Innovation, Sciences et Développement économique Canada
Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 3007993 C 2024/01/16

(11)(21) 3 007 993

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2016/12/09
(87) Date publication PCT/PCT Publication Date: 2017/06/15
(45) Date de délivrance/Issue Date: 2024/01/16
(85) Entrée phase nationale/National Entry: 2018/06/08
(86) N° demande PCT/PCT Application No.: US 2016/065964
(87) N° publication PCT/PCT Publication No.: 2017/100668
(30) Priorité/Priority: 2015/12/10 (US62/265,780)

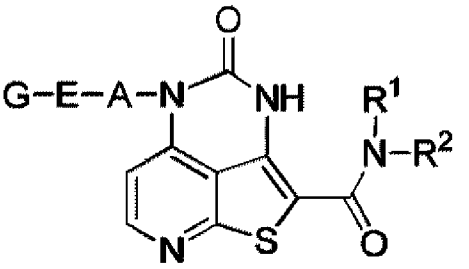
(51) Cl.Int./Int.Cl. *C07D 495/16* (2006.01),
A61K 31/519 (2006.01), *A61P 35/00* (2006.01)

(72) Inventeurs/Inventors:
ARORA, NIDHI, US;
BACANI, GENESIS M., US;
BARBAY, JOSEPH KENT, US;
BEMBENEK, SCOTT D., US;
CAI, MIN, CN;
CHEN, WEI, CN;
...

(73) Propriétaire/Owner:
JANSSEN PHARMACEUTICA NV, BE

(74) Agent: NORTON ROSE FULBRIGHT CANADA LLP/S.E.N.C.R.L., S.R.L.

(54) Titre : INHIBITEURS DE TYROSINE KINASE DE BRUTON ET LEURS PROCEDES D'UTILISATION
(54) Title: INHIBITORS OF BRUTON'S TYROSINE KINASE AND METHODS OF THEIR USE



(I')

(57) Abrégé/Abstract:
The present disclosure is directed to compounds of formula I and methods of their use and preparation, as well as compositions comprising compounds of formula I.

(11)(21) 3 007 993

(13) C

(72) **Inventeurs(suite)/Inventors(continued):** DECKHUT, CHARLOTTE POOLEY, US; EDWARDS, JAMES P., US; GHOSH, BRAHMANANDA, US; HAO, BAOYU, CN; KREUTTER, KEVIN D., US; LI, GANG, CN; TICHENOR, MARK S., US; VENABLE, JENNIFER D., US; WEI, JIANMEI, US; WIENER, JOHN J. M., US; WU, YAO, CN; ZHU, YAOPING, CN; ZHANG, FEIHUANG, CN; ZHANG, ZHENG, CN; XIAO, KUN, CN

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 June 2017 (15.06.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/100668 A1

(51) International Patent Classification:
C07D 495/16 (2006.01) *A61P 35/00* (2006.01)
A61K 31/519 (2006.01)

(21) International Application Number:
PCT/US2016/065964

(22) International Filing Date:
9 December 2016 (09.12.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/265,780 10 December 2015 (10.12.2015) US

(71) Applicant: **JANSSEN PHARMACEUTICA NV** [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

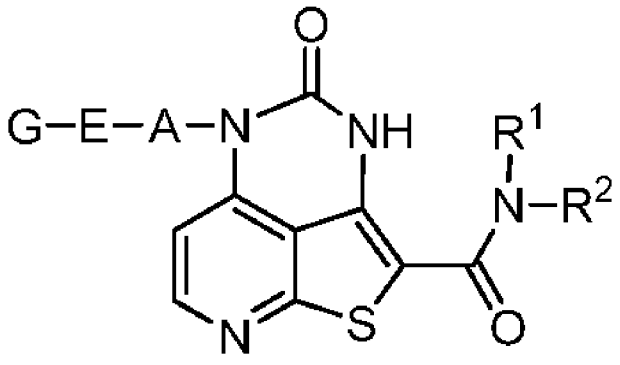
(72) Inventor; and
(71) Applicant : **ARORA, Nidhi** [US/US]; 3210 Merryfield Row, San Diego, California 92121 (US).

(72) Inventors: **BACANI, Genesis M.**; 3210 Merryfield Row, San Diego, California 92121 (US). **BARBAY, Joseph Kent**; Welsh & McKean Roads, Spring House, Pennsylvania 19477 (US). **BEMBENEK, Scott D.**; 3210 Merryfield Row, San Diego, California 92121 (US). **CAI, Min**; c/o Hutchinson Medipharma Limited, Building 4, 720 Cailun Road, Zhangjian Hi-Tech Park, Shanghai 201203 (CN). **CHEN, Wei**; c/o Hutchinson Medipharma Limited, Building 4, 720 Cailun Road, Zhangjian Hi-Tech Park, Shanghai 201203 (CN). **DECKHUT, Charlotte Pooley**; 3210 Merryfield Row, San Diego, California 92121 (US). **EDWARDS, James P.**; 3210 Merryfield Row, San Diego, California 92121 (US). **GHOSH, Brahmananda**; 1400 McKean Road, Spring House, Pennsylvania 19477 (US). **HAO, Baoyu**; c/o Hutchinson Medipharma Limited, Building 4, 720 Cailun Road, Zhangjian Hi-Tech Park, Shanghai 201203 (CN). **KREUTTER, Kevin**; c/o Janssen Research & Development LLC, 1400 McKean Road, Spring House, Pennsylvania 19477 (US). **LI, Gang**; c/o Hutchinson Medipharma Limited, Building 4, 720 Cailun Road, Zhangjian Hi-Tech Park, Shanghai 201203 (CN). **TICHENOR, Mark S.**; 3210 Merryfield Row, San Diego, California 92121 (US). **VENABLE, Jennifer D.**; 3210 Merryfield Row, San Diego, California 92121 (US). **WEI, Jianmei**; 3210 Merryfield Row, San Diego, California 92121 (US). **WIENER, John J. M.**; 3210 Merryfield Row, San Diego, California 92121 (US). **WU, Yao**; c/o Hutchinson Medipharma Limited, Building 4, 720 Cailun Road, Zhangjian Hi-Tech Park, Shanghai 201203 (CN). **ZHU, Yaoping**; c/o Hutchinson Medipharma Limited, Building 4, 720 Cailun Road, Zhangjian Hi-Tech Park, Shanghai 201203 (CN). **ZHANG, Feihuang**; c/o Hutchinson Medipharma Limited, Building 4, 720 Cailun Road, Zhangjian Hi-Tech Park, Shanghai 201203 (CN). **ZHANG, Zheng**; c/o Hutchinson Medipharma Limited, Building 4, 720 Cailun Road, Zhangjian Hi-Tech Park, Shanghai 201203 (CN). **XIAO, Kun**; c/o Hutchinson Medipharma Limited, Building 4, 720 Cailun Road, Zhangjian Hi-Tech Park, Shanghai 201203 (CN).

(74) Agents: **SHIRTZ, Joseph F.** et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933 (US).

[Continued on next page]

(54) Title: INHIBITORS OF BRUTON'S TYROSINE KINASE AND METHODS OF THEIR USE



(I')

(57) Abstract: The present disclosure is directed to compounds of formula I and methods of their use and preparation, as well as compositions comprising compounds of formula I.

WO 2017/100668 A1

WO 2017/100668 A1

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 3
CONTENANT LES PAGES 1 À 331

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 3
CONTAINING PAGES 1 TO 331

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

INHIBITORS OF BRUTON'S TYROSINE KINASE AND METHODS OF THEIR USE

TECHNICAL FIELD

The present disclosure is directed to small molecule tyrosine kinase inhibitors.

BACKGROUND

Rheumatoid arthritis ("RA") is a chronic, autoimmune, inflammatory disorder that affects the lining of the joints, causing painful swelling that can result in bone erosion and joint deformation. RA presents a significant societal impact – it has a relatively high prevalence (about 1% of the United States population suffers from RA), produces irreversible joint damage, and has a widespread occurrence of co-morbities. While many patients benefit from currently marketed biologic and small molecule medicines, most patients still suffered from the chronic pain and inflammation of the disease.

Cancer, in particular mantle cell lymphoma, chronic lymphocytic leukemia, macroglobulinemia, and multiple myeloma, continues to afflict patients. Alternative, effective treatments of cancer are still needed.

Human Bruton's tyrosine kinase ("Btk") is a ~76 kDa protein belonging to the Tec family of non-receptor tyrosine kinases. Tec kinases form the second largest family of cytoplasmic tyrosine kinases in mammalian cells, which consists of four other members in addition to BTK: the eponymous kinase TEC, ITK, TXK/RLK and BMX. Tec kinases are evolutionarily conserved throughout vertebrates. They are related to, but structurally distinct from, the larger Src and Syk kinase families. Tec family proteins are abundantly expressed in hematopoietic tissues and play important roles in the growth and differentiation of blood and endothelial cells in mammals.

Based upon Btk expression from IHC studies described in the art, Btk inhibition has the potential to modulate biology associated with B cells, macrophages, mast cells, osteoclasts, and platelet microparticles. Corneth, O.B., et al. Curr. Top. Microbiol. Immunol. *BTK Signaling in B Cell Differentiation and Autoimmunity.* 2015 Sept. 5. The role of B cells in RA is supported by the therapeutic benefit exhibited in the clinic upon B cell depletion with Rituximab™. Since auto-reactive antibodies play such a critical role in synovial inflammation, therapeutic modulation of the B cell compartment is an attractive mechanism to treat early RA and potentially modulate disease at the earliest stages. B cell depletion in murine models such as collagen-induced arthritis (CIA) prevents arthritis development. Svensson, et al. (1998) B cell-

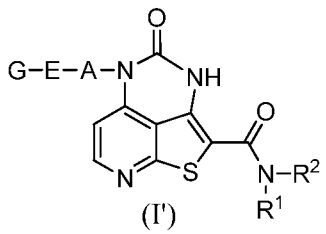
deficient mice do not develop type II collagen-induced arthritis (CIA). *Clin Exp Immunol* **111**, 521-526.

Use of Btk inhibitors in preclinical models support the role of Btk in B cell biology associated with RA. Btk inhibitors block antigen receptor-induced signaling at the earliest stages and subsequent B cell proliferation. In addition, critical aspects of antigen presentation function, such as antigen internalization and upregulation of co-stimulation molecules such as CD80 and CD86 and MHC-IIs can be blocked with Btk inhibitors (Kenny, E. F., et al. (2013) *PLoS One* **8**, e74103). Btk inhibitors exhibit efficacy in a variety of rodent arthritis models, whether dosed prophylactically or fully therapeutically (Di Paolo, J. A., et al. *Nat Chem Biol* (2011) **7**, 41-50; Liu, L., et al. (2011) *J Pharmacol Exp Ther* **338**, 154-163; Honigberg, L. A., et al. (2010) *Proc Natl Acad Sci U S A* **107**, 13075-13080; Evans, E. K., et al. (2013) *J Pharmacol Exp Ther* **346**, 219-228). In addition to ameliorating disease symptoms, Btk inhibition decreases autoantibody production and isotype switching, as well as epitope spreading from bovine collagen to rodent collagen. In addition, Btk inhibition shows significant reductions in inflammation scores as assessed by inflamed paw histopathology. Together, these data provide a rationale for testing Btk inhibitors in inflammatory autoimmune disorders where B cells play a major role. In addition, Btk is a clinically validated target for the treatment of hematological malignancies, with the irreversible covalent inhibitor (ICI) ibrutinib approved for treatment of B cell malignancies such as mantle cell lymphoma, chronic lymphocytic leukemia (CLL) and Waldenström's macroglobulinemia (Hendriks, R. W., et al. (2014) *Nat Rev Cancer* **14**, 219-232).

In view of Btk's role in a variety of immunological and oncological pathways, inhibitors of Btk are needed.

SUMMARY

The present disclosure is directed to compounds of formula I:



(I')

wherein

R^1 is H or C_{1-6}alkyl;

R^2 is $-C_{0-6}$alk-piperidinyl; $-C_{0-6}$alk-pyrrolidinyl; $-C_{0-6}$alk-oxazepanyl; $-C_{0-6}$alk-azetidinyl; $-C_{0-6}$alk-aziridinyl; $-C_{0-6}$alk-azepanyl; $-C_{0-6}$alk-quinuclidinyl; $-C_{0-6}$alk-imidazolidinyl;

-C_{0-6}alk-piperazinyl; -C_{0-6}alkmorpholinyl; –C_{0-6}alk-tetrahydropyranyl; or –C_{0-6}alk-tetrahydrofuranyl wherein the R^2 is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of

-NR^8-C(O)-$C(R^3)$=$CR^4(R^5)$; -C(O)-$C(R^3)$=$CR^4(R^5)$; oxo; halogen; -CN; -OH; -NR^6R^7; -C_{1-6}alkyl; -C_{1-6}alk-OH; -OC_{1-6}alkyl; -C_{3-6}cycloalkyl; -C_{1-6}haloalkyl; -C_{1-6}alkaryl; -SO_2-C_{1-6}alkyl; -SO_2-C_{2-6}alkenyl; -C(O)H; -C(O)-C_{1-6}alkyl; -C(O)-C_{3-6}cycloalkyl; -C(O)-C_{1-6}haloalkyl; -C(O)-C_{2-6}alkynyl; -C(O)-C_{6-10}aryl; -C(O)-heteroaryl; -C(O)-C_{1-6}alk-CN; -C(O)-C_{1-6}alk-OH; -C(O)-C_{1-6}alk-SO_2-C_{1-6}alkyl; -C(O)-O-C_{1-6}alkyl; -C(O)-C_{1-6}alk-NR^6R^7; -C(O)-C_{1-6}alk-O-C_{1-6}alkyl wherein the –C_{1-6}alk- is optionally substituted with –OH, -OC_{1-6}alkyl, or -NR^6R^7; and -C(O)-C_{0-6}alk-heterocycloalkyl wherein the -alk- is optionally substituted with oxo and the heterocycloalkyl is optionally substituted with -C_{1-6}alkyl; wherein

R^3 is H; -CN; halogen; -C_{1-6}haloalkyl; or -C_{1-6}alkyl;

R^4 and R^5 are each independently H; halogen; -C_{1-6}alkyl; -OC_{1-6}alkyl; -C_{0-6}alk-C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; -C_{0-6}alk-heterocycloalkyl optionally substituted with –C(O)C_{1-6}alkyl or -C_{1-6}alkyl; -C_{1-6}alk-OH; -C_{0-6}alk-NR^6R^7; -C_{1-6}alk-O-C_{1-6}alkyl; -C_{1-6}alk-NH-C_{0-6}alk-O-C_{1-6}alkyl; -C_{1-6}alk-$NHSO_2$-C_{1-6}alkyl; -C_{1-6}alk-SO_2-C_{1-6}alkyl; -NHC(O)-C_{1-6}alkyl; or –linker-PEG-Biotin; and

R^6 and R^7 are each independently H; -C_{1-6}alkyl; -C_{3-6}cycloalkyl; –C(O)H, or -CN; and

R^8 is H or C_{1-6}alkyl;

A is a bond, pyridyl; phenyl; napthalenyl; pyrimidinyl; pyrazinyl; pyridazinyl; benzo[d][1,3]dioxolyl optionally substituted with halogen; benzothiophenyl; or pyrazolyl; optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of -C_{1-6}alkyl; halogen; -SF_5; -OC_{1-6}alkyl; -C(O)-C_{1-6}alkyl; and -C_{1-6}haloalkyl;

E is –O-; a bond; -C(O)-NH-; -CH_2-; or -CH_2-O-;

G is H; -C_{3-6}cycloalkyl; -phenyl; -thiophenyl; -C_{1-6}alkyl; -pyrimidinyl; -pyridyl; -pyridazinyl; -benzofuranyl; -C_{1-6}haloalkyl; -heterocycloalkyl that contains an oxygen heteroatom; -phenyl-CH_2-O-phenyl; -C_{1-6}alk-O-C_{1-6}alkyl; -NR^6R^7; -SO_2C_{1-6}alkyl; or –OH; wherein the phenyl; thiophenyl; pyrimidinyl; pyridyl; pyridazinyl; or benzofuranyl is optionally

substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen; -C_{1-6}alkyl; -C_{1-6}haloalkyl; -OC_{1-6}haloalkyl; -C_{3-6}cycloalkyl; -OC_{1-6}alkyl; -CN; -OH; -C_{1-6}alk-O-C_{1-6}alkyl; -C(O)-NR^6R^7; and -C(O)-C_{1-6}alkyl;

or a stereoisomer or isotopic variant thereof;

or a pharmaceutically acceptable salt thereof.

Compositions comprising compounds of formula I are also described. Methods of using compounds of formula I are also within the scope of the disclosure.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The disclosure may be more fully appreciated by reference to the following description, including the following glossary of terms and the concluding examples. It is to be appreciated that certain features of the disclosed compositions and methods which are, for clarity, described herein in the context of separate aspects, may also be provided in combination in a single aspect. Conversely, various features of the disclosed compositions and methods that are, for brevity, described in the context of a single aspect, may also be provided separately or in any subcombination.

The term "alkyl," when used alone or as part of a substituent group, refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms ("C_{1-12}"), preferably 1 to 6 carbons atoms ("C_{1-6}"), in the chain. Examples of alkyl groups include methyl (Me, C_1alkyl) ethyl (Et, C_2alkyl), n-propyl (C_3alkyl), isopropyl (C_3alkyl), butyl (C_4alkyl), isobutyl (C_4alkyl), sec-butyl (C_4alkyl), tert-butyl (C_4alkyl), pentyl (C_5alkyl), isopentyl (C_5alkyl), tert-pentyl (C_5alkyl), hexyl (C_6alkyl), isohexyl (C_6alkyl), and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

When a range of carbon atoms is used herein, for example, C_{1-6}, all ranges, as well as individual numbers of carbon atoms are encompassed. For example, "C_{1-3}" includes C_{1-3}, C_{1-2}, C_{2-3}, C_1, C_2, and C_3.

The term "C_{1-6}alk" refers to an aliphatic linker having 1, 2, 3, 4, 5, or 6 carbon atoms and includes, for example, –CH_2-, –$CH(CH_3)$-, -$CH(CH_3)$-CH_2-, and –$C(CH_3)_2$-. The term "-C_0alk-" refers to a bond. In some aspects, the C_{1-6}alk can be substituted with an oxo group or an –OH group.

The term "alkenyl," when used alone or as part of a substituent group, refers to straight and branched carbon chains having from 2 to 12 carbon atoms ("C_{2-12}"), preferably 2 to 6 carbon atoms ("C_{2-6}"), wherein the carbon chain contains at least one, preferably one to two, more

preferably one double bond. For example, alkenyl moieties include, but are not limited to allyl, 1-propen-3-yl, 1-buten-4-yl, propa-1,2-dien-3-yl, and the like.

The term "alkynyl," when used alone or as part of a substituent group, refers to straight and branched carbon chains having from 2 to 12 carbon atoms ("C_{2-12}"), preferably 2 to 6 carbon atoms ("C_{2-6}"), wherein the carbon chain contains at least one, preferably one to two, more preferably one triple bond. For example, alkynyl moieties include, but are not limited to vinyl, 1-propyn-3-yl, 2-butyn-4-yl, and the like.

The term "aryl" refers to carbocylic aromatic groups having from 6 to 10 carbon atoms ("C_{6-10}") such as phenyl, naphthyl, and the like.

The term "cycloalkyl" refers to monocyclic, non-aromatic hydrocarbon groups having from 3 to 10 carbon atoms ("C_{3-10}"), preferably from 3 to 6 carbon atoms ("C_{3-6}"). Examples of cycloalkyl groups include, for example, cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl (C_5), cyclohexyl (C_6), 1-methylcyclopropyl (C_4), 2-methylcyclopentyl (C_4), adamantanyl (C_{10}), and the like.

The term "heterocycloalkyl" refers to any five to ten membered monocyclic or bicyclic, saturated ring structure containing at least one heteroatom selected from the group consisting of O, N and S. The heterocycloalkyl group may be attached at any heteroatom or carbon atom of the ring such that the result is a stable structure. Examples of suitable heterocycloalkyl groups include, but are not limited to, azepanyl, aziridinyl, azetidinyl, pyrrolidinyl, dioxolanyl, imidazolidinyl, pyrazolidinyl, piperazinyl, piperidinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, oxazepanyl, oxiranyl, oxetanyl, quinuclidinyl, tetrahyofuranyl, tetrahydropyranyl, piperazinyl, hexahydro-5H-[1,4]dioxino[2,3-c]pyrrolyl, benzo[d][1,3]dioxolyl, and the like.

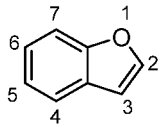
The term "heteroaryl" refers to a mono-or bicyclic aromoatic ring structure including carbon atoms as well as up to four heteroatoms selected from nitrogen, oxygen, and sulfur. Heteroaryl rings can include a total of 5, 6, 9, or 10 ring atoms ("C_{5-10}"). Examples of heteroaryl groups include but are not limited to, pyrrolyl, furyl, thiophenyl (thienyl), oxazolyl, imidazolyl, purazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furazanyl, indolizinyl, indolyl, isoindolinyl, indazolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, benzthiazolyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, isothiazolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, and the like.

The term "halogen" represents chlorine, fluorine, bromine, or iodine. The term "halo" represents chloro, fluoro, bromo, or iodo.

The term “haloalkyl” refers to an alkyl moiety wherein one or more of the hydrogen atoms has been replaced with one or more halogen atoms. One exemplary substitutent is fluoro. Preferred haloalkyl groups of the disclosure include trihalogenated alkyl groups such as trifluoromethyl groups.

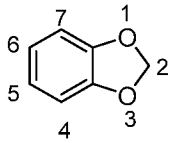
The term “oxo” refers to a =O moiety, wherein two hydrogens from the same carbon atom have be replaced with a carbonyl. For example, an oxo-substituted pyrrolidinyl moiety could be a pyrrolidin-2-one moiety or a pyrrolidin-3-one moiety.

The term “benzofuranyl” represents the following moiety:

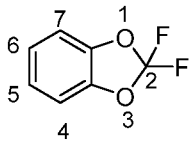


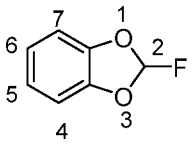
The benzofuranyl moiety can be attached through any one of the 2-, 3-, 4-, 5-, 6-, or 7-carbon atoms.

The term “benzo[d][1,3]dioxolyl” represents the following moiety:

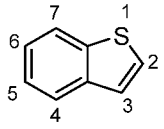


The benzo[d][1,3]dioxolyl moiety can be attached through any one of the 2-, 4-, 5-, 6-, or 7- carbon atoms. In those aspects wherein the “benzo[d][1,3]dioxolyl moiety is substituted with halogen,” the following moieties are preferred:





The term “benzothiophenyl” represents the following moiety:

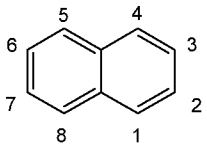


The benzothiophenyl moiety can be attached through any one of the 2-, 3-, 4-, 5-, 6-, or 7- carbon atoms.

The term “phenyl” represents the following moiety:

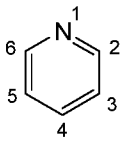
The phenyl moiety can be attached through any of the carbon atoms.

The term "napthalenyl" (i.e., naphthyl) represents the following moiety:



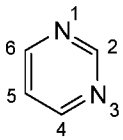
The naphthalenyl moiety can be attached through any one of the 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-position carbon atoms.

The term "pyridyl" represents the following moiety:



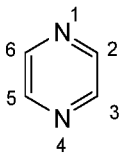
The pyridyl moiety can be attached through any one of the 2-, 3-, 4-, 5-, or 6-position carbon atoms.

The term "pyrimidinyl" represents the following moiety:



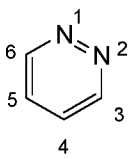
The pyrimidinyl moiety can be attached through any one of the 2-, 4-, 5-, or 6-position carbon atoms.

The term "pyrazinyl" represents the following moiety:



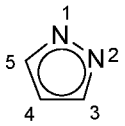
The pyrazinyl moiety can be attached through any one of the 2-, 3-, 5-, or 6-position carbon atoms.

The term "pyridazinyl" represents the following moiety:



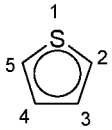
The pyridazinyl moiety can be attached through any one of the 3-, 4-, 5-, or 6-position carbon atoms.

The term "pyrazolyl" represents the following moiety:



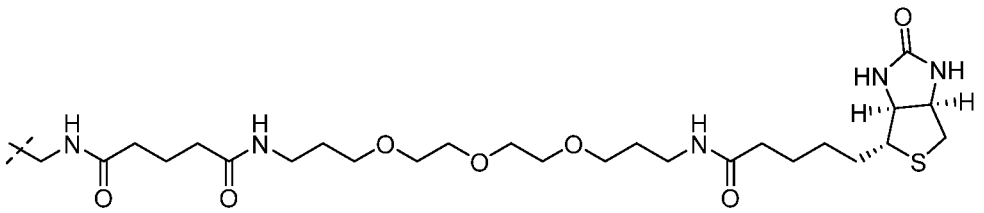
The pyrazolyl moiety can be attached through any one of the 1-, 2-, 3-, 4-, or 5-position carbon atoms.

The term "thiophenyl" represents the following moiety:

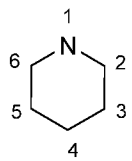


The thiophenyl moiety can be attached through any one of the 2-, 3-, 4-, or 5-position carbon atoms.

The term "linker-PEG-Biotin" refers to a moiety comprising –linker-PEG-CH_2-NH-biotinyl. Compounds of the disclosure that include a linker-PEG-Biotin moiety can be used according to any of the methods described herein. Alternatively, compounds of the disclosure that include a linker-PEG-Biotin moiety can be used as diagnostic probes according to methods known in the art. Preferred linkers are known in the art, with the linker –CH_2-NHC(O)-$(CH_2)_3$-C(O)-NH-CH_2- being particularly preferred. Preferred PEG moieties include at least two or three repeating –CH_2-CH_2-O- moieties. A preferred linker-PEG-Biotin moiety is



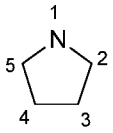
The term "piperidinyl" represents the following moiety:



Within the disclosure, when R^2 is a C_0alk-piperidinyl moiety, it can be attached to the compound of formula I through any one of the 2-, 3-, 4-, 5-, or 6-position atoms. In other aspects, when R^2 is a C_0alk-piperidinyl moiety, it can be attached to the compound of formula I

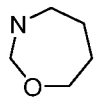
through any ring atom. Within the disclosure, when R^2 is a C_{1-6}alk-piperidinyl moiety, it can be attached to the compound of formula I through any one of the 1-, 2-, 3-, 4-, 5-, or 6-position atoms. When the piperidinyl moiety is a substituent, it can be attached through any one of the 1-, 2-, 3-, 4-, 5-, or 6-position atoms.

The term "pyrrolidinyl" represents the following moiety:

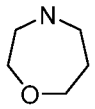


Within the disclosure, when R^2 is a C_0alk-pyrrolidinyl moiety, it can be attached to the compound of formula I through any one of the 2-, 3-, 4-, or 5-position atoms. In other aspects, when R^2 is a C_0alk-pyrrolidinyl moiety, it can be attached to the compound of formula I through any ring atom. Within the disclosure, when R^2 is a C_{1-6}alk-pyrrolidinyl moiety, it can be attached to the compound of formula I through any one of the 1-, 2-, 3-, 4-, or 5-position atoms. When the pyrrolidinyl moiety is a substituent, it can be attached through any one of the 1-, 2-, 3-, 4-, or 5-position atoms.

The term "oxazepanyl" refers to a 7-membered heterocycloalkyl moiety having one ring nitrogen atom and one ring oxygen atom. Examples include 1,3-oxazepanyl and 1,4-oxazepanyl moieties



1,3-oxazepanyl



1,4-oxazepanyl

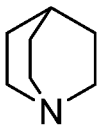
Within the disclosure, when R^2 is a C_0alk-oxazepanyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms. In other aspects, when R^2 is a C_0alk-oxazepanyl moiety, it can be attached to the compound of formula I through any ring nitrogen or carbon atom. Within the disclosure, when R^2 is a C_{1-6}alk-oxazepanyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms or nitrogen ring atom. When the oxazepanyl moiety is a substituent, it can be attached through any ring carbon atom or through the nitrogen atom.

The term "aziridinyl" represents a 3-membered heterocycloalkyl moiety having one ring nitrogen. Within the disclosure, when R^2 is a C_0alk-aziridinyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms. In other aspects, when R^2 is a C_{1-6}alk-aziridinyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms or the nitrogen ring atom. When the aziridinyl moiety is a substituent, it can be attached through any carbon atom or through the nitrogen atom.

The term "azetidinyl" represents a 4-membered heterocycloalkyl moiety having one ring nitrogen. Within the disclosure, when R^2 is an C_0alk-azetidinyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms. In other aspects, when R^2 is a C_{1-6}alk- azetidinyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms or the nitrogen ring atom. Within the disclosure, when R^2 is an C_{1-6}alk-azetidinyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms or the nitrogen ring atom. When the azetidinyl moiety is a substituent, it can be attached through any carbon atom or through the nitrogen atom.

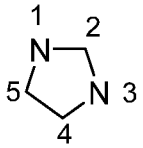
The term "azepanyl" represents a 7-membered heterocycloalkyl moiety having one ring nitrogen. Within the disclosure, when R^2 is an C_0alk-azepanyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms. In other aspects, when R^2 is a C_{1-6}alk-azepanyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms or the nitrogen ring atom. Within the disclosure, when R^2 is an C_{1-6}alk-azepanyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms or nitrogen ring atom. When the azepanyl moiety is a substitutent, it can be attached through any carbon atom or through the nitrogen atom.

The term "quinuclidinyl" represents the following moiety:



Within the disclosure, when R^2 is a quinuclidinyl moiety, or when the quinuclidinyl moiety is a substituent, it can be attached to the compound of formula I through any one of the ring carbon atoms.

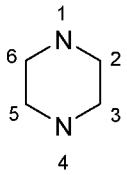
The term "imidazolidinyl" represents the following moiety:



Within the disclosure, when R^2 is an C_0alk-imidazolidinyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms. In other aspects, when R^2 is a C_{1-6}alk- imidazolidinyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms or the nitrogen ring atom. Within the disclosure, when R^2 is an C_{1-6}alk-imidazolidinyl moiety, it can be attached to the compound of formula I through any one of

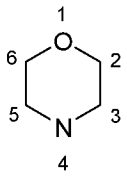
the ring carbon atoms or any nitrogen ring atom. When the imidazolidinyl moiety is a substituent, it can be attached through any one of the 1-, 2-, 3-, 4-, or 5-position atoms.

The term "piperazinyl" represents the following moiety:



Within the disclosure, when R^2 is a C_0alk-piperazinyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms. In other aspects, when R^2 is a C_{1-6}alk-piperazinyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms or the nitrogen ring atom. Within the disclosure, when R^2 is a C_{1-6}alk-piperazinyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms or nitrogen ring atoms. When the piperazinyl moiety is a substituent, it can be attached through any one of the 1-, 2-, 3-, 4-, 5-, or 6-position atoms.

The term "morpholinyl" represents the following moiety:



Within the disclosure, when R^2 is a C_0alk-morpholinyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms. In other aspects, when R^2 is a C_{1-6}alk-morpholinyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms or the nitrogen ring atom. Within the disclosure, when R^2 is a C_{1-6}alk-morpholinyl moiety, it can be attached to the compound of formula I through any one of the ring carbon atoms or nitrogen ring atom. When the morpholinyl moiety is a substituent, it can be attached through any one of the 2-, 3-, 4-, 5-, or 6-position atoms.

The term "tetrahydropyranyl" represents a 6-membered heterocycloalkyl moiety having one ring oxygen. The tetrahydropyranyl moiety can be attached through any carbon atom on the ring.

The term "tetrahydrofuranyl" represents a 5-membered heterocycloalkyl moiety having one ring oxygen. The tetrahydrofuranyl moiety can be attached through any carbon atom on the ring.

As used hereing, the term "compound(s) of formula I" includes those compounds of "formula I," as well as compounds of any of the formula I subgenera.

Within the scope of the disclosure, solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of product formation or isolation with pharmaceutically acceptable solvents such as water, ethanol, methanol, methyl tert-butyl ether (MTBE), diisopropyl ether (DIPE), ethyl acetate, isopropyl acetate, isopropyl alcohol, methyl isobutyl ketone (MIBK), methyl ethyl ketone (MEK), acetone, nitromethane, tetrahydrofuran (THF), dichloromethane (DCM), dioxane, heptanes, toluene, anisole, acetonitrile, and the like. In one aspect, solvates are formed using, but not limited to, Class 3 solvent(s). Categories of solvents are defined in, for example, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH),"Impurities: Guidelines for Residual Solvents, Q3C(R3), (November 2005). Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. In some embodiments, solvates of the described compounds, or pharmaceutically acceptable salts thereof, are conveniently prepared or formed during the processes described herein. In some embodiments, solvates of the compounds described herein are anhydrous. In some embodiments, the compounds described herein or pharmaceutically acceptable salts thereof, exist in unsolvated form. In some embodiments, the compounds described herein, or pharmaceutically acceptable salts thereof, exist in unsolvated form and are anhydrous.

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

"Pharmaceutically acceptable salt" refers to a salt of a compound of the disclosure that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid,

3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

"Pharmaceutically acceptable vehicle" refers to a diluent, adjuvant, excipient or carrier with which a compound of the disclosure is administered. A "pharmaceutically acceptable excipient" refers to a substance that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of a agent and that is compatible therewith. Examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

"Subject" includes humans. The terms "human," "patient," and "subject" are used interchangeably herein.

"Treating" or "treatment" of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (i.e., arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, "treating" or "treatment" refers to delaying the onset of the disease or disorder.

"Compounds of the present disclosure," and equivalent expressions, are meant to embrace compounds of the Formula (I) as described herein, which expression includes the pharmaceutically acceptable salts, and the solvates, e.g., hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

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

All isotopic variants of the compounds of the disclosure, radioactive or not, are intended to be encompassed within the scope of the disclosure.

It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers," for example, diastereomers, enantiomers, and atropisomers.

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

"Atropisomers" refer to stereoisomers that arise because of hindered rotation around a single bond.

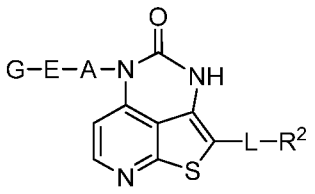
"Tautomers" refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci-and nitro-forms of phenyl nitromethane, that are likewise formed by treatment with acid or base.

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

The compounds of this disclosure may possess one or more asymmetric centers; such compounds can therefore be produced as individual (*R*)-or (*S*)-stereoisomers or as mixtures thereof.

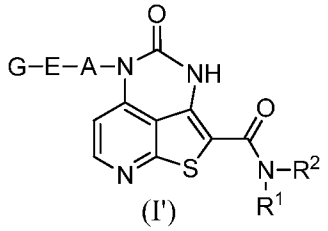
Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. Within the present disclosure, any open valency appearing on a carbon, oxygen, or nitrogen atom in any structure described herein indicates the presence of a hydrogen atom. Where a chiral center exists in a structure, but no specific stereochemistry is shown for that center, both enantiomers, separately or as a mixture, are encompassed by that structure. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

The present disclosure is directed to compounds of formula I:



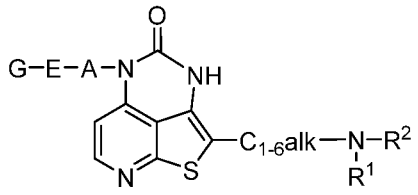
(I)

wherein L is -C(O)NR^1-, –C$_{1\text{-}6}$alk-NR^1-, a bond, or -NR^1-C(O)-. In preferred embodiments, L is -C(O)NR^1-, corresponding to compounds of formula I':



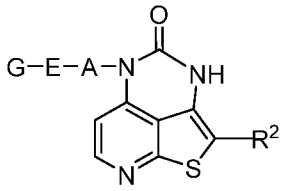
(I')

In other aspects, L is –C$_{1\text{-}6}$alk-NR^1-, corresponding to compounds of formula I":



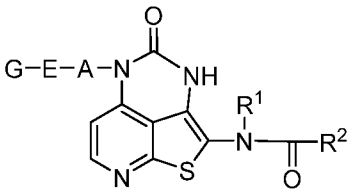
(I")

In other aspects, L is a bond, corresponding to compounds of formula I''':



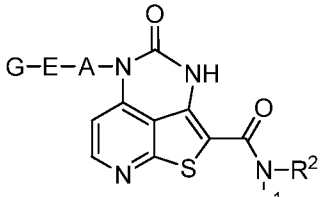
(I''')

In other aspects, L is -NR^1-C(O)-, corresponding to compounds of formula I'''':



(I'''')

A preferred embodiment of the disclosure is a compound of Formula (I) having the Formula (I'):



(I')

wherein

R^1 is H or C_{1-6}alkyl;

R^2 is –C_{0-6}alk-piperidinyl; –C_{0-6}alk-pyrrolidinyl; –C_{0-6}alk-oxazepanyl; –C_{0-6}alk-azetidinyl; –C_{0-6}alk-aziridinyl; –C_{0-6}alk-azepanyl; –C_{0-6}alk-quinuclidinyl; –C_{0-6}alk-imidazolidinyl; -C_{0-6}alk-piperazinyl; -C_{0-6}alkmorpholinyl; –C_{0-6}alk-tetrahydropyranyl; or –C_{0-6}alk-tetrahydrofuranyl wherein the R^2 is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of

-NR^8-C(O)-$C(R^3)$=$CR^4(R^5)$; -C(O)-$C(R^3)$=$CR^4(R^5)$; oxo; halogen; -CN; -OH; -NR^6R^7; -C_{1-6}alkyl; -C_{1-6}alk-OH; -OC_{1-6}alkyl; -C_{3-6}cycloalkyl; -C_{1-6}haloalkyl; -C_{1-6}alkaryl; -SO_2-C_{1-6}alkyl; -SO_2-C_{2-6}alkenyl; -C(O)H;

-C(O)-C_{1-6}alkyl; -C(O)-C_{3-6}cycloalkyl; -C(O)-C_{1-6}haloalkyl; -C(O)-C_{2-6}alkynyl; -C(O)-C_{6-10}aryl; -C(O)-heteroaryl; -C(O)-C_{1-6}alk-CN; -C(O)-C_{1-6}alk-OH; -C(O)-C_{1-6}alk-SO_2-C_{1-6}alkyl; -C(O)-O-C_{1-6}alkyl; -C(O)-C_{1-6}alk-NR^6R^7; -C(O)-C_{1-6}alk-O-C_{1-6}alkyl wherein the –C_{1-6}alk- is optionally substituted with –OH, -OC_{1-6}alkyl, or -NR^6R^7; and -C(O)-C_{0-6}alk-heterocycloalkyl wherein the -alk- is optionally substituted with oxo and the heterocycloalkyl is optionally substituted with -C_{1-6}alkyl; wherein

R^3 is H; -CN; halogen; -C_{1-6}haloalkyl; or -C_{1-6}alkyl;

R^4 and R^5 are each independently H; halogen; -C_{1-6}alkyl; -OC_{1-6}alkyl; -C_{0-6}alk-C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; -C_{0-6}alk-heterocycloalkyl optionally substituted with –C(O)C_{1-6}alkyl or -C_{1-6}alkyl; -C_{1-6}alk-OH; -C_{0-6}alk-NR^6R^7; -C_{1-6}alk-O-C_{1-6}alkyl; -C_{1-6}alk-NH-C_{0-6}alk-O-C_{1-6}alkyl; -C_{1-6}alk-$NHSO_2$-C_{1-6}alkyl; -C_{1-6}alk-SO_2-C_{1-6}alkyl; -NHC(O)-C_{1-6}alkyl; or –linker-PEG-Biotin; and

R^6 and R^7 are each independently H; -C_{1-6}alkyl; -C_{3-6}cycloalkyl; –C(O)H, or -CN; and

R^8 is H or C_{1-6}alkyl;

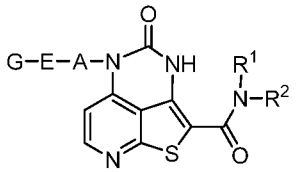
A is a bond, pyridyl; phenyl; napthalenyl; pyrimidinyl; pyrazinyl; pyridazinyl; benzo[d][1,3]dioxolyl optionally substituted with halogen; benzothiophenyl; or pyrazolyl; optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of -C_{1-6}alkyl; halogen; -SF_5; -OC_{1-6}alkyl; -C(O)-C_{1-6}alkyl; and -C_{1-6}haloalkyl;

E is –O-; a bond; -C(O)-NH-; -CH_2-; or -CH_2-O-; and

G is H; -C_{3-6}cycloalkyl; -phenyl; -thiophenyl; -C_{1-6}alkyl; -pyrimidinyl; -pyridyl; -pyridazinyl; -benzofuranyl; -C_{1-6}haloalkyl; -heterocycloalkyl that contains an oxygen heteroatom; -phenyl-CH_2-O-phenyl; -C_{1-6}alk-O-C_{1-6}alkyl; -NR^6R^7; -SO_2C_{1-6}alkyl; or –OH; wherein the phenyl; thiophenyl; pyrimidinyl; pyridyl; pyridazinyl; or benzofuranyl is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen; -C_{1-6}alkyl; -C_{1-6}haloalkyl; -OC_{1-6}haloalkyl; -C_{3-6}cycloalkyl; -OC_{1-6}alkyl; -CN; -OH; -C_{1-6}alk-O-C_{1-6}alkyl; -C(O)-NR^6R^7; and -C(O)-C_{1-6}alkyl.

Stereoisomers and isotopic variants of Formula I' are also within the scope of the disclosure. Pharmaceutically acceptable salts of Formula I' are also within the scope of the disclosure.

The present disclosure is preferably directed to compounds of Formula (I')



(I')

wherein

R^1 is H or C_{1-6}alkyl;

R^2 is selected from the group consisting of: C_{0-2}alk-piperidinyl; C_{0-2}alk-pyrrolidinyl; oxazepanyl; azetidinyl; azepanyl; quinuclidinyl; C_2alk-imidazolidinyl; C_2alk-piperazinyl; C_2alk-morpholinyl; tetrahydropyranyl; and C_{0-1}alk-tetrahydrofuranyl; wherein the R^2 is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of:

(C=O)-C(R^3)=CR^4(R^5); oxo; halogen; OH; NH_2; CN; C_{1-6}alkyl; C_{1-6}alk-OH; OC_{1-6}alkyl; C_{1-6}haloalkyl; C_{3-6}cycloalkyl; SO_2C_{1-6}alkyl; SO_2-C_{2-6}alkenyl; C_{1-2}alk-aryl; (C=O)H; (C=O)C_{1-6}alkyl; (C=O)C_{1-6}haloalkyl; (C=O)-C_{2-6}alkenyl; (C=O)-C_{2-6}alkynyl; (C=O)C_{3-6}cycloalkyl; (C=O)-phenyl; (C=O)-imidazolyl; (C=O)-C_{1-6}alkCN; (C=O)-C_{1-6}alk-OH; (C=O)-C_{1-6}alk-SO_2C_{1-6}alkyl; (C=O)-C_{1-6}alk-NR^6R^7; (C=O)-C_{1-6}alk-O-C_{1-6}alkyl wherein the -C_{1-6}alk- is optionally substituted with OH, OC_{1-6}alkyl, or NR^6R^7; (C=O)C_{0-1}alk-heterocycloalkyl wherein the -alk- is optionally substituted with oxo and the heterocycloalkyl is optionally substituted with C_{1-6}alkyl; and NH(C=O)-C(R^3)=CR^4(R^5);

wherein

R^3 is selected from the group consisting of: H, CN, halogen, C_{1-6}haloalkyl, and C_{1-6}alkyl;

R^4 and R^5 are each independently selected from the group consisting of: H; halogen; C_{1-6}alkyl; CH_2OH; C_{1-6}alk-OC_{1-6}alkyl; OC_{1-6}alkyl; C_{1-4}alk-NR^6R^7; C_{3-6}cycloalkyl substituted with NH_2 or CH_3; oxetanyl substituted with CH_3; 1-acetylpyrrolidin-2-yl; CH_2-pyrrolidinyl; CH_2-piperidinyl; $C(CH_3)_2$-piperidinyl; CH_2-morpholinyl; $C(CH_3)_2$-morpholinyl; CH_2-(4aR,7aS)-tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl; $C(CH_3)_2NH(CH_2CH_2OCH_3)$; $CH_2SO_2CH_3$; $CH_2NHSO_2CH_3$; NH(C=O)C_{1-6}alkyl; and linker-PEG-Biotin; and

R^6 and R^7 are each independently selected from the group consisting of: H, C_{1-6}alkyl, cyclopropyl, (C=O)H, and CN;

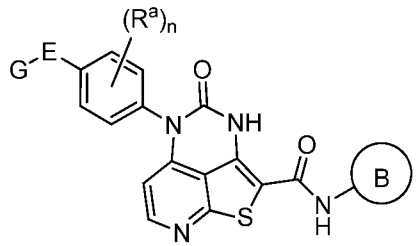
A is selected from the group consisting of: a bond, phenyl; naphthalenyl, pyridyl; pyrimidinyl; pyrazinyl; pyridazinyl; benzothiophenyl; and pyrazolyl; wherein the A is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of: C_{1-6}alkyl, halogen, OC_{1-6}alkyl, $(C=O)C_{1-6}$alkyl, and C_{1-6}haloalkyl;

E is selected from the group consisting of: -O-, a bond, (C=O)-NH, CH_2, and CH_2-O; and

G is selected from the group consisting of: H, C_{1-6}alkyl; C_{1-6}haloalkyl; C_{1-6}alk-OC_{1-6}alkyl; NR^6R^7; SO_2C_{1-6}alkyl; OH; C_{3-6}cycloalkyl; phenyl; thiophenyl; pyrimidinyl; pyridyl; pyridazinyl; benzofuranyl; ;heterocycloalkyl that contains an oxygen heteroatom; phenyl-CH_2-O-phenyl; wherein the phenyl, thiophenyl, pyrimidinyl, pyridyl, pyridazinyl, or benzofuranyl is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of: halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, OC_{1-6}haloalkyl, OC_{1-6}alkyl, OC_{1-6}alkyl-OC_{1-6}alkyl, C_{3-6}cycloalkyl, CN, OH, NH_2, $N(CH_3)_2$, C_{1-6}alk-OC_{1-6}alkyl, SO_2C_{1-6}alkyl, $(C=O)$-NR^6R^7, SF_5, and $(C=O)C_{1-6}$alkyl.

Stereoisomers and isotopic variants, pharmaceutically acceptable salts, N-oxides, and solvates of Formula I' are also within the scope of the disclosure.

An additional embodiment of the disclosure is directed to compounds of Formula (II'), as well as the stereoisomers, isotopic vairants, and pharmaceutically acceptable salt thereof:



(II')

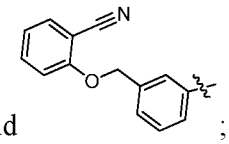
wherein

R^a is independently selected from the group consisting of: H, Cl, F, CH_3, and CF_3;

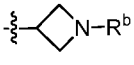
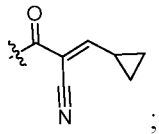
n is 0-2;

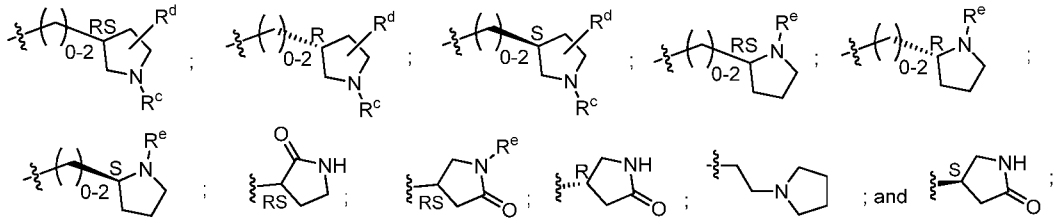
E is O;

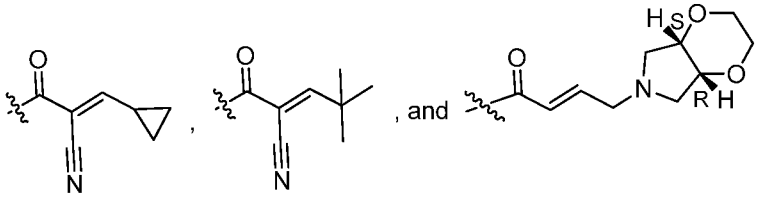
G is selected from the group consisting of: C_{3-6}cycloalkyl; oxetanyl; tetrahydrofuranyl; tetrahydropyranyl; benzofuran-7-yloxy; pyridyl; pyridyl substituted with CH_3; phenyl; phenyl substituted with one or two members independently selected from the group

consisting of: halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, OH, OC_{1-6}alkyl, OC_{1-6}haloalkyl, CH_2OCH_3, $(C=O)NH_2$, and C_{3-6}cycloalkyl; and  ;

Ring B is selected from the group consisting of:

(a)  ; where R^b is selected from the group consisting of: H; C_{1-6}alkyl, C_{3-6}cycloalkyl, $(C=O)CH=CH_2$, $(C=O)CH_2CH_2OCH_3$,$(C=O)CH_2CH_2SO_2CH_3$, and  ;

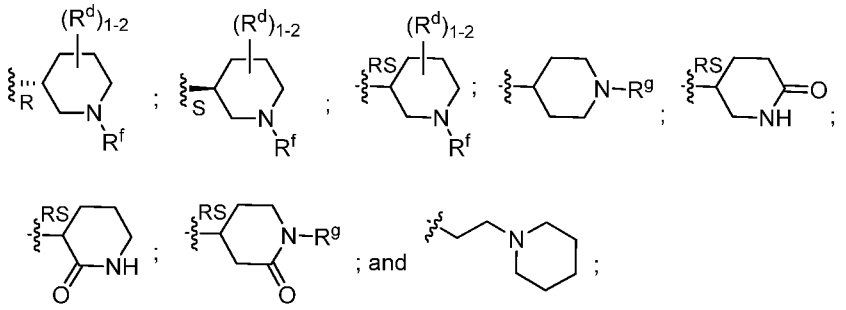
(b) 

where R^c is selected from the group consisting of: H, C_{1-6}alkyl, CN, $(C=O)C_{1-3}$alkyl, $(C=O)CH=CH_2$, C_{3-6}cycloalkyl, $(C=O)CH_2NH_2$, $(C=O)CH_2NH(CH_3)$, $(C=O)CH_2N(CH_3)_2$, $(C=O)CH_2CN$, CH_2-phenyl, $(C=O)CH_2Cl$, $(C=O)CH=CHCH_2NH_2$, $(C=O)CH_2CH_2OCH_3$, $(C=O)CH=CHCH_2NH(CH_3)$,$(C=O)CH=CHCH_2N(CH_3)_2$, $(C=O)CH=CHCH_2OH$, (C=O)-phenyl, $SO_2CH=CH_2$, $(C=O)CH_2CH_2SO_2CH_3$,  ;

R^d is selected from the group consisting of: H, F, OH, and OCH_3;

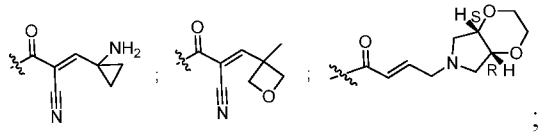
R^e is H or C_{1-6}alkyl;

(c)



where

R^d is selected from the group consisting of: H, F, OH, and OCH_3;

R^f is selected from the group consisting of: (C=O)-C(R^3)=CR^4(R^5); H; C_{1-6}alkyl; CN; (C=O)C_{1-3}alkyl; (C=O)C_{1-3}haloalkyl; (C=O)C_{2-6}alkenyl; (C=O)C_{2-6}alkynyl; (C=O)$(CH_2)_{1-2}OH$; (C=O)$(CH_2)_{1-2}OCH_3$; (C=O)H; (C=O)$(CH_2)_{0-1}CN$; (C=O)CH_2NH_2; (C=O)$(CH_2)_{1-2}NH(CH_3)$; (C=O)$(CH_2)_{1-2}N(CH_3)_2$; (C=O)$CH(CH_3)NH(CH_3)$; (C=O)$(CH_2)_{1-2}SO_2CH_3$; (C=O)$CH_2CH(CH_3)(OCH_3)$; (C=O)$CH(CH_3)CH_2(OH)$; (C=O)$CH(CH_3)CH_2(OCH_3)$; (C=O)$C(CH_3)_2CH_2(OCH_3)$; (C=O)$CH_2C(CH_3)_2(OCH_3)$; (C=O)$CH(NH_2)CH_2(OCH_3)$; (C=O)$CH(OCH_3)CH_2(OCH_3)$; (C=O)$CH(OH)CH_2(OCH_3)$;  ;C_{3-6}cycloalkyl; (C=O)$(CH_2)_{0-1}$azetidinyl; (C=O)oxetanyl; (C=O)tetrahydrofuranyl; (C=O)tetrahydropyranyl; (C=O)$(CH_2)_{0-1}$pyrrolidinyl, wherein said pyrrolidinyl is optionally substituted with CH_3; (C=O)$(CH_2)_{0-1}$piperidinyl; (C=O)$(CH_2)_{0-1}$morpholinyl; SO_2-C_{2-6}alkenyl; SO_2C_{1-6}alkyl; and linker-PEG-Biotin;

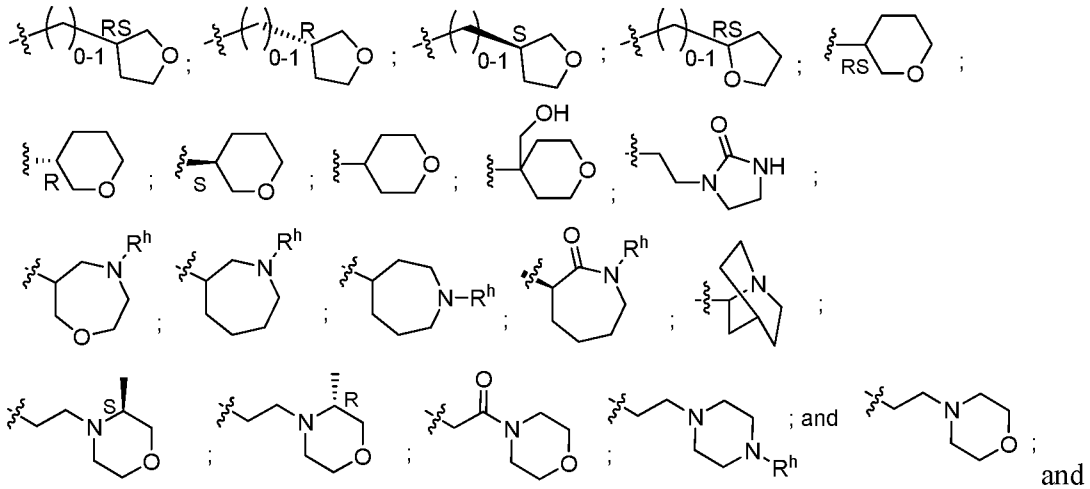
R^3 is selected from the group consisting of: H, CN, halogen, C_{1-6}haloalkyl, and C_{1-6}alkyl;

R^4 and R^5 are each independently selected from the group consisting of: H; halogen; C_{1-6}alkyl; CH_2OH; C_{1-6}alk-OC_{1-6}alkyl; OC_{1-6}alkyl; C_{1-4}alk-NR^6R^7; C_{3-6}cycloalkyl substituted with NH_2 or CH_3; oxetanyl substituted with CH_3; 1-acetylpyrrolidin-2-yl; CH_2-pyrrolidinyl; CH_2-piperidinyl; $C(CH_3)_2$-piperidinyl; CH_2-morpholinyl; $C(CH_3)_2$-morpholinyl; CH_2-(4aR,7aS)-tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl; $C(CH_3)_2NH(CH_2CH_2OCH_3)$; $CH_2SO_2CH_3$; $CH_2NHSO_2CH_3$; NH(C=O)C_{1-6}alkyl; and linker-PEG-Biotin; and

R^6 and R^7 are each independently selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl, and CN;

R^g is selected from the group consisting of: H, C_{1-6}alkyl, and CN; and

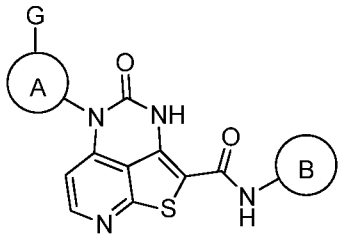
(d)



and

where R^h is selected from the group consisting of: H, CN, CH_3, and CH_2phenyl.

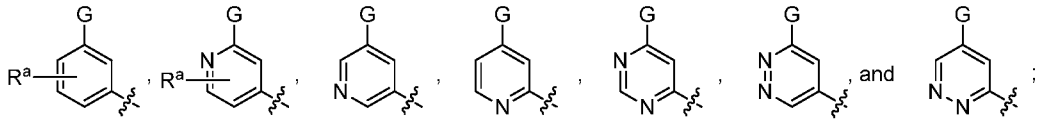
An additional embodiment of the disclosure is directed to compounds of Formula (III'), as well as the stereoisomers, isotopic vairants, and pharmaceutically acceptable salt thereof:



(III')

wherein

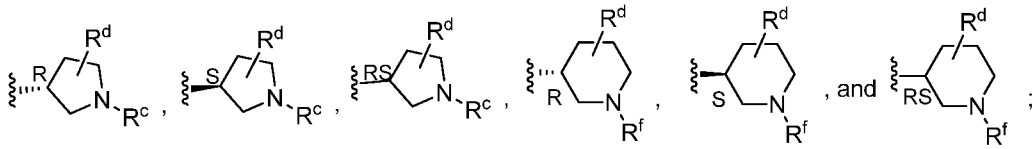
G-A is selected from the group consisting of:

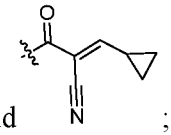


where G is phenyl; or phenyl substituted with one or two members independently selected from the group consisting of: halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, pyridyl, oxetan-3-yl, and tetrahydro-2H-pyran-4-yl;

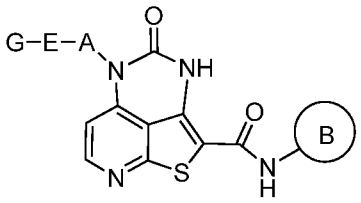
R^a is H or CH_3;

Ring B is selected from the group consisting of:



where R^c and R^f are independently selected from the group consisting of: H, C_{1-6}alkyl, $(C=O)CH=CH_2$, $(C=O)CH_2NH(CH_3)$, $(C=O)CH=CHCH_2N(CH_3)_2$, and  ; and R^d is selected from the group consisting of: H, OH and OCH_3.

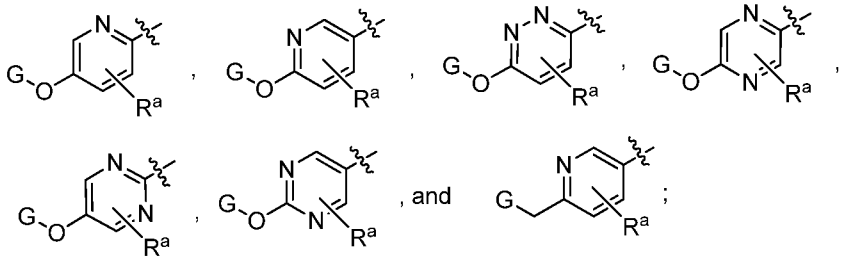
An additional embodiment of the disclosure is directed to compounds of Formula (IV'), as well as the stereoisomers, isotopic vairants, and pharmaceutically acceptable salt thereof:



(IV')

wherein

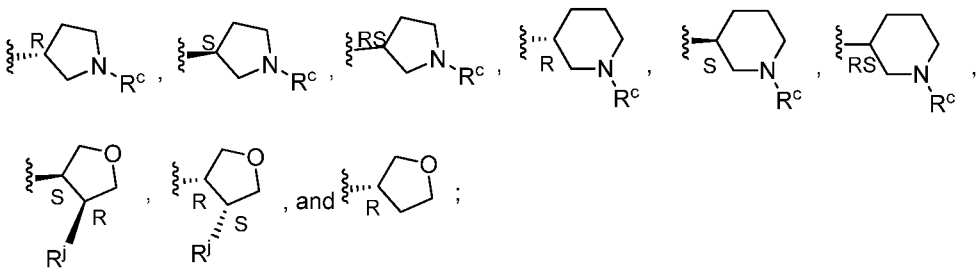
G-E-A is selected from the group consisting of:



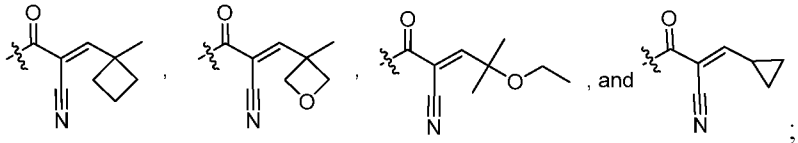
where G is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl, tetrahydro-2H-pyran-4-yl, pyridazin-3-yl, phenyl, and phenyl substituted with F;

R^a is H or CH_3;

Ring B is selected from the group consisting of:



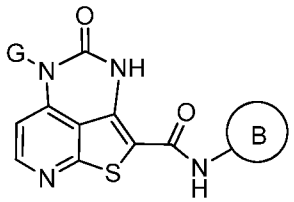
R^c is selected from the group consisting of: H, C_{1-6}alkyl, $(C=O)C_{1-3}$alkyl, $(C=O)CH=CH_2$, $(C=O)C_{1-6}$haloalkyl,



; and

R^j is selected from the group consisting of: H, NH_2, and $NH(C=O)CH=CH_2$.

An additional embodiment of the disclosure is directed to compounds of Formula (V'), as well as the stereoisomers, isotopic vairants, and pharmaceutically acceptable salt thereof:

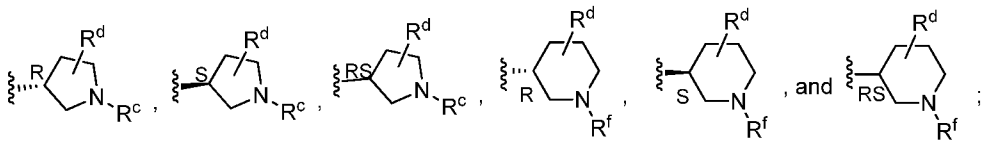


(V')

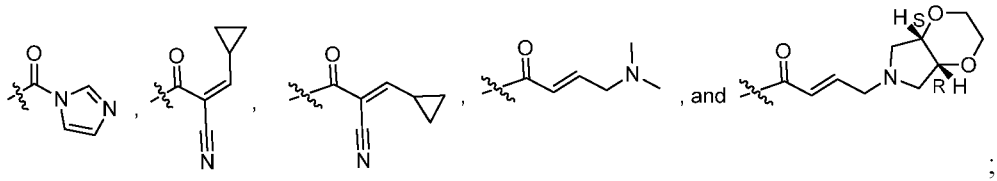
wherein

G is selected from the group consisting of: C_{1-6}alkyl; C_{1-6}haloalkyl; phenyl; phenyl substituted with one or two members independently selected from the group consisting of: halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, OC_{1-6}alkyl, OC_{1-6}haloalkyl, $(C=O)$-C_{1-6}alkyl, SF_5, OH, NH_2, $N(CH_3)_2$, $OCH_2CH_2OCH(CH_3)_2$, and SO_2C_{1-6}alkyl; benzo[d][1,3]dioxolyl optionally substituted with Cl; 2-methylpyridin-3-yl; 2-isopropylpyridin-4-yl; benzothiophenyl; napthalenyl; and 2,2-difluorobenzo[d][1,3]dioxol-5-yl;

Ring B is selected from the group consisting of:



where R^c and R^f are independently selected from the group consisting of: H, C_{1-6}alkyl, $(C=O)C_{1-3}$alkyl, $(C=O)CH=CH_2$, $(C=O)CH_2NHCH_3$,



;

and

R^d is H or OH.

According to the disclosure, R^1 is H or C_{1-6}alkyl. In some aspects, R^1 is C_{1-6}alkyl, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, or t-butyl. In preferred aspects, R^1 is H.

According to the disclosure R^2 is a C_{0-6} alk-heterocycloalkyl moiety that is unsubstituted or substituted with 1, 2, or 3 substituents. In those embodiments wherein R^2 is -C_0 alk-heterocycloalkyl, the heterocycloalkyl is directly attached to the compound of formula I through a bond. In those aspects wherein R^2 is a -C_{1-6} alk-heterocycloalkyl moiety, the heterocycloalkyl moiety is attached to the compound of formula I through an aliphatic linker having 1, 2, 3, 4, 5, or 6 carbon atoms, wherein the C_{1-6} alk includes, for example, –CH_2-, –$CH(CH_3)$-, -$CH(CH_3)$-CH_2-, and –$C(CH_3)_2$-. In some embodiments, the C_{1-6} alk linker is substituted by oxo, e.g, -CH_2-C(O)-. In preferred aspects, R^2 is -C_{0-1} alk-heterocycloalkyl, for example -C_0alk-heterocycloalkyl (i.e., -heterocycloalkyl) or -C_1 alk-heterocycloalkyl (i.e., -CH_2-heterocycloalkyl).

In preferred aspects, the R^2 heterocycloalkyl moiety is a 3-, 4-, 5-, or 6-membered heterocycloalkyl, preferably a 5- or 6-membered heterocycloalkyl, with a 6-membered heterocycloalkyl being most preferred. According to the disclosure, the heterocycloalkyl moiety can include one nitrogen atom, two nitrogen atoms, one nitrogen atom and one oxygen atom, or one oxygen atom. Preferred one nitrogen-containing heterocycloalkyl groups for R^2 are piperidinyl; pyrrolidinyl; azetidinyl; azepanyl; aziridinyl; and quinuclidinyl, with piperidinyl and pyrrolidinyl being preferred and piperidinyl being more preferred. Preferred two nitrogen-containing heterocycloalkyl groups for R^2 are imidazolidinyl and piperazinyl. Preferred one nitrogen, one oxygen containing heterocycloalkyl groups for R^2 are oxazepanyl, with 1,4-oxazepanyl being preferred; and morpholinyl. Preferred one oxygen-containing heterocycloalkyl groups for R^2 are tetrahydropyranyl and tetrahydrofuranyl.

In some aspects of the disclosure, R^2 is –C_{0-6}alk-piperidinyl, preferably –C_0 alk-piperidinyl or –C_1 alk-piperidinyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R^2 is –C_{0-6}alk-piperidinyl, preferably –C_0 alk-piperidinyl or –C_1 alk-piperidinyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any position on the piperidinyl ring. In preferred aspects, at least one substituent is attached through the piperidinyl nitrogen atom.

In some aspects of the disclosure, R^2 is –C_{0-6}alk-pyrrolidinyl, preferably –C_0 alk-pyrrolidinyl or –C_1 alk-pyrrolidinyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R^2 is –C_{0-6}alk-pyrrolidinyl, preferably

–C_0 alk-pyrrolidinyl or –C_1 alk-pyrrolidinyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any position on the pyrrolidinyl ring. In preferred aspects, at least one substituent is attached through the pyrrolidinyl nitrogen atom.

In some aspects of the disclosure, R^2 is –C_{0-6}alk- oxazepanyl, preferably –C_0 alk-oxazepanyl or –C_1 alk-oxazepanyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R^2 is –C_{0-6}alk- oxazepanyl, preferably –C_0 alk-oxazepanyl or –C_1 alk-oxazepanyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any position on the oxazepanyl ring. In some aspects, at least one substituent is attached through the oxazepanyl nitrogen atom.

In some aspects of the disclosure, R^2 is –C_{0-6}alk-azetidinyl, preferably –C_0 alk-azetidinyl or –C_1 alk-azetidinyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R^2 is –C_{0-6}alk-azetidinyl, preferably –C_0 alk-azetidinyl or –C_1 alk-azetidinyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any position on the azetidinyl ring. In some aspects, at least one substituent is attached through the azetidinyl nitrogen atom.

In some aspects of the disclosure, R^2 is –C_{0-6}alk-azepanyl, preferably –C_0 alk-azepanyl or –C_1 alk-azepanyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R^2 is –C_{0-6}alk-azepanyl, preferably –C_0 alk-azepanyl or –C_1 alk-azepanyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any position on the azepanyl ring. In some aspects, at least one substituent is attached through the azepanyl nitrogen atom.

In some aspects of the disclosure, R^2 is –C_{0-6}alk-aziridinyl, preferably –C_0 alk-aziridinyl or –C_1 alk-aziridinyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R^2 is –C_{0-6}alk-aziridinyl, preferably –C_0 alk-aziridinyl or –C_1 alk-aziridinyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any position on the aziridinyl ring. In some aspects, at least one substituent is attached through the azepanyl nitrogen atom.

In some aspects of the disclosure, R^2 is –C_{0-6}alk-quinuclidinyl, preferably –C_0 alk-quinuclidinyl or –C_1 alk-quinuclidinyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R^2 is –C_{0-6}alk-quinuclidinyl, preferably –C_0 alk-quinuclidinyl or –C_1 alk-quinuclidinyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any position on the quinuclidinyl ring.

In some aspects of the disclosure, R^2 is $-C_{0-6}$alk-imidazolidinyl, preferably $-C_0$ alk-imidazolidinyl or $-C_1$ alk-imidazolidinyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R^2 is $-C_{0-6}$alk-imidazolidinyl, preferably $-C_0$ alk-imidazolidinyl or $-C_1$ alk-imidazolidinyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any position on the imidazolidinyl ring. In some aspects, at least one substituent is attached through one of the imidazolidinyl nitrogen atoms.

In some aspects of the disclosure, R^2 is $-C_{0-6}$alk-piperazinyl, preferably $-C_0$ alk-piperazinyl or $-C_1$ alk-piperazinyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R^2 is $-C_{0-6}$alk-piperazinyl, preferably $-C_0$ alk-piperazinyl or $-C_1$ alk-piperazinyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any position on the piperazinyl ring. In some aspects, at least one substituent is attached through one of the piperazinyl nitrogen atoms.

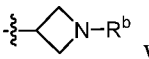
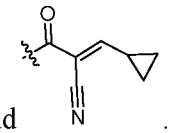
In some aspects of the disclosure, R^2 is $-C_{0-6}$alk-morpholinyl, preferably $-C_0$ alk-morpholinyl or $-C_1$ alk-morpholinyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R^2 is $-C_{0-6}$alk-morpholinyl, preferably $-C_0$ alk-morpholinyl or $-C_1$ alk-morpholinyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any position on the morpholinyl ring. In some aspects, at least one substituent is attached the morpholinyl nitrogen atom.

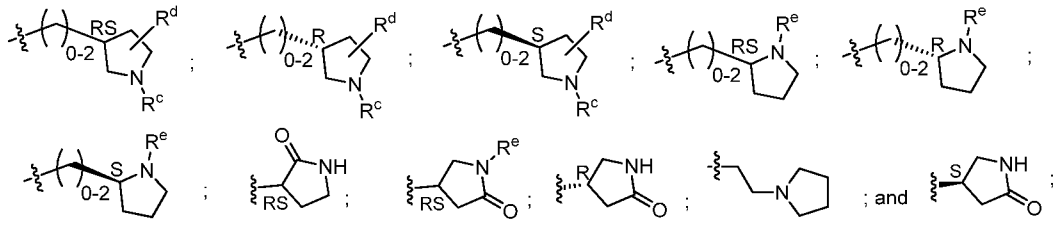
In some aspects of the disclosure, R^2 is $-C_{0-6}$alk-tetrahydropyranyl, preferably $-C_0$ alk-tetrahydropyranyl or $-C_1$ alk-tetrahydropyranyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R^2 is $-C_{0-6}$alk-tetrahydropyranyl, preferably $-C_0$ alk-tetrahydropyranyl or $-C_1$ alk-tetrahydropyranyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any carbon atom on the tetrahydropyranyl ring.

In some aspects of the disclosure, R^2 is $-C_{0-6}$alk-tetrahydrofuranyl, preferably $-C_0$ alk-tetrahydrofuranyl or $-C_1$ alk-tetrahydrofuranyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R^2 is $-C_{0-6}$alk-tetrahydrofuranyl, preferably $-C_0$ alk-tetrahydrofuranyl or $-C_1$ alk-tetrahydrofuranyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any carbon atom on the tetrahydrofuranyl ring.

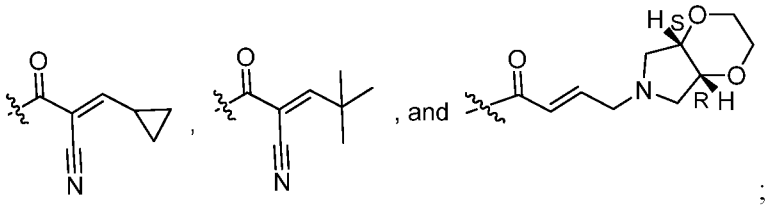
In preferred aspects of the disclosure, R^2 is piperidinyl, CH_2CH_2-piperidinyl, pyrrolidinyl, CH_2-pyrrolidinyl, or CH_2CH_2-pyrrolidinyl. In other preferred aspects, R^2 is

azetidinyl; azepanyl; quinuclidinyl; CH_2CH_2-imidazolidinyl; or CH_2CH_2-piperazinyl. In some aspects, R^2 is oxazepanyl or CH_2CH_2-morpholinyl, $CH_2(C=O)$-morpholinyl. In other aspects, R^2 is tetrahydropyranyl or tetrahydrofuranyl, or CH_2-tetrahydrofuranyl.

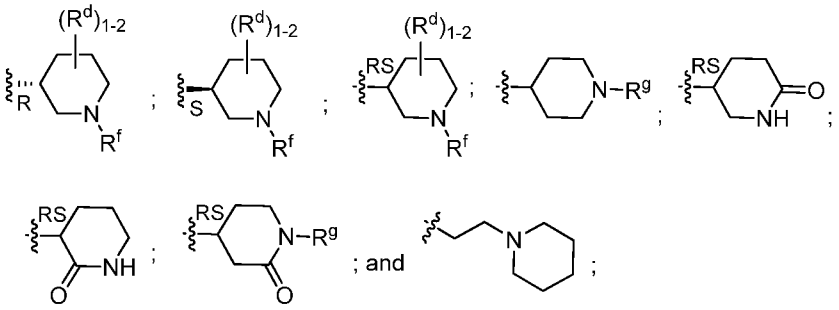
In some aspects, the R^2 moiety can be defined as "Ring B." In some aspects, particularly those wherein the compound is of Formula (II'), Ring B is  wherein R^b is selected from the group consisting of: H; C_{1-6}alkyl, C_{3-6}cycloalkyl, $(C=O)CH=CH_2$,  $(C=O)CH_2CH_2OCH_3$,$(C=O)CH_2CH_2SO_2CH_3$, and . In other aspects, Ring B is selected from the group consisting of:



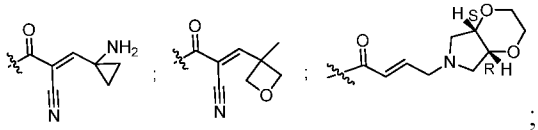
wherein R^c is selected from the group consisting of: H, C_{1-6}alkyl, CN, $(C=O)C_{1-3}$alkyl, $(C=O)CH=CH_2$, C_{3-6}cycloalkyl, $(C=O)CH_2NH_2$, $(C=O)CH_2NH(CH_3)$, $(C=O)CH_2N(CH_3)_2$, $(C=O)CH_2CN$, CH_2-phenyl, $(C=O)CH_2Cl$, $(C=O)CH=CHCH_2NH_2$, $(C=O)CH_2CH_2OCH_3$, $(C=O)CH=CHCH_2NH(CH_3)$,$(C=O)CH=CHCH_2N(CH_3)_2$, $(C=O)CH=CHCH_2OH$, $(C=O)$-phenyl, $SO_2CH=CH_2$, $(C=O)CH_2CH_2SO_2CH_3$,



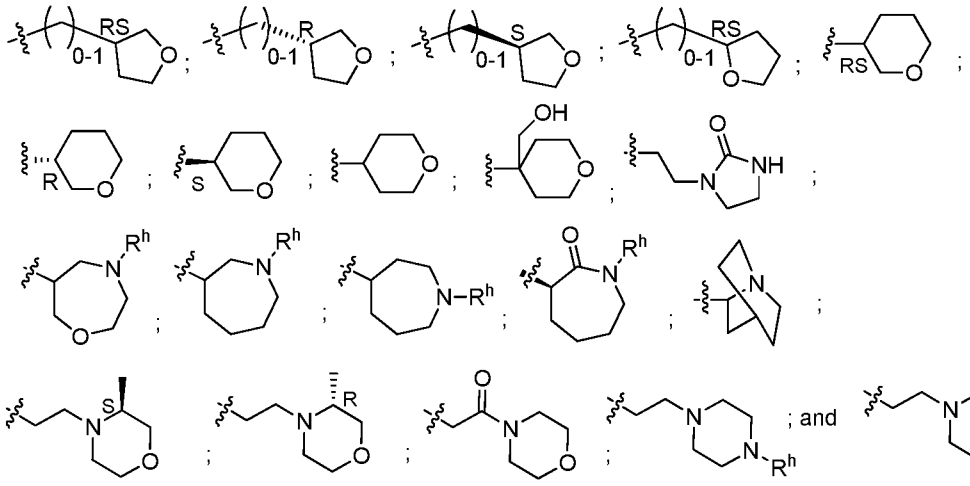
R^d is selected from the group consisting of: H, F, OH, and OCH_3; and R^e is H or C_{1-6}alkyl. In other aspects, Ring B is selected from the group consisting of



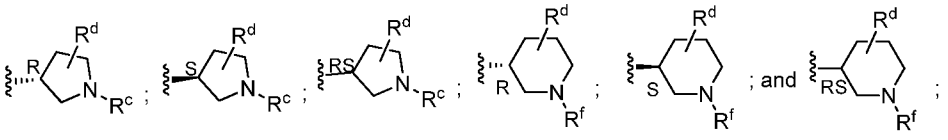
wherein R^d is selected from the group consisting of: H, F, OH, and OCH_3;
R^f is selected from the group consisting of: $(C=O)$-$C(R^3)=CR^4(R^5)$; H; C_{1-6}alkyl; CN; $(C=O)C_{1-3}$alkyl; $(C=O)C_{1-3}$haloalkyl; $(C=O)C_{2-6}$alkenyl; $(C=O)C_{2-6}$alkynyl; $(C=O)(CH_2)_{1-2}OH$; $(C=O)(CH_2)_{1-2}OCH_3$; $(C=O)H$; $(C=O)(CH_2)_{0-1}CN$; $(C=O)CH_2NH_2$; $(C=O)(CH_2)_{1-2}NH(CH_3)$; $(C=O)(CH_2)_{1-2}N(CH_3)_2$; $(C=O)CH(CH_3)NH(CH_3)$; $(C=O)(CH_2)_{1-2}SO_2CH_3$; $(C=O)CH_2CH(CH_3)(OCH_3)$; $(C=O)CH(CH_3)CH_2(OH)$; $(C=O)CH(CH_3)CH_2(OCH_3)$; $(C=O)C(CH_3)_2CH_2(OCH_3)$; $(C=O)CH_2C(CH_3)_2(OCH_3)$; $(C=O)CH(NH_2)CH_2(OCH_3)$; $(C=O)CH(OCH_3)CH_2(OCH_3)$; $(C=O)CH(OH)CH_2(OCH_3)$;



;C_{3-6}cycloalkyl; $(C=O)(CH_2)_{0-1}$azetidinyl; (C=O)oxetanyl; (C=O)tetrahydrofuranyl; (C=O)tetrahydropyranyl; $(C=O)(CH_2)_{0-1}$pyrrolidinyl, wherein said pyrrolidinyl is optionally substituted with CH_3; $(C=O)(CH_2)_{0-1}$piperidinyl; $(C=O)(CH_2)_{0-1}$morpholinyl; SO_2-C_{2-6}alkenyl; SO_2C_{1-6}alkyl; and linker-PEG-Biotin; wherein R^3 is selected from the group consisting of: H, CN, halogen, C_{1-6}haloalkyl, and C_{1-6}alkyl;
R^4 and R^5 are each independently selected from the group consisting of: H; halogen; C_{1-6}alkyl; CH_2OH; C_{1-6}alk-OC_{1-6}alkyl; OC_{1-6}alkyl; C_{1-4}alk-NR^6R^7; C_{3-6}cycloalkyl substituted with NH_2 or CH_3; oxetanyl substituted with CH_3; 1-acetylpyrrolidin-2-yl; CH_2-pyrrolidinyl; CH_2-piperidinyl; $C(CH_3)_2$-piperidinyl; CH_2-morpholinyl; $C(CH_3)_2$-morpholinyl; CH_2-(4aR,7aS)-tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl; $C(CH_3)_2NH(CH_2CH_2OCH_3)$; $CH_2SO_2CH_3$; $CH_2NHSO_2CH_3$; $NH(C=O)C_{1-6}$alkyl; and linker-PEG-Biotin; and
R^6 and R^7 are each independently selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl, and CN; and R^g is selected from the group consisting of: H, C_{1-6}alkyl, and CN. In other aspects, Ring B is selected from the group consisting of

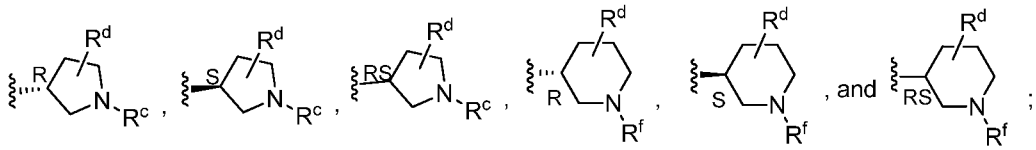


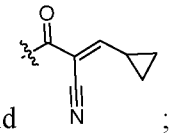
wherein R^h is selected from the group consisting of: H, CN, CH_3, and CH_2phenyl. In preferred aspects, Ring B is selected from the group consisting of

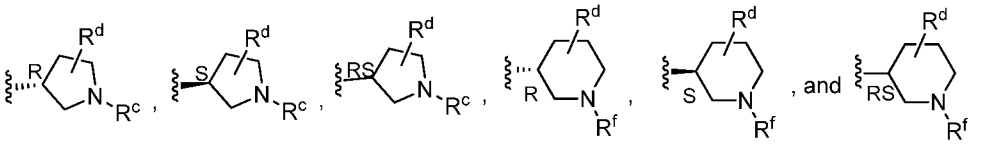


and R^c and R^f are $(C=O)CH=CH_2$; and R^d is H.

In some aspects, the R^2 moiety can be defined as "Ring B." In some aspects, particularly those wherein the compound is of Formula (III'), Ring B is selected from the group consisting of

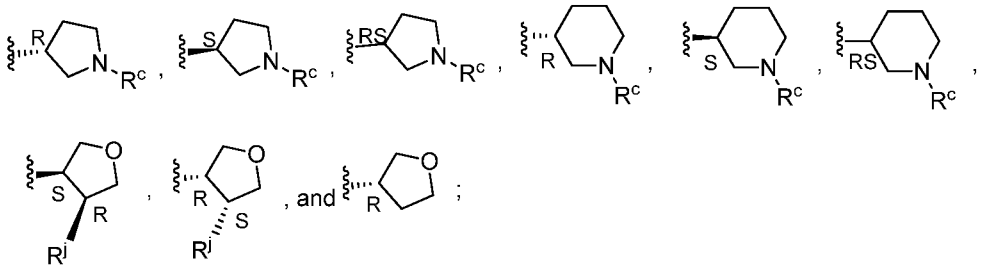


wherein R^c and R^f are independently selected from the group consisting of: H, $C_{1\text{-}6}$alkyl, $(C=O)CH=CH_2$, $(C=O)CH_2NH(CH_3)$, $(C=O)CH=CHCH_2N(CH_3)_2$, and  ; and R^d is selected from the group consisting of: H, OH and OCH_3. In preferred aspects, Ring B is selected from the group consisting of

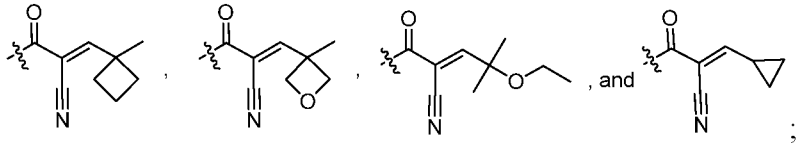


and R^c and R^f are $(C=O)CH=CH_2$; and R^d is H.

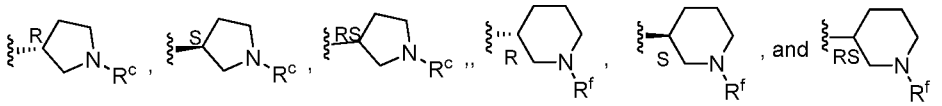
In some aspects, the R^2 moiety can be defined as "Ring B." In some aspects, particularly those wherein the compound is of Formula (IV'), Ring B is selected from the group consisting of



wherein R^c is selected from the group consisting of: H, C_{1-6}alkyl, $(C=O)C_{1-3}$alkyl, $(C=O)CH=CH_2$, $(C=O)C_{1-6}$haloalkyl,

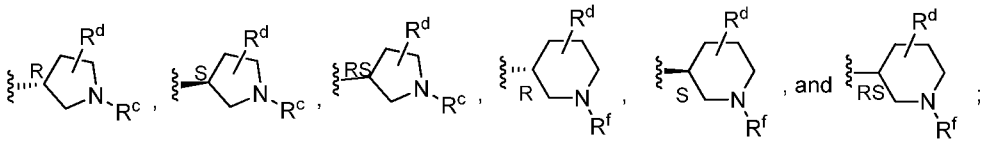


; and R^j is selected from the group consisting of: H, NH_2, and $NH(C=O)CH=CH_2$. In preferred aspects, Ring B is selected from the group consisting of

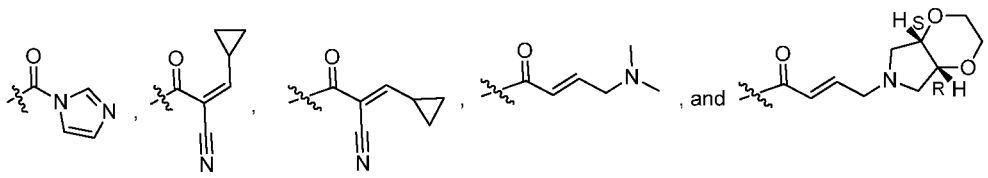


and R^c and R^f are $(C=O)CH=CH_2$.

In some aspects, the R^2 moiety can be defined as "Ring B." In some aspects, particularly those wherein the compound is of Formula (V'), Ring B is selected from the group consisting of



where R^c and R^f are independently selected from the group consisting of: H, C_{1-6}alkyl, $(C=O)C_{1-3}$alkyl, $(C=O)CH=CH_2$, $(C=O)CH_2NHCH_3$,



; and R^d is H or OH.

According to the disclosure, in some embodiments, the R^2 heterocycloalkyl is unsubstituted. In preferred aspects, the R^2 heterocycloalkyl is substituted with 1, 2, or 3 substituents. In preferred aspects, the R^2 heterocycloalkyl is substituted with 1 or 2 substituents, more preferably 1 substituent. In those aspects wherein the R^2 heterocycloalkyl is substituted, the substituents may be independently selected from the group consisting of

-NR^8-C(O)-$C(R^3)$=$CR^4(R^5)$; -C(O)-$C(R^3)$=$CR^4(R^5)$; oxo; halogen; -CN; -OH; -NR^6R^7; -C_{1-6}alkyl; -C_{1-6}alk-OH; -OC_{1-6}alkyl; -C_{3-6}cycloalkyl; -C_{1-6}haloalkyl; -C_{1-6}alkaryl; -SO_2C_{1-6}alkyl; -SO_2C_{2-6}alkenyl; -C(O)H; -C(O)-C_{1-6}alkyl; -C(O)-C_{3-6}cycloalkyl; -C(O)-C_{1-6}haloalkyl; -C(O)-C_{2-6}alkynyl; -C(O)-C_{6-10}aryl; -C(O)-heteroaryl; -C(O)-C_{1-6}alk-CN; -C(O)-C_{1-6}alk-OH; -C(O)-C_{1-6}alk-SO_2-C_{1-6}alkyl; -C(O)-O-C_{1-6}alkyl; -C(O)-C_{1-6}alk-NR^6R^7; -C(O)-C_{1-6}alk-O-C_{1-6}alkyl wherein the –alk- is optionally substituted with –OH, -OC_{1-6}alkyl, or -NR^6R^7; and -C(O)-C_{0-6}alk-heterocycloalkyl wherein the -alk- is optionally substituted with oxo and the heterocycloalkyl is optionally substituted with -C_{1-6}alkyl; and wherein R^3, R^4, R^5, R^6, R^7, and R^8 are as defined herein. In those aspects wherein the R^2 heterocycloalkyl is substituted, the substituents are preferably independently selected from the group consisting of -NR^8-C(O)-$C(R^3)$=$CR^4(R^5)$; -C(O)-$C(R^3)$=$CR^4(R^5)$; oxo; halogen; -CN; -OH; -NR^6R^7; -C_{1-6}alk-OH; -OC_{1-6}alkyl; -C_{3-6}cycloalkyl; -C_{1-6}haloalkyl; -C_{1-6}alkaryl; -SO_2C_{1-6}alkyl; -SO_2C_{2-6}alkenyl; -C(O)H; -C(O)-C_{1-6}alkyl; -C(O)-C_{3-6}cycloalkyl; -C(O)-C_{1-6}haloalkyl; -C(O)-C_{2-6}alkynyl; -C(O)-C_{6-10}aryl; -C(O)-heteroaryl; -C(O)-C_{1-6}alk-CN; -C(O)-C_{1-6}alk-OH; -C(O)-C_{1-6}alk-SO_2-C_{1-6}alkyl; -C(O)-C_{1-6}alk-NR^6R^7; -C(O)-C_{1-6}alk-O-C_{1-6}alkyl wherein the –alk- is optionally substituted with –OH, -OC_{1-6}alkyl, or -NR^6R^7; and -C(O)-C_{0-6}alk-heterocycloalkyl wherein the -alk- is optionally substituted with oxo and the heterocycloalkyl is optionally substituted with -C_{1-6}alkyl; and wherein R^3, R^4, R^5, R^6, R^7, and R^8 are as defined herein.

In some aspects, the R^2 heterocycloalkyl is substituted with an oxo moiety, for example one oxo moiety. In those aspects wherein the R^2 heterocycloalkyl is substituted with an oxo moiety, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with a halogen, for example a fluorine or chlorine. In some aspects, the R^2 heterocycloalkyl is substituted with one or two halogens, preferably one halogen. In those aspects wherein the R^2 heterocycloalkyl is substituted with a halogen, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with –CN. In some aspects, the R^2 heterocycloalkyl is substituted with one or two -CN, preferably one -CN. In those aspects wherein the R^2 heterocycloalkyl is substituted with -CN, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with –OH. In some aspects, the R^2 heterocycloalkyl is substituted with one or two -OH, preferably one -OH. In those aspects wherein the R^2 heterocycloalkyl is substituted with -OH, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with $–NR^6R^7$ wherein R^6 and R^7 are each independently H; -C_{1-6}alkyl, -C_{3-6}cycloalkyl; –C(O)H; or –CN. In preferred aspects, R^6 and R^7 are each independently H or -C_{1-6}alkyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with $–NR^6R^7$, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with -C_{1-6} alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. In some aspects, the R^2 heterocycloalkyl is substituted with one or two -C_{1-6}alkyl, preferably one -C_{1-6}alkyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with -C_{1-6}alkyl, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with -C_{1-6}alk-OH, for example, -C_{1-5}alk-OH, -C_{1-4}alk-OH, -C_{1-3}alk-OH, -C_{1-2}alk-OH, or -C_1alk-OH, wherein the –OH moiety can be attached to any carbon of the –C_{1-6}alk group, preferably the ω carbon. In some aspects, the R^2 heterocycloalkyl is substituted with one or two -C_{1-6}alk-OH, preferably one -C_{1-6}alk-OH. In those aspects wherein the R^2 heterocycloalkyl is substituted with -C_{1-6}alk-OH, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with -OC_{1-6}alkyl, for example, -O-C_{1-5}alkyl, -O-C_{1-4}alkyl, -O-C_{1-3}alkyl, -O-C_{1-2}alkyl, or -O-C_1alkyl. In some aspects, the R^2 heterocycloalkyl is substituted with one or two -OC_{1-6}alkyl, preferably one -OC_{1-6}alkyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with -OC_{1-6}alkyl, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some aspects, the R^2 heterocycloalkyl is substituted with one or two -C_{3-6}cycloalkyl, preferably one -C_{3-6}cycloalkyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with -C_{3-6}cycloalkyl, the heterocycloalkyl ring

may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with $-C_{1-6}$haloalkyl, for example, $-C_{1-5}$haloalkyl, $-C_{1-4}$haloalkyl, $-C_{1-3}$haloalkyl, $-C_{1-2}$haloalkyl, or $-C_1$haloalkyl, including $-CF_3$, $-CH_2CH_2F$, and the like. In some aspects, the R^2 heterocycloalkyl is substituted with one or two $-C_{1-6}$haloalkyl, preferably one $-C_{1-6}$haloalkyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with $-C_{1-6}$haloalkyl, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with $-C_{1-6}$alkaryl, for example, benzyl (i.e., $-CH_2$-phenyl). In some aspects, the R^2 heterocycloalkyl is substituted with one or two $-C_{1-6}$alkaryl, preferably one $-C_{1-6}$alkaryl. In those aspects wherein the R^2 heterocycloalkyl is substituted with $-C_{1-6}$alkaryl, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with $-SO_2C_{1-6}$alkyl, for example, $-SO_2$-C_{1-5}alkyl, $-SO_2$-C_{1-4}alkyl, $-SO_2$-C_{1-3}alkyl, $-SO_2$-C_{1-2}alkyl, or $-SO_2$-C_1alkyl. In some aspects, the R^2 heterocycloalkyl is substituted with one or two $-SO_2C_{1-6}$alkyl, preferably one $-SO_2C_{1-6}$alkyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with $-SO_2C_{1-6}$alkyl, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with $-SO_2C_{2-6}$alkenyl, for example, $-SO_2C_{2-5}$alkenyl, $-SO_2C_{2-4}$alkenyl, $-SO_2C_{2-3}$alkenyl, or $-SO_2C_2$alkenyl. In some aspects, the R^2 heterocycloalkyl is substituted with one or two $-SO_2C_{2-6}$alkenyl, preferably one $-SO_2C_{2-6}$alkenyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with $-SO_2C_{2-6}$alkenyl, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with –C(O)H. In some aspects, the R^2 heterocycloalkyl is substituted with one or two –C(O)H, preferably one –C(O)H. In those aspects wherein the R^2 heterocycloalkyl is substituted with –C(O)H, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with $-C(O)-C_{1-6}$alkyl, for example, $-C(O)-C_{1-5}$alkyl, $-C(O)-C_{1-4}$alkyl, $-C(O)-C_{1-3}$alkyl, $-C(O)-C_{1-2}$alkyl, or $-C(O)-C_1$alkyl. In some aspects, the R^2 heterocycloalkyl is substituted with one or two $-C(O)-C_{1-6}$alkyl, preferably one

–C(O)-C_{1-6}alkyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with –C(O)-C_{1-6}alkyl, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with –C(O)-C_{3-6}cycloalkyl, for example, –C(O)-cyclopropyl, –C(O)-cyclobutyl, –C(O)-cyclopentyl, or –C(O)-cyclohexyl. In some aspects, the R^2 heterocycloalkyl is substituted with one or two –C(O)-C_{3-6}cycloalkyl, preferably one –C(O)-C_{3-6}cycloalkyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with –C(O)-C_{3-6}cycloalkyl, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with –C(O)-C_{1-6}haloalkyl, for example, –C(O)–C_{1-5}haloalkyl, –C(O)–C_{1-4}haloalkyl, –C(O)–C_{1-3}haloalkyl, –C(O)–C_{1-2}haloalkyl, or –C(O)–C_1haloalkyl, including –C(O)–CF_3, –C(O)–CH_2CH_2F, and the like. In some aspects, the R^2 heterocycloalkyl is substituted with one or two –C(O)-C_{1-6}haloalkyl, preferably one –C(O)-C_{1-6}haloalkyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with –C(O)-C_{1-6}haloalkyl, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with –C(O)-C_{2-6}alkynyl, for example, –C(O)-C_{2-5}alkynyl, –C(O)-C_{2-4}alkynyl, –C(O)-C_{2-3}alkynyl, or –C(O)-C_2alkynyl. In some aspects, the R^2 heterocycloalkyl is substituted with one or two –C(O)-C_{2-6}alkynyl, preferably one -C(O)-C_{2-6}alkynyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with –C(O)-C_{2-6}alkynyl, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with –C(O)-C_{6-10}aryl, for example, –C(O)-phenyl or –C(O)-napthalenyl. In some aspects, the R^2 heterocycloalkyl is substituted with one or two –C(O)-C_{6-10}aryl, preferably one –C(O)-C_{6-10}aryl. In those aspects wherein the R^2 heterocycloalkyl is substituted with –C(O)-C_{6-10}aryl, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with –C(O)-heteroaryl, for example, –C(O)-pyrrolyl, –C(O)-thienyl, –C(O)-oxazolyl, –C(O)-pyrazolyl, –C(O)-pyridyl, –C(O)-pyrimidinyl, and the like. In some aspects, the R^2 heterocycloalkyl is substituted with one or two –C(O)-heteroaryl, preferably one –C(O)-heteroaryl. In those aspects wherein the R^2 heterocycloalkyl is substituted with –C(O)-heteroaryl, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with -C(O)-C_{1-6}alk-CN, for example, -C(O)-C_{1-5}alk-CN, -C(O)-C_{1-4}alk-CN, -C(O)-C_{1-3}alk-CN, -C(O)-C_{1-2}alk-CN, or -C(O)-C_1alk-CN. In some aspects, the R^2 heterocycloalkyl is substituted with one or two –C(O)-C_{1-6}alk-CN, preferably one –(C(O)-C_{1-6}alk-CN. In those aspects wherein the R^2 heterocycloalkyl is substituted with -C(O)-C_{1-6}alk-CN, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with -C(O)-C_{1-6}alk-OH, for example, -C(O)-C_{1-5}alk-OH, -C(O)-C_{1-4}alk-OH, -C(O)-C_{1-3}alk-OH, -C(O)-C_{1-2}alk-OH, or -C(O)-C_1alk-OH. In some aspects, the R^2 heterocycloalkyl is substituted with one or two –C(O)-C_{1-6}alk-OH, preferably one –C(O)-C_{1-6}alk-OH. The –OH moiety can be attached to any carbon of the –C_{1-6}alk group, preferably the ω carbon. In those aspects wherein the R^2 heterocycloalkyl is substituted with -C(O)-C_{1-6}alk-OH, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with -C(O)-C_{1-6}alk-SO_2-C_{1-6}alkyl, for example, -C(O)-C_{1-5}alk-SO_2-C_{1-5}alkyl, -C(O)-C_{1-4}alk-SO_2-C_{1-4}alkyl, -C(O)-C_{1-3}alk-SO_2-C_{1-3}alkyl, -C(O)-C_{1-2}alk-SO_2-C_{1-2}alkyl, or -C(O)-C_1alk-SO_2-C_1alkyl. In some aspects, the R^2 heterocycloalkyl is substituted with one or two -C(O)-C_{1-6}alk-SO_2-C_{1-6}alkyl, preferably one -C(O)-C_{1-6}alk-SO_2-C_{1-6}alkyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with -C(O)-C_{1-6}alk-SO_2-C_{1-6}alkyl, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with –C(O)-O-C_{1-6}alkyl, for example, –C(O)-O-C_{1-5}alkyl, –C(O)-O-C_{1-4}alkyl, -–C(O)-O-C_{1-3}alkyl, –C(O)-O-C_{1-2}alkyl, or –C(O)-O-C_1alkyl. In some aspects, the R^2 heterocycloalkyl is substituted with one or two –C(O)-O-C_{1-6}alkyl, preferably one -–C(O)-O-C_{1-6}alkyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with –C(O)-O-C_{1-6}alkyl, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with -C(O)-C_{1-6}alk-NR^6R^7, for example, -C(O)-C_{1-5}alk-NR^6R^7, -C(O)-C_{1-4}alk-NR^6R^7, -C(O)-C_{1-3}alk-NR^6R^7, -C(O)-C_{1-2}alk-NR^6R^7, or -C(O)-C_1alk-NR^6R^7, wherein R^6 and R^7 are each independently H; -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl; -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; –C(O)H, or –CN. In preferred aspects, R^6 and R^7 are each independently H, -C_{1-6}alkyl; or -C_{3-6}cycloalkyl, with H and -C_{1-6}alkyl being preferred, and H and –C_{1-2}alkyl being more preferred. In some

aspects, the R^2 heterocycloalkyl is substituted with one or two -C(O)-C_{1-6}alk-NR^6R^7, preferably one -C(O)-C_{1-6}alk-NR^6R^7. In those aspects wherein the R^2 heterocycloalkyl is substituted with -C(O)-C_{1-6}alk-NR^6R^7, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with -C(O)-C_{1-6}alk-O-C_{1-6}alkyl, for example, -C(O)-C_{1-5}alk-O-C_{1-5}alkyl, -C(O)-C_{1-4}alk-O-C_{1-4}alkyl, -C(O)-C_{1-3}alk-O-C_{1-3}alkyl, -C(O)-C_{1-2}alk-O-C_{1-2}alkyl, or -C(O)-C_1alk-O-C_1alkyl. In certain aspects wherein the R^2 heterocycloalkyl is substituted with -C(O)-C_{1-6}alk-O-C_{1-6}alkyl, the –C_{1-6}alk- is optionally substituted with –OH; -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl; or -NR^6R^7 (wherein R^6 and R^7 are each independently H; -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl; -C_{3-6}cycloalkyl; –C(O)H; or –CN). In preferred aspects, R^6 and R^7 are each independently H, -C_{1-6}alkyl; or -C_{3-6}cycloalkyl, with H and -C_{1-6}alkyl being preferred, and H and –C_{1-2}alkyl being more preferred. In some aspects, the –C_{1-6}alk- of the -C(O)-C_{1-6}alk-O-C_{1-6}alkyl moiety is substituted with –OH. In other aspects, the –C_{1-6}alk- is substituted with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. In some aspects, the R^2 heterocycloalkyl is substituted with one or two -C(O)-C_{1-6}alk-O-C_{1-6}alkyl, preferably one -C(O)-C_{1-6}alk-O-C_{1-6}alkyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with -C(O)-C_{1-6}alk-O-C_{1-6}alkyl, the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with -C(O)-C_{0-6}alk-heterocycloalkyl, for example, -C(O)-C_{0-5}alk-heterocycloalkyl, -C(O)-C_{0-4}alk-heterocycloalkyl, -C(O)-C_{0-3}alk-heterocycloalkyl, -C(O)-C_{0-2}alk-heterocycloalkyl, -C(O)-C_{0-1}alk-heterocycloalkyl, -C(O)-C_1alk-heterocycloalkyl, or -C(O)-C_0alk-heterocycloalkyl. Preferred substituent heterocycloalkyl groups include tetrahydrofuranyl, piperidinyl, pyrrolidinyl, and the like. In certain aspects wherein the R^2 heterocycloalkyl is substituted with -C(O)-C_{1-6}alk-heterocycloalkyl, the -C_{1-6}alk- is optionally substituted with oxo. In certain aspects wherein the R^2 heterocycloalkyl is substituted with -C(O)-C_{0-6}alk-heterocycloalkyl, the substituent heterocycloalkyl moiety can be unsubstituted or substituted with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with -C(O)-C_{0-6}alk-heterocycloalkyl, the R^2 heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In some aspects, the R^2 heterocycloalkyl is substituted with -NR^8-C(O)-C(R^3)=CR^4(R^5), wherein R^3, R^4, and R^5 are as described herein and R^8 is H or C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. In preferred aspects, R^8 is H. In these aspects, R^3 is H; -CN; halogen; -C_{1-6}haloalkyl; or -C_{1-6}alkyl. In some embodiments, R^3 is H. In other aspects, R^3 is –CN. In still other aspects, R^3 is halogen, for example F or Cl. In yet other aspects, R^3 is -C_{1-6}haloalkyl, for example, -C_{1-5}haloalkyl, –C_{1-4}haloalkyl, –C_{1-3}haloalkyl, -C_{1-2}haloalkyl, or –C_1haloalkyl, including –CF_3, –CH_2CH_2F, and the like. In further aspects, R^3 is -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with -NR^8-C(O)-C(R^3)=CR^4(R^5), the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In preferred aspects of the disclosure, the R^2 heterocycloalkyl is substituted with -C(O)-C(R^3)=CR^4(R^5). In these embodiments, R^3 is H; -CN; halogen; -C_{1-6}haloalkyl; or -C_{1-6}alkyl. In some embodiments, R^3 is H. In other aspects, R^3 is –CN. In still other aspects, R^3 is halogen, for example F or Cl. In yet other aspects, R^3 is -C_{1-6}haloalkyl, for example, -C_{1-5}haloalkyl, –C_{1-4}haloalkyl, –C_{1-3}haloalkyl, -C_{1-2}haloalkyl, or –C_1haloalkyl, including –CF_3, –CH_2CH_2F, and the like. In further aspects, R^3 is -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. In those aspects wherein the R^2 heterocycloalkyl is substituted with -C(O)-C(R^3)=CR^4(R^5), the heterocycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

In preferred aspects, the R^2 heterocycloalkyl is substituted with - C(O)-C(R^3)=CR^4(R^5); -C(O)-C_{1-6}alk-NR^6R^7; -C(O)-C_{1-6}alkyl; or –NR^6R^7. In more preferred aspects, the R^2 heterocycloalkyl is substituted with -C(O)-C(R^3)=CR^4(R^5). In other preferred aspects, the R^2 heterocycloalkyl is substituted with -C(O)-C_{1-6}alk-NR^6R^7; -C(O)-C_{1-6}alkyl; or –NR^6R^7; wherein R^6 and R^7 are each independently H or C_{1-6}alkyl.

