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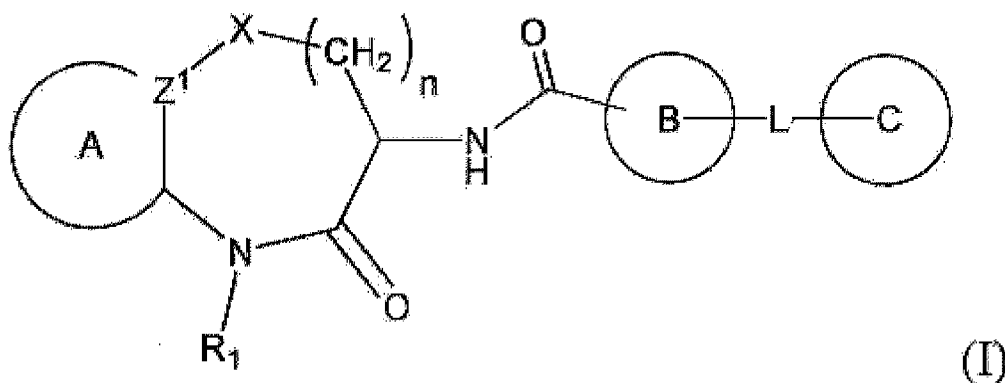
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(54) Title: BICYCLIC LACTAMS AND METHODS OF USE THEREOF



(57) Abrégé/Abstract:

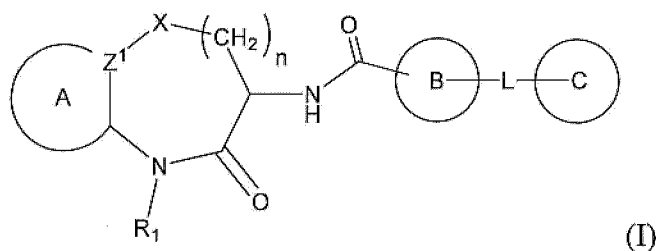
The invention relates to compounds having the general formula I: (see formula I) wherein R¹, X, Z¹, L, n, the A ring, the B ring, and the C ring are as described herein, pharmaceutical compositions including the compounds, and uses of the compounds relating to treatment or prophylaxis of irritable bowel disorders (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia-reperfusion injury of kidneys, liver and lungs, cisplatin-induced kidney injury, sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa, retinal degeneration, chronic kidney diseases, acute respiratory distress syndrome (ARDS) or chronic obstructive pulmonary disease (COPD).

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ABSTRACT

The invention relates to compounds having the general formula I:



wherein R^1 , X, Z^1 , L, n, the A ring, the B ring, and the C ring are as described herein,
pharmaceutical compositions including the compounds, and uses of the compounds relating to
treatment or prophylaxis of irritable bowel disorders (IBD), irritable bowel syndrome (IBS),
Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury,
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injury, sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis
pigmentosa, retinal degeneration, chronic kidney diseases, acute respiratory distress syndrome
(ARDS) or chronic obstructive pulmonary disease (COPD).

DEMANDE OU BREVET VOLUMINEUX

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CECI EST LE TOME 1 DE 4
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BICYCLIC LACTAMS AND METHODS OF USE THEREOF

FIELD OF THE INVENTION

5 The present invention relates to organic compounds useful for therapy and/or prophylaxis in a mammal, and in particular to inhibitors of RIP1 kinase useful for treating diseases and disorders associated with inflammation, cell death and others.

BACKGROUND OF THE INVENTION

10 Receptor-interacting protein-1 (“RIP1”) kinase is a serine/threonine protein kinase. RIP1 is a regulator of cell signaling that is involved, among other things, in the mediation of programmed cell death pathways, *e.g.*, necroptosis. The best studied form of necroptotic cell death is initiated by TNF α (tumor necrosis factor), but necroptosis can also be induced by other members of the TNF α death ligand family (Fas and TRAIL/Apo2L), interferons, Toll-like receptors (TLRs) signaling and viral infection via the DNA sensor DAI (DNA-dependent activator of interferon regulatory factor) [1-3].

15 Binding of TNF α to the TNFR1 (TNF receptor 1) prompts TNFR1 trimerization and formation of an intracellular complex, Complex-I. TRADD (TNF receptor associated death domain protein) binds to the intracellular death domain of TNFR1 and recruits the protein kinase RIP1 (receptor-interacting protein 1) through the death domain present in both proteins [4]. Following initial recruitment into TNFR1-associated signaling complex, RIP1 translocates to a secondary cytoplasmatic complex, Complex-II [5-7]. Complex-II is formed by the death domain containing protein FADD (Fas-associated Protein), RIP1, caspase-8 and cFLIP. If caspase-8 is not fully activated or its activity is blocked, the protein kinase RIP3 gets recruited to the complex, forming a necrosome, which will lead to necroptotic cell death initiation [8-10]. Once the necrosome is formed, RIP1 and RIP3 engage in a series of auto and cross phosphorylation events that are essential for necroptotic cell death. Necroptosis
20 can be completely blocked either by the kinase inactivating mutation in any of the two kinases, or chemically by RIP1 kinase inhibitors (necrostatins), or RIP3 kinase inhibitors [11-13]. Phosphorylation of RIP3 allows the binding and phosphorylation of pseudokinase MLKL (mixed
25

lineage kinase domain-like), a key component of necroptotic cell death [14, 15].

Necroptosis has crucial pathophysiological relevance in myocardial infarction, stroke, atherosclerosis, ischemia–reperfusion injury, inflammatory bowel diseases, retinal degeneration and a number of other common clinical disorders [16]. Therefore, selective inhibitors of RIP1 kinase activity are therefore desired as a potential treatment of diseases mediated by this pathway and associated with inflammation and/or necroptotic cell death.

Inhibitors of RIP1 kinase have been previously described. The first published inhibitor of RIP1 kinase activity was necrostatin 1 (Nec-1) [17]. This initial discovery was followed by modified versions of Nec-1 with various abilities to block RIP1 kinase activity [11, 18]. Recently, additional RIP1 kinase inhibitors have been described that differ structurally from necrostatin class of compounds [19, 20, 21].

References cited above:

- 1) Vanden Berghe, T., Linkermann, A., Jouan-Lanhout, S., Walczak, H. and Vandenabeele, P. (2014) Regulated necrosis: the expanding network of non-apoptotic cell death pathways. *Nature reviews. Molecular cell biology*. **15**, 135-147.
- 2) Newton, K. (2015) RIPK1 and RIPK3: critical regulators of inflammation and cell death. *Trends in cell biology*. **25**, 347-353.
- 3) de Almagro, M. C. and Vucic, D. (2015) Necroptosis: Pathway diversity and characteristics. *Semin Cell Dev Biol*. **39**, 56-62.
- 4) Chen, Z. J. (2012) Ubiquitination in signaling to and activation of IKK. *Immunological reviews*. **246**, 95-106.
- 5) O'Donnell, M. A., Legarda-Addison, D., Skountzos, P., Yeh, W. C. and Ting, A. T. (2007) Ubiquitination of RIP1 regulates an NF-kappaB-independent cell-death switch in TNF signaling. *Curr Biol*. **17**, 418-424.
- 6) Feoktistova, M., Geserick, P., Kellert, B., Dimitrova, D. P., Langlais, C., Hupe, M., Cain, K., MacFarlane, M., Hacker, G. and Leverkus, M. (2011) cIAPs block Ripoptosome formation, a

RIP1/caspase-8 containing intracellular cell death complex differentially regulated by cFLIP isoforms. *Molecular cell*. **43**, 449-463.

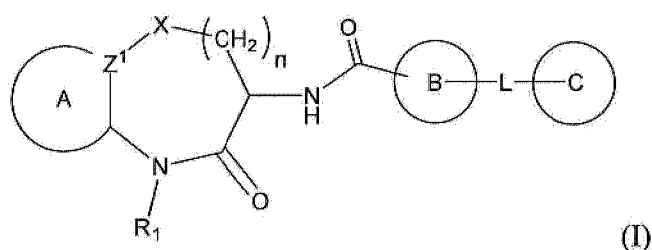
- 7) Bertrand, M. J., Milutinovic, S., Dickson, K. M., Ho, W. C., Boudreault, A., Durkin, J., Gillard, J. W., Jaquith, J. B., Morris, S. J. and Barker, P. A. (2008) cIAP1 and cIAP2 facilitate cancer cell survival by functioning as E3 ligases that promote RIP1 ubiquitination. *Mol Cell*. **30**, 689-700.
- 8) Wang, L., Du, F. and Wang, X. (2008) TNF- α induces two distinct caspase-8 activation pathways. *Cell*. **133**, 693-703.

- 9) He, S., Wang, L., Miao, L., Wang, T., Du, F., Zhao, L. and Wang, X. (2009) Receptor interacting protein kinase-3 determines cellular necrotic response to TNF- α . *Cell*. **137**, 1100-1111.
- 10) Cho, Y. S., Challa, S., Moquin, D., Genga, R., Ray, T. D., Guildford, M. and Chan, F. K. (2009) Phosphorylation-driven assembly of the RIP1-RIP3 complex regulates programmed necrosis and virus-induced inflammation. *Cell*. **137**, 1112-1123.
- 11) Degterev, A., Hitomi, J., Gernsheid, M., Ch'en, I. L., Korkina, O., Teng, X., Abbott, D., Cuny, G. D., Yuan, C., Wagner, G., Hedrick, S. M., Gerber, S. A., Lugovskoy, A. and Yuan, J. (2008) Identification of RIP1 kinase as a specific cellular target of necrostatins. *Nat Chem Biol*. **4**, 313-321.
- 12) Newton, K., Dugger, D. L., Wickliffe, K. E., Kapoor, N., de Almagro, M. C., Vucic, D., Komuves, L., Ferrando, R. E., French, D. M., Webster, J., Roose-Girma, M., Warming, S. and Dixit, V. M. (2014) Activity of protein kinase RIPK3 determines whether cells die by necroptosis or apoptosis. *Science*. **343**, 1357-1360.
- 13) Kaiser, W. J., Sridharan, H., Huang, C., Mandal, P., Upton, J. W., Gough, P. J., Schon, C. A., Marquis, R. W., Bertin, J. and Mocarski, E. S. (2013) Toll-like receptor 3-mediated necrosis via TRIF, RIP3, and MLKL. *The Journal of biological chemistry*. **288**, 31268-31279.
- 14) Zhao, J., Jitkaew, S., Cai, Z., Choksi, S., Li, Q., Luo, J. and Liu, Z. G. (2012) Mixed lineage kinase domain-like is a key receptor interacting protein 3 downstream component of TNF-induced necrosis. *Proceedings of the National Academy of Sciences of the United States of America*. **109**, 5322-5327.
- 15) Sun, L., Wang, H., Wang, Z., He, S., Chen, S., Liao, D., Wang, L., Yan, J., Liu, W., Lei, X. and Wang, X. (2012) Mixed Lineage Kinase Domain-like Protein Mediates Necrosis Signaling Downstream of RIP3 Kinase. *Cell*. **148**, 213-227.
- 16) Linkermann, A. and Green, D. R. (2014) Necroptosis. *The New England journal of medicine*. **370**, 455-465.
- 17) Degterev, A., Huang, Z., Boyce, M., Li, Y., Jagtap, P., Mizushima, N., Cuny, G. D., Mitchison, T. J., Moskowitz, M. A. and Yuan, J. (2005) Chemical inhibitor of nonapoptotic cell death with therapeutic potential for ischemic brain injury. *Nat Chem Biol*. **1**, 112-119.
- 18) Takahashi, N., Duprez, L., Grootjans, S., Cauwels, A., Nerinckx, W., DuHadaway, J. B., Goossens, V., Roelandt, R., Van Hauwermeiren, F., Libert, C., Declercq, W., Callewaert, N., Prendergast, G. C., Degterev, A., Yuan, J. and Vandenabeele, P. (2012) Necrostatin-1 analogues: critical issues on the specificity, activity and in vivo use in experimental disease models. *Cell Death Dis*. **3**, e437.

- 19) Harris, P. A., Bandyopadhyay, D., Berger, S. B., Campobasso, N., Capriotti, C. A., Cox, J. A., Dare, L., Finger, J. N., Hoffman, S. J., Kahler, K. M., Lehr, R., Lich, J. D., Nagilla, R., Nolte, R. T., Ouellette, M. T., Pao, C. S., Schaeffer, M. C., Smallwood, A., Sun, H. H., Swift, B. A., Totoritis, R. D., Ward, P., Marquis, R. W., Bertin, J. and Gough, P. J. (2013) Discovery of Small Molecule RIP1 Kinase Inhibitors for the Treatment of Pathologies Associated with Necroptosis. ACS medicinal chemistry letters. 4, 1238-1243.
- 20) Najjar, M., Suebsuwong, C., Ray, S. S., Thapa, R. J., Maki, J. L., Nogusa, S., Shah, S., Saleh, D., Gough, P. J., Bertin, J., Yuan, J., Balachandran, S., Cuny, G. D. and Degterev, A. (2015) Structure Guided Design of Potent and Selective Ponatinib-Based Hybrid Inhibitors for RIPK1. Cell Rep.
- 21) International Patent Publication No. WO 2014/125444.

SUMMARY OF THE INVENTION

Disclosed herein are compounds of formula I:



or pharmaceutically acceptable salts thereof, wherein

- R^1 is selected from the group consisting of H, C_1 - C_4 alkyl and C_1 - C_4 haloalkyl;
- the A ring is selected from the group consisting of cyclopropyl, 6 membered aryl, and 5 to 6 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the A ring is optionally substituted with:
- (a) 1 to 3 substituents selected from the group consisting of halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 thioalkyl, cyano, phenyl, benzyl, CH_2 -(C_3 - C_6 cycloalkyl), and CH_2CH_2 -(C_3 - C_6 cycloalkyl); wherein if a nitrogen atom in the A ring is substituted, the substituent is not halogen, cyano, or a C_1 - C_6

alkoxy, C₁-C₆ haloalkoxy or C₁-C₆ thioalkyl having an oxygen or sulfur atom directly bonded to the nitrogen atom;

(b) 1 substituent selected from the group consisting of C₄-C₆ heterocyclyl, C₅-C₆ heteroaryl, CH₂-(C₄-C₆ heterocyclyl), CH₂CH₂-(C₄-C₆ heterocyclyl), CH₂CH₂CH₂-(C₄-C₆ heterocyclyl), CH₂-(C₅-C₆ heteroaryl), CH₂CH₂-(C₅-C₆ heteroaryl); CH₂CH₂CH₂-(C₅-C₆ heteroaryl); and optionally a second substituent selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, and C₁-C₆ haloalkoxy; or

(c) two adjacent substituents which together form phenyl, C₅-C₆ heteroaryl, C₄-C₆ heterocyclyl or C₄-C₆ cycloalkyl;

the B ring is tetrazolyl or a 5 to 6 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the B ring is optionally substituted with 1 to 2 substituents selected from the group consisting of halogen, C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and cyano; and wherein if a nitrogen atom in the B ring is substituted, the substituent is not halogen, cyano, or a C₁-C₆ alkoxy, C₁-C₆ haloalkoxy or C₁-C₆ thioalkyl having an oxygen or sulfur atom directly bonded to the nitrogen atom;

the C ring is selected from the group consisting of phenyl, 5 to 6 membered heteroaryl, 4 to 7 membered cycloalkyl, and 4 to 7 membered heterocyclyl; wherein the C ring is optionally substituted with:

(a) 1 to 4 substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, cyano, phenyl, benzyl, CH₂-(C₃-C₆ cycloalkyl), and CH₂CH₂-(C₃-C₆ cycloalkyl); wherein if a nitrogen atom in the C ring is substituted, the substituent is not halogen, cyano, or a C₁-C₆ alkoxy, C₁-C₆ haloalkoxy or C₁-C₆ thioalkyl having an oxygen or sulfur atom directly bonded to the nitrogen atom;

(b) 1 to 2 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, CH₂-(C₄-C₆ heterocyclyl), CH₂CH₂-(C₄-C₆ heterocyclyl), and unsubstituted C₅-C₆ heteroaryl; or

(c) two adjacent substituents which together form phenyl, C₅-C₆ heteroaryl, C₄-C₆ heterocyclyl or C₄-C₆ cycloalkyl;

L is selected from the group consisting of a bond, O, S, NH, NCH₃, (CH₂)_m, CH(CH₃), C(CH₃)₂, CF₂, CH₂O, CH₂S, CH(OH), CH₂NH, and CH₂N(CH₃), or L is absent such that the B ring and the C ring are fused;

X is selected from the group consisting of O, S, SO, SO₂, CH₂, C(CH₃)₂, CF₂ and CHCF₃;

5 Z¹ is selected from the group consisting of:

- (i) C and N when the A ring is a 5 or 6 membered heteroaryl,
- (ii) C when the A ring is a 6 membered aryl, and
- (iii) CH when the A ring is cyclopropyl;

m is 1 or 4; and

10 n is 1 or 2;

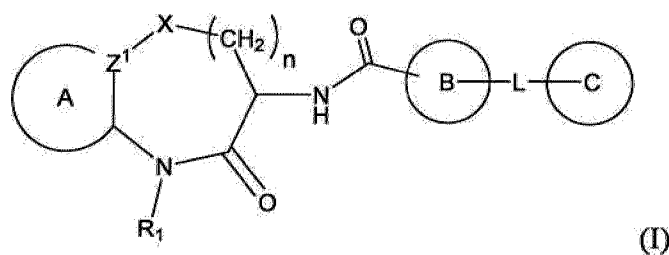
provided that if the A ring is 6 membered aryl or 6 membered heteroaryl, L is absent such that the B ring and the C ring are fused;

further provided that if the A ring is a 5 to 6 membered heteroaryl having 3 heteroatoms, two of said heteroatoms must be nitrogen;

15 further provided that if the A ring is unsubstituted 6 membered aryl and L is absent, the fused B and C rings are not unsubstituted indolyl or indolyl substituted by one or two halogen atoms; and

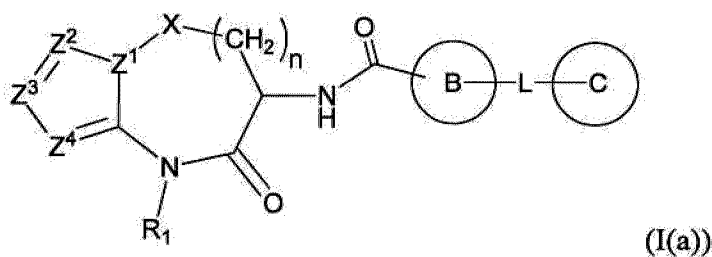
further provided that if the B ring is tetrazolyl, L is selected from the group consisting of CH₂, CH(CH₃), C(CH₃)₂, CF₂; and the C ring is phenyl.

In one aspect, the present invention provides a compound of formula I:



20

having the structure



or a pharmaceutically acceptable salt thereof, wherein

R₁ is selected from the group consisting of H and unsubstituted C₁-C₄ alkyl;

the A ring is selected from the group consisting of 5 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein two of said heteroatoms must be nitrogen; wherein the A ring is optionally substituted with:

- (a) 1 to 3 substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, cyano, phenyl, benzyl, CH₂-(C₃-C₆ cycloalkyl), and CH₂CH₂-(C₃-C₆ cycloalkyl); wherein if a nitrogen atom in the A ring is substituted, the substituent is not halogen, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, or cyano;
- (b) 1 substituent selected from the group consisting of C₄-C₆ heterocyclyl, C₅-C₆ heteroaryl, CH₂-(C₄-C₆ heterocyclyl), CH₂CH₂-(C₄-C₆ heterocyclyl), CH₂-(C₅-C₆ heteroaryl), and CH₂CH₂-(C₅-C₆ heteroaryl); and optionally a second substituent selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, and C₁-C₆ haloalkoxy; or
- (c) two adjacent substituents which together form phenyl, C₅-C₆ heteroaryl, C₄-C₆ heterocyclyl or C₄-C₆ cycloalkyl;

Z¹ is selected from the group consisting of C and N;

Z², Z³, and Z⁴ are each independently selected from the group consisting of CR^Z and NR⁸; each R^Z is independently selected from the group consisting of H, halogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, CH₂-(C₃-C₆ cycloalkyl), C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ thioalkyl, CH₂-(C₄-C₆ cycloalkoxy), CH₂-(C₄-C₆ thiocycloalkyl), phenyl, benzyl, 4 to 6 membered heterocyclyl, and 5 to 6 membered heteroaryl;

each R⁸ is either absent if the nitrogen atom to which it is attached has three bonds to other atoms, or R⁸ is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, CH₂-(C₃-C₆ cycloalkyl), C₁-C₆ haloalkyl, CH₂-(C₄-C₆ cycloalkoxy), CH₂-(C₄-C₆ thiocycloalkyl), phenyl, benzyl, C₃-C₆ cycloalkyl substituted by 1 to 2 fluorine atoms, (C₁-C₄ alkoxy)-C₁-C₂ alkyl, and CH₂-(C₃-C₆ cycloalkyl substituted by 1 to 2 fluorine atoms);

wherein Z¹ is N only if X is CH₂, CF₂, CH(CH₃), CH(CF₃), C(CH₃)₂, or CH(OH);

wherein if Z¹ is N, at least one of Z², Z³ or Z⁴ is CR^Z;

wherein if Z¹ is C, at least one of Z², Z³, and Z⁴ is NR⁸;

wherein, when Z^2 and Z^3 are each independently selected from the group consisting of CR^Z and NR^8 , Z^2 and Z^3 together with their respective R^Z and R^8 substituents may form a 6 membered aryl, 6 membered heteroaryl, 5 to 6 membered cycloalkyl or 5 to 6 membered heterocyclyl group;

wherein, when Z^3 and Z^4 are each independently selected from the group consisting of CR^Z and NR^8 , Z^3 and Z^4 together with their respective R^Z and R^8 substituents may form a 6 membered aryl, 6 membered heteroaryl, 5 to 6 membered cycloalkyl or 5 to 6 membered heterocyclyl group;

the B ring is tetrazolyl or a 5 to 6 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the B ring is optionally substituted with 1 to 2 substituents selected from the group consisting of halogen, C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy and cyano; and wherein if a nitrogen atom in the B ring is substituted, the substituent is not halogen, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 thioalkyl, or cyano; the C ring is selected from the group consisting of phenyl, 5 to 6 membered heteroaryl, 5 to 7 membered cycloalkyl, and 5 to 7 membered heterocyclyl; wherein the C ring is optionally substituted with:

(a) 1 to 4 substituents selected from the group consisting of halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 thioalkyl, cyano, phenyl, mono-fluorophenyl, di-fluorophenyl, benzyl, CH_2 -(C_3 - C_6 cycloalkyl), and CH_2CH_2 -(C_3 - C_6 cycloalkyl); wherein if a nitrogen atom in the C ring is substituted, the substituent is not halogen, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 thioalkyl, or cyano;

(b) 1 to 2 substituents selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, CH_2 -(C_4 - C_6 heterocyclyl), CH_2CH_2 -(C_4 - C_6 heterocyclyl), and unsubstituted C_5 - C_6 heteroaryl; or

(c) two adjacent substituents which together form phenyl, C_5 - C_6 heteroaryl, C_4 - C_6 heterocyclyl C_3 - C_6 cycloalkyl or C_4 cycloalkoxy;

L is selected from the group consisting of a bond, O, S, NH, NCH_3 , $(CH_2)_m$, $CH(CH_3)$, $C(CH_3)_2$, CF_2 , CH_2O , CH_2S , $CH(OH)$, CH_2NH , and $CH_2N(CH_3)$, or L is absent such that the B ring and the C ring are fused;

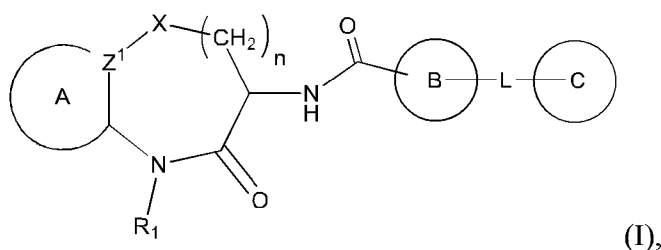
X is selected from the group consisting of O, S, SO, SO_2 , CH_2 , $C(CH_3)_2$, CF_2 and $CHCF_3$;

m is 1 or 4; and

n is 1 or 2;

provided that if the B ring is tetrazolyl, L is selected from the group consisting of CH_2 , $CH(CH_3)$, $C(CH_3)_2$, and CF_2 ; and the C ring is phenyl.

In another aspect, the present invention provides a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R₁ is selected from the group consisting of H and unsubstituted C₁-C₄ alkyl;

5 the A ring is 6 membered aryl; wherein the A ring is unsubstituted or substituted with one or two substituents selected from the group consisting of halogen and C₁₋₄ alkyl;

the B ring is tetrazolyl or a 5 to 6 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the B ring is optionally substituted with 1 to 2 substituents selected from the group consisting of halogen, C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄

10 haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and cyano; and wherein if a nitrogen atom in the B ring is substituted, the substituent is not halogen, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, or cyano; the C ring is selected from the group consisting of phenyl, 5 to 6 membered heteroaryl, 5 to 7 membered cycloalkyl, and 5 to 7 membered heterocyclyl; wherein the C ring is optionally substituted with:

(a) 1 to 4 substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, cyano, phenyl, mono-fluorophenyl, di-fluorophenyl, benzyl, CH₂-(C₃-C₆ cycloalkyl), and CH₂CH₂-(C₃-C₆ cycloalkyl); wherein if a nitrogen atom in the C ring is substituted, the substituent is not halogen, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, or cyano;

(b) 1 to 2 substituents selected from the group consisting of CH₂-(C₄-C₆ heterocyclyl), CH₂CH₂-(C₄-C₆ heterocyclyl), and unsubstituted C₅-C₆ heteroaryl; or

(c) two adjacent substituents which together form phenyl, C₅-C₆ heteroaryl, C₄-C₆ heterocyclyl C₃-C₆ cycloalkyl or C₄ cycloalkoxy;

L is absent such that the B ring and the C ring are fused;

X is selected from the group consisting of O, S, SO, SO₂, CH₂, C(CH₃)₂, CF₂ and CHCF₃;

25 Z¹ is C; and

n is 1 or 2;

provided that if the A ring is unsubstituted 6 membered aryl, the fused B and C rings are not unsubstituted indolyl or indolyl substituted by one or two halogen atoms; and
provided that if the A ring is unsubstituted 6 membered aryl, the C ring is not chlorothiophenyl.

5 In another aspect, the present invention provides a compound as exemplified herein, or a pharmaceutically acceptable salt thereof.

In the following description, all references to formula I also include subembodiments of formula I (i.e., formulae 1a, 1b, etc.).

10 Also disclosed herein are pharmaceutical compositions comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients. Specific embodiments include pharmaceutical compositions suitable for intravenous or oral delivery.

15 Also disclosed herein are oral formulations of a compound of formula I, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients suitable for oral delivery.

Also disclosed herein are parenteral formulations of a compound of formula I, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients suitable for parenteral delivery.

20 In some embodiments, disclosed herein are uses of a compound of formula I, or a pharmaceutically acceptable salt thereof, for the treatment of diseases and disorders. In some embodiments, the diseases and disorders to be treated are selected from the group consisting of irritable bowel disorders (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia-reperfusion injury of kidneys, liver and lungs, cisplatin-induced kidney injury, sepsis, systemic inflammatory response syndrome (SIRS),
25 pancreatitis, psoriasis, retinitis pigmentosa, retinal degeneration, chronic kidney diseases, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD).

In some embodiments, the disease or disorder to be treated is selected from the group consisting of inflammatory bowel diseases (including Crohn's disease and ulcerative colitis), psoriasis, retinal detachment, retinitis pigmentosa, macular degeneration, pancreatitis, atopic dermatitis, arthritis

(including rheumatoid arthritis, osteoarthritis, spondylarthritis, gout, systemic onset juvenile idiopathic arthritis (SoJIA), psoriatic arthritis), systemic lupus erythematosus (SLE), Sjogren's syndrome, systemic scleroderma, anti-phospholipid syndrome (APS), vasculitis, liver damage/diseases (non-alcohol steatohepatitis, alcohol steatohepatitis, autoimmune hepatitis autoimmune hepatobiliary diseases, primary sclerosing cholangitis (PSC), acetaminophen toxicity, hepatotoxicity), kidney damage/injury (nephritis, renal transplant, surgery, administration of nephrotoxic drugs e.g. cisplatin, acute kidney injury(AKI)), Celiac disease, autoimmune idiopathic thrombocytopenic purpura, transplant rejection, ischemia reperfusion injury of solid organs, sepsis, systemic inflammatory response syndrome (SIRS), cerebrovascular accident (CVA, stroke), myocardial infarction (MI), atherosclerosis, Huntington's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), allergic diseases (including asthma and atopic dermatitis), multiple sclerosis, type I diabetes, Wegener's granulomatosis, pulmonary sarcoidosis, Behcet's disease, interleukin-1 converting enzyme (ICE, also known as caspase-1) associated fever syndrome, chronic obstructive pulmonary disease (COPD), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), periodontitis, NEMO-deficiency syndrome (F-kappa-B essential modulator gene (also known as IKK gamma or IKKG) deficiency syndrome), HOIL-1 deficiency ((also known as RBCK1) heme-oxidized IRP2 ubiquitin ligase-1 deficiency), linear ubiquitin chain assembly complex (LUBAC) deficiency syndrome, hematological and solid organ malignancies, bacterial infections and viral infections (such as tuberculosis and influenza), and Lysosomal storage diseases (particularly, Gaucher Disease, and including GM2, Gangliosidosis, Alpha-mannosidosis, Aspartylglucosaminuria, Cholesteryl Ester storage disease, Chronic Hexosaminidase A Deficiency, Cystinosis, Danon disease, Fabry disease, Farber disease, Fucosidosis, Galactosialidosis, GM1 gangliosidosis, Mucopolidosis, Infantile Free Sialic Acid Storage Disease, Juvenile Hexosaminidase A Deficiency, Krabbe disease, Lysosomal acid lipase deficiency, Metachromatic Leukodystrophy, Mucopolysaccharidoses disorders, Multiple sulfatase deficiency, Niemann-Pick Disease, Neuronal Ceroid Lipofuscinoses, Pompe disease, Pycnodysostosis, Sandhoff disease, Schindler disease, Sialic Acid Storage Disease, Tay-Sachs and Wolman disease).

In some embodiments, the diseases and disorders to be treated are selected from the group consisting of irritable bowel disorders (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis,

ischemia–reperfusion injury of kidneys, liver and lungs, cisplatin-induced kidney injury, sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa and retinal degeneration.

5 In another aspect, the present invention provides a compound of the invention, or a pharmaceutically acceptable salt thereof, for use as a therapeutically active substance.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier.

10 In another aspect, the present invention provides a use of a compound of the invention, or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a disease or disorder selected from the group consisting of inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia–reperfusion injury of kidney, liver or lungs, cisplatin-induced kidney injury, sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa,
15 retinal degeneration, chronic kidney disease, acute respiratory distress syndrome (ARDS), and chronic obstructive pulmonary disease (COPD).

In another aspect, the present invention provides a use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder selected from the group consisting of inflammatory bowel disease
20 (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia–reperfusion injury of kidney, liver or lung, cisplatin-induced kidney injury, sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa, retinal degeneration, chronic kidney disease, acute respiratory distress syndrome (ARDS), and chronic obstructive pulmonary disease (COPD).

25 In another aspect, the present invention provides a compound of the invention, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of a disease or disorder selected from the group consisting of inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia–reperfusion injury of kidney, liver or lung, cisplatin-induced kidney injury,
30 sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa,

retinal degeneration, chronic kidney disease, acute respiratory distress syndrome (ARDS), and chronic obstructive pulmonary disease (COPD).

In some embodiments, disclosed herein are methods for the treatment or prevention of a disease or disorder with a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder is associated with inflammation and/or necroptosis. In some embodiments said disease or disorder is selected from the specific diseases and disorders recited herein.

In some embodiments, disclosed herein are methods of inhibiting RIP1 kinase activity by contacting a cell with a compound of formula I or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

As provided herein, all chemical formulae and generic chemical structures should be interpreted to provide proper valence and chemically stable bonds between atoms as understood by one of ordinary skill in the art. Where appropriate, substituents may be bonded to more than one adjacent atom (e.g., alkyl includes methylene where two bonds are present).

In the chemical formulae provided herein, “halogen” or “halo” refers to fluorine, chlorine, and bromine (*i.e.*, F, Cl, Br).

Alkyl, unless otherwise specifically defined, refers to an optionally substituted, straight-chain or branched C₁-C₁₂ alkyl group. In some embodiments, alkyl refers to a C₁-C₆ alkyl group. Exemplary alkyl groups include methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *tert*-butyl, *sec*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, and *n*-octyl. Substituted alkyl groups provided herein are substituted by one or more substituents selected from the group consisting of halogen, cyano, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, C₃-C₆ cycloalkyl, phenyl, OH, CO₂H, CO₂(C₁-C₄ alkyl), NH₂, NH(C₁-C₄ alkyl), N(C₁-C₄ alkyl)₂, NH(C=O)C₁-C₄ alkyl, (C=O)NH(C₁-C₄ alkyl), (C=O)N(C₁-C₄ alkyl)₂, S(C₁-C₄ alkyl), SO(C₁-C₄ alkyl), SO₂(C₁-C₄ alkyl), SO₂NH(C₁-C₄ alkyl), SO₂N(C₁-C₄ alkyl)₂, and NHSO₂(C₁-C₄ alkyl). In some embodiments, the substituted alkyl group has 1 or 2 substituents. In some embodiments, the alkyl group is unsubstituted.

Cycloalkyl, unless otherwise specifically defined, refers to an optionally substituted C₃-C₁₂

cycloalkyl group and includes fused, spirocyclic, and bridged bicyclic groups, wherein the substituents are selected from the group consisting of halogen, cyano, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, C₃-C₆ cycloalkyl, phenyl, OH, CO₂H, CO₂(C₁-C₄ alkyl), NH₂, NH(C₁-C₄ alkyl), N(C₁-C₄ alkyl)₂, NH(C=O)C₁-C₄ alkyl, (C=O)NH(C₁-C₄ alkyl), (C=O)N(C₁-C₄ alkyl)₂, S(C₁-C₄ alkyl), SO(C₁-C₄ alkyl), SO₂(C₁-C₄ alkyl), SO₂NH(C₁-C₄ alkyl), SO₂N(C₁-C₄ alkyl)₂, and NHSO₂(C₁-C₄ alkyl). In some embodiments, cycloalkyl refers to a C₃-C₆ cycloalkyl group. In some embodiments, the C₃-C₆ cycloalkyl group is optionally substituted with 1 to three halogen atoms. In some embodiments, the C₃-C₆ cycloalkyl group is optionally substituted with 1 to three fluorine atoms. Exemplary C₃-C₆ cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Exemplary C₃-C₁₂ cycloalkyl groups further include bicyclo[3.1.0]hexyl, bicyclo[2.1.1]hexyl,

cycloheptyl, bicycle[4.1.0]heptyl, spiro[4.2]heptyl, cyclooctyl, spiro[4.3]octyl, spiro[5.2]octyl, bicyclo[2.2.1]heptanyl, bicycle[2.2.2]octanyl, adamantanyl, decalanyl, and spiro[5.4]decanyl. Where appropriate, cycloalkyl groups may be fused to other groups such that more than one chemical bond exists between the cycloalkyl group and another ring system (e.g., the C ring of formula I). In some embodiments, the cycloalkyl group is unsubstituted.

Haloalkyl, unless otherwise specifically defined, refers to a straight-chain or branched C₁-C₁₂ alkyl group, wherein one or more hydrogen atoms are replaced by a halogen. In some embodiments, haloalkyl refers to a C₁-C₆ haloalkyl group. In some embodiments, 1 to 3 hydrogen atoms of the haloalkyl group are replaced by a halogen. In some embodiments, every hydrogen atom of the haloalkyl group is replaced by a halogen (e.g., trifluoromethyl). In some embodiments, the haloalkyl is as defined herein wherein the halogen in each instance is fluorine. Exemplary haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, trifluoroethyl, and pentafluoroethyl.

Alkoxy, unless otherwise specifically defined, refers to a straight-chain or branched C₁-C₁₂ alkyl group, wherein one or more oxygen atoms are present, in each instance between two carbon atoms. In some embodiments, alkoxy refers to a C₁-C₆ alkoxy group. In some embodiments, C₁-C₆ alkoxy groups provided herein have one oxygen atom. Exemplary alkoxy groups include methoxy, ethoxy, CH₂OCH₃, CH₂CH₂OCH₃, CH₂OCH₂CH₃, CH₂CH₂OCH₂CH₃, CH₂OCH₂CH₂CH₃, CH₂CH₂CH₂OCH₃, CH₂OCH(CH₃)₂, CH₂OC(CH₃)₃, CH(CH₃)OCH₃, CH₂CH(CH₃)OCH₃, CH(CH₃)OCH₂CH₃, CH₂OCH₂OCH₃, CH₂CH₂OCH₂CH₂OCH₃, and CH₂OCH₂OCH₂OCH₃.

Cycloalkoxy, unless otherwise specifically defined, refers to a C₄-C₁₀ or a C₄-C₆ alkoxy group as defined above wherein the group is cyclic and contains one oxygen atom. Exemplary cycloalkoxy groups include oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl.

Haloalkoxy, unless otherwise specifically defined, refers to a C₁-C₆ haloalkyl group as defined above, wherein one or two oxygen atoms are present, in each instance between two carbon atoms. In some embodiments, C₁-C₆ haloalkoxy groups provided herein have one oxygen atom. Exemplary haloalkoxy groups include OCF₃, OCHF₂ and CH₂OCF₃.

Thioalkyl, unless otherwise specifically defined, refers to a C₁-C₁₂ or a C₁-C₆ alkoxy group as defined above wherein the oxygen atom is replaced by a sulfur atom. In some embodiments, thioalkyl groups may include sulfur atoms substituted by one or two oxygen atoms (i.e., alkylsulfones and alkylsulfoxides). Exemplary thioalkyl groups are those exemplified in the definition of alkoxy above, wherein each oxygen atom is replaced by a sulfur atom in each instance.

Thiocycloalkyl, unless otherwise specifically defined, refers to a C₄-C₁₀ or a C₄-C₆ thioalkyl group as defined above wherein the group is cyclic and contains one sulfur atom. In

some embodiments, the sulfur atom of the thiocycloalkyl group is substituted by one or two oxygen atoms (i.e., a cyclic sulfone or sulfoxide). Exemplary thiocycloalkyl groups include thietanyl, thiolanyl, thianyl, 1,1-dioxothiolanyl, and 1,1-dioxothianyl.

Heterocyclyl, unless otherwise specifically defined, refers to a single saturated or partially unsaturated 4 to 8 membered ring that has at least one atom other than carbon in the ring, wherein the atom is selected from the group consisting of oxygen, nitrogen and sulfur; the term also includes multiple condensed ring systems that have at least one such saturated or partially unsaturated ring, which multiple condensed ring systems have from 7 to 12 atoms and are further described below. Thus, the term includes single saturated or partially unsaturated rings (e.g., 3, 4, 5, 6, 7 or 8 membered rings) from about 1 to 7 carbon atoms and from about 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the ring. The ring may be C-branched (i.e., substituted by C₁-C₄ alkyl). The ring may be substituted with one or more (e.g., 1, 2 or 3) oxo groups and the sulfur and nitrogen atoms may also be present in their oxidized forms. Exemplary heterocycles include but are not limited to azetidiny, tetrahydrofuranyl and piperidiny. The rings of the multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. It is to be understood that the individual rings of the multiple condensed ring system may be connected in any order relative to one another. It is also to be understood that the point of attachment of a multiple condensed ring system (as defined above for a heterocycle) can be at any position of the multiple condensed ring system. It is also to be understood that the point of attachment for a heterocycle or heterocycle multiple condensed ring system can be at any suitable atom of the heterocyclyl group including a carbon atom and a nitrogen atom. Exemplary heterocycles include, but are not limited to aziridiny, azetidiny, pyrrolidiny, piperidiny, homopiperidiny, morpholiny, thiomorpholiny, piperaziny, tetrahydrofuranyl, dihydrooxazolyl, tetrahydropyranly, tetrahydrothiopyranly, 1,2,3,4-tetrahydroquinolyl, benzoxazinyl, dihydrooxazolyl, chromanyl, 1,2-dihydropyridiny, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl, spiro[cyclopropane-1,1'-isoindoliny]-3'-one, isoindoliny-1-one, 2-oxa-6-azaspiro[3.3]heptanyl, imidazolidin-2-one N-methylpiperidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, phthalimide, 1,4-dioxane, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S,S-oxide, pyran, 3-pyrroline, thiopyran, pyrone, tetrahydrothiophene, quinuclidine, tropane, 2-azaspiro[3.3]heptane, (1R,5S)-3-azabicyclo[3.2.1]octane, (1s,4s)-2-azabicyclo[2.2.2]octane, (1R,4R)-2-oxa-5-azabicyclo[2.2.2]octane and pyrrolidin-2-one.

In some embodiments, the heterocyclyl is a C₄-C₁₀ heterocyclyl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. In some embodiments, the heterocyclyl group is neither bicyclic nor spirocyclic. In some embodiments, the heterocyclyl is a C₅-C₆ heterocyclyl having 1 to 3 heteroatoms, wherein at least 2 are

nitrogen if 3 heteroatoms are present.

Aryl, unless otherwise specifically defined, refers to a single all carbon aromatic ring or a multiple condensed all carbon ring system wherein at least one of the rings is aromatic and wherein the aryl group has 6 to 20 carbon atoms, 6 to 14 carbon atoms, 6 to 12 carbon atoms, or 6 to 10 carbon atoms. Aryl includes a phenyl radical. Aryl also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) having about 9 to 20 carbon atoms in which at least one ring is aromatic and wherein the other rings may be aromatic or not aromatic (i.e., carbocycle). Such multiple condensed ring systems are optionally substituted with one or more (e.g., 1, 2 or 3) oxo groups on any carbocycle portion of the multiple condensed ring system. The rings of the multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. It is to be understood that the point of attachment of a multiple condensed ring system, as defined above, can be at any position of the ring system including an aromatic or a carbocycle portion of the ring. Exemplary aryl groups include phenyl, indenyl, naphthyl, 1, 2, 3, 4-tetrahydronaphthyl, anthracenyl, and the like.

Heteroaryl, unless otherwise specifically defined, refers to a 5 to 6 membered aromatic ring that has at least one atom other than carbon in the ring, wherein the atom is selected from the group consisting of oxygen, nitrogen and sulfur; "heteroaryl" also includes multiple condensed ring systems having 8 to 16 atoms that have at least one such aromatic ring, which multiple condensed ring systems are further described below. Thus, "heteroaryl" includes single aromatic rings of from about 1 to 6 carbon atoms and about 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur. The sulfur and nitrogen atoms may also be present in an oxidized form provided the ring is aromatic. Exemplary heteroaryl ring systems include but are not limited to pyridyl, pyrimidinyl, oxazolyl or furyl. "Heteroaryl" also includes multiple condensed ring systems (e.g., ring systems comprising 2 or 3 rings) wherein a heteroaryl group, as defined above, is condensed with one or more rings selected from heteroaryls (to form for example a naphthyridinyl such as 1,8-naphthyridinyl), heterocycles, (to form for example a 1, 2, 3, 4-tetrahydronaphthyridinyl such as 1,2,3,4-tetrahydro-1,8-

naphthyridinyl), carbocycles (to form for example 5,6,7,8-tetrahydroquinolyl) and aryls (to form for example indazolyl) to form the multiple condensed ring system. Thus, a heteroaryl (a single aromatic ring or multiple condensed ring system) has 1 to 15 carbon atoms and about 1-6 heteroatoms within the heteroaryl ring. Such multiple condensed ring systems may be optionally substituted with one or more (e.g., 1, 2, 3 or 4) oxo groups on the carbocycle or heterocycle portions of the condensed ring. The rings of the multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. It is to be understood that the individual rings of the multiple condensed ring

system may be connected in any order relative to one another. It is also to be understood that the point of attachment of a multiple condensed ring system (as defined above for a heteroaryl) can be at any position of the multiple condensed ring system including a heteroaryl, heterocycle, aryl or carbocycle portion of the multiple condensed ring system. It is also to be understood that the point of attachment for a heteroaryl or heteroaryl multiple condensed ring system can be at any suitable atom of the heteroaryl or heteroaryl multiple condensed ring system including a carbon atom and a heteroatom (e.g., a nitrogen). Exemplary heteroaryls include but are not limited to pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, thienyl, indolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, furyl, oxadiazolyl, thiadiazolyl, quinolyl, isoquinolyl, benzothiazolyl, benzoxazolyl, indazolyl, quinoxalyl, quinazolyl, 5,6,7,8-tetrahydroisoquinolyl, benzofuranyl, benzimidazolyl, thianaphthenyl, pyrrolo[2,3-b]pyridinyl, quinazolinyl-4(3H)-one, triazolyl, 4,5,6,7-tetrahydro-1H-indazole and 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclo-penta[1,2-c]pyrazole.

As used herein, the term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

As used herein, the term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

As used herein a wavy line “~” that intersects a bond in a chemical structure indicates the point of attachment of the bond that the wavy bond intersects in the chemical structure to the remainder of a molecule.

As used herein, the term “C-linked” means that the group that the term describes is attached the remainder of the molecule through a ring carbon atom.

As used herein, the term “N-linked” means that the group that the term describes is attached to the remainder of the molecule through a ring nitrogen atom.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers can separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley &

Sons, Inc., New York, 1994. The compounds of the invention can contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which can occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

When a bond in a compound formula herein is drawn in a non-stereochemical manner (e.g. flat), the atom to which the bond is attached includes all stereochemical possibilities. When a bond in a compound formula herein is drawn in a defined stereochemical manner (e.g. bold, bold-wedge, dashed or dashed-wedge), it is to be understood that the atom to which the stereochemical bond is attached is enriched in the absolute stereoisomer depicted unless otherwise noted. In one embodiment, the compound may be at least 51% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 80% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 90% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 95% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 97% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 98% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 99% the absolute stereoisomer depicted.

As used herein, the term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

As used herein, the term "solvate" refers to an association or complex of one or more solvent molecules and a compound of the invention. Examples of solvents that form solvates

include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine. The term "hydrate" refers to the complex where the solvent molecule is water.

As used herein, the term "protecting group" refers to a substituent that is commonly employed to block or protect a particular functional group on a compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBZ) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include phenylsulfonyl, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfonyl)ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see P.G.M. Wuts and T.W. Greene, *Greene's Protective Groups in Organic Synthesis* 4th edition, Wiley-Interscience, New York, 2006.

As used herein, the term "mammal" includes, but is not limited to, humans, mice, rats, guinea pigs, monkeys, dogs, cats, horses, cows, pigs, and sheep.

As used herein, the term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of

the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S. M., et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds can be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds which are in a prodrug form. As used herein the term "prodrug" refers to those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

Prodrugs of the invention include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues, is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of a compound of the present invention. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes phosphoserine, phosphothreonine, phosphotyrosine, 4-hydroxyproline, hydroxylysine, demosine, isodemossine, gamma-carboxyglutamate, hippuric acid, octahydroindole-2-carboxylic acid, statine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, penicillamine, ornithine, 3-methylhistidine, norvaline, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, methyl-alanine, para-benzoylphenylalanine, phenylglycine, propargylglycine, sarcosine, methionine sulfone and tert-butylglycine.

Additional types of prodrugs are also encompassed. For instance, a free carboxyl group of a compound of the invention can be derivatized as an amide or alkyl ester. As another

example, compounds of this invention comprising free hydroxy groups can be derivatized as prodrugs by converting the hydroxy group into a group such as, but not limited to, a phosphate ester, hemisuccinate, dimethylaminoacetate, or phosphoryloxymethyloxycarbonyl group, as outlined in Fleisher, D. et al., (1996) Improved oral drug delivery: solubility limitations overcome by the use of prodrugs *Advanced Drug Delivery Reviews*, 19:115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers, wherein the acyl group can be an alkyl ester optionally substituted with groups including, but not limited to, ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in *J. Med. Chem.*, (1996), 39:10. More specific examples include replacement of the hydrogen atom of the alcohol group with a group such as (C₁₋₆)alkanoyloxymethyl, 1-((C₁₋₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁₋₆)alkanoyloxy)ethyl, (C₁₋₆)alkoxycarbonyloxymethyl, N-(C₁₋₆)alkoxycarbonylaminomethyl, succinoyl, (C₁₋₆)alkanoyl, alpha-amino(C₁₋₄)alkanoyl, arylacyl and alpha-aminoacyl, or alpha-aminoacyl-alpha-aminoacyl, where each alpha-aminoacyl group is independently selected from the naturally occurring L-amino acids, P(O)(OH)₂, -P(O)(O(C₁₋₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

For additional examples of prodrug derivatives, see, for example, a) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985) and *Methods in Enzymology*, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985); b) *A Textbook of Drug Design and Development*, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs," by H. Bundgaard p. 113-191 (1991); c) H. Bundgaard, *Advanced Drug Delivery Reviews*, 8:1-38 (1992); d) H. Bundgaard, et al., *Journal of Pharmaceutical Sciences*, 77:285 (1988); and e) N. Kakeya, et al., *Chem. Pharm. Bull.*, 32:692 (1984).

Additionally, the present invention provides for metabolites of compounds of the invention. As used herein, a "metabolite" refers to a product produced through metabolism in the body of a specified compound or salt thereof. Such products can result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound.

Metabolite products typically are identified by preparing a radiolabelled (e.g., ^{14}C or ^3H) isotope of a compound of the invention, administering it parenterally in a detectable dose (e.g., greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These

products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS, LC/MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well known to those skilled in the art. The metabolite products, so long as they are not otherwise found in vivo, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention can exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers, regioisomers and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present invention.

The term "composition," as used herein, is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "treat" and "treatment" refer to both therapeutic treatment and/or prophylactic treatment or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as, for example, the development or spread of cancer. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease or disorder, stabilized (i.e., not worsening) state of disease or disorder, delay or slowing of disease progression, amelioration or palliation of the disease state or disorder, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the disease or disorder as well as those prone to have the disease or disorder or those in which the disease or disorder is to be prevented.

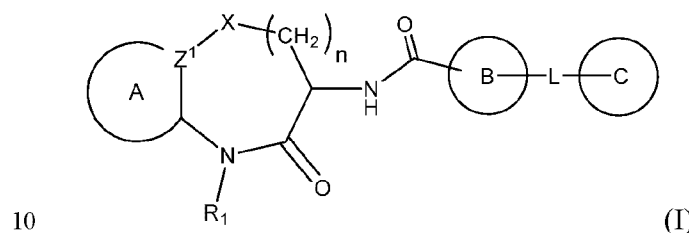
The phrase "therapeutically effective amount" or "effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more

symptoms of the particular disease, condition, or disorder described herein. For cancer therapy, efficacy can, for example, be measured by assessing the time to disease progression (TTP) and/or determining the response rate (RR).

5 The term "bioavailability" refers to the systemic availability (i.e., blood/plasma levels) of a given amount of drug administered to a patient. Bioavailability is an absolute term that indicates measurement of both the time (rate) and total amount (extent) of drug that reaches the general circulation from an administered dosage form.

INHIBITORS OF RIP1 KINASE

The present invention provides novel compounds having the general formula I:



wherein R^1 , X , Z^1 , L , n , the A ring, the B ring, and the C ring are as described herein.

In some embodiments of formula (I), the A ring is selected from the group consisting of cyclopropyl, 6 membered aryl, and 5 to 6 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the A ring is optionally substituted with:

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- (a) 1 to 3 substituents selected from the group consisting of halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 thioalkyl, cyano, phenyl, benzyl, CH_2 -(C_3 - C_6 cycloalkyl), and CH_2CH_2 -(C_3 - C_6 cycloalkyl); wherein if a nitrogen atom in the A ring is substituted, the substituent is not halogen, cyano, or a C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy or C_1 - C_6 thioalkyl having an oxygen or sulfur atom directly bonded to the nitrogen atom;
 - (b) 1 substituent selected from the group consisting of C_4 - C_6 heterocyclyl, C_5 - C_6 heteroaryl, CH_2 -(C_4 - C_6 heterocyclyl), CH_2CH_2 -(C_4 - C_6 heterocyclyl), CH_2 -(C_5 - C_6 heteroaryl), CH_2CH_2 -(C_5 - C_6 heteroaryl); and optionally a second substituent selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, and C_1 - C_6 haloalkoxy; or
 - (c) two adjacent substituents which together form phenyl, C_5 - C_6 heteroaryl, C_4 - C_6 heterocyclyl or C_4 - C_6 cycloalkyl; and
- 20
- 25

the C ring is selected from the group consisting of phenyl, 5 to 6 membered heteroaryl, 5 to 7 membered cycloalkyl, and 5 to 7 membered heterocyclyl; wherein the C ring is optionally substituted with:

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- (d) 1 to 4 substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, cyano, phenyl, benzyl, CH₂-(C₃-C₆ cycloalkyl), and CH₂CH₂-(C₃-C₆ cycloalkyl); wherein if a nitrogen atom in the C ring is substituted, the substituent is not halogen, cyano, or a C₁-C₆ alkoxy, C₁-C₆ haloalkoxy or C₁-C₆ thioalkyl having an oxygen or sulfur atom directly bonded to the nitrogen atom;
- (e) 1 to 2 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, CH₂-(C₄-C₆ heterocyclyl), CH₂CH₂-(C₄-C₆ heterocyclyl), and unsubstituted C₅-C₆ heteroaryl; or
- (f) two adjacent substituents which together form phenyl, C₅-C₆ heteroaryl, C₄-C₆ heterocyclyl or C₄-C₆ cycloalkyl.

In some embodiments, R¹ is selected from the group consisting of H, methyl, ethyl and isopropyl. In some embodiments, R¹ is H. In other embodiments, R¹ is methyl.

In some embodiments, X is CH₂. In some embodiments, X is CF₂. In some embodiments, X is O and Z¹ is C. In some embodiments, X is S and Z¹ is C.

In some embodiments, X is O, Z¹ is CH and the A ring is cyclopropyl.

In some embodiments, L is (CH₂)_m and m is 1 or 2. In some embodiments, L is (CH₂)_m and m is 1. In other embodiments, L is absent such that the B ring and the C ring are fused.

In some embodiments, n is 1.

In some embodiments, the A ring is cyclopropyl. In some embodiments, the A ring is unsubstituted cyclopropyl. In some embodiments, the A ring is cyclopropyl substituted by 1 to 2 C₁-C₄ alkyl groups. In some embodiments, the A ring is cyclopropyl substituted by one substituent selected from the group consisting of C₁-C₄ alkyl, phenyl or benzyl. In some embodiments, the A ring is cyclopropyl substituted by one or two halogens. In some embodiments, the A ring is as defined in this paragraph and n is 1. In some embodiments, the A ring is as defined in this paragraph, and X is selected from the group consisting of CH₂, C(CH₃)₂, CF₂ and CHCF₃.

In some embodiments, the A ring is a 5 membered heteroaryl having 1 to 2 nitrogen atoms and 0 to 1 oxygen or sulfur atoms as the only heteroatoms. In some embodiments, the A ring is a 5 membered heteroaryl having 1 to 2 nitrogen atoms and 0 to 1 oxygen or sulfur atoms as the only heteroatoms, wherein the 5 membered heteroaryl is unsubstituted or is substituted by C₁-C₄ alkyl. In some embodiments, the A ring is a 5 membered heteroaryl having 2 nitrogen atoms as the only heteroatoms, wherein the 5 membered heteroaryl is unsubstituted or is substituted by C₁-C₄ alkyl. In some embodiments wherein the A ring is as defined in this paragraph, X is CH₂ or O.

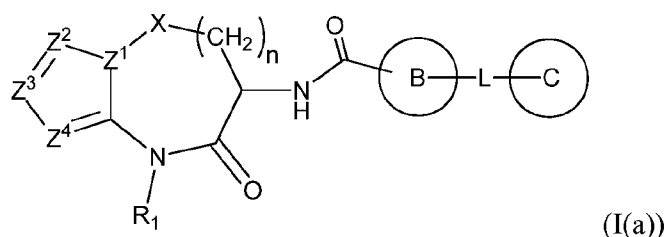
In some embodiments, the A ring is an unsubstituted 6 membered aryl. In some embodiments, the A ring is a 6 membered aryl substituted by one or two substituents selected from the group consisting of halogen and C₁-C₄ alkyl. In some embodiments, the A ring is a 6 membered aryl substituted by one or two substituents selected from the group consisting of halogen and methyl. In some embodiments, the A ring is a 6 membered aryl substituted by one or two substituents selected from the group consisting of fluoro and methyl.

In some embodiments, the B ring is a 5 or 6 membered heteroaryl having from 1 to 3 nitrogen atoms in the ring. In other embodiments, the B ring is a 5 or 6 membered heteroaryl having from 1 to 2 nitrogen atoms and from 0 to 1 oxygen or sulfur atoms in the ring. In some embodiments, the B ring is selected from the group consisting of furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl and triazolyl. In some embodiments, the B ring is pyrazolyl. In some embodiments, the B ring is imidazolyl. In some embodiments, the B ring is oxazolyl. In some embodiments, the B ring is thiazolyl. In some embodiments, the B ring is triazolyl. In some embodiments, the B ring is oxadiazolyl. In some embodiments, the B ring is pyridinyl or pyrimidinyl. In some embodiments of this paragraph, the B ring is unsubstituted.

In some embodiments wherein L is absent such that the B and C rings are fused, the C ring is a 5 to 7 membered heterocyclyl containing 1 to 2 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. In one embodiment wherein L is absent such that the B and C rings are fused, the C ring is a 5 to 7 membered heterocyclyl containing 1 heteroatom selected from the group consisting of nitrogen, oxygen and sulfur. In other embodiments wherein L is absent such that the B and C rings are fused, the C ring is a 5 to 7 membered cycloalkyl. In other embodiments wherein L is absent such that the B and C rings are fused, the C ring is phenyl. In some embodiments of this paragraph, the C ring is unsubstituted.

In some embodiments wherein L is present, the C ring is phenyl substituted by 1 or 2 substituents selected from the group consisting of halogen, C₁-C₄ alkyl, and C₁-C₄ alkoxy. In other embodiments wherein L is present, the C ring is unsubstituted phenyl.

In some embodiments, provided herein is a compound of formula I(a):



or a pharmaceutically acceptable salt thereof, wherein R¹, X, Z¹, L, n, the A ring, the B ring, and the C ring are as described herein, wherein

Z², Z³, and Z⁴ are each independently selected from the group consisting of CR^Z and NR⁸;

each R^Z is independently selected from the group consisting of H, halogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $CH_2(C_3$ - C_6 cycloalkyl), C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 thioalkyl, $CH_2(C_4$ - C_6 cycloalkoxy), $CH_2(C_4$ - C_6 thiocycloalkyl), phenyl, benzyl, 4 to 6 membered heterocyclyl; and 5 to 6 membered heteroaryl;

each R^8 is either absent if the nitrogen atom to which it is attached has three bonds to other atoms, or R^8 is selected from the group consisting of H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $CH_2(C_3$ - C_6 cycloalkyl), C_1 - C_6 haloalkyl, $CH_2(C_4$ - C_6 cycloalkoxy), $CH_2(C_4$ - C_6 thiocycloalkyl), phenyl, and benzyl;

wherein Z^1 is N only if X is CH_2 , CF_2 , $CH(CH_3)$, $CH(CF_3)$, $C(CH_3)_2$, or $CH(OH)$;

wherein if Z^1 is N, at least one of Z^2 , Z^3 or Z^4 is CR^Z ;

wherein, when Z^2 and Z^3 are each independently selected from CR^Z and NR^8 , Z^2 and Z^3 together with their respective R^Z and R^8 substituents may form a 6 membered aryl, 6 membered heteroaryl, 5 to 6 membered cycloalkyl or 5 to 6 membered heterocyclyl group;

wherein, when Z^3 and Z^4 are each independently selected from CR^Z and NR^8 , Z^3 and Z^4 together with their respective R^Z and R^8 substituents may form a 6 membered aryl, 6 membered heteroaryl, 5 to 6 membered cycloalkyl or 5 to 6 membered heterocyclyl group;

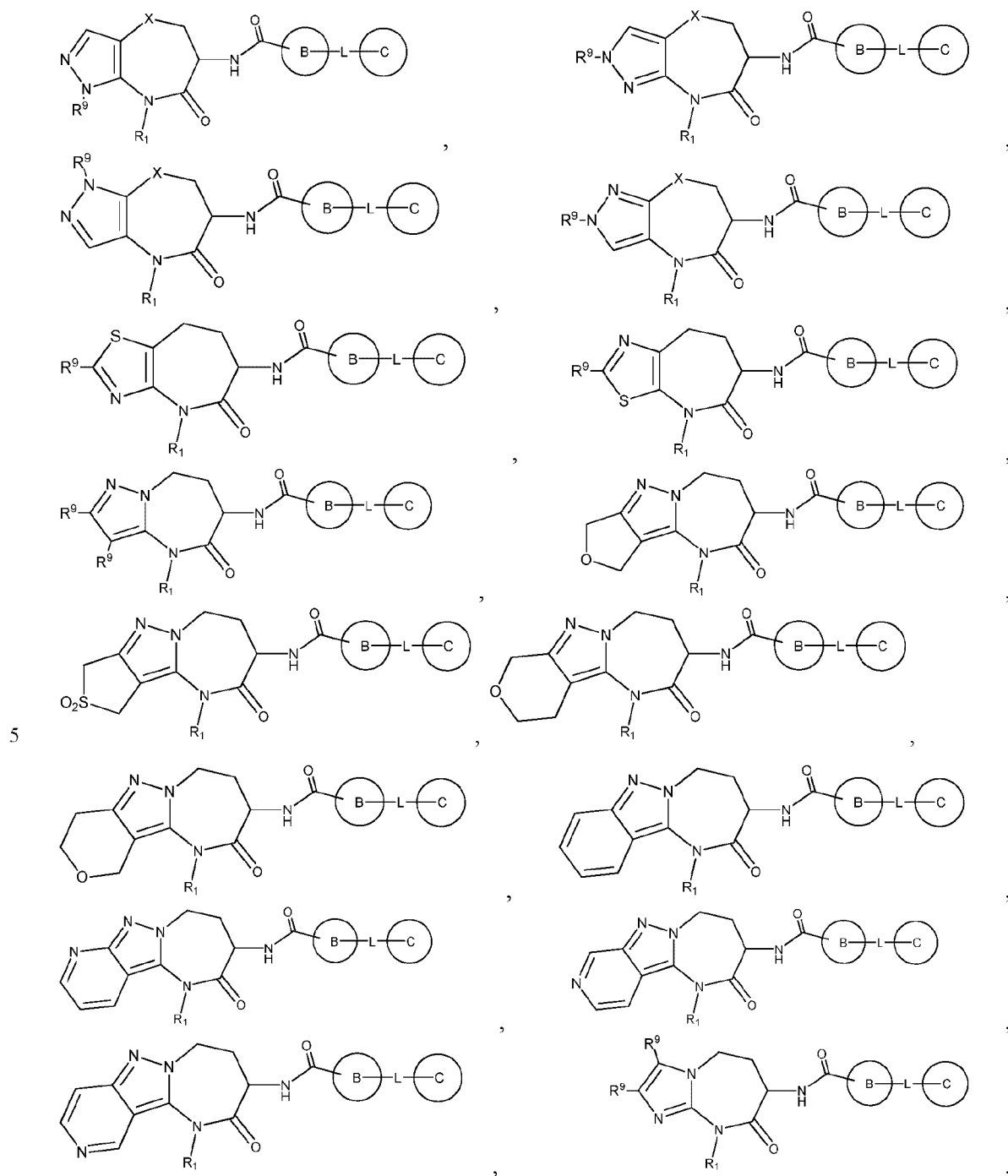
In some embodiments of formula I(a), R^1 is selected from H and CH_3 . In some embodiments, R^1 is H. In other embodiments, R^1 is CH_3 .

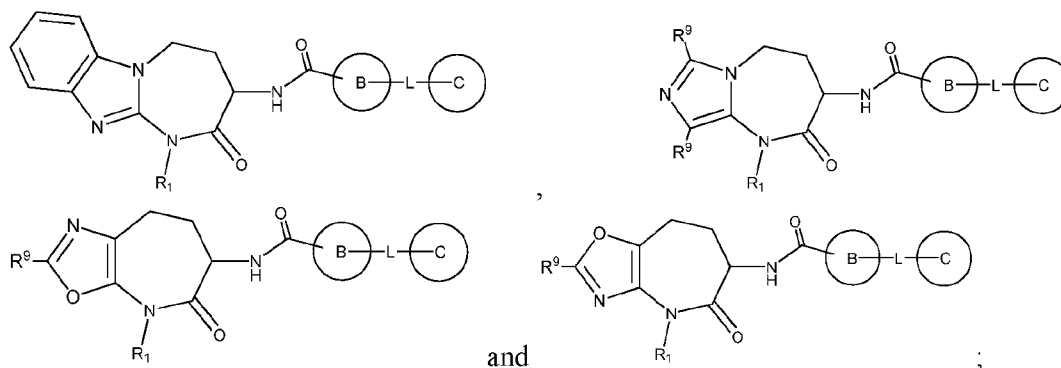
In some embodiments of formula I(a), X is CH_2 or O; Z^1 is C; and Z^2 , Z^3 , and Z^4 are each independently selected from the group consisting of CR^Z , NH, NCH_3 . In some embodiments of formula I(a), X is CH_2 or O; Z^1 is C; and Z^2 , Z^3 , and Z^4 are each independently selected from the group consisting of CH and NH.

In some embodiments of formula I(a), X is CH_2 ; Z^1 is N; and Z^2 , Z^3 , and Z^4 are each independently selected from the group consisting of CR^Z , NH, NCH_3 , wherein at least one of Z^2 , Z^3 , and Z^4 is CR^Z . In some embodiments of formula I(a), X is CH_2 ; Z^1 is N; and Z^2 , Z^3 , and Z^4 are each independently selected from the group consisting of CH and NH, wherein at least one of Z^2 , Z^3 , and Z^4 is CH.

In some embodiments of formula I(a), n is 1.

In some embodiments of formula I(a), the compound is of a formula selected from the group consisting of:

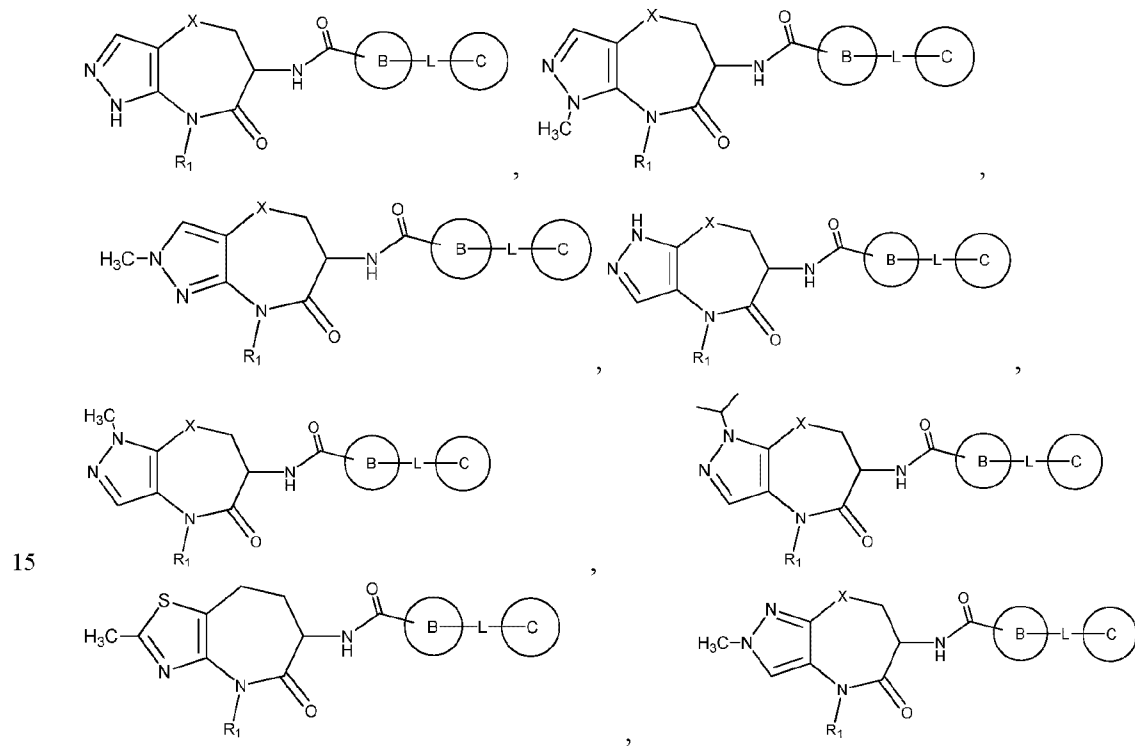


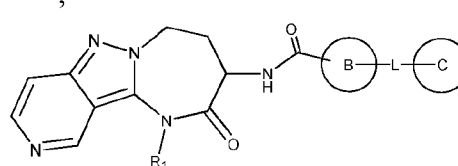
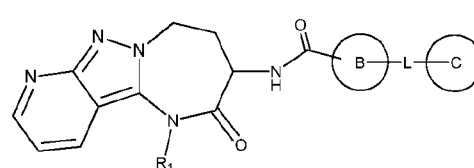
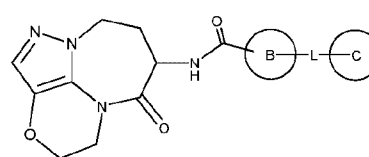
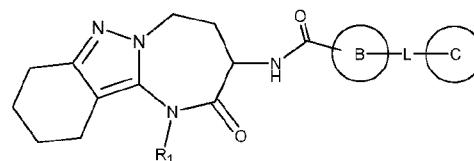
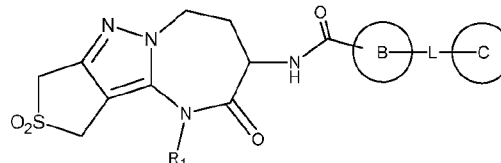
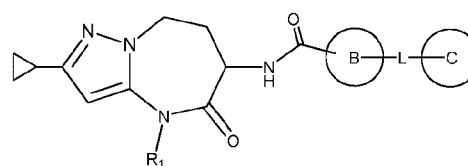
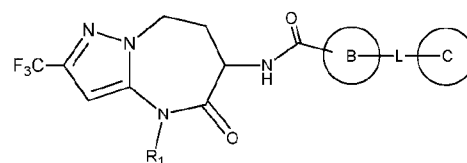
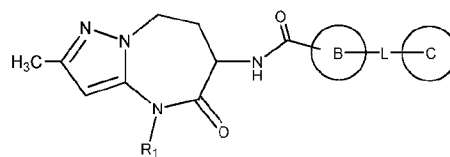
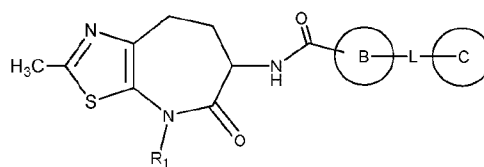


wherein each R^9 is independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyl substituted by 1 to 2 fluorine atoms, C_1 - C_6 haloalkyl, (C₁-C₄ alkoxy)- C_1 - C_2 alkyl, phenyl, benzyl, C_4 - C_6 heterocyclyl, CH_2 -(C_3 - C_6 cycloalkyl), CH_2 -(C_3 - C_6 cycloalkyl substituted by 1 to 2 fluorine atoms), and CH_2 -(C_4 - C_6 heterocyclyl).

In some embodiments, each R^9 is selected from the group consisting of hydrogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, $CH_2CH_2OCH_3$, C_3 - C_4 cycloalkyl, C_3 - C_4 cycloalkyl substituted by 1 to 2 fluorine atoms, CH_2 -(C_3 - C_4 cycloalkyl), CH_2 -(C_3 - C_4 cycloalkyl substituted by 1 to 2 fluorine atoms), and CH_2 -(C_4 heterocyclyl).

In some embodiments of formula I(a), the compound is of a formula selected from the group consisting of:

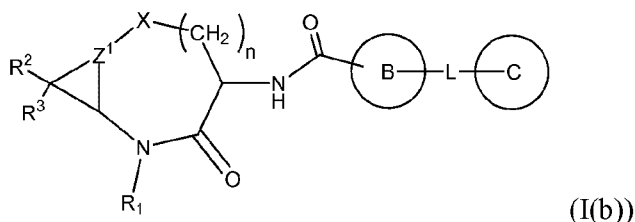






In some of the above embodiments of formula I(a), R¹ is H or methyl.

In some embodiments, provided herein is a compound of formula I(b):



or a pharmaceutically acceptable salt thereof, wherein R^1 , X, L, n, the A ring, the B ring, and the C ring are as described herein, wherein

5 Z^1 is CH; and

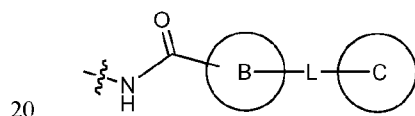
R^2 and R^3 are each independently selected from the group consisting of H, halo, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, CO_2 (C_1 - C_6 alkyl), phenyl, benzyl, 5 to 6 membered heterocyclyl, 5 to 6 membered heteroaryl, $-CH_2$ (C_3 - C_6 cycloalkyl), and $-CH_2$ (C_4 - C_6 heterocyclyl); provided that when each of R^2 and R^3 are other than H or halo, one must be C_1 - C_4 alkyl.

10 In some embodiments of formula I(b), R^2 and R^3 are each independently selected from the group consisting of H, fluoro, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, CO_2 (C_1 - C_6 alkyl), phenyl, benzyl, 5 to 6 membered heterocyclyl, 5 to 6 membered heteroaryl, $-CH_2$ (C_3 - C_6 cycloalkyl), and $-CH_2$ (C_4 - C_6 heterocyclyl); provided that when each of R^2 and R^3 are other than H or fluoro, one must be C_1 - C_4 alkyl.

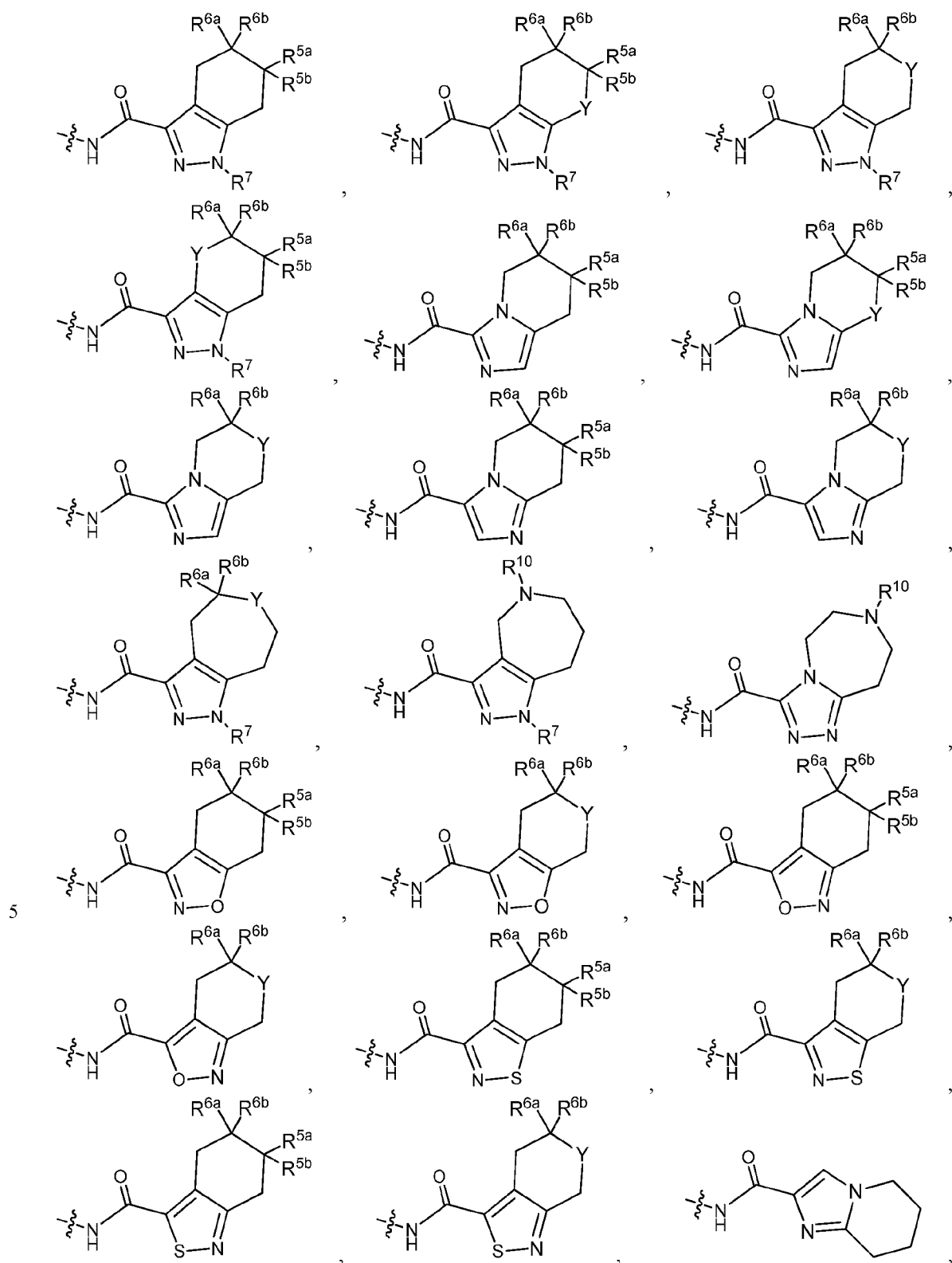
15 In some embodiments of formula I(b), R^2 and R^3 are each independently H or C_1 - C_6 alkyl.

In some embodiments of formula I(b), R^1 is H or methyl.

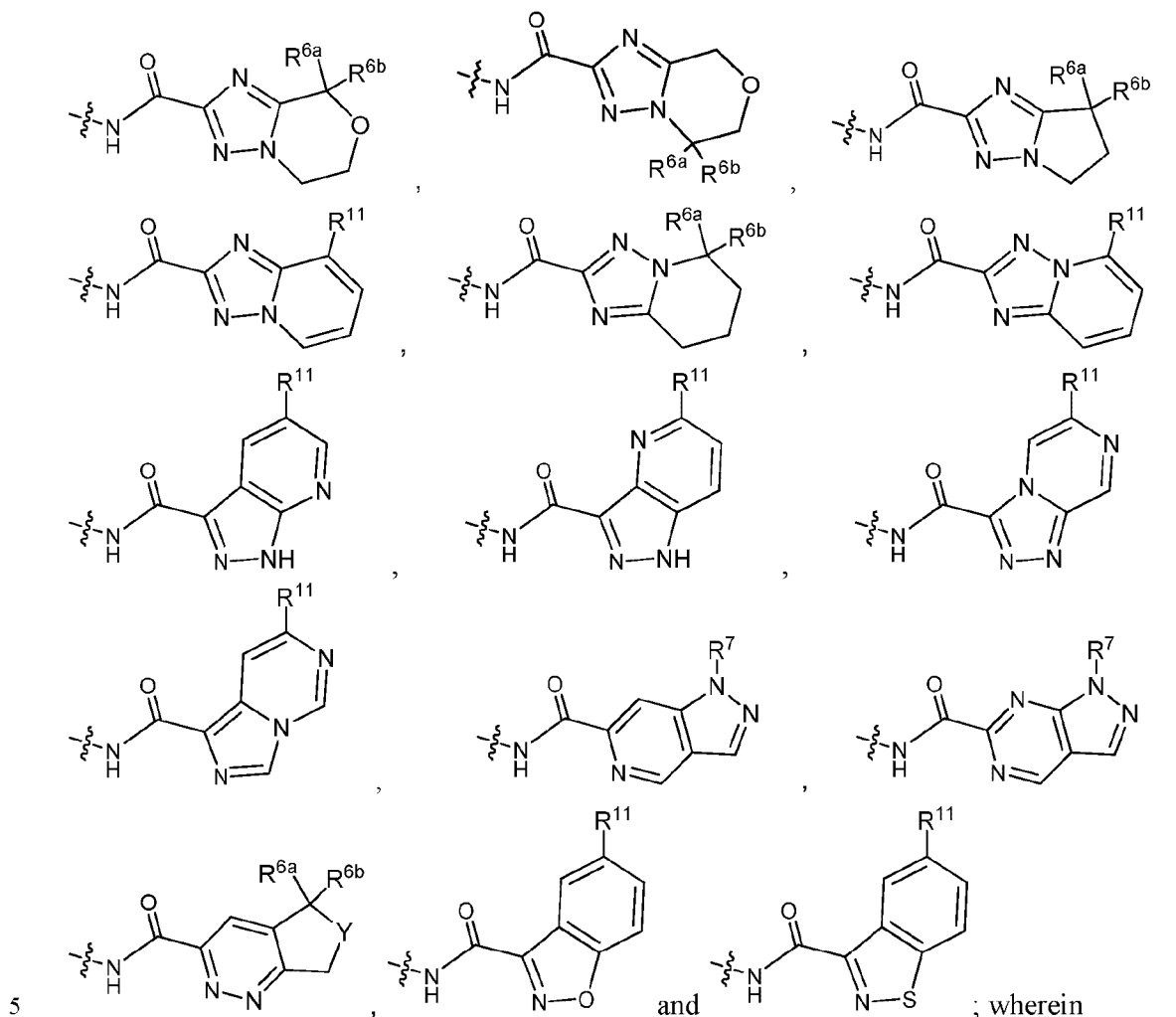
In some embodiments, provided herein is a compound of formula I, I(a) and I(b) wherein



is selected from the group consisting of:







Y is selected from the group consisting of O, S, SO and SO₂;

X¹, X² and X³ are each independently N or CH, wherein 1 or 2 of X¹, X² and X³ is N;

X⁴ and X⁵ are each independently N or CH;

10 R^{5a} and R^{5b}, are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, phenyl, benzyl, -CH₂(C₃-C₆ cycloalkyl); and 5 to 6 membered heteroaryl; wherein R^{5a} and R^{5b} together with the carbon to which they are attached may form a 3 to 5 membered cycloalkyl optionally substituted by one or two fluoro, or a 4 to 5 membered cycloalkoxy;

15 R^{6a} and R^{6b} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, phenyl, mono- or di-fluorophenyl, benzyl, -CH₂(C₃-C₆ cycloalkyl), and 5 to 6 membered heteroaryl; wherein R^{6a} and R^{6b} together with the carbon to which they are attached may form a 3 to 5 membered cycloalkyl optionally substituted by one or two fluoro, or a 4 to 5 membered cycloalkoxy;

wherein when R^{5a} and R^{6a} are each H, R^{5b} and R^{6b} may together form a 3 or 4 membered cycloalkyl;

and wherein only two of R^{5a} , R^{5b} , R^{6a} and R^{6b} may be other than H in each instance;

R^7 is selected from the group consisting of H, unsubstituted C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, and C_4 - C_6 cycloalkoxy;

R^{10} is selected from the group consisting of H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 haloalkyl, phenyl, and benzyl; and

R^{11} is selected from the group consisting of H, halogen, cyano, C_1 - C_4 alkyl, and C_1 - C_4 haloalkyl.

10 In some embodiments, Y is O.

In some embodiments, R^{5a} and R^{5b} are each H.

In some embodiments, R^{5a} and R^{5b} are each H; and R^{6a} and R^{6b} are each independently C_1 - C_4 alkyl. In some embodiments, R^{5a} and R^{5b} are each H; R^{6a} is H; and R^{6b} is C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or phenyl. In some embodiments, R^{5a} and R^{5b} are each H; R^{6a} is H; and R^{6b} is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl. In some embodiments, R^{5a} and R^{5b} are each H; R^{6a} is methyl; and R^{6b} is C_1 - C_4 alkyl or C_3 - C_4 cycloalkyl. In some embodiments, R^{5a} and R^{5b} are each H; R^{6a} is methyl; and R^{6b} is phenyl.

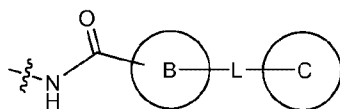
In some embodiments, R^{5a} and R^{6a} are each H, and R^{5b} and R^{6b} together form cyclopropyl or cyclobutyl; and Y is O.

20 In some embodiments, R^7 is H or methyl.

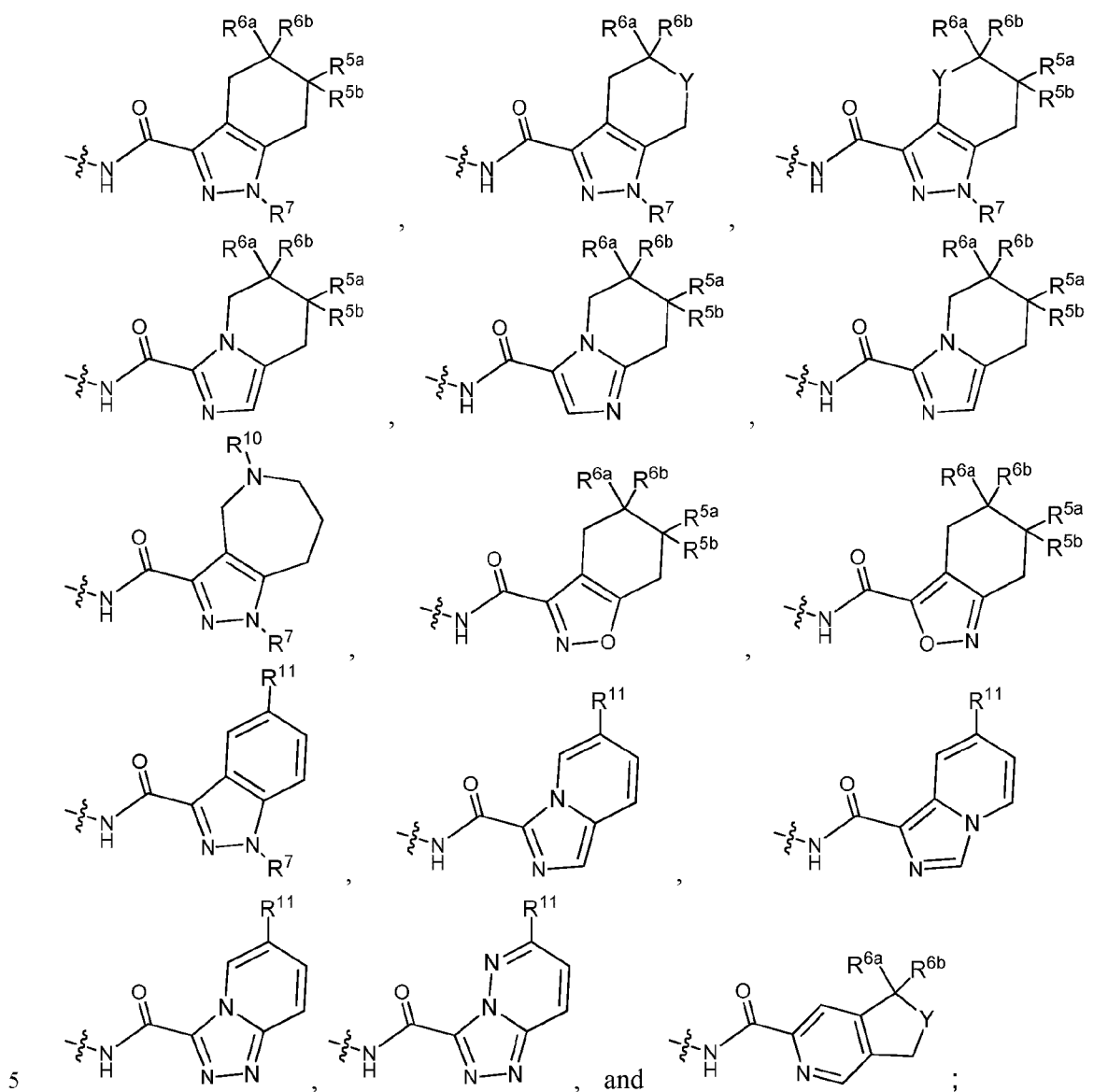
In some embodiments, R^{10} is selected from the group consisting of H, C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, phenyl, and benzyl.

In some embodiments, R^{11} is selected from the group consisting of H, halogen, methyl, and trifluoromethyl.

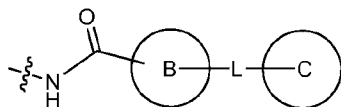
25 In some embodiments, provided herein is a compound of formula I, I(a) and I(b) wherein



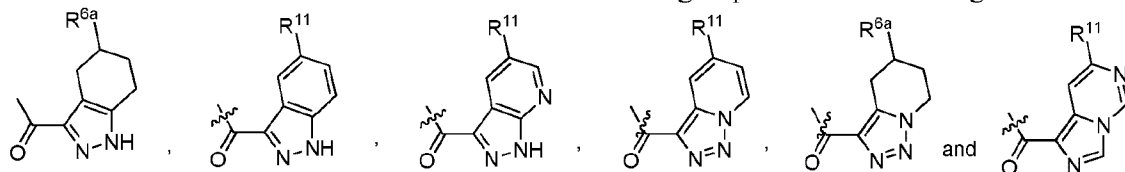
is selected from the group consisting of:



In some embodiments, provided herein is a compound of formula I, I(a) and I(b) wherein

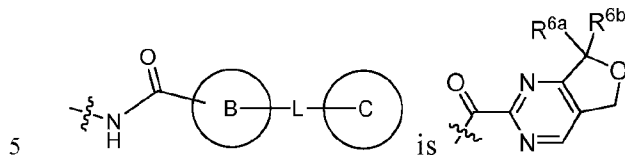


10 is selected from the group consisting of:



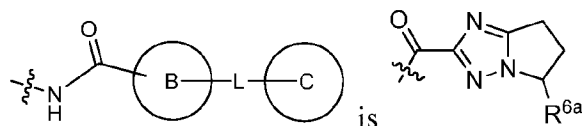
wherein R^{6a} and R¹¹ are as defined above. In some emodiments, R^{6a} is C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl or phenyl. In some emodiments, R¹¹ is C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl or phenyl.

In some embodiments, provided herein is a compound of formula I, I(a) or I(b) wherein



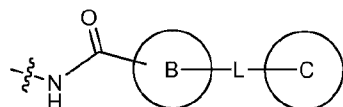
wherein R^{6a} and R^{6b} are as defined above. In some emodiments, R^{6a} and R^{6b} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl or phenyl; provided that if one of R^{6a} and R^{6b} is phenyl, the other is H. In some emodiments, R^{6a} and R^{6b} together form C₃-C₆ cycloalkyl.

10 In some embodiments, provided herein is a compound of formula I, I(a) or I(b) wherein

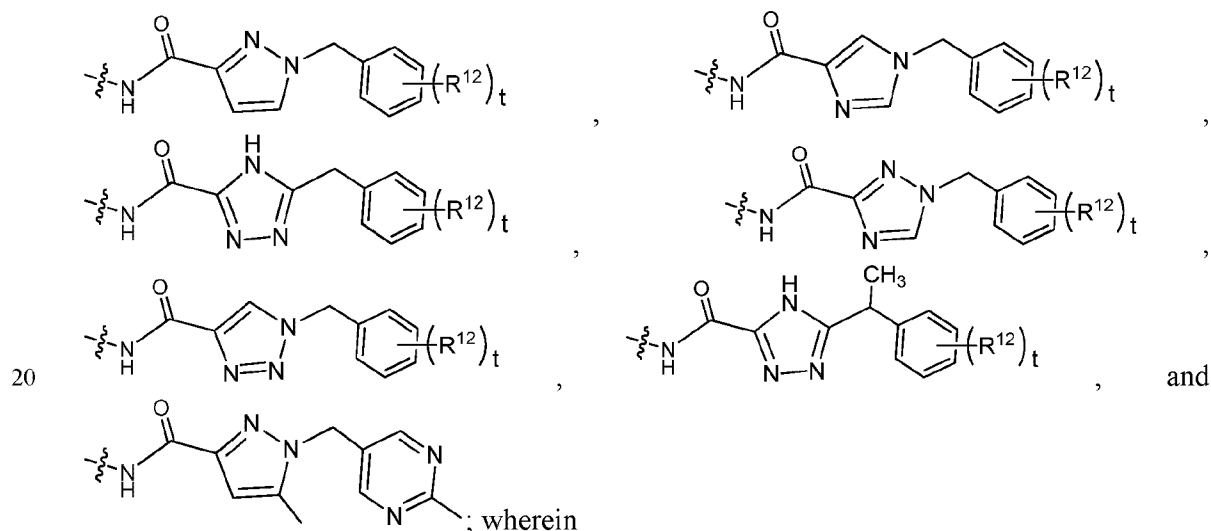


wherein R^{6a} is as defined above. In some emodiments, R^{6a} is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl or phenyl. In some emodiments, R^{6a} is phenyl.

15 In some embodiments, provided herein is a compound of formula I(a) or I(b), wherein



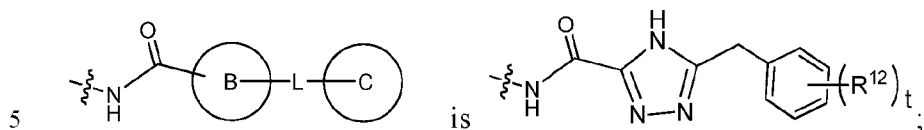
is selected from the group consisting of:



R^{12} is selected from the group consisting of halogen and methyl; and
 t is 0, 1 or 2.

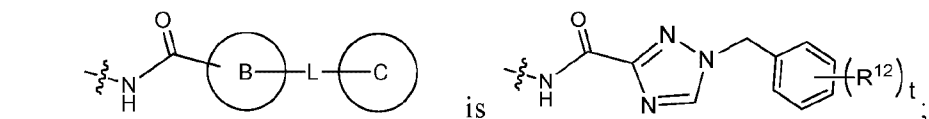
In some embodiments, R^{12} is fluoro and t is 1 or 2. In some embodiments, t is 0.

In some embodiments, provided herein is a compound of formula I(a) or I(b), wherein



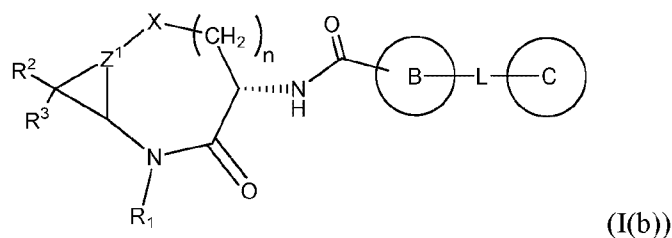
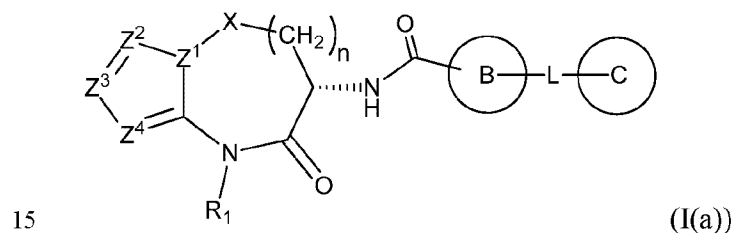
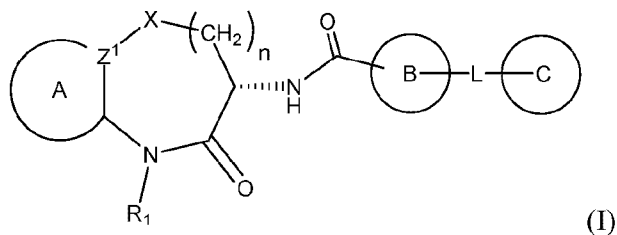
wherein R^{12} and t are as defined above. In some embodiments, each R^{12} is selected from fluoro and chloro. In some embodiments, each R^{12} is F and t is 1 or 2.

In some embodiments, provided herein is a compound of formula I(a) or I(b), wherein



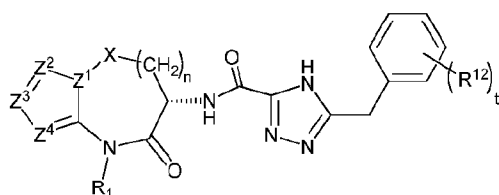
wherein R^{12} and t are as defined above. In some embodiments, each R^{12} is selected from fluoro and chloro. In some embodiments, each R^{12} is F and t is 1 or 2.

Also provided herein are specific stereoisomers of the compounds of each of the above embodiments of formulae I, I(a) and I(b):



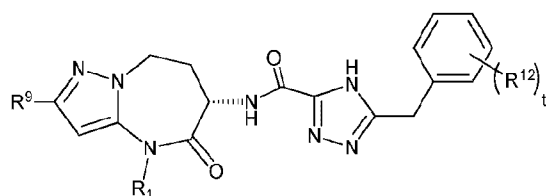
and each of the substituents are as defined above.

In some embodiments, provided herein is a compound of formula I(a) of the formula:



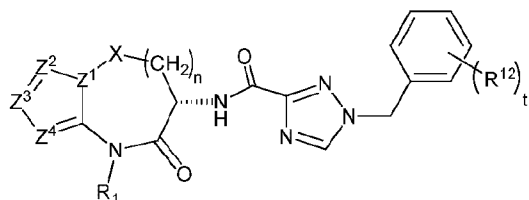
wherein each of the substituents are as defined above.

In some embodiments, provided herein is a compound of formula I(a) of the formula:



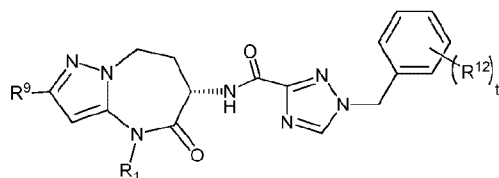
wherein R^1 is H, methyl or ethyl; R^9 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyl substituted by 1 to 2 fluorine atoms, C_1 - C_6 haloalkyl, $(C_1$ - C_4 alkoxy)- C_1 - C_2 alkyl, phenyl and benzyl; R^{12} is F or Cl; and t is 0, 1, 2 or 3. In some embodiments, R^1 is methyl; R^9 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, and C_3 - C_6 cycloalkyl substituted by 1 to 2 fluorine atoms; R^{12} is F; and t is 0, 1 or 2.

In some embodiments, provided herein is a compound of formula I(a) of the formula:



wherein each of the substituents are as defined above.

