_2H with a gradient of acetonitrile 10 to 60% in 15 min.

After concentration under vacuum and drying overnight, 80 mg of the title compound is obtained as a beige solid.

1H NMR (400 MHz, DMSO-d6) δ ppm 1.09 (br d, J=13 Hz, 1 H), 1.35 (dd, J=7, 2 Hz, 6 H), 1.48 - 1.56 (m, 1 H), 1.59 - 1.66 (m, 1 H), 1.97 - 2.07 (m, 1 H), 2.39 - 2.43 (m, 1 H), 2.64 - 2.74 (m, 1 H), 2.92 (br d, J=9 Hz, 1 H), 3.29 - 3.41 (m, 1 H), 3.53 (br s, 1 H), 4.03 (br dd, J=7, 4 Hz, 1 H), 4.54 - 4.68 (m, 2 H), 7.32 (d, J=5 Hz, 1 H), 7.37 (s, 1 H), 7.59 (d, J=6 Hz, 1 H), 8.25 (s, 2 H)

LCMS $[M+H]^+$ = 386 ; Rt = 0.62 ; Method A

Example 82 ; 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(1S,4S)-2-methyl-2-azabicyclo[2.2.1]heptan-6-yl]acetamide



To a solution of N-[(1R,4S)-2-azabicyclo[2.2.1]heptan-6-yl]-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide – example 88 (150 mg, 0,39 mmol) in 15 ml of MeOH, Formaldehyde solution (0,22 mL, 2,14 mmol), sodium cyanoborohydride (97,8 mg, 1,56 mmol) and acetic acid (0,018 ml, 0,32 mmol) are subsequently added and the mixture is stirred at 45°C overnight.

The reaction mixture is concentrated under reduced pressure and the residue diluted with AcOEt. The organic layers are washed with $NaHCO_3$ sat, water, dried over $MgSO_4$, filtered and concentrated under reduced pressure.

The residue is purified by reverse phase chromatography Waters SunFire PrepC18 OBD 30 x 100 mm column, water containing 0.1% HCO_2H with a gradient of acetonitrile 10 to 60% in 15 min.

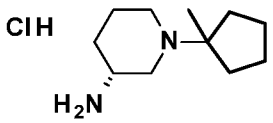
After concentration under vacuum and drying overnight, the title compound is obtained as a white solid (62 mg, 40% yield)

1H NMR (400 MHz, DMSO-d6) δ ppm 0.82 (dt, J=12, 3 Hz, 1 H), 1.28 (br d, J=10 Hz, 1 H), 1.37 (d, J=7 Hz, 6 H), 1.58 (br d, J=10 Hz, 1 H), 1.85 - 1.93 (m, 1 H), 2.18 - 2.25 (m, 4 H), 2.30 - 2.36 (m, 1 H), 2.67 - 2.72 (m, 1 H), 2.90 (br s, 1 H), 3.37 - 3.41 (m, 1 H), 3.91 - 3.98 (m, 1 H), 4.53 - 4.66 (m, 2 H), 7.32 (d, J=6 Hz, 1 H), 7.39 (s, 1 H), 7.59 (d, J=6 Hz, 1 H), 7.73 (br d, J=8 Hz, 1 H)

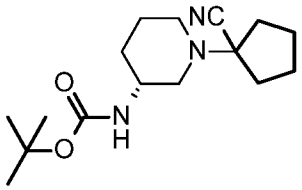
LCMS $[M+H]^+$ = 400 ; Rt = 0.62 ; Method A

Synthesis of amines building block

Intermediate 31 : (3R)-1-(1-methylcyclopentyl)piperidin-3-aminehydrochloride



Int 32: tert-butyl N-[(3R)-1-(1-cyanocyclopentyl)-3-piperidyl]carbamate

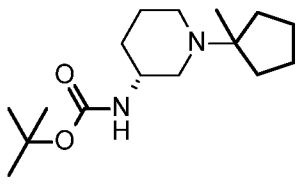


To a solution of tert-butyl N-[(3R)-3-piperidyl]carbamate (2 g, 9,98 mmol) and cyclopentanone (0,88 ml, 9,98 mmol) in 20 mL of DCM was added titanium(IV) isopropoxide (3,0 ml , 9,98 mmol) and the mixture was stirred at room temperature for 40 hours. Diethylaluminum cyanide (1M in toluene) (11,98 ml, 11,98 mmol) was added and the solution is stirred for an additional 20 hours. After dilution with DCM, water is added and the resulting mixture is filtered, washed with DCM and water. The aqueous layer is extracted with DCM. The organic layers are grouped, dried over MgSO4, filtered and concentrated under reduced pressure.