In other aspects, the R^2 is substituted with halogen; CN; OH; C_{1-6}alkyl; C_{1-6}haloalkyl; C_{1-6}alk-OH; OC_{1-6}alkyl; C_{3-6}cycloalkyl; NH_2; or C_{1-2}alkaryl. In yet other aspects, the R^2 is substituted with C=O)H; (C=O)C_{1-6}alkyl; (C=O)C_{3-6}cycloalkyl; (C=O)C_{1-6}haloalkyl; (C=O)-alkynyl; (C=O)-phenyl; (C=O)-C_{1-6}alkCN; (C=O)-C_{1-6}alk-OH; (C=O)-C_{1-6}alk-NR^6R^7; or (C=O)-C_{1-6}alk-O-C_{1-6}alkyl wherein the -C_{1-6}alk- is optionally substituted with OH, OC_{1-6}alkyl, or NR^6R^7. In some aspects, the R^2 is substituted with (C=O)C_{0-1}alk-heterocycloalkyl wherein the heterocycloalkyl is optionally substituted with C_{1-6}alkyl. In other aspects, the R^2 is substituted with SO_2alkyl, (C=O)-C_{1-6}alk-SO_2C_{1-6}alkyl, or SO_2-C_{2-6}alkenyl.

In those embodiments employing R^4 and R^5, that is, those aspects wherein the R^2 heterocycloalkyl is substituted with -C(O)-C(R^3)=CR^4(R^5) or -NR^8-C(O)-C(R^3)=CR^4(R^5), R^4 and R^5 are each independently H; halogen; -C_{1-6}alkyl; -OC_{1-6}alkyl; -C_{0-6}alk-C_{3-6}cycloalkyl optionally substituted with -C_{1-6}alkyl; -C_{1-6}alk-OH; -C_{0-6}alk-NR^6R^7; -C_{1-6}alk-O-C_{1-6}alkyl; -C_{1-6}alk-NH-C_{0-6}alk-O-C_{1-6}alkyl; -C_{0-6}alk-heterocycloalkyl optionally substituted with –C(O)C_{1-6}alkyl or -C_{1-6}alkyl; -C_{1-6}alk-NHSO_2-C_{1-6}alkyl; -C_{1-6}alk-SO_2-C_{1-6}alkyl; -NHC(O)-C_{1-6}alkyl; or linker-PEG-Biotin.

Within the scope of the disclosure, the double bond present in either -C(O)-C(R^3)=CR^4(R^5) or -NR^8-C(O)-C(R^3)=CR^4(R^5) may be of the *Z* or *E* configuration.

In some aspects, neither R^4 nor R^5 is H.

In most preferred aspects, each of R^4 and R^5 is H.

In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is halogen, for example F or Cl.

In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl.

In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl.

In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is -C_{0-6}alk-C_{3-6}cycloalkyl, for example, -C_{0-5}alk-C_{3-5}cycloalkyl, -C_{0-4}alk-C_{3-4}cycloalkyl, -C_{0-3}alk-C_3cycloalkyl, -C_{0-2}alk-C_{3-6}cycloalkyl, -C_{0-1}alk-C_{3-6}cycloalkyl, –C_0alk-C_{3-6}cycloalkyl or –C_1alk-C_{3-6}cycloalkyl. In these aspects, the cycloalkyl moiety can be unsubstituted or can be substituted with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The substitution can be a spiro-substitution or a non-spiro-substitution.

In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is -C_{0-6}alk-heterocycloalkyl, for example, -C_{1-6}alk-heterocycloalkyl, -C_{0-4}alk-heterocycloalkyl, -C_{0-3}alk-heterocycloalkyl, -C_{0-2}alk-heterocycloalkyl, -C_{0-1}alk-heterocycloalkyl, -C_1alk-heterocycloalkyl, or -C_0alk-heterocycloalkyl. In these aspects, the substituent heterocycloalkyl is preferably an oxygen-containing heterocycloalkyl, for example, tetrahydropyranyl, tetrahydrofuranyl, or oxetanyl. In other aspects, the heterocycloalkyl is a nitrogen-containing heterocycloalkyl, for example, pyrrolidinyl, aziridinyl, or piperidinyl. In certain of these aspects, the substituent heterocycloalkyl can be substituted with –C(O)C_{1-6}alkyl, for example, –C(O)C_{1-5}alkyl, –C(O)C_{1-4}alkyl, -C(O)C_{1-3}alkyl, -C(O)C_{1-2}alkyl, or -C(O)C_1alkyl.

In other aspects, the substituent heterocycloalkyl can be substituted with –C_{1-6}alkyl, for example, –C_{1-5}alkyl, –C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl.

In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is -C_{1-6}alk-OH, for example, -C_{1-5}alk-OH, -C_{1-4}alk-OH, -C_{1-3}alk-OH, -C_{1-2}alk-OH, or -C_1alk-OH. The –OH moiety can be attached to any carbon of the –C_{1-6}alk group, preferably the ω carbon.

In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is -C_{0-6}alk-NR^6R^7, for example, -C_{0-5}alk-NR^6R^7, -C_{0-4}alk-NR^6R^7, -C_{0-3}alk-NR^6R^7, -C_{0-2}alk-NR^6R^7, -C_{0-1}alk-NR^6R^7, C_1alk-NR^6R^7, or -C_0alk-NR^6R^7, wherein R^6 and R^7 are each independently H; -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl; -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; -C(O)H; or –CN. In preferred aspects, R^6 and R^7 are each independently H; -C_{1-6}alkyl; or -C_{3-6}cycloalkyl, more preferably, R^6 and R^7 are each independently H or -C_{1-6}alkyl.

In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is -C_{1-6}alk-O-C_{1-6}alkyl, for example, -C_{1-5}alk-O-C_{1-5}alkyl, -C_{1-4}alk-O-C_{1-4}alkyl, -C_{1-3}alk-O-C_{1-3}alkyl, -C_{1-2}alk-O-C_{1-2}alkyl, or -C_1alk-O-C_1alkyl.

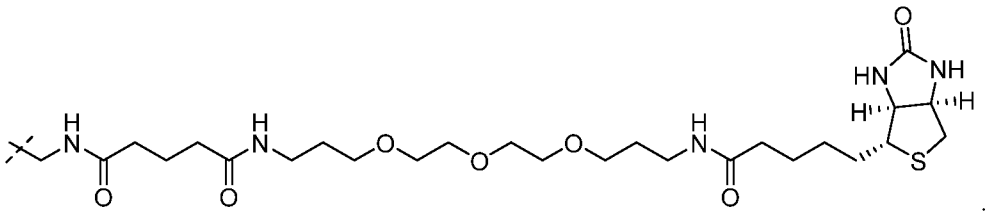
In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is -C_{1-6}alk-NH-C_{0-6}alk-O-C_{1-6}alkyl, for example, -C_{1-5}alk-NH-C_{0-6}alk-O-C_{1-5}alkyl, -C_{1-4}alk-NH-C_{0-6}alk-O-C_{1-4}alkyl, -C_{1-3}alk-NH-C_{0-6}alk-O-C_{1-3}alkyl, -C_{1-2}alk-NH-C_{0-6}alk-O-C_{1-2}alkyl, -C_1alk-NH-C_{0-6}alk-O-C_1alkyl, -C_{1-5}alk-NH-C_{0-6}alk-O-C_{1-5}alkyl, -C_{1-4}alk-NH-C_{1-5}alk-O-C_{1-4}alkyl, -C_{1-3}alk-NH-C_{1-4}alk-O-C_{1-3}alkyl, -C_{1-2}alk-NH-C_{1-3}alk-O-C_{1-2}alkyl, -C_1alk-NH-C_{1-2}alk-O-C_1alky, or -C_{1-6}alk-NH-C_0alk-O-C_{1-6}alkyl.

In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is -C_{1-6}alk-$NHSO_2$-C_{1-6}alkyl, for example, -C_{1-5}alk-$NHSO_2$-C_{1-5}alkyl -C_{1-4}alk-$NHSO_2$-C_{1-4}alkyl, -C_{1-3}alk-$NHSO_2$-C_{1-3}alkyl, -C_{1-2}alk-$NHSO_2$-C_{1-2}alkyl, or -C_1alk-$NHSO_2$-C_1alkyl.

In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is -C_{1-6}alk-SO_2-C_{1-6}alkyl, for example, -C_{1-5}alk-SO_2-C_{1-5}alkyl, -C_{1-4}alk-SO_2-C_{1-4}alkyl, -C_{1-3}alk-SO_2-C_{1-3}alkyl, -C_{1-2}alk-SO_2-C_{1-2}alkyl, or -C_1alk-SO_2-C_1alkyl.

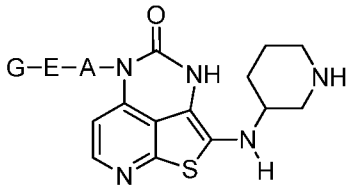
In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is -NHC(O)-C_{1-6}alkyl, for example, -NHC(O)-C_{1-5}alkyl, -NHC(O)-C_{1-4}alkyl, -NHC(O)-C_{1-3}alkyl, -NHC(O)-C_{1-2}alkyl, or -NHC(O)-C_1alkyl.

In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is linker-PEG-Biotin, preferably



In preferred aspects, one of R^4 and R^5 is H and the other of R^4 and R^5 is C_{1-6}alkyl (e.g., methyl, t-butyl); cycloalkyl (e.g., cyclopropyl); -C_{1-6}alk-NR^6R^7 (e.g., -CH_2-NH_2, -CH_2-$NHCH_3$, -CH_2-$N(CH_3)_2$, -$C(CH_3)_2$-NH_2, -$C(CH_3)_2$-$NHCH_3$, -$C(CH_3)_2$-$N(CH_3)_2$; -C1-6alk-O-C1-6alkyl (e.g., -$C(CH_3)_2$-OCH_3, -$C(CH_3)_2$-OCH_2CH_3); -C_{0-6}alk-heterocycloalkyl substituted with -C_{1-6}alkyl (e.g., -$C(CH_3)$-oxetanyl).

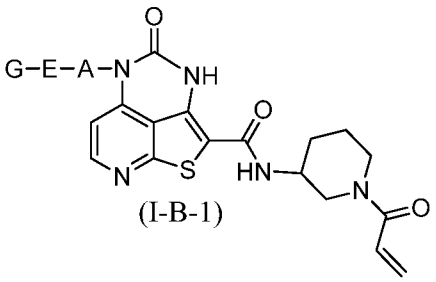
A preferred subgenus of formula I is:



(I-A)

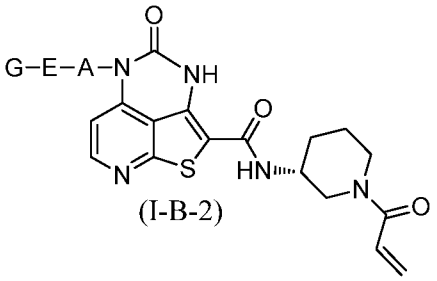
wherein the piperidinyl ring is substituted at the ring nitrogen with any 1 or 2 of the R^2 substituents defined herein.

Additional embodiments of the disclosure include compounds of Formula (I) having the subgenera of Formula (I-B-1) and Formula (I-B-2):



(I-B-1)

and



(I-B-2)

Within the scope of the disclosure, A can be a bond. Also within the scope of the disclosure, A can be pyridyl; phenyl; napthalenyl; pyrimidinyl; pyrazinyl; pyridazinyl; benzo[d][1,3]dioxolyl optionally substituted with halogen, preferably F; benzothiophenyl; or pyrazolyl. Also within the scope of the disclosure, A can be pyridyl; phenyl; napthalenyl; pyrimidinyl; pyrazinyl; pyridazinyl; benzothiophenyl; or pyrazolyl. Also according to the disclosure, any of the A moieties (excluding a bond) can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl; halogen, for example F or Cl; -SF_5; -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl; -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-5}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl; and -C_{1-6}haloalkyl, for example, –C_{1-5}haloalkyl, –C_{1-4}haloalkyl, –C_{1-3}haloalkyl, –C_{1-2}haloalkyl, or –C_1haloalkyl, including –CF_3, –CH_2CH_2F, and the like.

In some aspects, A is pyridyl. The pyridyl can be attached to any of the compounds of formula I (or its subgenera) through any ring carbon atom, but preferably it attached through the 2- or 3-position carbon. Preferably, the pyridyl is substituted with one or two substituents, preferably one substituent. The pyridyl substituent can be attached to any ring carbon atom of the pyridyl ring. In those embodiments wherein the pyridyl is attached to the compound of formula I through the 3-position carbon, the substituent is preferably attached to the pyridyl at the 2- or 4-position. The pyridyl can be substituted at any available ring carbon atom with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The pyridyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The pyridyl can be substituted at any available ring carbon atom with -SF_5. The pyridyl can be substituted at any available ring carbon atom with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The pyridyl can be substituted at any available ring carbon atom with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-5}alkyl, -C(O)-C_{1-4}alkyl,

-C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl. The pyridyl can be substituted at any available ring carbon atom with -C_{1-6}haloalkyl, for example, –C_{1-5}haloalkyl, –C_{1-4}haloalkyl, –C_{1-3}haloalkyl, –C_{1-2}haloalkyl, or –C_1haloalkyl, including –CF_3, CH_2CH_2F, and the like. Preferred substituents wherein A is pyridyl include -C_{1-6}alkyl, with -C_1alkyl being most preferred, and with one –C_1alkyl substituent being more preferred. Other preferred substituents include halogen, in particular F and Cl.

In some aspects, A is phenyl. Preferably, the phenyl is substituted with one or two substituents, preferably one substituent. The phenyl can be substituted at any available ring carbon atom with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The phenyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The phenyl can be substituted at any available ring carbon atom with -SF_5. The phenyl can be substituted at any available ring carbon atom with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The phenyl can be substituted at any available ring carbon atom with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-5}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl. The phenyl can be substituted at any available ring carbon atom with -C_{1-6}haloalkyl, for example, –C_{1-5}haloalkyl, –C_{1-4}haloalkyl, –C_{1-3}haloalkyl, –C_{1-2}haloalkyl, or –C_1haloalkyl, including –CF_3, CH_2CH_2F, and the like. The phenyl's substituent can be attached to any ring carbon atom of the phenyl ring, preferably ortho to the phenyl moiety's point of attachment to the compound of formula I. Preferred substituents wherein A is phenyl include -C_{1-6}alkyl, with -C_1alkyl being most preferred. Other preferred substituents include halogen, in particular F and Cl.

In some aspects, A is napthalenyl. Preferably, the napthalenyl is substituted with one or two substituents, preferably one substituent. The napthalenyl can be substituted at any available ring carbon atom with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The napthalenyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The napthalenyl can be substituted at any available ring carbon atom with -SF_5. The napthalenyl can be substituted at any available ring carbon atom with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The napthalenyl can be substituted at any available ring carbon atom with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-5}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl. The napthalenyl can be substituted at any available ring carbon atom with -C_{1-6}haloalkyl, for example, –C_{1-5}haloalkyl, –C_{1-4}haloalkyl, –C_{1-3}haloalkyl, –C_{1-2}haloalkyl, or –C_1haloalkyl, including –CF_3, CH_2CH_2F, and the like. The napthalenyl can be attached through any of its

carbon atoms to the compound of formula I. The napthalenyl substituent can be attached to any ring carbon atom of the napthalenyl ring, preferably ortho to the napthalenyl moiety's point of attachment to the compound of formula I. Preferred substituents wherein A is napthalenyl include -C_{1-6}alkyl, with -C_1alkyl being most preferred. Other preferred substituents include halogen, in particular F and Cl.

In some aspects, A is pyrimidinyl. The pyrimidinyl can be attached to any of the compounds of formula I (or its subgenera) through any ring carbon atom through any ring carbon atom. Preferably, the pyrimidinyl is substituted with one or two substituents, preferably one substituent. The pyrimidinyl can be substituted at any available ring carbon atom with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The pyrimidinyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The pyrimidinyl can be substituted at any available ring carbon atom with -SF_5. The pyrimidinyl can be substituted at any available ring carbon atom with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The pyrimidinyl can be substituted at any available ring carbon atom with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-5}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl. The pyrimidinyl can be substituted at any available ring carbon atom with -C_{1-6}haloalkyl, for example, –C_{1-5}haloalkyl, –C_{1-4}haloalkyl, –C_{1-3}haloalkyl, –C_{1-2}haloalkyl, or –C_1haloalkyl, including –CF_3, CH_2CH_2F, and the like. Preferred substituents wherein A is pyrimidinyl include -C_{1-6}alkyl, with -C_1alkyl being most preferred. Other preferred substituents include halogen, in particular F and Cl.

In some aspects, A is pyrazinyl. The pyrazinyl can be attached to any of the compounds of formula I (or its subgenera) through any ring carbon atom. Preferably, the pyrazinyl is substituted with one or two substituents, preferably one substituent. The pyrazinyl can be substituted at any available ring carbon atom with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The pyrazinyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The pyrazinyl can be substituted at any available ring carbon atom with -SF_5. The pyrazinyl can be substituted at any available ring carbon atom with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The pyrazinyl can be substituted at any available ring carbon atom with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-5}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl. The pyrazinyl can be substituted at any available ring carbon atom with -C_{1-6}haloalkyl, for example, –C_{1-5}haloalkyl, –C_{1-4}haloalkyl, –C_{1-3}haloalkyl, –C_{1-2}haloalkyl, or –C_1haloalkyl, including –CF_3, CH_2CH_2F, and the like. Preferred substituents wherein A is pyrazinyl include -C_{1-6}alkyl, with -

C_1alkyl being most preferred. Other preferred substituents include halogen, in particular F and Cl.

In some aspects, A is pyridazinyl. The pyridazinyl can be attached to any of the compounds of formula I (or its subgenera) through any ring carbon atom. Preferably, the pyridazinyl is substituted with one or two substituents, preferably one substituent. The pyridazinyl can be substituted at any available ring carbon atom with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The pyridazinyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The pyridazinyl can be substituted at any available ring carbon atom with -SF_5. The pyridazinyl can be substituted at any available ring carbon atom with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The pyridazinyl can be substituted at any available ring carbon atom with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-5}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl. The pyridazinyl can be substituted at any available ring carbon atom with -C_{1-6}haloalkyl, for example, –C_{1-5}haloalkyl, –C_{1-4}haloalkyl, –C_{1-3}haloalkyl, –C_{1-2}haloalkyl, or –C_1haloalkyl, including –CF_3, CH_2CH_2F, and the like. Preferred substituents wherein A is pyridazinyl include -C_{1-6}alkyl, with -C_1alkyl being most preferred. Other preferred substituents include halogen, in particular F and Cl.

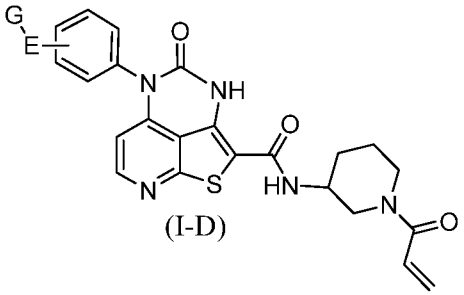
In some aspects, A is benzo[d][1,3]dioxolyl. The benzo[d][1,3]dioxolyl can be attached to any of the compounds of formula I (or its subgenera) through any ring carbon atom. The benzo[d][1,3]dioxolyl can be unsubstituted or can be substituted with one or two halogen, preferably F. Preferably, the benzo[d][1,3]dioxolyl is substituted with one or two other substituents. The benzo[d][1,3]dioxolyl can be substituted at any available ring carbon atom with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The benzo[d][1,3]dioxolyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The benzo[d][1,3]dioxolyl can be substituted at any available ring carbon atom with -SF_5. The benzo[d][1,3]dioxolyl can be substituted at any available ring carbon atom with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The benzo[d][1,3]dioxolyl can be substituted at any available ring carbon atom with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-5}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl. The benzo[d][1,3]dioxolyl can be substituted at any available ring carbon atom with -C_{1-6}haloalkyl, for example, –C_{1-5}haloalkyl, –C_{1-4}haloalkyl, –C_{1-3}haloalkyl, –C_{1-2}haloalkyl, or –C_1haloalkyl, including –CF_3, CH_2CH_2F, and the like.

In some aspects, A is benzothiophenyl. The benzothiophenyl can be attached to any of the compounds of formula I (or its subgenera) through any ring carbon atom. Preferably, the benzothiophenyl is substituted with one or two substituents, preferably one substituent. The benzothiophenyl can be substituted at any available ring carbon atom with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The benzothiophenyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The benzothiophenyl can be substituted at any available ring carbon atom with -SF_5. The benzothiophenyl can be substituted at any available ring carbon atom with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The benzothiophenyl can be substituted at any available ring carbon atom with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-5}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl. The benzothiophenyl can be substituted at any available ring carbon atom with -C_{1-6}haloalkyl, for example, –C_{1-5}haloalkyl, –C_{1-4}haloalkyl, –C_{1-3}haloalkyl, –C_{1-2}haloalkyl, or –C_1haloalkyl, including –CF_3, CH_2CH_2F, and the like.

In some aspects, A is pyrazolyl. The pyrazolyl can be attached to any of the compounds of formula I (or its subgenera) through any ring carbon atom. Preferably, the pyrazolyl is substituted with one or two substituents, preferably one substituent. The pyrazolyl can be substituted at any available ring carbon atom with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The pyrazolyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The pyrazolyl can be substituted at any available ring carbon atom with -SF_5. The pyrazolyl can be substituted at any available ring carbon atom with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The pyrazolyl can be substituted at any available ring carbon atom with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-5}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl. The pyrazolyl can be substituted at any available ring carbon atom with -C_{1-6}haloalkyl, for example, –C_{1-5}haloalkyl, –C_{1-4}haloalkyl, –C_{1-3}haloalkyl, –C_{1-2}haloalkyl, or –C_1haloalkyl, including –CF_3, CH_2CH_2F, and the like.

In preferred aspects, A is an unsubstituted or substituted phenyl, pyridyl, pyrimidyl, or pyrazinyl moiety, with pyridinyl being particularly preferred. In those aspects wherein the phenyl, pyridyl, pyrimidyl, or pyrazinyl moiety is substituted, the preferred substituents include –C_{1-6}alkyl (e.g., methyl) and halogen (e.g., F or Cl), with methyl being particularly preferred.

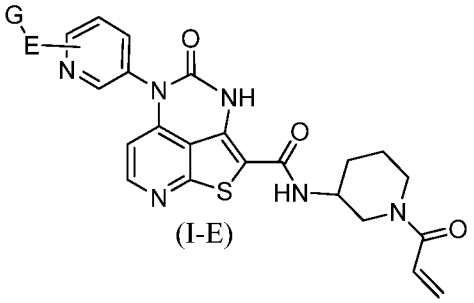
Additional embodiments of the disclosure are compounds of Formula (I) having the subgenera of Formula (I-D):



(I-D)

wherein the phenyl moiety can be unsubstituted or substituted with 1 or 2 substituents at any available carbon atom.

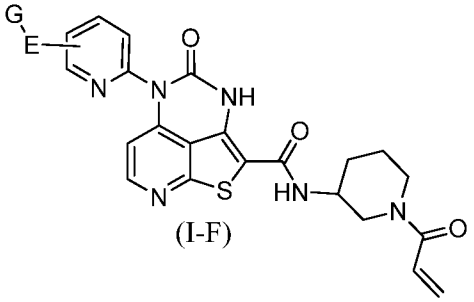
Additional embodiments of the disclosure are compounds of Formula (I) having the subgenera of Formula (I-E):



(I-E)

wherein the pyridyl moiety can be unsubstituted or substituted with 1 or 2 substituents at any available carbon atom.

Additional embodiments of the disclosure are compounds of Formula (I) having the subgenera of Formula (I-F):



(I-F)

wherein the pyridyl moiety can be unsubstituted or substituted with 1 or 2 substituents at any available carbon atom.

According to the disclosure, E is –O-; a bond; -C(O)-NH-; -CH_2-; or -CH_2-O-. The E moiety can be attached through any available carbon atom on the A moiety. The E moiety can also be attached through any available carbon atom on the G moiety.

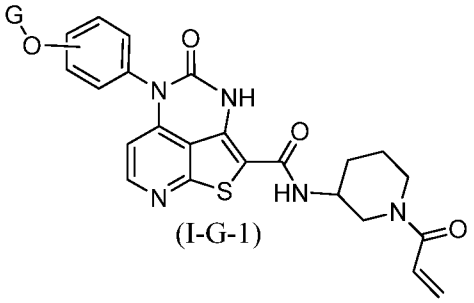
In preferred aspects, E is –O-. In other preferred aspects, E is a bond.

In some aspects of the disclosure, E is -C(O)-NH-, wherein the A-E-G moiety is A-C(O)-NH-G.

In other aspects of the disclosure, E is -CH_2-.

In yet other aspects of the disclosure, E is -CH_2-O-, wherein the A-E-G moiety is A-CH_2-O-G.

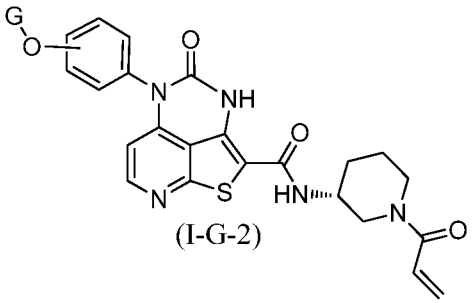
Additional embodiments of the disclosure are compounds of Formula (I) having the subgenera of Formula (I-G-1):



(I-G-1)

wherein the phenyl moiety can be unsubstituted or substituted with 1 or 2 substituents at any available carbon atom.

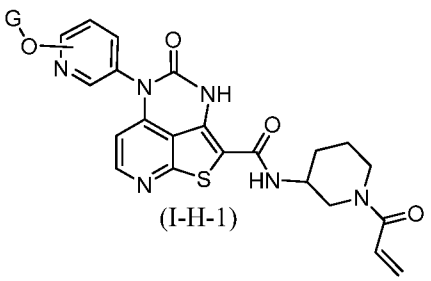
Additional embodiments of the disclosure are compounds of Formula (I) having the subgenera of Formula (I-G-2):



(I-G-2)

wherein the phenyl moiety can be unsubstituted or substituted with 1 or 2 substituents at any available carbon atom.

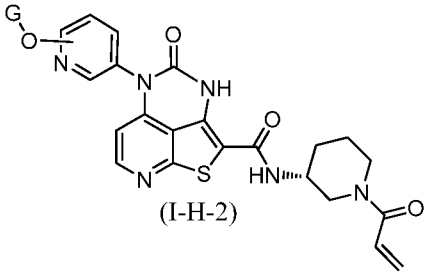
Additional embodiments of the disclosure are compounds of Formula (I) having the subgenera of Formula (I-H-1):



(I-H-1)

wherein the pyridyl moiety can be unsubstituted or substituted with 1 or 2 substituents at any available carbon atom.

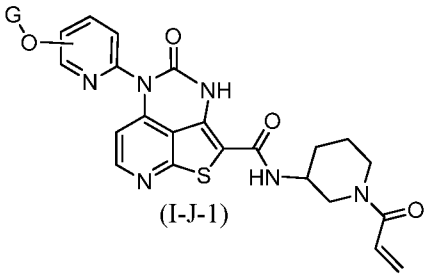
Additional embodiments of the disclosure are compounds of Formula (I) having the subgenera of Formula (I-H-2):



(I-H-2) I-H-2

wherein the pyridyl moiety can be unsubstituted or substituted with 1 or 2 substituents at any available carbon atom.

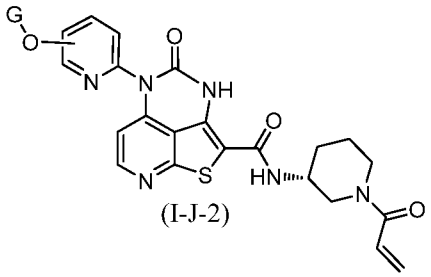
Additional embodiments of the disclosure are compounds of Formula (I) having the subgenera of Formula (I-J-1):



(I-J-1)

wherein the pyridyl moiety can be unsubstituted or substituted with 1 or 2 substituents at any available carbon atom.

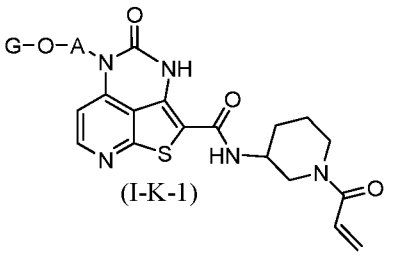
Additional embodiments of the disclosure are compounds of Formula (I) having the subgenera of Formula (I-J-2):



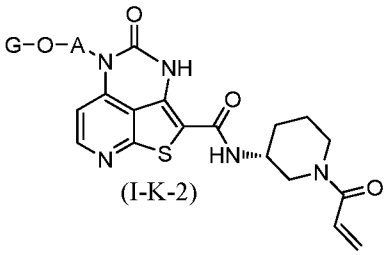
(I-J-2)

wherein the pyridyl moiety can be unsubstituted or substituted with 1 or 2 substituents at any available carbon atom.

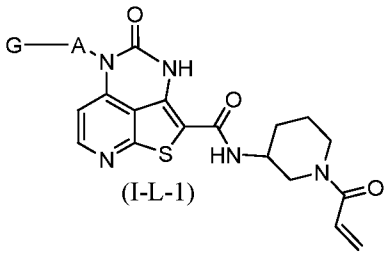
Other preferred subgenera of formula I are:


(I-K-1)

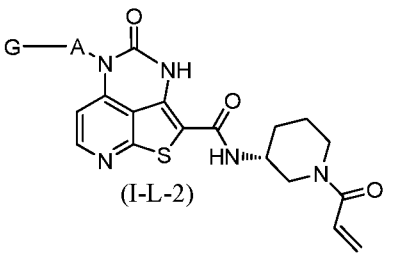
;


(I-K-2)

;


(I-L-1)

; and


(I-L-2)

;

According to the disclosure, G is H; -C_{3-6}cycloalkyl; -phenyl; -thiophenyl; -C_{1-6}alkyl; -pyrimidinyl; -pyridyl; -pyridazinyl; -benzofuranyl; -C_{1-6}haloalkyl; -heterocycloalkyl that contains an oxygen heteroatom; -phenyl-CH_2-O-phenyl; -C_{1-6}alk-O-C_{1-6}alkyl; -NR^6R^7; -SO_2C_{1-6}alkyl; or –OH; wherein the phenyl; pyridyl; pyridazinyl; pyrimidinyl; benzofuranyl; or thiophenyl is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen; -C_{1-6}alkyl; -C_{1-6}haloalkyl; -OC_{1-6}haloalkyl; -C_{3-6}cycloalkyl; -OC_{1-6}alkyl; -CN; -OH; -C_{1-6}alk-O-C_{1-6}alkyl; -C(O)-NR^6R^7; and -C(O)-C_{1-6}alkyl.

In some aspects, G is H.

In other aspects, G is -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

In some aspects, G is -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}lkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl.

In some aspects, G is -C_{1-6}haloalkyl, for example, –C_{1-5}haloalkyl, –C_{1-4}haloalkyl, –C_{1-3}haloalkyl, –C_{1-2}haloalkyl, or –C_1haloalkyl, including –CF_3, –CH_2CH_2F, and the like.

In other aspects, G is a -heterocycloalkyl that contains an oxygen heteroatom, for example, tetrahydropyranyl, tetrahydrofuranyl, or oxetanyl.

In preferred aspects, G is -phenyl-CH_2-O-phenyl. In these aspects, the -phenyl-CH_2-O-phenyl can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of halogen; -C_{1-6}alkyl; -C_{1-6}haloalkyl; -OC_{1-6}haloalkyl; -C_{3-6}cycloalkyl; -OC_{1-6}alkyl;

-CN; -OH; -C_{1-6}alk-O-C_{1-6}alkyl; -C(O)-NR^6R^7 (wherein R^6 and R^7 are as previously described herein); and -C(O)-C_{1-6}alkyl. The one or both of the phenyl rings of the -phenyl-CH_2-O-phenyl moiety can be substituted with halogen, for example F or Cl. The one or both of the phenyl rings of the -phenyl-CH_2-O-phenyl moiety can be substituted with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The one or both of the phenyl rings of the -phenyl-CH_2-O-phenyl moiety can be substituted with -C_{1-6}haloalkyl, for example, -C_{1-5}haloalkyl, -C_{1-4}haloalkyl, -C_{1-3}haloalkyl, -C_{1-2}haloalkyl, or -C_1haloalkyl. The one or both of the phenyl rings of the -phenyl-CH_2-O-phenyl moiety can be substituted with -OC_{1-6}haloalkyl, for example, -OC_{1-5}haloalkyl, -OC_{1-4}haloalkyl, -OC_{1-3}haloalkyl, -OC_{1-2}haloalkyl, or -OC_1haloalkyl. The one or both of the phenyl rings of the -phenyl-CH_2-O-phenyl moiety can be substituted with -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The one or both of the phenyl rings of the -phenyl-CH_2-O-phenyl moiety can be substituted with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The one or both of the phenyl rings of the -phenyl-CH_2-O-phenyl moiety can be substituted with –CN. The one or both of the phenyl rings of the -phenyl-CH_2-O-phenyl moiety can be substituted with –OH. The one or both of the phenyl rings of the -phenyl-CH_2-O-phenyl moiety can be substituted with -C_{1-6}alk-O-C_{1-6}alkyl, for example, -C_{1-5}alk-O-C_{1-5}alkyl, -C_{1-4}alk-O-C_{1-4}alkyl, -C_{1-3}alk-O-C_{1-3}alkyl, -C_{1-2}alk-O-C_{1-2}alkyl, or -C_1alk-O-C_1alkyl. The one or both of the phenyl rings of the -phenyl-CH_2-O-phenyl moiety can be substituted with -C(O)-NR^6R^7, wherein R^6 and R^7 are preferably each independently H; -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl; or -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More preferably, R^6 and R^7 are each independently H or -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The one or both of the phenyl rings of the -phenyl-CH_2-O-phenyl moiety can be substituted with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-65}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl.

In some aspects, G is -C_{1-6}alk-O-C_{1-6}alkyl, for example, -C_{1-5}alk-O-C_{1-5}alkyl, -C_{1-4}alk-O-C_{1-4}alkyl, -C_{1-3}alk-O-C_{1-3}alkyl, -C_{1-2}alk-O-C_{1-2}alkyl, or -C_1alk-O-C_1alkyl.

In other aspects, G is -NR^6R^7, wherein R^6 and R^7 are each independently H; -C_{1-6}alkyl; -C_{3-6}cycloalkyl; –C(O)H, or –CN. In these aspects, R^6 and R^7 are preferably each independently H; -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl; or -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More

preferably, R^6 and R^7 are each independently H or -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl.

In some aspects, G is -SO_2C_{1-6}alkyl, for example, -SO_2C_{1-5}alkyl, -SO_2C_{1-4}alkyl, -SO_2C_{1-3}alkyl, -SO_2C_{1-2}alkyl, or -SO_2C_1alkyl.

In some aspects, G is –OH.

In preferred aspects, G is phenyl. In these aspects, the phenyl can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of halogen; -C_{1-6}alkyl; -C_{1-6}haloalkyl; -OC_{1-6}haloalkyl; -C_{3-6}cycloalkyl; -OC_{1-6}alkyl; -CN; -OH; -C_{1-6}alk-O-C_{1-6}alkyl; -C(O)-NR^6R^7 (wherein R^6 and R^7 are as previously described herein); and -C(O)-C_{1-6}alkyl. The phenyl can be substituted with halogen, for example F or Cl. The phenyl can be substituted with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The phenyl can be substituted with -C_{1-6}haloalkyl, for example, -C_{1-5}haloalkyl, -C_{1-4}haloalkyl, -C_{1-3}haloalkyl, -C_{1-2}haloalkyl, or -C_1haloalkyl. The phenyl can be substituted with -OC_{1-6}haloalkyl, for example, -OC_{1-5}haloalkyl, -OC_{1-4}haloalkyl, -OC_{1-3}haloalkyl, -OC_{1-2}haloalkyl, or -OC_1haloalkyl. The phenyl can be substituted with -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The phenyl can be substituted with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The phenyl can be substituted with –CN. The phenyl can be substituted with –OH. The phenyl can be substituted with -C_{1-6}alk-O-C_{1-6}alkyl, for example, -C_{1-5}alk-O-C_{1-5}alkyl, -C_{1-4}alk-O-C_{1-4}alkyl, -C_{1-3}alk-O-C_{1-3}alkyl, -C_{1-2}alk-O-C_{1-2}alkyl, or -C_1alk-O-C_1alkyl. The phenyl can be substituted with -C(O)-NR^6R^7, wherein R^6 and R^7 are preferably each independently H; -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl; or -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More preferably, R^6 and R^7 are each independently H or -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The phenyl can be substituted with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-65}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl.

In some aspects, G is pyridyl. In these aspects, the pyridyl can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of halogen; -C_{1-6}alkyl; -C_{1-6}haloalkyl; -OC_{1-6}haloalkyl; -C_{3-6}cycloalkyl; -OC_{1-6}alkyl; -CN; -OH; -C_{1-6}alk-O-C_{1-6}alkyl; -C(O)-NR^6R^7 (wherein R^6 and R^7 are as previously described herein); and -C(O)-C_{1-6}alkyl. The pyridyl can be substituted with halogen, for example F or Cl. The pyridyl can be substituted

with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The pyridyl can be substituted with -C_{1-6}haloalkyl, for example, -C_{1-5}haloalkyl, -C_{1-4}haloalkyl, -C_{1-3}haloalkyl, -C_{1-2}haloalkyl, or -C_1haloalkyl. The pyridyl can be substituted with -OC_{1-6}haloalkyl, for example, -OC_{1-5}haloalkyl, -OC_{1-4}haloalkyl, -OC_{1-3}haloalkyl, -OC_{1-2}haloalkyl, or -OC_1haloalkyl. The pyridyl can be substituted with -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The pyridyl can be substituted with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The pyridyl can be substituted with –CN. The pyridyl can be substituted with –OH. The pyridyl can be substituted with -C_{1-6}alk-O-C_{1-6}alkyl, for example, -C_{1-5}alk-O-C_{1-5}alkyl, -C_{1-4}alk-O-C_{1-4}alkyl, -C_{1-3}alk-O-C_{1-3}alkyl, -C_{1-2}alk-O-C_{1-2}alkyl, or -C_1alk-O-C_1alkyl. The pyridyl can be substituted with -C(O)-NR^6R^7, wherein R^6 and R^7 are preferably each independently H; -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl; or -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More preferably, R^6 and R^7 are each independently H or -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The pyridyl can be substituted with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-65}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl.

In some aspects, G is pyridazinyl. In these aspects, the pyridazinyl can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of halogen; -C_{1-6}alkyl; -C_{1-6}haloalkyl; -OC_{1-6}haloalkyl; -C_{3-6}cycloalkyl; -OC_{1-6}alkyl; -CN; -OH; -C_{1-6}alk-O-C_{1-6}alkyl; -C(O)-NR^6R^7 (wherein R^6 and R^7 are as previously described herein); and -C(O)-C_{1-6}alkyl. The pyridazinyl can be substituted with halogen, for example F or Cl. The pyridazinyl can be substituted with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The pyridazinyl can be substituted with -C_{1-6}haloalkyl, for example, -C_{1-5}haloalkyl, -C_{1-4}haloalkyl, -C_{1-3}haloalkyl, -C_{1-2}haloalkyl, or -C_1haloalkyl. The pyridazinyl can be substituted with -OC_{1-6}haloalkyl, for example, -OC_{1-5}haloalkyl, -OC_{1-4}haloalkyl, -OC_{1-3}haloalkyl, -OC_{1-2}haloalkyl, or -OC_1haloalkyl. The pyridazinyl can be substituted with -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The pyridazinyl can be substituted with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The pyridazinyl can be substituted with –CN. The pyridazinyl can be substituted with –OH. The pyridazinyl can be substituted with -C_{1-6}alk-O-C_{1-6}alkyl, for example, -C_{1-5}alk-O-C_{1-5}alkyl, -C_{1-4}alk-O-C_{1-4}alkyl, -C_{1-3}alk-O-C_{1-3}alkyl, -C_{1-2}alk-O-C_{1-2}alkyl, or -C_1alk-O-C_1alkyl. The pyridazinyl can be substituted with -C(O)-NR^6R^7, wherein R^6 and R^7 are

preferably each independently H; -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl; or -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More preferably, R^6 and R^7 are each independently H or -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The pyridazinyl can be substituted with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-65}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl.

In some aspects, G is pyrimidinyl. In these aspects, the pyrimidinyl can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of halogen; -C_{1-6}alkyl; -C_{1-6}haloalkyl; -OC_{1-6}haloalkyl; -C_{3-6}cycloalkyl; -OC_{1-6}alkyl; -CN; -OH; -C_{1-6}alk-O-C_{1-6}alkyl; -C(O)-NR^6R^7 (wherein R^6 and R^7 are as previously described herein); and -C(O)-C_{1-6}alkyl. The pyrimidinyl can be substituted with halogen, for example F or Cl. The pyrimidinyl can be substituted with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The pyrimidinyl can be substituted with -C_{1-6}haloalkyl, for example, -C_{1-5}haloalkyl, -C_{1-4}haloalkyl, -C_{1-3}haloalkyl, -C_{1-2}haloalkyl, or -C_1haloalkyl. The pyrimidinyl can be substituted with -OC_{1-6}haloalkyl, for example, -OC_{1-5}haloalkyl, -OC_{1-4}haloalkyl, -OC_{1-3}haloalkyl, -OC_{1-2}haloalkyl, or -OC_1haloalkyl. The pyrimidinyl can be substituted with -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The pyrimidinyl can be substituted with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The pyrimidinyl can be substituted with –CN. The pyrimidinyl can be substituted with –OH. The pyrimidinyl can be substituted with -C_{1-6}alk-O-C_{1-6}alkyl, for example, -C_{1-5}alk-O-C_{1-5}alkyl, -C_{1-4}alk-O-C_{1-4}alkyl, -C_{1-3}alk-O-C_{1-3}alkyl, -C_{1-2}alk-O-C_{1-2}alkyl, or -C_1alk-O-C_1alkyl. The pyrimidinyl can be substituted with -C(O)-NR^6R^7, wherein R^6 and R^7 are preferably each independently H; -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl; or -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More preferably, R^6 and R^7 are each independently H or -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The pyrimidinyl can be substituted with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-65}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl.

In some aspects, G is benzofuranyl. In these aspects, the benzofuranyl can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of halogen; -C_{1-6}alkyl; -C_{1-6}haloalkyl; -OC_{1-6}haloalkyl; -C_{3-6}cycloalkyl; -OC_{1-6}alkyl; -CN; -OH; -C_{1-6}alk-O-C_{1-6}alkyl;

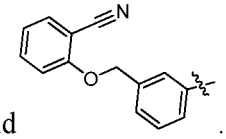
-C(O)-NR^6R^7 (wherein R^6 and R^7 are as previously described herein); and -C(O)-C_{1-6}alkyl. The benzofuranyl can be substituted with halogen, for example F or Cl. The benzofuranyl can be substituted with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The benzofuranyl can be substituted with -C_{1-6}haloalkyl, for example, -C_{1-5}haloalkyl, -C_{1-4}haloalkyl, -C_{1-3}haloalkyl, -C_{1-2}haloalkyl, or -C_1haloalkyl. The benzofuranyl can be substituted with -OC_{1-6}haloalkyl, for example, -OC_{1-5}haloalkyl, -OC_{1-4}haloalkyl, -OC_{1-3}haloalkyl, -OC_{1-2}haloalkyl, or -OC_1haloalkyl. The benzofuranyl can be substituted with -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The benzofuranyl can be substituted with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The benzofuranyl can be substituted with –CN. The benzofuranyl can be substituted with –OH. The benzofuranyl can be substituted with -C_{1-6}alk-O-C_{1-6}alkyl, for example, -C_{1-5}alk-O-C_{1-5}alkyl, -C_{1-4}alk-O-C_{1-4}alkyl, -C_{1-3}alk-O-C_{1-3}alkyl, -C_{1-2}alk-O-C_{1-2}alkyl, or -C_1alk-O-C_1alkyl. The benzofuranyl can be substituted with -C(O)-NR^6R^7, wherein R^6 and R^7 are preferably each independently H; -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl; or -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More preferably, R^6 and R^7 are each independently H or -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The benzofuranyl can be substituted with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-65}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl.

In some aspects, G is thiophenyl. In these aspects, the thiophenyl can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of halogen; -C_{1-6}alkyl; -C_{1-6}haloalkyl; -OC_{1-6}haloalkyl; -C_{3-6}cycloalkyl; -OC_{1-6}alkyl; -CN; -OH; -C_{1-6}alk-O-C_{1-6}alkyl; -C(O)-NR^6R^7 (wherein R^6 and R^7 are as previously described herein); and -C(O)-C_{1-6}alkyl. The thiophenyl can be substituted with halogen, for example F or Cl. The thiophenyl can be substituted with -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The thiophenyl can be substituted with -C_{1-6}haloalkyl, for example, -C_{1-5}haloalkyl, -C_{1-4}haloalkyl, -C_{1-3}haloalkyl, -C_{1-2}haloalkyl, or -C_1haloalkyl. The thiophenyl can be substituted with -OC_{1-6}haloalkyl, for example, -OC_{1-5}haloalkyl, -OC_{1-4}haloalkyl, -OC_{1-3}haloalkyl, -OC_{1-2}haloalkyl, or -OC_1haloalkyl. The thiophenyl can be substituted with -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The thiophenyl can be substituted with -OC_{1-6}alkyl, for example, -OC_{1-5}alkyl, -OC_{1-4}alkyl, -OC_{1-3}alkyl, -OC_{1-2}alkyl, or -OC_1alkyl. The thiophenyl can be substituted with –CN. The thiophenyl can be substituted with –OH. The

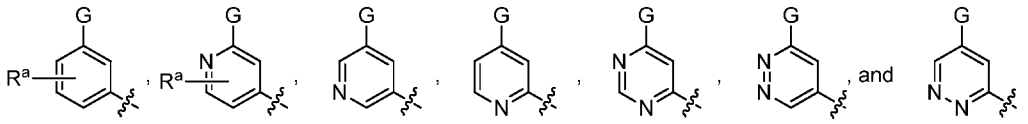
thiophenyl can be substituted with -C_{1-6}alk-O-C_{1-6}alkyl, for example, -C_{1-5}alk-O-C_{1-5}alkyl, -C_{1-4}alk-O-C_{1-4}alkyl, -C_{1-3}alk-O-C_{1-3}alkyl, -C_{1-2}alk-O-C_{1-2}alkyl, or -C_1alk-O-C_1alkyl. The thiophenyl can be substituted with -C(O)-NR^6R^7, wherein R^6 and R^7 are preferably each independently H; -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl; or -C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More preferably, R^6 and R^7 are each independently H or -C_{1-6}alkyl, for example, -C_{1-5}alkyl, -C_{1-4}alkyl, -C_{1-3}alkyl, -C_{1-2}alkyl, or -C_1alkyl. The thiophenyl can be substituted with -C(O)-C_{1-6}alkyl, for example, -C(O)-C_{1-65}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-C_{1-2}alkyl, or -C(O)-C_1alkyl.

In preferred aspects, G is unsubstituted or substituted phenyl, pyridyl, pyridizinyl, or pyrazinyl. In those aspects wherein G is substituted phenyl, pyridyl, pyridizinyl, or pyrazinyl, preferred substituents include C_{1-6}alkyl (e.g., methyl). In other preferred aspects, G is C_{1-6}alkyl (e.g., -isopropyl).

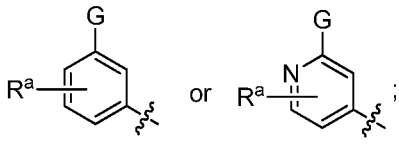
In preferred aspects, G is unsubstituted or substituted phenyl, pyridyl, pyridizinyl, or pyrazinyl and E is –CH_2- or O. In those aspects wherein G is substituted phenyl, pyridyl, pyridizinyl, or pyrazinyl and E is –CH_2- or O, preferred substituents include C_{1-6}alkyl (e.g., methyl). In other preferred aspects, G is C_{1-6}alkyl (e.g., -isopropyl) and E is –CH_2- or O.

In preferred embodiments, particularly those wherein the compounds are of Formula II', G is selected from the group consisting of C_{3-6}cycloalkyl; oxetanyl; tetrahydrofuranyl; tetrahydropyranyl; benzofuran-7-yloxy; pyridyl; pyridyl substituted with CH_3; phenyl; phenyl substituted with one or two members independently selected from the group consisting of: halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, OH, OC_{1-6}alkyl, OC_{1-6}haloalkyl, CH_2OCH_3, (C=O)NH_2, and C_{3-6}cycloalkyl; and  . In more preferred aspects, G is phenyl or phenyl substituted with C_{1-6}alkyl.

In preferred embodiments, particularly those wherein the compounds are of Formula III', G-A is selected from the group consisting of

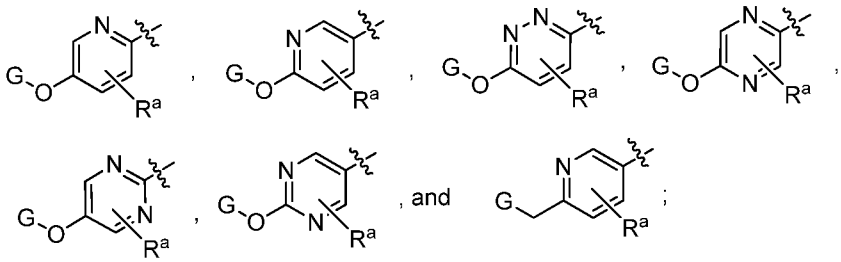


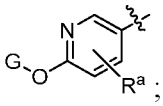
wherein G is phenyl; or phenyl substituted with one or two members independently selected from the group consisting of: halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, pyridyl, oxetan-3-yl, and tetrahydro-2H-pyran-4-yl; and R^a is H or CH_3. In more preferred aspects, G-A is



wherein G is phenyl, or phenyl substituted with C_{1-6}alkyl.

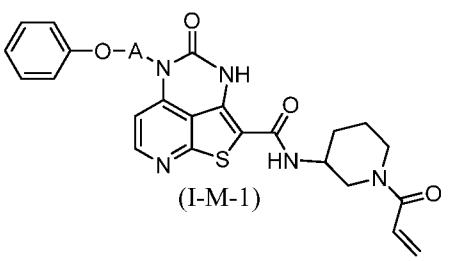
In preferred embodiments, particularly those wherein the compounds are of Formula IV', G-E-A is selected from the group consisting of:



where G is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl, tetrahydro-2H-pyran-4-yl, pyridazin-3-yl, phenyl, and phenyl substituted with F; and R^a is H or CH_3. In more preferred aspects, G-E-A is  ; R^a is CH_3; and G is phenyl.

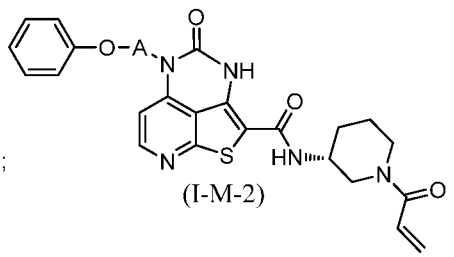
In preferred embodiments, particularly those wherein the compounds are of Formula V', G is selected from the group consisting of: C_{1-6}alkyl; C_{1-6}haloalkyl; phenyl; phenyl substituted with one or two members independently selected from the group consisting of: halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, OC_{1-6}alkyl, OC_{1-6}haloalkyl, (C=O)-C_{1-6}alkyl, SF_5, OH, NH_2, $N(CH_3)_2$, $OCH_2CH_2OCH(CH_3)_2$, and SO_2C_{1-6}alkyl; benzo[d][1,3]dioxolyl optionally substituted with Cl; 2-methylpyridin-3-yl; 2-isopropylpyridin-4-yl; benzothiophenyl; napthalenyl; and 2,2-difluorobenzo[d][1,3]dioxol-5-yl.

Preferred subgenera of formula I include:



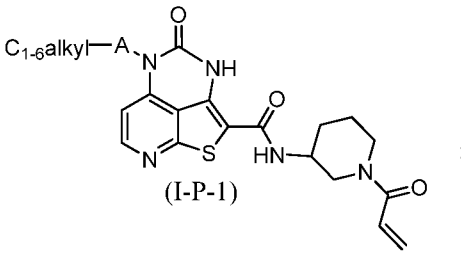
(I-M-1)

;

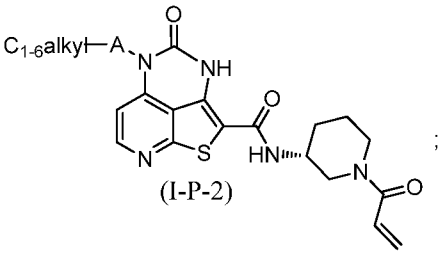


(I-M-2)

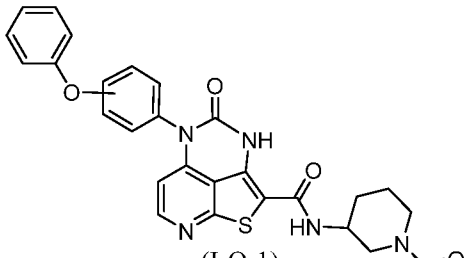
;



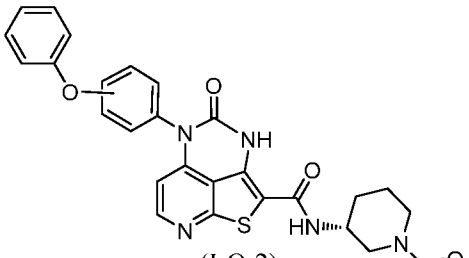
(I-P-1) ;



(I-P-2) ;

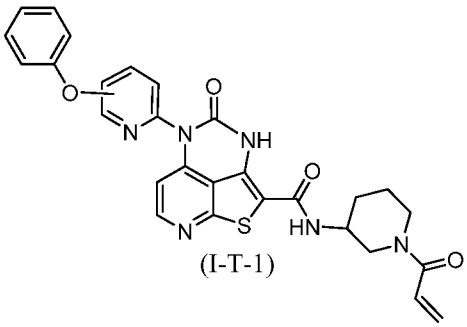


(I-Q-1) ;



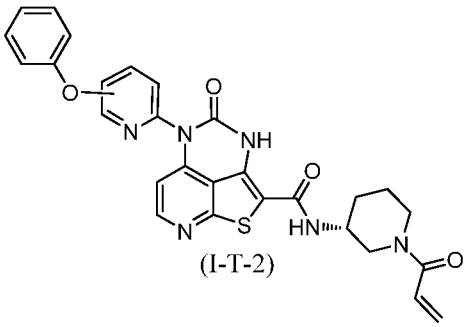
(I-Q-2) and

wherein the A phenyl is unsubstituted or substituted, preferably with $-C_{1-6}$alkyl.



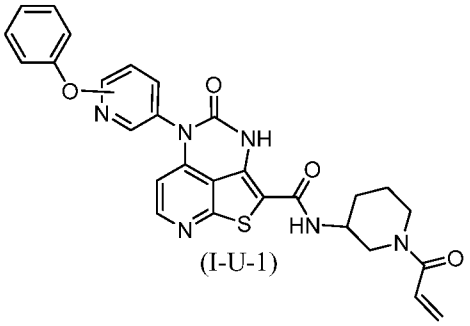
(I-T-1)

wherein the A pyridyl is unsubstituted or substituted, preferably with $-C_{1-6}$alkyl.



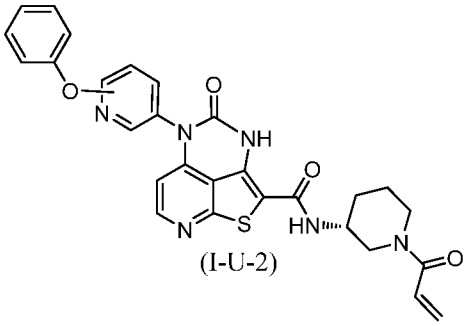
(I-T-2)

wherein the A pyridyl is unsubstituted or substituted, preferably with $-C_{1-6}$alkyl.



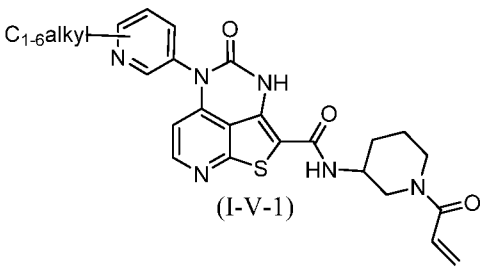
(I-U-1)

wherein the A pyridyl is unsubstituted or substituted, preferably with –C_{1-6}alkyl.



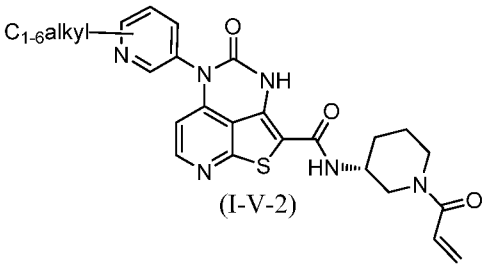
(I-U-2)

wherein the A pyridyl is unsubstituted or substituted, preferably with –C_{1-6}alkyl.



(I-V-1)

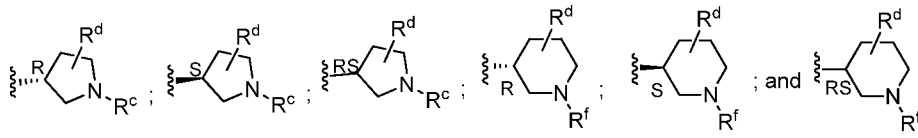
wherein the A pyridyl is unsubstituted or substituted, preferably with –C_{1-6}alkyl.



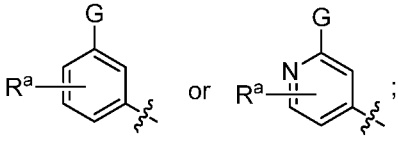
(I-V-2)

wherein the A pyridyl is unsubstituted or substituted, preferably with –C_{1-6}alkyl.

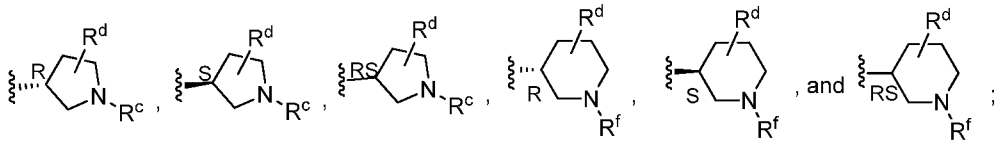
In those embodiments of the disclosure wherein the compounds are of Formula (II'), preferably R^a is H or CH_3; n is 1; E is O; G is phenyl or phenyl substituted with C_{1-6}alkyl;

Ring B is  and R^c and R^f are (C=O)CH=CH_2; and R^d is H.

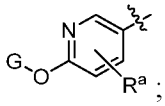
In those embodiments of the disclosure wherein the compounds are of Formula (III'),

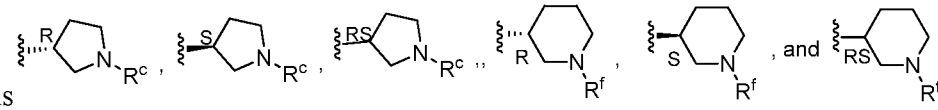
preferably G-A is  G is phenyl, or phenyl substituted with C_{1-6}alkyl;

Ring B is:

 and R^c and R^f are (C=O)CH=CH_2; and R^d is H.

In those embodiments of the disclosure wherein the compounds are of Formula (IV'),

preferably G-E-A is  ; R^a is CH_3; G is phenyl;

Ring B is  and R^c and R^f are (C=O)CH=CH_2.

A further embodiment of the present disclosure is a compound selected from the group consisting of:

N-((3R,5R)-1-Acryloyl-5-fluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-hydroxypiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-fluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-1-Acryloyl-5-hydroxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(3-fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-1-Acryloyl-5-methoxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-fluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-hydroxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-methoxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(benzofuran-7-yloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-(2,6-difluorophenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(2-ethylphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-fluoro-6-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-cyano-3-(3-methyloxetan-3-yl)acryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-(benzofuran-7-yloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-(methylamino)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(3-((2-Cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(4-Hydroxybut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Chloroacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Aminobut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-1-Acryloyl-4-fluoropyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,EZ)-N-(1-(2-Cyano-4-ethoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Hydroxybut-2-enoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(4-Cyano-1,4-oxazepan-6-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(cyclohexyloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-1-Acryloyl-4-methoxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyanopiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-1-Acryloyl-4-fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(*S)-(2-Methyl-4-phenoxyphenyl)- N-(1-(4-(methylamino)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-(cyclohexyloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4-methoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-13C-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(But-2-ynoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4-methyl-4-morpholinopent-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-fluoro-6-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-N-(1-propioloylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Fluoroacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Fluoroacryloyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-cyclopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3 H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2,6-Difluorophenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(5-chlorobenzo[d][1,3]dioxol-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-methoxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(But-2-ynoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-(Dimethylamino)acetyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Fluorophenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-ethyl-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4-methyl-4-(tetrahydro-2H-pyran-4-yl)pent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(2,6-difluorophenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-ethoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydrofuran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2,6-difluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(Benzofuran-7-yloxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Methoxypropanoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Methoxyphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Ethylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Hydroxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-(2-ethylphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2,3-dimethyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-(Dimethylamino)acetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-fluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydrofuran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2,6-dimethyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(pentafluorothio)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-Tetrahydro-2H-pyran-3-yl 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2,4-dimethylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-N-(1-(3-methoxypropanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydrofuran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1,6-Dimethylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Isopropylpyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-4-Fluoro-1-(3-methoxypropanoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Methoxyacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2 H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Cyanoazepan-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Hydroxypropanoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(But-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Isopropylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1,6-Dimethylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(3-(methylsulfonyl)propanoyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(But-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(3-(methylamino)propanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Fluoro-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydrofuran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Acryloylazetidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-13C-Acryloylpiperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((R)-2-Amino-3-methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4-methyl-4-morpholinopent-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-N-(1-(3-(methylsulfonyl)propanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-N-(1-(2-hydroxyacetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-N-(1-(2-methoxyacetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(But-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Isopropylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-ethyl-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((S)-2-Amino-3-methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(6-phenoxypyridazin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((S)-2-Hydroxy-3-methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Hydroxyacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-((R)-1-((S)-1-methylpyrrolidine-3-carbonyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-N-(1-(3-hydroxypropanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(4-Methyl-1,4-oxazepan-6-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-(Dimethylamino)propanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((S)-pyrrolidine-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-4-Fluoro-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Chloro-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)- N-(1-(2-Cyano-4-(dimethylamino)-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Fluoro-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(oxetane-3-carbonyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-N-methyl-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-5-Fluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Hydroxy-1-(3-methoxypropanoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Cyano-3-methylbut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Ethylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((S)-2,3-Dimethoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((R)-2-Hydroxy-3-methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(2-(trifluoromethyl)acryloyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-((R)-1-((R)-1-methylpyrrolidine-3-carbonyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(3-(methylsulfonyl)propanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(o-tolyloxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyclopropylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4-methyl-4-(piperidin-1-yl)pent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Aminoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4-(cyclopropylamino)-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-((6S)-6-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-4-Fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R)-1-(3-Methoxybutanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((S)-3-Methoxy-2-methylpropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Ethoxyphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R)-1-(3-Methoxy-2-methylpropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-5-Fluoro-1-methylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propioloylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(1-methyl-6-oxopiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Aminopropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-Fluoro-1-methylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1,3-Dimethylpiperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(2-oxopiperidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-fluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-5-Hydroxy-1-methylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Ethylphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(quinuclidin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(3-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-((6R)-6-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(5,5-Difluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2,6-difluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

13C-(R,Z)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

13C-(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-(cyclohexyloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-5-Hydroxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Cyanoacetyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Methylpiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-cyclopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Fluoro-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylazepan-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Methoxy-2,2-dimethylpropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Cyanoazepan-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((R)-2,3-Dimethoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3 H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((R)-pyrrolidine-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(4-(Hydroxymethyl)tetrahydro-2H-pyran-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-ethoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-fluorophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(4-Amino-2-cyano-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(3-(1-Aminocyclopropyl)-2-cyanoacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-Hydroxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((R)-tetrahydrofuran-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(3-Cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-4-Hydroxy-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Cyclopropylphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(5-oxopyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1,2-Dimethylpiperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Methacryloylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-(Cyclopropanecarbonyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylazepan-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((S)-tetrahydrofuran-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-4-Methoxy-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(5-chlorobenzo[d][1,3]dioxol-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(m-tolyloxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-4-Methoxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4-(ethylamino)-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyclopropylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(3-Fluorophenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Fluoro-4-phenoxyphenyl)-N-(1-(3-methoxypropanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(o-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(2-(2-oxoimidazolidin-1-yl)ethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(tetrahydro-2H-pyran-4-carbonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Hydroxyphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(3-Ethoxyacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Fluoro-6-methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Isopropylphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-5-Methoxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(3-methylbut-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(3-(Methoxymethyl)phenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(2-(trifluoromethoxy)phenoxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(3-Cyclopropyl-2-fluoroacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)azetidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Cyclopropylazetidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,EZ)-N-(1-(2-Cyano-3-methoxyacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(*S)-(5-Chlorobenzo[d][1,3]dioxol-4-yl)-N-(1-(2-cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,EZ)-N-(1-(2-Cyano-4-((2-methoxyethyl)amino)-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3 H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2,6-Difluoro-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Hydroxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N1-((E)-4-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-4-oxobut-2-en-1-yl)-N5-(15-oxo-19-((3aS,4R,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)glutaramide;

(R,E)-N-(1-(2-Cyano-4-methyl-4-(methylamino)pent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(5-Chlorobenzo[d][1,3]dioxol-4-yl)-N-(1-(2-cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(1-(3-(methylsulfonyl)propanoyl)azetidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-4-Hydroxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(2-(trifluoromethyl)phenoxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Hydroxy-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Methoxy-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Methoxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-(3-Methoxypropanoyl)azetidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-methylpent-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylazetidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(Cyclohexyloxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Ethylazetidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(Azetidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-N-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-fluorophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-chlorophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-phenyl-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(2-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-5-Methoxy-1-methylpiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-chloro-3-methylbut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(2-Fluorobut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Methyl-5-oxopyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Fluoro-3-methylbut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-4-(pentafluorothio)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-N-((1-methylpyrrolidin-2-yl)methyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-Hydroxy-1-methylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-Methoxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(pyrrolidin-2-ylmethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(p-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(5,5-Difluoro-1-methylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Isopropylazetidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4,4-Dimethylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(2-morpholinoethyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo- N-(pyrrolidin-2-ylmethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(2-Chlorobut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-phenoxy-2-(trifluoromethyl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(m-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Chloro-3-(trifluoromethyl)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2,3-Dimethyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-((1-methylpyrrolidin-3-yl)methyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Isopropoxyphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Cyclobutoxy-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-((1-methylpyrrolidin-2-yl)methyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(3,5-Difluorophenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-(Dimethylamino)acetyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-(trifluoromethyl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(p-tolyloxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-N-(2-(3-methylmorpholino)ethyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-(methylamino)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(pyridin-3-yloxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-chlorophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(4-Fluorophenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(2-(3-methylmorpholino)ethyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(Cyclopentyloxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(2-(1-methylpyrrolidin-2-yl)ethyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-fluorophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2,4-Difluorophenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(5-Fluoro-2-methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2,4-dimethylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(5-Fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(pyridin-2-yloxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(5-Fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Benzyl-2-oxoazepan-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-2-ylmethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(6-phenoxypyridazin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-Methoxy-1-methylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,EZ)-N-(1-(3-Cyclopropyl-2-(trifluoromethyl)acryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(o-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(2-morpholino-2-oxoethyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2,6-Dimethyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Hydroxypropanoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(5-Chlorobenzo[d][1,3]dioxol-4-yl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Ethylpiperidin-3-yl)-5-(4-(2-isopropylphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(5-chlorobenzo[d][1,3]dioxol-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Cyclopropoxy-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydrofuran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxy-2-(trifluoromethyl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Carbamoylphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-2-(piperazin-1-yl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one;

(R)-6-Methyl-4-oxo-5-(4-phenoxyphenyl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyanopiperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3,5-Dichlorophenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-Methyl-5-(2-methyl-4-phenoxyphenyl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Isopropoxy-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Ethoxy-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(tert-butyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Chlorophenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-phenyl-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-Methyl-5-(2-methyl-4-phenoxyphenyl)-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Methoxy-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Methoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(2-Methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3,4-Dichlorophenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-phenyl-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Methylpiperidin-3-yl)-4-oxo-5-(4-phenoxy-2-(trifluoromethyl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Methyl-6-phenoxypyridazin-3-yl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-methyl-6-phenoxypyridazin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Methylpiperidin-3-yl)-4-oxo-5-(o-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(5-Chlorobenzo[d][1,3]dioxol-4-yl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(pyridin-4-yloxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-(Dimethylamino)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-isopropyl-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methylpyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3,4-dichlorophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-Isopropyl-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-chloro-3-(trifluoromethyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Methoxy-3-methylbutanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(3-Acetamidoacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Chloroacryloyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Aminobut-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(vinylsulfonyl)pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-trideuteriomethylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(vinylsulfonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-(methylsulfonyl)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(2,3,4,5,6-pentadeuteriophenoxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-4-(2,3,4,5,6-pentadeuteriophenoxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-(methylamino)but-2-enoyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-(2,3,4,5,6-pentadeuteriophenoxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyanopiperidin-3-yl)-5-(2-methyl-4-(2,3,4,5,6-pentadeuteriophenoxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(2,3,4,5,6-pentadeuteriophenoxy)phenyl)-N-(1-(trideuteriomethyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(2,3,4,5,6-pentadeuteriophenoxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Aminobut-2-enoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-(methylsulfonamido)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-(Dimethylamino)acetyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyanobut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((S)-Azetidine-2-carbonyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-(3-methyloxetan-3-yl)acryloyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(2-Fluoro-4-(methylamino)but-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(2-(pyrrolidin-1-yl)acetyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-2-(((1-Acryloylpiperidin-3-yl)amino)methyl)-5-(2-methyl-4-phenoxyphenyl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(2-(methylamino)acetyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Aminoacetyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(2-(piperidin-1-yl)acetyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(2-morpholinoacetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Chloroacetyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Chloroacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-(thiophen-2-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-isopropoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-isopropoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(3-Cyclopropyl-2-methylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,EZ)-N-(1-(2-Chloro-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-morpholinobut-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(benzo[b]thiophen-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Isopropoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Isopropoxyphenyl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(4-(thiophen-2-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-phenoxybenzyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Methylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxybenzyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(Benzo[b]thiophen-5-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Methylpiperidin-3-yl)-4-oxo-5-(4-phenoxybenzyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(4-phenoxybenzyl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(trifluoromethoxy)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(trifluoromethoxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(4-(trifluoromethoxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-(trifluoromethoxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(naphthalen-2-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(1-benzyl-1H-pyrazol-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-3-yl)-N-(1-acryloylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-benzylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-4-yl)-N-(1-acryloylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-(Dimethylamino)acetyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-(Dimethylamino)acetyl)pyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(benzo[b]thiophen-2-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(Benzo[b]thiophen-2-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(Naphthalen-2-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Benzylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(1-Benzyl-1H-pyrazol-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-((4*S)-2-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(*R)-(2-Methyl-4-phenoxyphenyl)-N-((4*S)-2-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-((4*R)-2-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(*R)-(2-Methyl-4-phenoxyphenyl)-N-((4*R)-2-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(4-(Hydroxymethyl)tetrahydro-2H-pyran-4-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(4-(Hydroxymethyl)tetrahydro-2H-pyran-4-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Chloro-3-methylbut-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Chloro-3-methylbut-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-N-methyl-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-N-methyl-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-isopropyl-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-isopropyl-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Isopropyl-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Isopropyl-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*Z)-N-(1-(2-Cyano-4-methoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*Z)-N-(1-(2-Cyano-4-methoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*E)-N-(1-(2-Cyano-4-methoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*E)-N-(1-(2-Cyano-4-methoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((1-Acryloylpyrrolidin-3-yl)methyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-5-(4-phenoxyphenyl)-N-(pyrrolidin-3-ylmethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(1H-Imidazole-1-carbonyl)piperidin-3-yl)-5-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-methoxy-3-(trifluoromethyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-cyclobutoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-cyclobutoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-N-(2-oxopiperidin-3-yl)-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Methoxy-3-(trifluoromethyl)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Chloro-4-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Methyl-3-(trifluoromethyl)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-5-(4-phenoxyphenyl)-N-((tetrahydrofuran-2-yl)methyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Hydroxypyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Benzylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(3-phenoxyphenyl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-Methoxypiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-Methoxypiperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(*S)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(5-oxopyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(*S)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(5-oxopyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(*R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(5-oxopyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(*R)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(5-oxopyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*E)-N-(1-(But-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*E)-N-(1-(But-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*Z)-N-(1-(But-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*Z)-N-(1-(But-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*Z)-N-(1-(2-Cyano-4-ethoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*E)-N-(1-(2-Cyano-4-ethoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*Z)-N-(1-(2-Cyano-4-ethoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*E)-N-(1-(2-Cyano-4-ethoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-1-Acryloyl-5-methoxypiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-methoxypiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-1-Acryloyl-5-hydroxypiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-fluoropiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(4-Cyano-1,4-oxazepan-6-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-fluoropyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3 H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4-ethoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-methoxypyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)pyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-(methylamino)but-2-enoyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-(3-(methylsulfonyl)propanoyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Methoxyacetyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Acryloylazetidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-methyl-5-phenoxypyridin-2-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2',3'-difluoro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-1-Acryloyl-5-fluoropiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3'-fluoro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(4-cyclobutoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Hydroxybut-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2'-methyl-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-(trifluoromethoxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(6-phenoxypyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3'-chloro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-1-Acryloyl-4-methoxypyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,EZ)-N-(1-(2-Cyano-3-(3-methyloxetan-3-yl)acryloyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2'-chloro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Aminobut-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2',4'-difluoro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-benzylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3'-methyl-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-cyclohexylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Aminobut-2-enoyl)pyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4'-methyl-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Hydroxybut-2-enoyl)pyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-((R)-1-((S)-2-(methylamino)propanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-phenylpyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-phenoxypyrazin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-isopropylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(vinylsulfonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-3-yl)-N-(1-acryloylpyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-(methylsulfonamido)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-propylphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-cyclobutylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-trideuteriomethylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-phenylpyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-(pyridin-3-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(Ethylsulfonyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-(pyridin-2-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(3-Chloro-4-phenoxyphenyl)-N-(1-(4-(dimethylamino)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Isopropylpiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-fluoropyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-1-Acryloyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)pyrrolidine-3-carboxamide;

(R)-1-Acryloyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)pyrrolidine-3-carboxamide;

(R)-N-(1-(2-(Methylamino)acetyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((S)-3-Hydroxy-2-methylpropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-methoxypyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(4-Amino-2-fluorobut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(4-Amino-2-chlorobut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-3-yl)-N-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-3-yl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3'-Methyl-[1,1'-biphenyl]-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2'-Methyl-[1,1'-biphenyl]-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((E)-4-((4aR,7aS)-tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)but-2-enoyl)pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(2-phenoxypyrimidin-5-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-1-Acryloyl-5-hydroxypiperidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(3-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-(cyclohexyloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-(cyclopentyloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(2'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((R)-3-Hydroxy-2-methylpropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-isopropoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Acetylphenyl)-N-(1-acryloylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-(trifluoromethoxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-cyclopropylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-([1,1'-Biphenyl]-3-yl)-N-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((R)-3-Methoxy-2-methylpropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Chloro-4-phenoxyphenyl)-N-(1-(2-(dimethylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-([1,1'-Biphenyl]-3-yl)-N-(1-(4-(dimethylamino)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(*cis*)-1-Acryloyl-3-hydroxypiperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Chloro-4-phenoxyphenyl)-N-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Methoxyacetyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Chloro-4-phenoxyphenyl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-N-(6-oxopiperidin-3-yl)-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Fluoropyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4'-Methyl-[1,1'-biphenyl]-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Chloro-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acetylpiperidin-3-yl)-5-(3-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-chloro-4-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(2-phenylpyridin-4-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3*R*,5*R*)-5-Hydroxypiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-3-yl)-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Methoxypyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3*R*,5*R*)-1-Acryloyl-5-hydroxypiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Hydroxybut-2-enoyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-cyclobutylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyanopiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Methoxypropanoyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Cyanopiperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Methyl-5-phenoxypyridin-2-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(4-Hydroxybut-2-enoyl)piperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-(3-Methoxypropanoyl)piperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-3-amino-4-((3-cyclobutoxyphenyl)amino)thieno[2,3-b]pyridine-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

2-((1-Acryloylpiperidin-3-yl)amino)-5-(2-methyl-4-phenoxyphenyl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one;

(R)-5-([1,1'-Biphenyl]-3-yl)- N-(1-(2-(methylamino)acetyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(2-phenylpyridin-4-yl)-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Cyclobutylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(6-phenylpyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Cyclobutoxy-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

2-((1-Acryloylpiperidin-4-yl)amino)-5-(2-methyl-4-phenoxyphenyl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-methyl-3-(trifluoromethyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(4-Isopropoxy-2-methylphenyl)-4-oxo-N-((R)-1-((E)-4-((4aR,7aS)-tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)but-2-enoyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(4-cyclobutoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(4-phenylpyridin-2-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(3*R*,5*R*)-*tert*-Butyl 3-hydroxy-5-(4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(oxetan-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-(Cyclopentyloxy)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(trans-3-Hydroxypiperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-(Cyclohexyloxy)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

trans-tert-Butyl 3-hydroxy-4-(4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-4-Oxo-5-(5-phenylpyridin-3-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methoxypyrimidin-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(3-(trifluoromethoxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Cyclobutoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(3-(pyridin-2-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(6-phenylpyridin-2-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-(trifluoromethoxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(3S,4S)-tert-Butyl 3-fluoro-4-(4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)pyrrolidine-1-carboxylate;

(R)-5-(4-Cyclobutoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

tert-Butyl 4-(4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-tert-Butyl 3-(4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-5-(3-Cyclohexylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Isopropylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-(pyridin-4-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-(oxetan-3-yl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-isopropoxy-3-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Cyclobutylpyridin-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(6-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2,2-Difluorobenzo[d][1,3]dioxol-5-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Isopropoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-(tert-butyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(3S,4S)-tert-Butyl 3-methoxy-4-(4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)pyrrolidine-1-carboxylate;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(5-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(tert-butylsulfonyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Hydroxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Acetylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(5-Isopropoxy-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(6-phenoxypyridin-2-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-(tert-Butyl)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(3-(pyridin-4-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)- tert-Butyl 3-(5-(3-(tert-butyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-tert-Butyl 3-(5-(3-acetylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-5-(4-(tert-Butylsulfonyl)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-tert-Butyl 3-(5-(4-(tert-butylsulfonyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-tert-Butyl 3-(5-(4-(tert-butoxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-tert-Butyl 3-(5-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-tert-Butyl 3-(5-(6-cyclobutoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

N-((3R,4R)-1-Acryloyl-4-hydroxypiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Methyl-5-phenoxypyrazin-2-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-methyl-5-phenoxypyrazin-2-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,4R)-4-Hydroxypiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(cis-3-Hydroxypiperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-N-(2-oxopyrrolidin-3-yl)-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(R)-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(4-methyl-2-phenoxypyrimidin-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-phenoxypyrimidin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*R)-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(cis-4-Acrylamidotetrahydrofuran-3-yl)-5-(*S)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(6-cyclobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2',3'-difluoro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-hydroxypiperidin-3-yl)-5-(2',3'-difluoro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(3-methyl-2-phenylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-cyclohexylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(6-phenylpyridazin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-methoxypiperidin-3-yl)-5-(2',3'-difluoro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(6-phenoxypyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((*E)-3-((S)-1-Acetylpyrrolidin-2-yl)-2-cyanoacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-cyclobutoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((E)-3-((R)-1-Acetylpyrrolidin-2-yl)-2-cyanoacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((E)-4-((4aR,7aS)-tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)but-2-enoyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(6-phenylpyrimidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(6-cyclobutoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-methyl-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-isobutylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-cyclopentylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(cyclopentyloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(5-methyl-2-phenylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(2-isopropoxyethoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-isopropylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(5-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(5-phenoxypyrazin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-cyclobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([2,3'-Bipyridin]-4-yl)-N-(1-acryloylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(4-Methyl-6-phenoxypyridin-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(3-Chloro-4-phenoxyphenyl)-N-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(6-cyclobutoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(3-isopropylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2',3'-Difluoro-[1,1'-biphenyl]-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((1RS,2RS)-2-Aminocyclopentyl)-5-(*S)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-(tetrahydro-2H-pyran-4-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([2,2'-Bipyridin]-4-yl)-N-(1-acryloylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2',3'-Difluoro-[1,1'-biphenyl]-3-yl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-6-phenoxypyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(trans-1-Acryloyl-3-hydroxypiperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-6-phenoxypyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(Methylglycyl)piperidin-3-yl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(4-Methyl-2-phenoxypyrimidin-5-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-6-phenoxypyridin-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(5-phenoxypyrimidin-2-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Cyclopentylpyridin-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Isobutylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(6-phenylpyrimidin-4-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*R)-(4-methyl-2-phenoxypyrimidin-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Methyl-[1,1'-biphenyl]-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-cyclobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Isopropylpyridin-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(2-Methyl-6-phenoxypyridin-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(5-Methyl-2-phenylpyridin-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Isopropoxyethoxy)-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Cyclohexylpyridin-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(6-isopropoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Methyl-2-phenylpyridin-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-6-phenylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-6-phenylpyridin-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-cyclobutoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(3-methyl-2-phenylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(3-(tetrahydro-2H-pyran-4-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-tert-Butyl 3-(4-oxo-5-(3-(tetrahydro-2H-pyran-4-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-4-Oxo-5-(6-phenylpyridazin-4-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(6-phenoxypyridin-3-yl)-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-tert-Butyl 3-(5-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-5-(6-Cyclobutoxypyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3*S,4*R)-4-Acrylamidotetrahydrofuran-3-yl)-5-(*S)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(4-methyl-2-phenoxypyrimidin-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(2-phenoxypyrimidin-5-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(5-phenoxypyrimidin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-isobutylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-phenylpyridazin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((*3R,*4S)-4-Acrylamidotetrahydrofuran-3-yl)-5-(*S)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-isopropoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Isobutylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(5-phenylpyridazin-3-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*R)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-isopropoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(6-Isobutyl-4-methylpyridin-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(6-Isobutoxy-4-methylpyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(6-Isobutoxy-4-methylpyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(6-(Cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(6-(Cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(4-Methyl-2-phenoxypyrimidin-5-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(6-isobutyl-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(6-Isobutyl-4-methylpyridin-3-yl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-isobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-isobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-(cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-(cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-6-((tetrahydro-2 H-pyran-4-yl)oxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-((2-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-((6-methylpyridin-2-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-((2-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-(pyridin-3-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-((6-methylpyridin-2-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(6-(cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(5-(2-fluorophenoxy)pyridin-2-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(6-isobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N1-(15-Oxo-19-((3aR,4R,6aS)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)-N5-((E)-4-oxo-4-(3-(4-oxo-5-(5-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)but-2-en-1-yl)glutaramide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,EZ)-N-(1-(2-Cyano-3-(3-methyloxetan-3-yl)acryloyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(((S)-tetrahydrofuran-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-((5-methylpyridin-2-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(((R)-tetrahydrofuran-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

1-Acryloyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-isopropoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-(pyridazin-3-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-isobutyl-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-6-phenoxypyridin-3-yl)-4-oxo-N-(tetrahydrofuran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(6-Isopropoxy-4-methylpyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

2-(4-Acryloylpiperazin-1-yl)-5-(2-methyl-4-phenoxyphenyl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one;

(R)-5-(*S)-(6-(Cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(6-Isobutoxy-4-methylpyridin-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acetylpiperidin-3-yl)-5-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-1-(2-Cyano-3-cyclopropylacryloyl)-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

1-Cyano-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(4-(pyridazin-3-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-isopropoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)-1-propionylpiperidine-4-carboxamide;

(R)-5-(*R)-(6-Isopropoxy-4-methylpyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(1-propionylpiperidin-3-yl)-5-(4-(pyridin-2-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acetylpiperidin-3-yl)-4-oxo-5-(4-(pyridin-2-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acetylpiperidin-3-yl)-5-(2-methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-(pyridazin-3-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acetylpiperidin-3-yl)-4-oxo-5-(4-(pyridazin-3-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-isobutyl-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-1-(2-Cyano-4,4-dimethylpent-2-enoyl)-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

1-(2-Cyanoacetyl)-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

N-(5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)-1-propionylpiperidine-3-carboxamide;

1-(2-Cyanoacetyl)-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

1-Acryloyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

1-Ethyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

1-Cyano-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

1-Methyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-2-(4-methylpiperazin-1-yl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one;

(E)-4,4-Dimethyl-2-(4-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperazine-1-carbonyl)pent-2-enenitrile;

4-(5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperazine-1-carbonitrile;

5-(2-Methyl-4-phenoxyphenyl)-2-(4-propionylpiperazin-1-yl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one;

N-(5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

(E)-1-(2-Cyano-4,4-dimethylpent-2-enoyl)-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

(E)-1-(2-Cyano-3-cyclopropylacryloyl)-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

1-Methyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

1-Ethyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

N-(5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(vinylsulfonyl)pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyanopyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Cyanoacetyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(3-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2',3'-difluoro-4-methyl-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-(pyridin-2-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-(3-((2-cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-((R)-1-((R)-2-(methylamino)propanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((R)-Azetidine-2-carbonyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(3-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyanopiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-((R)-1-((S)-2-(methylamino)propanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(o-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(4-(3-((2-Cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-N-(1-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-(2-methoxyphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(4-(3-((2-Cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-N-(piperidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-5-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(4-phenoxyphenyl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-(3-((2-cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(4-(2-Methoxyphenoxy)-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Cyanopiperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-5-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((R)-pyrrolidine-2-carbonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Formylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(4-(pyridin-2-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-(2-Cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Cyanopiperidin-3-yl)-5-(4-(2-methoxyphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Cyanopiperidin-4-yl)-5-(4-(2-methoxyphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Formylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(o-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Cyanopiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acetylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Cyanopiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-(2-Cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((S)-pyrrolidine-2-carbonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(3-((2-cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)piperidin-3-yl)-5-(4-(2-methoxyphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(4-(piperidin-1-yl)but-2-enoyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-3-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Chloropropanoyl)piperidin-3-yl)-4-oxo-5-(5-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(4-(2-Methoxyphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-(Azetidin-1-yl)acetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-5-(4-phenoxyphenyl)-N-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Methylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(4-phenoxyphenyl)-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)piperidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Benzoylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(5-phenoxypyridin-2-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(4-(2-Methoxyphenoxy)-2-methylphenyl)-4-oxo-N-(piperidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(4-(2-Methoxyphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(Cyclopentyloxy)-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Methylpiperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)piperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(6-phenoxypyridin-3-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Isopropoxy-2-methylphenyl)-N-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Acetylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Benzylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-5-(4-phenoxyphenyl)-N-(piperidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-5-(4-phenoxyphenyl)-N-(2-(pyrrolidin-1-yl)ethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-5-(4-phenoxyphenyl)-N-(2-(piperazin-1-yl)ethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Acryloylpiperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Methylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-5-(4-phenoxyphenyl)-N-(2-(piperidin-1-yl)ethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(2-Morpholinoethyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-4-Oxo-5-(4-phenoxyphenyl)-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(2-(4-Methylpiperazin-1-yl)ethyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acetylpiperidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(3-(pyridin-3-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-5-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(3-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Benzoylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3,5-dichlorophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(o-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-(dimethylamino)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-(2-Cyanoacetyl)piperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Benzylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpiperidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-aminophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(Dimethylamino)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(m-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Chlorophenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(p-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Fluorophenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(tert-Butyl)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Isopropoxy-3-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Aminophenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-3-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(6-Isopropoxy-4-methylpyridin-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(6-isopropoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-(1-methylcyclobutyl)acryloyl)piperidin-3-yl)-5-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N1-((E)-4-((R)-3-(1-(2-Methyl-6-phenoxypyridin-3-yl)-2-oxo-1,2,3,5-tetrahydrocyclopenta[de]quinazoline-4-carboxamido)piperidin-1-yl)-4-oxobut-2-en-1-yl)-N5-(15-oxo-19-((3aR,4R,6aS)-2-oxooctahydrocyclopenta[d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)glutaramide;

(R,E)-N-(1-(2-Cyano-4-ethoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*R)-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-((2-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-((2-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-(pyridazin-3-yloxy)pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(5-(pyridazin-3-yloxy)pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-6-(pyridazin-3-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-6-(pyridazin-3-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-methyl-6-(pyridazin-3-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide; and

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-methyl-6-(pyridazin-3-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

and

stereoisomers or isotopic variants thereof; and pharmaceutically acceptable salts thereof.

The disclosure also relates to methods of using the compounds described herein to treat subjects diagnosed with or suffering from a disease, disorder, or condition mediated by Bruton's tyrosine kinase. These methods are accomplished by administering to the subject a compound of the disclosure in an amount sufficient to inhibit Bruton's tyrosine kinase.

In a further aspect, provided herein are methods for inhibiting Bruton's tyrosine kinase in a subject in need of treatment by administering to the subject a composition containing a therapeutically effective amount of at least one compound of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')). Some aspects of the disclosure are directed to methods of treating a subject suffering from an autoimmune disease by administering to the subject a composition containing a therapeutically effective amount of at least one compound of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')). In some aspects, the autoimmune disease is, e.g., inflammatory bowel disease, arthritis, lupus, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease Sjögren's syndrome, multiple sclerosis, Guillain-Barré syndrome, acute disseminated encephalomyelitis, Addison's disease, opsoclonus-myoclonus syndrome, ankylosing spondylitisis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, coeliac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behçet's disease, chronic fatigue, dysautonomia, endometriosis, interstitial cystitis, neuromyotonia, scleroderma, or vulvodynia. When used for the treatment of an autoimmune disease, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')) can be administered as single agents. Alternatively, when used for the treatment of an autoimmune disease, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')) can be administered in combination with other agents known to be useful for the treatment of autoimmune diseases.

Other embodiments of the disclosure are directed to methods of treating a subject suffering from a heteroimmune condition by administering to the subject a composition

containing a therapeutically effective amount of at least one compound of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')). In some aspects, the heteroimmune condition or disease is, e.g., graft versus host disease, transplantation, transfusion, anaphylaxis, allergy, type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, or atopic dermatitis. When used for the treatment of a heteroimmune condition, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (IV')) can be administered as single agents. Alternatively, when used for the treatment of a heteroimmune condition, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')) can be administered in combination with other agents known to be useful for the treatment of heteroimmune diseases.

Other embodiments of the disclosure are directed to methods of treating a subject suffering from an inflammatory disease by administering to the subject a composition containing a therapeutically effective amount of at least one compound of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')). In certain embodiments, the inflammatory disease is, e.g., asthma, appendicitis, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, hepatitis, hidradenitis suppurativa, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis, or vulvitis. When used for the treatment of an inflammatory disease, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V'))can be administered as single agents. Alternatively, when used for the treatment of an inflammatory disease, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')) can be administered in combination with other agents known to be useful for the treatment of inflammatory diseases.

Other embodiments of the disclosure are directed to methods of treating a subject suffering from cancer by administering to the subject a composition containing a therapeutically effective amount of at least one compound of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')). In one embodiment, the cancer is a B-cell proliferative disorder, e.g., diffuse large B cell lymphoma, follicular lymphoma, chronic

lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, or lymphomatoid granulomatosis. Cancers that are particularly suited to being treated with compounds of the disclosure include mantle cell lymphoma and chronic lymphocytic leukemia and macroglobulinemia, as well as multiple myeloma. In some embodiments, where the subject is suffering from a cancer, an anti-cancer agent is administered to the subject in addition to one of the above-mentioned compounds. In one embodiment, the anti-cancer agent is an inhibitor of mitogen-activated protein kinase signaling, e.g., U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002. When used for the treatment of cancer, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')) can be administered as single agents. Alternatively, when used for the treatment of cancer, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')) can be administered in combination with other agents known to be useful for the treatment of cancer.

Other embodiments of the disclosure are directed to methods of treating a subject suffering from a thromboembolic disorder by administering to the subject a composition containing a therapeutically effective amount of at least one compound of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')). In further embodiments, thromboembolic disorder is, e.g., myocardial infarct, angina pectoris, reocclusion after angioplasty, restenosis after angioplasty, reocclusion after aortocoronary bypass, restenosis after aortocoronary bypass, stroke, transitory ischemia, a peripheral arterial occlusive disorder, pulmonary embolism, or deep venous thrombosis. When used for the treatment of a thromboembolic disorder, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')) can be administered as single agents. Alternatively, when used for the treatment of a thromboembolic disorder, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')) can be administered in combination with other agents known to be useful for the treatment of thromboembolic disorders.

Other embodiments of the disclosure are directed to methods of treating a subject suffering from a respiratory disease by administering to the subject a composition containing a therapeutically effective amount of at least one compound of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')). In some aspects, the respiratory disease is asthma. In a further embodiment of this aspect, the respiratory disease includes, but is not limited to, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma. When used for the treatment of a respiratory disease, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')) can be administered as single agents. Alternatively, when used for the treatment of a respiratory disease, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')) can be administered in combination with other agents known to be useful for the treatment of respiratory diseases.

In another aspect are methods for preventing rheumatoid arthritis and osteoarthritis comprising administering to the subject, at least once, an effective amount of at least one compound of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')). When used for the treatment of rheumatoid arthritis or osteoarthritis, the compounds of Formula (I) can be administered as single agents. Alternatively, when used for the treatment of rheumatoid arthritis or osteoarthritis, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')) can be administered in combination with other agents known to be useful for the treatment of rheumatoid arthritis or osteoarthritis.

In another aspect are methods for treating inflammatory responses of the skin comprising administering to the subject, at least once, an effective amount of at least one compound of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')). Such inflammatory responses of the skin include, by way of example, dermatitis, contact dermatitis, eczema, urticaria, rosacea, and scarring. In another aspect are methods for reducing psoriatic lesions in the skin, joints, or other tissues or organs, comprising administering to the mammal an effective amount of a compound of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')). When used for the treatment of these conditions, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'),

Formula (IV') and Formula (V')) can be administered as single agents. Alternatively, when used for the treatment of these conditions, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')) can be administered in combination with other agents known to be useful for the treatment of these conditions.

In preferred aspects, compounds of the disclosure can be used to treat rheumatoid arthritis.

Compounds of the disclosure can also be used to treat systemic lupus erythematosus.

Compounds of the disclosure can also be used to treat pemphigus disorders and pemphigoid disorders.

In some aspects, the compounds of Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (V')) can be administered in combination with a CYP 3A4 inhibitor, according to methods known in the art.

In treatment methods according to the disclosure, an effective amount of a pharmaceutical agent according to the disclosure is administered to a subject suffering from or diagnosed as having such a disease, disorder, or condition. An "effective amount" means an amount or dose sufficient to generally bring about the desired therapeutic benefit in patients in need of such treatment for the designated disease, disorder, or condition. Effective amounts or doses of the compounds of the present disclosure may be ascertained by routine methods such as modeling, dose escalation studies or clinical trials, and by taking into consideration routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the compound, the severity and course of the disease, disorder, or condition, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the treating physician. An example of a dose is in the range of from about 0.001 to about 200 mg of compound per kg of subject's body weight per day, preferably about 0.05 to 100 mg/kg/day, or about 1 to 35 mg/kg/day, in single or divided dosage units (e.g., BID, TID, QID). For a 70-kg human, an illustrative range for a suitable dosage amount is from about 0.05 to about 7 g/day, or about 0.2 to about 2.5 g/day.

In addition, the compounds of the disclosure may be used in combination with additional active ingredients in the treatment of the above conditions. The additional active ingredients may be coadministered separately with a compound of the disclosure or included with such an agent in a pharmaceutical composition according to the disclosure. The combination may serve to increase efficacy (e.g., by including in the combination a compound potentiating the potency or

effectiveness of an active agent according to the disclosure), decrease one or more side effects, or decrease the required dose of the active agent according to the disclosure.

The compounds of the disclosure are used, alone or in combination with one or more additional active ingredients, to formulate pharmaceutical compositions of the disclosure. A pharmaceutical composition of the disclosure comprises: (a) an effective amount of at least one compound in accordance with the disclosure; and (b) a pharmaceutically acceptable excipient.

Delivery forms of the pharmaceutical compositions containing one or more dosage units of the active agents may be prepared using suitable pharmaceutical excipients and compounding techniques known or that become available to those skilled in the art. The compositions may be administered in the inventive methods by a suitable route of delivery, e.g., oral, parenteral, rectal, topical, or ocular routes, or by inhalation.

The preparation may be in the form of tablets, capsules, sachets, dragees, powders, granules, lozenges, powders for reconstitution, liquid preparations, or suppositories. Preferably, the compositions are formulated for intravenous infusion, topical administration, or oral administration.

For oral administration, the compounds of the disclosure can be provided in the form of tablets or capsules, or as a solution, emulsion, or suspension. To prepare the oral compositions, the compounds may be formulated to yield a dosage of, e.g., from about 0.05 to about 100 mg/kg daily, or from about 0.05 to about 35 mg/kg daily, or from about 0.1 to about 10 mg/kg daily. For example, a total daily dosage of about 5 mg to 5 g daily may be accomplished by dosing once, twice, three, or four times per day.

Oral tablets may include a compound according to the disclosure mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like. Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinyl-pyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, may be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating.

Capsules for oral administration include hard and soft gelatin capsules. To prepare hard gelatin capsules, compounds of the disclosure may be mixed with a solid, semi-solid, or liquid diluent. Soft gelatin capsules may be prepared by mixing the compound of the disclosure with water, an oil such as peanut oil or olive oil, liquid paraffin, a mixture of mono and di-glycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol.