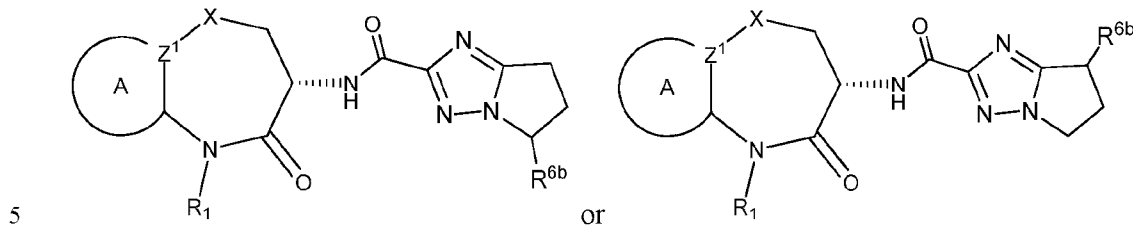
In some embodiments, provided herein is a compound of formula I(a) of the formula:



wherein R^1 is H, methyl or ethyl; R^9 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyl substituted by 1 to 2 fluorine atoms, C_1 - C_6 haloalkyl, $(C_1$ - C_4 alkoxy)- C_1 - C_2 alkyl, phenyl and benzyl; R^{12} is F or Cl; and t is 0, 1, 2 or 3. In some

embodiments, R^1 is methyl; R^9 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, and C_3 - C_6 cycloalkyl substituted by 1 to 2 fluorine atoms; R^{12} is F; and t is 0, 1 or 2.

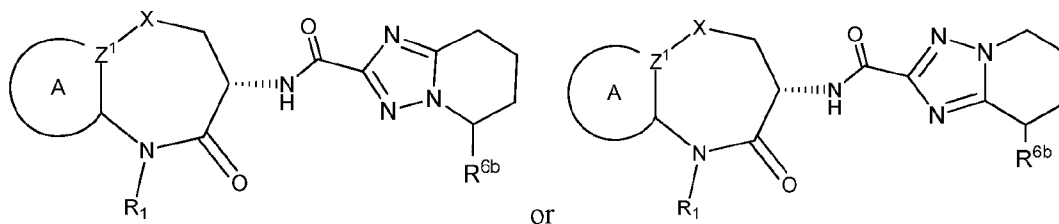
In some embodiments, provided herein is a compound of formula I(a) of the formula:



wherein R^1 , the A ring, Z^1 , X, and R^{6b} are as defined herein. In some embodiments, R^1 is H, methyl or ethyl. In some embodiments, R^1 is H or methyl; the A ring is 6 membered aryl or 5 membered heteroaryl; Z^1 is C or N; X is CH_2 or O; and R^{6b} is as defined herein. In some embodiments, R^1 is H or methyl; the A ring is 6 membered aryl or 5 membered heteroaryl; Z^1 is C or N; X is CH_2 or O; and R^{6b} is C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or phenyl.

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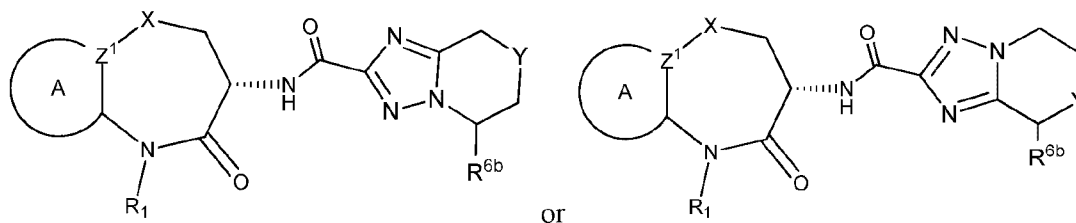
In some embodiments, provided herein is a compound of formula I(a) of the formula:



wherein R^1 , the A ring, Z^1 , X, and R^{6b} are as defined herein. In some embodiments, R^1 is H, methyl or ethyl. In some embodiments, R^1 is H or methyl; the A ring is 6 membered aryl or 5 membered heteroaryl; Z^1 is C or N; X is CH_2 or O; and R^{6b} is as defined herein. In some embodiments, R^1 is H or methyl; the A ring is 6 membered aryl or 5 membered heteroaryl; Z^1 is C or N; X is CH_2 or O; and R^{6b} is C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or phenyl.

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In some embodiments, provided herein is a compound of formula I(a) of the formula:

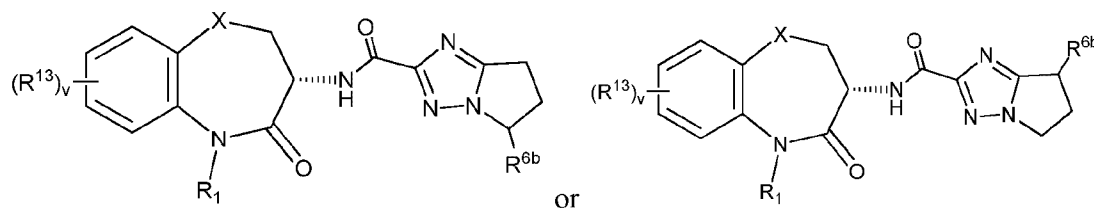


wherein R^1 , the A ring, Z^1 , X, and R^{6b} are as defined herein, and Y is NH or O. In some embodiments, R^1 is H, methyl or ethyl. In some embodiments, R^1 is H or methyl; the A ring is 6 membered aryl or 5 membered heteroaryl; Z^1 is C or N; X is CH_2 or O; and R^{6b} is as defined

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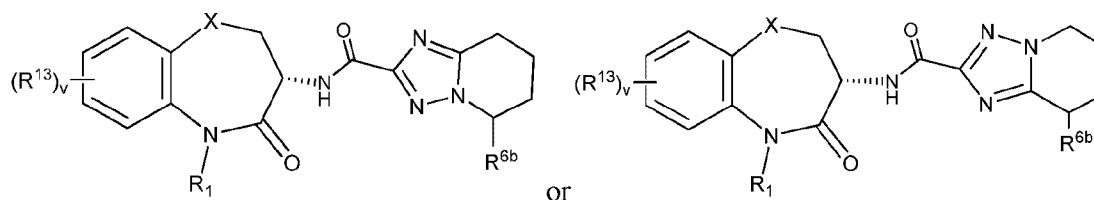
herein. In some embodiments, R^1 is H or methyl; the A ring is 6 membered aryl or 5 membered heteroaryl; Z^1 is C or N; X is CH_2 or O; and R^{6b} is C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or phenyl.

In some embodiments, provided herein is a compound of formula I(a) of the formula:



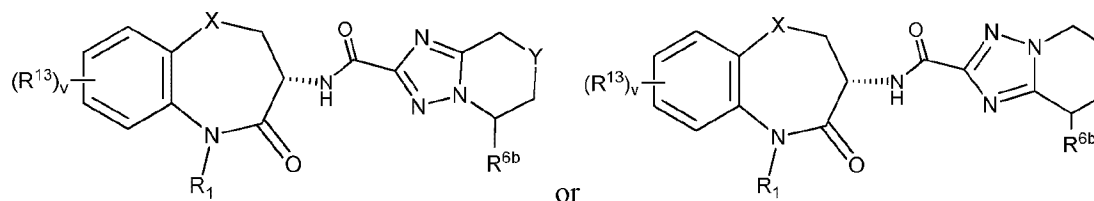
- 5 wherein each R^{13} is halo or C_1 - C_4 alkyl, v is 0 to 2; and R^1 , X, and R^{6b} are as defined herein. In some embodiments, R^1 is H, methyl or ethyl. In some embodiments, R^1 is H or methyl; X is CH_2 or O; and R^{6b} is as defined herein. In some embodiments, R^1 is H or methyl; the A ring is 6 membered aryl or 5 membered heteroaryl; Z^1 is C or N; X is CH_2 or O; and R^{6b} is C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or phenyl. In some embodiments, each R^{13} is F or methyl.

- 10 In some embodiments, provided herein is a compound of formula I(a) of the formula:



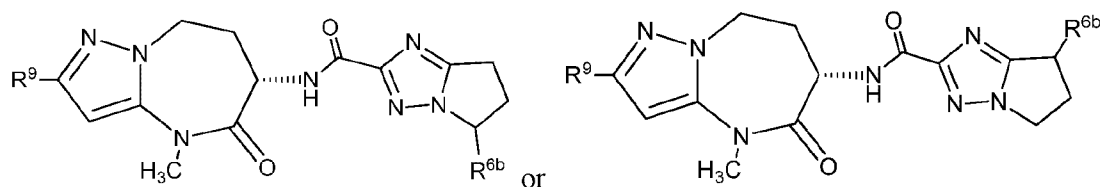
- wherein each R^{13} is halo or C_1 - C_4 alkyl, v is 0 to 2; and R^1 , X, and R^{6b} are as defined herein. In some embodiments, R^1 is H, methyl or ethyl. In some embodiments, R^1 is H or methyl; X is CH_2 or O; and R^{6b} is as defined herein. In some embodiments, R^1 is H or methyl; the A ring is 6 membered aryl or 5 membered heteroaryl; Z^1 is C or N; X is CH_2 or O; and R^{6b} is C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or phenyl. In some embodiments, each R^{13} is F or methyl.
- 15

In some embodiments, provided herein is a compound of formula I(a) of the formula:



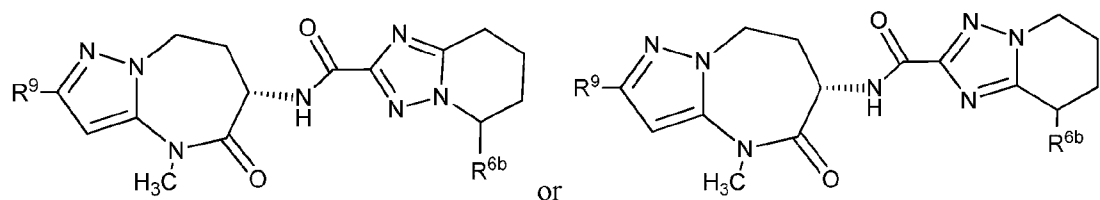
- wherein each R^{13} is halo or C_1 - C_4 alkyl, v is 0 to 2; Y is NH or O; and R^1 , X, and R^{6b} are as defined herein. In some embodiments, R^1 is H, methyl or ethyl. In some embodiments, R^1 is H or methyl; X is CH_2 or O; and R^{6b} is as defined herein. In some embodiments, R^1 is H or methyl; the A ring is 6 membered aryl or 5 membered heteroaryl; Z^1 is C or N; X is CH_2 or O; and R^{6b} is C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or phenyl. In some embodiments, each R^{13} is F or methyl.
- 20

In some embodiments, provided herein is a compound of formula I(a) of the formula:



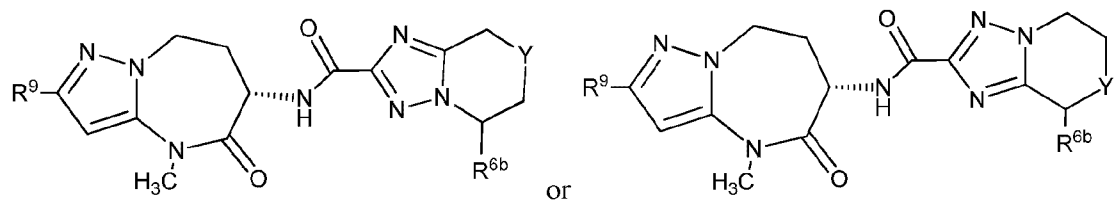
wherein R^9 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyl substituted by 1 to 2 fluorine atoms, C_1 - C_6 haloalkyl, (C_1 - C_4 alkoxy)- C_1 - C_2 alkyl, phenyl and benzyl; and R^{6b} is as defined herein. In some embodiments, R^9 is H, C_1 - C_4 alkyl, or C_3 - C_6 cycloalkyl; and R^{6b} is C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or phenyl optionally substituted by 1 to 4 substituents selected from the group consisting of halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 thioalkyl, cyano, phenyl, benzyl, CH_2 -(C_3 - C_6 cycloalkyl), and CH_2CH_2 -(C_3 - C_6 cycloalkyl). In some embodiments, R^9 is H, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl; and R^{6b} is C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, phenyl, fluorophenyl or di-fluorophenyl.

In some embodiments, provided herein is a compound of formula I(a) of the formula:



wherein R^9 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyl substituted by 1 to 2 fluorine atoms, C_1 - C_6 haloalkyl, (C_1 - C_4 alkoxy)- C_1 - C_2 alkyl, phenyl and benzyl; and R^{6b} is as defined herein. In some embodiments, R^9 is H, C_1 - C_4 alkyl, or C_3 - C_6 cycloalkyl; and R^{6b} is C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or phenyl optionally substituted by 1 to 4 substituents selected from the group consisting of halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 thioalkyl, cyano, phenyl, benzyl, CH_2 -(C_3 - C_6 cycloalkyl), and CH_2CH_2 -(C_3 - C_6 cycloalkyl). In some embodiments, R^9 is H, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl; and R^{6b} is C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, phenyl, fluorophenyl or di-fluorophenyl.

In some embodiments, provided herein is a compound of formula I(a) of the formula:



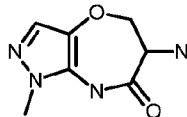
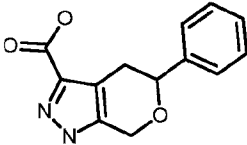
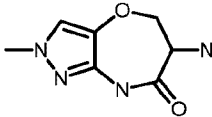
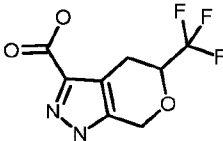
wherein Y is NH or O; R^9 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyl substituted by 1 to 2 fluorine atoms, C_1 - C_6 haloalkyl, (C_1 - C_4

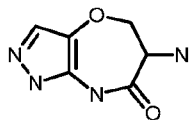
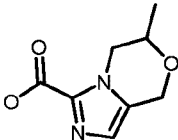
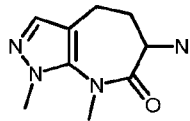
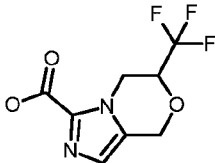
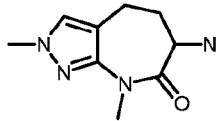
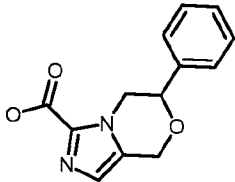
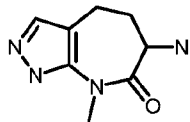
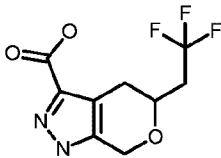
alkoxy)-C₁-C₂ alkyl, phenyl and benzyl; and R^{6b} is as defined herein. In some embodiments, R⁹ is H, C₁-C₄ alkyl, or C₃-C₆ cycloalkyl; and R^{6b} is C₁-C₄ alkyl, C₁-C₄ haloalkyl or phenyl optionally substituted by 1 to 4 substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, cyano, phenyl, benzyl, CH₂-(C₃-C₆ cycloalkyl), and CH₂CH₂-(C₃-C₆ cycloalkyl). In some embodiments, R⁹ is H, C₁-C₄ alkyl, C₃-C₆ cycloalkyl; and R^{6b} is C₁-C₄ alkyl, C₁-C₄ haloalkyl, phenyl, fluorophenyl or di-fluorophenyl.

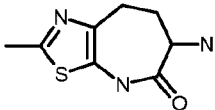
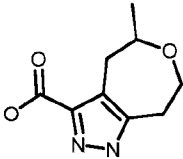
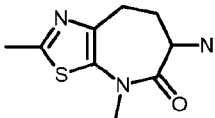
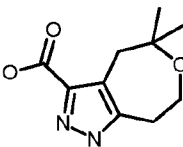
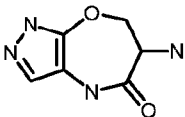
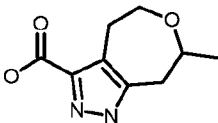
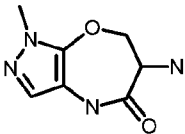
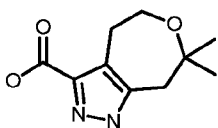
Also provided herein are embodiments corresponding to each of those described above, wherein each substituent is unsubstituted unless explicitly provided in the embodiment.

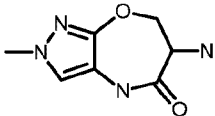
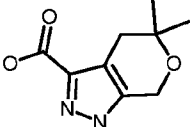
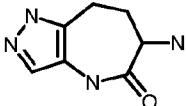
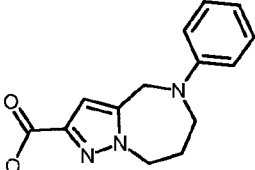
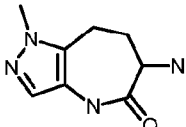
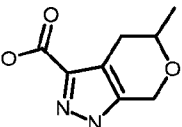
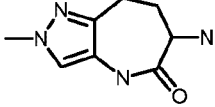
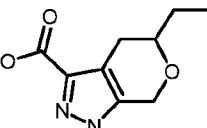
Particular compounds of formulae I, I(a), I(b) and II (hereafter referred to collectively as “formula I”) include the following, wherein each compound is the result of a condensation between a “left-hand side” amine (LHS Amine) of Table A, and a “right-hand side” carboxylic acid (RHS Acid) of Table A to form an amide of formula I. For simplicity, hydrogens are not shown. All possible combinations of a LHS Amine with a RHS Acid are contemplated and within the scope of the invention.

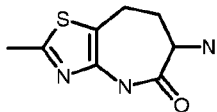
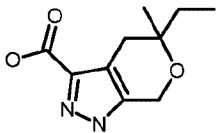
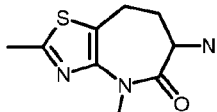
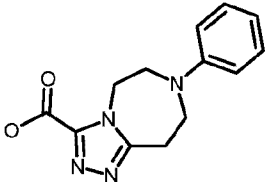
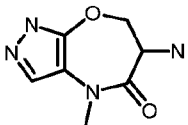
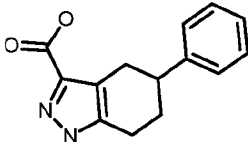
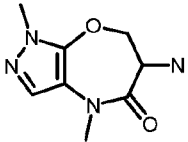
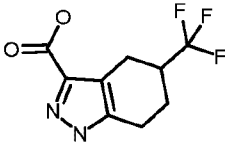
Table A

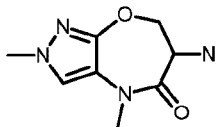
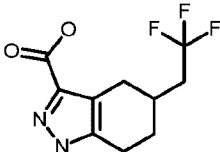
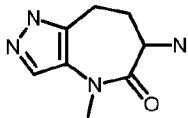
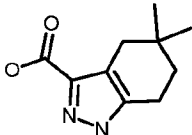
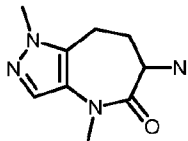
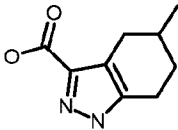
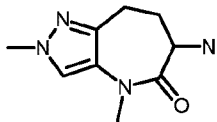
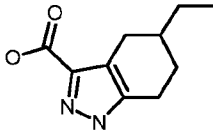
LHS Amine		RHS Acid	
1			1
2			2

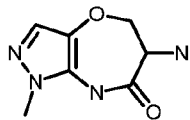
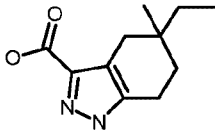
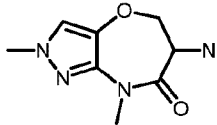
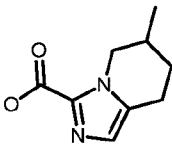
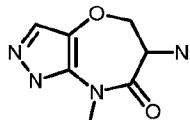
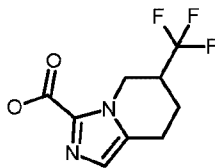
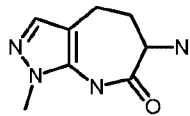
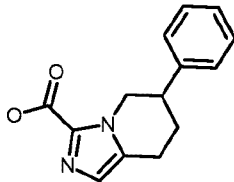
LHS Amine		RHS Acid	
3			3
4			4
5			5
6			6

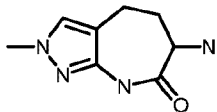
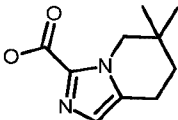
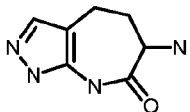
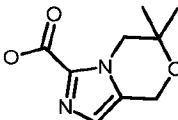
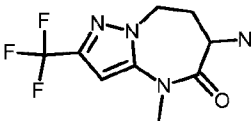
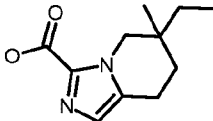
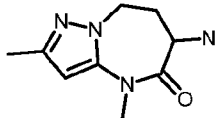
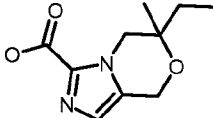
LHS Amine		RHS Acid	
7			7
8			8
9			9
10			10

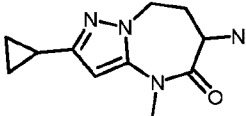
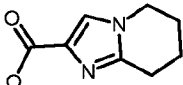
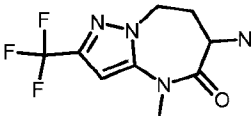
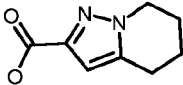
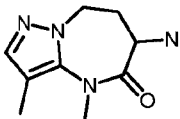
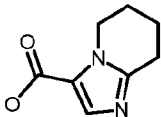
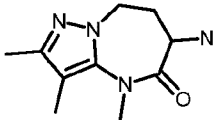
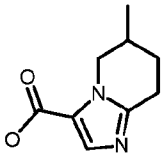
LHS Amine		RHS Acid	
11			11
12			12
13			13
14			14

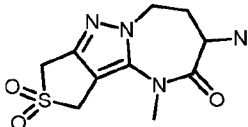
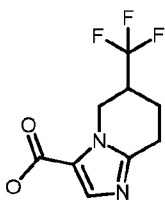
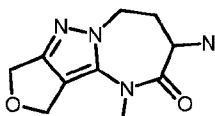
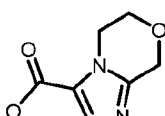
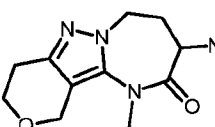
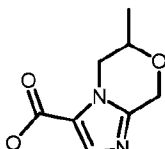
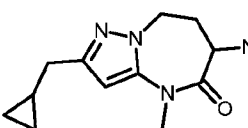
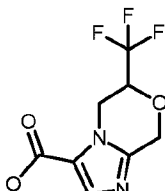
LHS Amine		RHS Acid	
15			15
16			16
17			17
18			18

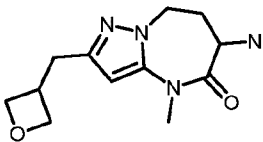
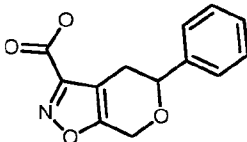
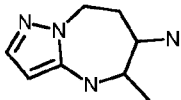
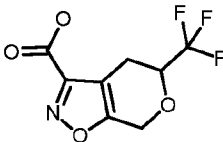
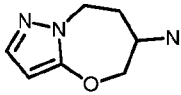
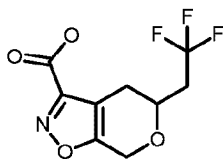
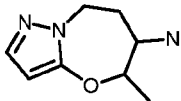
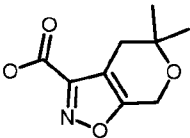
LHS Amine		RHS Acid	
19			19
20			20
21			21
22			22

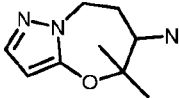
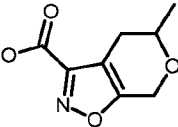
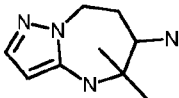
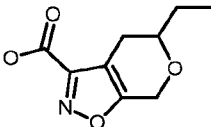
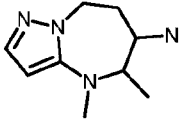
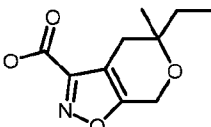
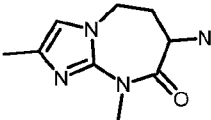
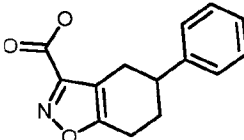
LHS Amine		RHS Acid	
23			23
24			24
25			25
26			26

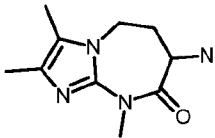
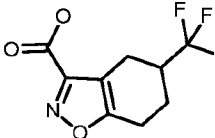
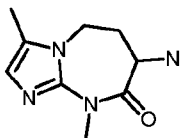
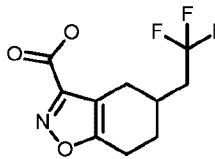
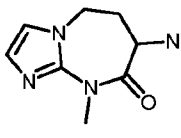
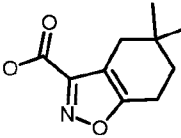
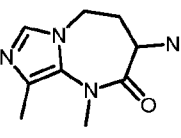
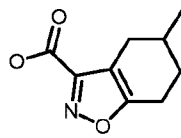
LHS Amine		RHS Acid	
27			27
28			28
29			29
30			30

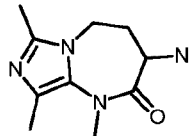
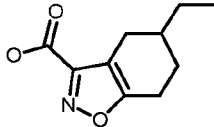
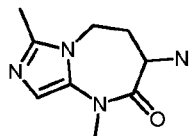
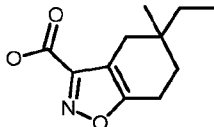
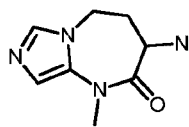
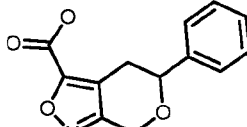
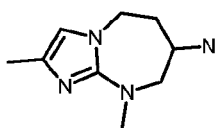
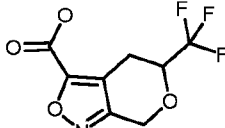
LHS Amine		RHS Acid	
31			31
32			32
33			33
34			34

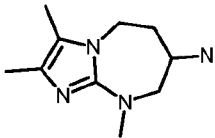
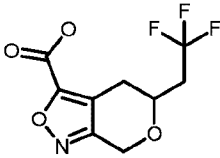
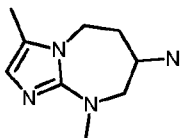
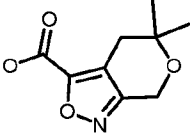
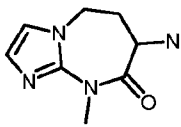
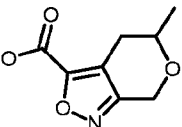
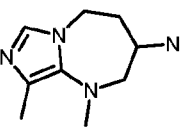
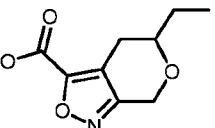
LHS Amine		RHS Acid	
35			35
36			36
37			37
38			38

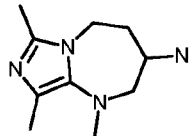
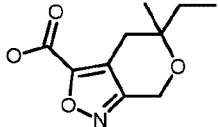
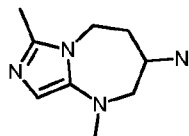
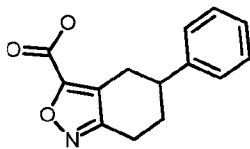
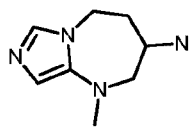
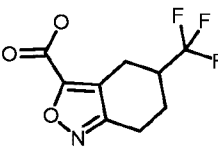
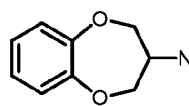
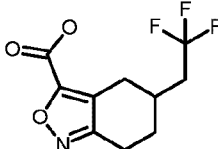
LHS Amine		RHS Acid	
39			39
40			40
41			41
42			42

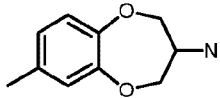
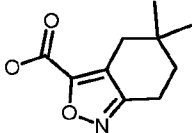
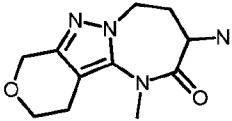
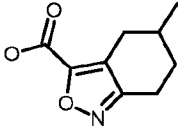
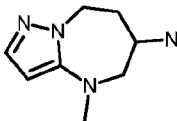
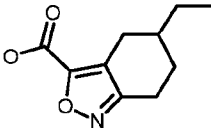
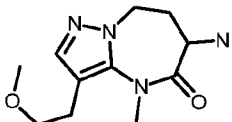
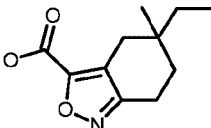
LHS Amine		RHS Acid	
43			43
44			44
45			45
46			46

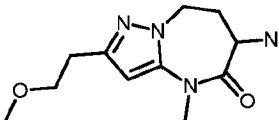
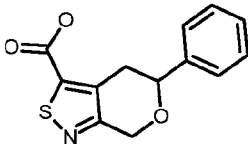
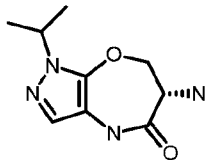
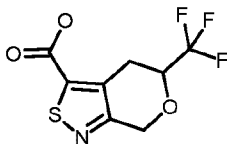
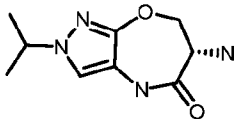
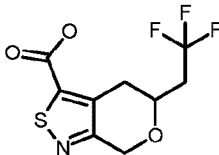
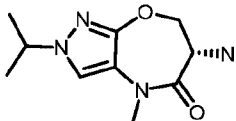
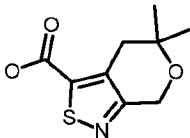
LHS Amine		RHS Acid	
47			47
48			48
49			49
50			50

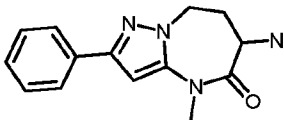
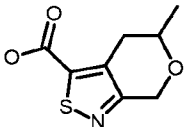
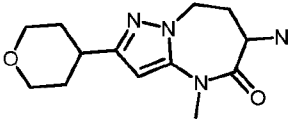
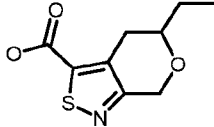
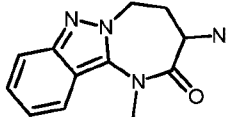
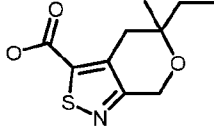
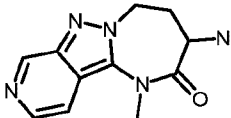
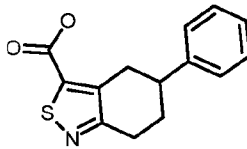
LHS Amine		RHS Acid	
51			51
52			52
53			53
54			54

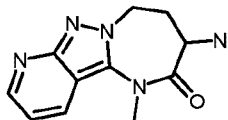
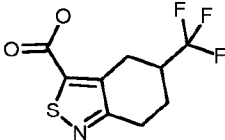
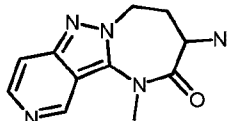
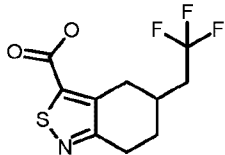
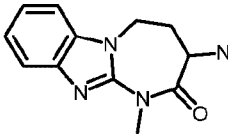
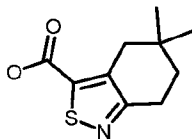
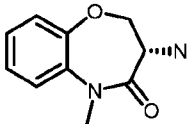
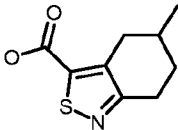
LHS Amine		RHS Acid	
55			55
56			56
57			57
58			58

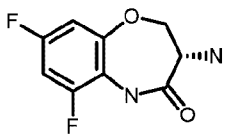
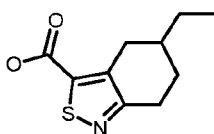
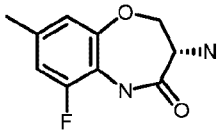
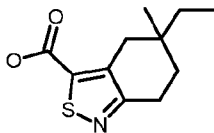
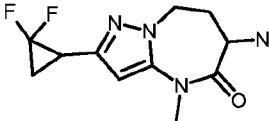
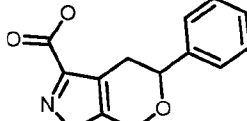
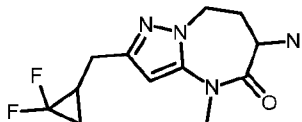
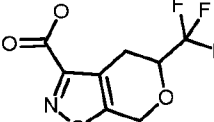
LHS Amine		RHS Acid	
59			59
60			60
61			61
62			62

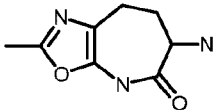
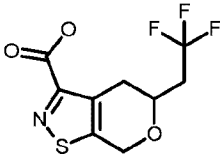
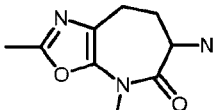
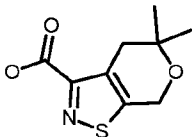
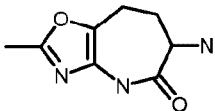
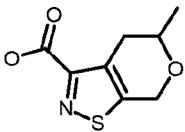
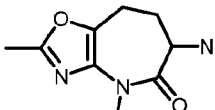
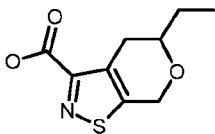
LHS Amine		RHS Acid	
63			63
64			64
65			65
66			66

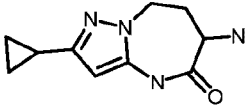
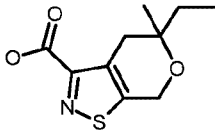
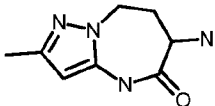
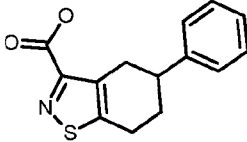
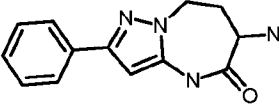
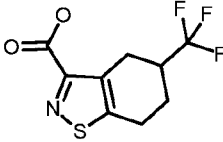
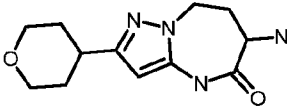
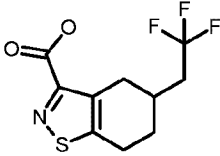
LHS Amine		RHS Acid	
67			67
68			68
69			69
70			70

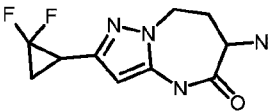
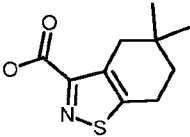
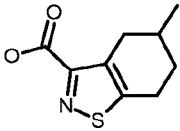
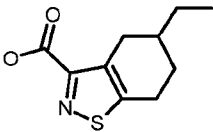
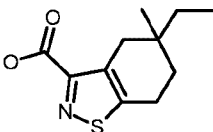
LHS Amine		RHS Acid	
71			71
72			72
73			73
74			74

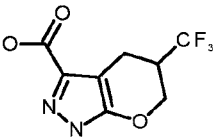
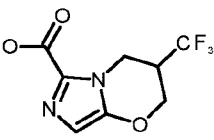
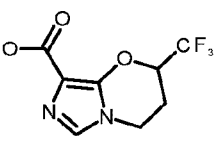
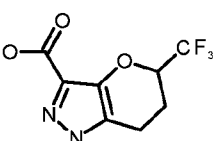
LHS Amine		RHS Acid	
75			75
76			76
77			77
78			78

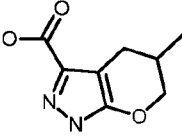
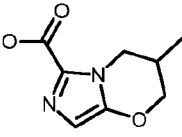
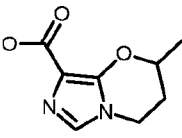
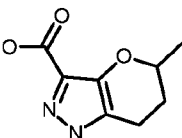
LHS Amine		RHS Acid	
79			79
80			80
81			81
82			82

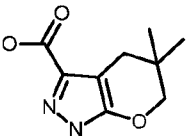
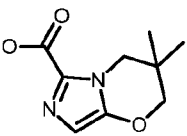
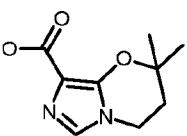
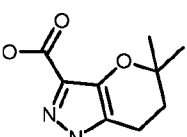
LHS Amine		RHS Acid	
83			83
84			84
85			85
86			86

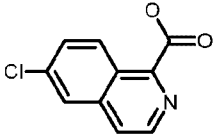
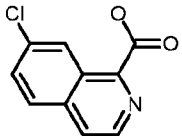
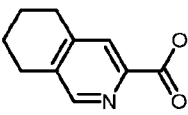
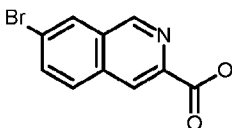
LHS Amine		RHS Acid	
87			87
88			88
89			89
90			90

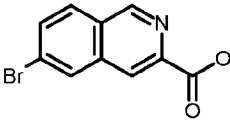
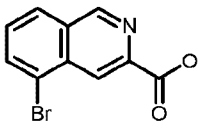
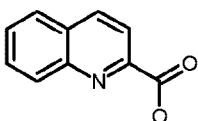
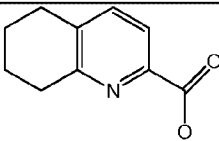
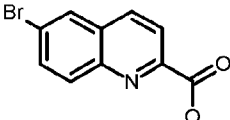
LHS Amine		RHS Acid	
91			91
			92
			93
			94

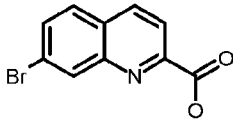
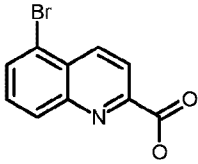
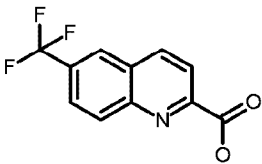
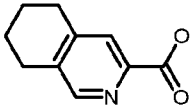
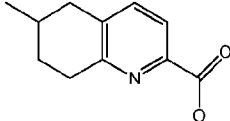
LHS Amine		RHS Acid	
			95
			96
			97
			98

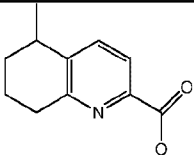
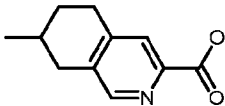
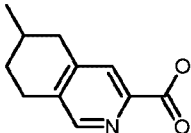
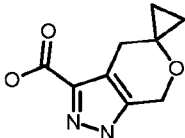
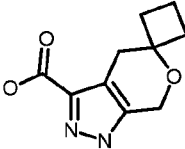
LHS Amine		RHS Acid	
			99
			100
			101
			102

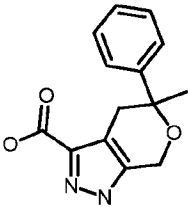
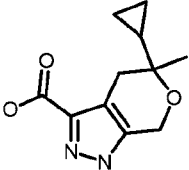
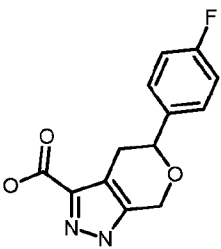
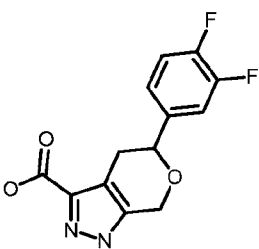
LHS Amine		RHS Acid	
			103
			104
			105
			106

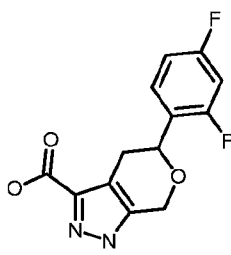
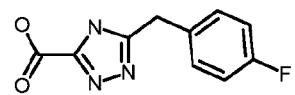
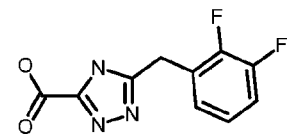
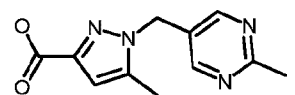
LHS Amine		RHS Acid	
		 <chem>Clc1ccc2c(c1)c(c[nH]2)C(=O)O</chem>	107
		 <chem>Clc1ccc2c(c1)c(c[nH]2)C(=O)O</chem>	108
		 <chem>C1CCC2=C(C1)C(=C)C(=CN2)C(=O)O</chem>	109
		 <chem>Brc1ccc2c(c1)c(c[nH]2)C(=O)O</chem>	110

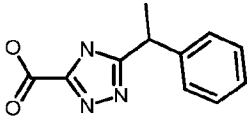
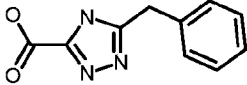
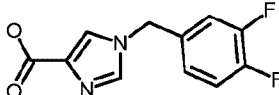
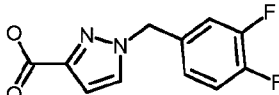
LHS Amine		RHS Acid	
		 <chem>O=C(O)c1ccc2cc(Br)ccc2n1</chem>	111
		 <chem>O=C(O)c1ccc2cc(Br)ccn2c1</chem>	112
		 <chem>O=C(O)c1ccc2ccncc2c1</chem>	113
		 <chem>O=C(O)c1ccc2c(c1)ccncc2</chem>	114
		 <chem>O=C(O)c1cc2cc(Br)ccc2n1</chem>	115

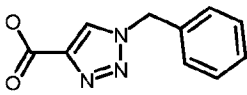
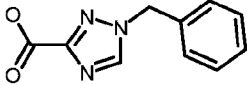
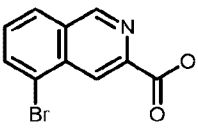
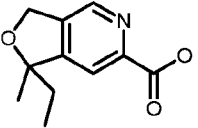
LHS Amine		RHS Acid	
		 <chem>O=C(O)c1ccc2cc(Br)ccc2n1</chem>	116
		 <chem>O=C(O)c1ccc2cc(Br)ccc2n1</chem>	117
		 <chem>O=C(O)c1ccc2cc(C(F)(F)F)ccc2n1</chem>	118
		 <chem>O=C(O)c1cnc2c1CCCCC2</chem>	119
		 <chem>O=C(O)c1cnc2c1CCCCC2</chem>	120

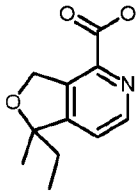
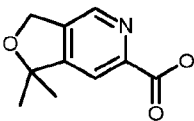
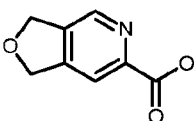
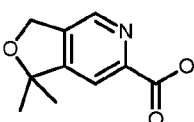
LHS Amine		RHS Acid	
			121
			122
			123
			124
			125

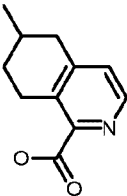
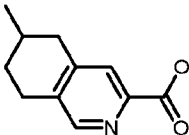
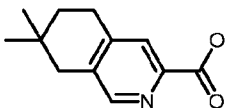
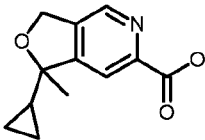
LHS Amine		RHS Acid	
			126
			127
			128
			129

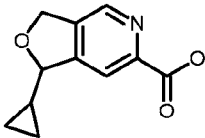
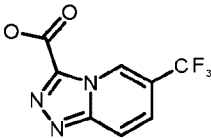
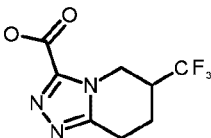
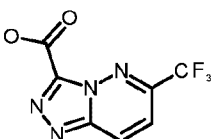
LHS Amine		RHS Acid	
		 <chem>O=C(O)c1nn2c(c1)COc3cc(F)c(F)cc32</chem>	130
		 <chem>O=C(O)c1nn2c(c1)CCc3ccc(F)cc32</chem>	131
		 <chem>O=C(O)c1nn2c(c1)CCc3cc(F)c(F)cc32</chem>	132
		 <chem>O=C(O)c1nn2c(c1)CCc3ccnc(C)n32</chem>	133

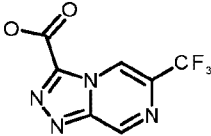
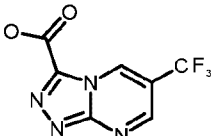
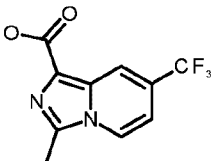
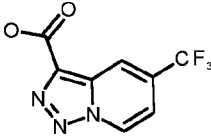
LHS Amine		RHS Acid	
		 <chem>CC1=NC2=C(N1)N=CN=C2C(=O)O</chem>	134
		 <chem>c1ccc(cc1)CC2=NC3=CC(=C(N2)N=CN3)C(=O)O</chem>	135
		 <chem>Fc1cc(cc(c1F)CN2C=CC(=O)O2)CC3=CN4C=CC(=O)O4</chem>	136
		 <chem>Fc1cc(cc(c1F)CN2C=CC(=O)O2)CC3=CN4C=CC(=O)O4</chem>	137

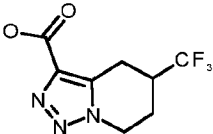
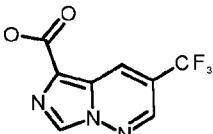
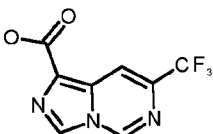
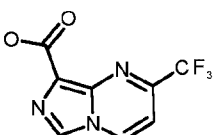
LHS Amine		RHS Acid	
			138
			139
			140
			141

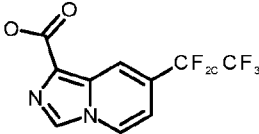
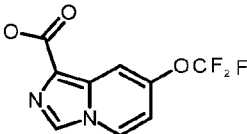
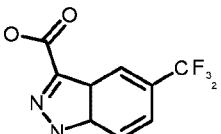
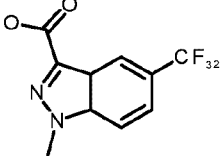
LHS Amine		RHS Acid	
			142
			143
			144
			145

LHS Amine		RHS Acid	
			146
			147
			148
			149

LHS Amine		RHS Acid	
		 <chem>O=C(O)c1cc(CCN2CC2)cnc1</chem>	150
		 <chem>O=C(O)c1nc2cc(C(F)(F)F)ncn2n1</chem>	151
		 <chem>O=C(O)c1nc2cc(C(F)(F)F)ncn2n1</chem>	152
		 <chem>O=C(O)c1nc2cc(C(F)(F)F)ncn2n1</chem>	153

LHS Amine		RHS Acid	
			154
			155
			156
			157

LHS Amine		RHS Acid	
			158
			159
			160
			161

LHS Amine		RHS Acid	
			162
			163
			164
			165

In one embodiment, provided herein is a compound of formula I selected from the group consisting of:

5a-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxamide;

- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1',4',5',7'-tetrahydrospiro[cyclopropane-1,6'-indazole]-3'-carboxamide;
- 5-(tert-butyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 5 N-((S)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxamide;
- N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-phenyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide;
- 10 5-methyl-N-((S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide;
- 5,5-dimethyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-4,7-dihydro-1H-pyrano[3,4-c]pyrazole-3-carboxamide;
- 15 N-((S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl)-5-phenyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide;
- 6-methyl-N-((S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl)-6,8-dihydro-5H-imidazo[5,1-c][1,4]oxazine-3-carboxamide;
- 6-methyl-N-((S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide;
- 20 (R)-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- (S)-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 25 (S)-2-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide;
- 5,5-dimethyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1,4,6,7-tetrahydroindazole-3-carboxamide;
- 5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide;
- 30 6-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxamide;

- N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(1H-pyrazol-1-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 1-ethyl-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-4-carboxamide;
- 5 1-ethyl-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide;
- (S)-1,1-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroisoquinoline-3-carboxamide;
- 10 N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- (S)-5,5-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide;
- 15 (S)-6,6-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxamide;
- 5-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- (S)-5-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- 20 H-1,2,4-triazole-3-carboxamide;
- 5-benzyl-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- 5-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- 25 5-benzyl-N-(4-methyl-5-oxo-2-(trifluoromethyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- 5-benzyl-N-(3,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 30 (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-indazole-3-carboxamide;

- N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- (R)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 5 (S)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-carboxamide;
- N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide;
- 10 (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxamide;
- N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-7-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-1-carboxamide;
- 15 (S)-N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- (R)-N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,5,6,7,8-hexahydrocyclohepta[c]pyrazole-3-carboxamide;
- 20 5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide;
- N-((S)-7-chloro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-5-methyl-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide;
- 25 5-(tert-butyl)-N-((S)-7-chloro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxamide;
- (S)-N-(7-chloro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxamide;
- 30 N-((S)-7-chloro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-5a-methyl-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxamide;

- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroquinoline-2-carboxamide;
- (S)-6-chloro-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxamide;
- 5 (S)-N-(7-chloro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- N-((S)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-3,4,5,5a,6,6a-hexahydrocyclopropa[e]indazole-1-carboxamide;
- (S)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 10 N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxamide;
- 5-methyl-N-((S)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 15 (S)-5-(tert-butyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-3,4,5,5a,6,6a-hexahydrocyclopropa[e]indazole-1-carboxamide;
- (R)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 20 (R)-5-(tert-butyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 5-methyl-N-((S)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[c]isoxazole-3-carboxamide;
- 25 5-methyl-N-((S)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide;
- 5-(tert-butyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide;
- 5-(tert-butyl)-N-((S)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide;
- 30 5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[c]isoxazole-3-carboxamide;

- 5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide;
- (S)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide;
- 5 (S)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[c]isoxazole-3-carboxamide;
- (R)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide;
- (R)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[c]isoxazole-3-carboxamide;
- 10 1-benzyl-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-1-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- 15 5-ethyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide;
- (S)-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxamide;
- N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxamide;
- 20 (S)-5-benzyl-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- (S)-5-chloro-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-indazole-3-carboxamide;
- 25 (S)-5-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- (S)-5-benzyl-N-(4-methyl-5-oxo-2-(trifluoromethyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxamide; and
- 30 (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide.

In one embodiment, provided herein is a compound of formula I selected from the group consisting of:

- 5-(tert-butyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 5 N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-phenyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide;
- 5,5-dimethyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-4,7-dihydro-1H-pyrano[3,4-c]pyrazole-3-carboxamide;
- 10 N-((S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl)-5-phenyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide;
- 6-methyl-N-((S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide;
- (R)-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 15 (S)-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 5,5-dimethyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1,4,6,7-tetrahydroindazole-3-carboxamide;
- N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(1H-pyrazol-1-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 20 1-ethyl-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide;
- (S)-1,1-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide;
- 25 N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 5-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- (S)-5-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- 30 5-benzyl-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;

- 5-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- 5-benzyl-N-(4-methyl-5-oxo-2-(trifluoromethyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- 5 5-benzyl-N-(3,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- (R)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 10 (S)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-carboxamide;
- 15 N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxamide;
- N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-7-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-1-carboxamide;
- 20 (R)-N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide;
- 25 N-((S)-7-chloro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-5-methyl-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide;
- 5-(tert-butyl)-N-((S)-7-chloro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- (S)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 30 N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxamide;

- 5-methyl-N-((S)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- (S)-5-(tert-butyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 5 (R)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- (R)-5-(tert-butyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 5-methyl-N-((S)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[c]isoxazole-3-carboxamide;
- 10 5-methyl-N-((S)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide;
- 5-(tert-butyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide;
- 15 5-(tert-butyl)-N-((S)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide;
- 5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[c]isoxazole-3-carboxamide;
- 5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide;
- 20 5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide;
- (S)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide;
- (S)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[c]isoxazole-3-carboxamide;
- 25 (R)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide;
- (R)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[c]isoxazole-3-carboxamide;
- 1-benzyl-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- 30 (S)-1-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;

5-ethyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide;

(S)-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxamide;

5 N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxamide;

(S)-5-benzyl-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;

10 (S)-5-chloro-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-indazole-3-carboxamide;

(S)-5-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;

(S)-5-benzyl-N-(4-methyl-5-oxo-2-(trifluoromethyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;

15 (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxamide; and

(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide.

20 In another embodiment, provided herein is a compound selected from the compounds of Tables 1, 2, 3, 4 and 5 below. In one embodiment, the compound is a compound of Table 1. In another embodiment, the compound is a compound of Table 2.

In one embodiment, provided herein is a compound selected from the group consisting of:

25 (S)-1-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;

(S)-1-benzyl-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;

5-ethyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide;

30 (S)-5-chloro-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-indazole-3-carboxamide;

(S)-5-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;

- (S)-5-benzyl-N-(4-methyl-5-oxo-2-(trifluoromethyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- (S)-N-((S)-6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- 5 (S)-N-((S)-6-fluoro-8-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- (R)-N-((S)-6-fluoro-8-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;
- (S)-5-methyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)benzo[d]isothiazole-3-carboxamide;
- 10 (S)-1-benzyl-N-(4-methyl-5-oxo-2-(trifluoromethyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-5-cyclopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-indazole-3-carboxamide;
- 15 (S)-5-(4-fluorobenzyl)-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- (S)-5-(2,3-difluorobenzyl)-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- 1-benzyl-N-(3,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- 20 1-benzyl-N-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-[1,3]diazepino[1,2-b]indazol-3-yl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(perfluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxamide;
- 25 (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-1H-indazole-3-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(perfluoroethyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4'H,6'H-spiro[cyclopentane-1,5'-pyrrolo[1,2-c][1,2,3]triazole]-3'-carboxamide;
- 30 (S)-1-isopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-carboxamide;

- (S)-N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide;
- N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]pyridine-6-carboxamide;
- 5 (S)-5-isopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[4,3-b]pyridine-3-carboxamide;
- 1-benzyl-N-(1-methyl-2-oxo-1,2,3,4,5,10-hexahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-5-chloro-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[4,3-b]pyridine-3-carboxamide;
- 10 1-benzyl-N-((S)-2-((S)-2,2-difluorocyclopropyl)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- 1-benzyl-N-((S)-2-((R)-2,2-difluorocyclopropyl)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- 15 (R)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide;
- (S)-1-benzyl-N-(9-methyl-8-oxo-6,7,8,9-tetrahydro-5H-imidazo[1,2-a][1,3]diazepin-7-yl)-1H-1,2,4-triazole-3-carboxamide;
- N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1-((R)-tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]pyridine-6-carboxamide;
- 20 (S)-1-benzyl-N-(4-methyl-5-oxo-4,5,6,7,8,9-hexahydropyrazolo[1,5-a][1,3]diazocin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-1-benzyl-N-(1-methyl-2-oxo-1,2,3,4,5,6-hexahydroimidazo[1,5-a][1,3]diazocin-3-yl)-1H-1,2,4-triazole-3-carboxamide;
- 25 (S)-1-(cyclopentylmethyl)-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- (R)-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1-(2,2,2-trifluoroethyl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide;
- (S)-1-(cyclopentylmethyl)-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- 30 (S)-1-(cyclohexylmethyl)-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;

- (S)-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-(4-fluorobenzyl)-1H-1,2,4-triazole-3-carboxamide;
- N-((S)-2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-((S)-1-phenylethyl)-1H-1,2,4-triazole-3-carboxamide;
- 5 (S)-1-benzyl-N-(3,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- (R)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5-dihydro-2H,3'H-spiro[furan-3,1'-furo[3,4-c]pyridine]-6'-carboxamide;
- (S)-1-(4-chlorobenzyl)-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- 10 (S)-1-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-1-benzyl-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- 15 6-isopropyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-2-(trifluoromethyl)imidazo[1,5-a]pyrimidine-8-carboxamide;
- 20 (S)-1-ethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[4,3-c]pyridine-6-carboxamide;
- 5-(2,4-difluorophenyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide;
- 25 5-(2,4-difluorophenyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide;
- (S)-7,7-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxamide;
- (S)-7,7-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,7-dihydrothieno[3,4-d]pyrimidine-2-carboxamide;
- 30 (S)-1-(2,3-difluorobenzyl)-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;

- (S)-1-(3,4-difluorobenzyl)-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-1-(2,4-difluorobenzyl)-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- 5 (S)-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-(4-fluorobenzyl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-(3,4-difluorobenzyl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-(2,4-difluorobenzyl)-1H-1,2,4-triazole-3-carboxamide;
- 10 (S)-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-(4-fluorobenzyl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-5-isopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-indazole-3-carboxamide;
- 15 1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1-(2,2,2-trifluoroethyl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-7-(trifluoromethyl)imidazo[1,5-c]pyrimidine-1-carboxamide;
- (S)-5-isopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[3,4-b]pyridine-3-carboxamide;
- 20 (S)-5-benzyl-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- (R)-N-((S)-6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide;
- 25 N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(1,1,1-trifluoropropyl)-1-cyclopropyl-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide;
- 1-cyclopropyl-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide;
- N-((S)-2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-(1-(4-fluorophenyl)ethyl)-1H-1,2,4-triazole-3-carboxamide;
- 30 (S)-1-(2,3-difluorobenzyl)-N-(2,3,4-trimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;

- (S)-1-(3,4-difluorobenzyl)-N-(2,3,4-trimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-1-benzyl-N-(2,3,4-trimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- 5 N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(perfluoroethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide;
- (S)-1-(2,4-difluorobenzyl)-N-(2,3,4-trimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-1-(4-fluorobenzyl)-N-(2,3,4-trimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- 10 1-(4-chlorobenzyl)-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(1,1,1-trifluoropropyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxamide;
- 15 (S)-1-benzyl-N-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-imidazo[1,5-a][1,3]diazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-2',3',5',6'-tetrahydro-3H-spiro[furo[3,4-c]pyridine-1,4'-pyran]-6-carboxamide;
- (S)-5-benzyl-N-(2,3,4-trimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide;
- 20 (S)-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-(2,6-difluorobenzyl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-(3,5-difluorobenzyl)-1H-1,2,4-triazole-3-carboxamide;
- 25 (S)-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-(2,5-difluorobenzyl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-1-(2,5-difluorobenzyl)-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;
- (S)-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-(2,3-dichlorobenzyl)-1H-1,2,4-triazole-3-carboxamide;
- 30 (S)-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-(2,4-dichlorobenzyl)-1H-1,2,4-triazole-3-carboxamide;

7-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-7-propyl-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxamide;

7-ethyl-7-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxamide;

5 1-(2,3-difluorobenzyl)-N-((R)-2-((R)-2,2-difluorocyclopropyl)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;

1-(2,4-difluorobenzyl)-N-((S)-2-((R)-2,2-difluorocyclopropyl)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;

10 1-(2,4-difluorobenzyl)-N-((R)-2-((R)-2,2-difluorocyclopropyl)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;

(S)-N-((S)-2-((R)-2,2-difluorocyclopropyl)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide;

1-(2,3-difluorobenzyl)-N-((S)-2-((S)-2,2-difluorocyclopropyl)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;

15 1-(3,4-difluorobenzyl)-N-((S)-2-((S)-2,2-difluorocyclopropyl)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;

1-(2,4-difluorobenzyl)-N-((S)-2-((S)-2,2-difluorocyclopropyl)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide;

20 N-((S)-2-((S)-2,2-difluorocyclopropyl)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-(4-fluorobenzyl)-1H-1,2,4-triazole-3-carboxamide;

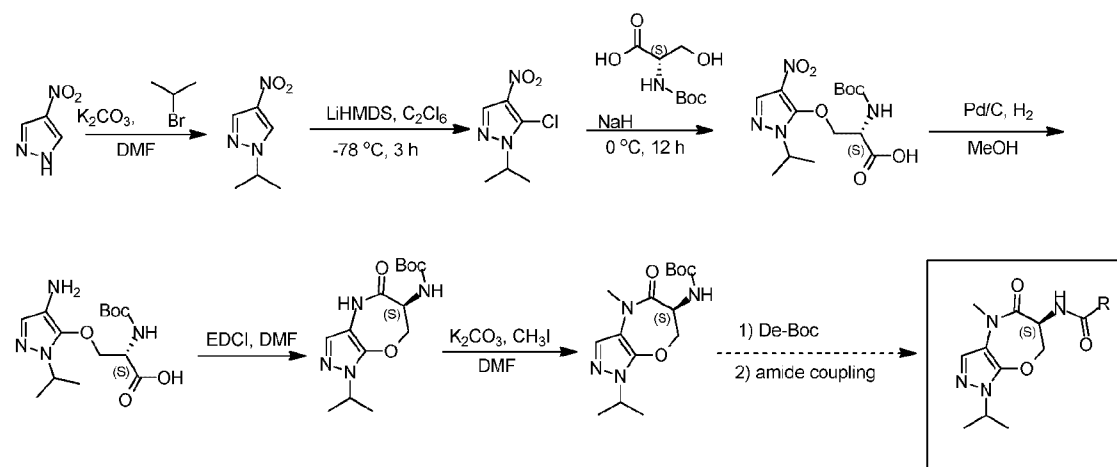
(S)-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-(2,3-difluorobenzyl)-1H-1,2,4-triazole-3-carboxamide; and

(S)-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-(4-fluorobenzyl)-4H-1,2,4-triazole-3-carboxamide.

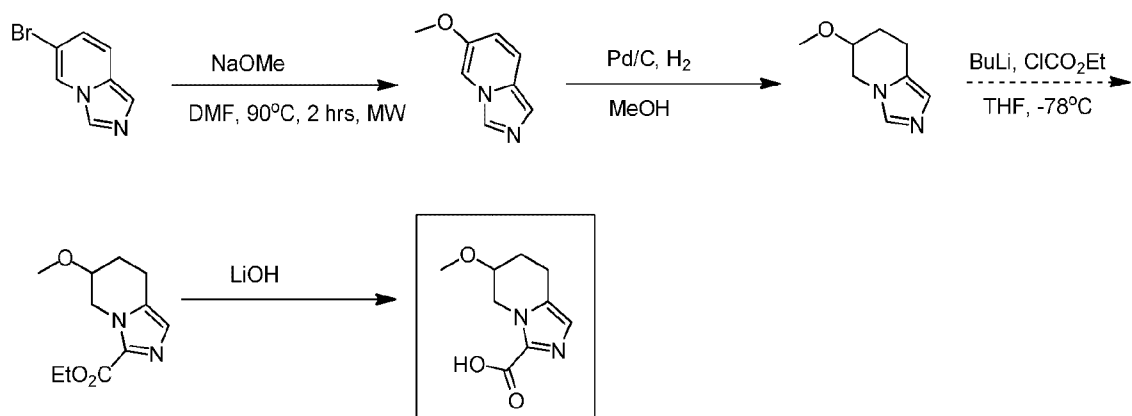
25 SYNTHESIS

Compounds of formula I may be prepared by the processes illustrated in the schemes below or by methods known to those of ordinary skill in the art. Scheme 1 below is an example of a method of preparing a compound of formula I, wherein “R” represent the “right-hand side” building block derived from the carboxylic acid intermediates of exemplary Schemes 2-14 and 26-35 (when L of formula I is absent) or is as prepared according to the procedures described in WO 2014/125444 (when L is present). Schemes 15-25 show illustrative methods for making the “left-hand side” lactam building blocks of compounds of formulae I, I(a) and I(b).

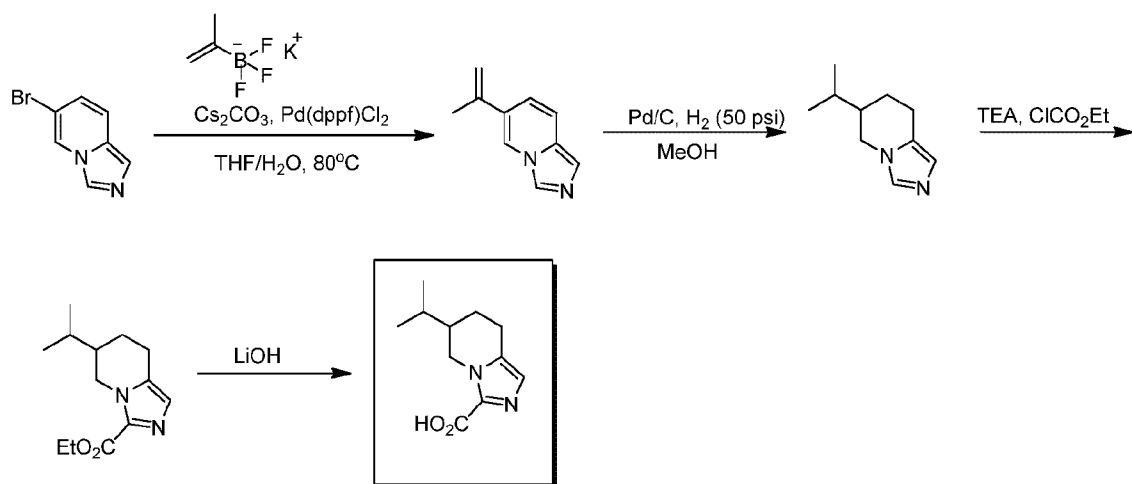
Scheme 1



Scheme 2

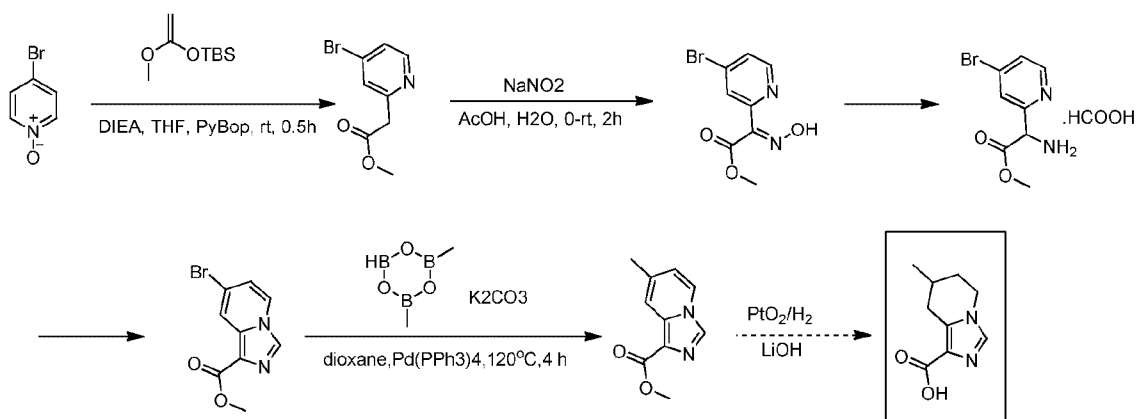


Scheme 3

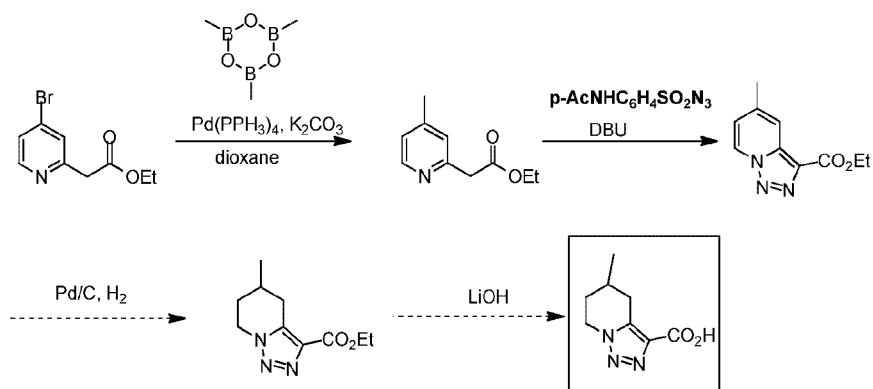


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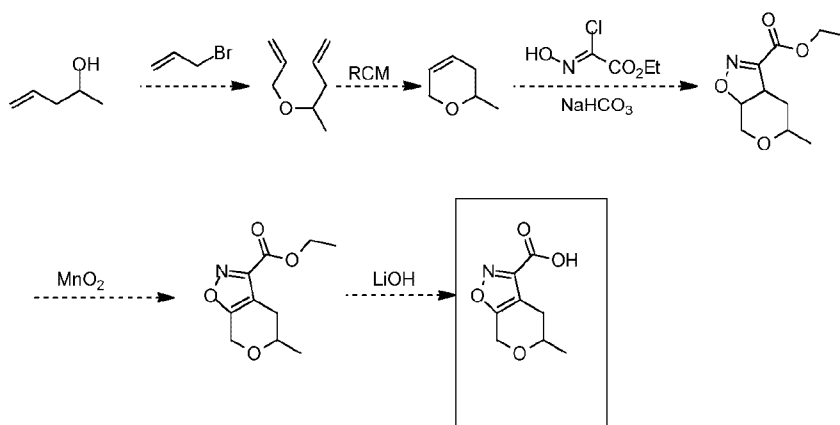
Scheme 4



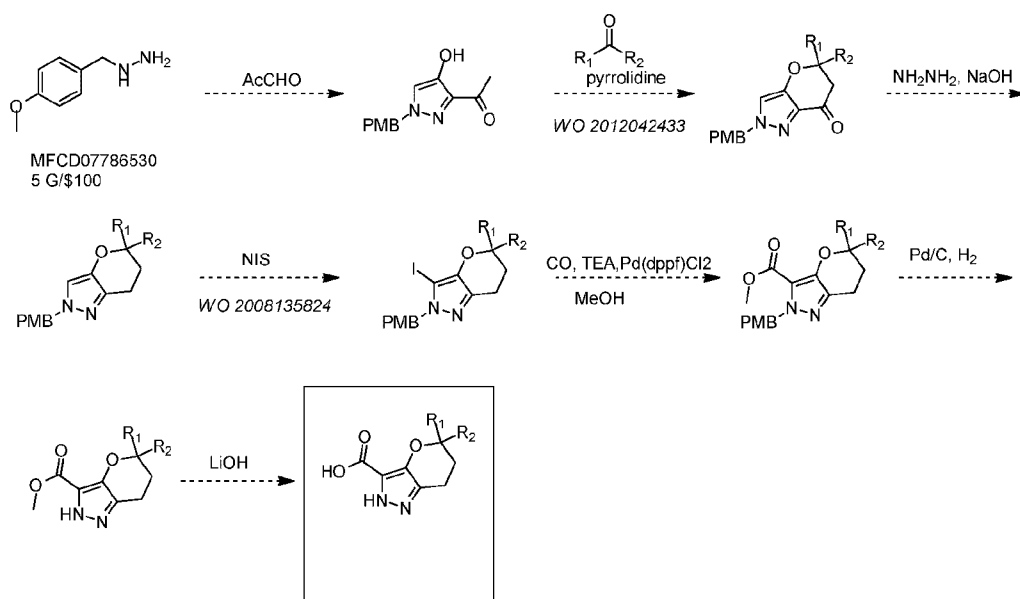
Scheme 5



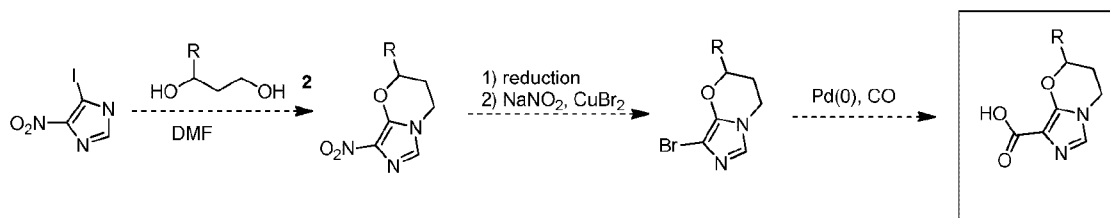
Scheme 6



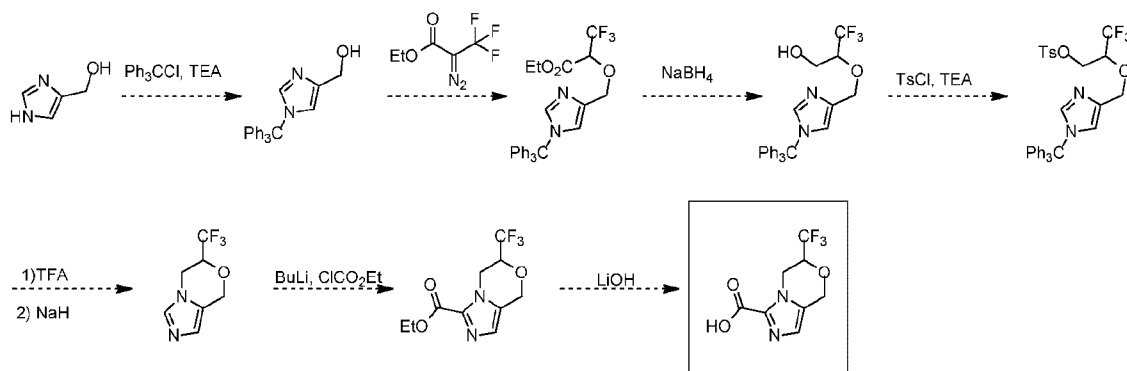
5 Scheme 7



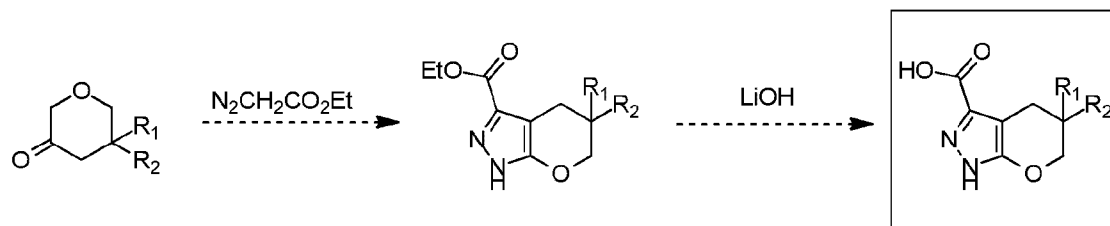
Scheme 8



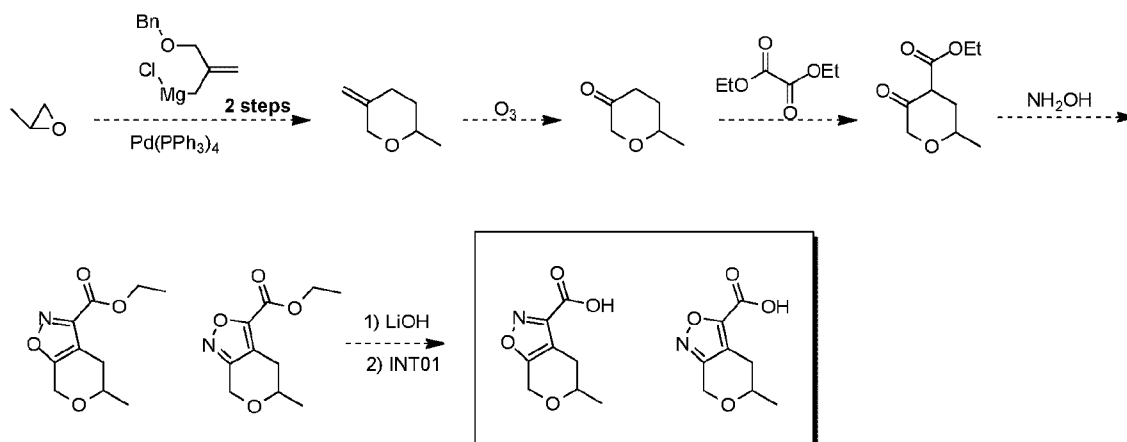
Scheme 9



5 Scheme 10

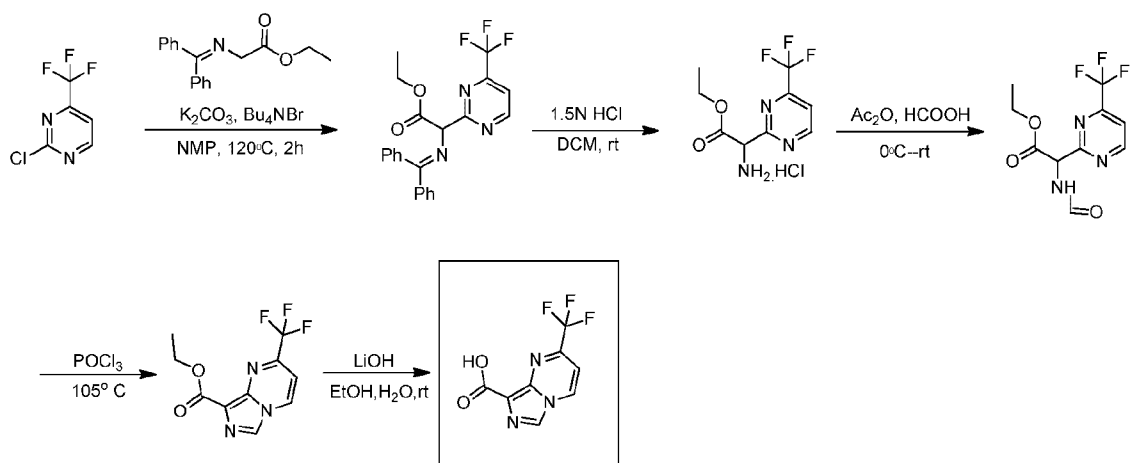


Scheme 11

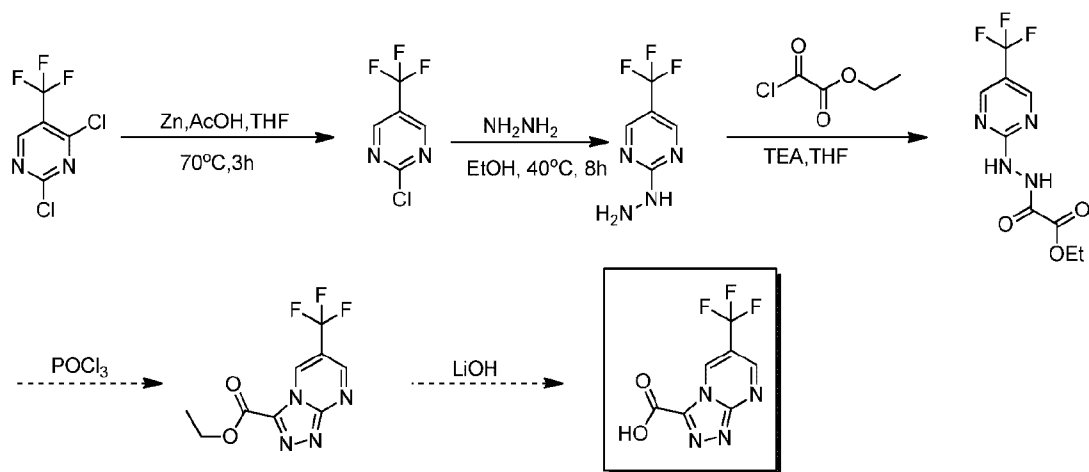


- 10 Isothiazoles are prepared in the same way shown in Scheme 11 by substituting NH₂-OH for NH₂-SH.

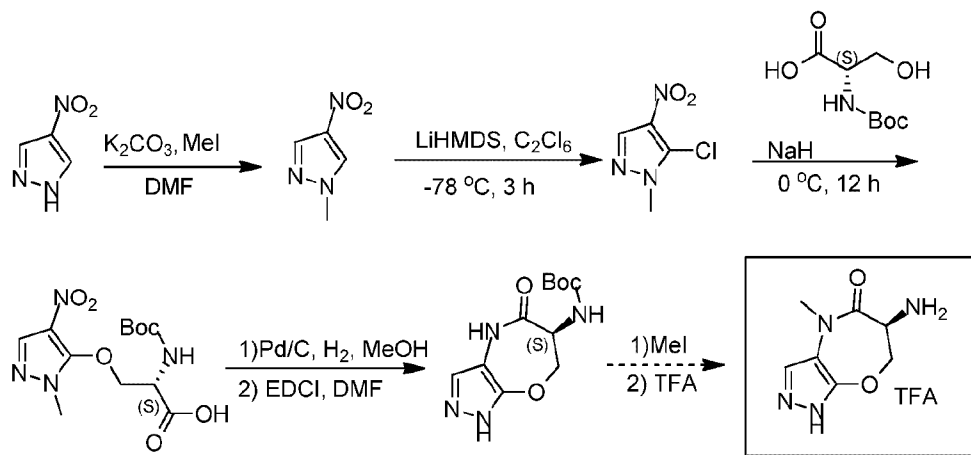
Scheme 12



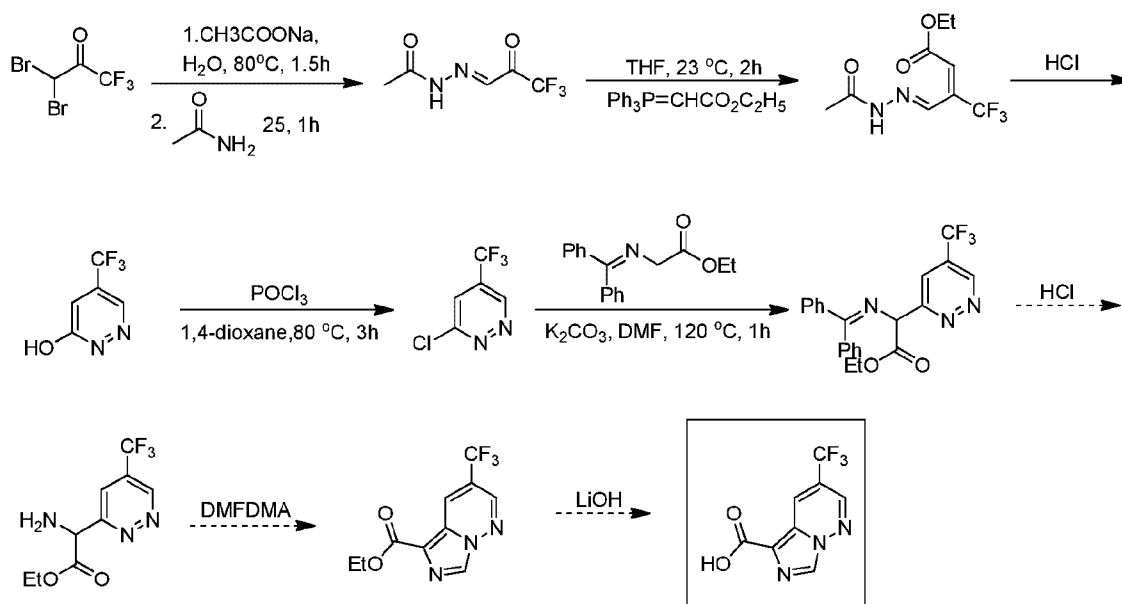
Scheme 13



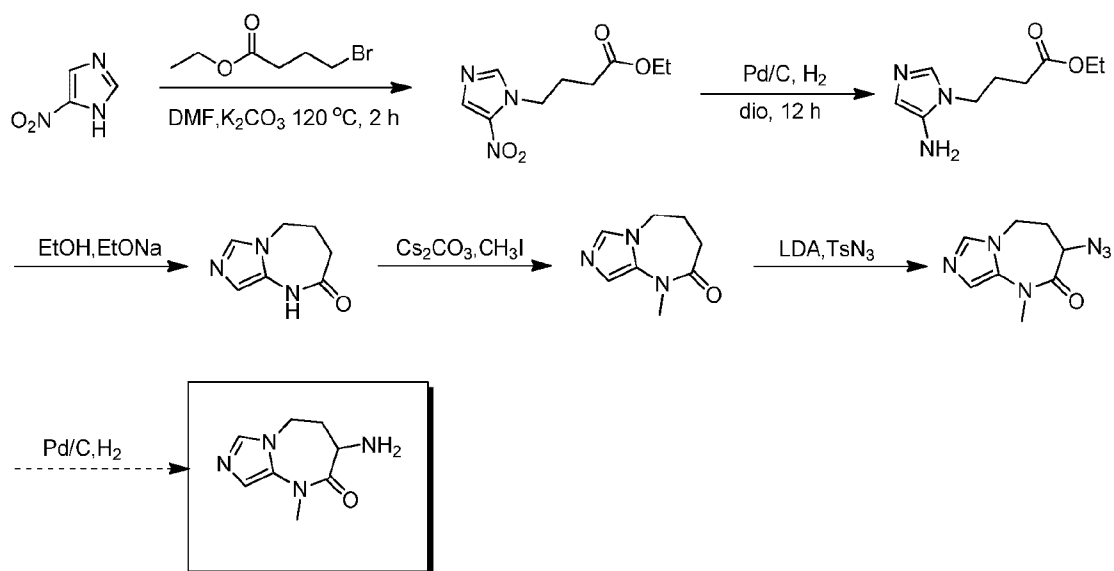
5 Scheme 14



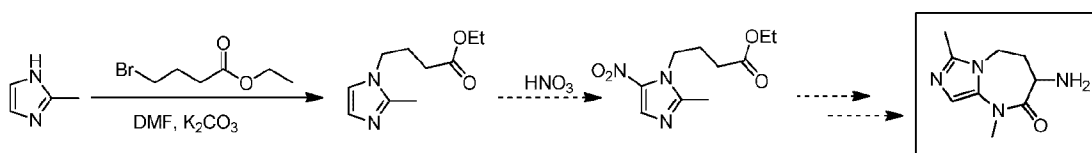
Scheme 15



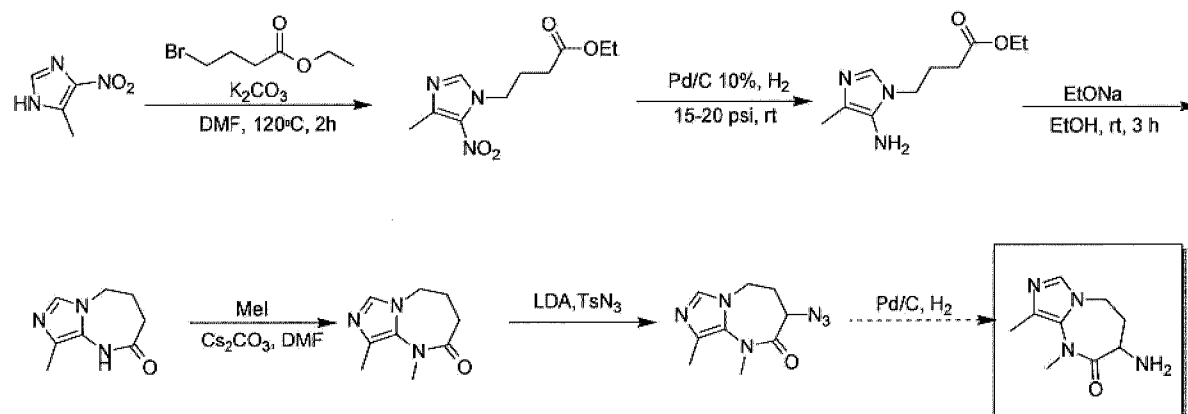
Scheme 16



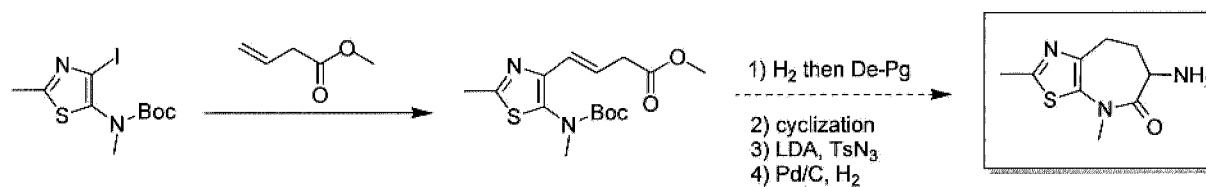
5 Scheme 17



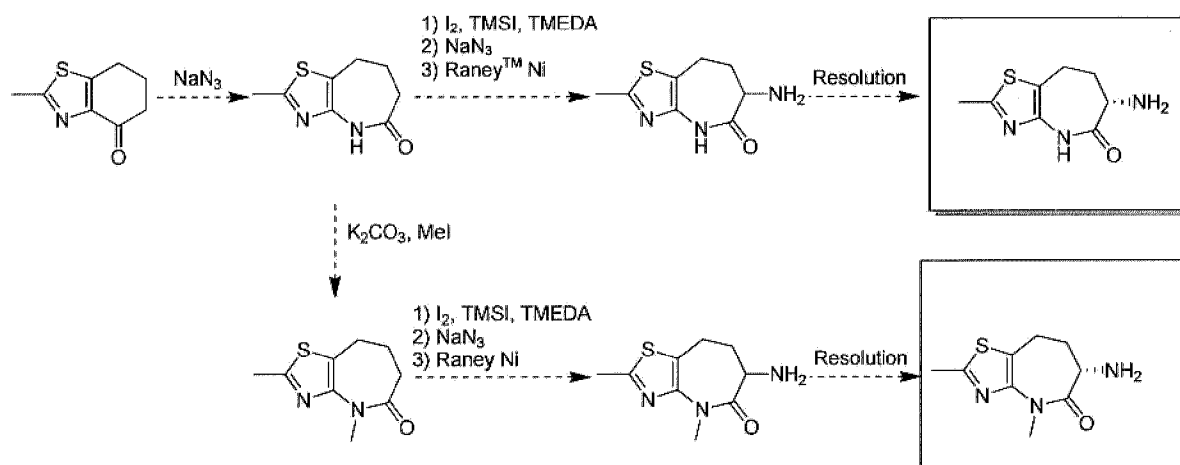
Scheme 18



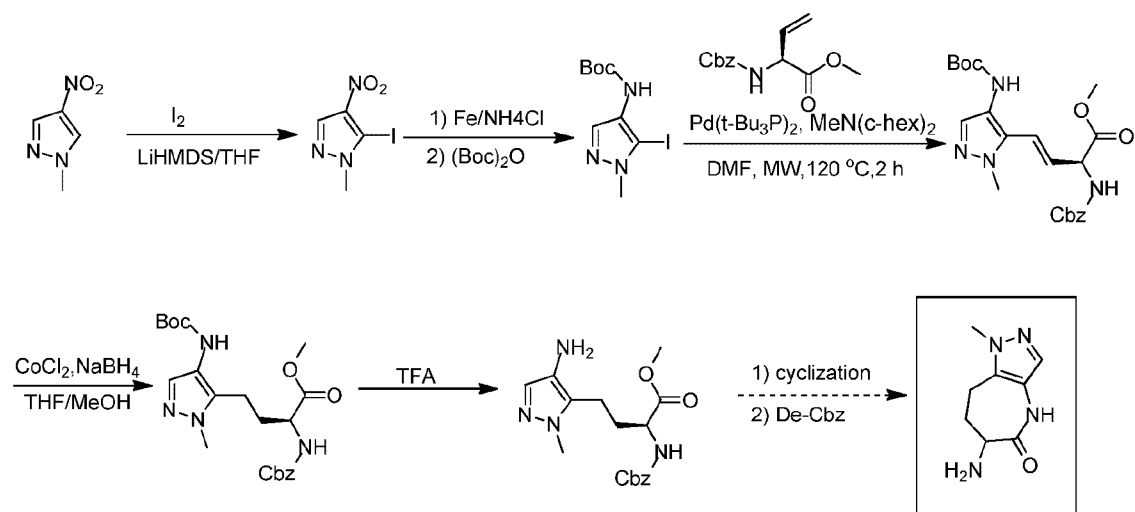
Scheme 19



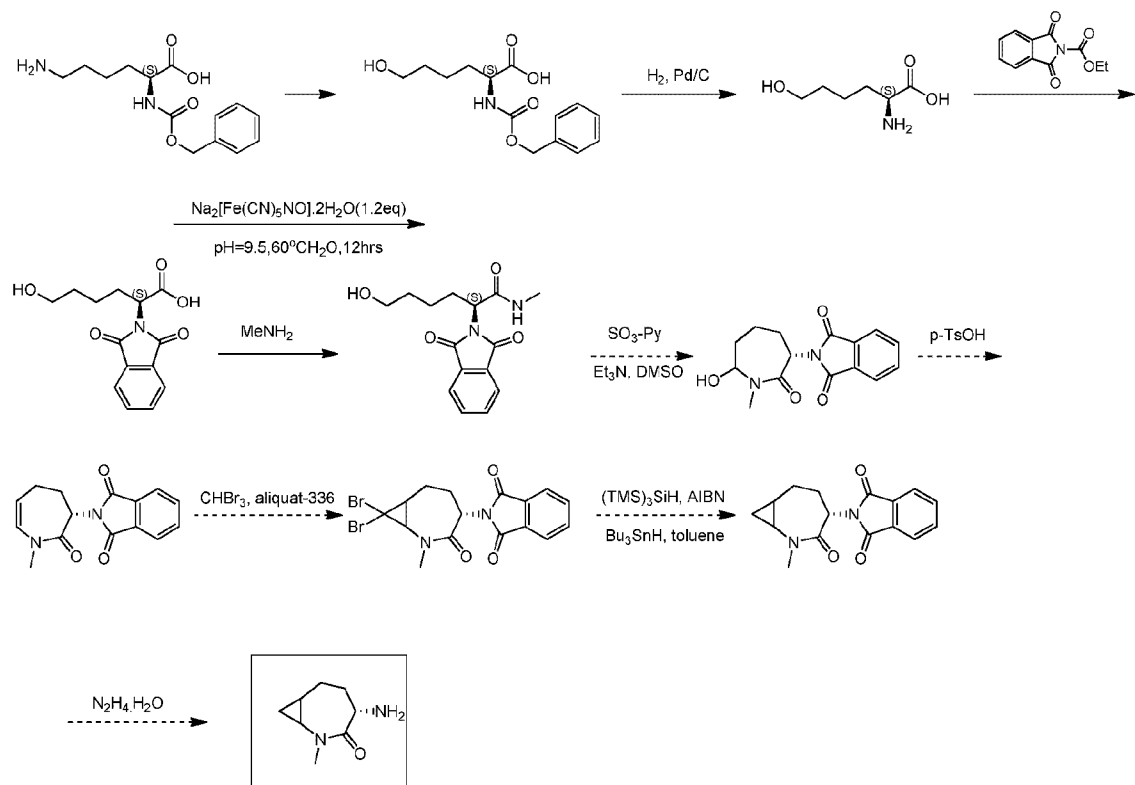
5 Scheme 20

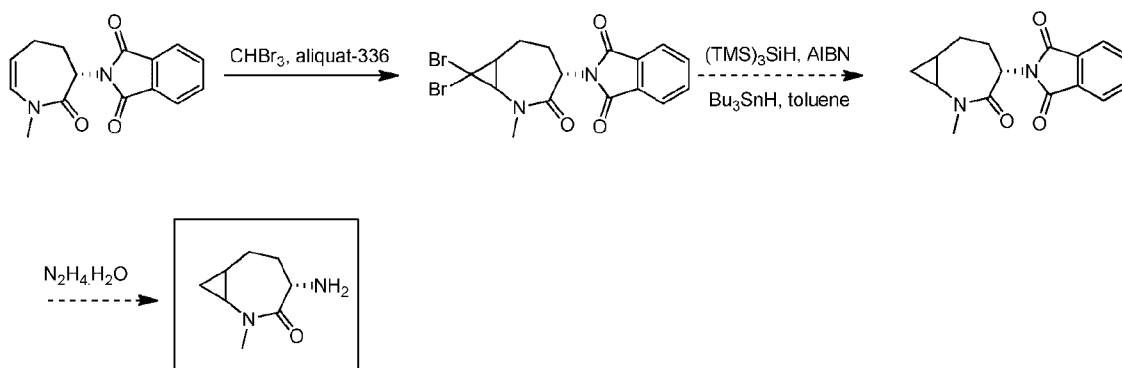
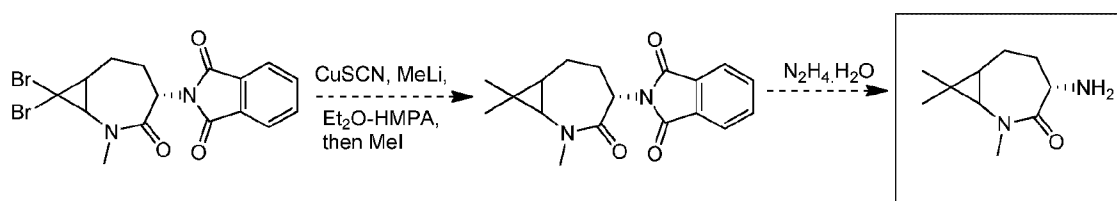


Scheme 21

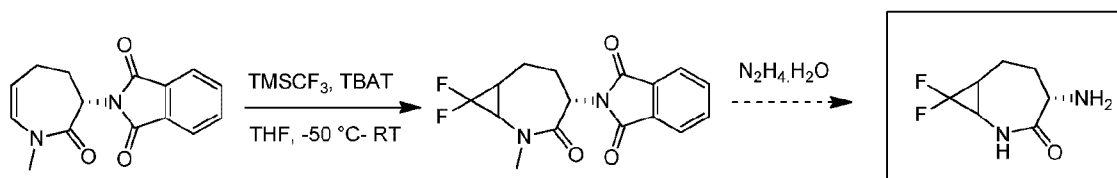
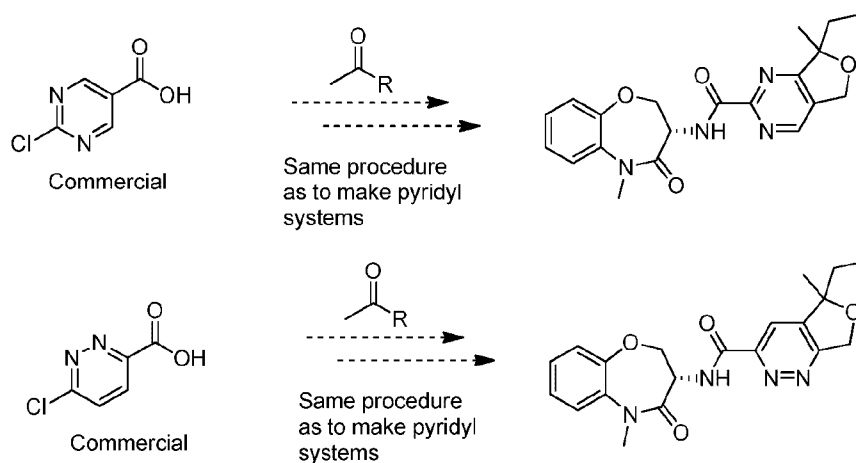