The residue is purified by flash chromatography on silica gel using Heptane/AcOEt (from 0% to 50%) to give the title compound (944 mg, 33% yield) as a yellow oil.

LCMS (method A): Rt = 1.17 min; MS m/z [M+H]+ 294

Int 33: tert-butyl N-[(3R)-1-(1-methylcyclopentyl)-3-piperidyl]carbamate

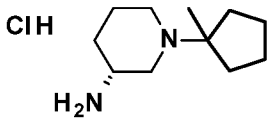


Under N2, a solution of tert-butyl N-[(3R)-1-(1-cyanocyclopentyl)-3-piperidyl]carbamate (300 mg, 1,02 mmol) in 5 mL of THF is cooled to 0°C and methylmagnesium bromide 3M in Et2O (1,70 ml , 5,11 mmol) is added dropwise. The mixture is stirred at 0°C for 1 hours and at rt overnight. The reaction is quenched with saturated aqueous NH4Cl and the aqueous layer is extracted with AcOEt. The organic layers are dried over MgSO4, filtered and concentrated under reduced pressure.

The residue is purified by Flash chromatography on silica gel using DCM/MeOH (from 0% to 10%) to give the title compound (85 mg, 30% yield) as a yellow oil.

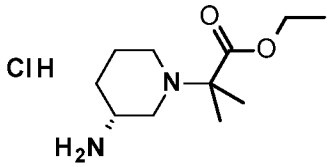
LCMS (method A): Rt = 0.54 min; MS m/z [M+H]+ 283

Int 31: (3R)-1-(1-methylcyclopentyl)piperidin-3-aminehydrochloride

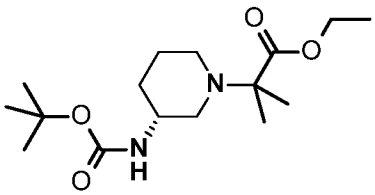


A solution of tert-butyl N-[(3R)-1-(1-methylcyclopentyl)-3-piperidyl]carbamate (85 mg, 0,30 mmol) in 5 mL of DCM was treated with hydrochloric acid 4M in dioxane (0.15 mL, 0,60mmol) and stirred 4 hours at rt. The reaction mixture concentrated under reduced pressure. The precipitate formed is filtered off to give 68 mg of an orange oil which is directly engaged in the next step.

Intermediate 34: ethyl 2-[(3R)-3-amino-1-piperidyl]-2-methyl-propanoate; hydrochloride



Int 35: ethyl 2-[(3R)-3-(tert-butoxycarbonylamino)-1-piperidyl]-2-methyl-propanoate

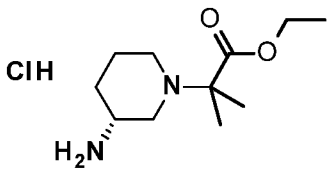


To a solution of tert-butyl N-[(3R)-3-piperidyl]carbamate (4 g, 20 mmol) in 80 ml of acetonitrile is added K2CO3 (6,8 g, 49,5 mmol) and Ethyl 2-bromoisobutyrate (5,76 g, 29,56 mmol).The mixture is stirred at 80°C for 72 hours. After cooling to rt, the mixture is diluted with water and

extracted twice with EtOAc. The combined organic layers are washed with brine and dried over Na_2SO_4, filtered off and concentrated under reduced pressure.
The residue is purified by flash chromatography on silica gel using heptane/EtOAc (from 0% to 30%) to give the title compound as a colorless oil (4,2 g, 66% yield).

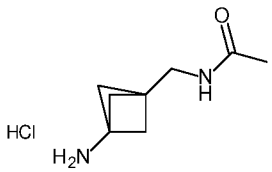
LCMS (method D): Rt = 1.71 min; MS m/z $[M+H]^+$ 315

Int 34: ethyl 2-[(3R)-3-amino-1-piperidyl]-2-methyl-propanoate; hydrochloride

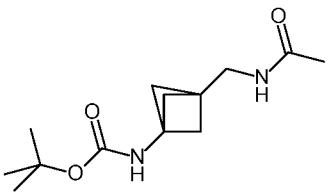


To a solution of ethyl 2-[(3R)-3-(tert-butoxycarbonylamino)-1-piperidyl]-2-methyl-propanoate (Int 35) (4,2 g, 13,4 mmol) in 40 ml of dioxane is added a solution of hydrochloric acid 4M in dioxane (34 ml, 136 mmol) and the mixture is stirred at room temperature for 20 hours. The mixture is then concentrated under reduced pressure and the residue is triturated in Et_2O. After drying overnight under vacuum in presence of P_2O_5, the title compound is obtained as a white solid (3,5 g, 98% yield).
LCMS (method B): Rt = 0.16 min; MS m/z $[M+H]^+$ 215