Liquids for oral administration may be in the form of suspensions, solutions, emulsions or syrups or may be lyophilized or presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may optionally contain: pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, e.g., oil (for example, almond oil or fractionated coconut oil), propylene glycol, ethyl alcohol, or water; preservatives (for example, methyl or propyl p-hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if desired, flavoring or coloring agents.

The active agents of this disclosure may also be administered by non-oral routes. For example, the compositions may be formulated for rectal administration as a suppository. For parenteral use, including intravenous, intramuscular, intraperitoneal, or subcutaneous routes, the compounds of the disclosure may be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity or in parenterally acceptable oil. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Such forms will be presented in unit-dose form such as ampules or disposable injection devices, in multi-dose forms such as vials from which the appropriate dose may be withdrawn, or in a solid form or pre-concentrate that can be used to prepare an injectable formulation. Illustrative infusion doses may range from about 1 to 1000 .mu.g/kg/minute of compound, admixed with a pharmaceutical carrier over a period ranging from several minutes to several days.

For topical administration, the compounds may be mixed with a pharmaceutical carrier at a concentration of about 0.1% to about 10% of drug to vehicle. Another mode of administering the compounds of the disclosure may utilize a patch formulation to affect transdermal delivery.

Compounds of the disclosure may alternatively be administered in methods of this disclosure by inhalation, via the nasal or oral routes, e.g., in a spray formulation also containing a suitable carrier.

Exemplary compounds useful in methods of the disclosure will now be described by reference to the illustrative synthetic schemes for their general preparation below and the specific

examples that follow. Artisans will recognize that, to obtain the various compounds herein, starting materials may be suitably selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent. Unless otherwise specified, the variables are as defined above in reference to Formula (I)(as well as Formula (I'), Formula (II'), Formula (III'), Formula (IV') and Formula (IV')). Reactions may be performed between the melting point and the reflux temperature of the solvent, and preferably between 0 °C and the reflux temperature of the solvent. Reactions may be heated employing conventional heating or microwave heating. Reactions may also be conducted in sealed pressure vessels above the normal reflux temperature of the solvent.

Compounds of the disclosure can be prepared using the knowledge of one skilled in the art in combination with the present disclosure. For example, compounds of the disclosure can be prepared according to the following schemes and examples.

Abbreviations

Table 1. Abbreviations and acronyms used herein include the following.

Table 1.

Term	Acronym/Abbreviation
Acetonitrile	ACN, MeCN
tert-Butylcarbamoyl	BOC
Di-tert-butyl dicarbonate	$(Boc)_2O$
Benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate	BOP
1,1'-Carbonyldiimidazole	CDI
Diatomaceous Earth	Celite® 545,
(1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate	COMU®

Term	Acronym/Abbreviation
1,8-Diazabicyclo[5.4.0]undec-7-ene	DBU
Methylene chloride, dichloromethane	DCM
Diisopropyl azodiformate	DIAD
N, *N*-Diisopropylethylamine	DIPEA, DIEA, Hunig's base
N,*N*-Dimethylformamide	DMF
4-Dimethylaminopyridine	DMAP
Dimethyl sulfoxide	DMSO
Deutero-dimethyl sulfoxide	DMSO-d_6
Diphenylphosphino ferrocene	dppf
Bis[(2-diphenylphosphino)phenyl] ether	DPEphos
Di-*tert*-butylphosphino ferrocene	dtbpf
1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide	EDCI, EDC, EDAC
Electrospray Ionisation	ESI
Ethyl Acetate	EtOAc, or EA, or AcOEt
Ethanol	EtOH
Flash Column Chromatography	FCC
2-(1H-9-Azobenzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate	HATU
Acetic Acid	HOAc, AcOH
1-Hydroxy-7-azabenzotriazole	HOAT, HOAt

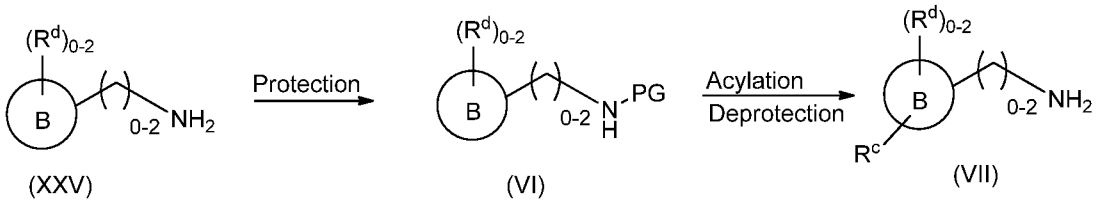
Term	Acronym/Abbreviation
1-Hydroxy-benzotriazole	HOBt
High-pressure liquid chromatography	HPLC
Isopropyl Alcohol	IPA
Deteromethanol	MeOD-d_4
Methanol	MeOH
Methanesulfonyl chloride	MsCl
Methyl tert-butyl ether	MTBE
Sodium methoxide	NaOMe
Tetrakis(triphenylphosphine)palladium(0)	$Pd(PPh_3)_4$
Palladium(II) acetate	$Pd(OAc)_2$
[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)	$Pd(dppf)Cl_2$
Palladium(II)bis(triphenylphosphine) dichloride, bis(triphenylphosphine)palladium(II) dichloride	$PdCl_2(PPh_3)_2$
Triphenylphosphine	PPh_3
Precipitate	ppt
p-Toluenesulfonic acid	*p*-TsOH, PTSA
(benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate)	PyBOP
Bromotripyrrolidinophosphonium hexafluorophosphate	PyBrOP®
Room temperature	rt
Supercritical Fluid Chromatography	SFC
Thionyl chloride	$SOCl_2$

Term	Acronym/Abbreviation
Tetrabutylammonium fluoride	TBAF
tert-Butyl(chloro)dimethylsilane	TBSCl
Triethyl amine	TEA
Trifluoroacetic acid	TFA
Trifluoroacetic anhydride	TFAA
Tetrahydrofuran	THF
Thin Layer Chromatography	TLC

PREPARATIVE EXAMPLES

Exemplary compounds useful in methods of the disclosure will now be described by reference to the illustrative synthetic schemes for their general preparation below and the specific examples to follow.

SCHEME 1



(XXV) (VI) (VII)

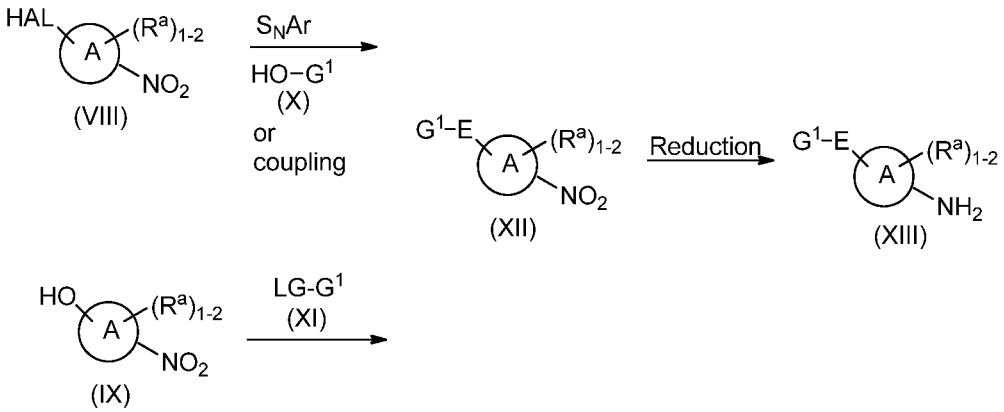
According to SCHEME 1, a compound of formula (VI), where ring B is a C_{4-10}heterocycloalkyl such as azetidinyl, pyrrolidinyl, piperidinyl, and the like; and PG is a suitable nitrogen protecting group such as BOC, is commercially available or is synthetically accessible employing conditions known to one skilled in the art, from a compound of formula (XXV). Acylation of a heterocycloalkyl compound of formula (VI), is achieved with a suitable acylating agent such as the anhydrides and halides of carboxylic acids such as acetic anhydride, propionic anhydride, prop-2-enoyl chloride, C_{1-6}alkyl(C=O)Cl, and the like, in the presence of a suitable base such as TEA, DIPEA, and the like, with or without the presence of a reagent such as DMAP, in a suitable solvent such as THF, DCM, and the like, at temperatures ranging from 0 °C to 25 °C, for a period of 2 to 6 h. Subsequent deprotection of the *tert*-butylcarbamate (BOC)

protecting group (PG), is accomplished by using an acid such as HCl, TFA, p-toluenesulfonic acid, in a solvent sich as MeOH, dioxane, or DCM. In a preferred embodiment, deprotection is achieved with HCl/MeOH or TFA/DCM, to provide a compound of formula (VII).

A compound of formula (VI), where ring B is a C_{5-6}cycloalkyl, and Y is NH_2 is prepared from a compound of formula (VI), where ring B is a C_{5-6}cycloalkyl, and Y is OH under Mitsonobu conditions. In two steps, reaction of a compound of formula (VI), where Y is OH, with triphenylphosphane, DIAD, and, phthalimide, followed by hydrazinolysis with hydrazine hydrate in a solvent such as EtOH, provides a compound of formula (VI), where ring B is a C_{5-6}cycloalkyl, PG is BOC, and Y is NH_2.

A compound of formula (VI), where ring B is a C_{5-6}cycloalkyl, PG is BOC, and Y is CO_2H, is reacted with diphenyl phosphorazidate (DPPA), phenylmethanol, and a base such as TEA, in a solvent such as toluene, at a temperature of about 100 °C, for a period of 18-24 h, to provide a compound (VI) where PG is BOC, and Y is NH-(C=O)OCH_2phenyl. Deprotection of the CBz, under conditions known to one skilled in the art, for example, hydrogenation using (H_2, 30 psi) using $Pd(OH)_2$, affords a compound of formula (VI), where PG is BOC, and Y is NH_2.

SCHEME 2



According to SCHEME 2, a synthetically accessible or commercially available compound of formula (VIII), where A is phenyl, or a six membered heteroaryl ring containing one or two nitrogen members, HAL is Br or F, and R^a is independently H, halogen, and CH_3, is reacted in an aromatic nucleophilic substitution reaction with a commercially available or synthetically accessible alcohol of formula G^1-OH (X), where G^1 is phenyl, C_{3-6}cycloalkyl, or C_{1-6}alkyl, a suitable base such as NaH, Na_2CO_3, $NaHCO_3$, K_2CO_3, Cs_2CO_3, and the like, in a

suitable solvent such as DMF, DMA, THF, dioxane, and the like, to provide a compound of formula (XII), where E is O.

In an alternate method, a compound of formula (XII), where E is O, is prepared from a compound of formula (VIII), where HAL is F, and R^a is OH, in a coupling reaction. For example, reaction of a compound of formula (VIII) with a commercially available or synthetically accessible aryl or heteroaryl boronic acid or ester such as phenyl boronic acid a metal catalyst such as copper (II) acetate, a base such as trimethylamine, in a solvent such as DCM, and the like, for a period of about 16 h, provides a compound of formula (XII) where R^a is F and E is O.

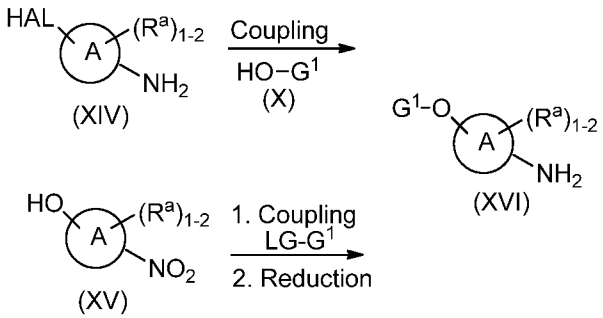
A compound of formula (IX), where R^a is C_{1-6}alkyl, is reacted with a commercially available or synthetically accessible compound of formula LG-G^1 (XI), where LG is a leaving group such as Cl, Br, I, or methanesulfonate, and G^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl, a suitable base such as NaH, Na_2CO_3, $NaHCO_3$, K_2CO_3, Cs_2CO_3, and the like, in a suitable solvent such as DMF, DMA, THF, dioxane, and the like, to provide a compound of formula (XII), where E is O, and G^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl.

A compound of formula (XII), where ring A is pyridyl, E is N-PG, and G^1 is C_{1-6}alkyl, is prepared from a compound of formula (VII), where HAL is Cl, and R^a is C_{1-6}alkyl. For example, 2-chloro-4-methyl-5-nitropyridine is reacted with an amine such as propan-2-amine, followed by reaction with DMAP, di-tert-butyl dicarbonate, in a solvent such as THF, to provide a compound of formula (XII), where ring A is pyridyl, E is N, substituted with a protecting group (BOC), and G^1 is C_{1-6}alkyl.

Reduction of the nitro moiety of a compound of formula (XII), where E is O or N-PG, G^1 is phenyl, C_{1-6}alkyl, C_{3-6}cycloalkyl, pyridyl, employing conditions known to one skilled in the art, for example, reduction with iron (Fe), in a solvent such as EtOH/water, in the presence of NH_4Cl or concentrated HCl, at a temperatures ranging from 0 °C to 25 °C, for a period of 2 to 6 h, provides the corresponding aniline of formula (XIII). Reduction of a nitro compound of formula (VII), is also achieved using hydrogenation conditions, for example, reaction with a palladium catalyst such as Pd/C, $Pd(OH)_2$, Pt/C and the like, in a suitable solvent such as THF, MeOH, EtOAc, or a mixture thereof, in the presence of H_2 (for example at atmospheric pressure or at 30 to 50 PSI), at temperatures ranging from rt to 50 °C, to provide an amine compound of formula (XIII). Reduction of a nitro compound of formula (XII), is also achieved employing Zn, ammonium chloride, in a suitable solvent or solvent mixture such as acetone/water, at a

temperature ranging from 0 °C to rt, for a period of about 2-6 h, to provide an amine compound of formula (XIII).

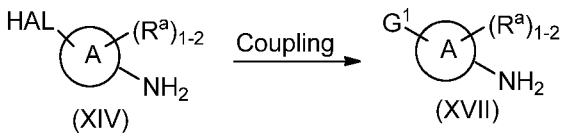
SCHEME 3



According to SCHEME 3, a compound of formula (XIV), where ring A is a suitably substituted phenyl or heteroaryl containing 1-2 nitrogen members, and HAL is I, Cl, or Br, and R^a is C_{1-6}alkyl, is reacted in a Copper-Catalyzed Cross-Coupling reaction with a compound of formula G^1-OH, where G^1 is phenyl, or heteroaryl containing 1-2 nitrogen members. For example, a compound of formula (XV) such as 2-chloro-4-methylpyrimidin-5-amine, is reacted with a compound of formula (X), such as phenol, a copper catalyst such as Cu, CuI, and the like, *N,N*-dimethylglycine, a base such as K_2CO_3, Cs_2CO_3, and the like, in a suitable solvent such as dioxane, DMSO, and the like, at a temperature of about 90 °C, for a period of 1 to 3 days, provides 4-methyl-2-phenoxypyrimidin-5-amine. In an alternate method, coupling reactions are performed in the absence of a catalyst, employing microwave or conventional heating, with a base such as K_2CO_3, in a solvent such as DMSO.

A compound of formula (XVI) is also prepared from a compound of formula (IX) in two steps. In a first step, coupling with a compound of formula (IX), where ring A is phenyl, or a heteroaryl ring containing 1-2 nitrogen members, R^a is C_{1-6}alkyl, is reacted with a compound of formula LG-G^1, where LG is Cl, and G^1 is C_{1-6}alkyl, phenyl, or 6 membered heteroaryl ring containing 1 to 2 nitrogen members as previously described. In a second step, reduction of the nitro moiety employing conditions known to one of skill in the art provides a compound of formula (XVI).

SCHEME 4

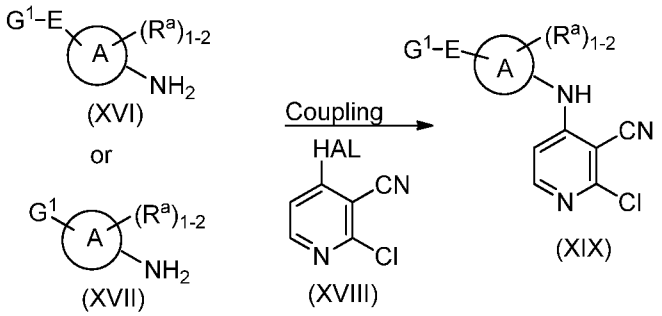


According to SCHEME 4, an aryl halide compound of formula (XIV), where ring A is phenyl, or a heteroaryl ring containing 1-2 nitrogen members, HAL is Cl, Br, and R^a is H or C_{1-}

$_{6}$alkyl, undergo a transition metal catalyzed cross-coupling reaction such as Suziki, Negishi, and Grignard reactions. For example, reaction of a compound of formula (XIV) with a commercially available or synthetically accessible alkyl or aryl boronic acid or ester, in the presence of a suitable palladium catalyst such as $Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd(dppf)Cl_2$, and the like, a base such as Cs_2CO_3, K_2CO_3, Na_2CO_3, and the like, in a suitable solvent such as ACN, THF, MeOH, EtOH, toluene, dioxane, water, or a mixture thereof, employing conventional or microwave heating, at temperatures ranging from 80 °C to 120 °C, for a period of 12, to 24 h, to provide a compound of formula (XVII), where G^1 is C_{1-6}alkyl, or phenyl.

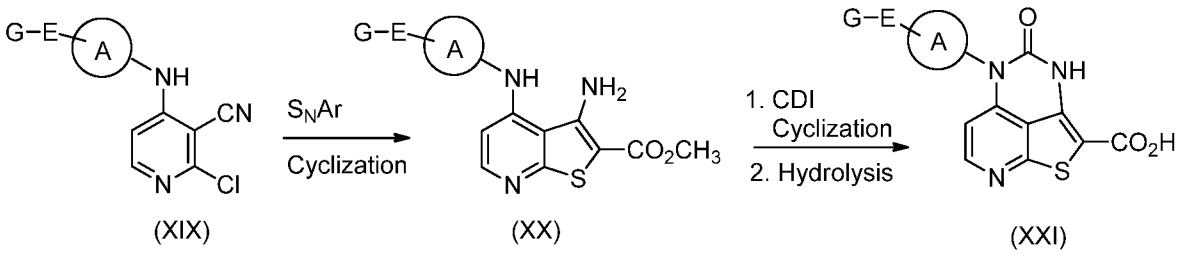
In a similar fashion, an aryl an aryl halide compound of formula (XIV), where ring A is phenyl, or a heteroaryl ring containing 1-2 nitrogen members, HAL is Cl, Br, and R^a is H or C_{1-6}alkyl, is reacted with a Grignard reagent such as such as isopropylmagnisium chloride, or an organozinc reagent such as isobutylzinc(II) bromide, cyclobutylzinc(II) bromide, and the like, in the presence of a palladium catalyst such as $Pd(dppf)Cl_2 \cdot DCM$, $Pd(dppf)_2Cl_2$, and the like, in a suitable solvent such THF, at temperatures ranging from -78 °C to the reflux temperature of the solvent, to provide a compound of formula (XVII), where G^1 is C_{1-6}alkyl.

SCHEME 5



According to SCHEME 5, aryl halides of formula (XVIII), where HAL is I, Cl or Br, undergo a palladium catalyzed arylation with a compound of formula (XVI) or (XVII), where G^1 is phenyl, and C_{3-6}cycloalkyl, R^a is H or C_{1-6}alkyl, in the presence of a palladium catalyst such as $Pd(OAc)_2$, $Pd_2(dba)_3$, and the like, a ligand such as Xantphos, S-Phos, BINAP, DPEPhos, a suitable base such as NaOtBu, Cs_2CO_3, K_3PO_4, and the like, in a suitable solvent such as ACN, THF, toluene, dioxane, and the like, employing conventional or microwave heating, at temperatures ranging from 60 to 120 °C, to provide a compound of formula (XIX), where E is a bond, or O.

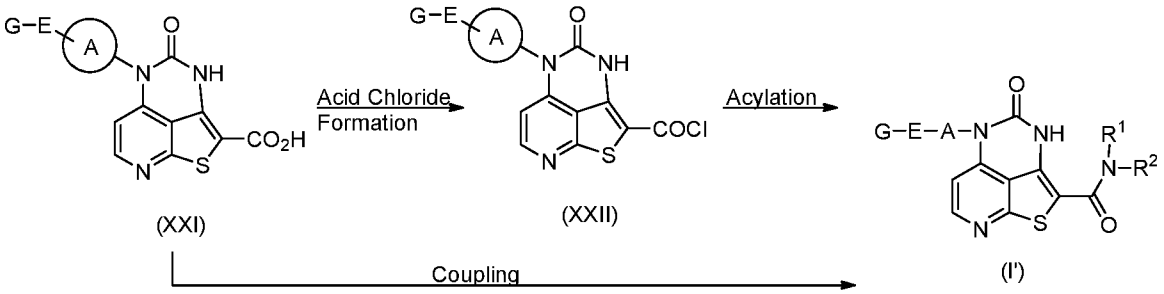
SCHEME 6



(XIX) (XX) (XXI)

According to SCHEME 6, a nitrile compound of formula (XIX) is reacted in a nucleophilic aromatic substitution reaction with ethyl thioacetate, under basic conditions, followed by ring closure, to afford a thienopyridine-carboxylate compound of formula (XX). A compound of formula (XXI) is prepared in two steps from a compound of formula (XX). In a first step, reaction of a compound of formula (XX) with CDI; in suitable solvent such as 1,dioxane, and the like; at reflux temperature; for a period of 12-24 h. In a second step, hydrolysis of the ester moiety, with a suitable base such as NaOH, LiOH, and the like, in a solvent such as MeOH, and the like, at temperatures ranging from rt to 50 °C, for a period of 12 to 24 h, affords an acid compound of formula (XXI).

SCHEME 7



(XXI) (XXII) (I')

According to SCHEME 7, an acid compound of fomula (XXI), as described above, is first converted to an acid chloride compound of formula (XXII). For example, a compound of formula (XXI) is treated with a chlorinating agent such as thionyl chloride and the like; in a solvent such as toluene, and the like, to form a compound of formula (XXII).

Coupling reactions are achieved by conventional amide bond forming techniques which are well known to one of skill in the art as depicted in SCHEME 5. For example, an acyl halide (eg, chloride) compound of formula (XXI), is reacted with a suitably substituted commercially available or synthetically accessible amine of formula (XXV), (VI), or (VII) in the presence of an excess of a tertiary amine, such as TEA, pyridine, and the like, optionally in the presence of a suitable catalyst such as DMAP, in a suitable solvent such as DCM or THF, at a temperature ranging from room temperature to the reflux temperature of the solvent, to provide a compound

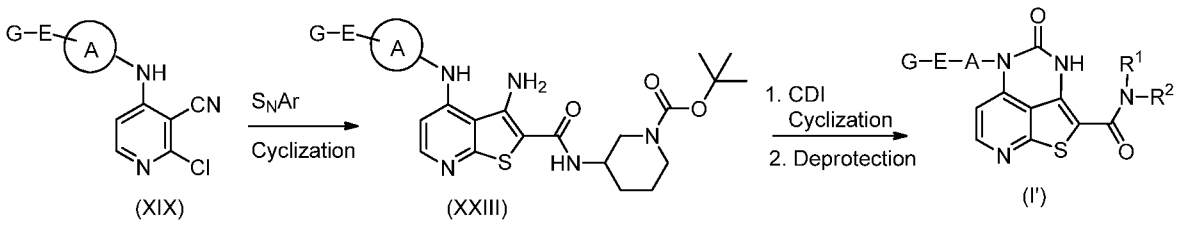
of Formula (I'). A variety of other amino acid coupling methodologies are used to couple the compounds of formula (XXI). Reaction of a suitably substituted commercially available or synthetically accessible amine of formula (XXV), (VI), or (VII); with a suitably substituted acid of formula (XXI) under amide bond forming conditions provides a compound of Formula (I'). In a preferred embodiment, a compound of formula (XXV), (VI), or (VII), either as a free base or as an acid salt, is reacted with an acid compound of formula (XXI), in the presence of a dehydrating agent such as HOBt/EDAC, HATU, HOAT, T3P®, and the like; a suitably selected base such as DIPEA, TEA, and the like; in an organic solvent or mixture thereof such as toluene, acetonitrile, ethyl acetate, DMF, THF, methylene chloride, and the like; to afford a compound of Formula (I'). In a particularly preferred embodiment, the dehydrating agent is HATU and the base is TEA or DIPEA. In cases where the amine compound of formula (XXV), (VI), or (VII) has a *tert*-butylcarbamate (BOC) protecting group (PG), removal of the *tert*-butylcarbamate (BOC) protecting group (PG), is accomplished by using an acid such as HCl, TFA, p-toluenesulfonic acid, in a solvent sich as MeOH, dioxane, or DCM. In a preferred embodiment, deprotection is achieved with HCl/MeOH or TFA/DCM.

A compound of Formula (I'), where R^2 is a suitably substituted C_{4-10}heterocycloalkyl, is reacted under reductive amination conditions with an suitable aldehyde such as formaldehyde, paraformaldehyde, a reducing agent such as $NaBH_4$, $NaBH(OAc)_3$, and the like, in a suitable solvent such as DCM, MeOH, THF, and the like, to afford a compound of Formula (I'), where R^2 is C_{4-10}heterocycloalkyl substituted with CH_3.

A compound of Formula (I'), where R^2 is C_{4-10}heterocycloalkyl, is reacted with acylating agent such as the anhydrides and halides of carboxylic acids such as acetic anhydride, prop-2-enoyl prop-2-enoate, propionic anhydride, C_{1-6}alkyl(C=O)Cl, and the like, under conditions previously described, to provide a compound of Formula (I'), where R^2 is C_{4-10}heterocycloalkyl substituted with $(C=O)C_{1-3}$alkyl, and $(C=O)C_{1-3}$alkenyl.

A compound of Formula (I'), where R^2 is C_{4-10}heterocycloalkyl is reacted with a suitable acid of such as CO_2H-C_{1-6}alkyl-N(R^6R^7), 2-(dimethylamino)acetic acid, cyanoacetic acid, Boc-sarcosine, 2-(*tert*-butoxycarbonylamino)acetic acid, (*E*)-4-(dimethylamino)but-2-enoic acid, acrylic acid, and the like, under amide bond forming conditions previously described conditions to provide a compound of Formula (I'). A deprotection step, employing conditions previously described is employed where applicable.

SCHEME 8



(XIX) (XXIII) (I')

According to SCHEME 8, a nitrile compound of formula (XIX) is reacted in a nucleophilic aromatic substitution reaction with *tert*-butyl -[(2-sulfanylacetyl)amino]piperidine-1-carboxylate, in a sealed vessel under high heat such as 150 °C for a period of time form 15 min to 1 hr, followed by ring closure, to afford a thienopyridine-carboxamide compound of formula (XXIII). A compound of Formula (I') is prepared in two steps from a compound of formula (XXIII). In a first step, reaction of a compound of formula (XXIII) with CDI; in suitable solvent such as dioxane, and the like; at reflux temperature; for a period of 12-24 h. In a second step, deprotection of the amine moiety, with a suitable acid such as HCl or TFA, and the like, in a solvent such as dioxane, and the like, at temperatures ranging from rt to 40 °C, for a period of 30 min to 24 h, affords an amine compound of Formula (I').

Compounds of Formula (I') may be converted to their corresponding salts using methods known to one of ordinary skill in the art. For example, an amine of Formula (I') is treated with trifluoroacetic acid, HCl, or citric acid in a solvent such as Et_2O, CH_2Cl_2, THF, MeOH, chloroform, or isopropanol to provide the corresponding salt form. Alternately, trifluoroacetic acid or formic acid salts are obtained as a result of reverse phase HPLC purification conditions. Cyrstalline forms of pharmaceutically acceptable salts of compounds of Formula (I') may be obtained in crystalline form by recrystallization from polar solvents (including mixtures of polar solvents and aqueous mixtures of polar solvents) or from non-polar solvents (including mixtures of non-polar solvents).

Where the compounds according to this disclosure have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present disclosure.

Compounds prepared according to the schemes described above may be obtained as single forms, such as single enantiomers, by form-specific synthesis, or by resolution. Compounds prepared according to the schemes above may alternately be obtained as mixtures of various forms, such as racemic (1:1) or non-racemic (not 1:1) mixtures. Where racemic and non-racemic mixtures of enantiomers are obtained, single enantiomers may be isolated using

conventional separation methods known to one of ordinary skill in the art, such as chiral chromatography, recrystallization, diastereomeric salt formation, derivatization into diastereomeric adducts, biotransformation, or enzymatic transformation. Where regioisomeric or diastereomeric mixtures are obtained, as applicable, single isomers may be separated using conventional methods such as chromatography or crystallization.

The following specific examples are provided to further illustrate the disclosure and various preferred embodiments.

EXAMPLES

In obtaining the compounds described in the examples below and the corresponding analytical data, the following experimental and analytical protocols were followed unless otherwise indicated.

Unless otherwise stated, reaction mixtures were magnetically stirred at rt (rt) under a nitrogen atmosphere. Where solutions were "dried," they were generally dried over a drying agent such as Na_2SO_4 or $MgSO_4$. Where mixtures, solutions, and extracts were "concentrated", they were typically concentrated on a rotary evaporator under reduced pressure. Reactions under microwave irradiation conditions were carried out in a Biotage Initiator or CEM (Microwave Reactor) Discover instrument.

Normal-phase silica gel chromatography (FCC) was performed on silica gel (SiO_2) using prepacked cartridges.

Preparative reverse-phase high performance liquid chromatography (RP HPLC) was performed on either:

An Agilent HPLC with an Xterra Prep RP18 column (5 μM, 30 x 100 or 50 x 150mm) or an XBridge C18 OBD column (5 μM, 30 x 100 or 50 x 150mm), and a mobile phase of 5% ACN in 20mM NH_4OH was held for 2 min, then a gradient of 5-99% ACN over 15 min, then held at 99% ACN for 5 min, with a flow rate of 40 or 80 mL/min.

or

A Shimadzu LC-8A Series HPLC with an Inertsil ODS-3 column (3 μm, 30 x 100mm, T = 45 °C), mobile phase of 5% ACN in H_2O (both with 0.05% TFA) was held for 1 min, then a gradient of 5-99% ACN over 6 min, then held at 99% ACN for 3 min, with a flow rate of 80 mL/min.

or

A Shimadzu LC-8A Series HPLC with an XBridge C18 OBD column (5 µm, 50 x 100mm), mobile phase of 5% ACN in H_2O (both with 0.05% TFA) was held for 1 min, then a gradient of 5-99% ACN over 14 min, then held at 99% ACN for 10 min, with a flow rate of 80 mL/min.

or

A Gilson HPLC with an XBridge C18 column (5µm, 100 x 50mm), mobile phase of 5-99% ACN in 20 mM NH_4OH over 10 min and then hold at 99 ACN for 2 min, at a flow rate of 80 mL/min.

Quality control testing includes identity, chemical, and radiochemical purity by HPLC using an XBridge C18 (5µm, 4.6 x 250 mm) column eluted with a mixture of methanol/ammonium acetate 5 mM, 65/35, v/v at a flow rate of 1 mL/min equipped with serial UV (280 nm) and gamma detection.

Preparative supercritical fluid high performance liquid chromatography (SFC) was performed either on a Jasco preparative SFC system, an APS 1010 system from Berger instruments, or a SFC-PICLAB-PREP 200 (PIC SOLUTION, Avignon, France). The separations were conducted at 100-150 bar with a flow rate ranging from 40-60 mL/min. The column was heated to 35-40 °C.

Mass spectra (MS) were obtained on an Agilent series 1100 MSD using electrospray ionization (ESI) in positive mode unless otherwise indicated. Calculated (calcd.) mass corresponds to the exact mass.

Nuclear magnetic resonance (NMR) spectra were obtained on Bruker model DRX spectrometers. Definitions for multiplicity are as follows: s = singlet, d = doublet, t= triplet, q = quartet, m = multiplet, br = broad. It will be understood that for compounds comprising an exchangeable proton, said proton may or may not be visible on an NMR spectrum depending on the choice of solvent used for running the NMR spectrum and the concentration of the compound in the solution.

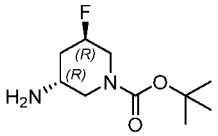
Chemical names were generated using ChemDraw Ultra 12.0, ChemDraw Ultra 14.0 (CambridgeSoft Corp., Cambridge, MA) or ACD/Name Version 10.01 (Advanced Chemistry).

Compounds designated as R* or S* are enantiopure compounds where the absolute configuration was not determined.

Chiral Resolution Method A. The atropisomers were chromatographed to isolate the two separate atropisomers, with the respective single atropisomers arbitrarily labeled as *S or *R to

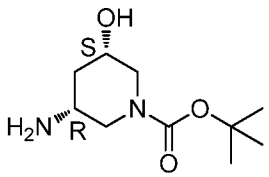
indicate that the compound is a single atropisomer of unknown absolute configuration. In cases for which absolute configuration of a single atropisomeric compound was determined, the atropisomers are named as either *S* or *R* throughout (with *S* corresponding to the alternate designations *aS*, S_a, or *P;* and with *R* corresponding to the alternate designations *aR*, R_a, or *M*). The purification was performed on a chiral SFC column (Stationary phase: Whelk O1 (*S,S*), 5 μm, 250 × 21.1mm column. The mobile phase was: 40% CO_2, 60% MeOH (0.2% formic acid).

Intermediate 1: *tert*-Butyl (3*R*,5*R*)-3-amino-5-fluoropiperidine-1-carboxylate.



A mixture of (3*R*,5*S*)-*tert*-butyl 3-azido-5-hydroxypiperidine-1-carboxylate (Intermediate 2, Step I) (1.5g, 6.19 mmol) in DCM at -78 °C was reacted by slow addition of DAST (1.2 g, 7.43 mmol). The reaction solution was stirred at -78 °C for 2 h and at rt for 16 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The organic layer was separated, washed with aqueous $NaHCO_3$ solution, water, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was reduced using conditions analogous to step J of Intermediate 2 to yield the title compound (660 mg, 44%) MS (ESI): mass calcd. for $C_{10}H_{19}FN_2O_2$, 218.1; m/z found, 219.1 $[M+H]^+$.

Intermediate 2: *tert*-Butyl (3R,5S)-3-amino-5-hydroxypiperidine-1-carboxylate.



Step A: (2*R*,4*S*)-Methyl 1-benzyl-4-hydroxypyrrolidine-2-carboxylate. To a round bottom flask were added methyl (2*R*,4*S*)-4-hydroxypyrrolidine-2-carboxylate (12 g, 83 mmol) and DCM (150 mL). To the reaction mixture were added triethylamine (33.3 g, 330 mmol) and benzylbromide (17 g, 99 mmol) at rt, and then was heated to reflux for 16 h. The reaction mixture was washed with saturated $NaHCO_3$, extracted with EtOAc, and dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound (9.2 g, 42%) as a colorless oil. MS (ESI): mass calcd. for $C_{10}H_{20}N_2O_3$, 216.1; m/z found, 217.1$[M+H]^+$.

Step B: (2*R*,4*S*)-Methyl 1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate. To a round bottom flask were added (2*R*,4*S*)-methyl 1-benzyl-4-hydroxypyrrolidine-2-carboxylate (9.2 g, 39 mmol), DCM (200 mL), triethylamine (7.90 g, 7.82 mmol), TBSCl (7.07 g, 47.0 mmol), and DMAP (48 mg, 0.39 mmol) at rt. The reaction mixture was heated to reflux for 16 h, cooled to rt, washed with saturated $NaHCO_3$, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound (13 g, 40%) as a colorless oil. MS (ESI): mass calcd. for $C_{19}H_{31}NO_3Si$, 349.2; m/z found, 350.1 $[M+H]^+$.

Step C: ((2*R*,4*S*)-1-Benzyl-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidin-2-yl)methanol. To a round bottom flask were added (2*R*,4*S*)-methyl 1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate (13 g, 37 mmol), THF (50 mL), and $LiBH_4$ (2.0 g, 93 mmol) at 0 °C. The reaction was allowed to warm to rt and was stirred for an additional 16 hrs at rt. The reaction mixture was washed with saturated $NaHCO_3$, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to obtain the title compound (6 g, 50%) as a yellow oil. MS (ESI): mass calcd. for $C_{18}H_{31}NO_2Si$, 321.2; m/z found, 322.1 $[M+H]^+$.

Step D: (3*S*,5*S*)-1-Benzyl-5-((*tert*-butyldimethylsilyl)oxy)piperidin-3-ol. To a round bottom flask were added ((2*R*,4*S*)-1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidin-2-yl)methanol (6.0 g, 19 mmol), THF (20 mL), and triethylamine (5.7 mL, 28 mmol). The reaction mixture was cooled to 0 °C and to this was added TFAA (5.9 g, 28 mmol). The reaction mixture was allowed to warm to rt and was reacted at rt for 16 h. The reaction mixture was washed with saturated $NaHCO_3$, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound (3 g, 50%) as a yellow oil. MS (ESI): mass calcd. for $C_{18}H_{31}NO_2Si$, 321.2.1; m/z found, 322.0 $[M+H]^+$.

Step E: (3*S*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)piperidin-3-ol. To a round bottom flask were added (3*S*,5*S*)-1-benzyl-5-((*tert*-butyldimethylsilyl)oxy)piperidin-3-ol (3.0 g, 9.3 mmol), EtOH (20 mL), and Pd/C (10% on activated carbon, 600 mg). To the reaction mixture was added H_2 and was reacted at rt for 16 h. The reaction mixture was filtered and concentrated to dryness to yield the title compound (2.4 g, quantitative) as a yellow oil. MS (ESI): mass calcd. for $C_{11}H_{25}NO_2Si$, 231.2; m/z found, 232.2 $[M+H]^+$.

Step F: *tert*-Butyl (3*S*,5*S*)-3-[*tert*-butyl(dimethyl)silyl]oxy-5-hydroxypiperidine-1-carboxylate. To a round bottom flask were added (3*S*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)piperidin-3-ol (2.4

g, 10 mmol), DCM (20 mL), triethylamine (2.1 g, 21 mmol), and $(Boc)_2O$ (2.7 g, 12 mmol) at 0 °C and was reacted at rt for 1 h. The reaction was quenched with saturated $NaHCO_3$, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound (3.3 g, 96%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{33}NO_4Si$, 331.2; m/z found, 332.1 $[M+H]^+$.

Step G: *tert*-Butyl (3*S*,5*S*)-3-[*tert*-butyl(dimethyl)silyl]oxy-5-methylsulfonyloxypiperidine-1-carboxylate. To a round bottom flask were added *tert*-butyl (3*S*,5*S*)-3-[*tert*-butyl(dimethyl)silyl]oxy-5-hydroxypiperidine-1-carboxylate (3.3 g, 10 mmol), DCM (20 mL), triethylamine (3 g, 29 mmol), and MsCl (1.7 g, 14.5 mmol) at 0 °C. The reaction mixture was allowed to warm to rt and was reacted at rt for 2 h. The reaction was quenched with saturated $NaHCO_3$, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield the title compound (4 g, 98%) as a yellow oil. MS (ESI): mass calcd. for $C_{17}H_{35}NO_6SSi$, 409.2; m/z found, 410.1 $[M+H]^+$.

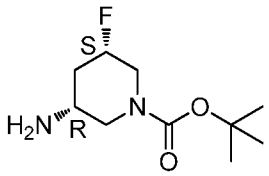
Step H: (3*R*,5*S*)-*tert*-Butyl 3-azido-5-((*tert*-butyldimethylsilyl)oxy)piperidine-1-carboxylate. To a round bottom flask were added *tert*-butyl (3*S*,5*S*)-3-[*tert*-butyl(dimethyl)silyl]oxy-5-methylsulfonyloxypiperidine-1-carboxylate (3.6 g, 8.8 mmol), DMF (20 mL), and NaN_3 (1.7 g, 26 mmol) at rt. The reaction was reacted at 70 °C for 72 h. The reaction was quenched with saturated $NaHCO_3$, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound (3.0 g, 96%) as a yellow oil.

Step I: (3*R*,5*S*)-*tert*-Butyl 3-azido-5-hydroxypiperidine-1-carboxylate. To a round bottom flask were added (3*R*,5*S*)-*tert*-butyl 3-azido-5-((*tert*-butyldimethylsilyl)oxy)piperidine-1-carboxylate (3.0 g, 8.4 mmol), THF (10 mL), and TBAF (1 M solution, 10 mL, 10 mmol) in sequence at 0 °C. The reaction solution was warmed to rt and reacted at rt for 16 h. The reaction was quenched by the addition of water, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated to dryness, and purified by flash column chromatography to yield the title compound (1.4 g, 69%) as a yellow oil. Mass calcd. for $C_{10}H_{18}N_4O_3$, 242.1. ^1H NMR (400 MHz, $CDCl_3$): δ 9.89-3.62 (m, 3H), 3.58-3.31 (m, 1H), 3.08-3.88 (m, 2H), 2.25-2.10 (m, 1H), 1.64-1.51 (m, 1H),1.42 (s, 9H).

Step J: (3*R*,5*S*)-*tert*-Butyl 3-amino-5-hydroxypiperidine-1-carboxylate. A mixture of (3*R*,5*S*)-*tert*-butyl 3-azido-5-hydroxypiperidine-1-carboxylate (500 mg, 2.06 mmol), Pd/C (10% on activated carbon, 200 mg), and MeOH (5 mL) were reacted at rt under H_2 for 16 h. The reaction

mixture was filtered and concentrated to dryness. No further purification (407 mg, 91% yield). MS (ESI): mass calcd. for $C_{10}H_{20}N_2O_3$, 216.1; m/z found, 217.0 $[M+H]^+$.

Intermediate 3: *tert*-Butyl (3R,5S)-3-amino-5-fluoropiperidine-1-carboxylate.

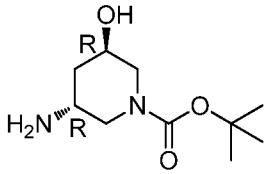


Step A: (3*R*,5*R*)-*tert*-Butyl 3-azido-5-hydroxypiperidine-1-carboxylate. The title compound was prepared using analogous conditions described in steps A-I of Intermediate 2, and using methyl (2*R*,4*R*)-4-hydroxypyrrolidine-2-carboxylate in place of methyl (2R,4S)-4-hydroxypyrrolidine-2-carboxylate in step A.

Step B: (3*R*,5*S*)-*tert*-Butyl 3-azido-5-fluoropiperidine-1-carboxylate. To a solution of (3*R*,5*R*)-*tert*-butyl 3-azido-5-hydroxypiperidine-1-carboxylate (1.5 g, 6.2 mmol) in dry DCM (50 mL) at -78 °C was added DAST (1.2 g, 7.4 mmol) slowly. The reaction solution was stirred at -78 °C for 2 h and at rt for 16 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution and the organic layer was separated and washed with aqueous $NaHCO_3$ solution and water, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound as a colorless oil (660 mg, 44% yield). $C_{10}H_{17}FN_4O_2$. ^1H NMR (400 MHz, $CDCl_3$): δ 4.80 (d, J = 46.5 Hz, 1H), 4.32 – 3.95 (m, 1H), 3.95 – 3.71 (m, 2H), 3.39-2.63 (m, 2H), 2.41-2.12 (m, 1H), 1.86-1.57 (m, 1H), 1.46 (s, 9H).

Step C: (3*R*,5*S*)-*tert*-Butyl 3-amino-5-fluoropiperidine-1-carboxylate. To a solution of (3*R*,5*S*)-*tert*-butyl 3-azido-5-fluoropiperidine-1-carboxylate (660 mg, 2.7 mmol) in MeOH (60 mL) was added Pd/C (10% Pd on C, 130 mg) and the mixture was stirred at rt under H_2 overnight, then filtered and concentrated to dryness to yield the title compound as a yellow oil (450 mg, 76% yield). MS (ESI): mass calcd. for $C_{10}H_{19}FN_2O_2$, 218.1; m/z found, 219.1 $[M+H]^+$.

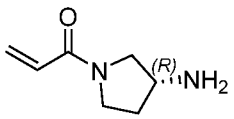
Intermediate 4: *tert*-Butyl (3*R*,5*R*)-3-amino-5-hydroxypiperidine-1-carboxylate.



The title compound was prepared using conditions analogous to Intermediate 2, steps A-J, and using (2R,4R)-4-hydroxypyrrolidine-2-carboxylic acid in place of methyl (2*R*,4*S*)-4-

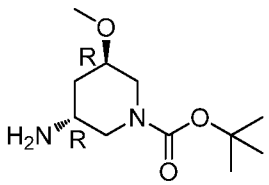
hydroxypyrrolidine-2-carboxylate in step A. MS (ESI): mass calcd. for $C_{10}H_{20}N_2O_3$, 216.1; m/z found, 217.1 $[M+H]^+$.

Intermediate 5: 1-[(3*R*)-3-Aminopyrrolidin-1-yl]prop-2-en-1-one.



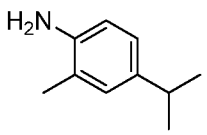
A solution of *tert*-butyl *N*-[(3*R*)-pyrrolidin-3-yl]carbamate (5.0 g, 27 mmol) and DIEA (4.156 g, 32.21 mmol) in DCM (60 mL) was cooled to 0 °C and prop-2-enoyl chloride (2.43 g, 26.8 mmol) was added portion wise and stirred at rt for 1 h. The mixture was concentrated to dryness and purified by flash column chromatography to get pure product, which was dissolved in concentrated HCl (30 mL) and MeOH (30 mL) and was stirred at rt for 0.5 h. The mixture was concentrated to dryness to give the title compound as a yellow oil (3.98 g, 83.9% yield). MS (ESI): mass calcd. for $C_7H_{12}N_2O$, 140.1; m/z found, 141.1 $[M+H]^+$.

Intermediate 6: *tert*-Butyl (3R,5R)-3-amino-5-methoxypiperidine-1-carboxylate.



The title compound was prepared using Method 2, steps A-J, and using (1*R*,3*S*)-3-hydroxycyclopentane carboxylic acid in place of methyl (2*R*,4*S*)-4-hydroxypyrrolidine-2-carboxylate in step A, and at step J, first the methyl ester is formed, followed by reduction to obtain *tert*-butyl (3*R*,5*R*)-3-amino-5-hydroxypiperidine-1-carboxylate. MS (ESI): mass calcd. for $C_{10}H_{20}N_2O_3$: 216.1; m/z found, 217.1 $[M+H]^+$.

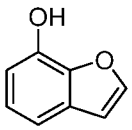
Intermediate 7: 4-Isopropyl-2-methyl-aniline.



To a solution of 4-iodo-2-methyl-aniline (4.0 g, 17 mmol) and $Pd(dppf)_2Cl_2$ (140 mg, 0.17 mmol) in THF (50 mL) was added isopropylmagnisium chloride (25.5 mL, 51.0 mmol) at -78 °C and was reacted at reflux for 4 h. The reaction was quenched with a saturated solution of NH_4Cl, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The

residue was purified by flash column chromatography to give the title compound as a brown solid (320 mg, 12%). MS (ESI): mass calcd. for $C_{10}H_{15}N$, 149.1; m/z found, 150.0 $[M+H]^+$.

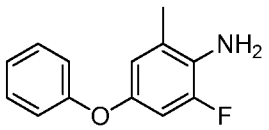
Intermediate 8: Benzofuran-7-ol.



Step A: 7-Methoxybenzofuran. To a round bottom flask were added 7-methoxy-2-benzofuran-2-carboxylic acid (5.0 g, 0.026 mol), copper (0.2 g, 3 mmol), and quinoline (30 mL). The reaction mixture was heated at reflux for 2 h. The mixture was filtered through Celite and washed with EtOAc, concentrated to dryness, and purified by flash column chromatography to yield the title compound (2.45 g, 64% yield) as a yellow oil. MS (ESI): mass calcd. for $C_9H_8O_2$, 148.1; m/z found, 149.0 $[M+H]^+$.

Step B: Benzofuran-7-ol. To a round bottom flask containing 7-methoxybenzofuran (2.45 g, 16.5 mmol) and anhydrous DCM (25 mL) was carefully added a solution of boron tribromide in DCM (1 M, 33 mL) at 0 °C. The reaction was allowed to warm to rt and stir at rt for 4 h. The reaction was quenched with water (20 mL), extracted with Et_2O, concentrated to dryness, and purified by flash column chromatography to yield the title compound (1.23 g, 55% yield) as a light-brown oil. MS (ESI): mass calcd. for $C_8H_6O_2$, 134.0.1; m/z found, 135.1 $[M+H]^+$.

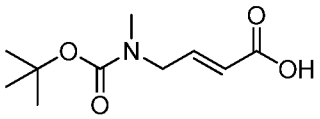
Intermediate 9: 2-Fluoro-6-methyl-4-phenoxyaniline.



Step A: 4-Bromo-2-fluoro-6-methylaniline. To a round bottom flask were added 2-fluoro-6-methylaniline (7 g, 56 mmol) and anhydrous DMF (100 mL). The reaction mixture was cooled in an ice bath, placed under a nitrogen atmosphere, and treated with *N*-bromosuccinimide (10 g, 56 mmol). The reaction was allowed to warm to rt and was stirred at rt for 10 min. The reaction mixture was poured into a water solution of diluted brine and extracted with EtOAc. The combined organic extracts were washed with diluted brine (3X), dried over anhydrous $MgSO_4$, filtered through a pad of silica, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound (6.84 g, 60% yield) as a yellow foam. MS (ESI): mass calcd. for C_7H_7BrFN, 203.0; m/z found, 204 $[M+H]^+$.

Step B: 2-Fluoro-6-methyl-4-phenoxyaniline. A mixture of 4-Bromo-2-fluoro-6-methylaniline (4.73 g, 23 mmol), phenol (4.4 g, 48 mmol), 1-Butylimidazole (1.4 g, 11 mmol), CuCl (230 mg, 2.3 mmol) and K_2CO_3 (6.5 g, 47 mmol) was degassed and heated at 120°C overnight. The mixture was cooled to room temperature, The mixture was concentrated and purified by ISCO using MeOH/H_2O as eluent to get the title compound as brown oil (2.23g, 44%). MS (ESI): mass calcd. for $C_{13}H_{12}FNO$, 217.1; m/z found, 218 $[M+H]^+$.

Intermediate 10: (E)-4-[tert-Butoxycarbonyl(methyl)amino]but-2-enoic acid.

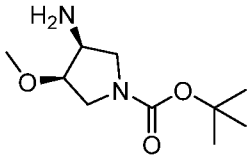


Step A: Methyl (*E*)-4-(methylamino)but-2-enoate. To a solution of methyl (*E*)-4-bromobut-2-enoate (1.79 g, 10 mmol) in THF (3 mL) was added methylamine (0.776 g, 25.0 mmol) at -20 °C over 30 min and then stirred at -5 °C for 2 h, filtered, and washed with THF. The filtrate was concentrated to dryness to give the title compound as a brown oil (0.96 g, 74%), which was used in the next step directly.

Step B: Methyl (*E*)-4-[*tert*-butoxycarbonyl(methyl)amino]but-2-enoate. To a solution of methyl (*E*)-4-(methylamino)but-2-enoate (0.96 g, 7.4 mmol) and Na_2CO_3 (1.58 g, 14.9 mmol) in THF (20 mL) and H_2O (20 mL) was added Boc_2O (3.24 g, 14.9 mmol) and the mixture was stirred at 25 °C for 3 h. The mixture was diluted with DCM, washed with brine several times, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to give the title compound as yellow liquid (0.68 g, 40% yield).

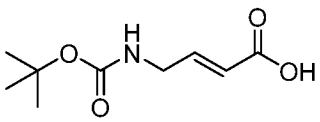
Step C: (*E*)-4-[*tert*-Butoxycarbonyl(methyl)amino]but-2-enoic acid. To a solution of methyl (*E*)-4-[*tert*-butoxycarbonyl(methyl)amino]but-2-enoate (0.68 g, 3.0 mmol) in THF (15 mL) and water (15 mL) was added LiOH•H_2O (0.498 g, 11.9 mmol) and the mixture was stirred at rt for 12 h. The pH of the mixture was adjusted to about 2, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give the title compound as light yellow liquid (0.41 g, 64% yield), which was used in the next step directly. MS (ESI): mass calcd. for $C_{11}H_{19}NO_4$, 229.1; m/z found, 130.0 $[M-Boc+H]^+$.

Intermediate 11: *tert*-Butyl (3*S*,4*R*)-3-amino-4-methoxypyrrolidine-1-carboxylate.



A mixture of *tert*-butyl (3*S*,4*R*)-3-amino-4-hydroxy-pyrrolidine-1-carboxylate (500 mg, 2.47 mmol), phthalic anhydride (439 mg, 2.97 mmol), triethylamine (500 mg, 4.94 mmol), and DMAP (60 mg, 0.49 mmol) in THF (20 mL) was stirred at reflux overnight. The reaction mixture was concentrated to dryness and the residue was purified by flash column chromatography to yield the intermediate as a white solid. This material was reacted with Ag_2O (1.142 g, 4.944 mmol) in MeI (10 mL) was stirred at reflux overnight. The reaction mixture was concentrated to dryness and the residue was purified by flash column chromatography to give the intermediate as a white solid. A solution of this material and $NH_2NH_2 \cdot H_2O$ (1 mL, 85%) in EtOH (5 mL) was stirred at reflux for 2 h. The solid was filtered off and the solvent was removed to give the title compound as an oil which was used without further purification in the next reaction.

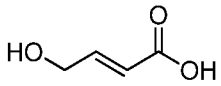
Intermediate 12: (*E*)-4-(*tert*-Butoxycarbonylamino)but-2-enoic acid.



Step A: (*E*)-4-Aminobut-2-enoic acid. To a round bottom flask were added (*E*)-4-bromobut-2-enoic acid (1 g, 6 mmol) and aqueous ammonia (10 mL) and was stirred at rt for 7 h. The mixture was concentrated to dryness to yield the title compound (0.61 g, 100%), which was used in the next step without purification.

Step B: (*E*)-4-(*tert*-Butoxycarbonylamino)but-2-enoic acid. To a round bottom flask containing a solution of (*E*)-4-aminobut-2-enoic acid (0.61 g, 6 mmol), Na_2CO_3 (1.3 g, 12 mmol), THF (15 mL), and H_2O (15 mL) was added Boc_2O (2.6 g, 12 mmol). The reaction mixture was stirred at 25 °C for 15 h. Then the mixture was extracted with EtOAc and the pH of the aqueous layer was adjusted to 2 with 1 M HCl. The acidic aqueous layer was extracted with EtOAc, washed with brine (3X), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield the title compound (0.24 g, 20% yield) as a white solid. MS (ESI): mass calcd. for $C_9H_{15}NO_4$; 201.1; m/z found, 102 $[M\text{-}Boc+H]^+$.

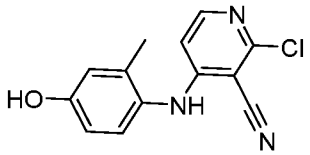
Intermediate 13: (E)-4-Hydroxybut-2-enoic acid.



Step A: Ethyl (*E*)-4-bromobut-2-enoate. To a round bottom flask containing ethyl (2*E*)-but-2-enoate (10.9 g, 87.6 mmol) and CCl_4 (100 mL) were added NBS (17 g, 96 mmol) and AIBN (4.3 g, 26 mmol). The reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was diluted with DCM and extracted with saturated $NaHCO_3$, water, and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness to yield the title compound (7.5 g, 44% yield) as an oil.

Step B: (*E*)-4-Hydroxybut-2-enoic acid. To a round bottom flask were added ethyl (*E*)-4-bromobut-2-enoate (2 g, 10 mmol), KOH (1.2 g, 21 mmol), and water (10 mL). The reaction mixture was stirred at 100 °C for 2 h, then acidified with 1 M HCl, and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to dryness to yield the title compound (560 mg, 53% yield) as a brown oil.

Intermediate 14: 2-Chloro-4-(4-hydroxy-2-methylanilino)pyridine-3-carbonitrile.

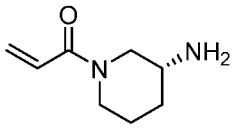


Step A: 2-Chloro-4-(4-methoxy-2-methylanilino)pyridine-3-carbonitrile. To a round bottom flask were added 2-chloro-4-iodopyridine-3-carbonitrile (1.7 g, 6.4 mmol), 4-methoxy-2-methylaniline (880 mg, 6.4 mmol), DPEPhos [bis(2-diphenylphosphinophenyl)ether] (690 mg, 1.3 mmol), palladium(II) acetate (145 mg, 0.646 mmol), K_3PO_4 (3.7 g, 0.017 mmol), and dioxane (15 mL). The reaction mixture was degassed and heated at 120 °C overnight. The mixture was cooled to rt, concentrated to dryness, and purified by flash column chromatography to yield the title compound (1.1 g, 63% yield) as a brown solid. MS (ESI): mass calcd. for $C_{14}H_{12}ClN_3O$, 273.1; m/z found, 274 $[M+H]^+$.

Step B: 2-Chloro-4-(4-hydroxy-2-methylanilino)pyridine-3-carbonitrile. To a round bottom flask containing a solution of 2-chloro-4-(4-methoxy-2-methylanilino)pyridine-3-carbonitrile (1.1 g, 4 mmol) in anhydrous DCM (15 mL) was carefully added a solution of boron tribromide in DCM (1 M, 4 mL, 4 mmol) at 0 °C. The reaction mixture was allowed to stir at rt for 4 h. The reaction was quenched with water (20 mL), extracted with ethyl ether, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound

(900 mg, 86% yield) as a yellow solid. MS (ESI): mass calcd. for $C_{13}H_{10}ClN_3O$, 259.1; m/z found, 260.0 $[M+H]^+$.

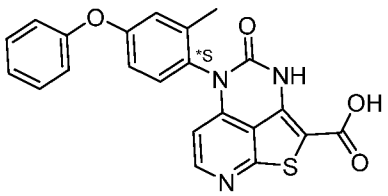
Intermediate 15: 1-[(3*R*)-3-Amino-1-piperidyl]prop-2-en-1-one.



Step A: (R)-tert-Butyl (1-acryloylpiperidin-3-yl)carbamate. To a solution of *tert*-butyl *N*-[(3*R*)-3-piperidyl]carbamate (2 g, 10 mmol) in DCM (30 mL) was added triethylamine (5 g, 50 mmol) and the reaction mixture was cooled to 0 °C. Prop-2-enoyl chloride (2.7 g, 30 mmol) was added slowly and was stirred overnight at rt. The reaction was extracted with H_2O and DCM, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. The crude product was used crude in the next step without further purification.

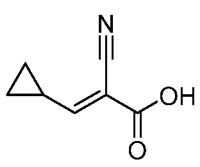
Step B: 1-[(3*R*)-3-Amino-1-piperidyl]prop-2-en-1-one. (R)-tert-Butyl (1-acryloylpiperidin-3-yl)carbamate (from Step A) was dissolved in MeOH and concentrated to dryness. Concentrated aqueous HCl was added, and the mixture was stirred for 2 h at rt. The reaction mixture was concentrated to dryness and the residue was used directly in the next step. MS (ESI): mass calcd. for $C_8H_{14}N_2O$, 154.1; m/z found, 155.1 $[M+H]^+$.

Intermediate 16: 5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



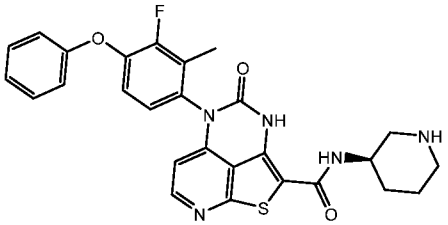
The title compound was prepared using Method 1, steps A-F in Example 1 (including Chiral Resolution Step A to obtain the **S* atropisomer). MS (ESI): mass calcd. for $C_{22}H_{15}N_3O_4S$, 417.1; m/z found, 418.2 $[M+H]^+$.

Intermediate 17: (E)-2-Cyano-3-cyclopropylprop-2-enoic acid.



A solution of cyanoacetic acid (1.34 g, 15.7 mmol), cyclopropanecarboxaldehyde (1.0 mL, 13 mmol), NH_4OAc (101 mg, 1.31 mmol), and HOAc (10 mL) in a 50 mL round bottom flask fitted with a stir bar under N_2 was warmed in a sand bath set at 110 °C. The reaction was run until LCMS and TLC showed the reaction had gone to completion. The reaction mixture was concentrated to dryness and water (20 mL) was added to the white solid. This mixture was concentrated dryness and repeated one time more. Water was added and the precipitate was filtered off to yield the title compound as a white solid (1.3 g, 72% yield). MS (ESI): mass calcd. for $C_7H_7NO_2$, 137.0; m/z found, 138.0 $[M+H]^+$.

Intermediate 18: (R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: 2-Bromo-3-fluoro-1-nitro-4-phenoxybenzene. To a mixture of a 2-bromo-3,4-difluoro-1-nitrobenzene (15.8 g, 66.4 mmol) and potassium carbonate (18.3 g, 132.8 mmol) in DMF (50 mL) was added phenol (6.25 g, 66.4 mmol) followed by stirring at 80 °C overnight. The title compound was collected by adding water to the reaction mixture and filtering to isolate a yellow solid (18 g, 87%).

Step B: 2-Fluoro-3-methyl-4-nitro-1-phenoxybenzene. Dimethylzinc as a 2 M solution in toluene (80.1 mL, 96.1 mmol) was slowly added to a mixture of 2-bromo-3-fluoro-1-nitro-4-phenoxybenzene (10 g, 32.0 mmol) and palladium-(diphenylphosphineoferrocenyl)-dichloride-methylene dichloride complex (1.33 g, 1.60 mmol) in dioxane (200 mL) at 40 °C. The mixture was stirred at 55 °C for 2 hours. After cooling to room temperature, methanol was slowly added followed by a saturated solution of ammonium chloride. The resulting mixture was extracted into ethyl acetate. The organic phase was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude oil was purified by flash chromatography on silica gel (PE/ethyl acetate, 9/1) to provide the crude as a yellow solid which is carried on to the next step without determining a yield.

Step C: 3-Fluoro-2-methyl-4-phenoxyaniline. Iron powder (4.5 g, 80.6 mmol) and NH_4Cl (4.5 g, 84.1 mmol) were added portion wise to a solution of 2-fluoro-3-methyl-4-nitro-1-

phenoxybenzene (product from step B) in EtOH (60 mL) and H_2O (20 mL) at rt. The resulting brown suspension was stirred at reflux during 2 hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over Na_2SO_4 anhydrous, filtered and concentrated under reduced pressure followed by purification by flash chromatography (silica gel, PE/ ethyl acetate, 10/1) to obtain the title compound as a yellow solid (2.42 g, 35%) MS (ESI): mass calcd. for $C_{13}H_{12}FNO$, 217.1; m/z found, 217.9 $[M+H]^+$.

Step D: 2-Chloro-4-((3-fluoro-2-methyl-4-phenoxyphenyl)amino)nicotinonitrile. A mixture of 3-fluoro-2-methyl-4-phenoxyaniline (2.4g, 11.0 mmol), 2-chloro-4-iodonicotinonitrile (2.9 g, 11.0 mmol), DPEPhos (1.19 g, 2.2 mmol), $Pd(AcO)_2$ (247.5 mg, 1.1 mmol), K_3PO_4 (4.68 g, 22.1 mmol) in dioxane (50 mL) was heated at reflux under N_2 for 4hr, then concentrated and purified by flash chromatography (silica gel, PE/ ethyl acetate, 10/1) to give the title compound as a yellow solid. (3.9 g, 99.8%) MS (ESI): mass calcd. for $C_{19}H_{13}ClFN_3O$, 353.1; m/z found, 354.0 $[M+H]^+$.

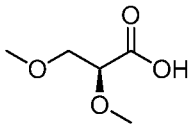
Step E: Methyl 3-amino-4-((3-fluoro-2-methyl-4-phenoxyphenyl)amino)thieno[2,3-b]pyridine-2-carboxylate. A mixture of 2-chloro-4-((3-fluoro-2-methyl-4-phenoxyphenyl)amino)nicotinonitrile (3.9 g,11.0 mmol), methyl 2-mercaptoacetate (2.3 g, 22.0 mmol) and NaOMe (1.17 g, 22.0 mmol) in MeOH (30 mL) was stirred at reflux for 16 hours. The precipitate was collected by filtration, dried under vacuo to give the title compound without purification. (3.2g, 69%). MS (ESI): mass calcd. for $C_{22}H_{18}FN_3O_3S$, 423.1; m/z found, 524.0 $[M+H]^+$.

Step F: Methyl 5-(3-fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate. CDI (4.9 g, 30.2 mmol) and Et_3N (0.5 mL) were added to a suspension of Methyl 3-amino-4-((3-fluoro-2-methyl-4-phenoxyphenyl)amino)thieno[2,3-b]pyridine-2-carboxylate (3.2 g, 7.56 mmol) in 1,4-dioxane (25 mL) at rt. The mixture was stirred at reflux for 3 hr, then concentrated and washed with MeOH to give the title compound as a yellow solid. (3.0 g, 99%) MS (ESI): mass calcd. for $C_{23}H_{16}FN_3O_4S$, 449.4; m/z found, 449.9 $[M+H]^+$.

Step G: 5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid. A mixture of Methyl 5-(3-fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate (3.0 g, 6.68 mmol) in MeOH/THF/H_2O (30/30/25 mL) was added $LiOH.H_2O$ (1.4 g, 33.4 mmol) and

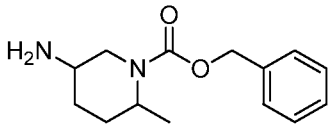
stirred at 60 °C overnight. The solvent was removed and acidified with 1N HCl. The title compound was collected by filtration to give a tan solid. (2.6 g, 90%)
MS (ESI): mass calcd. for $C_{22}H_{14}FN_3O_4S$, 435.4; m/z found, 435.9 $[M+H]^+$.
Step H: (R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A mixture of compound 5-(3-fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (650 mg, 1.49 mmol), *tert*-butyl (R)-3-aminopiperidine-1-carboxylate (598.03 mg, 2.99 mmol), Et_3N (301.6 mg, 2.99 mmol) and HATU (1.13 g, 2.99 mmol) in DMF (5 mL) was stirred at rt for 3 hr. Water was added and the precipitate isolated by filtration to give a pale yellow solid. The solid was dissolved in MeOH (8 mL) and acidified using HCl (8 mL). The resulting mixture was heated to 50 °C and stirred for 30 min, and then the solvent was removed to give the title compound as a yellow solid without further purification (680 mg, 82%). MS (ESI): mass calcd. for $C_{27}H_{24}FN_5O_3S$, 517.2; m/z found, 518.0 $[M+H]^+$.

Intermediate 19: (S)-2,3-Dimethoxypropanoic acid.



Step A: Methyl (S)-2-hydroxy-3-methoxypropanoate. To a solution of methyl (S)-oxirane-2-carboxylate (1 g, 9.80 mmol) in methanol (0.48 mL) was added was added Magnesium trifluoromethanesulfonate (790 mg, 2.45 mmol) at rt , and warmed to 40 °C for 16 hrs. Filtered and rinsed with DCM followed by concentration to obtain the title compound as a colorless oil (1.0 g, 76% yield).
Step B: Methyl (S)-2,3-dimethoxypropanoate. A mixture of Methyl (S)-2-hydroxy-3-methoxypropanoate (900 mg, 6.7 mmol) in DCM (10 mL) was treated with methyl iodide (1.90 g, 13.4 mmol) and silver oxide (2.32 g, 10 mmol) at rt. The mixture was warmed to 40 °C for 16 hours. Filtered and rinsed with DCM followed by concentration to give the title compound as a colorless oil (400 mg, 2.7 mmol, 40% yield).
Step C: (S)-2,3-Dimethoxypropanoic acid. A mixture of methyl (S)-2,3-dimethoxypropanoate (400 mg, 2.7 mmol), and lithium hydroxide hydrate (454 mg, 11 mmol) in DME (4 mL) and water (1 mL) stirred at rt for16 hrs. Adjusted pH to <7, extracted with DCM, and concentrated to give the title compound as a colorless oil without further purification or yield determination.

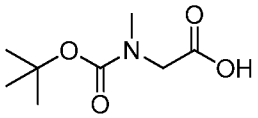
Intermediate 20: Benzyl 5-amino-2-methylpiperidine-1-carboxylate.



Step A: Benzyl 5-((*tert*-butoxycarbonyl)amino)-2-methylpiperidine-1-carboxylate. To a mixture of *tert*-butyl (6-methylpiperidin-3-yl)carbamate (900 mg, 4.2 mmol) in DCM, was added triethylamine (848 mg, 8.4 mmol) and benzoyl chloride (1.07 g, 6.3 mmol) which was allowed to stir at rt for 2 hrs. The crude reaction mixture was concentrated to a give the title compound without further purification (900 mg, 61% yield). MS (ESI): mass calcd. for $C_{19}H_{28}N_2O_4$, 348.2; m/z found, 349.1 $[M+H]^+$.

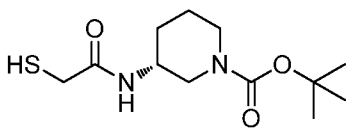
Step B: Benzyl 5-amino-2-methylpiperidine-1-carboxylate. A mixture of Benzyl 5-((*tert*-butoxycarbonyl)amino)-2-methylpiperidine-1-carboxylate (900 mg, 2.58 mmol), in methanol (5 mL), was added 1M HCl in methanol (5 mL). The mixture was allowed to stir at rt for 2 h. The crude reaction mixture was concentrated to a give the title compound without further purification (600 mg, 94% yield). MS (ESI): mass calcd. for $C_{14}H_{19}NO_2$, 233.1; m/z found, 234.0 $[M+H]^+$.

Intermediate 21: 2-[*tert*-Butoxycarbonyl(methyl)amino]acetic acid.



Sodium hydride (6.85 g, 171 mmol) was added to a mixture of (*tert*-butoxycarbonyl)glycine (10 g, 57.1 mmol) and methyl iodide (75 g, 528 mmol) in THF (600 mL) at 0 °C. The mixture was slowly allowed to warm to rt overnight. Water (300 mL) was added and extracted into ethyl acetate (2 x 500 mL). The aqueous layer was acidified to pH 3 with 1 M HCl extracted with ethyl acetate (2 x 500 mL). The combined organic layer was extracted with saturated aqueous sodium chloride (500 mL), dried ($MgSO_4$), filtration and concentrated to give the title compound as an oil (10 g, 91 %).

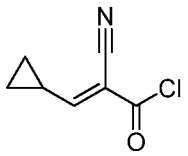
Intermediate 22: *tert*-Butyl (3R)-3-[(2-sulfanylacetyl)amino]piperidine-1-carboxylate.



A 20 mL microwave vial was charged with (*R*)-1-boc-3-aminopiperdine (5.0 g, 25 mmol). The vial was sealed, evacuated, and back-filled with argon three times. Methyl 2-mercaptoacetate

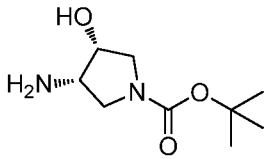
(6.7 mL, 170 mmol) was added via syringe in one portion and was heated to 150 °C in an oil bath. After 1 h 35 minutes, the mixture was cooled to rt and purified by flash column chromatography to yield a colorless oil (6.15 g. 90%).

Intermediate 23: (E)-2-Cyano-3-cyclopropylprop-2-enoyl chloride.



Step A: (E)-2-Cyano-3-cyclopropylacrylic acid. Combined cyanoacetic acid (1.34 g, 15.7 mmol), cyclopropyanecarboxyaldehyde (1.0 mL, 13 mmol), ammonium acetate (101 mg, 13.1 mmol) in acetic acid (10 ml) and warmed in a sand bath set at 110 °C for 2 hrs. The reaction mixture was concentrate to a solid and suspend in water (20 mL). The title compound was isolated by filtration and dried under vacuum to give the title compound (1.3 g, 72%) as a white solid.
Step B: (E)-2-Cyano-3-cyclopropylprop-2-enoyl chloride. To a suspension of (E)-2-cyano-3-cyclopropylacrylic acid (72.3 mg, 0.527 mmol) in $CDCl_3$ (5.2 mL) was added 1-chloro-N,N,2-trimethylpropenylamine (0.084 mL, 1.01 g/mL, 0.635 mmol). The resulting clear colorless solution was mixed for 5 minutes before direct use in subsequent reactions.

Intermediate 24: tert-Butyl (3S,4R)-3-amino-4-hydroxypyrrolidine-1-carboxylate.



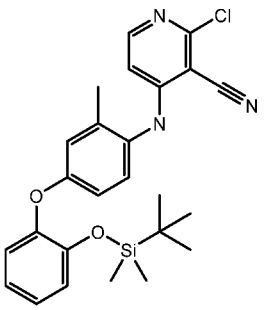
Step A: (3*S*,4*R*)-*tert*-Butyl 3-azido-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-1-carboxylate. A solution of methanesulfonyl chloride (11.66 g, 101.8 mmol) in DCM was added to a mixture of *tert*-butyl (3*R*,4*R*)-3-[*tert*-butyl(dimethyl)silyl]oxy-4-hydroxy-pyrrolidine-1-carboxylate (26.9 g, 84.8 mmol) and triethylamine (16.6 mL, 119 mmol) in DCM dropwise at 0 °C. The reaction mixture was stirred for 1.5 h at room temperature. The reaction mixture was taken up in water and extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue and sodium azide (11.2 g, 170 mmol) in DMF was heated at 120 °C for 13 h. The reaction mixture was poured into water and the mixture extracted with toluene. The organic layer was washed with brine, dried over anhydrous $MgSO_4$,

and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound (13.5 g, 47%).

Step B: *tert*-Butyl (3*S*,4*R*)-3-amino-4-[*tert*-butyl(dimethyl)silyl]oxy-pyrrolidine-1-carboxylate. A solution of (3*S*,4*R*)-*tert*-butyl 3-azido-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-1-carboxylate (13.5 g, 39.4 mmol) and Pd/C (10% on carbon, 400 mg, 0.376 mmol) in ethanol (150 mL) was hydrogenated under H_2-gas for 2 hours. The reaction mixture was filtered over Celite and concentrated to dryness to yield the title compound (12.36 g, 99.08% yield).

Step C: *tert*-Butyl (3*S*,4*R*)-3-amino-4-hydroxy-pyrrolidine-1-carboxylate. To a solution of *tert*-butyl (3*S*,4*R*)-3-amino-4-[*tert*-butyl(dimethyl)silyl]oxy-pyrrolidine-1-carboxylate (12.15 g, 38.39 mmol) in THF was added TBAF (52.2 mL, 52.2 mmol). The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated to dryness and water was added. The mixture was extracted with ethyl acetate and the organic layer was washed with water and brine several times. The water layer was extracted several times with chloroform. NaCl was added to the water layer and it was again extracted with chloroform. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound (7.8 g, 100% yield).

Intermediate 25: 4-((4-(2-((*tert*-Butyldimethylsilyl)oxy)phenoxy)-2-methylphenyl)amino)-2-chloronicotinonitrile.



Step A: 2-(3-Methyl-4-nitrophenoxy)phenol. The title compound was prepared in a manner analogous to Intermediate 27, Step A, using pyrocatechol.

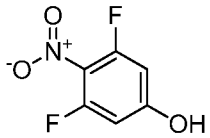
Step B: *tert*-Butyldimethyl(2-(3-methyl-4-nitrophenoxy)phenoxy)silane.

To a solution of 2-(3-methyl-4-nitrophenoxy)phenol (4.90 g, 20 mmol) in DCM (40 mL) were added Et_3N (3.03 g, 30 mmol) and TBSCl (3.31 g, 22 mmol) and stirred at room temperature for 3 hours. The reaction mixture was dispersed between DCM and saturated NH_4Cl aqueous

solution. The organic layer was collected, condensed and purified by flash chromatography eluting with PE/EA to yield the title compound (4.10 g, 57% yield)

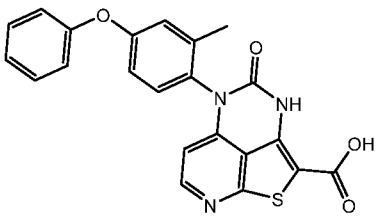
Step C: 4-((4-(2-((*tert*-Butyldimethylsilyl)oxy)phenoxy)-2-methylphenyl)amino)-2-chloronicotinonitrile. The title compound was prepared in a manner analogous to Intermediate 27, Steps B-C, using *tert*-butyldimethyl(2-(3-methyl-4-nitrophenoxy)phenoxy)silane in step B. MS (ESI): mass calcd. for $C_{25}H_{28}ClN_3O_2Si$:, 465.2; m/z found, 466.0 [M+H]+.

Intermediate 26: 3,5-Difluoro-4-nitrophenol.



To a solution of 3,5-difluorophenol (20.45 g, 157.2 mmol) in DCM (225 mL) was added fuming nitric acid (>90%, 7.86 mL, 157 mmol) dropwise over 10 minutes. The resulting orange solution was stirred in an ice bath for 50 min. The mixture was poured into water (200 mL) and the phases separated. The aqueous phase was extracted with DCM (50 mL) and EtOAc (2 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound (11.24 g, 40.8% yield) as a yellow solid. MS (ESI): mass calcd. for $C_6H_3F_2NO_3$, 175.0; m/z found, 174 $[M-H]^-$.

Intermediate 27: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



Step A: 2-Methyl-1-nitro-4-phenoxybenzene. To a round bottom flask were added phenol (42.5 g, 452 mmol), K_2CO_3 (125 g, 905 mmol), and DMF (500 mL). To the reaction mixture was added 5-fluoro-2-nitrotoluene (70.2 g, 452 mmol) and the reaction was stirred at 80 °C for 16 h under N_2. The reaction was diluted with saturated NH_4Cl and extracted with MTBE (3 × 400 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield the title compound (100 g, 92% yield) as a brown oil.

Step B: 2-Methyl-4-phenoxyaniline. To a solution of 2-methyl-1-nitro-4-phenoxybenzene (100 g, 436 mmol) in EtOH/H_2O (3:1 ratio, 2000 mL) were sequentially added NH_4Cl (117 g, 2180 mmol) and Fe (97 g, 1700 mmol). The reaction mixture was heated to reflux for 2 h, then the reaction was cooled to 25 °C and concentrated to dryness. To the residue was added water and EtOAc and the organic layer was separated, washed with saturated $NaHCO_3$ and saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness to yield the title compound (82 g, 90% yield).

Step C: 2-Chloro-4-(2-methyl-4-phenoxyanilino)pyridine-3-carbonitrile. To a round bottom flask under a N_2 atmosphere were added 2-methyl-4-phenoxyaniline (30 g, 150 mmol), 2-chloro-4-iodopyridine-3-carbonitrile (51.6 g, 195 mmol), and dioxane (200 mL), followed by bis(2-diphenylphosphinophenyl)ether (DPEphos) (16 g, 30 mmol), $Pd(OAc)_2$ (3.36 g, 15 mmol), and K_3PO_4 (89 g, 420 mmol). The reaction mixture was stirred at 100 °C overnight. The reaction mixture was filtered and purified flash column chromatography to yield the title compound (32 g, 63% yield) as a yellow solid.

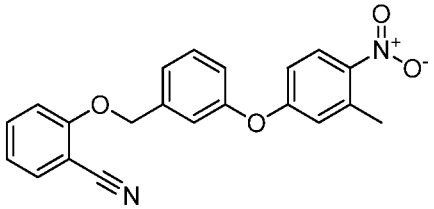
Step D: Methyl 3-amino-4-(2-methyl-4-phenoxyanilino)thieno[2,3-*b*]pyridine-2-carboxylate. To a round bottom flask were added 2-chloro-4-(2-methyl-4-phenoxyanilino)pyridine-3-carbonitrile (36 g, 107 mmol) in MeOH (150 mL). To this solution was added NaOMe (14.5 g, 268 mmol) in MeOH (30 mL), followed by methyl 2-sulfanylacetate (23 g, 217 mmol). The reaction mixture was refluxed overnight. The reaction mixture was cooled and the yellow precipitate was filtered off, washed with MeOH, and dried to yield the title compound (30 g, 75% yield) as a yellow solid.

Step E: Methyl 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate. To a round bottom flask were added methyl 3-amino-4-(2-methyl-4-phenoxyanilino)thieno[2,3-*b*]pyridine-2-carboxylate (30.6 g, 75.5 mmol), carbonyldiimidazole (49 g, 300 mmol), and 1,4-dioxane (500 ml). The reaction was stirred at reflux overnight. Then the reaction mixture was concentrated to dryness and to the residue was added to MeOH (200 mL) and the precipitate that formed was filtered off and dried to yield the title compound (28.1 g, 86%) as a yellow solid.

Step F: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid. To a round bottom flask were added methyl 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate (9.2 g, 21 mmol), lithium hydroxide (4.47 g, 106 mmol), THF (200 mL), MeOH (200 mL), and water (50 mL). The reaction mixture was stirred at 50 °C for 15 h. The mixture

was concentrated to dryness and diluted with H_2O. The pH was adjusted to 2 with 1 M HCl and the precipitate was filtered and dried to yield the title compound (8.1 g, 91% yield) as yellow solid. MS (ESI): mass calcd. for $C_{22}H_{15}N_3O_4S$, 417.1; m/z found, 418.1 $[M+H]^+$.

Intermediate 28: 2-((3-(3-Methyl-4-nitrophenoxy)benzyl)oxy)benzonitrile



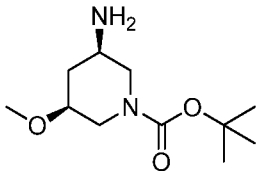
Step A: 3-(3-Methyl-4-nitrophenoxy)benzaldehyde. 4-fluoro-2-methyl-1-nitrobenzene (13 mL, 106.6 mmol), 3-hydroxybenzaldehyde (19.8 mL, 162 mmol) and K_2CO_3 (30.1 g, 217.9 mmol) were dissolved in DMF (123 mL) at rt under an atmosphere of argon. The mixture was warmed in a sand bath at 110 °C under N_2 for 5 hours. Cooled, filtered and extracted into ether partitioning away from a brine solution. The title compound was purified by silica chromatography (ethyl acetate/hexanes followed by DCM/methanol) (9.83 g, 36%) MS (ESI): mass calcd. for $C_{14}H_{11}NO_4$, 257.1; m/z found, 258.0 $[M+H]^+$.

Step B: (3-(3-Methyl-4-nitrophenoxy)phenyl)methanol. To a scintillation vial containing 3-(3-methyl-4-nitrophenoxy)benzaldehyde (13 g, 50.5 mmol) was added a stir bar and the vessel was purged with N_2. Dry MeOH (125 mL, dried over hot 3A sieves) was added via a syringe filter and the suspension was cooled to -10 °C. Sodium borohydride (1.1 g, 29 mmol) was added in one portion with mixing and the reaction was allowed to warm to rt over 30 min. The title compound was isolated by extracting into ethyl acetate from a solution of saturated aqueous NH_4Cl followed by drying over Na_2SO_4, filtration and concentration. (8.66 g, 66%) $C_{14}H_{13}NO_4$. ^1H NMR (500 MHz, Methanol-d4): δ 8.08 - 8.01 (m, 1H), 7.46 - 7.37 (m, 1H), 7.26 - 7.20 (m, 1H), 7.14 - 7.08 (m, 1H), 7.04 - 6.97 (m, 1H), 6.97 - 6.92 (m, 1H), 6.92 - 6.87 (m, 1H), 4.62 (s, 2H), 2.55 (s, 3H).

Step C: 2-((3-(3-Methyl-4-nitrophenoxy)benzyl)oxy)benzonitrile. (3-(3-methyl-4-nitrophenoxy)phenyl)methanol (8.13 g, 31.4 mmol), triphenylphosphine (9.97 g, 37.6 mmol) and DIAD (6.5 mL, 31.4 mmol) were dissolved in dry THF (118 mL) under an atmosphere of N_2. The suspension was cooled to -10 °C and 2-hydroxybenzonitrile (4.5 g, 37.6 mmol) was added in one portion with mixing. The reaction was allowed to warm to rt, followed by heating to 80 °C for 3 hours, 40 °C for 33 hours and 80 °C for 1.5 hours. Concentrated crude reaction mixture

onto silica and eluted through a plug of silica in a fritted funnel with ethyl acetate/hexanes, 4/1 to give the title compound. (8.65 g, 77%) MS (ESI): mass calcd. for $C_{21}H_{16}N_2O_4$, 360.1; m/z found, 361.0 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d4): δ 8.02 (d, J = 9.0 Hz, 1H), 7.68 - 7.55 (m, 2H), 7.53 - 7.41 (m, 1H), 7.41 - 7.29 (m, 1H), 7.29 - 7.14 (m, 2H), 7.14 - 7.01 (m, 2H), 6.99 - 6.85 (m, 2H), 5.27 (s, 2H), 2.53 (s, 3H).

Intermediate 29: *tert*-Butyl (3R,5S)-3-amino-5-methoxypiperidine-1-carboxylate.

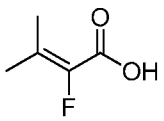


Step A: (3*R*,5*S*)-*tert*-Butyl 3-azido-5-hydroxypiperidine-1-carboxylate. The title compound was prepared using the method for Intermediate 2, steps A-J. Mass calcd. for $C_{10}H_{18}N_4O_3$, 242.1.1; ^1H NMR (400 MHz, $CDCl_3$): δ 3.85-3.68 (m, 3H), 3.60-3.49 (m, 1H), 3.16-3.00(m, 2H), 2.38-2.07 (m, 3H), 1.65-1.59 (m, 1H), 1.44 (s, 9H).

Step B: *tert*-Butyl (3*R*,5*S*)-3-azido-5-methoxypiperidine-1-carboxylate. A solution of (3*R*,5*S*)-*tert*-butyl 3-azido-5-hydroxypiperidine-1-carboxylate (200 mg, 0.83 mmol) and Ag_2O (152 mg, 1.24 mmol) in CH_3I (4 mL) was reacted at 60 °C for 16 h, filtered, and concentrated to dryness to give the title compound as a colorless oil (200 mg, 95%). Mass calcd. for $C_{11}H_{20}N_4O_3$, 256.2; ^1H NMR (400 MHz, $CDCl_3$): δ 4.39-4.00 (m, 3H), 3.37 (s, 3H), 3.36-3.29(m, 1H), 3.24-3.15 (m, 1H), 2.68-2.31 (m, 3H), 1.44 (s, 9H), 1.37-1.29 (m, 1H).

Step C: *tert*-Butyl (3*R*,5*S*)-3-amino-5-methoxypiperidine-1-carboxylate. A solution of *tert*-butyl (3*R*,5*S*)-3-azido-5-methoxypiperidine-1-carboxylate (200 mg, 0.78 mmol) and Pd/C (10% on carbon, 20 mg) in MeOH (10 mL) was reacted at rt under H_2 for 16 h. The reaction mixture was filtered and concentrated to dryness to give the title compound (170 mg, 95%), which was used in the next step without purification. MS (ESI): mass calcd. for $C_{11}H_{22}N_2O_3$, 230.30; m/z found, 231.1 $[M+H]^+$.

Intermediate 30: 2-Fluoro-3-methylbut-2-enoic acid.

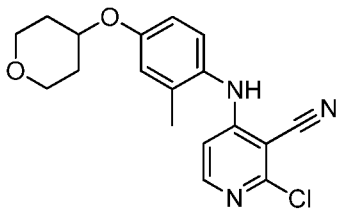


Step A: Ethyl 2-diethoxyphosphoryl-2-fluoroacetate. Ethyl 2-bromo 2-fluoroacetate (5.0 g, 27 mmol) was added to triethylphosphite (13 mL) and heated at 130 °C for 23 h. The resulting mixture was distilled under low pressure (1.4 mbar, 75-110 °C) to give the title compound as a yellowish oil (6.0 g, 92%).

Step B: Ethyl 2-fluoro-3-methylbut-2-enoate. To a dry 250 mL 2-neck round bottom flask that was purged with N_2 was added ethyl 2-diethoxyphosphoryl-2-fluoroacetate (500 mg, 2.07 mmol). Anhydrous THF (20 mL) was added and the reaction mixture was cooled to -70 °C, then BuLi (2.5 M in Hexane, 1 mL) was added dropwise. The reaction mixture was stirred for 2 h at -70 °C, then acetone (1 mL) was added and the reaction was warmed to rt and stirred overnight. The reaction was quenched by addition of an NH_4Cl solution and extracted with EtOAc. The organic layers was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness to give the title compound as a yellow oil (266 mg, 88.1% yield).

Step C: 2-Fluoro-3-methylbut-2-enoic acid. To a solution of ethyl 2-fluoro-3-methylbut-2-enoate (266 mg, 1.82 mmol) in dioxane (5 mL) and water (5 mL) was added NaOH (291.3 mg, 7.281 mmol) and was stirred for 10 min at 60 °C. The mixture was acidified with 2 M HCl to pH 2 and extracted with DCM. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to dryness to give the title compound as a yellow oil (181 mg, 84%).

Intermediate 31: 2-Chloro-4-(2-methyl-4-tetrahydropyran-4-yloxyanilino)pyridine-3-carbonitrile.



Step A: Tetrahydro-2H-pyran-4-yl methanesulfonate. To a solution of tetrahydro-2H-pyran-4-ol (2 g, 20 mmol) in DCM (20 mL) at 0 °C was added DIEA (3 g, 23.5 mmol), and methanesulfonyl chloride (2.46 g, 21.5 mmol). The reaction mixture was stirred at 0 °C for 1 hr, then at room temperature for 1.5 hrs. The mixture was poured into water, extracted into DCM. The organic layer was separated, washed with water, brine, dried over Na_2SO_4, and concentrated to give the title compound. (3.72 mg, quantitative).

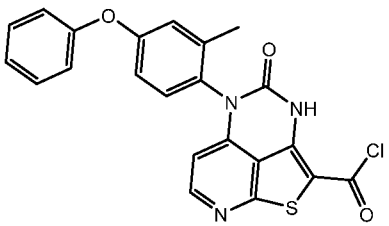
Step B: 4-(3-Methyl-4-nitrophenoxy)tetrahydro-2H-pyran. Tetrahydro-2H-pyran-4-yl methanesulfonate (3.53 g, 19.6 mmol) was dissolved in DMF (40 mL), followed by the addition of Cs_2CO_3 (9.57 g, 29.4 mmol) and 3-methyl-4-nitrophenol (3 g, 19.6 mmol). The mixture was

heated at 120 °C for 3 h, then cooled to rt, and diluted with water and extracted into EA. The combined organic layers were washed with brine and concentrated, then purified by chromatography with DCM/MeOH to get the target compound as a white solid. (2.87 g, 62%) MS (ESI): mass calcd. for $C_{12}H_{15}NO_4$, 237.1; m/z found, 238.3 $[M+H]^+$.

Step C: 2-Methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)aniline. 4-(3-methyl-4-nitrophenoxy)tetrahydro-2H-pyran (1.1 g, 4.6 mmol) was treated with Palladium on carbon (25 mg, 0.2 mmol) in methanol (20 mL) with a positive pressure of hydrogen gas at rt for 18 hours. The title compound was isolated after filtering through a pad of Celite and concentrating to give a brown solid. (0.81 g, 84%) MS (ESI): mass calcd. for $C_{12}H_{17}NO_2$, 207.1; m/z found, 208.1 $[M+H]^+$.

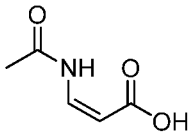
Step D: 2-Chloro-4-(2-methyl-4-tetrahydropyran-4-yloxyanilino)pyridine-3-carbonitrile. 2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)aniline (0.81 g, 3.9 mmol), 2-chloro-4-iodonicotinonitrile (1.3 g, 5.1 mmol), Cs_2CO_3 (2.54 g, 7.8 mmol), DPEPhos (0.42 g, 0.8 mmol), $Pd(OAc)_2$ (87.5 mg, 0.4 mmol) were dissolved in 1,4-dioxane (30 mL). The mixture was stirred at 80 °C overnight. The title compound was purified by flash chromatography (PE/EA) to give a yellow solid. (1.03 g, 80%) MS (ESI): mass calcd. for $C_{18}H_{18}ClN_3O_2$, 343.1; m/z found, 344.1 $[M+H]^+$.

Intermediate 32: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carbonyl chloride.



To a solution of 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 27) (500 mg, 1.2 mmol) in anhydrous DCM (20 mL) was added 2-drops of DMF and it was cooled to 0 °C. Next, oxalyl dichloride (762 mg, 6 mmol) was added slowly and it was stirred at 40 °C overnight, concentrated to dryness, and the residue was used in the next step without further purification or determined yield.

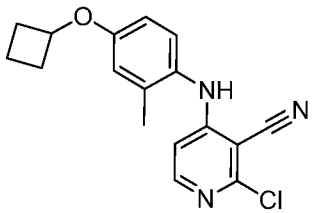
Intermediate 33: (Z)-3-Acetamidoprop-2-enoic acid.



Step A: Ethyl (*Z*)-3-acetamidoprop-2-enoate. To a solution of ethyl prop-2-ynoate (1.246 g, 12.70 mmol), acetamide (500 mg, 8.5 mmol), TFA (4.8 g, 42 mmol), and NaOAc (1.46 g, 16.9 mmol) in toluene (15 mL) was added $Pd(OAc)_2$ (95 mg, 0.42 mmol) at rt under N_2 and stirred at 70 °C overnight, concentrated to dryness, and purified by flash column chromatography to give the title compound as an oil (470 mg, 35% yield).

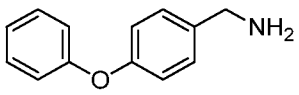
Step B: (*Z*)-3-Acetamidoprop-2-enoic acid. A solution of ethyl (*Z*)-3-acetamidoprop-2-enoate and $LiOH•H_2O$ in THF/H_2O (1/1) was stirred at 50 °C for 1 h, then the solution was acidified with 1 M HCl and extracted with EtOAc, combining the organic layers, and concentrated to dryness to give the title compound, which was used without further purification in the next step.

Intermediate 34: 2-Chloro-4-((4-cyclobutoxy-2-methylphenyl)amino)nicotinonitrile.



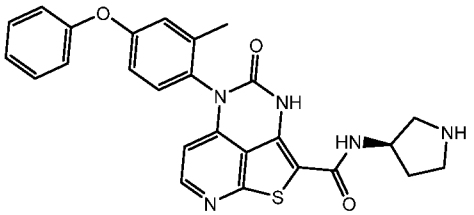
The title compound was prepared using Method 1, steps A-C in Example 1, and using 3-methyl-4-nitro-phenol and bromocyclobutane in place of phenol and 5-fluoro-2-nitrotoluene in step A, to yield the title compound. MS (ESI): mass calcd. for $C_{17}H_{16}ClN_3O$, 313.1; m/z found, 314.0 $[M+H]^+$.

Intermediate 35: (4-Phenoxyphenyl)methanamine.



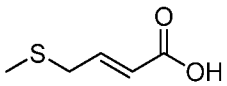
A solution of 4-phenoxybenzaldehyde (2.0 g, 10 mmol), hydroxylamine hydrochloride (700 mg, 10 mmol), EtOH (20 ml), and water (1 ml) was stirred at room temperature overnight. To the reaction mixture were added 10 N HCl (1 ml) and of Pd/C (10% on carbon, 320 mg) and was stirred under hydrogen for 30 min. The reaction mixture was filtrated through Celite and concentrated to dryness. The residue was purified by flash column chromatography to give the title compound as a white solid (1.5 g, 75% yield).

Intermediate 36: (R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared using Method 1, steps A-H (including Chiral Resolution Method A after step F to obtain the *S atropisomer) in Example 1, and using *tert*-butyl (3*R*)-3-aminocyclopentanecarboxylate in place of *tert*-butyl (3*R*,5*R*)-3-amino-5-fluoro-piperidine-1-carboxylate in step G, to yield the title compound. MS (ESI): mass calcd. for $C_{26}H_{23}N_5O_3S$, 485.2; m/z found, 486.1 $[M+H]^+$.

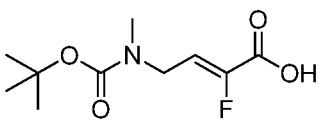
Intermediate 37: (E)-4-Methylsulfanylbut-2-enoic acid.



Step A: Methyl (*E*)-4-methylsulfanylbut-2-enoate. To a solution of methyl (*E*)-4-bromobut-2-enoate (1.507 g, 8.418 mmol) in MeCN (50 mL) was added 15% aqueous solution of NaSMe (0.59 g, 8.4 mmol) in water (4 mL) at -40 °C. The resulting mixture was warmed at 0 °C over a period of 1 h. The reaction was dispersed between EtOAc and water, the organic layer was collected, and concentrated to dryness to give the title compound (1.231 g, 100.0% yield) and was used in the next step without further purification.

Step B: (*E*)-4-Methylsulfanylbut-2-enoic acid. A solution of methyl (*E*)-4-methylsulfanylbut-2-enoate (1.231 g 8.418 mmol) and $LiOH•H_2O$ (1.413 g, 33.67 mmol) in THF (15 mL) and water (15 mL) was stirred at room temperature for 6 hours. The reaction was adjusted to pH = 3 using a 1 M aqueous solution of HCl and was dispersed between EtOAc and water. The organic layer was collected and concentrated to dryness to give the title compound (0.556 g, 50.0% yield), which was used in the next step without further purification.

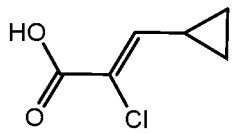
Intermediate 38: (Z)-4-[*tert*-Butoxycarbonyl(methyl)amino]-2-fluoro-but-2-enoic acid.



Step A: Ethyl 2-diethoxyphosphoryl-2-fluoro-acetate. A solution of ethyl 2-bromo 2-fluoroacetate (5.0 g, 27 mmol) in triethylphosphite (13 mL) was heated at 130 °C for 23 h. The resulting mixture was distilled under low pressure (1.4 mbar, 75-110 °C) to give the title compound as a yellowish oil (6.0 g, 92%).

Step B: (*Z*)-4-[*tert*-Butoxycarbonyl(methyl)amino]-2-fluoro-but-2-enoic acid. Ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate (2.0 g, 8.3 mmol) was placed in THF (5 mL) and cooled to 0 °C in ice-bath. Next, NaH (198 mg, 8.26 mmol) was added and stirred for 30 min at 0 °C. *tert*-Butyl *N*-methyl-*N*-(2-oxoethyl)carbamate (0.579 g, 3.34 mmol) was added to the reaction mixture slowly and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction was quenched by the addition of DCM and water. The organic layer was collected and washed with brine, dried over anhydrous $MgSO_4$, and concentrated to dryness. The residue was dissolved in dioxane (5 mL) and water (5 mL), and NaOH (1.321 g, 33.03 mmol) was added and was reacted for 10 min at rt. The mixture was acidified with 2 M HCl to pH~2 and extracted with DCM. The organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to dryness to give the title compound (500 mg, 26%).

Intermediate 39: (E/Z)-2-Chloro-3-cyclopropyl-prop-2-enoic acid.



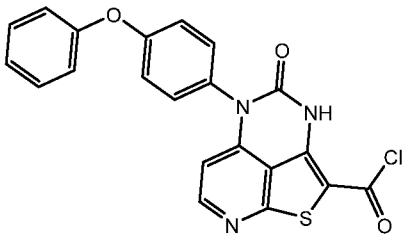
Step A: Ethyl 2,2-dichloro-2-diethoxyphosphoryl-acetate. A solution of 5% sodium hypochlorite (185 mL) was adjusted to pH 7.1 with 3 N HCl (10 mL) and ethyl 2-diethoxyphosphorylacetate (5.60 g, 25.0 mmol) was added drop wise at 0 °C with vigorous stirring over 30 min. After complete addition, the mixture was stirred for 5 min at rt and extracted with hexanes. The reaction mixture was concentrated to dryness gave the title compound as a colorless oil (0.86 g, 12% yield).

Step B: Ethyl 2-chloro-2-diethoxyphosphoryl-acetate. A solution of ethyl 2,2-dichloro-2-diethoxyphosphoryl-acetate (0.86 g, 2.9 mmol) in EtOH (6 mL) was cooled to 0 °C. A solution of sodium sulfite (0.74 g, 5.9 mmol) in water (20 mL) was added at a rate that the temperature could be kept around 15 °C. After the end of the addition the turbid solution was stirred at room temperature for 20 minutes before being extracted with chloroform (4 x 15 mL). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated to dryness to give the title compound as a yellow oil (0.47 g, 62% yield).

Step C: Ethyl (*E/Z*)-2-chloro-3-cyclopropyl-prop-2-enoate. To a solution of NaH (60% in oil, 87 mg, 3.6 mmol) in THF (10 mL) at 0 °C was added ethyl 2-chloro-2-diethoxyphosphoryl-acetate (0.47 g, 1.8 mmol) dropwise and stirred at 0 °C for 1 h. Then cyclopropanecarbaldehyde (127 mg, 1.82 mmol) was added dropwise and stirred at 0 °C for 1 h. The mixture was quenched with saturated NH_4Cl, extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, and concentrated to dryness to give the title compound as a yellow liquid (0.24 g, 76% yield).

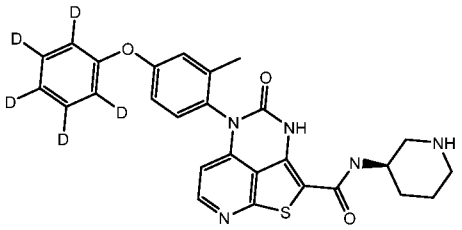
Step D: (*E/Z*)-2-Chloro-3-cyclopropyl-prop-2-enoic acid. To a solution of ethyl (*EZ*)-2-chloro-3-cyclopropyl-prop-2-enoate (0.24 g, 1.4 mmol) in dioxane (5 mL) and water (5 mL) was added KOH (0.385 g, 6.87 mmol) and the mixture was stirred at 60 °C for 2 h. The pH of the mixture was adjusted to about 2, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give the title compound as a light yellow solid (0.13 g, 65% yield), which was used in the next step directly.

Intermediate 40: 4-Oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carbonyl chloride.