Scheme 22



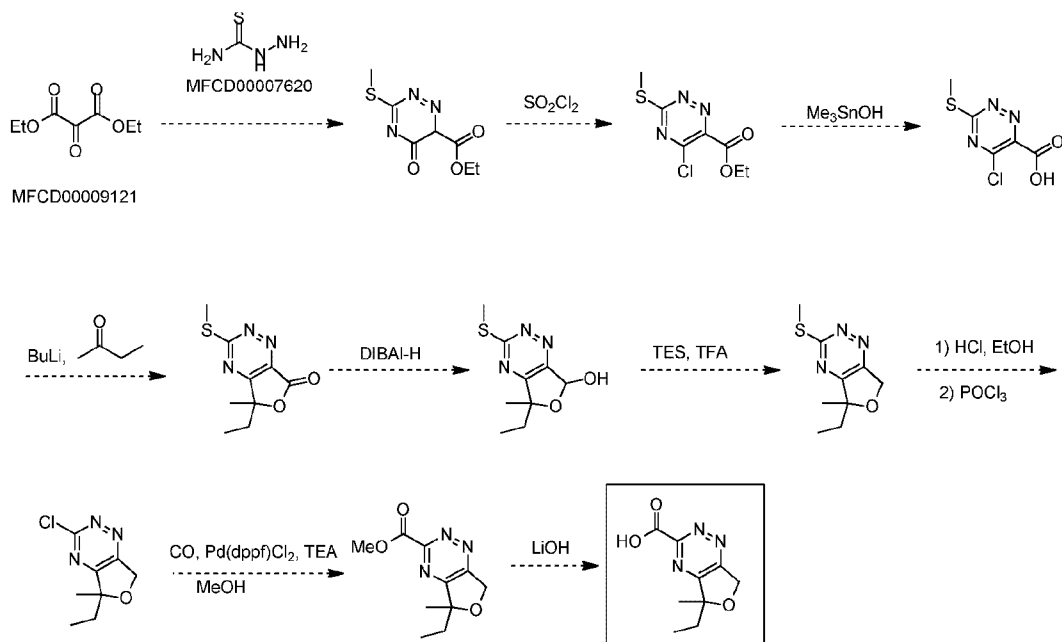
Scheme 23**Scheme 24**

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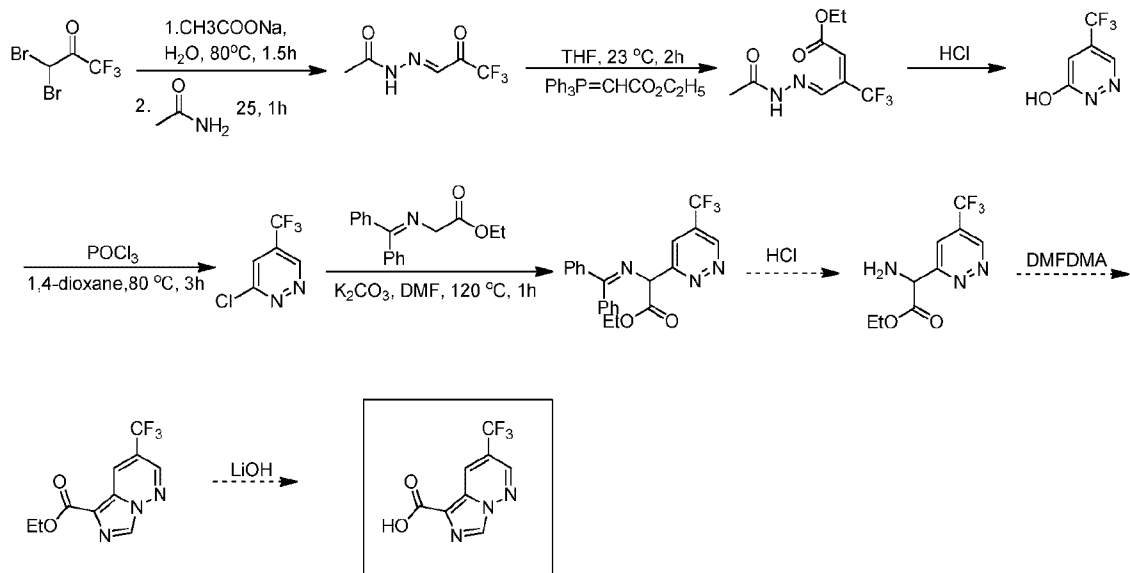
Scheme 25**Scheme 26**

10

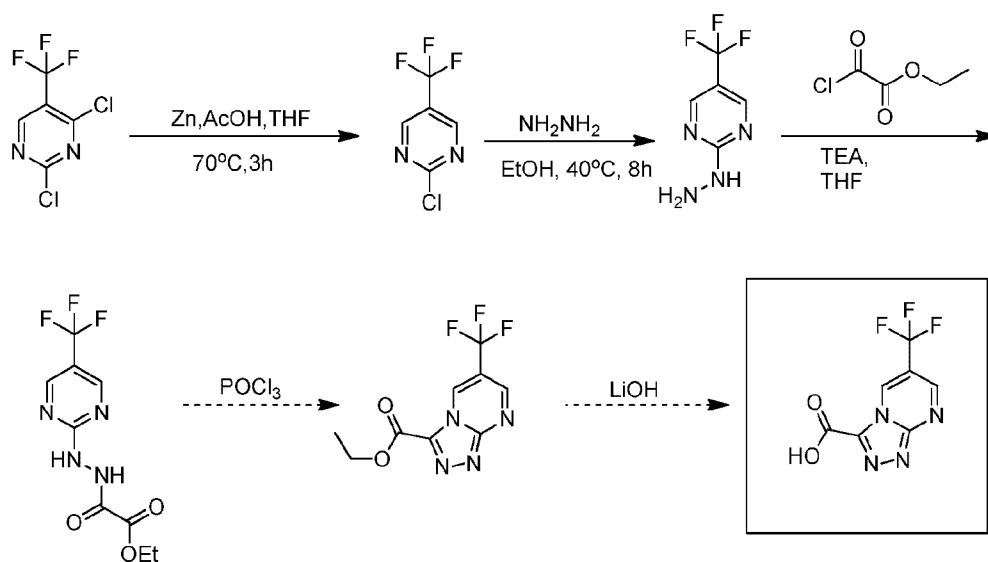
Scheme 27



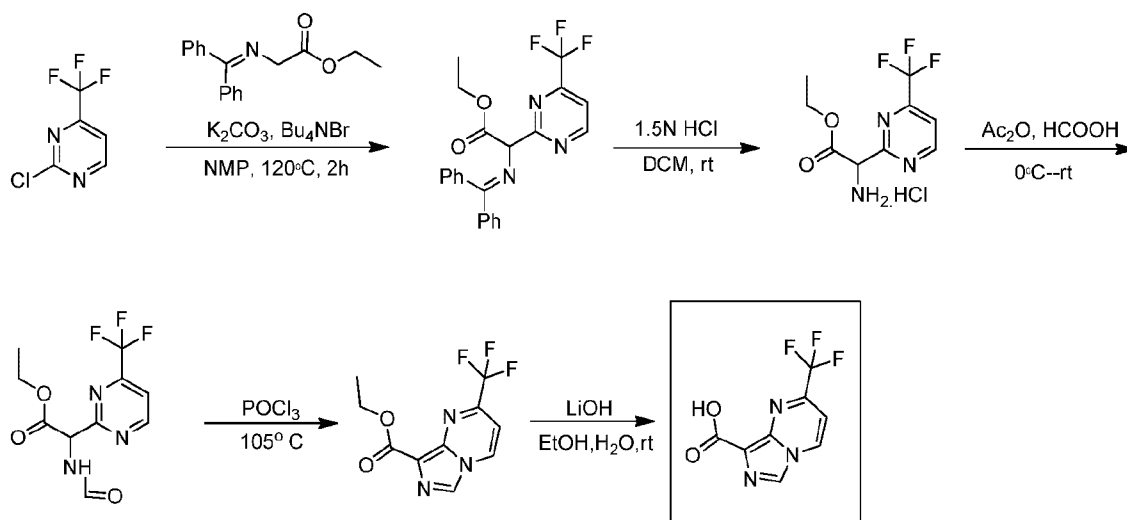
Scheme 28



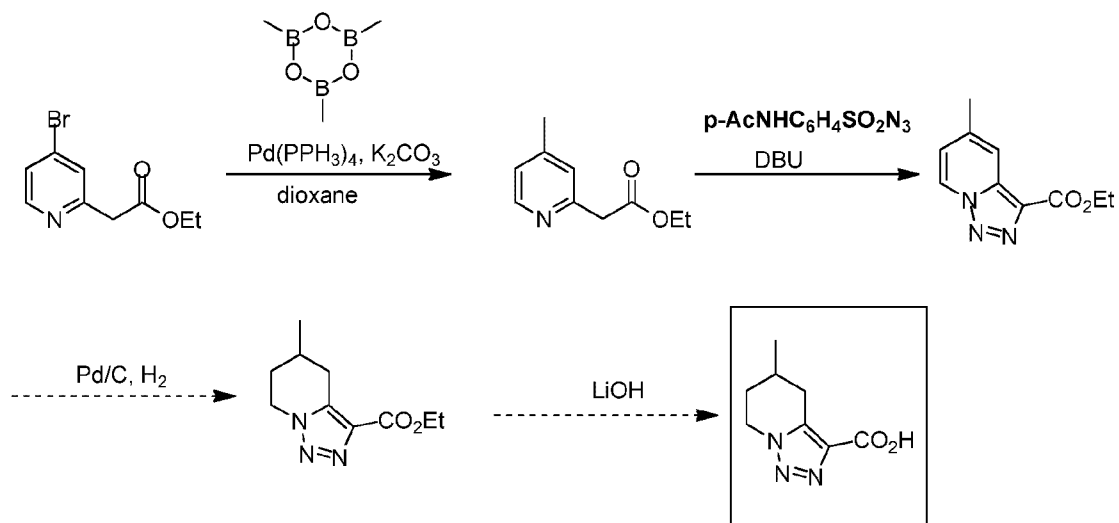
Scheme 29



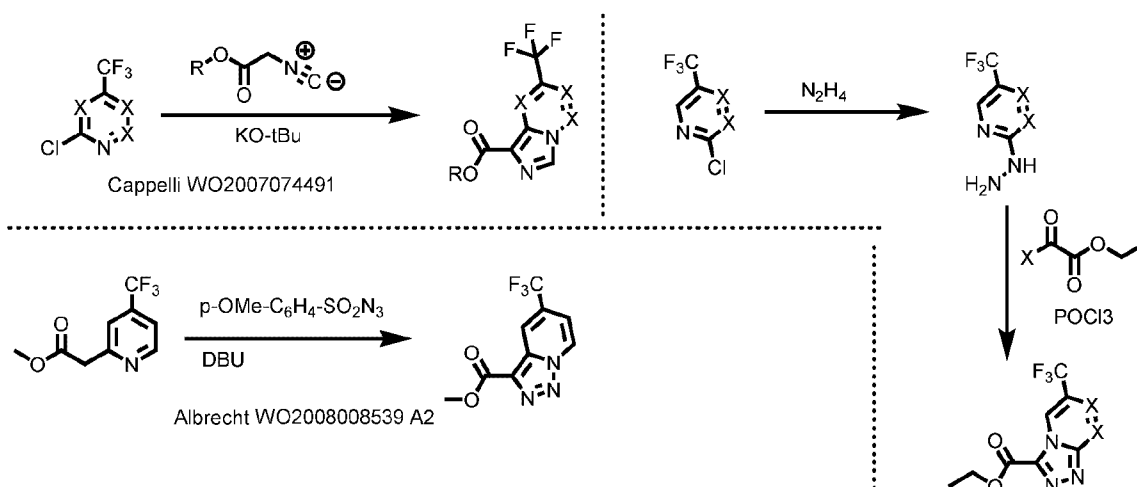
Scheme 30



Scheme 31

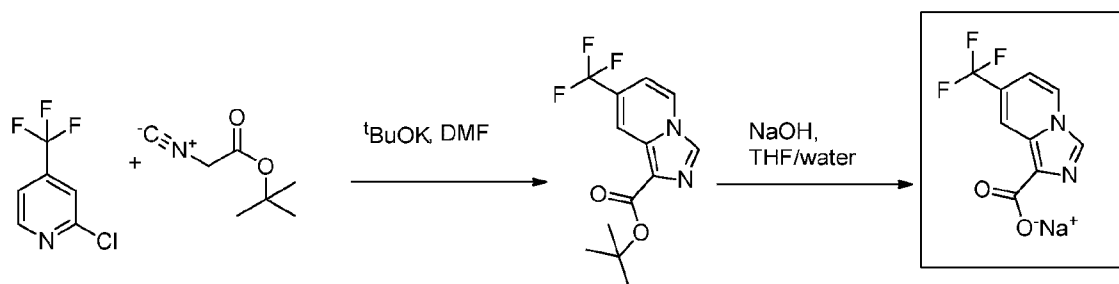


Scheme 32

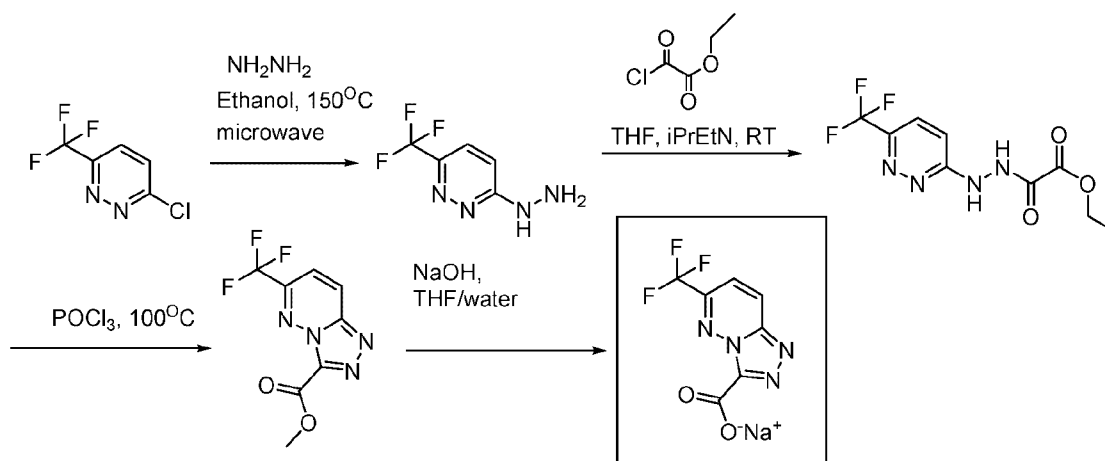


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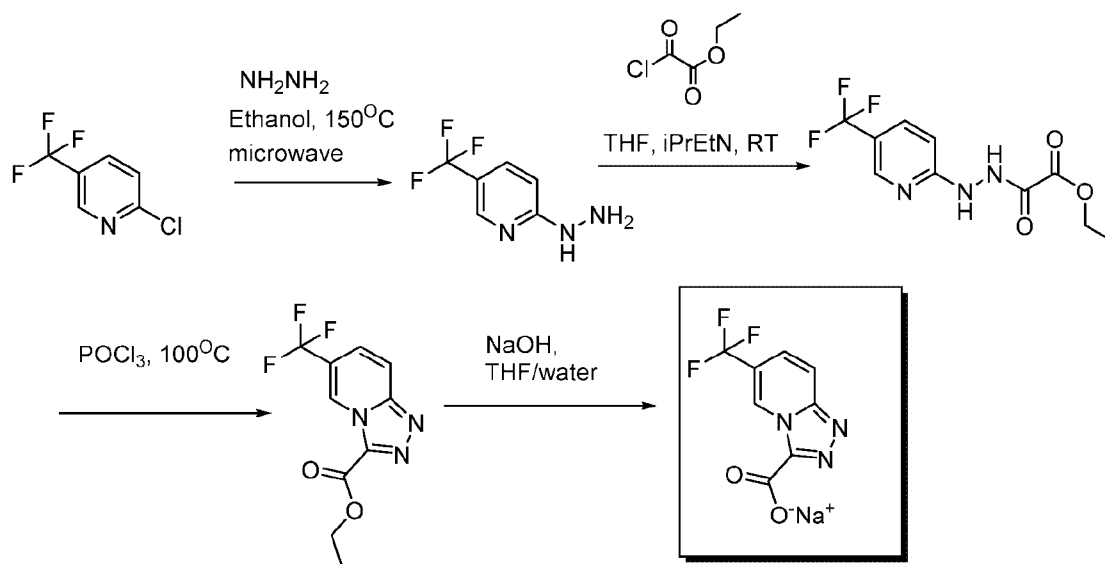
Scheme 33



Scheme 34



Scheme 35



5 PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

Provided herein are pharmaceutical compositions or medicaments containing the compounds of the invention (or stereoisomers, geometric isomers, tautomers, solvates, metabolites, isotopes, pharmaceutically acceptable salts, or prodrugs thereof), and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments. In one example, compounds of formula I may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of formula I is formulated in an acetate buffer, at pH 5. In another

embodiment, the compounds of formula I are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

5 Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. In some
10 embodiments, the “effective amount” of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to inhibit RIP1 kinase activity in order to provide a therapeutic effect in the mammal being treated. In addition, such an effective amount may be below the amount that is toxic to normal cells, or the mammal as a whole.

In one example, the pharmaceutically effective amount of the compound of the
15 invention administered intravenously or parenterally will be in the per dose range of about 0.1 to 100 mg/kg, alternatively about 0.1 to 20 mg/kg of patient body weight per day, or alternatively about 0.3 to 15 mg/kg/day.

In another embodiment, oral unit dosage forms, such as tablets and capsules, preferably contain from about 1 to about 1000 mg (*e.g.*, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg,
20 40 mg, 50 mg, 100 mg, 200 mg, 250 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, or 1000 mg) of the compound of the invention. The daily dose is, in certain embodiments, given as a single daily dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 mg to about 1,400 mg. This dosage regimen may be adjusted to provide the optimal therapeutic response.
25 The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In some embodiments, a low dose of the compound of the invention is administered in order to provide therapeutic benefit while minimizing or preventing adverse effects.

The compounds of the invention may be administered by any suitable means, including
30 oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. In specific embodiments, the compound of formula I is administered orally. In
35 other specific embodiments, the compound of formula I is administered intravenously.

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. *Remington: The Science and Practice of Pharmacy*. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. *Handbook of Pharmaceutical Excipients*. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which a compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe (GRAS) to be administered to a mammal. In general, safe solvents are non-toxic aqueous solvents such as water and other non-toxic solvents that are soluble or miscible in water. Suitable aqueous solvents include water, ethanol, propylene glycol, polyethylene glycols (e.g., PEG 400, PEG 300), etc. and mixtures thereof. The formulations can also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

Acceptable diluents, carriers, excipients and stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium

chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids
5 such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG). A active
10 pharmaceutical ingredient of the invention (e.g., compound of formula I or an embodiment thereof) can also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions,
15 nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington: The Science and Practice of Pharmacy: Remington the Science and Practice of Pharmacy (2005) 21st Edition, Lippincott Williams & Wilkins, Philadelphia, PA.

Sustained-release preparations of a compound of the invention (e.g., compound of formula I or an embodiment thereof) can be prepared. Suitable examples of sustained-release
20 preparations include semipermeable matrices of solid hydrophobic polymers containing a compound of formula I or an embodiment thereof, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinyl alcohol)), polylactides (U.S. Patent No. 3,773,919), copolymers of L-glutamic acid and
25 gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547, 1983), non-degradable ethylene-vinyl acetate (Langer et al., J. Biomed. Mater. Res. 15:167, 1981), degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate) and poly-D-(-)-3-hydroxybutyric acid (EP 133,988A). Sustained release compositions also include
30 liposomally entrapped compounds, which can be prepared by methods known per se (Epstein et al., Proc. Natl. Acad. Sci. U.S.A. 82:3688, 1985; Hwang et al., Proc. Natl. Acad. Sci. U.S.A. 77:4030, 1980; U.S. Patent Nos. 4,485,045 and 4,544,545; and EP 102,324A). Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol % cholesterol, the selected proportion being adjusted for
35 the optimal therapy.

In one example, compounds of formula I or an embodiment thereof may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the

dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of formula I (or an embodiment thereof) is formulated in an acetate buffer, at pH 5. In another embodiment, the compounds of formula I or an embodiment thereof are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

An example of a suitable oral dosage form provided herein is a tablet containing about 1 to about 500 mg (e.g., about 1 mg, 5 mg, 10 mg, 25mg, 30mg, 50mg, 80mg, 100mg, 150mg, 250mg, 300mg and 500mg) of the compound of the invention compounded with suitable amounts of anhydrous lactose, sodium croscarmellose, polyvinylpyrrolidone (PVP) K30, and magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment.

Formulations of a compound of the invention (e.g., compound of formula I or an embodiment thereof) can be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butanediol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables.

The amount of active ingredient that can be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans can contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which can vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion can contain from about 3 to 500 μ g of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which can contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which can include suspending agents and thickening agents.

The formulations can be packaged in unit-dose or multi-dose containers, for example sealed ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water, for injection immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described.

An embodiment, therefore, includes a pharmaceutical composition comprising a compound of formula I, or pharmaceutically acceptable salt thereof. In a further embodiment includes a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient.

When the binding target is located in the brain, certain embodiments of the invention provide for a compound of formula I (or an embodiment thereof) to traverse the blood-brain barrier. In these embodiments, the compounds provided herein exhibit sufficient brain penetration as potential therapeutics in neurological diseases. In some embodiments, brain penetration is assessed by evaluating free brain/plasma ratio (B_u/P_u) as measured *in vivo* pharmacokinetic studies in rodents or by other methods known to persons skilled in the art (see, e.g., Liu, X. et al., J. Pharmacol. Exp. Therap., 325:349-56, 2008).

Certain neurological diseases are associated with an increase in permeability of the blood-brain barrier, such that a compound of formula I (or an embodiment thereof) can be readily introduced to the brain. When the blood-brain barrier remains intact, several art-known approaches exist for transporting molecules across it, including, but not limited to, physical methods, lipid-based methods, and receptor and channel-based methods. Physical methods of transporting a compound of formula I (or an embodiment thereof) across the blood-brain barrier include, but are not limited to, circumventing the blood-brain barrier entirely, or by creating openings in the blood-brain barrier.

Circumvention methods include, but are not limited to, direct injection into the brain (see, e.g., Papanastassiou et al., Gene Therapy 9:398-406, 2002), interstitial infusion/convection-enhanced delivery (see, e.g., Bobo et al., Proc. Natl. Acad. Sci. U.S.A. 91:2076-2080, 1994), and implanting a delivery device in the brain (see, e.g., Gill et al., Nature Med. 9:589-595, 2003; and Gliadel Wafers™, Guildford).

Methods of creating openings in the barrier include, but are not limited to, ultrasound (see, e.g., U.S. Patent Publication No. 2002/0038086), osmotic pressure (e.g., by administration of hypertonic mannitol (Neuwelt, E. A., *Implication of the Blood-Brain Barrier and its Manipulation*, Volumes 1 and 2, Plenum Press, N.Y., 1989)), and permeabilization by, e.g., bradykinin or permeabilizer A-7 (see, e.g., U.S. Patent Nos. 5,112,596, 5,268,164, 5,506,206, and 5,686,416).

Lipid-based methods of transporting a compound of formula I (or an embodiment thereof) across the blood-brain barrier include, but are not limited to, encapsulating the a compound of formula I or I-I (or an embodiment thereof) in liposomes that are coupled to antibody binding fragments that bind to receptors on the vascular endothelium of the blood-brain barrier (see, e.g., U.S. Patent Publication No. 2002/0025313), and coating a compound of formula I (or an embodiment thereof) in low-density lipoprotein particles (see, e.g., U.S. Patent Publication No. 2004/0204354) or apolipoprotein E (see, e.g., U.S. Patent Publication No. 2004/0131692).

Receptor and channel-based methods of transporting a compound of formula I (or an embodiment thereof) across the blood-brain barrier include, but are not limited to, using glucocorticoid blockers to increase permeability of the blood-brain barrier (see, e.g., U.S. Patent Publication Nos. 2002/0065259, 2003/0162695, and 2005/0124533); activating potassium channels (see, e.g., U.S. Patent Publication No. 2005/0089473), inhibiting ABC drug transporters (see, e.g., U.S. Patent Publication No. 2003/0073713); coating a compound of formula I or I-I (or an embodiment thereof) with a transferrin and modulating activity of the one or more transferrin receptors (see, e.g., U.S. Patent Publication No. 2003/0129186), and cationizing the antibodies (see, e.g., U.S. Patent No. 5,004,697).

For intracerebral use, in certain embodiments, the compounds can be administered continuously by infusion into the fluid reservoirs of the CNS, although bolus injection may be acceptable. The inhibitors can be administered into the ventricles of the brain or otherwise introduced into the CNS or spinal fluid. Administration can be performed by use of an indwelling catheter and a continuous administration means such as a pump, or it can be administered by implantation, e.g., intracerebral implantation of a sustained-release vehicle. More specifically, the inhibitors can be injected through chronically implanted cannulas or chronically infused with the help of osmotic minipumps. Subcutaneous pumps are available that deliver proteins through a small tubing to the cerebral ventricles. Highly sophisticated pumps can be refilled through the skin and their delivery rate can be set without surgical intervention. Examples of suitable administration protocols and delivery systems involving a subcutaneous pump device or continuous intracerebroventricular infusion through a totally implanted drug delivery system are those used for the administration of dopamine, dopamine agonists, and cholinergic agonists to Alzheimer's disease patients and animal models for

Parkinson's disease, as described by Harbaugh, J. Neural Transm. Suppl. 24:271, 1987; and DeYebenes et al., Mov. Disord. 2: 143, 1987.

INDICATIONS AND METHODS OF TREATMENT

The compounds of the invention inhibit RIP1 kinase activity. Accordingly, the compounds of the invention are useful for the treatment of diseases and disorders mediated by this pathway and associated with inflammation and/or necroptotic cell death. Compounds of the invention are therefore useful for the treatment or prevention of a disease or disorder selected from the group consisting of irritable bowel disorders (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia–reperfusion injury of kidneys, liver and lungs, 5
cysplatin-induced kidney injury, sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa, retinal degeneration, chronic kidney diseases, acute respiratory distress syndrome (ARDS), and chronic obstructive pulmonary disease (COPD). 10

In another embodiment, compounds of the invention are useful for the treatment of one or more symptoms of the above diseases and disorders. In some embodiments, the disease or disorder is an irritable bowel disorder. In some embodiments, the disease or disorder is irritable bowel syndrome (IBS), Crohn's disease, or ulcerative colitis. In some embodiments, the disease or disorder is an ischemia–reperfusion injury of kidneys, liver and lungs. In some 15
embodiments, the disease or disorder is a chronic kidney disease. In some embodiments, the disease or disorder is acute respiratory distress syndrome (ARDS). In some embodiments, the disease or disorder is chronic obstructive pulmonary disease (COPD). 20

In some embodiments, the disease or disorder to be treated is selected from the group consisting of inflammatory bowel diseases (including Crohn's disease and ulcerative colitis), psoriasis, retinal detachment, retinitis pigmentosa, macular degeneration, pancreatitis, atopic 25
dermatitis, arthritis (including rheumatoid arthritis, osteoarthritis, spondylarthritis, gout, systemic onset juvenile idiopathic arthritis (SoJIA), psoriatic arthritis), systemic lupus erythematosus (SLE), Sjogren's syndrome, systemic scleroderma, anti-phospholipid syndrome (APS), vasculitis, liver damage/diseases (non-alcohol steatohepatitis, alcohol steatohepatitis, autoimmune hepatitis autoimmune hepatobiliary diseases, primary sclerosing cholangitis (PSC), acetaminophen toxicity, hepatotoxicity), kidney damage/injury (nephritis, renal 30
transplant, surgery, administration of nephrotoxic drugs e.g. cisplatin, acute kidney injury(AKI)), Celiac disease, autoimmune idiopathic thrombocytopenic purpura, transplant rejection, ischemia reperfusion injury of solid organs, sepsis, systemic inflammatory response syndrome (SIRS), cerebrovascular accident (CVA, stroke), myocardial infarction (MI), atherosclerosis, Huntington's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), allergic diseases (including asthma and atopic dermatitis), multiple sclerosis, type I diabetes, Wegener's granulomatosis, pulmonary 35

sarcoidosis, Behcet's disease, interleukin-1 converting enzyme (ICE, also known as caspase-1) associated fever syndrome, chronic obstructive pulmonary disease (COPD), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), periodontitis, NEMO-deficiency syndrome (F-kappa-B essential modulator gene (also known as IKK gamma or IKKG) deficiency syndrome), HOIL-1 deficiency ((also known as RBCK1) heme-oxidized IRP2 ubiquitin ligase-1 deficiency), linear ubiquitin chain assembly complex (LUBAC) deficiency syndrome, hematological and solid organ malignancies, bacterial infections and viral infections (such as tuberculosis and influenza), and Lysosomal storage diseases (particularly, Gaucher Disease, and including GM2, Gangliosidosis, Alpha-mannosidosis, Aspartylglucosaminuria, Cholesteryl Ester storage disease, Chronic Hexosaminidase A Deficiency, Cystinosis, Danon disease, Fabry disease, Farber disease, Fucosidosis, Galactosialidosis, GM1 gangliosidosis, Mucopolipidosis, Infantile Free Sialic Acid Storage Disease, Juvenile Hexosaminidase A Deficiency, Krabbe disease, Lysosomal acid lipase deficiency, Metachromatic Leukodystrophy, Mucopolysaccharidoses disorders, Multiple sulfatase deficiency, Niemann-Pick Disease, Neuronal Ceroid Lipofuscinoses, Pompe disease, Pycnodysostosis, Sandhoff disease, Schindler disease, Sialic Acid Storage Disease, Tay-Sachs and Wolman disease).

Also provided herein is the use of a compound of the invention in therapy. In some embodiments, provided herein is the use of a compound of the invention for the treatment or prevention of the above diseases and disorders. Also provided herein is the use of a compound of the invention in the manufacture of a medicament for the treatment or prevention of the above diseases and disorders.

Also provided herein is a method of treating a disease or disorder in a mammal in need of such treatment, said disease or disorder being selected from the group consisting of irritable bowel disorders (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia-reperfusion injury of kidneys, liver and lungs, cisplatin-induced kidney injury, sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa, retinal degeneration, chronic kidney diseases, acute respiratory distress syndrome (ARDS), and chronic obstructive pulmonary disease (COPD), wherein the method comprises administering to said mammal a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

Also provided herein is a method of treating a symptom of a disease or disorder in a mammal in need of such treatment, said disease or disorder being selected from the group consisting of irritable bowel disorders (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia-reperfusion injury of kidneys, liver and lungs, cisplatin-induced kidney injury,

sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa, retinal degeneration, chronic kidney diseases, acute respiratory distress syndrome (ARDS), and chronic obstructive pulmonary disease (COPD), wherein the method comprises administering to said mammal a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

Also provided herein is a method of treating a disease or disorder in a mammal in need of such treatment, said disease or disorder being selected from the group consisting of irritable bowel disorders (IBD), irritable bowel syndrome (IBS), Crohn's disease, and ulcerative colitis, wherein the method comprises orally administering to said mammal a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, as an orally acceptable pharmaceutical composition.

COMBINATION THERAPY

Compounds of the invention may be combined with one or more other compounds of the invention or one or more other therapeutic agent as any combination thereof, in the treatment of the diseases and disorders provided herein. For example, a compound of the invention may be administered simultaneously, sequentially or separately in combination with other therapeutic agents known to be useful for the treatment of a disease or disorder selected from those recited above.

In some embodiments, a compound provided herein may be combined with another therapeutically active agent as recited in WO 2016/027253. In such embodiments, the compound that inhibits RIP1 kinase in the combinations recited in WO 2016/027253 is replaced by a compound of formula I of the present disclosure.

As used herein "combination" refers to any mixture or permutation of one or more compounds of the invention and one or more other compounds of the invention or one or more additional therapeutic agent. Unless the context makes clear otherwise, "combination" may include simultaneous or sequentially delivery of a compound of the invention with one or more therapeutic agents. Unless the context makes clear otherwise, "combination" may include dosage forms of a compound of the invention with another therapeutic agent. Unless the context makes clear otherwise, "combination" may include routes of administration of a compound of the invention with another therapeutic agent.

Unless the context makes clear otherwise, "combination" may include formulations of a compound of the invention with another therapeutic agent. Dosage forms, routes of administration and pharmaceutical compositions include, but are not limited to, those described herein.

EXAMPLES

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

These examples serve to provide guidance to a skilled artisan to prepare and use the compounds, compositions and methods of the invention. While particular embodiment of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the inventions.

The chemical reactions in the examples described can be readily adapted to prepare a number of other compounds of the invention, and alternative methods for preparing the compounds of this invention are deemed to be within the scope of this invention. For example, the synthesis of non-exemplified compounds according to the invention can be successfully performed by modifications apparent to those skilled in the art, for example, by appropriately protecting interfering group, by utilizing other suitable reagents known in the art, for example, by appropriately protecting interfering groups by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions.

In the examples below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Commercially available reagents were purchased from suppliers such as Aldrich Chemical Company, Lancaster, TCI or Maybridge and were used without further purification unless otherwise indicated. The reactions set forth below were done generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried. ¹H NMR spectra were obtained in deuterated CDCl₃, d₆-DMSO, CH₃OD or d₆-acetone solvent solutions (reported in ppm) using or trimethylsilane (TMS) or residual non-deuterated solvent peaks as the reference standard. When peak multiplicities are reported, the following abbreviates are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet, br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hz (Hertz).

In the examples below, LCMS methods were performed for 10 or 30 minutes according to the following conditions:

Agilent 10 min LCMS Method: Experiments performed on an Agilent 1290 UHPLC coupled with Agilent MSD (6140) mass spectrometer using ESI as ionization source. The LC separation was using a Phenomenex XB-C18, 1.7mm, 50 × 2.1 mm column with a 0.4 ml / minute flow rate. Solvent A is water with 0.1% FA and solvent B is acetonitrile with 0.1% FA. The gradient consisted with 2 - 98% solvent B over 7 min and hold 98%B for 1.5 min following

equilibration for 1.5 min. LC column temperature is 40 °C. UV absorbance was collected at 220nm and 254nm and mass spec full scan was applied to all experiment.

Agilent 30 min LCMS Method: Experiments performed on an Agilent 1100 HPLC coupled with Agilent MSD mass spectrometer using ESI as ionization source. The LC separation was using an Agilent Eclipse XDB-C18, 3.5mm, 100 × 3.0 mm column with a 0.7 ml/minute flow rate. Solvent A is water with 0.1% FA and solvent B is acetonitrile with 0.1% FA. The gradient consisted with 2 - 98% solvent B over 25.5 min and hold 98%B for 2.5 min following equilibration for 1.5 min. UV absorbance were collected at 220nm and 254nm and mass spec full scan was applied to all experiment.

All abbreviations used to describe reagents, reaction conditions or equipment are intended to be consistent with the definitions set forth in the following list of Abbreviations. The chemical names of discrete compounds of the invention were typically obtained using the structure naming feature of ChemDraw naming program.

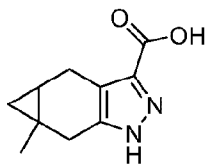
Abbreviations

ACN	Acetonitrile
Boc	<i>tert</i> -Butoxycarbonyl
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
HPLC	High Pressure Liquid Chromatography
LCMS	Liquid Chromatography Mass Spectrometry
RP	Reverse phase
RT or R _T	Retention time
SEM	2-(Trimethylsilyl)ethoxymethyl
THF	Tetrahydrofuran

PREPARATIVE EXAMPLES

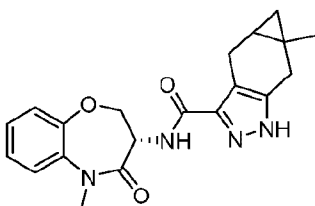
Example 1: Synthetic Method A

According to synthetic Method A, 5a-methyl-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxylic acid and similar carboxylic acid systems are prepared according to the paragraph below or from procedures described in *J. Med. Chem.* (2014), 57(13), 5714-5727; *J. Med. Chem.* (2015), 58(9), 3806-3816; and WO 2014023258 A1.



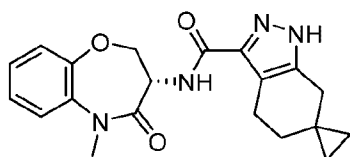
Step 1: 5a-methyl-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxylic acid

To a stirred solution of ethyl 5a-methyl-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxylate (200 mg, 0.907 mmol) in tetrahydrofuran (10 mL) and methanol (10 mL) was added a solution of 2M LiOH (0.69 mL, 1.36 mmol), and stirred at RT for 16 h. The reaction mixture was concentrated to dryness *in vacuo*, redissolved in water and neutralized with 1N HCl. The resulting crashed out solid was filtered, wash with water and dried affording 5a-methyl-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxylic acid (120 mg, 69% yield) used in the next step without any further purification.



Step 2: 5a-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxamide

To a screw cap vial 5a-methyl-4,4a,5,6-tetrahydro-1H-cyclopropa[f]indazole-3-carboxylic acid (20mg, 0.104 mmol), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (51 mg, 0.1357 mmol), (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one hydrochloride (26 mg, 0.115 mmol) was added and dissolved in N,N-dimethylformamide (3 mL). To the reaction mixture was added trimethylamine (0.101 mL, 0.728 mmol), the vial was capped and stirred at RT for 16 h. The mixture was concentrated to dryness *in vacuo* and the residue was purified by RP-HPLC affording 5a-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxamide (12mg, 31%): ^1H NMR (400 MHz, DMSO- d_6) δ 12.88 (s, 1H), 7.96 – 7.87 (m, 1H), 7.52 – 7.44 (m, 1H), 7.35 – 7.26 (m, 2H), 7.25 – 7.21 (m, 1H), 4.88 – 4.75 (m, 1H), 4.53 – 4.44 (m, 1H), 4.43 – 4.36 (m, 1H), 3.11 – 3.02 (m, 1H), 2.98 – 2.90 (m, 1H), 2.79 – 2.70 (m, 1H), 2.70 – 2.60 (m, 1H), 1.19 (s, 3H), 1.03 – 0.93 (m, 1H), 0.35 – 0.26 (m, 1H), 0.09 – 0.00 (m, 1H). LC-MS R_T = 4.98 min, m/z = 367.2 (M+H) $^+$.

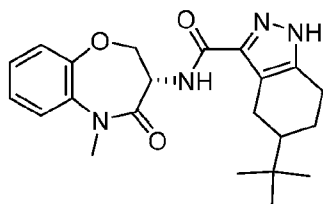
Example 2: Method A'**Step 1:**

(S)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1',4',5',7'-tetrahydrospiro[cyclopropane-1,6'-indazole]-3'-carboxamide

To a solution of 1'-((2-(trimethylsilyl)ethoxy)methyl)-1',4',5',7'-tetrahydrospiro[cyclopropane-1,6'-indazole]-3'-carboxylic acid (68 mg, 0.21 mmol) in N,N-dimethylformamide (0.350 mL) was added (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (40 mg, 0.21 mmol), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (86 mg, 1.3527 mmol) and triethylamine (0.171 mL, 0.0012 mmol) and stirred at RT for 16 h. The residue was dissolved in methanol (2 mL) and a 4M solution of HCl in dioxane (0.135 mL, 3.66 mmol,). The reaction mixture was stirred at RT for 16 h, concentrated to dryness *in vacuo* and the residue was purified by RP-HPLC affording (S)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1',4',5',7'-tetrahydrospiro[cyclopropane-1,6'-indazole]-3'-carboxamide (9 mg, 12% yield): ¹H NMR (400 MHz, DMSO-d₆) δ 12.84 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.35 – 7.26 (m, 2H), 7.25 – 7.21 (m, 1H), 4.90 – 4.76 (m, 1H), 4.56 – 4.32 (m, 2H), 2.68 – 2.55 (m, 2H), 2.48 – 2.42 (m, 2H), 1.53 – 1.37 (m, 2H), 0.42 – 0.33 (m, 4H). LC-MS R_T = 4.64 min, m/z = 367.2 (M+H)⁺.

Example 3: Method B

According to synthetic Method B, 5-(tert-butyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid and similar carboxylic acid systems are prepared according to the paragraph below or from procedures described in *J. Med. Chem.* (2014), 57(13), 5714-5727; *J. Med. Chem.* (2015), 58(9), 3806-3816; and WO 2014023258 A1.



5-(tert-butyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide

To a screw cap vial (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one hydrochloride (30mg, 0.131 mmol), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (75 mg, 0.197 mmol),

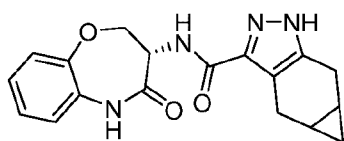
5 5-(tert-butyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (35 mg, 0.157 mmols) was added and dissolved in N,N-dimethylformamide (5 mL). To the reaction mixture was added trimethylamine (0.127 mL, 0.918 mmol), the vial was capped and stirred at RT for 16 h. The mixture was concentrated to dryness *in vacuo* and the residue was purified by RP-HPLC affording

10 5-(tert-butyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide

(9 mg, 14%): ^1H NMR (400 MHz, DMSO- d_6) δ 12.88 – 12.77 (m, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.35 – 7.26 (m, 2H), 7.27 – 7.19 (m, 1H), 4.88 – 4.77 (m, 1H), 4.55 – 4.35 (m, 2H), 2.86 – 2.65 (m, 2H), 2.19 – 2.05 (m, 1H), 2.01 – 1.91 (m, 1H), 1.37 – 1.17 (m, 2H), 0.89 (s, 9H). LCMS R_T = 5.52 min, m/z = 397.2 $[\text{M} + \text{H}]^+$.

15

Example 4: Method B'



Step 1:

20 **N-((S)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxamide**

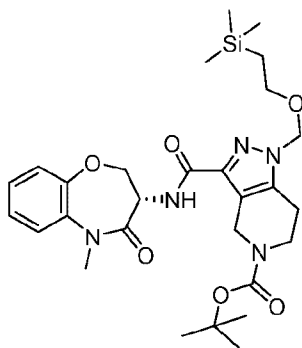
To a screw cap vial 1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxylic acid (44 mg, 0.247 mmol), 3-[bis(dimethylamino)methyl]-3H-benzotriazol-1-oxide hexafluorophosphate (127 mg, 0.3367 mmol),

25 (3S)-3-amino-3,5-dihydro-2H-1,5-benzoxazepin-4-one (40 mg, 0.225 mmol) was added and dissolved in N,N-dimethylformamide (3 mL). To the reaction mixture was added trimethylamine (0.094 mL, 0.673 mmol), the vial was capped and stirred at RT for 16 h. The mixture was concentrated to dryness *in vacuo* and the residue was purified by RP-HPLC affording

30 N-((S)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxamide (10.4 mg, 14%) as a white solid: ^1H NMR (400 MHz, DMSO- d_6) δ 12.87 (s, 1H), 10.12 (s, 1H), 8.02 – 7.87 (m, 1H), 7.22 – 7.05 (m, 4H), 4.87 – 4.66 (m, 1H), 4.55 – 4.32 (m, 2H), 3.23 – 3.09 (m, 1H), 3.00 – 2.62 (m, 4H), 2.15 – 2.01 (m, 1H), 1.32 – 1.09 (m, 2H), 0.62 – 0.40 (m, 1H), -0.05 – -0.14 (m, 1H). LCMS R_T = 4.21 min, m/z = 339.1 $[\text{M} + \text{H}]^+$.

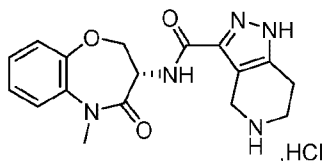
Example 5: Method C

According to synthetic Method C, 5-tert-butoxycarbonyl-1-(2-trimethylsilylethoxymethyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3-carboxylic acid and similar carboxylic acid systems are prepared according to the paragraph below or from procedures described in *J. Med. Chem.* (2014), 57(13), 5714-5727; *J. Med. Chem.* (2015), 58(9), 3806-3816; and WO 2014023258 A1.

**Step 1: tert-butyl**

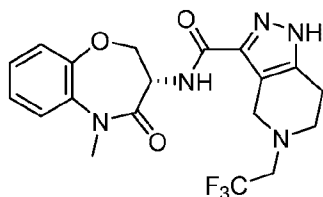
(S)-3-((5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)carbamoyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

To a solution of 5-tert-butoxycarbonyl-1-(2-trimethylsilylethoxymethyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3-carboxylic acid (455 mg, 1.15 mmol) in N,N-dimethylformamide (5 mL) was added (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (200 mg, 1.0405 mmol), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (524.83 mg, 1.3527 mmol) and N,N-diisopropylethylamine (1.27 mL, 7.2837 mmol) and stirred at RT for 16 h. To the reaction mixture was concentrated to dryness *in vacuo* and the residue was purified by flash column chromatography (silica gel, 100-200 mesh, 0 to 20% methanol in dichloromethane) to afford tert-butyl (S)-3-((5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)carbamoyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (523 mg, 88%) as a colorless oil: LCMS $R_T = 1.62$ min, $m/z = 572.1$ $[M + H]^+$.

**Step 2:**

(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxamide hydrochloride

To a stirred solution of tert-butyl 3-[[[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]carbamoyl]-1-(2-trimethylsilylet hoxymethyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (523 mg, 0.915 mmol) in methanol was added a 4M solution of HCl in dioxane (0.915 mL, 3.66 mmol). The reaction mixture was stirred at RT for 16 h and concentrated to dryness *in vacuo* to afford crude (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxamide hydrochloride (317 mg, 92%) used in the next step without further purification: LCMS $R_T = 0.77$ min, $m/z = 342.1$ $[M + H]^+$.

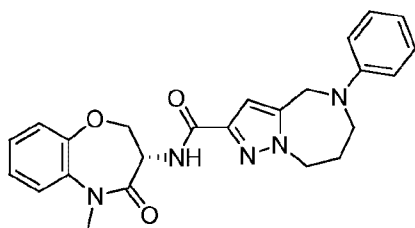


Step 3:

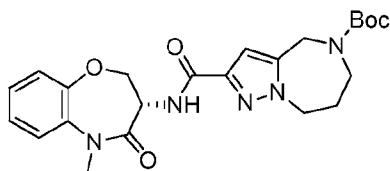
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxamide

To a stirred solution of N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-4,5,6,7-tetrahydro-1H-pyrazolo [4,3-c]pyridine-3-carboxamide hydrochloride (30 mg, 0.07941 mmol) in dichloromethane was added added N,N-diisopropylethylamine (0.0416 mL, 0.2382 mmol). To the reaction mixture was added 2,2,2-trifluoroethyltrifluoromethanesulphonate (24.70 mg, 0.1032 mmol) and was stirred at 35°C for 16 h. The reaction mixture was concentrated to dryness *in vacuo* and the residue was purified by RP-HPLC to afford (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxamide (13mg, 38%) as a white solid: ^1H NMR (400 MHz, DMSO- d_6) δ 13.03 (s, 1H), 8.01 (d, $J = 8.0$ Hz, 1H), 7.48 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.35 – 7.26 (m, 2H), 7.23 (dd, $J = 7.7, 1.8$ Hz, 1H), 4.87 – 4.75 (m, 1H), 4.58 – 4.47 (m, 1H), 4.44 – 4.35 (m, 1H), 3.74 (s, 2H), 2.89 (t, $J = 5.7$ Hz, 2H), 2.69 (t, $J = 5.6$ Hz, 2H).

Example 6: Method D

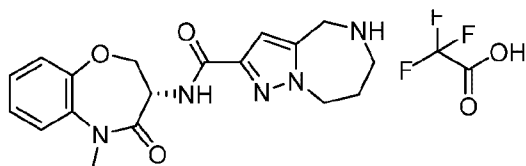


N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-phenyl-4,6,7,8-tetrahydro pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



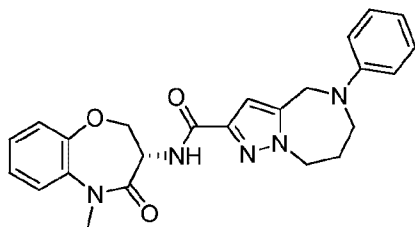
Step 1: tert-butyl 2-[[[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]carbamoyl]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate

- 5 To a solution of 5-tert-butoxycarbonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (500 mg, 1.78 mmol) in N,N-dimethylformamide (5 mL) was added (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (376 mg, 1.96 mmol), 1-hydroxybenzotriazole (288 mg, 2.13 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (409 mg, 2.13 mmol). The reaction mixture was stirred at RT for 2 h and then diluted with ethyl acetate (15 mL). The solution was washed with water (3 x 15 mL), brine (3 x 15 mL), dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by flash column chromatography (silica gel, 100-200 mesh, 0 to 50% ethyl acetate in petroleum ether) to afford tert-butyl 2-[[[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]carbamoyl]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (800 mg, 99% yield) as a light yellow oil: LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.72 min, ESI+ found [M+H] = 456.



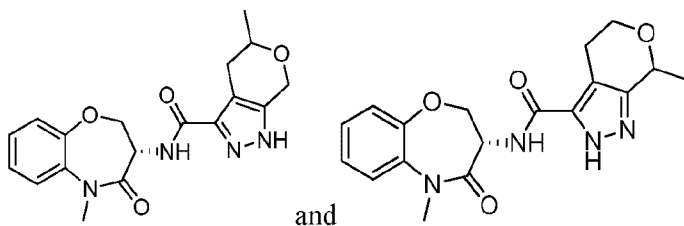
Step 2: N-[[[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide] 2,2,2-trifluoroacetate

- 20 To a solution of tert-butyl 2-[[[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]carbamoyl]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (780 mg, 1.71 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL). The reaction mixture was stirred at RT for 2 h and then concentrated to dryness *in vacuo* affording N-[[[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide] 2,2,2-trifluoroacetate (802 mg, 100% yield) as a yellow solid used as is in the next step: LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.29 min, ESI+ found [M+H] = 356.

**Step 3:****N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-phenyl-4,6,7,8-tetrahydro pyrazolo[1,5-a][1,4]diazepine-2-carboxamide**

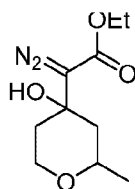
5 To a mixture of N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide 2,2,2-trifluoroacetate (197 mg, 0.42 mmol) in toluene (5 mL) was added copper(II) acetate (8 mg, 0.04 mmol), tetradecanoic acid (19 mg, 0.08 mmol), 2,6-lutidine (45 mg, 0.42 mmol) and phenylboronic acid (77 mg, 0.63 mmol) under oxygen (15 Psi). The reaction mixture was stirred at 25 °C for 12 h and concentrated to dryness in *vacuo*. The residue was purified by RP-HPLC (0-40% acetonitrile in water and 0.1% ammonium hydroxide) affording N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-phenyl-4,6,7,8-tetrahydro pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (2.5 mg, 1.4% yield) as white solid: ¹H NMR (400MHz, DMSO-d₆) δ 7.93 (d, *J* = 8.0 Hz, 1H), 7.51 - 7.44 (m, 1H), 7.35 - 7.18 (m, 3H), 7.10 (t, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.73 (s, 1H), 6.58 (t, *J* = 7.2 Hz, 1H), 4.83 - 4.64 (m, 3H), 4.54 - 4.40 (m, 3H), 4.37 - 4.34 (m, 1H), 3.93 - 3.79 (m, 2H), 3.29 (s, 3H), 1.84 - 1.82 (m, 2H). LCMS R_T = 2.45 min, *m/z* = 432.2 [M + H]⁺.

LCMS (0 to 60% acetonitrile in water + 0.05% ammonium bicarbonate over 3 mins) retention time 2.45 min, ESI+ found [M+H] = 432.2.

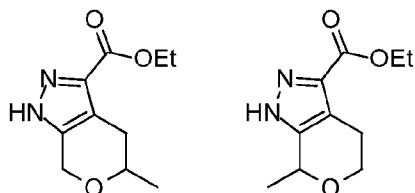
Example 7: Method E**5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide**

25 and

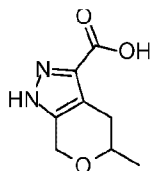
7-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-2,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide

Step 1:**Ethyl 2-diazo-2-(4-hydroxy-2-methyltetrahydro-2H-pyran-4-yl) acetate**

To a solution of ethyl 2-diazoacetate (8.0 g, 70.1 mmol) and 2-methyldihydro-2H-pyran-4(3H)-one (5.0 g, 43.8 mmol) in tetrahydrofuran (100 mL) was added lithium diisopropylamide (2 M in tetrahydrofuran, 39.5 mL, 79.0 mmol) at -78 °C under nitrogen. After addition, the reaction mixture was stirred at -78 °C for 1 h and then quenched by addition of saturated aqueous ammonium chloride (60 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 20% ethyl acetate in petroleum ether) to afford ethyl 2-diazo-2-(4-hydroxy-2-methyl-tetrahydropyran-4-yl)acetate (4.0 g, 40% yield).

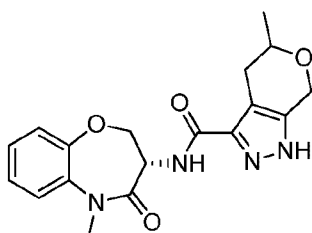
**Step 2: Ethyl 5-methyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate and ethyl 7-methyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate**

To a solution of ethyl 2-diazo-2-(4-hydroxy-2-methyl-tetrahydropyran-4-yl)acetate (3.0 g, 13.1 mmol) in pyridine (20 mL) was added phosphorus oxychloride (8.06 g, 52.6 mmol). The resulting mixture was stirred at 15 °C for 3 h and then poured into water (20 mL). The mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 25% ethyl acetate in petroleum ether) to afford a mixture of regio-isomer, which was further purified by RP-HPLC (15-45% acetonitrile in water and 0.05% ammonia) to afford ethyl 5-methyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate (300 mg, 10.9% yield) and ethyl 7-methyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate (300 mg, 1.427 mmol, 10.9% yield) as white solids.



Step 3: 5-methyl-1, 4, 5, 7-tetrahydropyrano [3, 4-c] pyrazole-3-carboxylic acid

To a solution of ethyl 5-methyl-2,4,5,7-tetrahydropyrano [3, 4-c] pyrazole-3-carboxylate (100 mg, 0.48 mmol) in tetrahydrofuran (3 mL) and water (3 mL) was added lithium hydroxide monohydrate (320 mg, 7.61 mmol). The reaction mixture was stirred at 15 °C for 15 h and then concentrated to dryness *in vacuo*. The residue was diluted with water (5 mL) and then adjusted to pH = 3 by adding 1 N hydrochloric acid. The mixture was extracted with dichloromethane (3 x 15 mL). The combined layers were dried over anhydrous sodium sulfate and concentrated to afford 5-methyl-1,4,5,7-tetrahydropyrano[3, 4-c]pyrazole-3-carboxylic acid (80 mg, 92.3% yield) as a white solid, which was used into next step without further purification.

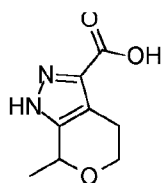


Step

4:

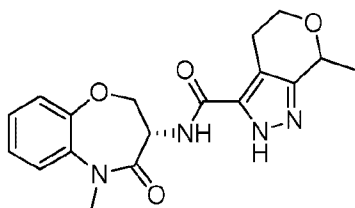
5-methyl-N-((3S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide

To a solution of (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (60 mg, 0.31 mmol) in N,N-dimethylformamide (5 mL) was added 1H-benzo[d][1,2,3]triazol-1-ol (50 mg, 0.37 mmol), *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (72 mg, 0.37 mmol) and 5-methyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylic acid (63 mg, 0.34 mmol). The reaction mixture was stirred at 15 °C for 1 h and then concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (28-58% acetonitrile in water and 0.05% hydrochloric acid) to afford 5-methyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide (55.7 mg, 49% yield) as a white solid: ¹H NMR (400MHz, Methanol-d₄) δ 7.44 - 7.40 (m, 1H), 7.35 - 7.26 (m, 2H), 7.25 - 7.20 (m, 1H), 5.01 - 4.97 (m, 1H), 4.82 - 4.77 (m, 1H), 4.72 - 4.70 (m, 1H), 4.61 - 4.57 (m, 1H), 4.41 - 4.33 (m, 1H), 3.70 - 3.66 (m, 1H), 3.41 (s, 3H), 2.87 - 2.82 (m, 1H), 2.50 - 2.44 (m, 1H), 1.32 (d, *J* = 6.0 Hz, 3H). LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 0.77 min, ESI+ found [M+H] = 357.0.



Step 5: 7-methyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylic acid

To a solution of ethyl 7-methyl-1,4,5,7-tetrahydropyrano[3,4-c]hpyrazole-3-carboxylate (100 mg, 0.48 mmol) in tetrahydrofuran (3 mL) and water (3 mL) was added lithium hydroxide monohydrate (320 mg, 7.61 mmol). The reaction mixture was stirred at 15 °C for 15 h and then concentrated to dryness *in vacuo*. The residue was diluted with water (5 mL) and then adjusted to pH = 3 by adding 1 N hydrochloric acid. The mixture was extracted with dichloromethane (3 x 15 mL). The combined layers were dried over anhydrous sodium sulfate and concentrated to afford 7-methyl-1,4,5,7-tetrahydropyrano[3,4-c]hpyrazole-3-carboxylic acid (~80 mg, 92.3% yield) as a white solid used in the next step without further purification.

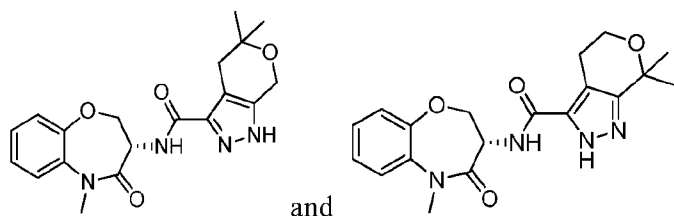


Step

6:

7-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-2,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide

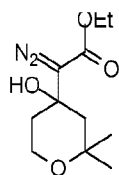
To a solution of (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (60 mg, 0.31 mmol) in N,N-dimethylformamide (5 mL) was added 1H-benzo[d][1,2,3]triazol-1-ol (50 mg, 0.37 mmol), *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (72 mg, 0.37 mmol) and 7-methyl-2,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylic acid (63 mg, 0.34 mmol). The reaction mixture was stirred at 15 °C for 1 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (25-48% acetonitrile in water and 0.05% hydrochloric acid) to afford 7-methyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-2,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide (39.8 mg, 35% yield) as a white solid: ¹H NMR (400MHz, Methanol-d₄) δ 7.44 - 7.40 (m, 1H), 7.35 - 7.26 (m, 2H), 7.25 - 7.20 (m, 1H), 4.99 - 4.91 (m, 1H), 4.77 - 4.75 (m, 1H), 4.62 - 4.56 (m, 1H), 4.41 - 4.33 (m, 1H), 4.19 - 4.12 (m, 1H), 3.62 - 3.60 (m, 1H), 3.41 (s, 3H), 2.80 - 2.73 (m, 1H), 1.47 (d, *J* = 6.8 Hz, 3H). LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 0.76 min, ESI+ found [M+H] = 357.0.

Example 8: Method F

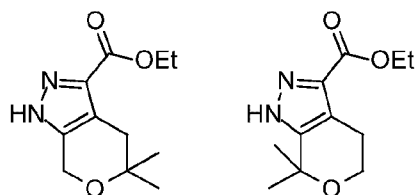
(S)-5,5-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide

5 and

(S)-7,7-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-2,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide

**Step 1: Ethyl 2-diazo-2-(4-hydroxy-2,2-dimethyltetrahydro-2H-pyran-4-yl) acetate**

- 10 To a solution of 2,2-dimethyl tetrahydropyran-4-one (5.0 g, 39.0 mmol) and ethyl diazoacetate (7.1 g, 62.4 mmol) in tetrahydrofuran (100 mL) was added lithium diisopropylamide (2 M in tetrahydrofuran, 35.1 mL, 70.2 mmol) at -78 °C under nitrogen. After addition, the reaction mixture was stirred at -78 °C for 1 h and then quenched by addition of saturated aqueous ammonium chloride (60 mL). The mixture was extracted with ethyl acetate (3 x 100 mL). The
- 15 combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 20% ethyl acetate in petroleum ether) to afford ethyl 2-diazo-2-(4-hydroxy-2,2-dimethyl-tetrahydropyran-4-yl) acetate (6.0 g, 63.5% yield) as a yellow oil use as is in the next step.

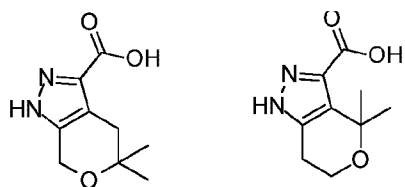


20

Step 2: ethyl 5,5-dimethyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate and ethyl 7,7-dimethyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate

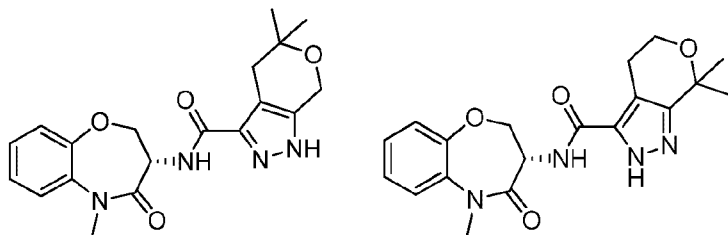
- To a solution of ethyl 2-diazo-2-(4-hydroxy-2,2-dimethyl-tetrahydropyran-4-yl) acetate (3.0 g, 12.38 mmol) in pyridine (60 mL) was added phosphorus oxychloride (7.6 g, 49.53 mmol). The
- 25 reaction mixture was stirred at 15 °C for 3 h and then poured into water (30 mL). The mixture

was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 25% ethyl acetate in petroleum ether) to afford a mixture of ethyl 7,7-dimethyl-4,5-dihydro-1H-pyrano[3,4-c]pyrazole-3-carboxylate and ethyl 7,7-dimethyl-4,5-dihydro-1H-pyrano[3,4-c]pyrazole-3-carboxylate (1.0 g, 36% yield, 1:1 mixture) as light yellow oil used as is in the next step: LCMS $R_T = 0.62$ min, $m/z = 224.8$ $[M + H]^+$. LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 0.615 min, ESI+ found $[M+H] = 224.8$.



Step 3: 5,5-dimethyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylic acid and 4,4-dimethyl-1,4,6,7-tetrahydropyrano[4,3-c]pyrazole-3-carboxylic acid

To a solution of ethyl 5,5-dimethyl-4,7-dihydro-2H-pyrano[3,4-c]pyrazole-3-carboxylate and ethyl 7,7-dimethyl-4,5-dihydro-1H-pyrano[3,4-c]pyrazole-3-carboxylate (200 mg, 0.9 mmol) in tetrahydrofuran (10 mL) and water (10 mL) was added lithium hydroxide monohydrate (299 mg, 7.1 mmol). The reaction mixture was stirred at 15 °C for 15 h and concentrated to dryness *in vacuo*. The residue was diluted with water (5 mL) and adjusted to pH = 3 with 1M hydrochloric acid. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo* to afford a crude mixture of 5,5-dimethyl-4,7-dihydro-1H-pyrano[3,4-c]pyrazole-3-carboxylic acid and 7,7-dimethyl-4,5-dihydro-1H-pyrano[3,4-c]pyrazole-3-carboxylic acid (120 mg, 68.6% yield) as a yellow oil used in the next step without any further purification.



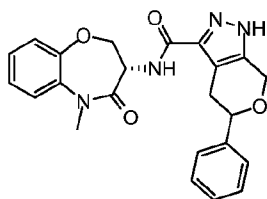
Step 4: (S)-5,5-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide

To a solution of (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (100 mg, 0.52 mmol) in N,N-dimethylformamide (5 mL) was added a mixture of 5,5-dimethyl-4,7-dihydro-1H-pyrano[3,4-c]pyrazole-3-carboxylic acid and 7,7-dimethyl-4,5-dihydro-2H-pyrano[3,4-c]pyrazole-3-carboxylic acid (118 mg, 0.60 mmol), 1H-benzo[d][1,2,3]triazol-1-ol (83 mg, 0.62 mmol) and N¹-((ethylimino)methylene)-N³,N³-dimethylpropane-1,3-diamine hydrochloride (99 mg, 0.52 mmol). The reaction mixture was stirred at 15 °C for 1 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (17-37% acetonitrile in water and 0.05% ammonia hydroxide) to afford:

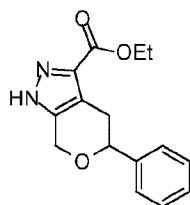
5,5-dimethyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-4,7-dihydro-1H-pyrano[3,4-c]pyrazole-3-carboxamide (59 mg, 30.7% yield) as white solid: ¹H NMR (400MHz, Methanol-d₄) δ 7.44 - 7.40 (m, 1H), 7.35 - 7.26 (m, 2H), 7.25 - 7.20 (m, 1H), 5.01 - 4.97 (m, 1H), 4.71 (s, 2H), 4.62 - 4.57 (m, 1H), 4.39 - 4.36 (m, 1H), 3.42 (s, 3H), 2.68 (s, 2H), 1.25 (s, 6H). LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 0.79 min, ESI+ found [M+H] = 371.0.

7,7-dimethyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-4,5-dihydro-2H-pyrano[3,4-c]pyrazole-3-carboxamide (20 mg, 10.4% yield) as white solid: ¹H NMR (400MHz, METHANOL-d₄) δ 13.10 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.34 - 7.22 (m, 3H), 4.87 - 4.80 (m, 1H), 4.55 - 4.49 (m, 1H), 4.42 - 4.37 (m, 1H), 3.73 (s, 2H), 3.31 (s, 3H), 2.58 - 2.20 (m, 2H), 1.39 (s, 6H). LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 0.78 min, ESI+ found [M+H] = 371.0.

Example 9: Method G



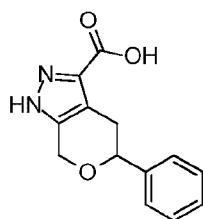
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-phenyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide



Step 1: Ethyl 5-phenyl-1,4,5,7-tetrahydropyrano [3,4-c] pyrazole-3-carboxylate

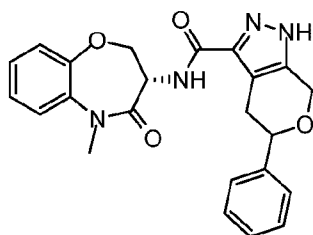
To a solution of 2-phenyltetrahydropyran-4-one (1.00 g, 5.68 mmol) in dimethyl sulfoxide (10 mL) was added ethyl diazoacetate (0.32 g, 2.84 mmol) and pyrrolidine (40.3 mg, 0.57 mmol) under nitrogen protection. The reaction mixture was stirred at RT for 12 h and diluted with

ethyl acetate (100 mL). The resulting mixture was washed with water (3 x 50 mL), brine (3 x 50 mL), dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 50% ethyl acetate in petroleum ether) to afford ethyl 5-phenyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate (180 mg, 12% yield) as a light yellow oil: LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.70 min, ESI+ found $[M+H] = 273$.



Step 2: 5-phenyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylic acid

To a solution of ethyl 5-phenyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate (100 mg, 0.37 mmol) in ethanol (4 mL) and water (4 mL) was added lithium hydroxide monohydrate (154 mg, 3.67 mmol). The reaction mixture was stirred at RT for 12 h and concentrated to dryness *in vacuo*. The residue was diluted with water (5 mL) and adjusted to pH = 5 with 1M hydrochloric acid. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo* to afford 5-phenyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylic acid (89 mg, 99% yield) as yellow oil used in the next step without any further purification: LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.62 min, ESI+ found $[M+H] = 245$.



Step 3:

N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-phenyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide

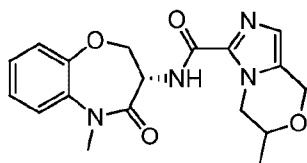
To a solution of 5-phenyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylic acid (88.0 mg, 0.36 mmol) in N,N-dimethylformamide (5 mL) was added 1H-benzo[d][1,2,3]triazol-1-ol (58 mg, 0.43 mmol), *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (83 mg, 0.43 mmol) and (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (76 mg, 0.40 mmol). The

reaction mixture was stirred at RT for 1 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (0-40% acetonitrile in water and 0.1% ammonia hydroxide) to afford

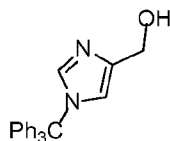
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-phenyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide (24 mg, 16% yield) as a white solid: ¹H NMR (400MHz, DMSO-d₆) δ 13.10 (br. s, 1H), 8.04 (br. s, 1H), 7.47 - 7.23 (m, 9H), 4.97 - 4.92 (m, 1H), 4.85 - 4.82 (m, 2H), 4.60 - 4.54 (m, 2H), 4.46 - 4.35 (m, 1H), 3.33 (s, 3H), 3.05 - 3.01 (m, 1H), 2.68 - 2.56 (m, 1H). LCMS R_T = 1.88 min, *m/z* = 419 [M + H]⁺.

LCMS (10- 80% acetonitrile in water + 0.05% ammonium bicarbonate over 3 mins) retention time 1.88/ min, ESI+ found [M+H] = 419.

10 Example 10: Method H

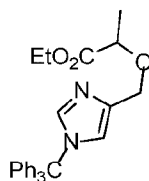


6-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6,8-dihydro-5H-imidazo[5,1-c][1,4]oxazine-3-carboxamide



15 Step 1: (1-trityl-1H-imidazol-4-yl) methanol

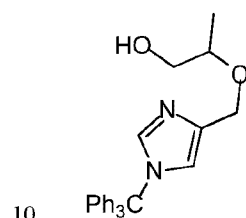
To a solution of (1H-imidazol-4-yl) methanol (5.0 g, 51.0 mmol) and triethylamine (15.5 g, 152.9 mmol) in N,N-dimethylformamide (100 mL) was slowly added (chloromethanetriyl)tribenzene (15.6 g, 56.1 mmol). After addition, the reaction mixture was stirred at RT for 3 h and then poured into water (300 mL). The resulting solid was collected by filtration, washed with water (2 x 100 mL) and recrystallized with dioxane (300 mL) to afford (1-trityl-1H-imidazol-4-yl)methanol (9.8 g, 56% yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆): δ 7.43 - 7.39 (m, 9H), 7.29 (s, 1H), 7.10 - 7.08 (m, 6H), 6.72 (s, 1H), 4.89 - 4.86 (m, 1H), 4.33 - 4.32 (d, *J* = 5.6 Hz, 2H).



25 Step 2: ethyl 2-((1-trityl-1H-imidazol-4-yl)methoxy)propanoate

To a solution of (1-trityl-1H-imidazol-4-yl)methanol (6.0 g, 17.6 mmol) in N,N-dimethylformamide (400 mL) was added sodium hydride (60%, 1.4 g, 35.2 mmol)

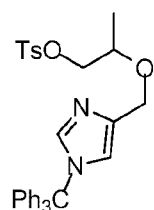
portionwise. After addition, the reaction mixture was stirred at RT for 2 h and ethyl 2-bromopropanoate (6.4 g, 35.2 mmol) was added. The resulting mixture was stirred at RT for another 15 h and quenched by addition of aqueous saturated ammonium chloride (300 mL). The mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 50% ethyl acetate in petroleum ether) to afford ethyl 2-((1-trityl-1H-imidazol-4-yl)methoxy)propanoate (2.0 g, 26% yield) as an orange oil; LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) R_T = 0.81 min, m/z = 449.1 $[M - C_2H_5 + CH_3 + Na]^+$.



Step 3: 2-((1-trityl-1H-imidazol-4-yl)methoxy)propan-1-ol

To a solution of ethyl 2-((1-trityl-1H-imidazol-4-yl)methoxy)propanoate (2.00 g, 4.54 mmol) in methanol (40 mL) was added sodium borohydride (0.86 g, 22.70 mmol) in small portions. After addition, the reaction mixture was stirred at 25°C for 16 h and then quenched by addition of saturated aqueous ammonium chloride (40 mL). The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo* to afford crude 2-((1-trityl-1H-imidazol-4-yl)methoxy)propan-1-ol (1.30 g, 72% yield) as colorless oil used in the next step without any further purification:

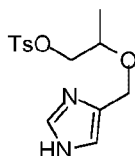
20 LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.80 min, ESI+ found $[M+Na] = 421.1$.



Step 4: 2-((1-trityl-1H-imidazol-4-yl)methoxy)propyl 4-methylbenzenesulfonate

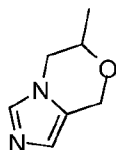
To a solution of 2-((1-trityl-1H-imidazol-4-yl)methoxy)propan-1-ol (1.3 g, 3.26 mmol) and triethylamine (1.0 g, 9.79 mmol) in dichloromethane (20 mL) was added 4-methylbenzene-1-sulfonyl chloride (0.8 g, 3.91 mmol) in small portions. After addition, the mixture was stirred at RT for 15 h. The reaction was washed with saturated sodium bicarbonate (2 x 15 mL), dried over sodium sulfate and concentrated to dryness *in vacuo* to afford crude 2-((1-trityl-1H-imidazol-4-yl)methoxy)propyl 4-methylbenzenesulfonate (1.8 g, 99% yield) as

a colourless oil used in the next step without any further purification: LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.86 min, ESI+ found $[M+H] = 553.1$.



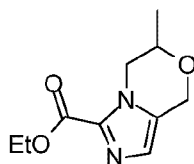
5 **Step 5: 2-((1H-imidazol-4-yl)methoxy)propyl 4-methylbenzenesulfonate 2,2,2-trifluoroacetate**

A mixture of 2-((1-trityl-1H-imidazol-4-yl)methoxy)propyl 4-methylbenzenesulfonate (1.8 g, 3.26 mmol) in 2,2,2-trifluoroacetic acid (20 mL) was stirred at RT for 3 h and concentrated to dryness *in vacuo* to afford crude 2-((1H-imidazol-4-yl)methoxy)propyl 4-methylbenzenesulfonate (1.0 g, 99% yield) as a red oil used in the next step without any further purification: LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.64 min, ESI+ found $[M+H] = 310.9$.



Step 6: 6-methyl-6,8-dihydro-5H-imidazo[5,1-c][1,4]oxazine

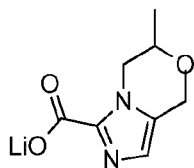
15 A mixture of 2-((1H-imidazol-4-yl)methoxy)propyl 4-methylbenzenesulfonate (1.0 g, 3.22 mmol) and cesium carbonate (3.2 g, 9.67 mmol) in N,N-dimethylformamide (20 mL) was heated at 80 °C for 15 h. After cooled, the mixture was poured into water (40 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% ethyl acetate in petroleum ether) to afford 6-methyl-6,8-dihydro-5H-imidazo[5,1-c][1,4]oxazine (0.2 g, 46% yield) as a white solid: LCMS (0 to 60% acetonitrile in water + 0.05% ammonium bicarbonate over 3 mins) retention time 1.19 min, ESI+ found $[M+H] = 139.1$.



25 **Step 7: ethyl 6-methyl-6,8-dihydro-5H-imidazo[5,1-c][1,4]oxazine-3-carboxylate**

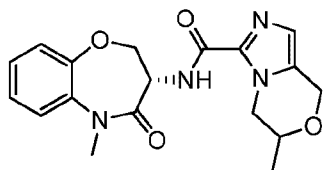
To a solution of 6-methyl-6,8-dihydro-5H-imidazo[5,1-c][1,4]oxazine (0.20 g, 1.45 mmol) and N-ethyl-N-isopropylpropan-2-amine (0.70 g, 5.79 mmol) in acetonitrile (2 mL) at -40 °C was added ethyl chloroformate (0.24 g, 2.17 mmol). After addition, the reaction mixture was

stirred at RT for 15 h and then concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 30% ethyl acetate in petroleum ether) to afford ethyl 6-methyl-6,8-dihydro-5H-imidazo[5,1-c][1,4]oxazine-3-carboxylate (0.09 g, 30% yield) as a colorless oil: LCMS $R_T = 1.52$ min, $m/z = 211.2$ $[M + H]^+$. LCMS (0 to 60% acetonitrile in water + 0.05% ammonium bicarbonate over 3 mins) retention time 1.52 min, ESI+ found $[M+H] = 211.2$.



Step 8: lithium 6-methyl-6,8-dihydro-5H-imidazo[5,1-c][1,4]oxazine-3-carboxylate

To a solution of ethyl 6-methyl-6,8-dihydro-5H-imidazo[5,1-c][1,4]oxazine-3-carboxylate (90 mg, 0.43 mmol) in ethanol (8 mL) and water (4 mL) was added lithium hydroxide hydrate (180 mg, 4.28 mmol). The mixture was stirred at RT for 1 h and concentrated to dryness *in vacuo* to afford lithium 6-methyl-6,8-dihydro-5H-imidazo[5,1-c][1,4]oxazine-3-carboxylate (71 mg, 90.7% yield) as white solid used in the next step without further purification.

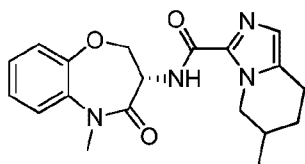


Step 9: 6-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6,8-dihydro-5H-imidazo[5,1-c][1,4]oxazine-3-carboxamide

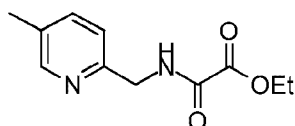
To a solution of lithium 6-methyl-6,8-dihydro-5H-imidazo[5,1-c][1,4]oxazine-3-carboxylate (71 mg, 0.39 mmol) in N,N-dimethylformamide (5 mL) was added 1H-benzo[d][1,2,3]triazol-1-ol (53 mg, 0.39 mmol), (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (50 mg, 0.26 mmol) and N^1 -(ethylimino)methylene)- N^3, N^3 -dimethylpropane-1,3-diamine hydrochloride (75 mg, 0.39 mmol). The mixture was stirred at 20 °C for 2 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (30-60% acetonitrile in water and 0.05% ammonium hydroxide) to afford 6-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6,8-dihydro-5H-imidazo[5,1-c][1,4]oxazine-3-carboxamide (37 mg, 39% yield) as a white solid: ^1H NMR (400 MHz, DMSO- d_6): δ 8.39 - 8.36 (m, 1H), 7.50 - 7.48 (m, 1H), 7.32 - 7.30 (m, 2H), 7.29 - 7.24 (m, 1H), 6.89 (s, 1H), 4.99 - 4.95 (m, 1H), 4.78 - 4.73 (m, 2H), 4.60 - 4.56 (m, 2H), 4.52 - 4.39 (m, 1H), 3.84 - 3.83 (m, 1H), 3.65 - 3.62 (m, 1H), 3.31 (s, 3H), 1.23 (d, $J = 6.4$ Hz, 3H). LCMS $R_T = 1.21$ min, $m/z = 357.2$ $[M + H]^+$. LCMS (10 to

80% acetonitrile in water + 0.03% trifluoacetic acid 2 mins) retention time 1.21 min, ESI+ found $[M+H] = 357.2$.

Example 11: Method I

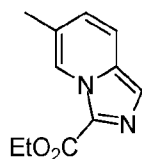


5 6-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide



Step1: ethyl 2-(((5-methylpyridin-2-yl)methyl)amino)-2-oxoacetate

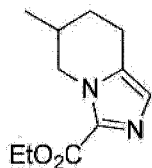
A solution of (5-methylpyridin-2-yl)methanamine (1.00 g, 8.19 mmol) and triethylamine (1.24 g, 12.28 mmol) in tetrahydrofuran (10 mL) was added ethyl oxalyl chloride (1.23 g, 9.00 mmol) at 0 °C. After addition, the reaction mixture was stirred at 20 °C for 10 h and then quenched with saturated aqueous sodium carbonate (20 mL). The solution was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 50% ethyl acetate in petroleum ether) to afford ethyl 2-[(5-methyl-2-pyridyl)methylamino]-2-oxo-acetate (1.20 mg, 66% yield) as brown oil: ^1H NMR (400 MHz, CDCl_3) δ 8.36 (s, 1H), 8.19 (br., s, 1H), 7.46 - 7.44 (m, 1H), 7.14 (d, $J = 8.0$ Hz, 1H), 4.56 (d, $J = 5.2$ Hz, 2H), 4.35 (q, $J = 7.2$ Hz, 2H), 2.30 (s, 3H), 1.36 (t, $J = 7.2$ Hz, 3H).



20 Step 2: ethyl 6-methylimidazo [1, 5-a] pyridine-3-carboxylate

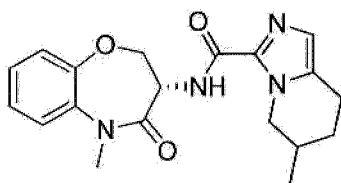
A mixture of ethyl 2-[(5-methyl-2-pyridyl)methylamino]-2-oxo-acetate (1.0 g, 4.5 mmol) and phosphorus oxychloride (28.0 g, 182.6 mmol) was heated at 100 °C for 10 h and concentrated to dryness *in vacuo*. The residue was poured into water (20 mL) and adjusted to pH = 8 by adding aqueous saturated sodium bicarbonate (20 mL). The resulting solution was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 70% ethyl acetate in petroleum ether) to afford ethyl 6-methylimidazo[1,5a]pyridine-3-carboxylate (250 mg, 27.2% yield) as brown solid: LCMS

(2 to 98% acetonitrile in water + 0.1% formic acid over 1.5 mins) retention time: 0.74 min, ESI+ found $[M+H] = 204.8$.



Step 3: ethyl 6-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxylate

- 5 A solution of ethyl 6-methylimidazo[1,5-a]pyridine-3-carboxylate (200 mg, 0.98 mmol) in methanol (5 mL) was treated with 10% palladium on carbon (200 mg, 0.19 mmol). The mixture was hydrogenated (50 psi) at 20 °C for 24 h and then filtered through Celite™. The filtrate was concentrated to dryness *in vacuo* to afford the crude ethyl 6-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxylate (200 mg, 98.1% yield) as colorless
10 oil used in the next step without any further purification: ^1H NMR (400 MHz, CDCl_3) δ 6.93 (s, 1H), 4.75 - 4.70 (m, 1H), 4.38 (q, $J = 7.2$ Hz, 2H), 3.68 - 3.62 (m, 1H), 2.99 - 2.94 (m, 1H), 2.77 - 2.75 (m, 1H), 1.96 - 1.93 (m, 2H), 1.47 - 1.40 (m, 4H), 1.13 (d, $J = 6.8$ Hz, 3H).



Step 4:

- 15 **6-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide**

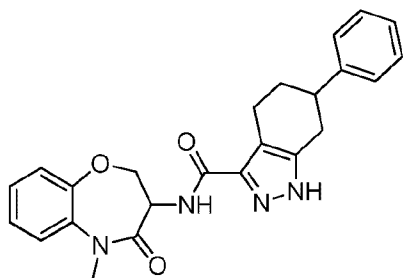
To a stirred solution of ethyl 6-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxylate (300 mg, 1.4 mmol) in ethanol (10 mL) and water (5 mL) was added lithium hydroxide (345 mg, 14.4 mmol). The mixture was stirred at 20 °C for 1 h and concentrated to dryness *in vacuo* pressure to afford
20 crude lithium 6-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxylate.

To a solution of crude lithium 6-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxylate (70 mg, 0.39 mmol) in N,N-dimethylformamide (5 mL) was added (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (50 mg, 0.26 mmol),

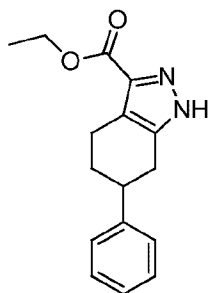
1H-benzo[d][1,2,3]triazol-1-ol (53 mg, 0.39 mmol) and N-1-((ethylamine)ethylene)-N₃,N₃-dimethylpropane-1,3-diamine hydrochloride (75 mg, 0.39 mmol). The mixture was stirred at 25 °C for 1 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (49% acetonitrile in water and 0.05% ammonia hydroxide) to afford
5 6-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide (29 mg, 31.4% yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 8.28 - 8.25 (m, 1H), 7.50 - 7.47 (m, 1H), 7.34 - 7.29 (m, 2H), 7.24 -

7.23 (m, 1H), 6.82 (s, 1H), 4.82 - 4.75 (m, 1H), 4.58 - 4.51 (m, 2H), 4.42 - 4.40 (m, 1H), 3.55 - 3.49 (m, 1H), 3.31 (s, 3H), 2.86 - 2.85 (m, 1H), 2.72 - 2.64 (m, 1H), 2.53 - 2.51 (m, 1H), 1.83 - 1.80 (m, 1 H), 1.38 - 1.32 (m, 1 H), 0.99 (d, $J = 6.4$ Hz, 3 H). LCMS (10 to 80% acetonitrile in water + 0.1% NH_4OH over 3 mins) retention time 1.90 min, ESI+ found $[\text{M}+\text{H}] = 355.2$.

5 Example 12: Method J

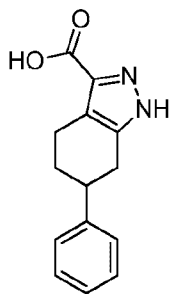


N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide



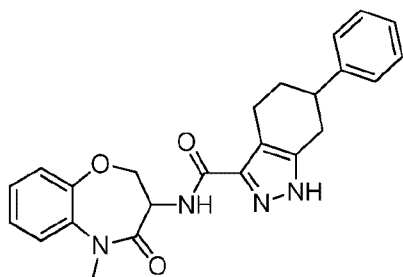
10 Step 1: ethyl 6-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

To a solution of 4-phenylcyclohexanone (2.0 g, 11.48 mmol) in dimethyl sulfoxide (20 mL) was added pyrrolidine (40.8 mg, 0.57 mmol). The mixture was stirred at 20 °C for 15 min, and ethyl 2-diazoacetate (654.8 mg, 5.74 mmol) was added. The resulting mixture was stirred at 20 °C for 15 h and then diluted with water (20 mL). The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 25% ethyl acetate in petroleum ether) to afford ethyl 6-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (830 mg, 53% yield) as a brown oil: ^1H NMR (400 MHz, CDCl_3) δ 7.35 - 7.32 (m, 2H), 7.27 - 7.22 (m, 3H), 4.39 - 4.33 (m, 2H), 3.08 - 2.97 (m, 3H), 2.81 - 2.72 (m, 2H), 2.15 - 2.12 (m, 1H), 1.95 - 1.89 (m, 1H), 1.38 - 1.34 (m, 3H). LCMS (10 to 80% acetonitrile in water + 0.05% ammonium bicarbonate over 3 mins) retention time 1.99 min, ESI+ found $[\text{M}+\text{H}] = 271.2$.



Step 2: 6-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid

To a solution of ethyl 6-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (400 mg, 1.5 mmol) in tetrahydrofuran (8 mL) and water (8 mL) was added lithium hydroxide monohydrate (354 mg, 14.8 mmol). The mixture was stirred at 20 °C for 22 h and concentrated to dryness *in vacuo*. The residue was diluted with water (10 mL) and adjusted to the pH = 3 with of 1M hydrochloric acid. The resulting solid was collected by filtration to afford crude 6-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (320 mg, 89.3% yield) as yellow solid used in the next step without further purification: LCMS (5 to 95% acetonitrile in water + 0.03% trifluoacetic acid over 1.5 mins) retention time 0.67 min, ESI+ found [M+H] = 242.9.



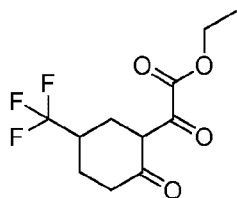
Step 3:

N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide

To a solution of 6-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (189 mg, 0.78 mmol) in N,N-dimethylformamide (5mL) was added 1H-benzo[d][1,2,3]triazol-1-ol (105 mg, 0.78 mmol), (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (100 mg, 0.52 mmol) and N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (150 mg, 0.78 mmol). The mixture was stirred at 20 °C for 1 h and then concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (40-70% acetonitrile in water and 0.05% ammonia hydrate) to afford N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide (77 mg, 34% yield as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 12.94 (s, 1H), 7.96 (d, *J* = 8.0, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.34 - 7.27 (m, 6H), 7.25 - 7.22 (m, 2H), 4.88 - 4.83 (m, 1H), 4.52 - 4.48 (m, 1H), 4.44 - 4.41 (m, 1H), 3.32 (s, 3H), 2.93 - 2.69 (m, 4H), 2.58 - 2.55 (m, 1H), 1.93 - 1.90 (m, 1H), 1.81 - 1.78 (m,

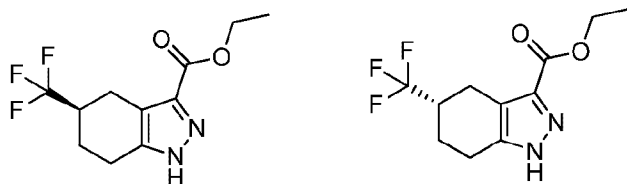
1H). LCMS (10 to 80% acetonitrile in water + 0.05% ammonium hydroxide over 3 mins) retention time 2.03 min, ESI+ found $[M+H] = 417.2$.

Example 13: Method K



5 Step 1: ethyl 2-oxo-2-[2-oxo-5-(trifluoromethyl)cyclohexyl]acetate

To a solution of 4-(trifluoromethyl)cyclohexanone (15.0 g, 90.3 mmol) in ethanol (45 mL) was added a solution of sodium ethoxide (6.8 g, 100.0 mmol) in ethanol (36 mL), following by diethyl oxalate (13.19 g, 90.29 mmol) at 0 °C. After addition, the mixture was allowed to warm to 25 °C and stirred for 15 h. The reaction mixture was concentrated to dryness *in vacuo* to afford crude ethyl 2-oxo-2-[2-oxo-5-(trifluoromethyl)cyclohexyl]acetate (33.0 g, 138% yield) as a yellow solid use in the next step without any further purification: LCMS (5 to 95% acetonitrile in water + 0.04% formic acid over 1.5mins) retention time 0.861min, ESI+ found $[M+H] = 266.9$.



15 Step 2: (R)-ethyl 5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate and (S)-ethyl 5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

To a solution of ethyl 2-oxo-2-[2-oxo-5-(trifluoromethyl)cyclohexyl]acetate (33.0 g, 90.3 mmol) in glacial acetic acid (33 mL) was added hydrazine hydrate (6.2 g, 124.0 mmol) at 0 °C. The mixture was stirred for 1 h at 25 °C, and then adjusted to pH=8 with aqueous sodium bicarbonate. The resulting mixture was extracted with methanol and dichloromethane (3 x 300 mL, methanol/dichloromethane = 5:95). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 50% ethyl acetate in petroleum ether) to afford racemic ethyl 5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (5.0 g, 21% yield) as a white solid. In a 500 mg batch, the enantiomers were separated by SFC to afford arbitrarily assigned enantiomers:

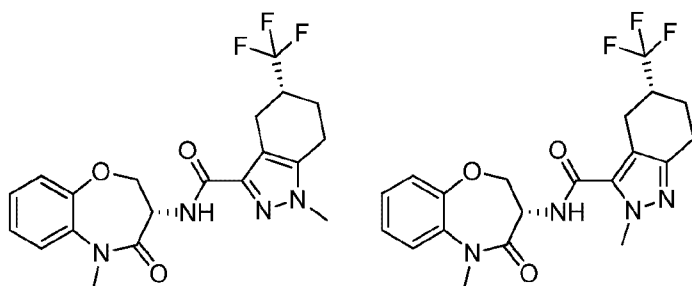
Peak 1 (Retention time: 3.36 min):

(R)-ethyl 5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (180 mg, 36% yield); Peak 2 (Retention time 3.66 min):

(S)-ethyl-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (132 mg, 26% yield)

SFC condition: Column: Lux Cellulose-2 150×4.6mm I.D., 3µm Mobile phase: A: CO₂ B: ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 5.5min and hold 40% for 3 min, then 5% of B for 2.5 min Flow rate: 2.5mL/min Column temperature: 40 °C.

Example 14: Method L

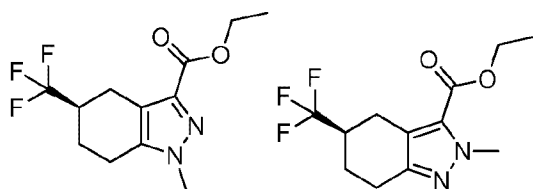


(5R)-1-methyl-N-[(3S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide and

(5R)-2-methyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide

Step 3:

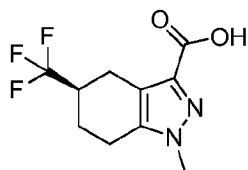
(R)-ethyl 1-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate and (R)-ethyl 2-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxylate



To a solution of arbitrarily assigned ethyl (R)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (180 mg, 0.69 mmol) in N,N-dimethylformamide (10 mL) was added potassium carbonate (104 mg, 0.76 mmol). After stirred for 30 min, methyl iodide (86 mg, 0.60 mmol) was added and stirring was continued for 15 h. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The residue which was purified by prep-TLC (30% ethyl acetate in petroleum ether) to afford (R)-ethyl 1-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (R_f = 0.2, 72 mg, 37% yield) and (R)-ethyl 2-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydro

-2H-indazole-3-carboxylate ($R_f = 0.5$, 53 mg, 28% yield): ^1H NMR (400MHz, CDCl_3) δ 4.40 - 4.35 (m, 2H), 3.80 (s, 3H), 3.22 - 3.15 (m, 1H), 2.81 - 2.50 (m, 3H), 2.38 - 2.40 (m, 1H), 2.31 - 2.19 (m, 1H), 1.82 - 1.67 (m, 1H), 1.38 (t, $J = 7.2$ Hz, 3H). LCMS $R_T = 0.835$ min, $m/z = 276.9$ $[\text{M} + \text{H}]^+$; ^1H NMR (400MHz, CDCl_3) δ 4.37 - 4.32 (m, 2H), 4.10 (s, 3H), 3.15 - 3.09 (m, 1H), 2.88 - 2.83 (m, 1H), 2.72 - 2.63 (m, 2H), 2.49 - 2.30 (m, 1H), 2.27 - 2.13 (m, 1H), 1.76 - 1.61 (m, 1H), 1.37 (t, $J = 7.2$ Hz, 3H). LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5mins) retention time 0.835min, ESI+ found $[\text{M} + \text{H}] = 276.9$ and retention time 0.895min, ESI+ found $[\text{M} + \text{H}] = 276.9$.

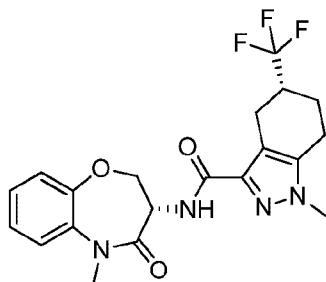
Step 4: (R)-1-methyl-5-(trifluoromethyl)-4, 5, 6, 7-tetrahydroindazole-3-carboxylic acid



10

To a solution of arbitrarily assigned ethyl (R)-1-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxylate (72 mg, 0.26 mmol) in ethanol (5 mL) and water (2 mL) was added potassium hydroxide (73 mg, 1.3 mmol). The mixture was stirred at 25 °C for 15 h and concentrated to dryness *in vacuo*. The residue was dissolved in water (5 mL) and adjusted the pH = 3 with 1 M hydrochloric acid. The solution was extracted with ethyl acetate (3 x 10 mL). The combined organic layer were washed with water (20 mL), brine (20 mL), dried over anhydrous sodium sulfate and concentrated to afford (R)-1-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxylic acid (52 mg, 80% yield) as a white solid used without further purification in the next step: LCMS (0 to 60% acetonitrile in water + 0.04% formic acid over 2 mins) retention time 1.10 min, ESI+ found $[\text{M} + \text{H}] = 249.0$.

20



Step 5:

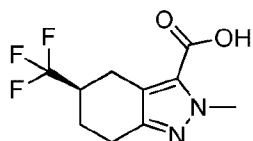
(5R)-1-methyl-N-[(3S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide

25

To a solution of (R)-1-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxylic acid (52 mg, 0.20 mmol) in N,N-dimethylformamide (4 mL) was added

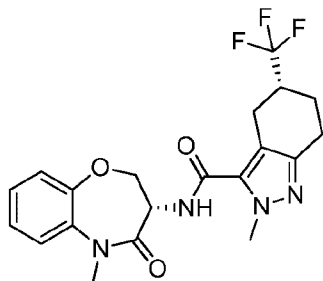
1-1*H*-benzo[d][1,2,3]triazol-1-ol (62 mg, 0.46 mmol), (3*S*)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (88 mg, 0.46 mmol), and *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (88 mg, 0.46 mmol). The reaction mixture was stirred at 25 °C for 12 h and

- 5 concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (25-55% acetonitrile in water and 0.225% formic acid) to afford (5*R*)-1-methyl-*N*-[(3*S*)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxamide (21 mg, 25% yield) as a white solid: ¹H NMR (400MHz, Methanol-*d*₄) δ 7.44 - 7.41 (m, 1H), 7.33 - 7.22 (m, 3H), 4.97 - 4.94 (m, 1H), 4.60 - 4.56 (m, 1H), 4.37- 4.31 (m, 1H), 3.77(s, 3H), 3.42 (s, 3H), 3.12 - 3.07 (m, 1H), 2.85 - 2.81 (m, 1H), 2.68 - 2.45 (m, 3H), 2.26 - 2.21 (m, 1H), 1.76 - 1.63 (m, 1H). LCMS (0 to 60% acetonitrile in water + 0.03% trifluoroacetic acid over 2mins) retention time 1.64 min, ESI+ found [M+H] = 423.2.



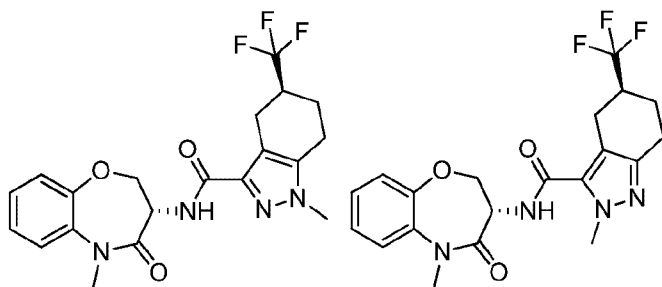
15 **Step 6: (R)-2-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxylic acid**

- To a solution of ethyl (R)-2-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxylate (53 mg, 0.19 mmol) in ethanol (5 mL) and water (2 mL) was added potassium hydroxide (62 mg, 1.1 mmol). The mixture was stirred at 25 °C for 15 h and concentrated to dryness *in vacuo*. The residue was dissolved in water (5 mL) and adjusted the pH = 3 with 1 M hydrochloric acid. The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo* to afford (R)-2-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole -3-carboxylic acid (53 mg, 99% yield) as a white solid used without further purification in the next step: LCMS (0 to 60% acetonitrile in water + 0.03% trifluoroacetic acid over 2mins) retention time 1.16 min, ESI+ found [M+H] = 249.0.

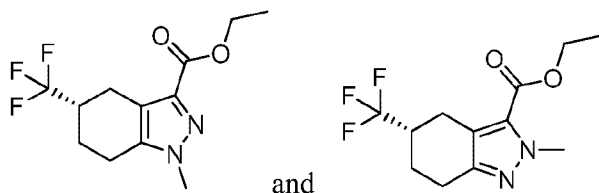


Step 7:**(5R)-2-methyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxamide**

To a solution of (5R)-2-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxylic acid (53 mg, 0.21 mmol) in N,N-dimethylformamide (4 mL) was added methyl (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (121 mg, 0.64 mmol), 1-1*H*-benzo[d][1,2,3]triazol-1-ol (86 mg, 0.64 mmol) and *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (122 mg, 0.64 mmol). The reaction mixture was stirred at 25 °C for 12 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (25-55% acetonitrile in water and 0.225% formic acid) to afford (5R)-1-methyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxamide (33 mg, 37% yield) as white solid: ¹H NMR (400MHz, CD₃OD) δ7.45 - 7.41 (m, 1H), 7.35 - 7.18 (m, 3H), 5.03 - 4.97 (m, 1H), 4.60 - 4.55 (m, 1H), 4.43 - 4.37 (m, 1H), 3.91 (s, 3H), 3.42 (s, 3H), 3.12 - 3.05 (m, 1H), 2.87 - 2.30 (m, 4H), 2.26 - 2.22 (m, 1H), 1.77 - 1.71 (m, 1H). LCMS (0 to 60% acetonitrile in water + 0.03% trifluoroacetic acid over 7 mins) retention time 6.00min, ESI+ found [M+H] = 423.1.