Intermediate 36: N-[(3-amino-1-bicyclo[1.1.1]pentanyl)methyl]-N-acetamide ; hydrochloride



Int 37: tert-butyl N-[3-(acetamidomethyl)-1-bicyclo[1.1.1]pentanyl]carbamate

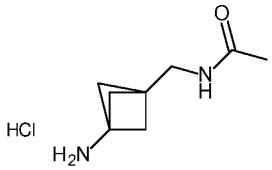


To a solution of tert-butyl N-[3-(aminomethyl)bicyclo[1.1.1]pentan-1-yl]carbamate (300 mg, 1.41 mmol) and DIPEA (1.23 ml, 7.07 mmol) in 10 ml of DCM is dropwise added acetyl chloride (80 µl, 1.13 mmol). The mixture is stirred at RT for 20 hours. The mixture is neutralized with a saturated aqueous solution of NH4Cl, then extracted with DCM. The organic layer is dried over Na_2SO_4, filtered off and concentrated under reduced pressure. After drying overnight under

vacuum in presence of P_2O_5, the title compound is obtained as a white solid (300 mg, 83% yield).

1H NMR (400 MHz, DMSO-d6) δ ppm 1.37 (s, 9 H), 1.73 (s, 6 H), 1.80 (s, 3 H), 3.17 (d, J=6 Hz, 2 H), 7.40 (br m, 1 H), 7.70 (m, 1H)

Int 36: N-[(3-amino-1-bicyclo[1.1.1]pentanyl)methyl]-N-acetamide ; hydrochloride



To a solution of tert-butyl N-[3-(acetamidomethyl)-1-bicyclo[1.1.1]pentanyl]carbamate (200 mg, 0.79 mmol) in 5 ml of dioxane is added a solution of hydrochloric acid 4M in dioxane (2 ml, 8 mmol) and the mixture is stirred at room temperature for 20 hours. The mixture is then concentrated under reduced pressure and the residue is triturated in Et2O. After drying overnight under vacuum in presence of P_2O_5, the title compound is obtained as a white solid (160 mg, 98% yield).

1H NMR (400 MHz, DMSO-d6) δ ppm 1.81 (s, 3 H), 1.83 (s, 6 H), 3.23 (d, J=6 Hz, 2 H), 7.86 (br m, 1 H), 8.56 (m, 3H)

Compounds of formula (I) underwent biochemical studies in order to assess their activities using the following *in vitro* methods:

IL-1β secretion assay

Monocytic THP-1 cells (DSMZ) were maintained in RPMI media (RPMI 1640 Medium (1×) +10% FBS, Eurobio CVFSVFOO-OU). Cells were then plated at 16,000 cells per well in 96-well round bottom cell culture plates (TPP, ref 92097) and maintained with RPMI and 0.1% Bovine Serum Albumin solution. Activation of the NLRP3 inflammasome requires both an NF-kB-dependent priming step and the addition of a NLRP3 activator. The priming step was induced by LPS (10ng/mL, Sigma, ref:L4391) for 3h at 37°C, then compound, in a 1:3.10 serial dilution series in DMSO 1:100, and the activator nigericin (Sigma Aldrich, ref : SML1779) 10µM (final concentration) were added to the cells and co-incubated for 2 h. 50 µL supernatant was removed, and IL-1β levels were monitored using an MSD assay (Electro Chemical Luminescence Immunoassay (ECLI) according to manufacturers' instructions.

TNF-α secretion assay

Monocytic THP-1 cells (DSMZ) were maintained in RPMI media (RPMI 1640 Medium (1×) +10% FBS, biowest S181H). Cells were then differentiated at 160,000 cells per well in 96-well

flat bottom cell culture plates with RPMI + 0.1% Bovine Serum Albumin solution and 0.5µM phorbol 12-myristate 13-acetate (PMA; Sigma, ref:P8139) overnight at 37°C. Experimental compounds were prepared and added as described above. TNF-α secretion was triggered by the addition of 0.5µg/mL LPS (invivoGen, tlrl-3pelps) and cells were incubated for 24 h. 2.5 µL supernatant was removed, and TNF-α levels were monitored using an MSD assay (mesoscale, K15049) according to manufacturers' instructions.