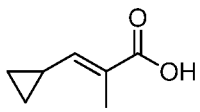
To a 50 mL flask with a stir bar were added 4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 58) (1.0 g, 2.5 mmol) and thionyl chloride (10.0 mL, 137 mmol) and was warmed in a sand bath to reflux for 1 hour. The reaction mixture was concentrated to dryness and added DCM was added and the reaction was concentrated to dryness to give the title compound (1.046 g, 100.0% yield), which was used without further purification.

Intermediate 41: (R)-5-(2-Methyl-4-(2,3,4,5,6-pentadeuteriophenoxy)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared using analogous conditions described in Method 1, steps A-H in Example 1, and using 2,3,4,5,6-pentadeuteriophenol in place of phenol in step A and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of *tert*-butyl (3*R*,5*R*)-3-amino-5-fluoro-piperidine-1-carboxylate in step G.

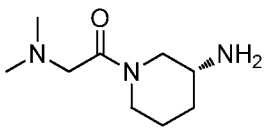
Intermediate 42: (E)-3-Cyclopropyl-2-methyl-prop-2-enoic acid.



Step A: Ethyl (*E*)-3-cyclopropyl-2-methyl-prop-2-enoate. A solution of ethyl 2-diethoxyphosphorylpropanoate (2.38 g, 10.0 mmol) in THF (30 mL) was cooled to -78 °C and *n*-BuLi (2.4 N, 4.58 mL) was added dropwise and stirred at -78 °C for 1 h. Then cyclopropanecarbaldehyde (0.70 g, 10 mmol) was added dropwise and stirred at -78 °C for 1 h. The mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness to give the title compound as a yellow liquid (1.13 g, 73.3% yield). MS (ESI): mass calcd. for $C_9H_{14}O_2$, 154.1; m/z found, 155.1 $[M+H]^+$.

Step B: (*E*)-3-Cyclopropyl-2-methyl-prop-2-enoic acid. To a solution of ethyl (*E*)-3-cyclopropyl-2-methyl-prop-2-enoate (1.13 g, 7.33 mmol) in dioxane (15 mL) and water (15 mL) was added KOH (2.056 g, 36.64 mmol) and the mixture was stirred at 60 °C for 2 h. The pH of the mixture was adjusted to about 2, then extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give the title compound as light yellow solid (0.77 g, 83% yield), which was used in the next step directly. MS (ESI): mass calcd. for $C_7H_{10}O_2$, 126.1; m/z found, 127.1 $[M+H]^+$.

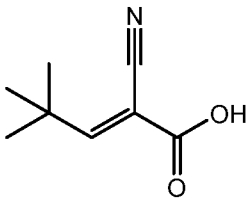
Intermediate 43: 1-[(3R)-3-Amino-1-piperidyl]-2-(dimethylamino)ethanone.



Step A: *tert*-Butyl *N*-[(3*R*)-1-[2-(dimethylamino)acetyl]-3-piperidyl]carbamate. A solution of *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate (400 mg, 2.0 mmol), 2-(dimethylamino)acetic acid (226 mg, 2.19 mmol), HATU (911 mg, 2.40 mmol), and triethylamine (0.557 mL, 4.00 mmol) in DMF (5 mL) was stirred at rt overnight, then poured into water. The mixture was extracted with EtOAc, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give the title compound as a yellow oil (399 mg, 70%).

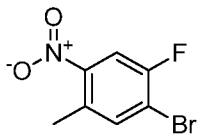
Step B: 1-[(3*R*)-3-Amino-1-piperidyl]-2-(dimethylamino)ethanone. A solution of *tert*-butyl *N*-[(3*R*)-1-[2-(dimethylamino)acetyl]-3-piperidyl]carbamate (200 mg, 0.70 mmol) in 2 M HCl in MeOH (2 mL) was stirred at rt overnight. The reaction was concentrated to dryness and the residue was used in next step without further purification (150 mg, quantitative). MS (ESI): mass calcd. for $C_9H_{19}N_3O$, 185.2; m/z found, 186.1 $[M+H]^+$.

Intermediate 44: (E)-2-Cyano-4,4-dimethyl-pent-2-enoic acid or (E)-2-cyano-4,4-dimethylpent-2-enoic acid.



A stirred solution of 2-cyanoacetic acid (1.70 g, 20 mmol), pivalaldehyde (1.72 g, 20 mmol) and NH_4OAc (60 mg, 0.8 mmol) in toluene was heated to reflux with Dean-Stark removal of water. When generation of water ceased, the mixture was cooled to room temperature and concentrated under reduced pressure to yield the title product as a yellow solid (2.13 g, 69% yield).

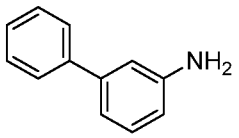
Intermediate 45: 1-Bromo-2-fluoro-5-methyl-4-nitrobenzene.



A solution of 4-bromo-5-fluoro-2-methylaniline (10.2 g, 50 mmol) and 3-chlorobenzenecarboperoxoic acid (34.5 g, 200 mmol) in DCE (10 mL) was stirred under nitrogen at reflux for 2 hours. After cooling to rt, the mixture was dispersed between DCM and saturated aqueous Na_2SO_3 solution. The organic layer was collected, concentrated to dryness

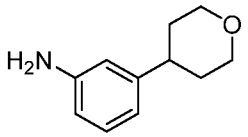
and purified by flash column chromatography to give the title compound as a brown oil (7.02 g, 60.0% yield).

Intermediate 46: [1,1'-Biphenyl]-3-amine.



To a solution of phenylboronic acid (12.193 g, 100.00 mmol) in MeOH (150 mL) were added sequentially Na_2CO_3 (21.198 g, 200.00 mmol) and 3-bromoaniline (17.202 g, 100.00 mmol), and then $Pd(OAc)_2$ (562 mg, 2.50 mmol) was added and the reaction was heated to reflux until a black suspension appeared. The reaction was cooled to room temperature, diluted with MeOH, and the black precipitate was removed by filtration. The filtrate was concentrated to dryness and the residue was added to water and DCM. The organic phase was collected, dried over anhydrous Na_2SO_4, and concentrated to dryness to give the title compound (18.373 g, 100.00% yield) as a brown oil. MS (ESI): mass calcd. for $C_{12}H_{11}N$, 169.22; m/z found, 170.0 $[M+H]^+$.

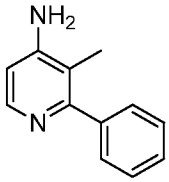
Intermediate 47: 3-(Tetrahydro-*2H*-pyran-4-yl)aniline.



Step A: 3-(3,6-Dihydro-2H-pyran-4-yl)aniline. A solution of 3-bromoaniline (0.9 mL, 8.10 mmol), 3,6-Dihydro-2*H*-pyran-4-boronic acid pinacol ester (5.11 g, 24.3 mmol) and X-phos-palladium precatalyst generation 1 (163 mg, 0.203 mmol) in dioxane (6.1 mL) and 0.5 M K_3PO_4 H_2O (12.2 mL) was stirred at 90 °C for 16 h. The reaction mixture was concentrated to dryness and the residue was purified by FCC (SiO_2, 0-10% MeOH (2 N NH3)/DMC) to give the title compound (320 mg, 17%).

Step B: 3-(Tetrahydro-*2H*-pyran-4-yl)aniline. A solution of 3-(3,6-dihydro-2H-pyran-4-yl)aniline (2.0 g, 4.87 mmol) in 1:1 MeOH:DCM (97 mL) was passed through an H-cube® hydrogenation flow reactor (recycling @ 80 °C, 1 atm, 1.5 mL/min, 10% Pd/C) for 16 h. The solution as concentrated then purified (FCC, EtOAc-hexanes) to give the title compound (548 mg, 63%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{21}N_5O_2S$, 407.1; m/z found, 408 $[M+H]^+$.

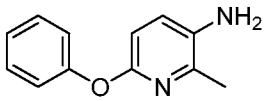
Intermediate 48: 3-Methyl-2-phenylpyridin-4-amine.



Step A: 3-Methyl-2-phenylpyridin-4-amine. To a solution of 4-bromo-2-chloro-3-methylpyridine (2.20 g, 10.7 mmol), *tert*-butyl carbamate (1.248 g, 10.66 mmol), $Pd(dppf)Cl_2$ (435 mg, 0.533 mmol), Xantphos (616 mg, 1.07 mmol), and Cs_2CO_3 (6.926 g, 21.31 mmol) in dioxane (60 mL) was heated at reflux under N_2 overnight. The reaction was concentrated to dryness and the residue was purified by flash column chromatography to give white solid that was used directly in the next step.

Step B: 3-Methyl-2-phenylpyridin-4-amine. 3-Methyl-2-phenylpyridin-4-amine was dissolved in dioxane and H_2O, $Pd(dppf)Cl_2$ (435 mg, 0.533 mmol), and Na_2CO_3 (2.259 g, 21.31 mmol) were added and stirred at reflux overnight . The reaction was concentrated to dryness and the residue was purified by flash column chromatography to give yellow solid. The yellow solid was dissolved in HCl and MeOH and stirred at 60 °C for 30 min. Then 1 M NaOH was added and was extracted with EtOAc (30 mL x 3) and concentrated to dryness to give the title compound (700 mg, 36% yield) as a pale yellow solid. MS (ESI): mass calcd. for $C_{12}H_{12}N_2$, 184.24; m/z found, 185.1 $[M+H]^+$.

Intermediate 49: 2-Methyl-6-phenoxypyridin-3-amine.

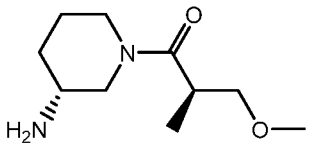


Step A: 2-methyl-3-nitro-6-phenoxypyridine. A round bottom flask containing 6-chloro-2-methyl-3-nitropyridine (50.1 g, 290 mmol) and CH_3CN (230 mL) was cooled at 0 °C. Phenol (41.0 g, 436 mmol) was added followed by Cs_2CO_3 (148 g, 454 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 15 h. The mixture was transferred to a 2L Erlenmeyer flask, then diluted with water to a total volume of 1.8 L. The resulting suspension was stirred at room temperature for 10 min, then the solid was isolated by filtration, rinsed with water and dried to yield the title compound (64.7 g, 97% yield) as a brown solid. MS (ESI): mass calcd. for $C_{12}H_{10}N_2O_3$, 230.07; m/z found, 231.0 $[M+H]^+$

Step B: 2-methyl-6-phenoxypyridin-3-amine. A round bottom flask containing 2-methyl-3-nitro-6-phenoxypyridine (64.7 g, 281 mmol) was treated with EtOH (500 mL) and a suspension of

10%Pd/C (4.17 g) in EtOH (300 mL). The mixture was degassed under vacuum and vented to an atmosphere of H_2. The reaction was stirred vigorously at room temperature for 7 h. The reaction mixture was filtered through celite, the filtrate was concentrated to about 400 mL, then water was added slowly until the total volume was 1.5 L. The resulting precipitate was filtered, and the filter cake was rinsed with water then dried under vaccum to provide the title compound (50.5 g, 90%) as an off-white solid. MS (ESI): mass calcd. for $C_{12}H_{12}N_2O$, 200.09; m/z found, 201.0 $[M+H]^+$

Intermediate 50: (2R)-1-[(3R)-3-Amino-1-piperidyl]-3-methoxy-2-methyl-propan-1-one.

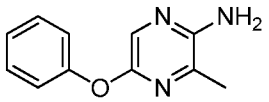


Step A: *tert*-Butyl *N*-[(3*R*)-1-[(2*S*)-2-hydroxypropanoyl]-3-piperidyl]carbamate. To a solution of (2*R*)-3-hydroxy-2-methyl-propanoic acid (78 mg, 0.75 mmol), HATU (342 mg, 0.90 mmol), and triethylamine (0.157 mL, 1.12 mmol) in DMF (3 mL) was added *tert*-butyl *N*-[(3*R*)-3-piperidyl]carbamate and the reaction was stirred at rt overnight. The reaction mixture was purified using flash column chromatography to give the title compound as a colorless liquid (138 mg, 68%).

Step B: *tert*-Butyl *N*-[(3*R*)-1-[(2*R*)-3-methoxy-2-methyl-propanoyl]-3-piperidyl]carbamate. A solution of *tert*-butyl *N*-[(3*R*)-1-[(2*S*)-2-hydroxypropanoyl]-3-piperidyl]carbamate (128 mg, 0.447 mmol), Ag_2O (311 mg, 1.34 mmol), MeI (1 mL), and DCM (2 mL) was sparged with N_2 and stirred at 40 °C for 3 days. The mixture was filtered through a pad of Celite and the filtrated was concentrated to dryness to give the title compound (121 mg, 91%), was used in next step without further purification.

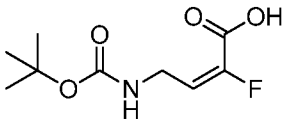
Step C: (2*R*)-1-[(3*R*)-3-Amino-1-piperidyl]-3-methoxy-2-methyl-propan-1-one. To a solution of 2 M HCl in MeOH (2 mL) was added *tert*-butyl *N*-[(3*R*)-1-[(2*R*)-3-methoxy-2-methyl-propanoyl]-3-piperidyl]carbamate (121 mg, 0.403 mmol). The reaction mixture was stirred at rt overnight. The reaction mixture was concentrated to dryness to give the title compound (73 mg, 90%), was used in next step without further purification. MS (ESI): mass calcd. for $C_{10}H_{20}N_2O_2$, 200.2; m/z found, 201.2 $[M+H]^+$.

Intermediate 51: 3-Methyl-5-phenoxy-pyrazin-2-amine.



A solution of 5-bromo-3-methyl-pyrazin-2-amine (1000 mg, 5.32 mmol), phenol (650 mg, 6.91 mmol), Cs_2CO_3 (2600 mg, 7.98 mmol), CuI (203 mg, 1.06 mmol), and N,N-dimethylglycine (110 mg, 1.06 mmol) in dioxane (5 mL) was degassed and heated to 90 °C under N_2 for 12 h. After cooling to room temperature, the mixture was diluted with EtOAc (100 mL) and water (100 mL) and the organic phase collected. The aqueous layer was extracted again with EtOAc (100 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to dryness. The residue was purified by flash column chromatography to give the title compound as a yellow oil (533 mg, 49.8% yield). MS (ESI): mass calcd. for $C_{11}H_{11}N_3O$, 201.1; m/z found, 202.1 $[M+H]^+$.

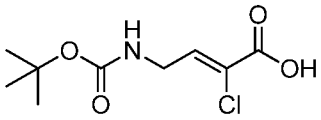
Intermediate 52: (E)-4-(*tert*-Butoxycarbonylamino)-2-fluoro-but-2-enoic acid.



Step A: Ethyl (E)-4-((*tert*-Butoxycarbonyl)amino)-2-fluorobut-2-enoate. A solution of ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate (500 mg, 2.07 mmol) in THF (5 mL) was cooled to 0 °C in ice-batch and NaH (60%, 50.0 mg, 2.07 mmol) was added and was stirred for 30 min. *tert*-Butyl (2-oxoethyl)carbamate was added to the reaction mixture slowly and the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was worked up with DCM and water. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to dryness to give the title compound.

Step B: (*E*)-4-(*tert*-Butoxycarbonylamino)-2-fluoro-but-2-enoic acid. The intermediate ethyl (E)-4-((*tert*-butoxycarbonyl)amino)-2-fluorobut-2-enoate was dissolved in dioxane (5 mL) and water (5 mL), and NaOH was added and was reacted for 10 min. The mixture was acidified with 2 M HCl to pH ~2 and extracted with DCM. The organics were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to dryness to give the title compound as a white solid (210 mg, 46% yield).

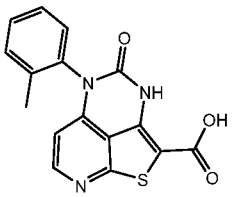
Intermediate 53: (Z)-4-(*tert*-Butoxycarbonylamino)-2-chloro-but-2-enoic acid.



Step A: Ethyl (*Z*)-4-(*tert*-butoxycarbonylamino)-2-chloro-but-2-enoate. A solution of NaH (60%, 0.186 g, 7.73 mmol) and THF (15 mL) was cooled to 0 °C and ethyl 2-chloro-2-diethoxyphosphoryl-acetate (1.0 g, 3.9 mmol) was added drop wise and stirred at 0 °C for 1 h. Then *tert*-butyl *N*-(2-oxoethyl)carbamate (0.615 g, 3.87 mmol) was added dropwise and stirred at 0 °C for 1 h. The mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness to give the title compound as yellow liquid (0.59 g, 58%).

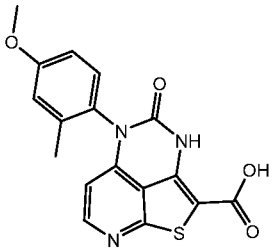
Step B: (*Z*)-4-(*tert*-Butoxycarbonylamino)-2-chloro-but-2-enoic acid. To a solution of ethyl (*Z*)-4-(*tert*-butoxycarbonylamino)-2-chloro-but-2-enoate (0.590 g, 2.24 mmol) in dioxane (10 mL) and H_2O (10 mL) was added KOH (0.628 g, 11.2 mmol) and the mixture was stirred at 60 °C for 2 h. Then the pH of the mixture was adjusted to about 2, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give the title compound as a light yellow solid (0.37 g, 70% yield), which was used in the next step directly.

Intermediate 54: 4-Oxo-5-(o-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



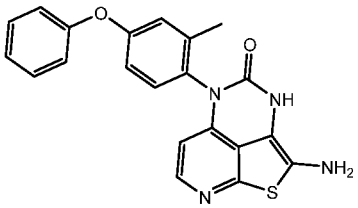
The title compound was prepared using Method 1, steps C-F in Example 1, using *o*-toluidine in place of 2-methyl-4-phenoxyaniline in step C. MS (ESI): mass calcd. for $C_{16}H_{11}N_3O_3S$, 325.1; m/z found, 326.0 $[M+H]^+$.

Intermediate 55: 5-(4-Methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



The title compound was prepared using Method 1, steps C-F, in Example 1, using 4-methoxy-2-methylaniline in place of 2-methyl-4-phenoxyaniline in step C. MS (ESI): mass calcd. for $C_{17}H_{13}N_3O_4S$, 355.1; m/z found, 356.0 $[M+H]^+$.

Intermediate 56: 2-Amino-5-(2-methyl-4-phenoxyphenyl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one.

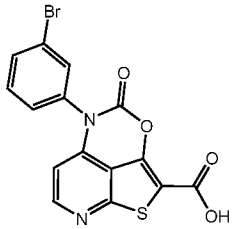


Step A: *tert*-Butyl (5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylen-2-yl)carbamate. 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 16) (200 mg, 0.479 mmol) was heated under reflux in redistilled thionyl chloride (0.50 mL) for 5 h. The thionyl chloride was removed under reduced pressure and the residue was taken up in dry acetone (2 mL), cooled to 0 °C, and sodium azide (500 mg, 7.69 mmol) was added dropwise with stirring and the solution was allowed to warm to 20 °C over 10 min. The reaction was diluted with water, extracted with EtOAc, and the solvent was removed under reduced pressure. The residue was taken up into *t*-butyl alcohol (37.5 mL) and was heated at reflux for 5 h. The reaction was concentrated to dryness to give the title compound (180 mg, 53.9% yield). MS (ESI): mass calcd. for $C_{26}H_{24}N_4O_4S$, 488.56; m/z found, 489.0 $[M+H]^+$.

Step B: 2-Amino-5-(2-methyl-4-phenoxyphenyl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one. To a solution of *tert*-butyl (5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylen-2-yl)carbamate (180 mg, 0.258 mmol) in DCM (10 mL) were added 2,6-lutidine (166 mg, 1.55 mmol) and trimethylsilyl trifluoromethanesulfonate (344 mg, 1.55 mmol) and was stirred at 20 °C for 2 h. The reaction was quenched by the addition of $NaHCO_3$ in ice water. The organic layer was separated and the aqueous layer was extracted with ethyl

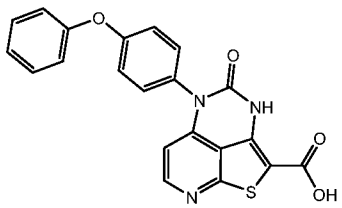
acetate (2 × 50 mL). The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by preparative HPLC (column: YMC-Actus Triart C18 150 × 30 mm, 5 μm, mobile phase A: water (0.075% TFA (aq.), V/V; B: acetonitrile, B in A from 35% to 65%, flow rate: 35 mL/min) to give the title compound (40 mg, 28% yield). MS (ESI): mass calcd. for $C_{21}H_{16}N_4O_2S$, 388.1; m/z found, 389.1 $[M+H]^+$.

Intermediate 57: 5-(3-Bromophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



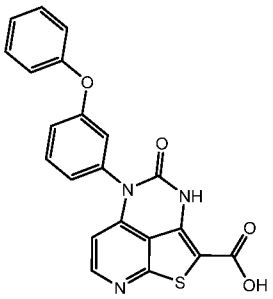
The title compound was prepared using Method 1, steps C-F in Example 1, and using 3-bromoaniline in place of 2-methyl-4-phenoxy-aniline in step C. MS (ESI): mass calcd. for $C_{15}H_8BrN_3O_3S$, 388.9; m/z found, 390.2 $[M+H]^+$.

Intermediate 58: 4-Oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



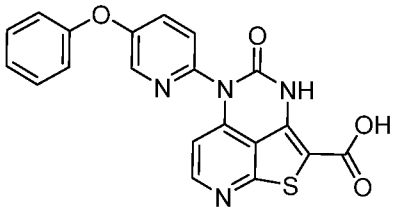
The title compound was prepared using Method 1, steps A-F in Example 1, using 4-fluoronitrobenzene in place of 5-fluoro-2-nitrotoluene in step A. MS (ESI): mass calcd. for $C_{21}H_{13}N_3O_4S$, 403.1; m/z found, 404.0 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d6): δ 8.36 (d, J = 5.5 Hz, 1H), 7.52 - 7.42 (m, 4H), 7.25 - 7.11 (m, 6H), 6.09 (d, J = 5.5 Hz, 1H).

Intermediate 59: 4-Oxo-5-(3-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



The title compound was prepared using Method 1, steps C-F, in Example 1, using 3-phenoxyaniline in place of 2-methyl-4-phenoxyaniline in step C. MS (ESI): mass calcd. for $C_{21}H_{13}N_3O_4S$, 403.1; m/z found, 404.1 $[M+H]^+$.

Intermediate 60: 4-Oxo-5-(5-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



Step A: 2-Nitro-5-phenoxypyridine. A round bottom flask containing 5-bromo-2-nitropyridine (300 g, 1480 mmol) and DMSO (1200 mL) was treated with phenol (167 g, 1770 mmol) followed by Cs_2CO_3 (722 g, 2220 mmol). The reaction mixture was stirred at 50 °C for 4 h. The mixture was transferred to a flask containing ice-water (5 L). The resulting precipitate was collected by filtration, rinsed with water, and dried at 70 °C under vacuum to yield the title compound (230 g, 72% yield) as a grey solid. MS (ESI): mass calcd. for $C_{11}H_8N_2O_3$, 216.05; m/z found, 217.0 $[M+H]^+$.

Step B: 5-Phenoxypyridin-2-amine. To a solution of 2-nitro-5-phenoxypyridine (100 g, 463 mmol) in MeOH (1.5 L) was added 10% Pd-C (10 g). The reaction mixture was stirred under an atmosphere of H_2 at room temperature for 24 hours. The mixture was filtered, and the filtrate was concentrated to dryness under vacuo to yield the title compound (85 g, 99% yield) as a yellow solid. MS (ESI): mass calcd. for $C_{11}H_{10}N_2O$, 186.08; m/z found, 187.1 $[M+H]^+$.

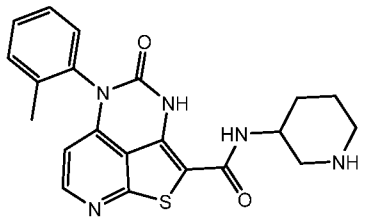
Step C: Methyl 3-amino-4-((5-phenoxypyridin-2-yl)amino)thieno[2,3-b]pyridine-2-carboxylate. To a round bottom flask containing 2-chloro-4-iodopyridine-3-carbonitrile (148 g, 559 mmol) and 5-phenoxypyridin-2-amine (80.0 g, 430 mmol) were added $Pd(OAc)_2$ (9.62 g, 43.0 mmol), followed by bis(2-diphenylphosphinophenyl)ether (DPEphos, 46.2 g, 85.9 mmol), and cesium

carbonate (350.0 g, 107.0 mmol). The reaction mixture was treated with 1,4-dioxane (2 L), the vessel was purged with N_2, then stirred at 105 °C for 3 h. Methyl 2-sulfanylacetate (68.4 g, 644 mmol) was added, and the reaction was heated for an additional 16 h at 105 °C. The reaction mixture was filtered, the filtrate was concentrated to dryness, and the residue was treated with MeOH (800 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (130 g, 77%) as a yellow solid. MS (ESI): mass calcd. for $C_{20}H_{16}N_4O3S$, 392.09; m/z found, 393.2 $[M+H]^+$.

Step D: Methyl 4-oxo-5-(5-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate. To a round bottom flask were added methyl 3-amino-4-((5-phenoxypyridin-2-yl)amino)thieno[2,3-b]pyridine-2-carboxylate (28.3 g, 72.1 mmol), carbonyldiimidazole (58.5 g, 361 mmol), and 1,4-dioxane (200 ml). The reaction was heated at reflux for 16 h. Then the reaction mixture was concentrated to dryness and the residue was treated with MeOH (200 mL). The resulting precipitate was isolated by filtration, rinsed with cold MeOH, and dried under vacuum to yield the title compound (21.0 g, 70% yield) as a yellow solid. MS (ESI): mass calcd. for $C_{21}H_{14}N_4O_4S$, 418.07; m/z found, 419.0 $[M+H]^+$.

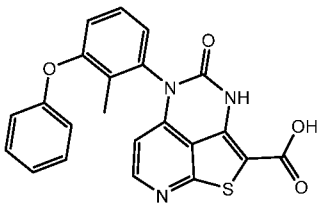
Step E: 4-Oxo-5-(5-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid. To a round bottom flask were added methyl 4-oxo-5-(5-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate (20.0 g, 47.8 mmol), lithium hydroxide (20.0 g, 476 mmol), THF (250 mL), MeOH (100 mL), and water (100 mL). The reaction mixture was stirred at 80 °C for 4 h. The mixture was concentrated to dryness and diluted with H_2O (100 mL). The pH was adjusted to 1 with 1 M HCl and the precipitate was filtered and dried to yield the title compound (18.0 g, 93% yield) as yellow solid. MS (ESI): mass calcd. for $C_{20}H_{12}N_4O_4S$, 404.06; m/z found, 405.0 $[M+H]^+$.

Intermediate 61: 4-Oxo-N-(piperidin-3-yl)-5-(o-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



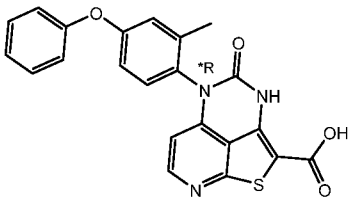
The title compound was prepared using Method 1, step G-H in Example 1, using using 4-oxo-5-(o-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 54) and *tert*-butyl-3-aminopiperidine-1-carboxylate in place of 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid and *tert*-butyl (3*R*,5*R*)-3-amino-5-fluoropiperidine-1-carboxylate. MS (ESI): mass calcd. for $C_{21}H_{21}N_5O_2S$, 407.1; m/z found, 408.1 $[M+H]^+$.

Intermediate 62: 5-(2-Methyl-3-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



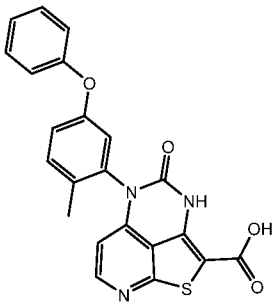
The title compound was prepared using Method 1, steps A-F, in Example 1, using 1-bromo-2-methyl-3-nitrobenzene in place of 4-fluoro-2-methyl-1-nitrobenzene in step A. MS (ESI): mass calcd. for $C_{22}H_{15}N_3O_4S$, 417.1; m/z found, 418.0 $[M+H]^+$.

Intermediate 63: (*R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



The title compound was prepared using Method 1, steps A-F in Example 1 (including Chiral resolution Method A after Step F to obtain the **R* atropisomer). MS (ESI): mass calcd. for $C_{22}H_{15}N_3O_4S$, 417.1; m/z found, 418.0 $[M+H]^+$.

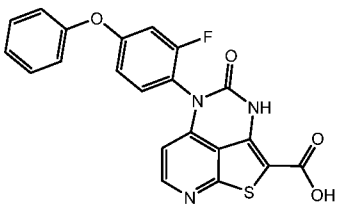
Intermediate 64: 5-(2-Methyl-5-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



Step A: 1-Methyl-2-nitro-4-phenoxybenzene. A mixture of 4-methyl-3-nitrophenol (3.06g, 20mmol), phenylboronic acid (4.88g, 40 mmol), $Cu(AcO)_2$ (5.20g, 40 mmol) and 4A MS (1.5g) in DCM was stirred at rt under oxygen overnight, then the reaction was filtratered and concentrated. The crude was purified using with ISCO elutiing with PE/EA to give the title compound (3.16g, 67%).

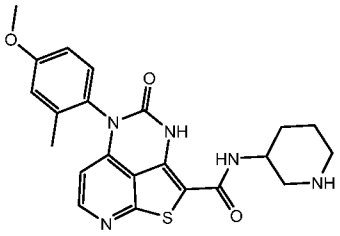
Step B: 5-(2-Methyl-5-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid. The title compound was prepared using Method 1, steps B-F, in Example 1, using 1-methyl-2-nitro-4-phenoxybenzene in place of 2-methyl-1-nitro-4-phenoxybenzene in step B. MS (ESI): mass calcd. for $C_{22}H_{15}N_3O_4S$, 417.1; m/z found, 418.0 $[M+H]^+$.

Intermediate 65: 5-(2-Fluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



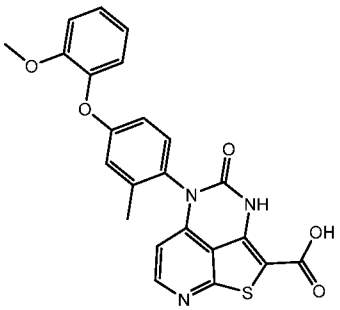
The title compound was prepared using conditions analogous to Intermediate 64, steps A-B, using 3-fluoro-4-nitrophenol in place of 4-methyl-3-nitrophenol. MS (ESI): mass calcd. for $C_{21}H_{12}FN_3O_4S$, 421.1; m/z found, 422.0 $[M+H]^+$.

Intermediate 66: 5-(4-Methoxy-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared using Method 1, step G in Example 1, and using 5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 55) and *tert*-butyl-3-aminopiperidine-1-carboxylate in place of 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid and *tert*-butyl (3*R*,5*R*)-3-amino-5-fluoropiperidine-1-carboxylate. MS (ESI): mass calcd. for $C_{22}H_{23}N_5O_3S$, 437.2; m/z found, 438.1 $[M+H]^+$.

Intermediate 67: 5-(4-(2-Methoxyphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



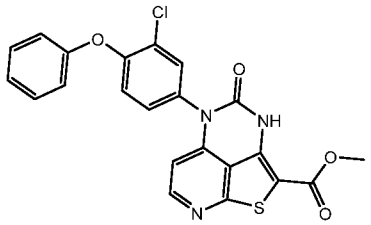
Step A: Methyl 5-(4-bromo-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate. The title compound was prepared using Method 1, steps C-E, in Example 1, using 4-bromo-2-methylaniline in place of 2-methyl-4-phenoxyaniline in step C as a yellow solid.

Step B: Methyl 5-(4-(2-methoxyphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate. The mixture of methyl 5-(4-bromo-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate (1.0 g, 2.2 mmol), 2-methoxyphenol (1.1 g, 8.9 mmol), Cs_2CO_3 (1.4 g, 4.4 mmol), CuCl (44 mg, 0.44 mmol), quinolin-8-ol (64 mg, 0.44 mmol) in NMP (10 mL) was stirred at 165 °C in sealed tube for 35 minutes. Then was purified by flash column chromatography eluting with PE/EA to yield the title compound (634 mg, 62% yield) as a grey solid.

Step C: 5-(4-(2-Methoxyphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid. The title compound was prepared using Method 1, step

F, in Example 1, using methyl 5-(4-(2-methoxyphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate in place of methyl 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate as a grey solid. MS (ESI): mass calcd. for $C_{23}H_{17}N_3O_5S$, 447.1; m/z found, 448.0 $[M+H]^+$.

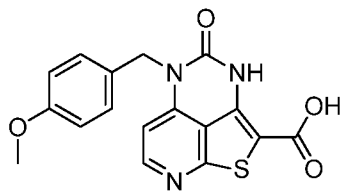
Intermediate 68: Methyl 5-(3-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate.



Step A: 3-Chloro-4-phenoxyaniline. The title compound was prepared using analogous conditions described in Method 1, steps A-B in Example 1, and using 2-chloro-1-fluoro-4-nitrobenzene in place of 5-fluoro-2-nitrotoluene in step A, to give the title compound. MS (ESI): mass calcd. for $C_{12}H_{10}ClNO$, 219.67; m/z found, 220.1 $[M+H]^+$.

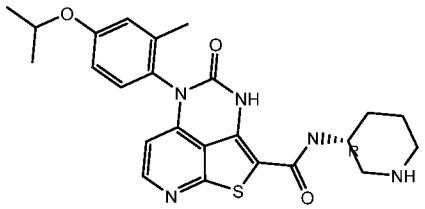
Step B: Methyl 5-(3-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate. The title compound was prepared using analogous conditions described in Example 534, step A, and using 3-chloro-4-phenoxyaniline and methyl 2-sulfanylacetate in place of 3-cyclobutylaniline and *tert*-butyl (3*R*)-3-[(2-sulfanylacetyl)amino]piperidine-1-carboxylate (Intermediate 22), to give the title compound. MS (ESI): mass calcd. for $C_{12}H_{10}ClNO$, 219.0; m/z found, 220.1 $[M+H]^+$.

Intermediate 69: 5-(4-Methoxybenzyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



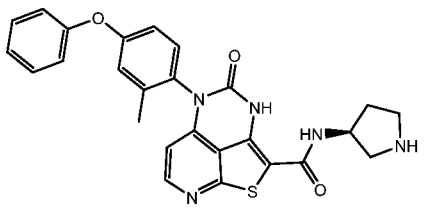
The title compound was prepared using Method 1, steps C-F in Example 1, using (4-methoxyphenyl)methanamine in place of 2-methyl-4-phenoxyaniline and DIPEA in place of Cs_2CO_3, $Pd(AcO)_2$ and DPEphos in step C. MS (ESI): mass calcd. for $C_{17}H_{13}N_3O_4S$, 355.1; m/z found, 356.0 $[M+H]^+$.

Intermediate 70: (R)-5-(4-Isopropoxy-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



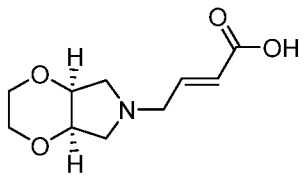
The title compound was prepared using Method 1, steps B-H in Example 1, and using 4-isopropoxy-2-methyl-1-nitrobenzene in place of 2-methyl-1-nitro-4-phenoxybenzene in step B, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of *tert*-butyl (3*R*,5*R*)-3-amino-5-fluoropiperidine-1-carboxylate in step G. MS (ESI): mass calcd. for $C_{24}H_{27}N_5O_3S$, 465.2; m/z found, 466.2 $[M+H]^+$.

Intermediate 71: (S)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared using Method 1, step G-H, in Example 1, using *tert*-butyl (S)-3-aminopyrrolidine-1-carboxylate in place of *tert*-butyl (3*R*,5*R*)-3-amino-5-fluoropiperidine-1-carboxylate in step G. MS (ESI): mass calcd. for $C_{26}H_{23}N_5O_3S$, 485.2; m/z found, 486.5 $[M+H]^+$.

Intermediate 72: (E)-4-((4aR,7aS)-Hexahydro-6H-[1,4]dioxino[2,3-c]pyrrol-6-yl)but-2-enoic acid.



Step A: Benzyl 3,4-dihydroxypyrrolidine-1-carboxylate. Benzyl 2,5-dihydro-1*H*-pyrrole-1-carboxylate (5.0 g, 25 mmol) was taken up in THF (40 mL) and water (15 mL) and to this solution were added OsO_4 (63 mg, 0.25 mmol) and 4-methylmorpholine 4-oxide (3.75 g, 32.0 mmol). The reaction was stirred at room temperature for 15 h. The reaction was concentrated to

dryness and the crude was partitioned between EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated to dryness, and purified by normal phase flash column chromatography (SiO_2) to give the title compound (4.8 g, 82% yield). MS (ESI): mass calcd. for $C_{12}H_{15}NO_4$, 237.25; m/z found, 238.1 $[M+H]^+$.

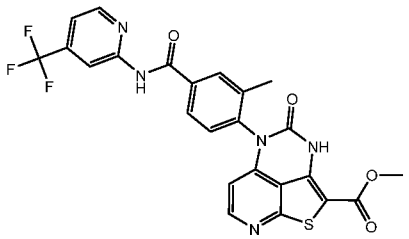
Step B: (4*aR*,7*aS*)-Benzyl tetrahydro-2*H*-[1,4]dioxino[2,3-*c*]pyrrole-6(3*H*)-carboxylate. To a solution of NaOH (9.00 g, 225 mmol) in water (30 mL) were added benzyl 3,4-dihydroxypyrrolidine-1-carboxylate (4.8 g, 20 mmol), and dichloroethane (30 mL). To this solution was added tetrabutylammonium fluoride (2.65 g, 10.1 mmol) and the mixture was stirred at 55 °C for 48 h. The mixture was extracted with DCM, concentrated to dryness, and purified by normal phase flash column chromatography (SiO_2) to give the title compound as a white solid (0.96 g, 18% yield). MS (ESI): mass calcd. for $C_{14}H_{17}NO_4$, 263.29; m/z found, 264.1 $[M+H]^+$.

Step C: (4*aR*,7*aS*)-3,4*a*,5,6,7,7*a*-Hexahydro-2*H*-[1,4]dioxino[2,3-*c*]pyrrole. A solution of (4*aR*,7*aS*)-benzyl tetrahydro-2*H*-[1,4]dioxino[2,3-*c*]pyrrole-6(3*H*)-carboxylate (0.96 g, 3.6 mmol), $Pd(OH)_2$ (51 mg, 0.36 mmol), and MeOH (10 mL) were reacted at room temperature for 3 h under H_2. The mixture was filtered and concentrated to dryness to give the title compound as a light yellow solid (0.43 g, 91% yield). MS (ESI): mass calcd. for $C_6H_{11}NO_2$, 129.16; m/z found, 130.4 $[M+H]^+$.

Step D: (*E*)-Methyl 4-((4*aR*,7*aS*)-tetrahydro-2*H*-[1,4]dioxino[2,3-*c*]pyrrol-6(3*H*)-yl)but-2-enoate. To a solution of methyl (*E*)-4-bromobut-2-enoate (42 mg, 0.23 mmol) and diisopropylethylamine (30 mg, 0.23 mmol) in THF (10 mL) was added (4*aR*,7*aS*)-3,4*a*,5,6,7,7*a*-hexahydro-2*H*-[1,4]dioxino[2,3-*c*]pyrrole (30 mg, 0.23 mmol), and was stirred at room temperature for 15 h. The mixture was concentrated to dryness to give the title compound (55 mg), which was used in the next step without further purification. MS (ESI): mass calcd. for $C_{11}H_{17}NO_4$, 227.26; m/z found, 228.1 $[M+H]^+$.

Step E: (*E*)-4-((4*aR*,7*aS*)-Tetrahydro-2*H*-[1,4]dioxino[2,3-*c*]pyrrol-6(3*H*)-yl)but-2-enoic acid. A solution of (E)-methyl 4-((4aR,7aS)-tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)but-2-enoate (55 mg, 0.24 mmol) and aqueous 4 M HCl (5 mL) was reacted at reflux for 1 h. The mixture was concentrated to dryness to give the title compound (55 mg, 106%), which was used without further purification.

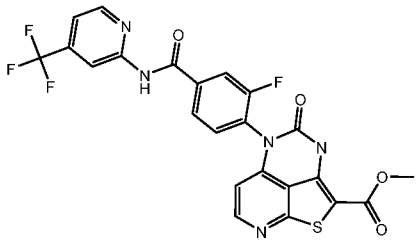
Intermediate 73: Methyl 5-(2-methyl-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate.



Step A: 3-Methyl-4-nitro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide. To a solution of 3-methyl-4-nitrobenzoic acid (3.0 g, 16.6 mmol) in DCM (100 mL) was added one drop of DMF and oxalyl dichloride (10.5 g, 82.8 mmol). The mixture was stirred at room temperature for 30 minutes, then concentrated and diluted in DCM, then added to a solution of 4-(trifluoromethyl)pyridin-2-amine (2.7 g, 16.6 mmol), triethylamine in DCM under ice-bath, stirred for 1 hour. The mixture was concentrated to yield the title compound as a yellow solid, which was used forward next step without further purification.

Step B: Methyl 5-(2-methyl-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate. The title compound was prepared using Method 1, steps B-E, in Example 1, using 3-methyl-4-nitro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide in place of 2-methyl-1-nitro-4-phenoxybenzene in step B.

Intermediate 74: Methyl 5-(2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate.

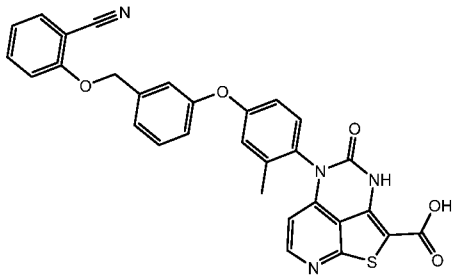


Step A: 3-Fluoro-4-nitro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide. To the suspension of 3-fluoro-4-nitrobenzoic acid acid (4.1 g, 22.1 mmol) in 30 ml of DCM was added Oxalyl chloride (3.0 g, 24.4 mmol) and 1 drop of DMF, then was stirred at room temperature for 4 hours. After concentration under vacuo to dryness, the residue was dissolved in 10 ml of DCM and was added a solution of 4-(trifluoromethyl)pyridin-2-amine (3.6 g, 22.1 mmol) in 30 ml of DCM, stirred at room temperature for 5 mins. The mixture was concentrated and purified by

ISCO using MeOH/H_2O as eluent to get the title compound as yellow solid acid (5.0 g, 69% yield).

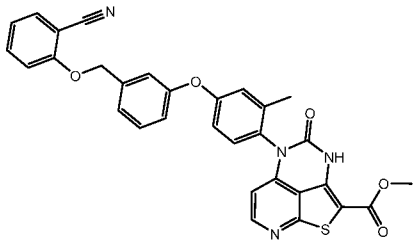
StepB: Methyl 5-(2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate. The title compound was prepared using Method 1, steps B-E in Example 1, using 3-fluoro-4-nitro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide in place of 2-methyl-1-nitro-4-phenoxybenzene in step B.

Intermediate 75: 5-(4-(3-((2-Cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



The title compound was prepared using Method 1, step F in Example 1, using methyl 5-(4-(3-((2-cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate (Intermediate 76) in place of methyl 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate. MS (ESI): mass calcd. for $C_{30}H_{20}N_4O_5S$, 548.1; m/z found, 549.0 $[M+H]^+$.

Intermediate 76: Methyl 5-(4-(3-((2-cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate.



Step A: 3-((*tert*-Butyldimethylsilyl)oxy)benzaldehyde. To a mixture of 3-hydroxybenzaldehyde (24.4 g, 200 mmol) in DCM (500 mL) was added Et_3N (30.3 g, 300 mmol) and TBSCl (33.1 g, 220 mmol) and stirred room temperature for 3 hours. The reaction was dispersed between DCM and saturated NH_4Cl aq solution. The organic layer was collected, condensed and was purified by flash column chromatography (PE/EA) to give the title compound (47.3 g, 100% yield). ^1H

NMR (400 MHz, DMSO-d6): δ ppm 10.01 (s, 1 H), 7.50 - 7.63 (m, 2 H), 7.37 (s, 1 H), 7.25 (d, J=7.50 Hz, 1 H), 1.01 (s, 9 H), 0.26 (s, 6 H)

Step B: (3-((*tert*-Butyldimethylsilyl)oxy)phenyl)methanol. To a mixture of 3-((*tert*-butyldimethylsilyl)oxy)benzaldehyde (47.3 g, 200 mmol) in MeOH (30 mL) cooled to 0 °C was added portion wise $NaBH_4$ (3.78 g, 100 mmol). After the addition was completed the reaction was stirred at room temperature for 2 hours. Volatiles were removed under vacuo. Water and EtOAc were added to the residue, the organic layer was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuo to provide target product as yellow oil, which was used forward next step without further purification. Mass calcd. for $C_{13}H_{22}O_2Si$, 238.1. ^1H NMR (400 MHz, DMSO-d6): δ ppm 0.18 - 0.27 (m, 6 H) 0.99 (s, 9 H) 4.48 (s, 2 H) 5.23 (br. s., 1 H) 6.69 - 6.78 (m, 1 H) 6.85 (s, 1 H) 6.93 (d, J=7.50 Hz, 1 H) 7.23 (t, J=7.94 Hz, 1 H).

Step C: 2-((3-((*tert*-Butyldimethylsilyl)oxy)benzyl)oxy)benzonitrile. To a mixture of (3-((*tert*-butyldimethylsilyl)oxy)phenyl)methanol (13.94 g, 60 mmol) in THF (200 mL) were sequentially added 2-hydroxybenzonitrile (8.58 g, 72 mmol), Ph_3P (18.88 g, 72 mmol) and DIAD (14.56 g, 72 mmol): dropwise at room temperature and the reaction was stirred for 1 hour. Saturated aqueous NH_4Cl and EtOAc were added, the organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, condensed under vacuo and was purified by flash column chromatography (PE/EA) to give the title compound (17.0 g, 83% yield).

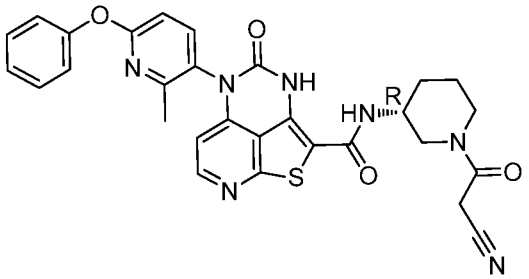
Step D: 2-((3-Hydroxybenzyl)oxy)benzonitrile. To a mixture of 2-((3-((*tert*-butyldimethylsilyl)oxy)benzyl)oxy)benzonitrile (17.0 g, 50 mmol) in THF (250 mL) was added a 1M solution TBAF (60 mL, 60 mmol) and the reaction was stirred at room temperature for 30 minutes. A saturated aqueous NH_4Cl solution and EtOAc were added, the organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, condensed and was purified by flash column chromatography(MeOH/DCM) to give the title compound (11.3 g, 100% yield).

Step E: 2-((3-(3-Methyl-4-nitrophenoxy)benzyl)oxy)benzonitrile. To a mixture of 2-((3-hydroxybenzyl)oxy)benzonitrile (11.3 g, 50 mmol), 4-fluoro-2-methyl-1-nitrobenzene (7.8 g, 50 mmol), K_2CO_3 (13.8 g, 10 0mmol) in 200 mL of DMSO was stirred under N_2 at 150 °C for 4 hours. The mixture was condensed and was purified by flash column chromatography (PE/EA) to give the title compound (15.1 g, 84% yield). MS (ESI): mass calcd. for $C_{21}H_{16}N_2O_4$, 360.1; m/z found, 361.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 - 7.98 (m, 1H), 7.74 - 7.62 (m, 1H), 7.62 - 7.39 (m, 6H), 7.39 - 7.31 (m, 1H), 7.22 - 7.17 (m, 1H), 7.09 - 6.97 (m, 3H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.55 (s, 1H), 5.21 (s, 2H), 2.58 (s, 3H).

Step F: 2-((3-(4-Amino-3-methylphenoxy)benzyl)oxy)benzonitrile. To a mixture of 2-((3-(3-methyl-4-nitrophenoxy)benzyl)oxy)benzonitrile (15.1 g, 42 mmol) in EtOH (420mL) and water (140 mL) were sequentially added NH_4Cl (11.2 g, 210 mmol), iron (9.38 g, 168 mmol) and the reaction mixture was stirred at reflux for 4 hours and then cooled to room temperature, The mixture was diluted with DCM (500 mL) and water (200 mL), the organic layer was collected, condensed and was purified by flash column chromatography (MeOH/water) to give the title compound (13.9 g, 100% yield). MS (ESI): mass calcd. for $C_{21}H_{18}N_2O_2$, 330.1; m/z found, 331.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (dd, J = 7.6, 1.7 Hz, 1H), 7.53 - 7.45 (m, 1H), 7.33 - 7.24 (m, 1H), 7.15 - 7.08 (m, 1H), 7.04 - 6.84 (m, 5H), 6.82 - 6.72 (m, 2H), 6.67 (d, J = 8.4 Hz, 1H), 5.14 (s, 2H), 2.15 (s, 3H).

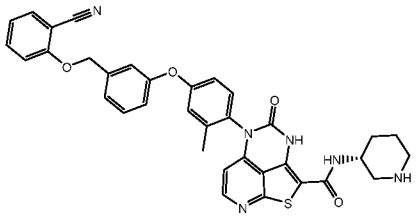
Step G: Methyl 5-(4-(3-((2-cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate. The title compound was prepared using Method 1, steps C-E in Example 1, using 2-((3-(4-amino-3-methylphenoxy)benzyl)oxy)benzonitrile in place of 2-methyl-4-phenoxyaniline in step C. MS (ESI): mass calcd. for $C_{31}H_{22}N_4O_5S$, 562.1; m/z found, 563.2 $[M+H]^+$.

Intermediate 77: (R)-N-(1-(2-Cyanoacetyl)piperidin-3-yl)-5-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



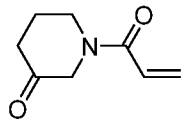
To a solution of (*R*)-5-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 711) (3.4 g, 6.8 mmol) in DCM (50 mL) was added triethylamine (2.06 g, 20.4 mmol) and was cooled to 0 °C. Next 2,5-dioxopyrrolidin-1-yl 2-cyanoacetate (1.86 g, 10.2 mmol) was added slowly and after the addition was complete, it was stirred at room temperature for 1 h. The reaction was washed with 1% HCl, $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was washed with DCM, the solid was collected by filtration and dried in a vacuum to give the title compound (3.0 g, 58% yield) as a yellow solid. MS (ESI): mass calcd. for $C_{29}H_{25}N_7O_4S$, 567.62; m/z found, 568.1 $[M+H]^+$.

Intermediate 78: (R)-5-(4-(3-((2-Cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



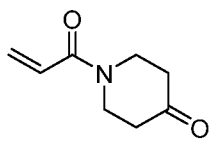
The title compound was prepared using Method 1, step G-H in Example 1, and using 5-(4-(3-((2-cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 75) and *tert*-butyl (*R*)-3-aminopiperidine-1-carboxylate in place of 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid and *tert*-butyl (3*R*,5*R*)-3-amino-5-fluoropiperidine-1-carboxylate. MS (ESI): mass calcd. for $C_{35}H_{30}N_6O_4S$, 630.2; m/z found, 631.0 $[M+H]^+$.

Intermediate 79: 1-Acryloylpiperidin-3-one.



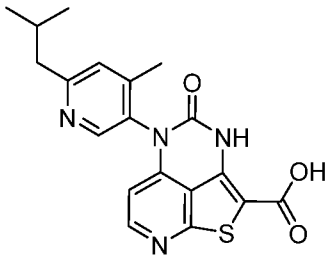
A solution of *tert*-butyl 3-oxopiperidine-1-carboxylate (1.00 g, 5.0 mmol) in 6 M HCl in MeOH (25 mL) was stirred at rt for 30 min, then concentrated to dryness. The residue was diluted in acetone/water (50 mL), and triethylamine (1.02 g, 10.0 mmol) and K_2CO_3 (1.39 g, 10.0 mmol) were added, followed by addition of prop-2-enoyl chloride (454 mg, 5.0 mmol). The mixture was stirred at rt for 18 h, extracted with EtOAc, the organic layers washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified by flash column chromatography to give the title compound as a white solid (480 mg, 62% yield). MS (ESI): mass calcd. for $C_8H_{11}NO_2$, 153.1; m/z found, 154.1 $[M+H]^+$.

Intermediate 80: 1-Acryloylpiperidin-4-one.



A solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (1.5 g, 7.5 mmol) in 6 M HCl in MeOH (25 mL) was stirred at rt for 30 min, then concentrated to dryness. The residue was diluted in acetone/water (30 mL), and triethylamine (2.28 g, 22.6 mmol) and K_2CO_3 (2.08 g, 15.1 mmol) were added, followed by the addition of prop-2-enoyl chloride (681 mg, 7.53 mmol). The mixture was stirred at rt for 18 h, then extracted with EtOAc and the organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified by flash column chromatography to give the title compound as a white solid (500 mg, 43%). MS (ESI): mass calcd. for C8H11NO2, 153.1; m/z found, 154.1 $[M+H]^+$.

Intermediate 81: 5-(6-Isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



Step A: 6-Isobutyl-4-methylpyridin-3-amine. To a 200 mL round bottom flask was were added 6-bromo-4-methylpyridin-3-amine (5.42 g, 29.0 mmol), a stir bar, and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (520 mg, 0.6 mmol). The vessel was evacuated then back filled with nitrogen. THF (20 mL) was added, followed by isobutylzinc(II) bromide (80 mL, 40 mmol) via syringe, then the reaction mixture was heated to 60 °C for 2 h. The reaction mixture was treated with saturated aqueous sodium bicarbonate (300 mL) and extracted with EtOAc (2 × 300 mL). The combined organic layers were dried ($MgSO_4$), concentrated to dryness, and the residue purified by flash column chromatography to give the title compound (3.65 g, 77% yield) as a brown solid. MS (ESI): mass calcd. for $C_{10}H_{16}N_2$, 164.1; m/z found, 165.1 $[M+H]^+$.

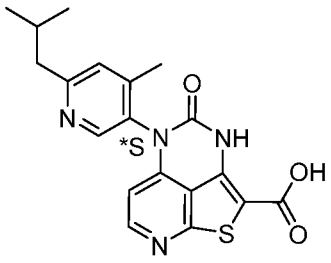
Step B: Methyl 3-amino-4-((6-isobutyl-4-methylpyridin-3-yl)amino)thieno[2,3-b]pyridine-2-carboxylate. To a round bottom flask under a N_2 atmosphere were added 6-isobutyl-4-methylpyridin-3-amine (53.5 g, 326 mmol), 2-chloro-4-iodopyridine-3-carbonitrile (94.8 g, 358 mmol), and dioxane (1000 mL), followed by bis(2-diphenylphosphinophenyl)ether (DPEphos) (10.5 g, 19.5 mmol), $Pd(OAc)_2$ (2.92 g, 13.0 mmol), and Cs_2CO_3 (265 g, 814 mmol). The reaction mixture was stirred at 105 °C overnight. The reaction mixture was filtered and concentrated. The residue was suspended in MeOH (400 mL) and stirred for 2 h at room

temperature. The resulting precipitate was isolated by filtration and dried under vacuum to give the title compound (75.3 g, 62% yield) as a yellow solid.

Step C: Methyl 5-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate. To a round bottom flask were added Methyl 3-amino-4-((6-isobutyl-4-methylpyridin-3-yl)amino)thieno[2,3-b]pyridine-2-carboxylate (30.0 g, 81 mmol), carbonyldiimidazole (CDI, 39.4 g, 243 mmol), trimethylamine (24.6 g, 243 mmol) and 1,4-dioxane (300 mL). The reaction was stirred at 100 °C for 6 h, then cooled to 50 °C. The resulting precipitate was collected by filtration, rinsed with MeOH and dried under vacuum to yield the title compound (27 g, 84%) as an off-white solid.

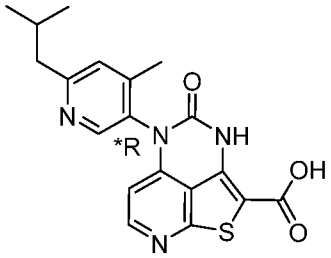
Step D: 5-(6-Isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid. To a round bottom flask were added methyl 5-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate (68.0 g, 172 mmol), lithium hydroxide (36.0 g, 858 mmol), and a mixture of 5:2:2 THF:MeOH:H_2O (4 L). The reaction mixture was stirred at 80 °C for 4.5 h. The mixture was concentrated to dryness and diluted with H_2O. The solution was acidified by the addition of 1 M HCl and the resulting precipitate was filtered and dried under vacuum to yield the title compound (63 g, 96% yield) as yellow solid. MS (ESI): mass calcd. for $C_{19}H_{18}N_4O_3S$, 382.11; m/z found, 383.1 $[M+H]^+$.

Intermediate 82: 5-(*S)-(6-Isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



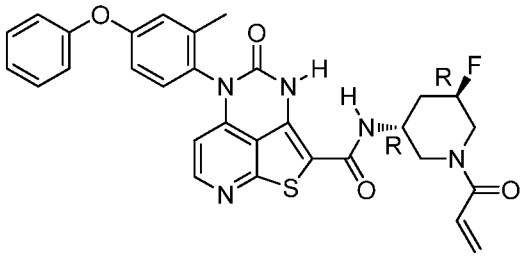
5-(6-Isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 81) was resolved using Chiral resolution Method B to obtain the title compound (*S atropisomer). MS (ESI): mass calcd. for $C_{19}H_{18}N_4O_3S$, 382.1; m/z found, 383.0 $[M+H]^+$.

Intermediate 83: 5-(*R)-(6-Isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid.



5-(6-Isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 81) was resolved using Chiral resolution Method B to obtain the title compound (*R atropisomer). MS (ESI): mass calcd. for $C_{19}H_{18}N_4O_3S$, 382.1; m/z found, 383.0 $[M+H]^+$.

Example 1: *N*-((3*R*,5*R*)-1-Acryloyl-5-fluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Method 1, Step A: 2-Methyl-1-nitro-4-phenoxybenzene. To a round bottom flask were added phenol (42.5 g, 452 mmol), K_2CO_3 (125 g, 905 mmol), and DMF (500 mL). To the reaction mixture was added 5-fluoro-2-nitrotoluene (70.2 g, 452 mmol) and the reaction was stirred at 80 °C for 16 h under N_2. The reaction was diluted with saturated NH_4Cl and extracted with MTBE (3 × 400 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield the title compound (100 g, 92% yield) as a brown oil.

Method 1, Step B: 2-Methyl-4-phenoxyaniline. To a solution of 2-methyl-1-nitro-4-phenoxybenzene (100 g, 436 mmol) in EtOH/H_2O (3:1 ratio, 2000 mL) were sequentially added NH_4Cl (117 g, 2180 mmol) and Fe (97 g, 1700 mmol). The reaction mixture was heated to reflux for 2 h, then the reaction was cooled to 25 °C and concentrated to dryness. To the residue was added water and EtOAc and the organic layer was separated, washed with saturated $NaHCO_3$ and saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness to yield the title compound (82 g, 90% yield).

Method 1, Step C: 2-Chloro-4-(2-methyl-4-phenoxyanilino)pyridine-3-carbonitrile. To a round bottom flask under a N_2 atmosphere were added 2-methyl-4-phenoxyaniline (30 g, 150 mmol), 2-chloro-4-iodopyridine-3-carbonitrile (51.6 g, 195 mmol), and dioxane (200 mL), followed by bis(2-diphenylphosphinophenyl)ether (DPEphos) (16 g, 30 mmol), $Pd(OAc)_2$ (3.36 g, 15 mmol), and K_3PO_4 (89 g, 420 mmol). The reaction mixture was stirred at 100 °C overnight. The reaction mixture was filtered and purified flash column chromatography to yield the title compound (32 g, 63% yield) as a yellow solid.

Method 1, Step D: Methyl 3-amino-4-(2-methyl-4-phenoxyanilino)thieno[2,3-*b*]pyridine-2-carboxylate. To a round bottom flask were added 2-chloro-4-(2-methyl-4-phenoxyanilino)pyridine-3-carbonitrile (36 g, 107 mmol) in MeOH (150 mL). To this solution was added NaOMe (14.5 g, 268 mmol) in MeOH (30 mL), followed by methyl 2-sulfanylacetate (23 g, 217 mmol). The reaction mixture was refluxed overnight. The reaction mixture was cooled and the yellow precipitate was filtered off, washed with MeOH, and dried to yield the title compound (30 g, 75% yield) as a yellow solid.

Method 1, Step E: Methyl 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate. To a round bottom flask were added methyl 3-amino-4-(2-methyl-4-phenoxyanilino)thieno[2,3-*b*]pyridine-2-carboxylate (30.6 g, 75.5 mmol), carbonyldiimidazole (CDI, 49 g, 300 mmol), and 1,4-dioxane (500 ml). The reaction was stirred at reflux overnight. Then the reaction mixture was concentrated to dryness and to the residue was added to MeOH (200 mL) and the precipitate that formed was filtered off and dried to yield the title compound (28.1 g, 86% yield) as a yellow solid.

Method 1, Step F: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid. To a round bottom flask were added Methyl 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate (9.2 g, 21 mmol), lithium hydroxide (4.47 g, 106 mmol), THF (200 mL), MeOH (200 mL), and water (50 mL). The reaction mixture was stirred at 50 °C for 15 h. The mixture was concentrated to dryness and diluted with H_2O. The pH was adjusted to 2 with 1 M aqueous HCl and the precipitate was filtered and dried to yield the title compound (8.1 g, 91% yield) as yellow solid.

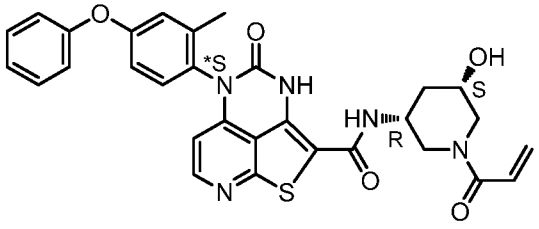
Method 1, Step G: tert-Butyl (3R,5R)-3-fluoro-5-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate. To a round bottom flask were added 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 27, 191 mg, 0.458 mmol), *tert*-butyl

(3*R*,5*R*)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1, 100 mg, 0.458 mmol), triethylamine (93 mg, 0.916 mmol), HATU (348 mg, 0.916 mmol), and DMF (3 mL). The reaction mixture was stirred at rt for 3 h. Water was added and the precipitate was collected by filtration to yield a pale yellow solid.

Method 1, Step H: N-((3R,5R)-5-fluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. tert-Butyl (3R,5R)-3-fluoro-5-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate was dissolved in MeOH (3 mL) and saturated aqueous HCl (3 mL) was added. The resulting mixture was heated to 50 °C for 30min. The reaction mixture was concentrated to dryness and the residue was purified by flash column chromatography to yield the title compound (Example 138, 80 mg, 31% yield over 2 steps) as a yellow solid.

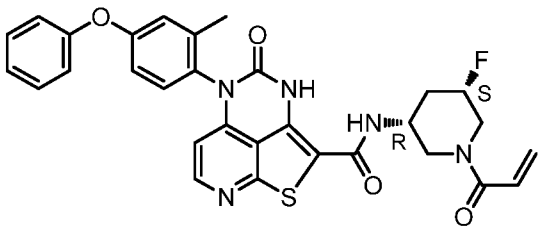
Method 1, Step I: *N*-((3*R*,5*R*)-1-Acryloyl-5-fluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a round bottom flask were added *N*-((3*R*,5*R*)-5-fluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 138, 40 mg, 0.077 mmol), triethylamine (23 mg, 0.054 mmol), and DCM (3 mL). Next, prop-2-enoyl chloride (5.0 mg, 0.054 mmol) was added dropwise at 0 °C, then stirred at rt for 1 h. The reaction mixture was concentrated to dryness and the residue purified by flash column chromatography to yield the title compound (22 mg, 48% yield) as a pale yellow solid. MS (ESI): mass calcd. for $C_{30}H_{26}FN_5O_4S$, 571.6; m/z found, 572.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.28 (d, *J* = 5.5Hz, 1H), 7.42-7.30 (m, 2H), 7.30-7.22 (m, 1H), 7.16-7.08 (m, 1H), 7.08-6.97 (m, 3H), 6.95-6.87 (m, 1H), 6.80-6.61 (m, 1H), 6.19-6.05 (m, 1H), 5.98 (d, *J* = 5.5Hz, 1H), 5.72-5.60 (m, 1H), 4.82-4.57(m, 1H), 4.17-4.05(m, 1H), 4.02-3.85(m, 2H), 3.55-3.28 (m, 2H), 2.39-2.18 (m, 1H), 2.04 (s, 3H), 2.0-1.91 (m, 1H).

Example 2: *N*-((3*R*,5*S*)-1-Acryloyl-5-hydroxypiperidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



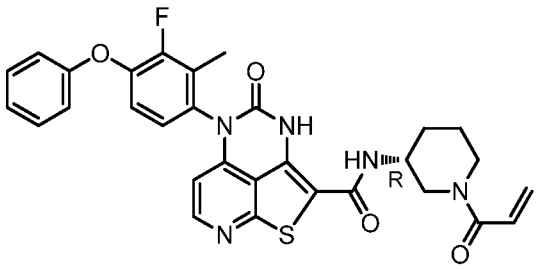
The title compound was prepared in a manner analogous to Method 1, steps A-I (including Chiral Resolution Step A to obtain the *S atropisomer) in Example 1, and using tert-butyl (3R,5S)-3-amino-5-hydroxypiperidine-1-carboxylate (Intermediate 2) in place of *tert*-butyl (3*R*,5*R*)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{27}N_5O_5S$, 569.6; m/z found, 570.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.36-8.27 (m, 1H), 7.45-7.37 (m, 2H), 7.33-7.26 (m, 1H), 7.21-7.14 (m, 1H), 7.11-7.02 (m, 3H), 7.00-6.92 (m, 1H), 6.85-6.65 (m, 1H), 6.21-6.09 (m, 1H), 6.06-6.02 (m, 1H), 5.75-5.61 (m, 1H), 4.20-3.75 (m, 4H), 3.66-3.55 (m, 2H), 2.21-2.12 (m, 1H), 2.11 (s, 3H), 1.90-1.77 (m, 1H).

Example 3: *N*-((3*R*,5*S*)-1-Acryloyl-5-fluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



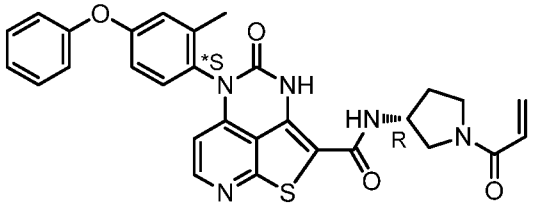
The titled compound was prepared using Method 1, steps A-I in Example 1, and using *tert*-butyl (3*R*,5*S*)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 3) in place of *tert*-butyl (3*R*,5*R*)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{26}FN_5O_4S$, 571.6; m/z found, 572.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.26 (s, 1H), 8.31 (d, J = 4.7 Hz, 1H), 8.26-8.00 (m, 1H), 7.57 – 7.29 (m, 3H), 7.29 – 6.91 (m, 5H), 6.88-6.65 (m, 1H), 6.11 (d, J = 16.7 Hz, 1H), 6.03-5.87 (m, 1H), 5.77-5.60 (m, 1H), 5.15-4.85 (m, 1H), 4.70-4.47 (m, 1H), 4.35-4.38 (m, 2H), 3.06 – 2.61 (m, 2H), 2.30-2.12 (m, 1H), 2.05 (s, 3H), 1.97-1.78 (m, 1H).

Example 4: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(3-fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



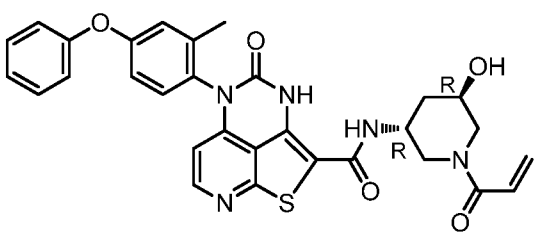
The title compound was prepared using analogous conditions described in Method 1, steps B-I in Example 1, and using 2-fluoro-3-methyl-4-nitro-1-phenoxybenzene (Intermediate 18, step B) in place of 2-methyl-4-phenoxyaniline in step B, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{26}FN_5O_4S$, 571.6; m/z found, 572.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.34 (d, J = 5.4 Hz, 1H), 7.41-7.34 (m, 2H), 7.22-7.11 (m, 2H), 7.10-7.04 (m, 3H), 6.84-6.72 (m, 1H), 6.19 (d, J = 17.0 Hz, 1H), 6.12 (d, J = 5.4 Hz, 1H), 5.76-5.69 (m, 1H), 4.56-4.48 (m, 0.5H), 4.32-4.25 (m, 0.5H), 4.4.20-4.13 (m, 0.5H), 4.02-3.88 (m, 1.5H), 3.22-3.12 (m, 1H), 2.95-2.83 (m, 1H), 2.12 (s, 3H), 2.07-2.00 (m, 1H), 1.90-1.82 (m, 1H), 1.78-1.66 (m, 1H), 1.63-1.54 (m, 1H).

Example 5: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



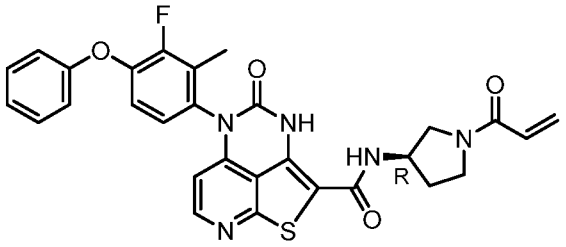
The title compound was prepared in a manner analogous to Method 1, steps A-I (including Chiral resolution Method A after Step F to obtain the **S* atropisomer) in Example 1, and using *tert*-butyl (3*R*)-3-aminopyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{29}H_{25}N_5O_4S$, 539.6; m/z found, 540.30 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.24 (s, 1H), 8.43-8.22 (m, 2H), 7.57 – 7.29 (m, 3H), 7.25-7.04 (m, 4H), 7.03-6.90 (m, 1H), 6.70-6.45 (m, 1H), 6.13 (d, J = 16.4 Hz, 1H), 6.05-6.88 (m, 1H), 5.73-5.57 (m, 1H), 4.60-4.30 (m, 1H), 3.91 – 3.36 (m, 4H), 2.24 – 1.89 (m, 5H).

Example 6: *N*-((3*R*,5*R*)-1-Acryloyl-5-hydroxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



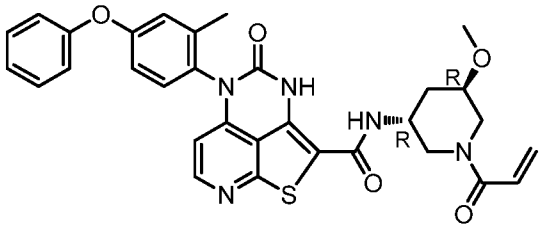
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using *tert*-butyl (3*R*,5*R*)-3-amino-5-hydroxypiperidine-1-carboxylate (Intermediate 4) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{27}N_5O_5S$, 569.6; m/z found, 570.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.34-8.18(m, 1H), 7.46 -7.36 (m, 2H), 7.33-7.22 (m, 1H), 7.20-7.13 (m, 1H), 7.13-7.02 (m, 3H), 7.00-6.94 (m, 1H), 6.88-6.70 (m, 1H), 6.25-6.10 (m, 1H), 6.05-5.92 (m, 1H), 5.76-5.67(m, 1H), 4.66-4.28 (m, 2H), 4.23-3.83 (m, 2.5H), 3.45-3.34 (m, 1H), 3.02-2.87 (m, 0.5H), 2.12 (s, 3H), 2.09-1.88 (m, 2H).

Example 7: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-5-(3-fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



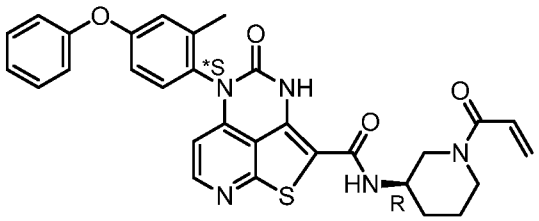
The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1, and using 1-[(3*R*)-3-aminopyrrolidin-1-yl]prop-2-en-1-one (Intermediate 5) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{29}H_{24}FN_5O_4S$, 557.6; m/z found, 558.4 $[M+H]^+$. ^1H NMR (400 MHz, a mixture of DMSO-d_6 and CD_3OD): δ 8.26 (d, J = 5.5Hz, 1H), 7.7.39-7.29 (m, 2H), 7.20-7.13 (m, 1H), 7.12-6.97 (m, 4H), 6.60-6.43 (m, 1H), 6.19-6.09 (m, 1H), 6.02 (d, J = 5.4Hz, 1H), 5.66-5.58 (m, 1H), 4.55-4.42 (m, 1H), 3.89-3.80 (m, 1H), 3.72-3.66 (m, 1H), 3.60-3.49 (m, 1H), 3.48-3.38 (m, 1H), 2.22-2.08 (m, 1H), 2.01 (s, 3H), 1.99-1.87 (m, 1H).

Example 8: *N*-((3*R*,5*R*)-1-Acryloyl-5-methoxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



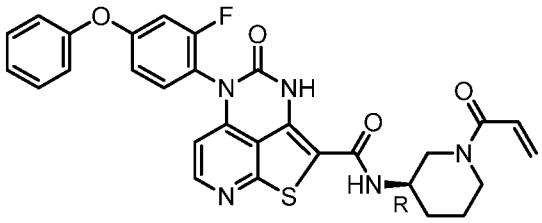
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using *tert*-butyl (3*R*,5*R*)-3-amino-5-methoxypiperidine-1-carboxylate (Intermediate 6) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{31}H_{29}N_5O_5S$, 583.7; m/z found, 584.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33 (d, J = 5.5 Hz, 1H), 7.52-7.37 (m, 2H), 7.38 -7.26 (m, 1H), 7.22-7.14 (m, 1H), 7.13 -7.03 (m, 3H), 7.01-6.94 (m, 1H), 6.89-6.68 (m, 1H), 6.25-6.13 (m, 1H), 6.07 (d, J = 5.6 Hz, 1H), 5.79-5.68 (m, 1H), 4.70-4.51 (m, 1H), 4.35 - 4.06 (m, 2H), 3.76 -3.55 (m, 1H), 3.41-3.33 (m, 3H), 3.27-3.08 (m, 1H), 3.02-2.69 (m, 1H), 2.33-2.10 (m, 4H),2.07-1.74 (m, 1H).

Example 9: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



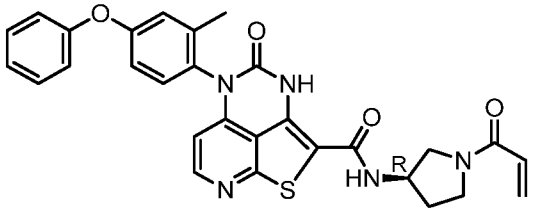
The title compound was prepared in a manner analogous to Method 1, steps A-I (including Chiral resolution Method A after Step F to obtain the **S* atropisomer) in Example 1, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{27}N_5O_4S$, 553.6; m/z found, 554.40 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33 (d, J = 5.5 Hz, 1H), 7.47-7.35 (m, 2H), 7.33-7.26 (m, 1H), 7.122-7.16 (m, 1H), 7.13 – 7.02 (m, 3H), 7.00-6.93 (m, 1H), 6.85-6.70 (m, 1H), 6.20 (d, J = 16.6 Hz, 1H), 6.14-6.04 (m, 1H), 5.77-5.67 (m, 1H), 4.58 – 3.88 (m, 3H), 3.25-3.10 (m, 1H), 2.99 – 2.84 (m, 1H), 2.13 (s, 3H), 2.09-1.97 (m, 1H), 1.91-1.82 (m, 1H), 1.79-1.65 (m, 1H), 1.64-1.50 (m, 1H).

Example 10: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(2-fluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



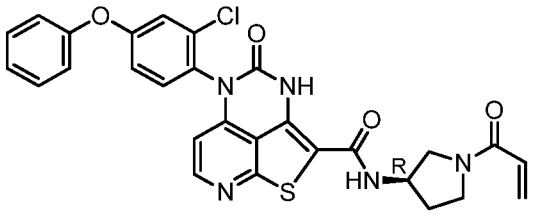
The title compound was prepared in a manner analogous to Method 1, steps C-I in Example 1, and using 2-fluoro-4-phenoxyaniline in place of 2-methyl-4-phenoxyaniline in step C and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{29}H_{24}FN_5O_4S$, 557.6; m/z found, 558.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.37 (s, 1H), 8.33 (d, J = 5.4 Hz, 1H), 8.22-8.05 (m, 1H), 7.64-7.51 (m, 1H), 7.51-7.38 (m, 2H), 7.28-7.20 (m, 1H), 7.20-7.09 (m, 3H), 6.99-6.90 (m, 1H), 6.86- 6.63 (m, 1H), 6.17 (d, J = 5.4 Hz, 1H), 6.07 (d, J = 16.6 Hz, 1H), 5.65 (d, J = 11.1 Hz, 1H), 4.53-4.07 (m, 1H), 4.08-3.88 (m, 1H), 3.84-3.65 (m, 1H), 3.11-2.91 (m, 1H), 2.78-2.56 (m, 1H), 2.00-1.83 (m, 1H), 1.80-1.69 (m, 1H), 1.68-1.54 (m, 1H), 1.47-1.30 (m, 1H).

Example 11: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



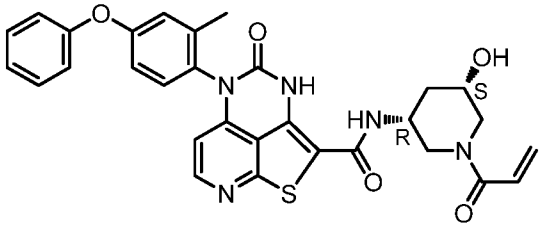
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using *tert*-butyl (3*R*)-3-aminopyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{29}H_{25}N_5O_4S$, 539.6; m/z found, 540.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.33-10.21 (m, 1H), 8.45-8.31 (m, 2H), 7.50-7.42 (m, 2H), 7.42-7.36 (m, 1H), 7.25-7.18 (m, 1H), 7.16-7.07 (m, 3H), 7.02-6.95 (m, 1H), 6.67-6.52 (m, 1H), 6.21-6.10 (m, 1H), 6.04-5.96 (m, 1H), 5.72-5.64 (m, 1H), 4.57-4.42 (m, 1H), 3.92-3.59 (m, 4H), 3.24-1.93 (m, 5H).

Example 12: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-5-(2-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



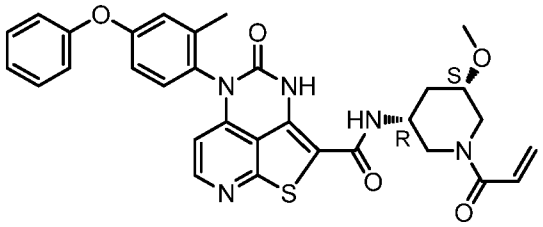
The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1 and using 2-chloro-4-fluoro-1-nitrobenzene in place of 2-methyl-4-fluoro-1-nitrobenzene for step A, and using 1-[(3*R*)-3-aminopyrrolidin-1-yl]prop-2-en-1-one (Intermediate5) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{28}H_{22}ClN_5O_4S$, 560.0; m/z found, 560.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.40 (s, 1H), 8.53-8.39 (m, 1H), 8.36-8.31 (m, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.51-7.45 (m, 2H), 7.35-7.31 (m, 1H), 7.26 (t, J = 7.1 Hz, 1H), 7.22-7.16 (m, 2H), 7.16-7.12 (m, 1H), 6.65-6.52 (m, 1H), 6.17-6.10 (m, 1H), 6.08-6.02 (m, 1H), 5.70-5.63 (m, 1H), 4.57-4.40 (m, 1H), 3.90-3.70 (m, 1H), 3.69-3.60 (m, 1H), 3.58-3.49 (m, 1H), 3.45-3.39 (m, 1H), 2.25-2.09 (m, 1H), 2.02-1.92 (m, 1H).

Example 13: *N*-((3*R*,5*S*)-1-Acryloyl-5-hydroxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



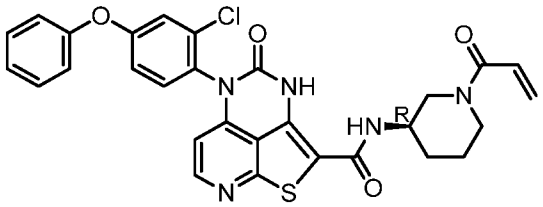
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using tert-butyl (3R,5S)-3-amino-5-hydroxypiperidine-1-carboxylate (Intermediate 2) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{27}N_5O_5S$, 569.17; m/z found, 570.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 10.31-10.09 (m, 1H), 8.36 (d, J = 5.3 Hz, 1H), 8.19-7.98 (m, 1H), 7.53-7.35 (m, 3H), 7.27-7.16 (m, 1H), 7.18-7.06 (m, 3H), 7.04-6.94 (m, 1H), 6.85-6.67 (m, 1H), 6.18-6.04 (m, 1H), 6.01 (d, J = 5.3 Hz, 1H), 5.77-5.62 (m, 1H), 4.33-4.13 (m, 1H), 4.06-3.79 (m, 2H), 3.10-2.87 (m, 2H), 2.70-2.52 (m, 1H), 2.13-1.95 (m, 4H), 1.70-1.56 (m, 1H).

Example 14: *N*-((3*R*,5*S*)-1-Acryloyl-5-methoxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



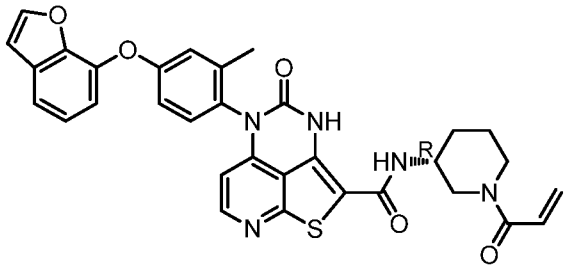
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1 and using tert-Butyl (3R,5S)-3-amino-5-methoxypiperidine-1-carboxylate (Intermediate 29) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{31}H_{29}N_5O_5S$, 583.7; m/z found, 584.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.39-8.29 (m, 1H), 7.47-7.36 (m, 2H), 7.30-7.27 (m, 1H), 7.20-7.15 (m, 1H), 7.12-7.03 (m, 3H), 7.02-6.93 (m, 1H), 6.85-6.60 (m, 1H), 6.17-6.05 (m, 2H), 5.79-5.60 (m, 1H), 4.44-4.26 (m, 1H), 4.23-4.12 (m, 1H), 4.03-3.92 (m, 1H), 3.68-3.55 (m, 2H), 3.53-3.45 (m, 3H), 3.44-3.35 (m, 1H), 2.17-2.09 (m, 4H), 2.02-1.96 (m, 1H).

Example 15: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(2-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



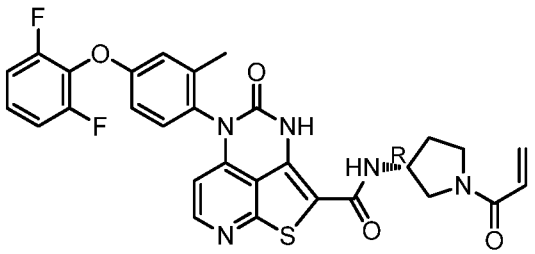
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1 and using 2-chloro-4-fluoro-1-nitrobenzene in place of 5-fluoro-2-nitrotoluene in step A and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{29}H_{24}ClN_5O_4S$, 574.1; m/z found, 574.3 $[M+H]^+$. ^1H NMR (400 MHz, CD3OD): δ 8.33 (d, J = 5.6 Hz, 1H), 7.78-7.73 (m, 1H), 7.52-7.45 (m, 1H), 7.36-7.21 (m, 2H), 7.10-7.02 (m, 2H), 7.00-6.88 (m, 2H), 6.88-6.70 (m, 1H), 6.28-6.14 (m, 1H), 6.07 (d, J = 5.6 Hz, 1H), 5.81-5.66 (m, 1H), 4.63-3.87 (m, 3H), 3.25-3.10 (m, 1H), 3.01-2.82 (m, 1H), 2.14 (s, 3H), 2.09-2.01 (m, 1H), 1.94-1.83 (m, 1H), 1.81-1.68 (m, 1H), 1.65-1.52 (m, 1H).

Example 16: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(4-(benzofuran-7-yloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



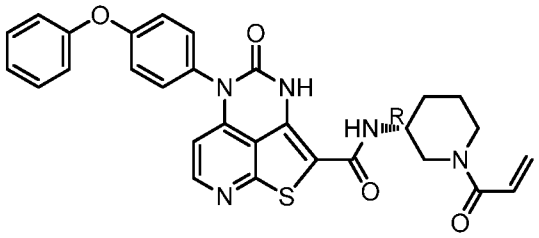
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using benzofuran-7-ol (Intermediate 8) in place of phenol in step A, and using (*R*)-*tert*-butyl 3-aminopiperidine-1-carboxylate place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{32}H_{27}N_5O_5S$, 593.7; m/z found, 594.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33 (d, J = 5.6 Hz, 1H), 7.78-7.73 (m, 1H), 7.52-7.45 (m, 1H), 7.36-7.21 (m, 2H), 7.10-7.02 (m, 2H), 7.00-6.88 (m, 2H), 6.88-6.70 (m, 1H), 6.28-6.14 (m, 1H), 6.07 (d, J = 5.6 Hz, 1H), 5.81-5.66 (m, 1H), 4.63-3.87 (m, 3H), 3.25-3.10 (m, 1H), 3.01-2.82 (m, 1H), 2.14 (s, 3H), 2.09-2.01 (m, 1H), 1.94-1.83 (m, 1H), 1.81-1.68 (m, 1H), 1.65-1.52 (m, 1H).

Example 17: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-5-(4-(2,6-difluorophenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



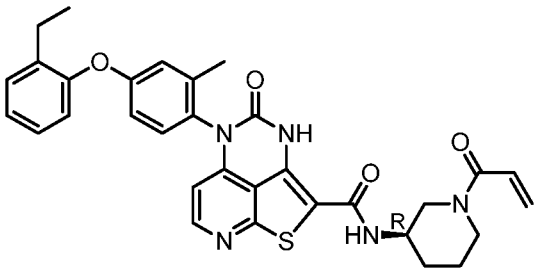
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using 2,6-difluorophenol in place of phenol in step A, and using (*R*)-*tert*-butyl 3-aminopyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{29}H_{23}F_2N_5O_4S$, 575.6; m/z found, 576.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.32 (d, J = 5.6 Hz, 1H), 7.38-7.27 (m, 2H), 7.22-7.11 (m, 2H), 7.04-6.99 (m, 1H), 6.96-6.89 (m, 1H), 6.73-6.51 (m, 1H), 6.34-6.20 (m, 1H), 6.08-6.00 (m, 1H), 5.80-5.64 (m, 1H), 4.71- 4.54 (m, 1H), 4.02-3.49 (m, 4H), 2.41-2.01 (m, 5H).

Example 18: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



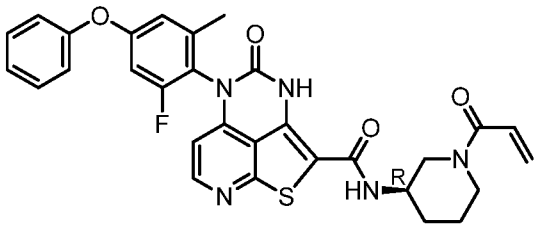
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using 4-fluoronitrobenzene in place of 5-fluoro-2-nitrotoluene in step A, and using (*R*)-*tert*-butyl 3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{29}H_{25}N_5O_4S$, 539.6; m/z found, 540.2 $[M+H]^+$. ^1H NMR (500 MHz, CD_3OD): δ 8.33 (d, J = 5.6 Hz, 1H), 7.48 - 7.32 (m, 4H), 7.27 - 7.07 (m, 5H), 6.90 - 6.68 (m, 1H), 6.21 (dd, J = 14.0, 5.4 Hz, 2H), 5.79 - 5.69 (m, 1H), 4.60 - 3.87 (m, 3H), 3.24 - 3.12 (m, 1H), 2.99 - 2.81 (m, 1H), 2.15 - 1.46 (m, 4H).

Example 19: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(4-(2-ethylphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



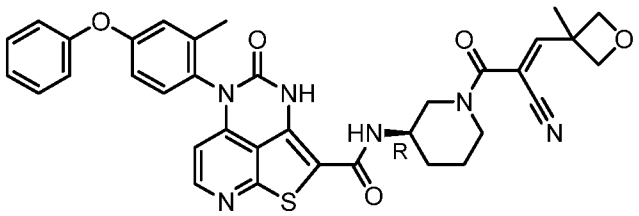
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using 2-ethylphenol in place of phenol in step A, and using (*R*)-*tert*-butyl 3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{32}H_{31}N_5O_4S$, 581.7; m/z found, 582.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.32 (d, J = 5.6 Hz, 1H), 7.36-7.30 (m, 1H), 7.27-7.20 (m, 2H), 7.18-7.12 (m, 1H), 7.00-6.93 (m, 2H), 6.88-6.83 (m, 1H), 6.83-6.71 (m, 1H), 6.25-6.12 (m, 1H), 6.05 (d, J = 5.6 Hz, 1H), 5.78-5.66 (m, 1H), 4.62-4.11 (m, 2H), 3.98-3.88 (m, 1H), 3.23-3.13 (m, 1H), 2.99-2.82 (m, 1H), 2.71-2.57 (m, 2H), 2.12-2.05 (m, 4H), 1.91-1.81 (m, 1H), 1.76-1.55 (m, 2H), 1.23-1.13 (m, 3H).

Example 20: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(2-fluoro-6-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps C-I in Example 1, and using 2-fluoro-6-methyl-4-phenoxyaniline (Intermediate 9) in place of 2-methyl-4-phenoxyaniline in step C, and using (*R*)-*tert*-butyl 3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{26}FN_5O_4S$, 571.6; m/z found, 572.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.37 (d, J = 5.5 Hz, 1H), 7.53-7.39 (m, 2H), 7.30-7.19 (m, 1H), 7.17-7.09 (m, 2H), 6.93-6.68 (m, 3H), 6.26-6.11(m, 2H), 5.84-5.63 (m, 1H), 4.62-3.83 (m, 3H), 3.25-3.10 (m, 1H), 3.03-2.83 (m, 1H), 2.16 (s, 3H), 2.11-2.02 (m, 1H), 1.95-1.52 (m, 3H).

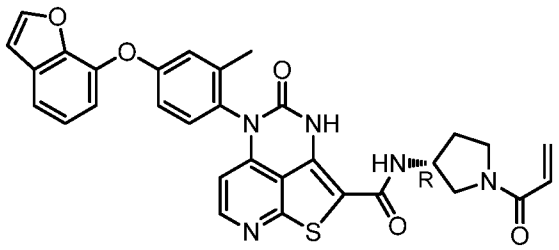
Example 21: (R,E)-N-(1-(2-cyano-3-(3-methyloxetan-3-yl)acryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a round bottom flask were added (R)-N-(1-(2-cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 874, 120 mg, 0.212 mmol), 3-methyloxetane-3-carbaldehyde (64 mg, 0.64 mmol), piperidine (0.3 mL), acetic acid (0.1 mL), dioxane (10 mL), and 4A molecular sieves (1 g) and the reaction mixture was stirred at 100 °C for 1 h under N_2. The mixture was concentrated to dryness and purified by flash column chromatography to yield the title compound (69 mg, 50% yield) as a white solid. MS (ESI): mass calcd. for $C_{35}H_{32}N_6O_5S$, 648.7; m/z found, 649.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33-8.27 (m, 1H), 7.42-7.35 (m, 2H), 7.33-7.23 (m, 2H), 7.20-7.12 (m, 1H), 7.10-7.01 (m, 3H), 6.99-6.92 (m, 1H), 6.07-6.01 (m, 1H), 5.08-4.92 (m,

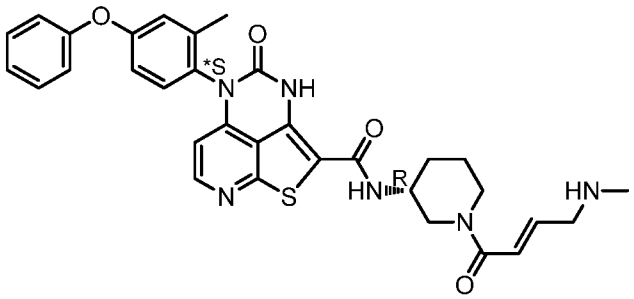
1H), 4.68-4.54 (m, 1H), 4.53-4.37 (m, 2H), 4.35-4.22 (m, 1H), 4.09-3.70 (m, 3H), 3.65-3.36 (m, 1H), 2.15-2.01 (m, 4H), 1.99-1.73 (m, 2H), 1.69-1.57 (m, 4H).

Example 22: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-5-(4-(benzofuran-7-yloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using benzofuran-7-ol (Intermediate 8) in place of phenol in step A, and using (*R*)-*tert*-butyl 3-aminopyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{31}H_{25}N_5O_5S$, 579.6; m/z found, 580.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.36 (d, J = 5.7 Hz, 1H), 7.77-7.73 (m, 1H), 7.52-7.46 (m, 1H), 7.32-7.21 (m, 2H), 7.08-7.02 (m, 2H), 7.00-6.87 (m, 2H), 6.70-6.53 (m, 1H), 6.33-6.24 (m, 1H), 6.12 (d, J = 5.7 Hz, 1H), 5.80-5.69 (m, 1H), 4.70-4.57 (m, 1H), 4.03-3.48 (m, 4H), 2.37-2.04 (m, 5H).

Example 23: (*R*,*E*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)-*N*-(1-(4-(methylamino)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

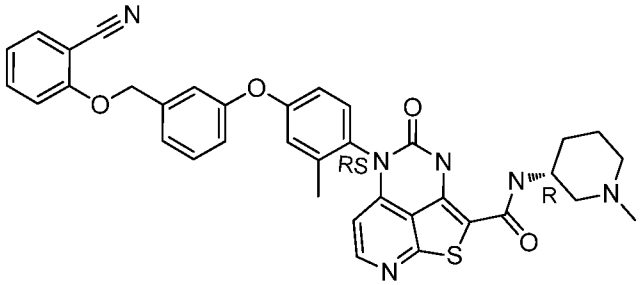


Step A: tert-butyl (R,E)-methyl(4-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-4-oxobut-2-en-1-yl)carbamate. The title compound was prepared in a manner analogous to Example 104 (including Chiral resolution Method A after Step F to obtain the **S* atropisomer), and using (R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-

2-carboxamide (Example 98) and (E)-4-[tert-Butoxycarbonyl(methyl)amino]but-2-enoic acid (Intermediate 10).

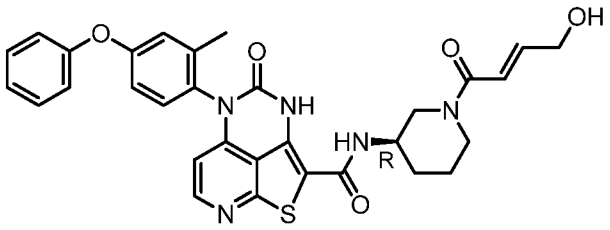
Step B: (*R*,*E*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)-*N*-(1-(4-(methylamino)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a flask containing tert-butyl (R,E)-methyl(4-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-4-oxobut-2-en-1-yl)carbamate (52 mg, 0.075 mmol) was added MeOH (4.0 mL) and concentrated aqueous HCl (4.0 mL). The reaction mixture was stirred at rt for 1 h, then the mixture was concentrated under reduced pressure and purified by silica gel chromatography to give the title compound (32 mg, 65%) as a white solid. MS (ESI): mass calcd. for $C_{32}H_{32}N_6O_4S$, 596.7; m/z found, 597.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.40 (s, 1H), 8.37-8.30 (m, 1H), 7.44-7.37 (m, 2H), 7.34-7.27 (m, 1H), 7.21-7.14 (m, 1H), 7.13-7.04 (m, 3H), 7.01-6.95 (m, 1H), 6.92-6.82 (m, 1H), 6.74-6.60 (m, 1H), 6.12-6.05 (m, 1H), 4.54-3.91 (m, 3H), 3.84-3.75 (m, 2H), 3.25-3.08 (m, 1H), 3.00-2.81 (m, 1H), 2.71 (s, 3H), 2.18-2.02 (m, 4H), 1.94-1.83 (m, 1H), 1.82-1.67 (m, 1H), 1.66-1.53 (m, 1H).

Example 24: (*R*)-5-(4-(3-((2-Cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



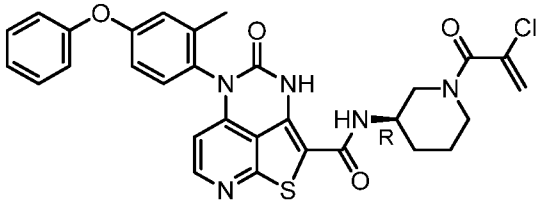
The title compound was prepared using the method from Example 52 Step B, and using (R)-5-(4-(3-((2-cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Intermediate 78) in place of (*R*)-5-(4-(2,6-difluorophenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. MS (ESI): mass calcd. for $C_{36}H_{32}N_6O_4S$, 644.7; m/z found, 645 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.30 (d, J = 5.4 Hz, 1H), 8.07 (d, J = 7.7 Hz, 1H), 7.80-7.70 (m, 1H), 7.69-7.60 (m, 1H), 7.53-7.44 (m, 1H), 7.37-7.23 (m, 3H), 7.17-7.05 (m, 3H), 7.04-6.93 (m, 1H), 5.95 (d, J = 5.5 Hz, 1H), 5.33 (s, 2H), 4.05-3.92 (m, 1H), 2.95-2.84 (m, 1H), 2.80-2.68 (m, 1H), 2.27 (s, 3H), 2.05 (s, 3H), 2.03-1.93 (m, 2H), 1.85-1.65 (m, 2H), 1.61-1.47 (m, 1H), 1.45-1.30 (m, 1H).

Example 25: (*S*,*E*)-*N*-(1-(4-Hydroxybut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



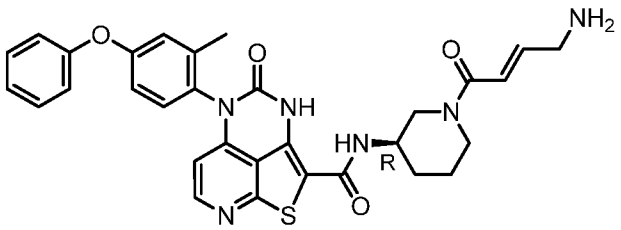
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G, and using (*E*)-4-hydroxybut-2-enoic acid (Intermediate 13) in place of prop-2-enoyl chloride in step I. MS (ESI): mass calcd. for $C_{31}H_{29}N_5O_5S$, 583.7; m/z found, 584.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33-8.29 (m, 1H), 7.42-7.35 (m, 2H), 7.33-7.28 (m, 1H), 7.19-7.12 (m, 1H), 7.10-7.02 (m, 3H), 6.99-6.94 (m, 1H), 6.88-6.77 (m, 1H), 6.71-6.61 (m, 1H), 6.08-6.03 (m, 1H), 4.53-3.90 (m, 5H), 3.24-3.12 (m, 1H), 2.97-2.84 (m, 1H), 2.11 (s, 3H), 2.09-2.00 (m, 1H), 1.89-1.81 (m, 1H), 1.77-1.65 (m, 1H), 1.63-1.50 (m, 1H).

Example 26: (*R*)-*N*-(1-(2-Chloroacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Example 104, using 2-chloroprop-2-enic acid and (R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869). MS (ESI): mass calcd. for $C_{30}H_{26}ClN_5O_4S$, 588.1; m/z found, 588.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.42-8.37 (m, 1H), 7.44-7.35 (m, 2H), 7.33-7.28 (m, 1H), 7.20-7.13 (m, 1H), 7.11-7.03 (m, 3H), 7.00-6.93 (m, 1H), 6.22-6.06 (m, 1H), 5.70 (s, 2H), 4.48-4.13 (m, 1H), 4.12-3.83 (m, 2H), 3.25-3.12 (m, 1H), 2.99-2.82 (m, 1H), 2.12 (s, 3H), 2.10-2.01 (m, 1H), 1.93-1.83 (m, 1H), 1.80-1.67 (m, 1H), 1.65-1.52 (m, 1H).

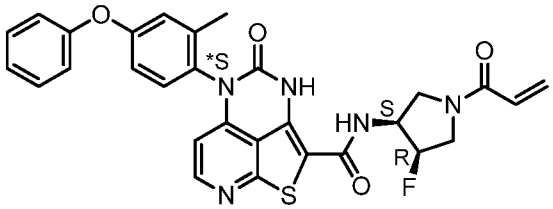
Example 27: (*R*,*E*)-*N*-(1-(4-Aminobut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: tert-butyl (R,E)-(4-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-4-oxobut-2-en-1-yl)carbamate. The title compound was prepared in a manner analogous to Example 104, using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate and (R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869).

Step B: (*R*,*E*)-*N*-(1-(4-Aminobut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared using the conditions described in Step B of Example 131 using tert-butyl (R,E)-(4-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-4-oxobut-2-en-1-yl)carbamate. MS (ESI): mass calcd. for $C_{31}H_{30}N_6O_4S$, 582.7; m/z found, 583.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.48 (s, 1H), 8.38-8.31 (m, 1H), 7.45-7.37 (m, 2H), 7.33-7.27 (m, 1H), 7.22-7.14 (m, 1H), 7.14-7.03 (m, 3H), 7.02-6.95 (m, 1H), 6.85-6.78 (m, 1H), 6.77-6.67 (m, 1H), 6.12-6.06 (m, 1H), 4.57-3.89 (m, 3H), 3.78-3.71 (m, 2H), 3.25-3.08 (m, 1H), 2.97-2.80 (m, 1H), 2.17-2.01 (m, 4H), 1.96-1.84 (m, 1H), 1.83-1.70 (m, 1H), 1.67-1.53 (m, 1H).