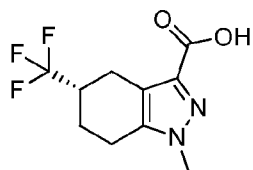
Example 15: Method M

(5S)-1-methyl-N-[(3S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide and
(5S)-2-methyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxamide



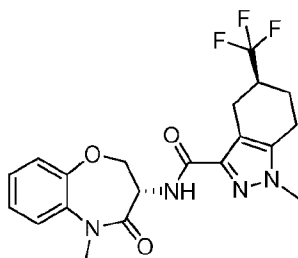
Step 1: (S)-ethyl 1-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate and
(S)-ethyl 2-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxylate

To a solution of ethyl (S)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (132 mg, 0.50 mmol) in N,N-dimethylformamide (10 mL) was added potassium carbonate (104 mg, 0.76 mmol). After stirred for 30 min, methyl iodide (86 mg, 0.60 mmol) was added and stirring was continued for 15 h. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (50 mL),
 5 brine (50 mL), dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The residue which was purified by prep-TLC (30% ethyl acetate in petroleum ether) to afford (S)-ethyl 1-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (R_f = 0.2, 38 mg, 27.5% yield) and (S)-ethyl
 10 2-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (R_f = 0.5, 86 mg, 62.3% yield) as a white solid: LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5mins) retention time 0.83min, ESI+ found $[M+H]^+ = 276.9$ and $R_T = 0.89$ min, $m/z = 276.9$ $[M+H]^+$.



15 **Step 2: (S)-1-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxylic acid**

To a solution of (S)-ethyl 1-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (38 mg, 0.14 mmol) in ethanol (5 mL) and water (2 mL) was added potassium hydroxide (38 mg, 0.69 mmol). The mixture was stirred at 25 °C for 15 h and concentrated to dryness *in vacuo*. The residue was dissolved in water (5 mL) and adjusted the
 20 pH = 3 with 1 M hydrochloric acid. The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over sodium sulfate and concentrated to dryness *in vacuo* to afford the product (R)-1-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxylic acid (38 mg, 100% yield) as a white solid: LCMS (0 to 60% acetonitrile in water + 0.03% trifluoroacetic acid over
 25 2 mins) retention time 1.12 min, ESI+ found $[M+H]^+ = 249.0$.

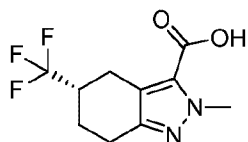


Step 3:

(5S)-1-methyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxamide

To a solution of (S)-1-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxylic acid (38 mg, 0.14 mmol) in N,N-dimethylformamide (4 mL) was added methyl (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (88 mg, 0.46 mmol), 1-1*H*-benzo[d][1,2,3]triazol-1-ol (62 mg, 0.46 mmol) and *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethyl propane-1,3-diamine hydrochloride (88 mg, 0.46 mmol). The reaction mixture was stirred at 25 °C for 12 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (25-55% acetonitrile in water and 0.225% formic acid) to afford (5S)-1-methyl-*N*-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxamide (31 mg, 52% yield) as a white solid: ¹H NMR (400MHz, Methanol-*d*₄) δ 7.46 - 7.40 (m, 1H), 7.36 - 7.20 (m, 3H), 4.99 - 4.94 (m, 1H), 4.60 - 4.56 (m, 1H), 4.38-4.33 (m, 1H), 3.79 (s, 3H), 3.41 (s, 3H), 3.11 - 3.06 (m, 1H), 2.85 - 2.81 (m, 1H), 2.67 - 2.46 (m, 3H), 2.25 - 2.21 (m, 1H), 1.75 - 1.67 (m, 1H). LCMS (0 to 60% acetonitrile in water + 0.03% trifluoroacetic acid over 7mins) retention time 6.20 min, ESI+ found [M+H] = 423.2.

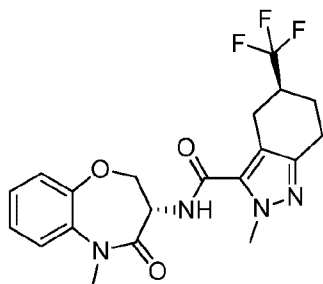
15



Step 4: (S)-2-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxylic acid

To a solution of (S)-ethyl 2-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1*H*-indazole-3-carboxylate (86 mg, 0.31 mmol) in ethanol (5 mL) and water (2 mL) was added potassium hydroxide (91 mg, 1.60 mmol). The mixture was stirred at 25 °C for 15 h and concentrated to dryness *in vacuo*. The residue was dissolved in water (5 mL) and adjusted the pH = 3 with 1 M hydrochloric acid. The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over sodium sulfate and concentrated to dryness *in vacuo* to afford (R)-2-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxylic acid (74 mg, 92% yield) as a white solid. LCMS (0 to 60% acetonitrile in water + 0.03% trifluoroacetic acid over 2 mins) retention time 1.17 min, ESI+ found [M+H] = 249.0.

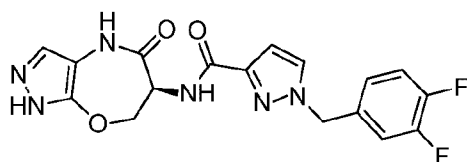
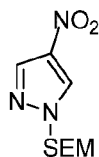
25



Step 5:**(5S)-2-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide**

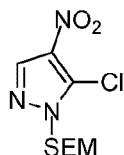
To a solution of (S)-2-methyl-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxylic acid (74 mg, 0.30 mmol) in N,N-dimethylformamide (4 mL) was added methyl (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (121 mg, 0.64 mmol), 1-1*H*-benzo[d][1,2,3]triazol-1-ol (86 mg, 0.64 mmol) and *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (122 mg, 0.64 mmol). The reaction mixture was stirred at 25 °C for 12 h and

concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (25-55% acetonitrile in water and 0.225% formic acid) to afford (5S)-2-methyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydroindazole-3-carboxamide (33 mg, 26% yield) as a white solid: ¹H NMR (400MHz, Methanol-d₄) δ 7.45 - 7.41 (m, 1H), 7.36 - 7.17(m, 3H), 4.98 - 4.94 (m, 1H), 4.60 - 4.55(m, 1H), 4.44 - 4.37 (m, 1H), 3.90 (s, 3H), 3.42 (s, 3H), 3.09 - 3.04 (m, 1H), 2.83 - 2.60 (m, 4H), 2.28 - 2.19 (m, 1H), 1.75 - 1.65 (m, 1H). LCMS (0 to 60% acetonitrile in water + 0.03% trifluoroacetic acid over 7mins) retention time 6.00 min, ESI+ found [M+H] = 423.2.

Example 16: Method N**(S)-1-(3,4-difluorobenzyl)-N-(5-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-b][1,4]oxazepin-6-yl)-1H-pyrazole-3-carboxamide****Step 1: 4-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole**

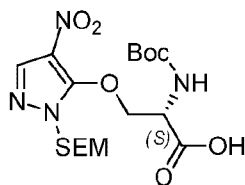
To a solution of 4-nitro-1*H*-pyrazole (30.0 g, 265 mmol) in tetrahydrofuran (400 mL) was added sodium hydride (60%, 15.9 g, 398 mmol) at 0 °C. The reaction mixture was stirred for 30 min, and (2-(chloromethoxy)ethyl)trimethylsilane (66.3 g, 398 mmol) was added at 0 °C. After addition, the mixture was stirred at 25 °C for 2 h and then quenched by addition of water (100 mL). The resulting mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 10% ethyl acetate in petroleum ether) to afford

4-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (60.0 g, 93% yield) used in the next step without further purification.



Step 2: 5-chloro-4-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole

- 5 To a solution of 4-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (20.0 g, 82.2 mmol) in tetrahydrofuran (300 mL) was added with lithium bis(trimethylsilyl)azanide (1M in tetrahydrofuran, 89.0 mL, 89.0 mmol) at -78 °C. The mixture was stirred for 30 min, and hexachloroethane (21.3 g, 90.1 mmol) was added dropwise. After addition, the mixture was allowed to warm to RT and stirred for 16 h. The reaction mixture was quenched by addition of
- 10 saturated aqueous ammonium chloride (80 mL) and extracted with ethyl acetate (3 x 80 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 10% ethyl acetate in petroleum ether) to afford 5-chloro-4-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (15.0 g, 66%
- 15 yield) as colorless oil: ¹H NMR (400 MHz, DMSO-d₆) δ 8.53 (s, 1H), 5.56 (s, 2H), 3.61 (t, *J* = 8.2 Hz, 2H), 0.86 (t, *J* = 8.2 Hz, 2H), 0.05 (s, 9H).

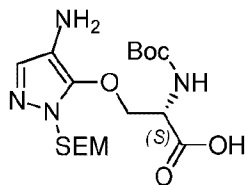


Step 3:

- (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-((4-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)oxy)propanoic acid

- To a solution of (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxypropanoic acid (1.77 g, 8.64 mmol) in N, N-dimethylformamide (50 mL) was added sodium hydride (60%, 691 mg, 17.28 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, and then 5-chloro-4-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (2.40 g, 8.64 mmol) was
- 25 added. The resulting mixture was stirred at 20 °C for 3 h and quenched by addition of 1M hydrochloric acid (30 mL). The mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 30% ethyl acetate in petroleum ether) to afford (*S*)-2-((*tert*-butoxycarbonyl)amino)-
- 30 -3-((4-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)oxy)propanoic acid (1.00 g,

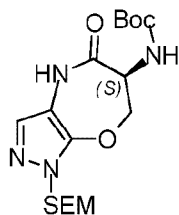
26% yield) as yellow oil. LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.99 min, ESI+ found $[M+H] = 469.1$.



Step 4:

5 (S)-3-((4-amino-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)oxy)-2-((tert-butoxycarbonyl)amino)propanoic acid

To a solution of (S)-2-((tert-butoxycarbonyl)amino)-3-((4-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)oxy)propanoic acid (600 mg, 1.34 mmol) in methanol (50 mL) was added 10% palladium on carbon (212 mg, 2.00 mmol). The resulting mixture was hydrogenated (50 psi) at 20 °C for 2 h and then filtered through Celite. The filtrate was concentrated to dryness *in vacuo* to afford crude (S)-3-((4-amino-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)oxy)-2-((tert-butoxycarbonyl)amino)propanoic acid (500 mg, 89% yield) as yellow oil: LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.831 min, ESI+ found $[M+H] = 417.2$.

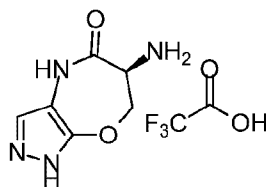


15

Step 5: (S)-tert-butyl (5-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-4,5,6,7-tetrahydro-1H-pyrazolo [3,4-b][1,4]oxazepin-6-yl)carbamate

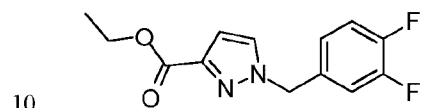
To a solution of (S)-3-((4-amino-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)oxy)-2-((tert-butoxycarbonyl)amino)propanoic acid (500 mg, 1.20 mmol) in N,N-dimethylformamide (10 mL) was added *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (275 mg, 1.44 mmol). The reaction mixture was stirred at 20 °C for 2 h and then concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 - 50% ethyl acetate in petroleum ether) to afford (S)-tert-butyl (5-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-b][1,4]oxazepin-6-yl)carbamate (300 mg, 63% yield) as yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.68 (s, 1H), 7.22 (s, 1H), 5.79 (s, 1H), 5.35 (d, *J* = 11.2 Hz, 1H), 5.22 (d, *J* = 11.2 Hz, 1H), 4.63 (d, *J* = 11.2 Hz, 1H), 4.53 (s, 1H), 4.24-4.20 (m, 1H), 3.62 (t, *J* = 8.2 Hz, 2H), 1.48 (s, 9H), 0.93 (t, *J* = 8.2 Hz, 2H), 0.01 (s, 9H).

25



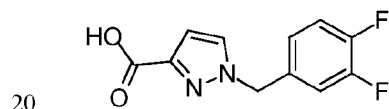
Step 6: (S)-6-amino-6,7-dihydro-1H-pyrazolo[3,4-b][1,4]oxazepin-5(4H)-one 2,2,2-trifluoroacetate

To a solution of (*S*)-*tert*-butyl (5-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-b][1,4]oxazepin-6-yl)carbamate (100 mg, 0.25 mmol) in dichloromethane (10 mL) was added 2,2,2-trifluoroacetic acid (565 mg, 5.00 mmol). The reaction mixture was stirred at 20 °C for 2 h and concentrated to dryness *in vacuo* to afford (*S*)-6-amino-6,7-dihydro-1H-pyrazolo[3,4-b][1,4]oxazepin-5(4H)-one 2,2,2-trifluoroacetate (70 mg, 99% yield) as a yellow solid used without further purification in the next step.



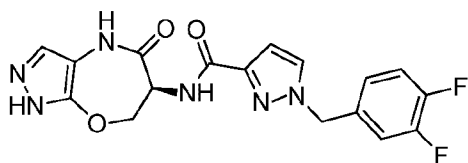
Step 7: ethyl 1-(3,4-difluorobenzyl)-1H-pyrazole-3-carboxylate

A mixture of ethyl 1H-pyrazole-3-carboxylate (1.4 g, 9.66 mmol), 4-(bromomethyl)-1,2-difluorobenzene (1.0 g, 4.83 mmol) and potassium hydroxide (0.27 g, 4.83 mmol) in tetrahydrofuran (100 mL) was stirred at 70 °C for 12 h. After cooling to RT, the mixture was filtered and the filtrate was concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% ethyl acetate in petroleum ether) to afford ethyl 1-(3,4-difluorobenzyl)-1H-imidazole-4-carboxylate (1.2 g, 93% yield) as white solid: LCMS (0 to 60% acetonitrile in water + 0.03% trifluoroacetic acid over 2 mins) retention time 1.25 min, ESI+ found [M+H] = 266.9.



Step 8: 1-(3,4-difluorobenzyl)-1H-pyrazole-3-carboxylic acid

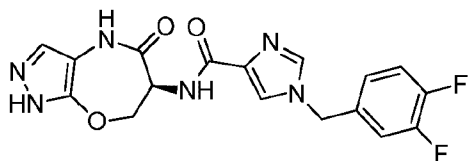
A mixture of ethyl methyl 1-(3,4-difluorobenzyl)-1H-imidazole-4-carboxylate (1.2 g, 4.51 mmol) in ethanol (40 mL) and water (5 mL) was potassium hydroxide (2.5 g, 45.07 mmol) was stirred at 25 °C for 13 h and concentrated to dryness *in vacuo*. The residue was dissolved with water (5 mL) and adjusted the pH = 3 by addition of 1M hydrochloric acid. The resulting solid was collected by filtration and dried under reduced pressure to afford 1-(3,4-difluorobenzyl)-1H-pyrazole-3-carboxylic acid (0.73 g, 68% yield) as a white solid: LCMS (0 to 60% acetonitrile in water + 0.03% trifluoroacetic acid over 2 mins) retention time 1.07 min, ESI+ found [M+H] = 238.9.



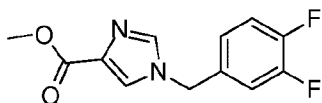
Step 9: (S)-1-(3,4-difluorobenzyl)-N-(5-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-b][1,4]oxazepin-6-yl)-1H-pyrazole-3-carboxamide

To a solution of (S)-6-amino-6,7-dihydro-1H-pyrazolo[3,4-b][1,4]oxazepin-5(4H)-one 2,2,2-trifluoroacetate (70.0 mg, 0.25 mmol) in N,N-dimethylformamide (5 mL) was added 1-(3,4-difluorobenzyl)-1H-pyrazole-3-carboxylic acid (71.4 mg, 0.30 mmol), 1H-benzo[d][1,2,3] triazol-1-ol (40.5 mg, 0.30 mmol) and *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (57.3 mg, 0.30 mmol). The reaction mixture was heated to 50 °C for 16 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (18-48% acetonitrile in water and 0.05% ammonia hydroxide) to afford (S)-1-(3,4-difluorobenzyl)-N-(5-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-b][1,4]oxazepin-6-yl)-1H-pyrazole-3-carboxamide (5.9 mg, 6.1% yield) as a white solid: ¹H NMR (400 MHz, CD₃OD) δ 7.78 (d, *J* = 2.4 Hz, 1H), 7.36 (s, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.26 - 7.20 (m, 2H), 7.14 - 7.10 (m, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 5.41 (s, 2H), 4.89 - 4.85 (m, 1H), 4.53 - 4.50 (m, 1H), 4.33 - 4.28 (m, 1H). LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.74 min, ESI+ found [M+H] = 389.0.

Example 17: Method O



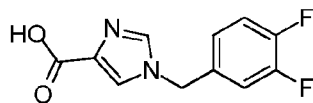
1-[(3,4-difluorophenyl)methyl]-N-[(6S)-5-oxo-1,4,6,7-tetrahydropyrazolo[3,4-b][1,4]oxazepin-6-yl]imidazole-4-carboxamide



Step 1: methyl 1-(3,4-difluorobenzyl)-1H-imidazole-4-carboxylate

A mixture of 4-(bromomethyl)-1,2-difluorobenzene (10.0 g, 48.3 mmol), 1H-imidazole-4-carboxylate (12.2 g, 96.6 mmol) and potassium hydroxide (5.4 g, 96.6 mmol) in tetrahydrofuran (100 mL) was heated at 70 °C for 12 h. After cooled, the mixture was filtered and the filtrate was concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% ethyl acetate in petroleum ether) to afford methyl 1-(3,4-difluorobenzyl)-1H-imidazole-4-carboxylate (5.0 g, 41% yield) as a

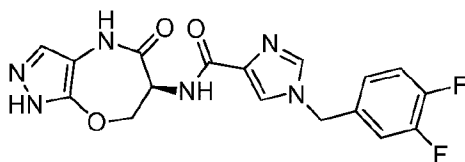
white solid: LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.70 min, ESI+ found $[M+H] = 252.8$.



Step 2: 1-(3,4-difluorobenzyl)-1H-imidazole-4-carboxylic acid

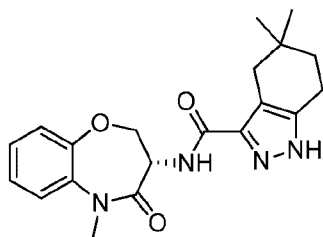
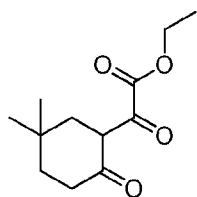
- 5 A mixture of methyl 1-(3,4-difluorobenzyl)-1H-imidazole-4-carboxylate (5.0 g, 19.07 mmol) in ethanol (50 mL) and water (5 mL) was added potassium hydroxide (5.4 g, 95.34 mmol). The mixture was stirred at 25 °C for 13 h and concentrated to dryness *in vacuo*. The residue was diluted with water (5 mL) and adjusted the pH = 3 by addition of 1M hydrochloric acid. The resulting solid was collected by filtration and dried under reduced pressure to afford 1-(3,4-difluorobenzyl)-1H-imidazole-4-carboxylic acid (4.5 g, 99.1% yield) as a white solid:

LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.22 min, ESI+ found $[M+H] = 238.8$.

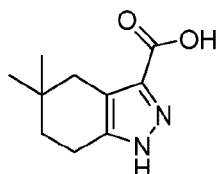


- 15 **Step 3:**
1-[(3,4-difluorophenyl)methyl]-N-[(6S)-5-oxo-1,4,6,7-tetrahydropyrazolo[3,4-b][1,4]oxazepin-6-yl]imidazole-4-carboxamide

- To a solution of (*S*)-6-amino-6,7-dihydro-1*H*-pyrazolo[3,4-*b*][1,4]oxazepin-5(4*H*)-one 2,2,2-trifluoroacetate (70 mg, 0.25 mmol) in N,N-dimethylformamide (5 mL) was added 1-(3,4-difluorobenzyl)-1*H*-imidazole-4-carboxylic acid (71 mg, 0.30 mmol), 1*H*-benzo[d][1,2,3]triazol-1-ol (41 mg, 0.30 mmol) and *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (57 mg, 0.30 mmol). The mixture was heated at 50 °C for 16 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (17-47% acetonitrile in water and 0.05% ammonia hydroxide) to afford (*S*)-1-(3,4-difluorobenzyl)-*N*-(5-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*][1,4]oxazepin-6-yl)-1*H*-imidazole-4-carboxamide (4.9 mg, 5.1% yield) as a white solid: ¹H NMR (400 MHz, CD₃OD) δ 7.79 (s, 1H), 7.74 (s, 1H), 7.36 (s, 1H), 7.32 - 7.24 (m, 2H), 7.14 - 7.05 (m, 1H), 5.26 (s, 2H), 4.82 - 4.50 (m, 1H), 4.51 - 4.48 (m, 1H), 4.31 - 4.26 (m, 1H). LCMS (10 to 80% acetonitrile in water + 0.05% ammonium hydroxide over 3 mins) retention time 1.36 min, ESI+ found $[M+H] = 389.1$.

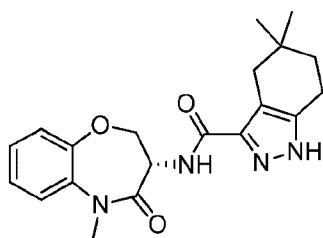
Example 18: Method P**5,5-dimethyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1,4,6,7-tetrahydroindazole-3-carboxamide****Step 1: ethyl 2-(5,5-dimethyl-2-oxocyclohexyl)-2-oxoacetate**

To a solution of 4,4-dimethylcyclohexanone (2.5 g, 19.8 mmol) in ethanol (30 mL) was added a solution of sodium ethoxide (1.5 g, 21.8 mmol) in ethanol (30 mL), followed by diethyl oxalate (2.9 g, 19.8 mmol) at 0 °C. After addition, the mixture was stirred at 25 °C for 15 h and concentrated to dryness *in vacuo* to afford crude ethyl 2-(5,5-dimethyl-2-oxocyclohexyl)-2-oxoacetate (4.5 g, 100% yield) as a yellow solid used in the next step without further purification.

**Step 2: 5,5-dimethyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid**

To a solution of ethyl 2-(5,5-dimethyl-2-oxocyclohexyl)-2-oxoacetate (4.47 g, 21.8 mmol) in glacial acetic acid (5 mL) was added hydrazine hydrate (0.18 g, 21.8 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 h and then adjusted to pH = 8 by addition of aqueous sodium bicarbonate. The resulting mixture was extracted with methanol and dichloromethane (3 x 300 mL, methanol/dichloromethane = 5:95). The combined organic extracts were washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 30% ethyl acetate in petroleum ether) to afford ethyl 5,5-dimethyl-4,5,6,7-tetrahydro- 1H-indazole-3-carboxylate (700 mg). The above material was dissolved in THF (10 mL) and water (2 mL), and added lithium hydroxide monohydrate (500 mg, 11.9 mmol). The mixture was stirred at 25 °C for 12 h and concentrated to dryness *in*

vacuo. The residue was diluted with water (10 mL) and washed with ethyl acetate (2 x 20 mL). The aqueous layer was then adjust to pH = 3 by addition of 1M HCl. The solution was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo* to afford
 5,5-dimethyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (100 mg, 2.5% yield over 2
 steps) as a white solid: LCMS (5to 95% acetonitrile in water + 0.04% formic acid over
 1.5mins) retention time 0.66 min, ESI+ found [M+H] = 195.1.

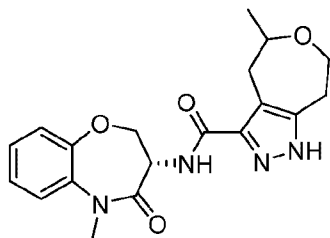


Step 3:

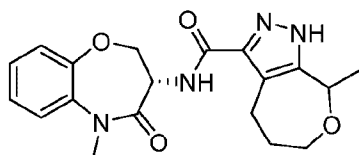
5,5-dimethyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1,4,6,7-tetrahydroindazole-3-carboxamide

To a solution of 5,5-dimethyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (100 mg, 0.51 mmol) in N,N-dimethylformamide (5 mL) was added 1H-benzo[d][1,2,3]triazol-1-ol (76 mg, 0.56 mmol), (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (108 mg, 0.56 mmol) and N-1-((ethylamine)ethylene)-N₃,N₃-dimethylpropane-1,3-diamine hydrochloride (108 mg, 0.56 mmol). The mixture was stirred at 25 °C for 1 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (45-75% acetonitrile in water and 0.05% hydrochloric acid) to afford 5,5-dimethyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1,4,6,7-tetrahydroindazole-3-carboxamide (30 mg, 15.8% yield) as white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.31 – 7.19 (m, 3H), 4.82 – 4.77 (m, 1H), 4.51 – 4.34 (m, 2H), 3.29 (s, 3H), 2.57 – 2.52 (m, 2H), 2.32 (s, 2H), 1.45 (t, *J* = 6.4 Hz, 2H), 0.88 (s, 6H). LCMS (5to 95% acetonitrile in water + 0.04% formic acid over 1.5mins) retention time 0.86 min, ESI+ found [M+H] = 369.0.

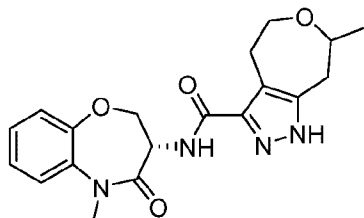
Example 19: Method Q



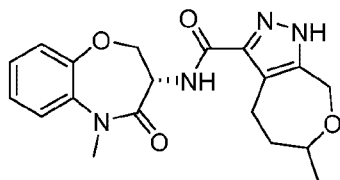
5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide



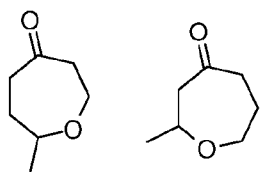
8-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxamide



5 **7-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide**



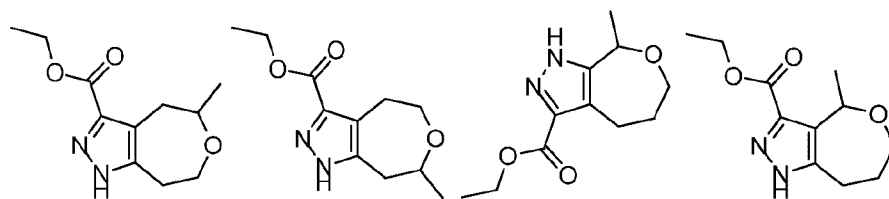
6-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxamide



10

Step 1: 7-methyloxepan-4-one and 2-methyloxepan-4-one

To a solution of 2-methyldihydro-2H-pyran-4(3H)-one (3.0 g, 26.68 mmol) in dichloromethane (60 mL) and boron fluoride ethyl ether (8.1 mL, 48% ethyl ether) was added trimethylsilyldiazomethane (14.5 mL, 28.91 mmol, 2 M in hexane) dropwise at -30 °C. After addition, the resulting solution was stirred for 1 h at -30 °C and quenched by addition of saturated sodium bicarbonate (30 mL). The resulting mixture was extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 30% ethyl acetate in petroleum ether) to afford a mixture of 7-methyloxepan-4-one and 2-methyloxepan-4-one (1.2 g, 35.1% yield) as a yellow oil used in the next step without further purification.



Step 2: ethyl 5-methyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylate;

ethyl 7-methyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylate;

ethyl 8-methyl-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxylate and

5 ethyl 6-methyl-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxylate

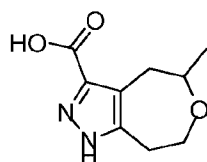
To a solution of 7-methyloxepan-4-one and 2-methyloxepan-4-one (1.00 g, 7.8 mmol) in dimethyl sulfoxide (30 mL) was added ethyl diazoacetate (1.07 g, 9.4 mmol), pyrrolidine (0.11 g, 1.56 mmol). The mixture was stirred at 20 °C for 16 h and diluted with water (20 mL). The solution was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were
 10 washed with water (3 x 25 mL), dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% ethyl acetate in petroleum ether) to afford:

ethyl 5-methyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylate (120 mg, 6.9% yield) as a yellow solid: ¹H NMR (400MHz, CDCl₃) δ 4.38 (q, *J* = 6.8 Hz, 2H), 4.24 - 4.20 (m, 1H), 3.63 - 3.55 (m, 2H), 3.45 - 3.41 (m, 1H), 3.06 - 3.05 (m, 1H), 2.97 - 2.89 (m, 1H), 2.70 - 2.63 (m, 1H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.33 (d, *J* = 6.4 Hz, 3H);

ethyl 7-methyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylate (120 mg, 6.9% yield) as yellow solid: ¹H NMR (400MHz, CDCl₃) δ 4.38 (q, *J* = 7.2 Hz, 2H), 4.26 - 4.22 (m, 1H), 3.67 - 3.56 (m, 1H), 3.54 - 3.49 (m, 1H), 3.37 - 3.32 (m, 1H), 3.04 - 2.90 (m, 1H), 2.90 - 2.83 (m, 2H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.32 (d, *J* = 6.0 Hz, 3H);

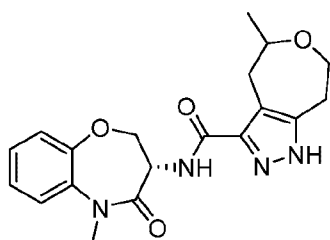
ethyl 8-methyl-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxylate (250 mg, 14.3% yield) as yellow solid: ¹H NMR (400MHz, CDCl₃) δ 4.60 - 4.55 (m, 1H), 4.44 - 4.35 (m, 2H), 4.33 - 4.28 (m, 1H), 3.86 - 3.79 (m, 1H), 3.39 - 3.34 (m, 1H), 2.80 - 2.76 (m, 1H), 1.90 - 1.83 (m, 2H), 1.65 (d, *J* = 6.4 Hz, 3H), 1.39 (t, *J* = 7.2 Hz, 3H) and

25 ethyl 6-methyl-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxylate (250 mg, 14.3% yield) as a yellow solid: ¹H NMR (400MHz, CDCl₃) δ 4.92 (d, *J* = 14.4 Hz, 1H), 4.52 (d, *J* = 14.4 Hz, 1H), 4.41 - 4.35 (m, 2H), 3.86 - 3.82 (m, 1H), 3.43 - 3.37 (m, 1H), 2.70 - 2.65 (m, 1H), 2.00 - 1.92 (m, 1H), 1.64 - 1.61 (m, 1H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.29 (d, *J* = 6.4 Hz, 3H).



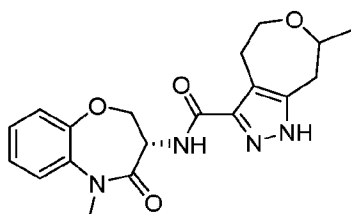
Step 3: 5-methyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylic acid

To a solution of ethyl 5-methyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylate (110 mg, 0.49 mmol) in tetrahydrofuran (5 mL) and water (1 mL) was added lithium hydroxide (118 mg, 4.91 mmol). The mixture was stirred at 20 °C for 20 h and then concentrated to dryness *in vacuo*. The residue was diluted with water (30 mL) and adjusted pH = 3 by addition of 1 M hydrochloric acid. The resulting solution was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo* to afford the crude 5-methyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylic acid (100 mg, 100% yield) as a white solid: LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.86 min, ESI+ found [M+H] = 196.9.

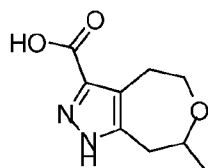


Step 4:
5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide

To a solution of 5-methyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylic acid (50.0 mg, 0.25 mmol) in N,N-dimethylformamide (5 mL) was added 1H-benzo[d][1,2,3]triazol-1-ol (41.3 mg, 0.31 mmol), *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (58.6 mg, 0.31 mmol) and (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (53.9 mg, 0.28 mmol). The reaction mixture was stirred at 25 °C for 1 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (50-80% methanol in water and 0.05% ammonia) to afford 5-methyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide (30.0 mg, 32% yield) as a white solid: ¹H NMR (400MHz, DMSO-d₆) δ 12.94 (s, 1H), 8.01 - 7.99 (m, 1H), 7.49 - 7.47 (m, 1H), 7.32 - 7.28 (m, 2H), 7.24 - 7.21 (m, 1H), 4.82 - 4.79 (m, 1H), 4.42 - 4.39 (m, 1H), 4.37 - 4.35 (m, 1H), 4.07 - 4.04 (m, 1H), 3.49 - 3.45 (m, 3H), 3.31 (s, 3H), 2.87 - 2.80 (m, 2H), 2.49 - 2.35 (m, 1H), 1.13 (d, *J* = 6.0 Hz, 3H). LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.78 min, ESI+ found [M+H] = 371.0.

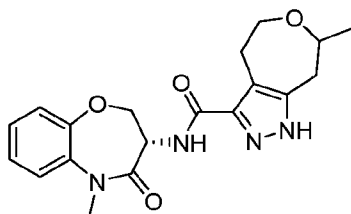


7-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide



5 Step 5: 7-methyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylic acid

To a solution of ethyl 7-methyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylate (120 mg, 0.54 mmol) in tetrahydrofuran (5 mL) and water (1 mL) was added lithium hydroxide (128 mg, 5.35 mmol). The mixture was stirred at 20 °C for 20 h and then concentrated to dryness *in vacuo*. The residue was diluted with water (30 mL) and adjusted pH = 3 by addition of 1 M hydrochloric acid. The resulting solution was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo* to afford crude 7-methyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylic acid (100 mg, 95% yield) as a white solid used without further purification in the next step: LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.85 min, ESI+ found [M+H] = 197.0.



Step

6:

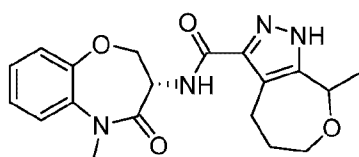
7-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide

To a solution of 7-methyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylic acid (50.0 mg, 0.25 mmol) in N,N-dimethylformamide (5 mL) was added 1H-benzo[d][1,2,3]triazol-1-ol (41.3 mg, 0.31 mmol), *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (58.6 mg, 0.31 mmol) and (3*S*)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (53.9 mg, 0.28 mmol). The reaction mixture was stirred at 25 °C for 1 h and concentrated to dryness *in vacuo*.

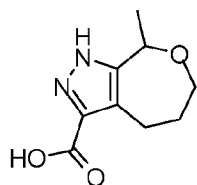
The residue was purified by RP-HPLC (50-80% methanol in water and 0.05% ammonia) to afford

7-methyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide (20 mg, 21% yield) as a white solid: ^1H NMR (400MHz, DMSO- d_6) δ 12.92 (s, 1H), 8.00 - 7.97 (m, 1H), 7.49 - 7.47 (m, 1H), 7.32 - 7.28 (m, 2H), 7.24 - 7.23 (m, 1H), 4.84 - 4.79 (m, 1H), 4.50 - 4.44 (m, 1H), 4.42 - 4.39 (m, 1H), 4.05 - 4.01 (m, 1H), 3.61 - 3.58 (m, 1H), 3.38 - 3.36 (m, 1H), 3.31 (s, 3H), 3.30 - 3.26 (m, 1H), 2.87 - 2.83 (m, 1H), 2.71 - 2.65 (m, 1H), 2.61 - 2.50 (m, 1H), 1.19 (d, J = 6.4 Hz, 3H).

LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.78 min, ESI+ found $[M+H]^+ = 371.0$.

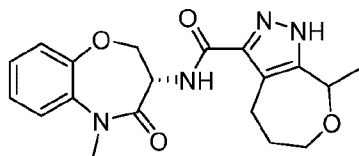


8-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxamide



15 Step 7: 8-methyl-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxylic acid

To a solution of ethyl 8-methyl-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxylate (250 mg, 1.11 mmol) in tetrahydrofuran (5 mL) and water (1 mL) was added lithium hydroxide (267 mg, 11.15 mmol). The mixture was stirred at 20 °C for 20 h and concentrated to dryness *in vacuo*. The residue was diluted with water (30 mL) and adjusted pH = 3 by addition of 1 M hydrochloric acid. The resulting solution was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo* to afford crude 8-methyl-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxylic acid (200 mg, 91% yield) as a white solid: LCMS (0 to 60% acetonitrile in water + 0.03% trifluoroacetic acid over 2.0 mins) retention time 1.26 min, ESI+ found $[M+H]^+ = 197.2$.



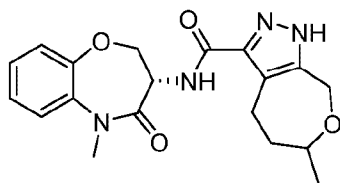
Step

8:

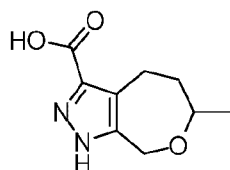
8-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxamide

To a solution of 8-methyl-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxylic acid (70.0 mg, 0.35 mmol) in N,N-dimethylformamide (5 mL) was added 1H-benzo[d][1,2,3]triazol-1-ol (57.9 mg, 0.43 mmol), N¹-((ethylimino)methylene)-N³,N³-dimethylpropane-1,3-diamine hydrochloride (82.1 mg, 0.43 mmol), and (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (75.4 mg, 0.39 mmol). The reaction mixture was stirred at 25 °C for 1 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (21-51% acetonitrile in water and 0.05% ammonia) to afford

8-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxamide (65 mg, 49% yield) as a white solid: ¹H NMR (400MHz, DMSO-d₆) δ 12.90 (s, 1H), 8.00 (br. s, 1H), 7.50 - 7.47 (m, 1H), 7.33 - 7.28 (m, 2H), 7.26 - 7.24 (m, 1H), 4.84 - 4.81 (m, 1H), 4.63 - 4.60 (m, 1H), 4.48 - 4.39 (m, 2H), 4.09 - 4.07 (m, 1H), 3.73 - 3.70 (m, 1H), 3.32 (s, 3H), 3.20 - 3.17 (m, 1H), 2.70 - 2.65 (m, 1H), 1.78 - 1.70 (m, 1H), 1.62 - 1.59 (m, 1H), 1.48 (d, *J* = 6.8 Hz, 3H). LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.78 min, ESI+ found [M+H] = 371.0.



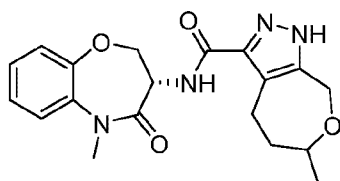
20

6-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxamide**Step 9: 6-methyl-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxylic acid**

To a solution of ethyl 6-methyl-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxylate (250 mg, 1.11 mmol) in tetrahydrofuran (5 mL) and water (1 mL) was added lithium hydroxide (267 mg, 11.15 mmol). The mixture was stirred at 20 °C for 20 h and concentrated to dryness *in vacuo*. The residue was diluted with water (30 mL) and adjusted pH = 3 by addition of 1 M hydrochloric acid. The resulting solution was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo*

30

to afford the crude 6-methyl-4,5,6,8-tetrahydro-1*H*-oxepino[3,4-*c*]pyrazole-3-carboxylic acid (200 mg, 91% yield) as a white solid: LCMS (0 to 60% acetonitrile in water + 0.03% trifluoroacetic acid over 2.0 mins) retention time 1.27 min, ESI+ found [M+H]⁺=197.2.



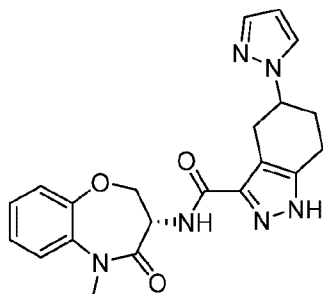
5 Step 10:

6-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,8-tetrahydro-1*H*-oxepino[3,4-*c*]pyrazole-3-carboxamide

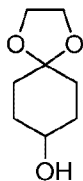
To a solution of 6-methyl-4,5,6,8-tetrahydro-1*H*-oxepino[3,4-*c*]pyrazole-3-carboxylic acid (70.0 mg, 0.35 mmol) in N,N-dimethylformamide (5 mL) was added
 10 1*H*-benzo[d][1,2,3]triazol-1-ol (57.9 mg, 0.43 mmol),
*N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (82.1 mg, 0.43 mmol) and (3*S*)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (75.4 mg, 0.39 mmol). The reaction mixture was stirred at 25 °C for 1 h and concentrated to dryness *in vacuo*.
 The residue was purified by RP-HPLC (23-53% acetonitrile in water and 0.05% ammonia) to
 15 afford

6-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,8-tetrahydro-1*H*-oxepino[3,4-*c*]pyrazole-3-carboxamide (62 mg, 47% yield) as a white solid: ¹H NMR (400MHz, DMSO-*d*₆) δ 8.05 - 8.03 (m, 1H), 7.50 - 7.47 (m, 1H), 7.33 - 7.23 (m, 3H), 4.84 - 4.80 (m, 1H), 4.70 (d, *J* = 14.8 Hz, 1H), 4.49 - 4.40 (m, 3H), 3.78 - 3.74 (m, 1H), 3.31 (s, 3H), 3.30 - 3.24 (m, 1H), 2.49 - 2.47 (m, 1H), 1.83 - 1.78 (m, 1H), 1.41 - 1.32 (m, 1H), 1.15 (d, *J* = 6.0 Hz, 3H). LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.79 min, ESI+ found [M+H]⁺=371.1.

Example 20: Method R

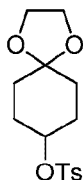


25 N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(1*H*-pyrazol-1-yl)-4,5,6,7-tetrahydro-1*H*-indazole-3-carboxamide



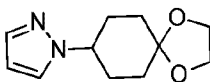
Step 1: 1,4-dioxaspiro[4.5]decan-8-ol

To a solution of 1,4-dioxaspiro[4.5]decan-8-one (10.0 g, 64.0 mmol) in methanol (150 mL) was added sodium borohydride (2.5 g, 66.1 mmol) at 0 °C. The mixture was warmed to 20 °C for 3 h and then poured into water (150 mL). The resulting mixture was extracted with dichloromethane (3 x 200 mL). The combined organic phases were filtered through a cotton plug, and the filtrate was concentrated to dryness *in vacuo* to afford 1,4-dioxaspiro[4.5]decan-8-ol (7.0 g, 69% yield) used without further purification in the next step: ¹H NMR (400 MHz, CDCl₃) δ 3.95 - 3.91 (m, 4H), 3.80 - 3.77 (m, 1H), 1.87 - 1.80 (m, 4H), 1.69 - 1.56 (m, 5H).



Step 2: 1,4-dioxaspiro[4.5]decan-8-yl 4-methylbenzenesulfonate

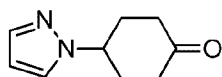
A solution of 1,4-dioxaspiro[4.5]decan-8-ol (7.0 g, 44.25 mmol) in pyridine (70 mL) was treated with 4-methylbenzenesulfonyl chloride (10.1 g, 53.1 mmol). The reaction mixture was stirred at 20 °C for 16 h and then quenched by addition of brine (50 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The combined organics were washed with 0.5 M HCl (100 mL), saturated aqueous sodium bicarbonate (100 mL), brine (100 mL), dried over sodium sulfate and concentrated to dryness *in vacuo* to afford 1,4-dioxaspiro[4.5]decan-8-yl 4-methylbenzenesulfonate (10.0 g, 72.3% yield) as a clear liquid used without further purification in the next step: ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 4.63 - 4.60 (m, 1H), 3.93 - 3.86 (m, 4H), 2.42 (s, 3H), 1.84 - 1.76 (m, 6H), 1.54 - 1.50 (m, 2H).



Step 3: 1-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-pyrazole

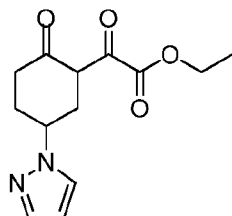
To a mixture of sodium hydride (60%, 0.97 g, 24.24 mmol) in N,N-dimethylformamide (5 mL) was slowly added 1H-pyrazole (1.65 g, 24.24 mmol) at 0° C. The reaction mixture stirred for 30 min, and 1,4-dioxaspiro[4.5]decan-8-yl 4-methylbenzenesulfonate (6.26 g, 20.03 mmol) was added. After addition, the reaction mixture was stirred at 0° C for 10 min and at 60° C for 5 h. The reaction mixture was cooled and quenched by addition of water (30 mL). The mixture

was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 50% ethyl acetate in petroleum ether) to afford 1-(1,4-dioxaspiro[4.5]dec-8-yl)-1H-pyrazole (2.0 g, 48% yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 7.73 (d, *J* = 2.0 Hz, 1H), 7.41 (d, *J* = 1.6 Hz, 1H), 6.20 (t, *J* = 2.0 Hz, 1H), 4.29 - 4.21 (m, 1H), 3.87 - 3.90 (m, 4H), 1.98 - 1.93 (m, 4H), 1.75 - 1.65 (m, 4H).



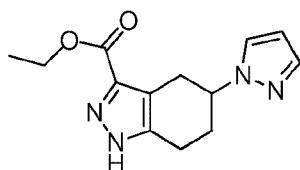
Step 4: 4-(1H-pyrazol-1-yl)cyclohexanone

- 10 A solution of 1-(1,4-dioxaspiro[4.5]dec-8-yl)-1H-pyrazole (2.0 g, 9.60 mmol) and 36 % HCl (4.9 g, 48.02 mmol) in THF (20 ml) was stirred at ambient temperature for 20 h. The mixture was diluted with water (30 mL) and then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo* to afford crude 4-(1H-pyrazol-1-yl)cyclohexanone (1.5 g, 95% yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 7.81 (d, *J* = 2.4 Hz, 1H), 7.45 (d, *J* = 1.6 Hz, 1H), 6.26 (t, *J* = 1.8 Hz, 1H), 4.74 - 4.67 (m, 1H), 2.59 - 2.52 (m, 2H), 2.33 - 2.17 (m, 6H).



Step 5: ethyl 2-oxo-2-(2-oxo-5-(1H-pyrazol-1-yl)cyclohexyl)acetate

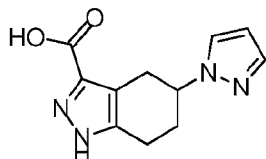
- 20 To a solution of 4-pyrazol-1-ylcyclohexanone (1.2 g, 7.31 mmol) in ethanol (15 mL) was added a solution of sodium ethanoxide in ethanol (10 mL) at 0 °C. The reaction mixture was stirred for further 10 min and diethyl oxalate (1.1 g, 7.31 mmol) was added. The resulting mixture was stirred at RT for 20 h and concentrated to dryness *in vacuo* to afford ethyl 2-oxo-2-(2-oxo-5-pyrazol-1-yl-cyclohexyl)acetate (2.0 g, over 100% yield) as a yellow solid use in the next step without further purification.



Step 6: ethyl 5-(1H-pyrazol-1-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

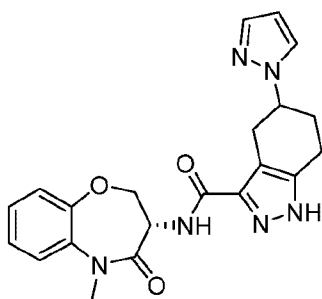
To a solution of ethyl 2-oxo-2-(2-oxo-5-pyrazol-1-yl-cyclohexyl)acetate (1.90 g, 7.19 mmol) in acetic acid (10 mL) was added 50% hydrazine in water (0.52 g, 8.04 mmol) at 0 °C. The

mixture was stirred at 25 °C for 1 h and then quenched by addition of saturated aqueous sodium bicarbonate. The mixture was extracted with methanol/dichloromethane (3 x 50 mL, 1:10). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% ethyl acetate in petroleum ether) to afford ethyl 5-(1H-pyrazol-1-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (1.0 g, 53% yield) as a yellow solid: LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.61 min, ESI+ found [M+H] = 260.9.



10 Step 7: 5-(1H-pyrazol-1-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid

To a solution of ethyl 5-(1H-pyrazol-1-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (200 mg, 0.77 mmol) in tetrahydrofuran (5 mL) and water (1 mL) was added lithium hydroxide (92 mg, 3.83 mmol). The mixture was stirred at RT for 20 h and concentrated to dryness *in vacuo*. The residue was diluted with water (10 mL) and then adjusted to pH = 3 by addition of 1 N hydrochloric acid. The solution was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo* to afford 5-(1H-pyrazol-1-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (100 mg, 56% yield) as a white solid: LCMS (0 to 60% acetonitrile in water + 0.03% trifluoroacetic acid over 3 mins) retention time 1.36 min, ESI+ found [M+H] = 233.2.



20 Step 8:

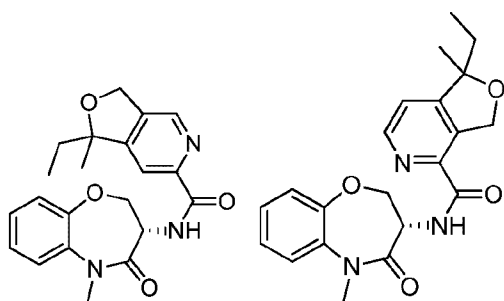
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(1H-pyrazol-1-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide

To a solution of 1H-benzo[d][1,2,3]triazol-1-ol (49 mg, 0.36 mmol) in N,N-dimethylformamide (5 mL) was added N¹-((ethylimino)methylene)-N³,N³-dimethylpropane-1,3-diamine hydrochloride (69 mg, 0.36 mmol), 6,6-dimethyl-1,4,5,8-tetrahydrooxepino[3,4-c]pyrazole-3-carboxylic acid (63 mg, 0.30 mmol) and (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (64 mg, 0.33 mmol).

The reaction mixture was stirred at RT for 1 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (28-58% acetonitrile in water and 0.05% ammonia) to afford

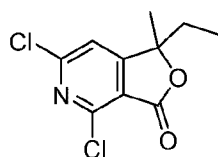
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(1H-pyrazol-1-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide (60 mg, 49% yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 13.00 (br. s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 2.0 Hz, 1H), 7.50 - 7.42 (m, 2H), 7.35 - 7.19 (m, 3H), 6.26 - 6.18 (m, 1H), 4.87 - 4.77 (m, 1H), 4.62 - 4.46 (m, 2H), 4.44 - 4.36 (m, 1H), 3.31 (s, 3H), 3.20 - 3.10 (m, 1H), 2.98 - 2.65 (m, 3H), 2.25 - 2.09 (m, 2H). LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.78 min, ESI+ found [M+H]⁺ = 407.1.

10 Example 21: Method S



1-ethyl-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide and

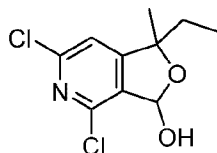
1-ethyl-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-4-carboxamide



Step 1: 4,6-dichloro-1-ethyl-1-methylfuro[3,4-c]pyridin-3(1H)-one

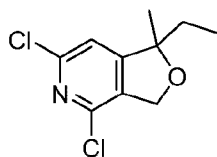
n-BuLi (2.5 M in hexane, 16 mL, 40 mmol) was added dropwise to a solution of diisopropylamine (4.7 g, 46.5 mmol) at -78 °C. The mixture was stirred at -78 °C for 40 min and a solution of 2,6-dichloronicotinic acid (3 g, 15.6 mmol) in tetrahydrofuran (30 mL) was added dropwise to the reaction mixture at -78 °C and the resultant mixture was stirred at -78 °C for 3 h. Butanone (10 g, 139 mmol) was added dropwise to the reaction mixture at -78 °C and the reaction mixture was warmed slowly to RT and stirred for 16 h. The reaction mixture was cooled to 0 °C, quenched with sat. ammonium chloride to pH 7 and acidified with 3 N HCl to pH 4. The mixture was extracted with ethyl acetate (30 mL x 4). The combined organic layers were combined, dried over sodium sulphate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 8 : 1 to 6 : 1 to 4 : 1 ethyl

acetate : petroleum ether) to afford 4,6-dichloro-1-ethyl-1-methylfuro[3,4-c]pyridin-3(1H)-one as a brown solid (1.3 g, Yield 34%). LCMS: m/z = 246.0/ 248.1 [M+1]. Column: MERCK RP18 (50-3). Mobile phase: H₂O(0.01%TFA) (A) / ACN(0.01% TFA)(B) Elution program: Gradient from 10 to 95% of B in 1.8min at 2.0ml/min. Temperature: 45°C. 3 min gradient.



Step 2: 4,6-dichloro-1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridin-3-ol

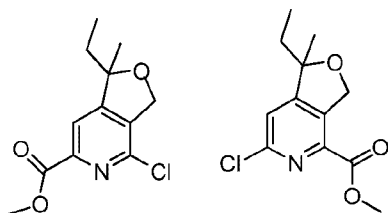
To a stirred suspension of 4,6-dichloro-1-ethyl-1-methylfuro[3,4-c]pyridin-3(1H)-one (1.3 g, 5.28 mmol) in toluene (30 mL) was added diisobutyl aluminium hydride (1 M in toluene, 12 mL, 12 mmol) at -78°C. The reaction mixture was stirred at -78°C for 1.5 h and quenched with saturated ammonium chloride (50 mL) dropwise at -78°C. The mixture was warmed slowly to RT and stirred for 30 min. The reaction mixture was filtered and the filtrate was extracted with ethyl acetate (30 mL x 3). The combined organic layers were combined, dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 4 : 1 to 2 : 1 ethyl acetate : petroleum ether) to afford 4,6-dichloro-1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridin-3-ol (1 g, Yield 76%) as a colorless oil. LCMS: m/z = 248.0/ 250.1 [M+1]. Column: MERCK RP18 (50-3). Mobile phase: H₂O(0.01%TFA) (A) / ACN(0.01% TFA)(B) Elution program: Gradient from 10 to 95% of B in 1.8min at 2.0ml/min. Temperature: 45°C. 3 min gradient.



Step 3: 4,6-dichloro-1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine

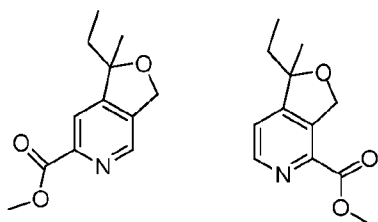
To a stirred solution of 4,6-dichloro-1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridin-3-ol (1 g, 4.06 mmol) in dichloromethane (10 mL) was added dropwise trifluoroacetic acid (1.5 mL, 20.1 mmol) at 0°C and the mixture was stirred at 0°C for 30 min. Triethylsilane (2 mL, 12.55 mmol) was added dropwise to the reaction mixture at 0°C and the reaction mixture was warmed slowly to RT and stirred at RT for 2 h. The reaction mixture was concentrated to dryness *in vacuo*. The residue was dissolved in ethyl acetate (50 mL) and adjusted to pH = 7 by addition of saturated sodium bicarbonate. The ethyl acetate layer was separated, dried over sodium sulphate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 8 : 1 ethyl acetate : petroleum ether) to afford 4,6-dichloro-1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine (0.83 g, Yield 88%) was got as

a white solid. LCMS: m/z = 232.1/ 234.1 [M+1]. Column: MERCK RP18 (50-3). Mobile phase: H₂O(0.01%TFA) (A) / ACN(0.01% TFA)(B) Elution program: Gradient from 10 to 95% of B in 1.8min at 2.0ml/min. Temperature: 45°C. 3 min gradient.



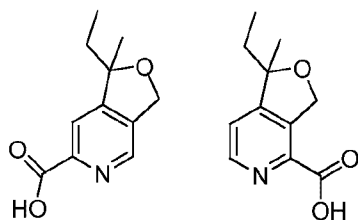
5 **Step 1: methyl 4-chloro-1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine-6-carboxylate and methyl 6-chloro-1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine-4-carboxylate**

To a solution of 4,6-dichloro-1-ethyl-1-methyl-3H-furo[3,4-c]pyridine (0.50 g, 2.15 mmol) in methanol (10 mL) was added [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.16 g, 0.22 mmol) and triethylamine (2.18 g, 21.54 mmol). The reaction mixture was stirred at 80 °C for 15 h under the carbon monoxide (25 psi). After cooling to RT the reaction mixture was concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 30% ethyl acetate in petroleum ether) to afford methyl 4-chloro-1-ethyl-1-methyl-3H-furo[3,4-c]pyridine-6-carboxylate and methyl 6-chloro-1-ethyl-1-methyl-3H-furo[3,4-c]pyridine-4-carboxylate (140 mg (3:1 mixture), 0.55 mmol, 25.5% yield mixture) as a light yellow oil used as is in the next step without further purification.



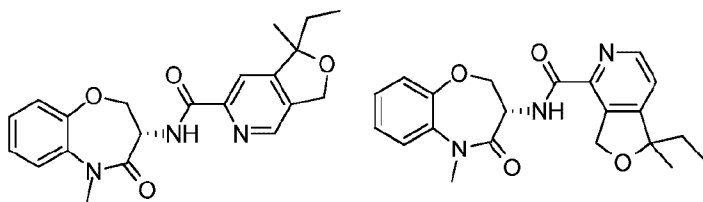
Step 2: methyl 1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine-6-carboxylate and methyl 1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine-4-carboxylate

20 To a solution of methyl 4-chloro-1-ethyl-1-methyl-3H-furo[3,4-c]pyridine-6-carboxylate and methyl 6-chloro-1-ethyl-1-methyl-3H-furo[3,4-c]pyridine-4-carboxylate (140 mg, 0.55 mmol) in methanol (10 mL) was added 10% palladium (437 mg, 0.41 mmol) on carbon. The reaction mixture was hydrogenated (15 psi) at 20 °C for 1 h and then filtered through Celite. The filtrate was concentrated to dryness *in vacuo* to afford methyl 1-ethyl-1-methyl-3H-furo[3,4-c]pyridine-4-carboxylate and methyl 1-ethyl-1-methyl-3H-furo[3,4-c]pyridine-6-carboxylate (100 mg, 82.6% yield) as a yellow oil: LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.65 min, ESI+ found [M+H] = 222.



Step 3: 1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine-6-carboxylic acid and 1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine-4-carboxylic acid

To a solution of methyl 1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine-6-carboxylate and methyl 1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine-4-carboxylate (100 mg, 0.46 mmol) in tetrahydrofuran (5 mL) and water (5 mL) was added lithium hydroxide monohydrate (202 mg, 4.81 mmol). The reaction mixture was stirred at 15 °C for 15 h and concentrated to dryness *in vacuo*. The residue was diluted with water (5 mL) and adjusted to pH = 3 by addition of 1 M hydrochloric acid. The mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo* to afford 1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine-6-carboxylic acid and 1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine-4-carboxylic acid (50 mg, 50.5 % yield) as a yellow oil used in the next step without further purification.



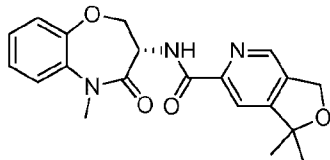
Step 4: 1-ethyl-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide and 1-ethyl-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-4-carboxamide

To a solution of 1-ethyl-1-methyl-3H-furo[3,4-c]pyridine-6-carboxylic acid and 1-ethyl-1-methyl-3H-furo[3,4-c]pyridine-4-carboxylic acid (3:1 mixture, 41 mg, 0.20 mmol) in N,N-dimethylformamide (5 mL) was added *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (59 mg, 0.31 mmol), (3*S*)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (50 mg, 0.26 mmol) and 1*H*-benzo[d][1,2,3]triazol-1-ol (35 mg, 0.26 mmol). The reaction mixture was stirred at 15 °C for 1 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (40-70% acetonitrile in water and 0.05% ammonia hydroxide) to afford:

1-ethyl-1-methyl-N-[(3*S*)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-3H-furo[3,4-c]pyridine-6-carboxamide (15 mg, 20.7% yield) as white solid and

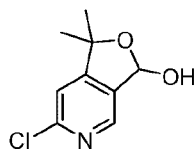
1-ethyl-1-methyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-3H-furo[3,4-c]pyridine-4-carboxamide (7 mg, 9.6% yield) as a white solid: ^1H NMR (400MHz, CD_3OD) δ 8.57 (s, 1H), 7.86 (s, 1H), 7.45 - 7.43 (m, 1H), 7.39 - 7.29 (m, 2H), 7.26 - 7.25 (m, 1H), 5.16 (d, $J = 3.6$ Hz, 2H), 5.05 - 5.00 (m, 1H), 4.67 - 4.62 (m, 1H), 4.41 (t, $J = 9.6$, 1H), 3.43 (s, 3H), 1.88 - 1.82 (m, 2H), 1.46 (s, 3H), 0.77 (t, $J = 7.2$, 3H); LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) $R_T = 0.87$ min, $m/z = 382.0$ $[\text{M} + \text{H}]^+$ and ^1H NMR (400MHz, CD_3OD) δ 8.60 (d, $J = 5.6$ Hz, 1H), 7.45 - 7.42 (m, 2H), 7.34 - 7.24 (m, 3H), 5.33 - 5.28 (m, 2H), 5.02 - 4.97 (m, 1H), 5.16 (d, $J = 3.6$ Hz, 2H), 5.05 - 5.00 (m, 1H), 4.63 (t, $J = 10.0$ Hz, 1H), 4.41 (t, $J = 9.6$ Hz, 1H), 3.43 (s, 3H), 1.87 - 1.81 (m, 2H), 1.45 (s, 3H), 0.75 (t, $J = 7.6$ Hz, 3H); LCMS (10 to 80% acetonitrile in water + 0.03% trifluoroacetic acid over 2.0 mins) $R_T = 1.17$ min, $m/z = 382.3$ $[\text{M} + \text{H}]^+$.

Example 22: Method T



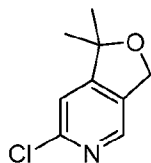
(S)-1,1-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide

6-chloro-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one and similar starting materials for Method T are commercially purchased or prepared according to exemplary procedures shown in: WO 2005080342 A1; WO 2005074939 A1; and WO 2004029026 A1.



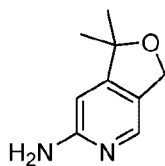
Step 1: 6-chloro-1,1-dimethyl-1,3-dihydrofuro[3,4-c]pyridin-3-ol

A stirred solution of 6-chloro-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one (18.5 g, 0.09362 mol) in dry toluene (300 mL) at RT under nitrogen was cooled to -70°C was added dropwise diisobutylaluminum hydride (197.24 mL, 0.18724 mol, 1M in Toluene) and the reaction mixture and allowed to stir at -70°C for 3h. The reaction mixture was quenched with saturated ammonium chloride solution and filtered. The filtrate was extracted with ethyl acetate (2x 200 mL) and the combined organic layer was washed the water, brine, dried over anhydrous sodium sulphate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 30% ethyl acetate : petroleum ether) to afford 6-chloro-1,1-dimethyl-1,3-dihydrofuro[3,4-c]pyridin-3-ol (17.5g, 94%): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.4 (s, 1H), 7.65 (s, 1H), 7.2- 6.40 br., s, 1H), 6.35 (s, 1H), 1.35 (s, 3H), 1.23 (s, 3H).



Step 2: 6-chloro-1,1-dimethyl-1,3-dihydrofuro[3,4-c]pyridine

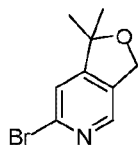
6-chloro-1,1-dimethyl-1,3-dihydrofuro[3,4-c]pyridin-3-ol (17.5 g, 0.0877 mol) was dissolved in dry dichloromethane and cooled to 0°C under nitrogen. To the stirred solution was added dropwise trifluoroacetic acid (32.66 ml 0.438 mol.) and stirred for 30 min at 0°C. Triethyl silane (42.47 ml, 0.263 mol) was added to the reaction mixture at 0°C and stirred at RT for 3h. The reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with dichloromethane (2 x 200 mL). The combined organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 30% ethyl acetate : petroleum ether) to afford 6-chloro-1,1-dimethyl-1,3-dihydrofuro[3,4-c]pyridine (15.2 g, 94%): LCMS $R_T = 1.55$ min, $m/z = 184.04$ $[M + H]^+$. Column : Acquity UPLC BEH C-18 (2.1X50 mm) 1.7 μ ; MP :A: 0.05%FA in Water, B: 0.05%FA in Acetonitrile; T/%B : 0/10,0.5/10, 1/35, 1.5/45, 2.3/90, 3.2/90, 3.6/10, 4/10; Flow : 0.55 mL; Diluent : ACN+WATER(70:30); Column temp :35°C.



Step 3: 1,1-dimethyl-1,3-dihydrofuro[3,4-c]pyridin-6-amine

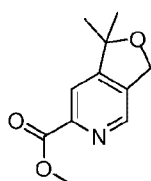
To a stirred solution of 6-chloro-1,1-dimethyl-1,3-dihydrofuro[3,4-c]pyridine (15.0 g, 0.082 mol) in dry tetrahydrofuran was added benzophenone imine (15.39 g, 0.085 mol.) and cesium carbonate (39.92g, 0.12254) under a nitrogen atmosphere. The resulting solution was degassed with nitrogen for 10 min and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (1.88g, 0.003 mol) and palladium(II) acetate (0.440 g, 0.002 mol.) were added under a nitrogen atmosphere. Reaction mixture was heated at reflux for 11 h. Reaction was cooled to RT, filtered through Celite and washed with ethyl acetate. The filtrate was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated to dryness *in vacuo*. The residue was dissolved in tetrahydrofuran, cooled to 0°C and 2N HCl (30 mL) was added to reaction mixture and stirred at to RT for 3 h. The reaction mixture was poured into water, extracted with ether and the aqueous layer was adjusted to pH = 8 by addition of sodium bicarbonate. The mixture was extracted with ethyl acetate (2 x 200mL), dried over anhydrous sodium sulphate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 5% methanol in dichloromethane) to afford

1,1-dimethyl-1,3-dihydrofuro[3,4-c]pyridin-6-amine (3g, 29%) as a white solid: LCMS R_T = 1.09 min, m/z = 165.11 $[M + H]^+$.



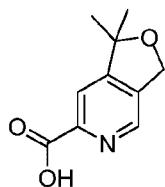
Step 4: 6-bromo-1,1-dimethyl-1,3-dihydrofuro[3,4-c]pyridine

- 5 To a solution of 1,1-dimethyl-3H-furo[3,4-c]pyridin-6-amine (200 mg, 1.22 mmol) in hydrobromic acid (0.06 mL, 1.22 mmol) was added sodium nitrite (210 mg, 3.05 mmol) in water (0.2 mL) and bromine (0.12 mL, 2.44 mmol) at -25 °C. The reaction was stirred at -25 °C for 1 h and warmed to 15 °C over 30 min. The solution was diluted with 5 M sodium hydroxide (20 mL) and extracted with dichloromethane (3 x 20mL). The combined organic layer were
10 dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 50% ethyl acetate in petroleum ether) to afford 6-bromo-1,1-dimethyl-3H-furo[3,4-c]pyridine (150 mg, 54% yield) as a colorless oil use in the next step without further purification.



Step 5: methyl 1,1-dimethyl-1,3-dihydrofuro[3,4-c]pyridine-6-carboxylate

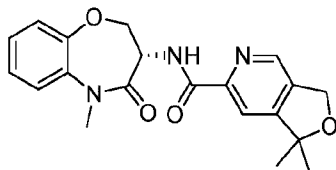
- To a solution of 6-bromo-1,1-dimethyl-3H-furo[3,4-c]pyridine (150 mg, 0.66 mmol) in methanol (10 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (48 mg, 0.07 mmol) and triethylamine (665 mg, 6.58 mmol). The reaction mixture was stirred at 80 °C for 15 h under the carbon monoxide (25 psi). The reaction mixture was concentrated
20 to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 50% ethyl acetate in petroleum ether) to afford methyl 1,1-dimethyl-3H-furo[3,4-c]pyridine-6-carboxylate (100 mg, 73.4% yield) as a pale yellow oil: LCMS (10 to 80% acetonitrile in water + 0.03% trifluoroacetic acid over 2.0 mins) retention time 0.97 min, ESI+ found $[M+H] = 208.2$.



25

Step 6: 1,1-dimethyl-1,3-dihydrofuro[3,4-c]pyridine-6-carboxylic acid

To a solution of methyl 1,1-dimethyl-3H-furo[3,4-c]pyridine-6-carboxylate (100 mg, 0.48 mmol) in tetrahydrofuran (5 mL) and water (5 mL) was added lithium hydroxide monohydrate (202 mg, 4.83 mmol). The reaction mixture was stirred at 15 °C for 15 h and then concentrated to dryness *in vacuo*. The residue was diluted with water (5 mL) and then adjusted to pH = 3 by addition of 1 M hydrochloric acid. The mixture was extracted with dichloromethane (3 × 15 mL). The combined layers were dried over sodium sulfate and concentrated to afford crude 1,1-dimethyl-3H-furo[3,4-c]pyridine-6-carboxylic acid (50 mg, 53.9% yield) as a yellow oil used in the next step without further purification.

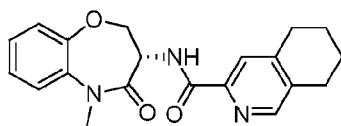


Step 7:

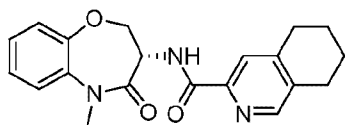
S)-1,1-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide

To a solution of (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (50 mg, 0.26 mmol) in N,N-dimethylformamide (5 mL) was added 1,1-dimethyl-3H-furo[3,4-c]pyridine-6-carboxylic acid (56 mg, 0.29 mmol), *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (60 mg, 0.31 mmol) and 1*H*-benzo[d][1,2,3]triazol-1-ol (42 mg, 0.31 mmol). The reaction mixture was stirred at 15 °C for 1 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (35-65% acetonitrile in water and 0.05% ammonia hydroxide) to afford 1,1-dimethyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-3H-furo[3,4-c]pyridine-6-carboxamide (18 mg, 18.8% yield) as a white solid: ¹H NMR (400MHz, CD₃OD) δ 8.57 (s, 1H), 7.91 (s, 1H), 7.44 - 7.43 (m, 1H), 7.34 - 7.31 (m, 2H), 7.26 - 7.25 (m, 1H), 5.15 (s, 2H), 5.05 - 5.00 (m, 1H), 4.65 - 4.62 (m 1H), 4.43 - 3.98 (m, 1H), 3.43 (s, 3H), 1.49 (s, 6H). LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.84 min, ESI+ found [M+H]⁺=368.0.

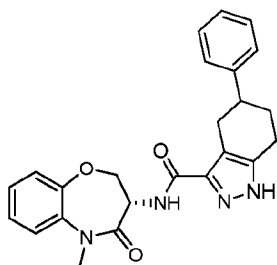
Example 23: Method U



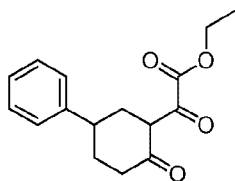
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroisoquinoline-3-carboxamide

**Step 1:****(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroisoquinoline-3-carboxamide**

- 5 To a solution of 5,6,7,8-tetrahydroisoquinoline-3-carboxylic acid (80 mg, 0.45 mmol) in N,N-dimethylformamide (5 mL) was added (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (96 mg, 0.50 mmol), N^1 -((ethylimino)methylene)- N^3,N^3 -dimethylpropane-1,3-diamine hydrochloride (104 mg, 0.54 mmol) and 1-hydroxybenzotriazole (73 mg, 0.54 mmol). The reaction mixture was stirred at
- 10 RT for 12 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (0-40% acetonitrile in water and 0.1% ammonia hydroxide) to afford (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroisoquinoline-3-carboxamide (26 mg, 16.5% yield) as white solid: ^1H NMR (400MHz, CD_3OD) δ 8.32 (s, 1H), 7.71 (s, 1H), 7.43 (d, $J = 6.0$ Hz, 1H), 7.37 - 7.19 (m, 3H), 5.02 - 4.97 (m, 1H),
- 15 4.64 - 4.60 (m, 1H), 4.37 (t, $J = 10.8$ Hz, 1H), 3.42 (s, 3H), 2.83 - 2.81 (m, 4H), 1.87 - 1.82 (m, 4H). LCMS (10- 80% acetonitrile in water + 0.03% trifluoroacetic over 2 mins) retention time 1.15 min, ESI+ found $[\text{M}+\text{H}] = 352.2$.

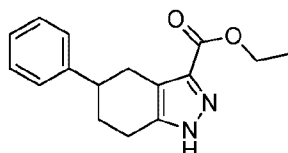
Example 24: Method V

- 20 **N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide**

**Step 1: ethyl 2-oxo-2-(2-oxo-5-phenylcyclohexyl)acetate**

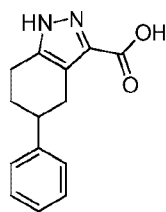
- To a solution of 4,4-dimethylcyclohexanone (2.50 g, 19.8 mmol) in ethanol (30 mL) was added
- 25 a solution of sodium ethoxide (1.48 g, 21.8 mmol) in ethanol (30 mL), followed by diethyl oxalate (2.9 g, 19.8 mmol) at 0 °C. After addition, the mixture was stirred at 25 °C for 15 h and

concentrated to dryness *in vacuo* to afford crude ethyl 2-oxo-2-(2-oxo-5-phenylcyclohexyl)acetate (5.4 g, 99.4% yield) as a yellow solid used in the next step without further purification.



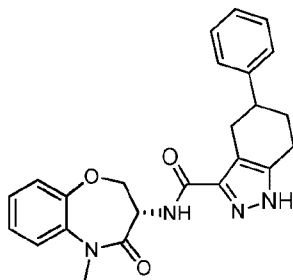
5 **Step 2: ethyl 5-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate**

To a solution of ethyl 2-oxo-2-(2-oxo-5-phenylcyclohexyl)acetate (5.4 g, 19.7 mmol) in glacial acetic acid (5 mL) was added hydrazine hydrate (1.09 g, 21.8 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 h and then adjusted to pH = 8 by addition of aqueous sodium bicarbonate. The resulting solid was collected by filtration and dried to afford crude ethyl 5-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (1.5 g, 28% yield) use in the next step without further purification.



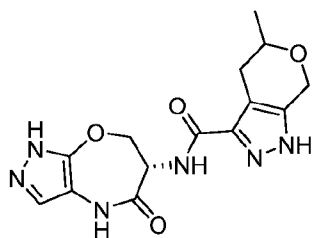
Step 3: 5-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid

To a solution of ethyl 5-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (405 mg, 1.5 mmol) in tetrahydrofuran (8 mL) and water (4 mL) was added lithium hydroxide hydrate (621 mg, 14.8 mmol). The mixture was stirred at 25 °C for 25 h and concentrated to dryness *in vacuo*. The residue was diluted with water (5 mL) and adjusted the pH = 3 by addition of 1 N hydrochloric acid. The resulting solid was collected by filtration and dried to afford crude 5-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (330 mg, 90.9% yield) as white solid: LCMS (5 to 95% acetonitrile in water + 0.03% formic acid over 1.5 mins) retention time 0.77 min, ESI+ found [M+H] = 242.9.



Step 4:**N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide**

To a stirred solution of 5-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (94 mg, 0.39 mmol) in N,N-dimethylformamide (5 mL) was added (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (50 mg, 0.26 mmol), 1-hydroxybenzotriazole (53 mg, 0.39 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimidehydrochloride (75 mg, 0.39 mmol). The mixture was stirred at 20 °C for 1 h and then concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (42-72% acetonitrile in water and 0.05% ammonia hydroxide) to afford N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide (73 mg, 67.6% yield) as white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 12.95 (s, 1H), 7.97 - 7.95 (m, 1H), 7.48 - 7.45 (m, 1H), 7.33 - 7.25 (m, 6H), 7.23 - 7.17 (m, 2H), 4.85 - 4.78 (m, 1H), 4.54 - 4.47 (m, 1H), 4.42 - 4.37 (m, 1H), 3.31 (s, 3H), 2.98 - 2.92 (m, 1H), 2.88 - 2.83 (m, 1H), 2.72 - 2.67 (m, 2H), 2.56 - 2.53 (m, 1H), 1.98 - 1.89 (m, 2H). LCMS (10 to 80% acetonitrile in water + 0.03% trifluoroacetic acid over 3 mins) retention time 1.19 min, ESI+ found [M+H] = 417.3.

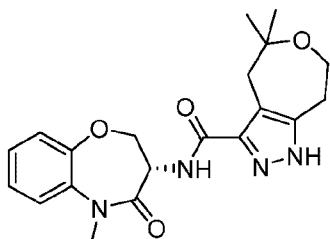
Example 25: Method W**5-methyl-N-((S)-5-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-b][1,4]oxazepin-6-yl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide**

To a solution of (S)-6-amino-6,7-dihydro-1H-pyrazolo[3,4-b][1,4]oxazepin-5(4H)-one 2,2,2-trifluoroacetate (70 mg, 0.25 mmol) in N,N-dimethylformamide (5 mL) was added 1H-benzo[d][1,2,3]triazol-1-ol (41 mg, 0.30 mmol), 5-methyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylic acid (55 mg, 0.30 mmol), and N¹-((ethylimino)methylene)-N³,N³-dimethylpropane-1,3-diamine hydrochloride (57 mg, 0.30 mmol). The reaction mixture was heated at 50 °C for 16 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (0 to 27% acetonitrile in water and 0.05% hydrochloric acid) to afford 5-methyl-N-((S)-5-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-b][1,4]oxazepin-6-yl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide (3.3 mg, 4%) as a white solid: ¹H NMR (400 MHz, CD₃OD) δ 7.52 (s, 1H), 4.91 - 4.74 (m, 3H), 4.58 - 4.54 (m, 1H), 4.39 - 4.35 (m, 1H), 3.75 - 3.71 (m, 1H), 3.00 - 2.88 (m, 1H), 2.55 - 2.51 (m, 1H), 1.36 (d, J = 3.2 Hz, 3H). LCMS

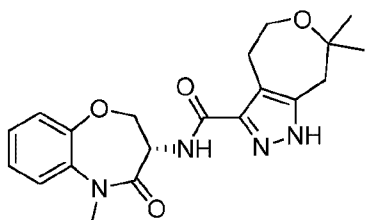
(5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.35 min, ESI+ found $[M+H]^+ = 333.0$.

Example 26: Method X

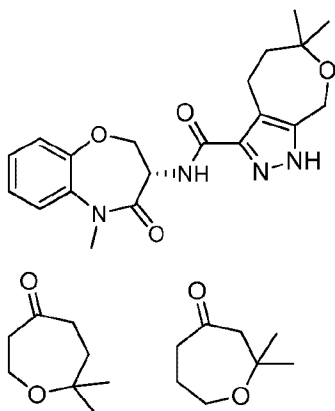
- (S)-5,5-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide



- (S)-7,7-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide



- (S)-6,6-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxamide

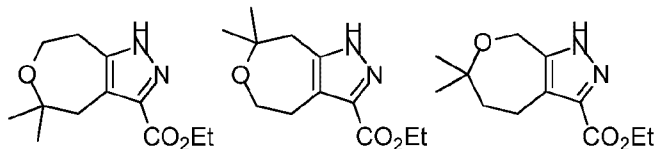


Step 1: 7, 7-dimethyloxepan-4-one and 2, 2-dimethyloxepan-4-one

- To a solution of 2, 2-dimethyltetrahydropyran-4-one (10.4 g, 81.14 mmol) in dichloromethane (40 mL) and boron fluoride ethyl ether (11.2 mL, 48% ethyl ether) was added (diazomethyl)trimethylsilane (48.0 mL, 96.0 mmol, 2 M in hexane) dropwise at -30 °C. After addition, the resulting solution was stirred for 1 h at -30 °C and then quenched by addition of saturated sodium bicarbonate (30 mL). The resulting mixture was extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over anhydrous

sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 18% ethyl acetate in petroleum ether) to afford a mixture of 7,7-dimethyloxepan-4-one and 2,2-dimethyloxepan-4-one (2.6 g, 22.5% yield, ratio 1:1) as a pale yellow oil.

- 5 **Step 2: ethyl 5,5-dimethyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylate; ethyl 7,7-dimethyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylate; ethyl 6,6-dimethyl-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxylate**



- 10 To a solution of 7,7-dimethyloxepan-4-one and 2,2-dimethyloxepan-4-one (2.6 g, 18.3 mmol) and pyrrolidine (85 mg, 1.2 mmol) in dimethyl sulfoxide (20 mL) was slowly added ethyl diazoacetate (1.39 g, 12.2 mmol). After addition, the reaction was stirred at 22 °C for 16 h and poured into water (30 mL). The mixture was then extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water (2 x 30 mL) and brine (30 mL), dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 18% ethyl acetate in petroleum ether) to afford a mixture of three regio-isomers (900 mg, 20.6% yield) as yellow oil. The regio-isomers were separated by SFC to afford:

- Peak 1 (Retention time 3.31 min), ethyl 5,5-dimethyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c] pyrazole-3-carboxylate (200 mg): ¹H NMR (400 MHz, CDCl₃) δ 4.38 - 4.33 (m, 2H), 3.88 (t, *J* = 6.0 Hz, 2H), 3.11 (s, 2H), 2.97 (t, *J* = 6.00 Hz, 2H), 1.37 (t, *J* = 6.00 Hz, 2H), 1.21 (s, 6H)

Peak 2 (Retention time 3.37 min), ethyl 7,7-dimethyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c] pyrazole-3-carboxylate (150 mg) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 4.39 - 4.34 (m, 2H), 3.92 - 3.87 (m, 2H), 3.08 - 3.03 (m, 2H), 2.98 (s, 2H), 1.38 (t, *J* = 6.0 Hz, 3H), 1.23 (s, 6H)

- 25 Peak 3 (Retention time 6.30 min), ethyl 6,6-dimethyl-4,5,6,8-tetrahydro-1H-oxepino[3,4-c] pyrazole-3-carboxylate (150 mg) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 4.68 (s, 2H), 4.40 - 4.35 (m, 2H), 3.00 - 2.92 (m, 2H), 1.95 - 1.88 (m, 2H), 1.39 (t, *J* = 6.0 Hz, 3H), 1.33 (s, 6H).

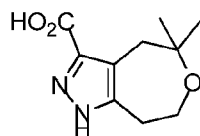
SFC conditions:

- Column: Chiralpak AD-3 150×4.6mm I.D., 3μm Mobile phase: A: CO₂ B: ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min

Flow rate: 2.5mL/min Column temp.: 35°C

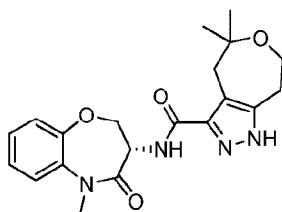
Column: Chiralpak AY 150×4.6mm I.D., 3µm Mobile phase: A: CO₂ B: iso-propanol

(0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min Flow rate: 2.5mL/min Column temp.: 35°C



5 **Step 3: 5,5-dimethyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylic acid**

To a solution of ethyl 5,5-dimethyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylate (200 mg, 0.84 mmol) in tetrahydrofuran (5 mL) and water (1 mL) was added lithium hydroxide (100 mg, 4.20 mmol). The mixture was stirred at 20 °C for 20 h and concentrated to dryness *in vacuo*. The residue was diluted with water (30 mL) and adjusted to pH = 3 by addition of 1 N hydrochloric acid. The solution was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo* to afford 5,5-dimethyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylic acid (160 mg, 90.7% yield) as a white solid: LCMS (0 to 60% acetonitrile in water + 0.03% trifluoroacetic acid over 15 3 mins) retention time 1.76 min, ESI+ found [M+H]⁺=211.2.

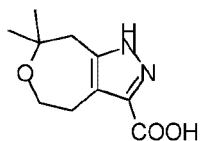


Step 4:

(S)-5,5-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide

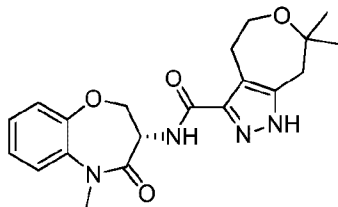
20 To a solution of 1-hydroxybenzotriazole (54 mg, 0.40 mmol) in N,N-dimethylformamide (5 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimidehydrochloride (77 mg, 0.40 mmol) 5,5-dimethyl-1,4,7,8-tetrahydrooxepino[4,5-c]pyrazole-3-carboxylic acid (70 mg, 0.33 mmol) and (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (70 mg, 0.37 mmol). The reaction mixture was stirred at 25 °C for 1 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (26-56% acetonitrile in water and 0.05% ammonia) to afford (S)-5,5-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide (95 mg, 74.9% yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 12.93 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.49 - 7.47 (m, 1H), 7.35 - 7.19 (m, 3H), 4.85 - 4.78 (m, 1H), 4.52 - 4.46 (m, 1H), 4.41 - 4.37 (m, 1H), 3.77 - 3.75 (m, 30

2H), 3.31 (s, 3H), 3.01 (s, 2H), 2.82 - 2.79 (m, 2H), 1.04 (s, 6H). LCMS R_T = 0.80 min, m/z = 385.1 $[M + H]^+$. LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.80 min, ESI+ found $[M+H] = 385.1$.



5 **Step 5: 7,7-dimethyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylic acid**

To a solution of ethyl 7,7-dimethyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylate (150 mg, 0.63 mmol) in tetrahydrofuran (5 mL) and water (1 mL) was added lithium hydroxide (75 mg, 3.15 mmol). The mixture was stirred at 20 °C for 20 h and concentrated to dryness *in vacuo*. The residue was diluted with water (20 mL) and adjusted to pH = 3 by addition of 1 N hydrochloric acid. The solution was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo* to afford 7,7-dimethyl-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxylic acid (95 mg, 71.8% yield) as a white solid: LCMS R_T = 1.80 min, m/z = 211.2 $[M + H]^+$. LCMS (0 to 60% acetonitrile in water + 0.03% trifluoroacetic acid over 3 mins) retention time 1.80 min, ESI+ found $[M+H] = 211.2$.



Step 6:

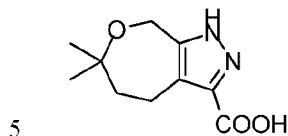
20 **(S)-7,7-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide**

To a solution of 1-hydroxybenzotriazole (39.2 mg, 0.29 mmol) in N,N-dimethylformamide (5 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimidehydrochloride (55.6 mg, 0.29 mmol), 7,7-dimethyl-1,4,5,8-tetrahydrooxepino[4,5-c]pyrazole-3-carboxylic acid (50.0 mg, 0.24 mmol) and (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (50.3 mg, 0.26 mmol). The reaction mixture was stirred at 25 °C for 1 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (26-56% acetonitrile in water and 0.05% ammonia) to afford

(S)-7,7-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide (65 mg, 70.5% yield) as a white solid: ^1H NMR (400 MHz, DMSO- d_6) δ 12.91 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.50 - 7.48 (m, 1H),

7.36 - 7.19 (m, 3H), 4.85 - 4.78 (m, 1H), 4.54 - 4.37 (m, 2H), 3.73 - 3.71 (m, 2H), 3.31 (s, 3H), 2.89 - 2.79 (m, 4H), 1.12 (s, 3H), 1.11 (s, 3H). LCMS $R_T = 0.79$ min, $m/z = 385.1$ $[M + H]^+$.

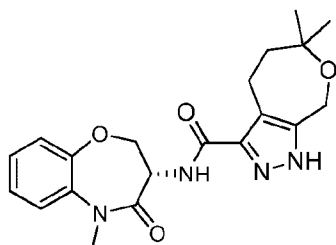
LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.79 min, ESI+ found $[M+H] = 385.1$.



Step 7: 6,6-dimethyl-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxylic acid

To a solution of ethyl 6,6-dimethyl-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxylate (100 mg, 0.42 mmol) in tetrahydrofuran (5 mL) and water (1 mL) was added lithium hydroxide (50 mg, 2.10 mmol). The mixture was stirred at 23 °C for 20 h and concentrated to dryness *in vacuo*. The residue was diluted with water (20 mL) and adjusted to pH = 3 by addition of 1 N hydrochloric acid. The solution was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo* to afford crude 6,6-dimethyl-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxylic acid (70 mg, 79.3% yield) as a white solid: LCMS $R_T = 1.86$ min, $m/z = 211.2$ $[M + H]^+$.

LCMS (0 to 60% acetonitrile in water + 0.03% trifluoroacetic acid over 3 mins) retention time 1.86 min, ESI+ found $[M+H] = 211.2$.



Step 8:

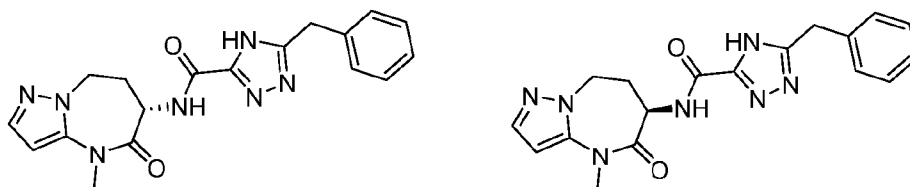
20 (S)-6,6-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxamide

To a solution of 1-hydroxybenzotriazole (54 mg, 0.40 mmol) in N,N-dimethylformamide (5 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimidehydrochloride (77 mg, 0.40 mmol), 6,6-dimethyl-1,4,5,8-tetrahydrooxepino[3,4-c]pyrazole-3-carboxylic acid (70 mg, 0.33 mmol) and (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (70 mg, 0.37 mmol). The reaction mixture was stirred at 25 °C for 1 h and concentrated to dryness *in vacuo*. The residue was purified by RP-HPLC (55-85% methanol in water and 0.05% ammonia) to afford (S)-6,6-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxamide (95 mg, 74.9% yield) as a white solid:

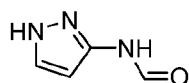
^1H NMR (400 MHz, DMSO- d_6) δ 12.93 (br. s, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.39 - 7.16 (m, 3H), 4.83 - 4.81 (m, 1H), 4.61 - 4.33 (m, 4H), 3.31 (s, 3H), 2.80 - 2.70 (m, 2H), 1.85 - 1.70 (m, 2H), 1.20 (s, 6H). LCMS R_T = 0.81 min, m/z = 385.1 $[\text{M} + \text{H}]^+$.

LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention
 5 time 0.81 min, ESI+ found $[\text{M} + \text{H}] = 385.1$.

Example 27: Method Y



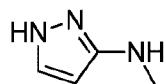
(S)-5-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)
 10 -4H-1,2,4-triazole-3-carboxamide and
 (R)-5-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)
)-4H-1,2,4-triazole-3-carboxamide



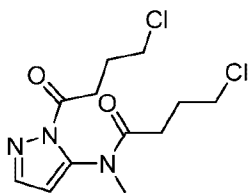
Step 1: N-(1H-pyrazol-3-yl)formamide

15 A solution of 1H-pyrazol-3-amine (2.5 g, 30.09 mmol) in formic acid (10 mL) was heated to 110 °C for 2 h in a sealed vessel. After this time, the reaction mixture was concentrated *in vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% 3:1 isopropyl acetate:methanol in heptane) affording N-(1H-pyrazol-3-yl)formamide (2.75 g, 82%) as a white solid used as is in the next step: LCMS R_T = 0.25 min, m/z = 112 $[\text{M} + \text{H}]^+$.

20 **Step 2: N-methyl-1H-pyrazol-3-amine**

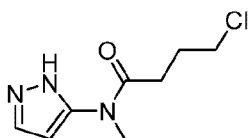


To a solution of N-(1H-pyrazol-3-yl)formamide (2.75 g, 24.8 mmol) in anhydrous tetrahydrofuran (100 mL) cooled to 0 °C under nitrogen was slowly added a solution of lithium aluminum hydride (2 M in tetrahydrofuran, 37.1 mL, 74.3 mmol) under nitrogen. The reaction
 25 mixture was allowed to warm to RT and was stirred for 16 h. After this time, the reaction was quenched with solid sodium sulfate decahydrate and stirred at RT for 30 mins. The resulting mixture was diluted with isopropyl acetate, filtered through Celite, and concentrated *in vacuo* to afford N-methyl-1H-pyrazol-3-amine (1.97 g, 82% yield) as an orange oil used as in the next step without further purification.



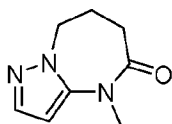
Step 3: 4-chloro-*N*-(1-(4-chlorobutanoyl)-1*H*-pyrazol-5-yl)-*N*-methylbutanamide

To a stirred solution of *N*-methyl-1*H*-pyrazol-5-amine (200 mg, 2.06 mmol) in anhydrous dichloromethane (10 mL) cooled to 0 °C was added *N,N*-diisopropylethylamine (1.08 mL, 6.18 mmol) followed by dropwise addition of 4-chlorobutanoyl chloride (0.697 g, 4.94 mmol) under nitrogen. To the resulting mixture was added 4-dimethylaminopyridine (0.025 g, 0.21 mmol), and the reaction mixture was stirred at RT for 16 h. The reaction mixture was partially concentrated *in vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 50% isopropyl acetate in heptane) affording 4-chloro-*N*-(1-(4-chlorobutanoyl)-1*H*-pyrazol-5-yl)-*N*-methylbutanamide as a colorless oil (0.450 g, 71%) used as is in the next step: LCMS $R_T = 1.35$ min, $m/z = 306$ $[M + H]^+$.



Step 4: 4-chloro-*N*-methyl-*N*-(1*H*-pyrazol-5-yl)butanamide

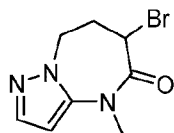
To a stirred solution of 4-chloro-*N*-(1-(4-chlorobutanoyl)-1*H*-pyrazol-5-yl)-*N*-methylbutanamide (0.338 g, 1.10 mmol) in ethanol (2 mL) was added sodium hydroxide (1 mol/L) in water (1.10 mL, 1.10 mmol) and the mixture was left to stand at RT for 5 min. The reaction mixture was concentrated to dryness *in vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording 4-chloro-*N*-methyl-*N*-(1*H*-pyrazol-5-yl)butanamide as a white solid (0.185 g, 83%) used in the next step without further purification: LCMS $R_T = 0.86$ min, $m/z = 202$ $[M + H]^+$.



Step 5: 4-methyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-5(6*H*)-one

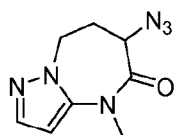
To a solution of 4-chloro-*N*-methyl-*N*-(1*H*-pyrazol-5-yl)butanamide (0.185 g, 0.92 mmol) in *N,N*-dimethylformamide (4 mL) was added cesium carbonate (0.597 g, 1.83 mmol) and stirred at RT for 16 h. The reaction mixture was filtered through Celite and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording

4-methyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-5(6*H*)-one as a viscous colorless oil (0.123 g, 81%) used as is in the next step: LCMS $R_T = 0.76$ min, $m/z = 166$ $[M + H]^+$.



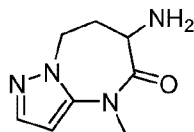
Step 6: 6-bromo-4-methyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-5(6*H*)-one

- 5 To a solution of 4-methyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-5(6*H*)-one (0.123 g, 0.745 mmol) cooled to -78°C in dry tetrahydrofuran (5 mL) was added dropwise a solution of lithium bis(trimethylsilyl)amide (1 mol/L) in dry tetrahydrofuran (2.23 mL, 2.23 mmol) under nitrogen. The resulting solution was stirred at -78°C for 30 min and N-bromosuccinimide (0.265 g, 1.49 mmol) was added and stirred at -78°C for 2 h. The reaction mixture was
- 10 quenched with saturated sodium bisulfite (50 mL) and extracted with isopropyl acetate (3 x 50 mL), dried over sodium sulfate and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording
- 15 6-bromo-4-methyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-5(6*H*)-one as a pale yellow oil (0.083 g, 46%) use as is in the next step: LCMS $R_T = 0.83$ min, $m/z = 244$ $[M + H]^+$.



Step 7: 6-azido-4-methyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-5(6*H*)-one

- To a solution of 6-bromo-4-methyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-5(6*H*)-one (0.083 g, 0.30 mmol) in N, N-dimethylformamide (1 mL) was added sodium azide (0.026 g, 0.41 mmol) and the reaction mixture was stirred at RT for 2 h. The reaction mixture was
- 20 diluted with isopropyl acetate, filtered through Celite, and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording
- 25 6-azido-4-methyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-5(6*H*)-one as a pale orange oil (0.067 g, 96%) used as is in the next step: LCMS $R_T = 0.93$ min, $m/z = 207$ $[M + H]^+$.

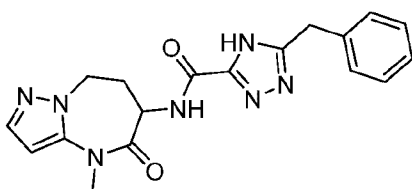


Step 8: 6-amino-4-methyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-5(6*H*)-one

To a solution of 6-azido-4-methyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-5(6*H*)-one (0.067 g, 0.32 mmol) in methanol (2 mL) was added 10% Pd/C (0.069 g, 0.065 mmol), a

balloon of hydrogen, and the mixture was stirred at RT for 16 h. The reaction mixture was filtered through Celite and concentrated to dryness *in vacuo* affording 6-amino-4-methyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-5(6*H*)-one as a viscous oil (0.055 g, 94%) used in the next step without further purification: LCMS $R_T = 0.25$ min, $m/z =$

5 $181 [M + H]^+$.



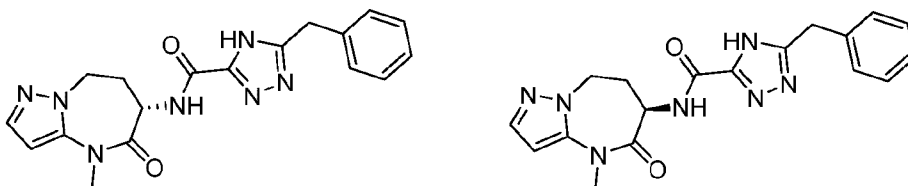
Step 9:

5-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-6-yl)-4*H*-1,2,4-triazole-3-carboxamide

10 To a stirred solution of 6-amino-4-methyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-5(6*H*)-one (0.055 g, 0.31 mmol) in *N,N*-dimethylformamide (2 mL) was added 5-benzyl-4*H*-1,2,4-triazole-3-carboxylic acid (0.074 g, 0.37 mmol), ((3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)oxy)tri(pyrrolidin-1-yl)phosphonium

15 hexafluorophosphate(V) (0.182 g, 0.34 mmol) and *N,N*-diisopropylethylamine (0.160 mL, 0.92 mmol). After stirring at RT for 16 h the reaction mixture was loaded directly for purification by RP-HPLC (0 to 35% acetonitrile in water and 0.1% formic acid) affording 5-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-6-yl)-4*H*-1,2,4-triazole-3-carboxamide as a white solid (0.029 mg, 26%): ^1H NMR (400 MHz, DMSO- d_6) δ 14.42 (s, 1H), 8.56 (s, 1H), 7.49 (d, $J = 2.0$ Hz, 1H), 7.38 – 7.16 (m, 5H), 6.34 (d, $J = 2.0$ Hz, 1H), 4.42 – 4.13 (m, 3H), 4.11 (s, 2H), 3.24 (s, 3H), 2.69 – 2.53 (m, 1H), 2.47 – 2.32 (m, 1H). LCMS $R_T = 3.35$ min, $m/z = 366.2 [M + H]^+$.