Data interpretation

IC_{50} values were calculated from the plot of percentage of inhibition versus the inhibitor concentration by a logistics fit according to: y = A2 + (A1 — A2)/ (1 + (x/ IC_{50})^p) where y is the %-inhibition at the inhibitor concentration, x. A1 is the lowest inhibition value, *i.e.,* 0 %, and A2 the maximum inhibition value, *i.e.,* 100 %. The exponent, p, is the Hill coefficient. The curve fitting was conducted with an internally developed software.

Brain over plasma ratio evaluation

A solution of 3 mg of compound in a generic vehicle (Glycofurol/solutol/Dextrose 5%: 10%/5%/85%, adjusted at pH3), final concentration 0.2 mg/ml, are stirred overnight at ambient temperature whilst protected from light.

Female C57Bl6 mice between the ages of 8 –12 weeks are administered with the prepared solution, as single intravenous dose of 1 mg/kg into the tail vein with a dose volume of 5 ml/kg. A total of 3 animal replicates are evaluated for each compound utilizing a terminal sampling approach. After 0.25h post dosing, under anesthesia, 400 µL of blood and the whole brain are collected. Blood sample is centrifuged at 4°C for 10 minutes at 1500 g; brain is weighted, homogenized using deionized water to give a final ratio of (1/2: w/v). Plasma and brain concentrations are measured by an exploratory LC-MS/MS method.

Individual brain over plasma concentration ratio is calculated for each animal, and geometric mean value is reported.

The IC_{50} values for the compounds disclosed herein were generally less than 10 µM, more particularly less than 1 µM, as indicated in the table below:

Exp Nr	IL1b IC_{50} (µM)	TNF-a inhibition @ 10µM	TNF-a inhibition @ 3µM	Ratio brain/plasma
1	0.661	**-17,7**	**-5,1**	

Exp Nr	IL1b IC_{50} (µM)	TNF-a inhibition @ 10µM	TNF-a inhibition @ 3µM	Ratio brain/plasma
2	0.577	**-51,5**	**3,3**	
3	0.335	**-8,2**	**3,1**	
4	0.054	**7,5**	**21,5**	
5	1.230	**-14,1**	**-18,2**	
6	0.158			**7.58**
7	1.790			
8	0.801	**-21,8**	**-10,0**	
9	9.560			
10	0.101	**-11,9**	**3,0**	**5.84**
11	0.045	**-12,7**	**20,1**	**3.20**
12	0.540			
13	0.168	**22,2**	**5,2**	
14	0.237	**-18,8**	**-0,5**	
15	2.740			
16	1.520			
17	0.300	**31,4**	**11,2**	
18	0.236	**21,6**	**9,6**	**1.56**
19	0.225	**-22,7**	**27,7**	
20	0.185	**-26,0**	**-6,1**	
21	0.060	**13,5**	**11,7**	
22	0.400	**14,5**	**-2,9**	
23	0.311	**3,3**	**1,8**	
24	2.890	**15,5**	**12,0**	
25	0.768			
26	1.990			
27	1.030			
28	0.775	**-45,5**	**34,4**	
29	1.140			
30	1.200			
31	0.030	**32,5**	**10,5**	
32	3.060			
33	2.750			
34	6.160			
35	2.380	**5,7**	**23,0**	
35	0.516			
37	0.045			
38	1.300			
39	2.230			
40	0.259			
41	0.037			**1.56**
42	1.150			
43	0.133			**0.42**

Exp Nr	IL1b IC_{50} (µM)	TNF-a inhibition @ 10µM	TNF-a inhibition @ 3µM	Ratio brain/plasma
44	0,278			
45	1.530			
46	8.200			
47	1.030			
48	0,0589			
49	0,027			
50	0,650			
51	>10.000			
52	0,082			
53	1,07			
54	1,71			
55	3,23			
56	1,47			
57	1,01			
58	0,657			
59	0,034			**1.15**
60	0,130			
61	0,159			
62	0,850			
63	1,66			
64	0,109			
65	3,80			
66	2,07			
67	0,446			
68	2,28			
69	3,43			
70	0,148			
71	0,07			
72	>10,00			
73	>10,00			
74	0.344			
75	0.157			
76	0.978			
77	0.078			
78	0.326			
79	0.029			
80	0.322			
81	>10,00			
82	4.50			
83	1.88			
84	5.95			
85	>10,00			

Exp Nr	IL1b IC_{50} (µM)	TNF-a inhibition @ 10µM	TNF-a inhibition @ 3µM	Ratio brain/plasma
86	>10,00			
87	>10,00			
88	>10,00			

It is therefore apparent that the compounds of formula (I) have an inhibitory activity on NOD-like receptor protein 3 (NLRP3) inflammasome.