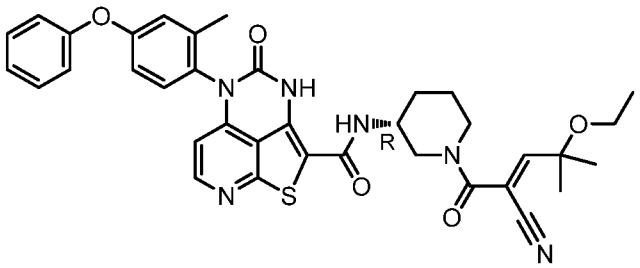
Example 28: *N*-((3*S*,4*R*)-1-Acryloyl-4-fluoropyrrolidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-I (including Chiral resolution Method A after Step F to obtain the **S* atropisomer) in Example 1, and using *tert*-butyl (3*S*,4*R*)-3-amino-4-fluoropyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for

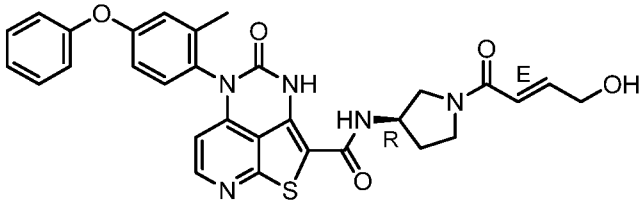
$C_{29}H_{24}FN_5O_4S$, 557.6; m/z found, 558.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.37-8.30 (m, 1H), 7.45-7.37 (m, 2H), 7.33-7.26 (m, 1H), 7.21-7.14 (m, 1H), 7.11-7.02 (m, 3H), 7.00-6.92 (m, 1H), 6.67-6.53 (m, 1H), 6.36-6.26 (m, 1H), 6.12-6.05 (m, 1H), 5.81-5.74 (m, 1H), 5.39-5.16 (m, 1H), 4.19-3.84 (m, 3H), 3.81-3.52 (m, 2H), 2.12 (s, 3H).

Example 29: (*R*,*EZ*)-*N*-(1-(2-Cyano-4-ethoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a round bottom flask were added (*R*)-*N*-(1-(2-cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 874, 200 mg, 0.35 mmol), 2-ethoxy-2-methylpropanal (123 mg, 1.1 mmol), piperdine (0.3 mL), and EtOH (5 mL) and was stirred at rt for 15 h. Then the reaction mixture was concentrated to dryness and purified by flash column chromatography to yield the title compound (154 mg, 63.0% yield) as a light yellow solid. MS (ESI): mass calcd. for $C_{36}H_{36}N_6O_5S$, 664.8; m/z found, 665.8 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.35-8.31 (m, 1H), 7.43-7.37 (m, 2H), 7.33-7.27 (m, 1H), 7.20-7.14 (m, 1H), 7.11-7.03 (m, 3H), 7.00-6.95 (m, 1H), 6.92-6.69 (m, 1H), 6.12-6.05 (m, 1H), 4.62-3.89 (m, 3H), 3.60-3.34 (m, 3H), 3.19-2.86 (m, 1H), 2.21-2.20 (m, 4H), 1.96-1.85 (m, 1H), 1.80-1.62 (m, 2H), 1.50-1.21 (m, 9H).

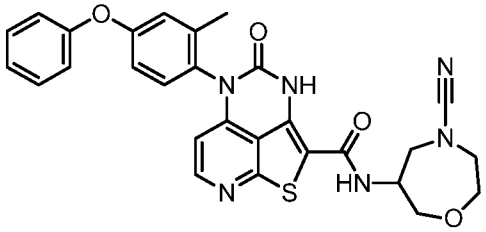
Example 30: (*R*,*E*)-*N*-(1-(4-Hydroxybut-2-enoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared using the method in Example 104, and using (*E*)-4-hydroxybut-2-enoic acid (Intermediate 13) in place of methylsulfonylpropanoic acid.

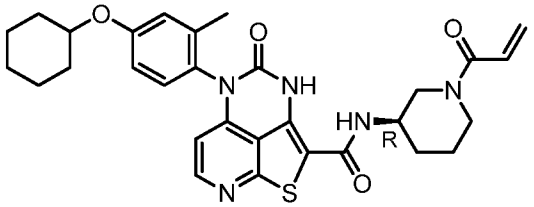
MS (ESI): mass calcd. for $C_{30}H_{27}N_5O_5S$, 569.6; m/z found, 570.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.24 (s, 1H), 8.32 (d, J = 5.4 Hz, 1H), 7.49-7.40 (m, 2H), 7.36 (d, J = 8.6 Hz, 1H), 7.23-7.15 (m, 1H), 7.14-7.03 (m, 3H), 7.02-6.90 (m, 1H), 6.81-6.67 (m, 1H), 6.46-6.25 (m, 1H), 5.96 (d, J = 5.2 Hz, 1H), 5.09-4.90 (m, 1H), 4.57-4.37 (m, 1H), 4.21-4.05 (m, 2H), 3.88-3.38 (m, 4H), 2.22-2.08 (m, 1H), 2.05 (s, 3H), 2.01-1.90 (m, 1H).

Example 31: *N*-(4-Cyano-1,4-oxazepan-6-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using *tert*-butyl 6-amino-1,4-oxazepane-4-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G, and using bromocyanide in place of prop-2-enoyl chloride in step I. MS (ESI): mass calcd. for $C_{28}H_{24}N_6O_4S$, 540.6; m/z found, 541.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 10.26 (s, 1H), 8.40-8.26 (m, 1H), 8.19 (s, 1H), 7.49-7.37 (m, 2H), 7.37-7.28 (m, 1H), 7.21-7.14 (m, 1H), 7.14-7.02 (m, 3H), 6.99-6.91 (m, 1H), 6.04-5.86 (m, 1H), 4.38-4.22 (m, 1H), 3.90-3.81 (m, 1H), 3.80-3.66 (m, 3H), 3.57-3.50 (m, 1H), 3.41-3.35 (m, 3H), 2.03 (s, 3H).

Example 32: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(4-(cyclohexyloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

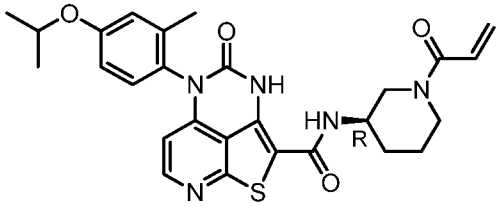


Step A: 2-Chloro-4-[4-(cyclohexoxy)-2-methylanilino]pyridine-3-carbonitrile. To a round bottom flask containing 2-chloro-4-(4-hydroxy-2-methylanilino)pyridine-3-carbonitrile (Intermediate 14) (1 g, 4 mmol), cyclohexanol (1.16 g, 11.6 mmol), PPh_3 (1.5 g, 5.7 mmol), and THF (20 mL) at 0 °C was added DIAD (1.17 g, 5.79 mmol). The mixture was stirred at rt

overnight. The mixture was concentrated to dryness and the residue was purified by flash column chromatography to yield the title compound (400 mg, 30% yield) as a yellow solid.

Step B: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(4-(cyclohexyloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps D-I in Example 1, and using 2-chloro-4-[4-(cyclohexoxy)-2-methylanilino]pyridine-3-carbonitrile in place of 2-chloro-4-(2-methyl-4-phenoxyanilino)pyridine-3-carbonitrile in step D, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{33}N_5O_4S$, 559.7; m/z found, 560.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.43 (s, 1H), 8.30 (d, J = 5.5 Hz, 1H), 7.23-7.15 (m, 1H), 7.02-6.95 (m, 1H), 6.94-6.89 (m, 1H), 6.87-6.71 (m, 1H), 6.27-6.14 (m, 1H), 6.03 (d, J = 5.5 Hz, 1H), 5.79-5.67 (m, 1H), 4.55-3.88 (m, 4H), 3.25-3.11 (m, 1H), 3.01-2.80 (m, 1H), 2.10 (s, 3H), 2.06-1.94 (m, 3H), 1.90-1.69 (m, 4H), 1.65-1.36 (m, 7H).

Example 33: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



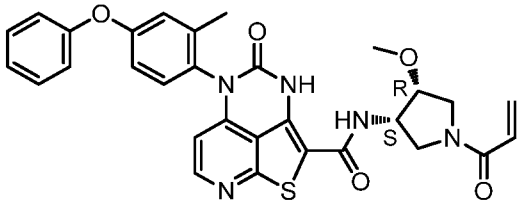
Step A: 4-Isopropoxy-2-methyl-1-nitrobenzene. To a round bottom flask were added 3-methyl-4-nitrophenol (5.0 g, 33 mmol), K_2CO_3 (9.0 g, 65 mmol), DMF (20 mL), and 2-iodopropane (8.3 g, 460 mmol) and the reaction was stirred at 80 °C overnight. Water was added to the mixture and a yellow precipitate formed. The mixture was filtered and the precipitate was washed with water and dried under vacuum to yield the title compound (5.0 g, 78% yield).

Step B: 4-Isopropoxy-2-methylaniline. To a round bottom flask were added 4-isopropoxy-2-methyl-1-nitrobenzene (5.0 g, 26 mmol) and MeOH (100 mL). The reaction mixture was evacuated under reduced pressure and filled with N_2 (3x) and Pd/C (10% on carbon; 500 mg) was added. The mixture was evacuated under reduced pressure and filled with N_2 (3x), then evacuated under reduced pressure and filled with H_2. The mixture was stirred under H_2 atmosphere overnight. The mixture was filtered over diatomaceous earth and concentrated to dryness to yield the title compound (3.5 g, 83% yield).

Step C: 2-Chloro-4-(4-isopropoxy-2-methylanilino)pyridine-3-carbonitrile. To a round bottom flask were added 4-isopropoxy-2-methylaniline (1 g, 6 mmol), 2-chloro-4-iodopyridine-3-carbonitrile (2.0 g, 7.6 mmol), DPEPhos [bis(2-diphenylphosphinophenyl)ether] (650 mg, 1.2 mmol), palladium(II) acetate (135 mg, 0.600 mmol), and K_3PO_4 (3.5 g, 16 mmol). The reaction mixture was degassed and heated at 120 °C overnight. The mixture was cooled to rt, concentrated to dryness, and purified by flash column chromatography to yield the title compound (2.34 g, 65.0% yield) as a yellow solid.

Step D: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps D-I in Example 1, and using 2-chloro-4-(4-isopropoxy-2-methylanilino)pyridine-3-carbonitrile in place of 2-chloro-4-(2-methyl-4-phenoxyanilino)pyridine-3-carbonitrile in step D, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{29}N_5O_4S$, 519.6; m/z found, 520.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.18 (s, 1H), 8.30 (d, J = 5.4 Hz, 1H), 8.18-8.01 (m, 1H), 7.33-7.15 (m, 1H), 7.04-6.87 (m, 2H), 6.85-6.67 (m, 1H), 6.22-6.02 (m, 1H), 5.89 (d, J = 5.4 Hz, 1H), 5.74-5.60 (m, 1H), 4.78-4.56 (m, 1H), 4.57 -3.86 (m, 2H), 3.84-3.68 (m, 1H), 3.17 - 2.90 (m, 1H), 2.85- 2.59 (m, 1H), 2.03 (s, 3H), 1.98-1.88 (m, 1H), 1.82-1.55 (m, 2H), 1.52-1.36 (m, 1H), 1.35-1.24 (m, 6H).

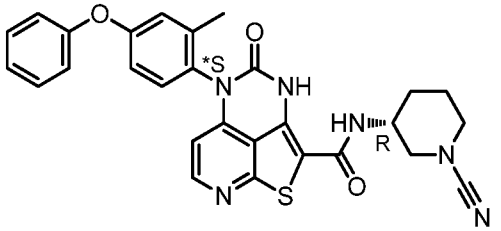
Example 34: *N*-((3*S*,4*R*)-1-Acryloyl-4-methoxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using *tert*-butyl (3*S*,4*R*)-3-amino-4-methoxypyrrolidine-1-carboxylate (Intermediate 11) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{27}N_5O_5S$, 569.6; m/z found, 570.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD and DMSO-d_6): δ 8.29 (d, J = 5.4Hz, 1H), 7.44-7.35 (m, 2H), 7.32-7.26 (m, 1H), 7.18-7.10 (m, 1H), 7.10-7.00 (m, 3H), 6.98-6.90 (m, 1H), 6.62-6.47 (m, 1H), 6.23-6.10 (m, 1H), 5.98

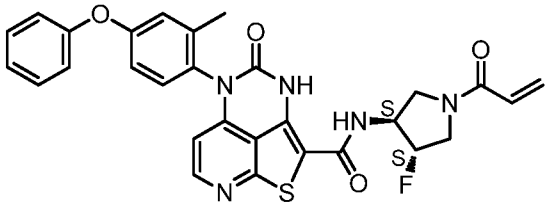
(d, J = 5.5Hz, 1H), 5.72-5.63(m, 1H), 4.75-4.49(m, 1H), 4.05-3.90 (m, 2H), 3.82-3.60 (m, 2H), 3.52-3.41 (m, 1H), 3.36-3.27 (m, 3H), 2.05 (s, 3H).

Example 35: (*R*)-*N*-(1-Cyanopiperidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



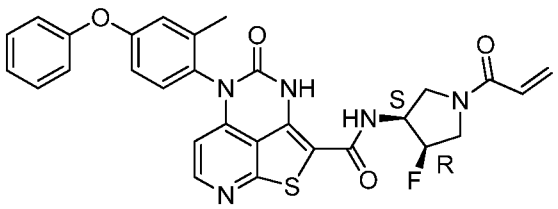
The title compound was prepared in a manner analogous to Method 1, steps A-I (including Chiral resolution Method A after Step F to obtain the **S* atropisomer) in Example 1, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G, and using bromocyanide in place of prop-2-enoyl chloride in step I. MS (ESI): mass calcd. for $C_{28}H_{24}N_6O_3S$, 524.6; m/z found, 525.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.18 (br, 1H), 8.36-8.25 (m, 1H), 8.23-8.08 (br, 1H), 7.46-7.39 (m, 2H), 7.37-7.30 (m, 1H), 7.20-7.16 (m, 1H), 7.13-7.05 (m, 3H), 6.99-6.92 (m, 1H), 6.00-5.86 (m, 1H), 3.97-3.90 (m, 1H), 2.98-2.90 (m, 2H), 2.03 (s, 3H), 2.01-1.90 (m, 1H), 1.90-1.83 (m, 1H), 1.82-1.73 (m, 1H), 1.66-1.51 (m, 2H), 1.51-1.34 (m, 1H).

Example 36: N-((3S,4S)-1-Acryloyl-4-fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



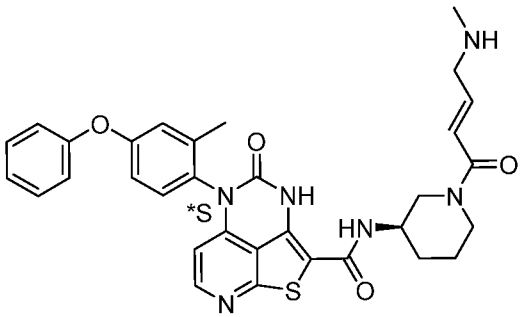
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using *tert*-butyl (3*S*,4*S*)-3-amino-4-fluoropyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{29}H_{24}FN_5O_4S$, 557.6; m/z found, 558.1 $[M+H]^+$. ^{1}H NMR (400 MHz, CD_3OD): δ 8.33 (d, J = 5.5Hz, 1H), 7.47-7.37 (m, 2H), 7.34-7.27 (m, 1H), 7.24-7.13 (m, 1H), 7.13-7.02 (m, 3H), 7.02-6.94 (m, 1H), 6.70-6.56 (m, 1H), 6.39-6.28 (m, 1H), 6.08 (d, J = 5.5Hz, 1H), 5.83-5.74 (m, 1H), 5.35-5.16 (m, 1H), 4.76-4.65 (m, 1H), 4.10-3.74 (m, 4H), 2.12 (s, 3H).

Example 37: N-((3S,4R)-1-Acryloyl-4-fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



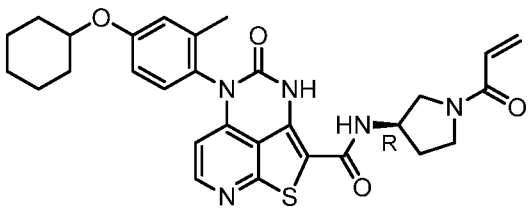
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using *tert*-butyl (3*S*,4*R*)-3-amino-4-fluoropyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{29}H_{24}FN_5O_4S$, 557.6; m/z found, 558.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6 and CD_3OD): δ 8.28 (d, J = 5.2Hz, 1H), 7.42-7.21 (m, 3H), 7.16-7.07 (m, 1H), 7.07-6.97 (m, 3H), 6.95-6.88 (m, 1H), 6.61-6.45 (m, 1H), 6.25-6.15 (m, 1H), 5.98 (d, J = 5.4Hz, 1H), 5.74-5.64 (m, 1H), 5.35-5.10 (m, 1H), 4.81-4.61 (m, 1H), 4.06-3.84 (m, 2H), 3.80-3.47 (m, 2H), 2.04 (s, 3H).

Example 38: (*R*,*E*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)- *N*-(1-(4-(methylamino)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



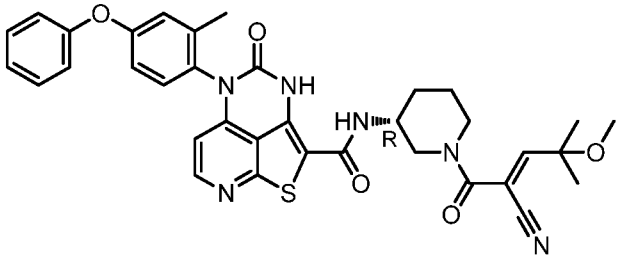
The title compound was prepared in a manner analogous to Example 104, using (E)-4-[*tert*-Butoxycarbonyl(methyl)amino]but-2-enoic acid (Intermediate 10) and (R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 98). MS (ESI): mass calcd. for $C_{32}H_{32}N_6O_4S$, 596.7; m/z found, 597.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.46 (s, 1H), 8.38-8.31 (m, 1H), 7.45-7.37 (m, 2H), 7.33-7.27 (m, 1H), 7.22-7.14 (m, 1H), 7.14-7.03 (m, 3H), 7.02-6.95 (m, 1H), 6.92-6.83 (m, 1H), 6.74-6.61 (m, 1H), 6.12-6.06 (m, 1H), 4.57-3.89 (m, 3H), 3.86-3.76 (m, 2H), 3.25-3.08 (m, 1H), 2.97-2.83 (m, 1H), 2.71 (s, 3H), 2.17-2.01 (m, 4H), 1.96-1.84 (m, 1H), 1.83-1.70 (m, 1H), 1.67-1.53 (m, 1H).

Example 39: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-5-(4-(cyclohexyloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared as for using steps A-I in Example 33, and using iodocyclohexane in place of 2-iodopropane in Step 1 and *tert*-butyl (3*R*)-3-aminopyrrolidine-1-carboxylate in place of tert-butyl (R)-3-aminopiperidine-1-carboxylate in Step G. MS (ESI): mass calcd. for $C_{29}H_{31}N_5O_4S$, 545.7; m/z found, 546.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33 (d, J = 5.6 Hz, 1H), 7.30-7.20 (m, 1H), 7.04-6.99 (m, 1H), 6.98-6.93 (m, 1H), 6.73-6.55 (m, 1H), 6.37-6.26 (m, 1H), 6.06 (d, J = 5.6 Hz, 1H), 5.85-5.71 (m, 1H), 4.73-4.58 (m, 1H), 4.47 - 4.36 (m, 1H), 4.07-3.52 (m, 4H), 2.43-2.11 (m, 5H), 2.07-2.00 (m, 2H), 1.89-1.80 (m, 2H), 1.68 - 1.41 (m, 6H).

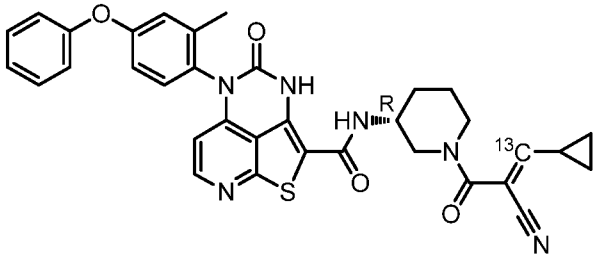
Example 40: (*R*,*E*)-*N*-(1-(2-Cyano-4-methoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a round bottom flask were added (*R*)-*N*-(1-(2-cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 874, 250 mg, 0.44 mmol), 2-methoxy-2-methylpropanal (225 mg, 2.2 mmol), EtOH (5 mL), and piperdine (75 mL) The reaction mixture was stirred at rt for 1 h, concentrated to dryness, and purified by flash column chromatography to yield the title compound (80 mg, 28% yield) as a white solid. MS (ESI): mass calcd. for $C_{35}H_{34}N_6O_5S$, 650.7; m/z found, 651.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.32 (d, J = 5.6 Hz, 1H), 7.47-7.36 (m, 2H), 7.34-7.26 (m, 1H), 7.22-7.14(m, 1H), 7.12-7.02 (m, 3H), 7.01-6.94 (m, 1H), 6.92-6.69 (m, 1H), 6.06 (d, J

= 5.5Hz, 1H), 4.56- 3.83 (m, 3H), 3.6-3.32 (m, 1H), 3.29-3.22 (m, 3H), 3.18-2.82 (m, 1H), 2.17-2.02 (m, 4H), 1.98-1.84 (m, 1H), 1.81-1.57 (m, 2H), 1.51-1.32 (m, 6H).

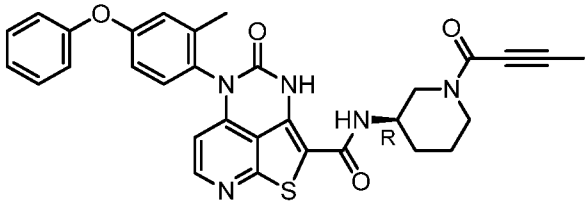
Example 41: (*R*,*E*)-*N*-(1-(2-Cyano-3-^{13}C-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: ^{13}C-Cyclopropanecarbaldehyde. A solution of ^{13}C-DMF (500 mg, 6.75 mmol) in THF (10 mL) was slowly added to cyclopropane magnesium bromide in THF (0.5 M, 14.8 mL, 7.42 mmol) cooled in an ice bath under N_2 over a period of 5 minutes. The mixture was brought to room temperature and stirred for 1 h. The mixture was acidified with 3 M aqueous HCl, extracted with Et_2O, dried over anhydrous Na_2SO_4, and concentrated to dryness to give the title compound as a pale yellow oil, which was used in the next step without purification.

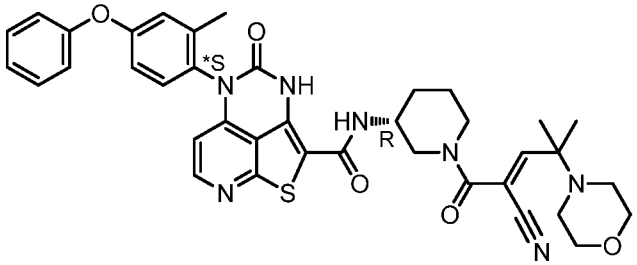
Step B: (*R*,*E*)-*N*-(1-(2-Cyano-3-^{13}C-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (*R*)-*N*-(1-(2-cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 874, 200 mg, 0.35 mmol) and ^{13}C-cyclopropanecarbaldehyde (100 mg, 1.4 mmol) in EtOH (5 mL) was added piperidine (60 mg, 0.70 mmol) and was stirred at room temperature overnight. The reaction was concentrated to dryness and purified by normal phase flash column chromatography (SiO_2) to give the title compound (22 mg, 91% yield) as a yellow solid. MS (ESI): mass calcd. for $C_{34}H_{30}N_6O_4S$, 619.7; m/z found, 620.2 $[M+H]^+$. ^{1}H NMR (400 MHz, CD_3OD): δ 8.28 (d, *J* = 5.6Hz, 1H), 7.39-7.31 (m, 2H), 7.28-7.21 (m, 1H), 7.16-7.07 (m, 1H), 7.07-6.96 (m, 3H), 6.95-6.85 (m, 1H), 6.72-6.19 (m, 1H), 5.98 (d, *J* = 5.6Hz, 1H), 4.24-4.08 (m, 3H), 3.99-3.83 (m, 2H), 2.04 (s, 3H), 1.98-1.88(m, 2H), 1.83-1.74 (m, 1H), 1.69-1.60 (m, 1H), 1.54-1.45 (m, 1H), 1.16-1.05 (m, 2H), 0.95-0.83 (m, 1H), 0.81-0.74 (m, 1H).

Example 42: (*R*)-*N*-(1-(But-2-ynoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared using the method in Example 104, and using but-2-ynoic acid in place of 3-methylsulfonylpropanoic acid. MS (ESI): mass calcd. for $C_{31}H_{27}N_5O_4S$, 565.6; m/z found, 566.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD and DMSO-d_6): δ 8.32-8.27 (m, 1H), 7.40-7.33 (m, 2H), 7.31-7.26 (m, 1H), 7.17-7.10 (m, 1H), 7.09-7.00 (m, 3H), 6.96-6.89 (m, 1H), 6.00-5.95 (m, 1H), 4.40-3.73 (m, 3H), 3.29-3.02 (m, 1H), 2.92-2.64 (m, 1H), 2.07 (s, 3H), 1.99-1.91 (m, 4H), 1.85-1.73 (m, 1H), 1.69-1.59 (m, 1H), 1.53-1.37 (m, 1H).

Example 43: (*R*,*E*)-*N*-(1-(2-Cyano-4-methyl-4-morpholinopent-2-enoyl)piperidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



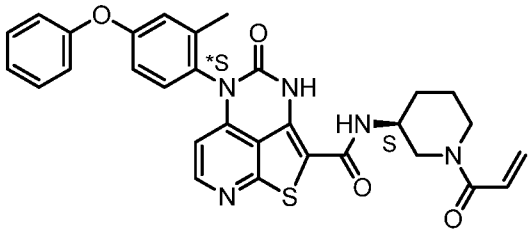
Step A: (*R*)-*N*-(1-(2-Cyanoacetyl)piperidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

The title compound was prepared in a manner analogous to Example 104, using 2-cyanoacetic acid and (R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 98).

Step B: (*R*,*E*)-*N*-(1-(2-Cyano-4-methyl-4-morpholinopent-2-enoyl)piperidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a sealed tube were added (*R*)-*N*-(1-(2-cyanoacetyl)piperidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (50 mg, 0.09 mmol), 2-methyl-2-morpholinopropanal (20 mg, 0.13 mmol), piperidine (9 mg, 0.1 mmol), and EtOH (3 mL). The sealed tube was heated to 105 °C

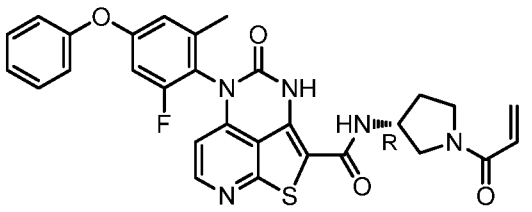
overnight, cooled to rt, and the residue purified by flash column chromatography to yield the title compound (39 mg, 63% yield) as a yellow solid. MS (ESI): mass calcd. for $C_{38}H_{39}N_7O_5S$, 705.8; m/z found, 706.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33 (d, J = 5.5 Hz, 1H), 7.47-7.37 (m, 2H), 7.33-7.26 (m, 1H), 7.23-7.14 (m, 1H), 7.12-7.03 (m, 3H), 7.01-6.94 (m, 1H), 6.90-6.78 (m, 1H), 6.07 (d, J = 5.6 Hz, 1H), 4.55-3.82 (m, 3H), 3.81-3.63 (m, 4H), 3.47-3.35 (m, 0.5H), 3.29 -2.86 (m, 1.5H), 2.71-2.51 (m, 4H), 2.12 (s, 3H), 2.07-1.60 (m, 4H), 1.41-1.24 (m, 6H).

Example 44: (*S*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1 (including Chiral resolution Method A after Step F to obtain the **S* atropisomer), and using *tert*-butyl (3*S*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{27}N_5O_4S$, 553.6; m/z found, 554.0 $[M+H]^+$. ^1H NMR (500 MHz, CD_3OD): δ 8.29 (d, J = 6.5 Hz, 1H), 7.47 - 7.33 (m, 2H), 7.29 (d, J = 8.4 Hz, 1H), 7.24 - 6.94 (m, 5H), 6.88 - 6.73 (m, 1H), 6.20 (d, J = 17.3 Hz, 1H), 6.13 - 5.97 (m, 1H), 5.80 - 5.62 (m, 1H), 4.64 - 3.88 (m, 3H), 3.26 - 3.12 (m, 1H), 3.04 - 2.89 (m, 1H), 2.18 - 2.02 (m, 4H), 1.99 - 1.47 (m, 3H).

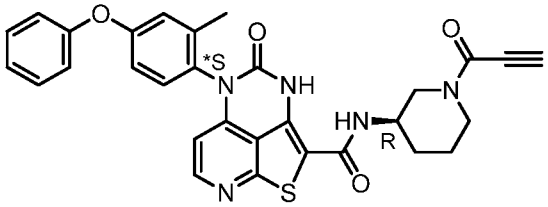
Example 45: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-5-(2-fluoro-6-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps C-G in Example 1, and using 2-fluoro-6-methyl-4-phenoxyaniline (Intermediate 9) in place of 2-methyl-4-phenoxyaniline in step C, and using 1-[(3*R*)-3-aminopyrrolidin-1-yl]prop-2-en-1-one

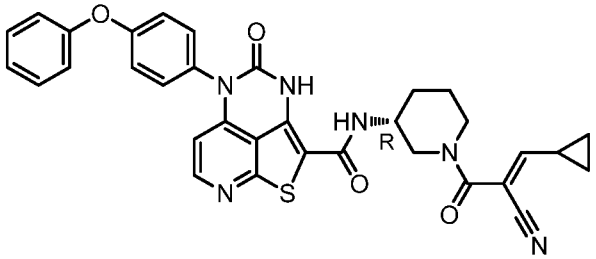
(Intermediate 5) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{29}H_{24}FN_5O_4S$, 557.6; m/z found, 558.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.36-8.28 (br, 1H), 7.57-7.41 (m, 2H), 7.34-7.10 (m, 3H), 6.95-6.85 (m, 1H), 6.83-6.76 (m, 1H), 6.75-6.55 (m, 1H), 6.42-6.25 (m, 1H), 6.17-6.04 (m, 1H), 5.86-5.70 (m, 1H), 4.77-4.57 (m, 1H), 4.18 -3.51 (m, 4H), 2.48 -1.94 (m, 5H).

Example 46: (R)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-N-(1-propioloylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared using a method analogous to Example 75, using prop-2-ynoic acid and (R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 98). MS (ESI): mass calcd. for $C_{30}H_{25}N_5O_4S$, 551.6; m/z found, 552.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.40-8.26 (m, 1H), 7.43-7.34 (m, 2H), 7.29-7.21 (m, 1H), 7.20-7.13 (m, 1H), 7.12-7.03 (m, 3H), 7.00-6.93 (m, 1H), 6.09-6.03 (m, 1H), 4.50-4.36 (m, 1H), 4.33-4.13 (m, 1H), 4.05-3.77 (m, 2H), 3.38-3.19 (m, 1H), 3.06-2.85 (m, 1H), 2.16-2.01 (m, 4H), 1.95-1.84 (m, 1H), 1.79-1.67 (m, 1H), 1.64-1.49 (m, 1H).

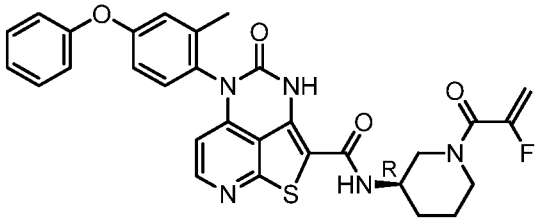
Example 47: (*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared using a method analogous to Example 75, using (*E*)-2-cyano-3-cyclopropylprop-2-enoic acid (Intermediate 17) and (R)-4-oxo-5-(4-phenoxyphenyl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 860). MS (ESI): mass calcd. for $C_{33}H_{28}N_6O_4S$, 604.7; m/z found, 605.1 $[M+H]^+$. ^1H NMR (500

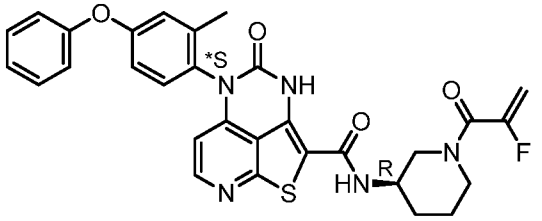
MHz, CD_3OD): δ 8.32 (dd, *J* = 5.7, 1.6 Hz, 1H), 7.50 - 7.31 (m, 4H), 7.29 - 6.99 (m, 5H), 6.63 - 6.46 (m, 1H), 6.28 - 6.10 (m, 1H), 5.48 (d, *J* = 1.4 Hz, 1H), 4.53 - 3.87 (m, 3H), 2.21 - 0.70 (m, 11H).

Example 48: (*R*)-*N*-(1-(2-Fluoroacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared using a method analogous to Example 75, using 2-fluoroprop-2-enoic acid and (R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869). MS (ESI): mass calcd. for $C_{30}H_{26}FN_5O_4S$, 571.6; m/z found, 572.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.32 (d, J = 5.6 Hz, 1H), 7.46-7.35 (m, 2H), 7.32-7.23 (m, 1H), 7.21-7.12 (m, 1H), 7.12-7.02 (m, 3H), 7.00-6.91 (m, 1H), 6.09-6.05 (m, 1H), 5.28-5.06 (m, 2H), 4.51-3.84 (m, 3H), 3.25-2.85 (m, 2H), 2.11 (s, 3H), 2.09-1.99 (m, 1H), 1.96-1.82 (m, 1H), 1.77-1.53 (m, 2H).

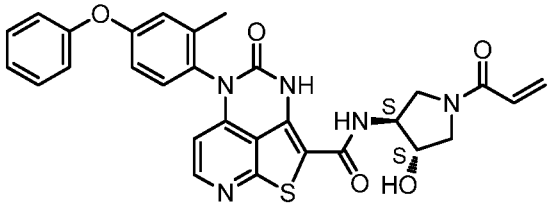
Example 49: (*R*)-*N*-(1-(2-Fluoroacryloyl)piperidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a round bottom flask were added (R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 98, 31 mg, 0.062 mmol), were added DMF (3 mL), 2-fluoroacrylic acid (9 mg, 0.01 mmol), triethylamine (21 mg, 0.188 mmol), HATU (47 mg, 0.124 mmol). The reaction mixture was stirred at rt for 2 h. Water was added and the precipitate was collected by filtration, then purified by silica gel chromatograph to give the title compound as a light yellow solid.

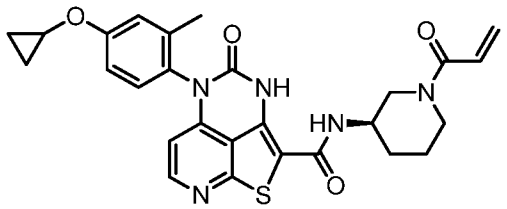
MS (ESI): mass calcd. for $C_{30}H_{26}FN_5O_4S$, 571.6; m/z found, 572.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.34 (d, J = 5.5 Hz, 1H), 7.47 – 7.36 (m, 2H), 7.33-7.25 (m, 1H), 7.22-7.14 (m, 1H), 7.13-7.03 (m, 3H), 7.02-6.94 (m, 1H), 6.08 (d, J = 5.6 Hz, 1H), 5.30-5.10 (m, 2H), 4.63 – 3.77 (m, 3H), 3.29 – 2.75 (m, 2H), 2.15 (s, 3H), 2.10 – 2.00 (m, 1H), 1.95-1.84 (m, 1H), 1.80 – 1.69 (m, 1H), 1.67-1.55 (m, 1H).

Example 50: *N*-((3*S*,4*S*)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using *tert*-butyl (3*S*,4*S*)-3-amino-4-hydroxypyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{29}H_{25}N_5O_5S$, 555.6; m/z found, 556.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.31 (d, J = 5.5Hz, 1H), 7.45-7.35 (m, 2H), 7.35-7.27 (m, 1H), 7.21-7.12 (m, 1H), 7.11-7.00 (m, 3H), 7.00-6.93 (m, 1H), 6.66-6.54 (m, 1H), 6.34-6.24 (m, 1H), 6.06 (d, J = 5.5Hz, 1H), 5.76 (dt, J = 10.5, 1.9, 1H), 4.50-4.32 (m, 2H), 4.09-3.49 (m, 4H), 2.11 (s, 3H).

Example 51: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(4-cyclopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3 *H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



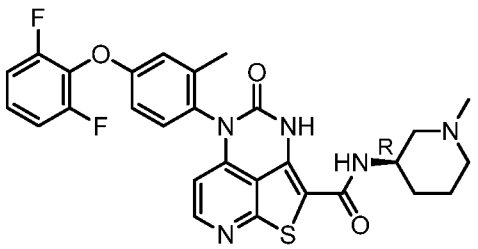
Step A: 4-(Cyclopropoxy)-2-methyl-1-nitrobenzene. To a reaction vial were added 3-methyl-4-nitrophenol (3.1 g, 20 mmol), bromocyclopropane (4.9 g, 40 mmol), KI (3.4 g, 20 mmol), cesium carbonate (6.6 g, 20 mmol), and NMP (20 mL) and was heated to 170 °C for 2 h in the microwave. The mixture was diluted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, concentrated to dryness, and purified by flash column chromatography to yield the title compound (0.85 g, 22% yield) as a brown liquid.

Step B: 4-(Cyclopropoxy)-2-methylaniline. A mixture of 4-(cyclopropoxy)-2-methyl-1-nitrobenzene (450 mg, 2.3 mmol) and Pd/C (24 mg, 0.23 mmol) in MeOH (15 mL) was stirred for 5 h under H_2. The reaction was filtered and the filtrate was concentrated to dryness to yield the title compound (310 mg, 82% yield) as a brown liquid, which was used in the next step without purification.

Step C: 2-Chloro-4-[4-(cyclopropoxy)-2-methylanilino]pyridine-3-carbonitrile. To a round bottom flask were added 4-(cyclopropoxy)-2-methylaniline (420 mg, 2.6 mmol), 2-chloro-4-iodopyridine-3-carbonitrile (885 mg, 3.35 mmol), $Pd(OAc)_2$ (58 mg, 0.26 mmol), DPEphos (280 mg, 0.51 mmol), cesium carbonate (1.7 g, 5.2 mmol), and dioxane (20 mL) and was stirred at 110 °C for 15 h under N_2. The mixture was concentrated to dryness and purified by flash column chromatography to yield the title compound (530 mg, 69% yield) as a light yellow solid.

Step D: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(4-cyclopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3 *H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps D-I in Example 1, and using 2-chloro-4-[4-(cyclopropoxy)-2-methylanilino]pyridine-3-carbonitrile in place 2-chloro-4-(2-methyl-4-phenoxyanilino)pyridine-3-carbonitrile in step D, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 27) in step G. MS (ESI): mass calcd. for $C_{27}H_{27}N_5O_4S$, 517.6; m/z found, 518.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.35-8.26 (m, 1H), 7.27-7.20 (m, 1H), 7.15-7.04 (m, 2H), 6.85-6.71 (m, 1H), 6.24-6.13 (m, 1H), 6.07-6.00 (m, 1H), 5.77-5.67 (m, 1H), 4.61-3.87 (m, 3H), 3.87-3.76 (m, 1H), 3.22-3.08 (m, 1H), 2.96-2.81 (m, 1H), 2.16-1.98 (m, 4H), 1.92-1.80 (m, 1H), 1.79-1.65 (m, 1H), 1.64-1.50 (m, 1H), 0.88-0.77 (m, 2H), 0.76-0.67 (m, 2H).

Example 52: (*R*)-5-(4-(2,6-Difluorophenoxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

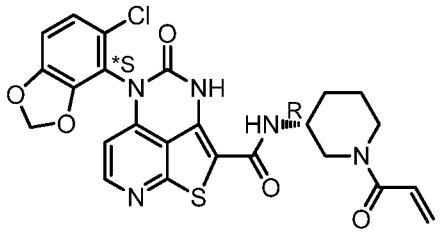


Step A: (*R*)-5-(4-(2,6-Difluorophenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a

manner analogous to Method 1, steps A-H in Example 1, using 2,6-difluorophenol in place of phenol in step A, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 27) in step G.

Step B: (*R*)-5-(4-(2,6-Difluorophenoxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a round bottom flask were added (*R*)-5-(4-(2,6-difluorophenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (120 mg, 0.22 mmol) and DCM (5 mL) and was treated with formaldehyde (0.5 mL, 37 wt. % in H_2O). To the stirred reaction was added $NaBH(AcO)_3$ (95 mg, 0.45 mmol) and the reaction was maintained at rt for 1 h. The reaction was concentrated to dryness and the residue purified by flash column chromatography to yield the title compound (59 mg, 43% yield) as a yellow solid. MS (ESI): mass calcd. for $C_{28}H_{25}F_2N_5O_3S$, 549.6; m/z found, 550.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.33-8.25 (m, 1H), 8.12-8.00 (m, 1H), 7.48-7.29 (m, 4H), 7.11-7.05 (m, 1H), 6.99-6.89 (m, 1H), 5.94-5.84 (m, 1H), 4.01-3.93 (m, 1H), 2.90-2.84 (m, 1H), 2.76-2.69 (m, 1H), 2.25 (s, 3H), 2.07 (s, 3H), 2.01-1.96 (m, 2H), 1.91 (s, 3H), 1.84-1.76 (m, 1H), 1.76-1.67 (m, 1H), 1.62-1.49 (m, 1H), 1.44-1.32 (m, 1H).

Example 53: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(**S*)-(5-chlorobenzo[*d*][1,3]dioxol-4-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

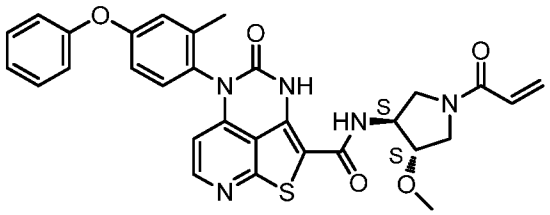


Step A: 2-Chloro-4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyridine-3-carbonitrile. A mixture of 2,4-dichloropyridine-3-carbonitrile (1.6 g, 9.3 mmol), 5-chloro-1,3-benzodioxol-4-amine (1.6 g, 9.3 mmol), DPEphos (1.0 g, 1.9 mmol), $Pd(AcO)_2$ (0.21 g, 0.93 mmol), and K_3PO_4 (5.0 g, 23 mmol) in dioxane (80 mL) was heated at reflux under N_2 overnight. The reaction was concentrated to dryness and the residue was purified by flash column chromatography to yield the title compound (2.2 g, 77% yield) as a yellow solid.

Step B: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(**S*)-(5-chlorobenzo[*d*][1,3]dioxol-4-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared

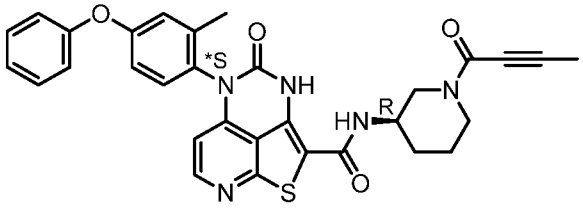
in a manner analogous to Method 1, steps D-I in Example 1 (including Chiral resolution Method A after Step F to obtain the *S atropisomer), and using 2-chloro-4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyridine-3-carbonitrile in place of 2-chloro-4-(2-methyl-4-phenoxyanilino)pyridine-3-carbonitrile in step D, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 27) in step G. MS (ESI): mass calcd. for $C_{24}H_{20}ClN_5O_5S$, 526.0; m/z found, 526.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.38 (d, *J* = 5.5Hz, 1H), 7.11 (d, *J* = 8.4Hz, 1H), 7.00 (d, *J* = 8.4Hz, 1H), 6.85-6.70 (m, 1H), 6.25 (d, *J* = 5.5Hz, 1H), 6.23-6.15 (m, 1H), 6.11-6.07 (m, 2H), 5.78-5.65 (m, 1H), 4.56-4.48 (m, 0.5H), 4.31-4.23 (m, 0.5H), 4.20-4.12 (m, 0.5H), 4.05-3.87 (m, 1.5H), 3.25-3.11 (m, 1H), 2.97 -2.85 (m, 1H), 2.12-2.01 (m, 1H), 1.91-1.82 (m, 1H), 1.79-1.65 (m, 1H), 1.63-1.52 (m, 1H).

Example 54: *N*-((3*S*,4*S*)-1-Acryloyl-4-methoxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using *tert*-butyl (3*S*,4*S*)-3-amino-4-methoxypyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{27}N_5O_5S$, 569.6; m/z found, 570.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33 (d, *J* = 5.3Hz, 1H), 7.46-7.36 (m, 2H), 7.35-7.26 (m, 1H), 7.22-7.13(m, 1H), 7.13-7.02 (m, 3H), 7.02-6.94(m, 1H), 6.68-6.53 (m, 1H), 6.37-6.23 (m, 1H), 6.08 (d, *J* = 5.5Hz, 1H), 5.83-5.71 (m, 1H), 4.66-4.56 (m, 1H), 4.08 -3.77 (m, 3H), 3.75-3.62 (m, 2H), 3.52-3.45 (m, 3H), 2.12 (s, 3H).

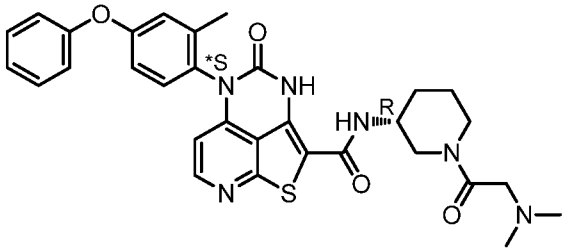
Example 55: (*R*)-*N*-(1-(But-2-ynoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: (*R*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1 (including Chiral resolution Method A after Step F to obtain the **S* atropisomer), and using *tert*-butyl (3*S*,4*S*)-3-amino-4-methoxypyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

Step B: (*R*)-*N*-(1-(But-2-ynoyl)piperidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A mixture of (*R*)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 98, 25 mg, 0.050 mmol), but-2-ynoic acid (25 mg, 0.30 mmol), HATU (50 mg, 0.13 mmol), and triethylamine (20 mg, 0.20 mmol) in DMF (2 mL) was reacted at rt for 2 h. The reaction was quenched with H_2O (20 mL), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound as a white solid. MS (ESI): mass calcd. for $C_{31}H_{27}N_5O_4S$, 565.6; m/z found, 566.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.38-8.27 (m, 1H), 7.46-7.36 (m, 2H), 7.33-7.26 (m, 1H), 7.22-7.14 (m, 1H), 7.12-7.04 (m, 3H), 7.00-6.92 (m, 1H), 6.11-6.04 (m, 1H), 4.48-4.22 (m, 2H), 4.13-3.92 (m, 1H), 3.40-3.16 (m, 1H), 3.06-2.80 (m, 1H), 2.12 (s, 3H), 2.08-1.97 (m, 4H), 1.94-1.80 (m, 1H), 1.79-1.67 (m, 1H), 1.66-1.51 (m, 1H).

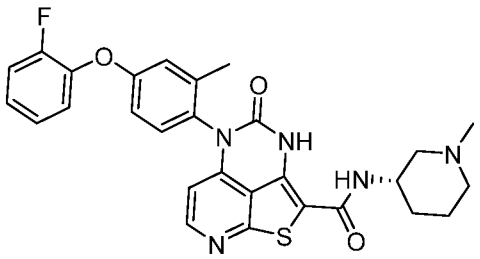
Example 56: (*R*)-*N*-(1-(2-(Dimethylamino)acetyl)piperidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: *tert*-Butyl *N*-[(3*R*)-1-[2-(dimethylamino)acetyl]-3-piperidyl]carbamate. A solution of *tert*-butyl *N*-[(3*R*)-3-piperidyl]carbamate (400 mg, 2 mmol), 2-(dimethylamino)acetic acid (226 mg, 2.19 mmol), HATU (0.91 mg, 2.4 mmol), and triethylamine (0.56 mL, 4.0 mmol) in DMF (5 mL) was stirred at rt overnight, then poured into water. The mixture was extracted with EtOAc and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield the title compound as a yellow oil.

Step B: (*R*)-*N*-(1-(2-(Dimethylamino)acetyl)piperidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3 *H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1 (including Chiral resolution Method A after Step F to obtain the **S* atropisomer), and using 1-[(3*R*)-3-amino-1-piperidyl]-2-(dimethylamino)ethanone (Intermediate 43) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{31}H_{32}N_6O_4S$, 584.7; m/z found, 585.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.26 (d, *J* = 5.5 Hz, 1H), 7.43-7.34 (m, 2H), 7.29-7.21 (m, 1H), 7.20-7.13 (m, 1H), 7.12-7.03 (m, 3H), 7.00-6.93 (m, 1H), 6.00 (d, *J* = 5.5 Hz, 1H), 4.26-3.74 (m, 3H), 3.61-3.40 (m, 2H), 3.27-3.04 (m, 2H), 2.49-2.34 (m, 6H), 2.12 (s, 3H), 2.05-1.96 (m, 1H), 1.93-1.70 (m, 2H), 1.68-1.52 (m, 1H).

Example 57: (*R*)-5-(4-(2-Fluorophenoxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

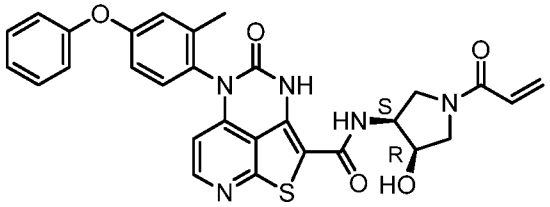


Step A: (*R*)-5-(4-(2-Fluorophenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A solution of 5-(4-(2-fluorophenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (218 mg, 0.501 mmol), *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate (100 mg, 0.5 mmol), and HATU (380 mg, 1.0 mmol) in DMF (3 mL) was stirred at rt for 3 hr. Water was added and the precipitate that formed was filtered to give a pale yellow solid. The solid was dissolved in MeOH (4 mL) and HCl (4 mL), and the resulting mixture was heated to 50 °C for 30 min. The reaction was concentrated to dryness to yield the title compound (200 mg, 72% yield) as a yellow solid, which was used in the next step reaction without further purification.

Step B: (*R*)-5-(4-(2-Fluorophenoxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (*R*)-5-(4-(2-fluorophenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (110 mg, 0.21 mmol) and formaldehyde (0.3 mL, 37 wt. % in H_2O) in MeOH (5 mL) was added $NaBH(OAc)_3$ (135 mg, 0.640 mmol) and was stirred at rt

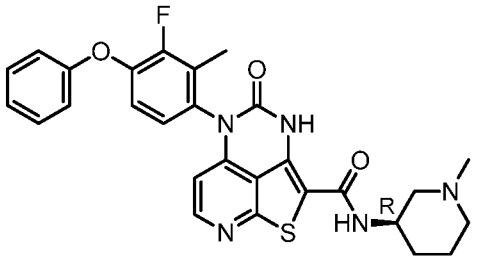
for 1 h. The reaction was concentrated to dryness and purified by flash column chromatography to yield the title compound (67 mg, 54% yield) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{26}FN_5O_3S$, 531.6; m/z found, 532.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.54 (s, 1H), 8.33-8.21 (m, 1H), 7.39-7.31 (m, 1H), 7.31-7.18 (m, 4H), 7.06-6.98 (m, 1H), 6.98-6.88 (m, 1H), 6.06-5.97 (m, 1H), 4.32-4.19 (m, 1H), 3.44-3.33 (m, 1H), 3.22-3.08 (m, 1H), 2.77-2.60 (m, 5H), 2.15-2.06 (m, 3H), 2.04-1.90 (m, 2H), 1.88-1.74 (m, 1H), 1.69-1.55 (m, 1H).

Example 58: *N*-((3*S*,4*R*)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using *tert*-butyl (3*S*,4*R*)-3-amino-4-hydroxypyrrolidine-1-carboxylate (Intermediate 24) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{29}H_{25}N_5O_5S$, 555.6; m/z found, 556.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.30 (d, J = 5.5Hz, 1H), 7.44-7.35 (m, 2H), 7.33-7.27 (m, 1H), 7.19-7.12 (m, 1H), 7.12-7.01 (m, 3H), 7.00-6.93 (m, 1H), 6.67-6.51 (m, 1H), 6.32-6.22(m, 1H), 6.05 (d, J = 5.5Hz, 1H), 5.80-5.68 (m, 1H), 4.65-4.52 (m, 1H), 4.51-4.38 (m, 1H), 4.06-3.85 (m, 1H), 3.73-3.49 (m, 3H), 2.10 (s, 3H).

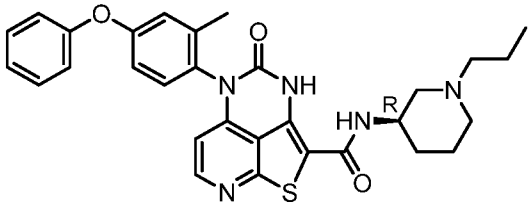
Example 59: (*R*)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a mixture of (*R*)-5-(3-fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Intermediate 18) (50 mg, 0.1 mmol) and formaldehyde (0.3 mL, 37 wt. % in H_2O) in MeOH (6 mL) was added $NaBH(OAc)_3$

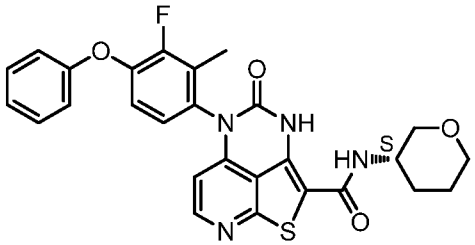
(62 mg, 0.29 mmol). The reaction mixture was stirred at rt for 1 h, concentrated to dryness, and purified by flash column chromatography to yield the title compound (36 mg, 64% yield) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{26}FN_5O_3S$, 531.6; m/z found, 532.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.48 (s, 1H), 8.39-8.29 (m, 1H), 7.43-7.34 (m, 2H), 7.23-7.11 (m, 2H), 7.11-7.03 (m, 3H), 6.18-6.10 (m, 1H), 4.31-4.21 (m, 1H), 3.50-3.36 (m, 1H), 3.26-3.16 (m, 1H), 2.82-2.64 (m, 5H), 2.12 (s, 3H), 2.04-1.96 (m, 2H), 1.88-1.77 (m, 1H), 1.70-1.57(m, 1H).

Example 60: (*R*)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(1-propylpiperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



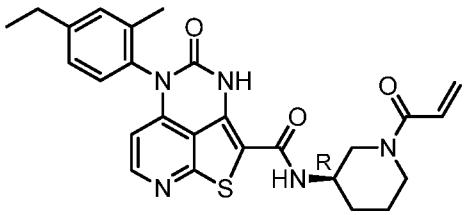
To a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.30 mmol) in MeOH (5 mL) was added propanal (0.045 mL, 0.6 mmol). It was stirred at rt for 10 min, then $NaBH(OAc)_3$ (190 mg, 0.90 mmol) was added and the mixture was stirred at rt overnight. The pH was adjusted to pH >7 with 2 M aqueous NaOH and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound (75 mg, 46% yield) as a yellow solid. MS (ESI): mass calcd. for $C_{30}H_{31}N_5O_3S$, 541.7; m/z found, 542.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6 and CD_3OD): δ 8.25 (d, J = 5.0 Hz, 1H), 7.47-7.32 (m, 2H), 7.32-7.22 (m, 1H), 7.19-7.11 (m, 1H), 7.10-6.99 (m, 3H), 6.97-6.86 (m, 1H), 5.93 (d, J = 4.7 Hz, 1H), 4.06-3.95 (m, 1H), 2.96-2.83 (m, 1H), 2.79-2.64 (m, 1H), 2.38-2.25 (m, 2H), 2.15-1.98 (m, 5H), 1.86-1.77 (m, 1H), 1.74-1.65 (m, 1H), 1.62-1.53 (m, 1H), 1.53-1.38 (m, 3H), 0.84 (t, J = 7.0 Hz, 3H).

Example 61: (*S*)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(tetrahydro-2*H*-pyran-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared using analogous conditions described in Method 1, steps B-I in Example 1, and using 2-fluoro-3-methyl-4-nitro-1-phenoxybenzene (Intermediate 18, step B) in place of 2-methyl-4-phenoxyaniline in step B, and using (3*S*)-tetrahydropyran-3-amine in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{23}FN_4O_4S$, 518.6; m/z found, 519.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.27 (d, J = 5.0Hz, 1H), 7.42-7.27(m, 2H), 7.25-7.16 (m, 1H), 7.14-6.98 (m, 4H), 6.03 (d, *J* = 5.2Hz, 1H), 392-3.84 (m, 1H), 3.80-3.70 (m, 2H), 3.30-3.12 (m, 2H), 2.02 (s, 3H), 1.92-1.83 (m, 1H), 1.67-1.49 (m, 3H).

Example 62: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(4-ethyl-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

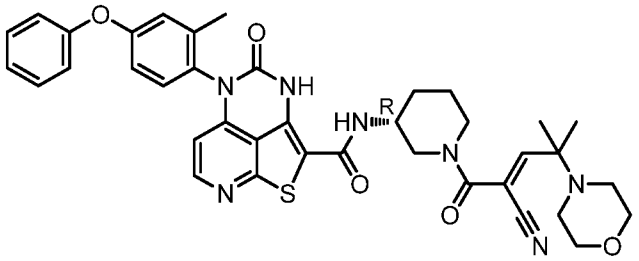


Step A: 4-Ethyl-2-methylaniline. To a mixture of 4-bromo-2-methylaniline (1.86 g, 10 mmol), Cs_2CO_3 (10 g, 30 mmol), and $Pd(dppf)Cl_2$ (146 mg, 0.200 mmol) in a Schlenk tube under a N_2 atmosphere was added dry THF (30 mL). To the stirred suspension was added trialkylborane (3.0 mL, 1 M in THF, 3.0 mmol) in one portion, and the mixture was refluxed for 5 h. The reaction was cooled to 0 °C and quenched by the addition of 10% aqueous NaOH and 30% aqueous H_2O_2. After stirring for 30 min at rt, the mixture was extracted with EtOAc. The combined organic layers were washed with aqueous $FeSO_4$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound (1.1 g, 83% yield) as a white solid.

Step B: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(4-ethyl-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps C-I in Example 1, and using 4-ethyl-2-methylaniline in place of 2-

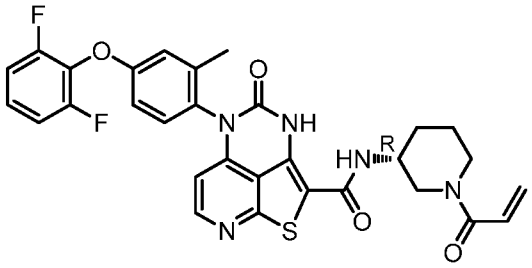
methyl-4-phenoxyaniline in step C, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{26}H_{27}N_5O_3S$, 489.6; m/z found, 490.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 8.30 (d, J = 5.5 Hz, 1H), 8.08 (s, 1H), 7.36-7.14 (m, 3H), 6.89- 6.64 (m, 1H), 6.09 (d, J = 16.7 Hz, 1H), 5.85 (d, J = 5.5 Hz, 1H), 5.67 (d, J = 10.5 Hz, 1H), 4.52-4.14 (m, 1H), 4.08 – 3.92 (m, 1H), 3.80-3.60 (m, 1H), 3.15-2.88 (m, 1H), 2.79-2.59 (m, 3H), d 2.80-2.60 (m, 3H), 1.99-1.89 (m, 1H), 1.78-1.58 (m, 2H), 1.50-1.32 (m, 1H), 1.23 (t, J = 7.6 Hz, 3H).

Example 63: (*R*,*E*)-*N*-(1-(2-Cyano-4-methyl-4-(tetrahydro-2*H*-pyran-4-yl)pent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



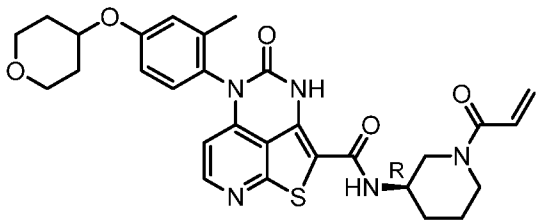
To a sealed tube were added (*R*)-*N*-(1-(2-cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 874, 150 mg, 0.27 mmol), 2-methyl-2-morpholinopropanal (65 mg, 0.41 mmol), piperidine (30 mg, 0.35 mmol), and EtOH (3 mL) and was heated to 105 °C overnight, cooled to rt, concentrated to dryness, and the residue purified by flash column chromatography to yield the title compound (37 mg, 96% yield) as yellow solid. MS (ESI): mass calcd. for $C_{38}H_{39}N_7O_5S$, 705.8; m/z found, 706.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.31 (d, J = 5.5 Hz, 1H), 7.47-7.36 (m, 2H), 7.35-7.26 (m, 1H), 7.21-7.14 (m, 1H), 7.12-7.04 (m, 3H), 7.01-6.93 (m, 1H), 6.89-6.78 (m, 1H), 6.08-6.02 m, 1H), 4.52-3.87 (m, 3H), 3.80-3.61 (m, 4H), 3.52-3.35 (m, 1H), 3.25-2.85 (m, 1H), 2.74-2.51 (m, 4H), 2.15-2.10 (m, 3H), 2.08-1.57 (m, 4H), 1.36-1.26 (m, 6H).

Example 64: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(4-(2,6-difluorophenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



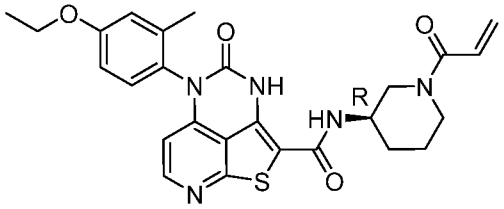
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using 2,6-difluorophenol in place of phenol in step A, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{25}F_2N_5O_4S$, 589.6; m/z found, 590.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.29 (d, J = 5.6 Hz, 1H), 7.40-7.26 (m, 2H), 7.21-7.10 (m, 2H), 7.04-6.98 (m, 1H), 6.95-6.88 (m, 1H), 6.85-6.70 (m, 1H), 6.27-6.12 (m, 1H), 6.05-5.98(m, 1H), 5.78-5.64 (m, 1H), 4.61-3.84 (m, 3H), 3.24-3.07 (m, 1H), 2.98-2.79 (m, 1H), 2.15-2.10 (m, 3H), 2.09-1.98 (m, 1H), 1.94-1.48 (m, 3H).

Example 65: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-((tetrahydro-2*H*-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps D-I in Example 1, and using 2-chloro-4-(2-methyl-4-tetrahydropyran-4-yloxyanilino)pyridine-3-carbonitrile (Intermediate 31) in place of 2-chloro-4-(2-methyl-4-phenoxyanilino)pyridine-3-carbonitrile in step D, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{29}H_{31}N_5O_5S$, 561.7; m/z found, 562.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.31-8.27 (m, 1H), 7.25-7.20 (m, 1H), 7.05-7.01 (m, 1H), 6.99-6.95 (m, 1H), 6.81-6.77 (m, 1H), 6.22-6.17 (m, 1H), 6.04-6.00 (m, 1H), 5.74-5.69 (m, 1H), 4.68-4.58 (m, 1H), 4.33-4.11 (m, 1H), 4.07-3.85 (m, 4H), 3.65-3.57 (m, 2H), 3.21-3.18 (m, 1H), 2.93-2.86 (m, 1H), 2.11 (s, 3H), 2.09-2.02 (m, 3H), 1.89-1.83 (m, 1H), 1.80-1.69 (m, 3H), 1.55-1.50 (m, 1H).

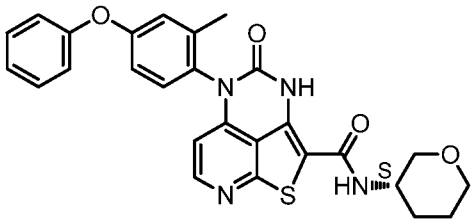
Example 66: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(4-ethoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: 4-Ethoxy-2-methyl-1-nitrobenzene. To a mixture of 3-methyl-4-nitrophenol (5.0 g, 33 mmol) and K_2CO_3 (13.6 g, 98.6 mmol) in DMF (25 mL) was added bromoethane (8.9 g, 82 mmol) and the reaction was stirred at 80 °C overnight. Water was added to the reaction mixture and a yellow solid was precipitated. The precipitate was filtered, washed with water, and dried to yield the title compound (4.5 g, 76% yield) as a yellow solid.

Step B: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(4-ethoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps B-I in Example 1, using 4-ethoxy-2-methyl-1-nitrobenzene in place of 2-methyl-1-nitro-4-phenoxybenzene in step B, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{26}H_{27}N_5O_4S$, 505.6; m/z found, 506.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33-8.22 (m, 1H), 7.29-7.16 (m, 1H), 7.01-6.88 (m, 2H), 6.87- 6.70 (m, 1H), 6.26-6.12 (m, 1H), 6.04-5.94 (m, 1H), 5.77-5.65 (m, 1H), 4.57-3.89 (m, 5H), 3.21-3.05 (m, 1H), 2.96-2.77 (m, 1H), 2.10 (s, 3H), 2.07-1.99 (m, 1H), 1.88-1.80 (m, 1H), 1.78-1.49 (m, 2H), 1.44-1.35 (m, 3H).

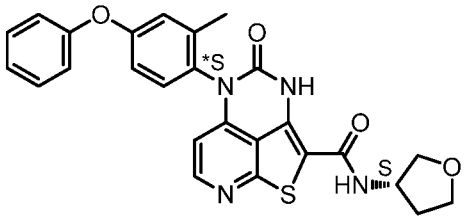
Example 67: (*S*)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(tetrahydro-2*H*-pyran-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1, and using (3*S*)-tetrahydropyran-3-amine in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{24}N_4O_4S$, 500.6; m/z found, 501.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.23 (s,

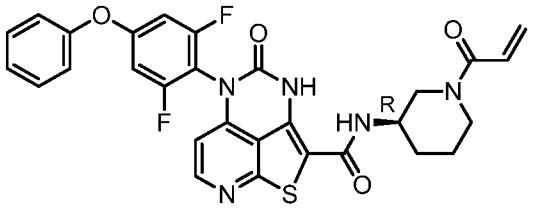
1H), 8.33 (d, *J* = 5.5 Hz, 1H), 7.96 (d, *J* = 7.4 Hz, 1H), 7.51-7.41 (m, 2H), 7.41-7.33 (m, 1H), 7.26-7.16 (m, 1H), 7.15-7.04 (m, 3H), 7.03-6.90 (m, 1H), 5.97 (d, *J* = 5.4 Hz, 1H), 4.00-3.84 (m, 1H), 3.84-3.69 (m, 2H), 3.25-3.12 (m, 2H), 2.06 (s, 3H), 1.97-1.85 (m, 1H), 1.78-1.50 (m, 3H).

Example 68: (*S*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(tetrahydrofuran-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-G (including Chiral resolution Method A after Step F to obtain the **S* atropisomer) in Example 1, and using (3*S*)-tetrahydrofuran-3-amine in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{26}H_{22}N_4O_4S$, 486.5; m/z found, 487.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.40-8.27(m, 1H), 7.40-7.35 (m, 2H), 7.34-7.24 (m, 1H), 7.23-7.14 (m, 1H), 7.13 – 7.02 (m, 3H), 7.00-6.92 (m, 1H), 6.08 (d, *J* = 4.7 Hz, 1H), 4.65-4.50 (m, 1H), 4.06 – 3.90 (m, 2H), 3.88-3.65 (m, 2H), 2.35-2.21 (m, 1H), 2.13 (s, 3H), 2.06-1.95 (m, 1H).

Example 69: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(2,6-difluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

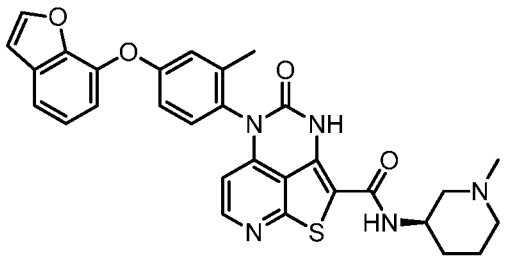


Step A: 1,3-Difluoro-2-nitro-5-phenoxybenzene. 3,5-Difluoro-4-nitrophenol (Intermediate 26) (493 mg, 2.82 mmol) was dissolved in CH_3CN (45 mL, 860 mmol) and (2-trimethylsilylphenyl) trifluoromethanesulfonate (1.0 mL, 4.2 mmol) was added, followed by cesium fluoride (1.28 g, 8.45 mmol). The reaction was stirred at rt overnight under argon. The reaction was washed with saturated aqueous NaCl (50 mL) and the aqueous phase was extracted with Et_2O (50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to

dryness. The product was purified by flash column chromatography to yield the title compound (450.7 mg, 63.70% yield) as a yellow oil.

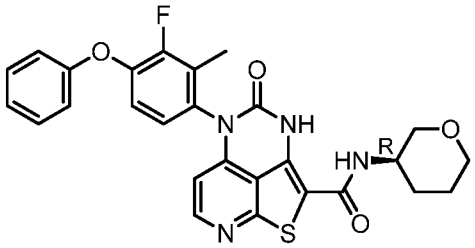
Step B: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(2,6-difluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps B-I in Example 1, using 1,3-difluoro-2-nitro-5-phenoxybenzene in place of 2-methyl-4-phenoxyaniline in step B and tert-butyl (R)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{29}H_{23}F_2N_5O_4S$, 575.6; m/z found, 576.3 $[M+H]^+$. 1H NMR (400 MHz, CDCl3) δ9.51 (s, 1H), 8.43 (d, J = 5.05 Hz, 1H), 7.46 (t, J = 7.83 Hz, 2H), 7.28 – 7.31 (m, 1H), 7.12 – 7.16 (m, 2H), 6.69 (d, J = 9.09 Hz, 2H), 6.62 (dd, J = 16.67, 10.61 Hz, 1H), 6.25 – 6.51 (m, 1H), 6.16 – 6.24 (m, 1H), 5.70 – 5.82 (m, 1H), 5.38 – 5.52 (m, 1H), 3.87 – 4.22 (m, 2H), 3.27 – 3.77 (m, 3H), 1.87 – 2.13 (m, 2H), 1.62 – 1.85 (m, 2H).

Example 70: (*R*)-5-(4-(Benzofuran-7-yloxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



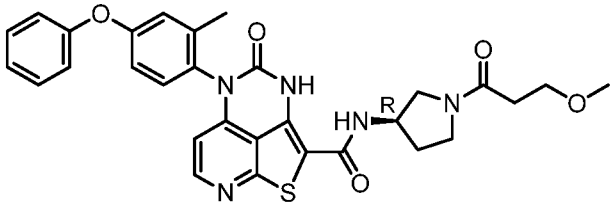
The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1, and using benzofuran-7-ol (Intermediate 8) in place of phenol in step A, and using (3*R*)-1-methylpiperidin-3-amine in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{27}N_5O_4S$, 553.6; m/z found, 554.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.41 (s, 1H), 8.35-8.29 (m, 1H), 7.77-7.72 (m, 1H), 7.51-7.45 (m, 1H), 7.31-7.22 (m, 2H), 7.07-7.02 (m, 2H), 6.98- 6.93 (m, 1H), 6.92-6.88 (m, 1H), 6.10-6.05 (m, 1H), 4.33 - 4.18 (m, 1H), 3.47-3.36 (m, 1H), 3.26-3.14 (m, 1H), 2.91-2.68 (m, 5H), 2.10 (s, 3H), 2.06-1.96 (m, 2H), 1.89-1.74 (m, 1H), 1.73-1.59 (m, 1H).

Example 71: (*R*)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(tetrahydro-2*H*-pyran-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



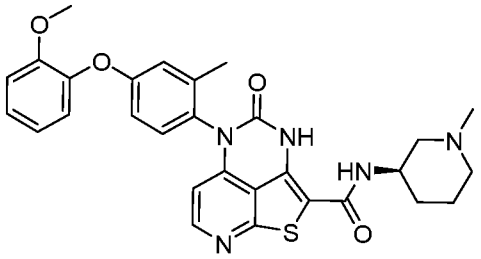
The title compound was prepared using analogous conditions described in Method 1, steps B-I in Example 1, and using 2-fluoro-3-methyl-4-nitro-1-phenoxybenzene (Intermediate 18, step B) in place of 2-methyl-4-phenoxyaniline in step B, and using (3*R*)-tetrahydropyran-3-amine in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{23}FN_4O_4S$, 518.6; m/z found, 519 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6 and CD_3OD): δ 8.27 (d, J = 5.5 Hz, 1H), 7.42-7.28 (m, 2H), 7.23-7.15 (m, 1H), 7.13-6.96 (m, 4H), 6.03 (d, J = 5.5 Hz, 1H), 3.93-3.83 (m, 1H), 3.80-3.69 (m, 2H), 3.28-3.12 (m, 2H), 2.02 (s, 3H), 1.92-1.84 (m, 1H), 1.66-1.50 (m, 3H).

Example 72: (*R*)-*N*-(1-(3-Methoxypropanoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared using the method in Example 104, and using 3-methoxypropanoic acid in place of 3-methylsulfonylpropanoic acid. MS (ESI): mass calcd. for $C_{30}H_{29}N_5O_5S$, 571.6; m/z found, 572.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.32 (d, J = 5.6, 1H), 7.43-7.35 (m, 2H), 7.33-7.25 (m, 1H), 7.21-7.12 (m, 1H), 7.12-7.03 (m, 3H), 7.01-6.92 (m, 1H), 6.07 (d, J = 5.6, 1H), 4.66-4.53 (m, 1H), 3.82-3.70 (m, 1H), 3.68-3.60 (m, 3H), 3.56-3.38 (m, 2H), 3.34-3.30 (m, 3H), 2.62-2.54 (m, 2H), 2.35-2.17 (m, 1H), 2.16-1.99 (m, 4H).

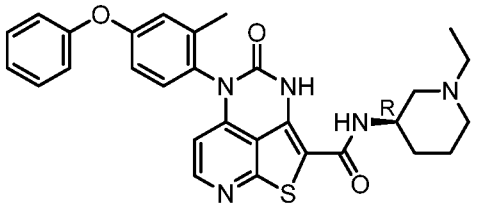
Example 73: (*R*)-5-(4-(2-Methoxyphenoxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: (R)-5-(4-(2-methoxyphenoxy)-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of 5-(4-(2-methoxyphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 67, 200 mg, 0.45 mmol) in DCM (50 mL) was added a drop of DMF and then oxalyl chloride (284 mg, 2.24 mmol). The reaction was stirred at rt for 3 h, concentrated to dryness, and diluted in DCM. Triethylamine (226 mg, 2.24 mmol) and *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate (107 mg, 0.536 mmol) were added, stirred at rt for 1 h, concentrated to dryness, and purified by flash column chromatography to a yellow solid. The solid was diluted in MeOH, concentrated HCl was added and the solution was concentrated to dryness to yield the title compound (150 mg, 59% yield) as a yellow solid.

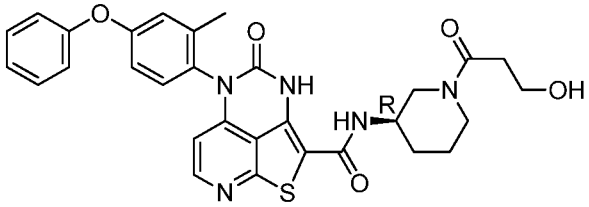
Step B: (*R*)-5-(4-(2-Methoxyphenoxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a mixture of (*R*)-5-(4-(2-methoxyphenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (98 mg, 0.17 mmol) and formaldehyde (0.5 mL, 37 wt. % in H_2O) in MeOH (15 mL) was added $NaBH(OAc)_3$ (110 mg, 0.52 mmol), then stirred at rt for 1 h, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a white solid (52 mg, 56% yield). MS (ESI): mass calcd. for $C_{29}H_{29}N_5O_4S$, 543.6; m/z found, 544.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.29 (d, J = 5.3 Hz, 1H), 8.08 (d, J = 7.5 Hz, 1H), 7.28-7.20 (m, 2H), 7.16-7.08 (m, 1H), 7.05-6.97 (m, 1H), 6.96-6.86 (m, 1H), 6.82-6.68 (m, 1H), 5.88 (d, J = 5.3 Hz, 1H), 3.42-3.90 (m, 1H), 3.78 (s, 3H), 2.97-2.85 (m, 1H), 2.81-2.66 (m, 1H), 2.28 (s, 3H), 2.11-1.95 (m, 5H), 1.82-1.65 (m, 2H), 1.61-1.48 (m, 1H), 1.46-1.30 (m, 1H).

Example 74: (*R*)-*N*-(1-Ethylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.30 mmol) in DCM (10 mL) was added acetaldehyde (99 mg, 2.3 mmol). After stirring at rt for 10 min, $NaBH(OAc)_3$ (190 mg, 0.90 mmol) was added. The mixture was stirred at rt overnight and the pH was adjusted to pH >7 with 2 M aqueous NaOH. The reaction mixture was concentrated to dryness and the residue was purified using flash column chromatography to yield the title compound (44 mg, 27% yield) as a yellow solid. MS (ESI): mass calcd. for $C_{29}H_{29}N_5O_3S$, 527.6; m/z found, 528.2 $[M+H]^+$. ^1H NMR (400 MHz, a mixture of DMSO-d6 and CD3OD): δ 8.23 (d, J = 5.4 Hz, 1H), 7.42-7.31 (m, 2H), 7.30-7.20 (m, 1H), 7.16-7.10 (m, 1H), 7.08-7.98 (m, 3H), 6.95-6.83 (m, 1H), 5.91 (d, J = 5.4 Hz, 1H), 4.03-3.95 (m, 1H), 2.99-2.88 (m, 1H), 2.78-2.71 (m, 1H), 2.46-2.38 (m, 2H), 2.09-1.97 (m, 5H), 1.85-1.75 (m, 1H), 1.75-1.65 (m, 1H), 1.60-1.48 (m, 1H), 1.46-1.38 (m, 1H), 1.01 (t, J = 7.1 Hz, 3H).

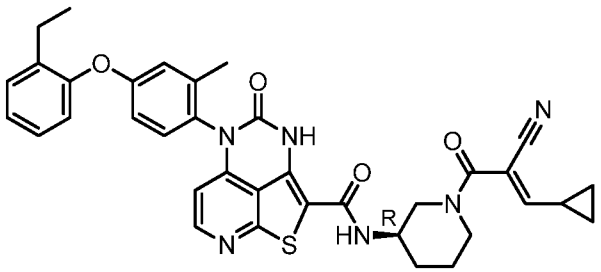
Example 75: (*R*)-*N*-(1-(3-Hydroxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 120 mg, 0.22 mmol), 3-hydroxypropanoic acid (40 mg, 0.45 mmol), HATU (110 mg, 0.29 mmol), diisopropylethylamine (58 mg, 0.45 mmol) in DMF (5 mL) was stirred at rt for 2 h. The reaction was purified by HPLC to yield the title compound (58 mg, 44% yield) as white solid. MS (ESI): mass calcd. for $C_{30}H_{29}N_5O_5S$, 571.6; m/z found, 572.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.34-8.25 (m, 1H), 7.43-7.35 (m, 2H), 7.35-7.28 (m, 1H), 7.19-7.12 (m, 1H), 7.11-7.02 (m, 3H), 7.00-6.93 (m, 1H), 6.09-6.02 (m, 1H), 4.54-4.03 (m, 2H), 3.98-3.78 (m, 3H), 3.18-3.00 (m, 1H),

2.88-2.46 (m, 3H), 2.11 (s, 3H), 2.08-1.98 (m, 1H), 1.90-1.78 (m, 1H), 1.76-1.60 (m, 1H), 1.62-1.45 (m, 1H).

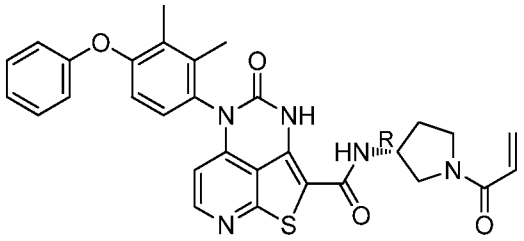
Example 76: (*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-(2-ethylphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: (*R*)-5-(4-(2-Ethylphenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using 2-ethylphenol in place of phenol in step A, and using *tert*-butyl (3*R*)-3-aminopyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

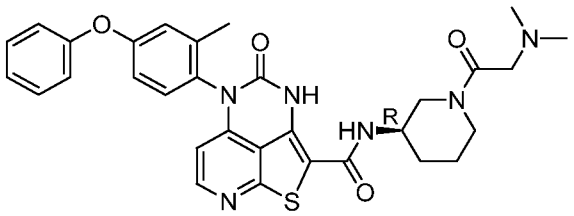
Step B: (*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-(2-ethylphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a mixture of (*R*)-5-(4-(2-ethylphenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (70 mg, 0.13 mmol) and triethylamine (28 mg, 0.28 mmol) in DMF (2 mL) were added (*E*)-2-cyano-3-cyclopropylprop-2-enoic acid (Intermediate 17) (36 mg, 0.26 mmol) and HATU (100 mg, 0.27 mmol) and was reacted at rt for 20 min. The reaction was quenched with H_2O (10 mL), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to obtain the title compound (60 mg, 97% yield) as a white solid. MS (ESI): mass calcd. for $C_{36}H_{34}N_6O_4S$, 646.8; m/z found, 647.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.37-8.29 (m, 1H), 7.35-7.29 (m, 1H), 7.27-7.20 (m, 2H), 7.18-7.12 (m, 1H), 7.00-6.93 (m, 2H), 6.88-6.83 (m, 1H), 6.57-6.47 (m, 1H), 6.07-6.03 (m, 1H), 4.33-4.06 (m, 1H), 4.15-3.93 (m, 2H), 3.28-2.98 (m, 2H), 2.68-2.59 (m, 2H), 2.10 (s, 3H), 2.08-1.94 (m, 2H), 1.92-1.85 (m, 1H), 1.84-1.56 (m, 2H), 1.27-1.56 (m, 5H), 1.07-1.78 (m, 2H).

Example 77: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-5-(2,3-dimethyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



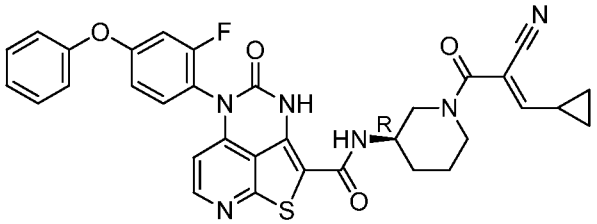
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using 1-fluoro-2,3-dimethyl-4-nitrobenzene in place of 5-fluoro-2-nitrotoluene in step A, and using tert-butyl (R)-3-aminopyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{27}N_5O_4S$, 553.6; m/z found, 554.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD and DMSO-d_6): δ 8.26-8.11 (br, 1H), 7.34-7.28 (m, 2H), 7.09 (d, J = 8.3 Hz, 1H), 7.06-7.00 (m, 1H), 6.95-6.88 (m, 2H), 6.84 (d, J = 8.6 Hz, 1H), 6.60-6.47 (m, 1H), 6.17-6.10 (m, 1H), 5.94-5.79 (m, 1H), 5.66-5.60 (m, 1H), 4.55-4.44 (m, 1H), 3.75-3.67 (m, 1H), 3.64-3.57 (m, 1H), 3.55-3.45 (m, 1H), 3.45-3.36 (m, 1H), 2.16 (s, 3H), 2.15-2.06 (m, 1H), 2.01 (s, 3H), 1.96-1.91 (m, 1H).

Example 78: (*R*)-*N*-(1-(2-(Dimethylamino)acetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 120 mg, 0.22 mmol) in DMF (2 mL) was added 2-(dimethylamino)acetic acid (47 mg, 0.34 mmol), HATU (102 mg, 0.268 mmol), and triethylamine (0.128 mL, 0.896 mmol). The mixture was stirred at rt overnight, then purified by flash column chromatography to yield the title compound (36 mg, 26% yield) as a yellow solid. MS (ESI): mass calcd. for $C_{31}H_{32}N_6O_4S$, 584.7; m/z found, 585.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.26 (d, J = 5.5, 1H), 7.45-7.35 (m, 2H), 7.32-7.23 (m, 1H), 7.20-7.12 (m, 1H), 7.11-7.00 (m, 3H), 7.00-6.90 (m, 1H), 6.00 (d, J = 4.9, 1H), 4.06-3.91 (m, 2H), 3.79-3.59 (m, 1H), 3.50-3.39 (m, 2H), 3.23-3.06 (m, 2H), 2.52-2.31 (m, 6H), 2.10 (s, 3H), 2.06-1.97 (m, 1H), 1.79-1.89 (m, 1H), 1.74-1.49 (m, 2H).

Example 79: (*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-fluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

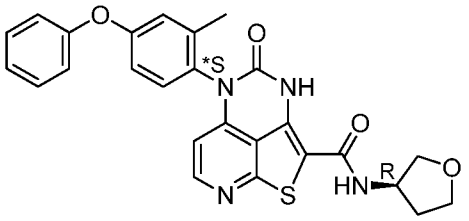


Step A: 2-Fluoro-1-nitro-4-phenoxybenzene. To a mixture of 3-fluoro-4-nitrophenol (2.0 g, 13 mmol), phenylboronic acid (2.33 g, 19.1 mmol), $Cu(OAc)_2$ (4.6 g, 25 mmol), and triethylamine (6.4 g, 64 mmol) in DCM (60 mL) was added molecular sieves (4A powder <50 μm, 2 g). The mixture was stirred at rt under N_2 overnight, filtered, concentrated to dryness, and purified by flash column chromatography to yield the title compound (2.7 g, 91% yield) as a yellow solid.

Step B: (*R*)-5-(2-Fluoro-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps B-H in Example 1, and using 2-fluoro-1-nitro-4-phenoxybenzene in place of 2-methyl-1-nitro-4-phenoxybenzene in step B and *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

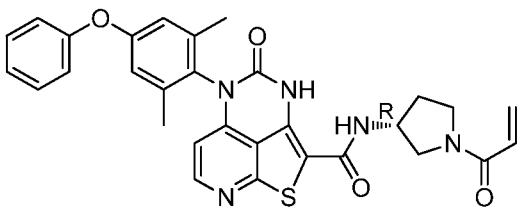
Step C: (*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-fluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A solution of (*R*)-5-(2-fluoro-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (150 mg, 0.30 mmol), (E)-2-cyano-3-cyclopropylprop-2-enoic acid (Intermediate 17) (61 mg, 45 mmol), HATU (2.27 g, 5.96 mmol), and triethylamine (150 mg, 1.5 mmol) in DMF (4 mL) was stirred at rt for 2 h, then purified by flash column chromatography to yield the title compound (124 mg, 67% yield) as a white solid. MS (ESI): mass calcd. for $C_{33}H_{27}FN_6O_4S$, 622.7; m/z found, 623.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.32 (d, J = 5.5 Hz, 1H), 8.21 (s, 1H), 7.62-7.50 (m, 1H), 7.50-7.39 (m, 2H), 7.28-7.19 (m, 1H), 7.19-7.08 (m, 3H), 6.99-6.89 (m, 1H), 6.66-6.47 (m, 1H), 6.15 (d, J = 5.4 Hz, 1H), 4.04-4.00 (m, 1H), 3.99-3.72 (m, 2H), 3.10-2.68 (m, 2H), 2.00-1.71 (m, 3H), 1.70-1.58 (m, 1H), 1.56-1.37 (m, 1H), 1.18-1.05 (m, 2H), 1.02-0.68 (m, 2H).

Example 80: (*R*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(tetrahydrofuran-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



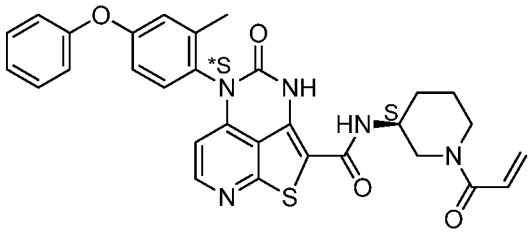
A solution of 5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 16) (30 mg, 0.072 mmol), HATU (55 mg, 0.15 mmol), and triethylamine (22 mg, 0.22 mmol) in anhydrous DMF (3 mL) was stirred at rt. After 10 min, (3*R*)-tetrahydrofuran-3-amine (10 mg, 0.12 mmol) was added and the mixture was stirred for 2 h. The crude mixture was purified by flash column chromatography to yield the title compound (27 mg, 99% yield) as a slight yellow solid. MS (ESI): mass calcd. for $C_{26}H_{22}N_4O_4S$, 486.5; m/z found, 487.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33 (d, *J* = 5.5 Hz, 1H), 7.46 – 7.35 (m, 2H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.21-7.13 (m, 1H), 7.12-7.03 (m, 3H), 7.00-6.94 (m, 1H), 6.07 (d, *J* = 5.5 Hz, 1H), 4.65 – 4.53 (m, 1H), 4.03 – 3.88 (m, 2H), 3.87-3.76 (m, 1H), 3.75-3.66 (m, 1H), 2.36-2.22 (m, 1H), 2.12 (s, 3H), 2.06 – 1.97 (m, 1H).

Example 81: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-5-(2,6-dimethyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



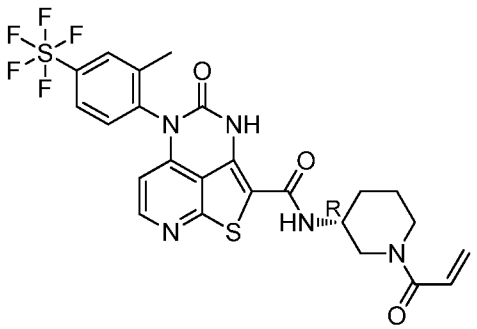
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, using 5-fluoro-1,3-dimethyl-2-nitrobenzene in place of 5-fluoro-2-nitrotoluene in step A and *tert*-butyl (3*R*)-3-aminopyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{27}N_5O_4S$, 553.6; m/z found, 554.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD and DMSO-d_6): δ 8.36-8.27 (m, 1H), 7.41-7.31 (m, 2H), 7.17-7.10 (m, 1H), 7.08-7.01 (m, 2H), 6.84 (s, 2H), 6.61-6.48 (m, 1H), 6.20-6.13 (m, 1H), 5.98-5.92 (m, 1H), 5.69-5.61 (m, 1H), 4.59-4.46 (m, 1H), 3.96-3.84 (m, 1H), 3.75-3.69 (m, 1H), 3.63-3.45 (m, 2H), 2.27-2.02 (m, 2H), 2.01 (s, 6H).

Example 82: (*S*)-N-(1-acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1 (including Chiral resolution Method A after Step F to obtain the *S* atropisomer), and using *tert*-butyl (3*S*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{27}N_5O_4S$, 553.6; m/z found, 554.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.34-8.22 (m, 1H), 7.45-7.36 (m, 2H), 7.33-7.23 (m, 1H), 7.21-7.13 (m, 1H), 7.13-7.03 (m, 3H), 7.01-6.93 (m, 1H), 6.87-6.72 (m, 1H), 6.29-6.14 (m, 1H), 6.08-5.96 (m, 1H), 5.79-5.68 (m, 1H), 4.53-3.95 (m, 3H), 3.28-3.10 (m, 1H), 3.04-2.84 (m, 1H), 2.15-2.02 (m, 4H), 1.96-1.83 (m, 1H), 1.82-1.68 (m, 1H), 1.63-1.49 (m, 1H).

Example 83: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(pentafluorothio)phenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

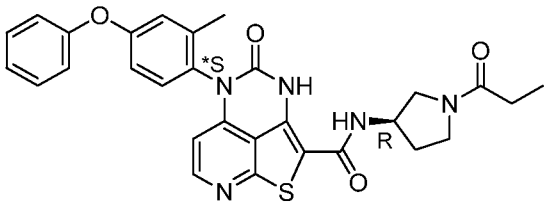


Step A: 2-Methyl-4-(pentafluorosulfanyl)aniline. To a stirred solution of 2-methyl-4-(pentafluorosulfanyl)nitrobenzene (1.5 g, 5.7 mmol) in ethanol (50 mL) was added Fe powder (1.28 g, 22.8 mmol), followed by the slow addition of concentrated HCl (2.5 mL) at 0 °C. The mixture was stirred at rt for 1 h and the reaction was quenched by pouring into ice water and neutralized with sodium carbonate. The reaction was extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield the title compound (1.13 g, 85% yield) as a yellow oil.

Step B: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(pentafluorothio)phenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared

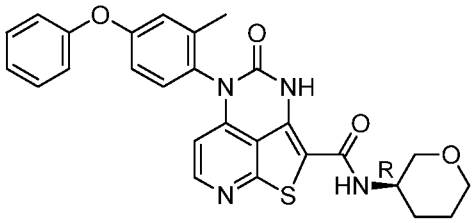
in a manner analogous to Method 1, steps C-G in Example 1, and using 2-methyl-4-(pentafluorosulfanyl)aniline in place of 2-methyl-4-phenoxyaniline in step C, and using 1-[(3*R*)-3-amino-1-piperidyl]prop-2-en-1-one (Intermediate 15) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{24}H_{22}F_5N_5O_3S_2$, 587.6; m/z found, 588.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.36-8.28 (m, 1H), 8.02-7.96 (m, 1H), 7.93-7.85 (m, 1H), 7.66-7.58 (m, 1H), 6.85-6.73 (m, 1H), 6.25-6.15 (m, 1H), 6.06-6.00 (m, 1H), 5.79-5.68 (m, 1H), 4.59-3.89 (m, 3H), 3.25-3.12 (m, 1H), 3.00-2.84 (m, 1H), 2.28 (s, 3H), 2.12-1.99 (m, 1H), 1.92-1.82 (m, 1H), 1.80-1.66 (m, 1H), 1.66-1.53 (m, 1H).

Example 84: (*R*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(1-propionylpyrrolidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



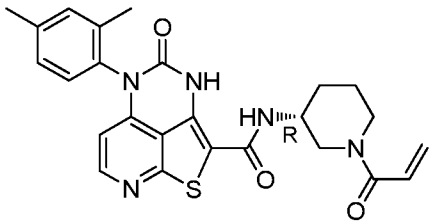
To a solution of (*R*)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(pyrrolidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Intermediate 36, 60 mg, 0.12 mmol), DCM (2 mL), and triethylamine (30 mg, 0.3 mmol) was added propanoyl propanoate (39 mg, 0.3 mmol) in DCM (2 mL) dropwise and stirred at room temperature for 2 h. The reaction mixture was concentrated to dryness and purified by normal phase flash column chromatography (SiO_2), then by preparative TLC to yield the title compound (27 mg, 42%) as a yellow solid. MS (ESI): mass calcd. for $C_{29}H_{27}N_5O_4S$, 541.6; m/z found, 542.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 9.45 (s, 1H), 8.39-8.33 (m, 1H), 7.43-7.34 (m, 2H), 7.21-7.13 (m, 2H), 7.13-7.07 (m, 2H), 7.03-7.00 (m, 1H), 6.98-6.93 (m, 1H), 6.06-6.00 (m, 1H), 5.76-5.63 (m, 1H), 4.73-4.59 (m, 1H), 3.91-3.78 (m, 1H), 3.74-3.35 (m, 3H), 2.41-2.20 (m, 3H), 2.14-2.10 (m, 3H), 2.09-1.86 (m, 1H), 1.22-1.13 (m, 3H).

Example 85: (*R*)-Tetrahydro-2*H*-pyran-3-yl 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate.



To a solution of 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 27, 150 mg, 0.36 mmol) in DCM (60 mL) was added a drop of DMF, then oxalyl chloride (230 mg, 1.8 mmol) was added. The reaction was stirred at rt for 3 h, concentrated to dryness, and diluted in DCM. Next, triethylamine (180 mg, 1.8 mmol) and (3*R*)-tetrahydropyran-3-amine (54 mg, 0.54 mmol) were added and the reaction was stirred at rt for 1 h, then concentrated to dryness, and purified by flash column chromatography to yield the title compound (115 mg, 64.1% yield) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{24}N_4O_4S$, 500.6; m/z found, 501.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.31 (d, J = 5.5 Hz, 1H), 7.98 (d, J = 7.5 Hz, 1H), 7.50-7.38 (m, 2H), 7.37-7.30 (m, 1H), 7.24-7.15 (m, 1H), 7.15-7.03 (m, 3H), 7.00-6.92 (m, 1H), 5.95 (d, J = 5.4 Hz, 1H), 3.94-3.85 (m, 1H), 3.85-3.70 (m, 2H), 3.25-3.12 (m, 2H), 2.04 (s, 3H), 1.96-1.85 (m, 1H), 1.73-1.51 (m, 3H).

Example 86: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(2,4-dimethylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

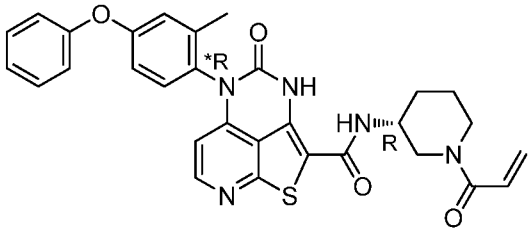


Step A: 5-(2,4-Dimethylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid. The title compound was prepared in a manner analogous to Method 1, steps C-F in Example 1, and using 2,4-dimethylaniline in place of 2-methyl-4-phenoxyaniline in step C.

Step B: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(2,4-dimethylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of 5-(2,4-dimethylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (200 mg, 0.59 mmol) and 1-[(3*R*)-3-amino-1-piperidyl]prop-2-en-1-one (Intermediate 15, 300 mg, 1.9 mmol) in anhydrous DMF were added HATU (570 mg, 1.5 mmol) and diisopropylethylamine (260 mg, 2.0 mmol) and the mixture stirred overnight at rt. The reaction mixture was purified by flash column chromatography, then preparative TLC to yield the title compound as a yellow solid. MS (ESI):

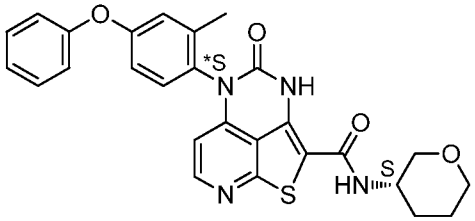
mass calcd. for $C_{25}H_{25}N_5O_3S$, 475.6; m/z found, 476.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.31-10.12 (m, 1H), 8.30 (d, J = 5.5Hz, 1H), 8.14-8.00 (m, 1H), 7.28-7.25 (m, 1H), 7.25-7.17 (m, 2H), 6.85-6.69 (m, 1H), 6.14-6.02 (m, 1H), 5.86 (d, J = 5.5Hz, 1H), 5.71-5.62 (m, 1H), 4.51-4.14 (m, 1H), 4.07-3.91 (m, 1H), 3.83-3.69 (m, 1H), 3.13-2.91 (m, 1H), 2.79-2.60 (m, 1H), 2.35 (s, 3H), 2.04 (s, 3H), 1.97-1.87 (m, 1H), 1.81-1.71 (m, 1H), 1.71-1.56 (m, 1H), 1.50-1.32 (m, 1H).

Example 87: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(**R*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1 (including Chiral resolution Method A after Step F to obtain the **R* atropisomer), and using *tert*-butyl (R)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{27}N_5O_4S$, 553.6; m/z found, 554.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.32 (d, J = 5.6 Hz, 1H), 7.49-7.36 (m, 2H), 7.30 (d, J = 8.6 Hz, 1H), 7.22-7.16 (m, 1H), 7.13-7.02 (m, 3H), 7.00-6.93 (m, 1H), 6.87-6.70 (m, 1H), 6.25-6.13 (m, 1H), 6.07 (d, J = 5.5 Hz, 1H), 5.79-5.67 (m, 1H), 4.57-3.89 (m, 3H), 3.25-3.10 (m, 1H), 2.99-2.80 (m, 1H), 2.12 (s, 3H), 2.08-2.00 (m, 1H), 1.94-1.82 (m, 1H), 1.79-1.66 (m, 1H), 1.65-1.52 (m 1H).

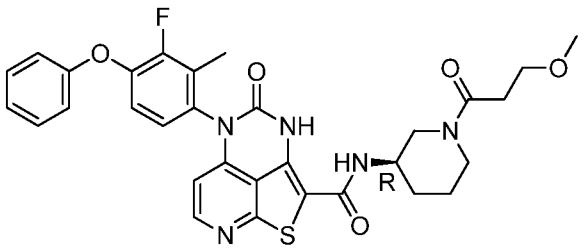
Example 88: (*S*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(tetrahydro-2*H*-pyran-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1 (including Chiral resolution Method A after Step F to obtain the **S* atropisomer), and using (S)-

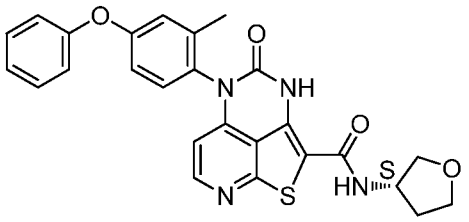
tetrahydro-2H-pyran-3-amine in place of *tert*-butyl (3*R*,5*R*)-3-amino-5-fluoropiperidine-1-carboxylate in step G. MS (ESI): mass calcd. for $C_{27}H_{24}N_4O_4S$, 500.6; m/z found, 501.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD and DMSO-d_6): δ 8.27 (d, J = 5.5 Hz, 1H), 7.43 – 7.32 (m, 2H), 7.27 (d, J = 8.6 Hz, 1H), 7.17-7.09 (m, 1H), 7.08-6.97 (m, 3H), 6.95-6.86 (m, 1H), 5.96 (d, J = 5.5 Hz, 1H), 3.96-3.87 (m, 1H), 3.84-3.78 (m, 1H), 3.77-3.69 (m, 1H), 3.33-3.25 (m, 1H), 3.24-3.15 (m, 1H), 2.04 (s, 3H), 1.98-1.87 (m, 1H), 1.70-1.54 (m, 3H).