20



Step 10:

25 **(S)-5-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-6-yl)-4*H*-1,2,4-triazole-3-carboxamide and**
(R)-5-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-6-yl)-4*H*-1,2,4-triazole-3-carboxamide

5-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepin-6-yl)-4*H*-1,2,4-triazole-3-carboxamide was further purified by chiral SFC (ID column, 30% methanol +

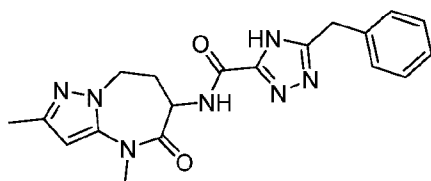
30

0.1% ammonium hydroxide isocratic elution) affording arbitrarily assigned enantiomers (S)-5-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4-H-1,2,4-triazole-3-carboxamide (0.012 g, 11%) and (R)-5-benzyl-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4-H-1,2,4-triazole-3-carboxamide (0.012 g, 11%) as white solids:

Analytical data for the first eluting enantiomer (arbitrarily assigned S configuration): SFC R_T (ID column, 30% methanol + 0.1% ammonium hydroxide isocratic elution, 2.5 min method): 0.545 min, 100% ee: ^1H NMR (400 MHz, DMSO- d_6) δ 14.44 (s, 1H), 8.54 (s, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.35 – 7.20 (m, 5H), 6.34 (d, J = 2.0 Hz, 1H), 4.42 – 4.13 (m, 3H), 4.10 (s, 2H), 3.24 (s, 3H), 2.65 – 2.53 (m, 1H), 2.44 – 2.30 (m, 1H). LCMS R_T = 3.35 min, m/z = 366.1 $[\text{M} + \text{H}]^+$.

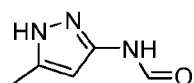
Analytical data for the second eluting enantiomer (arbitrarily assigned R configuration): SFC R_T : 0.908 min, 99% ee: ^1H NMR (400 MHz, DMSO- d_6) δ 14.43 (s, 1H), 8.54 (s, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.43 – 7.13 (m, 5H), 6.34 (d, J = 2.0 Hz, 1H), 4.42 – 4.13 (m, 3H), 4.10 (s, 2H), 2.67 – 2.52 (m, 1H), 2.46 – 2.29 (m, 1H). LCMS R_T = 3.35 min, m/z = 366.2 $[\text{M} + \text{H}]^+$.

Example 28: Method Z



3:

5-benzyl-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide



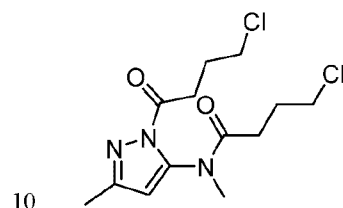
Step 1: N-(5-methyl-1H-pyrazol-3-yl)formamide

A solution of 5-methyl-1H-pyrazol-3-amine (1.8 g, 18.5 mmol) in formic acid (10 mL) was heated to 110 °C for 3 h in a sealed vessel. After this time, the reaction mixture was concentrated in *vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 15% methanol in dichloromethane) affording N-(5-methyl-1H-pyrazol-3-yl)formamide (1.96 g, 85%) as an off-white solid used as is in the next step: LCMS R_T = 0.50 min, m/z = 126 $[\text{M} + \text{H}]^+$.



Step 2: N,5-dimethyl-1H-pyrazol-3-amine

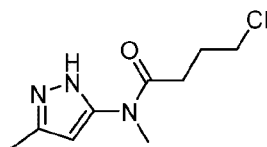
To a solution of N-(5-methyl-1H-pyrazol-3-yl)formamide (1.96 g, 15.7 mmol) in anhydrous tetrahydrofuran (50 mL) cooled to 0 °C under nitrogen was slowly added a solution of lithium aluminum hydride (2 M in tetrahydrofuran, 23.5 mL, 47.0 mmol) under nitrogen. The reaction mixture was allowed to warm to RT and was stirred for 16 h. After this time, the reaction was quenched with solid sodium sulfate decahydrate and stirred at RT for 30 mins. The resulting mixture was diluted with isopropyl acetate, filtered through Celite, and concentrated *in vacuo* to afford N,5-dimethyl-1H-pyrazol-3-amine (1.79 g, 103% yield) as a yellow oil used in the next step without further purification.

**Step 3: 4-chloro-N-[1-(4-chlorobutanoyl)-5-methyl-pyrazol-3-yl]-N-methyl-butanamide**

To a stirred solution of N,5-dimethyl-1H-pyrazol-3-amine (1.74 g, 15.7 mmol) in anhydrous dichloromethane (50 mL) cooled to 0 °C was added *N,N*-diisopropylethylamine (8.19 mL, 47.0 mmol) followed by dropwise addition of 4-chlorobutanoyl chloride (5.3 g, 37.6 mmol) under nitrogen. To the resulting mixture was added 4-dimethylaminopyridine (0.191 g, 1.57 mmol), and the reaction mixture was stirred at RT for 16 h. The reaction mixture was partially concentrated *in vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 50% isopropyl acetate in heptane) affording 4-chloro-N-[1-(4-chlorobutanoyl)-5-methyl-pyrazol-3-yl]-N-methyl-butanamide (2.37 g, 47%) as an orange oil used as is in the next step: LCMS $R_T = 1.43$ min, $m/z = 320$ $[M + H]^+$.

15

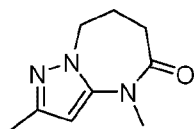
20

**Step 4: 4-chloro-N-methyl-N-(5-methyl-1H-pyrazol-3-yl)butanamide**

To a stirred solution of 4-chloro-N-[1-(4-chlorobutanoyl)-5-methyl-pyrazol-3-yl]-N-methyl-butanamide (2.37 g, 7.4 mmol) in ethanol (20 mL) was added sodium hydroxide (1 mol/L) in water (7.4 mL, 7.4 mmol) and the mixture was left to stand at RT for 5 min. The reaction mixture was concentrated to dryness *in vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording 4-chloro-N-methyl-N-(5-methyl-1H-pyrazol-3-yl)butanamide (1.4 g, 88%) as a yellow oil used in the next step without further purification: LCMS $R_T = 0.99$ min, $m/z = 216$ $[M + H]^+$.

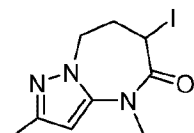
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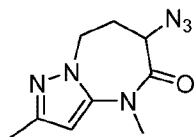
Step 5: 2,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

To a solution of 4-chloro-N-methyl-N-(5-methyl-1H-pyrazol-3-yl)butanamide (1.4 g, 6.5 mmol) in acetonitrile (10 mL) was added cesium carbonate (3.2 g, 13.0 mmol), and the resulting suspension was stirred at RT for 16 h. The reaction mixture was filtered through Celite and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording 2,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.655 g, 56%) as a viscous colorless oil used as is in the next step: LCMS $R_T = 0.91$ min, $m/z = 180$ $[M + H]^+$.



Step 6: 6-iodo-2,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

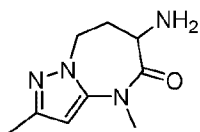
To a solution of 2,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.655 g, 3.65 mmol) in dry dichloromethane (20 mL) under nitrogen cooled to $\sim -10^\circ\text{C}$ in a salt/ice bath was added N,N,N',N'-tetramethylethylenediamine (2.55 g, 22 mmol) followed by iodotrimethylsilane (4.4 g, 22 mmol). The resulting solution was stirred in the salt/ice bath for 1.5 h, after which time was added iodine (2.8 g, 11 mmol). The mixture continued to stir in the salt/ice bath for another 2 h, after which time the reaction mixture was quenched with saturated sodium bisulfite (50 mL). The layers were separated, and the aqueous was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording 6-iodo-2,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one as a brown solid (0.874 g, 78%) used as is in the next step: LCMS $R_T = 1.03$ min, $m/z = 306$ $[M + H]^+$.



Step 7: 6-azido-2,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

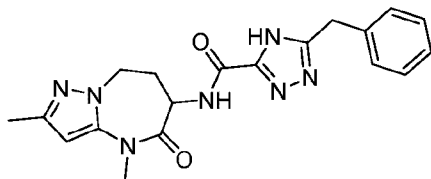
To a solution of 6-iodo-2,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.874 g, 2.86 mmol) in N,N-dimethylformamide (2 mL) was added sodium azide (0.223 g, 3.44 mmol), and the reaction mixture was stirred at RT for 2 h. The reaction mixture was diluted with isopropyl acetate, filtered through Celite, and concentrated to dryness *in vacuo*.

The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording 6-amino-2,4-dimethyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepin-5(6H)-one as a pale orange oil (0.606 g, 96%) used as is in the next step: LCMS $R_T = 0.99$ min, $m/z = 221$ $[M + H]^+$.



Step 8: 6-amino-2,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

To a solution of 6-amino-2,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.606 g, 2.75 mmol) in tetrahydrofuran (5 mL) was added water (1 mL) followed by polymer-bound triphenylphosphine (2.75 g, ~3 mmol/g loading). The mixture was shaken at RT for 16 h, filtered through Celite and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 20% methanol in dichloromethane) affording 6-amino-2,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one as a colorless oil (0.500 g, 94%) used as is in the next step: LCMS $R_T = 0.54$ min, $m/z = 195$ $[M + H]^+$.



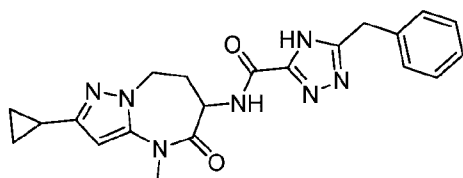
Step 9:

5-benzyl-N-(2,4-dimethyl-5-oxo-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide

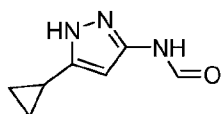
To a stirred solution of 6-amino-2,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.029 g, 0.15 mmol) in N,N-dimethylformamide (2 mL) was added 5-benzyl-4H-1,2,4-triazole-3-carboxylic acid (0.037 g, 0.18 mmol), ((3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)oxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V) (0.095 g, 0.18 mmol) and N,N-diisopropylethylamine (0.078 mL, 0.45 mmol). After stirring at RT for 16 h the reaction mixture was loaded directly for purification by RP-HPLC (5 to 50% acetonitrile in water and 0.1% formic acid) affording 6-amino-2,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one as a white solid (0.029 g, 51%): ^1H NMR (400 MHz, DMSO- d_6) δ 14.39 (s, 1H), 8.53 (s, 1H), 7.36 – 7.21 (m, 6H), 6.13 (s, 1H), 4.39 – 4.21 (m, 2H), 4.18 – 4.01 (m, 4H), 3.22 (s, 3H), 2.57 (ddd, J = 12.8,

8.0, 4.9 Hz, 1H), 2.41 – 2.29 (m, 1H), 2.17 (s, 3H). LCMS R_T = 3.58 min, m/z = 380.2 $[M + H]^+$.

Example 29: Method AA

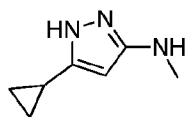


5 5-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide



Step 1: N-(5-cyclopropyl-1H-pyrazol-3-yl)formamide

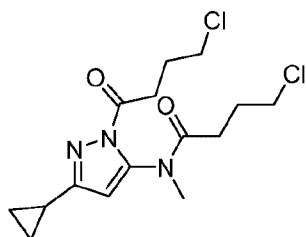
A solution of 5-cyclopropyl-1H-pyrazol-3-amine (2.0 g, 16.2 mmol) in formic acid (10 mL)
 10 was heated to 110 °C for 3 h in a sealed vessel. After this time, the reaction mixture was concentrated *in vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 15% methanol in dichloromethane) affording N-(5-cyclopropyl-1H-pyrazol-3-yl)formamide (1.74 g, 71%) as an off-white solid used as is in the next step: LCMS R_T = 0.86 min, m/z = 152 $[M + H]^+$.



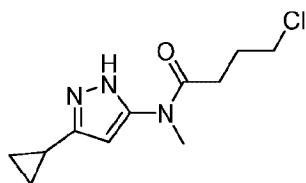
15

Step 2: 5-cyclopropyl-N-methyl-1H-pyrazol-3-amine

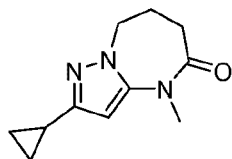
To a solution of N-(5-cyclopropyl-1H-pyrazol-3-yl)formamide (1.74 g, 11.5 mmol) in anhydrous tetrahydrofuran (50 mL) cooled to 0 °C was slowly added a solution of lithium aluminum hydride (2 M in tetrahydrofuran, 17.3 mL, 34.5 mmol) under nitrogen. The reaction
 20 mixture was allowed to warm to RT and was stirred for 16 h. After this time, the reaction was quenched with solid sodium sulfate decahydrate and stirred at RT for 30 mins. The resulting mixture was diluted with isopropyl acetate, filtered through Celite, and concentrated *in vacuo* to afford 5-cyclopropyl-N-methyl-1H-pyrazol-3-amine (1.70 g, 110% yield) as an orange oil used in the next step without further purification.

**Step 3:****4-chloro-N-[1-(4-chlorobutanoyl)-5-cyclopropyl-pyrazol-3-yl]-N-methyl-butanamide**

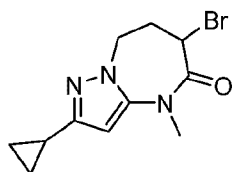
To a stirred solution of 5-cyclopropyl-N-methyl-1H-pyrazol-3-amine (0.760 g, 5.5 mmol) in anhydrous dichloromethane (50 mL) cooled to 0 °C was added *N,N*-diisopropylethylamine (2.90 mL, 16.6 mmol) followed by dropwise addition of 4-chlorobutanoyl chloride (1.87 g, 13.3 mmol) under nitrogen. To the resulting mixture was added 4-dimethylaminopyridine (0.068 g, 0.55 mmol), and the reaction mixture was stirred at RT for 16 h. The reaction mixture was partially concentrated *in vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 50% isopropyl acetate in heptane) affording 4-chloro-N-[1-(4-chlorobutanoyl)-5-cyclopropyl-pyrazol-3-yl]-N-methyl-butanamide (1.18 g, 62%) as an orange oil used as is in the next step: LCMS $R_T = 1.50$ min, $m/z = 346$ $[M + H]^+$.

**Step 4: 4-chloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)-N-methyl-butanamide**

To a stirred solution of 4-chloro-N-[1-(4-chlorobutanoyl)-5-cyclopropyl-pyrazol-3-yl]-N-methyl-butanamide (1.18 g, 3.4 mmol) in ethanol (5 mL) was added sodium hydroxide (1 mol/L) in water (3.4 mL, 3.4 mmol) and the mixture was left to stand at RT for 5 min. The reaction mixture was concentrated to dryness *in vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording 4-chloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)-N-methyl-butanamide (0.540 g, 66%) as a colorless oil used as is in the next step: LCMS $R_T = 1.08$ min, $m/z = 242$ $[M + H]^+$.

**Step 5: 2-cyclopropyl-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one**

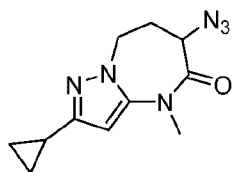
To a solution of 4-chloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)-N-methyl-butanamide (0.540 g, 2.2 mmol) in acetonitrile (10 mL) was added cesium carbonate (1.46 g, 4.5 mmol), and the resulting suspension was stirred at RT for 16 h. The reaction mixture was filtered through Celite and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording
 5 2-cyclopropyl-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.332 g, 72%) as a pink oil used as is in the next step: LCMS $R_T = 0.98$ min, $m/z = 206$ $[M + H]^+$.



Step 6:

10 6-bromo-2-cyclopropyl-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

To a solution of 2-cyclopropyl-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.332 g, 1.6 mmol) cooled to -78°C in dry tetrahydrofuran (8 mL) was added dropwise a solution of lithium bis(trimethylsilyl)amide (1 mol/L) in anhydrous tetrahydrofuran (3.23 mL, 3.23 mmol) under nitrogen. The resulting solution was stirred at -78°C for 30 min and
 15 N-bromosuccinimide (0.432 g, 2.42 mmol) was added and stirred at -78°C for 2 h. The reaction mixture was quenched with saturated sodium bisulfite (50 mL) and extracted with isopropyl acetate (3 x 50 mL), dried over sodium sulfate and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 4% methanol
 in dichloromethane) affording
 20 6-bromo-2-cyclopropyl-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one as a pale yellow oil (0.210 g, 46%) used as is in the next step: LCMS $R_T = 1.06$ min, $m/z = 284$ $[M + H]^+$.

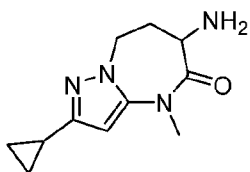


Step 7:

25 6-azido-2-cyclopropyl-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

To a solution of 6-bromo-2-cyclopropyl-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.210 g, 0.74 mmol) in N,N-dimethylformamide (1.5 mL) was added sodium azide (0.058 g, 0.89 mmol), and the reaction mixture was stirred at RT for 2 h. The reaction mixture was diluted
 30 with isopropyl acetate, filtered through Celite, and concentrated to dryness *in vacuo*. The

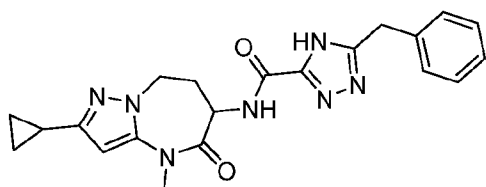
resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording 6-amino-2-cyclopropyl-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one as a yellow oil (0.109 g, 60%) used as is in the next step: LCMS $R_T = 1.05$ min, $m/z = 247$ $[M + H]^+$.



Step 8:

6-amino-2-cyclopropyl-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

To a solution of 6-amino-2-cyclopropyl-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.109 g, 0.44 mmol) in tetrahydrofuran (2 mL) was added water (0.4 mL) followed by polymer-bound triphenylphosphine (0.44 g, ~3 mmol/g loading). The mixture was shaken at RT for 16 h, filtered through Celite and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 20% methanol in dichloromethane) affording 6-amino-2-cyclopropyl-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one as a colorless oil (0.096 g, 99%) used as is in the next step. LCMS $R_T = 0.73$ min, $m/z = 221$ $[M + H]^+$.



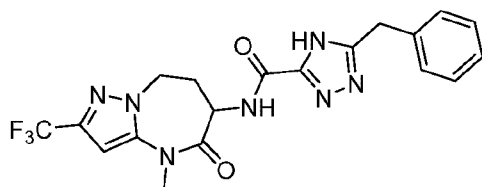
Step 9:

5-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide

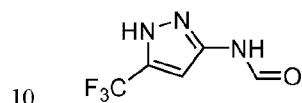
To a stirred solution of 6-amino-2-cyclopropyl-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.033 g, 0.15 mmol) in *N,N*-dimethylformamide (2 mL) was added 5-benzyl-4H-1,2,4-triazole-3-carboxylic acid (0.037 g, 0.18 mmol), ((3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)oxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V) (0.095 g, 0.18 mmol) and *N,N*-diisopropylethylamine (0.078 mL, 0.45 mmol). After stirring at RT for 16 h the reaction mixture was loaded directly for purification by RP-HPLC (5 to 50% acetonitrile in water and 0.1% formic acid) affording

5-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide as a white solid (0.038 g, 62%): ¹H NMR (400 MHz, DMSO-d₆) δ 8.51 (d, J = 7.8 Hz, 1H), 7.36 – 7.19 (m, 5H), 6.06 (s, 1H), 4.37 – 4.20 (m, 2H), 4.16 – 4.02 (m, 3H), 3.20 (s, 3H), 2.65 – 2.53 (m, 1H), 2.40 – 2.27 (m, 1H), 1.91 – 1.80 (m, 1H), 0.92 – 0.81 (m, 2H), 0.73 – 0.60 (m, 2H). LCMS R_T = 3.95 min, *m/z* = 406.2 [M + H]⁺.

Example 30: Method BB

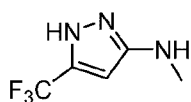


5-benzyl-N-[4-methyl-5-oxo-2-(trifluoromethyl)-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl]-4H-1,2,4-triazole-3-carboxamide



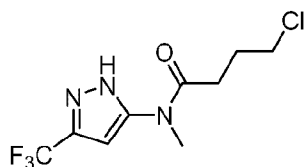
Step 1: N-[5-(trifluoromethyl)-1H-pyrazol-3-yl]formamide

A solution of 5-(trifluoromethyl)-1H-pyrazol-3-amine (2.3 g, 15.2 mmol) in formic acid (10 mL) was heated to 110 °C for 3 h in a sealed vessel. After this time, the reaction mixture was concentrated *in vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 15% methanol in dichloromethane) affording N-[5-(trifluoromethyl)-1H-pyrazol-3-yl]formamide (2.15 g, 79%) as an off-white solid used as is in the next step: LCMS R_T = 0.85 min, *m/z* = 180 [M + H]⁺.



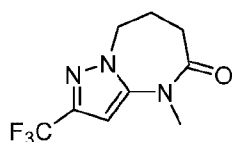
Step 2: N-methyl-5-(trifluoromethyl)-1H-pyrazol-3-amine

To a solution of N-[5-(trifluoromethyl)-1H-pyrazol-3-yl]formamide (2.15 g, 12.0 mmol) in anhydrous tetrahydrofuran (50 mL) cooled to 0 °C under nitrogen was slowly added a solution of lithium aluminum hydride (2 M in tetrahydrofuran, 18.0 mL, 36.0 mmol) under nitrogen. The reaction mixture was allowed to warm to RT gradually and was stirred for 16 h. After this time, the reaction was quenched with solid sodium sulfate decahydrate and stirred at RT for 30 min. The resulting mixture was diluted with isopropyl acetate, filtered through Celite, and concentrated *in vacuo* to afford N-methyl-5-(trifluoromethyl)-1H-pyrazol-3-amine (2.3 g, 120% yield) as an orange oil used in the next step without further purification.



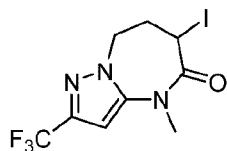
Step 3: 4-chloro-N-methyl-N-[5-(trifluoromethyl)-1H-pyrazol-3-yl]butanamide

To a stirred solution of N-methyl-5-(trifluoromethyl)-1H-pyrazol-3-amine (2.3 g, 14 mmol) in anhydrous dichloromethane (50 mL) cooled to 0 °C was added *N,N*-diisopropylethylamine (7.3 mL, 42.0 mmol) followed by dropwise addition of 4-chlorobutanoyl chloride (4.7 g, 33 mmol) under nitrogen. To the resulting mixture was added 4-dimethylaminopyridine (0.170 g, 1.4 mmol), and the reaction mixture was stirred at RT 16 h. The reaction mixture was partially concentrated *in vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording 4-chloro-N-methyl-N-[5-(trifluoromethyl)-1H-pyrazol-3-yl]butanamide (1.03 g, 27%) as an orange solid used as is in the next step: LCMS $R_T = 1.18$ min, $m/z = 270$ $[M + H]^+$.



Step 4: 4-methyl-2-(trifluoromethyl)-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

To a solution of 4-chloro-N-methyl-N-[5-(trifluoromethyl)-1H-pyrazol-3-yl]butanamide (1.0 g, 3.8 mmol) in acetonitrile (10 mL) was added cesium carbonate (2.5 g, 7.7 mmol), and the resulting suspension was stirred at RT for 16 h. The reaction mixture was filtered through Celite and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 70% isopropyl acetate in heptane) affording 4-methyl-2-(trifluoromethyl)-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.420 g, 47%) as a yellow solid used as is in the next step: LCMS $R_T = 1.05$ min, $m/z = 234$ $[M + H]^+$.

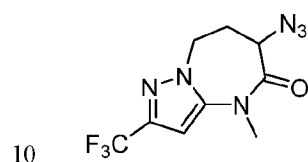


Step 5:

6-iodo-4-methyl-2-(trifluoromethyl)-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

To a solution of 4-methyl-2-(trifluoromethyl)-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.420 g, 1.80 mmol) in dry dichloromethane (20 mL) under nitrogen cooled to ~ -10 °C in a salt/ice bath was added *N,N,N',N'*-tetramethylethylenediamine (1.26 g, 10.8 mmol) followed by iodotrimethylsilane (2.2 g, 10.8 mmol). The resulting solution was stirred in the salt/ice bath

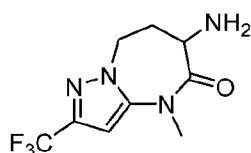
for 1.5 h, after which time was added iodine (1.4 g, 5.4 mmol). The mixture continued to stir in the salt/ice bath for another 2 h, after which time the reaction mixture was quenched with saturated sodium bisulfite (50 mL). The layers were separated, and the aqueous was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried over sodium sulfate and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 60% isopropyl acetate in heptane) affording 6-iodo-4-methyl-2-(trifluoromethyl)-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one as a white solid (0.470 g, 73%) used as is in the next step: LCMS $R_T = 1.25$ min, $m/z = 360$ $[M + H]^+$.



Step 6:

6-azido-4-methyl-2-(trifluoromethyl)-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

To a solution of 6-iodo-4-methyl-2-(trifluoromethyl)-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.470 g, 1.3 mmol) in N,N-dimethylformamide (2 mL) was added sodium azide (0.102 g, 1.57 mmol), and the reaction mixture was stirred at RT for 2 h. The reaction mixture was diluted with isopropyl acetate, filtered through Celite, and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 70% isopropyl acetate in heptane) affording 6-azido-4-methyl-2-(trifluoromethyl)-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one as a white solid (0.330 g, 92%) used as is in the next step: LCMS $R_T = 1.21$ min, $m/z = 275$ $[M + H]^+$.

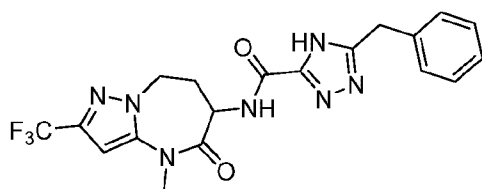


Step 7:

6-amino-4-methyl-2-(trifluoromethyl)-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

To a solution of 6-azido-4-methyl-2-(trifluoromethyl)-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.330 g, 1.2 mmol) in tetrahydrofuran (5 mL) was added water (1 mL) followed by polymer-bound triphenylphosphine (1.2 g, ~3 mmol/g loading). The mixture was shaken at RT for 16 h, filtered through Celite and concentrated to dryness *in vacuo*. The resulting residue was

purified by column chromatography (silica gel, 100-200 mesh, 0 to 20% methanol in dichloromethane) affording 6-amino-4-methyl-2-(trifluoromethyl)-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one as a colorless oil (0.260 g, 87%) used as is in the next step: LCMS $R_T = 0.89$ min, $m/z = 249$ $[M + H]^+$.

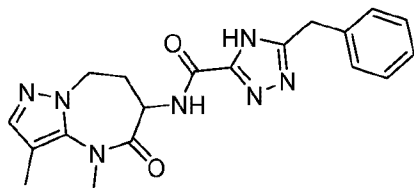


Step 8:

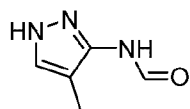
5-benzyl-N-[4-methyl-5-oxo-2-(trifluoromethyl)-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl]-4H-1,2,4-triazole-3-carboxamide

To a stirred solution of 6-amino-2,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.037 g, 0.15 mmol) in *N,N*-dimethylformamide (2 mL) was added 5-benzyl-4H-1,2,4-triazole-3-carboxylic acid (0.037 g, 0.18 mmol), ((3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)oxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V) (0.095 g, 0.18 mmol) and *N,N*-diisopropylethylamine (0.078 mL, 0.45 mmol). After stirring at RT for 16 h the reaction mixture was loaded directly for purification by RP-HPLC (5 to 50% acetonitrile in water and 0.1% formic acid) affording 5-benzyl-N-[4-methyl-5-oxo-2-(trifluoromethyl)-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl]-4H-1,2,4-triazole-3-carboxamide as a white solid (0.039 g, 60%): ^1H NMR (400 MHz, DMSO- d_6) δ 14.42 (s, 1H), 8.64 (s, 1H), 7.47 – 7.13 (m, 5H), 6.93 (s, 1H), 4.53 – 4.41 (m, 1H), 4.41 – 4.26 (m, 2H), 4.11 (s, 2H), 3.27 (s, 3H), 2.74 – 2.57 (m, 1H). LCMS $R_T = 4.33$ min, $m/z = 434.1$ $[M + H]^+$.

Example 31: Method CC

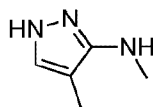


5-benzyl-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide



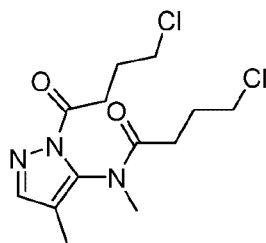
Step 1: N-(4-methyl-1H-pyrazol-3-yl)formamide

A solution of 4-methyl-1H-pyrazol-3-amine (1.3 g, 13.4 mmol) in formic acid (10 mL) was heated to 110 °C for 3 h in a sealed vessel. After this time, the reaction mixture was concentrated *in vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 15% methanol in dichloromethane) affording N-(4-methyl-1H-pyrazol-3-yl)formamide (1.44 g, 86%) as an off-white solid used as is in the next step: LCMS $R_T = 0.37$ min, $m/z = 126$ $[M + H]^+$.



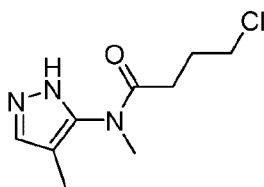
Step 2: N,4-dimethyl-1H-pyrazol-3-amine

To a solution of N-(4-methyl-1H-pyrazol-3-yl)formamide (1.44 g, 11.5 mmol) in anhydrous tetrahydrofuran (50 mL) cooled to 0 °C under nitrogen was slowly added a solution of lithium aluminum hydride (2 M in tetrahydrofuran, 17.3 mL, 34.5 mmol) under nitrogen. The reaction mixture was allowed to warm to RT and was stirred for 16 h. After this time, the reaction was quenched with solid sodium sulfate decahydrate and stirred at RT for 30 mins. The resulting mixture was diluted with isopropyl acetate, filtered through Celite, and concentrated *in vacuo* to afford N,4-dimethyl-1H-pyrazol-3-amine (1.29 g, 101% yield) as a yellow oil used in the next step without further purification.



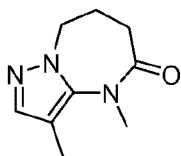
Step 3: 4-chloro-N-[1-(4-chlorobutanoyl)-4-methyl-pyrazol-3-yl]-N-methyl-butanamide

To a stirred solution of N,4-dimethyl-1H-pyrazol-3-amine (1.28 g, 11.5 mmol) in anhydrous dichloromethane (50 mL) cooled to 0 °C was added *N,N*-diisopropylethylamine (6.03 mL, 34.6 mmol) followed by dropwise addition of 4-chlorobutanoyl chloride (3.9 g, 27.6 mmol) under nitrogen. To the resulting mixture was added 4-dimethylaminopyridine (0.141 g, 1.15 mmol), and the reaction mixture was stirred at RT 16 h. The reaction mixture was partially concentrated *in vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording 4-chloro-N-[1-(4-chlorobutanoyl)-4-methyl-pyrazol-3-yl]-N-methyl-butanamide (2.2 g, 60%) as an orange oil used as is in the next step: LCMS $R_T = 1.32$ min, $m/z = 320$ $[M + H]^+$.



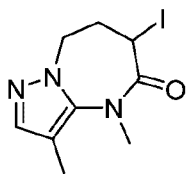
Step 4: 4-chloro-N-methyl-N-(4-methyl-1H-pyrazol-3-yl)butanamide

To a stirred solution of 4-chloro-N-[1-(4-chlorobutanoyl)-4-methyl-pyrazol-3-yl]-N-methyl-butanamide (2.2 g, 6.9 mmol) in ethanol (20 mL) was added sodium hydroxide (1 mol/L) in water (6.9 mL, 6.9 mmol) and the mixture was left to stand at RT for 5 min. The reaction mixture was concentrated to dryness *in vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording 4-chloro-N-methyl-N-(4-methyl-1H-pyrazol-3-yl)butanamide (1.18 g, 80%) as a yellow oil used as is in the next step: LCMS $R_T = 0.99$ min, $m/z = 216$ $[M + H]^+$.



Step 5: 3,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

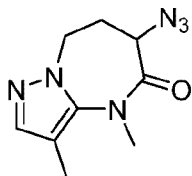
To a solution of 4-chloro-N-methyl-N-(4-methyl-1H-pyrazol-3-yl)butanamide (1.47 g, 6.8 mmol) in acetonitrile (20 mL) was added cesium carbonate (8.9 g, 27.2 mmol), and the resulting suspension was stirred at RT for 48 h. The reaction mixture was filtered through Celite and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording 3,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.510 g, 42%) as a viscous white solid used as is in the next step: LCMS $R_T = 0.86$ min, $m/z = 180$ $[M + H]^+$.



Step 6: 6-iodo-3,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

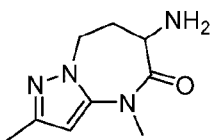
To a solution of 3,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.450 g, 2.51 mmol) in dry dichloromethane (20 mL) under nitrogen cooled to $\sim -10^\circ\text{C}$ in a salt/ice bath was added N,N,N',N'-tetramethylethylenediamine (1.75 g, 15.1 mmol) followed by iodotrimethylsilane (3.0 g, 15.1 mmol). The resulting solution was stirred in the salt/ice bath for 1.5 h, after which time was added iodine (1.91 g, 7.5 mmol). The mixture continued to stir in the salt/ice bath for another 2 h, after which time the reaction mixture was quenched with

saturated sodium bisulfite (50 mL). The layers were separated, and the aqueous was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried over sodium sulfate and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording
 5 6-iodo-3,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one as a brown solid (0.420 g, 55%) used as is in the next step: LCMS $R_T = 0.99$ min, $m/z = 306$ $[M + H]^+$.



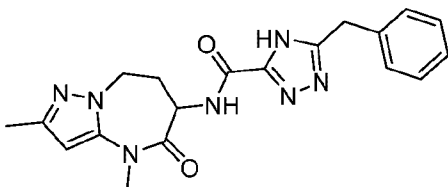
Step 7: 6-azido-3,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

To a solution of 6-iodo-3,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one
 10 (0.420 g, 1.4 mmol) in N,N-dimethylformamide (2 mL) was added sodium azide (0.107 g, 1.65 mmol), and the reaction mixture was stirred at RT for 2 h. The reaction mixture was diluted with isopropyl acetate, filtered through Celite, and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording
 15 6-azido-3,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one as a pale orange oil (0.289 g, 95%) used as is in the next step: LCMS $R_T = 0.80$ min, $m/z = 221$ $[M + H]^+$.



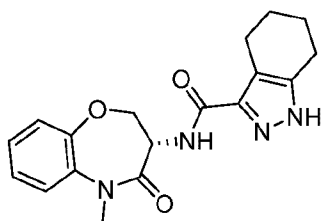
Step 8: 6-amino-3,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

To a solution of 6-azido-3,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one
 20 (0.289g, 1.31 mmol) in tetrahydrofuran (5 mL) was added water (1 mL) followed by polymer-bound triphenylphosphine (1.31 g, ~3 mmol/g loading). The mixture was shaken at RT for 16 h, filtered through Celite and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 20% methanol in dichloromethane) affording
 25 6-amino-3,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one as a colorless oil (0.146 g, 57%) used as is in the next step: LCMS $R_T = 0.65$ min, $m/z = 195$ $[M + H]^+$.

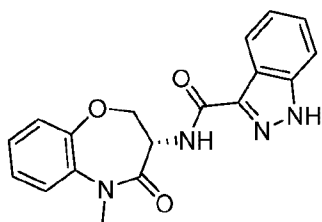


Step 9:**5-benzyl-N-(3,4-dimethyl-5-oxo-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide**

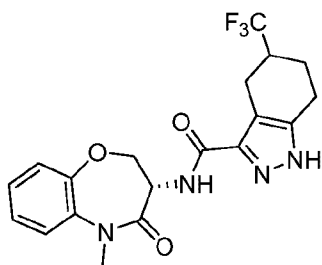
To a stirred solution of 6-amino-3,4-dimethyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.029 g, 0.15 mmol) in N,N-dimethylformamide (2 mL) was added 5-benzyl-4H-1,2,4-triazole-3-carboxylic acid (0.037 g, 0.18 mmol), ((3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)oxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V) (0.095 g, 0.18 mmol) and *N,N*-diisopropylethylamine (0.078 mL, 0.45 mmol). After stirring at RT for 16 h the reaction mixture was loaded directly for purification by RP-HPLC (5 to 50% acetonitrile in water and 0.1% formic acid) affording 5-benzyl-N-(3,4-dimethyl-5-oxo-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide as a white solid (0.036 g, 63%): ¹H NMR (400 MHz, DMSO-d₆) δ 14.41 (s, 1H), 8.45 (d, J = 7.6 Hz, 1H), 7.39 – 7.12 (m, 6H), 4.40 – 3.99 (m, 5H), 3.21 (s, 3H), 2.62 – 2.51 (m, 1H), 2.36 – 2.21 (m, 1H), 2.01 (s, 3H). LCMS R_T = 3.61 min, *m/z* = 380.2 [M + H]⁺.

Example 32: Method DD**Step 1:****(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide**

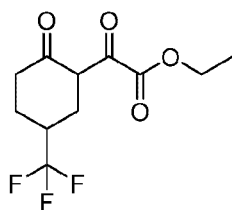
To a stirred solution of (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (0.025 g, 0.13 mmol) in N,N-dimethylformamide (1 mL) was added 4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (0.026 g, 0.16 mmol), ((3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)oxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V) (0.078 g, 0.14 mmol) and *N,N*-diisopropylethylamine (0.045 mL, 0.26 mmol). After stirring at RT for 16 h the reaction mixture was loaded directly for purification by RP-HPLC (5 to 60% acetonitrile in water and 0.1% formic acid) affording (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide as a white solid (0.017 g, 38%): ¹H NMR (400 MHz, DMSO-d₆) δ 12.83 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.37 – 7.20 (m, 3H), 4.82 (dt, J = 11.3, 7.8 Hz, 1H), 4.49 (dd, J = 11.4, 9.8 Hz, 1H), 4.40 (dd, J = 9.8, 7.7 Hz, 1H), 3.31 (s, 3H), 2.62 – 2.53 (m, 4H), 1.75 – 1.57 (m, 4H). LCMS R_T = 4.21 min, *m/z* = 341.2 [M + H]⁺.

Example 33: Method EE**(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-indazole-3-carboxamide**

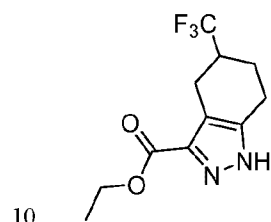
- 5 To a stirred solution of (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (0.025 g, 0.13 mmol) in N,N-dimethylformamide (1 mL) was added 1H-indazole-3-carboxylic acid (0.026 g, 0.16 mmol), ((3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)oxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V) (0.078 g, 0.14 mmol) and *N,N*-diisopropylethylamine (0.045 mL, 0.26 mmol). After stirring at RT for 16 h the reaction mixture was loaded directly for purification by RP-HPLC (5 to 60% acetonitrile in water and 0.1% formic acid) affording (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-indazole-3-carboxamide as a white solid (0.015 g, 34%): ¹H NMR (400 MHz, DMSO-d₆) δ 13.71 (s, 1H), 8.39 (d, J = 8.1 Hz, 1H), 8.06 (dt, J = 8.2, 1.0 Hz, 1H), 7.63 (dt, J = 8.5, 0.9 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.42 (ddd, J = 8.4, 6.9, 1.1 Hz, 1H), 7.38 – 7.19 (m, 4H), 4.95 (dt, J = 11.6, 7.9 Hz, 1H), 4.63 (dd, J = 11.6, 9.9 Hz, 1H), 4.47 (dd, J = 9.9, 7.7 Hz, 1H), 3.34 (s, 3H). LCMS R_T = 4.32 min, *m/z* = 337.1 [M + H]⁺.

Example 34: Method FF

- 20 **N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide**

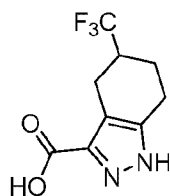
**Step 1: ethyl 2-oxo-2-(2-oxo-5-(trifluoromethyl)cyclohexyl)acetate**

To a stirred solution of sodium ethoxide (2.68 mol/L) in ethanol (2.7 mL, 7.2 mmol) cooled to 0 °C was added dropwise a solution of 4-(trifluoromethyl)cyclohexanone (1 g, 6 mmol) in diethyl oxalate (1 g, 7.2 mmol). The reaction mixture was warmed to RT and stirred for 4 h. The reaction was then quenched with an aqueous solution of 5% citric acid (75 mL) and
 5 extracted with isopropyl acetate (3 x 75 mL). The combined organic extracts were dried over sodium sulfate and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 50% isopropyl acetate in heptane) affording ethyl 2-oxo-2-(2-oxo-5-(trifluoromethyl)cyclohexyl)acetate as a yellow oil (0.623 g, 39%) used as is in the next step: LCMS $R_T = 1.34$ min, $m/z = 267$ $[M + H]^+$.



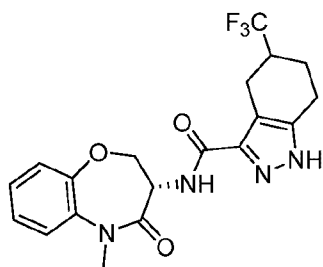
Step 2: ethyl 5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

To a solution of ethyl 2-oxo-2-(2-oxo-5-(trifluoromethyl)cyclohexyl)acetate (0.623 g, 2.34 mmol) in acetic acid (5 mL) was added hydrazine hydrate (300 mg, 4.68 mmol). The reaction mixture was heated to 80 °C for 16 h. The reaction mixture was concentrated to dryness *in vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl
 15 acetate in heptane) affording ethyl 5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (0.425 g, 69%) as a white solid used as in the next step: LCMS $R_T = 1.23$ min, $m/z = 263$ $[M + H]^+$.

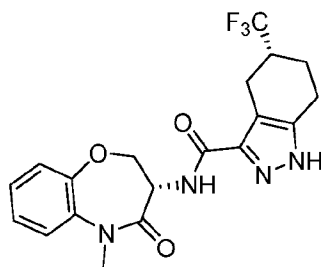
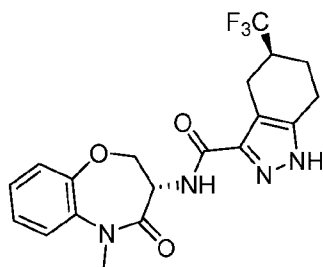


Step 3: 5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid

To a solution of ethyl 5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (0.425 g, 1.62 mmol) in methanol (4 mL) was added sodium hydroxide (1 mol/L) in water (4.05 mL, 4.05 mmol). The reaction mixture was stirred at RT for 16 h. After this time, the mixture was concentrated *in vacuo* to remove methanol. The remaining solution was added to
 25 hydrochloric acid (1 mol/L) in water (50 mL). The resulting precipitate was collected, washed with 1 M hydrochloric acid, and dried thoroughly to afford 5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (0.164 g, 42% yield) as a white solid used in the next step without further purification: LCMS $R_T = 1.03$ min, $m/z = 235$ $[M + H]^+$.

**Step 4:****N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide**

- 5 To a stirred solution of (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (0.035 g, 0.18 mmol) in *N,N*-dimethylformamide (2 mL) was added 5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (0.051 g, 0.22 mmol), ((3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)oxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V) (0.109 g, 0.2 mmol) and *N,N*-diisopropylethylamine (0.095 mL, 0.55 mmol). After stirring at RT for 16 h the reaction mixture was loaded directly for purification by RP-HPLC (20 to 60% acetonitrile in water and 0.1% formic acid) affording N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4, 5,6,7-tetrahydro-1H-indazole-3-carboxamide (0.037 g, 50%) as a white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.53 – 7.45 (m, 1H), 7.37 – 7.20 (m, 3H), 4.83 (dt, *J* = 11.5, 8.1 Hz, 1H), 4.52 (ddd, *J* = 11.3, 10.7, 3.9 Hz, 1H), 4.40 (ddd, *J* = 10.0, 7.7, 2.5 Hz, 1H), 3.31 (s, 3H), 2.98 (dt, *J* = 16.0, 4.4 Hz, 1H), 2.85 – 2.54 (m, 3H), 2.49 – 2.38 (m, 1H), 2.15 – 2.01 (m, 1H), 1.71 – 1.53 (m, 1H). LCMS *R*_T = 4.95 min, *m/z* = 409.1 [*M* + *H*]⁺.

**Step 5:****(5S)-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide and (5R)-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide**

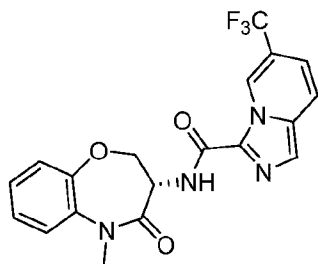
- 25 N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4, 5,6,7-tetrahydro-1H-indazole-3-carboxamide was further purified by chiral SFC (SFC conditions: Column: Regis Whelk O-1 (s,s)50×4.6mm I.D., 3μm Mobile phase: A: CO₂

B:Methanol (0.1% NH₄OH) Isocratic: 25% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar) affording arbitrarily assigned diastereomers (5S)-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide (0.015 g, 20 %) and
 5 (5R)-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide (0.013 g, 17%) as white solids:

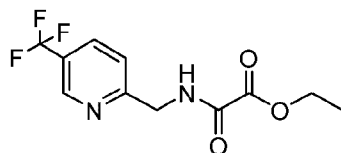
Analytical data for the first eluting diastereomer (arbitrarily assigned S,S configuration): SFC R_T (Whelk O-1 (S,S) column, 25% methanol + 0.1% ammonium hydroxide isocratic elution, 2.5 min method): 1.01 min, 100% ee: ¹H NMR (400 MHz, DMSO-d₆) δ 12.97 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.68 – 7.41 (m, 1H), 7.41 – 7.06 (m, 3H), 4.83 (dt, J = 11.4, 7.7 Hz, 1H), 4.51 (dd, J = 11.5, 9.8 Hz, 1H), 4.40 (dd, J = 9.8, 7.7 Hz, 1H), 3.31 (s, 3H), 2.98 (dd, J = 16.0, 5.1 Hz, 1H), 2.86 – 2.74 (m, 1H), 2.74 – 2.57 (m, 2H), 2.47 – 2.37 (m, 1H), 2.16 – 2.02 (m, 1H), 1.72 – 1.51 (m, 1H). LCMS R_T = 4.95 min, m/z = 409.1 [M + H]⁺.

Analytical data for the second eluting diastereomer (arbitrarily assigned R,S configuration):
 15 SFC R_T 1.13 min, 98% ee: ¹H NMR (400 MHz, DMSO-d₆) δ 13.00 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.63 – 7.39 (m, 1H), 7.43 – 7.11 (m, 3H), 4.83 (dt, J = 11.4, 7.8 Hz, 1H), 4.52 (dd, J = 11.5, 9.8 Hz, 1H), 4.41 (dd, J = 9.9, 7.7 Hz, 1H), 3.31 (s, 3H), 2.99 (dd, J = 16.0, 5.1 Hz, 1H), 2.85 – 2.74 (m, 1H), 2.74 – 2.58 (m, 2H), 2.48 – 2.38 (m, 1H), 2.16 – 2.03 (m, 1H), 1.71 – 1.53 (m, 1H). LCMS R_T = 4.95 min, m/z = 409.1 [M + H]⁺.

20 **Example 35: Method GG**



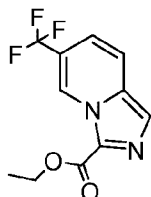
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-carboxamide



25 **Step 1: ethyl 2-oxo-2-[[5-(trifluoromethyl)-2-pyridyl]methylamino]acetate**

To a solution of [5-(trifluoromethyl)-2-pyridyl]methanamine (1.0 g, 5.7 mmol) in anhydrous tetrahydrofuran cooled to 0 °C under nitrogen was added triethylamine (1.19 mL, 8.5 mmol) followed by ethyl 2-chloro-2-oxoacetate (0.85 g, 6.25 mmol). The reaction mixture warmed to

RT slowly and stirred for 16 h. The reaction mixture was concentrated to dryness *in vacuo* and partitioned between isopropyl acetate (100 mL) and saturated aqueous sodium bicarbonate (50 mL). The organic layer was washed with brine (50 mL), dried over sodium sulfate, and concentrated to dryness *in vacuo* affording ethyl 2-oxo-2-[[5-(trifluoromethyl)-2-pyridyl]methylamino]acetate (1.2 g, 77%) as an orange solid used in the next step without further purification: LCMS $R_T = 1.05$ min, $m/z = 277$ $[M + H]^+$.



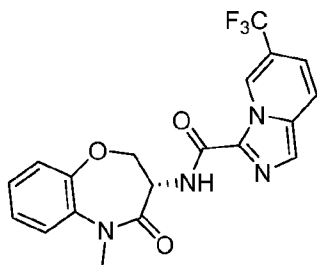
Step 2: ethyl 6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-carboxylate

A suspension of ethyl 2-oxo-2-[[5-(trifluoromethyl)-2-pyridyl]methylamino]acetate (1.2 g, 4.3 mmol) in phosphoryl chloride (12 mL, 129 mmol) was heated to 100 °C for 16 h. The reaction mixture was concentrated to dryness *in vacuo*, diluted with dichloromethane/methanol/trimethylamine (85:5:10) and purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording ethyl 6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-carboxylate as a brown solid (0.460 g, 32%) used as is in the next step: LCMS $R_T = 1.26$ min, $m/z = 259$ $[M + H]^+$.



Step 3: sodium 6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-carboxylate

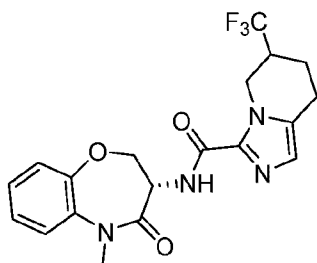
To a solution of ethyl 6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-carboxylate (0.100 g, 0.39 mmol) in tetrahydrofuran (2 mL) was added sodium hydroxide (1 mol/L) in water (0.47 mL, 0.47 mmol). The reaction mixture stirred at RT for 16 h, concentrated to dryness *in vacuo* affording sodium 6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-carboxylate as a brown solid used in the next step without further purification: LCMS $R_T = 0.93$ min, $m/z = 231$ $[M + H]^+$.



Step 4:**N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-carboxamide**

To a stirred solution of [(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]ammonium chloride (0.074 g, 0.32 mmol) in N,N-dimethylformamide (1.5 mL) was added sodium 6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-carboxylate (0.097 g, 0.39 mmol), ((3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)oxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V) (0.210 g, 0.39 mmol) and *N,N*-diisopropylethylamine (0.17 mL, 0.97 mmol). After stirring at RT for 16 h the reaction mixture was loaded directly for purification by column chromatography (silica gel, 100-200 mesh, 0 to 70% isopropyl acetate in heptane) affording

N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-carboxamide as a yellow solid (0.118 g, 91%): ¹H NMR (400 MHz, DMSO-d₆) δ 9.66 (p, J = 1.2 Hz, 1H), 8.78 (d, J = 8.0 Hz, 1H), 8.03 (dt, J = 9.6, 0.9 Hz, 1H), 7.81 (d, J = 0.8 Hz, 1H), 7.58 – 7.46 (m, 1H), 7.41 – 7.19 (m, 4H), 4.91 (dt, J = 11.6, 7.8 Hz, 1H), 4.69 (dd, J = 11.6, 9.9 Hz, 1H), 4.46 (dd, J = 9.9, 7.7 Hz, 1H), 3.33 (s, 3H). LCMS R_T = 5.64 min, *m/z* = 405.1 [M + H]⁺.

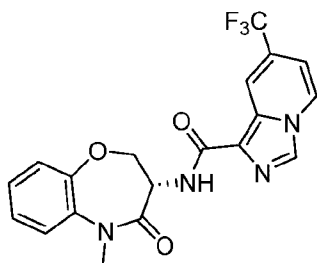
Example 36: Method HH**N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide**

To a solution of N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-carboxamide (0.034 g, 0.084 mmol) in methanol (2 mL) was added palladium hydroxide (10 wt% loading, 0.020 g) followed by a balloon of hydrogen. The reaction mixture was stirred at RT for 16 h, filtered through Celite and concentrated to dryness *in vacuo* affording

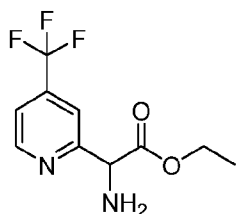
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide (34 mg, 99%) as a yellow oil: ¹H NMR (400 MHz, DMSO-d₆) δ 8.35 (d, J = 8.0 Hz, 1H), 7.54 – 7.45 (m, 1H), 7.37 – 7.19 (m, 3H), 6.89 (d, J = 0.8 Hz, 1H), 4.91 – 4.69 (m, 2H), 4.57 (ddd, J = 11.6, 9.8, 3.6 Hz, 1H), 4.40 (ddd, J = 9.8, 7.6, 2.0 Hz, 1H), 4.12 – 4.01 (m, 2H), 3.31 (s, 3H), 3.04 – 2.92 (m, 1H), 2.84 –

2.69 (m, 1H), 2.15 – 2.04 (m, 1H), 1.83 – 1.67 (m, 1H). LCMS $R_T = 5.07$ min, $m/z = 409.1$ [$M + H$] $^+$.

Example 37: Method II

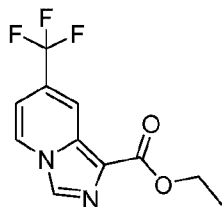


- 5 **N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxamide**



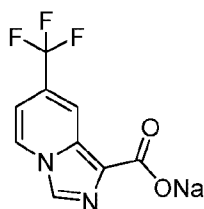
Step 1: ethyl 2-amino-2-[4-(trifluoromethyl)-2-pyridyl]acetate

- To a stirred suspension of sodium hydride (95%, 0.631 g, 25 mmol) in
 10 N,N-dimethylformamide (50 mL) cooled to 0 °C was added ethyl
 2-(benzhydrylideneamino)acetate (5.35 g, 20 mmol). After stirring the reaction for 30 min at
 0 °C, 2-chloro-4-(trifluoromethyl)pyridine (4 g, 22 mmol) was added. The reaction mixture
 was warmed to RT and stirred for 4 h. Hydrochloric acid (1 mol/L) in water (50 mL) was
 added, and the resulting mixture stirred at RT for 3 h. The mixture was diluted with isopropyl
 15 acetate (100 mL) and neutralized with saturated aqueous sodium bicarbonate (50 mL). The
 layers were separated, and the aqueous was extracted with isopropyl acetate (2 x 100 mL). The
 combined organics were dried over sodium sulfate, concentrated to dryness *in vacuo*, and
 purified by column chromatography (silica gel, 100-200 mesh, 0 to 10% methanol in
 dichloromethane) affording ethyl 2-amino-2-[4-(trifluoromethyl)-2-pyridyl]acetate (0.630 g,
 20 13%) used as is in the next step: LCMS $R_T = 0.93$ min, $m/z = 249$ [$M + H$] $^+$.



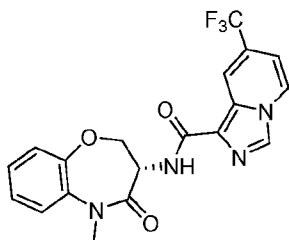
Step 2: ethyl 7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxylate

To a solution of ethyl 2-amino-2-[4-(trifluoromethyl)-2-pyridyl]acetate (0.630 g, 0.254 mmol) in toluene (5 mL) was added N,N-dimethylformamide dimethyl acetal (0.44 mL, 3.3 mmol), and the resulting mixture was heated to 80 °C in a sealed vessel for 16 h. The reaction mixture was then concentrated to dryness *in vacuo* and purified by column chromatography (silica gel, 100-200 mesh, 0 to 5% methanol in dichloromethane) affording ethyl 7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxylate (0.147 g, 22%) as a white solid used as is in the next step: LCMS $R_T = 1.19$ min, $m/z = 259$ $[M + H]^+$.



Step 3: sodium 7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxylate

To a stirred solution of ethyl 7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxylate (0.147 g, 0.57 mmol) in tetrahydrofuran (2 mL) was added sodium hydroxide (1 mol/L) in water (1.4 mL, 1.4 mmol). The resulting mixture was heated to 50 °C for 6 h, concentrated to dryness *in vacuo* affording sodium 7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxylate as a white solid used as is in the next step: LCMS $R_T = 0.95$ min, $m/z = 231$ $[M + H]^+$.



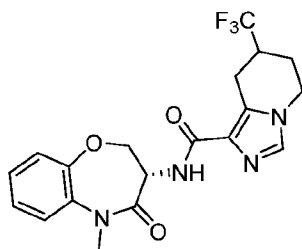
Step 4:

N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxamide

To a stirred solution of [(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]ammonium chloride (0.052 g, 0.23 mmol) in N,N-dimethylformamide (1.5 mL) was added sodium 7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxylate (0.069 g, 0.27 mmol), ((3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)oxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V) (0.148 g, 0.27 mmol) and N,N-diisopropylethylamine (0.12 mL, 0.68 mmol). After stirring at RT for 16 h the reaction mixture was loaded directly for purification by RP-HPLC (30 to 70% acetonitrile in water and 0.1% formic acid) affording N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxamide (0.067 g, 73%) as a white solid: ^1H NMR (400 MHz, DMSO- d_6) δ 8.71 – 8.66 (m, 2H), 8.36 – 8.25 (m, 2H), 7.55 – 7.47 (m, 1H), 7.39 – 7.21 (m, 3H), 7.12 (dd, J

= 7.4, 1.9 Hz, 1H), 4.92 (dt, J = 11.5, 7.8 Hz, 1H), 4.60 (dd, J = 11.5, 9.8 Hz, 1H), 4.47 (dd, J = 9.8, 7.7 Hz, 1H), 3.33 (s, 3H). LCMS R_T = 5.03 min, m/z = 405.1 $[M + H]^+$.

Example 38: Method JJ

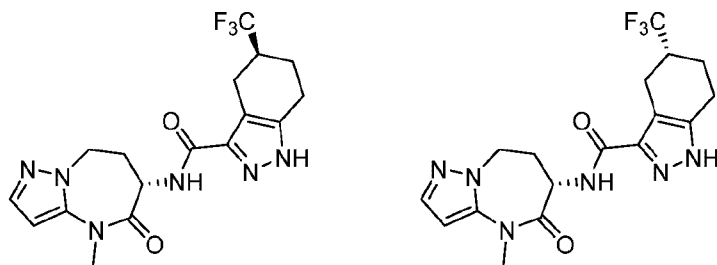


5 N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxamide

To a solution of N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-7-(trifluoromethyl)imidazo[1,5-a]pyridine-1-carboxamide (0.050 g, 0.12 mmol) in methanol (2 mL) was added palladium hydroxide (10 wt% loading, 0.030 g) followed by a balloon of hydrogen. The reaction mixture
10 was stirred at RT for 16 h, filtered through Celite and concentrated to dryness *in vacuo* affording

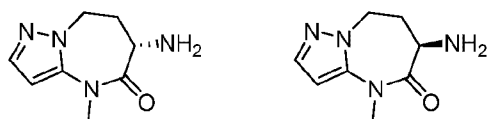
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-7-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-1-carboxamide (31 mg, 61%) as a yellow oil: ^1H NMR (400
15 MHz, DMSO- d_6) δ 7.88 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.53 – 7.45 (m, 1H), 7.36 – 7.20 (m, 3H), 4.81 (dt, J = 11.2, 7.9 Hz, 1H), 4.54 – 4.36 (m, 2H), 4.33 – 4.23 (m, 1H), 3.95 (tt, J = 12.4, 4.4 Hz, 1H), 3.39 – 3.33 (m, 1H), 3.31 (s, 3H), 3.05 – 2.86 (m, 1H), 2.80 – 2.64 (m, 1H), 2.26 – 2.12 (m, 1H), 1.95 – 1.78 (m, 1H). LCMS R_T = 4.46 min, m/z = 409.1 $[M + H]^+$.

Example 39: Method KK



20

(5S)-N-[(6S)-4-methyl-5-oxo-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide and
(5R)-N-[(6S)-4-methyl-5-oxo-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide

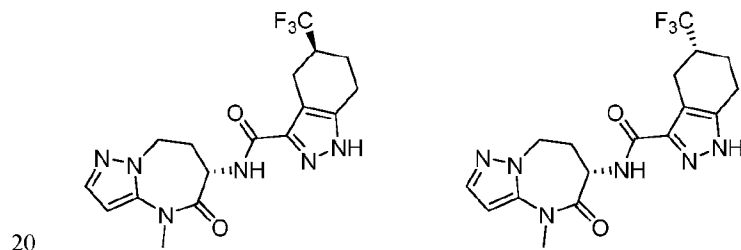


25

Step 1: (6S)-6-amino-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one and (6R)-6-amino-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one

To a solution of 6-azido-4-methyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepin-5(6H)-one (0.500 g, 2.42 mmol) in methanol (10 mL) was added 10% Pd/C (0.258 g, 0.242 mmol), a
 5 balloon of hydrogen, and the mixture was stirred at RT for 16 h. The reaction mixture was filtered through Celite, concentrated to dryness *in vacuo*, and purified by column chromatography (silica gel, 100-200 mesh, 0 to 20% methanol in dichloromethane) affording 6-amino-4-methyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepin-5(6H)-one (0.210 g, 48%) as
 a viscous oil. The resulting compound was further purified by chiral SFC (Chiralpak AD
 10 150×21.2mm I.D column., 5µm Mobile phase: A: CO₂ B: Methanol (0.1% NH₄OH) Isocratic 25% B for 6.0 min. Flow rate: 70mL/min Column temperature: 40 °C. BPR: 100 bar) affording
 arbitrarily assigned distereomers
 (6S)-6-amino-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.074 g, 17 %) and (6R)-6-amino-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.074 g,
 15 17%) as viscous oils used as is in the next step.

Analytical data for the first eluting enantiomer (arbitrarily assigned S configuration): SFC R_T (AD column, 25% methanol + 0.1% ammonium hydroxide isocratic elution, 2.5 min method): 0.42 min, 98% ee; Analytical data for the second eluting enantiomer (arbitrarily assigned R configuration): SFC R_T = 0.69 min, 97% ee.



Step 2:

(5S)-N-[(6S)-4-methyl-5-oxo-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide and
(5R)-N-[(6S)-4-methyl-5-oxo-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide
 25

To a stirred solution of (6S)-6-amino-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.022 g, 0.12 mmol) in N,N-dimethylformamide (2 mL) was added 5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (0.034 g, 0.15 mmol),
 30 ((3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)oxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V) (0.080 g, 0.15 mmol) and N,N-diisopropylethylamine (0.064 mL, 0.37 mmol). After stirring at RT for 16 h the reaction mixture was loaded directly for

purification by RP-HPLC (20 to 60% acetonitrile in water and 0.1% formic acid) affording N-[(6S)-4-methyl-5-oxo-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide (0.040 g, 83%) as a white solid.

The resulting compound was further purified by chiral SFC (SFC conditions: Column: Lux Cellulose-1 50×4.6mm I.D., 3µm Mobile phase: A: CO₂ B: Methanol (0.1% NH₄OH) Isocratic: 20% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar) affording arbitrarily assigned diastereomers (5R)-N-[(6S)-4-methyl-5-oxo-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide (0.019 g, 38 %) and (5S)-N-[(6S)-4-methyl-5-oxo-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl]-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide (0.019 g, 38%) as white solids:

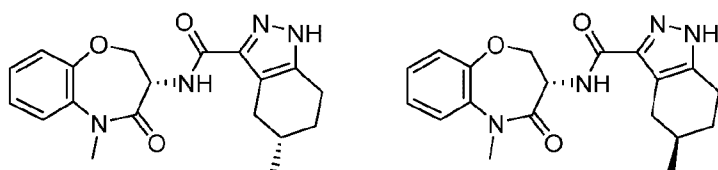
Analytical data for the first eluting diastereomer (arbitrarily assigned R,S configuration): SFC R_T (Lux Cellulose-1 column, 25% methanol + 0.1% ammonium hydroxide isocratic elution, 2.5 min method): 1.23 min, 100% ee: ¹H NMR (400 MHz, DMSO-d₆) δ 12.97 (s, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 2.1 Hz, 1H), 6.32 (d, J = 2.0 Hz, 1H), 4.42 – 4.24 (m, 2H), 4.23 – 4.12 (m, 1H), 3.25 (s, 3H), 3.05 – 2.93 (m, 2H), 2.84 – 2.74 (m, 1H), 2.74 – 2.54 (m, 3H), 2.39 – 2.25 (m, 1H), 2.15 – 2.04 (m, 1H), 1.72 – 1.55 (m, 1H). LCMS R_T = 3.97 min, *m/z* = 397.1 [M + H]⁺.

Analytical data for the second eluting diastereomer (arbitrarily assigned S,S configuration): SFC R_T 1.59 min, 100% ee: ¹H NMR (400 MHz, DMSO-d₆) δ 12.98 (s, 1H), 8.08 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 6.33 (d, J = 2.0 Hz, 1H), 4.45 – 4.09 (m, 3H), 3.25 (s, 3H), 3.01 (dd, J = 16.0, 5.1 Hz, 1H), 2.87 – 2.56 (m, 4H), 2.47 – 2.25 (m, 2H), 2.18 – 2.02 (m, 1H), 1.74 – 1.52 (m, 1H). LCMS R_T = 3.95 min, *m/z* = 397.1 [M + H]⁺.

Examples 40-43: Chiral Separation of Compounds

Supercritical fluid chromatography (SFC) was performed on select compounds of the invention in order to obtain chiral separation of stereoisomers. SFC chiral conditions are as follows. All isolated peaks were arbitrarily assigned.

Example 40:



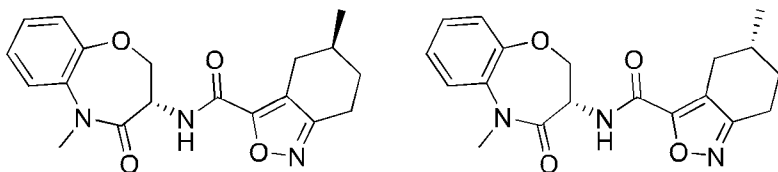
(S)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide and R)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide

Prep:

SFC condition: Column: Chiralcel™ OX 150 x 21.2mm I.D., 5µm Mobile phase: A: CO₂ B: Methanol (0.1% NH₄OH) Isocratic: 45% B in 6min Flow rate: 70mL/min Column temperature: 40 °C, BPR: 100 bar (Peak 2: 4.5 min) and SFC condition: Column: Chiralcel OX 150 x 21.2mm I.D., 5µm Mobile phase: A: CO₂ B: Methanol (0.1% NH₄OH) Isocratic: 45% B in 6min Flow rate: 70mL/min Column temperature: 40 °C, BPR: 100 bar (Peak 1: 4.0 min).

Analytical:

SFC condition: Column: Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO₂ B: Methanol (0.1% NH₄OH) Isocratic: 40% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar (Peak 2: 1.200 min) and SFC condition: Column: Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO₂ B: Methanol (0.1% NH₄OH) Isocratic: 40% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar (Peak 1: 1.031 min).

Example 41:

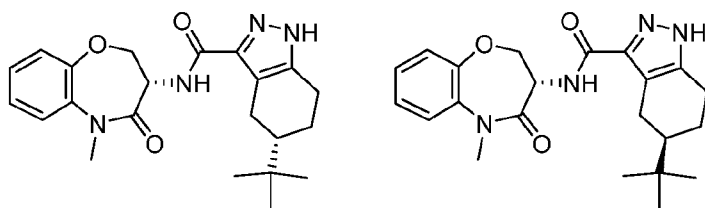
(S)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[c]isoxazole-3-carboxamide and (R)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[c]isoxazole-3-carboxamide

Prep:

SFC condition: Column: Chiralpak AD 150 x 21.2mm I.D., 5µm Mobile phase: A: CO₂ B: Ethanol (0.1% NH₄OH) Isocratic: 25% B in 6.0min Flow rate: 70mL/min Column temperature: 40 °C, BPR: 100 bar (Peak 1: 2.6 min) and SFC condition: Column: Chiralpak AD 150 x 21.2mm I.D., 5µm Mobile phase: A: CO₂ B: Ethanol (0.1% NH₄OH) Isocratic: 25% B in 6.0min Flow rate: 70mL/min Column temperature: 40 °C, BPR: 100 bar (Peak 2: 3.0 min).

Analytical:

SFC condition: Column: Chiralpak AD 50×4.6mm I.D., 3µm Mobile phase: A: CO₂ B: Ethanol (0.1% NH₄OH) Isocratic: 20% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar (Peak1: 0.862 min) and SFC condition: Column: Chiralpak AD 50×4.6mm I.D., 3µm Mobile phase: A: CO₂ B: Ethanol (0.1% NH₄OH) Isocratic: 20% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar (Peak 2: 0.957 min).

Example 42:

(S)-5-(tert-butyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide and

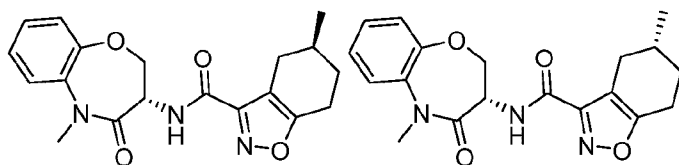
5 (R)-5-(tert-butyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide

Prep:

SFC condition: Column: Lux Cellulose-3 150x 21.2mm I.D., 5 μ m Mobile phase: A: CO₂ B:Methanol (0.1% NH₄OH) Isocratic: 15% B in 6min Flow rate: 70mL/min Column
10 temperature: 40 °C, BPR: 100 bar (Peak 2: 2.5 min) and SFC condition: Column: Lux Cellulose-3 150x 21.2mm I.D., 5 μ m Mobile phase: A: CO₂ B:Methanol (0.1% NH₄OH) Isocratic: 15% B in 6min Flow rate: 70mL/min Column temperature: 40 °C, BPR: 100 bar (Peak 1: 2.0 min).

Analytical:

15 SFC condition: Column: Lux Cellulose-3 50x4.6mm I.D., 3 μ m Mobile phase: A: CO₂ B:Methanol (0.1% NH₄OH) Isocratic: 15% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar (Peak 2: 0.551 min) and SFC condition: Column: Lux Cellulose-3 50x4.6mm I.D., 3 μ m Mobile phase: A: CO₂ B:Methanol (0.1% NH₄OH) Isocratic: 15% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar (Peak 1:
20 0.0.470 min).

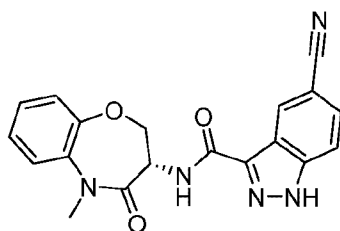
Example 43:**Prep:**

25 SFC condition: Column: Chiralpak ID 150 x 21.2mm I.D., 5 μ m Mobile phase: A: CO₂ B: Ethanol (0.1% NH₄OH) Isocratic: 40% B in 6min Flow rate: 70mL/min Column temperature: 40 oC, BPR: 100 bar (Peak 1: 2.0 min) and SFC condition: Column: Chiralpak ID 150 x 21.2mm I.D., 5 μ m Mobile phase: A: CO₂ B: Ethanol (0.1% NH₄OH) Isocratic: 40% B in 6min Flow rate: 70mL/min Column temperature: 40 oC, BPR: 100 bar (Peak 2: 3.25 min).

Analytical:

SFC condition: Column: Chiralpak ID 50×4.6mm I.D., 3µm Mobile phase: A: CO₂ B: Ethanol (0.1% NH₄OH) Isocratic: 30% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar (Peak 1: 0.888 min) and SFC condition: Column: Chiralpak ID 50×4.6mm I.D., 3µm Mobile phase: A: CO₂ B: Ethanol (0.1% NH₄OH) Isocratic: 30% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar (Peak 2: 1.424 min).

Examples 44-82 were prepared according to the above procedures and synthetic schemes as shown in Table 1 below.

Example 83

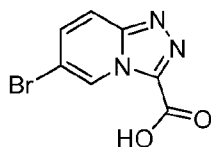
(S)-5-cyano-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-indazole-3-carboxamide

Method B

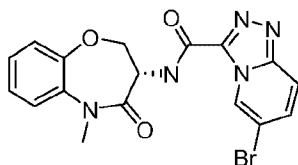
(33 mg, 59% yield)

¹H NMR (400 MHz, DMSO-*d*₆) δ 14.23 (s, 1H), 8.68 – 8.59 (m, 1H), 8.52 – 8.43 (m, 1H), 7.87 – 7.74 (m, 2H), 7.58 – 7.48 (m, 1H), 7.42 – 7.18 (m, 3H), 5.00 – 4.88 (m, 1H), 4.73 – 4.60 (m, 1H), 4.53 – 4.41 (m, 1H), 3.33 (s, 3H). LC-MS R_T = 4.57 min, m/z = 362.1 (M+H)⁺.

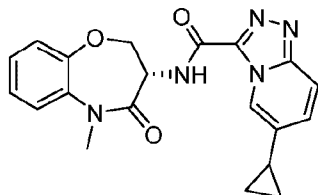
LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.57 min, ESI⁺ found [M+H] = 362.1.

**Step 1: 6-bromo-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylic acid**

In a screw cap vial, ethyl 6-bromo-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate (70 mg, 0.259 mmol) was dissolved in tetrahydrofuran (1 mL) and methanol (0.2 mL). To the reaction was then added lithium hydroxide (0.20 mL, 0.388 mmol) and stirred at RT for 18 h. Upon completion, reaction was concentrated to dryness *in vacuo* to afford crude 6-bromo-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylic acid (62 mg, 98% yield) used as is in the next step.

**Step 2:****(S)-6-bromo-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide**

- 5 To a screw cap vial (S)-3-amino-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one hydrochloride (58 mg, 0.255 mmol), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (120 mg, 0.316 mmol), and 6-bromo-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylic acid (62 mg, 0.243 mmol) was added and dissolved in N,N-dimethylformamide (5 mL). To the reaction mixture was added trimethylamine (0.136 mL, 0.973 mmol), the vial was capped and stirred at RT for 16 h. The mixture was concentrated to dryness *in vacuo* and the residue was purified by RP-HPLC affording (S)-6-bromo-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide (92 mg, 90% yield), used as is in the next step.

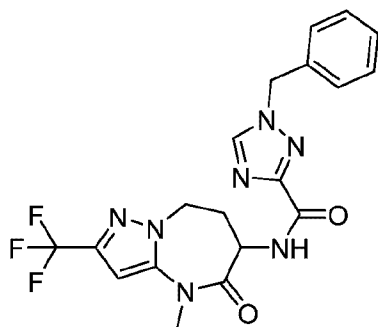
Example 84**Step 3:**

- 20 **(S)-6-cyclopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide**
- In a microwave vial, (S)-6-bromo-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide (92 mg, 0.221 mmol), potassium cyclopropyltrifluoroborate (68.9 mg, 0.442 mmol), palladium(II) acetate (4.96mg, 0.022mmol), di(adamantan-1-yl)(butyl)phosphine (12.51mg, 0.0332mmol), and cesium carbonate (288.1mg, 0.884mmol) were added and purged with N₂ for 2 min. To the vial was then added toluene (4.42ml, 41.8mmol) and water (0.442ml, 24.54mmol) and the reaction was allowed to stir 110°C for 18 h. The mixture was concentrated to dryness *in vacuo* and the residue was purified by RP-HPLC affording (S)-6-cyclopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-[1,2,4]t

riazolo[4,3-a]pyridine-3-carboxamide (18mg, 21% yield): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.31 (d, $J = 8.0$ Hz, 1H), 9.25 – 9.20 (m, 1H), 7.99 (dd, $J = 9.7, 1.0$ Hz, 1H), 7.72 (dd, $J = 9.7, 1.8$ Hz, 1H), 7.59 – 7.49 (m, 1H), 7.42 – 7.22 (m, 3H), 5.02 – 4.87 (m, 1H), 4.81 – 4.67 (m, 1H), 4.54 – 4.41 (m, 1H), 1.79 – 1.69 (m, 1H), 1.03 – 0.93 (m, 2H), 0.80 – 0.69 (m, 2H). LC-MS $R_T = 4.66$ min, $m/z = 378.1$ ($\text{M}+\text{H}$) $^+$.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.66 min, ESI+ found $[\text{M}+\text{H}] = 378.1$.

Example 85

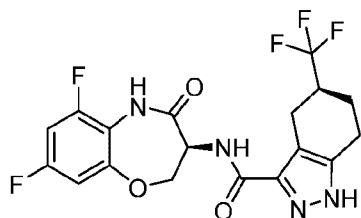


Step 1:
1-benzyl-N-(4-methyl-5-oxo-2-(trifluoromethyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide

Method B

To a screw cap vial
 15 6-amino-4-methyl-2-(trifluoromethyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepin-5(6H)-one (74mg, 0.298 mmol),
 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (158 mg, 0.417 mmol), 1-benzyl-1H-1,2,4-triazole-3-carboxylic acid (76mg, 0.358 mmol) was added and dissolved in N,N-dimethylformamide (5 mL). To the
 20 reaction mixture was added trimethylamine (0.166 mL, 1.19 mmol), the vial was capped and stirred at RT for 16 h. The mixture was concentrated to dryness *in vacuo* and the residue was purified by RP-HPLC affording
 1-benzyl-N-(4-methyl-5-oxo-2-(trifluoromethyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide (77mg, 59% yield): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.82 (s, 1H), 8.63 (d, $J = 7.6$ Hz, 1H), 7.49 – 7.19 (m, 5H), 6.93 (s, 1H), 5.49 (s, 2H), 4.51 – 4.42 (m, 1H), 4.39 – 4.27 (m, 2H), 3.27 (s, 3H), 2.72 – 2.59 (m, 1H), 2.48 – 2.42 (m, 1H). LC-MS $R_T = 4.34$ min, $m/z = 434.1$ ($\text{M}+\text{H}$) $^+$.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.34 min, ESI+ found $[\text{M}+\text{H}] = 434.1$.

Example 86

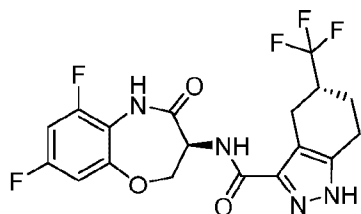
5 **(S)-N-((S)-6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide**

Method B

(20mg, 29% yield)

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.02 (s, 1H), 10.03 (s, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.31 – 7.16 (m, 1H), 7.12 – 6.96 (m, 1H), 4.95 – 4.81 (m, 1H), 4.69 – 4.56 (m, 1H), 4.56 – 4.44 (m, 1H), 3.10 – 2.95 (m, 1H), 2.87 – 2.58 (m, 3H), 2.17 – 2.03 (m, 1H), 1.72 – 1.55 (m, 1H).
 10 LC-MS R_T = 5.03 min, *m/z* = 434.1 (M+H)⁺.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 5.03 min, ESI+ found [M+H] = 434.1.

Example 87

15

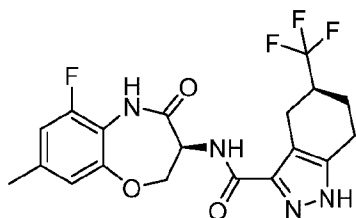
(R)-N-((S)-6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide

Method B

20 (12mg, 17% yield)

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.02 (s, 1H), 10.03 (s, 1H), 8.02 (d, *J* = 7.7 Hz, 1H), 7.49 – 7.12 (m, 1H), 7.12 – 6.87 (m, 1H), 5.06 – 4.81 (m, 1H), 4.67 – 4.55 (m, 1H), 4.55 – 4.45 (m, 1H), 3.08 – 2.95 (m, 1H), 2.87 – 2.59 (m, 3H), 2.20 – 2.02 (m, 1H), 1.76 – 1.56 (m, 1H).
 LC-MS R_T = 5.01 min, *m/z* = 434.1 (M+H)⁺.

25 LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 5.01 min, ESI+ found [M+H] = 434.1.

Example 88

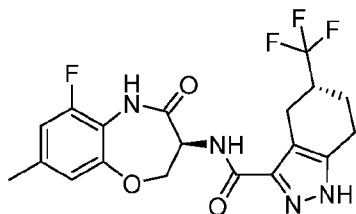
(S)-N-((S)-6-fluoro-8-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide

5 **Method B**

(29mg, 42% yield)

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 9.95 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.05 – 6.93 (m, 1H), 6.93 – 6.83 (m, 1H), 4.90 – 4.77 (m, 1H), 4.60 – 4.51 (m, 1H), 4.49 – 4.41 (m, 1H), 3.06 – 2.95 (m, 1H), 2.85 – 2.74 (m, 1H), 2.74 – 2.58 (m, 2H), 2.47 – 2.42 (m, 1H), 2.30 (s, 3H), 2.14 – 2.09 (m, 1H), 1.70 – 1.56 (m, 1H). LC-MS R_T = 5.20 min, *m/z* = 427.1 (M+H)⁺.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 5.20 min, ESI+ found [M+H] = 427.1.

Example 89

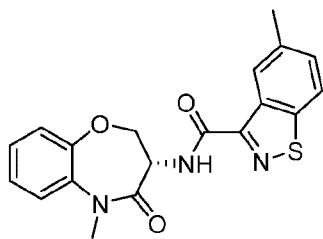
15 **(R)-N-((S)-6-fluoro-8-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide**

Method B

(19mg, 27% yield)

20 ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 9.95 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.07 – 6.92 (m, 1H), 6.92 – 6.80 (m, 1H), 4.97 – 4.74 (m, 1H), 4.63 – 4.49 (m, 1H), 4.49 – 4.37 (m, 1H), 3.07 – 2.94 (m, 1H), 2.87 – 2.74 (m, 1H), 2.74 – 2.59 (m, 2H), 2.48 – 2.42 (m, 1H), 2.30 (s, 3H), 2.18 – 2.02 (m, 1H), 1.72 – 1.55 (m, 1H). LC-MS R_T = 5.19 min, *m/z* = 427.1 (M+H)⁺.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 5.19 min, ESI+ found [M+H] = 427.1.

Example 90

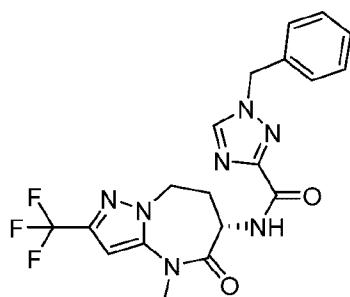
(S)-5-methyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)benzo[d]isothiazole-3-carboxamide

5 **Method B**

(24mg, 24% yield)

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.89 (d, $J = 8.0$ Hz, 1H), 8.48 – 8.40 (m, 1H), 8.23 – 8.14 (m, 1H), 7.59 – 7.46 (m, 2H), 7.40 – 7.20 (m, 3H), 4.99 – 4.86 (m, 1H), 4.72 – 4.62 (m, 1H), 4.54 – 4.42 (m, 1H), 3.34 (s, 3H), 2.46 (s, 3H). LC-MS $R_T = 5.97$ min, $m/z = 368.1$ ($\text{M}+\text{H}$) $^+$.

- 10 LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 5.97 min, ESI+ found $[\text{M}+\text{H}] = 368.1$.

Example 91

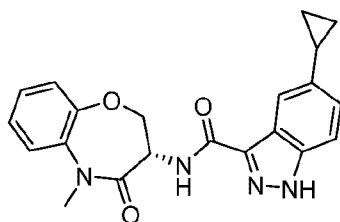
- 15 **(S)-1-benzyl-N-(4-methyl-5-oxo-2-(trifluoromethyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide**

Method B

(35mg, 27% yield)

- ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.82 (s, 1H), 8.63 (d, $J = 7.6$ Hz, 1H), 7.46 – 7.17 (m, 5H), 6.93 (s, 1H), 5.49 (s, 2H), 4.52 – 4.43 (m, 1H), 4.39 – 4.27 (m, 2H), 3.27 (s, 3H), 2.70 – 2.58 (m, 20 1H), 2.47 – 2.42 (m, 1H). LC-MS $R_T = 4.63$ min, $m/z = 434.1$ ($\text{M}+\text{H}$) $^+$.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.63 min, ESI+ found $[\text{M}+\text{H}] = 434.1$.

Example 92

(S)-5-cyclopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-indazole-3-carboxamide

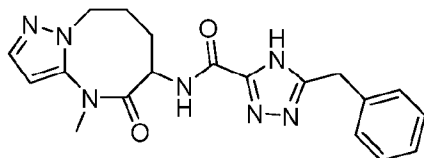
5 Method B

(13.8mg, 25% yield)

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.58 (s, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 7.78 – 7.70 (m, 1H), 7.58 – 7.46 (m, 2H), 7.39 – 7.22 (m, 3H), 7.16 (dd, *J* = 8.7, 1.7 Hz, 1H), 5.03 – 4.83 (m, 1H), 4.67 – 4.57 (m, 1H), 4.52 – 4.42 (m, 1H), 2.10 – 1.96 (m, 1H), 1.00 – 0.91 (m, 2H), 0.68 – 0.59 (m, 2H). LC-MS R_T = 5.36 min, *m/z* = 377.1 (M+H)⁺.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 5.36 min, ESI+ found [M+H] = 377.1.

Example 93 (general for all 8 membered lactams)



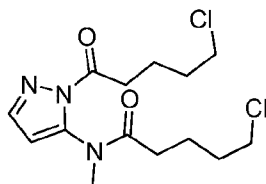
15 5-benzyl-N-(4-methyl-5-oxo-4,5,6,7,8,9-hexahydropyrazolo[1,5-a][1,3]diazocin-6-yl)-4H-1,2,4-triazole-3-carboxamide

All NMR spectra were recorded in DMSO-*d*₆/ CD₃OD/ CDCl₃ solution in 5mm o.d. tubes [Wilmad NMR tubes (Sigma-Aldrich), 5mm Thin Wall, 7" Length] at 300.0 K and were collected on Bruker Avance NMRS-400 at 400 MHz for ¹H. The chemical shifts (δ) are relative to CDCl₃ (CDCl₃ = 7.26 ppm), *d*₆-DMSO (*d*₆-DMSO = 2.5 ppm), CD₃OD (CD₃OD = 3.3 ppm) and expressed in ppm. The chemical shifts in CDCl₃, *d*₆-DMSO and CD₃OD are relative to tetramethylsilane (TMS, = 0.00 ppm) and expressed in ppm.

All LC-MS were done using following methods;

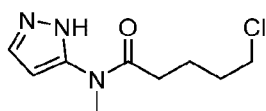
Column- ZORBAX EXT (4.6X50mm, 5u), (mobile phase: from 90% [10 mM NH₄OAc in water] and 10% [CH₃CN] to 70% [10 mM NH₄OAc in water] and 30% [CH₃CN] in 1.5 min, further to 10% [10 mM NH₄OAc in water] and 90% [CH₃CN] in 3.0 min, held this mobile phase composition up to 4.0 min and finally back to initial condition in 5.0 min). Flow = 1.2ml/min.

Column- Restek Ultra AQ C18 (30 x 2.1 mm, 3u), (mobile phase: 98% [0.05% HCOOH in water] and 2% [CH₃CN] held for 0.75 min, then to 90% [0.05% HCOOH in water] and 10% [CH₃CN] in 1.0 min, further to 2% [0.05% HCOOH in water] and 98% [CH₃CN] in 2.0 min, held this mobile phase composition up to 2.25 min and finally back to initial condition in 3.0 min). Flow = 1.5 ml/min



Step 1: 5-chloro-N-(1-(5-chloropentanoyl)-1H-pyrazol-5-yl)-N-methylpentanamide

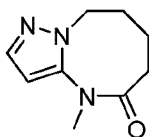
To a stirred solution of N,5-dimethyl-1H-pyrazol-3-amine (0.500 g, 5.15 mmol) in anhydrous dichloromethane (25 mL) cooled to 0 °C was added *N,N*-diisopropylethylamine (2.0 mL, 15.4 mmol) followed by dropwise addition of 5-chloropentanoyl chloride (1.65 mL, 12.9 mmol) under nitrogen. To the resulting mixture was added 4-dimethylaminopyridine (33.0 mg, 0.515 mmol), and the reaction mixture was stirred at RT for 6 h. The mixture was diluted with dichloromethane (2 x 125 mL), and washed with saturated sodium bicarbonate (1 x 100 mL), water (1 x 100 mL), brine (1 x 100 mL), dried over sodium sulphate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 20 to 30% ethyl acetate in hexane) to afford 5-chloro-N-(1-(5-chloropentanoyl)-1H-pyrazol-5-yl)-N-methylpentanamide (1.3 g, 76%) as a yellow oil: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.36 (s, 1H); 6.8 (br. s, 1H); 3.69-3.64 (m, 5H); 3.31 (s, 3H); 3.10-3.07 (m, 2H); 2.55 (br. s, 1H); 1.80-1.62 (m, 8H). LCMS *R*_T = 3.46 min, *m/z* = 334 (M+H)⁺.



Step 2: 5-chloro-N-methyl-N-(1H-pyrazol-5-yl)pentanamide

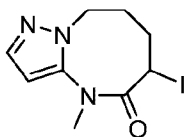
To a stirred solution of 5-chloro-N-(1-(5-chloropentanoyl)-1H-pyrazol-5-yl)-N-methylpentanamide (12.5 g, 37.4 mmol) in ethanol (70 mL) was added sodium hydroxide (1.5 g, 37.4 mmol) in water (37 mL) and the mixture was left to stand at RT for 5 min. The reaction mixture was concentrated to dryness *in vacuo*, diluted with water (200 mL) and extracted with ethyl acetate (3 x 150 mL). The filtrate was washed with water, brine, dried over sodium sulphate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 50 to 60% ethyl acetate in hexane) to afford 5-chloro-N-methyl-N-(1H-pyrazol-5-yl)pentanamide (6 g, 74%) as a yellow sticky solid: ¹H

NMR (400 MHz, DMSO- d_6) δ 12.76 (br. s, 1H); 7.75 (s, 1H); 6.22 (s, 1H); 3.55 (br. s, 2H); 3.09 (s, 3H); 2.17 (br. s, 2H); 1.60 (br. s, 4H). LCMS R_T = 2.45 min, m/z = 216.3 (M + H)⁺.



Step 3: 4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one

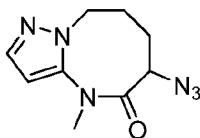
- 5 To a solution of 5-chloro-N-methyl-N-(1H-pyrazol-5-yl)pentanamide (5.0 g, 23.2 mmol) in anhydrous acetonitrile (200 mL) was added cesium carbonate (15.11 g, 46.4 mmol) and stirred at RT for 16 h. The reaction mixture was concentrated to dryness *in vacuo* and the residue was diluted with ethyl acetate (200mL) and washed with water (2 x 200 mL), brine (1 x 100 mL), dried over sodium sulphate and concentrated to dryness *in vacuo*. The residue was purified by
10 column chromatography (silica gel, 100-200 mesh, 40 to 50% ethyl acetate in hexane) to afford 4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one (3.4g, 82%) as a yellow solid: ¹H NMR (400 MHz, DMSO- d_6) δ 7.49 (s, 1H); 6.28 (s, 1H); 4.33-4.28 (m, 1H); 3.78-3.71 (m, 1H); 3.15 (s, 3H); 2.30-2.24 (m, 1H); 1.93-1.88 (m, 2H); 1.67-1.57 (m, 2H); 1.38-1.42 (m, 1H). LCMS R_T = 1.64 min, m/z = 180 (M + H)⁺.



15

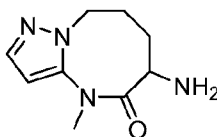
Step 4: 6-iodo-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one

- To a solution of 5-chloro-N-methyl-N-(1H-pyrazol-5-yl)pentanamide (3.4 g, 19.0 mmol) in dry dichloromethane (100 mL) under nitrogen cooled to $\sim -10^\circ\text{C}$ in a salt/ice bath was added N,N,N',N'-tetramethylethylenediamine (17.1 mL, 113.8 mmol) followed by
20 iodotrimethylsilane (15.8 mL, 113.8 mmol). The resulting solution was stirred in the salt/ice bath for 1.5 h, after which time was added iodine (14.44 g, 56.9 mmol). The mixture continued to stir in the salt/ice bath for another 2 h, after which time the reaction mixture was diluted with water (100 mL). The layers were separated, and the aqueous was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with sodium bisulfite (1 x 150 mL),
25 water (1 x 100 mL), brine (1 x 100 mL) and dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo* to afford 6-iodo-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one (5.5 g, 95%) as a light yellow oil, used as is in the next step: ¹H NMR (400 MHz, DMSO- d_6) δ 7.54 (s, 1H); 6.39 (s, 1H); 4.33-4.26 (m, 1H); 4.04-4.00 (m, 1H); 3.78-3.71 (m, 1H); 3.17 (s, 3H); 2.32-2.27 (m,
30 2H); 1.93-1.61 (m, 2H). LCMS R_T = 2.63 min, m/z = 306 (M + H)⁺.



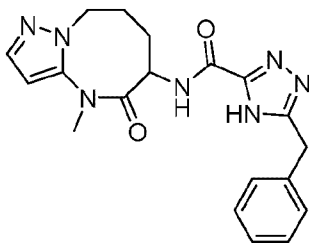
Step 5: 6-azido-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one

To a solution of 6-iodo-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one (1.3 g, 4.26 mmol) in N,N-dimethylformamide (15 mL) was added sodium azide (1.10 g, 17.0 mmol), and the reaction mixture was stirred at RT for 17 h. The reaction mixture was diluted with ethyl acetate (200 mL), washed with water (3 x 100 mL), brine (1 x 100 mL), dried over sodium sulfate and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 30 to 50% ethyl acetate in heptane) affording azido-6-azido-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one (0.500 g, 53%) as a yellow solid (0.606 g, 96%): ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.53 (s, 1H); 6.37 (s, 1H); 4.34-4.29 (m, 1H); 3.87-3.80 (m, 1H); 3.18 (s, 3H); 3.17-3.15 (m, 1H); 2.05-1.95 (m, 3H); 1.68-1.57 (m, 1H). LCMS R_T = 2.72 min, *m/z* = 221.2 (M + H)⁺.



Step 6: 6-amino-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one

To a solution of 6-azido-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one (2.2 g, 9.98 mmol) in methanol (50 mL) was added 10% palladium on carbon (1.0 g) under argon. The reaction mixture was stirred under hydrogen (balloon pressure) at RT for 17 h. The reaction mixture was filtered through Celite, the cake washed with 5% methanol in dichloromethane and the combined filtrate was concentrated to dryness *in vacuo* affording 6-amino-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one (1.65 g, 85%) as a viscous brown liquid used as is in the next step: ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.51 (s, 1H); 6.29 (s, 1H); 4.29-4.24 (m, 1H); 3.78-3.71 (m, 1H); 3.17 (s, 3H); 2.74-2.70 (m, 1H); 1.96-1.88 (m, 3H); 1.66-1.60 (m, 3H). LCMS R_T = 1.42 min, *m/z* = 195.2 (M + H)⁺.



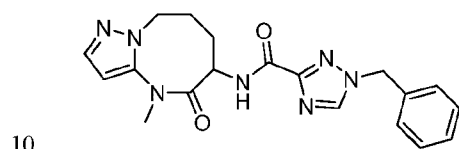
5-benzyl-N-(4-methyl-5-oxo-4,5,6,7,8,9-hexahydropyrazolo[1,5-a][1,3]diazocin-6-yl)-4H-1,2,4-triazole-3-carboxamide

Method B

(58mg, 75% yield)

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.27 (s, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.29 – 7.21 (m, 3H), 6.36 (d, *J* = 2.0 Hz, 1H), 4.42 – 4.29 (m, 1H), 4.09 (s, 2H), 3.97 – 3.80 (m, 2H), 3.21 (s, 3H), 2.07 – 1.96 (m, 1H), 1.93 – 1.77 (m, 2H), 1.66 – 1.53 (m, 1H). LCMS R_T = 3.61 min, *m/z* = 380.2 = (M + H)⁺.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.61 min, ESI+ found [M+H] = 380.2.

Example 94

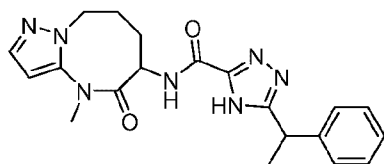
1-benzyl-N-(4-methyl-5-oxo-4,5,6,7,8,9-hexahydropyrazolo[1,5-a][1,3]diazocin-6-yl)-1H-1,2,4-triazole-3-carboxamide

Method B

(104mg, 80% yield)

15 ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.80 (s, 1H), 8.24 (d, *J* = 7.0 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.39 – 7.27 (m, 5H), 6.36 (d, *J* = 2.0 Hz, 1H), 5.47 (s, 2H), 4.42 – 4.28 (m, 1H), 3.98 – 3.77 (m, 2H), 3.21 (s, 3H), 2.08 – 1.95 (m, 1H), 1.92 – 1.76 (m, 2H), 1.67 – 1.54 (m, 1H). LCMS R_T = 3.72 min, *m/z* = 380.2 = (M + H)⁺.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.72 min, ESI+ found [M+H] = 380.2.

Example 95

N-(4-methyl-5-oxo-4,5,6,7,8,9-hexahydropyrazolo[1,5-a][1,3]diazocin-6-yl)-5-(1-phenylethyl)-4H-1,2,4-triazole-3-carboxamide

Method B

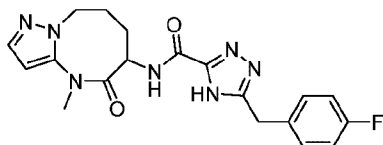
(34mg, 56% yield)

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.31 – 8.20 (m, 1H), 7.59 – 7.54 (m, 1H), 7.36 – 7.17 (m, 6H), 6.41 – 6.32 (m, 1H), 4.47 – 4.24 (m, 2H), 4.02 – 3.76 (m, 2H), 3.22 (s, *J* = 2.4 Hz, 3H), 2.05 –

1.97 (m, 1H), 1.92 – 1.76 (m, 2H), 1.64 – 1.58 (m, 4H). LCMS R_T = 3.85 min, m/z = 394.2 = (M + H)⁺.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.85 min, ESI+ found [M+H] = 394.2.