The compounds of formula (I) may thus be used as inhibitors of NOD-like receptor protein 3 (NLRP3) inflammasome pathway.

The compounds of formula (I) may thus be used as medicaments, especially medicaments which are inhibitors of NOD-like receptor protein 3 (NLRP3) inflammasome pathway.

Thus, according to another of its aspects, a subject of the present disclosure is medicaments that comprise a compound of formula (I), or an addition salt thereof with a pharmaceutically acceptable acid.

These medicaments are employed therapeutically in the treatment of neurodegenerative diseases, in particular Parkinson's disease, Multiple System Atrophy, Alzheimer's Disease, Multiple Sclerosis, Amyotrophic Lateral Sclerosis or Brain injury.

According to another embodiment, the present disclosure relates to pharmaceutical compositions comprising as active principle, a compound of formula (I). These pharmaceutical compositions contain an effective dose of at least one compound of formula (I), or a pharmaceutically acceptable salt of the said compound.

These pharmaceutical compositions may also contain at least one pharmaceutically acceptable excipient.

The said excipients are chosen, according to the pharmaceutical form and the desired mode of administration, from the usual excipients known to those skilled in the art.

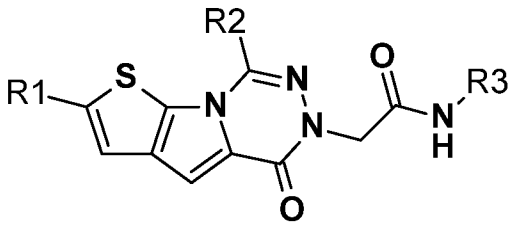
The compounds of formula (I) may be used in the treatment of pathologies involving NOD-like receptor protein 3 (NLRP3) inflammasome pathway.

The present disclosure, according to another of its aspects, also provides a method of treating the pathologies indicated above.

Thus, described is also a method of treating Parkinson's disease, Multiple System Atrophy, Alzheimer's Disease, Multiple Sclerosis, Amyotrophic Lateral Sclerosis or Brain injury, including administering to a subject in need thereof a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof.

CLAIMS

1. Compound of the formula (I)



(I)

in which:

R1 represents a hydrogen atom, a halogen atom, -(C_1-C_2)-alkyl group,

R2 represents a -(C_1-C_3)alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from a hydroxy group, -(C_1-C_3)-alkoxy group, or a -(C_3-C_4)cycloalkyl group,

R3 is selected from

- a -(C_5-C_8)bicycloalkyl group being unsubstituted or substituted with one -(C_1-C_3)alkyl group being unsubstituted or substituted with one or two -NH(CO)Me groups,
- a -(C_4-C_7)heterocycloalkyl group with nitrogen as heteroatom, being unsubstituted or substituted with one or more substituents independently selected from
  - a halogen atom,
  - an oxo group,
  - -(C_1-C_4)-alkyl group, being unsubstituted or substituted with 1 to 3 substituents independently selected from a hydroxy group, -(C_1-C_2)-alkyl group, a halogen atom, a -(C_1-C_2)-alkoxy group, a nitrile group, a -C(O)O(C_1-C_3) group, or a -(C_3-C_8)-cycloalkyl group being unsubstituted or substituted by one or more halogen group,
  - -(C_3-C_6)-cycloalkyl group, being unsubstituted or substituted by one or more (C_1-C_2) alkyl group,
  - –(CO)-(C_1-C_2)-alkyl group,
  - a heterocycloalkyl group, or
  - a heteroaryl group being unsubstituted or substituted with one or more -(C_1-C_4)alkyl group,

- a -hetero(C_6-C_9)bicycloalkyl group with nitrogen as heteroatom, optionally substituted with one or more substituents independently selected from
  - a -(C_3-C_4)cycloalkyl group, or
  - a -(C_1-C_3)alkyl group,

or

- a mono, or bicycloheteroaryl group, being unsubstituted or substituted with one or more substituents independently selected from
  - a -(C_1-C_4)-alkyl group,
  - a -(C_1-C_4)-alkoxy group, or
  - a halogen atom,

or a pharmaceutically acceptable salt thereof.