Example 89: (*R*)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-*N*-(1-(3-methoxypropanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



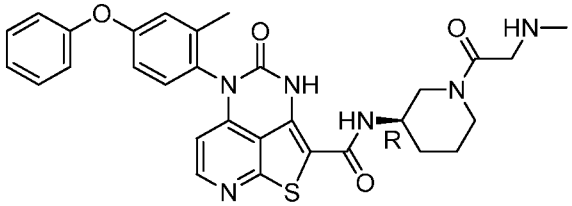
A solution of (*R*)-5-(3-fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Intermediate 18) (80 mg, 0.16 mmol), 3-methoxypropanoic acid (32 mg, 0.31 mmol), triethylamine (31 mg, 0.31 mmol), and HATU (118 mg, 0.310 mmol) in DMF (2 mL) was stirred at rt for 1 hr. Water was added and the precipitate was filtered to give a crude product, which was purified by flash column chromatography to yield the title compound (73 mg, 77% yield) as a white solid. MS (ESI): mass calcd. for $C_{31}H_{30}FN_5O_5S$, 603.7; m/z found, 604.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.39-8.26 (m, 1H), 7.45-7.31 (m, 2H), 7.24-7.18 (m, 1H), 7.17-7.10 (m, 1H), 7.09-7.02(m, 3H), 6.16-6.07 (m, 1H), 4.53-4.29 (m, 1H), 4.13-3.85 (m, 2H), 3.70-3.60 (m, 2H), 3.32 (s, 3H), 3.17-2.98 (m, 1H), 2.86-2.63 (m, 3H), 2.12 (s, 3H), 2.07-1.97 (m, 1H), 1.88-1.75 (m, 1H), 1.1.73-1.46 (m, 2H).

Example 90: (*S*)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(tetrahydrofuran-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a solution of 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 27, 100 mg, 0.24 mmol) in DCM (25 mL) was added a drop of DMF, then oxalyl chloride (150 mg, 1.2 mmol) was added. The reaction was stirred at rt for 3 h, concentrated to dryness, and diluted in DCM again. Next, triethylamine (120 mg, 1.2 mmol) and (3*S*)-tetrahydrofuran-3-amine (31 mg, 0.36 mmol) were added and stirred at rt for 1 h. The reaction mixture was concentrated dryness and purified by flash column chromatography to yield the title compound (60 mg, 51% yield) as a yellow solid. MS (ESI): mass calcd. for $C_{26}H_{22}N_4O_4S$, 486.5; m/z found, 487.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.25 (s, 1H), 8.37-8.27 (m, 2H), 7.49-7.39 (m, 2H), 7.37 (d, J = 8.6 Hz, 1H), 7.24-7.15 (m, 1H), 7.13-7.04 (m, 3H), 7.02-6.93 (m, 1H), 5.96 (d, J = 5.5 Hz, 1H), 4.52-4.37 (m, 1H), 3.90-3.78 (m, 2H), 3.74-3.65 (m, 1H), 3.63-3.57 (m, 1H), 2.20-2.08 (m, 1H), 2.05 (s, 3H), 1.98-1.87 (m, 1H).

Example 91: (*R*)-5-(2-Methyl-4-phenoxyphenyl)-*N*-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

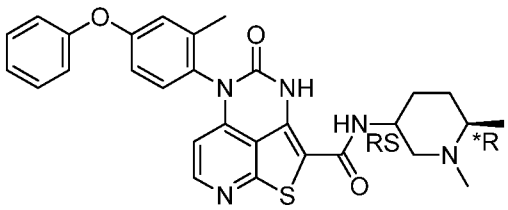


Step A: (*R*)-*tert*-Butyl methyl(2-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-2-oxoethyl)carbamate. To a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 200 mg, 0.40 mmol) in DMF (3 mL) were added 2-[*tert*-butoxycarbonyl(methyl)amino]acetic acid (Intermediate 21, 114 mg, 0.603 mmol), HATU (230 mg, 0.60 mmol), and triethylamine (0.23 mL, 1.6 mmol). The mixture was stirred at rt overnight, then purified by flash column chromatography to yield the title compound (198 mg, 73.0% yield) as a yellow solid.

Step B: (*R*)-5-(2-Methyl-4-phenoxyphenyl)-*N*-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a round bottom flask were added (*R*)-*tert*-butyl methyl(2-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-2-oxoethyl)carbamate (198 mg, 0.300 mmol) and HCl in MeOH (3 M, 3 mL) and was stirred at rt for 4 h, then the pH was adjusted to pH >7 with 2 M aqueous NaOH. The mixture was purified by flash column chromatography to

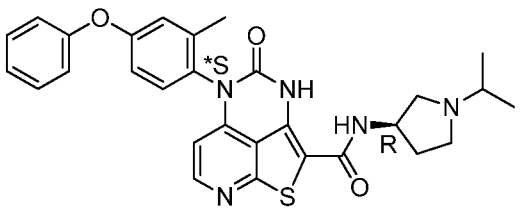
yield the title compound as a yellow solid (95 mg, 56% yield). MS (ESI): mass calcd. for $C_{30}H_{30}N_6O_4S$, 570.7; m/z found, 571.2 $[M+H]^+$. ^1H NMR (400 MHz, a mixture solution of DMSO-d_6 and CD_3OD): δ 8.02-7.98 (m, 1H), 7.39-7.32 (m, 2H), 7.14-7.08 (m, 2H), 7.07-7.01 (m, 2H), 6.99-6.96 (m, 1H), 6.92-6.84 (m, 1H), 5.69-5.62 (m, 1H), 4.10-3.92 (m, 1H), 3.92-3.83 (m, 1H), 3.72-3.52 (m, 2H), 3.52-3.36 (m, 2H), 3.32-3.21 (m, 1H), 2.31-2.23 (m, 3H), 2.01 (s, 3H), 1.95-1.86 (m, 1H), 1.81-1.59 (m, 2H), 1.54-1.41 (m, 1H).

Example 92: *N*-(1,6-Dimethylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



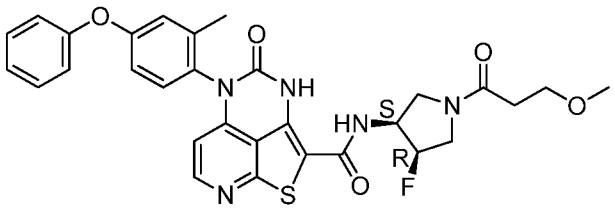
A mixture of 5-(2-Methyl-4-phenoxyphenyl)-*N*-((6*R*)-6-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 173, 150 mg, 0.29 mmol), $NaBH(OAc)_3$ (123 mg, 0.580 mmol), and formaldehyde (1 mL, 37 wt. % in H_2O) in DCM (5 mL) was reacted at 80 °C for 2 h. The reaction mixture was concentrated to dryness, saturated aqueous $NaHCO_3$ was added, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound as a yellow solid. MS (ESI): mass calcd. for $C_{29}H_{29}N_5O_3S$, 527.6; m/z found, 528.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.42 (s, 1H), 8.37-8.30 (m, 1H), 7.45-7.37 (m, 2H), 7.33-7.26 (m, 1H), 7.21-7.14 (m, 1H), 7.11-7.02 (m, 3H), 7.00-6.92 (m, 1H), 6.12-6.05 (m, 1H), 4.36-4.23 (m, 1H), 3.63-3.56 (m, 1H), 3.06-2.95 (m, 1H), 2.89-2.79 (m, 4H), 2.11 (s, 3H), 2.12-1.99 (m, 2H), 1.81-1.63 (m, 2H), 1.41-1.32 (m, 3H).

Example 93: (*R*)-*N*-(1-Isopropylpyrrolidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(pyrrolidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Intermediate 36, 60 mg, 0.12 mmol) dissolved in acetone was stirred for 10 min, then $NaBH(OAc)_3$ (100 mg, 0.5 mmol) was added slowly and the mixture was stirred for 2 h. Next, NaOH (2 mL) was added and the mixture was purified by flash column chromatography, then preparative TLC to yield the title compound as a yellow solid (11 mg, 17%). MS (ESI): mass calcd. for $C_{29}H_{29}N_5O_3S$, 527.6; m/z found, 528.2 $[M+H]^+$. -H NMR (400 MHz, DMSO-d6): δ 8.42 (s, 1H), 8.25 (d, J = 5.4 Hz, 1H), 7.47-7.39 (m, 2H), 7.33-7.27 (m, 1H), 7.21-7.15 (m, 1H), 7.12-7.08 (m, 2H), 7.07-7.04 (m, 1H), 6.98-6.92 (m, 1H), 5.87 (d, J = 5.4 Hz, 1H), 4.45-4.31 (m, 1H), 2.95-2.75 (m, 2H), 2.64-2.55 (m, 2H), 2.20-2.09 (m, 1H), 2.03 (s, 3H), 2.01-1.92 (m, 1H), 1.84-1.73 (m, 1H), 1.09-1.00 (m, 6H).

Example 94: *N*-((3*S*,4*R*)-4-Fluoro-1-(3-methoxypropanoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

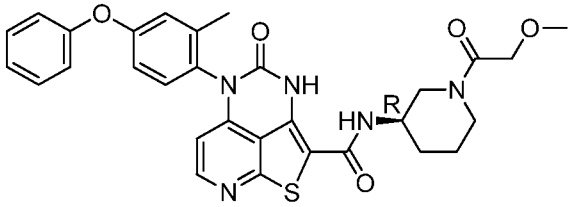


Step A: *N*-((3*S*,4*R*)-4-Fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using *tert*-butyl (3*S*,4*R*)-3-amino-4-fluoropyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

Step B: *N*-((3*S*,4*R*)-4-Fluoro-1-(3-methoxypropanoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A mixture of *N*-((3*S*,4*R*)-4-fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (80 mg, 0.16 mmol), 3-methoxypropanoic acid (33 mg, 0.32 mmol), triethylamine (32 mg, 0.32 mmol), and HATU (120 mg, 0.32 mmol) in DMF (3 mL) was stirred at rt for 1 h, then water was added and the precipitate was collected by filtration and purified by flash column chromatography to yield the title compound as a white solid (75 mg, 78% yield). MS (ESI): mass calcd. for $C_{30}H_{28}FN_5O_5S$, 589.6; m/z found, 590.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33 (d, *J* = 5.3Hz, 1H), 7.43-7.34 (m, 2H), 7.34-7.26 (m, 1H), 7.20-7.12 m, 1H), 7.12-7.02 (m, 3H), 6.99-6.94 (m, 1H), 6.07

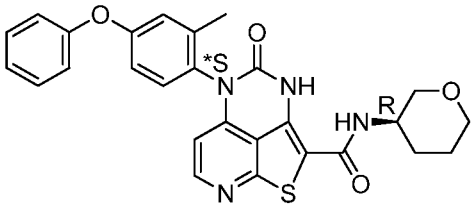
(d, *J* = 5.2Hz, 1H), 5.36-5.14 (m, 1H), 4.80-4.63 (m, 1H), 4.07-3.45 (m, 6H), 3.33 (s, 3H), 2.68-2.51 (m, 2H), 2.11 (s, 3H).

Example 95: (*R*)-*N*-(1-(2-Methoxyacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 120 mg, 0.22 mmol) in DMF (2 mL) were added 2-methoxyacetic acid (0.026 mL, 0.34 mmol), HATU (100 mg, 0.27 mmol), and DMF (2 mL). The mixture was stirred at rt overnight, then purified by flash column chromatography to yield the title compound as a yellow solid (83 mg, 63%). MS (ESI): mass calcd. for $C_{30}H_{29}N_5O_5S$, 571.6; m/z found, 572.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.32 (d, *J* = 5.5, 1H), 7.45-7.35 (m, 2H), 7.33-7.27 (m, 1H), 7.20-7.12 (m, 1H), 7.12-7.02 (m, 3H), 7.02-6.93 (m, 1H), 6.07 (d, *J* = 5.3, 1H), 4.29-4.09 (m, 3H), 4.02-3.85 (m, 2H), 3.39 (s, 3H), 3.11-3.01 (m, 1H), 2.86-2.74 (m, 1H), 2.11 (s, 3H), 2.09-2.00 (m, 1H), 1.88-1.78 (m, 1H), 1.76-1.52 (m, 2H).

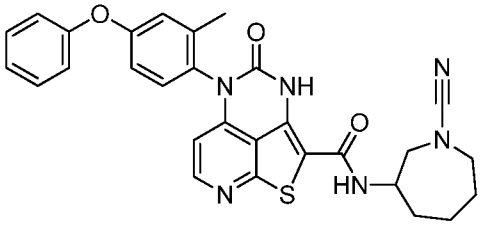
Example 96: (*R*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(tetrahydro-2 *H*-pyran-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of 5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 16) (30 mg, 0.07 mmol), HBTU (55 mg, 0.15 mmol), and triethylamine (22 mg, 0.22 mmol) in anhydrous DMF (3 mL) was stirred at rt. After 10 min, (3*R*)-tetrahydropyran-3-amine (11 mg, 0.11 mmol) was added and the mixture was stirred for 2 h at rt. The crude mixture was purified by flash column chromatography to yield the title compound as a slight yellow solid (25 mg, 69% yield). MS (ESI): mass calcd. for

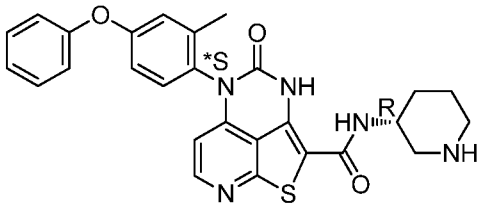
$C_{27}H_{24}N_4O_4S$, 500.6; m/z found, 501.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD and DMSO-d_6): δ 8.28 (d, J = 5.5 Hz, 1H), 7.41-7.33 (m, 2H), 7.28 (d, J = 8.7 Hz, 1H), 7.18-7.10 (m, 1H), 7.09-6.97 (m, 3H), 6.96-6.86 (m, 1H), 5.96 (d, J = 5.5 Hz, 1H), 3.98-3.91 (m, 1H), 3.85 – 3.69 (m, 2H), 3.35-3.24 (m, 1H), 3.25-3.17 (m, 1H), 2.04 (s, 3H), 1.96-1.87 (m, 1H), 1.74 – 1.53 (m, 3H).

Example 97: *N*-(1-Cyanoazepan-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using *tert*-butyl 3-aminoazepane-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G, and using bromocyanide in place of prop-2-enoyl chloride in step I. MS (ESI): mass calcd. for $C_{29}H_{26}N_6O_3S$, 538.6; m/z found, 539.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6 and CD_3OD): δ 8.28 (d, J = 5.5 Hz, 1H), 7.41-7.32 (m, 2H), 7.28 (d, J = 8.6 Hz, 1H), 7.16-7.08 (m, 1H), 7.09-6.99 (m, 3H), 6.94-6.90 (m, 1H), 5.99 (d, J = 5.5 Hz, 1H), 4.18-4.09 (m, 1H), 3.48-3.37 (m, 1H), 3.36-3.27 (m, 1H), 3.25-3.17 (m, 2H), 2.05 (s, 3H), 1.95-1.80 (m, 3H), 1.72-1.60 (m, 2H), 1.55-1.42 (m, 1H).

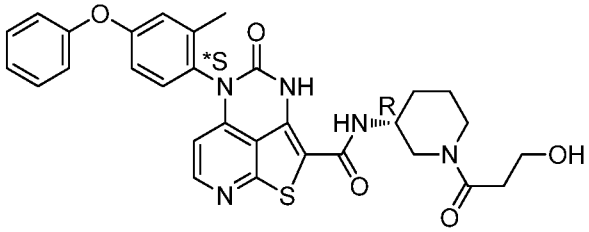
Example 98: (*R*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1 (including Chiral resolution Method A after Step F to obtain the **S* atropisomer), and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{25}N_5O_3S$, 499.6; m/z found, 500.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.20 (d, J = 5.6 Hz, 1H), 7.48-7.34 (m, 2H), 7.27-7.21 (m, 1H), 7.19-7.13 (m, 1H), 7.11-7.03 (m, 3H), 7.00-

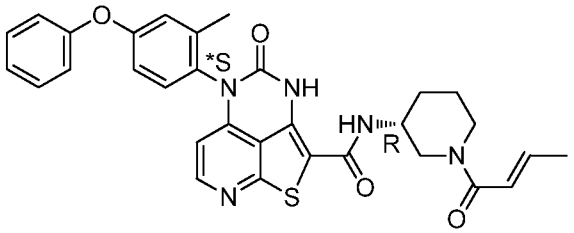
6.94 (m, 1H), 5.94 (d, J = 5.6 Hz, 1H), 4.19-4.06 (m, 1H), 3.29-3.21 (m, 1H), 3.15-3.00 (m, 1H), 2.89-2.70 (m, 2H), 2.11 (s, 3H),2.08-1.86 (m, 2H), 1.79-1.64 (m, 2H).

Example 99: (*R*)-*N*-(1-(3-Hydroxypropanoyl)piperidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution containing (*R*)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 98, 39 mg, 0.073 mmol), 3-hydroxypropanoic acid (13 mg, 0.14 mmol), HATU (36 mg, 0.095 mmol), and diisopropylethylamine (24 mg, 0.18 mmol) in DMF (5 mL) was stirred at rt for 2 h. The mixture was purified by flash column chromatography to yield the title compound as a white solid (15 mg, 36% yield). MS (ESI): mass calcd. for $C_{30}H_{29}N_5O_5S$, 571.6; m/z found, 572.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.36-8.30 (m, 1H), 7.44-7.37 (m, 2H), 7.33-7.27 (m, 1H), 7.21-7.14 (m, 1H), 7.12-7.03 (m, 3H), 7.01-6.95 (m, 1H), 6.11-6.05 (m, 1H), 4.51-3.90 (m, 3H), 3.88-3.79 (m, 2H), 3.20-3.05 (m, 1H), 2.90-2.75 (m, 1H), 2.73-2.58 (m, 2H), 2.12 (s, 3H), 2.09-2.01 (m, 1H), 1.91-1.77 (m, 1H), 1.77-1.64 (m, 1H), 1.64-1.45 (m, 1H).

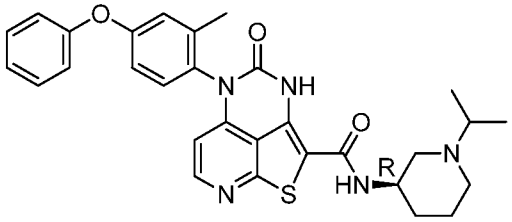
Example 100: (*R*,*E*)-*N*-(1-(But-2-enoyl)piperidin-3-yl)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 98, 45 mg, 0.090 mmol), (*E*)-but-2-enoic acid (15.5 mg, 0.18 mmol), HATU (68 mg, 0.18 mmol), triethylamine (18 mg, 0.18 mmol) in DMF (1 mL) was stirred at rt for 4 h. The mixture was purified by flash column chromatography to yield the title compound as a yellow solid (51 mg, 100% yield). MS (ESI):

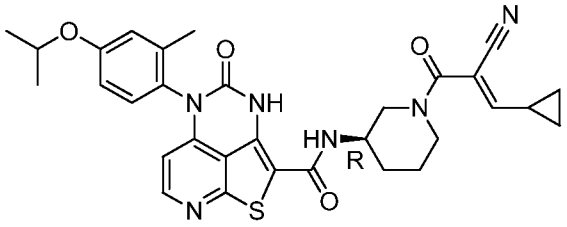
mass calcd. for $C_{31}H_{29}N_5O_4S$, 567.7; m/z found, 568.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.21 (br, 1H), 8.35-8.26 (m, 1H), 8.22-8.02 (br, 1H), 7.45-7.40 (m, 2H), 7.36-7.31 (m, 1H), 7.20-7.16 (m, 1H), 7.12-7.08 (m, 2H), 7.08-7.05 (m, 1H), 6.98-6.93 (m, 1H), 6.69-6.59 (m, 1H), 6.55-6.35 (m, 1H), 5.97-5.89 (m, 1H), 4.49-4.04 (m, 1H), 4.04-3.90 (m, 1H), 3.77-3.72 (m, 1H), 2.92-2.85 (m, 1H), 2.76-2.60 (m, 1H), 2.03 (s, 3H), 1.94-1.88 (m, 1H), 1.83-1.77 (m, 3H), 1.76-1.70 (m, 1H), 1.66-1.57 (m, 1H), 1.47-1.37 (s, 1H).

Example 101: (*R*)-*N*-(1-Isopropylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A mixture of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.30 mmol) in acetone (10 mL) was stirred at rt for 10 min, then $NaBH(OAc)_3$ (190 mg, 0.90 mmol) was added. The mixture was stirred at rt overnight and adjusted to pH >7 with 2 M aqueous NaOH. The reaction mixture was concentrated to dryness and the residue purified by flash column chromatography to yield the title compound as a yellow solid (52 mg, 32% yield). MS (ESI): mass calcd. for $C_{30}H_{31}N_5O_3S$, 541.7; m/z found, 542.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6 and CD_3OD): δ 8.23 (d, J = 4.7, 1H), 7.43-7.31 (m, 2H), 7.31-7.21 (m, 1H), 7.19-7.11 (m, 1H), 7.11-6.97 (m, 3H), 6.96-6.85 (m, 1H), 5.91 (d, J = 4.7, 1H), 4.04-3.95 (m, 1H), 2.98-2.71 (m, 3H), 2.32-2.19 (m, 2H), 2.03 (s, 3H), 1.86-1.77 (m, 1H), 1.77-1.67 (m, 1H), 1.60-1.47 (m, 1H), 1.47-1.37 (m, 1H), 1.01 (d, J = 5.7, 6H).

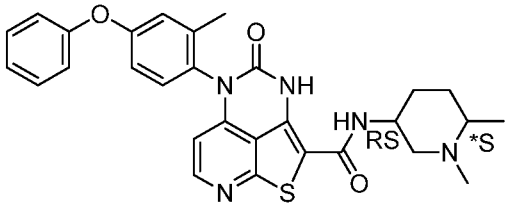
Example 102: (*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: 4-Isopropoxy-2-methyl-1-nitrobenzene. To a mixture of 3-methyl-4-nitrophenol (5.0 g, 33 mmol) and K_2CO_3 (9.0 g, 65 mmol) in DMF (20 mL) was added 2-iodopropane (8.3 g, 49 mmol) and the reaction was stirred at 80 °C overnight. Water was added to the mixture to yield a precipitate, then filtered, washed with water, and dried to yield the title compound as a yellow solid (5.0 g, 78% yield).

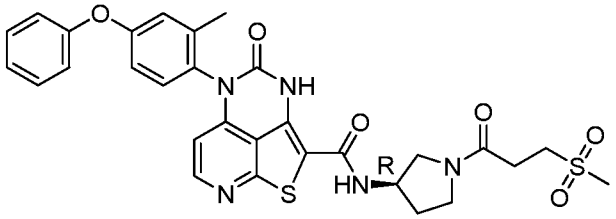
Step B: (*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a stirred solution of (*R*)-5-(4-Isopropoxy-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Intermediate 70, 80 mg, 0.17 mmol) in DMF (3 mL) were added (*E*)-2-cyano-3-cyclopropylprop-2-enoic acid (Intermediate 17) (28 mg, 0.20 mmol), HATU (78 mg, 0.20 mmol), and diisopropylethylamine (0.05 mL) and was stirred at rt overnight. The reaction was concentrated to dryness and the residue was partitioned between ethyl acetate and water. The organic layer was separated, shaken with brine, and dried over anhydrous Na_2SO_4. The residue was purified by flash column chromatography to yield the title compound as yellow solid (37 mg, 37% yield). MS (ESI): mass calcd. for $C_{31}H_{32}N_6O_4S$, 584.7; m/z found, 585.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.45-8.28 (m, 1H), 8.22-8.05 (m, 1H), 7.34-7.18 (m, 1H), 7.11-6.87 (m, 2H), 6.71-6.54 (m, 1H), 6.01-5.85 (m, 1H), 4.82-4.57 (m, 1H), 3.98-3.77 (m, 2H), 3.07-2.87 (m, 1H), 2.05 (s, 3H), 1.98-1.44 (m, 6H), 1.41-1.21 (m, 6H), 1.26-1.11 (m, 3H), 1.09-0.75 (m, 2H).

Example 103: *N*-(1,6-Dimethylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



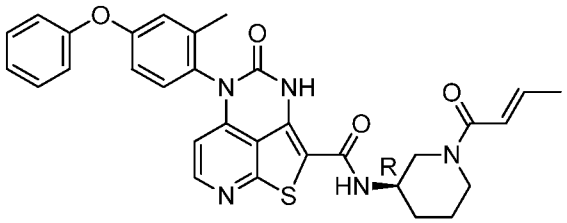
The title compound was made as described in Example 92, and in Step B the other isomer was isolated by flash column chromatography to yield the title compound as a yellow solid. MS (ESI): mass calcd. for $C_{29}H_{29}N_5O_3S$, 527.6; m/z found, 528.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.45 (s, 1H), 8.37-8.30 (m, 1H), 7.45-7.37 (m, 2H), 7.33-7.26 (m, 1H), 7.21-7.14 (m, 1H), 7.11-7.02 (m, 3H), 7.00-6.92 (m, 1H), 6.12-6.05 (m, 1H), 4.39-4.28 (m, 1H), 3.48-3.35 (m, 1H), 3.29-3.17 (m, 2H), 2.85-2.75 (m, 3H), 2.11 (s, 3H), 2.01-1.86 (m, 4H), 1.43-1.35 (m, 3H).

Example 104: (*R*)-5-(2-Methyl-4-phenoxyphenyl)-*N*-(1-(3-(methylsulfonyl)propanoyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(pyrrolidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 159, 100 mg, 0.21 mmol), 3-methylsulfonylpropanoic acid (35 mg, 0.23 mmol), HATU (160 mg, 0.42 mmol), and triethylamine (42 mg, 0.42 mmol) in DMF (2 mL) was stirred at rt for 2 h, then purified by flash column chromatography to yield the title compound as a white solid (41 mg, 32% yield). MS (ESI): mass calcd. for $C_{30}H_{29}N_5O_6S_2$, 619.7; m/z found, 620.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 8.43- 8.23 (m, 2H), 7.48-7.40 (m, 2H), 7.37 (d, J = 8.6 Hz, 1H), 7.23-7.15 (m, 1H), 7.14-7.06 (m, 3H), 7.02-6.90 (m, 1H), 5.97 (dd, J = 5.4, 2.4 Hz, 1H), 4.61-4.35 (m, 1H), 3.87-3.32 (m, 6H), 3.00 (s, 3H), 2.78-2.65 (m, 2H), 2.24-2.08 (m, 1H), 2.05 (s, 3H), 2.03-1.87 (m, 1H).

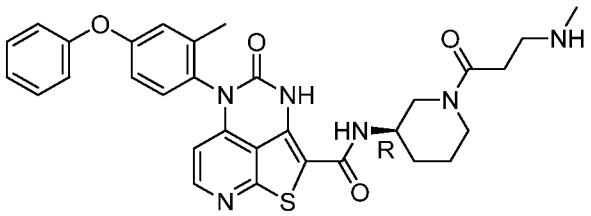
Example 105: (*R*,*E*)-*N*-(1-(But-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a mixture of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.30 mmol) and (*E*)-but-2-enoic acid (52 mg, 0.60 mmol) in DMF (2 mL) were added HATU (230 mg, 0.60 mmol), and triethylamine (60 mg, 0.60 mmol) and was stirred at rt for 4 h. The mixture was purified by flash column chromatography to yield the title compound as yellow solid (124 mg, 73.0% yield). MS (ESI): mass calcd. for $C_{31}H_{29}N_5O_4S$, 567.7; m/z found, 568.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 8.31 (d, J = 5.4 Hz, 1H), 8.06 (br, 1H), 7.45-7.38 (m, 2H), 7.38-7.33

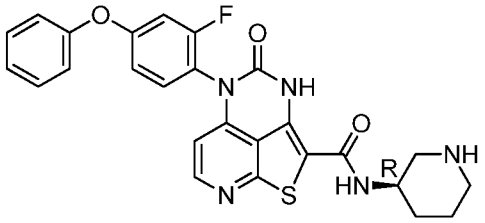
(m, 1H), 7.20-7.14 (m, 1H), 7.13-7.03 (m, 3H), 6.98-6.92 (m, 1H), 6.71-6.58 (m, 1H), 6.52-6.39 (m, 1H), 5.95 (d, J = 5.4 Hz, 1H), 4.47-4.12 (m, 1H), 4.06-3.90 (m, 1H), 3.78-3.68 (m, 1H), 3.11-2.87 (m, 1H), 2.73-2.55 (m, 1H), 2.03 (s, 3H), 1.93-1.87 (m, 1H), 1.83-1.76 (m, 3H), 1.76-1.69 (m, 1H), 1.67-1.55 (m, 1H), 1.43-1.31 (m, 1H).

Example 106: (*R*)-5-(2-Methyl-4-phenoxyphenyl)-*N*-(1-(3-(methylamino)propanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a stirred suspension of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 200 mg, 0.40 mmol) in DMF (3 mL) were added 3-[*tert*-butoxycarbonyl(methyl)amino]propanoic acid (165 mg, 0.812 mmol), HATU (230 mg, 0.61 mmol), and diisopropylethylamine (105 mg, 0.812 mmol). The resulting mixture was stirred at rt overnight. The solvent was removed and the residue was partitioned between ethyl acetate and water. The organic layer was separated, shaken with brine, and dried over anhydrous Na_2SO_4. The residue was purified by flash column chromatography to yield the intermediate compound as a yellow solid. The intermediate compound was treated with concentrated HCl (2 mL) in MeOH (15 mL) at rt for about 2 h. After concentrating to dryness, the crude material was purified by flash column chromatography to yield the title compound as a yellow solid (150 mg, 59% yield). MS (ESI): mass calcd. for $C_{31}H_{32}N_6O_4S$, 584.7; m/z found, 585.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.43 (s, 1H), 8.37-8.30 (m, 1H), 7.45-7.36 (m, 2H), 7.33-7.26 (m, 1H), 7.22-7.14 (m, 1H), 7.13-7.04 (m, 3H), 7.01-6.93 (m, 1H), 6.11-6.04 (m, 1H), 4.58-4.32 (m, 1H), 4.12 -3.72 (m, 2H), 3.27-2.78 (m, 6H), 2.74-2.67 (m, 3H), 2.12 (s, 3H), 2.08-1.99 (m, 1H), 1.93-1.49 (m, 3H).

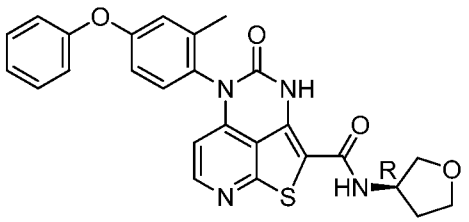
Example 107: (*R*)-5-(2-Fluoro-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: 2-Fluoro-1-nitro-4-phenoxybenzene. To a mixture of 3-fluoro-4-nitrophenol (2.0 g, 13 mmol), phenylboronic acid (2.3 g, 19 mmol), $Cu(OAc)_2$ (4.6 g, 25 mmol), and triethylamine (6.4 g, 64 mmol) in DCM (60 mL) was added molecular sieves (4A powder <50 μm, 2 g). The mixture was stirred at rt under N_2 overnight, filtered, concentrated to dryness, and purified by normal phase flash column chromatography (SiO2) to yield the title compound as a yellow solid (2.7 g, 91% yield).

Step B: (*R*)-5-(2-Fluoro-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps B-H in Example 1, and using 2-Fluoro-1-nitro-4-phenoxybenzene in place 2-methyl-1-nitro-4-phenoxybenzene in Step B and and *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{26}H_{22}FN_5O_3S$, 503.5; m/z found, 623.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 9.07 (s, 1H), 8.42-8.34 (m, 1H), 8.30 (d, J = 7.0 Hz, 1H), 7.65-7.54 (m, 1H), 7.53-7.41 (m, 2H), 7.32-7.22 (m, 1H), 7.21-7.12 (m, 3H), 7.02-6.94 (m, 1H), 6.21 (d, J = 5.4 Hz, 1H), 4.26-4.05 (m, 1H), 3.25-3.08 (m, 2H), 2.93-2.72 (m, 2H), 1.97-1.80 (m, 2H), 1.79-1.52 (m, 2H).

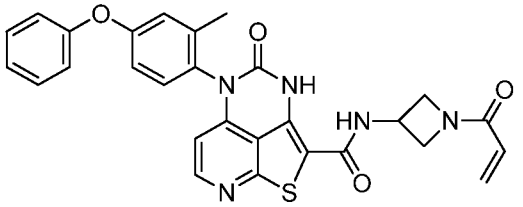
Example 108: (*R*)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(tetrahydrofuran-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a solution of 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Intermediate 27, 150 mg, 0.36 mmol) in DCM (60 mL) was added a drop of DMF, then oxalyl chloride (230 mg, 1.8 mmol) was added. The reaction was stirred at rt for 3 h, concentrated to dryness, and diluted in DCM. To this solution was added triethylamine (180 mg, 1.8 mmol) and (3*R*)-tetrahydrofuran-3-amine (55 mg, 0.63 mmol)

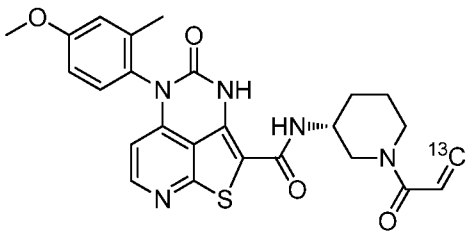
and was stirred at rt for 1 h, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a yellow solid (61 mg, 34% yield). MS (ESI): mass calcd. for $C_{26}H_{22}N_4O_4S$, 486.5; m/z found, 487.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.27 (s, 1H), 8.39-8.25 (m, 2H), 7.55-7.32 (m, 3H), 7.27-7.17 (m, 1H), 7.17-7.05 (m, 3H), 7.04-6.91 (m, 1H), 5.98 (d, J = 5.4 Hz, 1H), 4.55-4.37 (m, 1H), 3.96-3.81 (m, 2H), 3.75-3.66 (m, 1H), 3.65-3.55 (m, 1H), 2.22-2.12 (m, 1H), 2.07 (s, 3H), 1.99-1.87 (m, 1H).

Example 109: *N*-(1-Acryloylazetidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using *tert*-butyl 3-aminoazetidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{28}H_{23}N_5O_4S$, 525.6; m/z found, 526.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6 and CD_3OD): δ 8.29 (d, J = 5.5 Hz, 1H), 7.43-7.33 (m, 2H), 7.31-7.23 (m, 1H), 7.17-7.09 (m, 1H), 7.08-6.98 (m, 3H), 6.97-6.89 (m, 1H), 6.37-6.23 (m, 1H), 6.20-6.08 (m, 1H), 5.98 (d, J = 5.5 Hz, 1H), 5.71-5.60 (m, 1H), 4.81-4.69 (m, 1H), 4.58-4.47 (m, 1H), 4.24-4.17 (m, 2H), 4.04-3.97 (m, 1H), 2.04 (s, 3H).

Example 110: (*R*)-*N*-(1-^{13}C-Acryloylpiperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



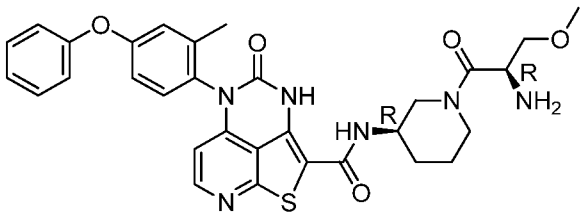
Step A: ^{13}C-Acrylic acid. To a round bottom flask were added malonic acid (1.7 g, 16 mmol), ^{13}C-formaldehyde (0.50 g, 16 mmol, 37 wt. % in H_2O), and dry pyridine (7 mL) and stirred at reflux for 2 h. Concentrated H_2SO_4 was added dropwise to neutralize the cooled reaction

mixture. The mixture was diluted with H_2O, extracted with Et_2O, dried over anhydrous Na_2SO_4, and concentrated to dryness to yield the title compound as a yellow liquid.

Step B: (*R*)-5-(4-Methoxy-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps C-H in Example 1, and using 4-methoxy-2-methylaniline in place of 2-methyl-4-phenoxyaniline in step C, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

Step C: (*R*)-*N*-(1-^{13}C-Acryloylpiperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A mixture of (*R*)-5-(4-methoxy-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (500 mg, 1.1 mmol), ^{13}C-acrylic acid (154 mg, 2.11 mmol), EDCI (300 mg, 1.6 mmol), HOBt (210 mg, (1.6 mmol), and triethylamine (270 mg, 2.6 mmol) in DMF (8 mL) was stirred at rt for 2 h. The reaction mixture was first purified by HPLC, then by flash column chromatography, and finally by TLC to yield the title compound as a pink solid (8 mg, 1.5%). MS (ESI): mass calcd. for $C_{25}H_{25}N_5O_4S$, 492.6; m/z found, 493.2 $[M+H]^+$. ^{1}H NMR (400 MHz, CD_3OD): δ 8.33-8.27 (m, 1H), 7.27-7.20 (m, 1H), 7.04-6.98 (m, 1H), 6.98-6.91 (m, 1H), 6.86-6.73 (m, 1H), 6.45-5.47 (m, 3H), 4.54-3.91 (m, 3H), 3.85 (s, 3H), 3.24-3.09 (m, 1H), 2.97-2.80 (m, 1H), 2.13 (s, 3H), 2.12-2.00 (m, 1H), 1.92-1.82 (m, 1H), 1.80-1.67 (m, 1H), 1.67-1.51 (m, 1H).

Example 111: *N*-((*R*)-1-((*R*)-2-Amino-3-methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

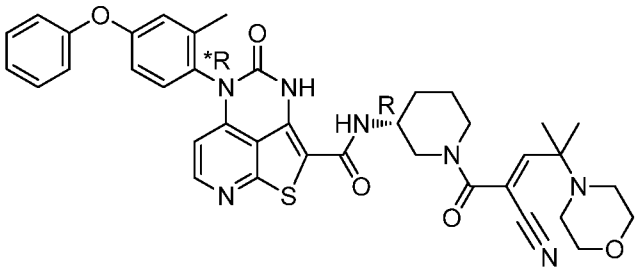


Step A: *tert*-Butyl ((*R*)-3-methoxy-1-((*R*)-3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-1-oxopropan-2-yl)carbamate. To a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.30 mmol) in DMF (3 mL) were added 2-(*tert*-butoxycarbonylamino)-3-methoxy-propanoic acid (99

mg, 0.45 mmol), HATU (140 mg, 0.36 mmol), and triethylamine (0.086 mL, 0.62 mmol). The reaction mixture was stirred at rt for 4 h. The reaction mixture was purified by flash column chromatography to yield the title compound as a yellow solid (186 mg, 88% yield).

Step B: *N*-((*R*)-1-((*R*)-2-Amino-3-methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A solution of *tert*-butyl ((*R*)-3-methoxy-1-((*R*)-3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-1-oxopropan-2-yl)carbamate (186 mg, 0.265 mmol) and HCl/MeOH (2 M in MeOH, 4 mL). The reaction mixture was stirred at rt for 4 h, then the pH was adjusted pH >7 with 2 M aqueous NaOH. The mixture was purified by flash column chromatography to yield the title compound as a yellow solid (71 mg, 44% yield). MS (ESI): mass calcd. for $C_{31}H_{32}N_6O_5S$, 600.7; m/z found, 601.2 $[M+H]^+$. ^1H NMR (400 MHz, CD3OD): δ 8.30-8.15 (m, 1H), 7.46-7.35 (m, 2H), 7.31-7.21 (m, 1H), 7.19-7.12 (m, 1H), 7.12-7.01 (m, 3H), 7.00-6.91 (m, 1H), 6.04-5.89 (m, 1H), 4.38-4.26 (m, 1H), 4.18-4.04 (m, 1H), 4.01-3.89 (m, 1H), 3.63-3.44 (m, 3H), 3.41-3.33 (m, 2H), 3.18-2.76 (m, 1H), 2.11 (s, 3H), 2.02-1.91 (m, 1H), 1.86-1.76 (m, 1H), 1.68-1.54 (m, 1H).

Example 112: (*R*,*E*)-*N*-(1-(2-Cyano-4-methyl-4-morpholinopent-2-enoyl)piperidin-3-yl)-5-(**R*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

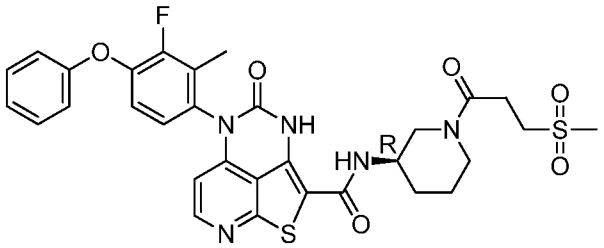


Step A: (*R*)-*N*-(1-(2-Cyanoacetyl)piperidin-3-yl)-5-(**R*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a stirred solution of (*R*)-5-(**R*)-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 300, 80 mg, 0.16 mmol) in DMF (3 mL) were added 2-cyanoacetic acid (30 mg, 0.35 mmol), HATU (120 mg, 0.54 mmol), and diisopropylethylamine (45 mg, 0.35 mmol). The resulting mixture was stirred at rt overnight, concentrated to dryness, and the residue was partitioned between ethyl acetate and water. The organic layer was separated, shaken with brine, and dried over anhydrous Na_2SO_4. The residue

was purified by flash column chromatography to yield the title compound as a yellow solid (68 mg, 75% yield).

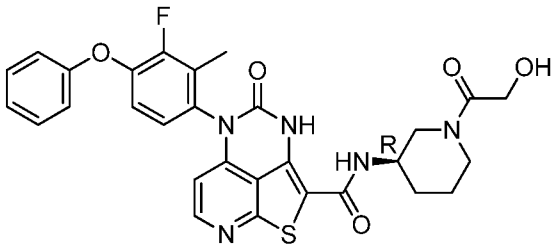
Step B: (*R*,*E*)-*N*-(1-(2-Cyano-4-methyl-4-morpholinopent-2-enoyl)piperidin-3-yl)-5-(**R*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a sealed reaction tube were added (*R*)-*N*-(1-(2-cyanoacetyl)piperidin-3-yl)-5-(**R*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (68 mg, 0.12 mmol), 2-methyl-2-morpholinopropanal (28 g, 0.18 mmol), piperidine (15 mg, 0.18 mmol), and EtOH (2 mL). The tube was sealed and heated to 105 °C overnight, cooled to rt, and the residue purified by flash column chromatography to yield the title compound as yellow solid (39 mg, 46% yield). MS (ESI): mass calcd. for $C_{38}H_{39}N_7O_5S$, 705.8; m/z found, 706.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.40-8.25 (m, 1H), 7.48-7.34 (m, 2H), 7.33-7.23 (m, 1H), 7.25-7.14 (m, 1H), 7.13-7.04 (m, 3H), 7.01-6.94 (m, 1H), 6.90-6.80 (m, 1H), 6.13-6.05 (m, 1H), 4.64-3.96 (m, 3H), 3.81-3.60 (m, 4H), 3.24-2.83 (m, 2H), 2.69-2.51 (m, 4H), 2.12 (s, 3H), 2.05-1.52 (m, 4H), 1.34-1.26 (m, 6H).

Example 113: (*R*)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-*N*-(1-(3-(methylsulfonyl)propanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



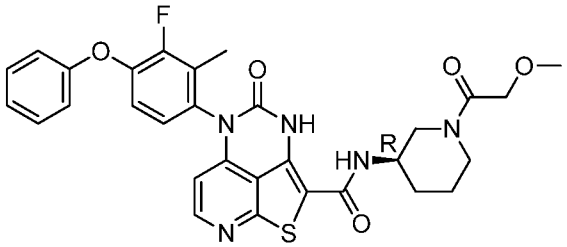
A mixture of (*R*)-5-(3-fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Intermediate 18) (80 mg, 0.16 mmol), 3-methylsulfonylpropanoic acid (47 mg, 0.31 mmol), triethylamine (31 mg, 0.31 mmol), and HATU (118 mg, 0.31 mmol) in DMF (2 mL) was stirred at rt for 1 h, then water was added and the precipitate was collected by filtration. The residue was purified by flash column chromatography to yield the title compound as a white solid (70 mg, 68% yield). MS (ESI): mass calcd. for $C_{31}H_{30}FN_5O_6S_2$, 651.7; m/z found, 652.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.39-8.29 (m, 1H), 7.44-7.33 (m, 2H), 7.22-7.09 (m, 2H), 7.09-7.04 (m, 3H), 6.16-6.08 (m, 1H), 4.44-4.14 (m, 1H), 4.10-3.79 (m, 2H), 3.49-3.38 (m, 2H), 3.24-3.11 (m, 1H), 3.06-2.89 (m, 6H), 2.12 (s, 3H), 2.09-2.01 (m, 1H), 1.92-1.78 (m, 1H), 1.75-1.52 (m, 2H).

Example 114: (*R*)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-*N*-(1-(2-hydroxyacetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(3-fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Intermediate 18) (80 mg, 0.16 mmol), 2-hydroxyacetic acid (24 mg, 0.31 mmol), triethylamine (31 mg, 0.31 mmol), and HATU (118 mg, 0.310 mmol) in DMF (2 mL) was stirred at rt for 1 h, then water was added and the precipitate was collected by filtration. The residue was purified by flash column chromatography to yield the title compound as a white solid (60 mg, 67% yield). MS (ESI): mass calcd. for $C_{29}H_{26}FN_5O_5S$, 575.6; m/z found, 576.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.37-8.25 (m, 1H), 7.43-7.32 (m, 2H), 7.23-7.17 (m, 1H), 7.16-7.10 (m, 1H), 7.09-7.02(m, 3H), 6.18-6.04 (m, 1H), 4.56-4.17 (m, 3H), 3.97-3.58 (m, 2H), 3.08-2.96 (m, 1H), 2.91-2.75 (m, 1H), 2.11 (s, 3H), 2.08-1.97 (m, 1H), 1.88-1.76 (m, 1H), 1.73-1.49 (m, 2H).

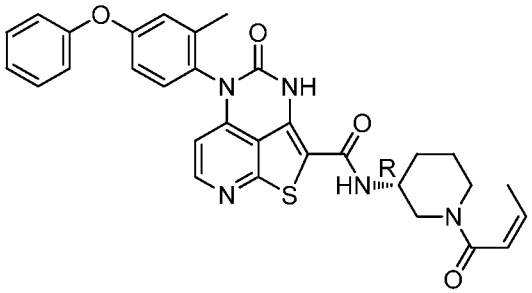
Example 115: (*R*)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-*N*-(1-(2-methoxyacetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A mixture of (*R*)-5-(3-fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Intermediate 18) (80 mg, 0.16 mmol), 2-methoxyacetic acid (28 mg, 0.31 mmol), triethylamine (31 mg, 0.31 mmol), and HATU (118 mg, 0.310 mmol) in DMF (2 mL) was stirred at rt for 1 h, then water was added and the precipitate was collected by filtration. The residue was purified by flash column chromatography to yield the title compound as a white solid (60 mg, 66% yield). MS (ESI): mass calcd. for $C_{30}H_{28}FN_5O_5S$, 589.6; m/z found, 590.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.40-8.24 (m,

1H), 7.44-7.31 (m, 2H), 7.24-7.17 (m, 1H), 7.16-7.10 (m, 1H), 7.09-7.01 (m, 3H), 6.16-6.06 (m, 1H), 4.52-4.10 (m, 3H), 3.99-3.69 (m, 2H), 3.38 (s, 3H), 3.12-2.96 (m, 1H), 2.87-2.70 (m, 1H), 2.11 (s, 3H), 2.07-1.97 (m, 1H), 1.87-1.76 (m, 1H), 1.75-1.47 (m, 2H).

Example 116: (*R*,*Z*)-*N*-(1-(But-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



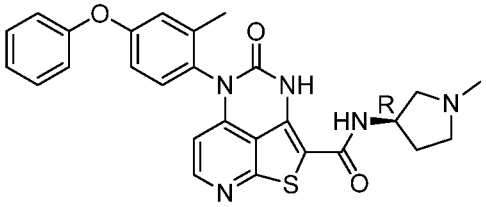
Step A: 1,3-Dibromobutan-2-one. To a solution butan-2-one (0.72 g, 10 mmol) in hydrobromic acid (3 mL) in a 3-neck flask equipped with a condenser and a bubble trap filled with sodium hydroxide was added bromine (3.2 g, 20 mmol) at 0 °C over 20 minutes. The mixture was stirred 1 h before the heavier organic phase was separated. The product was used without further purification (2.30 g, 100% yield).

Step B: (*Z*)-But-2-enoic acid. 1,3-Dibromobutan-2-one (2.3 g, 10.0 mmol) was added to a 2 M aqueous solution of potassium carbonate (100 mL) at 0 °C. The mixture was stirred for 16 h at rt using a condenser. The aqueous solution was extracted with diethyl ether to remove unreacted material. The aqueous phase was then acidified with 37% hydrochloric acid to a pH of 2 and extracted with diethyl ether. The ether layers were dried over anhydrous $MgSO_4$ and filtered. The product was used without further purification (166 mg, 19% yield).

Step C: (*R*,*Z*)- *N*-(1-(But-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A mixture of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 300 mg, 0.58 mmol), (*Z*)-but-2-enoic acid (100 mg, 1.2 mmol), HATU (290 mg, 0.76 mmol), and diisopropylethylamine (190 mg, 1.5 mmol) in DMF (5 mL) was stirred at rt for 2 h. The mixture was purified by HPLC to yield the title compound as white solid (45 mg, 13% yield). MS (ESI): mass calcd. for $C_{31}H_{29}N_5O_4S$, 567.7; m/z found, 568.3 $[M+H]^+$. ^1H NMR (400 MHz, CD3OD): δ 8.37-8.30 (m, 1H), 7.45-7.36 (m, 2H), 7.35-7.26 (m, 1H), 7.21-7.13 (m, 1H), 7.13-7.02 (m, 3H), 7.02-6.93 (m, 1H), 6.88-6.38 (m, 1H), 6.15-5.99 (m,

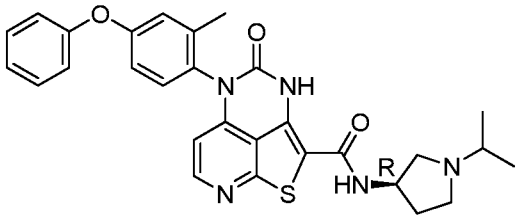
2H), 4.60-3.85 (m, 3H), 3.21-3.04 (m, 1H), 2.97-2.80 (m, 1H), 2.38-1.96 (m, 5H), 1.90-1.78 (m, 3H), 1.78-1.63 (m, 1H), 1.63-1.50 (m, 1H)

Example 117: (*R*)-5-(2-Methyl-4-phenoxyphenyl)-*N*-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1, and using (*R*)-1-methylpyrrolidin-3-amine in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{25}N_5O_3S$, 499.6; m/z found, 500.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6 and CD_3OD): δ 8.23 (d, J = 5.5 Hz, 1H), 7.42-7.34 (m, 2H), 7.29-7.23 (m, 1H), 7.17-7.10 (m, 1H), 7.08-7.04 (m, 2H), 7.03-7.00 (m, 1H), 6.95-6.88 (m, 1H), 5.90 (d, J = 5.5 Hz, 1H), 4.47-4.37 (m, 1H), 2.86-2.76 (m, 2H), 2.68-2.61 (m, 1H), 2.58-2.50 (m, 1H), 2.36 (s, 3H), 2.25-2.15 (m, 1H), 2.03 (s, 3H), 1.88-1.80 (m, 1H).

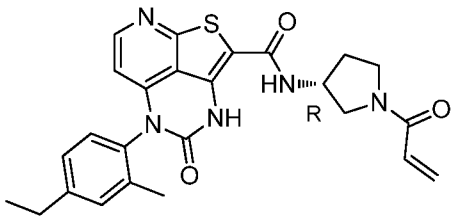
Example 118: (*R*)-*N*-(1-Isopropylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(pyrrolidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 159, 150 mg, 0.31 mmol) in acetone was stirred for 10 min, then $NaBH(OAc)_3$ (130 mg, 0.60 mmmol) was added slowly and the mixture was stirred for 2 h. Next, NaOH (2 mL) was added and the mixture was purified by flash column chromatography, then preparative TLC to yield the title compound as a yellow solid (47 mg, 30% yield). MS (ESI): mass calcd. for $C_{29}H_{29}N_5O_3S$, 527.6; m/z found, 528.1 $[M+H]^+$. ^1H NMR (400 MHz, CDCl3): δ 8.34 (d, J = 5.2 Hz, 1H), 7.44-7.34 (m, 2H), 7.20-7.14 (m, 2H), 7.13-7.06 (m, 2H), 7.00 (s, 1H), 6.98-6.93 (m, 1H), 6.25-6.11 (m, 1H), 6.00 (d, J = 5.2

Hz, 1H), 4.68-4.58 (br, 1H), 3.10-3.01 (m, 1H), 2.90-2.80 (m, 1H), 2.74-2.64 (m, 1H), 2.49-2.31 (m, 3H), 2.12 (s, 3H), 1.83-1.70 (m, 1H), 1.23-1.07 (m, 6H).

Example 119: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-5-(4-ethyl-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



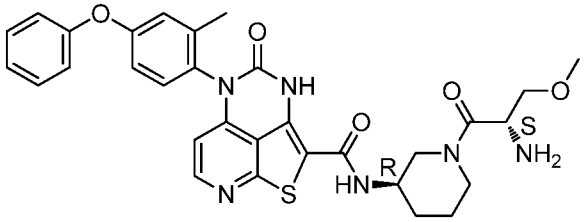
Step A: 4-Ethyl-2-methylaniline. To a mixture of 4-bromo-2-methylaniline (1.86 g, 10.0 mmol), Cs_2CO_3 (9.8 g, 30 mmol), and Pd(dppf)Cl_2 (146 mg, 0.200 mmol) in a Schlenk tube under a N_2 atmosphere was added dry THF (30 mL). To the stirred suspension was added trialkylborane (30 mL, 1 M solution in THF, 30 mmol) in one portion, and the mixture was refluxed for 5 h. The reaction was cooled to 0 °C and quenched by the addition of 10% aqueous NaOH and 30% aqueous H_2O_2. After stirring for 30 min at rt, the mixture was extracted with EtOAc. The combined organic layers were washed successively with aqueous $FeSO_4$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound as a white solid (1.1 g, 83% yield).

Step B: 5-(4-Ethyl-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid. The title compound was prepared in a manner analogous to Method 1, steps C-F in Example 1, and using 4-ethyl-2-methylaniline in place of 2-methyl-4-phenoxyaniline in step C.

Step C: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-5-(4-ethyl-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A solution of 5-(4-ethyl-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (150 mg, 0.42 mmol), 1-[(3R)-3-aminopyrrolidin-1-yl]prop-2-en-1-one (Intermediate 5, 119 mg, 0.850 mmol), HATU (320 mg, 0.85 mmol), and triethylamine (214 mg, 2.12 mmol) in DMF (4 mL) was stirred at rt for 2 h. The residue was purified by flash column chromatography to yield the title compound as a yellow solid (50 mg, 25% yield). MS (ESI): mass calcd. for $C_{25}H_{25}N_5O_3S$, 475.6; m/z found, 476.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.25 (s, 1H), 8.42-8.22 (m, 2H), 7.35-7.16 (m, 3H), 6.71-6.48 (m, 1H), 6.23-6.05 (m, 1H), 5.85 (d, J = 5.5 Hz, 1H), 5.73-5.60 (m, 1H),

4.60-4.37(m, 1H), 3.91-3.38 (m, 4H), 2.65 (q, *J* = 7.5 Hz, 2H), 2.24-2.07 (m, 1H), 2.05 (s, 3H), 2.03-1.89 (m, 1H), 1.23 (t, *J* = 7.6 Hz, 3H).

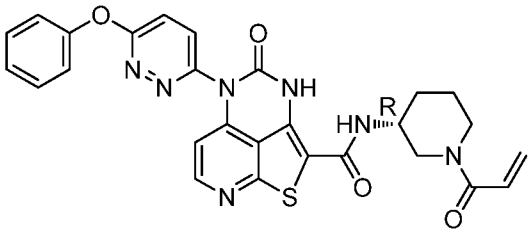
Example 120: *N*-((*R*)-1-((*S*)-2-Amino-3-methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: *tert*-Butyl ((*S*)-3-methoxy-1-((*R*)-3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-1-oxopropan-2-yl)carbamate. A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.30 mmol), (2*S*)-2-(*tert*-butoxycarbonylamino)-3-methoxypropanoic acid (99 mg, 0.45 mmol), HATU (137 mg, 0.360 mmol), and triethylamine (0.086 mL, 0.62 mmol) in DMF (3 mL) was stirred at rt overnight, then purified by flash column chromatography to yield the title compound as a yellow solid (188 mg, 89%).

Step B: *N*-((*R*)-1-((*S*)-2-Amino-3-methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A solution of *tert*-butyl ((*S*)-3-methoxy-1-((*R*)-3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-1-oxopropan-2-yl)carbamate (188 mg, 0.268 mmol) in HCl/MeOH (3 mL) was stirred at rt overnight, then the pH was adjusted to pH >7 with 2 M aqueous NaOH, and purified by flash column chromatography to yield the title compound as a yellow solid (83 mg, 99% yield). MS (ESI): mass calcd. for $C_{31}H_{32}N_6O_5S$, 600.7; m/z found, 601.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.06 (d, *J* = 5.5, 1H), 7.43-7.31 (m, 2H), 7.22-7.05 (m, 4H), 7.04-7.00 (m, 1H), 6.99-6.91 (m, 1H), 5.79 (d, *J* = 5.6, 1H), 4.13-3.94 (m, 3H), 3.56-3.51 (m, 1H), 3.46-3.39 (m, 1H), 3.39-3.34 (m, 2H), 3.33-3.37 (m, 3H), 3.25-3.20 (m, 1H), 2.16-2.01 (m, 4H), 1.96-1.78 (m, 2H), 1.68-1.51 (m, 1H).

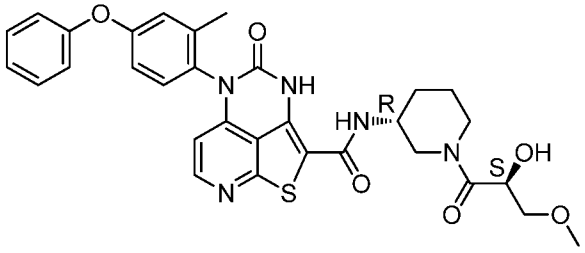
Example 121: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(6-phenoxypyridazin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



StepA: 6-Phenoxypyridazin-3-amine. A solution of 6-chloropyridazin-3-amine (1.3 g, 10 mmol), phenol (3.8 g, 40 mmol), and NaOH (1.6 g, 40 mmol) in water (10 mL) was stirred at 190 °C in a sealed tube for 16 h. The mixture was dispersed between EtOAc and water. Another reaction on the same scale was carried out. The organic layers were combined, concentrated to dryness, and purified by flash column chromatography to yield the title compound (0.50 g, 27% yield).

Step B: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(6-phenoxypyridazin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps C-G in Example 1, and using 6-phenoxypyridazin-3-amine in place of 2-methyl-4-phenoxyaniline in step C, and using 1-[(3*R*)-3-amino-1-piperidyl]prop-2-en-1-one (Intermediate 15) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{23}N_7O_4S$, 541.6; m/z found, 542.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.23-8.15 (m, 1H), 7.93-7.84 (m, 1H), 7.58 (d, J = 9.2 Hz, 1H), 7.51-7.44 (m, 2H), 7.33-7.25 (m, 3H), 6.83-6.74 (m, 1H), 6.28-6.14 (m, 2H), 5.75-5.67 (m, 1H), 4.22-4.11 (m, 1H), 3.98-3.91 (m, 1H), 3.07-2.93 (m, 1H), 2.15-1.95 (m, 2H), 1.94-1.78 (m, 2H), 1.67-1.49 (m, 2H).

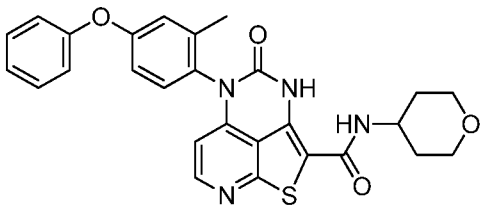
Example 122: *N*-((*R*)-1-((*S*)-2-Hydroxy-3-methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.30 mmol), (2*S*)-2-hydroxy-3-methoxy-propanoic acid (54 mg, 0.45 mmol), HATU (170 mg, 0.45 mmol), and triethylamine (0.084 mL, 0.60 mmol) in DMF (3 mL) was stirred at rt for 4 h, then purified by

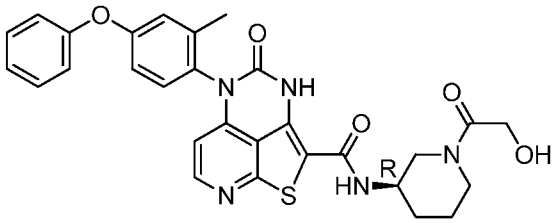
flash column chromatography and preparative TLC to yield the title compound as a yellow solid (24 mg, 13%). MS (ESI): mass calcd. for $C_{31}H_{31}N_5O_6S$, 601.7; m/z found, 602.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33 (d, J = 5.6 Hz, 1H), 7.44-7.36 (m, 2H), 7.35-7.28 (m, 1H), 7.21-7.15 (m, 1H), 7.13-7.03 (m, 3H), 7.03-6.95 (m, 1H), 6.07 (d, J = 5.6 Hz, 1H), 4.69-4.61 (m, 1H), 4.44-4.17 (m, 1H), 4.13-3.89 (m, 2H), 3.71-3.64 (m, 1H), 3.61-3.50 (m, 1H), 3.47-3.35 (m, 3H), 3.22-3.10 (m, 1H), 2.01-1.86 (m, 1H), 2.12 (s, 3H), 2.07-1.99 (m, 1H), 1.88-1.80 (m, 1H), 1.79-1.49 (m, 2H).

Example 123: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(tetrahydro-2*H*-pyran-4-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1, and using tetrahydropyran-4-amine in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{24}N_4O_4S$, 500.6; m/z found, 501.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6 and CD_3OD): δ 8.29-8.25 (m, 1H), 7.39-7.32 (m, 2H), 7.28-7.23 (m, 1H), 7.16-7.09 (m, 1H), 7.07-6.99 (m, 3H), 6.94-6.89 (m, 1H), 5.99-5.95 (m, 1H), 4.02-3.97 (m, 1H), 3.91-3.83 (m, 2H), 3.42-3.32 (m, 2H), 2.05 (s, 3H), 1.79-1.70 (m, 2H), 1.67-1.55 (m, 2H).

Example 124: (*R*)-*N*-(1-(2-Hydroxyacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



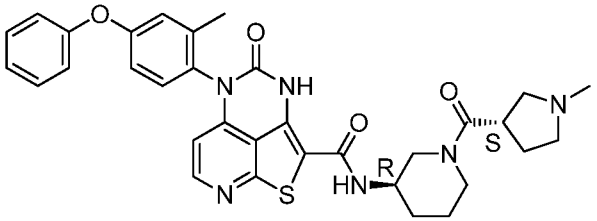
Step A: Benzyl *N*-[(3*R*)-1-(2-hydroxyacetyl)-3-piperidyl]carbamate. A mixture of benzyl *N*-[(3*R*)-3-piperidyl]carbamate (1.0 g, 3.3 mmol), 2-hydroxyacetic acid (225 mg, 3.00 mmol), HATU (1.24 g, 3.26 mmol), and triethylamine (0.450 mL, 3.26 mmol) in MeCN (10 mL) was stirred at 30 °C for 3 h. The reaction mixture was diluted with EtOAc, washed with 1 M aqueous

HCl (3x), saturated aqueous $NaHCO_3$ (3x) and saturated brine (1x). After filtration and concentration to dryness, the residue was purified by flash column chromatography to yield the title compound as a clear oil (400 mg, 42%).

Step B: 1-[(3*R*)-3-Amino-1-piperidyl]-2-hydroxyethanone. A mixture of benzyl *N*-[(3*R*)-1-(2-hydroxyacetyl)-3-piperidyl]carbamate (400 mg, 1.4 mmol) and Pd/C (10%, 50 mg) in MeOH (10 mL) was reacted at rt overnight under H_2. The reaction mixture was filtered and concentrated to dryness to yield the title compound as a clear oil (210 mg, 95%), which is used in the next step without further purification.

Step C: (*R*)-*N*-(1-(2-Hydroxyacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1, and using 1-[(3*R*)-3-amino-1-piperidyl]-2-hydroxyethanone in place of *tert*-butyl (3*R*)-3-aminopyrrolidine-1-carboxylate in step G. MS (ESI): mass calcd. for $C_{29}H_{27}N_5O_5S$, 557.6; m/z found, 558.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 8.32 (d, J = 5.4 Hz, 1H), 8.11 (s, 1H), 7.46-7.40 (m, 2H), 7.36 (d, J = 8.5 Hz, 1H), 7.21-7.17 (m, 1H), 7.12-7.06 (m, 3H), 6.99-6.95 (m, 1H), 5.96 (d, J = 5.2 Hz, 1H), 4.61-4.28 (m, 1H), 4.13-4.05 (m, 3H), 3.81-3.77 (m, 1H), 3.72-3.53 (m, 1H), 2.99-2.64 (m, 2H), 2.05 (s, 3H), 1.93-1.89 (m, 1H), 1.75-1.71 (m, 1H), 1.67-1.55 (m, 1H), 1.50-1.36 (m, 1H).

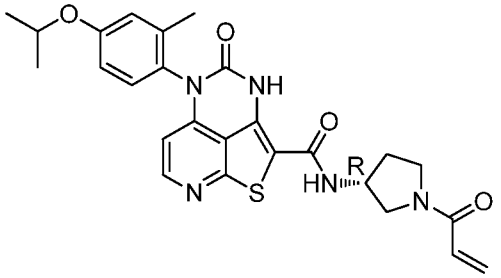
Example 125: 5-(2-Methyl-4-phenoxyphenyl)-*N*-((*R*)-1-((*S*)-1-methylpyrrolidine-3-carbonyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a solution of 5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-((*R*)-1-((*S*)-pyrrolidine-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (120 mg, 0.20 mmol) in DCM (2 mL) were added formaldehyde (0.5 mL, 37 wt. % in H_2O) and sodium $NaBH(OAc)_3$ (200 mg, 0.94 mmol) and was reacted at rt overnight. The reaction was quenched with H_2O (10 mL), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the

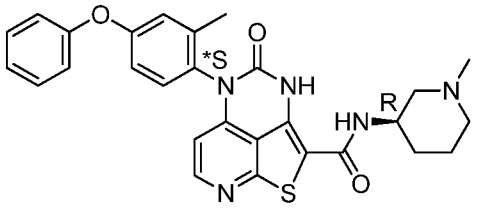
title compound as a yellow solid (54 mg, 44% yield). MS (ESI): mass calcd. for $C_{33}H_{34}N_6O_4S$, 610.7; m/z found, 611.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.30-8.22 (m, 1H), 7.44-7.34 (m, 2H), 7.30-7.23 (m, 1H), 7.19-7.12 (m, 1H), 7.10-7.02 (m, 3H), 7.00-6.93 (m, 1H), 6.04-5.94 (m, 1H), 4.35-4.19 (m, 1H), 4.17-3.81 (m, 2H), 3.60-3.46 (m, 1H), 3.27-3.19 (m, 1H), 3.16-2.95 (m, 2H), 2.95-2.84 (m, 2H), 2.80-2.70 (m, 1H), 2.59-2.44 (m, 3H), 2.15-2.00 (m, 6H), 1.93-1.71 (m, 2H), 1.66-1.50 (m, 1H).

Example 126: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using 3-methyl-4-nitrophenol and 2-iodopropane in place of phenol and 5-fluoro-2-nitrotoluene in step A, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of *tert*-butyl (3*R*)-3-aminopyrrolidine-1-carboxylate in step. MS (ESI): mass calcd. for $C_{26}H_{27}N_5O_4S$, 505.6; m/z found, 506.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.28 (d, J = 5.4 Hz, 1H), 7.26-7.18 (m, 1H), 7.00-6.87 (m, 2H), 6.69-6.51 (m, 1H), 6.34-6.21 (m, 1H), 6.06-5.97 (m, 1H), 5.79-5.69 (m, 1H), 4.74-4.53 (m, 2H), 4.04-3.48 (m, 4H), 2.43-1.98 (m, 5H), 1.42-1.29 (m, 6H).

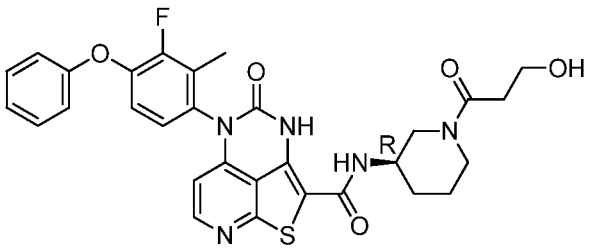
Example 127: (*R*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared using an analogous method to Example 52 Step B using (R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 98). MS (ESI): mass calcd. for $C_{28}H_{27}N_5O_3S$,

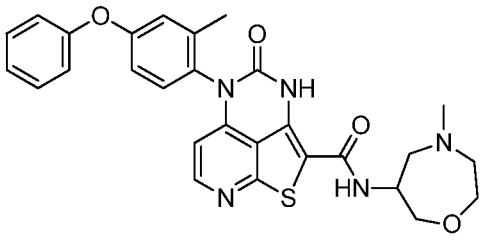
513.6; m/z found, 514.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.30 (d, J = 5.6, 1H), 7.43-7.35 (m, 2H), 7.31-7.26 (m, 1H), 7.20-7.14 (m, 1H), 7.12-7.08 (m, 2H), 7.08-7.03 (m, 1H), 7.01-6.95 (m, 1H), 6.05 (d, J = 5.6, 1H), 4.24-4.11 (m, 1H), 3.02-2.90 (m, 1H), 2.78-2.68 (m, 1H), 2.36 (s, 3H), 2.29-2.16 (m, 2H), 2.12 (s, 3H), 1.95-1.78 (m, 2H), 1.74-1.63 (m, 1H), 1.57-1.45 (m, 1H).

Example 128: (*R*)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-*N*-(1-(3-hydroxypropanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(3-fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Intermediate 18) (80 mg, 0.16 mmol), 3-hydroxypropanoic acid (28 mg, 0.31 mmol), triethylamine (31 mg, 0.31 mmol), and HATU (120 mg, 0.31 mmol) in DMF (2 mL) was stirred at rt for 1 h. The reaction was quenched by the addition of water and the precipitate collected by filtration. The residue was purified by flash column chromatography to yield the title compound as a white solid (32 mg, 35% yield). MS (ESI): mass calcd. for $C_{30}H_{28}FN_5O_5S$, 589.6; m/z found, 590.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.43-8.23 (m, 1H), 7.45-7.32 (m, 2H), 7.25-7.17 (m, 1H), 7.16-7.10 (m, 1H), 7.09-7.01 (m, 3H), 6.18-6.06 (m, 1H), 4.52-4.07 (m, 2H), 3.95-3.76 (m, 3H), 3.18-3.00 (m, 1H), 2.80-2.47 (m, 3H), 2.11 (s, 3H), 2.07-1.98 (m, 1H), 1.88-1.76 (m, 1H), 1.74-1.47 (m, 2H).

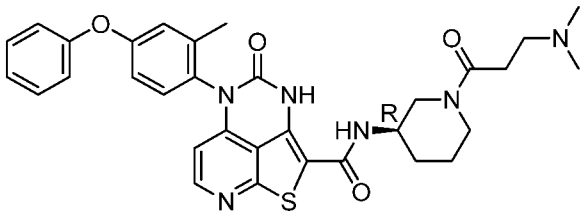
Example 129: *N*-(4-Methyl-1,4-oxazepan-6-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: 5-(2-Methyl-4-phenoxyphenyl)-*N*-(1,4-oxazepan-6-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using *tert*-butyl 6-amino-1,4-oxazepane-4-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

Step B: *N*-(4-Methyl-1,4-oxazepan-6-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of 5-(2-methyl-4-phenoxyphenyl)-*N*-(1,4-oxazepan-6-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (259 mg, 0.502 mmol) in DCM (10 mL) were added formaldehyde (2 mL, 37 wt. % in H_2O) and $NaBH(OAc)_3$ (213 mg, 1.00 mmol) and stirred at rt for 4 h. To the reaction mixture were added DCM (50 mL), MeOH (5 mL), water (30 mL), and an aqueous solution of NH_4OH (2 mL). The organic layer was collected, concentrated to dryness, and purified by flash column chromatography, then by preparative TLC to yield the title compound as a yellow solid (156 mg, 56.0% yield). MS (ESI): mass calcd. for $C_{28}H_{27}N_5O_4S$, 529.6; m/z found, 530.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.29 (d, J = 5.3 Hz, 1H), 8.14-8.00 (m, 1H), 7.45-7.38 (m, 2H), 7.34 (d, J = 8.6 Hz, 1H), 7.20-7.15 (m, 1H), 7.13-7.03 (m, 3H), 6.99-6.92 (m, 1H), 5.99-5.89 (d, J = 5.4 Hz, 1H), 4.34-4.25 (m, 1H), 3.83-3.77 (m, 1H), 2.78-2.53 (m, 4H), 2.33 (s, 3H), 2.03 (s, 3H).

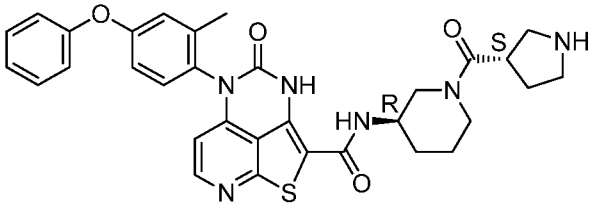
Example 130: (*R*)-*N*-(1-(3-(Dimethylamino)propanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 200 mg, 0.4 mmol) in DMF (3 mL) were added 3-(dimethylamino)propanoic acid (95 mg, 0.81 mmol), HATU (230 mg, 0.61 mmol), and diisopropylethylamine (105 mg, 0.812 mmol) and stirred at rt overnight. The reaction was concentrated to dryness and the residue was partitioned between EtOAc and water. The organic layer was separated, shaken with brine, dried over anhydrous Na_2SO_4, and purified by flash column chromatography to yield the title compound as a yellow solid (95 mg, 40%

yield). MS (ESI): mass calcd. for $C_{32}H_{34}N_6O_4S$, 598.7; m/z found, 599.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.32-8.21 (m, 1H), 7.46-7.35 (m, 2H), 7.32-7.24(m, 1H), 7.21-7.13 (m, 1H), 7.12- 7.03 (m, 3H), 7.01-6.92 (m, 1H), 6.07-5.97 (m, 1H), 4.47-4.11 (m, 1H), 4.07-3.69 (m, 2H), 3.24-3.03 (m, 3H), 3.02-2.75 (m, 3H), 2.66-2.59 (m, 6H), 2.11 (s, 3H), 2.07-1.99 (m, 1H), 1.95-1.53 (m, 3H).

Example 131: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-((*R*)-1-((*S*)-pyrrolidine-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

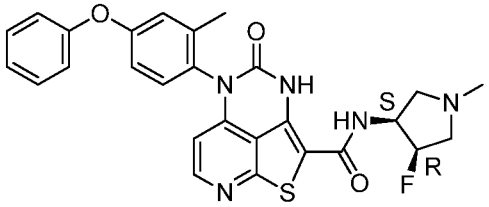


Step A: (*S*)-*tert*-Butyl 3-((*R*)-3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carbonyl)pyrrolidine-1-carboxylate. A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 300 mg, 0.6 mmol), (3*S*)-1-*tert*-butoxycarbonylpyrrolidine-3-carboxylic acid (260 mg, 1.2 mmol), HATU (456 mg, 1.20 mmol), and triethylamine (120 mg. 1.2 mmol) in DMF (5 mL) was reacted at rt for 2 h, then quenched with H_2O (10 mL), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound as a yellow solid (300 mg, 72% yield).

Step B: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-((*R*)-1-((*S*)-pyrrolidine-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (*S*)-*tert*-butyl 3-((*R*)-3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carbonyl)pyrrolidine-1-carboxylate (300 mg, 0.43 mmol) in MeOH (6 mL) was added HCl (37%, 2 mL) and was reacted at rt for 1 h, then quenched with a saturated solution of $NaHCO_3$ (20 mL), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield the title compound as a yellow solid (200 mg, 78% yield). MS (ESI): mass calcd. for $C_{32}H_{32}N_6O_4S$, 596.7; m/z found, 597.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.48 (s, 1H), 8.35-8.26 (m, 1H), 7.46-7.35 (m, 2H), 7.35-7.28 (m, 1H), 7.19-7.12 (m, 1H), 7.08-7.04 (m, 3H), 7.00-6.93 (m, 1H), 6.09-6.02 (m, 1H),

4.53-4.31 (m, 1H), 4.21-3.86 (m, 2H), 3.75-3.47 (m, 3H), 3.41-3.34 (m, 2H), 3.26-2.68 (m, 2H), 2.46-2.21 (m, 1H), 2.13-2.01 (m, 5H),1.94-1.54 (m, 3H).

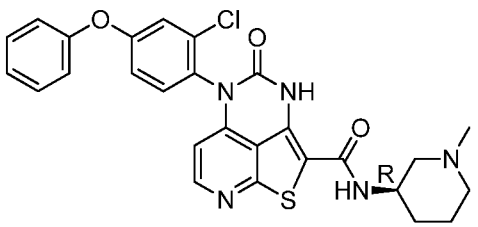
Example 132: *N*-((3*S*,4*R*)-4-Fluoro-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: *N*-((3*S*,4*R*)-4-Fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using *tert*-butyl (3*S*,4*R*)-3-amino-4-fluoropyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

Step B: *N*-((3*S*,4*R*)-4-Fluoro-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of *N*-((3*S*,4*R*)-4-fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (100 mg, 0.2 mmol) and formaldehyde (0.3 mL, 37 wt. % in H_2O) in MeOH (4 mL) was added $NaBH(OAc)_3$ (126 mg, 0.597 mmol) and stirred at rt for 1 h, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a white solid (100 mg, 95% yield). MS (ESI): mass calcd. for $C_{27}H_{24}FN_5O_3S$, 517.6; m/z found, 518.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.32 (d, J = 5.5Hz, 1H), 7.44-7.34 (m, 2H), 7.29 (d, J = 8.6Hz, 1H), 7.20-7.12 (m, 1H), 7.12-7.03 (m, 3H), 6.96 (dd, J = 8.6, 2.8Hz, 1H), 6.06 (d, J = 5.5Hz, 1H), 5.26-5.05 (m, 1H), 4.73-4.61 (m, 1H), 3.15-3.00 (m, 1H), 2.98-2.81 (m, 3H), 2.44 (s, 3H), 2.11 (s, 3H).

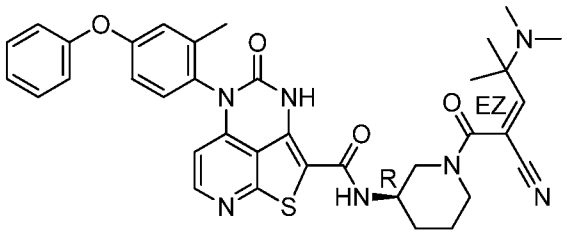
Example 133: (*R*)-5-(2-Chloro-4-phenoxyphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: (*R*)-5-(2-Chloro-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using 2-chloro-4-fluoro-1-nitrobenzene in place of 5-fluoro-2-nitrotoluene in step A, and using *tert*-butyl (3*R*)-3-aminopyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

Step B: (*R*)-5-(2-Chloro-4-phenoxyphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (*R*)-5-(2-chloro-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (104 mg, 0.20 mmol) in DCM (5 mL) were added formaldehyde (0.5 mL, 37 wt. % in H_2O) and $NaBH(OAc)_3$ (85 mg, 0.4 mmol) and stirred at rt for 4 h. To the reaction mixture were added DCM (50 mL), MeOH (5 mL), and water (30 mL). The organic layer was collected, concentrated to dryness, and purified by flash column chromatography to yield the title compound as yellow solid (15 mg, 14% yield). MS (ESI): mass calcd. for $C_{27}H_{24}ClN_5O_3S$, 534.0; m/z found, 534.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.85-8.75 (m, 1H), 8.01 (d, J = 5.5 Hz, 1H), 7.49-7.43 (m, 2H), 7.36-7.32 (m, 1H), 7.26-7.20 (m, 2H), 7.19-7.15 (m, 2H), 7.07-7.02 (m, 1H), 5.62 (d, J = 5.4 Hz, 1H), 3.95-3.83 (m, 1H), 2.81-2.69 (m, 1H), 2.14 (s, 3H), 2.02-1.91 (m, 2H), 1.86-1.76 (m, 2H), 1.71-1.64 (m, 1H), 1.56-1.29 (m, 2H).

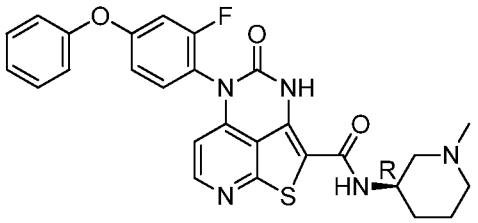
Example 134: (*R*,*Z*)- *N*-(1-(2-Cyano-4-(dimethylamino)-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a round bottom flask were added (*R*)-*N*-(1-(2-cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 874, 150 mg, 0.26 mmol), 2-(dimethylamino)-2-methylpropanal (92 mg, 0.80 mmol), piperidine (0.3 mL), AcOH (0.1 mL), dioxane (10 mL), and 4A molecular sieves (1 g) and was stirred at 100 °C for 1 h under N_2. The mixture was concentrated to dryness and purified by flash column chromatography to yield the title compound as a yellow solid (103 mg, 52.8%

yield). MS (ESI): mass calcd. for $C_{36}H_{37}N_7O_4S$, 663.8; m/z found, 664.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.37 (s, 1H), 8.34-8.30 (m, 1H), 7.42-7.35 (m, 2H), 7.32-7.25 (m, 1H), 7.20-7.12 (m, 1H), 7.11-7.02 (m, 3H), 6.99-6.94 (m, 1H), 6.92-6.76 (m, 1H), 6.09-6.04 (m, 1H), 4.44-3.80 (m, 3H), 3.25-2.87 (m, 2H), 2.49-2.31 (m, 6H), 2.13-2.00 (m, 4H), 1.96-1.85 (m, 1H), 1.80-1.58 (m, 2H), 1.45-1.30 (m, 6H).

Example 135: (*R*)-5-(2-Fluoro-4-phenoxyphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



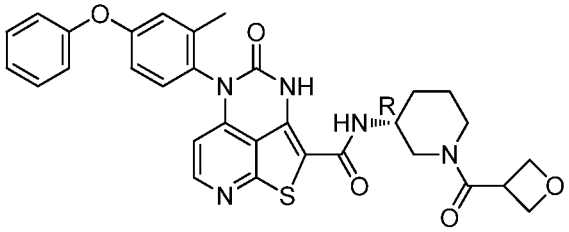
Step A: 2-Fluoro-1-nitro-4-phenoxybenzene. To a solution of 3-fluoro-4-nitrophenol (2.33 g, 19.1 mmol), phenylboronic acid (2.00 g, 12.7 mmol), $Cu(OAc)_2$ (4.624 g, 25.46 mmol), and triethylamine (6.435 g, 63.65 mmol) in DCM (60 mL) was added molecular sieves (4A powder, <50 μm, 2.0 g). The mixture was stirred at room temperature under N_2 overnight. The reaction was filtered and concentrated to dryness. The residue was purified by normal phase flash column chromatography (SiO_2) to yield the title compound as a yellow solid (2.7 g, 91% yield). MS (ESI): mass calcd. for $C_{12}H_8FNO_3$, 233.20; m/z found, 233.9 $[M+H]^+$.

Step B: (*R*)-5-(2-Fluoro-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps B-H in Example 1, and using 2-fluoro-1-nitro-4-phenoxybenzene, Pd/C, and MeOH in place of -methyl-1-nitro-4-phenoxybenzene, Fe, EtOH/H_2O, and NH_4Cl 2 in step B, and using 2-fluoro-4-phenoxyaniline in place of 2-methyl-4-phenoxyaniline in step C, and using (*R*)-*tert*-butyl 3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

Step C: (*R*)-5-(2-Fluoro-4-phenoxyphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A solution of (*R*)-5-(2-fluoro-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (100 mg, 0.2 mmol) and formaldehyde (1 mL, 37 wt. % in H_2O) in MeOH (10 mL) was added $NaBH(OAc)_3$ (212 mg, 1.00 mmol) and then stirred at room temperature for 1 h, concentrated to dryness, and purified by normal phase flash column chromatography (SiO_2) to

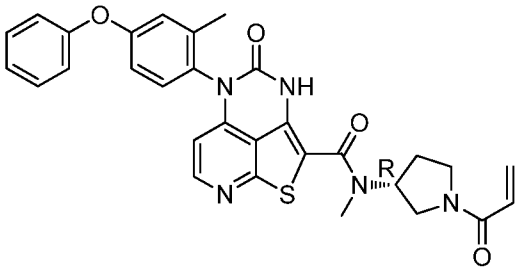
yield the title compound as a yellow solid (62 mg, 60% yield). MS (ESI): mass calcd. for $C_{27}H_{24}FN_5O_3S$, 517.6; m/z found, 517.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.32 (d, J = 7.5 Hz, 1H), 8.23-8.17 (m, 2H), 7.55-7.37 (m, 3H), 7.31-7.14 (m, 3H), 7.14-7.06 (m, 1H), 6.98-6.87 (m, 1H), 6.02 (d, J = 5.4 Hz, 1H), 3.98-3.86 (m, 1H), 2.88-2.77 (m, 1H), 2.72-2.57 (m, 1H), 2.22 (s, 3H), 2.05-1.88 (m, 2H), 1.84-1.63 (m, 2H), 1.58-1.43 (m, 1H), 1.39-1.25 (m, 1H).

Example 136: (*R*)-5-(2-Methyl-4-phenoxyphenyl)-*N*-(1-(oxetane-3-carbonyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



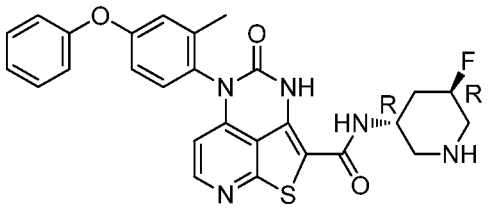
A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 100 mg, 0.2 mmol), oxetane-3-carboxylic acid (30 mg, 0.29 mmol), triethylamine (40 mg, 0.40 mmol), and HATU (150 mg, 0.40 mmol) in DMF (5 mL) was reacted at rt for 2 h, quenched with H_2O (10 mL), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound as an off white solid (48 mg, 41% yield). MS (ESI): mass calcd. for $C_{31}H_{29}N_5O_5S$, 583.7; m/z found, 584.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD and DMSO-d_6): δ 8.41-8.34 (m, 1H), 7.50-7.41 (m, 2H), 7.38-7.33 (m, 1H), 7.27-7.18 (m, 1H), 7.17-7.09 (m, 3H), 7.06-6.97 (m, 1H), 6.12-6.05 (m, 1H), 5.08-4.89 (m, 1H), 4.89-4.75 (m, 4H), 4.28-4.18 (m, 1H), 4.04-3.78 (m, 1H), 3.68-3.38 (m, 1H), 3.01-2.93 (m, 1H), 2.85-2.75 (m, 1H), 2.20-2.11 (m, 3H), 2.09-2.03 (m, 1H), 1.93-1.81 (m, 1H), 1.76-1.64 (m, 1H), 1.63-1.52 (m, 1H).

Example 137: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-*N*-methyl-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



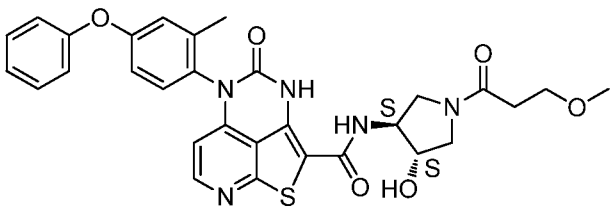
The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using *tert*-butyl (3*R*)-3-(methylamino)pyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{30}H_{27}N_5O_4S$, 553.6; m/z found, 554.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.84 (s, 1H), 8.37 – 8.17 (m, 1H), 7.48 – 7.41 (m, 2H), 7.36 (d, J = 8.6 Hz, 1H), 7.26-7.15 (m, 1H), 7.14 – 7.04 (m, 3H), 7.03-6.89 (m, 1H), 6.64 – 6.48 (m, 1H), 6.19 – 6.04 (m, 1H), 6.00 – 5.89 (m, 1H), 5.75-5.58 (m, 1H), 4.98 – 4.73 (m, 1H), 3.89 – 3.34 (m, 4H), 3.08 – 2.95 (m, 3H), 2.29 – 2.09 (m, 2H), 2.06 (s, 3H).

Example 138: *N*-((3*R*,5*R*)-5-Fluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



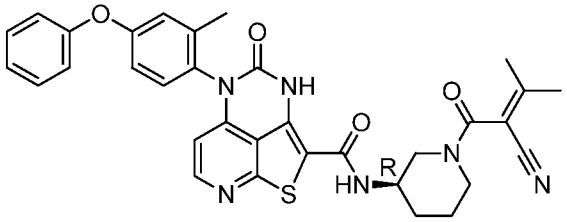
A solution of 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxylic acid (Method 1, Example 1, Steps A-F, 191 mg, 0.458 mmol), *tert*-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (100 mg, 0.458 mmol), triethylamine (92 mg, 0.92 mmol), and HATU (348 mg, 0.916 mmol) in DMF (3 mL) was stirred at rt for 3 h. The reaction was quenched by the addition of water and the precipitate collected by filtration. The solid was dissolved in MeOH (3 mL) and HCl (3 mL) and the solution was heated with stirring at 50 °C for 30 min, concentrated to dryness, and the residue purified by flash column chromatography to yield the title compound as a yellow solid (80 mg, 31% yield). MS (ESI): mass calcd. for $C_{27}H_{24}FN_5O_3S$, 517.6; m/z found, 518.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33 (d, J = 5.5Hz, 1H), 7.47-7.36 (m, 2H), 7.34-7.27 (m, 1H), 7.21-7.13 (m, 1H), 7.14-7.03 (m, 3H), 7.02-6.94 (m, 1H), 6.07 (d, J = 5.5Hz, 1H), 4.76-4.54 (m, 1H), 4.18-4.08 (m, 1H), 3.17-3.01 (m, 2H), 2.79-2.59 (m, 2H), 2.36-2.24 (m, 1H), 2.12 (s, 3H), 1.94-1.83 (m, 1H).

Example 139: *N*-((3*S*,4*S*)-4-Hydroxy-1-(3-methoxypropanoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of *N*-((3*S*,4*S*)-4-hydroxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 236) (100 mg, 0.2 mmol), 3-methoxypropanoic acid (41 mg, 0.40 mmol), triethylamine (40 mg, 0.40 mmol), and HATU (151 mg, 0.398 mmol) in DMF (3 mL) was stirred at rt for 1 h. Water was added and the precipitate was filtered to give a crude, which was purified by flash column chromatography to yield the title compound as a white solid (65 mg, 54% yield). MS (ESI): mass calcd. for $C_{30}H_{29}N_5O_6S$, 587.6; m/z found, 588.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.31 (d, J = 5.4Hz, 1H), 7.44-7.35 (m, 2H), 7.33-7.27 (m, 1H), 7.20-7.12 (m, 1H), 7.11-7.02 (m, 3H), 7.00-6.93 (m, 1H), 6.06 (d, J = 5.5Hz, 1H), 4.44-4.29 (m, 2H), 4.01-3.84 (m, 1H), 3.74-3.57 (m, 4H), 3.52-3.41 (m, 1H), 3.32 (s, 3H), 2.65-2.55 (m, 2H), 2.11 (s, 3H).

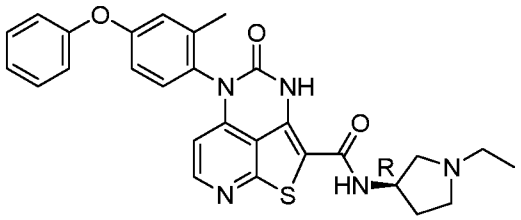
Example 140: (*R*)-*N*-(1-(2-Cyano-3-methylbut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.30 mmol) and 2-cyano-3-methylbut-2-enoic acid (75 mg, 0.60 mmol) in DMF (2 mL) were added HATU (228 mg, 0.600 mmol) and triethylamine (61 mg, 0.60 mmol) and stirred at rt for 4 h. The mixture was purified by flash column chromatography to yield the title product as a yellow solid (105 mg, 58.0% yield). MS (ESI): mass calcd. for $C_{33}H_{30}N_6O_4S$, 606.7; m/z found, 607.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.23 (br, 1H), 8.37-8.25 (m, 1H), 8.21-8.04 (m, 1H), 7.47-7.38 (m, 2H), 7.38-7.30 (m, 1H), 7.20-7.14 (m, 1H), 7.14-7.03 (m, 3H), 7.00-6.91 (m, 1H), 6.02-

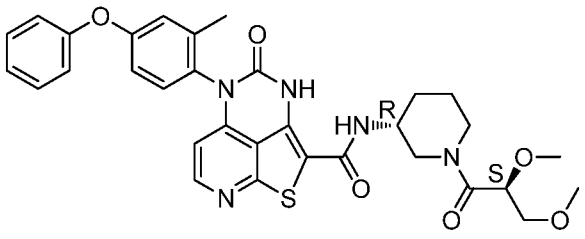
5.87 (m, 1H), 4.39-4.09 (m, 1H), 3.82-3.62 (m, 2H), 3.16-3.02 (m, 1H), 2.88-2.73 (m, 1H), 2.11-2.01 (m, 6H), 1.97-1.92 (m, 1H), 1.92-1.87 (m, 3H), 1.83-1.75 (m, 1H), 1.70-1.59 (m, 1H), 1.48-1.38 (m, 1H).

Example 141: (*R*)-*N*-(1-Ethylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(pyrrolidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 159, 150 mg, 0.31 mmol) in MeOH (5 mL) was added acetaldehyde (1 mL) slowly and was stirred for 10 min. Then $NaBH(OAc)_3$ (127 mg, 0.600 mmol) was added slowly and the mixture was stirred for 2 h. NaOH (2 mL) was added and the mixture was purified by flash column chromatography, then preparative TLC to yield the title compound as a yellow solid (58 mg, 36% yield). MS (ESI): mass calcd. for $C_{28}H_{27}N_5O_3S$, 513.6; m/z found, 514.1 $[M+H]^+$. ^1H NMR (400 MHz, CDCl3): δ 8.41-8.31 (m, 1H), 7.49-7.34 (m, 2H), 7.22-7.15 (m, 2H), 7.15-7.08 (m, 2H), 7.02 (s, 1H), 7.00-6.94 (m, 1H), 6.33-6.11 (m, 1H), 6.02 (d, J = 3.9 Hz, 1H), 4.76-4.56 (m, 1H), 3.13-3.03 (m, 1H), 2.92-2.85 (m, 1H), 2.67-2.55 (m, 3H), 2.47-2.39 (m, 1H), 2.35-2.28 (m, 1H), 2.14 (s, 3H), 1.88-1.77 (m, 1H), 1.24-1.13 (m, 3H).

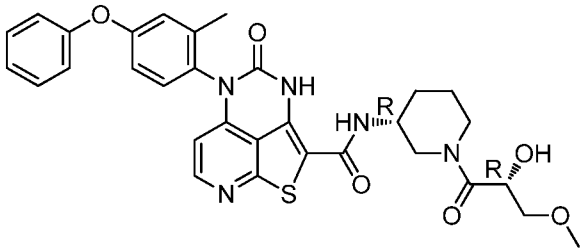
Example 142: *N*-((*R*)-1-((*S*)-2,3-Dimethoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a solution of (S)-2,3-dimethoxypropanoic acid (Intermediate 19) (50 mg, 0.37 mmol) in DCM (5 mL) was added oxalyl dichloride (2 mL) and was stirred at 60 °C overnight. The reaction was

concentrated to dryness and dissolved in DCM (5 mL). This mixture was added to a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 80 mg, 0.16 mmol) and triethylamine (40 mg, 0.40 mmol) in DCM (5 mL) and reacted at room temperature for 30 minutes. The reaction was quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated to dryness, and purified by normal phase flash column chromatography (SiO_2) to yield the title compound (35 mg, 36%) as an off white solid. MS (ESI): mass calcd. for $C_{32}H_{33}N_5O_6S$, 615.7; m/z found, 616.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD and DMSO-d_6): δ 8.43-8.30 (m, 1H), 7.50-7.38 (m, 2H), 7.37-7.27 (m, 1H), 7.27-7.17 (m, 1H), 7.17-7.07 (m, 3H), 7.04-6.95 (m, 1H), 6.14-6.07 (m, 1H), 4.53-4.36 (m, 3H), 4.34-3.84 (m, 3H), 3.72-3.56 (m, 2H), 3.44-3.34 (m, 4H), 3.22-3.03 (m, 1H), 3.01-2.77 (m, 1H), 2.19-2.11(m, 3H), 2.10-2.01 (m, 1H), 1.93-1.81 (m, 1H), 1.78-1.49 (m, 2H).

Example 143: *N*-((*R*)-1-((*R*)-2-Hydroxy-3-methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

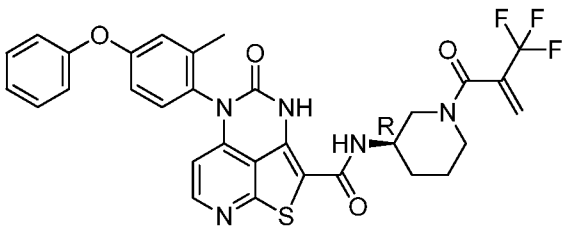


Step A: (2*R*)-Oxirane-2-carboxylic acid, sodium salt. To a solution of methyl (2*R*)-oxirane-2-carboxylate (170 mg, 1.7 mmol) in MeOH (1 mL) in an ice-salt bath was added a solution of NaOH (73 mg, 1.8 mmol) in MeOH (2 mL) dropwise over 10 min. The reaction mixture was stirred at rt overnight, then ether (5 mL) was added. The mixture was left to stand at -10 °C for 1 h, and the precipitate was collected, washed with ether, dried in vacuo to yield the title compound as a white solid (170 mg, 92%).

Step B: 5-(2-methyl-4-phenoxyphenyl)-N-((R)-1-((R)-oxirane-2-carbonyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 200 mg, 0.40 mmol), (2*R*)-oxirane-2-carboxylic acid (89 mg, 0.80 mmol), HATU (115 mg, 0.600 mmol), and diisopropylethylamine (0.219 mL, 1.20 mmol) in DMF (3 mL) was stirred at rt for 15 min, then purified by flash column chromatography to yield the title compound as a yellow solid (160 mg, 70% yield).

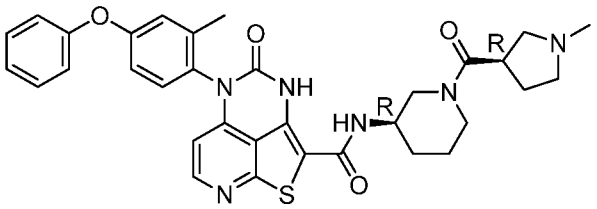
Step C: *N*-((*R*)-1-((*R*)-2-Hydroxy-3-methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A mixture of (*R*)-*N*-(1-(cyclopropanecarbonyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (150 mg, 0.26 mmol) and NaOMe in MeOH (0.5 M, 9 mL) was stirred at 100 °C in a microwave tube for 5 min, concentrated to dryness, and the residue purified by flash column chromatography to yield the title compound as a yellow solid (40 mg, 25% yield). MS (ESI): mass calcd. for $C_{31}H_{31}N_5O_6S$, 601.7; m/z found, 602.8 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33 (d, *J* = 5.6 Hz, 1H), 7.44-7.36 (m, 2H), 7.35-7.26 (m, 1H), 7.20-7.13 (m, 1H), 7.11-7.04 (m, 3H), 7.00-6.95 (m, 1H), 6.07 (d, *J* = 5.5 Hz, 1H), 4.75-4.60 (m, 1H), 4.48-4.17 (m, 1H), 4.10-3.89 (m, 2H), 3.72-3.52 (m, 2H), 3.44-3.33 (m, 3H), 3.23-3.09 (m, 1H), 3.00-2.79 (m, 1H), 2.12 (s, 3H), 2.09-2.01 (m, 1H), 1.91-1.80 (m, 1H), 1.79-1.49 (m, 2H).

Example 144: (*R*)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(1-(2-(trifluoromethyl)acryloyl)piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.28 mmol), 2-(trifluoromethyl)prop-2-enoic acid (78 mg, 0.56 mmol), HATU (138 mg, 0.364 mmol), and diisopropylethylamine (72 mg, 0.56 mmol) in DMF (5 mL) was stirred at rt for 2 h. The mixture was purified first by HPLC and then by flash column chromatography to yield the title compound as white solid (18 mg, 10% yield). MS (ESI): mass calcd. for $C_{31}H_{26}F_3N_5O_4S$, 621.6; m/z found, 622.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.34-8.27 (m, 1H), 7.42-7.34 (m, 2H), 7.33-7.26 (m, 1H), 7.19-7.12 (m, 1H), 7.10-7.01 (m, 3H), 6.98-6.92 (m, 1H), 6.22-6.14 (m, 1H), 6.08-6.03 (m, 1H), 5.99-5.87 (m, 1H), 4.57-4.32 (m, 1H), 4.12-3.78 (m, 2H), 3.22-3.06 (m, 1H), 2.95-2.80 (m, 1H), 2.11-2.05 (m, 4H), 1.97-1.79 (m, 1H), 1.79-1.65 (m, 1H), 1.63-1.53 (m, 1H).