5 Example 96



5-(4-fluorobenzyl)-N-(4-methyl-5-oxo-4,5,6,7,8,9-hexahydropyrazolo[1,5-a][1,3]diazocin-6-yl)-4H-1,2,4-triazole-3-carboxamide

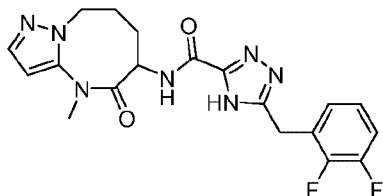
Method B

10 (24mg, 40% yield)

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.32 – 8.22 (m, 1H), 7.61 – 7.49 (m, 1H), 7.34 – 7.25 (m, 2H), 7.18 – 7.09 (m, 2H), 6.41 – 6.31 (m, 1H), 4.41 – 4.28 (m, 1H), 4.09 (s, 2H), 3.98 – 3.79 (m, 2H), 3.21 (s, 3H), 2.08 – 1.96 (m, 1H), 1.94 – 1.77 (m, 2H), 1.68 – 1.52 (m, 1H). LCMS R_T = 3.72 min, m/z = 398.1 = (M + H)⁺.

15 LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.72 min, ESI+ found [M+H] = 398.1

Example 97



5-(2,3-difluorobenzyl)-N-(4-methyl-5-oxo-4,5,6,7,8,9-hexahydropyrazolo[1,5-a][1,3]diazocin-6-yl)-4H-1,2,4-triazole-3-carboxamide.

20

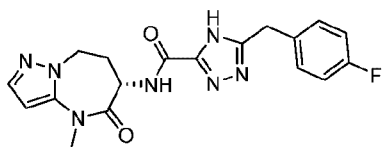
Method B

(41mg, 60% yield)

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.34 – 8.25 (m, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.39 – 7.27 (m, 1H), 7.23 – 7.10 (m, 2H), 6.35 (d, *J* = 2.0 Hz, 1H), 4.41 – 4.29 (m, 1H), 4.17 (s, 2H), 3.97 – 3.78 (m, 2H), 3.21 (s, 3H), 2.07 – 1.97 (m, 1H), 1.96 – 1.77 (m, 2H), 1.67 – 1.53 (m, 1H). LCMS R_T = 3.81 min, m/z = 416.2 (M + H)⁺.

25

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.81 min, ESI+ found [M+H] = 416.2

Example 98

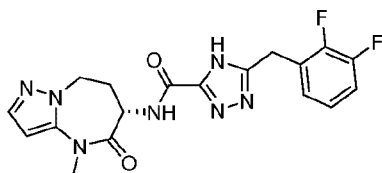
(S)-5-(4-fluorobenzyl)-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide

5 **Method B**

(55mg, 94% yield)

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.57 – 8.50 (m, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.38 – 7.24 (m, 2H), 7.20 – 7.08 (m, 2H), 6.34 (d, *J* = 2.1 Hz, 1H), 4.42 – 4.25 (m, 2H), 4.24 – 4.13 (m, 1H), 4.09 (s, 2H), 3.25 (s, 3H), 2.67 – 2.53 (m, 1H), 2.44 – 2.29 (m, 1H). LCMS R_T = 3.63 min, *m/z* = 384.1 (M + H)⁺.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.63 min, ESI⁺ found [M+H] = 384.1.

Example 99

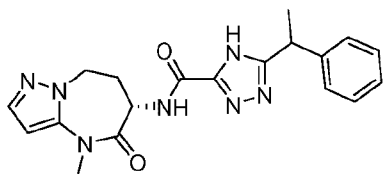
15 **(S)-5-(2,3-difluorobenzyl)-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide**

Method B

(42mg, 80% yield)

20 ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.62 – 8.51 (m, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.39 – 7.28 (m, 1H), 7.23 – 7.09 (m, 2H), 6.34 (d, *J* = 2.0 Hz, 1H), 4.41 – 4.26 (m, 2H), 4.23 – 4.14 (m, 3H), 3.24 (s, 3H), 2.62 – 2.55 (m, 1H), 2.44 – 2.33 (m, 1H). LCMS R_T = 3.71 min, *m/z* = 402.1 (M + H)⁺.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.71 min, ESI⁺ found [M+H] = 402.1.

Example 100

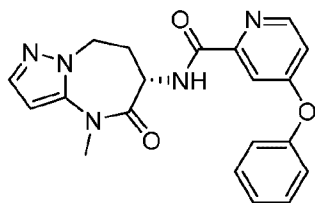
N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-(1-phenylethyl)-4H-1,2,4-triazole-3-carboxamide

5 Method B

(54mg, 74% yield)

^1H NMR (400 MHz, DMSO- d_6) δ 8.52 (s, 1H), 7.49 (d, $J = 2.0$ Hz, 1H), 7.36 – 7.18 (m, 6H), 6.34 (d, $J = 2.0$ Hz, 1H), 4.42 – 4.26 (m, 4H), 4.24 – 4.13 (m, 1H), 3.25 (s, 3H), 1.63 (d, $J = 7.3$ Hz, 3H). LCMS $R_T = 3.75$ min, $m/z = 380.2$ ($M + H$) $^+$.

- 10 LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.75 min, ESI+ found $[M+H] = 380.2$.

Example 101

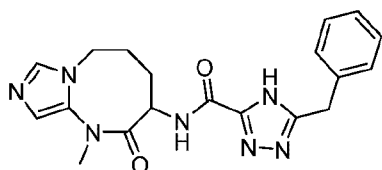
- 15 **(S)-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4-phenoxypicolinamide**

Method B

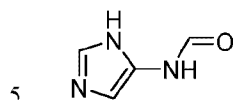
(22mg, 35% yield)

- 20 ^1H NMR (400 MHz, DMSO- d_6) δ 8.92 (d, $J = 7.8$ Hz, 1H), 8.62 – 8.54 (m, 1H), 7.57 – 7.45 (m, 3H), 7.39 – 7.30 (m, 2H), 7.27 – 7.17 (m, 3H), 6.33 (d, $J = 2.0$ Hz, 1H), 4.44 – 4.14 (m, 3H), 3.25 (s, 3H), 2.74 – 2.61 (m, 1H), 2.41 – 2.27 (m, 1H). LCMS $R_T = 4.59$ min, $m/z = 378.2$ ($M + H$) $^+$.

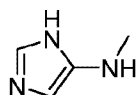
LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.59 min, ESI+ found $[M+H] = 378.2$.

Example 102

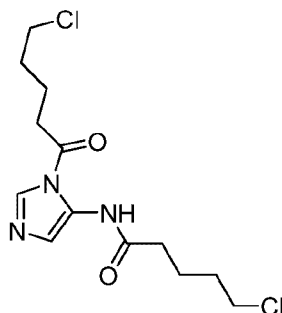
5-benzyl-N-(1-methyl-2-oxo-1,2,3,4,5,6-hexahydroimidazo[1,5-a][1,3]diazocin-3-yl)-4H-1,2,4-triazole-3-carboxamide

**Step 1: N-(1H-imidazol-5-yl)formamide**

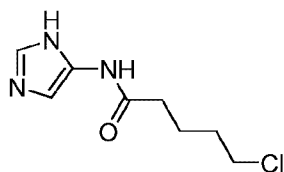
A solution of 3H-imidazol-4-ylamine (7.9g, 96.2mmol) in formic acid (32ml) was heated at 110°C for 2h in a sealed vessel. Reaction mass was cooled to RT and concentrated to dryness *in vacuo*. The residue was co-distilled with methanol (3 x 60ml) affording
 10 N-(3H-imidazol-4-yl)-formamide (9.0 g, 84.18%) as white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.38 (s, 1H), 10.51 (s, 1H), 8.16 (s, 1H), 7.61 (d, *J* = 8.6 Hz, 1H), 6.47 (s, 1H).

**Step 2: N-methyl-1H-imidazol-5-amine**

To a stirred solution of N-(3H-imidazol-4-yl)-formamide (4.5g, 40.5 mmol) in tetrahydrofuran
 15 (170mL) at ice cooled condition was added lithium aluminum hydride (2M solution in tetrahydrofuran, 61 mL, 121.6 mmol) very slowly under nitrogen and the reaction mixture was allowed to warm at RT gradually and stirred for 6h. The reaction was quenched with solid sodium sulfate and stirred at RT for 30 min. The reaction mixture was diluted with ethyl acetate and filtered through Celite bed and the filtrate was concentrated to dryness *in vacuo* to afford
 20 crude N-methyl-1H-imidazol-5-amine (3.17g, 81%) as colorless liquid, use as is in the next step.

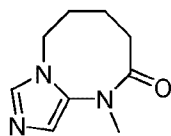
**Step 3: 5-chloro-N-(1-(5-chloropentanoyl)-1H-imidazol-5-yl)pentanamide**

To a stirred solution of N-methyl-1H-imidazol-5-amine (6.1 g, 62.1 mmol) in anhydrous dichloromethane (300 mL) cooled to 0 °C was added *N,N*-diisopropylethylamine (32.8 mL, 188.4 mmol) followed by dropwise addition of 5-chloropentanoyl chloride (19.5 mL, 150.7 mmol) under nitrogen. To the resulting mixture was added 4-dimethylaminopyridine (0.767 mg, 6.28 mmol), and the reaction mixture was stirred at RT for 16 h. The reaction mixture was concentrated to dryness *in vacuo* and the resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 20 to 25% ethyl acetate in hexane) affording 5-chloro-N-(1-(5-chloropentanoyl)-1H-imidazol-5-yl)pentanamide (17.5 g, 83%) as a yellow oil: LCMS $R_T = 1.67$ min, $m/z = 334.3$ $[M]^+$, 336.3 $[M+2]^+$



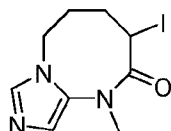
Step 4: 5-chloro-N-(1H-imidazol-5-yl)pentanamide

To a stirred solution of 5-chloro-N-(1-(5-chloropentanoyl)-1H-imidazol-5-yl)pentanamide (17.5 g, 52.4 mmol) in ethanol (105 mL) was added sodium hydroxide (2.1 g, 52.4 mmol) in water (52.5 mL) and the mixture was left to stand at RT for 5 min. The reaction mixture was concentrated to dryness *in vacuo*, diluted with water (200mL) and extracted with ethyl acetate (3 x 150 mL). The filtrate was washed with water, brine, dried over sodium sulphate and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 45 to 50% ethyl acetate in hexane) to afford 5-chloro-N-(1H-imidazol-5-yl)pentanamide (8.8 g, 78%) as a yellow oil: ^1H NMR (400 MHz, DMSO- d_6) δ 12.77 (s, 1H), 7.75 (s, 1H), 6.22 (s, 1H), 3.56 (br. s, 2H), 3.09 (s, 3H), 2.17 (s, 1H), 1.99 (br. s, 2H), 1.60 (br. s, 4H). LCMS $R_T = 2.57$ min, $m/z = 216.1$ (M+H) $^+$.



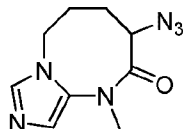
Step 5: 1-methyl-3,4,5,6-tetrahydroimidazo[1,5-a][1,3]diazocin-2(1H)-one

To a solution of 5-chloro-N-(1H-imidazol-5-yl)pentanamide (8.8 g, 40.8 mmol) in anhydrous acetonitrile (350 mL) was added cesium carbonate (26.6 g, 81.6 mmol) and stirred at RT for 16 h. The reaction mixture was concentrated to dryness *in vacuo* and the residue was purified by column chromatography (silica gel, 100-200 mesh, 45 to 50% ethyl acetate in hexane) to afford 1-methyl-3,4,5,6-tetrahydroimidazo[1,5-a][1,3]diazocin-2(1H)-one (5.6 g, 77%) as yellow solid: ^1H NMR (400 MHz, DMSO- d_6) δ 7.49 (s, 1H), 6.28 (s, 1H), 4.30 (br. d, $J = 14.09$ Hz), 3.75 (t, $J = 12.1$ Hz, 1H), 3.15 (s, 3H), 2.29-2.25 (m, 1H), 1.93-1.89 (m, 2H), 1.67-1.55 (m, 2H), 1.44-1.38 (m, 1H). LCMS $R_T = 1.90$ min, $m/z = 180.2$ (M + H) $^+$.



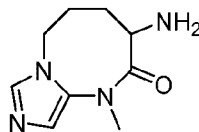
Step 6: 3-iodo-1-methyl-3,4,5,6-tetrahydroimidazo[1,5-a][1,3]diazocin-2(1H)-one

To a solution of 1-methyl-3,4,5,6-tetrahydroimidazo[1,5-a][1,3]diazocin-2(1H)-one (0.730 mg, 4.1 mmol) in dry dichloromethane (65 mL) under nitrogen cooled to $\sim -10^{\circ}\text{C}$ in a salt/ice bath was added N,N,N',N'-tetramethylethylenediamine (6.5 mL, 24.4 mmol) followed by iodotrimethylsilane (3.5 mL, 24.4 mmol). The resulting solution was stirred in the salt/ice bath for 1.5 h, after which time was added iodine (3.1 g, 12.2 mmol). The mixture continued to stir in the salt/ice bath for another 2 h, after which time the reaction mixture was diluted with water (100 mL). The layers were separated, and the aqueous was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with sodium bisulfite (1 x 150 mL), water (1 x 100 mL), brine (1 x 100 mL) and dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo* to afford 3-iodo-1-methyl-3,4,5,6-tetrahydroimidazo[1,5-a][1,3]diazocin-2(1H)-one (1.15 g, 93% crude yield) as a light yellow solid, used as is in the next step: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.54 (s, 1H), 6.42 – 6.39 (s, 1H), 4.29 (dd, $J = 14.6, 3.9$ Hz, 1H), 4.06-3.98 (m, 1H), 3.78-3.71 (m, 2H), 3.16 (s, 3H), 2.31-2.26 (s, 2H), 1.84-1.81 (m, 1H), 1.72-1.61 (m, 1H). LCMS $R_T = 2.54$ min, $m/z = 306.1$ ($M + H$) $^{+}$.



Step 7: 3-azido-1-methyl-3,4,5,6-tetrahydroimidazo[1,5-a][1,3]diazocin-2(1H)-one

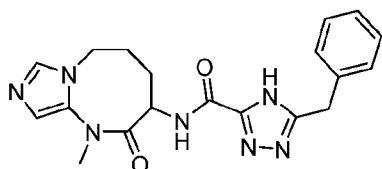
To a solution of 3-iodo-1-methyl-3,4,5,6-tetrahydroimidazo[1,5-a][1,3]diazocin-2(1H)-one (1.1 g, 3.61 mmol crude) in N,N-dimethylformamide (15 mL) was added sodium azide (0.94 g, 14.4 mmol), and the reaction mixture was stirred at RT for 17 h. The reaction mixture was diluted with ethyl acetate (200 mL), washed with water (3 x 100 mL), brine (1 x 100 mL), dried over sodium sulfate and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 25 to 30% ethyl acetate in hexane) affording 3-azido-1-methyl-3,4,5,6-tetrahydroimidazo[1,5-a][1,3]diazocin-2(1H)-one (0.600 g, 76 %) as a yellow solid: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.53 (s, 1H), 6.38 (s, 1H), 4.32 (d, $J = 14.7$ Hz, 1H), 3.84 (t, $J = 12.2$ Hz, 1H), 3.22 (s, 3H), 3.21-3.17 (m, 1H), 2.05-1.98 (m, 3H), 1.26-1.23 (m, 1H). LCMS $R_T = 1.33$ min, $m/z = 221.3$ ($M + H$) $^{+}$.



Step 8: 3-amino-1-methyl-3,4,5,6-tetrahydroimidazo[1,5-a][1,3]diazocin-2(1H)-one

To a solution of 3-azido-1-methyl-3,4,5,6-tetrahydroimidazo[1,5-a][1,3]diazocin-2(1H)-one (0.400 mg, 1.82 mmol) in methanol (12 mL) was added 10% palladium on carbon (0.200 g) under argon. The reaction mixture was stirred under hydrogen (balloon pressure) at RT for 3 h.

- 5 The reaction mixture was filtered through Celite, the cake washed with methanol and the combined filtrate was concentrated to dryness *in vacuo* affording 3-amino-1-methyl-3,4,5,6-tetrahydroimidazo[1,5-a][1,3]diazocin-2(1H)-one (0.27 mg, 77%) as a light yellow liquid used as is in the next step: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.51 (s, 1H), 6.30 (s, 1H), 4.27 (dd, $J = 14.4, 5.3$ Hz, 1H), 3.75 (t, $J = 11.3$ Hz, 1H), 3.17 (s, 3H),
 10 2.73-2.67 (m, 1H), 1.99-1.87 (m, 2H), 1.661.47 (m, 3H). LCMS $R_T = 3.64$ min, $m/z = 195.1$ ($M + H$) $^+$.

**Step 9:**

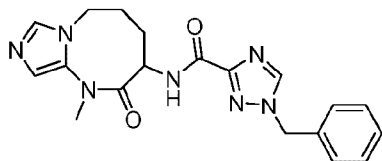
- 15 **5-benzyl-N-(1-methyl-2-oxo-1,2,3,4,5,6-hexahydroimidazo[1,5-a][1,3]diazocin-3-yl)-4H-1,2,4-triazole-3-carboxamide**

Method B

(19.6 mg, 25% yield)

- ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.31 – 8.21 (m, 1H), 7.56 (d, $J = 2.0$ Hz, 1H), 7.37 – 7.18 (m, 5H), 6.59 (s, 0H), 6.36 (d, $J = 2.0$ Hz, 1H), 4.41 – 4.29 (m, 1H), 4.09 (s, 2H), 3.98 – 3.76 (m, 2H), 3.21 (s, 3H), 2.06 – 1.98 (m, 1H), 1.93 – 1.79 (m, 2H), 1.68 – 1.52 (m, 1H). LCMS $R_T =$
 20 3.46 min, $m/z = 380.2$ ($M + H$) $^+$.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.46 min, ESI+ found $[M+H] = 380.2$.

Example 103

25

- 1-benzyl-N-(1-methyl-2-oxo-1,2,3,4,5,6-hexahydroimidazo[1,5-a][1,3]diazocin-3-yl)-1H-1,2,4-triazole-3-carboxamide**

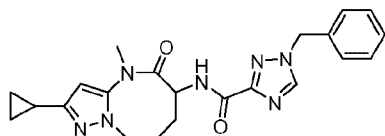
Method B

(44mg, 56% yield)

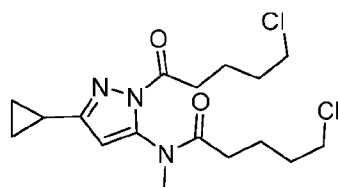
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.80 (s, 1H), 8.24 (d, $J = 7.1$ Hz, 1H), 7.56 (d, $J = 2.0$ Hz, 1H), 7.42 – 7.26 (m, 6H), 6.36 (d, $J = 2.0$ Hz, 1H), 5.47 (s, 2H), 4.42 – 4.29 (m, 1H), 3.97 – 3.76 (m, 2H), 3.21 (s, 3H), 2.07 – 1.97 (m, 1H), 1.92 – 1.77 (m, 2H), 1.68 – 1.53 (m, 1H). LCMS $R_T = 3.55$ min, $m/z = 380.2$ ($M + H$) $^+$.

- 5 LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.55 min, ESI+ found $[M+H] = 380.2$.

Example 104



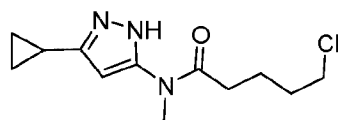
- 10 **1-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-4,5,6,7,8,9-hexahydropyrazolo[1,5-a][1,3]diazocin-6-yl)-1H-1,2,4-triazole-3-carboxamide**



Step 1:

5-chloro-N-(1-(5-chloropentanoyl)-3-cyclopropyl-1H-pyrazol-5-yl)-N-methylpentanamide

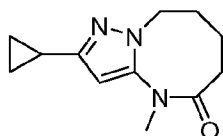
- 15 To a stirred solution of N,5-dimethyl-1H-pyrazol-3-amine (6 g, 43.7 mmol) in anhydrous dichloromethane (300 mL) cooled to 0 °C was added *N,N*-diisopropylethylamine (22.8 mL, 131.2 mmol) followed by dropwise addition of 5-chloropentanoyl chloride (13.5 mL, 104.96 mmol) under nitrogen. To the resulting mixture was added 4-dimethylaminopyridine (0.534 mg, 4.37 mmol), and the reaction mixture was stirred at RT for 16 h. The reaction mixture was
- 20 concentrated to dryness *in vacuo* to afford 5-chloro-N-(1-(5-chloropentanoyl)-3-cyclopropyl-1H-pyrazol-5-yl)-N-methylpentanamide (1.3 g, 76%) as a yellow oil used as is in the next step: LCMS $R_T = 1.79$ min, $m/z = 374.1$ (M) $^+$, 376.1($M+2$) $^+$



- 25 **Step 2: 5-chloro-N-(3-cyclopropyl-1H-pyrazol-5-yl)-N-methylpentanamide**

To a stirred solution of 5-chloro-N-(1-(5-chloropentanoyl)-3-cyclopropyl-1H-pyrazol-5-yl)-N-methylpentanamide (21.5 g, crude) in ethanol (115 mL) was added sodium hydroxide (2.29 g, 57.4 mmol) in water

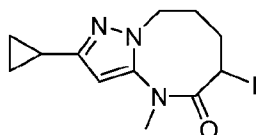
(57.6 mL) and the mixture was left to stand at RT for 5 min. The reaction mixture was concentrated to dryness *in vacuo*, and the residue was purified by column chromatography (silica gel, 100-200 mesh, 45 to 50% ethyl acetate in hexane) to afford 5-chloro-N-(3-cyclopropyl-1H-pyrazol-5-yl)-N-methylpentanamide (4.2 g, 34%) as a yellow oil, used as is in the next step: ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.47 (s, 1H), 5.89 (s, 1H), 3.56 (br. s, 2H), 3.04 (s, 3H), 2.18 (br. s, 2H), 1.87 (br. s, 1H), 1.61-1.57 (m, 4H), 0.92 (d, *J* = 6 Hz, 2H), 0.69 (br. s, 2H). LCMS R_T = 1.49 min, *m/z* = 256 (M)⁺, 258 (M+2)⁺



Step 3:

2-cyclopropyl-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one

To a solution of 5-chloro-N-(3-cyclopropyl-1H-pyrazol-5-yl)-N-methylpentanamide (4.2 g, 19.47 mmol) in anhydrous acetonitrile (200 mL) was added cesium carbonate (12.69 g, 38.95 mmol) and stirred at RT for 16 h. The reaction mixture was concentrated to dryness *in vacuo* and the residue was purified by column chromatography (silica gel, 100-200 mesh, 45 to 50% ethyl acetate in hexane) to afford 2-cyclopropyl-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one (3.5 g, 82%) as an off white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 5.99 (s, 1H), 4.30 (br. d, *J* = 10.04 Hz), 3.64 (t, *J* = 12.32 Hz, 1H), 3.11 (s, 3H), 2.27-2.22 (m, 1H), 1.87-1.78 (m, 3H), 1.69 (t, *J* = 11.8 Hz), 1.54-1.51 (m, 1H), 1.39-1.33 (m, 1H), 0.85-0.82 (m, 2H), 0.63 (br. s, 2H). LCMS R_T = 1.39 min, *m/z* = 220.0 (M + H)⁺.



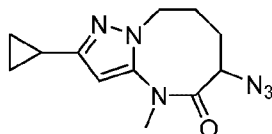
Step 4:

2-cyclopropyl-6-iodo-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one

To a solution of 2-cyclopropyl-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one (2.5 g, 11.4 mmol) in dry dichloromethane (65 mL) under nitrogen cooled to ~ -10 °C in a salt/ice bath was added N,N,N',N'-tetramethylethylenediamine (18.2 mL, 68.4 mmol) followed by iodotrimethylsilane (9.7 mL, 68.4 mmol). The resulting solution was stirred in the salt/ice bath for 1.5 h, after which time was added iodine (8.6 g, 34.2 mmol). The mixture continued to stir in the salt/ice bath for another 2 h, after which time the reaction mixture was diluted with water (100 mL). The layers were separated, and the aqueous was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with sodium bisulfite (1 x 150 mL), water (1

x 100 mL), brine (1 x 100 mL) and dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo* to afford 2-cyclopropyl-6-iodo-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one (4g, crude yield) as a light yellow oil, used as is in the next step.

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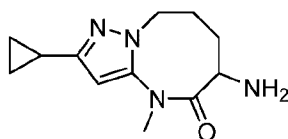


Step 4:

6-azido-2-cyclopropyl-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one.

To a solution of 2-cyclopropyl-6-iodo-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one (4 g, 15.4 mmol crude) in N,N-dimethylformamide (60 mL) was added sodium azide (3 g, 65.0 mmol), and the reaction mixture was stirred at RT for 17 h. The reaction mixture was diluted with ethyl acetate (200 mL), washed with water (3 x 100 mL), brine (1 x 100 mL), dried over sodium sulfate and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 25 to 30% ethyl acetate in hexane) affording 6-azido-2-cyclopropyl-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one (2 g, 66 % over two steps) as a yellow solid (0.606 g, 96%): ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.08 (s, 1H), 4.20 (dd, *J* = 14.8, 5.2 Hz, 1H), 3.72 (dd, *J* = 14.8, 11.5 Hz, 1H), 3.30-3.17 (m, 1H), 3.18 (s, 3H), 1.99-1.92 (m, 3H), 1.95 (s, 2H), 1.85-1.80 (m, 1H), 1.65-1.60 (m, 1H), 0.85 (dd, *J* = 8.4, 2.4 Hz, 3H), 0.64 (dd, *J* = 7.4, 5.1 Hz, 2H). LCMS *R*_T = 1.51 min, *m/z* = 261.1 (M + H)⁺.

20



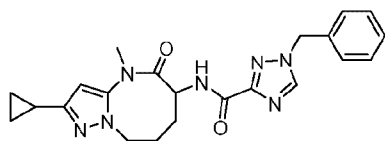
Step 5:

6-amino-2-cyclopropyl-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one

To a solution of 6-azido-2-cyclopropyl-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one (3 g, 11.5 mmol) in methanol (50 mL) was added 10% palladium on carbon (1.5 g) under argon. The reaction mixture was stirred under hydrogen (balloon pressure) at RT for 3 h. The reaction mixture was filtered through Celite, the cake washed with methanol and the combined filtrate was concentrated to dryness *in vacuo* affording

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6-amino-2-cyclopropyl-4-methyl-6,7,8,9-tetrahydropyrazolo[1,5-a][1,3]diazocin-5(4H)-one (2.2 g, 82%) as a viscous yellow liquid used as is in the next step: ^1H NMR (400 MHz, DMSO- d_6) δ 6.00 (s, 1H), 4.15 (dd, J = 14.2, 4.9 Hz, 1H), 3.64 (dd, J = 14.2, 11.4 Hz, 1H), 3.13 (s, 3H), 2.74 (d, J = 7.3 Hz, 1H), 1.95 (s, 1H), 1.83-1.82 (m, 2H), 1.63-1.52 (m, 3H), 0.85 (d, J = 6.5 Hz, 2H), 0.63 (s, 2H). LCMS R_T = 2.12 min, m/z = 235.2 ($M + H$) $^+$.



Step 6:

1-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-4,5,6,7,8,9-hexahydropyrazolo[1,5-a][1,3]diazocin-6-yl)-1H-1,2,4-triazole-3-carboxamide

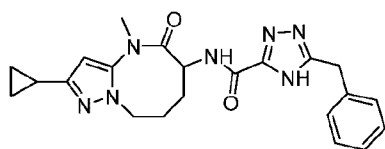
10 Method B

(29mg, 65% yield)

^1H NMR (400 MHz, DMSO- d_6) δ 8.80 (s, 1H), 8.21 (d, J = 7.1 Hz, 1H), 7.39 – 7.24 (m, 5H), 6.07 (s, 1H), 5.47 (s, 2H), 4.32 – 4.15 (m, 1H), 3.98 – 3.67 (m, 2H), 3.17 (s, 3H), 2.03 – 1.72 (m, 4H), 1.67 – 1.50 (m, 1H), 0.93 – 0.79 (m, 2H), 0.77 – 0.53 (m, 2H). LCMS R_T = 4.11 min, m/z = 420.2 ($M + H$) $^+$.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.11 min, ESI+ found $[M+H] = 420.2$.

Example 105



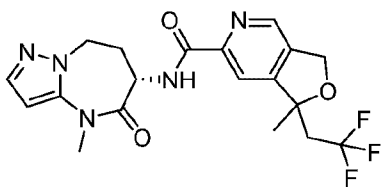
20 5-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-4,5,6,7,8,9-hexahydropyrazolo[1,5-a][1,3]diazocin-6-yl)-4H-1,2,4-triazole-3-carboxamide

Method B

(8.4 mg, 19% yield)

^1H NMR (400 MHz, DMSO- d_6) δ 8.44 (s, 0H), 8.28 – 8.17 (m, 1H), 7.42 – 7.18 (m, 4H), 6.68 (s, 1H), 6.07 (s, 1H), 4.29 – 4.18 (m, 1H), 4.09 (s, 2H), 3.93 – 3.72 (m, 2H), 3.17 (s, 3H), 2.03 – 1.74 (m, 4H), 1.65 – 1.50 (m, 1H), 0.91 – 0.81 (m, 2H), 0.71 – 0.56 (m, 2H). LCMS R_T = 3.97 min, m/z = 420.2 ($M + H$) $^+$.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.97 min, ESI+ found $[M+H] = 420.2$.

Example 106

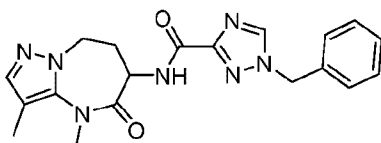
1-methyl-N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1-(2,2,2-trifluoroethyl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide

5 Method B

(50mg, 71% yield)

^1H NMR (400 MHz, DMSO- d_6) δ 8.94 – 8.88 (m, 1H), 8.67 (s, 1H), 8.14 (s, 1H), 7.51 (d, J = 2.0 Hz, 1H), 6.35 (d, J = 2.0 Hz, 1H), 5.19 – 5.11 (m, 2H), 4.45 – 4.33 (m, 2H), 4.31 – 4.16 (m, 1H), 3.27 (s, 3H), 3.14 – 3.03 (m, 1H), 2.99 – 2.87 (m, 1H), 2.78 – 2.62 (m, 1H), 2.41 – 2.29 (m, 1H), 1.50 (s, 3H). LCMS R_T = 4.22 min, m/z = 424.1 ($M + H$) $^+$.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.22 min, ESI+ found $[M+H] = 424.1$.

Example 107

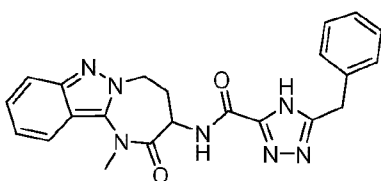
15 1-benzyl-N-(3,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide

Method B

(50mg, 64% yield)

^1H NMR (400 MHz, DMSO- d_6) δ 8.81 (s, 1H), 8.41 (d, J = 7.7 Hz, 1H), 7.44 – 7.25 (m, 6H), 5.48 (s, 2H), 4.34 – 4.12 (m, 3H), 3.21 (s, 3H), 2.61 – 2.53 (m, 1H), 2.29 – 2.19 (m, 1H), 2.01 (s, 3H). LCMS R_T = 3.71 min, m/z = 380.2 ($M + H$) $^+$.

LCMS (2 to 98% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.71 min, ESI+ found $[M+H] = 380.2$.

Example 108

25

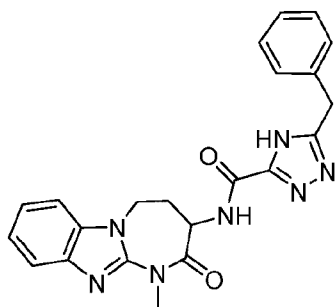
5-benzyl-N-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-[1,3]diazepino[1,2-b]indazol-3-yl)-4H-1,2,4-triazole-3-carboxamide

5-benzyl-N-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-[1,3]diazepino[1,2-b]indazol-3-yl)-4H-1,2,4-triazole-3-carboxamide was prepared from 1H-indazole-3-amine according to Method Z.

- 5 Yield of final step: 0.057 g, 70%: ^1H NMR (400 MHz, DMSO- d_6) δ 7.76 (dt, J = 8.5, 1.0 Hz, 1H), 7.62 (dt, J = 8.8, 0.9 Hz, 1H), 7.38 – 7.18 (m, 6H), 7.12 (ddd, J = 8.5, 6.6, 0.9 Hz, 1H), 4.61 (dd, J = 10.7, 4.1 Hz, 2H), 4.22 (dt, J = 11.4, 8.0 Hz, 1H), 4.11 (s, 2H), 3.47 (s, 3H), 2.18 (t, J = 7.4 Hz, 1H), 1.47 (d, J = 7.5 Hz, 1H). LC-MS R_T = 4.08 min, m/z = 416.2 ($M+H$) $^+$.

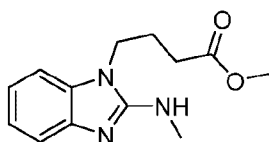
LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.08 min, ESI+ found $[M+H] = 416.2$.

Example 109



METHOD G2

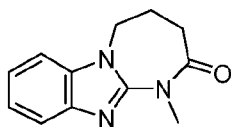
- 15 **5-benzyl-N-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[4,5]imidazo[1,2-a][1,3]diazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide**



Step 1: methyl 4-[2-(methylamino)benzimidazol-1-yl]butanoate

- To a solution of N-methyl-1H-benzimidazol-2-amine (1.36 g, 9.24 mmol, 1.00) in acetonitrile (40 mL) was added cesium carbonate (12 g, 37.0 mmol, 4 equiv) followed by methyl 4-bromobutanoate (1.40 mL, 2.01 g, 11.1 mmol, 1.0 equiv). The reaction mixture was stirred overnight at RT, then was filtered through Celite and concentrated to dryness *in vacuo*. The residue was purified by flash column chromatography (silica gel, 100-200 mesh, 0 to 10% methanol in dichloromethane) to afford methyl 4-[2-(methylamino)benzimidazol-1-yl]butanoate (0.65 g, 28%) as an orange oil.

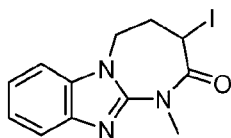
- 25 LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 0.88 min, ESI+ found $[M+H] = 248$.



Step 2: 1-methyl-4,5-dihydro-3H-[1,3]diazepino[1,2-a]benzimidazol-2-one

To a solution of methyl 4-[2-(methylamino)benzimidazol-1-yl]butanoate (0.650 g, 2.63 mmol) in methanol (3 mL) was added a solution of 1M aqueous sodium hydroxide (2.89 mL, 2.891 mmol, 1.100 equiv). The reaction mixture stirred at RT for 1 h. The mixture was concentrated to dryness *in vacuo* and resuspended in N,N-dimethylformamide (5 mL), and to it was added N,N-diisopropylethylamine (1.38 mL, 7.89 mmol, 3 equiv) followed by (7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (1.71 g, 3.15 mmol, 1.2 equiv). The reaction stirred 4 h at RT. The reaction mixture was diluted with isopropyl acetate (50 mL), then washed with water (50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to dryness *in vacuo*. The residue was purified by flash column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) to afford the product 1-methyl-4,5-dihydro-3H-[1,3]diazepino[1,2-a]benzimidazol-2-one (0.41 g, 72%) as a yellow solid.

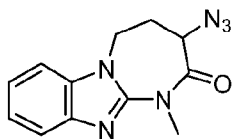
LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 0.96 min, ESI+ found $[M+H] = 216$.



Step 3: 3-iodo-1-methyl-4,5-dihydro-3H-[1,3]diazepino[1,2-a]benzimidazol-2-one

To a solution of 1-methyl-4,5-dihydro-3H-[1,3]diazepino[1,2-a]benzimidazol-2-one (0.375 g, 1.74 mmol) in dichloromethane (10 mL) cooled in a salt/ice bath was added N,N,N',N'-tetramethylethylenediamine (1.58 mL, 10.45 mmol, 6 equiv) followed by iodotrimethylsilane (1.491 mL, 10.45 mmol, 6 equiv). The reaction mixture was stirred for 1.5 h in the salt/ice bath, then was added iodine (1.33 g, 5.23 mmol, 3 equiv), and the mixture was stirred in the cooling bath for another 2 h. The reaction was then quenched by the addition of a saturated sodium sulfite solution (50 mL). The layers were separated, and the aqueous was extracted two more times with dichloromethane (2 x 50 mL). The combined organics were dried over sodium sulfate, filtered and concentrated to dryness *in vacuo*. The residue was purified by flash column chromatography (silica gel, 100-200 mesh, 0 to 50% isopropyl acetate in heptane) to afford 3-iodo-1-methyl-4,5-dihydro-3H-[1,3]diazepino[1,2-a]benzimidazol-2-one (0.445 g, 75% yield) as a white solid.

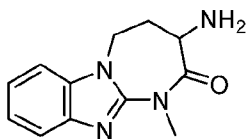
LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 1.06 min, ESI+ found $[M+H] = 342$.



Step 4: 3-azido-1-methyl-4,5-dihydro-3H-[1,3]diazepino[1,2-a]benzimidazol-2-one

- 5 To a solution of 3-iodo-1-methyl-4,5-dihydro-3H-[1,3]diazepino[1,2-a]benzimidazol-2-one (0.45 mg, 1.30 mmol) in N,N-dimethylformamide (2 mL) was added sodium azide (0.101 g, 1.57 mmol, 1.2 equiv). The reaction mixture was stirred for 2 h at RT, filtered through Celite, and concentrated to dryness *in vacuo*. The residue was purified by flash column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) to afford
- 10 3-azido-1-methyl-4,5-dihydro-3H-[1,3]diazepino[1,2-a]benzimidazol-2-one (0.315 g, 94%) as a white solid.

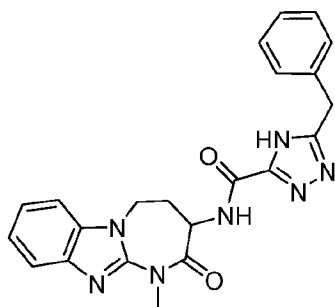
LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 1.04 min, ESI+ found $[M+H] = 257$.



Step 5: 3-amino-1-methyl-4,5-dihydro-3H-[1,3]diazepino[1,2-a]benzimidazol-2-one

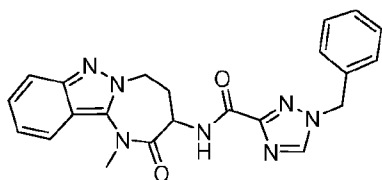
- To a solution of 3-azido-1-methyl-4,5-dihydro-3H-[1,3]diazepino[1,2-a]benzimidazol-2-one (0.315 g, 1.23 mmol, 1 equiv) in tetrahydrofuran (5 mL) was added water (1 mL) and polystyrene-bound triphenylphosphine resin (1.23 g, ~3 mmol/g loading, 3.69 mmol, 3 equiv). The reaction mixture was shaken for 16 h at RT, then was filtered through Celite and
- 20 concentrated to dryness *in vacuo*. The residue was purified by flash column chromatography (silica gel, 100-200 mesh, 0 to 15% methanol in dichloromethane) to afford 3-amino-1-methyl-4,5-dihydro-3H-[1,3]diazepino[1,2-a]benzimidazol-2-one (0.197 g, 70%) as a colorless oil.

- LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 0.76 min,
- 25 ESI+ found $[M+H] = 231$.

**Step 6:****5-benzyl-N-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[4,5]imidazo[1,2-a][1,3]diazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide**

- 5 To a solution of 3-amino-1-methyl-4,5-dihydro-3H-[1,3]diazepino[1,2-a]benzimidazol-2-one (0.028 g, 0.12 mmol) in N,N-dimethylformamide (2 mL) was added 5-benzyl-4H-1,2,4-triazole-3-carboxylic acid (0.037 g, 0.18 mmol, 1.5 equiv), N,N-diisopropylamine (0.064 mL, 0.047 g, 0.36 mmol, 3 equiv), and (7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (0.076 mg, 0.14 mmol, 1.15 equiv). The reaction mixture was stirred for 16 h at RT, diluted with isopropyl acetate (25 mL), washed with water (25 mL) and brine (25 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to dryness *in vacuo*. The residue was purified by preparative RP-HPLC (5 to 50% acetonitrile in H₂O + 0.1% formic acid) to afford 5-benzyl-N-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[4,5]imidazo[1,2-a][1,3]diazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide (0.014 g, 27%) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 14.32 (s, 1H), 8.61 (s, 1H), 7.67 – 7.58 (m, 2H), 7.36 – 7.19 (m, 7H), 4.72 – 4.61 (m, 1H), 4.49 (dt, J = 11.5, 7.8 Hz, 1H), 4.19 – 3.98 (m, 3H), 3.42 (s, 3H), 2.76 – 2.60 (m, 1H), 2.61 – 2.51 (m, 1H). LC-MS R_T = 3.97 min, m/z = 416.2 (M+H)⁺.

- LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.97 min, ESI+ found [M+H] = 416.2.

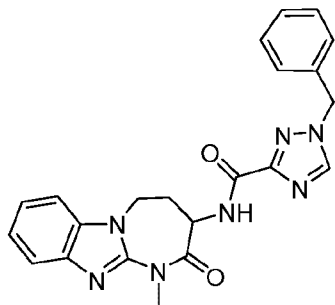
Example 110**1-benzyl-N-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-[1,3]diazepino[1,2-b]indazol-3-yl)-1H-1,2,4-triazole-3-carboxamide**

- 25 1-benzyl-N-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-[1,3]diazepino[1,2-b]indazol-3-yl)-1H-1,2,4-triazole-3-carboxamide was prepared from 1H-indazole-3-amine according to Methods Z and G1. Yield of final step: 0.033 g, 52%: ¹H NMR (400 MHz, DMSO-d₆) δ 8.81 (s, 1H), 8.57

(d, $J = 7.7$ Hz, 1H), 7.76 (dt, $J = 8.5, 1.0$ Hz, 1H), 7.62 (dt, $J = 8.8, 0.9$ Hz, 1H), 7.43 – 7.25 (m, 6H), 7.12 (ddd, $J = 8.5, 6.6, 0.9$ Hz, 1H), 5.47 (s, 2H), 4.65 – 4.56 (m, 2H), 4.22 (dt, $J = 11.5, 7.9$ Hz, 1H), 3.47 (s, 3H), 2.79 – 2.65 (m, 1H), 2.61 – 2.51 (m, 1H). LC-MS $R_T = 4.26$ min, $m/z = 416.2$ ($M+H$)⁺.

- 5 LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.26 min, ESI+ found $[M+H] = 416.2$.

Example 111

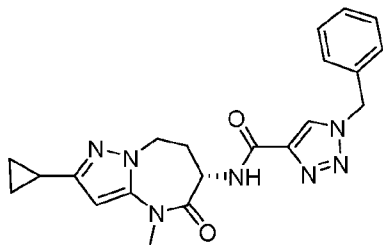


- 10 1-benzyl-N-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[4,5]imidazo[1,2-a][1,3]diazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide was prepared from 3-amino-1-methyl-4,5-dihydro-3H-[1,3]diazepino[1,2-a]benzimidazol-2-one according to Method G1. Yield: 0.011 g, 22%. ¹H NMR (400 MHz, DMSO-d₆) δ 8.83 (s, 1H), 8.69 (d, $J = 7.6$ Hz, 1H), 7.68 – 7.56 (m, 2H), 7.43 – 7.17 (m, 8H), 5.49 (s, 2H), 4.71 – 4.60 (m, 1H), 4.48 (dt, $J = 11.5, 7.7$ Hz, 1H), 4.05 (ddd, $J = 14.6, 12.8, 6.5$ Hz, 1H), 3.42 (s, 3H), 2.76 – 2.62 (m, 1H), 2.56 – 2.45 (m, 1H). LC-MS $R_T = 4.08$ min, $m/z = 416.2$ ($M+H$)⁺.
- 15

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.08 min, ESI+ found $[M+H] = 416.2$.

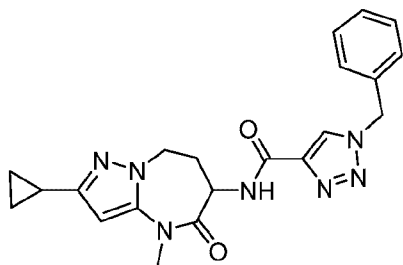
Example 112

METHOD G3



20

(S)-1-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,3-triazole-4-carboxamide

**Step 1:****1-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,3-triazole-4-carboxamide**

5 To a solution of 6-amino-2-cyclopropyl-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (0.029 g, 0.13 mmol, 1 equiv) in N,N-dimethylformamide (2 mL) was added 1-benzyltriazole-4-carboxylic acid (0.040 g, 0.20 mmol, 1.5 equiv), N,N-diisopropylethylamine (0.069 mL, 0.40 mmol, 3 equiv), and
 10 (7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (0.082 g, 0.15 mmol, 1.15 equiv). The reaction mixture was stirred overnight, then was diluted with isopropyl acetate (25 mL), washed with water (25 mL) and brine (25 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to dryness *in vacuo*. The residue was purified by preparative RP-HPLC (5 to 50% acetonitrile in H₂O + 0.1% formic acid) to afford
 15 1-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,3-triazole-4-carboxamide (0.030 g, 56% yield) as a white solid.

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.46 min, ESI⁺ found [M+H] = 406.2

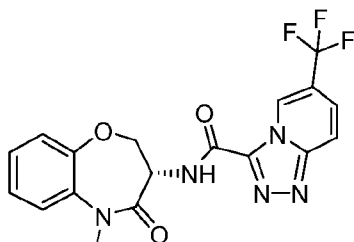
1-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,3-triazole-4-carboxamide was further purified by chiral SFC (Whelk O-1 column, 40% methanol + 0.1% ammonium hydroxide isocratic elution) affording arbitrarily assigned enantiomers (R)-
 1-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,3-triazole-4-carboxamide (0.014 g, 26%) and
 25 (S)-5-1-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,3-triazole-4-carboxamide (0.013 g, 24%) as white solids:

Analytical data for the first eluting enantiomer (arbitrarily assigned R configuration): SFC R_T (Whelk O-1 column, 40% methanol + 0.1% ammonium hydroxide isocratic elution, 2.5 min method): 0.773 min, 100% ee: ¹H NMR (400 MHz, DMSO-d₆) δ 8.66 (s, 1H), 8.60 (d, J = 7.9 Hz, 1H), 7.54 – 7.15 (m, 5H), 6.05 (s, 1H), 5.65 (s, 2H), 4.39 – 4.19 (m, 3H), 4.09 (ddd, J = 14.6, 12.6, 6.5 Hz, 1H), 3.19 (s, 3H), 2.62 – 2.52 (m, 1H), 2.40 – 2.28 (m, 1H), 1.85 (tt, J = 8.4, 5.0 Hz, 1H), 0.89 – 0.81 (m, 2H), 0.75 – 0.58 (m, 2H) LCMS R_T = 4.46 min, *m/z* = 406.2 (M+H)⁺.

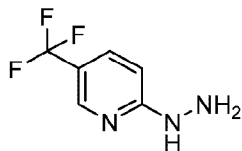
Analytical data for the second eluting enantiomer (arbitrarily assigned S configuration): SFC R_T : 0.960 min, 100% ee: ^1H NMR (400 MHz, DMSO- d_6) δ 8.66 (s, 1H), 8.60 (d, J = 7.9 Hz, 1H), 7.56 – 7.18 (m, 5H), 6.05 (s, 1H), 5.65 (s, 2H), 4.46 – 4.16 (m, 2H), 4.16 – 3.97 (m, 1H), 3.19 (s, 3H), 2.62 – 2.52 (m, 1H), 2.42 – 2.28 (m, 1H), 1.85 (tt, J = 8.4, 5.0 Hz, 1H), 0.91 – 0.80 (m, 2H), 0.73 – 0.59 (m, 2H). LCMS R_T = 4.42 min, m/z = 406.2 ($M+H$) $^+$.

Example 113

METHOD G4



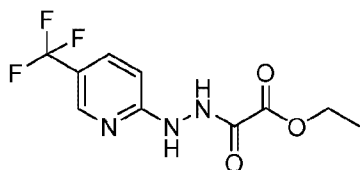
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide



Step 1: [5-(trifluoromethyl)-2-pyridyl]hydrazine

To a solution of 2-chloro-5-(trifluoromethyl)pyridine (1.0 g, 5.5 mmol) in ethanol (10 mL) in a large microwave vial was added hydrazine hydrate (1.25 mL, 22 mmol, 4 equiv). The vial was capped and heated in a microwave to 150 °C for 1 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (50 mL) and extracted with isopropyl acetate (3 x 75 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated to dryness *in vacuo* to afford [5-(trifluoromethyl)-2-pyridyl]hydrazine (0.95 g, 97%) as a tan solid, which was used in the next step without further purification.

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 0.77 min, ESI+ found $[M+H] = 178$.

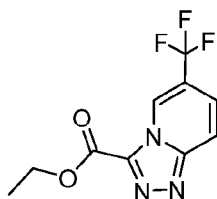


Step 2: ethyl 2-oxo-2-[2-[5-(trifluoromethyl)-2-pyridyl]hydrazino]acetate

To a solution of [5-(trifluoromethyl)-2-pyridyl]hydrazine (0.95mg, 5.4 mmol) in tetrahydrofuran (25 mL) cooled to 0 °C was added N,N-diisopropylethylamine (1.87 mL, 10.7

mmol, 2 equiv) followed by ethyl 2-chloro-2-oxo-acetate (0.66 mL, 5.9 mmol, 1.1 equiv). The reaction mixture was allowed to slowly warm to RT with stirring for 16 h. The mixture was concentrated to dryness *in vacuo* and purified by flash column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording ethyl 2-oxo-2-[2-[5-(trifluoromethyl)-2-pyridyl]hydrazino]acetate (0.63 g, 42%) as an orange solid.

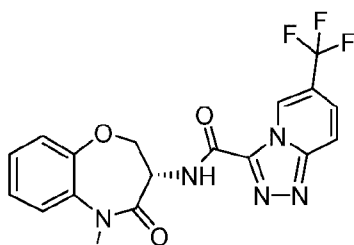
LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 1.15 min, ESI+ found $[M+H] = 278$.



Step 3: ethyl 6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate

A suspension of ethyl 2-oxo-2-[2-[5-(trifluoromethyl)-2-pyridyl]hydrazino]acetate (0.63 g, 2.27 mmol) in phosphoryl chloride (6 mL, 64.6 mmol, 28.4 equiv) was heated to 100 °C for 16 h. The reaction mixture was cooled to RT and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% iPrOAc in heptane) affording ethyl 6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate (0.266 g, 45%) as an off-white solid.

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 1.23 min, ESI+ found $[M+H] = 260$.



Step 4:

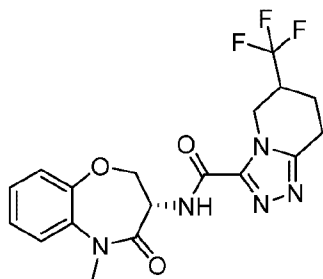
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide

To a solution of ethyl 6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate (0.266 g, 1.02 mmol) dissolved in tetrahydrofuran (4 mL) was added 1M aqueous sodium hydroxide (1.23 mL). The reaction mixture was stirred for 1 h at RT, then concentrated to dryness *in vacuo*. The residue was resuspended in N,N-dimethylformamide (2 mL), and to it was added [(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]ammonium chloride (0.040 g, 0.18 mmol), N,N-diisopropylethylamine (0.092 mL, 0.067 g, 0.52 mmol), and (7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (0.114 g, 0.21

mmol). The reaction mixture was stirred for 16 h at RT, then was purified directly by preparative RP-HPLC (20-60% acetonitrile in water + 0.1% formic acid) affording (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide (0.035 g, 49%) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 9.49 – 9.40 (m, 2H), 8.25 – 8.14 (m, 1H), 7.83 (dd, J = 9.6, 1.8 Hz, 1H), 7.58 – 7.49 (m, 1H), 7.40 – 7.19 (m, 3H), 4.95 (dt, J = 11.6, 7.8 Hz, 1H), 4.76 (dd, J = 11.7, 9.9 Hz, 1H), 4.47 (dd, J = 9.9, 7.7 Hz, 1H), 3.34 (s, 3H). LC-MS R_T = 4.09 min, m/z = 406.1 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.09 min, ESI⁺ found [M+H] = 406.1

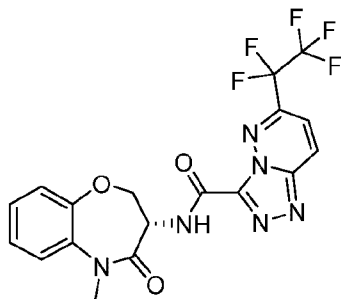
METHOD G5



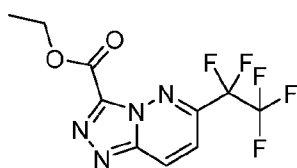
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide

To a solution of (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide (0.046 g, 0.11 mmol) in methanol (2 mL) was added palladium hydroxide (10 wt%, 0.024 g, 0.017 mmol, 0.15 equiv). The reaction mixture stirred under a balloon of hydrogen gas for 16 h at RT, then was filtered through Celite and concentrated to dryness *in vacuo*. The residue was purified by flash column chromatography (silica gel, 100-200 mesh, 0 to 10% methanol in dichloromethane) affording N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide (0.034 g, 73%) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 8.96 (d, J = 8.0 Hz, 1H), 7.55 – 7.47 (m, 1H), 7.37 – 7.20 (m, 3H), 4.89 – 4.79 (m, 1H), 4.72 – 4.54 (m, 2H), 4.41 (ddd, J = 9.8, 7.6, 3.4 Hz, 1H), 4.06 (dd, J = 13.3, 10.4 Hz, 1H), 3.31 (s, 3H), 3.23 – 3.05 (m, 2H), 3.00 – 2.86 (m, 1H), 2.22 – 2.10 (m, 1H), 1.99 – 1.83 (m, 1H). LC-MS R_T = 4.56 min, m/z = 410.1 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.56 min, ESI⁺ found [M+H] = 410.1

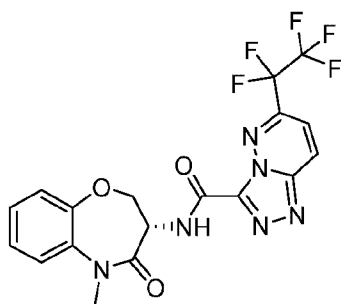
Example 114**METHOD G6**

(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(perfluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxamide

**Step 1: ethyl****6-(1,1,2,2,2-pentafluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxylate**

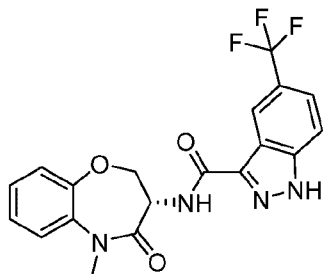
To a solution of ethyl 6-chloro-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxylate (0.2 g, 0.88 mmol) in N,N-dimethylformamide (2 mL) was added (1,1,2,2,2-Pentafluoroethyl)(1,10-phenanthroline-κN1,κN10)copper (0.384 g, 1.06 mmol, 1.2 equiv). The reaction mixture was heated to 90 °C for 24 h, then was diluted with isopropyl acetate (25 mL) and water (25 mL). The layers were separated, and the aqueous was extracted two more times with isopropyl acetate (2 x 25 mL). The combined organics were washed with water and brine, dried over sodium sulfate, filtered and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording ethyl 6-(1,1,2,2,2-pentafluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxylate (0.031 g, 11%) as a pale yellow solid.

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 1.20 min, ESI+ found [M+H] = 311.



Step 2:**(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(perfluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxamide**

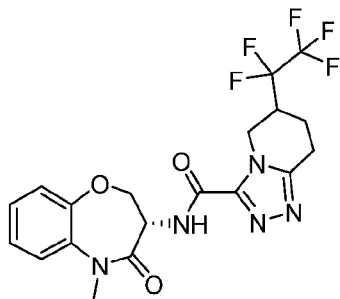
To a solution of ethyl 6-(1,1,2,2,2-pentafluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxylate (0.031 g, 0.10 mmol) dissolved in methanol (1 mL) was added 1M aqueous sodium hydroxide (0.15 mL). The reaction mixture was stirred for 1 h at 0 °C, then concentrated to dryness *in vacuo*. The residue was resuspended in N,N-dimethylformamide (2 mL), and to it was added [(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]ammonium chloride (0.025 g, 0.1 mmol), N,N-diisopropylethylamine (0.057 mL, 0.33 mmol), and (7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (0.071 g, 0.13 mmol). The reaction mixture was stirred for 16 h at RT, then was purified directly by preparative RP-HPLC (20-60% acetonitrile in water + 0.1% formic acid) affording (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide (0.015 g, 30%) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 9.30 (d, J = 7.8 Hz, 1H), 8.90 – 8.79 (m, 1H), 7.93 (d, J = 9.8 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.41 – 7.23 (m, 3H), 4.97 (dt, J = 11.4, 7.8 Hz, 1H), 4.62 (dd, J = 11.5, 9.9 Hz, 1H), 4.52 (dd, J = 9.9, 7.8 Hz, 1H), 3.35 (s, 3H). LC-MS R_T = 4.81 min, m/z = 457.1 (M+H)⁺. LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.81 min, ESI+ found [M+H] = 457.1

Example 115**METHOD G7**

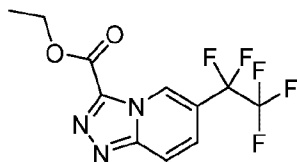
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-1H-indazole-3-carboxamide

To a solution of [(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]ammonium chloride (0.030 g, 0.13 mmol) in N,N-dimethylformamide (2 mL) was added 5-(trifluoromethyl)-1H-indazole-3-carboxylic acid (0.036 g, 0.16 mmol, 1.2 equiv), N,N-diisopropylethylamine (0.046 mL, 0.26 mmol, 2 equiv), and (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (0.078 g, 0.14 mmol, 1.1 equiv). The reaction mixture was stirred overnight at RT, then was purified directly by preparative RP-HPLC (20 to 70% acetonitrile in water + 0.1% formic acid) affording (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-1H-indazole-3-carboxamide (0.036 mg, 67%) as a light brown solid: ¹H NMR (400 MHz, DMSO-d₆) δ 14.15 (s, 1H), 8.62 (d, J = 8.0 Hz, 1H), 8.55 – 8.28 (m, 1H), 7.91 – 7.83 (m, 1H), 7.75 – 7.68 (m, 1H), 7.56 – 7.49 (m, 1H), 7.40 – 7.22 (m, 3H), 4.96 (dt, J = 11.6, 7.8 Hz, 1H), 4.66 (dd, J = 11.6, 9.9 Hz, 1H), 4.48 (dd, J = 9.9, 7.7 Hz, 1H), 3.34 (s, 3H). LC-MS R_T = 5.43 min, m/z = 405.1 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 5.43 min, ESI⁺ found [M+H] = 405.1

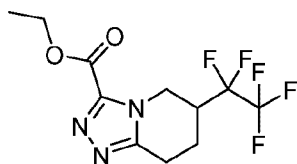
Example 116**METHOD G13**

N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(perfluoroethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide



Step 1: ethyl 6-(1,1,2,2,2-pentafluoroethyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate

- 5 To a solution of ethyl 6-bromo-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate (0.100 g, 0.37 mmol) in N,N-dimethylformamide (2 mL) was added (1,1,2,2,2-Pentafluoroethyl)(1,10-phenanthroline-κN1,κN10)copper (0.201 g, 0.56 mmol, 1.5 equiv). The reaction mixture was heated to 90 °C for 24 h, then was diluted with isopropyl acetate (25 mL) and water (25 mL). The layers were separated, and the aqueous was extracted two more times with isopropyl acetate (2 x 25 mL). The combined organics were washed with water and brine, dried over sodium sulfate, filtered and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording ethyl 6-(1,1,2,2,2-pentafluoroethyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate (0.055 mg, 0.18 mmol, 48%) as an off white solid.
- 15 LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 1.24 min, ESI+ found [M+H] = 310

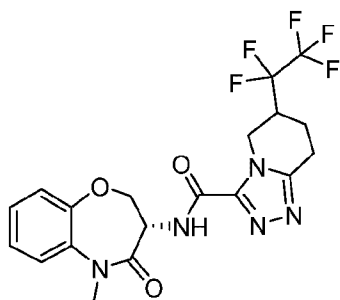


Step 2: ethyl

- 6-(1,1,2,2,2-pentafluoroethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate**
- 20 **ylate**

- To a solution of ethyl 6-(1,1,2,2,2-pentafluoroethyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate (0.055 g, 0.18 mmol) in methanol (2 mL) was added palladium hydroxide (10 wt%, 0.037 g, 0.027 mmol, 0.15 equiv). The reaction mixture stirred for 16 h at RT under a balloon of hydrogen. The reaction mixture was then filtered through Celite and concentrated to dryness *in vacuo* affording ethyl 6-(1,1,2,2,2-pentafluoroethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate (0.055 g, 98%) as a white solid which was used without further purification.
- 25

- LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 1.14 min, ESI+ found [M+H] = 314
- 30

**Step 3:****N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(perfluoroethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide**

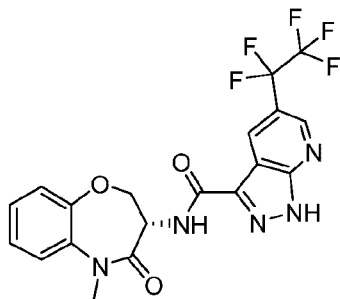
5 To a solution of ethyl 6-(1,1,2,2,2-pentafluoroethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate (0.055 g, 0.18 mmol) dissolved in methanol (1 mL) was added 1M aqueous sodium hydroxide (0.200 mL). The reaction mixture was stirred for 1 h at RT, then concentrated to dryness *in vacuo*. The residue was resuspended in N,N-dimethylformamide (2 mL), and to it was added

10 [(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]ammonium chloride (0.030 g, 0.13 mmol), N,N-diisopropylethylamine (0.069 mL, 0.39 mmol), and (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (0.086 g, 0.16 mmol). The reaction mixture was stirred for 16 h at RT, then was purified directly by preparative RP-HPLC (20-60% acetonitrile in water + 0.1% formic acid) affording

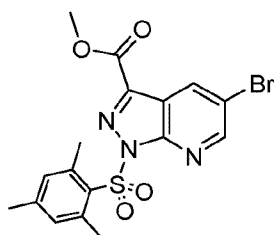
15 N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(perfluoroethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide (0.049 g, 81%) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 8.95 (dd, J = 8.1, 1.3 Hz, 1H), 7.50 (ddd, J = 7.3, 1.9, 0.9 Hz, 1H), 7.38 – 7.26 (m, 2H), 7.26 – 7.20 (m, 1H), 4.89 – 4.78 (m, 1H), 4.72 – 4.59 (m, 2H), 4.40 (ddd, J = 9.8, 7.6, 3.3 Hz, 1H), 4.13 – 4.02 (m, 1H), 3.32 (s, 3H), 3.17 – 3.08 (m, 1H), 3.00 –

20 2.88 (m, 1H), 2.26 – 2.15 (m, 1H), 2.01 – 1.83 (m, 1H). LC-MS R_T = 5.00 min, m/z = 460.1 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 5.00 min, ESI+ found [M+H] = 460.1

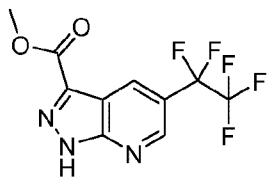
Example 117**METHOD G8**

(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(perfluoroethyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxamide

**Step 1: methyl****5-bromo-1-(2,4,6-trimethylphenyl)sulfonyl-pyrazolo[3,4-b]pyridine-3-carboxylate**

To a suspension of methyl 5-bromo-1H-pyrazolo[3,4-b]pyridine-3-carboxylate (0.500 g, 1.95 mmol) in tetrahydrofuran (10 mL) was added triethylamine (0.544 mL, 3.93 mmol, 2 equiv), 2-mesitylenesulfonyl chloride (0.475 g, 2.15 mmol, 1.1 equiv), and 4-(dimethylamino)pyridine 0.024mg, 0.20 mmol, 0.1 equiv). The reaction mixture was stirred at RT for 16 h, then was concentrated to dryness *in vacuo* affording methyl 5-bromo-1-(2,4,6-trimethylphenyl)sulfonyl-pyrazolo[3,4-b]pyridine-3-carboxylate (0.855 g, 99%) as an orange solid which was used in the next step without further purification.

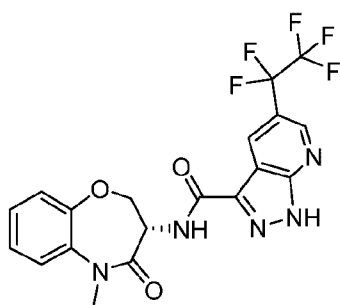
LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 1.77 min, ESI+ found [M+H] = 440

**Step 2: methyl 5-(1,1,2,2,2-pentafluoroethyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxylate**

To a solution of methyl 5-bromo-1-(2,4,6-trimethylphenyl)sulfonyl-pyrazolo[3,4-b]pyridine-3-carboxylate (0.855 g, 1.95 mmol) in 1-methyl-2-pyrrolidinone was added (1,1,2,2,2-pentafluoroethyl)(1,10-

phenanthroline- κ N1, κ N10)copper (0.990 g, 2.73 mmol, 1.4 equiv). The reaction mixture was heated to 80°C for 24 h, then was diluted with water (100 mL) and extracted with isopropyl acetate (3 x 50 mL). The combined organics were washed with water (75 mL) and brine (75 mL), dried over sodium sulfate, and concentrated to dryness *in vacuo*. The residue was purified by flash column chromatography (silica gel, 100-200 mesh, 0 to 25% isopropyl acetate in heptane) affording methyl 5-(1,1,2,2,2-pentafluoroethyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxylate (0.020 g, 3%) as a pale yellow oil.

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 1.24 min, ESI+ found $[M+H] = 296$



Step 3:

(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(perfluoroethyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxamide

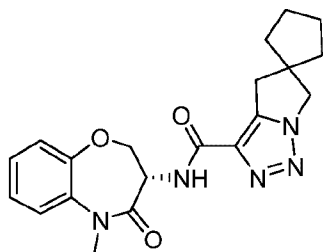
To a solution of methyl 5-(1,1,2,2,2-pentafluoroethyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxylate (0.020 g, 0.07 mmol) dissolved in methanol (1 mL) was added 1M aqueous sodium hydroxide (0.135 mL). The reaction mixture was stirred at 70 °C for 16 h, then concentrated to dryness *in vacuo*. The residue was resuspended in N,N-dimethylformamide (2 mL), and to it was added [(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]ammonium chloride (0.030 g, 0.13 mmol), N,N-diisopropylethylamine (0.069 mL, 0.39 mmol), and (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (0.086 g, 0.16 mmol). The reaction mixture was stirred for 16 h at RT, then was purified directly by preparative RP-HPLC (20-70% acetonitrile in water + 0.1% formic acid) affording (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(perfluoroethyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxamide (0.005 g, 17%) as a white solid: ^1H NMR (400 MHz, DMSO- d_6) δ 14.87 (s, 1H), 8.92 (d, $J = 2.2$ Hz, 1H), 8.82 (d, $J = 8.0$ Hz, 1H), 8.68 (d, $J = 2.2$ Hz, 1H), 7.54 – 7.50 (m, 1H), 7.38 – 7.22 (m, 3H), 4.95 (dt, $J = 11.6, 7.9$ Hz, 1H), 4.69 (dd, $J = 11.6, 9.9$ Hz, 1H), 4.47 (dd, $J = 9.9, 7.7$ Hz, 1H), 3.33 (s, 3H). LC-MS $R_T = 5.43$ min, $m/z = 456.1$ ($M+H$) $^+$.

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 5.43 min, ESI+ found $[M+H] = 456.1$

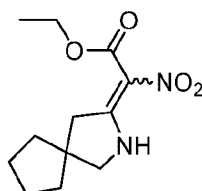
Example 118

METHOD G9

5

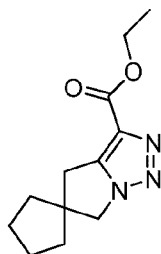


(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4'H,6'H-spiro[cyclopentane-1,5'-pyrrolo[1,2-c][1,2,3]triazole]-3'-carboxamide



Step 1: ethyl 2-(8-azaspiro[4.4]nonan-7-ylidene)-2-nitroacetate

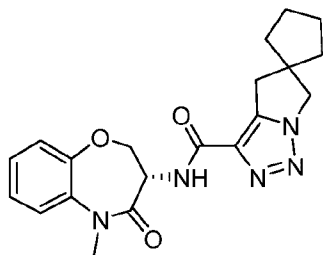
- 10 To a solution of 8-azaspiro[4.4]nonan-7-one (1.39 g, 10 mmol) in dichloromethane (50 mL) was added potassium carbonate (4.15 g, 30 mmol, 3 equiv) and trimethyloxonium tetrafluoroborate (2.96 g, 20 mmol, 2 equiv). The reaction mixture was stirred for 16 h at RT, then was diluted with water (100 mL) and the layers separated. The aqueous was extracted two more times with dichloromethane (2 x 75 mL). The combined organics were washed with brine
- 15 (50 mL), dried over sodium sulfate, and concentrated to dryness *in vacuo*. The residue was resuspended in ethyl nitroacetate (4.45 mL, 40 mmol, 4 equiv) and heated to 70 °C for 7 h. After cooling to rt, the mixture was purified directly by flash column chromatography (silica gel, 100-200 mesh, 0 to 50% isopropyl acetate in heptane) affording ethyl 2-(8-azaspiro[4.4]nonan-7-ylidene)-2-nitroacetate (1.09 g, 43%) as a yellow oil.
- 20 LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 1.25 min, ESI+ found $[M+H] = 255$



Step 2: ethyl spiro[4,6-dihydropyrrolo[1,2-c]triazole-5,1'-cyclopentane]-3-carboxylate

To a solution of ethyl (2E)-2-(8-azaspiro[4.4]nonan-7-ylidene)-2-nitro-acetate (1.09 g, 4.29 mmol) in acetic acid (13.4 mL) cooled to 0 °C was added zinc dust (1.68 g, 25.7 mmol, 6 equiv). The reaction mixture was warmed to RT and stirred for 1 h. After this time, the mixture was
 5 filtered through Celite, the filtrate was cooled to 0 °C, and to it was added trifluoroacetic acid (1.13 mL, 15.0 mmol, 3.5 equiv) followed by tert-butyl nitrite (1.68 mL, 14.1 mmol, 3.3 equiv). The reaction mixture was warmed to RT and stirred for 2 h. After this time, water (13.4 mL) was added, and then the entire mixture was concentrated to dryness *in vacuo*. The residue was purified by flash column chromatography (silica gel, 100-200 mesh, 0 to 70% isopropyl acetate
 10 in heptane) affording ethyl spiro[4,6-dihydropyrrolo[1,2-c]triazole-5,1'-cyclopentane]-3-carboxylate (0.410 g, 47%).

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 1.18 min, ESI+ found [M+H] = 236

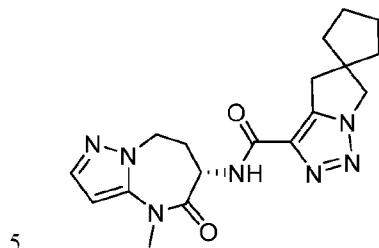


15 **Step 3:**
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4'H,6'H-spiro[cyclopentane-1,5'-pyrrolo[1,2-c][1,2,3]triazole]-3'-carboxamide

To a solution of ethyl spiro[4,6-dihydropyrrolo[1,2-c]triazole-5,1'-cyclopentane]-3-carboxylate (0.105 g, 0.45
 20 mmol) dissolved in methanol (1 mL) was added 1M aqueous sodium hydroxide (0.893 mL). The reaction mixture was stirred at 50 °C for 1 h, then concentrated to dryness *in vacuo*. The residue was resuspended in N,N-dimethylformamide (2 mL), and to it was added [(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]ammonium chloride (0.035 g, 0.15 mmol), N,N-diisopropylethylamine (0.080 mL, 0.46 mmol), and
 25 (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (0.100 g, 0.18 mmol). The reaction mixture was stirred for 16 h at RT, then was purified directly by preparative RP-HPLC (20-60% acetonitrile in water + 0.1% formic acid) affording (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(perfluoroethyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxamide (0.039 g, 66%) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 8.39 (d, J = 8.0 Hz, 1H), 7.53 – 7.46 (m, 1H), 7.38 – 7.19 (m, 3H), 4.84 (dt, J = 11.6, 7.9 Hz, 1H), 4.61 (dd, J = 11.6, 9.9 Hz, 1H), 4.40 (dd, J = 9.9, 7.7 Hz, 1H), 4.25 (d, J = 0.9
 30 Hz, 2H).

Hz, 2H), 3.31 (s, 3H), 2.88 (s, 2H), 1.80 – 1.62 (m, 8H). LC-MS R_T = 4.82 min, m/z = 382.2 ($M+H$)⁺.

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.82 min, ESI+ found $[M+H]$ = 382.2

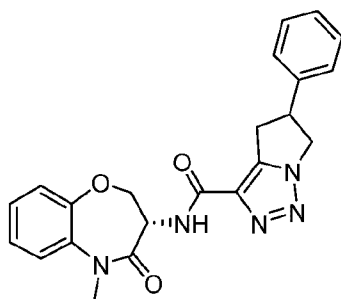


(S)-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4'H,6'H-spiro[cyclopentane-1,5'-pyrrolo[1,2-c][1,2,3]triazole]-3'-carboxamide

(S)-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4'H,6'H-spiro[cyclopentane-1,5'-pyrrolo[1,2-c][1,2,3]triazole]-3'-carboxamide was prepared from
 10 (S)-6-amino-4-methyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepin-5(6H)-one according to METHOD G9. Yield of final step: 0.019 g, 30%: ¹H NMR (400 MHz, DMSO-d₆) δ 8.49 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 6.32 (d, J = 2.0 Hz, 1H), 4.43 – 4.27 (m, 2H), 4.25 (d, J = 1.0 Hz, 2H), 4.19 (ddd, J = 14.6, 12.7, 6.6 Hz, 1H), 3.25 (s, 3H), 2.89 (s, 2H), 2.58 (ddd, J = 12.9, 8.0, 5.0 Hz, 1H), 2.47 – 2.35 (m, 1H), 1.81 – 1.59 (m, 8H). LC-MS R_T = 3.80 min, m/z =
 15 370.2 ($M+H$)⁺.

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.80 min, ESI+ found $[M+H]$ = 370.2

Example 119



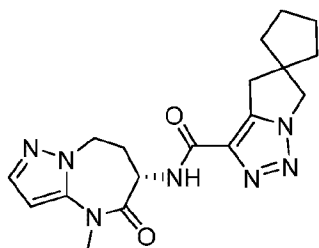
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-phenyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole-3-carboxamide

N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-phenyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole-3-carboxamide was prepared from 4-phenyl-2-pyrrolidinone according to METHOD G9. Yield of final step: 0.048 g, 78%: ¹H NMR (400 MHz, DMSO-d₆)
 25 δ 8.45 (d, J = 8.1 Hz, 1H), 7.53 – 7.45 (m, 1H), 7.42 – 7.20 (m, 8H), 4.91 – 4.81 (m, 2H), 4.63

(ddd, $J = 11.6, 9.9, 1.5$ Hz, 1H), 4.49 – 4.31 (m, 3H), 3.48 – 3.38 (m, 1H), 3.32 (s, 3H), 3.00 (dd, $J = 16.3, 8.4$ Hz, 1H). LC-MS $R_T = 4.93$ min, $m/z = 404.1$ ($M+H$)⁺.

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.93 min, ESI+ found $[M+H] = 404.1$

5 Example 120



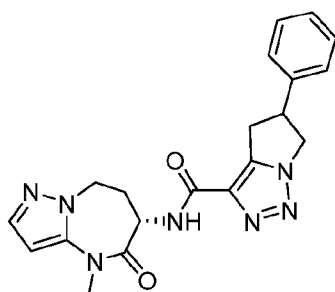
(S)-N-(4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-4'H,6'H-spiro[cyclopentane-1,5'-pyrrolo[1,2-c][1,2,3]triazole]-3'-carboxamide was prepared according to Method G9.

1H NMR (400 MHz, DMSO-d₆) δ 8.55 (d, $J = 7.8$ Hz, 1H), 7.49 (d, $J = 2.0$ Hz, 1H), 7.42 – 7.32 (m, 4H), 7.32 – 7.24 (m, 1H), 6.32 (d, $J = 2.0$ Hz, 1H), 4.85 (ddd, $J = 11.3, 8.1, 3.6$ Hz, 1H), 4.50 – 4.27 (m, 3H),

4.20 (ddd, $J = 14.6, 12.6, 6.6$ Hz, 1H), 3.48 – 3.38 (m, 1H), 3.25 (d, $J = 1.6$ Hz, 3H), 3.01 (dd, $J = 16.4, 8.3$ Hz, 1H), 2.66 – 2.54 (m, 1H), 2.48 – 2.37 (m, 1H).

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.97 min, ESI+ found $[M+H] = 392.2$

Example 121



N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-phenyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole-3-carboxamide

N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-phenyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole-3-carboxamide was prepared from (S)-6-amino-4-methyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepin-5(6H)-one and 4-phenyl-2-pyrrolidinone according to METHOD G9. Yield of final step: 0.013 g, 19%. ¹H

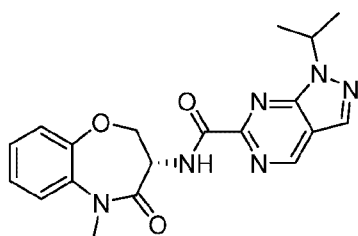
NMR (400 MHz, DMSO-d₆) δ 8.55 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.42 – 7.32 (m, 4H), 7.32 – 7.24 (m, 1H), 6.32 (d, J = 2.0 Hz, 1H), 4.85 (ddd, J = 11.3, 8.1, 3.6 Hz, 1H), 4.50 – 4.27 (m, 3H),

4.20 (ddd, J = 14.6, 12.6, 6.6 Hz, 1H), 3.48 – 3.38 (m, 1H), 3.25 (d, J = 1.6 Hz, 3H), 3.01 (dd, J = 16.4, 8.3 Hz, 1H), 2.66 – 2.54 (m, 1H), 2.48 – 2.37 (m, 1H). LC-MS R_T = 3.97 min, m/z = 392.2 ($M+H$)⁺.

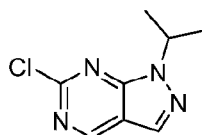
LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.97 min, ESI+ found $[M+H]$ = 392.2.

Example 122

10 METHOD G10



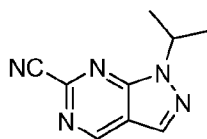
(S)-1-isopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-carboxamide



15 Step 1: 6-chloro-1-isopropyl-pyrazolo[3,4-d]pyrimidine

To a solution of 6-chloro-1H-pyrazolo[3,4-d]pyrimidine (0.417 g, 2.70 mmol) in 1-methyl-2-pyrrolidinone (2 mL) was added potassium carbonate (0.745 g, 5.40 mmol, 2 equiv) and 2-iodopropane (0.540 mL, 5.4 mmol, 2 equiv). The reaction mixture was stirred for 3 h at 60 °C, then was diluted with dichloromethane, filtered through Celite, and concentrated to dryness *in vacuo*. The residue was purified by flash column chromatography (silica gel, 100-200 mesh, 0 to 50% isopropyl acetate in heptane) affording 6-chloro-1-isopropyl-pyrazolo[3,4-d]pyrimidine (0.240 g, 45%) as a white solid.

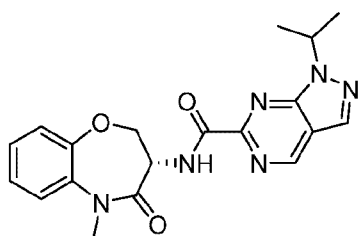
LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 1.11 min, ESI+ found $[M+H]$ = 197.



25 Step 2: 1-isopropylpyrazolo[3,4-d]pyrimidine-6-carbonitrile

To a solution of sodium cyanide (0.071 g, 1.46 mmol, 1.2 equiv) in water (1.5 mL) was added 1,4-diazabicyclo[2.2.2]octane (0.025 mL, 0.24 mmol, 0.20000 equiv), followed by a solution of 6-chloro-1-isopropyl-pyrazolo[3,4-d]pyrimidine (0.240 g, 1.2205 mmol, 1 equiv) in dimethyl sulfoxide (1.5 mL). The reaction mixture stirred for 16 h at RT, then was diluted with water (50 mL) and extracted with isopropyl acetate (3 x 50 mL). The combined organics were washed with brine (75 mL), dried over sodium sulfate, filtered and concentrated to dryness *in vacuo*. The residue was purified by flash column chromatography (silica gel, 100-200 mesh, 0 to 50% isopropyl acetate in heptane) affording 1-isopropylpyrazolo[3,4-d]pyrimidine-6-carbonitrile (0.036 g, 16%) as an orange solid.

- LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 1.14 min, ESI+ found [M+H] = 188.

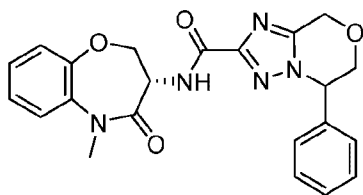


Step

3:

- (S)-1-isopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-carboxamide**

- To a suspension of 1-isopropylpyrazolo[3,4-d]pyrimidine-6-carbonitrile (0.036 g, 0.19 mmol) in water (0.5 mL) was added 1M aqueous sodium hydroxide (0.577 mL). The reaction mixture was stirred at 50 °C for 2 h, then concentrated to dryness *in vacuo*. The residue was resuspended in N,N-dimethylformamide (2 mL), and to it was added [(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]ammonium chloride (0.035 g, 0.15 mmol), N,N-diisopropylethylamine (0.080 mL, 0.46 mmol), and (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (0.100 g, 0.18 mmol). The reaction mixture was stirred for 16 h at RT, then was purified directly by preparative RP-HPLC (5-50% acetonitrile in water + 0.1% formic acid) affording (S)-1-isopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-carboxamide (0.028 g, 48%) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 9.46 (s, 1H), 9.13 (d, J = 7.8 Hz, 1H), 8.51 (s, 1H), 7.58 – 7.49 (m, 1H), 7.39 – 7.24 (m, 3H), 5.27 (p, J = 6.7 Hz, 1H), 4.92 (dt, J = 11.1, 7.9 Hz, 1H), 4.65 – 4.49 (m, 2H), 3.35 (s, 3H), 1.53 (dd, J = 6.7, 0.8 Hz, 6H). LC-MS R_T = 4.44 min, m/z = 381.1 (M+H)⁺.
- LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.44 min, ESI+ found [M+H] = 381.1

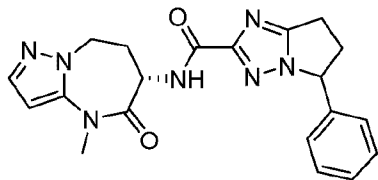
Example 123

N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-phenyl-5,6-dihydro-8H-[1,2,4]triazolo[5,1-c][1,4]oxazine-2-carboxamide

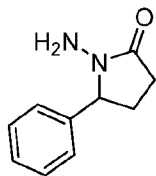
- 5 N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-phenyl-5,6-dihydro-8H-[1,2,4]triazolo[5,1-c][1,4]oxazine-2-carboxamide was prepared from 5-phenylmorpholin-3-one and (3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]ammonium chloride according to METHOD G11. Yield of final step: 0.025 g, 39%: ¹H NMR (400 MHz, DMSO-d₆) δ 8.48 (d, J = 8.0 Hz, 1H), 7.54 – 7.46 (m, 1H), 7.43 – 7.16 (m, 8H), 5.65 (t, J = 4.5 Hz, 1H), 5.13 (d, J = 15.7 Hz, 1H), 5.04 – 4.96 (m, 1H), 4.81 (dt, J = 11.5, 7.9 Hz, 1H), 4.59 (dd, J = 11.6, 9.9 Hz, 1H), 4.44 – 4.31 (m, 2H), 3.30 (s, 3H). LC-MS R_T = 4.57 min, m/z = 420.1 (M+H)⁺.
- 10

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 4.57 min, ESI⁺ found [M+H] = 420.1

15 **Example 124**

METHOD G11

N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-phenyl-1,6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



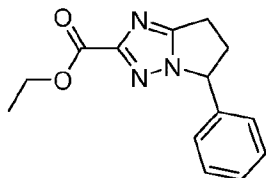
20

Step 1: 1-amino-5-phenylpyrrolidin-2-one

- To a solution of 5-phenylpyrrolidin-2-one (0.200 g, 1.24 mmol) in 1,2-dimethoxyethane (8 mL) was added sodium hydride (60% suspension in mineral oil, 0.099 g, 2.48 mmol, 2 equiv). The reaction mixture was stirred for 30 mins at RT, then was cooled to 0 °C. To the cooled mixture was added a solution of O-mesitylenesulfonylhydroxylamine (0.610 g, 2.83 mmol, 2.3
- 25

equiv) in 1,2-dimethoxyethane (5 mL). The resulting mixture was warmed to RT and stirred for 16 h. The reaction was quenched with methanol (0.1 mL) and concentrated to dryness *in vacuo*. The residue was purified by flash column chromatography (silica gel, 100-200 mesh, 0 to 7.5% methanol in isopropyl acetate) affording 1-amino-5-phenyl-pyrrolidin-2-one (0.195 g, 89%) as a white solid.

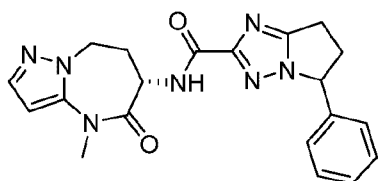
LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 1.11 min, ESI+ found $[M+H] = 177$.



Step 2: ethyl 5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxylate

- To a suspension of 1-amino-5-phenyl-pyrrolidin-2-one (0.150 g, 0.85 mmol) in toluene (1.5 mL) was added acetic acid (0.15 mL, 2.6 mmol, 3 equiv) followed by ethyl 2-amino-2-thioxo-acetate (0.125 g, 0.94 mmol, 1.1 equiv). The reaction mixture was heated to 90 °C and stirred for 16 h. The mixture was loaded directly onto silica gel and purified by flash column chromatography (silica gel, 100-200 mesh, 0 to 100% isopropyl acetate in heptane) affording ethyl 5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxylate (0.024 g, 11%) as a colorless oil.

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 2 mins) retention time 1.09 min, ESI+ found $[M+H] = 258$.



- Step 3:**
N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide

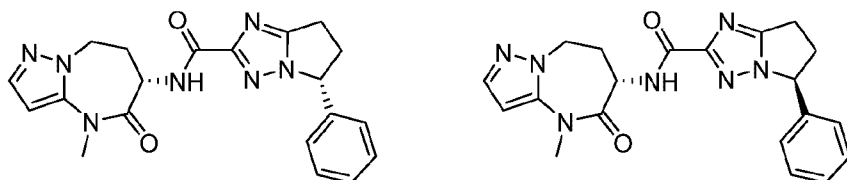
- To a solution of ethyl 5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxylate (0.024 g, 0.09 mmol) in tetrahydrofuran (0.5 mL) was added 1M aqueous sodium hydroxide (0.187 mL). The reaction mixture was stirred at 50 °C for 1 h, then concentrated to dryness *in vacuo*. The residue was resuspended in N,N-dimethylformamide (2 mL), and to it was added (S)-6-amino-4-methyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepin-5(6H)-one (0.030 g, 0.17 mmol), N,N-diisopropylethylamine (0.087 mL, 0.50 mmol), and (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (0.109 g, 0.20

mmol). The reaction mixture was stirred for 16 h at RT, then was purified directly by preparative RP-HPLC (20-60% acetonitrile in water + 0.1% formic acid) affording N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide (0.023 g, 34%) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 8.50 (t, J = 7.5 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.44 – 7.32 (m, 3H), 7.27 – 7.20 (m, 2H), 6.33 (dd, J = 2.0, 1.0 Hz, 1H), 5.57 (dd, J = 8.2, 5.9 Hz, 1H), 4.41 – 4.24 (m, 2H), 4.24 – 4.12 (m, 1H), 3.24 (d, J = 1.1 Hz, 3H), 3.22 – 3.06 (m, 2H), 3.05 – 2.94 (m, 1H), 2.61 – 2.52 (m, 2H), 2.44 – 2.30 (m, 1H). LC-MS R_T = 3.73 min, m/z = 392.2 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.1% formic acid over 10 mins) retention time 3.73 min, ESI+ found [M+H] = 392.2

Examples 125 and 126

METHOD G12



(R)-N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide and (S)-N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide (1:1)

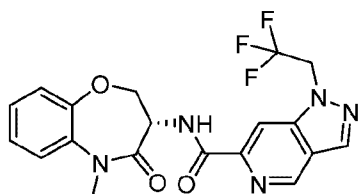
N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide was further purified by chiral SFC (Lux Cellulose-4 column, 50% methanol + 0.1% ammonium hydroxide isocratic elution) affording arbitrarily assigned diastereomers (R)-N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide (0.006 g, 9%) and (S)-N-((S)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide (0.006 g, 9%) as white solids:

Analytical data for the first eluting diastereomer (arbitrarily assigned R,S configuration): SFC R_T (Lux Cellulose-4 column, 50% methanol + 0.1% ammonium hydroxide isocratic elution, 2.5 min method): 1.14 min, 100% ee: ¹H NMR (400 MHz, DMSO-d₆) δ 8.51 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.44 – 7.32 (m, 3H), 7.28 – 7.20 (m, 2H), 6.33 (d, J = 2.0 Hz, 1H), 5.57 (dd, J = 8.2, 5.9 Hz, 1H), 4.41 – 4.32 (m, 1H), 4.32 – 4.23 (m, 1H), 4.23 – 4.13 (m, 1H), 3.24 (s, 3H), 3.21 – 3.14 (m, 1H), 3.14 – 3.04 (m, 1H), 3.04 – 2.93 (m, 1H), 2.63 – 2.52 (m, 2H), 2.37 (td, J = 12.5, 6.6 Hz, 1H). LCMS R_T = 3.76 min, m/z = 392.2 (M+H)⁺.

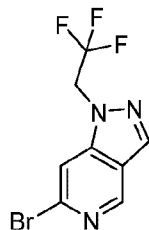
Analytical data for the second eluting diastereomer (arbitrarily assigned S,S configuration):
 SFC R_T: 1.84 min, 100% ee: ¹H NMR (400 MHz, DMSO-d₆) δ 8.49 (d, J = 7.7 Hz, 1H), 7.48
 (d, J = 2.0 Hz, 1H), 7.43 – 7.32 (m, 3H), 7.26 – 7.21 (m, 2H), 6.33 (d, J = 2.0 Hz, 1H), 5.57 (dd,
 J = 8.3, 5.8 Hz, 1H), 4.41 – 4.24 (m, 2H), 4.24 – 4.12 (m, 1H), 3.24 (s, 3H), 3.22 – 3.06 (m, 2H),
 3.05 – 2.94 (m, 1H), 2.61 – 2.52 (m, 2H), 2.42 – 2.31 (m, 1H). LCMS R_T = 3.76 min, m/z =
 392.2 (M+H)⁺.

Example 127

METHOD C1

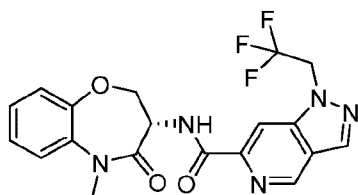


10 N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1-(2,2,2-trifluoroethyl)pyrazolo[4,3-c]pyridine-6-carboxamide



Step 1: 6-bromo-1-(2,2,2-trifluoroethyl)-1H-pyrazolo[4,3-c]pyridine

A solution of 6-bromo-1H-pyrazolo[4,3-c]pyridine (1.0 g, 5.05 mmol) in
 N,N-dimethylformamide (9.2 mL) was cooled to 0 °C and sodium hydride (60 mass% in oil,
 0.460 g, 11.5 mmol) was added. After 5 min, 2,2,2-trifluoroethyl trifluoromethanesulfonate
 (3.0 g, 12.9 mmol) was added. The reaction stirred at 0 °C for 10 min and then was warmed to
 RT and stirred for an additional 18 h. The reaction mixture was sealed with a yellow cap and
 heated at 60 °C for 1 h. After cooling to RT, the reaction was diluted with water and isopropyl
 acetate. The aqueous layer was extracted with isopropyl acetate (3 x 100 mL). The combined
 organic layers were washed with brine, dried with magnesium sulfate, concentrated to dryness
in vacuo, and the residue was purified by flash column chromatography (silica gel, 0% to 50%
 isopropyl acetate - heptane) to give 6-bromo-1-(2,2,2-trifluoroethyl)pyrazolo[4,3-c]pyridine
 (0.925 g, 3.30 mmol, 65% Yield): ¹H NMR (400 MHz, DMSO-d₆) δ 8.95 (s, 1H), 8.47 (s, 1H),
 8.20 (s, 1H), 5.47 (q, J = 8.8 Hz, 2H). LRMS R_T = 1.25 min, m/z = 281 (M+H)⁺.



Step 2: N-[(3*S*)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1-(2,2,2-trifluoroethyl)pyrazolo[4,3-*c*]pyridine-6-carboxamide

Palladium(II) acetate (3.1 mg, 0.0134 mmol),
 5 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (7.9 mg, 0.0134 mmol),
 6-bromo-1-(2,2,2-trifluoroethyl)pyrazolo[4,3-*c*]pyridine (75 mg, 0.268 mmol),
 (3*S*)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (77.2 mg, 0.402 mmol) were
 added to a screw-cap vial (not dried). A septum was put on the vial and secured with electrical
 tape. Nitrogen was then purged through the reaction vial for 15 min. The solids were dissolved
 10 in toluene (0.53 mL), and triethylamine (0.110 mL, 0.803 mmol) was added. The reaction flask
 was purged with a balloon for carbon monoxide for 5 minutes. The vial, with the balloon of
 carbon monoxide, was placed in a 80 °C heating block and was allowed to stir for 16 h. (NOTE:
 no solvent remained after heating for 16 h). The crude residue was dissolved in isopropyl
 acetate, and filtered through Celite. The crude residue was purified by flash column
 15 chromatography (silica gel, 0% to 60% isopropyl acetate in heptane) to afford
 N-[(3*S*)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1-(2,2,2-trifluoroethyl)pyrazolo
 [4,3-*c*]pyridine-6-carboxamide (102.6 mg, 0.242 mmol, 90% Yield) as a yellow solid: ¹H
 NMR (400 MHz, DMSO-*d*₆) δ 9.26 (d, *J* = 1.2 Hz, 1H), 9.06 (d, *J* = 8.0 Hz, 1H), 8.59 (d, *J* = 0.8
 Hz, 1H), 8.52 (bs, 1H), 7.57 – 7.47 (m, 1H), 7.40 – 7.24 (m, 3H), 5.75 – 5.60 (m, 2H), 4.93 (dt,
 20 *J* = 10.8, 8.0 Hz, 1H), 4.62 – 4.48 (m, 2H), 3.35 (s, 3H). LRMS R_T = 5.04 min, *m/z* = 420.1
 (M+H)⁺.

Prep HPLC Information:

Column: Phenomenex Gemini-NX C18 5um, 110A (50 x 30 mm)

Mobile Phase: 0.1 % Ammonium Hydroxide in Water (A) / Acetonitrile (B)

25 Elution Program

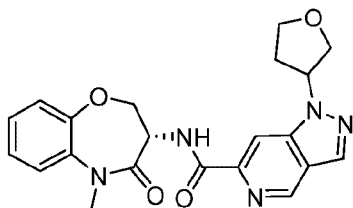
Gradient: 20 to 60% B

Pressure: 900 psi

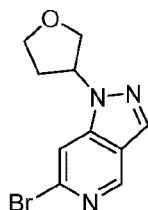
Flow Rate: 60 mL/min

Column Temperature: 25 °C

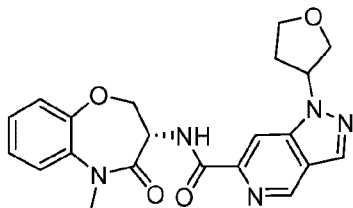
30 Wavelength: 220 nm

Example 128**METHOD C2**

N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-*c*]pyridine-6-carboxamide

**Step 1: 6-bromo-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-*c*]pyridine**

A suspension of sodium hydride (60 mass% in oil, 0.480 g, 12.0 mmol) in N,N-dimethylformamide (9.2 mL) was cooled to 0 °C and 6-bromo-1H-pyrazolo[4,3-*c*]pyridine (1.0 g, 5.05 mmol) was added. After 5 min, 3-bromotetrahydrofuran (1.80 g, 11.9 mmol) was added. The reaction stirred at 0 °C for 10 min, warmed to RT and stirred for an additional 18 h. Additional sodium hydride (60 mass% in oil, 0.230 g, 5.75 mmol) and 3-bromotetrahydrofuran (0.90 g, 5.96 mmol) was added. The reaction was sealed with a yellow cap and heated at 60 °C for 4 h. After cooling to RT, the reaction was diluted with water and isopropyl acetate. The aqueous layer was extracted with isopropyl acetate. The combined organic layers were washed with brine, dried with magnesium sulfate, concentrated to dryness *in vacuo*, and the residue was purified by flash column chromatography (silica gel, 0% to 50% isopropyl acetate in heptane) to give 6-bromo-1-tetrahydrofuran-3-yl-pyrazolo[4,3-*c*]pyridine (0.579 g, 2.16 mmol, 43% Yield): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.89 (s, 1H), 8.34 (s, 1H), 8.06 (s, 1H), 5.63 – 5.37 (m, 1H), 4.21 – 3.98 (m, 2H), 3.98 – 3.72 (m, 2H), 2.65 – 2.36 (m, 1H), 2.36 – 2.19 (m, 1H). LRMS R_T = 1.03 min, *m/z* = 269 (M+H)⁺.