2. Compound according to claim 1 wherein:

R1 represents a hydrogen atom, a halogen atom chosen between bromine and chlorine atom, a methyl group,

R2 represents a -(C_1-C_3)alkyl group chosen between methyl, ethyl, propyl and isopropyl group being unsubstituted or substituted with 1 substituent independently selected from a hydroxy group, methoxy group, or a cyclopropyl group,

R3 is selected from

- a bicyclopentyl group being substituted with one -(C_1-C_3)alkyl group being unsubstituted or substituted with one -NH(CO)Me group,
- a -(C_4-C_6) heterocycloalkyl group with nitrogen as heteroatom, being unsubstituted or substituted with one or more substituents independently selected from
  - a fluorine atom,
  - an oxo group,
  - a -(C_1-C_4)-alkyl group, being unsubstituted or substituted with 1 to 3 substituents independently selected from a hydroxy group, a methyl group, a fluorine atom, a methoxy group, a nitrile group, a -C(O)O(C_1-C_2) group, or a -(C_3-C_6)-cycloalkyl group being unsubstituted or substituted by one fluorine atom,
  - a -(C_3-C_5)-cycloalkyl group, being unsubstituted or substituted by one or more methyl group,
  - a –(CO)-methyl group,
  - a heterocyclopropyl group,

- an imidazole group, being unsubstituted or substituted with one methyl group,

➢ a -hetero(C_6-C_9)bicycloalkyl group with nitrogen as heteroatom, optionally substituted with one or more substituents independently selected from

- a -(C_3-C_4) cycloalkyl group, or
- a methyl group,

or

➢ a mono, or bicycloheteroaryl group, being unsubstituted or substituted with one or two substituents independently selected from

➢ a methyl group,
➢ a methoxy group, or
➢ a fluorine atom,

or a pharmaceutically acceptable salt thereof.

3. Compound according to any one of claims 1 or 2 wherein

R1 represents a hydrogen atom, a halogen atom chosen between a bromine and a chlorine atom,

R2 represents a -(C_1-C_3)alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from a hydroxy group, or a -(C_3-C_4)cycloalkyl group,

R3 is selected from

➢ -(C_5-C_8)bicycloalkyl group being unsubstituted or substituted with one -(C_1-C_3)alkyl group being unsubstituted or substituted with one or two -NH(CO)Me groups,

➢ a -(C_4-C_7)heterocycloalkyl group with nitrogen as heteroatom, being unsubstituted or substituted with one or more substituents independently selected from

- -(C_1-C_4)-alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from a hydroxy group, a methyl group, a fluorine atom, a methoxy group, a nitrile group, a -C(O)O(C_1-C_3) group, -(C_3-C_5)-cycloalkyl group being unsubstituted or substituted by one or more fluorine atom,
- -(C_3-C_6)-cycloalkyl group, being unsubstituted or substituted by one or more -(C_1-C_2)-alkyl group, or
- a heterocycloalkyl group,

➢ -hetero(C_6-C_8) bicycloalkyl group with nitrogen as heteroatom, optionally substituted with one or more -(C_3-C_4)cycloalkyl group,

or

- a mono, or bicycloheteroaryl group, being unsubstituted or substituted with one fluorine atom,

or a pharmaceutically acceptable salt thereof.

4. Compound according to any one of claims 1 to 3 wherein R1 represents a hydrogen atom or a pharmaceutically acceptable salt thereof.

5. Compound according to any one of claims 1 to 4 wherein R1 represents a bromine atom or a pharmaceutically acceptable salt thereof.

6. Compound according to any one of claims 1 to 5 wherein R1 represents a chlorine atom or a pharmaceutically acceptable salt thereof.

7. Compound according to any one of claims 1 to 6 wherein R2 represents a -iPr group or a pharmaceutically acceptable salt thereof.

8. Compound according to any one of claims 1 to 7 wherein R2 represents a -cyclopropyl group or a pharmaceutically acceptable salt thereof.

9. Compound according to any one of claims 1 to 8 wherein R3 represents a –(C_4-C_7)heterocycloalkyl group with nitrogen as heteroatom, being unsubstituted or substituted with one or more substituents independently selected from

- -(C_1-C_4)-alkyl group, being unsubstituted or substituted with 1 to 3 substituents independently selected from a hydroxy group, -(C_1-C_2)-alkyl group, a fluorine atom, -(C_1-C_2)-alkoxy group, a nitrile group, a -C(O)O(C_1-C_3) group, -(C_3-C_5)-cycloalkyl group being unsubstituted or substituted by one or more fluorine atom,
- -(C_3-C_6)-cycloalkyl group, being unsubstituted or substituted by one or more (C_1-C_2) alkyl group, or
- a heterocyclopropyl group.

or a pharmaceutically acceptable salt thereof.