Example 145: 5-(2-Methyl-4-phenoxyphenyl)-*N*-((*R*)-1-((*R*)-1-methylpyrrolidine-3-carbonyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



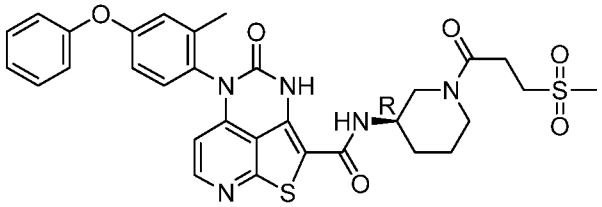
Step A: (*R*)-*tert*-Butyl 3-((*R*)-3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carbonyl)pyrrolidine-1-carboxylate. A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 300 mg, 0.6 mmol), (3*R*)-1-*tert*-butoxycarbonylpyrrolidine-3-carboxylic acid (260 mg, 1.2 mmol), HATU (456 mg, 1.20 mmol), and triethylamine (121 mg, 1.20 mmol) in DMF (5 mL) was reacted at rt for 2 h. The reaction was quenched with H_2O (10 mL), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound as a yellow solid (350 mg, 83% yield).

Step B: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-((*R*)-1-((*R*)-pyrrolidine-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (*R*)-*tert*-butyl 3-((*R*)-3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carbonyl)pyrrolidine-1-carboxylate (350 mg, 0.50 mmol) in MeOH (5 mL) was added HCl (37%, 2 mL) and was reacted at rt for1 h. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (20 mL), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield the title compound as a yellow solid (200 mg, 67% yield).

Step C: 5-(2-Methyl-4-phenoxyphenyl)-*N*-((*R*)-1-((*R*)-1-methylpyrrolidine-3-carbonyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of 5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-((*R*)-1-((*R*)-pyrrolidine-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (150 mg, 0.25 mmol) in DCM (2 mL) were added formaldehyde (0.5 mL, 37 wt. % in H_2O) and $NaBH(OAc)_3$ (200 mg, 0.94 mmol) and was stirred at rt overnight. The reaction was quenched with H_2O (10 mL), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound as a yellow solid (120 mg, 78% yield). MS (ESI): mass calcd. for $C_{33}H_{34}N_6O_4S$, 610.7; m/z found, 611.2 $[M+H]^+$. ^1H

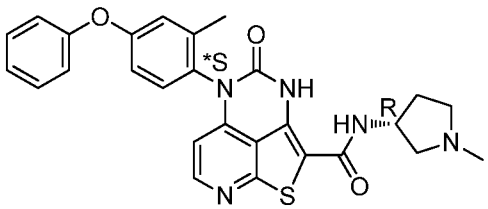
NMR (400 MHz, CD_3OD): δ 8.43 (s, 1H), 8.35-8.27 (m, 1H), 7.43-7.35 (m, 2H), 7.34-7.27 (m, 1H), 7.19-7.12 (m, 1H), 7.10-7.00 (m, 3H), 6.99-6.92 (m, 1H), 6.11-6.00 (m, 1H), 4.57-4.32 (m, 1H), 4.26-3.81 (m, 2H), 3.81-3.60 (m, 2H), 3.53-3.31 (m, 3H), 3.22-3.00 (m, 1H), 2.96-2.89 (m, 3H), 2.88-2.41 (m, 2H), 2.22-1.98 (m, 5H), 1.93-1.47 (m, 3H).

Example 146: (*R*)-5-(2-Methyl-4-phenoxyphenyl)-*N*-(1-(3-(methylsulfonyl)propanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 120 mg, 0.22 mmol), 3-methylsulfonylpropanoic acid (68 mg, 0.45 mmol), HATU (110 mg, 0.29 mmol), and diisopropylethylamine (58 mg, 0.45 mmol) in DMF (5 mL) was stirred at rt for 2 h. The mixture was purified by HPLC to yield the title compound as white solid (85 mg, 60% yield). MS (ESI): mass calcd. for $C_{31}H_{31}N_5O_6S_2$, 633.7; m/z found, 634.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.34-8.30 (m, 1H), 7.42-7.36 (m, 2H), 7.32-7.27 (m, 1H), 7.19-7.13 (m, 1H), 7.10-7.03 (m, 3H), 6.99-6.95 (m, 1H), 6.08-6.04 (m, 1H), 4.44-4.13 (m, 1H), 4.08-3.79 (m, 2H), 3.50-3.39 (m, 2H), 3.24-3.11 (m, 1H), 3.08-2.83 (m, 6H), 2.12 (s, 3H), 2.08-2.00 (m, 1H), 1.91-1.76 (m, 1H), 1.77-1.52 (m, 2H).

Example 147: (*R*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)-*N*-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



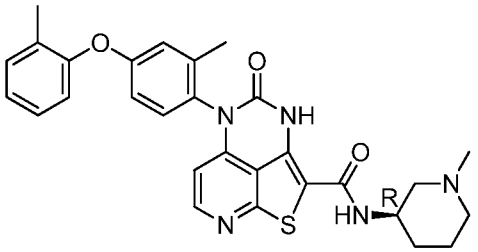
Step A: *tert*-butyl *N*-[(3*R*)-1-Methylpyrrolidin-3-yl]carbamate. To a solution of *tert*-butyl *N*-[(3*R*)-pyrrolidin-3-yl]carbamate (500 mg, 2.68 mmol) in MeOH (5 mL) was added formaldehyde (0.4 mL, 37 wt. % in H_2O) and was stirred at rt for 5 min. Next, sodium cyanoborohydride (506 mg, 8.05 mmol) was added and was stirred at rt overnight. The reaction mixture was

concentrated to dryness and the residue was added to EtOAc and H_2O, and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness to yield the title compound as a yellow oil (536 mg, 100%).

Step B: (3*R*)-1-Methylpyrrolidin-3-amine. A solution of *tert*-butyl *N*-[(3*R*)-1-methylpyrrolidin-3-yl]carbamate (536 mg, 2.84 mmol) in HCl and MeOH (2 M, 2 mL) was stirred at rt for 4 h. The reaction mixture was concentrated to dryness to yield the title compound (322 mg, 88%), which was used in next step without further purification.

Step C: (*R*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)-*N*-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1 (including Chiral resolution Method A after Step F to obtain the **S* atropisomer), and using (3*R*)-1-methylpyrrolidin-3-amine in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{25}N_5O_3S$, 499.6; m/z found, 500.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.29 (d, J = 5.6 Hz, 1H), 7.47-7.35 (m, 2H), 7.31-7.25 (m, 1H), 7.21-7.14 (m, 1H), 7.12-7.04 (m, 3H), 7.02-6.94 (m, 1H), 6.03 (d, J = 5.6 Hz, 1H), 4.61-4.53 (m, 1H), 3.02-2.91 (m, 2H), 2.85-2.78 (m, 1H), 2.69-2.63 (m, 1H), 2.50 (s, 3H), 2.43-2.35 (m, 1H), 2.12 (s, 3H), 1.99-1.88 (m, 1H).

Example 148: (*R*)-5-(2-Methyl-4-(*o*-tolyloxy)phenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

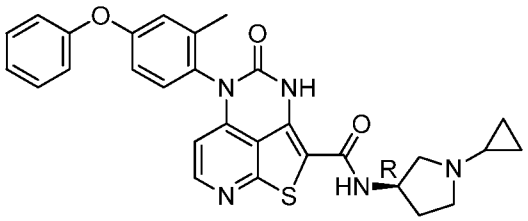


Step A: (*R*)-5-(2-Methyl-4-(*o*-tolyloxy)phenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using o-cresol in place of phenol in step A, and using (*R*)-*tert*-butyl 3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G to yield the title compound.

Step B: (*R*)-5-(2-Methyl-4-(*o*-tolyloxy)phenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (*R*)-5-(2-methyl-4-(*o*-tolyloxy)phenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-

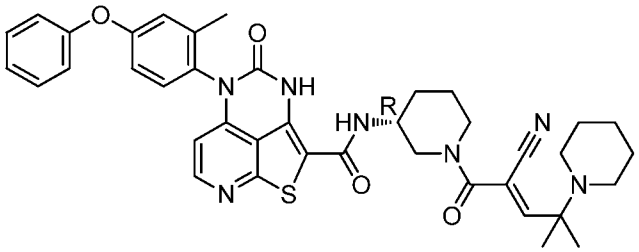
carboxamide (80 mg, 0.16 mmol) in DCM (5 mL), were added formaldehyde (0.5 ml, 37 wt. % in H_2O) and $NaBH(OAc)_3$ (100 mg, 0.47 mmol) and reacted at rt for 20 min. The reaction was quenched with H_2O (10 mL), extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound as a yellow solid (26 mg, 31% yield). MS (ESI): mass calcd. for $C_{29}H_{29}N_5O_3S$, 527.6; m/z found, 528.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.38-8.27 (m, 1H), 7.32-7.27 (m, 1H), 7.27-7.19 (m, 2H), 7.18-7.07 (m, 1H), 7.03-6.90 (m, 2H), 6.88-6.80 (m, 1H), 6.11-6.02 (m, 1H), 4.35-4.15 (m, 1H), 3.45-3.34 (m, 1H), 3.26-3.13 (m, 1H), 2.81-2.65 (m, 5H), 2.22 (s, 3H), 2.09 (s, 3H), 2.03-1.96 (m, 2H), 1.86-1.75 (m, 1H), 1.66-1.57 (m, 1H).

Example 149: (*R*)-*N*-(1-Cyclopropylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



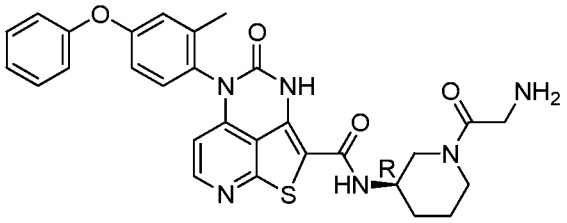
To a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(pyrrolidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 159, 200 mg, 0.41 mmol) in MeOH (5 mL) was added (1-ethoxycyclopropoxy)-trimethylsilane (209 mg, 1.20 mmol) slowly and was stirred for 10 min, then $NaBH_4CN$ (77 mg, 1.2 mmol) and AcOH (6 mg, 0.1 mmol) was added slowly and the mixture was stirred for 2 h. NaOH (2 mL) was added and the mixture was purified first by flash column chromatography, then by preparative TLC to yield the title compound as a yellow solid (65 mg, 29% yield). MS (ESI): mass calcd. for $C_{29}H_{27}N_5O_3S$, 525.6; m/z found, 526.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 9.50-9.35 (m, 1H), 8.33 (d, J = 5.4Hz, 1H), 7.46-7.33 (m, 2H), 7.20-7.13 (m, 2H), 7.13-7.05 (m, 2H), 6.99 (s, 1H), 6.97-6.91 (m, 1H), 5.96 (d, J = 5.4Hz, 1H), 5.18-4.95 (m, 1H), 3.99-3.60 (m, 2H), 3.37-2.92 (m, 2H), 2.72-2.58 (m, 1H), 2.49-2.25 (m, 2H), 2.11 (d, J = 2.4, 3H), 1.51-1.28 (m, 2H), 1.01-0.75 (m, 2H).

Example 150: (*R*,*E*)-*N*-(1-(2-Cyano-4-methyl-4-(piperidin-1-yl)pent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a sealed tube were added (*R*)-*N*-(1-(2-cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 874, 150 mg, 0.265 mmol), 2-methyl-2-(1-piperidyl)propanal (65 mg, 0.42 mmol), piperidine (30 mg, 0.35 mmol), and EtOH (3 mL) and the tube was sealed and heated to 105 °C overnight, cooled to rt, and the residue purified by flash column chromatography to yield the title compound as a yellow solid (78 mg, 42% yield). MS (ESI): mass calcd. for $C_{39}H_{41}N_7O_4S$, 703.9; m/z found, 704.30 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.32 (d, J = 5.6 Hz, 1H), 7.46 -7.37 (m, 2H), 7.33-7.26 (m, 1H), 7.22-7.15 (m, 1H), 7.14-7.05 (m, 3H), 7.02-6.95 (m, 1H), 6.94-6.75 (m, 1H), 6.09-6.03 (m, 1H), 4.52-3.71 m, 3H), 3.57 – 3.34 (m, 1H), 3.24-2.91 (m, 1H), 266-2.41 (m, 4H), 2.16-2.10 (m, 3H), 2.09-1.86 (m, 2H), 1.85-1.53 (m, 6H), 1.50-1.36 (m, 2H), 1.35-1.24 (m, 6H).

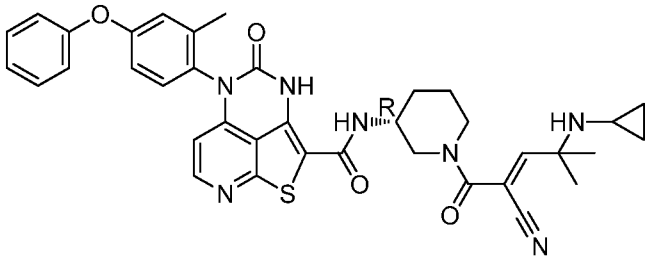
Example 151: (*R*)-*N*-(1-(2-Aminoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: (*R*)-*tert*-Butyl (2-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-2-oxoethyl)carbamate. To a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.30 mmol) in DMF (3 mL) were added 2-(*tert*-butoxycarbonylamino)acetic acid (79 mg, 0.45 mmol), HATU (137 mg, 0.360 mmol), and triethylamine (0.167 mL, 1.20 mmol). The reaction mixture was stirred at rt for 4 h and was purified by flash column chromatography to yield the title compound as a yellow solid (171 mg, 86% yield).

Step B: (*R*)-*N*-(1-(2-Aminoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A solution of (*R*)-*tert*-butyl (2-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-2-oxoethyl)carbamate (171 mg, 0.260 mmol) and HCl/MeOH (2 M, 3 mL) was stirred at rt for 4 h, then the pH was adjusted to pH >7 with 2 M aqueous NaOH, and purified by flash column chromatography to yield the title compound as a yellow solid (95 mg, 65% yield). MS (ESI): mass calcd. for $C_{29}H_{28}N_6O_4S$, 556.6; m/z found, 557.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.09-8.01 (m, 1H), 7.42-7.31 (m, 2H), 7.20-7.05 (m, 4H), 7.04-6.99 (m, 1H), 6.99-6.93 (m, 1H), 5.83-5.73 (m, 1H), 4.16-4.02 (m, 1H), 3.99-3.91 (m, 1H), 3.86-3.73 (m, 1H), 3.62-3.48 (m, 2H), 3.42-3.30 (m, 1H), 3.27-3.16 (m, 1H), 2.10 (s, 3H), 2.07-2.00 (m, 1H), 1.93-1.76 (m, 2H), 1.65-1.51 (m, 1H).

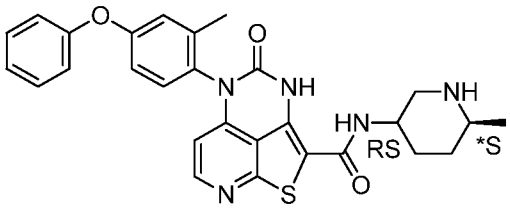
Example 152: (*R*,*E*)-*N*-(1-(2-Cyano-4-(cyclopropylamino)-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: 3-Bromo-3-methylbutanal. To a solution of 3-methylbutanal (500 mg, 5.80 mmol) in Et_2O (3 mL) was added slowly a bromine/dioxane complex (720 mg, 2.90 mmol) while cooling with ice-water. The reaction mixture was stirred at rt for 4 h, and then 10% aqueous $Na_2S_2O_4$ was added. After stirring at rt for 15 min, the mixture was extracted with Et_2O/H_2O, the organic layer was collected, washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness to yield the title compound as a pale yellow liquid (510 mg, 52%).
Step B: 2-(Cyclopropylamino)-2-methylpropanal. To a solution of 3-bromo-3-methylbutanal (450 mg, 2.73 mmol) in Et_2O (10 mL) was added cyclopropanamine (545 mg, 9.55 mmol). The reaction mixture was stirred at rt overnight, then extracted with an Et_2O/water mixture. The organic layer was collected, washed with Et_2O, dried over anhydrous Mg_2SO_4, filtered, and concentrated to dryness to yield the title compound as a pale yellow liquid (197 mg, 57%).
Step C: (*R*,*E*)-*N*-(1-(2-Cyano-4-(cyclopropylamino)-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-

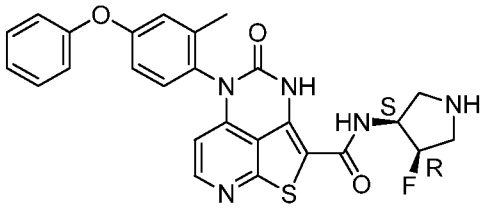
carboxamide. To a solution of (*R*)-*N*-(1-(2-cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 874, 163 mg, 0.288 mmol) and 2-(cyclopropylamino)-2-methylpropanal (110 mg, 0.86 mmol) in *i*PrOH (5 mL) was added piperdine (0.014 mL, 0.14 mmol) and was stirred at 40 °C overnight, concentrated to dryness, and the residue purified by flash column chromatography to yield the title compound as a yellow solid (19 mg, 10% yield). MS (ESI): mass calcd. for $C_{37}H_{37}N_7O_4S$, 675.8; m/z found, 676.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.25-8.18 (m, 1H), 7.73-7.64 (m, 1H), 7.44-7.35 (m, 2H), 7.26-7.20 (m, 1H), 7.19-7.14 (m, 1H), 7.11-7.07 (m, 2H), 7.07-7.03 (m, 1H), 6.99-6.94 (m, 1H), 6.03-5.90 (m, 1H), 4.07-3.81 (m, 2H), 3.64-3.43 (m, 1H), 3.06-3.08 (m, 1H), 2.71-2.57 (m, 1H), 2.15-2.01 (m, 5H), 1.98-1.88 (m, 1H), 1.76-1.68 (m, 1H), 1.65-1.53 (m, 6H), 1.34-1.29 (m, 1H), 1.11-0.89 (m, 4H).

Example 153: 5-(2-Methyl-4-phenoxyphenyl)-*N*-((6*S*)-6-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



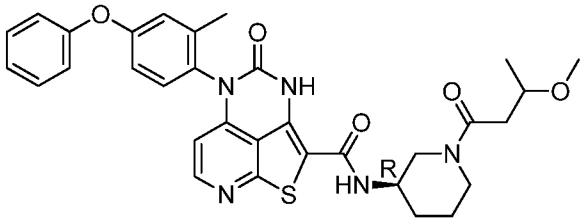
The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using benzyl 5-amino-2-methylpiperidine-1-carboxylate (Intermediate 20) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G and TFA in place of MeOH and aqueous HCl in Step H. Example 153 and Example 173 were separated from the same reaction mixture by flash column chromatography (C-18, MeOH/H_2O) followed by preparative TLC. MS (ESI): mass calcd. for $C_{28}H_{27}N_5O_3S$, 513.6; m/z found, 544.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.40-8.32 (m, 1H), 7.45-7.37 (m, 2H), 7.33-7.26 (m, 1H), 7.21-7.14 (m, 1H), 7.11-7.02 (m, 3H), 7.00-6.92 (m, 1H), 6.12-6.05 (m, 1H), 4.39-4.28 (m, 1H), 3.63-3.50 (m, 1H), 3.46-3.37 (m, 1H), 3.37-3.33 (m, 1H), 2.11 (s, 3H), 2.06-1.83 (m, 4H), 1.43-1.35 (m, 3H).

Example 154: *N*-((3*S*,4*R*)-4-Fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



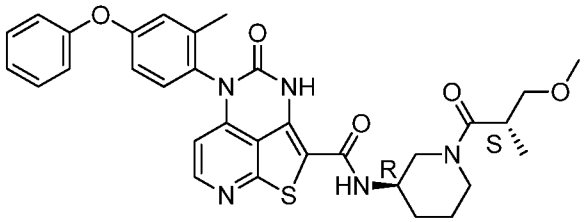
The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using *tert*-butyl (3*S*,4*R*)-3-amino-4-fluoropyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{26}H_{22}FN_5O_3S$, 503.5; m/z found, 504.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6 and CD_3OD): δ 8.37-8.25 (m, 1H), 7.42-7.30(m, 2H), 7.29-7.21 (m, 1H), 7.16-7.09 (m, 1H), 7.08-6.98 (m, 3H), 6.95-6.88 (m, 1H), 6.06-5.96 (m, 1H), 5.39-5.18 (m, 1H), 4.83-4.66 (m, 1H), 3.67-3.54 (m, 3H), 3.44-3.35 (m, 1H), 2.04 (s, 3H).

Example 155: *N*-((3*R*)-1-(3-Methoxybutanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



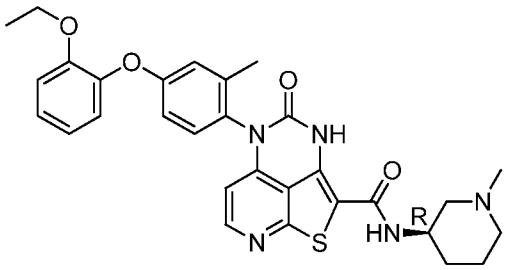
To a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.30 mmol) and 3-methoxybutanoic acid (265 mg, 0.900 mmol) in anhydrous DMF (2 mL) were added HATU (342 mg, 0.900 mmol) and diisopropylethylamine (156 mg, 1.20 mmol) and the mixture was stirred overnight at rt. The reaction mixture was purified by flash column chromatography, then preparative TLC to yield the title compound (41 mg, 23%) as a white solid. MS (ESI): mass calcd. for $C_{32}H_{33}N_5O_5S$, 599.7; m/z found, 600.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.26 (s, 1H), 8.35-8.09 (m, 2H), 7.48-7.42 (m, 2H), 7.38-7.31 (m, 1H), 7.23-7.17 (m, 1H), 7.16-7.10 (m, 2H), 7.10-7.08 (m, 1H), 7.01-6.95 (m, 1H), 5.93 (s, 1H), 4.49-4.11 (m, 1H), 3.99-3.64 (m, 3H), 3.23-3.16 (m, 3H), 3.09-2.90 (m, 1H), 2.75-2.54 (m, 2H), 2.38-2.22 (m, 1H), 2.06 (s, 3H), 1.99-1.88 (m, 1H), 1.81-1.70 (m, 1H), 1.69-1.54 (m, 1H), 1.52-1.31 (m, 1H), 1.14-1.07 (m, 3H).

Example 156: *N*-((*R*)-1-((*S*)-3-Methoxy-2-methylpropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.28 mmol), (2*S*)-3-methoxy-2-methylpropanoic acid (43 mg, 0.36 mmol), HATU (137 mg, 0.360 mmol), and triethylamine (0.125 mL, 0.897 mmol) in DMF (3 mL) was stirred at rt overnight. The reaction mixture was purified by flash column chromatography to yield the title compound as a white solid (120 mg, 70% yield). MS (ESI): mass calcd. for $C_{32}H_{33}N_5O_5S$, 599.7; m/z found, 600.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.34 (d, J = 5.5, 1H), 7.45-7.38 (m, 2H), 7.34-7.27 (m, 1H), 7.23-7.14 (m, 1H), 7.12-7.03 (m, 3H), 7.01-6.94 (m, 1H), 6.08 (d, J = 5.5, 1H), 4.36-4.27 (m, 1H), 4.20-3.87 (m, 2H), 3.65-3.55 (m, 1H), 3.36 (s, 3H), 3.27-3.17 (m, 2H), 3.15-2.75 (m, 2H), 2.13 (s, 3H), 2.09-2.00 (m, 1H), 1.92-1.70 (m, 2H), 1.63-1.49 (m, 1H), 1.10-0.99 (m, 3H).

Example 157: (*R*)-5-(4-(2-Ethoxyphenoxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

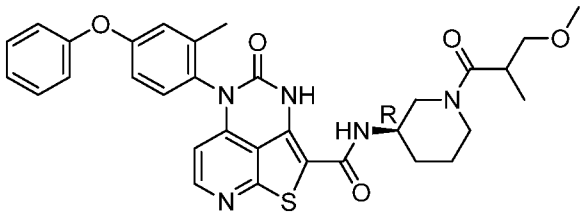


Step A: (*R*)-5-(4-(2-Ethoxyphenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using 2-ethoxyphenol in place of phenol in step A, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

Step B: (*R*)-5-(4-(2-Ethoxyphenoxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (*R*)-5-(4-(2-

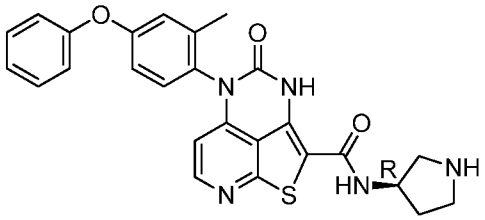
ethoxyphenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (542 mg, 0.997 mmol) in DCM (10 mL) were added formaldehyde (1 mL, 37 wt. % in H_2O) and $NaBH(OAc)_3$ (423 mg, 2.00 mmol) and stirred at rt for 4 h. To the reaction mixture were added DCM (50 mL), MeOH (5 mL), water (30 mL), and an aqueous solution of NH_4OH (2 mL). The organic layer was separated, concentrated to dryness, and purified by flash column chromatography, then by preparative TLC to yield the title compound as a yellow solid (90 mg, 26% yield). MS (ESI): mass calcd. for $C_{30}H_{31}N_5O_4S$, 557.7; m/z found, 558.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.29 (d, J = 5.5 Hz, 1H), 8.09-7.97 (m, 1H), 7.26 (d, J = 8.7 Hz, 1H), 7.22-7.15 (m, 2H), 7.14-7.10 (m, 1H), 7.01-6.96 (m, 1H), 6.94-6.91 (m, 1H), 6.79 (dd, J = 8.6, 2.9 Hz, 1H), 5.86 (d, J = 5.5 Hz, 1H), 4.04 (q, J = 7.0 Hz, 2H), 3.99-3.93 (m, 1H), 2.91-2.84 (m, 1H), 2.76-2.68 (m, 1H), 2.26 (s, 3H), 2.01 (s, 3H), 2.02-1.92 (m, 2H), 1.82-1.74 (m, 1H), 1.74-1.66 (m, 1H), 1.59-1.48 (m, 1H), 1.42-1.32 (m, 1H), 1.19 (t, J = 7.0 Hz, 3H).

Example 158: *N*-((3*R*)-1-(3-Methoxy-2-methylpropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



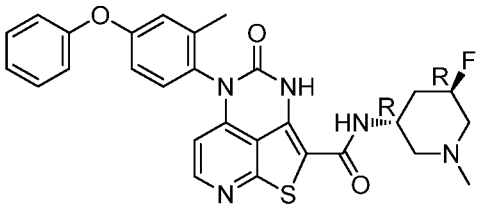
To a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 110 mg, 0.22 mmol) in DMF (3 mL) were added 3-methoxy-2-methylpropanoic acid (39 mg, 0.33 mmol), HATU (100 mg, 0.26 mmol) and triethylamine (0.123 mL, 0.880 mmol) and was stirred at rt for 4 h. The reaction mixture was purified by flash column chromatography to yield the title compound as a white solid (70 mg, 52% yield). MS (ESI): mass calcd. for $C_{32}H_{33}N_5O_5S$, 599.7; m/z found, 600.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.32 (d, *J* = 5.5, 1H), 7.46-7.36 (m, 2H), 7.33-7.28 (m, 1H), 7.21-7.15 (m, 1H), 7.11-7.03 (m, 3H), 7.00-6.94 (m, 1H), 6.07 (d, *J* = 5.5, 1H), 4.38-4.23 (m, 1H), 4.20-3.88 (m, 2H), 3.62-3.52 (m, 1H), 3.38-3.31 (m, 3H), 3.26-3.19 (m, 2H), 3.15-3.01 (m, 1H), 2.86-2.73 (m, 1H), 2.12 (s, 3H), 2.07-2.01 (m, 1H), 1.89-1.79 (m, 1H), 1.76-1.66 (m, 1H), 1.61-1.45 (s, 1H), 1.15-1.01 (m, 3H).

Example 159: (*R*)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(pyrrolidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



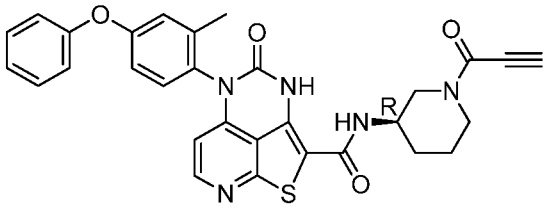
The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using *tert*-butyl (3*R*)-3-aminopyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{26}H_{23}N_5O_3S$, 485.6; m/z found, 486.1 $[M+H]^+$. ^1H NMR (400 MHz, CDCl3): δ 8.31 (d, J = 5.5 Hz, 1H), 7.41-7.33 (m, 2H), 7.19-7.12 (m, 2H), 7.11-7.05 (m, 2H), 7.01-6.97 (m, 1H), 6.97-6.91 (m, 1H), 6.44-6.27 (m, 1H), 5.97 (d, J = 5.5 Hz, 1H), 4.64-4.50 (m, 1H), 3.25-3.10 (m, 2H), 3.06-2.89 (m, 2H), 2.30-2.17 (m, 1H), 2.11 (s, 3H), 1.84-1.72 (m, 1H).

Example 160: *N*-((3*R*,5*R*)-5-Fluoro-1-methylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



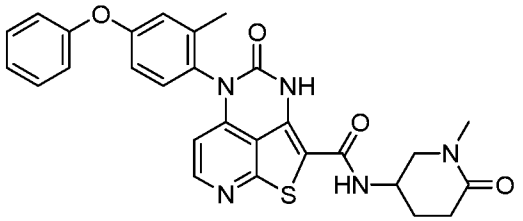
To a solution of *N*-((3*R*,5*R*)-5-fluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 138, 23 mg, 0.044 mmol) and formaldehyde (0.3 mL, 37 wt. % in H_2O) in MeOH (2 mL) was added $NaBH(OAc)_3$ (3.2 mg, 0.015 mmol) and stirred at rt overnight, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a white solid (21 mg, 86% yield). MS (ESI): mass calcd. for $C_{28}H_{26}FN_5O_3S$, 531.6; m/z found, 532.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.27 (d, *J* = 5.5Hz, 1H), 7.39-7.30 (m, 2H), 7.25 (d, *J* = 8.6Hz, 1H), 7.15-7.07 (m, 1H), 7.06-6.98 (m, 3H), 6.91 (dd, *J* = 8.6, 2.8Hz, 1H), 5.98 (d, *J* = 5.5Hz, 1H), 4.76-4.56 (m, 1H), 4.16-4.08 (m, 1H), 2.79-2.64 (m, 2H), 2.28 (s, 1H), 2.26 (s, 3H), 2.19-2.06 (m, 2H), 2.04 (s, 3H), 1.75-1.63 (m, 1H).

Example 161: (*R*)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(1-propioloylpiperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



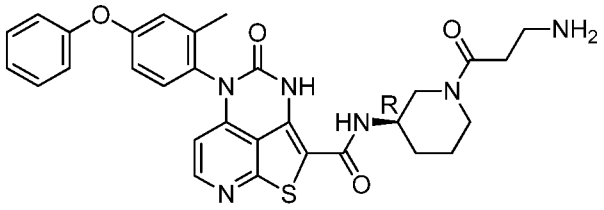
A solution of (*R*)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.28 mmol), prop-2-ynoic acid (42 mg, 0.60 mmol), HATU (148 mg, 0.390 mmol), and diisopropylethylamine (77 mg, 0. 60 mmol) in DMF (5 mL) was stirred at rt for 2 h. The reaction mixture was purified by HPLC to yield the title compound as a yellow solid (82 mg, 49% yield). MS (ESI): mass calcd. for $C_{30}H_{25}N_5O_4S$, 551.6; m/z found, 552.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD and DMSO-d_6): δ 8.30-8.24 (m, 1H), 7.40-7.32 (m, 2H), 7.31-7.25 (m, 1H), 7.15-7.08 (m, 1H), 7.07-6.98 (m, 3H), 6.93-6.88 (m, 1H), 5.98-5.93 (m, 1H), 4.39-3.74 (m, 4H), 3.26-3.05 (m, 1H), 2.86-2.67 (m, 1H), 2.03 (s, 3H), 1.98-1.89 (m, 1H), 1.84-1.70 (m, 1H), 1.69-1.57 (m, 1H), 1.53-1.33 (m, 1H).

Example 162: 5-(2-Methyl-4-phenoxyphenyl)-*N*-(1-methyl-6-oxopiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1, and using 5-amino-1-methylpiperidin-2-one in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{28}H_{25}N_5O_4S$, 527.6; m/z found, 528.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.36-8.25 (m, 2H), 7.50-7.39 (m, 2H), 7.35 (d, J = 8.6 Hz, 1H), 7.25-7.15 (m, 1H), 7.14-7.04 (m, 3H), 7.00-6.92 (m, 1H), 5.95 (d, J = 5.5 Hz, 1H), 4.31-4.15 (m, 1H), 3.50-3.36 (m, 2H), 2.79 (s, 3H), 2.37-2.25 (m, 2H), 2.05 (s, 3H), 1.97-1.83 (m, 2H).

Example 163: (*R*)-*N*-(1-(3-Aminopropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

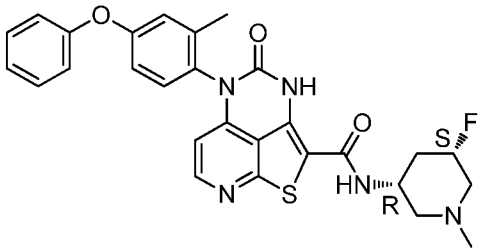


Step A: 3-(*tert*-Butoxycarbonylamino)propanoic acid. To a solution of 3-aminopropanoic acid (1.0 g, 11 mmol) in DCM (50 mL) at 0 °C under a N_2 atmosphere were added DMAP (137 mg, 1.12 mmol) and *tert*-butoxycarbonyl *tert*-butyl carbonate (3.0 g, 14 mmol). The reaction was warmed to rt overnight. The reaction mixture was concentrated to dryness and was used in the next step without purification (1.5 g, 70% yield).

Step B: (*R*)-*tert*-Butyl (3-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-3-oxopropyl)carbamate. To a stirred solution of (R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.30 mmol) in DMF (3 mL) were added 3-(*tert*-butoxycarbonylamino)propanoic acid (170 mg, 0.90 mmol), HATU (230 mg, 0.60 mmol), and diisopropylethylamine (120 mg, 0.93 mmol) and stirred at rt overnight. The solvent was removed and the residue was partitioned between ethyl acetate and water. The organic layer was separated, shaken with brine, and dried over anhydrous Na_2SO_4. The residue was purified by flash column chromatography to yield the title compound as brown solid (50 mg, 25% yield).

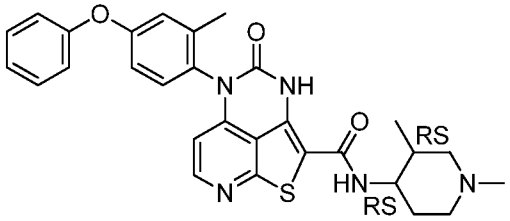
Step C: (*R*)-*N*-(1-(3-Aminopropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (*R*)-*tert*-Butyl (3-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-3-oxopropyl)carbamate (50 mg, 0.075 mmol) in MeOH (15 mL) was added concentrated HCl (1 mL) and was stirred at rt for about 2 h. The reaction was concentrated to dryness and purified by flash column chromatography to yield the title compound as a yellow solid (26 mg, 57% yield). MS (ESI): mass calcd. for $C_{30}H_{30}N_6O_4S$, 570.7; m/z found, 571.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.49 (s, 1H), 8.29-8.21 (m, 1H), 7.44-7.33 (m, 2H), 7.28-7.22 (m, 1H), 7.18-7.10 (m, 1H), 7.10-7.01 (m, 3H), 6.99-6.91 (m, 1H), 6.04-5.94 (m, 1H), 4.29-4.06 (m, 1H), 4.05-3.60 (m, 2H), 3.20-3.09(m, 3H), 3.00-2.74 (m, 2H), 2.13-2.06 (m, 3H), 2.05-1.52 (m, 5H).

Example 164: *N*-((3*R*,5*S*)-5-Fluoro-1-methylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



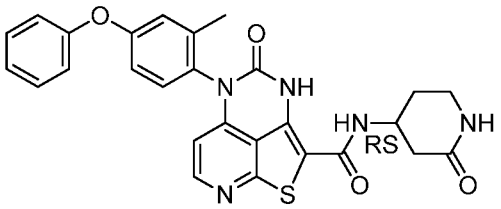
To a solution of *N*-((3*R*,5*S*)-5-fluoropiperidin-*3*-yl)-5-*(*2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 167, 90 mg, 0.16 mmol) and formaldehyde (0.5 mL, 37 wt. % in H_2O) in methanol (25 mL) was added $NaBH(OAc)_3$ (102 mg, 0.481 mmol) and was stirred at rt for 16 h, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a white solid (78 mg, 84% yield). MS (ESI): mass calcd. for $C_{28}H_{26}FN_5O_3S$, 531.6; m/z found, 532.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.29 (d, *J* = 5.5 Hz, 1H), 8.15 (s, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.37-7.30 (m, 1H), 7.23 – 7.15 (m, 1H), 7.14 – 7.05 (m, 3H), 7.00-6.95 (m, 1H), 5.93 (d, *J* = 5.4 Hz, 1H), 4.91 (d, *J* = 47.4 Hz, 1H), 4.27-4.15 (m, 1H), 2.91 – 2.80 (m, 2H), 2.19 (s, 3H), 2.15 – 1.88 (m, 6H), 1.78-1.50 (m, 1H).

Example 165: *N*-(1,3-Dimethylpiperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



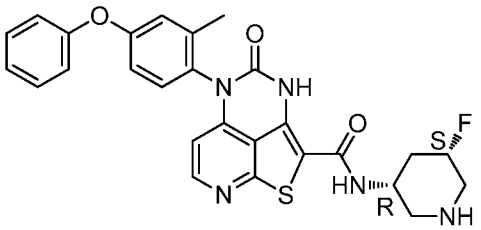
To a solution of 5-(2-methyl-4-phenoxyphenyl)-*N*-(3-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 172, 90 mg, 0.18 mmol) and formaldehyde (0.5 mL, 37 wt. % in H_2O) in methanol (15 mL) was added $NaBH(OAc)_3$ (111 mg, 0.524 mmol) and was stirred at rt for 3 h, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a yellow solid (71 mg, 77% yield). MS (ESI): mass calcd. for $C_{29}H_{29}N_5O_3S$, 527.6; m/z found, 528.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.37-8.20 (m, 1H), 7.45-7.34 (m, 2H), 7.34 – 7.20 (m, 1H), 7.20 – 7.11 (m, 1H), 7.11 – 7.02 (m, 3H), 6.99-6.93 (m, 1H), 6.10-5.94 (m, 1H), 4.35-4.15 (m, 0.5H), 3.74 – 3.55 (m, 0.5H), 3.10-2.68 (m, 3H), 2.65-2.37 (m, 3H), 2.35-2.20 (m, 1H), 2.12 (s, 3H), 2.05 – 1.70 (m, 3H), 1.08 – 0.91 (m, 3H).

Example 166: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(2-oxopiperidin-4-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



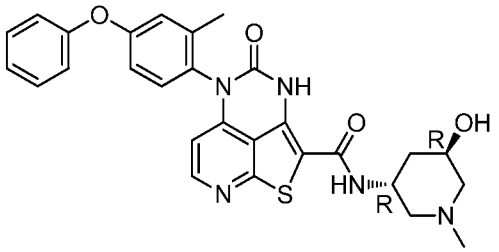
The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1, and using 4-aminopiperidin-2-one in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{23}N_5O_4S$, 513.6; m/z found, 514.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.46-8.30 (br, 1H), 8.30-8.20 (m, 1H), 7.60-7.54 (m, 1H), 7.45-7.39 (m, 2H), 7.34-7.26 (m, 1H), 7.20-7.15 (m, 1H), 7.12-7.07 (m, 2H), 7.07-7.03 (m, 1H), 6.97-6.92 (m, 1H), 5.93-5.83 (m, 1H), 4.20-4.13 (m, 1H), 3.22-3.13 (m, 2H), 2.45-2.41 (m, 1H), 2.31-2.23 (m, 1H), 2.03 (s, 3H), 1.96-1.91 (m, 1H), 1.77-1.68 (m, 1H).

Example 167: *N*-((3*R*,5*S*)-5-fluoropiperidin-*3*-yl)-5-*(*2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



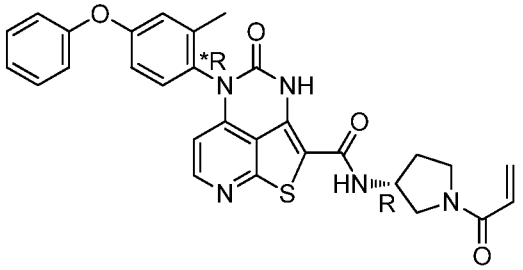
The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using tert-butyl (3R,5S)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 3) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{24}FN_5O_3S$, 517.6; m/z found, 518.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.29 (d, J = 5.5 Hz, 1H), 8.15 (s, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.52-7.38 (m, 2H), 7.34 (d, J = 8.6 Hz, 1H), 7.24-7.15 (m, 1H), 7.15-7.03 (m, 3H), 7.02-6.91 (m, 1H), 5.93 (d, J = 5.5 Hz, 1H), 4.90 (s, 0.5H), 4.78 (s, 0.5H), 4.20-4.09 (m, 1H), 3.05-2.90 (m, 2H), 2.79-2.51 (m, 2H), 2.20-2.07 (m, 1H), 2.04 (s, 3H), 1.98-1.72 (m, 1H).

Example 168: *N*-((3*R*,5*R*)-5-Hydroxy-1-methylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



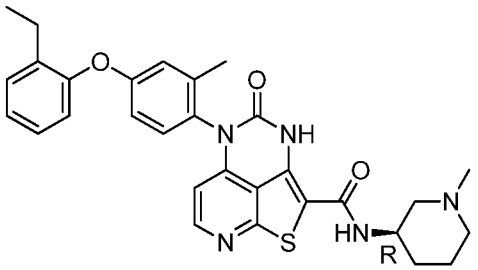
A solution of *N*-((3*R*,5*R*)-5-hydroxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 179, 80 mg, 0.16 mmol) in DCM (5 mL) was treated with formaldehyde (0.5 mL, 37 wt. % in H_2O). To the stirred reaction mixture was added $NaBH(OAc)_3$ (100 mg, 0.47 mmol) and the reaction mixture was maintained at rt for 1 h, and then concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound as a yellow solid (53 mg, 59% yield). MS (ESI): mass calcd. for $C_{28}H_{27}N_5O_4S$, 529.6; m/z found, 530.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.44 (s, 1H), 8.36-8.30 (m, 1H), 7.46-7.37 (m, 2H), 7.34-7.27 (m, 1H), 7.21-7.14 (m, 1H), 7.13-7.04 (m, 3H), 7.01-6.94 (m, 1H), 6.11-6.04 (m, 1H), 4.76-4.61 (m, 1H), 4.28-4.21 (m, 1H), 3.48-3.36 (m, 1H), 3.24-3.10 (m, 1H), 3.08 -2.95 (m, 1H), 2.84-2.75 (m, 4H), 2.12 (s, 3H), 2.09-1.99 (m, 1H), 1.96-1.82 (m, 1H).

Example 169: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-5-(**R*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1 (including Chiral resolution Method A after Step F to obtain the **R* atropisomer), and using *tert*-butyl (3*R*)-3-aminopyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{29}H_{25}N_5O_4S$, 539.6; m/z found, 540.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 8.42-8.25 (m, 2H), 7.52 – 7.31 (m, 3H), 7.24-7.05 (m, 4H), 7.02-6.90 (m, 1H), 6.68-6.48 (m, 1H), 6.13 (d, J = 18.0 Hz, 1H), 6.03-5.93 (m, 1H), 5.72-5.57 (m, 1H), 4.60-4.32 (m, 1H), 3.91-3.35 (m, 4H), 2.24 – 1.91 (m, 5H).

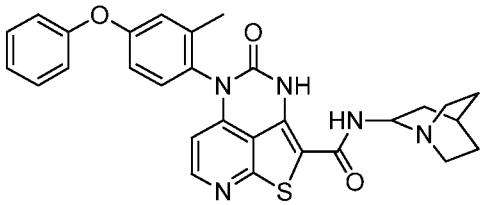
Example 170: (*R*)-5-(4-(2-Ethylphenoxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: (*R*)-5-(4-(2-Ethylphenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using 2-ethylphenol in place of phenol in step A, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

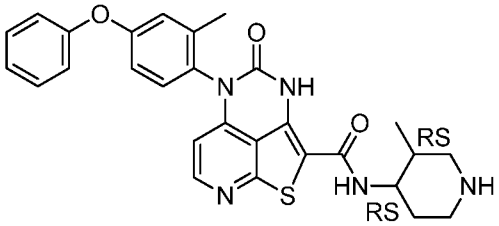
Step B: (*R*)-5-(4-(2-Ethylphenoxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (*R*)-5-(4-(2-ethylphenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (60 mg, 0.11 mmol) in DCM (2 mL) were added formaldehyde (0.5 mL, 37 wt. % in H_2O) and $NaBH(OAc)_3$ (70 mg, 0.33 mmol) and was reacted at rt for 20 min. The reaction was quenched by the addition of H_2O (10 mL), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography and preparative TLC to yield the title compound as a yellow solid (51 mg, 82% yield). MS (ESI): mass calcd. for $C_{30}H_{31}N_5O_3S$, 541.7; m/z found, 544.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.28 (d, J = 5.6Hz, 1H), 7.35-7.29 (m, 1H), 7.27-7.20 (m, 2H), 7.18-7.12 (m, 1H), 7.00-6.93 (m, 2H), 6.88-6.83 (m, 1H), 6.02 (d, J = 5.6Hz, 1H), 4.21-4.06 (m, 1H), 2.96-2.87 (m, 1H), 2.76-2.68 (m, 1H), 2.66-2.56 (m, 2H), 2.33 (s, 3H), 2.26-2.13 (m, 2H), 2.09 (s, 3H), 1.91-1.78 (m, 2H), 1.72-1.63 (m, 1H), 1.55-1.48 (m, 1H), 1.22-1.16 (m, 3H).

Example 171: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(quinuclidin-2-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



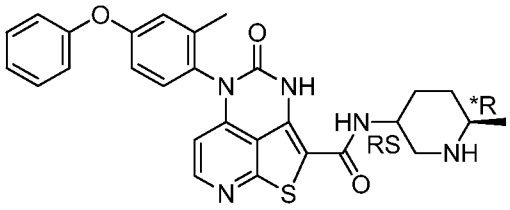
The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1, and using 3-aminoquinuclidine and THF in place of *tert*-butyl (3*R*,5*R*)-3-amino-5-fluoropiperidine-1-carboxylate and DMF in step G. MS (ESI): mass calcd. for $C_{29}H_{27}N_5O_3S$, 525.6; m/z found, 526.0 $[M+H]^+$. 1H NMR (500 MHz, DMSO-d6) δ 8.82 (s, 1H), 8.42 - 8.08 (m, 1H), 7.59 - 7.40 (m, 2H), 7.40 - 7.07 (m, 6H), 7.07 - 6.90 (m, 1H), 6.05 - 5.70 (m, 1H), 4.08 (s, 1H), 3.10 - 2.69 (m, 5H), 2.14 - 1.93 (m, 6H), 1.86 - 1.67 (m, 2H), 1.67 - 1.47 (m, 1H).

Example 172: 5-(2-Methyl-4-phenoxyphenyl)-*N*-(3-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



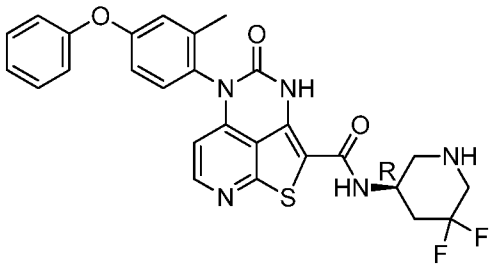
The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using *tert*-butyl 4-amino-3-methylpiperidine-1-carboxylate and THF in place of *tert*-butyl (3*R*,5*R*)-3-amino-5-fluoropiperidine-1-carboxylate and DMF in step G. MS (ESI): mass calcd. for $C_{28}H_{27}N_5O_3S$, 513.6; m/z found, 514.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD and DMSO-d_6): δ 8.34 – 8.24 (m, 1H), 7.44 – 7.33 (m, 2H), 7.28 (d, J = 8.5 Hz, 1H), 7.18-7.09 (m, 1H), 7.10 – 6.99 (m, 3H), 6.97-6.86 (m, 1H), 5.99-5.90 (m, 1H), 4.38 – 4.15 (m, 0.5H), 3.86-3.78 (m, 0.5H), 3.35 – 3.14 (m, 2H), 3.12 – 2.92 (m, 2H), 2.77-2.62 (m, 0.5H), 2.33 – 2.18 (m, 0.5H), 2.03 (s, 3H), 1.97 – 1.77 (m, 2H), 0.98-0.85 (m, 3H).

Example 173: 5-(2-Methyl-4-phenoxyphenyl)-*N*-((6*R*)-6-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



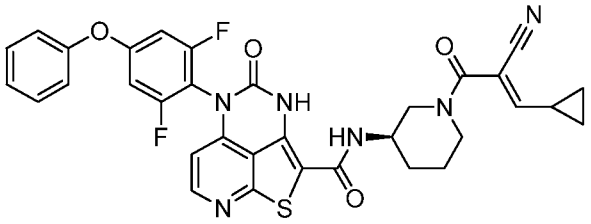
The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using benzyl 5-amino-2-methylpiperidine-1-carboxylate (Intermediate 20) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G and TFA in place of MeOH and aqueous HCl in Step H. Example 153 and Example 173 were separated from the same reaction mixture by flash column chromatography (C-18, MeOH/H_2O) followed by preparative TLC. MS (ESI): mass calcd. for $C_{28}H_{27}N_5O_3S$, 513.6; m/z found, 544.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.40-8.33 (m, 1H), 7.45-7.37 (m, 2H), 7.33-7.26 (m, 1H), 7.21-7.14 (m, 1H), 7.11-7.02 (m, 3H), 7.00-6.92 (m, 1H), 6.12-6.05 (m, 1H), 4.33-4.17 (m, 1H), 3.60-3.48 (m, 1H), 3.23-3.15 (m, 1H), 2.97-2.84 (m, 1H), 2.15-2.04 (m, 5H), 1.84-1.73 (m, 1H), 1.67-1.58 (m, 1H), 1.41-1.32 (m, 3H).

Example 174: (*R*)-*N*-(5,5-Difluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using *tert*-butyl (5*R*)-5-amino-3,3-difluoropiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{23}F_2N_5O_3S$, 535.6; m/z found, 535.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.32 (d, J = 5.5 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.47-7.41 (m, 2H), 7.36 (d, J = 8.6 Hz, 1H), 7.22-7.18 (m, 1H), 7.16-7.05 (m, 3H), 7.01-6.95 (m, 1H), 5.96 (d, J = 5.5 Hz, 1H), 4.10-4.00 (m, 1H), 3.03-2.90 (m, 2H), 2.80-2.66 (m, 1H), 2.45-2.40 (m, 1H), 2.37-2.27 (m, 1H), 2.05 (s, 3H), 2.02-1.94 (m, 1H).

Example 175: (*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2,6-difluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: 1,3-Difluoro-2-nitro-5-phenoxybenzene. To a solution of 3,5-difluoro-4-nitrophenol (Intermediate 26) (493 mg, 2.82 mmol) in CH_3CN (45 mL) was added (2-trimethylsilylphenyl) trifluoromethanesulfonate (1.0 mL, 4.2 mmol), followed by cesium fluoride (1.28 g, 8.45 mmol). The mixture was stirred at rt overnight (argon needle inlet). The reaction mixture was washed with saturated aqueous NaCl (50 mL) and the aqueous phase was extracted once with Et_2O (50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a yellow oil mass (450.7 mg. 64%)

Step B: 2,6-difluoro-4-phenoxyaniline: The title compound was prepared in a manner analogous to Method 1, step B in Example 1, and using 1,3-difluoro-2-nitro-5-phenoxybenzene in place of 2-Methyl-1-nitro-4-phenoxybenzene in step B.

Step C: 2-Chloro-4-(2,6-difluoro-4-phenoxyanilino)pyridine-3-carbonitrile. The title compound was prepared in a manner analogous to Method 1, step C in Example 1, and using 2,6-difluoro-4-phenoxyaniline in place of 2-Methyl-4-phenoxyaniline in step C.

Step D: *tert*-Butyl (3*R*)-3-[(2-sulfanylacetyl)amino]piperidine-1-carboxylate. A 20 mL microwave vial was charged with (*R*)-1-boc-3-aminopiperdine (5.0 g, 25 mmol). The vial was sealed, evacuated, and back-filled with argon three times. Methyl 2-mercaptoacetate (6.7 mL, 170 mmol) was added via syringe in one portion and was heated to 150 °C in an oil bath. After 1 h 35 minutes, the mixture was cooled to rt and purified by flash column chromatography to yield a colorless oil (6.15 g. 90%).

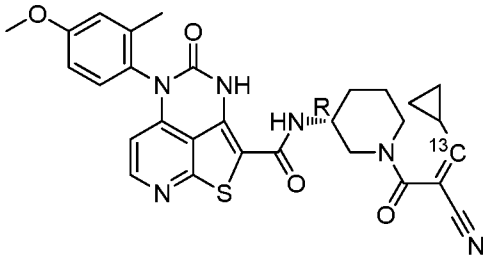
Step E: (*R*)-*tert*-Butyl 3-(3-amino-4-((2,6-difluoro-4-phenoxyphenyl)amino)thieno[2,3-*b*]pyridine-2-carboxamido)piperidine-1-carboxylate. To the sealed tube containing 2-chloro-4-(2,6-difluoro-4-phenoxyanilino)pyridine-3-carbonitrile (580 mg, 1.6 mmol) was added a 0.56 M solution of *tert*-butyl (3*R*)-3-[(2-sulfanylacetyl)amino]piperidine-1-carboxylate in dioxane (3.5 mL, 1.9 mmol). The resulting brown suspension was heated in the sealed tube under argon at

150 °C in an oil bath for 15 minutes. The mixture was cooled to rt and was used directly in the next reaction.

Step F: (*R*)-*tert*-butyl 3-(5-(2,6-difluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3 *H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate. To a solution of (*R*)-*tert*-butyl 3-(3-amino-4-((2,6-difluoro-4-phenoxyphenyl)amino)thieno[2,3-*b*]pyridine-2-carboxamido)piperidine-1-carboxylate (966 mg, 1.62 mmol) in dioxane (3.5 mL) was added CDI (1.05 g, 6.49 mmol) and was heated at 150 °C in an oil bath for 10 minutes. The mixture was cooled to rt and was partitioned between EtOAc (50 mL) and water (50 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL) and the combined organic extracts were washed with saturated aqueous NaCl (50 mL). The organic phase was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to dryness and the residue was purified by flash column chromatography to yield the title compound as a tan solid (562 mg, 56%).

Step G: (*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2,6-difluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A suspension of (*R*)-5-(2,6-difluoro-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 235) (28.6 mg, 0.0548 mmol) in THF (2 mL) was sonicated to produce a milky suspension. To this suspension was added triethylamine (11 µL, 0.082 mmol) followed by a solution of (*E*)-2-cyano-3-cyclopropylprop-2-enoyl chloride (Intermediate 23) (0.060 mmol) in $CHCl_3$ (from step H above). The reaction mixture was stirred at rt for 1 h, concentrated to dryness, and purified by flash column chromatography and HPLC to yield the title compound as a white solid (17.9 mg, 51%). MS (ESI): mass calcd. for $C_{33}H_{26}F_2N_6O_4S$, 640.7; m/z found, 641.3 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 9.42 - 9.68 (m, 1H), 8.45 (d, J = 5.56 Hz, 1H), 7.39 - 7.55 (m, 2H), 7.29 (t, J = 7.33 Hz, 1H), 7.14 (d, J = 7.58 Hz, 2H), 6.70 (d, J = 9.09 Hz, 2H), 6.28 (d, J = 6.06 Hz, 1H), 4.13 – 4.22 (m, 1H), 3.39-4.02 (m, 3H), 1.65 – 2.16 (m, 6H), 1.21 – 1.33 (m, 3H), 0.92 – 1.04 (m, 1H).

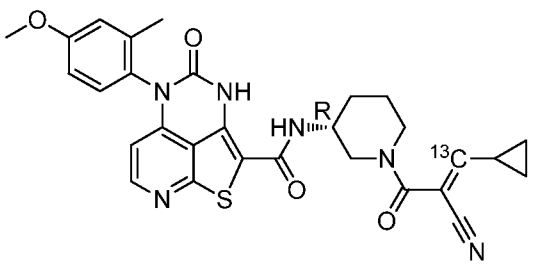
Example 176: ^{13}C-(*R*,*Z*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: ^{13}C-Cyclopropanecarbaldehyde. A solution of ^{13}C-*N*,*N*-dimethylformamide (500 mg, 6.75 mmol) in THF (10 mL) was slowly added to cyclopropylmagnesiumbromide in THF (0.5 M, 15 mL, 7.4 mmol) in an ice bath under N_2 over a period of 5 min. The mixture was brought to rt and stirred for 1 h, then the mixture was acidified with 3 M aqueous HCl, extracted with Et_2O, dried over anhydrous Na_2SO_4, and concentrated to dryness to yield the title compound as a pale yellow oil (320 mg, 62%), which was used without purification in next step.

Step B: ^{13}C-(*R*,*Z*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A solution of (*R*)-5-(4-methoxy-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (prepared as in Example 110, Step B, 250 mg, 0.57 mmol), 2-cyanoacetic acid (97 mg, 1.1 mmol), triethylamine (115 mg, 1.14 mmol), and HATU (434 mg, 1.14 mmol) in DMF (3 mL) was stirred at rt for 3 h. The reaction was quenched by the addition of water and the precipitate was filtered to give a pale yellow solid. To a mixture of this solid and ^{13}C-cyclopropanecarbaldehyde (122 mg, 1.71 mmol) in EtOH (5 mL) was added piperidine (97 mg, 1.1 mmol) and was stirred at rt for 1 h, concentrated to dryness, and purified by by flash chromatography (C-18, MeOH/H_2O) to yield the title compound as a white solid (12 mg, 4%). MS (ESI): mass calcd. for $C_{29}H_{28}N_6O_4S$, 557.6; m/z found, 558.4 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6 and CD_3OD): δ 8.25 (d, *J* = 5.3 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 6.97 (s, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 6.53-6.01(m, 1H), 5.86 (d, *J* = 5.3 Hz, 1H), 4.39-4.21 (m, 1H), 3.90-3.84 (m, 1H), 3.78 (s, 3H), 3.72-3.63 (m, 1H), 3.30-3.13 (m, 1H), 2.95-2.84 (m, 1H), 2.03 (s, 3H), 2.00-1.89 (m, 2H), 1.86-1.78 (m, 1H), 1.68-1.63 (m, 1H), 1.52-1.44 (m, 1H), 1.09-0.97 (m, 2H), 0.82-0.75 (m, 2H).

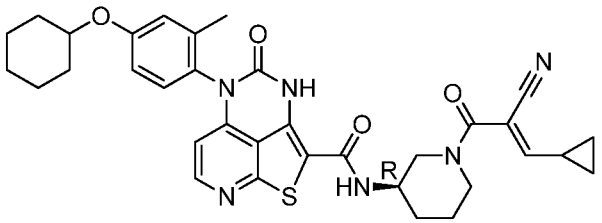
Example 177: ^{13}C-(*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was made using the same procedure as described in Example 176, but the other isomer was isolated by flash chromatography (C-18, MeOH/H_2O). MS (ESI): mass calcd. for $C_{29}H_{28}N_6O_4S$, 557.6; m/z found, 558.4 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6 and

CD_3OD): δ 8.26 (d, *J* = 5.4 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 6.97 (s, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.77-6.24 (m, 1H), 5.88 (d, *J* = 5.4 Hz, 1H), 3.95-3.82 (m, 2H), 3.78 (s, 3H), 3.71-3.57 (m, 1H), 3.10-2.76 (m, 2H), 2.03 (s, 3H), 1.97-1.86 (m, 2H), 1.82-1.75 (m, 1H), 1.71-1.61 (m, 1H), 1.503-1.43(m, 1H), 1.16-1.09 (m, 2H), 1.00-0.88 (m, 1H), 0.84-0.77 (m, 1H).

Example 178: (*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-(cyclohexyloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



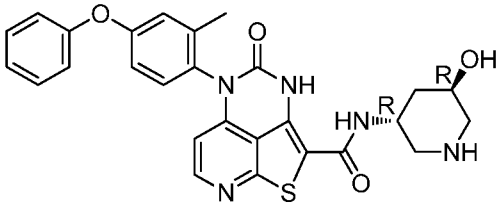
Step A: 2-Chloro-4-[4-(cyclohexoxy)-2-methylanilino]pyridine-3-carbonitrile. To a cold (0 °C) solution of 2-chloro-4-(4-hydroxy-2-methylanilino)pyridine-3-carbonitrile (Intermediate 14) (1.0 g, 3.8 mmol), cyclohexanol (1.16 g, 11.6 mmol), and PPh_3 (1.5 g, 5.7 mmol) in THF (20 mL) was added DIAD (1.17 g, 5.79 mmol) and was stirred at rt overnight. The mixture was concentrated to dryness and the residue was purified by flash column chromatography to yield the title compound as a yellow solid (400 mg, 30% yield).

Step B: (*R*)-5-(4-(Cyclohexyloxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps D-H in Example 1, and using 2-chloro-4-[4-(cyclohexoxy)-2-methylanilino]pyridine-3-carbonitrile in place of 2-chloro-4-(2-methyl-4-phenoxyanilino)pyridine-3-carbonitrile in step D, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

Step C: (*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-(cyclohexyloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a stirred solution of (*R*)-5-(4-(cyclohexyloxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (100 mg, 0.20 mmol) in DMF (3 mL) were added (*E*)-2-cyano-3-cyclopropylprop-2-enoic acid (Intermediate 17) (43 mg, 0.31 mmol), HATU (120 mg, 0.32 mmol), and diisopropylethylamine (67 mg, 0.52 mmol) and was stirred at rt overnight, concentrated to dryness, and the residue partitioned between ethyl acetate and water. The organic layer was separated, shaken with brine, and dried over anhydrous

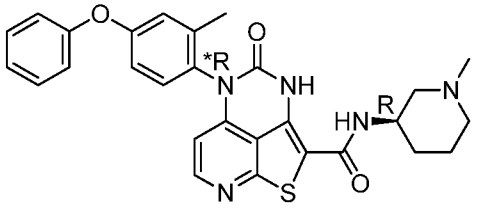
Na_2SO_4. The residue was purified by flash column chromatography to yield the title compound as a brown solid (26 mg, 16% yield). MS (ESI): mass calcd. for $C_{34}H_{36}N_6O_4S$, 624.8; m/z found, 625.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.46 (s, 1H), 8.31 (d, J = 5.5 Hz, 1H), 7.22-7.14(m, 1H), 7.01-6.95 (m, 1H), 6.95-6.88 (m, 1H), 6.60-6.48 (m, 1H), 6.03 (d, J = 5.5 Hz, 1H), 4.44-4.33 (m, 1H), 4.11-3.94 (m, 2H), 2.10 (s, 3H), 2.06-1.95 (m, 4H), 1.94-1.65 (m, 5H), 1.64-1.26 (m, 10H), 1.25-1.14 (m, 2H), 1.06-0.77 (m, 2H).

Example 179: *N*-((3*R*,5*R*)-5-Hydroxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using *tert*-butyl (3*R*,5*R*)-3-amino-5-hydroxypiperidine-1-carboxylate (Intermediate 4) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{25}N_5O_4S$, 515.6; m/z found, 516.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.24 (d, J = 5.6 Hz, 1H), 7.45-7.35 (m, 2H), 7.29-7.23(m, 1H), 7.20-7.13 (m, 1H), 7.12-7.04 (m, 3H), 7.00-6.94 (m, 1H), 5.98 (d, J = 5.6 Hz, 1H), 4.52-4.37 (m, 1H), 4.09-3.98 (m, 1H), 3.22-3.11 (m, 1H), 2.91-2.81 (m, 2H), 2.76-2.65 (m, 1H), 2.12 (s, 3H), 2.07-1.87 (m, 2H).

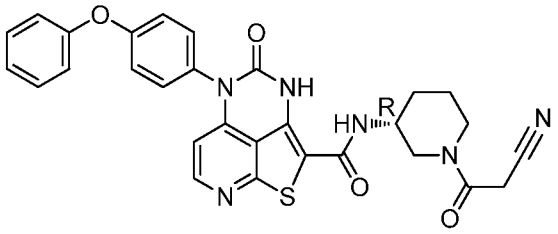
Example 180: (*R*)-5-(**R*)-(2-Methyl-4-phenoxyphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1 (including Chiral resolution Method A after Step F to obtain the **R* atropisomer), and using (3*R*)-1-methylpiperidin-3-amine in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{28}H_{27}N_5O_3S$, 513.6; m/z found, 514.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.31 (d, J = 5.5, 1H), 7.46-7.36 (m, 2H),

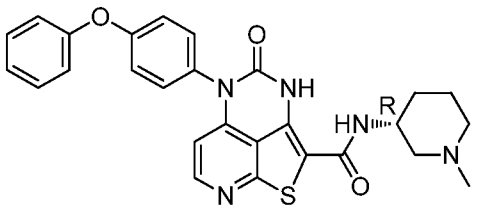
7.33-7.24 (m, 1H), 7.22-7.14 (m, 1H), 7.12-7.02 (m, 3H), 7.02-6.93 (m, 1H), 6.05 (d, J = 5.6, 1H), 4.24-4.11 (m, 1H), 3.02-2.89 (m, 1H), 2.80-2.66 (m, 1H), 2.36 (s, 3H), 2.31-2.17 (m, 2H), 2.12 (s, 3H), 1.94-1.80 (m, 2H), 1.75-1.61 (m, 1H), 1.56-1.45 (m, 1H).

Example 181: (*R*)-*N*-(1-(2-Cyanoacetyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To an oven dried microwave vial with a stir bar under Ar were added (*R*)-4-oxo-5-(4-phenoxyphenyl)-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 860, 313.4 mg, 0.523 mmol), cyanoacetic acid (72 mg, 0.84 mmol), HATU (258 mg, 0.680 mmol), and triethylamine (0.147 mL, 1.04 mmol) in THF (2.1 mL) and was warmed in the microwave for 5 min at 100 °C. The reaction mixture was filtered and purified by HPLC to yield the title compound (203 mg, 58% yield). MS (ESI): mass calcd. for $C_{29}H_{24}N_6O_4S$, 552.6; m/z found, 553.0 $[M+H]^+$. ^1H NMR (500 MHz, CD_3OD): δ 8.42 - 8.24 (m, 1H), 7.50 - 7.37 (m, 4H), 7.24 - 7.05 (m, 5H), 6.27 - 6.13 (m, 1H), 4.53 - 4.30 (m, 1H), 4.03 - 3.60 (m, 4H), 3.23 - 2.68 (m, 2H), 2.16 - 1.48 (m, 4H).

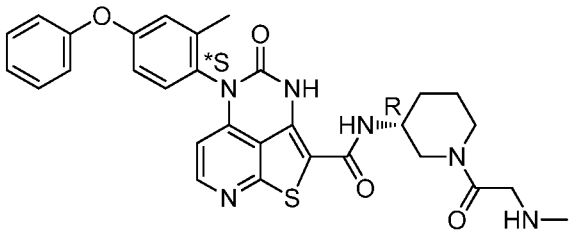
Example 182: (*R*)-*N*-(1-Methylpiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To an oven dried microwave vial with a stir bar under Ar were added (*R*)-4-oxo-5-(4-phenoxyphenyl)-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 860, 69.5 mg, 0.143 mmol), sodium cyanoborohydride (19.7 mg, 0.313 mmol), and MeOH (3 mL) and was cooled to 0 °C in an ice bath. Next, was added via a syringe was aqueous formaldehyde (0.01 mL, 37 wt. % in H_2O) and allowed to slowly warm to rt. The reaction mixture was filtered and purified by HPLC to yield the title compound as a white fluffy

solid (25.3 mg, 35% yield). MS (ESI): mass calcd. for $C_{27}H_{25}N_5O_3S$, 499.6; m/z found, 500.1 $[M+H]^+$. ^1H NMR (500 MHz, CD_3OD): δ 8.27 (d, J = 5.6 Hz, 1H), 7.50 - 7.31 (m, 4H), 7.24 - 7.03 (m, 6H), 6.14 (d, J = 5.6 Hz, 1H), 4.27 - 4.05 (m, 1H), 2.99 - 2.63 (m, 2H), 2.33 (s, 3H), 2.25 - 2.07 (m, 2H), 1.97 - 1.41 (m, 4H).

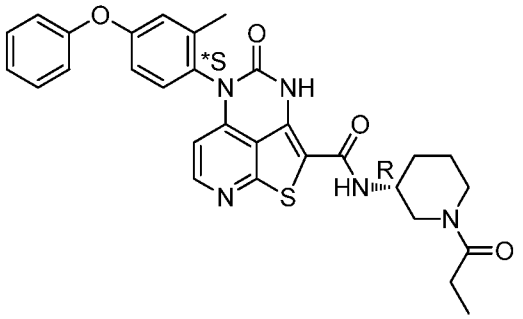
Example 183: (*R*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)-*N*-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: (*R*)-*tert*-Butyl methyl(2-(3-(5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-2-oxoethyl)carbamate. To a solution of (*R*)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 98, 30 mg, 0.056 mmol), 2-[*tert*-butoxycarbonyl(methyl)amino]acetic acid (Intermediate 21) (16 mg, 0.085 mmol), HATU (28 mg, 0.074 mmol), and triethylamine (0.031 mL, 0.22 mmol) were added to DMF (1.5 mL). The reaction mixture was stirred at rt overnight, then purified by flash column chromatography and preparative TLC to yield the title compound as a yellow solid.

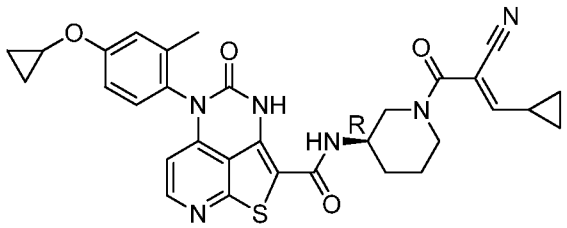
Step B: (*R*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)-*N*-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A solution of (*R*)-*tert*-butyl methyl(2-(3-(5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-2-oxoethyl)carbamate (25 mg, 0.037 mmol) in HCl/MeOH (2 M, 2 mL) was stirred at rt for 4 h, then the pH was adjusted to pH >7 with saturated $NaHCO_3$, and purified by flash column chromatography and preparative TLC to yield the title compound as a yellow solid (5 mg, 24% yield). MS (ESI): mass calcd. for $C_{30}H_{30}N_6O_4S$, 570.7; m/z found, 571.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.16-8.07 (m, 1H), 7.43-7.35 (m, 2H), 7.23-7.12 (m, 2H), 7.11-7.05 (m, 2H), 7.04-7.01 (m, 1H), 7.01-6.91 (m, 1H), 5.90-5.75 (m, 1H), 4.26-4.09 (m, 2H), 3.97-3.89 (m, 1H), 3.84-3.78 (m, 1H), 3.73-3.55 (m, 2H), 3.48-3.41 (m, 1H), 2.60-2.49 (m, 3H), 2.15-2.08 (m, 3H), 2.02-1.87 (m, 3H), 1.85-1.73 (m, 1H), 1.67-1.56 (m, 1H).

Example 184: (*R*)-5-(**S*)-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(1-propionylpiperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(**S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 98, 30 mg, 0.06 mmol), triethylamine (15 mg, 0.015 mmol), and propanoyl propanoate (15 mg, 0.12 mmol) in DCM (15 mL) was stirred for 30 min at rt. The mixture was purified by flash column chromatography to yield the title compound as yellow solid (19 mg, 57% yield). MS (ESI): mass calcd. for $C_{30}H_{29}N_5O_4S$, 555.6; m/z found, 556.6 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.34-8.28 (m, 1H), 7.51-7.35 (m, 2H), 7.34-7.27 (m, 1H), 7.21-7.13 (m, 1H), 711-7.02 (m, 3H), 7.00-6.93 (m, 1H), 6.09-6.01 (m, 1H), 4.54-3.83 (m, 3H), 3.16-2.97 (m, 1H), 2.85-2.65 (m, 1H), 2.59-2.36 (m, 2H), 2.15-2.09 (m, 3H), 2.09- 2.00 (m, 1H), 1.91-1.51 (m, 3H), 1.17-1.09 (m, 3H).

Example 185: (*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-cyclopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

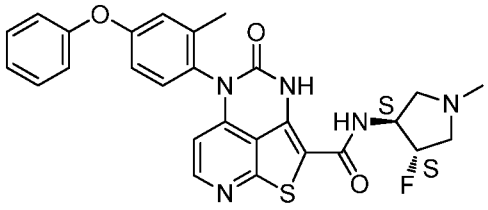


Step A: 4-cyclopropoxy-2-methyl-1-nitrobenzene. The title compound was prepared using the method from Example 33, Step A, using bromocyclopropane in place of 2-iodopropane.

Step B: (R)-5-(4-Cyclopropoxy-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps B-H in Example 1, and using 4-cyclopropoxy-2-methyl-1-nitrobenzene in place of 2-methyl-1-nitro-4-phenoxybenzene in Step B, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

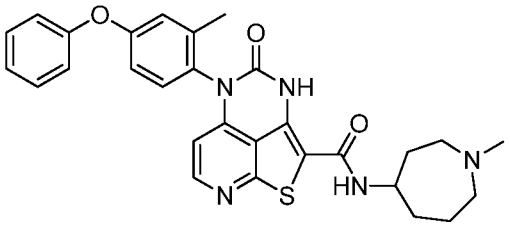
Step C: (*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-cyclopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A solution of (*R*)-5-(4-cyclopropoxy-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (80 mg, 0.17 mmol), (*E*)-2-cyano-3-cyclopropylprop-2-enoic acid (Intermediate 17) (48 mg, 0.35 mmol), HATU (85 mg, 0.22 mmol), and diisopropylethylamine (44 mg, 0.35 mmol) in DMF (5 mL) was stirred at rt for 2 h. The mixture was purified by HPLC to yield the title compound as a white solid (27 mg, 27% yield). MS (ESI): mass calcd. for $C_{31}H_{30}N_6O_4S$, 582.7; m/z found, 583.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33-8.27 (m, 1H), 7.25-7.20 (m, 1H), 7.14-7.10 (m, 1H), 7.10-7.04 (m, 1H), 6.57-6.49 (m, 1H), 6.04-5.99 (m, 1H), 4.14-3.93 (m, 3H), 3.89-3.79 (m, 1H), 3.25-3.05 (m, 2H), 2.12 (s, 3H), 2.09-1.95 (m, 2H), 1.93-1.83 (m, 1H), 1.82-1.70 (m, 1H), 1.68-1.59 (m, 1H), 1.25-1.15 (m, 2H), 1.01-0.91 (m, 1H), 0.87-.077 (m, 3H), 0.75-0.69 (m, 2H).

Example 186: *N*-((3*S*,4*S*)-4-Fluoro-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a solution of *N*-((3*S*,4*S*)-4-fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 218, 100 mg, 0.2 mmol) and formaldehyde (0.5 mL, 37 wt. % in H_2O) in MeOH (5 mL) was added $NaBH(OAc)_3$ (127 mg, 0.597 mmol) and was stirred at rt for 1 h, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a white solid (86 mg, 80% yield). MS (ESI): mass calcd. for $C_{27}H_{24}FN_5O_3S$, 517.6; m/z found, 518.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.28 (d, J = 5.5Hz, 1H), 7.42-7.35 (m, 2H), 7.35-7.30 (m, 1H), 7.18-7.12 (m, 1H), 7.09-7.01 (m, 3H), 6.99-6.92 (m, 1H), 6.04 (d, J = 5.5Hz, 1H), 5.39-5.18 (m, 1H), 4.66-4.51 (m, 1H), 3.64-3.53 (m, 1H), 3.43-3.37 (m, 1H), 3.36-3.30(m, 1H), 3.05-2.95 (m, 1H), 2.70 (s, 3H), 2.08 (s, 3H).

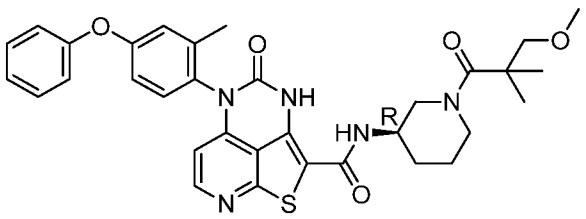
Example 187: 5-(2-Methyl-4-phenoxyphenyl)-*N*-(1-methylazepan-4-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: *N*-(Azepan-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using *tert*-butyl 4-aminoazepane-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

Step B: 5-(2-Methyl-4-phenoxyphenyl)-*N*-(1-methylazepan-4-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of *N*-(azepan-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (100 mg, 0.2 mmol) and formaldehyde (0.4 mL, 37 wt. % in H_2O) in MeOH (5 mL) was added $NaBH(OAc)_3$ (124 mg, 0.585 mmol) and was stirred at rt for 1 h, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a yellow solid (70 mg, 68% yield). MS (ESI): mass calcd. for $C_{29}H_{29}N_5O_3S$, 527.6; m/z found, 528.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.24 (d, *J* = 5.4 Hz, 1H), 7.45-7.33 (m, 2H), 7.32-7.22 (m, 1H), 7.22-12 (m, 1H), 7.11-7.01 (m, 3H), 7.01-6.92 (m, 1H), 5.98 (d, *J* = 5.4 Hz, 1H), 4.27-4.15 (m, 1H), 3.09-2.98 (m, 1H), 2.96-2.79 (m, 3H), 2.54 (s, 3H), 2.16-2.06 (m, 5H), 2.02-1.87 (m, 2H), 1.83-1.70 (m, 2H).

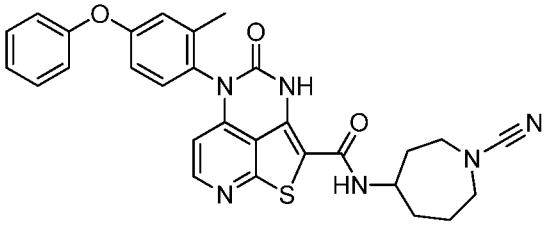
Example 188: (*R*)-*N*-(1-(3-Methoxy-2,2-dimethylpropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 110 mg, 0.22 mmol) in DMF (3 mL) were added 3-methoxy-2,2-dimethylpropanoic acid (44 mg, 0.33 mmol), HATU (100 mg, 0.26 mmol), and triethylamine (0.123 mL, 0.880 mmol) and was stirred at rt for 4 h. The reaction mixture was purified by flash column chromatography to yield the title compound as a yellow solid 50 mg, 36% yield). MS (ESI): mass calcd. for $C_{33}H_{35}N_5O_5S$, 613.7; m/z found,

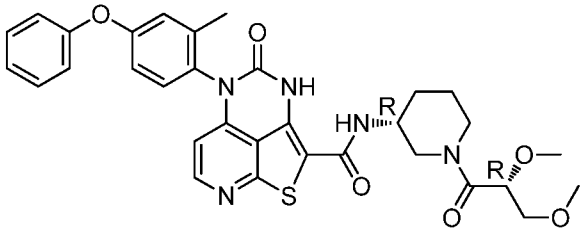
614.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33 (d, J = 5.6, 1H), 7.46-7.36 (m, 2H), 7.34-7.26 (m, 1H), 7.20-7.13 (m, 1H), 7.12-7.02 (m, 3H), 7.00-6.91 (m, 1H), 6.13-6.02 (m, 1H), 4.44-4.23 (m, 2H), 4.03-3.92 (m, 1H), 3.60-3.51 (m, 1H), 3.47-3.39 (m, 1H), 3.36 (s, 3H), 3.01-2.92 (m, 1H), 2.92-2.83 (m, 1H), 2.12 (s, 3H), 2.08-2.01 (m, 1H), 1.85-1.79 (m, 1H), 1.77-1.65 (m, 1H), 1.63-1.50 (m, 1H), 1.30 (s, 6H).

Example 189: *N*-(1-Cyanoazepan-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-I in Example 1, and using *tert*-butyl 4-aminoazepane-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G, and using bromocyanide in place of prop-2-enoyl chloride in step I. MS (ESI): mass calcd. for $C_{29}H_{26}N_6O_3S$, 538.6; m/z found, 539.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.32 (d, J = 5.6 Hz, 1H), 7.44-7.36 (m, 2H), 7.28 (d, J = 8.6 Hz, 1H), 7.21-7.13 (m, 1H), 7.12-7.03 (m, 3H), 7.01-6.92 (m, 1H), 6.07 (d, J = 5.6 Hz, 1H), 4.12-4.00 (m, 1H), 3.50-3.38 (m, 2H), 3.33-3.30 (m, 1H), 3.28-3.24 (m, 1H), 2.14-2.08 (m, 4H), 2.05-1.88 (m, 3H), 1.85-1.69 (m, 2H).

Example 190: *N*-((*R*)-1-((*R*)-2,3-Dimethoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3 *H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



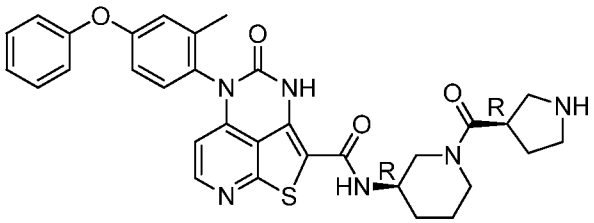
Step A: Methyl (2*R*)-2-hydroxy-3-methoxypropanoate. To a solution of methyl cyclopropanecarboxylate (1.0 g, 9.8 mmol) in MeOH (1 mL) was added $Mg_2(SO_3CF_3)_2$ (4.05 g, 11.7 mmol) at rt and warmed to 40 °C for 16 h. The reaction mixture was filtered, washed with DCM, and concentrated to dryness to yield the title compound as a colorless oil (900 mg, 69%).

Step B: Methyl (2*R*)-2,3-dimethoxypropanoate. To a solution of methyl (2*R*)-2-hydroxy-3-methoxypropanoate (900 mg, 6.7 mmol) in DCM (10 mL) were added methyl iodide (1.90 g, 13.4 mmol) and Ag_2O (2.32 g, 10.0 mmol) at rt. The reaction was warmed to 40 °C for 16 h, filtered, washed with DCM, and concentrated to dryness to yield the title compound as a colorless oil (400 mg, 40%).

Step C: (2*R*)-2,3-Dimethoxypropanoic acid. A solution of methyl (2*R*)-2,3-dimethoxypropanoate (400 mg, 2.7 mmol), $LiOH•H_2O$ (454 mg, 10.8 mmol) in dimethoxymethane (4 mL) and H_2O (1 mL) was reacted at rt for16 h. The pH was adjusted to pH <7, extracted with DCM, concentrated to remove the DCM, which yielded the title compound as a colorless oil as a solution in dimethoxymethane (3.0 g).

Step D: *N*-((*R*)-1-((*R*)-2,3-Dimethoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3 *H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (2*R*)-2,3-dimethoxypropanoic acid (50 mg, 0.37 mmol) in DCM (5 mL) was added oxalyl dichloride (2 mL) and reacted at 60 °C overnight. The reaction mixture was concentrated to dryness and dissolved in DCM (5 mL). The mixture was added to solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 80 mg, 0.16 mmol) and triethylamine (40 mg, 0.40 mmol) in DCM (5 mL) and reacted at rt for 30 min. The reaction was quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound as an off white solid (30 mg, 30%). MS (ESI): mass calcd. for $C_{32}H_{33}N_5O_6S$, 615.7; m/z found, 616.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.41-8.27 (m, 1H), 7.46-7.34 (m, 2H), 7.33-7.26 (m, 1H), 7.27-7.17 (m, 1H), 7.15-7.02 (m, 3H), 7.02-6.95 (m, 1H), 6.12-6.03 (m, 1H), 4.68-4.47 (m, 3H), 4.41-3.89 (m, 3H), 3.77-3.55 (m, 2H), 3.44-3.36 (m, 4H), 3.52-3.12 (m, 1H), 3.01-2.77 (m, 1H), 2.19-2.11(m, 3H), 2.07-2.01 (m, 1H), 1.93-1.81 (m, 1H), 1.78-1.49 (m, 2H).

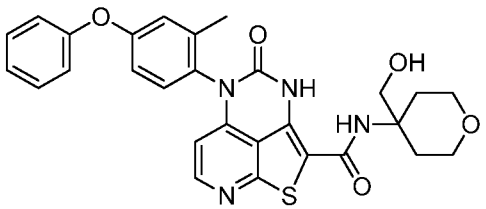
Example 191: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-((*R*)-1-((*R*)-pyrrolidine-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: (*R*)-*tert*-butyl 3-((*R*)-3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carbonyl)pyrrolidine-1-carboxylate. A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 300 mg, 0.60 mmol), (3*R*)-1-*tert*-butoxycarbonylpyrrolidine-3-carboxylic acid (258 mg, 1.20 mmol), HATU (456 mg, 1.20 mmol), and triethylamine (121 mg, 1.20 mmol) in DMF (5 mL) was reacted at rt for 2 h. The reaction was quenched with H_2O (10 mL), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound as a yellow solid (350 mg, 83% yield).

Step B: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-((*R*)-1-((*R*)-pyrrolidine-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (*R*)-*tert*-butyl 3-((*R*)-3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carbonyl)pyrrolidine-1-carboxylate (350 mg, 0.50 mmol) in MeOH (5 mL) was added HCl (37%, 2 mL) and was reacted at rt for 1 h. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (20 mL), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to yield the title compound as a yellow solid (200 mg, 67% yield). MS (ESI): mass calcd. for $C_{32}H_{32}N_6O_4S$, 596.7; m/z found, 597.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.43 (s, 1H), 8.36-8.30 (m, 1H), 7.44-7.34 (m, 2H), 7.33-7.25 (m, 1H), 7.20-7.13 (m, 1H), 7.11-7.02 (m, 3H), 7.00-6.92 (m, 1H), 6.13-6.03 (m, 1H), 4.52-4.33 (m, 1H), 4.24-3.87 (m, 2H), 3.75-3.61 (m, 2H), 3.44-3.31 (m, 3H), 3.09-2.62 (m, 2H), 2.40-2.15 (m, 1H), 2.15-1.99 (m, 5H), 1.92-1.50 (m, 3H).

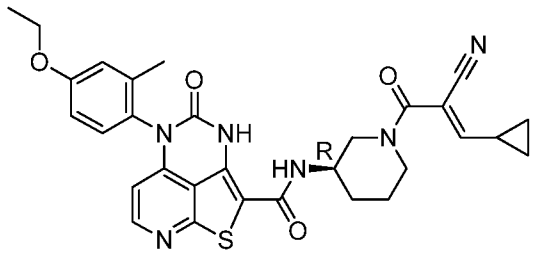
Example 192: *N*-(4-(Hydroxymethyl)tetrahydro-2*H*-pyran-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1, and using (4-aminotetrahydropyran-4-yl)methanol in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{28}H_{26}N_4O_5S$, 530.6; m/z found, 531.7 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 10.14 (s,

1H), 8.35-8.23 (m, 1H), 7.48-7.41 (m, 2H), 7.38-7.30 (m, 1H), 7.24-7.17 (m, 1H), 7.16-7.06 (m, 3H), 7.01-6.94 (m, 1H), 6.00-5.86 (m, 1H), 5.08-4.90 (m, 1H), 3.71-3.52 (m, 6H), 2.29-2.12 (m, 2H), 2.06 (s, 3H), 1.68-1.56 (m, 2H).

Example 193: (*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-ethoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



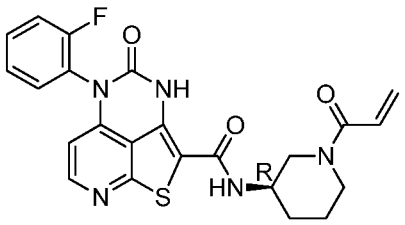
Step A: Step A: 4-Ethoxy-2-methyl-1-nitrobenzene. To a mixture of 3-methyl-4-nitrophenol (5.0 g, 33 mmol) and K_2CO_3 (13.6 g, 98.6 mmol) in DMF (25 mL) was added bromoethane (8.9 g, 82 mmol) and the reaction was stirred at 80 °C overnight. Water was added to the reaction mixture and a yellow solid was precipitated. The precipitate was filtered, washed with water, and dried to yield the title compound (4.5 g, 76% yield) as a yellow solid.

Step B: (*R*)-5-(4-Ethoxy-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps B-H in Example 1, and using 4-ethoxy-2-methyl-1-nitrobenzene in place of 2-methyl-1-nitro-4-phenoxybenzene Step B, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

Step C: (*R*,*E*)-*N*-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-ethoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a stirred suspension of (*R*)-5-(4-ethoxy-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (100 mg, 0.22 mmol) in DMF (3 mL) were added (*E*)-2-cyano-3-cyclopropylprop-2-enoic acid (Intermediate 17) (36 mg, 0.26 mmol), HATU (100 mg, 0.26 mmol), and diisopropylethylamine (60 mg, 0.46 mmol) and was stirred at rt overnight. The reaction mixture was concentrated to dryness and the residue was partitioned between ethyl acetate and water. The organic layer was separated, shaken with brine, dried over anhydrous Na_2SO_4, and purified by flash column chromatography to yield the title compound as a brown solid (73 mg, 56% yield). MS (ESI): mass calcd. for $C_{30}H_{30}N_6O_4S$, 570.7; m/z found, 571.9 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.29 (d, J = 5.2 Hz, 1H), 7.26-7.16 (m, 1H),

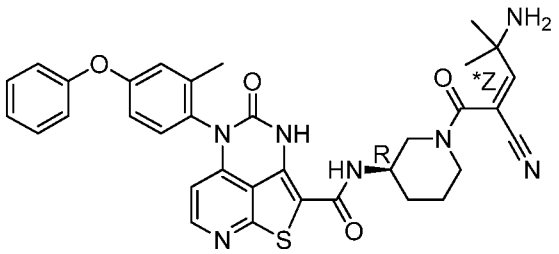
7.01-6.94(m, 1H), 6.93-6.87 (m, 1H), 6.60-6.47 (m, 1H), 6.04-5.97 (m, 1H), 4.27-3.88 (m, 5H), 3.25-3.00 (m, 1H), 2.14-2.09 (m, 3H), 2.09-1.49 (m, 6H), 1.46-1.35 (m, 3H), 1.25-1.13 (m, 2H), 1.04-0.70 (m, 2H).

Example 194: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-5-(2-fluorophenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps C-I in Example 1, and using 2-fluoroaniline in place of 2-methyl-4-phenoxyaniline in step C, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{23}H_{20}FN_5O_3S$, 465.5; m/z found, 466.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.37 (s, 1H), 8.33 (d, J = 5.4 Hz, 1H), 8.24-8.03 (m, 1H), 7.68-7.54 (m, 2H), 7.54-7.46 (m,, 1H), 7.44-7.33 (m, 1H), 6.87-6.64 (m, 1H), 6.15-5.97 (m, 2H), 5.65 (d, J = 10.6 Hz, 1H), 4.55 -4.11 (m, 1H), 4.10-3.88 (m, 1H), 3.79-3.69 (br, 1H), 3.14- 2.90 (m, 1H), 2.83-2.57 (m, 1H), 2.05-1.85 (m, 1H), 1.83-1.52 (m, 2H), 1.52-1.29 (m, 1H).

Example 195: (*R*,*Z*)-*N*-(1-(4-Amino-2-cyano-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

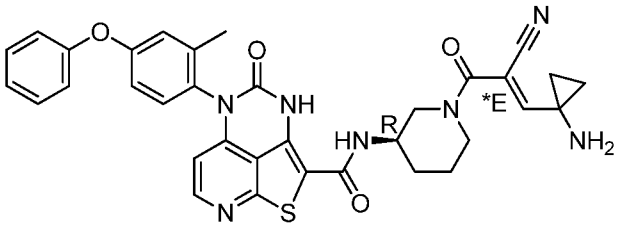


Step A: (*R*,*Z*)-*tert*-Butyl (4-cyano-2-methyl-5-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-5-oxopent-3-en-2-yl)carbamate. A solution of ((*R*)-*N*-(1-(2-cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 874, 300 mg, 0.53 mmol), *tert*-butyl *N*-(1,1-dimethyl-2-oxo-ethyl)carbamate (297 mg,

1.59 mmol), piperdine (0.5 mL), acetic acid (0.2 mL), dioxane (15 mL), and 4A molecular sieves (1 g) were added to a flask and stirred at 100 °C for 1 h under N_2. The mixture was concentrated to dryness and purified by flash column chromatography to yield the title compound as a light yellow solid (188 mg, 48.2% yield).

Step B: (*R,Z*)-*N*-(1-(4-Amino-2-cyano-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (*R,Z*)-*tert*-butyl (4-cyano-2-methyl-5-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-5-oxopent-3-en-2-yl)carbamate (188 mg, 0.255 mmol) in MeOH (5 mL) was added concentrated HCl (5 mL) and stirred at rt for 10 min. The mixture was concentrated to dryness, diluted with DCM, washed with saturated $NaHCO_3$ and brine, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a yellow solid (151 mg, 90.6% yield). MS (ESI): mass calcd. for $C_{34}H_{33}N_7O_4S$, 635.7; m/z found, 636.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.28-8.20 (m, 1H), 7.83-7.63 (m, 1H), 7.42-7.34 (m, 2H), 7.28-7.21 (m, 1H), 7.18-7.11 (m, 1H), 7.09-7.00 (m, 3H), 6.98-6.92 (m, 1H), 6.01-5.95 (m, 1H), 4.30-3.73 (m, 3H), 3.36-3.25 (m, 2H), 2.14-2.04 (m, 4H), 2.01-1.83 (m, 2H), 1.75-1.62 (m, 1H), 1.60-1.46 (m, 6H).

Example 196: (*R,E*)-*N*-(1-(3-(1-Aminocyclopropyl)-2-cyanoacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

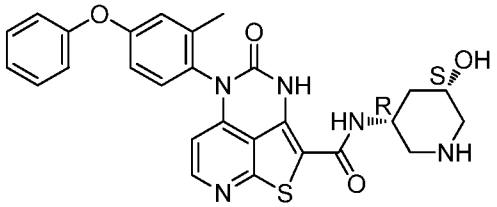


Step A: (*R,E*)-*tert*-butyl (1-(2-cyano-3-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-3-oxoprop-1-en-1-yl)cyclopropyl)carbamate. A solution of ((*R*)-*N*-(1-(2-cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 874, 150 mg, 0.26 mmol), *tert*-butyl *N*-(1-formylcyclopropyl)carbamate (147 mg, 0.795 mmol), piperidine (0.3 mL), acetic acid (0.1 mL), dioxane (10 mL), and 4A molecular sieves(1 g) was stirred at 100 °C for 1 h under N_2. The mixture was concentrated to dryness and

purified by flash column chromatography to yield the title compound as a light yellow solid (153 mg, 78.5% yield).

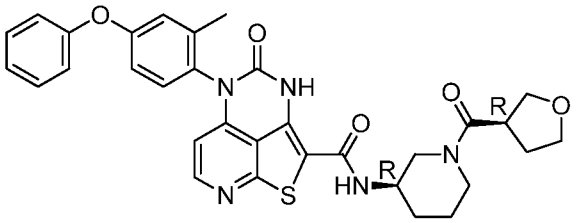
Step B: (*R*,*E*)-*N*-(1-(3-(1-Aminocyclopropyl)-2-cyanoacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (*R*,*E*)-*tert*-butyl (1-(2-cyano-3-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-3-oxoprop-1-en-1-yl)cyclopropyl)carbamate (153 mg, 0.21 mmol) in MeOH (4 mL) was added TFA (1 mL) and was stirred at rt for 20 min. The mixture was concentrated to dryness, diluted with DCM, washed with saturated $NaHCO_3$ and brine, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a brown solid (68 mg, 51% yield). MS (ESI): mass calcd. for $C_{34}H_{31}N_7O_4S$, 633.7; m/z found, 634.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD and DMSO-d_6): δ 8.36-8.18 (m, 1H), 7.59-7.18 (m, 4H), 7.18-6.85 (m, 5H), 6.03-5.84 (m, 1H), 4.66-4.39 (m, 1H), 4.12-3.69 (m, 2H), 3.07-2.67 (m, 2H), 2.10-1.77 (m, 6H), 1.77-1.48 (m, 3H), 1.39-1.11 (m, 2H).

Example 197: *N*-((3*R*,5*S*)-5-Hydroxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



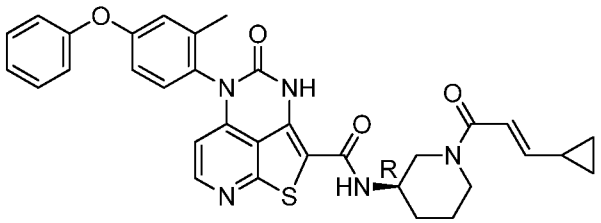
The title compound was prepared using using Method 1, steps A-H in Example 1, using *tert*-butyl (3*R*,5*S*)-3-amino-5-hydroxypiperidine-1-carboxylate (Intermediate 2) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{25}N_5O_4S$, 515.6; m/z found, 516.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.37-8.27 (m, 1H), 7.47-7.35 (m, 2H), 7.35-7.28 (m, 1H), 7.23-7.12 (m, 1H), 7.13-7.03 (m, 3H), 7.02-6.94 (m, 1H), 6.07 (d, J = 5.6Hz, 1H), 4.41-4.25 (m, 1H), 4.12-4.00 (m, 1H), 3.29-3.19 (m, 2H), 3.14-3.02 (m, 1H), 3.00-2.89 (m, 1H), 2.26-2.15 (m, 1H), 2.14-2.07 (m, 3H), 1.90-1.80 (m, 1H).

Example 198: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-((*R*)-1-((*R*)-tetrahydrofuran-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 90 mg, 0.18 mmol), (3*R*)-tetrahydrofuran-3-carboxylic acid (88 mg, 0.76 mmol), HATU (168 mg, 0.44 mmol), and triethylamine (45 mg, 0.45 mmol) in DMF (5 mL) was reacted at rt for 2 h. The reaction was quenched by the addition of H_2O (10 mL), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound as a yellow solid (52 mg, 48% yield). MS (ESI): mass calcd. for $C_{32}H_{31}N_5O_5S$, 597.7; m/z found, 598.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.35-8.27 (m, 1H), 7.43-7.35 (m, 2H), 7.32-7.28 (m, 1H), 7.19-7.12 (m, 1H), 7.12-7.00 (m, 3H), 6.99-6.92 (m, 1H), 6.11-6.00 (m, 1H), 4.52-4.29 (m, 1H), 4.21-3.79 (m, 6H), 3.52-3.38 (m, 1H), 3.22-3.00 (m, 1H), 2.87-2.69 (m, 1H), 2.39-2.14 (m, 1H), 2.14-2.09 (m, 3H),2.09-1.97 (m, 2H), 1.88-1.50 (m, 3H).

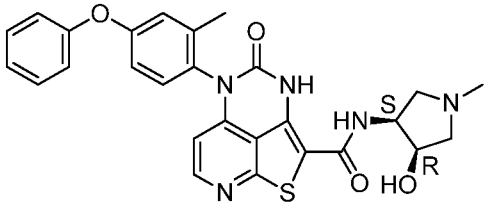
Example 199: (*R*,*E*)-*N*-(1-(3-Cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 100 mg, 0.2 mmol) and (*E*)-3-cyclopropylprop-2-enoic acid (500 mg, 4.5 mmol) in anhydrous DMF (5 mL) were added HATU (228 mg, 0.600 mmol) and diisopropylethylamine (130 mg, 1.0 mmol) and was stirred overnight at rt. The reaction mixture was purified by flash column chromatography, then preparative TLC to yield the title compound as a yellow solid (41 mg, 34% yield). MS (ESI): mass calcd. for $C_{33}H_{31}N_5O_4S$, 593.7; m/z found, 594.1 $[M+H]^+$. ^1H NMR (400 MHz, CDCl3): δ 9.51-9.41 (m, 1H), 8.34 (d, J = 5.4 Hz, 1H), 7.42-7.35 (m, 2H), 7.20-7.13 (m, 2H), 7.12-7.06 (m, 2H), 7.01-6.98 (m, 1H), 6.97-6.92 (m, 1H), 6.52-6.33 (m, 2H), 6.00 (d, J = 5.4 Hz, 1H), 4.16-4.06 (m, 1H),

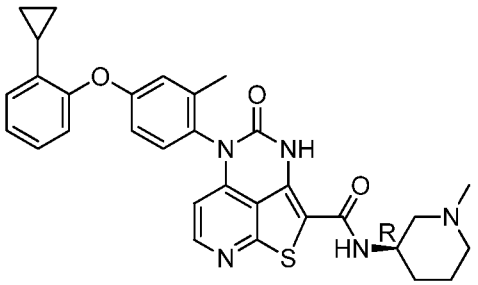
4.01-3.78 (m, 1H), 3.63-3.27 (m, 2H), 2.14-2.09 (m, 3H), 2.05-1.92 (m, 1H), 1.81-1.58 (m, 5H), 0.96-0.82 (m, 2H), 0.76-0.42 (m, 2H).