**Step 2:**

N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-*c*]pyridine-6-carboxamide

Palladium(II) acetate (2.6 mg, 0.0112 mmol),
 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (6.6 mg, 0.0112 mmol),
 5 6-bromo-1-tetrahydrofuran-3-yl-pyrazolo[4,3-*c*]pyridine (60 mg, 0.224 mmol),
 (3*S*)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (64.5 mg, 0.336 mmol) were
 added to a screw-cap vial (not dried). A septum was put on the vial and secured with electrical
 tape. Nitrogen was then purged through the reaction vial for 15 min. The solids were dissolved
 in toluene (0.45 mL), and then triethylamine (0.095 mL, 0.671 mmol) was added. The reaction
 10 flask was purged with a balloon for carbon monoxide for 5 minutes. The vial, with the balloon
 of carbon monoxide, was placed in a 80 °C heating block and was allowed to stir for 17 h.
 (NOTE: no solvent remained after heating for 17 h). The crude residue was dissolved in
 isopropyl acetate, filtered through Celite and concentrated to dryness *in vacuo*. The residue
 was purified by flash column chromatography (silica gel, 0% to 75% isopropyl acetate in
 15 heptane) to give
 N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-*c*]pyridine-6-carboxamide (55 mg, 60% Yield): ¹H NMR (400 MHz,
 DMSO-*d*₆) δ 9.20 (d, *J* = 0.8 Hz, 1H), 9.02 (d, *J* = 8.0 Hz, 1H), 8.47 - 8.46 (m, 1H), 8.40 - 8.36
 (m, 1H), 7.57 - 7.47 (m, 1H), 7.39 - 7.24 (m, 3H), 5.73 - 5.66 (m, 1H), 4.96 - 4.89 (m, 1H),
 20 4.61 - 4.50 (m, 2H), 4.14 - 4.01 (m, 2H), 3.96 - 3.82 (m, 2H), 3.35 (s, 3H), 2.51 - 2.39 (m, 1H),
 2.34 - 2.19 (m, 1H). LRMS *R*_T = 4.49 min, *m/z* = 408.2 (M+H)⁺.

Prep HPLC Information:

Column: Phenomenex Gemini-NX C18 5um, 110A (50 x 30 mm)

Mobile Phase: 0.1 % Ammonium Hydroxide in Water (A) / Acetonitrile (B)

25 Elution Program

Gradient: 20 to 60% B

Pressure: 900 psi

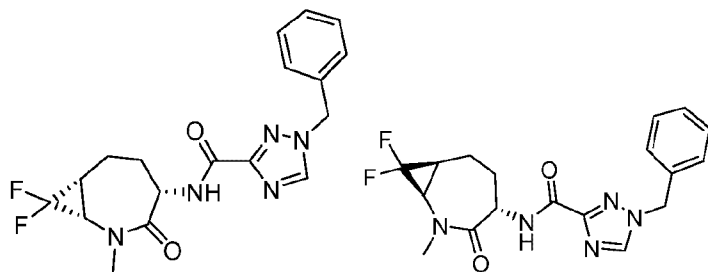
Flow Rate: 60 mL/min

Column Temperature: 25 °C

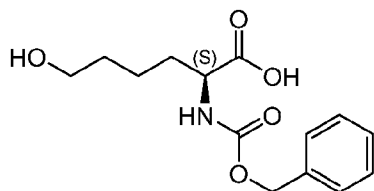
30 Wavelength: 230 nm

Examples 129 and 130

METHOD C3

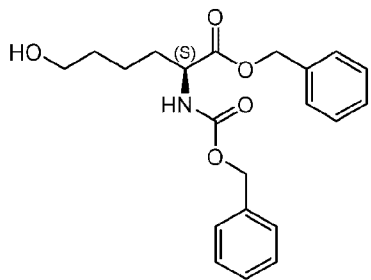


1-benzyl-N-((1*S*,4*S*,7*R*)-8,8-difluoro-2-methyl-3-oxo-2-azabicyclo[5.1.0]octan-4-yl)-1*H*-1,2,4-triazole-3-carboxamide and
 1-benzyl-N-((1*R*,4*S*,7*S*)-8,8-difluoro-2-methyl-3-oxo-2-azabicyclo[5.1.0]octan-4-yl)-1*H*-1,2,4-triazole-3-carboxamide



Step 1: (S)-2-(((benzyloxy)carbonyl)amino)-6-hydroxyhexanoic acid

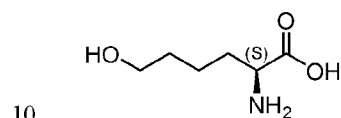
((Benzyloxy)carbonyl)-L-lysine (150 g, 535 mmol) was dissolved in water (1.5 L), and the solution was warmed to 60°C and adjusted to pH = 9.5 with 4M NaOH, disodium pentacyano(nitroso)iron(II) dihydrate (168 g, 642 mmol) was added slowly with vigorous stirring over 10 min. The reaction mixture was stirred at 60 °C for and maintained pH = 9.5 with 4N NaOH for 12 h. The reaction mixture was filtered through a bed of Celite, the filtrate was cautiously acidified with hydrochloric acid to pH = 1, and then extracted with ethyl acetate (3 x 1000 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate, filtered and concentrated to dryness *in vacuo* to afford (S)-2-(((benzyloxy)carbonyl)amino)-6-hydroxyhexanoic acid (260 g, crude) as a brown oil, use without further purification in the next step.



Step 2: benzyl (S)-2-(((benzyloxy)carbonyl)amino)-6-hydroxyhexanoate

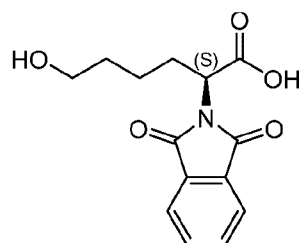
A mixture of (S)-2-(((benzyloxy)carbonyl)amino)-6-hydroxyhexanoic acid (130 g, 462

mmol), cesium carbonate (75 g, 231 mmol), bromomethylbenzene (79. g, 462 mmol) in N,N-dimethylformamide (1 L) and the mixture was stirred at 10 °C for 18 h under nitrogen atmosphere. The reaction mixture was filtered, the filtrate was diluted with water (5 L), the aqueous phase was extracted with ethyl acetate (3 x 1 L). The combined organic was washed
 5 with brine (200 mL), dried with anhydrous sodium sulfate, filtered and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (silica gel, 100-200 mesh, 50:1 to 0:1 ethyl acetate in petroleum ether) affording benzyl (S)-2-(((benzyloxy)carbonyl)amino)-6-hydroxyhexanoate (222 g, 65%) as a white oil, use without further purification in the next step: HPLC R_T = 3.16 min



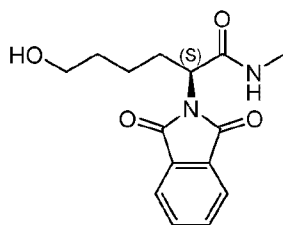
Step 3: (S)-2-amino-6-hydroxyhexanoic acid

To a solution of (S)-2-(((benzyloxy)carbonyl)amino)-6-hydroxyhexanoate (222 g, 598 mmol) in methanol (1 L) was added 10% Pd/C (20 g) under a nitrogen atmosphere. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred
 15 under hydrogen (50 psi) at 50 °C for 2 hrs. The reaction mixture was filtered and the filtrate was concentrated to dryness *in vacuo* to give (S)-2-amino-6-hydroxyhexanoic acid (85 g, 577 mmol, 97% yield) as a white solid, used without further purification in the next step: TLC (Petroleum ether/Ethyl acetate=2/1, R_f = 0.45)



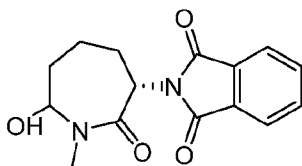
Step 4: (S)-2-(1,3-dioxoisindolin-2-yl)-6-hydroxyhexanoic acid

To a mixture of (S)-2-amino-6-hydroxyhexanoic acid (50 g, 340 mmol), ethyl 1,3-dioxoisindoline-2-carboxylate (74 g, 340 mmol) was added sodium carbonate (36 g, 340 mmol) in water (500 mL) was stirred at 10 °C for 2. The reaction mixture was adjust pH = 1 and extracted with ethyl acetate (3 x 250 mL). The combined organic layers were washed with
 25 brine (100 mL), dried over sodium sulfate, filtered and concentrated to dryness *in vacuo*. The residue was washed with 2-methoxy-2-methylpropane (300 mL) and dried to afford (S)-2-(1,3-dioxoisindolin-2-yl)-6-hydroxyhexanoic acid (47 g, 50%) as a white solid, use without further purification in the next step: HPLC R_T = 1.83 min



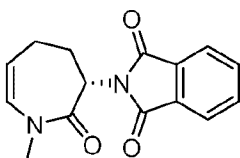
Step 5: (S)-2-(1,3-dioxoisindolin-2-yl)-6-hydroxy-N-methylhexanamide

A mixture of (S)-2-(1,3-dioxoisindolin-2-yl)-6-hydroxyhexanoic acid (32 g, 115 mmol), 3-(ethyliminomethyleneamino)-N,N-dimethylpropan-1-amine (33 g, 173 mmol), benzotriazol-1-ol (16 g, 115 mmol) and methanamine (2 M solution in tetrahydrofuran, 144 mL, 287.5 mmol) in tetrahydrofuran (320 mL) was degassed and purged with nitrogen, and the reaction mixture was stirred at 10 °C for 2 h under a nitrogen atmosphere. To the reaction mixture was added water (200 mL) and the mixture was extracted with ethyl acetate (3 x 100 mL). The combined was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 200:1, 50:1 methanol in dichloromethane) to afford (S)-2-(1,3-dioxoisindolin-2-yl)-6-hydroxy-N-methylhexanamide (16.5 g, 49% yield), used as is in the next step



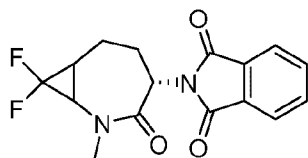
Step 6: 2-((3S)-7-hydroxy-1-methyl-2-oxoazepan-3-yl)isoindoline-1,3-dione

To a solution of (S)-2-(1,3-dioxoisindolin-2-yl)-6-hydroxy-N-methylhexanamide (13.8 g, 48mmol) in dimethylsulfoxide (84 mL) were added triethylamine (24 g, 238 mmol, 33 mL) and sulfur trioxide pyridine complex (38 g, 238 mmol) at 0°C under an argon atmosphere and the mixture was stirred at 10-20°C for 2.5 h. The reaction mixture was quenched with water and treated with 1N HCl, and then extracted with ethyl acetate (3 x 100 mL). The organic layer was washed with brine, dried over sodium sulfate and concentrated to dryness *in vacuo* to afford 2-((3S)-7-hydroxy-1-methyl-2-oxoazepan-3-yl)isoindoline-1,3-dione (21.2 g, crude) as off-white oil, which was used in the next step without further purification: TLC (dichloromethane/Methanol = 10/1, R_f = 0.43)



Step 7: (S)-2-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-azepin-3-yl)isoindoline-1,3-dione

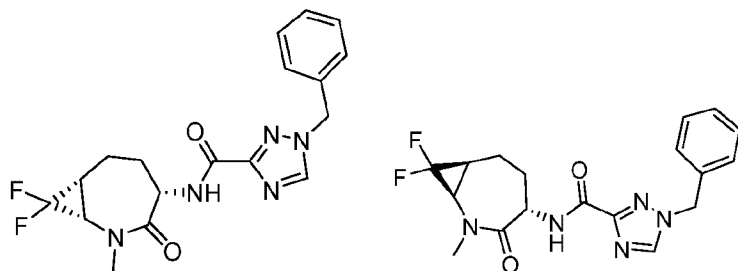
A solution of (S)-2-(1,3-dioxoisindolin-2-yl)-6-hydroxy-N-methylhexanamide (21.2 g, 73 mmol) and p-toluenesulfonic acid monohydrate (839 mg, 4.4 mmol) in toluene (200 mL) was stirred under reflux for 1.5 h. After allowing to cool to RT, the reaction mixture was diluted with ethyl acetate (500 mL) and washed with saturated aqueous sodium bicarbonate (200 mL) and brine (100 mL). The organic layer was dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was washed with ethyl acetate (10 mL) and dried to afford (S)-2-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-azepin-3-yl)isoindoline-1,3-dione (4.6 g, 23%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 7.88 (dd, *J* = 5.52, 3.01 Hz, 2H), 7.71 - 7.77 (m, 2H), 5.96 (dd, *J* = 9.03, 1.51 Hz, 1H), 5.35 - 5.45 (m, 1H), 5.04 (dd, *J* = 10.79, 3.26 Hz, 1H), 3.10 (s, 3H), 2.46 - 2.57 (m, 1H), 2.23 - 2.40 (m, 2H), 1.61 (s, 1H).



Step 1:

2-((4S)-8,8-difluoro-2-methyl-3-oxo-2-azabicyclo[5.1.0]octan-4-yl)isoindoline-1,3-dione

A solution of sodium chlorodifluoroacetate (1.42 g, 9.25 mmol) in diglyme (5.9 mL) was added dropwise to a refluxing solution of 2-[(3S)-1-methyl-2-oxo-4,5-dihydro-3H-azepin-3-yl]isoindoline-1,3-dione (0.250 g, 0.925 mmol) in diglyme (10 mL) over 25 minutes. After addition, the reaction was allowed to stir for an additional 10 minutes at reflux. After cooling to RT, the reaction mixture was concentrated to dryness *in vacuo* and the residue was purified by flash column chromatography (silica gel, 0% to 70% isopropyl acetate in heptane) affording 2-[(4S)-8,8-difluoro-6-methyl-5-oxo-6-azabicyclo[5.1.0]octan-4-yl]isoindoline-1,3-dione (0.270 g, 0.843 mmol, 91% yield) as an inseparable ~6.8:1 mixture of diastereomers: ¹H NMR (400 MHz, Chloroform-*d*) δ (major isomer) 7.90 - 7.81 (m, 2H), 7.75 - 7.70 (m, 2H), 5.44 (dd, *J* = 11.6, 8.0 Hz, 1H), 3.66-3.30 (m, 1H), 3.26 - 3.11 (m, 1H), 3.02 (s, 3H), 2.25 - 2.15 (m, 1H), 2.04 - 1.90 (m, 2H), 1.85 - 1.72 (m, 1H). LRMS R_T = 1.29 min, *m/z* = 321 (M+H)⁺.



Step 2:

1-benzyl-N-((1S,4S,7R)-8,8-difluoro-2-methyl-3-oxo-2-azabicyclo[5.1.0]octan-4-yl)-1H-1,2,4-triazole-3-carboxamide and

1-benzyl-N-((1*R*,4*S*,7*S*)-8,8-difluoro-2-methyl-3-oxo-2-azabicyclo[5.1.0]octan-4-yl)-1*H*-1,2,4-triazole-3-carboxamide

- Hydrazine (0.087 mL, 2.72 mmol) was added to a solution of 2-[(4*S*)-8,8-difluoro-6-methyl-5-oxo-6-azabicyclo[5.1.0]octan-4-yl]isoindoline-1,3-dione and (~6.8:1 dr, 0.290 g, 0.905 mmol) in ethanol (9.1 mL). The reaction was heated at 80 °C for 2 h. After cooling to RT, the reaction was filtered through a short plug of Celite using ethanol. The filtrate was concentrated to dryness *in vacuo* to afford (4*S*)-4-amino-8,8-difluoro-6-methyl-6-azabicyclo[5.1.0]octan-5-one (88.9 mg, 0.467 mmol, 51.6% Yield). The crude residue was used in the next step without further purification.
- (7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (0.138 g, 0.254 mmol) was added to a solution of (4*S*)-4-amino-8,8-difluoro-6-methyl-6-azabicyclo[5.1.0]octan-5-one (44 mg, 0.231 mmol), 1-benzyl-1,2,4-triazole-3-carboxylic acid (58 mg, 0.289 mmol), and *N,N*-diisopropylethylamine (0.120 mL, 0.694 mmol), in *N,N*-dimethylformamide (2.3 mL). The reaction was allowed to stir at RT for 18 h before being concentrated to dryness *in vacuo*. The crude residue was purified by preparative reverse phase HPLC affording arbitrarily assigned 1-benzyl-N-((1*S*,4*S*,7*R*)-8,8-difluoro-2-methyl-3-oxo-2-azabicyclo[5.1.0]octan-4-yl)-1*H*-1,2,4-triazole-3-carboxamide (56.7 mg, 0.151 mmol, 65% Yield) and 1-benzyl-N-((1*R*,4*S*,7*S*)-8,8-difluoro-2-methyl-3-oxo-2-azabicyclo[5.1.0]octan-4-yl)-1*H*-1,2,4-triazole-3-carboxamide (5.7 mg, 6.6 %): 1-benzyl-N-((1*S*,4*S*,7*R*)-8,8-difluoro-2-methyl-3-oxo-2-azabicyclo[5.1.0]octan-4-yl)-1*H*-1,2,4-triazole-3-carboxamide (arbitrarily assigned): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81 (s, 1H), 8.19 (m, 2H), 7.45 – 7.20 (m, 5H), 5.49 (s, 2H), 5.00 (dt, *J* = 10.8, 7.2 Hz, 1H), 3.72 – 3.49 (m, 1H), 2.90 (s, 3H), 2.43 – 1.96 (m, 4H), 1.61 (m, 1H), 1.27 (m, 1H). LRMS *R*_T = 4.18 min, *m/z* = 376.1 (M+H)⁺.

Prep HPLC Information:

Column: Phenomenex Gemini-NX C18 5um, 110A (50 x 30 mm)

Mobile Phase: 0.1 % Ammonium Hydroxide in Water (A) / Acetonitrile (B)

Elution Program

Gradient: 20 to 60% B

Pressure: 800 psi

Flow Rate: 60 mL/min

Column Temperature: 25 °C

Wavelength: 210 nm

and

1-benzyl-N-((1*R*,4*S*,7*S*)-8,8-difluoro-2-methyl-3-oxo-2-azabicyclo[5.1.0]octan-4-yl)-1*H*-1,2,4-triazole-3-carboxamide (arbitrarily assigned): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.82 (s, 1H), 8.58 (d, *J* = 4.4 Hz, 1H), 7.43 – 7.27 (m, 5H), 5.48 (s, 2H), 4.43 – 4.33 (m, 1H), 3.27 – 3.14 (m, 1H), 2.80 (s, 3H), 2.55 – 2.43 (m, 1H), 2.10 – 2.00 (m, 3H), 1.30 – 1.10 (m, 1H). LRMS *R*_T = 3.90 min, *m/z* = 376.1 (M+H)⁺.

Prep HPLC Information:

Column: Phenomenex Gemini-NX C18 5μm, 110A (50 x 30 mm)

Mobile Phase: 0.1 % Ammonium Hydroxide in Water (A) / Acetonitrile (B)

10 Elution Program

Gradient: 20 to 60% B

Pressure: 800 psi

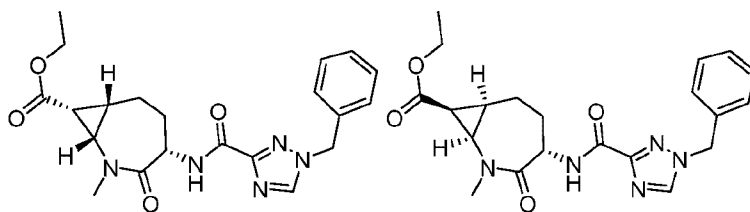
Flow Rate: 60 mL/min

Column Temperature: 25 °C

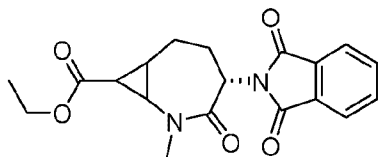
15 Wavelength: 210 nm

Example 131 and 132

METHOD C3 & C4



20 **Ethyl(1*S*,4*S*,7*S*,8*R*)-4-(1-benzyl-1*H*-1,2,4-triazole-3-carboxamido)-2-methyl-3-oxo-2-azabicyclo[5.1.0]octane-8-carboxylate** and **ethyl(1*R*,4*S*,7*R*,8*S*)-4-(1-benzyl-1*H*-1,2,4-triazole-3-carboxamido)-2-methyl-3-oxo-2-azabicyclo[5.1.0]octane-8-carboxylate**

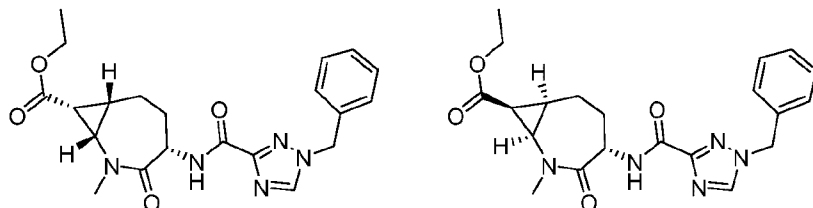


Step 1: ethyl

25 **(4*S*)-4-(1,3-dioxoisindolin-2-yl)-2-methyl-3-oxo-2-azabicyclo[5.1.0]octane-8-carboxylate**

A solution of ethyl diazoacetate (15 mass% in toluene, 1.3 mL, 1.5 mmol) in dichloromethane (3 mL) was added dropwise to a solution of the

2-[(3*S*)-1-methyl-2-oxo-4,5-dihydro-3H-azepin-3-yl]isoindoline-1,3-dione (0.20 g, 0.74 mmol) and rhodium(II) acetate (6.9 mg, 0.030 mmol) in dichloromethane (5.2 mL), over a period of 4 h. After, the reaction was allowed to stir for an additional 12 h. The reaction was then filtered through Celite using isopropyl acetate. The filtrate was concentrated to dryness *in vacuo* and the residue was purified by flash column chromatography (silica gel, 0% to 70% isopropyl acetate in heptane) to give ethyl (4*S*)-4-(1,3-dioxoisindolin-2-yl)-6-methyl-5-oxo-6-azabicyclo[5.1.0]octane-8-carboxylate (0.145 g, 0.407 mmol, 55% Yield). LRMS $R_T = 1.28$ min, $m/z = 357$ ($M+H$)⁺.



10 **Step 2:** **ethyl (1*S*,4*S*,7*S*,8*R*)-4-(1-benzyl-1H-1,2,4-triazole-3-carboxamido)-2-methyl-3-oxo-2-azabicyclo[5.1.0]octane-8-carboxylate and ethyl (1*R*,4*S*,7*R*,8*S*)-4-(1-benzyl-1H-1,2,4-triazole-3-carboxamido)-2-methyl-3-oxo-2-azabicyclo[5.1.0]octane-8-carboxylate**

15 Hydrazine (0.040 mL, 1.18 mmol) was added to a solution of ethyl (4*S*)-4-(1,3-dioxoisindolin-2-yl)-6-methyl-5-oxo-6-azabicyclo[5.1.0]octane-8-carboxylate (0.140 g, 0.393 mmol) in ethanol (3.9 mL). The reaction was heated at 80 °C for 2 h. After cooling to RT, the reaction was filtered through a short plug of Celite using ethanol. The filtrate was concentrated to dryness *in vacuo* and the residue was submitted to the next step without further purification.

(7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (0.235 g, 0.432 mmol) was added to a solution of the crude residue, 1-benzyl-1,2,4-triazole-3-carboxylic acid (99.8 mg, 0.491 mmol), and N,N-diisopropylethylamine (0.21 mL, 1.18 mmol), in N,N-dimethylformamide (3.9 mL). The reaction was allowed to stir at RT for 18h before being concentrated to dryness *in vacuo*. The crude residue was purified by reverse phase preparative HPLC to afford arbitrarily assigned ethyl (1*S*,4*S*,7*S*,8*R*)-4-(1-benzyl-1H-1,2,4-triazole-3-carboxamido)-2-methyl-3-oxo-2-azabicyclo[5.1.0]octane-8-carboxylate (23.5 mg, 0.057 mmol, 14.5% Yield) and ethyl (1*R*,4*S*,7*R*,8*S*)-4-(1-benzyl-1H-1,2,4-triazole-3-carboxamido)-2-methyl-3-oxo-2-azabicyclo[5.1.0]octane-8-carboxylate (15.6 mg, 0.038 mmol, 9.7% Yield).

Ethyl

(1*S*,4*S*,7*S*,8*R*)-4-(1-benzyl-1H-1,2,4-triazole-3-carboxamido)-2-methyl-3-oxo-2-azabicyclo[5.1.0]octane-8-carboxylate: ¹H NMR (400 MHz, DMSO-d₆) δ 8.81 (s, 1H), 8.15 (d, J = 7.6 Hz,

1H), 7.46 – 7.19 (m, 4H), 5.49 (s, 2H), 5.07 (dt, J = 10.8, 7.2 Hz, 1H), 4.09 (m, 2H), 3.41 – 3.20 (m, 1H), 2.85 (s, 3H), 2.30 – 2.12 (m, 2H), 2.01 – 1.77 (m, 2H), 1.60 – 1.43 (m, 1H), 1.21 (t, J = 7.2 Hz, 3H), 1.15 – 0.95 (m, 1H). LRMS R_T = 4.19 min, m/z = 412.2 (M+H)⁺.

Prep HPLC Information:

5 Column: Es Industries Pyridyl Amide (150 x 30 mm)

Mobile Phase: Carbon Dioxide (A) / Methanol w/ 0.1% Ammonium Hydroxide (B)

Elution Program

Gradient: 5 to 60% B

Pressure: 2500 psi

10 Flow Rate: 100 mL/min

Column Temperature: 40 °C

Wavelength: 254 nm

Ethyl

(1*R*,4*S*,7*R*,8*S*)-4-(1-benzyl-1*H*-1,2,4-triazole-3-carboxamido)-2-methyl-3-oxo-2-azabicyclo[5.1.0]octane-8-carboxylate: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.43 – 7.27 (m, 5H), 5.49 (s, 2H), 4.98 (dt, J = 11.2, 7.6 Hz, 1H), 4.16 – 4.02 (m, 2H), 3.38 – 3.27 (m, 1H), 2.74 (s, 3H), 2.30-2.22 (m, 1H), 2.16 – 1.94 (m, 2H), 1.97 – 1.83 (m, 2H), 1.80-1.74 (m, 1H), 1.68-1.61 (m, 1H), 1.20 (t, J = 7.2 Hz, 3H). LRMS R_T = 4.22 min, m/z = 412.2 (M+H)⁺.

20 Prep HPLC Information:

Column: Es Industries Pyridyl Amide (150 x 30 mm)

Mobile Phase: Carbon Dioxide (A) / Methanol w/ 0.1% Ammonium Hydroxide (B)

Elution Program

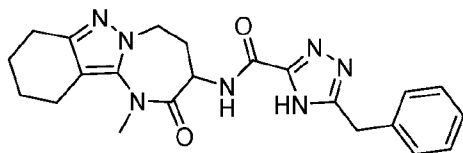
Gradient: 5 to 60% B

25 Pressure: 2500 psi

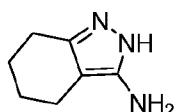
Flow Rate: 100 mL/min

Column Temperature: 40 °C

Wavelength: 254 nm

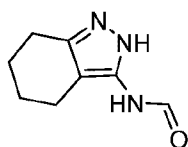
Example 133**METHOD X1**

5-benzyl-N-(1-methyl-2-oxo-2,3,4,5,8,9,10,11-octahydro-1H-[1,3]diazepino[1,2-b]indazol-3-yl)-4H-1,2,4-triazole-3-carboxamide

**Step 1: 4,5,6,7-tetrahydro-2H-indazol-3-amine**

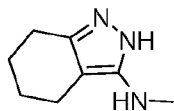
To a solution of 2-oxocyclohexanecarbonitrile (1.71 g, 13.2 mmol) in toluene (23 mL) was added hydrazine (0.485 mL, 14.5 mmol), and the reaction was stirred at 85 °C for 5 h. The reaction mixture was concentrated to dryness *in vacuo* and the residue was used in the next step without further purification: LCMS R_T = 0.80 min; m/z = 138 (M + H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

**Step 2: N-(4,5,6,7-tetrahydro-2H-indazol-3-yl)formamide**

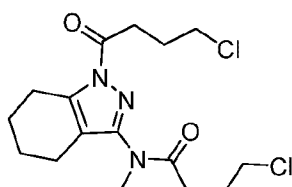
3-Amino-4,5,6,7-tetrahydro-1H-indazole (1.10 g, 7.7 mmol) and formic acid (4.7 mL, 120 mmol) were mixed together, and the reaction was stirred at 110 °C for 3 h. The reaction mixture was concentrated to dryness *in vacuo* and the residue was purified by column chromatography (silica gel, 100-200 mesh, 0-15% methanol in dichloromethane) affording N-(4,5,6,7-tetrahydro-2H-indazol-3-yl)formamide (1.143 g, 90% yield) as yellow solid: ¹H NMR (400 MHz, DMSO-d₆) δ 11.92 (s, 1H), 9.85 (dd, J = 7.9, 3.4 Hz, 1H), 8.51 (d, J = 11.0 Hz, 0.55H), 8.08 (d, J = 1.7 Hz, 0.35H), 2.54 – 2.50 (m, 2H), 2.32 (td, J = 6.0, 1.9 Hz, 2H), 1.77 – 1.55 (m, 4H), tautomers were found in NMR; LCMS R_T = 1.43 min; m/z = 166 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

**Step 3: N-methyl-4,5,6,7-tetrahydro-2H-indazol-3-amine**

To a solution of N-(4,5,6,7-tetrahydro-1H-indazol-3-yl)formamide (2.08 g, 12.6 mmol) in tetrahydrofuran (120 mL) was added lithium aluminum hydride (2 mol/L) in tetrahydrofuran (20.0 mL, 40.0 mmol) at 0 °C, and the reaction was stirred at 25 °C for 6 h. Sodium sulfate decahydrate was added, and the mixture was stirred for 18 h. The mixture was filtered through celite, and ethyl acetate was used to rinse the solid. The combined liquid was concentrated to dryness *in vacuo* to afford N-methyl-4,5,6,7-tetrahydro-1H-indazol-3-amine (2.03 g, 106% yield) as colorless oil used without further purification: ¹H NMR (400 MHz, DMSO-d₆) δ 10.83 (s, 1H), 4.54 (s, 1H), 2.64 (d, *J* = 5.3 Hz, 3H), 2.45 – 2.37 (m, 2H), 2.23 – 2.15 (m, 2H), 1.69 – 1.56 (m, 4H); LCMS R_T = 1.30 min; *m/z* = 152 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



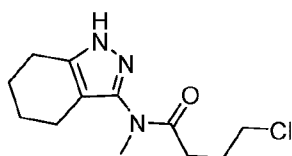
Step

4:

4-chloro-N-(1-(4-chlorobutanoyl)-4,5,6,7-tetrahydro-1H-indazol-3-yl)-N-methylbutanamide

To a solution of N-methyl-4,5,6,7-tetrahydro-1H-indazol-3-amine (2.03 g, 13.4 mmol) and N,N-dimethylpyridin-4-amine (163.7 mg, 1.340 mmol) in dichloromethane (53 mL) and N,N-diisopropylethylamine (5.84 mL) was added 4-chlorobutyryl chloride (3.462 mL, 30.82 mmol) at 0 °C, and the reaction was stirred at 0 °C for 30 min then at 25 °C for 8 h. The reaction mixture was concentrated to dryness *in vacuo* and the residue was purified by column chromatography (silica gel, 100-200 mesh, 0-40% ethyl acetate in heptane) affording 4-chloro-N-[1-(4-chlorobutanoyl)-4,5,6,7-tetrahydroindazol-3-yl]-N-methyl-butamide (3.44 g, 71% yield) as oil: LCMS R_T = 3.11 min; *m/z* = 360 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

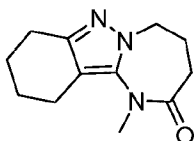


Step 5: 4-chloro-N-methyl-N-(4,5,6,7-tetrahydro-1H-indazol-3-yl)butanamide

To a solution of 4-chloro-N-[1-(4-chlorobutanoyl)-4,5,6,7-tetrahydroindazol-3-yl]-N-methyl-butamide (3.44 g, 9.55 mmol) in ethanol (17 mL) was added sodium hydroxide (1 mol/L) in water (9.5 mL, 9.55 mmol), and the reaction was stirred at 25 °C for 5 min. The reaction mixture was

concentrated to dryness *in vacuo* and the residue was used without further purification: LCMS $R_T = 2.10$ min; $m/z = 256$ (M+H)⁺.

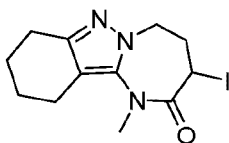
LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



5 Step 6: 1-methyl-4,5,8,9,10,11-hexahydro-1H-[1,3]diazepino[1,2-b]indazol-2(3H)-one

To a solution of 4-chloro-N-methyl-N-(4,5,6,7-tetrahydro-1H-indazol-3-yl)butanamide (2.81 g, 11.0 mmol) in N,N-dimethylformamide (49 mL) was added cesium carbonate (5.37 g, 16.5 mmol), and the reaction was stirred at 65 °C for 18 h. The reaction mixture was diluted with ethyl acetate and water, and the two layers were separated. The aqueous layer was extracted by
 10 ethyl acetate. The organic layers were combined, washed by water and brine, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0-100% ethyl acetate in heptane) affording 1-methyl-4,5,8,9,10,11-hexahydro-3H-[1,3]diazepino[1,2-b]indazol-2-one (2.03 g, 63% yield) as a white solid: ¹H NMR (400 MHz, Chloroform-d) δ 4.18 (t, $J = 6.7$ Hz, 2H), 3.24 (s, 3H), 2.65 (dd, $J = 6.4, 5.6$ Hz, 2H), 2.53 – 2.42 (m, 2H), 2.42 – 2.25 (m, 4H), 1.90
 15 – 1.74 (m, 4H); ¹H NMR (400 MHz, DMSO-d₆) δ 4.13 – 4.04 (m, 2H), 2.73 (d, $J = 0.6$ Hz, 3H), 2.56 – 2.47 (m, 2H), 2.43 (t, $J = 5.9$ Hz, 2H), 2.23 – 2.07 (m, 4H), 1.79 – 1.61 (m, 4H); LCMS $R_T = 1.78$ min; $m/z = 220$ (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



20

Step

7:

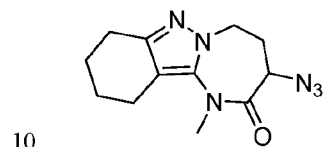
3-iodo-1-methyl-4,5,8,9,10,11-hexahydro-1H-[1,3]diazepino[1,2-b]indazol-2(3H)-one

To a solution of 1-methyl-4,5,8,9,10,11-hexahydro-3H-[1,3]diazepino[1,2-b]indazol-2-one (1.00 g, 3.42 mmol) in dichloromethane (29 mL) was added
 25 N,N,N',N'-tetramethylethylenediamine (3.09 mL, 20.5 mmol) at -10 °C (1/1 salt/ice bath), followed by fresh iodotrimethylsilane (2.93 mL, 20.5 mmol), and the reaction was stirred in salt/ice bath (at -10 ~ -15 °C) for 1.5 h. Iodine (2.60 g, 10.3 mmol) was added, and the reaction was stirred in salt/ice bath (at -10 ~ -15 °C) for 2 h. The crude mixture was diluted with ethyl acetate and sodium sulfite, and the two layers were separated. The aqueous layer was extracted
 30 by ethyl acetate. The organic layers were combined, washed by water and brine, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The residue

was purified by column chromatography (silica gel, 100-200 mesh, 0-70% ethyl acetate in dichloromethane) affording

3-iodo-1-methyl-4,5,8,9,10,11-hexahydro-3H-[1,3]diazepino[1,2-b]indazol-2-one (0.87 g, 74% yield) as white powder: ^1H NMR (400 MHz, Chloroform- d) δ 4.56 (dd, J = 9.3, 7.7 Hz, 1H), 4.23 – 4.13 (m, 2H), 3.29 (s, 3H), 3.02 – 2.89 (m, 1H), 2.81 – 2.70 (m, 1H), 2.69 – 2.62 (m, 2H), 2.53 – 2.43 (m, 2H), 1.93 – 1.69 (m, 4H); ^1H NMR (400 MHz, DMSO- d_6) δ 4.56 (dd, J = 8.7, 7.8 Hz, 1H), 4.14 – 4.07 (m, 2H), 3.17 (s, 3H), 2.91 – 2.77 (m, 1H), 2.62 – 2.54 (m, 1H), 2.47 – 2.39 (m, 2H), 1.82 – 1.63 (m, 4H); LCMS R_T = 1.25 min; m/z = 346 ($M+H$) $^+$.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

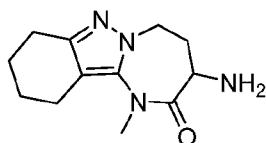


Step 8:

3-azido-1-methyl-4,5,8,9,10,11-hexahydro-1H-[1,3]diazepino[1,2-b]indazol-2(3H)-one

To a solution of 3-iodo-1-methyl-4,5,8,9,10,11-hexahydro-3H-[1,3]diazepino[1,2-b]indazol-2-one (880 mg, 2.55 mmol) in N,N -dimethylformamide (3.0 mL) was added sodium azide (222 mg, 3.3142 mmol), and the reaction was stirred at 25 °C for 4 h. The crude mixture was diluted with ethyl acetate and water, and the two layers were separated. The aqueous layer was extracted by ethyl acetate. The organic layers were combined, washed by water and brine, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The crude residue was used without further purification: LCMS R_T = 2.10 min; m/z = 261 ($M+H$) $^+$.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

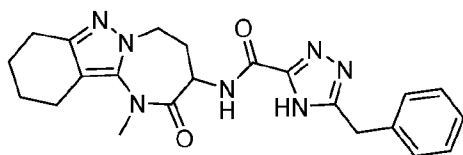


Step 9:

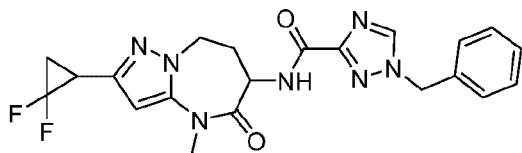
3-amino-1-methyl-4,5,8,9,10,11-hexahydro-1H-[1,3]diazepino[1,2-b]indazol-2(3H)-one

To a solution of 3-azido-1-methyl-4,5,8,9,10,11-hexahydro-3H-[1,3]diazepino[1,2-b]indazol-2-one (330 mg, 1.27 mmol) in tetrahydrofuran (5.3 mL) and water (1.2 mL) was added triphenylphosphine, polymer-bound (7.61 mmol), and the reaction was stirred at 25 °C for 18 h. The crude mixture was filtered through celite, and concentrated to dryness *in vacuo*. The crude residue was used without further purification: LCMS R_T = 1.39 min; m/z = 235 ($M+H$) $^+$.

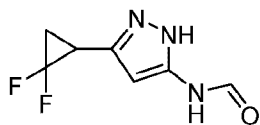
LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

**Step 10:****5-benzyl-N-(1-methyl-2-oxo-2,3,4,5,8,9,10,11-octahydro-1H-[1,3]diazepino[1,2-b]indazol-3-yl)-4H-1,2,4-triazole-3-carboxamide**

- 5 To a solution of 5-benzyl-4H-1,2,4-triazole-3-carboxylic acid (32 mg, 0.16 mmol) in N,N-dimethylformamide (0.1 mL) and acetonitrile (0.25 mL) was added 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (62 mg, 0.16 mmol) at 0 °C, and the reaction was stirred at 0 °C for 20 min. 3-Amino-1-methyl-4,5,8,9,10,11-hexahydro-3H-[1,3]diazepino[1,2-b]indazol-2-one (25 mg, 0.11 mmol) was added. The reaction was stirred at 25 °C for 18 h. The reaction mixture was concentrated to dryness *in vacuo* and the residue was purified by RP-HPLC affording 5-benzyl-N-(1-methyl-2-oxo-4,5,8,9,10,11-hexahydro-3H-[1,3]diazepino[1,2-b]indazol-3-yl)-4H-1,2,4-triazole-3-carboxamide (11 mg, 25% yield) as white powder: ¹H NMR (400 MHz, DMSO-d₆) δ 8.30 (d, *J* = 7.7 Hz, 1H), 7.38 – 7.16 (m, 5H), 4.35 – 4.08 (m, 3H), 4.06 (s, 2H), 3.19 (s, 3H), 2.65 – 2.51 (m, 3H), 2.49 – 2.40 (m, 2H), 2.27 – 2.16 (m, 1H), 1.87 – 1.59 (m, 4H); LCMS R_T = 4.15 min; *m/z* = 420.2 (M+H)⁺.

Example 134**METHOD X2**

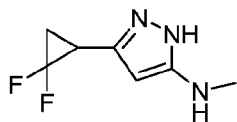
- 20 **1-benzyl-N-(2-(2,2-difluorocyclopropyl)-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide**

**Step 1: N-[5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl]formamide**

- 25 To a solution of 5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-amine (1.01 g, 6.35 mmol) in toluene (9.40 mL) was added formic acid (3.8 mL), and the reaction was stirred at 110 °C for 3 h. The crude mixture was concentrated to dryness *in vacuo*, and the residue was purified by column chromatography (silica gel, 100-200 mesh, 0-100% ethyl acetate in dichloromethane) affording N-[5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl]formamide (420 mg, 35% yield) as

light brown solid: ^1H NMR (400 MHz, DMSO- d_6) δ 12.42 (s, 1H), 10.47 (s, 0.70H), 10.10 (s, 0.30H), 8.62 (d, $J = 11.0$ Hz, 0.30H), 8.14 (d, $J = 1.8$ Hz, 0.80H), 6.39 (s, 0.70H), 5.90 (d, $J = 1.9$ Hz, 0.30H), 3.04 – 2.85 (m, 1H), 2.15 – 2.00 (m, 1H), 1.96 – 1.81 (m, 1H); tautomers were found in NMR; LCMS $R_T = 1.18$ min; $m/z = 188$ (M+H) $^+$.

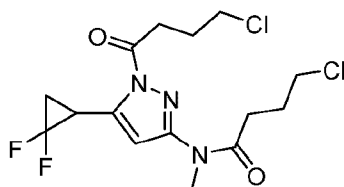
- 5 LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



Step 2: 5-(2,2-difluorocyclopropyl)-N-methyl-1H-pyrazol-3-amine

To a solution of N-[5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl]formamide (787 mg, 4.2 mmol) in tetrahydrofuran (37 mL) was added lithium aluminum hydride (2 mol/L) in
 10 tetrahydrofuran (6.38 mL, 12.6 mmol) at 0 °C, and the reaction was stirred at 25 °C for 6 h. Sodium sulfate decahydrate was added, and the mixture was stirred for 18 h. The mixture was filtered through celite, and ethyl acetate was used to rinse the solid. The combined liquid was concentrated to dryness *in vacuo* affording
 5-(2,2-difluorocyclopropyl)-N-methyl-1H-pyrazol-3-amine (950 mg) as colorless oil used
 15 without further purification: ^1H NMR (400 MHz, DMSO- d_6) δ 11.45 (s, 1H), 5.23 (bs, 1H), 2.81 – 2.66 (m, 1H), 2.61 (d, $J = 5.3$ Hz, 3H), 1.98 – 1.87 (m, 1H), 1.77 – 1.65 (m, 1H); LCMS $R_T = 1.06$ min; $m/z = 174$ (M+H) $^+$.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



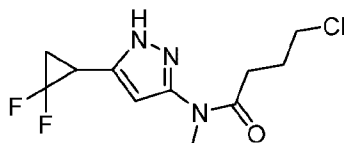
Step 3:

4-chloro-N-(1-(4-chlorobutanoyl)-5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl)-N-methylbutanamide

To a solution of 5-(2,2-difluorocyclopropyl)-N-methyl-1H-pyrazol-3-amine (810 mg, 4.7 mmol) and N,N-dimethylpyridin-4-amine (57 mg, 0.47 mmol) in dichloromethane (19 mL)
 25 and N,N-diisopropylethylamine (2.0 mL, 12 mmol) was added 4-chlorobutyryl chloride (1.2 mL, 10 mmol) at 0 °C, and the reaction was stirred at 0~25°C for 18 h. The reaction mixture was concentrated to dryness *in vacuo* and the crude residue was purified by column chromatography (silica gel, 100-200 mesh, 0-50% ethyl acetate in heptane) affording
 4-chloro-N-(1-(4-chlorobutanoyl)-5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl)-N-methylbut
 30 anamide (332 mg, 56% yield): ^1H NMR (400 MHz, DMSO- d_6) δ 6.86 (s, 1H), 3.74 (t, $J = 6.5$ Hz, 2H), 3.71 – 3.62 (m, 2H), 3.43 – 3.33 (m, 2H), 3.23 (t, $J = 7.3$ Hz, 2H), 2.73 – 2.62 (m, 2H),

2.18 – 1.87 (m, 6H), CH₃ was not seen in NMR, probably overlapping with HDO peak at 3.30 ppm; LCMS R_T = 3.07 min; *m/z* = 382 (M+H)⁺.

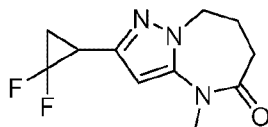
LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



5 **Step 4: 4-chloro-N-(5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl)-N-methylbutanamide**

To a solution of 4-chloro-N-[1-(4-chlorobutanoyl)-5-(2,2-difluorocyclopropyl)pyrazol-3-yl]-N-methylbutanamide (332 mg, 0.87 mmol) in ethanol (1.4 mL) was added sodium hydroxide (1 mol/L) in water (0.87 mL), and the reaction was stirred at 25 °C for 5 min. The reaction mixture was concentrated to dryness *in vacuo* and the residue was used without further purification: LCMS R_T = 2.03 min; *m/z* = 278 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

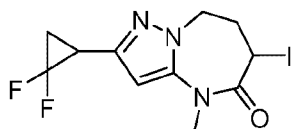


Step 5:

15 **2-(2,2-difluorocyclopropyl)-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one**

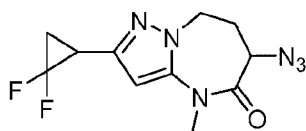
To a solution of 4-chloro-N-[5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl]-N-methylbutanamide (240 mg, 0.86 mmol) in N,N-dimethylformamide (3.9 mL) was added cesium carbonate (422 mg, 1.30 mmol), and the reaction was stirred at 65 °C for 18 h. The crude mixture was diluted with ethyl acetate and citric acid solution (10% aq.), and the two layers were separated. The aqueous layer was extracted by ethyl acetate. The organic layers were combined, washed by water and brine, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography (silica gel, 100-200 mesh, 0-75% ethyl acetate in dichloromethane) affording 2-(2,2-difluorocyclopropyl)-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (118 mg, 56% yield) as colorless oil: ¹H NMR (400 MHz, DMSO-d₆) δ 6.18 – 6.13 (m, 1H), 4.21 – 4.12 (m, 2H), 3.15 (s, 3H), 2.86 (td, *J* = 12.1, 8.0 Hz, 1H), 2.27 – 2.17 (m, 4H), 2.03 – 1.90 (m, 1H), 1.88 – 1.75 (m, 1H); LCMS R_T = 1.70 min; *m/z* = 242 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

**Step 6:****2-(2,2-difluorocyclopropyl)-6-iodo-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one**

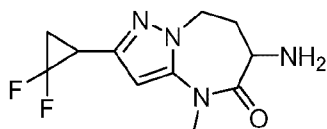
5 To a solution of 2-(2,2-difluorocyclopropyl)-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (118 mg, 0.49 mmol) in dichloromethane (4.0 mL) cooled to -10 °C in a salt/ice bath was added N,N,N',N'-tetramethylethylenediamine (0.44 mL, 2.9 mmol), followed by iodotrimethylsilane (0.42 mL, 2.9 mmol), and the reaction was stirred at -10 °C for 1.5 h. Iodine (372 mg, 1.47 mmol) was added, and the reaction was stirred for 2 h. The crude mixture was diluted with ethyl acetate and sodium sulfite solution, and the two layers were separated. The aqueous layer was extracted by ethyl acetate. The organic layers were combined, washed by water and brine, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography (silica gel, 100-200 mesh, 0-70% ethyl acetate in heptane) affording 2-(2,2-difluorocyclopropyl)-6-iodo-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (53 mg, 29% yield) as white solid: ¹H NMR (400 MHz, Chloroform-d) δ 5.95 (dd, *J* = 2.4, 1.1 Hz, 1H), 4.62 (ddd, *J* = 9.2, 7.4, 4.7 Hz, 1H), 4.31 – 4.14 (m, 2H), 3.33 (s, 3H), 3.05 – 2.89 (m, 1H), 2.84 – 2.67 (m, 2H), 1.91 – 1.76 (m, 1H), 1.78 – 1.65 (m, 1H); LCMS *R*_T = 2.15 min; *m/z* = 368 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

**Step 7:****6-azido-2-(2,2-difluorocyclopropyl)-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one**

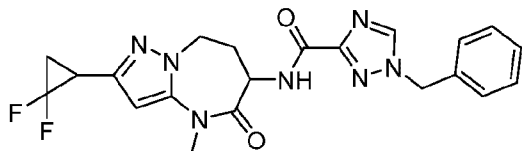
25 To a solution of 2-(2,2-difluorocyclopropyl)-6-iodo-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (53 mg, 0.14 mmol) in N,N-dimethylformamide (0.20 mL) was added sodium azide (11.6 mg, 0.17 mmol), and the reaction was stirred at 25 °C for 2 h. The crude mixture was used without further purification: LCMS *R*_T = 2.06 min; *m/z* = 283 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

**Step 8:****6-amino-2-(2,2-difluorocyclopropyl)-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one**

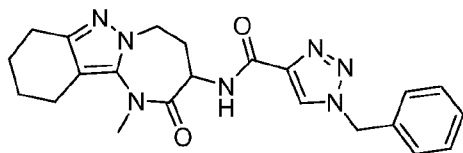
5 To a solution of 6-amino-2-(2,2-difluorocyclopropyl)-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (41 mg, 0.14 mmol) in tetrahydrofuran (0.5 mL) and water (0.15 mL) was added polymer-bound triphenylphosphine (0.87 mmol), and the reaction was stirred at 25 °C for 18 h. The crude mixture was filtered through celite, and concentrated to dryness *in vacuo*. The crude material was used without further purification: LCMS $R_T = 1.19$ min; $m/z = 257$ (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

**Step 9:****1-benzyl-N-[2-(2,2-difluorocyclopropyl)-4-methyl-5-oxo-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl]-1,2,4-triazole-3-carboxamide**

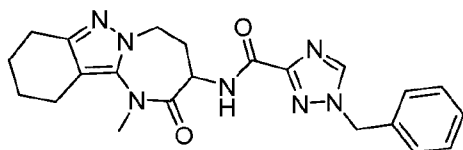
15 To a solution of 1-benzyl-1H-1,2,4-triazole-3-carboxylic acid (62 mg, 0.29 mmol) in N,N-dimethylformamide (1.0 mL) was added 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (112 mg, 0.29 mmol) at 0 °C, and the reaction was stirred at 0 °C for 20 min.

6-Amino-2-(2,2-difluorocyclopropyl)-4-methyl-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-5-one (37 mg, 0.14 mmol, 37 mg) was added. The reaction was stirred at 25 °C for 18 h. The crude material was purified by RP-HPLC affording 1-benzyl-N-[2-(2,2-difluorocyclopropyl)-4-methyl-5-oxo-7,8-dihydro-6H-pyrazolo[1,5-a][1,3]diazepin-6-yl]-1,2,4-triazole-3-carboxamide (36.5 mg, 57%) as white powder: ¹H NMR (400 MHz, DMSO-d₆) δ 8.82 (s, 1H), 8.54 (d, *J* = 7.8 Hz, 1H), 7.44 – 7.25 (m, 5H), 6.34 – 6.23 (m, 1H), 5.48 (s, 2H), 4.36 – 4.25 (m, 2H), 4.23 – 4.09 (m, 1H), 3.22 (d, *J* = 2.1 Hz, 3H), 2.99 – 2.78 (m, 1H), 2.67 – 2.53 (m, 1H), 2.44 – 2.31 (m, 1H), 2.02 – 1.80 (m, 2H); LCMS $R_T = 4.36$ min; $m/z = 442.2$ (M+H)⁺.

Example 135**METHOD X3****Step 1:**

5 **1-benzyl-N-(1-methyl-2-oxo-2,3,4,5,8,9,10,11-octahydro-1H-[1,3]diazepino[1,2-b]indazol-3-yl)-1H-1,2,3-triazole-4-carboxamide**

To a solution of 1-benzyl-1H-1,2,3-triazole-4-carboxylic acid (75 mg, 0.35 mmol) in N,N-dimethylformamide (1.0 mL) was added 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (136 mg, 0.35 mmol) at 0 °C, and the reaction was stirred at 0 °C for 20 min. 3-Amino-1-methyl-4,5,8,9,10,11-hexahydro-3H-[1,3]diazepino[1,2-b]indazol-2-one (41 mg, 0.17 mmol) was added. The reaction was stirred at 25 °C for 18 h. The crude material was purified by RP-HPLC affording 1-benzyl-N-(1-methyl-2-oxo-2,3,4,5,8,9,10,11-octahydro-1H-[1,3]diazepino[1,2-b]indazol-3-yl)-1H-1,2,3-triazole-4-carboxamide (42 mg, 57% yield) as white powder: ¹H NMR (400 MHz, DMSO-d₆) δ 8.65 (s, 1H), 8.49 (d, *J* = 7.7 Hz, 1H), 7.46 – 7.25 (m, 5H), 5.65 (s, 2H), 4.41 – 4.03 (m, 3H), 3.18 (s, 3H), 2.59 – 2.51 (m, 3H), 2.48 – 2.40 (m, 2H), 2.35 – 2.22 (m, 1H), 1.86 – 1.57 (m, 4H); LCMS *R*_T = 4.55 min; *m/z* = 420.2 (M+H)⁺.

Example 136**Step 1:**

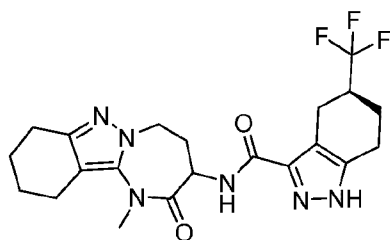
20 **1-benzyl-N-(1-methyl-2-oxo-2,3,4,5,8,9,10,11-octahydro-1H-[1,3]diazepino[1,2-b]indazol-3-yl)-1H-1,2,4-triazole-3-carboxamide**

To a solution of 1-benzyl-1H-1,2,4-triazole-3-carboxylic acid (75 mg, 0.35 mmol) in N,N-dimethylformamide (1.0 mL) was added 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (136 mg, 0.35 mmol) at 0 °C, and the reaction was stirred at 0 °C for 20 min. 3-Amino-1-methyl-4,5,8,9,10,11-hexahydro-3H-[1,3]diazepino[1,2-b]indazol-2-one (41 mg, 0.17 mmol) was added. The reaction was stirred at 25 °C for 18 h. The crude material was purified by RP-HPLC affording 1-benzyl-N-(1-methyl-2-oxo-4,5,8,9,10,11-hexahydro-3H-[1,3]diazepino[1,2-b]indazol-3-yl)

-1,2,4-triazole-3-carboxamide (40 mg, 54% yield) as white powder: ^1H NMR (400 MHz, DMSO- d_6) δ 8.82 (s, 1H), 8.38 (d, $J = 7.7$ Hz, 1H), 7.46 – 7.24 (m, 5H), 5.48 (s, 2H), 4.37 – 4.06 (m, 3H), 3.19 (s, 3H), 2.66 – 2.52 (m, 3H), 2.48 – 2.39 (m, 2H), 2.32 – 2.17 (m, 1H), 1.87 – 1.59 (m, 4H); LCMS $R_T = 4.35$ min; $m/z = 420.2$ (M+H) $^+$.

5 Example 137

METHOD X3



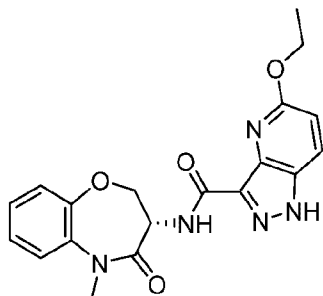
Step 1:

(5S)-N-(1-methyl-2-oxo-2,3,4,5,8,9,10,11-octahydro-1H-[1,3]diazepino[1,2-b]indazol-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide

To a solution of (*S*)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (61 mg, 0.26 mmol) in N,N-dimethylformamide (1.0 mL) was added 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (136 mg, 0.35 mmol) at 0 °C, and the reaction was stirred at 0 °C for 20 min. 3-Amino-1-methyl-4,5,8,9,10,11-hexahydro-3H-[1,3]diazepino[1,2-b]indazol-2-one (41 mg, 0.17 mmol) was added. The reaction was stirred at 25 °C for 18 h. The crude material was purified by RP-HPLC affording (*S*)-N-(1-methyl-2-oxo-2,3,4,5,8,9,10,11-octahydro-1H-[1,3]diazepino[1,2-b]indazol-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide (28.3 mg, 34% yield): ^1H NMR (400 MHz, DMSO- d_6) δ 12.97 (s, 1H), 7.97 (d, $J = 7.8$ Hz, 1H), 4.37 – 4.03 (m, 3H), 3.19 (s, 3H), 3.06 – 2.95 (m, 1H), 2.84 – 2.74 (m, 1H), 2.72 – 2.52 (m, 5H), 2.50 – 2.40 (m, 3H), 2.28 – 2.16 (m, 1H), 2.14 – 2.08 (m, 1H), 1.88 – 1.55 (m, 5H); LCMS $R_T = 4.84$ min; $m/z = 451.2$ (M+H) $^+$.

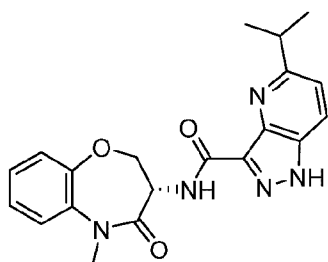
Example 138

25 METHOD X4

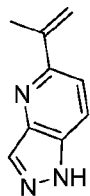


Step 1:**5-ethoxy-N-[(3*S*)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1H-pyrazolo[4,3-*b*]pyridine-3-carboxamide**

To a solution of 5-ethoxy-1H-pyrazolo[4,3-*b*]pyridine-3-carboxylic acid (40 mg, 0.19 mmol) in N,N-dimethylformamide (1.0 mL) was added 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (76 mg, 0.19 mmol) at 0 °C, and the reaction was stirred at 0 °C for 20 min. (3*S*)-3-Amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (25 mg, 0.13 mmol) was added. The reaction was stirred at 25 °C for 18 h. The reaction mixture was purified by RP-HPLC affording 5-ethoxy-N-[(3*S*)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1H-pyrazolo[4,3-*b*]pyridine-3-carboxamide (11.5 mg, 23% yield) as white powder: ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.90 (bs, 1H), 9.15 (d, *J* = 7.1 Hz, 1H), 8.06 (d, *J* = 9.1 Hz, 1H), 7.54 – 7.46 (m, 1H), 7.40 – 7.23 (m, 3H), 6.92 (d, *J* = 9.1 Hz, 1H), 5.10 – 4.95 (m, 1H), 4.72 – 4.57 (m, 3H), 4.31 (dd, *J* = 11.3, 9.8 Hz, 1H), 3.37 (s, 3H), 1.44 (t, *J* = 7.0 Hz, 3H); LCMS *R*_T = 4.80 min; *m/z* = 382.1 (M+H)⁺.

Example 139**METHOD X5**

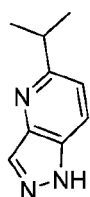
5-isopropenyl-N-[(3*S*)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1H-pyrazolo[4,3-*b*]pyridine-3-carboxamide

**Step 1: 5-isopropenyl-1H-pyrazolo[4,3-*b*]pyridine**

Bis(tricyclohexylphosphine)palladium(0) (129 mg, 0.19 mmol), 5-chloro-1H-pyrazolo[4,3-*b*]pyridine (301 mg, 1.9 mmol) and isopropenylboronic acid pinacol ester (471 mg, 2.66 mmol) were mixed in acetonitrile (6.0 mL) and sodium carbonate (2 mol/L) in water (2.9 mL, 5.7 mmol), and the reaction was microwaved at 110 °C for 2 h. The crude

mixture was diluted with ethyl acetate and citric acid solution (5% in water) to pH 9, and the two layers were separated. The aqueous layer was extracted by ethyl acetate. The organic layers were combined, washed by water and brine, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography (silica gel, 100-200 mesh, 0-50% ethyl acetate in dichloromethane) affording 5-isopropenyl-1H-pyrazolo[4,3-b]pyridine (274 mg, 58% yield) as white powder: ¹H NMR (400 MHz, DMSO-d₆) δ 13.27 (s, 1H), 8.27 (s, 1H), 7.96 (dd, *J* = 8.9, 1.0 Hz, 1H), 7.75 (d, *J* = 8.9 Hz, 1H), 5.91 – 5.83 (m, 1H), 5.38 (d, *J* = 1.5 Hz, 1H), 2.22 (dd, *J* = 1.5, 0.8 Hz, 3H); LCMS R_T = 1.44 min; *m/z* = 160 (M+H)⁺.

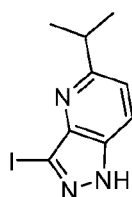
LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



Step 2: 5-isopropenyl-1H-pyrazolo[4,3-b]pyridine

To a solution of 5-isopropenyl-1H-pyrazolo[4,3-b]pyridine (201 mg, 0.82 mmol) in ethyl acetate (4.0 mL) and methanol (1.0 mL) was added palladium on activated carbon (10% wt) (86 mg), and the reaction was stirred with H₂ balloon at 65 °C for 4 h. The crude mixture was filtered through celite, and the celite was washed with ethyl acetate. The organic layers were combined and concentrated to dryness *in vacuo*, and the crude residue (244 mg) was used without further purification: ¹H NMR (400 MHz, DMSO-d₆) δ 13.15 (s, 1H), 8.18 (s, 1H), 7.91 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 1H), 3.15 (hept, *J* = 6.9 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 6H); LCMS R_T = 1.18 min; *m/z* = 162 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

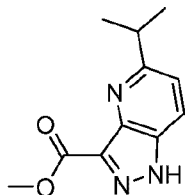


Step 3: 3-iodo-5-isopropenyl-1H-pyrazolo[4,3-b]pyridine

To a solution of 5-isopropenyl-1H-pyrazolo[4,3-b]pyridine (219 mg, 0.96 mmol) in N,N-dimethylformamide (4.85 mL) was added potassium hydroxide (162 mg, 2.9 mmol), followed by iodine (441 mg, 1.74 mmol), and the reaction was stirred at 50 °C for 1 h, and then at 25 °C for 1 h. The crude mixture was diluted with ethyl acetate and washed by sodium sulfite solution till color of organic layer did not change. The aqueous layers were combined and extracted by ethyl acetate. The organic layers were combined, washed by water and brine, dried

over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography (silica gel, 100-200 mesh, 0-40% ethyl acetate in heptane) affording 3-iodo-5-isopropyl-1H-pyrazolo[4,3-b]pyridine (192 mg, 69% yield) as white powder: ^1H NMR (400 MHz, DMSO- d_6) δ 13.60 (s, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 8.7 Hz, 1H), 3.18 (hept, J = 6.9 Hz, 1H), 1.29 (d, J = 6.9 Hz, 6H); LCMS R_T = 1.22 min; m/z = 288 (M+H) $^+$.

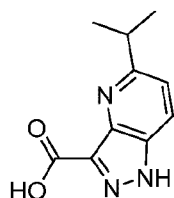
LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



Step 4: methyl 5-isopropyl-1H-pyrazolo[4,3-b]pyridine-3-carboxylate

- 3-Iodo-5-isopropyl-1H-pyrazolo[4,3-b]pyridine (110 mg, 0.38 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (44 mg, 0.076 mmol) and palladium(II) acetate (8.6 mg, 0.038 mmol) were mixed in triethylamine (0.80 mL, 5.75 mmol), methanol (1.6 mL) and N,N-dimethylformamide (1.2 mL), and the yellow solution was stirred under atmosphere of carbon monoxide at room temperature for 10 min and then at 60 °C for 2 days.
- The crude mixture was to dryness *in vacuo* and the crude residue was purified by column chromatography (silica gel, 100-200 mesh, 0-30% ethyl acetate in dichloromethane) affording methyl 5-isopropyl-1H-pyrazolo[4,3-b]pyridine-3-carboxylate (96 mg, 114% yield) as off-white powder: ^1H NMR (400 MHz, DMSO- d_6) δ 13.95 (bs, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 8.8 Hz, 1H), 3.90 (s, 3H), 3.20 (hept, J = 6.9 Hz, 1H), 1.30 (d, J = 6.9 Hz, 6H); LCMS R_T = 1.13 min; m/z = 220 (M+H) $^+$.

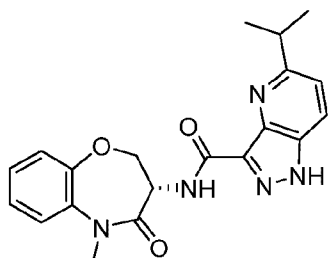
LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



Step 5: 5-isopropyl-1H-pyrazolo[4,3-b]pyridine-3-carboxylic acid

- To a solution of methyl 5-isopropyl-1H-pyrazolo[4,3-b]pyridine-3-carboxylate (83 mg, 0.38 mmol) in tetrahydrofuran (2.0 mL), water (1.0 mL) and methanol (1.0 mL) was added sodium hydroxide (150 mg, 3.8 mmol), and the reaction was stirred at 40 °C for 4 h. Hydrochloric acid solution (1.0 M) was added and the final pH was 3. The solution was concentrated to dryness *in vacuo*, and the crude residue was used without further purification: LCMS R_T = 1.37 min; m/z = 206 (M+H) $^+$.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



Step 6:

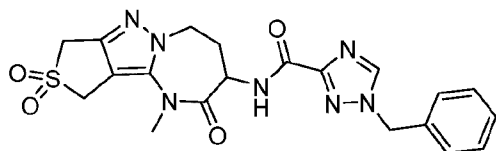
5-isopropyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1H-pyrazolo[4,3-b]pyridine-3-carboxamide

To a solution of 5-isopropyl-1H-pyrazolo[4,3-b]pyridine-3-carboxylic acid (40 mg, 0.19 mmol) in N,N-dimethylformamide (1.0 mL) was added 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (91 mg, 0.23412 mmol) at 0 °C, and the reaction was stirred at 0 °C for 20 min. (3S)-3-Amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (25 mg, 0.13 mmol) was added. The reaction was stirred at 25 °C for 18 h. The crude material was purified by RP-HPLC affording

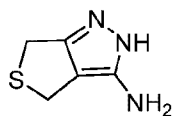
5-isopropyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1H-pyrazolo[4,3-b]pyridine-3-carboxamide (43.2 mg, 87% yield) as white powder: ¹H NMR (400 MHz, DMSO-d₆) δ 13.88 (bs, 1H), 9.65 (d, *J* = 7.2 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.38 – 7.26 (m, 3H), 5.04 (dt, *J* = 11.3, 7.3 Hz, 1H), 4.66 (dd, *J* = 9.8, 7.4 Hz, 1H), 4.32 (dd, *J* = 11.3, 9.8 Hz, 1H), 3.37 (s, 3H), 3.30 – 3.24 (m, 1H), 1.41 (d, *J* = 6.8 Hz, 6H); LCMS R_T = 4.92 min; *m/z* = 380.2 (M+H)⁺.

Example 140

METHOD X6



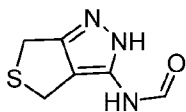
1-benzyl-N-(1-methyl-9,9-dioxido-2-oxo-1,2,3,4,5,10-hexahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide



Step 1: 2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-amine

To a solution of 4-cyano-3-tetrahydrothiophenone (1.01 g, 7.78 mmol) in toluene (11.5 mL) was added hydrazine (0.33 mL, 9.7 mmol), and the reaction was stirred at 90 °C for 10 h. The reaction mixture was concentrated to dryness *in vacuo* and the residue was used without further purification: LCMS $R_T = 1.29$ min; $m/z = 170$ (M+H)⁺.

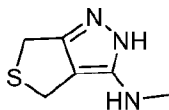
- 5 LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



Step 2: N-(4,6-dihydro-2H-thieno[3,4-c]pyrazol-3-yl)formamide

- 4,6-dihydro-1H-thieno[3,4-c]pyrazol-3-amine (442 mg, 2.98 mmol) and formic acid (1.3 mL) were mixed together, and the reaction was stirred at 110 °C for 3 h. The crude reaction mixture was diluted with ethyl acetate (300 mL) and water (30 mL), and sodium hydroxide solution (aq, 50% w/w) was added dropwise at 0 °C to change the pH of aqueous layer to 7. The two layers were separated. The aqueous layer was extracted by ethyl acetate (50 mL x 2). The organic layers were combined, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The crude residue (2.68 g yellow solid) was used without further purification: LCMS $R_T = 1.39$ min; $m/z = 170$ (M+H)⁺.

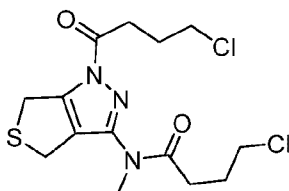
LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



Step 3: N-methyl-4,6-dihydro-2H-thieno[3,4-c]pyrazol-3-amine

- To a solution of N-(4,6-dihydro-1H-thieno[3,4-c]pyrazol-3-yl)formamide (2.68 g, 15.8 mmol) in tetrahydrofuran (201 mL) was added lithium aluminum hydride (2 mol/L) in tetrahydrofuran (23.8 mL, 47.5 mmol) at 0 °C, and the reaction was stirred at 25 °C for 2.5 h, resulting in a brown solution. Sodium sulfate decahydrate was added, and the mixture was stirred for 18 h. The mixture was filtered through celite, and ethyl acetate was used to rinse the celite solid. The combined liquid was concentrated to dryness *in vacuo*, and the crude residue (3.43 g) was used without further purification: LCMS $R_T = 1.58$ min; $m/z = 156$ (M+H)⁺.

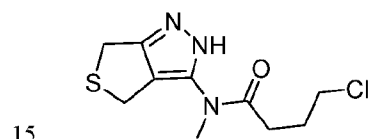
LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



Step 4:**4-chloro-N-[1-(4-chlorobutanoyl)-4,6-dihydrothieno[3,4-c]pyrazol-3-yl]-N-methyl-butanamide**

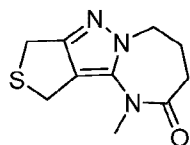
To a solution of N-methyl-4,6-dihydro-1H-thieno[3,4-c]pyrazol-3-amine (3.43 g, 22.1 mmol) and N,N-dimethylpyridin-4-amine (270 mg, 2.21 mmol) in dichloromethane (88 mL) and N,N-diisopropylethylamine (7.71 mL, 44.2 mmol) was added 4-chlorobutyryl chloride (4.47 mL, 39.8 mmol) at 0 °C, and the reaction was stirred at 0 °C for 30 min then at 25 °C for 2 h. The reaction solution was diluted with ethyl acetate (350 mL), and washed by water (final pH~7). The organic layer was dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0-30% ethyl acetate in heptane) affording 4-chloro-N-[1-(4-chlorobutanoyl)-4,6-dihydrothieno[3,4-c]pyrazol-3-yl]-N-methyl-butanamide (3.785 g, 47% yield) as yellow oil: LCMS $R_T = 3.46$ min; $m/z = 364$ (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

**Step 5: 4-chloro-N-(4,6-dihydro-1H-thieno[3,4-c]pyrazol-3-yl)-N-methyl-butanamide**

To a solution of 4-chloro-N-[1-(4-chlorobutanoyl)-4,6-dihydrothieno[3,4-c]pyrazol-3-yl]-N-methyl-butanamide (3.78 g, 10.4 mmol) in ethanol (16 mL) was added sodium hydroxide (1 mol/L) in water (10 mL, 10 mmol), and the reaction was stirred at 0 °C for 15 min. The crude mixture was diluted with ethyl acetate and water, and the two layers were separated. The aqueous layer was extracted by ethyl acetate. The organic layers were combined, washed by water and brine, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The crude material (3.40 g white solid) was used without further purification: LCMS $R_T = 1.87$ min; $m/z = 260$ (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

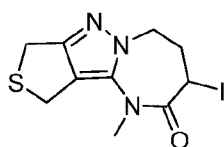
**Step 6:****1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one**

To a solution of 4-chloro-N-(4,6-dihydro-1H-thieno[3,4-c]pyrazol-3-yl)-N-methyl-butanamide (2.70 g, 10.4

mmol) in N,N-dimethylformamide (47 mL) was added cesium carbonate (4.41 g, 13.5 mmol), and the reaction was stirred at 60 °C for 1.5 h. The crude mixture was diluted with ethyl acetate and citric acid to pH 8, and the two layers were separated. The aqueous layer was extracted by ethyl acetate twice. The organic layers were combined, washed by water and brine, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography (silica gel, 100-200 mesh, 0-10% methanol in dichloromethane) affording

1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one (1.91 g, 62% yield) as slightly yellow oil, which crystalized upon scratch or addition of crystal seed: ¹H NMR (400 MHz, DMSO-d₆) δ 4.14 (t, *J* = 6.7 Hz, 2H), 3.88 (s, 4H), 3.12 (s, 3H), 2.33 – 2.15 (m, 4H); ¹H NMR (400 MHz, Chloroform-d) δ 4.21 (t, *J* = 6.8 Hz, 2H), 4.03 – 3.95 (m, 2H), 3.89 – 3.82 (m, 2H), 3.23 (s, 3H), 2.50 – 2.30 (m, 4H); LCMS R_T = 1.66 min; *m/z* = 224 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

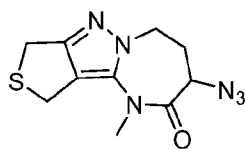


Step 7:

3-iodo-1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one

To a solution of 1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one (1001 mg, 3.3621 mmol, 75% wt purity) in dichloromethane (28 mL) was added N,N,N',N'-tetramethylethylenediamine (4.05 mL, 27 mmol) at -20 °C (acetone-dry-ice bath), followed by iodotrimethylsilane (3.84 mL, 27 mmol), and the reaction was stirred in acetone-dry-ice bath (-20 ~ -15 °C) for 3 h. Iodine (3.41 g, 13.5 mmol) was added, and the reaction was stirred in acetone-dry-ice bath (at -15 ~ -10 °C) for 2 h. The crude mixture was diluted with ethyl acetate and sodium thiosulfate solution (10% aq., 10 mL), and the two layers were separated. The aqueous layer was extracted by ethyl acetate. The organic layers were combined, washed by water and brine, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography (silica gel, 100-200 mesh, 0-50% ethyl acetate in heptane) affording 3-iodo-1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one (0.80 g, 68% yield) as off-white solid: ¹H NMR (400 MHz, Chloroform-d) δ 4.65 (dd, *J* = 8.5, 7.6 Hz, 1H), 4.19 (ddd, *J* = 8.3, 5.9, 1.5 Hz, 2H), 4.03 – 3.95 (m, 2H), 3.93 – 3.85 (m, 2H), 3.29 (s, 3H), 3.05 – 2.89 (m, 1H), 2.85 – 2.71 (m, 1H); LCMS R_T = 1.97 min; *m/z* = 350 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

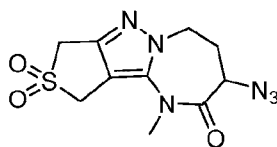


Step 8:

3-azido-1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one

To a solution of 3-iodo-1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one (310 mg, 0.89 mmol) in N,N-dimethylformamide (3.50 mL) was added sodium azide (89 mg, 1.33 mmol), and the reaction was stirred at 25 °C for 2 h. The reaction mixture was concentrated to dryness *in vacuo* and was diluted with ethyl acetate and water (pH~8). The two layers were separated. The aqueous layer was extracted by ethyl acetate twice. The organic layers were combined, washed by water and brine, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The crude material (436 mg) was used without further purification: LCMS R_T = 1.07 min; m/z = 265 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



Step 9:

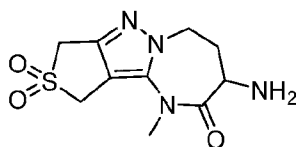
3-azido-1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one 9,9-dioxide

To a solution of 3-azido-1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one (355 mg, 1.34 mmol) in acetic acid (0.081 mL, 1.41 mmol) and dichloromethane (11 mL) was added 3-chloroperoxybenzoic acid (722 mg, 3.22 mmol) at 0 °C, and the reaction was stirred at 0 °C for 1 h. Second portion of 3-chloroperoxybenzoic acid (96 mg, 0.43 mmol) was added, and the reaction was stirred at 25 °C for 30 min. The crude mixture was diluted with ethyl acetate. The organic solution was washed by water and brine, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography (silica gel, 100-200 mesh, 0-60% ethyl acetate in heptane) affording

3-azido-1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one 9,9-dioxide (360 mg, 90% yield) as white solid: ¹H NMR (400 MHz, Chloroform-d) δ

4.55 – 4.39 (m, 1H), 4.33 – 4.16 (m, 5H), 3.91 (dd, $J = 10.6, 7.9$ Hz, 1H), 3.32 (s, 3H), 2.88 – 2.74 (m, 1H), 2.30 (dddd, $J = 13.5, 10.7, 6.6, 1.8$ Hz, 1H); ^1H NMR (400 MHz, DMSO- d_6) δ 4.53 (d, $J = 14.7$ Hz, 1H), 4.48 – 4.25 (m, 5H), 4.13 (dd, $J = 11.3, 7.9$ Hz, 1H), 3.25 (s, 3H), 2.84 – 2.64 (m, 1H), 2.17 (dddd, $J = 13.2, 11.4, 6.1, 1.7$ Hz, 1H); LCMS $R_T = 1.52$ min; $m/z = 297$ (M+H) $^+$.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

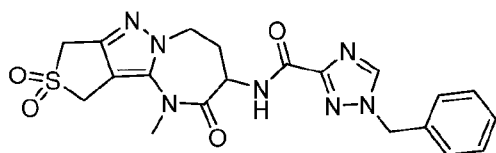


Step 10:

3-amino-1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one 9,9-dioxide

To a suspension of 3-azido-1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one 9,9-dioxide (291 mg, 0.84 mmol) in tetrahydrofuran (6.9 mL) and water (0.93 mL) was added polymer-bound triphenylphosphine (5.1 mmol), and the reaction was stirred at 25 °C for 12 h. The reaction mixture was filtered through celite, and the celite solid was rinsed by a solution of methanol in dichloromethane (10% v/v) twice. The solutions were combined and concentrated to dryness *in vacuo*, and the crude material (284 mg) was used without further purification: LCMS $R_T = 0.52$ min; $m/z = 271$ (M+H) $^+$.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins).



Step 11:

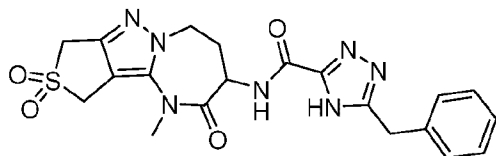
1-benzyl-N-(1-methyl-9,9-dioxido-2-oxo-1,2,3,4,5,10-hexahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide

To a suspension of 1-benzyl-1H-1,2,4-triazole-3-carboxylic acid (68 mg, 0.32 mmol) in N,N-dimethylformamide (1.0 mL) and N,N-diisopropylethylamine (0.055 mL, 0.32 mmol) was added 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (123 mg, 0.32 mmol) at 0 °C, and the reaction was stirred at 0 °C for 20 min, resulting in a yellow solution. 3-Amino-1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one 9,9-dioxide (57 mg, 0.21 mmol) was added. The reaction was stirred at 25 °C for 18 h. The reaction mixture was concentrated to dryness *in vacuo* and the residue was purified by

RP-HPLC

affording

1-benzyl-N-(1-methyl-9,9-dioxido-2-oxo-1,2,3,4,5,10-hexahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide (61 mg, 63% yield) as white powder: ^1H NMR (400 MHz, DMSO- d_6) δ 8.82 (s, 1H), 8.49 (d, J = 7.7 Hz, 1H), 7.46 – 7.23 (m, 5H), 5.49 (s, 2H), 4.56 – 4.33 (m, 6H), 4.34 – 4.19 (m, 1H), 3.20 (s, 3H), 2.73 – 2.60 (m, 1H), 2.41 – 2.28 (m, 1H); LCMS R_T = 3.47 min; m/z = 456.1 ($M+H$) $^+$.

Example 141

5-benzyl-N-(1-methyl-9,9-dioxido-2-oxo-1,2,3,4,5,10-hexahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide

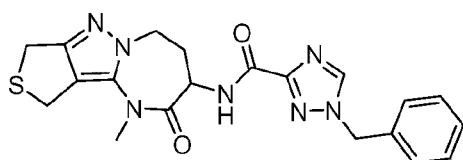
Step

1:

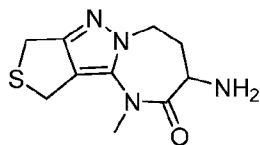
5-benzyl-N-(1-methyl-9,9-dioxido-2-oxo-1,2,3,4,5,10-hexahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide

To a suspension of 5-benzyl-4H-1,2,4-triazole-3-carboxylic acid (65 mg, 0.32 mmol) in N,N-dimethylformamide (1.0 mL) and N,N-diisopropylethylamine (0.052 mL, 0.32 mmol) was added 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (123 mg, 0.32 mmol) at 0 °C, and the reaction was stirred at 0 °C for 20 min, resulting in a yellow solution.

3-Amino-1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one 9,9-dioxide (57 mg, 0.21 mmol) was added. The reaction was stirred at 25 °C for 18 h. The reaction mixture was concentrated to dryness *in vacuo* and the residue was purified by RP-HPLC

Example 142**METHOD X7**

1-benzyl-N-(1-methyl-2-oxo-1,2,3,4,5,10-hexahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide

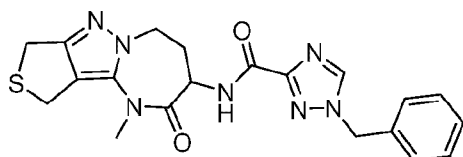


Step 1:

3-amino-1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one

To a solution of 3-azido-1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one (235 mg, 0.89 mmol) in tetrahydrofuran (3.0 mL) and water (1.0 mL) was added polymer-bound triphenylphosphine, (5.4 mmol), and the reaction was stirred at 25 °C for 5 h. The reaction mixture was filtered through celite, and the celite solid was rinsed by a solution of methanol in dichloromethane (10% v/v, 3 mL) twice. The organic solutions were combined and concentrated to dryness *in vacuo*, and the crude material (285 mg) was used without further purification: LCMS $R_T = 1.3$ min; $m/z = 239$ (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



Step 2:

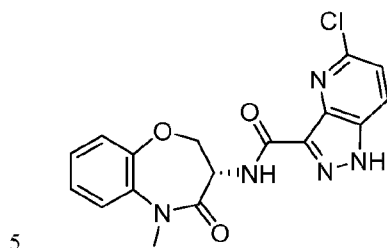
1-benzyl-N-(1-methyl-2-oxo-1,2,3,4,5,10-hexahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide

To a suspension of 1-benzyl-1H-1,2,4-triazole-3-carboxylic acid (71 mg, 0.33 mmol) in N,N-dimethylformamide (1.0 mL) and N,N-diisopropylethylamine (0.050 mL, 0.29 mmol) was added 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (129 mg, 0.33 mmol) at 0 °C, and the reaction was stirred at 0 °C for 20 min, resulting in a yellow solution. 3-Amino-1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one (53 mg, 0.22 mmol) was added. The reaction was stirred at 25 °C for 18 h. The crude material was purified by RP-HPLC affording 1-benzyl-N-(1-methyl-2-oxo-1,2,3,4,5,10-hexahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide (75 mg, 80% yield) as white powder: ¹H NMR (400 MHz, DMSO-d₆) δ 8.82 (s, 1H), 8.45 (d, $J = 7.7$ Hz, 1H, NH), 7.44 – 7.26 (m, 5H),

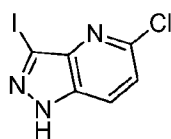
5.48 (s, 2H), 4.40 (dt, $J = 11.4, 7.8$ Hz, 1H), 4.31 – 4.12 (m, 2H), 3.99 – 3.78 (m, 4H), 3.19 (s, 3H), 2.73 – 2.56 (m, 1H), 2.37 – 2.21 (m, 1H); LCMS $R_T = 3.99$ min; $m/z = 424.1$ (M+H)⁺.

Example 143

METHOD X8



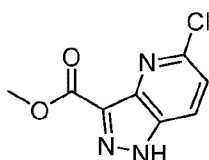
5-chloro-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1H-pyrazolo[4,3-b]pyridine-3-carboxamide



Step 1: 5-chloro-3-iodo-1H-pyrazolo[4,3-b]pyridine

- 10 To a solution of 5-chloro-1H-pyrazolo[4,3-b]pyridine (501 mg, 3.16 mmol) in N,N-dimethylformamide (16 mL) was added potassium hydroxide (532 mg, 9.49 mmol), followed by iodine (1.45 g, 5.70 mmol) at 0 °C, and the reaction was stirred at 0 °C for 30 min, then at 25 °C for 30 min, and finally at 50 °C for 1 h. The crude mixture was diluted with ethyl acetate and washed by sodium sulfite solution till color of organic layer did not change. The
- 15 aqueous layers were combined and extracted by ethyl acetate. The organic layers were combined, washed by water and brine, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo* affording 5-chloro-3-iodo-1H-pyrazolo[4,3-b]pyridine (770 mg, 87% yield) used without further purification: ¹H NMR (400 MHz, DMSO-d₆) δ 13.89 (s, 1H), 8.10 (d, $J = 8.8$ Hz, 1H), 7.48 (d, $J = 8.8$ Hz, 1H); LCMS $R_T = 1.92$ min; $m/z =$
- 20 280 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

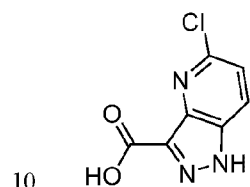


Step 2: methyl 5-chloro-1H-pyrazolo[4,3-b]pyridine-3-carboxylate

- 5-chloro-3-iodo-1H-pyrazolo[4,3-b]pyridine (250 mg, 0.85 mmol),
- 25 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (49 mg, 0.085 mmol,) and palladium(II)

acetate (9.5 mg, 0.042 mmol) were mixed in triethylamine (2.6 mL), methanol (2.6 mL) and N,N-dimethylformamide (2.5 mL), and the yellow solution was stirred under atmosphere of carbon monoxide at room temperature for 10 min and then at 70 °C for 2 days. The crude mixture was concentrated to dryness *in vacuo*, and the crude residue was purified by column chromatography (silica gel, 100-200 mesh, 0-50% ethyl acetate in dichloromethane) affording methyl 5-chloro-1H-pyrazolo[4,3-b]pyridine-3-carboxylate (0.12 g, 67% yield) as off-white powder: ¹H NMR (400 MHz, DMSO-d₆) δ 14.36 (s, 1H), 8.23 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 3.92 (s, 3H); LCMS R_T = 1.48 min; *m/z* = 212 (M+H)⁺.

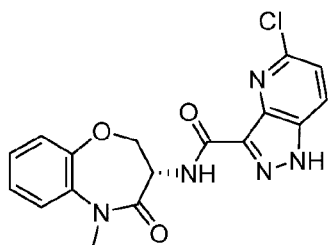
LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



Step 3: 5-chloro-1H-pyrazolo[4,3-b]pyridine-3-carboxylic acid

To a solution of methyl 5-chloro-1H-pyrazolo[4,3-b]pyridine-3-carboxylate (30.0 mg, 0.142 mmol) in tetrahydrofuran (1.0 mL) and methanol (0.25 mL) was added sodium hydroxide (1 mol/L) in water (0.25 mL), and the reaction was stirred at 25 °C for 8 h. Hydrochloric acid solution (1.0 M, 0.60 mL) was added, resulting in a clear solution with pH ~6. The solution was concentrated to dryness *in vacuo*, and the crude material was used without further purification: LCMS R_T = 0.91 min; *m/z* = 198 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



20 Step 4:

5-chloro-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1H-pyrazolo[4,3-b]pyridine-3-carboxamide

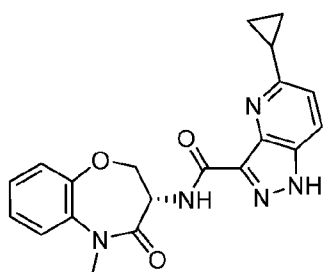
To a solution of 5-chloro-1H-pyrazolo[4,3-b]pyridine-3-carboxylic acid (35 mg, 0.18 mmol) in N,N-dimethylformamide (1.0 mL) was added 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (70 mg, 0.18 mmol) and N,N-diisopropylethylamine (0.042 mL) at 0 °C, and the reaction was stirred at 0 °C for 20 min. (3S)-3-Amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (23 mg, 0.12 mmol) was added.

The reaction was stirred at 25 °C for 18 h. The crude material was purified by RP-HPLC affording

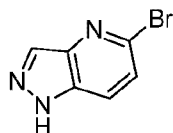
5-chloro-N-[(3*S*)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1H-pyrazolo[4,3-*b*]pyridine-3-carboxamide (12 mg, 27% yield) as white powder: ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.22 (bs, 1H), 8.75 (d, *J* = 7.3 Hz, 1H), 8.24 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.52 (dd, *J* = 6.9, 2.5 Hz, 1H), 7.39 – 7.24 (m, 3H), 4.97 (dt, *J* = 11.4, 7.4 Hz, 1H), 4.59 (dd, *J* = 9.9, 7.5 Hz, 1H), 4.44 (dd, *J* = 11.4, 9.9 Hz, 1H), 3.36 (s, 3H); LCMS *R*_T = 4.37 min; *m/z* = 372.1 (M+H)⁺.

Example 144

10 METHOD X9



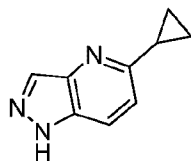
5-cyclopropyl-N-[(3*S*)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1H-pyrazolo[4,3-*b*]pyridine-3-carboxamide



15 Step 1: 5-bromo-1H-pyrazolo[4,3-*b*]pyridine

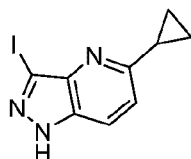
To a suspension of 5-chloro-1H-pyrazolo[4,3-*b*]pyridine (81 mg, 0.51 mmol) in propionitrile (0.51 mL) was added bromotrimethylsilane (0.135 mL, 1.0 mmol), and the reaction was stirred at 100 °C for 16 h.. Second portion of bromotrimethylsilane (0.14 mL, 1.0 mmol) was added, and the suspension was stirred at 110 °C for 6 h. The crude mixture was quenched with ice-water. Sodium carbonate was added to change the pH to 9. The aqueous layer was extracted by a solution of methanol in ethyl acetate (10% v/v) twice. The organic layers were combined, washed by water and brine, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The crude material (189 mg beige solid) was used without further purification: ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.59 (s, 1H), 8.29 (d, *J* = 1.0 Hz, 1H), 8.02 (dd, *J* = 8.7, 1.0 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H); LCMS *R*_T = 1.63 min; *m/z* = 198 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



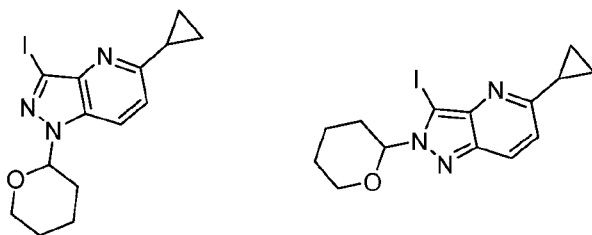
Step 2: 5-cyclopropyl-1H-pyrazolo[4,3-b]pyridine

- To a solution of 5-bromo-1H-pyrazolo[4,3-b]pyridine (77 mg, 0.37 mmol), palladium(II) acetate (8.3 mg, 0.037 mmol) and S-Phos (31 mg, 0.074 mmol) in tetrahydrofuran (1.5 mL) was added cyclopropylzinc bromide (0.5 mol/L) in tetrahydrofuran (4 mL, 2.2 mmol), and the reaction was stirred at 110 °C for 18 h. The crude mixture was diluted with ethyl acetate and citric acid solution (10% aq.) to pH 9, and the two layers were separated. The aqueous layer was extracted by ethyl acetate. The organic layers were combined, washed by water and brine, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography (silica gel, 100-200 mesh, 0-50% ethyl acetate in dichloromethane) to afford 5-cyclopropyl-1H-pyrazolo[4,3-b]pyridine (33 mg, 56% yield) as white powder: ¹H NMR (400 MHz, DMSO-d₆) δ 13.12 (bs, 1H), 8.10 (s, 1H), 7.93 – 7.82 (m, 1H), 7.28 (d, *J* = 8.7 Hz, 1H), 2.27 – 2.16 (m, 1H), 0.99 – 0.92 (m, 4H); LCMS *R*_T = 1.06 min; *m/z* = 160 (M+H)⁺.
- LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



Step 3: 5-cyclopropyl-3-iodo-1H-pyrazolo[4,3-b]pyridine

- To a solution of 5-cyclopropyl-1H-pyrazolo[4,3-b]pyridine (290 mg, 1.82 mmol) in N,N-dimethylformamide (9.26 mL) was added potassium hydroxide (307 mg, 5.52 mmol), followed by iodine (832 mg, 3.3 mmol) at 25 °C, and the reaction was stirred at 50 °C for 1 h. The crude mixture was diluted with ethyl acetate and washed by sodium sulfide solution till color of organic layer did not change. The aqueous layers were combined and extracted by ethyl acetate. The organic layers were combined, washed by water and brine, dried over magnesium sulfate, filtered through celite, and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography (silica gel, 100-200 mesh, 0-30% ethyl acetate in dichloromethane) affording 5-cyclopropyl-3-iodo-1H-pyrazolo[4,3-b]pyridine (122 mg, 23% yield) as white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 13.56 (s, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 2.30 – 2.20 (m, 1H), 1.05 – 0.93 (m, 4H); *R*_T = 1.22 min; *m/z* = 286 (M+H)⁺.
- LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)



Step 4: 5-cyclopropyl-3-iodo-1-tetrahydropyran-2-yl-pyrazolo[4,3-b]pyridine and 5-cyclopropyl-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[4,3-b]pyridine

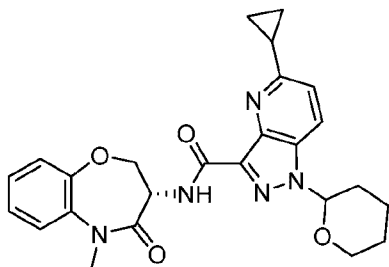
To a suspension of 5-cyclopropyl-3-iodo-1H-pyrazolo[4,3-b]pyridine (67 mg, 0.23 mmol) in dichloromethane (2.0 mL) was added 4-methylbenzenesulfonamide hydrate (4.45 mg, 0.023 mmol), followed by 3,4-dihydro-2H-pyran (59 mg, 0.70 mmol), and the reaction was stirred at 25 °C for 18 h, resulting in a colorless solution. More 3,4-dihydro-2H-pyran (59 mg, 0.705 mmol) was added, and the reaction solution was kept at 40 °C for 3.5 h. The solution was concentrated to dryness *in vacuo*, and the crude residue was purified by column chromatography (silica gel, 100-200 mesh, 0-30% dichloromethane in heptane) affording 5-cyclopropyl-3-iodo-1-tetrahydropyran-2-yl-pyrazolo[4,3-b]pyridine (31 mg, 36% yield) and 5-cyclopropyl-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[4,3-b]pyridine (15 mg, 18% yield):

Analytical data for one isomer: ¹H NMR (400 MHz, DMSO-d₆) δ 7.97 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 5.88 – 5.78 (m, 1H), 4.02 – 3.90 (m, 1H), 3.78 – 3.65 (m, 1H), 2.49 – 2.38 (m, 1H), 2.30 – 2.16 (m, 1H), 2.13 – 1.91 (m, 1H), 1.83 – 1.39 (m, 3H), 1.06 – 0.93 (m, 4H); LCMS *R*_T = 1.47 min; *m/z* = 370 (M+H)⁺.

Analytical data for the other isomer: ¹H NMR (400 MHz, DMSO-d₆) δ 8.08 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 5.83 (dd, *J* = 9.7, 2.4 Hz, 1H), 3.91 – 3.83 (m, 1H), 3.78 – 3.65 (m, 1H), 2.38 – 2.21 (m, 2H), 2.07 – 1.91 (m, 2H), 1.79 – 1.40 (m, 3H), 1.07 – 0.91 (m, 4H); LCMS *R*_T = 1.62 min; *m/z* = 370 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

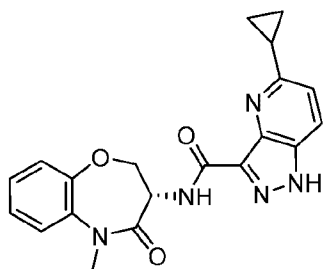
Note: following Step 5 and 6 below, both isomers afforded 5-cyclopropyl-N-[(3*S*)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1H-pyrazolo[4,3-b]pyridine-3-carboxamide (i.e., final product).



Step 5:**5-cyclopropyl-N-((3*S*)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[4,3-*b*]pyridine-3-carboxamide**

5-cyclopropyl-3-iodo-1-tetrahydropyran-2-yl-pyrazolo[4,3-*b*]pyridine (31 mg, 0.084 mmol),
 5 (3*S*)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one hydrochloride (29 mg, 0.13 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (7.3 mg, 0.013 mmol) and palladium(II) acetate (1.9 mg, 0.0084 mmol) were mixed in triethylamine (0.076 mL), *N,N*-dimethylformamide (0.10 mL) and toluene (5 mL), and the yellow solution was stirred under atmosphere of carbon monoxide at room temperature for 10 min and then at 80 °C for 18
 10 h. The crude mixture was concentrated to dryness *in vacuo*, and the crude residue was purified by column chromatography (silica gel, 100-200 mesh, 0-40% ethyl acetate in dichloromethane) affording 5-cyclopropyl-N-[(3*S*)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1-tetrahydropyran-2-yl-pyrazolo[4,3-*b*]pyridine-3-carboxamide (20 mg, 52% yield) as light brown solid:
 15 LCMS $R_T = 3.30$ min; $m/z = 462$ (M+H)⁺.

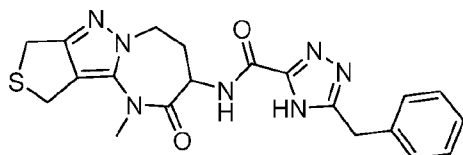
LCMS (5 to 95% acetonitrile in water + 0.05% formic acid over 5 mins)

**Step 6:****5-cyclopropyl-N-[(3*S*)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1*H*-pyrazolo[4,3-*b*]pyridine-3-carboxamide**

To a solution of 5-cyclopropyl-N-[(3*S*)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1-tetrahydropyran-2-yl-pyrazolo[4,3-*b*]pyridine-3-carboxamide (20 mg, 0.043 mmol) in methanol (0.26 mL) and dichloromethane (0.50 mL) was added hydrochloride (4 mol/L) in 1,4-dioxane (0.12 mL,
 25 0.48 mmol), and the reaction was stirred at 25 °C for 1 h. *N,N*-diisopropylethylamine (0.11 mL) was added. The crude mixture was concentrated to dryness *in vacuo*. The crude material was purified by RP-HPLC affording 5-cyclopropyl-N-[(3*S*)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1*H*-pyrazolo[4,3-*b*]pyridine-3-carboxamide (13.2 mg, 81% yield) as white powder: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.50 (d, *J* = 7.2 Hz, 1H), 8.03 (d, *J* = 8.7 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.38 – 7.27 (m, 3H), 5.01 (dt, *J* = 11.3, 7.3 Hz, 1H, CHN), 4.64 (dd, *J* = 9.8, 7.4

Hz, 1H), 4.29 (dd, $J = 11.3, 9.9$ Hz, 1H), 3.38 (s, 3H), 2.41 – 2.28 (m, 1H, Ar-CH), 1.43 – 1.33 (m, 1H), 1.27 – 1.17 (m, 1H), 1.15 – 1.05 (m, 2H); LCMS $R_T = 4.73$ min; $m/z = 378.2$ (M+H)⁺.