10. Compounds of formula (I) according to claim 1 which are selected from the following list:

1 (R)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide

2 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(thiazol-5-yl) acetamide

3 N-((R)-1-((S)-2-hydroxypropyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5] pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

4 (R)-N-(1-cyclopropylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d] [1,2,4]triazin-6(5H)-yl)acetamide

5 (R)-2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4] triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate

6 (R)-2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclopropylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate

7 2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(thiazol-5-yl)acetamide

8 (R)-2-(2-bromo-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4] triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide

9 (R)-2-(8-isopropyl-2-methyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate

10 (R)-2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4] triazin-6(5H)-yl)-N-(1-cyclobutylpiperidin-3-yl)acetamide formate

11 (R)-N-(1-cyclobutylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d] [1,2,4]triazin-6(5H)-yl)acetamide formate

12 N-(benzo[d]thiazol-6-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

13 (R)-2-(2-chloro-8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclopropylpiperidin-3-yl)acetamide

14 (R)-N-(1-isobutylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4] triazin-6(5H)-yl)acetamide

15 N-(benzo[d]thiazol-5-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

16 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(6-methoxypyridin-3-yl)acetamide

17 (R)-N-(1-(cyclopentylmethyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo [1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

18 N-((3R)-1-((2,2-difluorocyclopropyl)methyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno [3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide compound with formaldehyde

19 (R)-N-(1-(2-hydroxyethyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno [3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide compound with formaldehyde

20 (R)-N-(1-cyclobutylpiperidin-3-yl)-2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d] [1,2,4]triazin-6(5H)-yl)acetamide

21 (R)-2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclopropylpiperidin-3-yl)acetamide

22 2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-((R)-1-((S)-2-hydroxypropyl)piperidin-3-yl)acetamide

23 (R)-N-(1-(2-hydroxy-2-methylpropyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate

24 (R)-2-(8-cyclopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methylpiperidin-3-yl)acetamide formate

25 N-((R)-1-cyclobutylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)propanamide formate

26 N-((R)-1-cyclopropylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)propanamide formate

27 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methyl-1H-indazol-6-yl)acetamide formate

28 (R)-N-(1-(cyclopropylmethyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate

29 (R)-2-(2-chloro-8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclobutylpiperidin-3-yl)acetamide formate

30 (R)-2-(2-chloro-8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclopropylpiperidin-3-yl)acetamide formate

31 (R)-2-(2-bromo-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-cyclobutylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate

32 (R)-N-(1-cyclobutylpiperidin-3-yl)-2-(8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

33 (R)-N-(1-cyclopropylpiperidin-3-yl)-2-(8-(methoxymethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide 2,2,2-trifluoroacetate

34 2-(2-chloro-8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(5,5-difluoro-1-methylpiperidin-3-yl)acetamide 2,2,2-trifluoroacetate

35 N-(5,5-difluoro-1-methylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

36 (R)-N-(1-(2-fluoroethyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate

37 N-(1-(tert-butyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate

38 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-(2,2,2-trifluoroethyl)piperidin-3-yl)acetamide 2,2,2-trifluoroacetate

39 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(quinuclidin-3-yl)acetamide

40 (R)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-(oxetan-3-yl)piperidin-3-yl)acetamide

41 (R)-N-(1-(3-fluoropropyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno [3',2':4,5] pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate

42 (R)-N-(1-acetylpiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4] triazin-6(5H)-yl)acetamide

43 (R)-N-(1-((3,3-difluorocyclobutyl)methyl)piperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide formate

44 N-((R)-1-cyclopropylpiperidin-3-yl)-2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5]pyrrolo [1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

45 (R)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-(1-methyl-1H-imidazol-2-yl)piperidin-3-yl)acetamide

46 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methyl-2-oxopiperidin-4-yl)acetamide

47 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(1-methyl-6-oxopiperidin-3-yl)acetamide

48 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(3R)-1-isopropyl-3-piperidyl]acetamide

49 N-[(3R)-1-cyclopentyl-3-piperidyl]-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo [6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide

50 N-((R)-1-cyclobutylpiperidin-3-yl)-2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5]pyrrolo [1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

51 N-((R)-1-cyclopropylpiperidin-3-yl)-2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5]pyrrolo [1,2d][1,2,4]triazin-6(5H)-yl)acetamide