Example 200: *N*-((3*S*,4*R*)-4-Hydroxy-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a solution of *N*-((3*S*,4*R*)-4-hydroxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 241, 100 mg, 0.2 mmol) and formaldehyde (0.5 mL, 37 wt. % in H_2O) in MeOH (5 mL) was added $NaBH(OAc)_3$ (127 mg, 0.597 mmol) and stirred at rt overnight, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a yellow solid (53 mg, 50% yield). MS (ESI): mass calcd. for $C_{27}H_{25}N_5O_4S$, 515.6; m/z found, 516.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.33-8.17 (m, 1H), 7.43-7.33 (m, 2H), 7.33-7.23 (m, 1H), 7.18-7.09 (m, 1H), 7.10-7.00 (m, 3H), 7.00-6.90 (m, 1H), 6.04-5.93 (m, 1H), 4.57-4.37 (m, 2H), 3.14-2.94 (m, 2H), 2.87-2.69 (m, 2H), 2.47 (s, 3H), 2.09 (s, 3H).

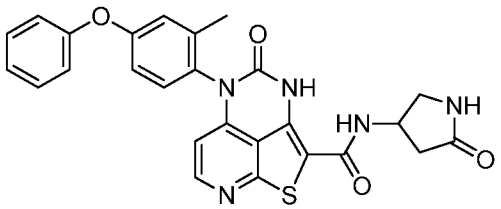
Example 201: (*R*)-5-(4-(2-Cyclopropylphenoxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: (*R*)-5-(4-(2-Cyclopropylphenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using 2-cyclopropylphenol in place of phenol in step A, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

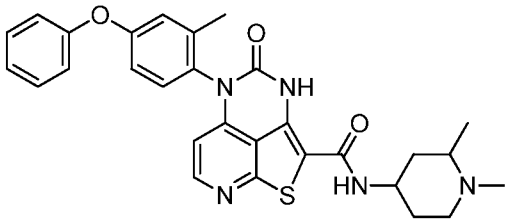
Step B: (*R*)-5-(4-(2-Cyclopropylphenoxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (*R*)-5-(4-(2-cyclopropylphenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (100 mg, 0.19 mmol) in DCM (10 mL) was added formaldehyde (30 mg, 1.0 mmol, 37 wt. % in H_2O) and after stirring at rt for 10 min, $NaBH(OAc)_3$ (78 mg, 0.37 mmol) was added. The mixture was stirred at rt overnight, then the pH was adjusted to pH >7 with 2 M aqueous NaOH, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound as a yellow solid (45 mg, 44% yield). MS (ESI): mass calcd. for $C_{31}H_{31}N_5O_3S$, 553.7; m/z found, 554.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6 and CD_3OD): δ 8.24 (d, *J* = 5.5, 1H), 7.29-7.20 (m, 1H), 7.19-7.06 (m, 2H), 7.02-6.89 (m, 3H), 6.86-6.76 (m, 1H), 5.89 (d, *J* = 5.5, 1H), 4.06-3.93 (m, 1H), 2.91-2.76 (m, 1H), 2.70-2.59 (m, 1H), 2.23 (s, 3H), 2.08-1.92 (m, 6H), 1.82-1.66 (m, 2H), 1.59-1.48 (m, 1H), 1.43-1.32 (m, 1H), 0.90-0.80 (m, 2H), 0.67-0.57 (m, 2H).

Example 202: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(5-oxopyrrolidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



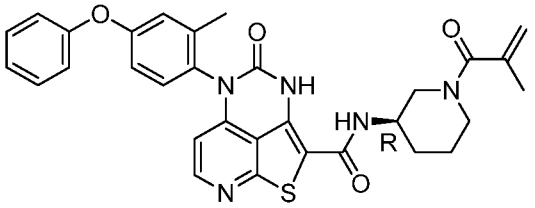
The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1, and using 4-aminopyrrolidin-2-one in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{26}H_{21}N_5O_4S$, 499.5; m/z found, 500.7 $[M+H]^+$. ^1H NMR (400 MHz, a mixture of CD3OD and DMSO-d6): δ 8.25-8.16 (m, 1H), 7.40-7.32 (m, 2H), 7.27-7.18 (m, 1H), 7.15-7.08 (m, 1H), 7.07-7.01 (m, 2H), 7.01-7.98 (m, 1H), 6.92-6.88 (m, 1H), 5.93-5.84 (m, 1H), 4.67-4.52 (m, 1H), 3.63-3.57 (m, 1H), 3.25-3.19 (m, 1H), 2.58-2.51 (m, 1H), 2.36-2.29 (m, 1H), 2.01 (s, 3H).

Example 203: *N*-(1,2-Dimethylpiperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



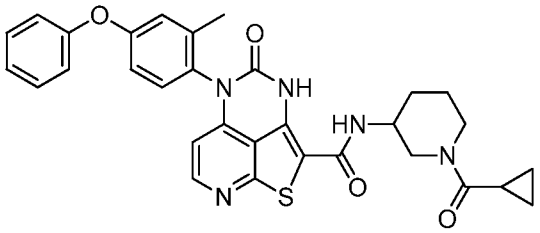
To a solution of 5-(2-methyl-4-phenoxyphenyl)-*N*-(2-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 258, 150 mg, 0.29 mmol) and formaldehyde (0.6 mL, 37 wt. % in H_2O) in MeOH (30 mL) was added $NaBH(OAc)_3$ (186 mg, 0.878 mmol) and was stirred at rt for 3 h, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a yellow solid (110 mg, 71% yield). MS (ESI): mass calcd. for $C_{29}H_{29}N_5O_3S$, 527.6; m/z found, 528.7 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD and DMSO-d_6): δ 8.23 (d, J = 5.5 Hz, 1H), 7.46 – 7.32 (m, 2H), 7.27 (d, J = 8.5 Hz, 1H), 7.19 – 7.10 (m, 1H), 7.09-6.98 (m, 3H), 6.97-6.85 (m, 1H), 5.89 (d, J = 5.4 Hz, 1H), 3.90 – 3.64 (m, 2H), 2.98-2.75 (m, 1H), 2.24 (s, 3H), 2.20 – 2.11 (m, 1H), 2.03 (s, 3H), 1.89-1.72 (m, 2H), 1.69-1.53 (m, 1H), 1.43-1.28 (m, 1H), 1.05 (d, J = 6.2 Hz, 3H).

Example 204: (*R*)-*N*-(1-Methacryloylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



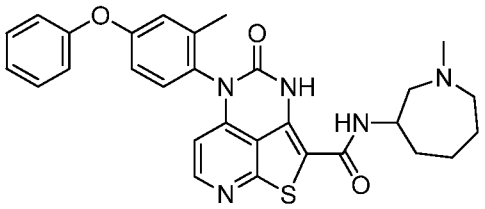
A solution (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.28 mmol), 2-methylprop-2-enoic acid (52 mg, 0.60 mmol), HATU (148 mg, 0.390 mmol), and diisopropylethylamine (77 mg, 0.60 mmol) in DMF (5 mL) was stirred at rt for 2 h. The mixture was purified by HPLC to yield the title compound as a brown solid (105 mg, 66.1% yield). MS (ESI): mass calcd. for $C_{31}H_{29}N_5O_4S$, 567.7; m/z found, 568.7 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD and DMSO-d_6): δ 8.27-8.22 (m, 1H), 7.38-7.31 (m, 2H), 7.31-7.24 (m, 1H), 7.14-7.07 (m, 1H), 7.07-6.98 (m, 3H), 6.94-6.87 (m, 1H), 5.97-5.91 (m, 1H), 5.17-4.93 (m, 2H), 4.05-3.89 (m, 1H), 3.86-3.74 (m, 2H), 3.08-2.62 (m, 2H), 2.05-1.99 (m, 3H), 1.96-1.88 (m, 1H), 1.84 (s, 3H), 1.78-1.69 (m, 1H), 1.67-1.58 (m, 1H), 1.49-1.39 (m, 1H).

Example 205: *N*-(1-(Cyclopropanecarbonyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps A-G in Example 1, and using 1-(cyclopropylcarbonyl)-3-piperidinamine HCl in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{31}H_{29}N_5O_4S$, 567.7; m/z found, 568.0 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d4) δ 8.34 (d, J = 5.5 Hz, 1H), 7.46 - 7.36 (m, 2H), 7.30 (d, J = 8.5 Hz, 1H), 7.21 - 7.13 (m, 1H), 7.13 - 7.03 (m, 3H), 6.98 (dd, J = 8.5, 2.8 Hz, 1H), 6.09 (d, J = 5.5 Hz, 1H), 4.51 (d, J = 63.3 Hz, 1H), 4.34 (s, 1H), 4.20 (d, J = 13.6 Hz, 1H), 3.97 (d, J = 38.8 Hz, 1H), 3.30 - 3.15 (m, 1H), 2.99 - 2.81 (m, 1H), 2.13 (s, 3H), 2.00 (s, 1H), 1.95 - 1.08 (m, 3H), 0.99 - 0.69 (m, 4H).

Example 206: 5-(2-Methyl-4-phenoxyphenyl)-*N*-(1-methylazepan-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

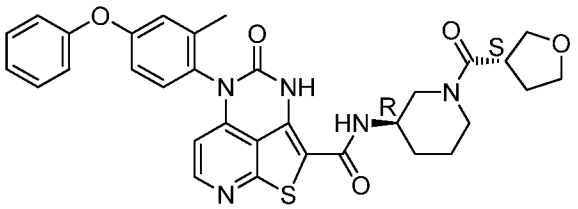


Step A: *N*-(Azepan-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using *tert*-butyl 3-aminoazepane-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

Step B: 5-(2-Methyl-4-phenoxyphenyl)-*N*-(1-methylazepan-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of *N*-(azepan-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (100 mg, 0.2 mmol) and formaldehyde (0.3 mL, 37 wt. % in H_2O) in MeOH was added $NaBH(OAc)_3$ (124 mg, 0.585 mmol) and stirred at rt for 1 h, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a white solid (70 mg, 63% yield). MS (ESI): mass calcd. for $C_{29}H_{29}N_5O_3S$, 527.6; m/z found, 528.5 $[M+H]^+$. ^1H NMR (400 MHz,

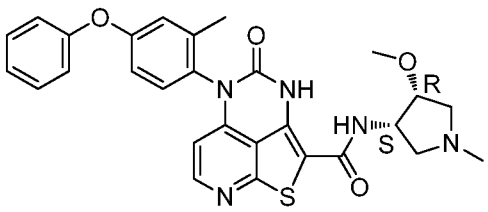
CD_3OD): δ 8.50 (s, 1H), 8.31 (d, *J* = 5.6 Hz, 1H), 7.42-7.36 (m, 2H), 7.31-7.27 (m, 1H), 7.19-7.12 (m, 1H), 7.11-7.03 (m, 3H), 6.97 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.06 (d, *J* = 5.6 Hz, 1H), 4.31-4.21 (m, 1H), 3.43-3.30 (m, 2H), 3.27-3.12 (m, 2H), 2.84 (s, 3H), 2.15-2.04 (m, 1H), 2.08 (s, 3H), 2.01-1.83 (m, 4H), 1.74-1.62 (m, 1H).

Example 207: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-((*R*)-1-((*S*)-tetrahydrofuran-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 120 mg, 0.24 mmol), (3*S*)-tetrahydrofuran-3-carboxylic acid (100 mg, 0.86 mmol), HATU (150 mg, 0.40 mmol), and triethylamine (80 mg, 0.79 mmol) in DMF (5 mL) was reacted at rt for 2 h. The reaction was quenched with H_2O (10 mL), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography to yield the title compound as an off white solid (57 mg, 40% yield). MS (ESI): mass calcd. for $C_{32}H_{31}N_5O_5S$, 597.7; m/z found, 598.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.32-8.27 (m, 1H), 7.42-7.29 (m, 3H), 7.19-7.09 (m, 1H), 7.09-7.00 (m, 3H), 6.97-6.90 (m, 1H), 6.04-5.98 (m, 1H), 4.60-4.31 (m, 1H), 4.26-4.08 (m, 1H), 3.94-3.85 (m, 1H), 3.85-3.66 (m, 4H), 3.52-3.37 (m, 1H), 3.15-2.92 (m, 1H), 2.81-2.59 (m, 1H), 2.15-1.97 (m, 6H), 1.89-1.73 (m, 1H),1.73-1.41 (m, 2H).

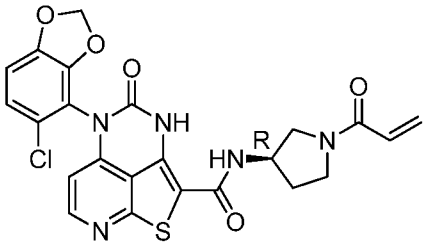
Example 208: *N*-((3*S*,4*R*)-4-Methoxy-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



To a solution of *N*-((3*S*,4*R*)-4-methoxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 211, 100 mg, 0.19

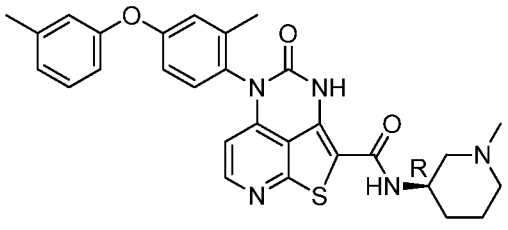
mmol) and formaldehyde (0.4 mL, 37 wt. % in H_2O) in MeOH (5 mL) was added $NaBH(OAc)_3$ (123 mg, 0.582 mmol) and was stirred at rt for 1 h. The reaction mixture was concentrated to dryness and purified by flash column chromatography to yield the title compound as a yellow solid (54 mg, 52% yield). MS (ESI): mass calcd. for $C_{28}H_{27}N_5O_4S$, 529.6; m/z found, 530.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD and DMSO-d_6): δ 8.23 (d, J=5.4Hz, 1H), 7.41-7.28 (m, 2H), 7.28-7.18 (m, 1H), 7.14-7.06(m, 1H), 7.06-6.95 (m, 3H), 6.94-6.85 (m, 1H), 5.94 (d, J = 5.4Hz, 1H), 4.60-4.51 (m, 1H), 3.96-3.86 (m, 1H), 3.27 (s, 3H), 2.92-2.78 (m, 2H), 2.71-2.59 (m, 2H), 2.32 (s, 3H), 2.03 (s, 3H).

Example 209: (*R*)-*N*-(1-Acryloylpyrrolidin-3-yl)-5-(5-chlorobenzo[*d*][1,3]dioxol-4-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps C-I in Example 1, and using 5-chloro-1,3-benzodioxol-4-amine and 2,4-dichloropyridine-3-carbonitrile in place of 2-methyl-4-phenoxyaniline and 2-chloro-4-iodopyridine-3-carbonitrile in step C, and using *tert*-butyl (3*R*)-3-aminopyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{23}H_{18}ClN_5O_5S$, 511.9; m/z found, 512.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.37 (d, J = 5.5Hz, 1H), 7.12 (d, J = 8.4Hz, 1H), 7.01 (d, J = 8.4Hz, 1H), 6.70-6.52 (m, 1H), 6.32-6.23 (m, 2H), 6.13-6.07(m, 2H), 5.82-5.67 (m, 1H), 4.67-4.57 (m, 1H), 4.01-3.51 (m, 4H), 2.40-2.21 (m, 1H), 2.19-2.03 (m, 1H).

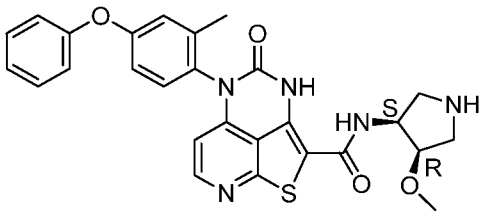
Example 210: (*R*)-5-(2-Methyl-4-(*m*-tolyloxy)phenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



Step A: (*R*)-5-(2-Methyl-4-(*m*-tolyloxy)phenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using *m*-cresol in place of phenol in step A, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

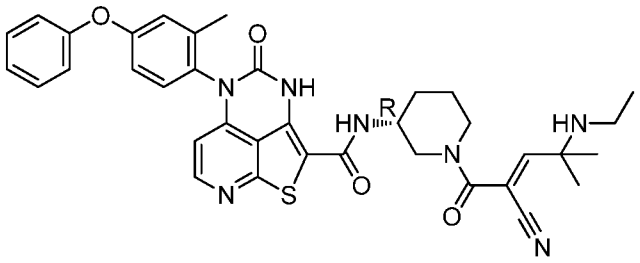
Step B: (*R*)-5-(2-Methyl-4-(*m*-tolyloxy)phenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (*R*)-5-(2-methyl-4-(*m*-tolyloxy)phenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (88 mg, 0.17 mmol) in DCM (5 mL) was added formaldehyde (0.5 mL, 37 wt. % in H_2O) and $NaBH(OAc)_3$ (73 mg, 0.34 mmol) and stirred at rt for 4 h. The mixture was diluted with DCM (50 mL), MeOH (5 mL), and water (30 mL). The organic layer was collected, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a yellow solid (62 mg, 65% yield). MS (ESI): mass calcd. for $C_{29}H_{29}N_5O_3S$, 527.6; m/z found, 528.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.26 (d, J = 5.3 Hz, 1H), 8.05 (br, 1H), 7.33-7.26 (m, 2H), 7.05-7.01 (m, 1H), 7.00-6.97 (m, 1H), 6.95-6.90 (m, 2H), 6.89-6.85 (m, 1H), 5.88 (d, J = 5.4 Hz, 1H), 3.95-3.87 (m, 1H), 2.84-2.78 (m, 1H), 2.70-2.61 (m, 1H), 2.30 (s, 3H), 2.18 (s, 3H), 2.02 (s, 3H), 1.93-1.83 (m, 2H), 1.79-1.73 (m, 1H), 1.69-1.63 (m, 1H), 1.54-1.45 (m, 1H), 1.35-1.27 (m, 1H).

Example 211: *N*-((3*S*,4*R*)-4-Methoxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared using steps A-H in Example 1, and using *tert*-butyl (3*S*,4*R*)-3-amino-4-methoxypyrrolidine-1-carboxylate (Intermediate 11) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{25}N_5O_4S$, 515.6; m/z found, 516.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD and DMSO-d_6): δ 8.29 (d, *J* = 5.5Hz, 1H), 7.43-7.30 (m, 2H), 7.26 (d, *J* = 8.6Hz, 1H), 7.15-7.08 (m, 1H), 7.07-6.99 (m, 3H), 6.92 (dd, *J* = 8.6, 2.8Hz, 1H), 6.00 (d, *J* = 5.5Hz, 1H), 4.67-4.60 (m, 1H), 4.10-4.03(m, 1H), 3.53-3.45 (m, 2H), 3.36 (s, 3H), 3.35-3.27 (m, 2H), 2.04 (s, 3H).

Example 212: (*R*,*E*)-*N*-(1-(2-Cyano-4-(ethylamino)-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

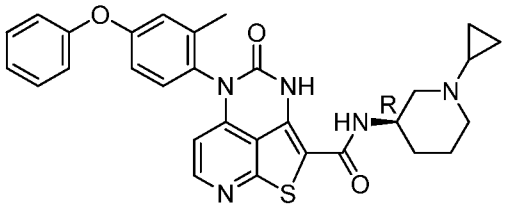


Step A: 3-Bromo-3-methylbutanal. To a solution of 3-methylbutanal (1.0 g, 12 mmol) in Et_2O (10 mL) was slowly added bromine-1,4-dioxane complex (1.44 g, 5.81 mmol) while cooling with ice water. The reaction mixture was stirred at rt overnight, then 10% aqueous $Na_2S_2O_4$ was added. After stirring at rt for 30 min, the mixture was extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness to yield the title compound as a yellow liquid (1.1 g, 56%)

Step B: 3-(Ethylamino)-3-methylbutanal. To a solution of 3-bromo-3-methylbutanal (650 mg, 3.94 mmol) in Et_2O (10 mL) was added ethyl amine (0.773 mL, 11.8 mmol) while cooling with ice-water. The reaction mixture was stirred at rt overnight, then concentrated to dryness and the residue used in next step without purification.

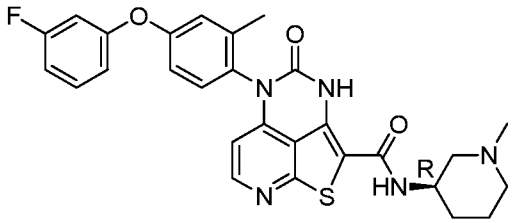
Step C: (*R*,*E*)-*N*-(1-(2-Cyano-4-(ethylamino)-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A solution of (*R*)-*N*-(1-(2-cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 874, 98 mg, 0.17 mmol), 3-(ethylamino)-3-methylbutanal (60 mg, 0.52 mmol), and piperidine (0.0085 mL, 0.086 mmol) in CH_3CN (5 mL) was stirred at 60 °C overnight, concentrated to dryness, and the residue purified by flash column chromatography to yield the title compound as a yellow solid (20 mg, 17% yield). MS (ESI): mass calcd. for $C_{36}H_{37}N_7O_4S$, 663.8; m/z found, 664.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.12-8.03 (m, 1H), 7.63-7.51 (m, 1H), 7.42-7.35 (m, 2H), 7.19-7.12 (m, 2H), 7.11-7.07 (m, 2H), 7.06-7.02 (m, 1H), 6.98-6.93 (m, 1H), 5.84-5.78 (m, 1H), 4.05-3.95 (m, 1H), 3.76-3.69 (m, 1H), 3.64-3.56 (m, 2H), 3.54-3.45 (m, 1H), 3.24-3.17 (m, 1H), 2.16-2.08 (m, 5H), 2.08-1.97 (m, 2H), 1.75-1.70 (m, 1H), 1.58-1.45 (m, 6H), 1.18-1.12 (m, 3H).

Example 213: (*R*)-*N*-(1-Cyclopropylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 150 mg, 0.30 mmol), (1-ethoxycyclopropoxy)trimethylsilane (209 mg, 1.20 mmol), $NaBH_3CN$ (38 mg, 0.60 mmol), and acetic acid (2 drops) in MeOH (10 mL) was heated at 55 °C overnight. The product was purified by flash column chromatography to yield the title compound as a white solid (76 mg, 41% yield). MS (ESI): mass calcd. for $C_{30}H_{29}N_5O_3S$, 539.6; m/z found, 540.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.34-8.30 (m, 1H), 8.21 (s, 1H), 7.43-7.36 (m, 2H), 7.31-7.26 (m, 1H), 7.19-7.13 (m, 1H), 7.11-7.03 (m, 3H), 6.99-6.94 (m, 1H), 6.09-6.06 (m, 1H), 4.20-4.09 (m, 1H), 4.34-4.30 (m, 1H), 3.16-3.06 (m, 1H), 2.66-2.53 (m, 2H), 2.22-2.12 (m, 1H), 2.11 (s, 3H), 1.98-1.80 (m, 2H), 1.74-1.52 (m, 2H), 0.71-0.59 (m, 4H).

Example 214: (*R*)-5-(4-(3-Fluorophenoxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

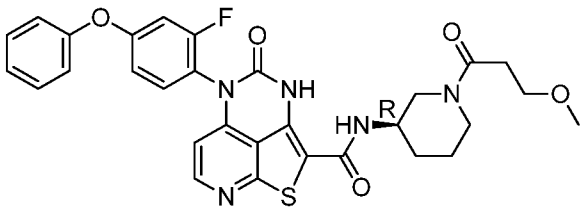


Step A: (*R*)-5-(4-(3-Fluorophenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps A-H in Example 1, and using 3-fluorophenol in place of phenol in step A, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

Step B: (*R*)-5-(4-(3-Fluorophenoxy)-2-methylphenyl)-*N*-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. To a solution of (*R*)-5-(4-(3-fluorophenoxy)-2-methylphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (96 mg, 0.19 mmol) in DCM (5 mL) were added

formaldehyde (0.5 mL, 37 wt. % in H_2O) and $NaBH(OAc)_3$ (78 mg, 0.37 mmol) and was stirred at rt for 4 h. To the mixture was added DCM (50 mL), MeOH (5 mL), and water (30 mL) and the organic layer was collected, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a yellow solid (58 mg, 56% yield). MS (ESI): mass calcd. for $C_{28}H_{26}FN_5O_3S$, 531.6; m/z found, 532.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6): δ 8.24 (d, J = 5.2 Hz, 1H), 8.11 (br, 1H), 7.47-7.39 (m, 1H), 7.38-7.28 (m, 1H), 7.16-7.08 (m, 1H), 7.05-6.95 (m, 3H), 6.94-6.88 (m, 1H), 5.90 (d, J = 5.1 Hz, 1H), 3.95-3.87 (m, 1H), 2.84-2.77 (m, 1H), 2.69-2.60 (m, 1H), 2.18 (s, 3H), 2.03 (s, 3H), 1.95-1.84 (m, 2H), 1.80-1.71 (m, 1H), 1.70-1.62 (m, 1H), 1.53-1.43 (m, 1H), 1.36-1.25 (m, 1H).

Example 215: (*R*)-5-(2-Fluoro-4-phenoxyphenyl)-*N*-(1-(3-methoxypropanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



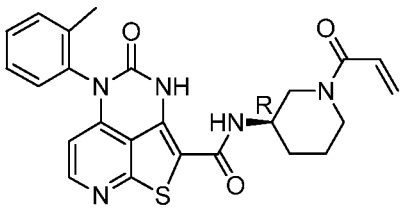
Step A: 2-Fluoro-1-nitro-4-phenoxybenzene. To a solution of 3-fluoro-4-nitrophenol (2.0 g, 13 mmol), phenylboronic acid (2.33 g, 19.1 mmol), $Cu(OAc)_2$ (4.62 g, 25.5 mmol), and triethylamine (6.44 g, 6.37 mmol) in DCM (60 mL) was added 4A molecular sieves (powder <50 μm, 2 g). The mixture was stirred at rt under N_2 overnight, then filtered, concentrated to dryness, and purified by flash column chromatography to yield the title compound as a yellow solid (2.7 g, 91% yield).

Step B: (*R*)-5-(2-Fluoro-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. The title compound was prepared in a manner analogous to Method 1, steps B-H in Example 1, and using 2-fluoro-1-nitro-4-phenoxybenzene in place of 2-methyl-1-nitro-4-phenoxybenzene in step B, and using *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G.

Step C: (*R*)-5-(2-Fluoro-4-phenoxyphenyl)-*N*-(1-(3-methoxypropanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. A solution of (*R*)-5-(2-fluoro-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (150 mg, 0.30 mmol), 3-methoxypropanoic acid (27 mg, 0.26 mmol), HATU (227 mg, 0.596 mmol), and triethylamine (60 mg, 0.60 mmol) in DMF (4

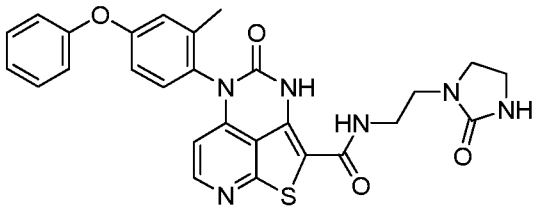
mL) was stirred at rt for 2 h, then purified by flash column chromatography to yield the title compound as a white solid (103 mg, 58.1% yield). MS (ESI): mass calcd. for $C_{30}H_{28}FN_5O_5S$, 589.6; m/z found, 590.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.39 (s, 1H), 8.34 (d, J = 5.5 Hz, 1H), 8.22-7.89 (m, 1H), 7.65-7.51 (m, 1H), 7.51-7.40 (m, 2H), 7.30-7.22 (m, 1H), 7.21-7.09 (m, 3H), 6.99-6.89 (m, 1H), 6.17 (d, J = 5.4 Hz, 1H), 4.49-4.08 (m, 1H), 3.97-3.62 (m, 2H), 3.58-3.46 (m, 2H), 3.22-3.15 (m, 3H), 3.05-2.80 (m, 1H), 2.68-2.49 (m, 3H), 1.98-1.83 (m, 1H), 1.81-1.51 (m, 2H), 1.49-1.26 (m, 1H).

Example 216: (*R*)-*N*-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(*o*-tolyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared in a manner analogous to Method 1, steps C-G in Example 1, and using 2-methylaniline in place of 2-methyl-4-phenoxyaniline for step C, and using 1-[(3*R*)-3-amino-1-piperidyl]prop-2-en-1-one (Intermediate 15) in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{24}H_{23}N_5O_3S$, 461.5; m/z found, 462.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.29 (d, J = 5.5, 1H), 7.48-7.39 (m, 3H), 7.35-7.30 (m, 1H), 6.86-6.71 (m, 1H), 6.25-6.14 (m, 1H), 5.96 (d, J = 5.5, 1H), 5.76-5.67 (m, 1H), 4.56-4.26 (m, 1H), 4.21-3.90 (m, 2H), 3.20-3.11 (m, 1H), 2.65-2.82 (m, 1H), 2.16 (s, 3H), 2.09-2.01 (m, 1H), 1.90-1.82 (m, 1H), 1.80-1.22 (m, 1H), 1.63-1.52 (m, 1H).

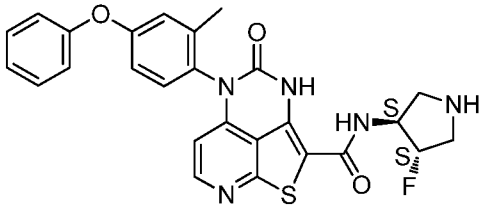
Example 217: 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(2-(2-oxoimidazolidin-1-yl)ethyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared using analogous conditions described in Method 1, steps A-G in Example 1, and using 1-(2-aminoethyl)imidazolidin-2-one in place of tert-butyl (3R,5R)-3-

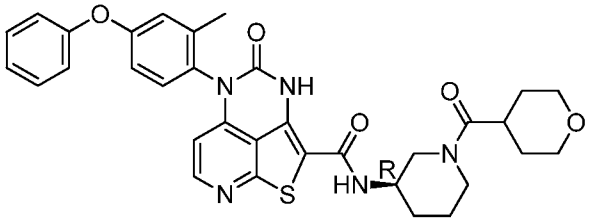
amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{27}H_{24}N_6O_4S$, 528.6; m/z found, 528.9 $[M+H]^+$. ^1H NMR (500 MHz, $CDCl_3$): δ 9.55 (s, 1H), 8.32 (s, 1H), 7.44 - 7.35 (m, 2H), 7.23 - 7.15 (m, 3H), 7.14 - 7.07 (m, 2H), 7.00 (d, *J* = 2.7 Hz, 1H), 6.99 - 6.91 (m, 1H), 5.97 (d, *J* = 5.2 Hz, 1H), 4.94 (s, 1H), 3.70 - 3.56 (m, 4H), 3.56 - 3.40 (m, 4H), 2.13 (s, 3H).

Example 218: *N*-((3*S*,4*S*)-4-Fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



The title compound was prepared using analogous conditions described in Method 1, steps A-H in Example 1, and using *tert*-butyl (3*S*,4*S*)-3-amino-4-fluoropyrrolidine-1-carboxylate in place of tert-butyl (3R,5R)-3-amino-5-fluoropiperidine-1-carboxylate (Intermediate 1) in step G. MS (ESI): mass calcd. for $C_{26}H_{22}FN_5O_3S$, 503.5; m/z found, 504.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.26 (d, *J* = 5.5Hz, 1H), 7.46-7.35 (m, 2H), 7.28 (d, *J* = 8.6Hz, 1H), 7.19-7.12 (m, 1H), 7.12-.02 (m, 3H), 7.00-6.92 (m, 1H), 6.01 (d, *J* = 5.5Hz, 1H), 5.28-5.11 (m, 1H), 4.56-4.46 (m, 1H), 3.49-3.42 (m, 1H), 3.41-3.34 (m, 1H), 3.25-3.15 (m, 1H), 3.06-2.99 (m, 1H), 2.11 (s, 3H).

Example 219: (*R*)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-*N*-(1-(tetrahydro-2*H*-pyran-4-carbonyl)piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.



A solution of (*R*)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-*N*-(piperidin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide (Example 869, 90 mg, 0.18 mmol), tetrahydropyran-4-carboxylic acid (88 mg, 0.67 mmol), HATU (168 mg, 0.442 mmol), and triethylamine (45 mg, 0.45 mmol) in DMF (5 mL) was reacted at rt for 2 h. The reaction was quenched by the addition of H_2O (10 mL), extracted with DCM, dried over anhydrous Na_2SO_4,

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 3
CONTENANT LES PAGES 1 À 331

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 3
CONTAINING PAGES 1 TO 331

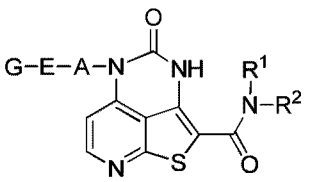
NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

What is Claimed:

1. A compound of Formula (I'), and pharmaceutically acceptable salts, stereoisomers, isotopes, N-oxides, or solvates thereof,



(I')

wherein

R^1 is H or C_{1-6}alkyl;

R^2 is selected from the group consisting of: C_{0-2}alk-piperidinyl; C_{0-2}alk-pyrrolidinyl; oxazepanyl; azetidinyl; azepanyl; quinuclidinyl; C_2alk-imidazolidinyl; C_2alk-piperazinyl; C_2alk-morpholinyl; tetrahydropyranyl; and C_{0-1}alk-tetrahydrofuranyl; wherein the R^2 is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of:

(C=O)-C(R^3)=CR^4(R^5); oxo; halogen; OH; NH_2; CN; C_{1-6}alkyl; C_{1-6}alk-OH; OC_{1-6}alkyl; C_{1-6}haloalkyl; C_{3-6}cycloalkyl; SO_2C_{1-6}alkyl; SO_2-C_{2-6}alkenyl; C_{1-2}alk-aryl; (C=O)H; (C=O)C_{1-6}alkyl; (C=O)C_{1-6}haloalkyl; (C=O)-C_{2-6}alkenyl; (C=O)-C_{2-6}alkynyl; (C=O)C_{3-6}cycloalkyl; (C=O)-phenyl; (C=O)-imidazolyl; (C=O)-C_{1-6}alkCN; (C=O)-C_{1-6}alk-OH; (C=O)-C_{1-6}alk-SO_2C_{1-6}alkyl; (C=O)-C_{1-6}alk-NR^6R^7; (C=O)-C_{1-6}alk-O-C_{1-6}alkyl wherein the -C_{1-6}alk- is optionally substituted with OH, OC_{1-6}alkyl, or NR^6R^7; (C=O)C_{0-1}alk-heterocycloalkyl wherein the -alk- is optionally substituted with oxo and the heterocycloalkyl is optionally substituted with C_{1-6}alkyl; and NH(C=O)-C(R^3)=CR^4(R^5);

wherein

R^3 is selected from the group consisting of: H, CN, halogen, C_{1-6}haloalkyl, and C_{1-6}alkyl;

R^4 and R^5 are each independently selected from the group consisting of: H; halogen; C_{1-6}alkyl; CH_2OH; C_{1-6}alk-OC_{1-6}alkyl; OC_{1-6}alkyl; C_{1-4}alk-NR^6R^7; C_{3-6}cycloalkyl substituted with NH_2 or CH_3; oxetanyl substituted with CH_3; 1-

Date Reçue/Date Received 2023-04-13

acetylpyrrolidin-2-yl; CH_2-pyrrolidinyl; CH_2-piperidinyl; $C(CH_3)_2$-piperidinyl; CH_2-morpholinyl; $C(CH_3)_2$-morpholinyl; CH_2-(4aR,7aS)-tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl; $C(CH_3)_2NH(CH_2CH_2OCH_3)$; $CH_2SO_2CH_3$; $CH_2NHSO_2CH_3$; $NH(C=O)C_{1-6}$alkyl; and linker-PEG-Biotin; and

R^6 and R^7 are each independently selected from the group consisting of: H, C_{1-6}alkyl, cyclopropyl, (C=O)H, and CN;

A is selected from the group consisting of: a bond, phenyl; naphthalenyl, pyridyl; pyrimidinyl; pyrazinyl; pyridazinyl; benzothiophenyl; and pyrazolyl; wherein the A is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of: C_{1-6}alkyl, halogen, OC_{1-6}alkyl, $(C=O)C_{1-6}$alkyl, and C_{1-6}haloalkyl;

E is selected from the group consisting of: -O-, a bond, (C=O)-NH, CH_2, and CH_2-O; and

G is selected from the group consisting of: H, C_{1-6}alkyl; C_{1-6}haloalkyl; C_{1-6}alk-OC_{1-6}alkyl; NR^6R^7; SO_2C_{1-6}alkyl; OH; C_{3-6}cycloalkyl; phenyl; thiophenyl; pyrimidinyl; pyridyl; pyridazinyl; benzofuranyl; ;heterocycloalkyl that contains an oxygen heteroatom; phenyl-CH_2-O-phenyl; wherein the phenyl, thiophenyl, pyrimidinyl, pyridyl, pyridazinyl, or benzofuranyl is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of: halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, OC_{1-6}haloalkyl, OC_{1-6}alkyl, OC_{1-6}alkyl-OC_{1-6}alkyl, C_{3-6}cycloalkyl, CN, OH, NH_2, $N(CH_3)_2$, C_{1-6}alk-OC_{1-6}alkyl, SO_2C_{1-6}alkyl, (C=O)-NR^6R^7, SF_5, and $(C=O)C_{1-6}$alkyl; and

stereoisomers or isotopic variants thereof;

or pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein R^1 is H.

3. The compound of claim 1 or claim 2, wherein R^2 is piperidinyl, CH_2CH_2-piperidinyl, pyrrolidinyl, CH_2-pyrrolidinyl, or CH_2CH_2-pyrrolidinyl.

4. The compound of claim 1 or claim 2, wherein R^2 is azetidinyl; azepanyl; quinuclidinyl; CH_2CH_2-imidazolidinyl; or CH_2CH_2-piperazinyl.

5. The compound of claim 1 or claim 2, wherein R^2 is oxazepanyl or CH_2CH_2-morpholinyl, $CH_2(C=O)$-morpholinyl.

Date Reçue/Date Received 2023-04-13

6. The compound of claim 1 or claim 2, wherein R^2 is tetrahydropyranyl or tetrahydrofuranyl, or CH_2-tetrahydrofuranyl.

7. The compound of any one of claims 1-6, wherein R^2 is unsubstituted.

8. The compound of any one of claims 1 to 6, wherein R^2 is substituted with 1 or 2 substitutents.

9. The compound of any one of claims 1 to 6 or 8, wherein R^2 is substituted with oxo.

10. The compound of any one of claims 1 to 6, 8, or 9, wherein R^2 is substituted with halogen; CN; OH; C_{1-6}alkyl; C_{1-6}haloalkyl; C_{1-6}alk-OH; OC_{1-6}alkyl; C_{3-6}cycloalkyl; NH_2; or C_{1-2}alkaryl.

11. The compound of any one of claims 1 to 6 or 8, wherein R^2 is substituted with (C=O)H; (C=O)C_{1-6}alkyl; (C=O)C_{3-6}cycloalkyl; (C=O)C_{1-6}haloalkyl; (C=O)-alkynyl; (C=O)-phenyl; (C=O)-C_{1-6}alkCN; (C=O)-C_{1-6}alk-OH; (C=O)-C_{1-6}alk-NR^6R^7; or (C=O)-C_{1-6}alk-O-C_{1-6}alkyl wherein the -C_{1-6}alk- is optionally substituted with OH, OC_{1-6}alkyl, or NR^6R^7.

12. The compound of any one of claims 1 to 6 or 8, wherein R^2 is substituted with (C=O)C_{0-1}alk-heterocycloalkyl wherein the heterocycloalkyl is optionally substituted with C_{1-6}alkyl.

13. The compound of any one of claims 1 to 6 or 8, wherein R^2 is substituted with SO_2alkyl, (C=O)-C_{1-6}alk-SO_2C_{1-6}alkyl, or SO_2-C_{2-6}alkenyl.

14. The compound of any one of claims 1 to 6 or 8, wherein R^2 is substituted with (C=O)-$C(R^3)$=$CR^4(R^5)$.

15. The compound of claim 14, wherein R^3 is H.

16. The compound of claim 14, wherein R^3 is CN.

17. The compound of claim 14, wherein R^3 is F or Cl.

18. The compound of claim 14, wherein R^3 is C_{1-6}haloalkyl or C_{1-6}alkyl.

Date Reçue/Date Received 2023-04-13

19. The compound of any one of claims 14 to 18, wherein one of R^4 and R^5 is H.

20. The compound of any one of claims 14 to 18, wherein R^4 is H and R^5 is H.

21. The compound of any one of claims 14 to 19, wherein one of R^4 and R^5 is halogen, C_{1-6}alkyl, C_{1-6}alk-OH, OC_{1-6}alkyl, C_{1-6}alk-OC_{1-6}alkyl, or C_{0-6}alkC_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl.

22. The compound of any one of claims 14 to 19, wherein one of R^4 and R^5 is CH_2NH_2, $CH_2NH(CH_3)$, $CH_2N(CH_3)_2$, $C(CH_3)_2N(CH_3)_2$, $C(CH_3)_2NH(CH_3)$, $C(CH_3)_2NH_2$, $C(CH_3)_2NH(CH_2CH_3)$, $C(CH_3)_2$NH-cyclopropyl, $NH(C{=}O)C_{1-6}$alkyl, or $C(CH_3)_2NH(CH_2CH_2OCH_3)$.

23. The compound of any one of claims 14 to 19, wherein one of R^4 and R^5 is C_{3-6}cycloalkyl substituted with NH_2 or CH_3; oxetanyl substituted with CH_3; 1-acetylpyrrolidin-2-yl; CH_2-pyrrolidinyl; CH_2-piperidinyl; $C(CH_3)_2$-piperidinyl; CH_2-morpholinyl; $C(CH_3)_2$-morpholinyl; or CH_2-(4aR,7aS)-tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl.

24. The compound of any one of claims 14 to 19, wherein one of R^4 and R^5 is or $NH(C{=}O)$-C_{1-6}alkyl.

25. The compound of any one of claims 14 to 19, wherein one of R^4 and R^5 is $CH_2SO_2CH_3$ or $CH_2NHSO_2CH_3$.

26. The compound of any one of claims 1 to 25, wherein A is phenyl.

27. The compound of any one of claims 1 to 25, wherein A is pyridyl.

28. The compound of any one of claims 1 to 25, wherein A is pyrimidinyl.

29. The compound of any one of claims 1 to 25, wherein A is pyrazinyl.

30. The compound of any one of claims 1 to 29, wherein A is substituted with 1 or 2 substitutents.

Date Reçue/Date Received 2023-04-13

31. The compound of any one of claims 1 to 30, wherein A is substituted with CH_3.

32. The compound of any one of claims 1 to 31, wherein E is O.

33. The compound of any one of claims 1 to 31, wherein E is a bond.

34. The compound of any one of claims 1 to 31, wherein E is (C=O)-NH, CH_2, or CH_2O.

35. The compound of any one of claims 1 to 34, wherein G is C_{1-6}alkyl; C_{1-6}haloalkyl; C_{1-6}alk-OC_{1-6}alkyl; or C_{3-6}cycloalkyl.

36. The compound of any one of claims 1 to 34, wherein G is C_{1-6}alkyl or C_{3-6}cycloalkyl.

37. The compound of any one of claims 1 to 34, wherein G is NH_2, $N(CH_3)_2$ or OH.

38. The compound of any one of claims 1 to 34, wherein G is heterocycloalkyl that contains an oxygen heteroatom.

39. The compound of any one of claims 1 to 34, wherein G is phenyl.

40. The compound of any one of claims 1 to 34, wherein G is pyridyl.

41. The compound of any one of claims 1 to 34, wherein G is pyrimidinyl or pyridazinyl.

42. The compound of any one of claims 1 to 34, wherein G is benzofuranyl or thiophenyl.

43. The compound of any one of claims 1 to 34, wherein G is phenyl-CH_2-O-phenyl.

44. The compound of any one of claims 1 to 43, wherein G is substituted with 1 or 2 substitutents.

45. The compound of any one of claims 1 to 44, wherein G is substituted with halogen.

46. The compound of any one of claims 1 to 44, wherein G is substituted with C_{1-6}alkyl, C_{1-6}haloalkyl, OC_{1-6}alkyl, OC_{1-6}haloalkyl, C_{1-6}alk-OC_{1-6}alkyl, (C=O)-C_{1-6}alkyl, or C_{3-6}cycloalkyl.

47. The compound of any one of claims 1 to 44, wherein G is substituted with CN.

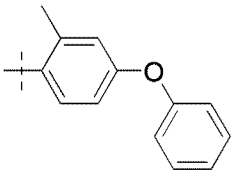
Date Reçue/Date Received 2023-04-13

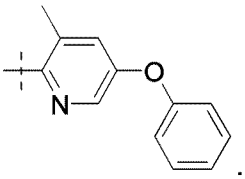
48. The compound of any one of claims 1 to 44, wherein G is substituted with OH.

49. The compound of any one of claims 1 to 44, wherein G is substituted with (C=O)-NR^6R^7.

50. The compound of any one of claims 1 to 25, wherein A-E-G is phenyl-O-phenyl or pyridyl-O-phenyl.

51. The compound of any one of claims 1 to 25, wherein A-E-G is



or


.

52. The compound of claim 1, wherein R^1 is H; R^2 is piperidinyl substituted with 1 or 2 substituents wherein one of the substituents is (C=O)-$C(R^3)$=$CR^4(R^5)$, wherein R^3, R^4, and R^5 are each H; A is phenyl or pyridyl substituted with CH_3; E is O; and G is phenyl.

53. The compound of claim 56, wherein R^2 is substituted with 1 substituent that is (C=O)-$C(R^3)$=$CR^4(R^5)$.

54. A compound selected from the group consisting of:

N-((3R,5R)-1-Acryloyl-5-fluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-hydroxypiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-fluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-1-Acryloyl-5-hydroxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(3-fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-1-Acryloyl-5-methoxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-fluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-hydroxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-methoxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(benzofuran-7-yloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-(2,6-difluorophenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(2-ethylphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-fluoro-6-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-cyano-3-(3-methyloxetan-3-yl)acryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-(benzofuran-7-yloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-(methylamino)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(3-((2-Cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(4-Hydroxybut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Chloroacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Aminobut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-1-Acryloyl-4-fluoropyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,EZ)-N-(1-(2-Cyano-4-ethoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Hydroxybut-2-enoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(4-Cyano-1,4-oxazepan-6-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(cyclohexyloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-1-Acryloyl-4-methoxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyanopiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

N-((3S,4R)-1-Acryloyl-4-fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(*S)-(2-Methyl-4-phenoxyphenyl)- N-(1-(4-(methylamino)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-(cyclohexyloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4-methoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-13C-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(But-2-ynoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4-methyl-4-morpholinopent-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-fluoro-6-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-N-(1-propioloylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Fluoroacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Fluoroacryloyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-cyclopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3 H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-5-(4-(2,6-Difluorophenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(5-chlorobenzo[d][1,3]dioxol-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-methoxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(But-2-ynoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-(Dimethylamino)acetyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Fluorophenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-ethyl-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4-methyl-4-(tetrahydro-2H-pyran-4-yl)pent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(2,6-difluorophenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-ethoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(S)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydrofuran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2,6-difluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(Benzofuran-7-yloxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Methoxypropanoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Methoxyphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Ethylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Hydroxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-(2-ethylphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2,3-dimethyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-(Dimethylamino)acetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-fluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydrofuran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2,6-dimethyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(S)-N-(1-acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(pentafluorothio)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-Tetrahydro-2H-pyran-3-yl 5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxylate;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2,4-dimethylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-N-(1-(3-methoxypropanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydrofuran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1,6-Dimethylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Isopropylpyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-4-Fluoro-1-(3-methoxypropanoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Methoxyacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2 H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

N-(1-Cyanoazepan-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Hydroxypropanoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(But-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Isopropylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1,6-Dimethylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(3-(methylsulfonyl)propanoyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(But-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(3-(methylamino)propanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Fluoro-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydrofuran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Acryloylazetidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-13C-Acryloylpiperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((R)-2-Amino-3-methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R,E)-N-(1-(2-Cyano-4-methyl-4-morpholinopent-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-N-(1-(3-(methylsulfonyl)propanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-N-(1-(2-hydroxyacetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-N-(1-(2-methoxyacetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(But-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Isopropylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-ethyl-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((S)-2-Amino-3-methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(6-phenoxypyridazin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((S)-2-Hydroxy-3-methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Hydroxyacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-((R)-1-((S)-1-methylpyrrolidine-3-carbonyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Fluoro-2-methyl-4-phenoxyphenyl)-N-(1-(3-hydroxypropanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(4-Methyl-1,4-oxazepan-6-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-(Dimethylamino)propanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((S)-pyrrolidine-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-4-Fluoro-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Chloro-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)- N-(1-(2-Cyano-4-(dimethylamino)-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Fluoro-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(oxetane-3-carbonyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-N-methyl-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-5-Fluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Hydroxy-1-(3-methoxypropanoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Cyano-3-methylbut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Ethylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

N-((R)-1-((S)-2,3-Dimethoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((R)-2-Hydroxy-3-methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(2-(trifluoromethyl)acryloyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-((R)-1-((R)-1-methylpyrrolidine-3-carbonyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(3-(methylsulfonyl)propanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(o-tolyloxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyclopropylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4-methyl-4-(piperidin-1-yl)pent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Aminoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4-(cyclopropylamino)-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-((6S)-6-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-4-Fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R)-1-(3-Methoxybutanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((S)-3-Methoxy-2-methylpropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-5-(4-(2-Ethoxyphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R)-1-(3-Methoxy-2-methylpropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-5-Fluoro-1-methylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propioloylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(1-methyl-6-oxopiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Aminopropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-Fluoro-1-methylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1,3-Dimethylpiperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(2-oxopiperidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-fluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-5-Hydroxy-1-methylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Ethylphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(quinuclidin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

5-(2-Methyl-4-phenoxyphenyl)-N-(3-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-((6R)-6-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(5,5-Difluoropiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2,6-difluoro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

13C-(R,Z)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

13C-(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-(cyclohexyloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-5-Hydroxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Cyanoacetyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Methylpiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-cyclopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Fluoro-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylazepan-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Methoxy-2,2-dimethylpropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Cyanoazepan-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((R)-2,3-Dimethoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3 H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((R)-pyrrolidine-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(4-(Hydroxymethyl)tetrahydro-2H-pyran-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-ethoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-fluorophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(4-Amino-2-cyano-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(3-(1-Aminocyclopropyl)-2-cyanoacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-Hydroxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((R)-tetrahydrofuran-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(3-Cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-4-Hydroxy-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Cyclopropylphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(5-oxopyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1,2-Dimethylpiperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Methacryloylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-(Cyclopropanecarbonyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylazepan-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((S)-tetrahydrofuran-3-carbonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-4-Methoxy-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(5-chlorobenzo[d][1,3]dioxol-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(m-tolyloxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-4-Methoxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4-(ethylamino)-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyclopropylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(3-Fluorophenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Fluoro-4-phenoxyphenyl)-N-(1-(3-methoxypropanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(o-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(2-(2-oxoimidazolidin-1-yl)ethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Fluoropyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(tetrahydro-2H-pyran-4-carbonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Hydroxyphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(3-Ethoxyacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Fluoro-6-methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Isopropylphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-5-Methoxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(3-methylbut-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(3-(Methoxymethyl)phenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(2-(trifluoromethoxy)phenoxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(3-Cyclopropyl-2-fluoroacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)azetidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Cyclopropylazetidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,EZ)-N-(1-(2-Cyano-3-methoxyacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R,E)-5-(*S)-(5-Chlorobenzo[d][1,3]dioxol-4-yl)-N-(1-(2-cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,EZ)-N-(1-(2-Cyano-4-((2-methoxyethyl)amino)-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3 H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2,6-Difluoro-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Hydroxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N1-((E)-4-(3-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)-4-oxobut-2-en-1-yl)-N5-(15-oxo-19-((3aS,4R,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)glutaramide;

(R,E)-N-(1-(2-Cyano-4-methyl-4-(methylamino)pent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(5-Chlorobenzo[d][1,3]dioxol-4-yl)-N-(1-(2-cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(1-(3-(methylsulfonyl)propanoyl)azetidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-4-Hydroxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(2-(trifluoromethyl)phenoxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Hydroxy-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Methoxy-1-methylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

N-((3S,4S)-4-Methoxypyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-(3-Methoxypropanoyl)azetidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-methylpent-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylazetidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(Cyclohexyloxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Ethylazetidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(Azetidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-N-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-fluorophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-chlorophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-phenyl-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(2-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-5-Methoxy-1-methylpiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-(2-chloro-3-methylbut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(2-Fluorobut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Methyl-5-oxopyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Fluoro-3-methylbut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-4-(pentafluorothio)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-N-((1-methylpyrrolidin-2-yl)methyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-Hydroxy-1-methylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-Methoxypiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(pyrrolidin-2-ylmethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(p-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(5,5-Difluoro-1-methylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Isopropylazetidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4,4-Dimethylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

5-(2-Methyl-4-phenoxyphenyl)-N-(2-morpholinoethyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo- N-(pyrrolidin-2-ylmethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(2-Chlorobut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-phenoxy-2-(trifluoromethyl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(m-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Chloro-3-(trifluoromethyl)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2,3-Dimethyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-((1-methylpyrrolidin-3-yl)methyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Isopropoxyphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Cyclobutoxy-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-((1-methylpyrrolidin-2-yl)methyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(3,5-Difluorophenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-(Dimethylamino)acetyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-(trifluoromethyl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-5-(2-Methyl-4-(p-tolyloxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-N-(2-(3-methylmorpholino)ethyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-(methylamino)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(pyridin-3-yloxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-chlorophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(4-Fluorophenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(2-(3-methylmorpholino)ethyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(Cyclopentyloxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(2-(1-methylpyrrolidin-2-yl)ethyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-fluorophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2,4-Difluorophenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(5-Fluoro-2-methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2,4-dimethylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-5-(5-Fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(pyridin-2-yloxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(5-Fluoro-2-methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydro-2H-pyran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Benzyl-2-oxoazepan-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-2-ylmethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(6-phenoxypyridazin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-Methoxy-1-methylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,EZ)-N-(1-(3-Cyclopropyl-2-(trifluoromethyl)acryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(o-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(2-morpholino-2-oxoethyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2,6-Dimethyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Hydroxypropanoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(5-Chlorobenzo[d][1,3]dioxol-4-yl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Ethylpiperidin-3-yl)-5-(4-(2-isopropylphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(5-chlorobenzo[d][1,3]dioxol-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Cyclopropoxy-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(tetrahydrofuran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxy-2-(trifluoromethyl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Carbamoylphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-2-(piperazin-1-yl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one;

(R)-6-Methyl-4-oxo-5-(4-phenoxyphenyl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyanopiperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3,5-Dichlorophenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-Methyl-5-(2-methyl-4-phenoxyphenyl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Isopropoxy-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Ethoxy-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(tert-butyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-5-(*S)-(2-Methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Chlorophenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-phenyl-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-Methyl-5-(2-methyl-4-phenoxyphenyl)-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Methoxy-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Methoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(2-Methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(5-Chlorobenzo[d][1,3]dioxol-4-yl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

; (R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-isopropyl-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3,4-dichlorophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-chloro-3-(trifluoromethyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Methoxy-3-methylbutanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(3-Acetamidoacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Chloroacryloyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Aminobut-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(vinylsulfonyl)pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-trideuteriomethylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(vinylsulfonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-(methylsulfonyl)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(2,3,4,5,6-pentadeuteriophenoxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-4-(2,3,4,5,6-pentadeuteriophenoxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R,E)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-(methylamino)but-2-enoyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-(2,3,4,5,6-pentadeuteriophenoxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyanopiperidin-3-yl)-5-(2-methyl-4-(2,3,4,5,6-pentadeuteriophenoxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(2,3,4,5,6-pentadeuteriophenoxy)phenyl)-N-(1-(trideuteriomethyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(2,3,4,5,6-pentadeuteriophenoxy)phenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Aminobut-2-enoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-(methylsulfonamido)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-(Dimethylamino)acetyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyanobut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((S)-Azetidine-2-carbonyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-(3-methyloxetan-3-yl)acryloyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(2-Fluoro-4-(methylamino)but-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(2-(pyrrolidin-1-yl)acetyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-2-(((1-Acryloylpiperidin-3-yl)amino)methyl)-5-(2-methyl-4-phenoxyphenyl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(2-(methylamino)acetyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-(2-Aminoacetyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(2-(piperidin-1-yl)acetyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(2-morpholinoacetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Chloroacetyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Chloroacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-(thiophen-2-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-isopropoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-isopropoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(3-Cyclopropyl-2-methylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,EZ)-N-(1-(2-Chloro-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-morpholinobut-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(benzo[b]thiophen-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Isopropoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Isopropoxyphenyl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-4-Oxo-N-(piperidin-3-yl)-5-(4-(thiophen-2-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-phenoxybenzyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Methylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxybenzyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(Benzo[b]thiophen-5-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(trifluoromethoxy)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(trifluoromethoxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(4-(trifluoromethoxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-(trifluoromethoxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(naphthalen-2-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(1-benzyl-1H-pyrazol-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-3-yl)-N-(1-acryloylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-benzylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-4-yl)-N-(1-acryloylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-(2-(Dimethylamino)acetyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-(Dimethylamino)acetyl)pyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(benzo[b]thiophen-2-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Benzylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-((4*S)-2-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(*R)-(2-Methyl-4-phenoxyphenyl)-N-((4*S)-2-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-((4*R)-2-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(*R)-(2-Methyl-4-phenoxyphenyl)-N-((4*R)-2-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(4-(Hydroxymethyl)tetrahydro-2H-pyran-4-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(4-(Hydroxymethyl)tetrahydro-2H-pyran-4-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Chloro-3-methylbut-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Chloro-3-methylbut-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-N-methyl-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Acryloylpyrrolidin-3-yl)-N-methyl-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-isopropyl-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-isopropyl-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Isopropyl-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Isopropyl-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*Z)-N-(1-(2-Cyano-4-methoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*Z)-N-(1-(2-Cyano-4-methoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*E)-N-(1-(2-Cyano-4-methoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*E)-N-(1-(2-Cyano-4-methoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((1-Acryloylpyrrolidin-3-yl)methyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-5-(4-phenoxyphenyl)-N-(pyrrolidin-3-ylmethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-cyclobutoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-cyclobutoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-N-(2-oxopiperidin-3-yl)-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-5-(3-Chloro-4-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Methyl-3-(trifluoromethyl)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-5-(4-phenoxyphenyl)-N-((tetrahydrofuran-2-yl)methyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Hydroxypyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Benzylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(3-phenoxyphenyl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-Methoxypiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-5-Methoxypiperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(*S)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(5-oxopyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(*S)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(5-oxopyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(*R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(5-oxopyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(*R)-5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(5-oxopyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*E)-N-(1-(But-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*E)-N-(1-(But-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R,*Z)-N-(1-(But-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*Z)-N-(1-(But-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*Z)-N-(1-(2-Cyano-4-ethoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*E)-N-(1-(2-Cyano-4-ethoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*Z)-N-(1-(2-Cyano-4-ethoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,*E)-N-(1-(2-Cyano-4-ethoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-1-Acryloyl-5-methoxypiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-methoxypiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-1-Acryloyl-5-hydroxypiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-fluoropiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(4-Cyano-1,4-oxazepan-6-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-fluoropyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3 H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4-ethoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

N-((3S,4S)-1-Acryloyl-4-methoxypyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)pyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-(methylamino)but-2-enoyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-(3-(methylsulfonyl)propanoyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Methoxyacetyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Acryloylazetidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-methyl-5-phenoxypyridin-2-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2',3'-difluoro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-1-Acryloyl-5-fluoropiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3'-fluoro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(4-cyclobutoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Hydroxybut-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2'-methyl-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-(trifluoromethoxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(6-phenoxypyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3'-chloro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-1-Acryloyl-4-methoxypyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,EZ)-N-(1-(2-Cyano-3-(3-methyloxetan-3-yl)acryloyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2'-chloro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Aminobut-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2',4'-difluoro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-benzylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3'-methyl-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-cyclohexylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R,E)-N-(1-(4-Aminobut-2-enoyl)pyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4'-methyl-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Hydroxybut-2-enoyl)pyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-((R)-1-((S)-2-(methylamino)propanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-phenylpyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-phenoxypyrazin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-isopropylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(vinylsulfonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-3-yl)-N-(1-acryloylpyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-(4-(methylsulfonamido)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-propylphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-cyclobutylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-(1-trideuteriomethylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-phenylpyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-(pyridin-3-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(Ethylsulfonyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-(pyridin-2-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(3-Chloro-4-phenoxyphenyl)-N-(1-(4-(dimethylamino)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Isopropylpiperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-fluoropyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-1-Acryloyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)pyrrolidine-3-carboxamide;

(R)-1-Acryloyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)pyrrolidine-3-carboxamide;

(R)-N-(1-(2-(Methylamino)acetyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((S)-3-Hydroxy-2-methylpropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-1-Acryloyl-4-methoxypyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,Z)-N-(1-(4-Amino-2-fluorobut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R,Z)-N-(1-(4-Amino-2-chlorobut-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-3-yl)-N-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-3-yl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3'-Methyl-[1,1'-biphenyl]-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2'-Methyl-[1,1'-biphenyl]-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((E)-4-((4aR,7aS)-tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)but-2-enoyl)pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(2-phenoxypyrimidin-5-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5R)-1-Acryloyl-5-hydroxypiperidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(3-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-(cyclohexyloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-(cyclopentyloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(2'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((R)-3-Hydroxy-2-methylpropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-isopropoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Acetylphenyl)-N-(1-acryloylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-(trifluoromethoxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-cyclopropylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-([1,1'-Biphenyl]-3-yl)-N-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((R)-3-Methoxy-2-methylpropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Chloro-4-phenoxyphenyl)-N-(1-(2-(dimethylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-([1,1'-Biphenyl]-3-yl)-N-(1-(4-(dimethylamino)but-2-enoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(*cis*)-1-Acryloyl-3-hydroxypiperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Chloro-4-phenoxyphenyl)-N-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Methoxyacetyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Chloro-4-phenoxyphenyl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-N-(6-oxopiperidin-3-yl)-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Fluoropyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-5-(4'-Methyl-[1,1'-biphenyl]-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Chloro-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acetylpiperidin-3-yl)-5-(3-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-chloro-4-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(2-phenylpyridin-4-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3*R*,5*R*)-5-Hydroxypiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-3-yl)-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4S)-4-Methoxypyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3*R*,5*R*)-1-Acryloyl-5-hydroxypiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-Hydroxybut-2-enoyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-cyclobutylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyanopiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Methoxypropanoyl)piperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Cyanopiperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-5-(3-Methyl-5-phenoxypyridin-2-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(4-Hydroxybut-2-enoyl)piperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-(3-Methoxypropanoyl)piperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-3-amino-4-((3-cyclobutoxyphenyl)amino)thieno[2,3-b]pyridine-2-carboxamide;

(R)-5-([1,1'-Biphenyl]-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

2-((1-Acryloylpiperidin-3-yl)amino)-5-(2-methyl-4-phenoxyphenyl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one;

(R)-5-([1,1'-Biphenyl]-3-yl)- N-(1-(2-(methylamino)acetyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(2-phenylpyridin-4-yl)-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Cyclobutylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(6-phenylpyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Cyclobutoxy-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

2-((1-Acryloylpiperidin-4-yl)amino)-5-(2-methyl-4-phenoxyphenyl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-methyl-3-(trifluoromethyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(4-Isopropoxy-2-methylphenyl)-4-oxo-N-((R)-1-((E)-4-((4aR,7aS)-tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)but-2-enoyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(4-cyclobutoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-4-Oxo-5-(4-phenylpyridin-2-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(3*R*,5*R*)-*tert*-Butyl 3-hydroxy-5-(4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(oxetan-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-(Cyclopentyloxy)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(trans-3-Hydroxypiperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-(Cyclohexyloxy)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

trans-tert-Butyl 3-hydroxy-4-(4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-4-Oxo-5-(5-phenylpyridin-3-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methoxypyrimidin-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(3-(trifluoromethoxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Cyclobutoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(3-(pyridin-2-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(6-phenylpyridin-2-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-(trifluoromethoxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(3S,4S)-tert-Butyl 3-fluoro-4-(4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)pyrrolidine-1-carboxylate;

(R)-5-(4-Cyclobutoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

tert-Butyl 4-(4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-tert-Butyl 3-(4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-5-(3-Cyclohexylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Isopropylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-(pyridin-4-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-(oxetan-3-yl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-isopropoxy-3-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Cyclobutylpyridin-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(6-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2,2-Difluorobenzo[d][1,3]dioxol-5-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Isopropoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-(tert-butyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(3S,4S)-tert-Butyl 3-methoxy-4-(4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)pyrrolidine-1-carboxylate;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(5-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(tert-butylsulfonyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Hydroxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Acetylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,4R)-1-Acryloyl-4-hydroxypiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Methyl-5-phenoxypyrazin-2-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-methyl-5-phenoxypyrazin-2-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,4R)-4-Hydroxypiperidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(cis-3-Hydroxypiperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-N-(2-oxopyrrolidin-3-yl)-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(R)-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(4-methyl-2-phenoxypyrimidin-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-phenoxypyrimidin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*R)-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(cis-4-Acrylamidotetrahydrofuran-3-yl)-5-(*S)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(6-cyclobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2',3'-difluoro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-hydroxypiperidin-3-yl)-5-(2',3'-difluoro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(3-methyl-2-phenylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-cyclohexylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(6-phenylpyridazin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3R,5S)-1-Acryloyl-5-methoxypiperidin-3-yl)-5-(2',3'-difluoro-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(6-phenoxypyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

N-((R)-1-((*E)-3-((S)-1-Acetylpyrrolidin-2-yl)-2-cyanoacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-cyclobutoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((E)-3-((R)-1-Acetylpyrrolidin-2-yl)-2-cyanoacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((E)-4-((4aR,7aS)-tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)but-2-enoyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(6-phenylpyrimidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(6-cyclobutoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-methyl-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-isobutylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-cyclopentylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(cyclopentyloxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(5-methyl-2-phenylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(2-isopropoxyethoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-isopropylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(5-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(5-phenoxypyrazin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-cyclobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([2,3'-Bipyridin]-4-yl)-N-(1-acryloylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(4-Methyl-6-phenoxypyridin-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(3-Chloro-4-phenoxyphenyl)-N-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(6-cyclobutoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(3-isopropylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2',3'-Difluoro-[1,1'-biphenyl]-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((1RS,2RS)-2-Aminocyclopentyl)-5-(*S)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(3-(tetrahydro-2H-pyran-4-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-([2,2'-Bipyridin]-4-yl)-N-(1-acryloylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2',3'-Difluoro-[1,1'-biphenyl]-3-yl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-5-(2-Methyl-6-phenoxypyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(trans-1-Acryloyl-3-hydroxypiperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-6-phenoxypyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(Methylglycyl)piperidin-3-yl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(4-Methyl-2-phenoxypyrimidin-5-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-6-phenoxypyridin-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3S,4R)-1-Acryloyl-4-hydroxypyrrolidin-3-yl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(5-phenoxypyrimidin-2-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Cyclopentylpyridin-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Isobutylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(6-phenylpyrimidin-4-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*R)-(4-methyl-2-phenoxypyrimidin-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Methyl-[1,1'-biphenyl]-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-cyclobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Isopropylpyridin-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(2-Methyl-6-phenoxypyridin-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(5-Methyl-2-phenylpyridin-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(2-Isopropoxyethoxy)-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Cyclohexylpyridin-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(6-isopropoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(3-Methyl-2-phenylpyridin-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-6-phenylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-6-phenylpyridin-4-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-cyclobutoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(3-methyl-2-phenylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(3-(tetrahydro-2H-pyran-4-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-tert-Butyl 3-(4-oxo-5-(3-(tetrahydro-2H-pyran-4-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-4-Oxo-5-(6-phenylpyridazin-4-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-4-Oxo-5-(6-phenoxypyridin-3-yl)-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-tert-Butyl 3-(5-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidine-1-carboxylate;

(R)-5-(6-Cyclobutoxypyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((3*S,4*R)-4-Acrylamidotetrahydrofuran-3-yl)-5-(*S)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(4-methyl-2-phenoxypyrimidin-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(2-phenoxypyrimidin-5-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(5-phenoxypyrimidin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-isobutylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-phenylpyridazin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((*3R,*4S)-4-Acrylamidotetrahydrofuran-3-yl)-5-(*S)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-isopropoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Isobutylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(5-phenylpyridazin-3-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*R)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-isopropoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(6-Isobutyl-4-methylpyridin-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(6-Isobutoxy-4-methylpyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(6-Isobutoxy-4-methylpyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(6-(Cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*R)-(6-(Cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(4-Methyl-2-phenoxypyrimidin-5-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(6-isobutyl-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(6-Isobutyl-4-methylpyridin-3-yl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-isobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-isobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-(cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-(cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-6-((tetrahydro-2 H-pyran-4-yl)oxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-((2-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-((6-methylpyridin-2-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-((2-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-(pyridin-3-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-((6-methylpyridin-2-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(6-(cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(5-(2-fluorophenoxy)pyridin-2-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(6-isobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N1-(15-Oxo-19-((3aR,4R,6aS)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)-N5-((E)-4-oxo-4-(3-(4-oxo-5-(5-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)piperidin-1-yl)but-2-en-1-yl)glutaramide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,EZ)-N-(1-(2-Cyano-3-(3-methyloxetan-3-yl)acryloyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(((S)-tetrahydrofuran-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-((5-methylpyridin-2-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-(((R)-tetrahydrofuran-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

1-Acryloyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-isopropoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-(pyridazin-3-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-isobutyl-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(2-Methyl-6-phenoxypyridin-3-yl)-4-oxo-N-(tetrahydrofuran-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(6-Isopropoxy-4-methylpyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

2-(4-Acryloylpiperazin-1-yl)-5-(2-methyl-4-phenoxyphenyl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one;

(R)-5-(*S)-(6-(Cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(6-Isobutoxy-4-methylpyridin-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acetylpiperidin-3-yl)-5-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(E)-1-(2-Cyano-3-cyclopropylacryloyl)-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

1-Cyano-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(4-(pyridazin-3-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-isopropoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)-1-propionylpiperidine-4-carboxamide;

(R)-5-(*R)-(6-Isopropoxy-4-methylpyridin-3-yl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(1-propionylpiperidin-3-yl)-5-(4-(pyridin-2-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acetylpiperidin-3-yl)-4-oxo-5-(4-(pyridin-2-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acetylpiperidin-3-yl)-5-(2-methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-(pyridazin-3-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acetylpiperidin-3-yl)-4-oxo-5-(4-(pyridazin-3-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(6-isobutyl-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(E)-1-(2-Cyano-4,4-dimethylpent-2-enoyl)-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

1-(2-Cyanoacetyl)-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

N-(5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)-1-propionylpiperidine-3-carboxamide;

1-(2-Cyanoacetyl)-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

1-Acryloyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

1-Ethyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

1-Cyano-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

1-Methyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-2-(4-methylpiperazin-1-yl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one;

(E)-4,4-Dimethyl-2-(4-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperazine-1-carbonyl)pent-2-enenitrile;

4-(5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperazine-1-carbonitrile;

5-(2-Methyl-4-phenoxyphenyl)-2-(4-propionylpiperazin-1-yl)-3H-1-thia-3,5,8-triazaacenaphthylen-4(5H)-one;

N-(5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-3-carboxamide;

(E)-1-(2-Cyano-4,4-dimethylpent-2-enoyl)-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

(E)-1-(2-Cyano-3-cyclopropylacryloyl)-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

Date Reçue/Date Received 2023-04-13

1-Methyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

1-Ethyl-N-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

N-(5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylen-2-yl)piperidine-4-carboxamide;

(R)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(vinylsulfonyl)pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyanopyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Cyanoacetyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(3-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Methoxypropanoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2',3'-difluoro-4-methyl-[1,1'-biphenyl]-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R,E)-5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(4-(pyridin-2-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-(3-((2-cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-((R)-1-((R)-2-(methylamino)propanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-((R)-1-((R)-Azetidine-2-carbonyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(3-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Cyanopiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-((R)-1-((S)-2-(methylamino)propanoyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(o-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(4-(3-((2-Cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-N-(1-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-(2-methoxyphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(4-(3-((2-Cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-N-(piperidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-5-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-4-Oxo-5-(4-phenoxyphenyl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-(3-((2-cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)piperidin-3-yl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(4-(2-Methoxyphenoxy)-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Cyanopiperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-Cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-5-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((R)-pyrrolidine-2-carbonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Formylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(4-(pyridin-2-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-(2-Cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Cyanopiperidin-3-yl)-5-(4-(2-methoxyphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Cyanopiperidin-4-yl)-5-(4-(2-methoxyphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Formylpiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(o-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Cyanopiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acetylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

N-(1-Cyanopiperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-(2-Cyanoacetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((R)-1-((S)-pyrrolidine-2-carbonyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-(3-((2-cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)piperidin-3-yl)-5-(4-(2-methoxyphenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-(4-(piperidin-1-yl)but-2-enoyl)piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-3-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpiperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(S,E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)pyrrolidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(3-Chloropropanoyl)piperidin-3-yl)-4-oxo-5-(5-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(4-(2-Methoxyphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-(2-(Azetidin-1-yl)acetyl)piperidin-3-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-5-(4-phenoxyphenyl)-N-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Methylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(4-phenoxyphenyl)-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(4-(Dimethylamino)but-2-enoyl)piperidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Benzoylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(5-phenoxypyridin-2-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(4-(2-Methoxyphenoxy)-2-methylphenyl)-4-oxo-N-(piperidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(4-(2-Methoxyphenoxy)-2-methylphenyl)-N-(1-methylpiperidin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-5-(4-(Cyclopentyloxy)-2-methylphenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Methylpiperidin-4-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(E)-N-(1-(2-Cyano-4,4-dimethylpent-2-enoyl)piperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-5-(6-phenoxypyridin-3-yl)-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Isopropoxy-2-methylphenyl)-N-(1-(2-(methylamino)acetyl)piperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Acetylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Benzylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-5-(4-phenoxyphenyl)-N-(piperidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-5-(4-phenoxyphenyl)-N-(2-(pyrrolidin-1-yl)ethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-5-(4-phenoxyphenyl)-N-(2-(piperazin-1-yl)ethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-Acryloylpiperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-5-(2-Methyl-4-phenoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Methylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

4-Oxo-5-(4-phenoxyphenyl)-N-(2-(piperidin-1-yl)ethyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(2-Morpholinoethyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(S)-4-Oxo-5-(4-phenoxyphenyl)-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(2-(4-Methylpiperazin-1-yl)ethyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acetylpiperidin-3-yl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(3-(pyridin-3-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-5-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(3-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Benzoylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3,5-dichlorophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-4-oxo-5-(o-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(3-(dimethylamino)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N-(1-(2-Cyanoacetyl)piperidin-4-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S)-N-(1-Benzylpyrrolidin-3-yl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(S,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(4-methoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-(1-propionylpiperidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-aminophenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-5-(4-(Dimethylamino)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(m-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Chlorophenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-4-Oxo-N-(piperidin-3-yl)-5-(p-tolyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-Fluorophenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(4-(tert-Butyl)phenyl)-4-oxo-N-(piperidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-5-(*S)-(6-Isopropoxy-4-methylpyridin-3-yl)-4-oxo-N-(pyrrolidin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(6-isopropoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-(1-methylcyclobutyl)acryloyl)piperidin-3-yl)-5-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

N1-((E)-4-((R)-3-(1-(2-Methyl-6-phenoxypyridin-3-yl)-2-oxo-1,2,3,5-tetrahydrocyclopenta[de]quinazoline-4-carboxamido)piperidin-1-yl)-4-oxobut-2-en-1-yl)-N5-(15-oxo-19-((3aR,4R,6aS)-2-oxooctahydrocyclopenta[d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)glutaramide;

(R,E)-N-(1-(2-Cyano-4-ethoxy-4-methylpent-2-enoyl)piperidin-3-yl)-5-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R,E)-N-(1-(2-Cyano-3-cyclopropylacryloyl)piperidin-3-yl)-5-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*R)-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-((2-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-((2-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*R)-(2-methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(2-methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-(pyridazin-3-yloxy)pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-4-oxo-5-(5-(pyridazin-3-yloxy)pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(2-methyl-6-(pyridazin-3-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(2-methyl-6-(pyridazin-3-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(4-methyl-6-(pyridazin-3-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide; and

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(4-methyl-6-(pyridazin-3-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

or

pharmaceutically acceptable salts thereof.

55. A compound selected from the group consisting of:

Date Reçue/Date Received 2023-04-13

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(R)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(6-phenoxypyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-phenoxypyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(R)-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(4-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-4-oxo-5-(5-phenoxypyrimidin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

(R)-N-(1-Acryloylpiperidin-3-yl)-5-(*S)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide; and

(R)-N-(1-Acryloylpyrrolidin-3-yl)-5-(*S)-(2-methyl-6-phenoxypyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide, or

pharmaceutically acceptable salts thereof.

56. A pharmaceutical composition comprising at least one compound of any one of claims 1 to 55 and at least one pharmaceutically acceptable excipient.

57. The pharmaceutical composition of claim 56, comprising at least one compound of claim 54 and at least one pharmaceutically acceptable excipient.

58. The pharmaceutical composition of claims 56 comprising at least one compound of claim 55 and at least one pharmaceutically acceptable excipient.

Date Reçue/Date Received 2023-04-13

59. Use of an effective amount of at least one compound as defined in any one of claims 1 to 55 or the pharmaceutical composition of any one of claims 56-58 for the treatment of a subject suffering from or diagnosed with a disease, disorder, or medical condition mediated by Bruton's tyrosine kinase activity.

60. Use of at least one compound as defined in any one of claims 1 to 55 in the manufacture of a medicament for the treatment of a subject suffering from or diagnosed with a disease, disorder, or medical condition mediated by Bruton's tyrosine kinase activity.

61. Use of an effective amount of at least one compound as defined in any one of claims 1 to 55 or the pharmaceutical composition of any one of claims 56-58 for the treatment of cancer in a subject.

62. Use of at least one compound as defined in any one of claims 1 to 55 in the manufacture of a medicament for the treatment of cancer in a subject.

63. The use of claim 61 or 62, wherein the cancer is mantle cell lymphoma, chronic lymphocytic leukemia, macroglobulinemia, or multiple myeloma.

64. Use of an effective amount of at least one compound as defined in any one of claims 1 to 55 or the pharmaceutical composition of any one of claims 56-58 for the treatment of systemic lupus erythematosus in a patient.

65. Use of at least one compound as defined in any one of claims 1 to 55 in the manufacture of a medicament for the treatment of systemic lupus erythematosus in a patient.

66. Use of an effective amount of at least one compound as defined in any one of claims 1 to 55 or the pharmaceutical composition of any one of claims 56-58 for the treatment of a pemphigus disorder or a pemphigoid disorder in a patient.

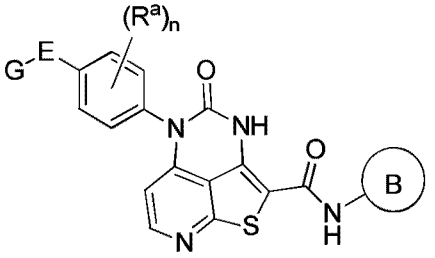
67. Use of at least one compound as defined in any one of claims 1 to 55 in the manufacture of a medicament for the treatment of a pemphigus disorder or a pemphigoid disorder in a patient.

Date Reçue/Date Received 2023-04-13

68. Use of an effective amount of at least one compound as defined in any one of claims 1 to 55 or the pharmaceutical composition of any one of claims 56-58 for the treatment of rheumatoid arthritis in a patient.

69. Use of at least one compound as defined in any one of claims 1 to 55 in the manufacture of a medicament for the treatment of rheumatoid arthritis in a patient.

70. A compound of claim 1 having the structure of Formula (II'), and stereoisomers, isotopic variants, or pharmaceutically acceptable salts thereof of Formula (II');



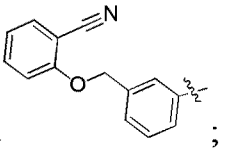
(II')

wherein

R^a is independently selected from the group consisting of: H, Cl, F, CH_3, and CF_3;

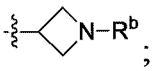
n is 0-2;

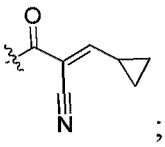
E is O;

G is selected from the group consisting of: C_{3-6}cycloalkyl; oxetanyl; tetrahydrofuranyl; tetrahydropyranyl; benzofuran-7-yloxy; pyridyl; pyridyl substituted with CH_3; phenyl; phenyl substituted with one or two members independently selected from the group consisting of: halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, OH, OC_{1-6}alkyl, OC_{1-6}haloalkyl, CH_2OCH_3, $(C=O)NH_2$, and C_{3-6}cycloalkyl; and  ;

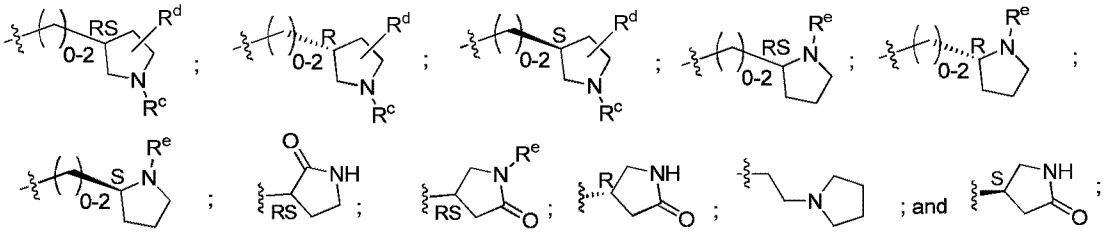
Ring B is selected from the group consisting of:

Date Reçue/Date Received 2023-04-13

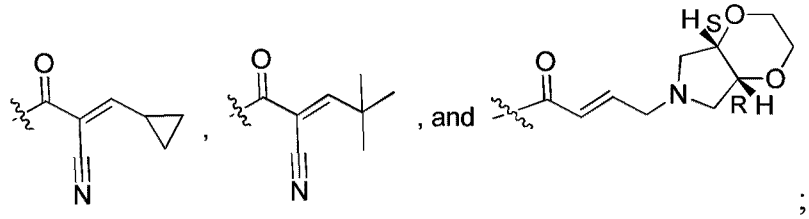
(a)  ; wherein R^b is selected from the group consisting of: H; C_{1-6}alkyl, C_{3-6}cycloalkyl, $(C=O)CH=CH_2$, $(C=O)CH_2CH_2OCH_3$,$(C=O)CH_2CH_2SO_2CH_3$, and

 ;

(b)



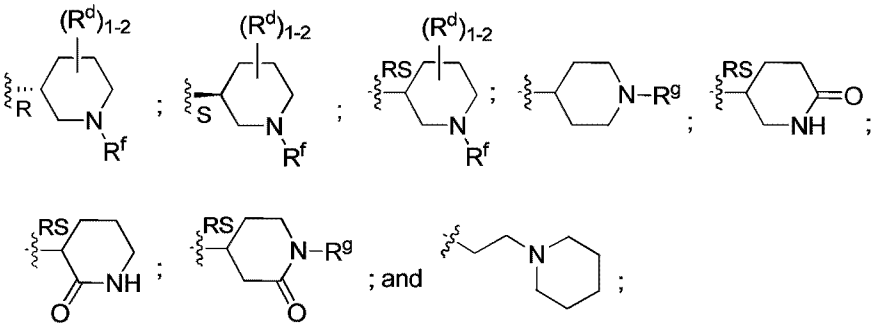
wherein R^c is selected from the group consisting of: H, C_{1-6}alkyl, CN, $(C=O)C_{1-3}$alkyl, $(C=O)CH=CH_2$, C_{3-6}cycloalkyl, $(C=O)CH_2NH_2$, $(C=O)CH_2NH(CH_3)$, $(C=O)CH_2N(CH_3)_2$, $(C=O)CH_2CN$, CH_2-phenyl, $(C=O)CH_2Cl$, $(C=O)CH=CHCH_2NH_2$, $(C=O)CH_2CH_2OCH_3$, $(C=O)CH=CHCH_2NH(CH_3)$,$(C=O)CH=CHCH_2N(CH_3)_2$, $(C=O)CH=CHCH_2OH$, $(C=O)$-phenyl, $SO_2CH=CH_2$, $(C=O)CH_2CH_2SO_2CH_3$,

 ;

R^d is selected from the group consisting of: H, F, OH, and OCH_3;

R^e is H or C_{1-6}alkyl;

(c)



wherein

R^d is selected from the group consisting of: H, F, OH, and OCH_3;

R^f is selected from the group consisting of: (C=O)-C(R^3)=CR^4(R^5); H; C_{1-6}alkyl; CN; (C=O)C_{1-3}alkyl; (C=O)C_{1-3}haloalkyl; (C=O)C_{2-6}alkenyl; (C=O)C_{2-6}alkynyl; (C=O)$(CH_2)_{1-2}OH$; (C=O)$(CH_2)_{1-2}OCH_3$; (C=O)H; (C=O)$(CH_2)_{0-1}CN$; (C=O)CH_2NH_2; (C=O)$(CH_2)_{1-2}NH(CH_3)$; (C=O)$(CH_2)_{1-2}N(CH_3)_2$; (C=O)$CH(CH_3)NH(CH_3)$; (C=O)$(CH_2)_{1-2}SO_2CH_3$; (C=O)$CH_2CH(CH_3)(OCH_3)$; (C=O)$CH(CH_3)CH_2(OH)$; (C=O)$CH(CH_3)CH_2(OCH_3)$; (C=O)$C(CH_3)_2CH_2(OCH_3)$; (C=O)$CH_2C(CH_3)_2(OCH_3)$; (C=O)$CH(NH_2)CH_2(OCH_3)$; (C=O)$CH(OCH_3)CH_2(OCH_3)$; (C=O)$CH(OH)CH_2(OCH_3)$; C_{3-6}cycloalkyl; (C=O)$(CH_2)_{0-1}$azetidinyl; (C=O)oxetanyl; (C=O)tetrahydrofuranyl; (C=O)tetrahydropyranyl; (C=O)$(CH_2)_{0-1}$pyrrolidinyl, wherein said pyrrolidinyl is optionally substituted with CH_3; (C=O)$(CH_2)_{0-1}$piperidinyl; (C=O)$(CH_2)_{0-1}$morpholinyl; SO_2-C_{2-6}alkenyl; SO_2C_{1-6}alkyl; and linker-PEG-Biotin;

R^3 is selected from the group consisting of: H, CN, halogen, C_{1-6}haloalkyl, and C_{1-6}alkyl;

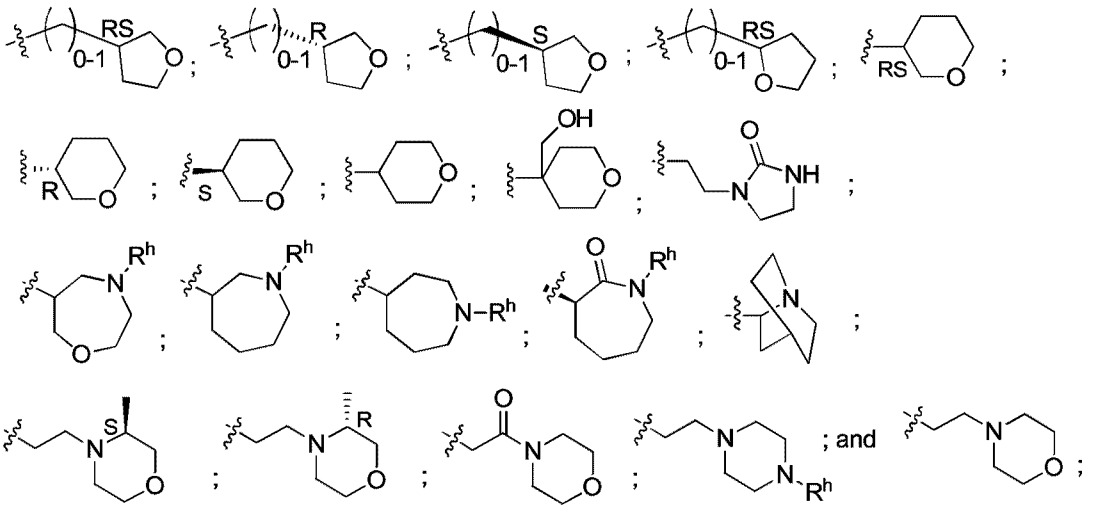
R^4 and R^5 are each independently selected from the group consisting of: H; halogen; C_{1-6}alkyl; CH_2OH; C_{1-6}alk-OC_{1-6}alkyl; OC_{1-6}alkyl; C_{1-4}alk-NR^6R^7; C_{3-6}cycloalkyl substituted with NH_2 or CH_3; oxetanyl substituted with CH_3; 1-acetylpyrrolidin-2-yl; CH_2-pyrrolidinyl; CH_2-piperidinyl; $C(CH_3)_2$-piperidinyl; CH_2-morpholinyl; $C(CH_3)_2$-morpholinyl; CH_2-(4aR,7aS)-tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl; $C(CH_3)_2NH(CH_2CH_2OCH_3)$; $CH_2SO_2CH_3$; $CH_2NHSO_2CH_3$; NH(C=O)C_{1-6}alkyl; and linker-PEG-Biotin; and

R^6 and R^7 are each independently selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl, and CN;

R^g is selected from the group consisting of: H, C_{1-6}alkyl, and CN; and

(d)

Date Reçue/Date Received 2023-04-13

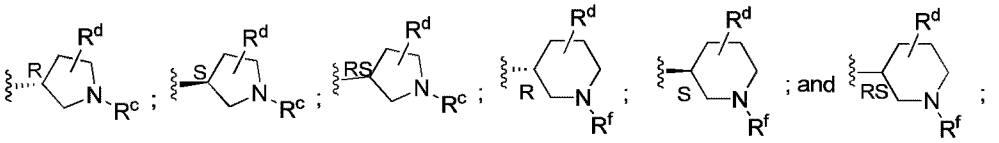


and wherein R^h is selected from the group consisting of: H, CN, CH_3, and CH_2phenyl.

71. The compound of claim 70, wherein R^a is H or CH_3; n is 1; E is O;

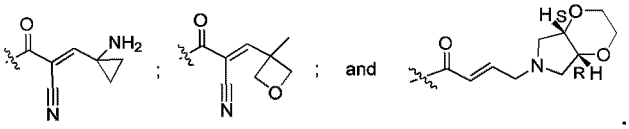
G is phenyl or phenyl substituted with C_{1-6}alkyl;

Ring B is selected from the group consisting of

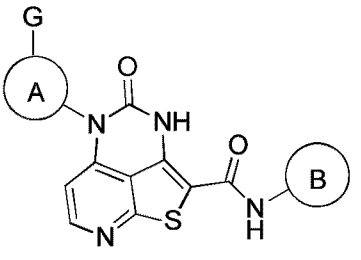


R^c and R^f are $(C=O)CH=CH_2$; and R^d is H.

72. The compound of claim 70, wherein R^f is selected from the group consisting of



73. The compound of claim 1 having the structure of Formula (III'), and stereoisomers, isotopic variants, or pharmaceutically acceptable salts of Formula (III');

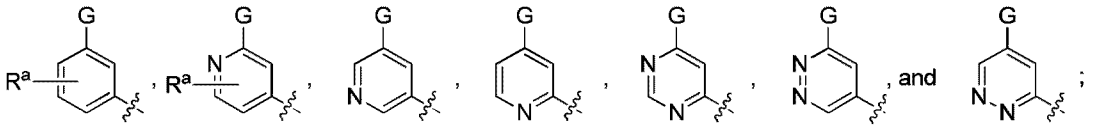


(III')

Date Reçue/Date Received 2023-04-13

wherein

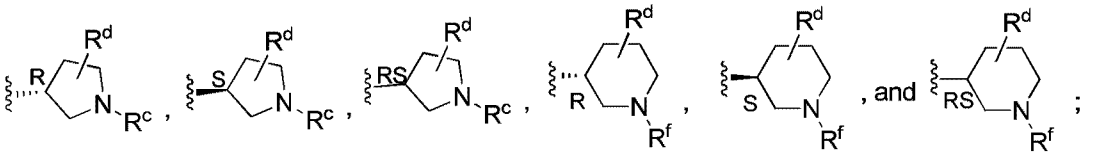
G-A is selected from the group consisting of:



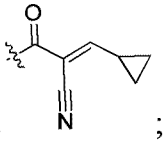
wherein G is phenyl; or phenyl substituted with one or two members independently selected from the group consisting of: halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, pyridyl, oxetan-3-yl, and tetrahydro-2H-pyran-4-yl;

R^a is H or CH_3;

Ring B is selected from the group consisting of:



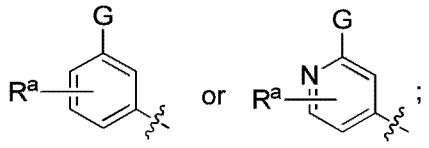
wherein R^c and R^f are independently selected from the group consisting of: H, C_{1-6}alkyl,



$(C=O)CH=CH_2$, $(C=O)CH_2NH(CH_3)$, $(C=O)CH=CHCH_2N(CH_3)_2$, and ;

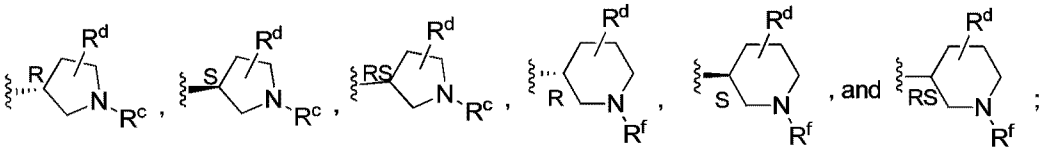
and R^d is selected from the group consisting of: H, OH and OCH_3.

74. The compound of claim 73, wherein

G-A is  ;

G is phenyl, or phenyl substituted with C_{1-6}alkyl;

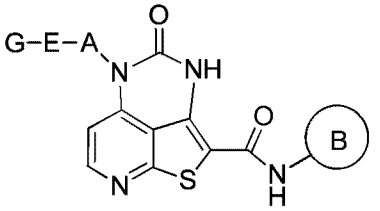
Ring B is selected from the group consisting of



and R^c and R^f are $(C=O)CH=CH_2$; and R^d is H.

Date Reçue/Date Received 2023-04-13

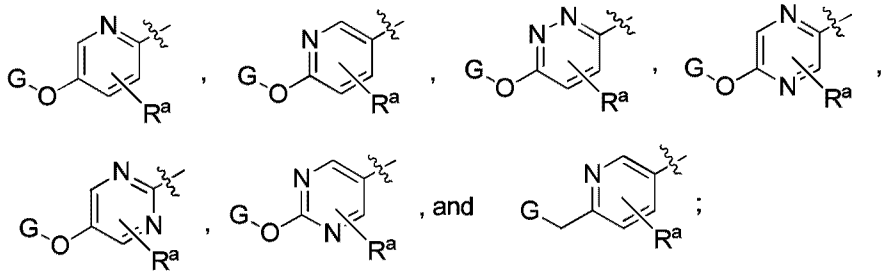
75. The compound of claim 1 having the structure of Formula (IV'), and stereoisomers, isotopic variants, or pharmaceutically acceptable salts of Formula (IV'):



(IV')

wherein

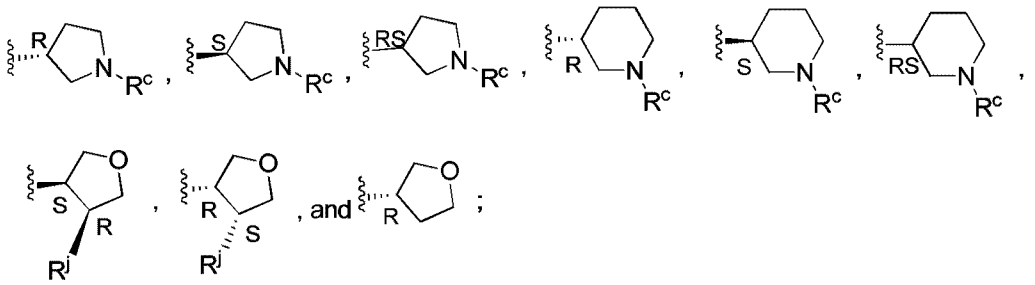
G-E-A is selected from the group consisting of:



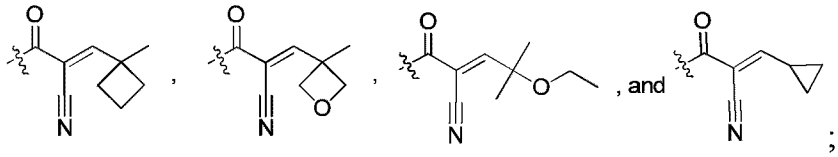
wherein G is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl, tetrahydro-2H-pyran-4-yl, pyridazin-3-yl, phenyl, and phenyl substituted with F;

R^a is H or CH_3;

Ring B is selected from the group consisting of:



R^c is selected from the group consisting of: H, C_{1-6}alkyl, $(C=O)C_{1-3}$alkyl, $(C=O)CH=CH_2$, $(C=O)C_{1-6}$haloalkyl,

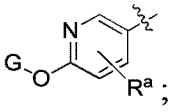


; and

R^j is selected from the group consisting of: H, NH_2, and $NH(C=O)CH=CH_2$.

Date Reçue/Date Received 2023-04-13

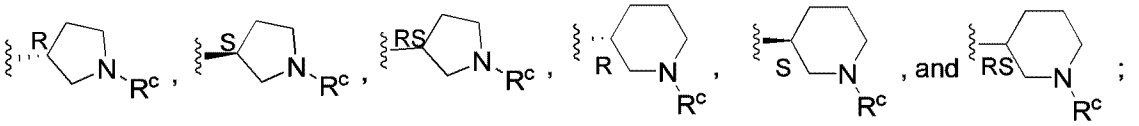
76. The compound of claim 75, wherein

G-E-A is  ;

R^a is CH_3;

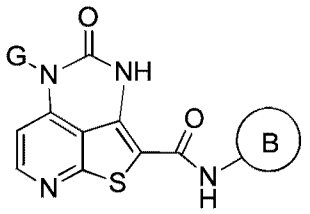
G is phenyl;

Ring B is selected from the group consisting of



and R^c is $(C=O)CH=CH_2$.

77. The compound of claim 1 having the structure of Formula (V'), and stereoisomers, isotopic variants, or pharmaceutically acceptable salts of Formula (V'):

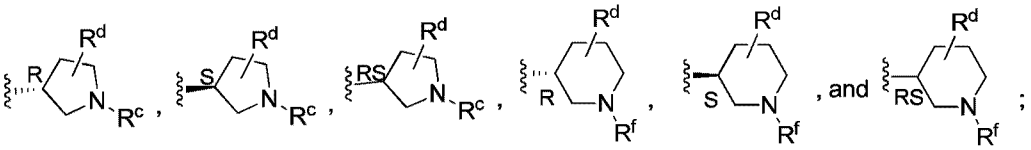


(V')

wherein

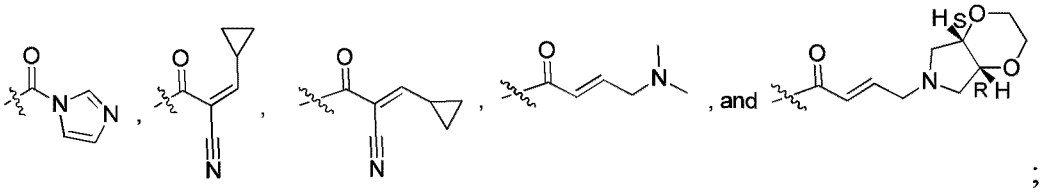
G is selected from the group consisting of: C_{1-6}alkyl; C_{1-6}haloalkyl; phenyl; phenyl substituted with one or two members independently selected from the group consisting of: halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, OC_{1-6}alkyl, OC_{1-6}haloalkyl, $(C=O)$-C_{1-6}alkyl, SF_5, OH, NH_2, $N(CH_3)_2$, $OCH_2CH_2OCH(CH_3)_2$, and SO_2C_{1-6}alkyl; benzo[d][1,3]dioxolyl optionally substituted with Cl; 2-methylpyridin-3-yl; 2-isopropylpyridin-4-yl; benzothiophenyl; napthalenyl; and 2,2-difluorobenzo[d][1,3]dioxol-5-yl;

Ring B is selected from the group consisting of:



Date Reçue/Date Received 2023-04-13

wherein R^e and R^f are independently selected from the group consisting of: H, C_{1-6}alkyl, $(C=O)C_{1-3}$alkyl, $(C=O)CH=CH_2$, $(C=O)CH_2NHCH_3$,

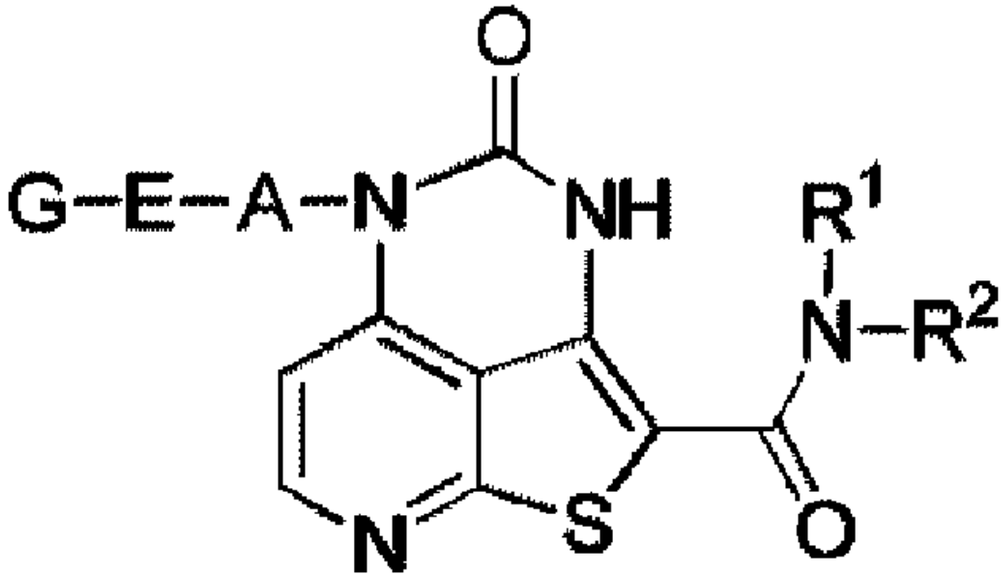


;

and

R^d is H or OH.

Date Reçue/Date Received 2023-04-13



(I')