52 (R)-N-(1-cyclopropylpiperidin-3-yl)-2-(8-(2-hydroxypropan-2-yl)-5-oxothieno [3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

53 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(2-methylpyrazol-3-yl)acetamide

54 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(1-methylpyrazol-3-yl)acetamide

55 N-[(1-tert-butyl-5-oxo-pyrrolidin-3-yl)methyl]-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide

56 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(3-pyridyl)acetamide

57 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[rac-(3R)-1-(2,2-dimethylcyclobutyl)-3-piperidyl]acetamide

58 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(2-pyridyl)acetamide

59 2-(4-bromo-12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(1-tert-butyl-3-piperidyl)acetamide

60 N-[(3R)-1-cyclopropyl-3-piperidyl]-2-(12-ethyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide

61 N-[(3R)-1-cyclopropylazepan-3-yl]-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide

62 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(3R)-1-methylazepan-3-yl]acetamide

63 N-(1-cyclopropyl-5,5-difluoropiperidin-3-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide 2,2,2-trifluoroacetate

64 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-((3R)-1-(1-methoxypropan-2-yl)piperidin-3-yl)acetamide

65 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-(2-methoxypyridin-4-yl)acetamide

66 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-pyrimidin-4-yl-acetamide

67 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(4-pyridyl)acetamide

68 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(6-methyl-3-pyridyl)acetamide

69 2-(12-ethyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(3R)-1-[(2S)-2-hydroxypropyl]-3-piperidyl]acetamide

70 N-(5-fluoropyrimidin-4-yl)-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide

71 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(3R)-1-(1-methylcyclopentyl)-3-piperidyl]acetamide

72 N-[(3R)-1-cyclopropylpiperidin-3-yl]-2-(9-oxo-12-propyl-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide

73 2-(12-ethyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[(3R)-1-methyl-3-piperidyl]acetamide

74N-[3-(acetamidomethyl)bicyclo[1.1.1]pentan-1-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

75 N-[(3R)-1-(cyanomethyl)piperidin-3-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

76N-[(3R)-1-methylpyrrolidin-3-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4] triazin-6(5H)-yl)acetamide

77 N-[(3R)-1-(2-cyanoethyl)piperidin-3-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

78 N-[(3R)-1-[(2R)-2-hydroxypropyl]piperidin-3-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo [1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

79N-[(3R)-1-(1-hydroxy-2-methylpropan-2-yl)piperidin-3-yl]-2-(8-isopropyl-5-oxothieno [3',2':4,5] pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

80 ethyl 2-methyl-2-[3-[[2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetyl]amino]piperidin-1-yl]propanoate

81 N-((R)-1-cyclobutylpiperidin-3-yl)-2-(8-(1-hydroxyethyl)-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

82 N-[(1R,4R)-2-methyl-2-azabicyclo[2.2.1]heptan-6-yl]-2-(8-isopropyl-5-oxothieno[3',2':4,5] pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

83 N-(2-methyl-2-azaspiro[3.3]heptan-6-yl)-2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)acetamide

84 2-(8-isopropyl-5-oxothieno[3',2':4,5]pyrrolo[1,2-d][1,2,4]triazin-6(5H)-yl)-N-pyrimidin-5-ylacetamide

85 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-(2-oxo-4-piperidyl)acetamide

86 N-(1-cyclopropylpyrrolidin-3-yl)-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo [6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamide

87 2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)-N-[rac-(3R)-1-tert-butylpyrrolidin-3-yl]acetamide

88 N-[(1S,4R)-2-azabicyclo[2.2.1]heptan-6-yl]-2-(12-isopropyl-9-oxo-3-thia-1,10,11-triazatricyclo[6.4.0.02,6]dodeca-2(6),4,7,11-tetraen-10-yl)acetamidehydrochloride

11. Medicament, characterized in that it comprises a compound of formula (I) according to any one of claims 1 to 10, or pharmaceutically acceptable salt thereof.

12. Pharmaceutical composition, characterized in that it comprises a compound of formula (I) according to any one of claims 1 to 10.

13. Compound of formula (I) according to any one of claims 1 to 10, for use as inhibitors of NOD-like receptor protein 3 (NLRP3) inflammasome.

14. Compound of formula (I) according to any one of claims 1 to 10, for use in the treatment of Parkinson's disease, Multiple System Atrophy, Alzheimer's disease, frontotemporal Dementia, Multiple Sclerosis, Amyotrophic Lateral Sclerosis or brain injury.