Example 145



5-benzyl-N-(1-methyl-2-oxo-1,2,3,4,5,10-hexahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide

Step 1:
5-benzyl-N-(1-methyl-2-oxo-1,2,3,4,5,10-hexahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide

- To a solution of 5-benzyl-4H-1,2,4-triazole-3-carboxylic acid (113 mg, 0.556 mmol) in N,N-dimethylformamide (1.5 mL) and N,N-diisopropylethylamine (0.0776 mL, 0.44 mmol) was added 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (216 mg, 0.56 mmol,) at 0 °C, and the reaction was stirred at 0 °C for 20 min, resulting in a brown solution.
- 3-Amino-1-methyl-1,4,5,10-tetrahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-2(3H)-one (53 mg, 0.22 mmol) was added. The reaction was stirred at 25 °C for 18 h. The crude material was purified by RP-HPLC affording 5-benzyl-N-(1-methyl-2-oxo-1,2,3,4,5,10-hexahydro-8H-thieno[3',4':3,4]pyrazolo[1,5-a][1,3]diazepin-3-yl)-4H-1,2,4-triazole-3-carboxamide (54 mg, 57% yield) as white powder: ¹H NMR (400 MHz, DMSO-d₆) δ 14.40 (bs, 1H), 8.48 (bs, 1H), 7.42 – 7.16 (m, 5H), 4.40 (dt, $J = 11.4, 7.8$ Hz, 1H), 4.32 – 4.15 (m, 2H), 4.11 (s, 2H), 4.02 – 3.78 (m, 4H), 3.19 (s, 3H), 2.69 – 2.56 (m, 1H), 2.40 – 2.25 (m, 1H); LCMS $R_T = 3.87$ min; $m/z = 424.1$ (M+H)⁺.

Examples 146-170 were prepared according to the Methods above and were purified according the Chiral Methods section below. Table 2 provides data for these compounds.

CHIRAL METHODS

Example #	SFC analytical method	SFC prep method
149	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar	SFC condition: Column: ES Industries AD 150 x 21.2mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 25% B in 6min Flow rate: 70mL/min Column temperature: 40

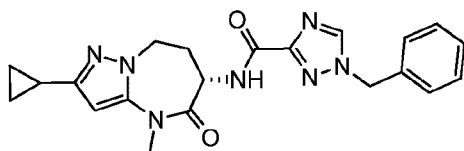
		oC, BPR: 100 bar
147	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 oC, BPR: 120 bar	SFC condition: Column: ES Industries AD150 x 21.2mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 25% B in 6min Flow rate: 70mL/min Column temperature: 40 oC, BPR: 100 bar
148	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 oC, BPR: 120 bar	SFC condition: Column: ES Industries AD150 x 21.2mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 25% B in 6min Flow rate: 70mL/min Column temperature: 40 oC, BPR: 100 bar
150	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 oC, BPR: 120 bar	SFC condition: Column:Chiralcel OJ 250×21.1mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 20% in 10 min B Flow rate: 70mL/min Column temperature: 40 oC, BPR: 100 bar
149	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 oC, BPR: 120 bar	SFC condition: Column:Chiralcel OJ 250×21.1mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 20% B in 10 min Flow rate: 70mL/min Column temperature: 40 oC, BPR: 100 bar
153	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 oC, BPR: 120 bar	SFC condition: Column:Chiralcel OJ 250×21.1mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 15% B in 10 min Flow rate: 70mL/min Column temperature: 40 oC, BPR: 100 bar

152	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar	SFC condition: Column:Chiralcel OJ 250×21.1mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 15% B in 10 min Flow rate: 70mL/min Column temperature: 40 °C, BPR: 100 bar
154	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar	SFC condition: Column: Chiralcel OX 250 x 21.2 mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 40% B in 6min Flow rate: 70mL/min Column temperature: 40 °C, BPR: 100 bar
156	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar	SFC condition: Column: Chiralcel OX 250 x 21.2 mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 40% B in 6min Flow rate: 70mL/min Column temperature: 40 °C, BPR: 100 bar
155	SFC condition: Column:Chiralpak AD 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar	SFC condition: Column: Chiralpak AD 150 x 21.2 mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 30% B in 6min Flow rate: 70mL/min Column temperature: 40 °C, BPR: 100 bar
161	SFC condition: Column:Phenomenex Lux Cellulose-3 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar	SFC condition: Column: Phenomenex Lux Cellulose-3 150 x 21.2 mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 15% B in 6min Flow rate: 70mL/min Column temperature: 40 °C, BPR: 100 bar

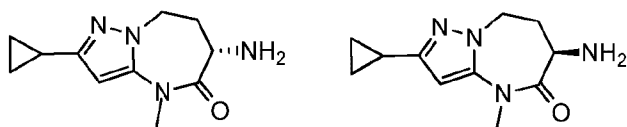
168	SFC condition: Column:Phenomenex Lux Cellulose-3 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 oC, BPR: 120 bar	SFC condition: Column: Phenomenex Lux Cellulose-3 150 x 21.2 mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 15% B in 6min Flow rate: 70mL/min Column temperature: 40 oC, BPR: 100 bar
159	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 oC, BPR: 120 bar	SFC condition: Column: ES Industries AD 150 x 30 mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient:5-60% B in 6min Flow rate: 100mL/min Column temperature: 40 oC, BPR: 100 bar
169	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 oC, BPR: 120 bar	SFC condition: Column: ES Industries AS 150 x 30 mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient:5-60% B in 6min Flow rate: 100mL/min Column temperature: 40 oC, BPR: 100 bar
170	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 oC, BPR: 120 bar	SFC condition: Column: ES Industries AD 150 x 30 mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) 5-60% B in 10min Flow rate: 100mL/min Column temperature: 40 oC, BPR: 100 bar
162	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 oC, BPR: 120 bar	SFC condition: Column: ES Industries AD 150 x 30 mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) 5-60% B in 10min Flow rate: 100mL/min Column temperature: 40 oC, BPR: 100 bar

157	SFC condition: Column: Chiralpak AD 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 oC, BPR: 120 bar	SFC condition: Column: Chiralpak AD 150 x 30.0 mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 35% B in 6min Flow rate: 150mL/min Column temperature: 25 oC, BPR: 100 bar
167	SFC condition: Column: Chiralpak AD 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 oC, BPR: 120 bar	SFC condition: Column: Chiralpak AD 150 x 30.0 mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 35% B in 6min Flow rate: 150mL/min Column temperature: 25 oC, BPR: 100 bar
163	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 oC, BPR: 120 bar	SFC condition: Column:Cellulose-1 150×21.1mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 25% B in 10 min Flow rate: 70mL/min Column temperature: 40 oC, BPR: 100 bar
160	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 oC, BPR: 120 bar	SFC condition: Column:Cellulose-1 150×21.1mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Isocratic: 30% B in 10 min Flow rate: 70mL/min Column temperature: 40 oC, BPR: 100 bar
166	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 oC, BPR: 120 bar	SFC condition: Column: ES Industries AD 150 x 30 mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) 5-60% B in 10min Flow rate: 100mL/min Column temperature: 40 oC, BPR: 100 bar

158	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar	SFC condition: Column: ES Industries AD 150 x 30 mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) 5-60% B in 10min Flow rate: 100mL/min Column temperature: 40 °C, BPR: 100 bar
165	SFC condition: Column:Chiralcel OX 50×4.6mm I.D., 3µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) Gradient: 5-60% B in 2.5min Flow rate: 4mL/min Column temperature: 40 °C, BPR: 120 bar	SFC condition: Column: ES Industries AD 150 x 30 mm I.D., 5µm Mobile phase: A: CO ₂ B:Methanol (0.1% NH ₄ OH) 5-60% B in 10min Flow rate: 100mL/min Column temperature: 40 °C, BPR: 100 bar

Example 171**WX Method ZZZ**

(S)-1-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide



Step

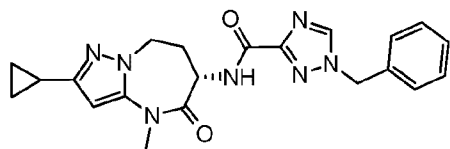
1:

(S)-6-amino-2-cyclopropyl-4-methyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepin-5(6H)-one and

(R)-6-amino-2-cyclopropyl-4-methyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepin-5(6H)-one

6-amino-2-cyclopropyl-4-methyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepin-5(6H)-one was underwent SFC separation to get peak 1 as (S)-6-amino-2-cyclopropyl-4-methyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepin-5(6H)-one and peak 2 as (R)-6-amino-2-cyclopropyl-4-methyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepin-5(6H)-one.

SFC condition: Column: Chiralpak OD 250 x 30mm I.D., 5 μ m Mobile phase: A: CO₂ B: Ethanol (0.05% NH₄OH) Isocratic: 20% B in 6min Flow rate: 50 mL/min Column temperature: 40 °C, BPR: 100 bar (Peak 1: 3.11 min) (Peak 2: 3.53 min).



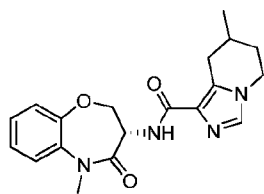
5 Step 2:

(S)-1-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide

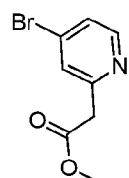
A mixture of (S)-6-amino-2-cyclopropyl-4-methyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepin-5(6H)-one (200 mg, 0.91 mmol), 1-benzyl-1H-1,2,4-triazole-3-carboxylic acid (0.19 g, 0.91 mmol), 1H-benzo[d][1,2,3]triazol-1-ol (180 mg, 1.36 mmol) and *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (260 mg, 1.36 mmol) in N,N-dimethylformamide (5 mL) was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by RP-HPLC (acetonitrile 30-60%/0.1% HCl in water) to afford (S)-1-benzyl-N-(2-cyclopropyl-4-methyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide (120 mg, 32%) as a white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.83 (s, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 7.41 – 7.28 (m, 5H), 6.06 (s, 1H), 5.48 (s, 2H), 4.34 – 4.22 (m, 2H), 4.12 – 4.04 (m, 1H), 3.19 (s, 3H), 2.61 – 2.54 (m, 1H), 2.37 – 2.29 (m, 1H), 1.88 – 1.81 (m, 1H), 0.89 – 0.81 (m, 2H), 0.70 – 0.61 (m, 2H). LCMS R_T = 0.98 min; *m/z* = 406.1 (M+H)⁺.

LCMS (10 to 80% acetonitrile in water + 0.03% trifluoroacetic acid over 2.0 mins) retention time 0.98 min, ESI⁺ found [M+H]⁺ = 406.2.

WX METHOD B



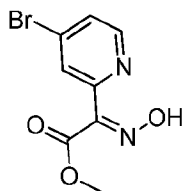
25 7-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-1-carboxamide



Step 1: methyl 2-(4-bromopyridin-2-yl) acetate

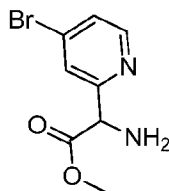
A mixture of 1-(tert-butyldimethylsilyloxy)-1-methoxyethene (2.2 g, 11.5 mmol), 4-bromopyridinen-oxide (1.0 g, 5.7 mmol), N,N-diisopropylethylamine (2.2 g, 17.2 mmol) and bromo[tri(1-pyrrolidinyl)] phosphonium hexafluorophosphate (3.0 g, 6.3 mmol) in tetrahydrofuran (20 mL) was stirred at 25 °C for 1 h and then diluted with ethyl acetate (30 mL). The resulting mixture was washed with water (3 × 30 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 100 - 200 mesh, 0 to 10% ethyl acetate in petroleum ether) to afford methyl 2-(4-bromopyridin-2-yl) acetate (1.0 g, 75%): LCMS R_T = 0.52 min; m/z = 232.0 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.03% trifluoacetic acid over 1.5 mins) retention time 0.520 min, ESI+ found [M+H] = 232.0

**Step 2: (E)-methyl 2-(4-bromopyridin-2-yl)-2-(hydroxyimino) acetate**

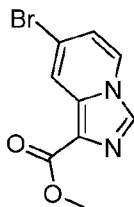
To a solution of methyl 2-(4-bromopyridin-2-yl) acetate (4.0 g, 17.4 mmol) in acetic acid (60 mL) was added sodium nitrite (1.2 g, 17.4 mmol) in water (30 mL) at 0 °C. After addition, the mixture was stirred at 25 °C for 40 min. Water (30 mL) was added and the mixture was stirred for an additional 1 h. The reaction was concentrated to dryness under reduced pressure and the residue was taken up in ethyl acetate (100 mL), washed with water (2 × 50 mL), brine (50 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was then purified by column chromatography (silica gel, 100 - 200 mesh, 0 to 20% methanol in dichloromethane) to afford (E)-methyl 2-(4-bromopyridin-2-yl)-2-(hydroxyimino) acetate (3.6 g, 80%) as yellow oil: LCMS R_T = 0.65 min; m/z = 261.0 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.03% trifluoacetic acid over 1.5 mins) retention time 0.651 min, ESI+ found [M+H] = 261.0

**Step 3: methyl 2-amino-2-(4-bromopyridin-2-yl) acetate**

A mixture of zinc (1.8 g, 27.8 mmol) and (E)-methyl 2-(4-bromopyridin-2-yl)-2-(hydroxyimino) acetate (3.6 g, 13.9 mmol) in methanol (56 mL) and water (36 mL) was slowly added formic acid (36 mL, 961.9 mmol) over 30 min at 0 °C.

After addition, the mixture was stirred at 25 °C for 5 h and then diluted with ethyl acetate (50 mL). The organic layer was washed with water (3 × 30 mL). The combined aqueous layers were concentrated under reduced pressure to afford crude methyl 2-amino-2-(4-bromopyridin-2-yl) acetate (3.0 g, 88%) as yellow oil, used as is in the next step without further purification.

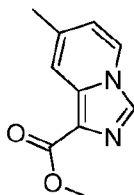


Step 4: methyl 7-bromoimidazo [1,5-a]pyridine-1-carboxylate

A mixture of methyl 2-amino-2-(4-bromo-2-pyridyl) acetate (500 mg, 2.0 mmol) and triethyl orthoformate (2 mL, 2.0 mmol) was heated at 150 °C under microwave conditions for 10 min.

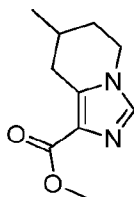
The mixture was concentrated under reduced pressure and purified by preparative TLC (50% ethyl acetate in petroleum ether) to afford methyl 7-bromoimidazo[1,5-a]pyridine-1-carboxylate (210 mg, 40%) as brown oil: LCMS R_T = 0.65 min; m/z = 257.0 ($M+H$)⁺.

LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.654 min, ESI+ found $[M+H]$ = 257.0



Step 5: methyl 7-methylimidazo [1,5-a]pyridine-1-carboxylate

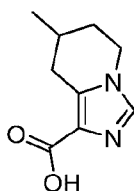
A mixture of methyl 7-bromoimidazo[1,5-a]pyridine-1-carboxylate (210 mg, 0.8 mmol), potassium carbonate (227 mg, 1.7 mmol) and trimethylboroxine (310 mg, 2.5 mmol) in 1,4-dioxane (5 mL) was treated with tetrakis(triphenylphosphine) palladium(0) (47 mg, 0.04 mmol). The resulting mixture was heated to 120 °C for 4 h under nitrogen. The mixture was filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (50% ethyl acetate in petroleum ether) to afford methyl 7-methylimidazo[1,5-a]pyridine-1-carboxylate (110 mg, 70%) as a yellow solid, used in the next step without further purification.



Step 6: methyl 7-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-1-carboxylate

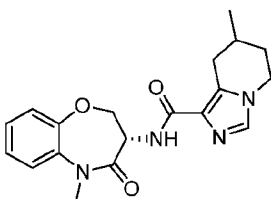
A mixture of methyl 7-methylimidazo[1,5-a]pyridine-1-carboxylate (90 mg, 0.47 mmol) and 10% palladium on carbon (50 mg, 0.05 mmol) in methanol (10 mL) was hydrogenated (50 psi) at 25°C for 18 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (7% methanol in dichloromethane) affording methyl 7-methyl-5,6,7,8-tetrahydro imidazo[1,5-a]pyridine-1-carboxylate (50 mg, 54%) as yellow oil: LCMS $R_T = 1.24$ min; $m/z = 195.1$ ($M+H$)⁺.

LCMS (10 to 80% acetonitrile in water + 0.05% ammonium bicarbonate over 3 mins) retention time 1.239 min, ESI+ found $[M+H] = 195.1$



Step 7: 7-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-1-carboxylic acid

To a solution of methyl 7-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-1-carboxylate (18 mg, 0.09 mmol) in tetrahydrofuran (2 mL) and water (2 mL) was added lithium hydroxide (11 mg, 0.46 mmol). The resulting mixture was stirred at 25°C for 12 h, adjusted to pH = 4 by addition of hydrochloric acid (1.0 M) and concentrated under reduced pressure. The residue was extracted with dichloromethane (30 mL) and ethyl acetate (1 × 30 mL). The combined organic layers were concentrated under reduced pressure to afford 7-methyl-5,6,7,8-tetrahydroimidazo [1,5-a]pyridine-1-carboxylic acid (15 mg, 90%) as white solids, used in the next step without further purification.



Step 8: 7-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-1-carboxamide

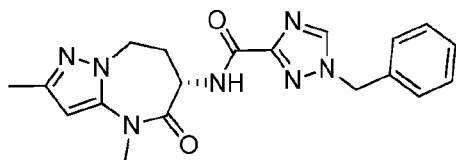
To a solution of 7-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-1-carboxylic acid (22 mg, 0.12 mmol) and (3S)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (23 mg, 0.12

mmol) in N,N-dimethylformamide (2 mL) was added (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (76 mg, 0.15 mmol). The resulting mixture was stirred for 12 h at 25 °C and then concentrated to dryness under reduced pressure. The residue was purified by RP-HPLC (27-57% methanol in water and 0.05% ammonia hydroxide) to afford 7-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-1-carboxamide (6.6 mg, 15%) as a white solid: ¹H NMR (400 MHz, CD₃OD) δ 7.55 – 7.53 (m, 1H), 7.43 – 7.41 (m, 1H), 7.32 – 7.29 (m, 2H), 7.11 – 6.92 (m, 1H), 4.97 – 4.96 (m, 1H), 4.59 – 4.55 (m, 1H), 4.35 – 4.21 (m, 2H), 3.94 – 3.93 (m, 1H), 3.42 – 3.41 (m, 3H), 3.31 – 3.24 (m, 1H), 2.41 – 2.34 (m, 1H), 2.01 – 1.98 (m, 2H), 1.63 – 1.59 (m, 1H), 1.12 – 1.09 (m, 3H). LCMS R_T = 0.74 min; *m/z* = 355.0 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.03% trifluoacetic acid over 1.5 mins) retention time 0.740 min, ESI+ found [M+H] = 355.0.

Example 172

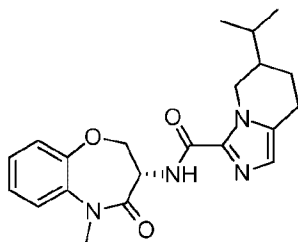
15 WX METHOD PP



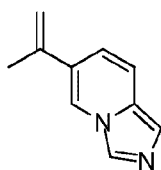
(S)-1-benzyl-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide

A mixture of 1-benzyltriazole-4-carboxylic acid (20 mg, 0.10 mmol), (S)-6-amino-2,4-dimethyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepin-5(6H)-one (15 mg, 0.08 mmol), *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethyl propane-1,3-diamine hydrochloride (22 mg, 0.11 mmol) and 1H-benzo[d][1,2,3] triazol-1-ol (19 mg, 0.11 mmol) in N,N-dimethylformamide (5 mL) was stirred at 25 °C for 2 h. The reaction was concentrated under reduced pressure and the residue was purified by RP-HPLC (acetonitrile 17 - 47%/0.05% ammonium bicarbonate in water) to afford (S)-1-benzyl-N-(2,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,3]diazepin-6-yl)-1H-1,2,4-triazole-3-carboxamide (12.1 mg, 39%) as white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.85 (s, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 7.39 – 7.29 (m, 5H), 6.13 (s, 1H), 5.49 (s, 2H), 4.15 – 4.10 (m, 2H), 4.08 – 4.06 (m, 1H), 3.21 (s, 3H), 2.59 – 2.54 (m, 1H), 2.35 – 2.29 (m, 1H), 2.16 (s, 3H). LCMS R_T = 0.909 min; *m/z* = 380.4 (M+H)⁺.

LCMS (10 to 80% acetonitrile in water + 0.03% trifluoacetic acid over 2.0 mins) retention time 0.909 min, ESI+ found [M+H] = 380.4.

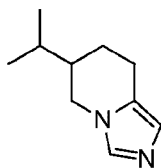
Example 173**WX Method D**

6-isopropyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide

**Step 1: 6-(prop-1-en-2-yl)imidazo[1,5-a]pyridine**

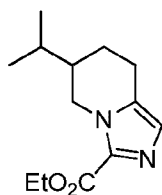
A mixture of 6-bromoimidazo[1,5-a]pyridine (500 mg, 2.5 mmol), potassium isopropyl trifluoroborate (750 mg, 5.0 mmol), cesium carbonate (1.654 g, 5.0 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (185 mg, 0.1 mmol) in tetrahydrofuran (20 mL) and water (2 mL) was heated at 80 °C for 3 h under nitrogen. After cooled, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified with preparative TLC (10% methanol in dichloromethane) to afford 6-(prop-1-en-2-yl)imidazo[1,5-a]pyridine (300 mg, 74%) as brown oil. LCMS R_T = 0.26 min; m/z = 158.8 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.26 min, ESI+ found [M+H] = 158.8

**Step 2: 6-isopropyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine**

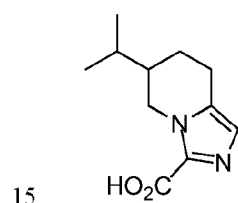
A mixture of 6-(prop-1-en-2-yl)imidazo[1,5-a]pyridine (300 mg, 1.9 mmol) and 10% palladium on carbon (202 mg, 0.2 mmol) in methanol (30 mL) was hydrogenated (50 psi) at 20 °C for 72 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (10% methanol in dichloromethane) to

afford 6-isopropyl-5,6,7,8-tetrahydroimidazo [1,5-a]pyridine (150 mg, 48%) as brown oil, used in the next step without further purification.



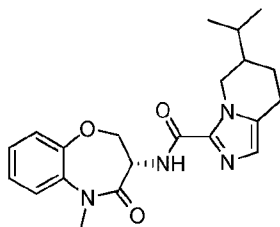
Step 3: ethyl 6-isopropyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxylate

- 5 To a solution of 6-isopropyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine (300 mg, 1.8 mmol) in tetrahydrofuran (5 mL) was added n-butyllithium (2.5 M, 1.1 mL, 2.7 mmol) at -78 °C. Stirring at -78°C was continued for 1 h, then ethyl chloroformate (1300 mg, 12.3 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 1 h and quenched by addition of saturated aqueous ammonium chloride (10 mL). The mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 100 - 200 mesh, 100% dichloromethane) to afford ethyl 6-isopropyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxylate (100 mg, 23%) as brown oil, used in the next step without further purification.



Step 4: 6-isopropyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxylic acid

- A mixture of 6-isopropyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxylate (100 mg, 0.45 mmol) and potassium hydroxide (252 mg, 4.5 mmol) in ethanol (5 mL) and water (1 mL) was stirred at 25 °C for 12 h. The solvent was removed under reduced pressure. The residue was diluted with water (10 mL) and adjusted to pH = 4 by addition of hydrochloric acid (2.0 M). The mixture was concentrated under reduced pressure to afford crude 6-isopropyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine -3-carboxylic acid (80 mg, 85%) as a white solid, , used in the next step without further purification.



25 Step

5:

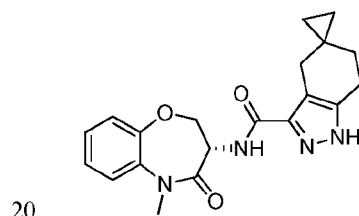
6-isopropyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide

A mixture of (S)-3-amino-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one (40 mg, 0.2 mmol), 6-isopropyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxylic acid (43 mg, 0.2 mmol), 1*H*-benzo[d][1,2,3]triazol-1-ol (42 mg, 0.3 mmol) and *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (59 mg, 0.3 mmol) in *N,N*-dimethylformamide (5 mL) was stirred at 25 °C for 16 h. After evaporation of the solvent under reduced pressure, the residue was purified by RP-HPLC (acetonitrile 46-76%/0.05% ammonia hydroxide in water) to afford 6-isopropyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide (10 mg, 14%): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.27 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 6.8 Hz, 1H), 7.35 – 7.26 (m, 2H), 7.25 – 7.21 (m, 1H), 6.81 (s, 1H), 4.83 – 4.75 (m, 1H), 4.63 – 4.51 (m, 2H), 4.43 – 4.37 (m, 1H), 3.69 – 3.62 (m, 1H), 3.31 (s, 3H), 2.95 – 2.87 (m, 1H), 2.67 – 2.58 (m, 1H), 1.93 – 1.85 (m, 1H), 1.68 – 1.54 (m, 2H), 1.41 – 1.28 (m, 1H), 0.92 – 0.88 (m, 6H). LCMS *R*_T = 0.84 min; *m/z* = 393.1 (M+H)⁺.

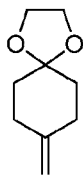
LCMS (5 to 95% acetonitrile in water + 0.03% trifluoacetic acid over 1.5 mins) retention time 0.84 min, ESI+ found [M+H] = 393.1

Example 174

WX METHOD FF



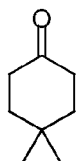
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1',4',6',7'-tetrahydrospiro[cyclopropane-1,5'-indazole]-3'-carboxamide



Step 1: 8-methylene-1,4-dioxaspiro[4.5]decane

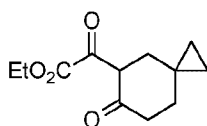
25 To a suspension of (bromomethyl)triphenylphosphonium (34.12 g, 96.04 mmol) in tetrahydrofuran (200 mL) was added potassium *tert*-butoxide (10.8 g, 96.0 mmol) portionwise at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and then a solution of 1,4-dioxaspiro[4.5]decan-8-one (5.0 g, 32.0 mmol) in tetrahydrofuran (20 mL) was added dropwise. After addition, the reaction mixture was slowly warmed to 23 °C and stirred for 18

- h. The reaction mixture was quenched by addition of water (120 mL) and extracted with ethyl acetate (3×200 mL). The combined organic layers were washed with brine (100 mL) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 5% ethyl acetate in petroleum ether) to afford
- 5 8-methylene-1,4-dioxaspiro[4.5]decane (3.9 g, 79%) as yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 4.67 (s, 2H), 3.98 (s, 4H), 2.37 – 2.30 (m, 4H), 1.73 – 1.70 (m, 4H).



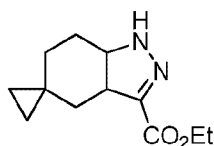
Step 2: Spiro[2.5]octan-6-one

- To a solution of 8-methylene-1,4-dioxaspiro[4.5]decane (3.9 g, 25.3 mmol) in toluene (7.2 mL) was added diethylzinc (1.0 M, 63.2 mL, 63.2 mmol) at -40 °C. The mixture was stirred for 10
- min and then diiodomethane (33.9 g, 126.4 mmol) added dropwise. After addition, the resulting mixture was allowed to warm to 24 °C and stirred for 18 h. The reaction mixture was poured onto ice-cooled saturated aqueous ammonium chloride (30 mL) and extracted with ethyl acetate (3×60 mL). The combined organic extracts were washed with water (30 mL), dried
- 15 over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 5% ethyl acetate in petroleum ether) affording a colorless oil. A mixture of this oil and trifluoroacetic acid (2.9 mL, 38.9 mmol) in tetrahydrofuran (8 mL) and water (7 mL) was stirred at 23 °C for 2 h. The mixture was adjusted to pH = 7 by addition of aqueous sodium hydroxide (2 M) and extracted with diethyl
- 20 ether (3×30 mL). The combined organic layers were washed water (20 mL), brine (20 mL), dried over sodium sulfate and concentrated under reduced pressure affording crude spiro[2.5]octan-6-one (1.4 g, 44.6% over 2 steps) as colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 2.40 (t, J = 6.8 Hz, 4H), 1.67 (t, J = 6.4 Hz, 4H), 0.47 (s, 4H).



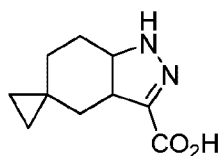
Step 3: Ethyl 2-oxo-2-(6-oxospiro[2.5]octan-7-yl)acetate

- To a solution of spiro[2.5]octan-6-one (500 mg, 4.03 mmol) in ethanol (5 mL) was added sodium ethanoxide and diethyl oxalate (588 mg, 4.0 mmol) at 0 °C. After addition, the mixture was allowed to warm to 20 °C and stirred for 20 h. The solvent was removed under reduced pressure affording crude ethyl 2-oxo-2-(6-oxospiro[2.5]octan-7-yl)acetate (800 mg, 88%) as a
- 30 yellow solid, used as is in the next step without further purification.

**Step 4:****Ethyl spiro[1,3a,4,6,7,7a-hexahydroindazole-5,1'-cyclopropane]-3-carboxylate**

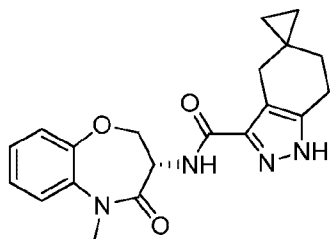
To a solution of ethyl 2-oxo-2-(6-oxospiro[2.5]octan-7-yl)acetate (800 mg, 3.57 mmol) in glacial acetic acid (3 mL) was added hydrazine (0.12 mL, 3.92 mmol) at 0 °C. The mixture was stirred for 18 h at 23 °C and then extracted with ethyl acetate (3 × 30 mL). The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 30% ethyl acetate in petroleum ether) affording ethyl spiro[1,3a,1,4,6,7-tetrahydroindazole-5,1'-cyclopropane]-3-carboxylate (50 mg, 6.4%) as a pale yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 4.41 – 4.30 (m, 2H), 2.76 (t, *J* = 6.0 Hz, 2H), 2.62 (s, 2H), 1.62 (t, *J* = 6.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 0.44 (s, 4H). LCMS R_T = 0.817 min; *m/z* = 220.9 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.817 min, ESI+ found [M+H] = 220.9.

**Step 5:****Spiro[1,3a,4,6,7,7a-hexahydroindazole-5,1'-cyclopropane]-3-carboxylic acid**

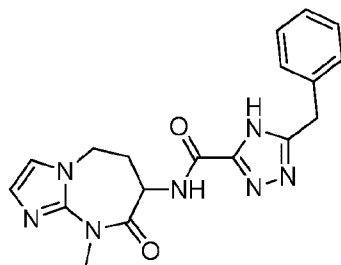
A mixture of ethyl spiro[1,3a,1,4,6,7-tetrahydroindazole-5,1'-cyclopropane]-3-carboxylate (50 mg, 0.23 mmol) and lithium hydroxide hydrate (27 mg, 1.13 mmol) in tetrahydrofuran (5 mL) and water (2 mL) was stirred at 23 °C for 18 h. The organic solvent was removed under reduced pressure and the aqueous residue was adjusted to pH = 5 by addition of hydrochloric acid (1.0 M). The solution was then extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure affording crude spiro[1,3a,1,4,6,7-tetrahydro indazole-5,1'-cyclopropane]-3-carboxylic acid (40 mg, 91%) as a white solid: LCMS R_T = 1.456 min; *m/z* = 193.2 (M+H)⁺.

LCMS (0 to 60% acetonitrile in water + 0.04% formic acid over 3 mins) retention time 1.456 min, ESI+ found [M+H] = 193.2.

**Step 6****(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1',4',6',7'-tetrahydrospiro[cyclopropane-1,5'-indazole]-3'-carboxamide**

- 5 A mixture of spiro[1,3a,1,4,6,7-tetrahydroindazole-5,1'-cyclopropane]-3-carboxylic acid (40 mg, 0.21 mmol), (3s)-3-amino-5-methyl-2,3-dihydro-1,5-benzoxazepin-4-one (44 mg, 0.23 mmol), 1*H*-benzo[d][1,2,3]triazol-1-ol (33 mg, 0.25 mmol) and *N*¹-((ethylimino)methylene)-*N*³,*N*³-dimethylpropane-1,3-diamine hydrochloride (45 mg, 0.25 mmol) in *N,N*-dimethylformamide (5 mL) was stirred at 25 °C for 1 h. The reaction was concentrated under reduced pressure and the residue was purified by RP-HPLC (acetonitrile 38-68%/0.05% ammonia in water) affording (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1',4',6',7'-tetrahydrospiro[cyclopropane-1,5'-indazole]-3'-carboxamide (18.7 mg, 24%) as a white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.90 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 6.0 Hz, 1H), 7.37 – 7.16 (m, 3H), 4.85 – 4.75 (m, 1H), 4.53 – 4.44 (m, 1H), 4.42 – 4.35 (m, 1H), 3.31 (s, 3H), 2.63 (t, *J* = 5.6 Hz, 2H), 2.41 (s, 2H), 1.49 (t, *J* = 5.6 Hz, 2H), 0.46 – 0.20 (m, 4H). LCMS R_T = 0.856 min; *m/z* = 367.1 (M+H)⁺.

LCMS (5 to 95% acetonitrile in water + 0.03% trifluoroacetic acid over 1.5 mins) retention time 0.856 min, ESI+ found [M+H] = 367.1.

Example 175**WX METHOD RRRRRR****5-benzyl-N-(9-methyl-8-oxo-6,7,8,9-tetrahydro-5H-imidazo[1,2-a][1,3]diazepin-7-yl)-4H-1,2,4-triazole-3-carboxamide**

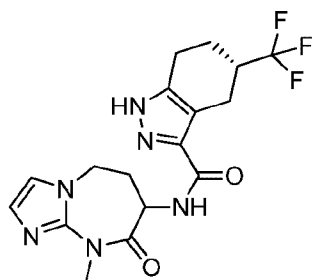
- 25 A mixture of (5-benzyl-4H-1,2,4-triazole-3-carboxylic acid (22 mg, 0.11 mmol), 7-amino-9-methyl-6,7-dihydro-5H-imidazo[1,2-a][1,3]diazepin-8(9H)-one (20 mg, 0.11

mmol), N^1 -((ethylimino)methylene)- N^3,N^3 -dimethyl propane-1,3-diamine hydrochloride (26 mg, 0.13 mmol) and 1*H*-benzo[d][1,2,3] triazol-1-ol (18 mg, 0.13 mmol) in *N,N*-dimethylformamide (4 mL) was stirred at 25 °C for 12 h. The reaction was concentrated under reduced pressure and the residue was purified by RP-HPLC (14 - 24% methanol in water and 0.05% ammonia hydroxide) to afford 5-benzyl-*N*-(9-methyl-8-oxo-6,7,8,9-tetrahydro-5*H*-imidazo[1,2-*a*][1,3]diazepin-7-yl)-4*H*-1,2,4-triazole-3-carboxamide (5 mg, 12%) as white solid: ^1H NMR (400 MHz, CD_3OD) δ 7.34 – 7.22 (m, 5H), 7.09 (s, 1H), 6.96 (s, 1H), 4.53 – 4.48 (m, 1H), 4.32 – 4.26 (m, 1H), 4.16 (s, 2H), 4.10 – 4.02 (m, 1H), 3.38 (s, 3H), 2.77 – 2.90 (m, 1H), 2.29 – 2.21 (m, 1H). LCMS R_T = 1.21 min; m/z = 366.1 ($\text{M}+\text{H}$) $^+$.

LCMS (0 to 60% acetonitrile in water + 0.05% ammonium bicarbonate over 3 mins) retention time 1.21 min, ESI+ found $[\text{M}+\text{H}] = 366.1$.

Example 176

WX METHOD SSSSSS



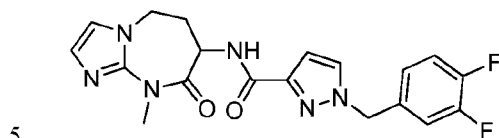
(5*S*)-*N*-(9-methyl-8-oxo-6,7,8,9-tetrahydro-5*H*-imidazo[1,2-*a*][1,3]diazepin-7-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1*H*-indazole-3-carboxamide

A mixture of (5*S*)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1*H*-indazole-3-carboxylic acid (26 mg, 0.11 mmol), 7-amino-9-methyl-6,7-dihydro-5*H*-imidazo[1,2-*a*][1,3]diazepin-8(9*H*)-one (20 mg, 0.11 mmol), N^1 -((ethylimino)methylene)- N^3,N^3 -dimethyl propane-1,3-diamine hydrochloride (26 mg, 0.13 mmol) and 1*H*-benzo[d][1,2,3] triazol-1-ol (18 mg, 0.13 mmol) in *N,N*-dimethylformamide (4 mL) was stirred at 25 °C for 12 h. The reaction was concentrated under reduced pressure and the residue was purified by RP-HPLC (17 - 47% methanol in water and 0.05% ammonia hydroxide) to afford (5*S*)-*N*-(9-methyl-8-oxo-6,7,8,9-tetrahydro-5*H*-imidazo[1,2-*a*][1,3]diazepin-7-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1*H*-indazole-3-carboxamide (10.7 mg, 24%) as white solid: ^1H NMR (400 MHz, CD_3OD) δ 7.09 (d, J = 1.2 Hz, 1H), 6.96 (d, J = 1.2 Hz, 1H), 4.52 – 4.47 (m, 1H), 4.32 – 4.26 (m, 1H), 4.07 – 4.05 (m, 1H), 3.39 (s, 3H), 3.14 – 3.10 (m, 1H), 2.88 – 2.84 (m, 2H), 2.76 – 2.70 (m, 1H), 2.64 – 2.48 (m, 2H), 2.21 – 2.20 (m, 2H), 1.74 – 1.69 (m, 1H). LCMS R_T = 0.69 min; m/z = 397.0 ($\text{M}+\text{H}$) $^+$.

LCMS (5 to 95% acetonitrile in water + 0.03% trifluoacetic acid over 1.5 mins) retention time 0.69 min, ESI+ found $[M+H] = 397.0$.

Example 177

WX METHOD TTTTTT



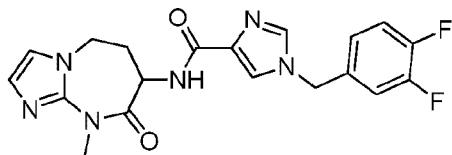
1-(3,4-difluorobenzyl)-N-(9-methyl-8-oxo-6,7,8,9-tetrahydro-5H-imidazo[1,2-a][1,3]diazepin-7-yl)-1H-pyrazole-3-carboxamide

A mixture of 1-[(3,4-difluorophenyl)methyl]pyrazole-3-carboxylic acid (26 mg, 0.11 mmol), 7-amino-9-methyl-6,7-dihydro-5H-imidazo[1,2-a][1,3]diazepin-8(9H)-one (20 mg, 0.11 mmol), N^1 -((ethylimino)methylene)- N^3,N^3 -dimethyl propane-1,3-diamine hydrochloride (26 mg, 0.13 mmol) and 1H-benzo[d][1,2,3] triazol-1-ol (18 mg, 0.13 mmol) in N,N-dimethylformamide (4 mL) was stirred at 25 °C for 12 h. The reaction was concentrated under reduced pressure and the residue was purified by RP-HPLC (30 - 40% methanol in water and 0.05% ammonia hydroxide) to afford 1-(3,4-difluorobenzyl)-N-(9-methyl-8-oxo-6,7,8,9-tetrahydro-5H-imidazo[1,2-a][1,3]diazepin-7-yl)-1H-pyrazole-3-carboxamide (10.8 mg, 24%) as white solid: ^1H NMR (400 MHz, CD_3OD) δ 7.75 (d, $J = 2.4$ Hz, 1H), 7.27 – 7.21 (m, 2H), 7.09 – 7.01 (m, 2H), 6.95 (d, $J = 1.2$ Hz, 1H), 6.75 – 6.74 (m, 1H), 5.38 (s, 2H), 4.53 – 4.48 (m, 1H), 4.31 – 4.26 (m, 1H), 4.06 – 4.03 (m, 1H), 3.38 (s, 3H) 2.85 – 2.79 (m, 1H), 2.29 – 2.23 (m, 1H). LCMS $R_T = 1.99$ min; $m/z = 401.1$ ($M+H$) $^+$.

LCMS (0 to 60% acetonitrile in water + 0.03% ammonium bicarbonate over 3 mins) retention time 1.99 min, ESI+ found $[M+H] = 401.1$.

Example 178

WX METHOD UUUUUU



1-(3,4-difluorobenzyl)-N-(9-methyl-8-oxo-6,7,8,9-tetrahydro-5H-imidazo[1,2-a][1,3]diazepin-7-yl)-1H-imidazole-4-carboxamide

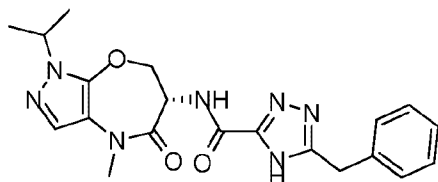
A mixture of 1-[(3,4-difluorophenyl)methyl]imidazole-4-carboxylic acid (26 mg, 0.11 mmol), 7-amino-9-methyl-6,7-dihydro-5H-imidazo[1,2-a][1,3]diazepin-8(9H)-one (20 mg, 0.11 mmol), N^1 -((ethylimino)methylene)- N^3,N^3 -dimethyl propane-1,3-diamine hydrochloride (26 mg, 0.13 mmol) and 1H-benzo[d][1,2,3] triazol-1-ol (18 mg, 0.13 mmol) in

N,N-dimethylformamide (4 mL) was stirred at 25 °C for 12 h. The reaction was concentrated under reduced pressure and the residue was purified by RP-HPLC (13 - 43% methanol in water and 0.05% ammonia hydroxide) to afford 1-(3,4-difluorobenzyl)-N-(9-methyl-8-oxo-6,7,8,9-tetrahydro-5H-imidazo[1,2-a][1,3]diazepin-7-yl)-1H-imidazole-4-carboxamide (13.1 mg, 29%) as white solid: ¹H NMR (400 MHz, CD₃OD) δ 7.78 (s, 1H), 7.67 (s, 1H), 7.28 – 7.23 (m, 2H), 7.11 – 7.08 (m, 2H), 6.94 (d, *J* = 1.6 Hz, 1H), 5.23 (s, 2H), 4.50 – 4.46 (m, 1H), 4.31 – 4.26 (m, 1H), 4.07 – 4.02 (m, 1H), 3.38 (s, 3H), 2.86 – 2.80 (m, 1H), 2.25 – 2.19 (m, 1H). LCMS R_T = 1.85 min; *m/z* = 401.1 (M+H)⁺.

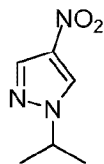
LCMS (0 to 60% acetonitrile in water + 0.05% ammonium bicarbonate over 3 mins) retention time 1.85 min, ESI+ found [M+H] = 401.1.

Example 179

WX METHOD DDDDDD

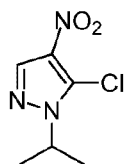


(S)-5-benzyl-N-(1-isopropyl-4-methyl-5-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-b][1,4]oxazepin-6-yl)-4H-1,2,4-triazole-3-carboxamide



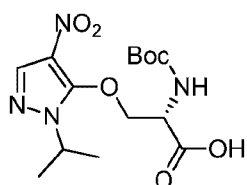
Step1: 1-isopropyl-4-nitro-1H-pyrazole

To a solution of 4-nitro-1H-pyrazole (10.0 g, 88.4 mmol) in N, N-dimethylformamide (50 mL) was added potassium carbonate (36.7 g, 265.3 mmol) and stirred at 25 °C for 1 h, then 2-iodopropane (17.6 mL, 176.9 mmol) was added. The mixture was stirred at 25 °C for 12 h and then concentrated under reduced pressure. The residue was diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried over sodium sulfate and concentrated under reduced pressure to afford 1-isopropyl-4-nitro-pyrazole (11.0 g, 80%) as yellow solid: ¹H NMR (400MHz, CD₃OD) δ 8.58 (s, 1H), 8.09 (s, 1H), 4.61 - 4.54 (m, 1H), 1.52 (d, *J* = 6.4 Hz, 6H).



Step 2: 5-chloro-1-isopropyl-4-nitro-1H-pyrazole

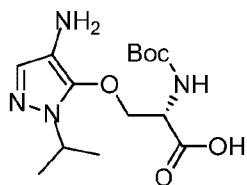
To a cooled (- 78 °C) solution of 1-isopropyl-4-nitro-pyrazole (5.0 g, 32.2 mmol) in tetrahydrofuran (50 mL) was added lithium bis(trimethylsilyl)azanide (1.0 M, 34.9 mL, 34.9 mmol) dropwise. The mixture was stirred at - 78 °C for 30 min and then hexachloroethane (8.36 g, 35.3 mmol) was added. The mixture was stirred at 25 °C for 18 h and quenched by addition of saturated aqueous ammonium chloride (80 mL). The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 100 - 200 mesh, 0 to 10% ethyl acetate in petroleum ether) to afford 5-chloro-1-isopropyl-4-nitro-pyrazole (5.0 g, 82%) as colorless solid: ¹H NMR (400MHz, CD₃OD) δ 8.26 (s, 1H), 4.85 - 4.80 (m, 1H), 1.49 (d, *J* = 6.8 Hz, 6H).

**Step****3:**

(S)-2-((tert-butoxycarbonyl)amino)-3-((1-isopropyl-4-nitro-1H-pyrazol-5-yl)oxy)propanoic acid

To a solution of (S)-2-((tert-butoxycarbonyl)amino)-3-hydroxypropanoic acid (4.38 g, 21.4 mmol) in N,N-dimethylformamide (30 mL) was added sodium hydride (1.1 g, 28.5 mmol, 60%) at 0 °C. The mixture was stirred at 0 °C for 1 h. At which time 5-chloro-1-isopropyl-4-nitro-pyrazole (2.7 g, 14.2 mmol) was added. After addition, the mixture was stirred at 20 °C for another 3 h, and then quenched by addition of water (30 mL). The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water (30 mL), brine (30 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica (0 - 100% ethyl acetate in petroleum ether) to afford (S)-2-((tert-butoxycarbonyl)amino)-3-((1-isopropyl-4-nitro-1H-pyrazol-5-yl)oxy)propanoic acid (0.7 g, 14%) as yellow oil: LCMS *R*_T = 0.68 min; *m/z* = 302.9 (M+H)⁺.

LCMS (5- 95% acetonitrile in water + 0.03% trifluoroacetic over 1.5 mins) retention time 0.68 min, ESI+ found [M-55] = 302.9.



DEMANDE OU BREVET VOLUMINEUX

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

CECI EST LE TOME 1 DE 4
CONTENANT LES PAGES 1 À 332

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 4
CONTAINING PAGES 1 TO 332

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

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

1. A compound of formula I:



R₁ is selected from the group consisting of H and unsubstituted C₁-C₄ alkyl;

the B ring is tetrazolyl or a 5 to 6 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the B ring is optionally substituted with 1 to 2 substituents selected from the group consisting of halogen, C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and cyano; and wherein if a nitrogen atom in the B ring is substituted, the substituent is not halogen, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, or cyano;

(a) 1 to 4 substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, cyano, phenyl, monofluorophenyl, di-fluorophenyl, benzyl, CH₂-(C₃-C₆ cycloalkyl), and CH₂CH₂-(C₃-C₆ cycloalkyl); wherein if a nitrogen atom in the C ring is substituted, the substituent is not halogen, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, or cyano;

(c) two adjacent substituents which together form phenyl, C₅-C₆ heteroaryl, C₄-C₆ heterocyclyl, C₃-C₆ cycloalkyl, or C₄ cycloalkoxy;

X is selected from the group consisting of O, S, SO, SO₂, CH₂, C(CH₃)₂, CF₂ and CHCF₃;

n is 1 or 2;

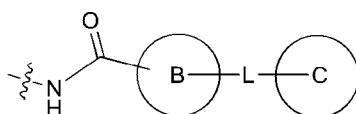
provided that if the A ring is unsubstituted 6 membered aryl, the fused B and C rings are not unsubstituted indolyl or indolyl substituted by one or two halogen atoms; and
provided that if the A ring is unsubstituted 6 membered aryl, the C ring is not chlorothiophenyl.

5 2. The compound or salt of claim 1, wherein the A ring is a 6 membered aryl substituted with one or two substituents selected from the group consisting of halogen and methyl.

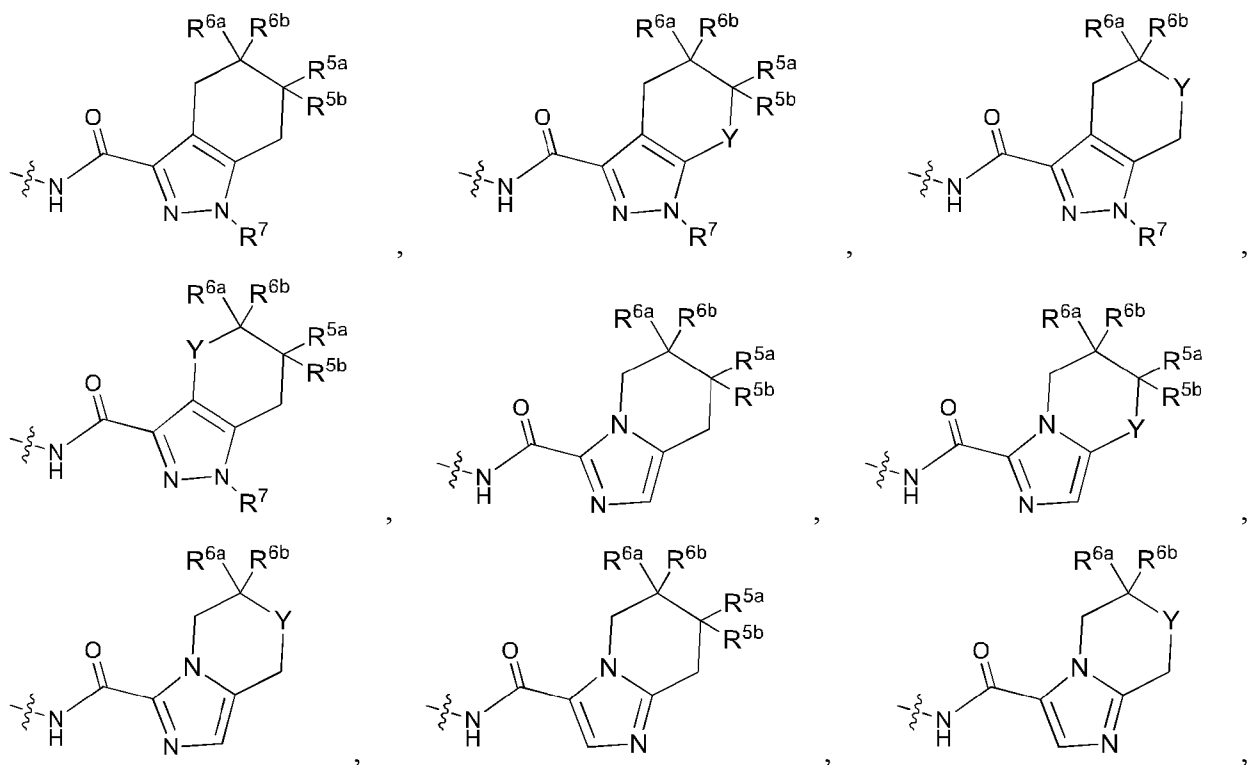
3. The compound or salt of claim 1, wherein the A ring is a 6 membered aryl substituted with one or two substituents selected from the group consisting of fluoro and methyl.

10

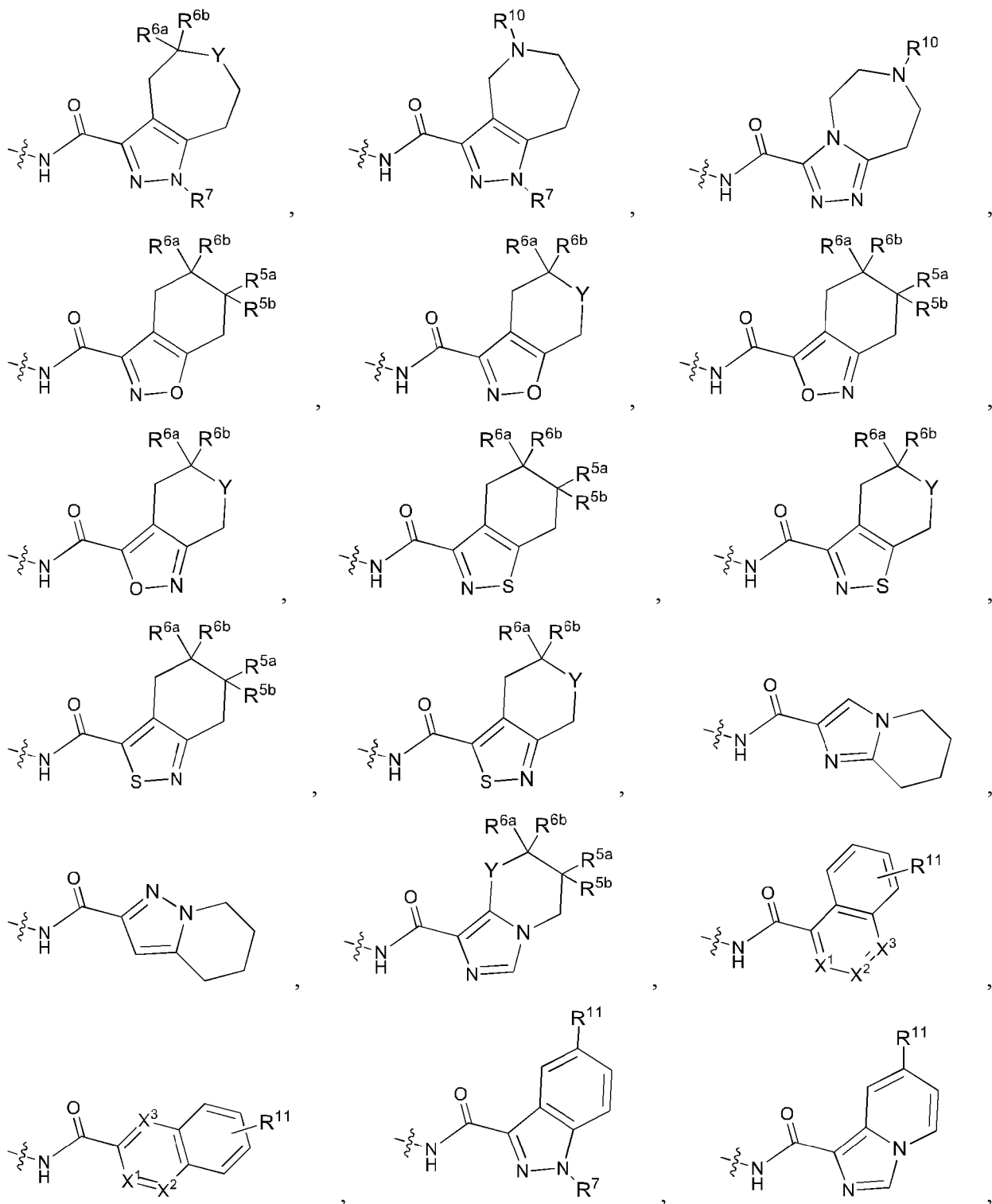
4. The compound or salt according to any one of claims 1-3, wherein:

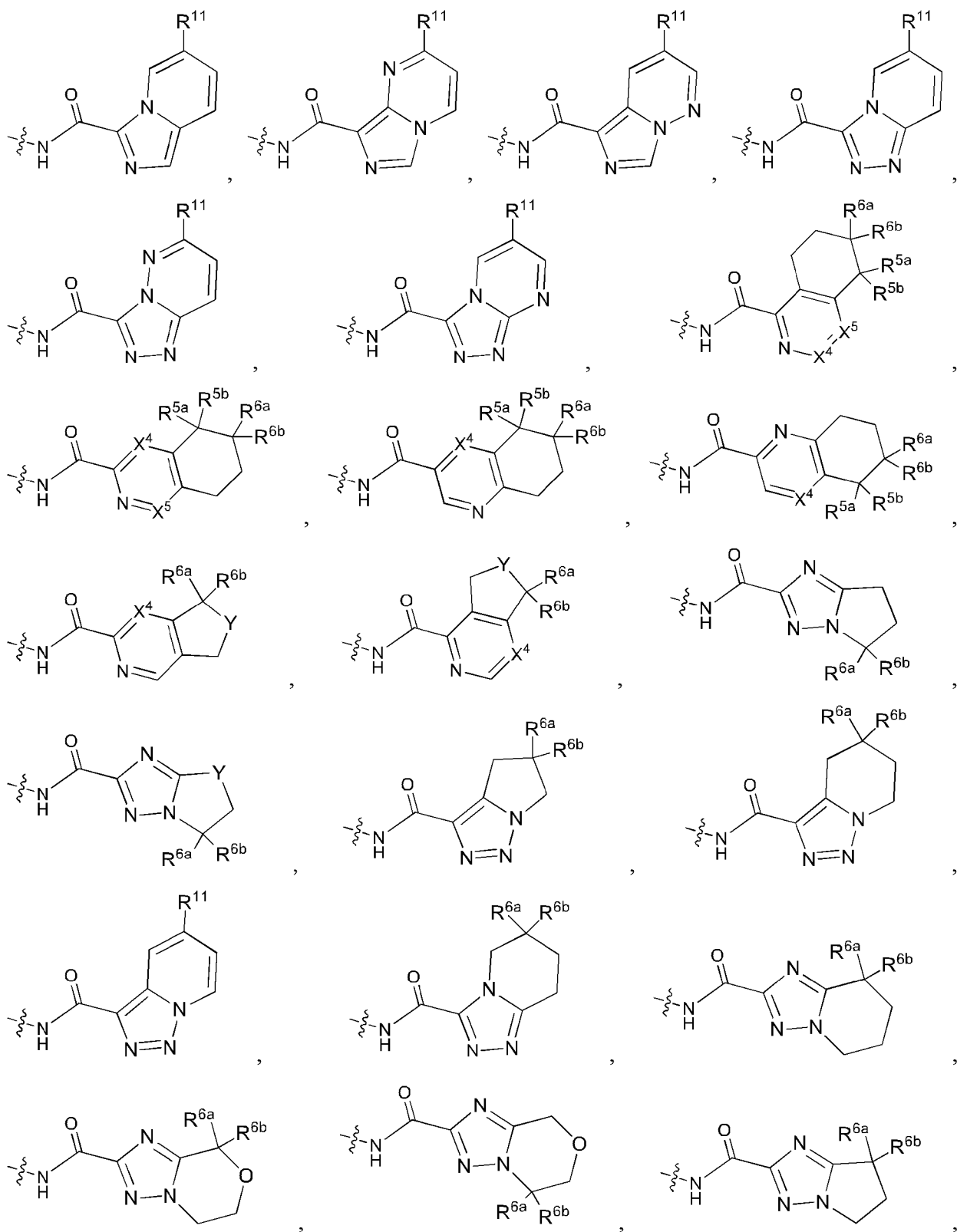


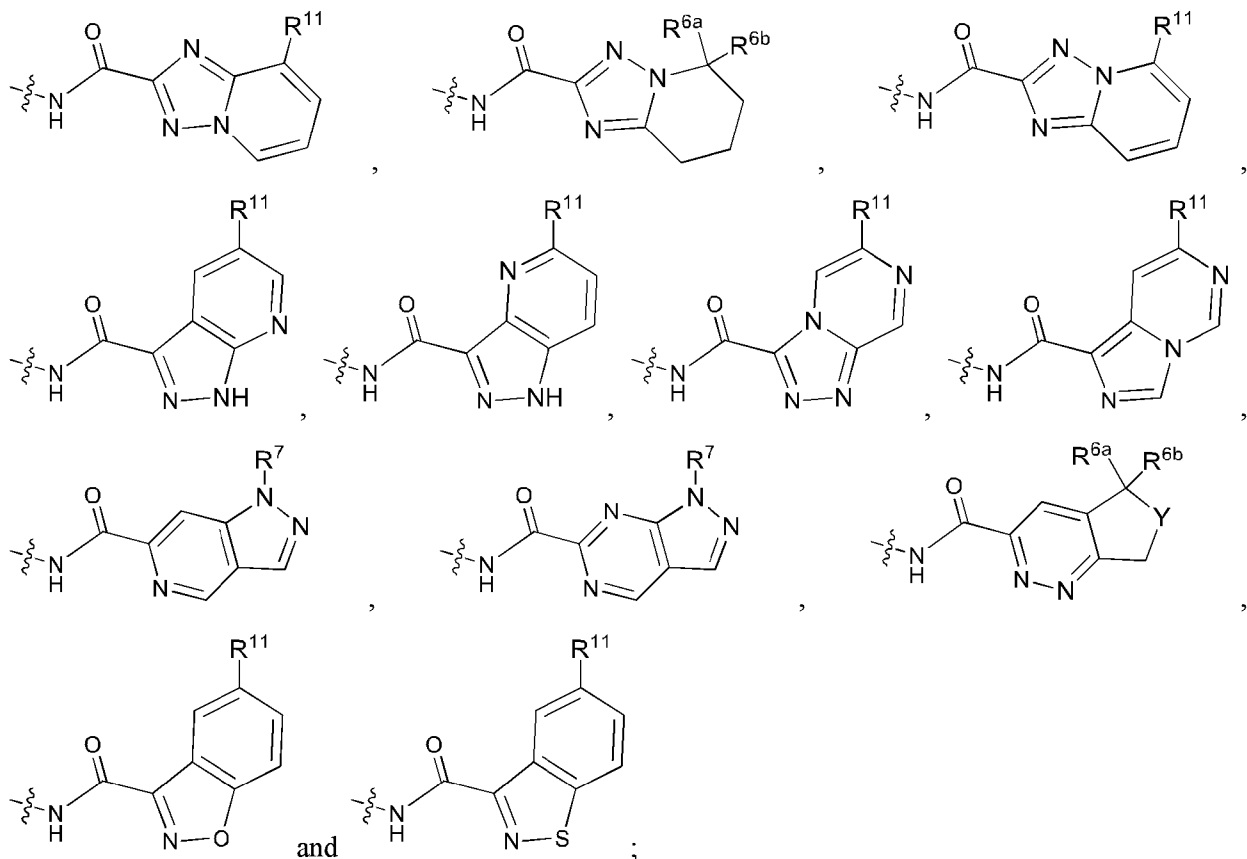
is selected from the group consisting of:



15







5 wherein:

Y is selected from the group consisting of O, S, SO and SO₂;

X¹, X² and X³ are each independently N or CH, wherein 1 or 2 of X¹, X² and X³ is N;

X⁴ and X⁵ are each independently N or CH;

10 R^{5a} and R^{5b}, are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, phenyl, benzyl, -CH₂(C₃-C₆ cycloalkyl), and 5 to 6 membered heteroaryl; wherein R^{5a} and R^{5b} together with the carbon to which they are attached may form a 3 to 4 membered cycloalkyl or a 4 membered cycloalkoxy;

15 R^{6a} and R^{6b} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, phenyl, mono-fluorophenyl, di-fluorophenyl, benzyl, -CH₂(C₃-C₆ cycloalkyl), and 5 to 6 membered heteroaryl; wherein R^{6a} and R^{6b} together with the carbon to which they are attached may form a 3 to 4 membered cycloalkyl or a 4 membered cycloalkoxy;

wherein when R^{5a} and R^{6a} are each H, R^{5b} and R^{6b} may together form a 3 or 4 membered cycloalkyl;

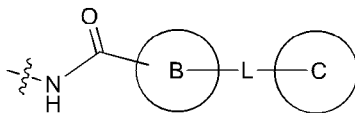
and wherein only two of R^{5a}, R^{5b}, R^{6a} and R^{6b} may be other than H in each instance;

R⁷ is selected from the group consisting of H and unsubstituted C₁-C₄ alkyl;

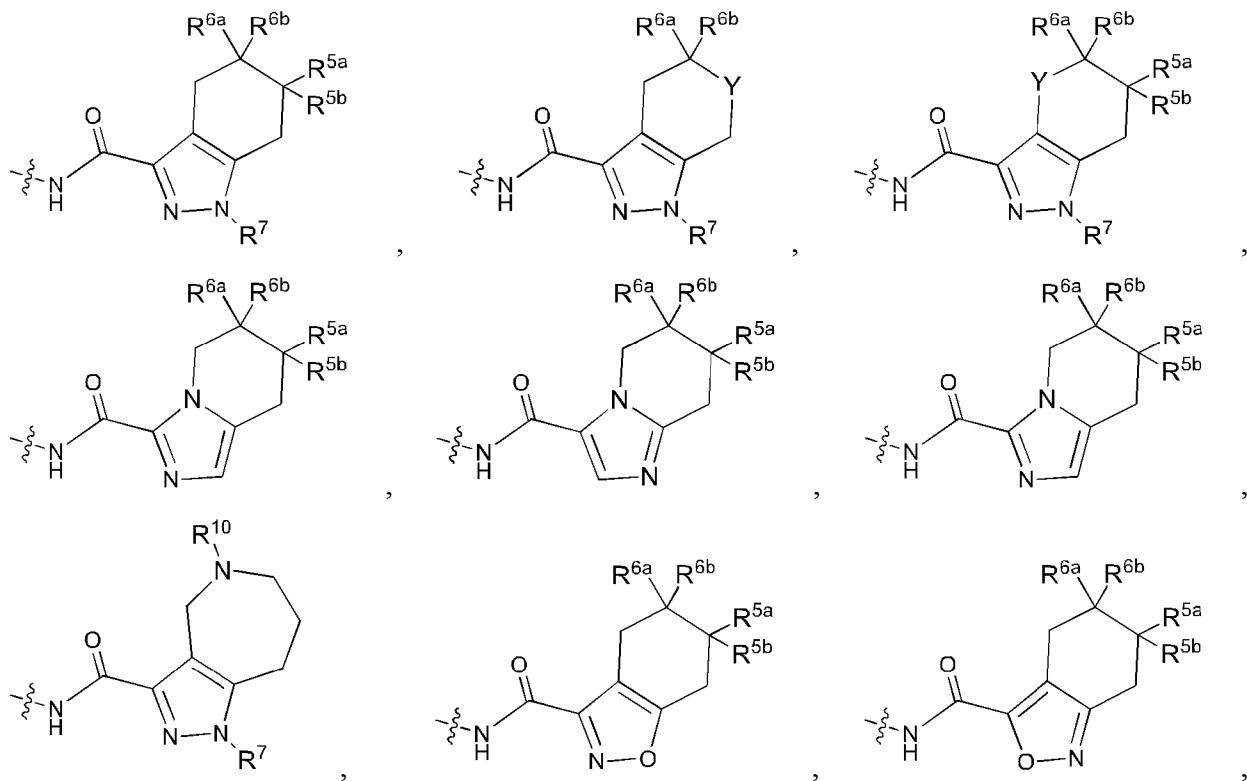
R¹⁰ is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, phenyl, and benzyl; and

R¹¹ is selected from the group consisting of H, halogen, C₁-C₄ alkyl, and C₁-C₄ haloalkyl.

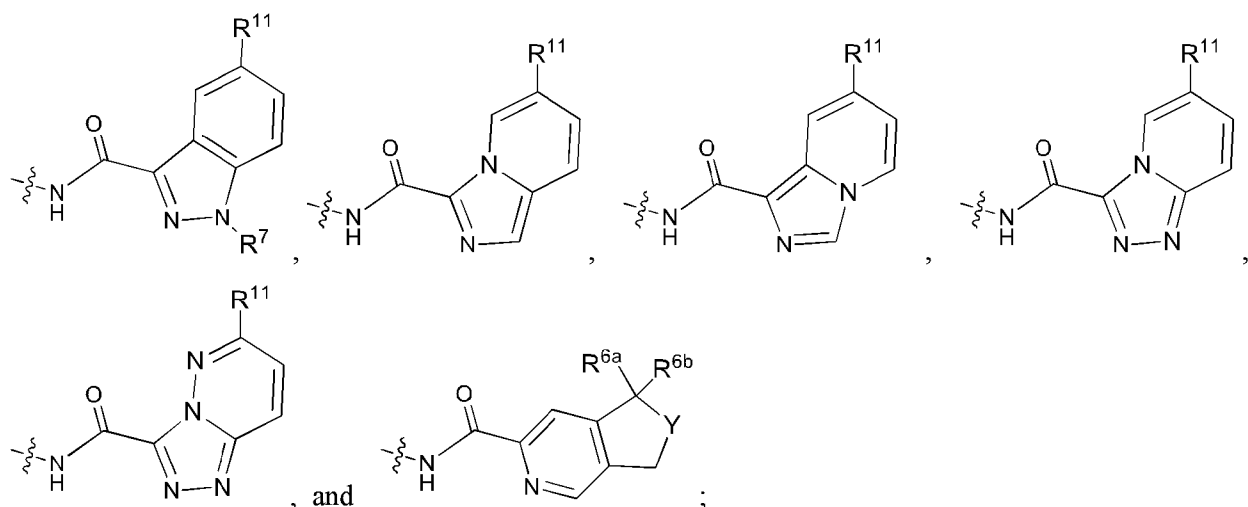
5. The compound or salt according to claim 4, wherein:



is selected from the group consisting of:



10



wherein:

R^{5a} and R^{5b} are each H; or

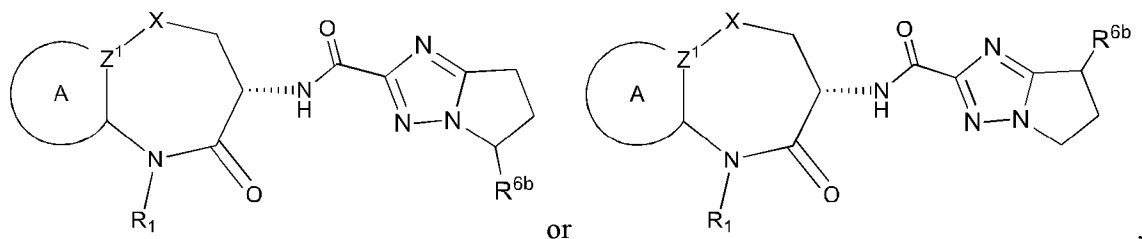
5 R^{5a} and R^{6a} are each H, and R^{5b} and R^{6b} together form cyclopropyl or cyclobutyl.

6. The compound or salt according to claim 4 or 5, wherein Y is O.

7. The compound or salt according to any one of claims 4-6, wherein R^{5a} and R^{5b} are each H.

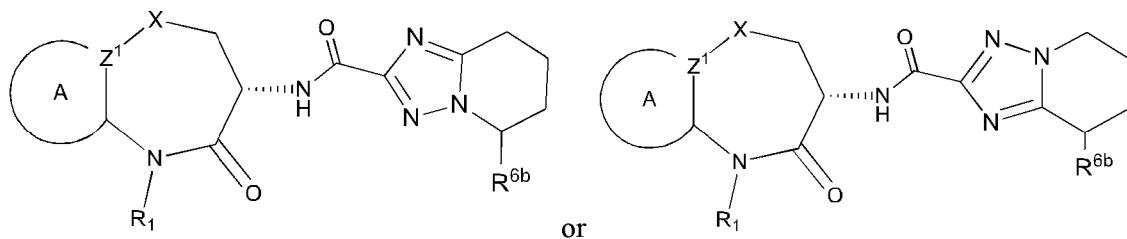
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8. The compound or salt according to claim 1, wherein the compound is of the formula:



wherein R^{6b} is selected from the group consisting of H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, phenyl, mono-fluorophenyl, di-fluorophenyl, benzyl, $-CH_2(C_3$ - C_6 cycloalkyl),
 15 and 5 to 6 membered heteroaryl.

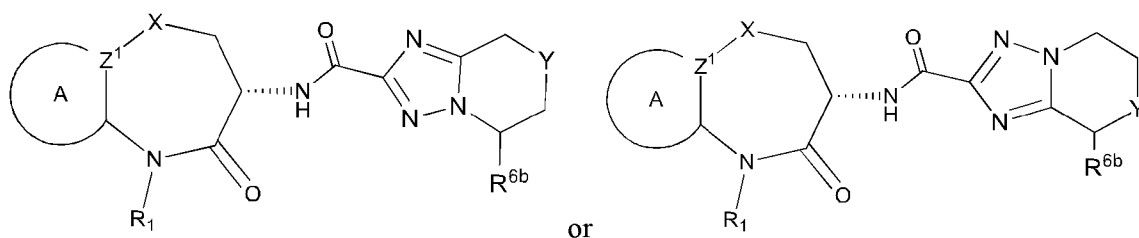
9. The compound or salt according to claim 1, wherein the compound is of the formula:



wherein R^{6b} is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, phenyl, mono-fluorophenyl, di-fluorophenyl, benzyl, -CH₂(C₃-C₆ cycloalkyl), and 5 to 6 membered heteroaryl.

5

10. The compound or salt according to claim 1, wherein the compound is of the formula:



wherein Y is NH or O; and R^{6b} is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, phenyl, mono-fluorophenyl, di-fluorophenyl, benzyl, -CH₂(C₃-C₆ cycloalkyl), and 5 to 6 membered heteroaryl.

10

11. The compound or salt according to any one of claims 8-10, wherein R_1 is H or methyl; and X is CH₂ or O.

15

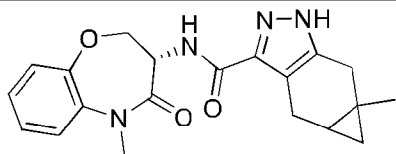
12. The compound or salt according to any one of claims 8-10, wherein R_1 is H or methyl; X is CH₂ or O; and R^{6b} is selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ haloalkyl, phenyl, fluorophenyl and di-fluorophenyl.

13. The compound or salt according to any one of claims 1-10, wherein R_1 is H or CH₃.

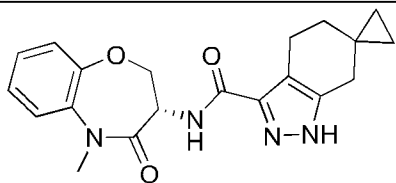
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14. The compound or salt according to any one of claims 1-13, wherein n is 1.

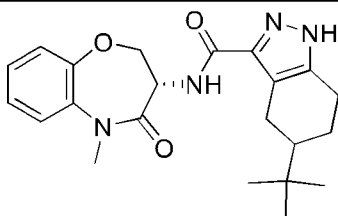
15. A compound which is:



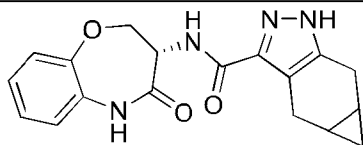
5a-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxamide



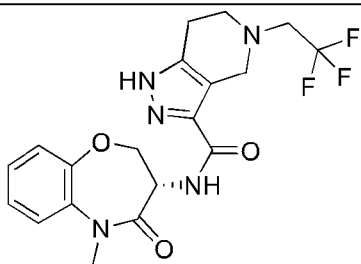
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1',4',5',7'-tetrahydrospiro[cyclopropane-1,6'-indazole]-3'-carboxamide



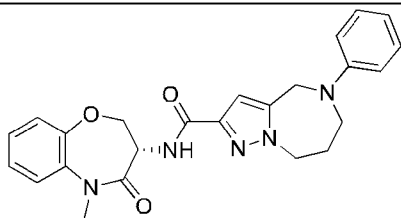
5-(tert-butyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide



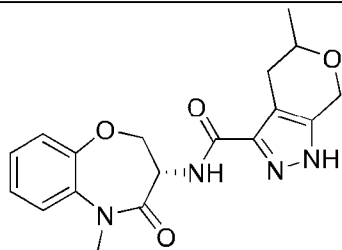
N-((S)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxamide



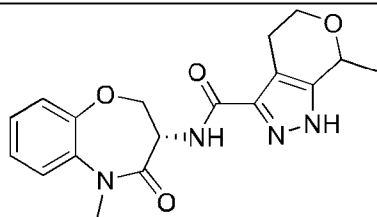
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxamide



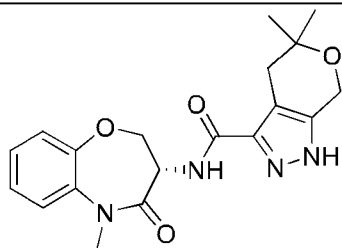
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-phenyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



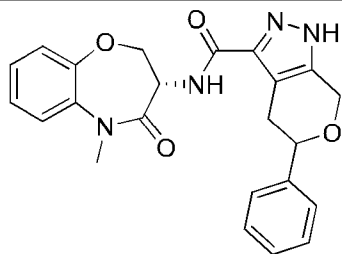
5-methyl-N-((S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide



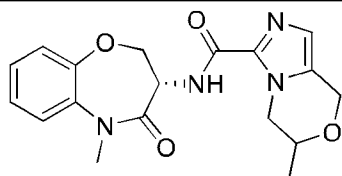
7-methyl-N-((S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl)-2,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide



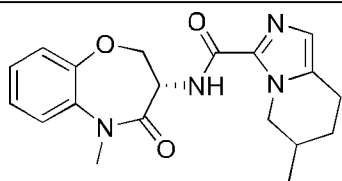
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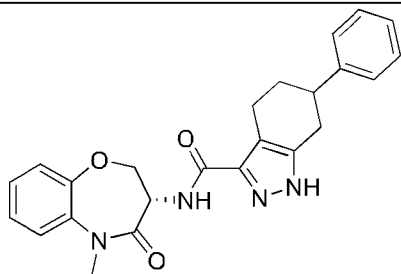
N-((S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl)-5-phenyl-1,4,5,7-tetrahydropyrazolo[3,4-c]pyrazole-3-carboxamide



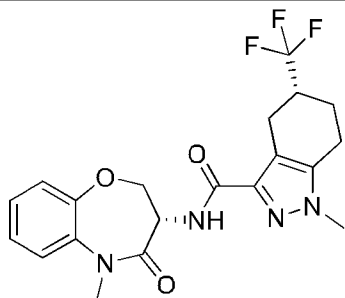
6-methyl-N-((S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl)-6,8-dihydro-5H-imidazo[5,1-c][1,4]oxazine-3-carboxamide



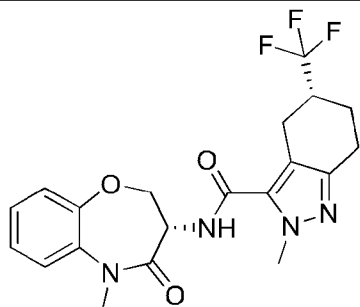
6-methyl-N-((S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide



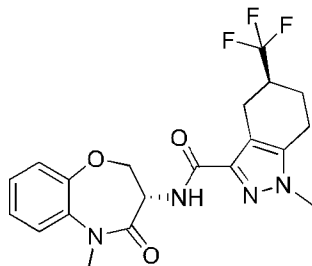
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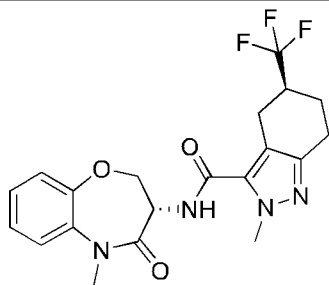
(R)-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide



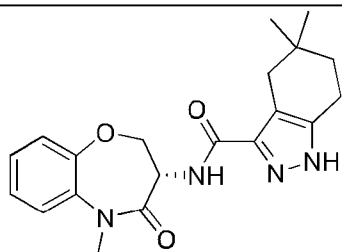
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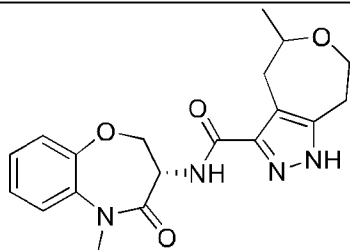
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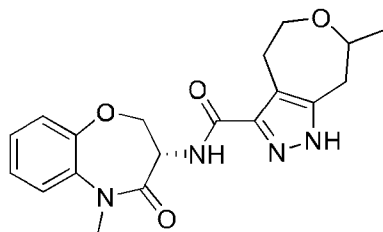
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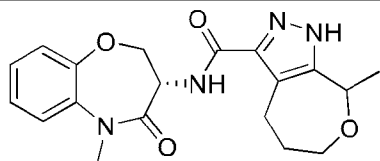
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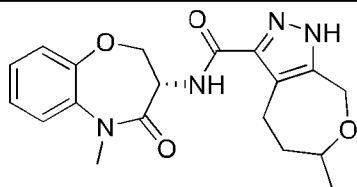
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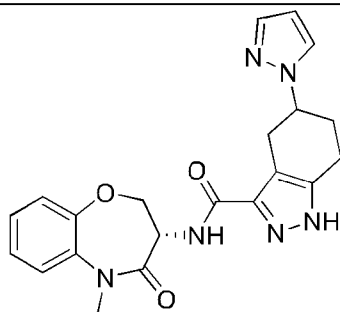
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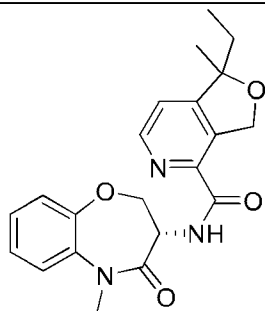
8-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxamide



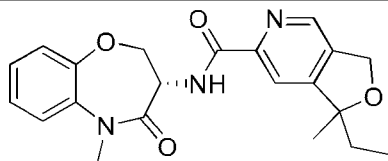
6-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,8-tetrahydro-1H-oxepino[3,4-c]pyrazole-3-carboxamide



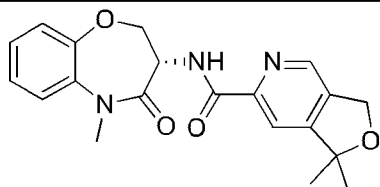
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(1H-pyrazol-1-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide



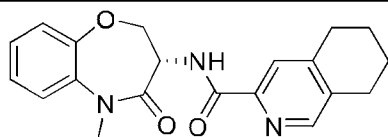
1-ethyl-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-4-carboxamide



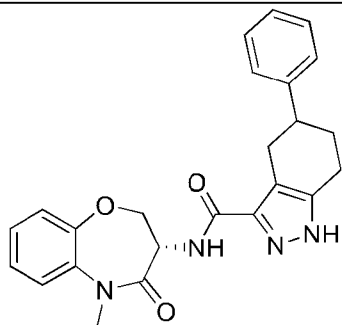
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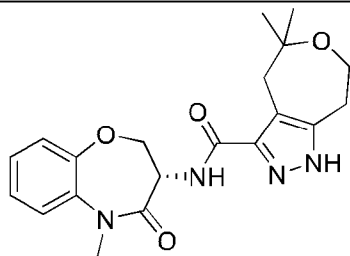
(S)-1,1-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide



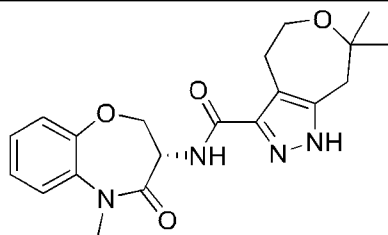
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroisoquinoline-3-carboxamide



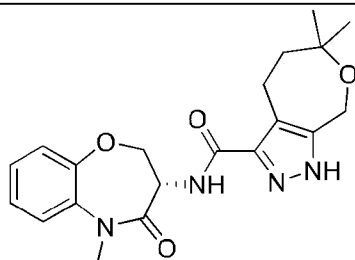
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide



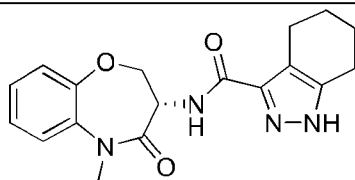
(S)-5,5-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,7,8-tetrahydro-1H-oxepino[4,5-c]pyrazole-3-carboxamide



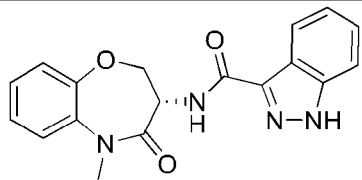
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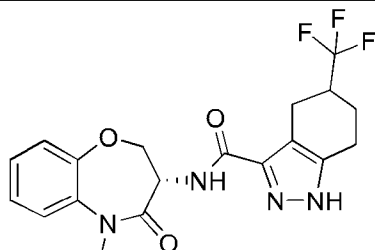
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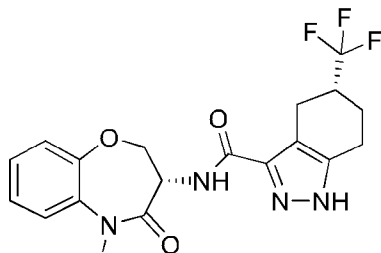
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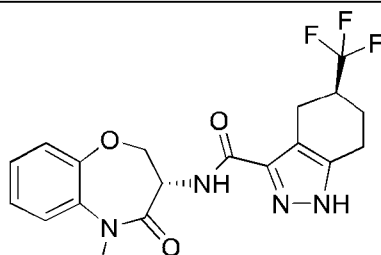
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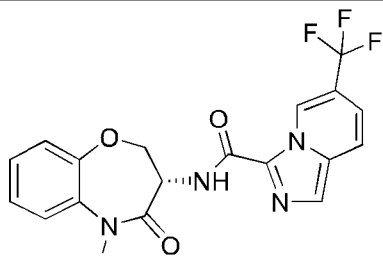
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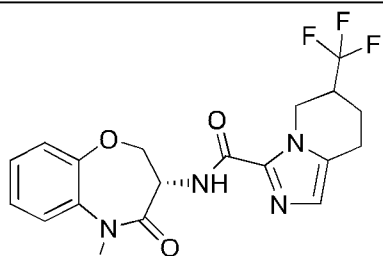
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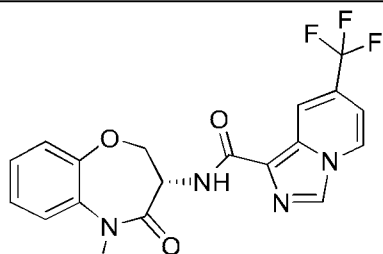
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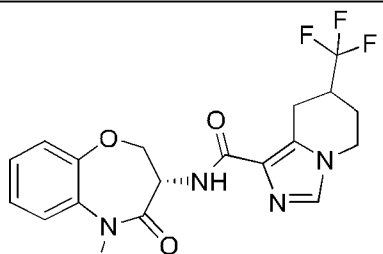
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-carboxamide



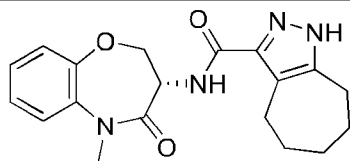
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide



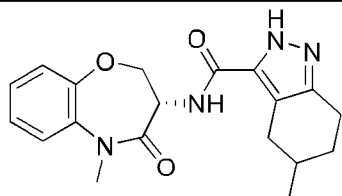
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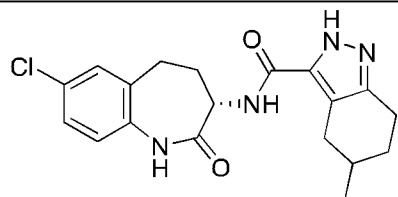
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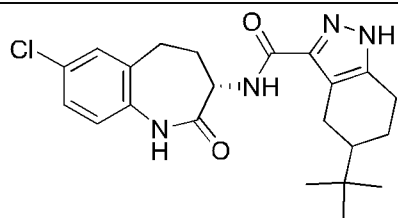
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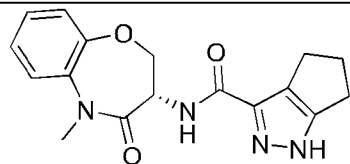
5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide



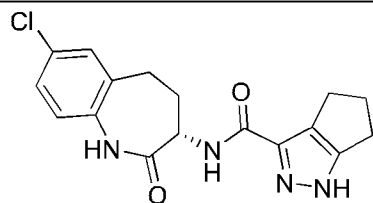
N-((S)-7-chloro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-5-methyl-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide



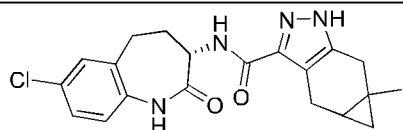
5-(tert-butyl)-N-((S)-7-chloro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide



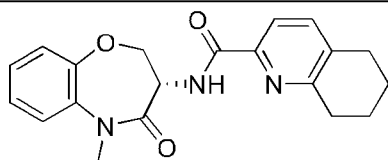
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxamide



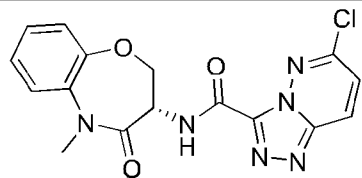
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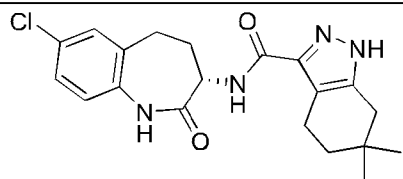
N-((S)-7-chloro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-5a-methyl-1,4,4a,5,5a,6-hexahydrocyclopropa[f]indazole-3-carboxamide



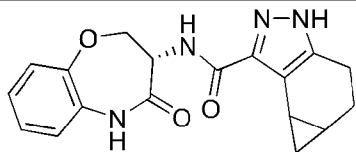
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroquinoline-2-carboxamide



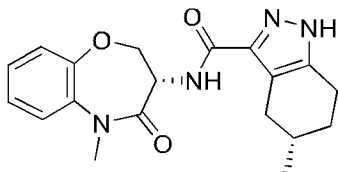
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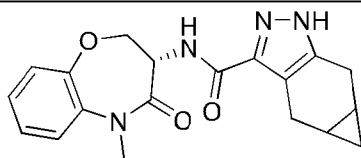
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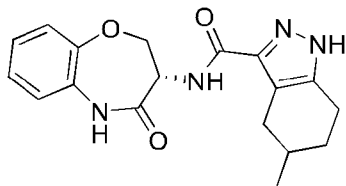
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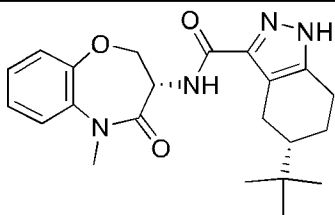
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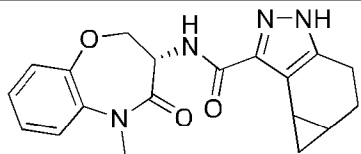
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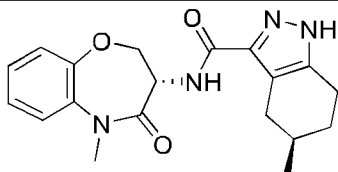
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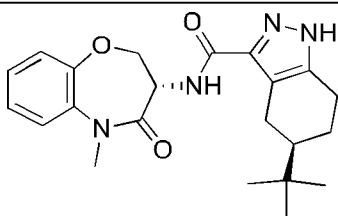
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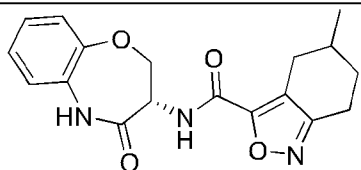
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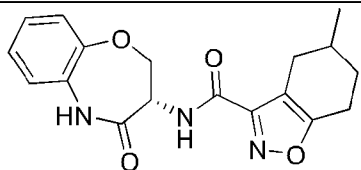
(R)-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide



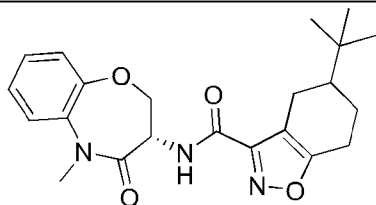
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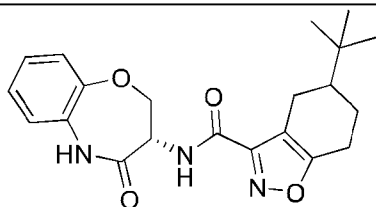
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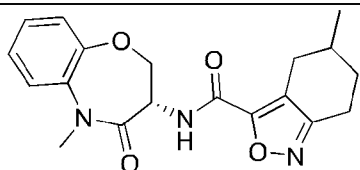
5-methyl-N-((S)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide



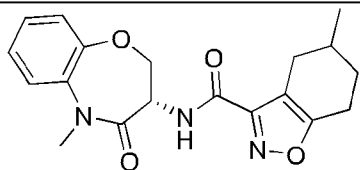
5-(tert-butyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide



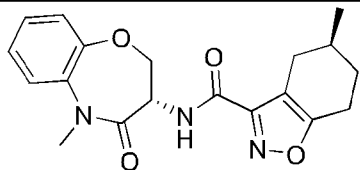
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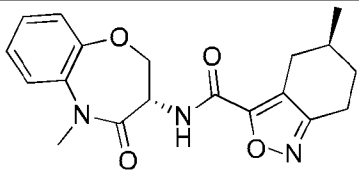
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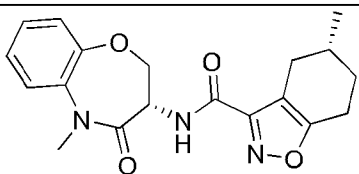
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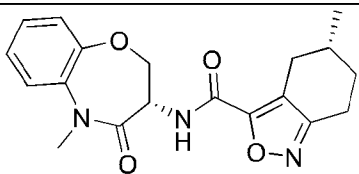
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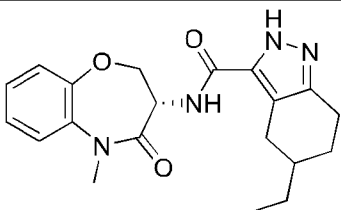
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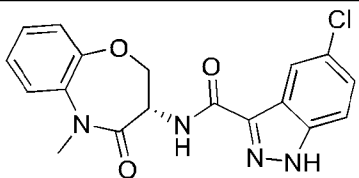
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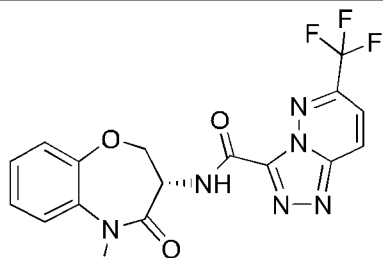
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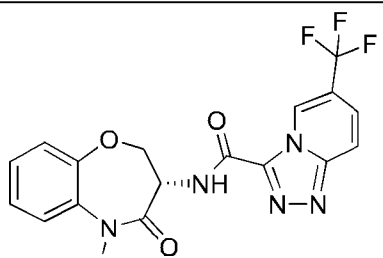
5-ethyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide



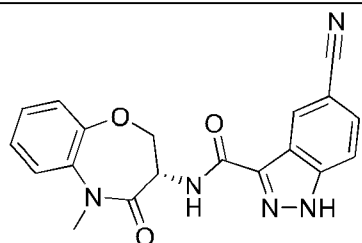
(S)-5-chloro-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-indazole-3-carboxamide



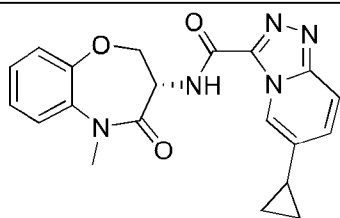
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxamide



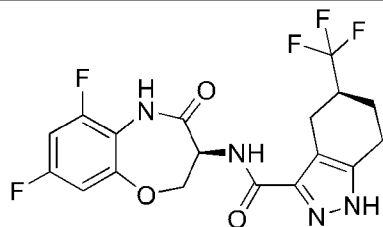
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide



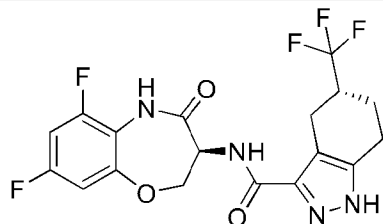
(S)-5-cyano-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-indazole-3-carboxamide



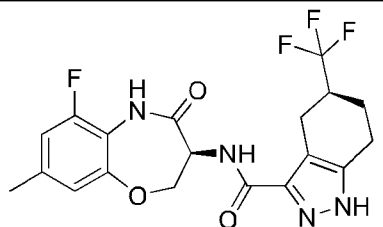
(S)-6-cyclopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide



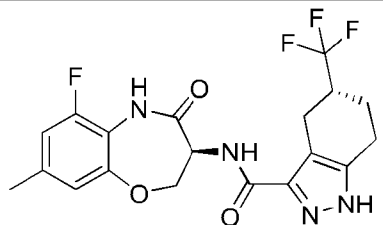
(S)-N-((S)-6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide



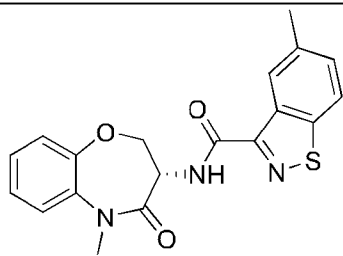
(R)-N-((S)-6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide



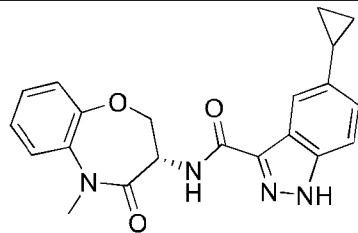
(S)-N-((S)-6-fluoro-8-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide



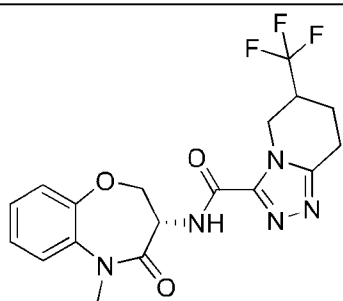
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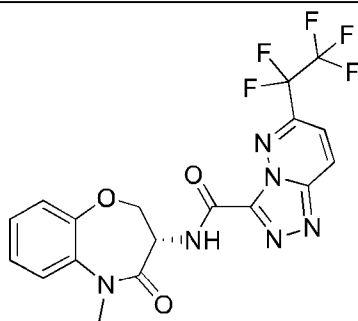
(S)-5-methyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)benzo[d]isothiazole-3-carboxamide



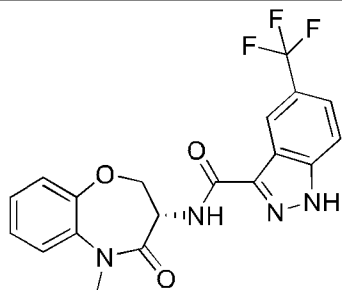
(S)-5-cyclopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-indazole-3-carboxamide



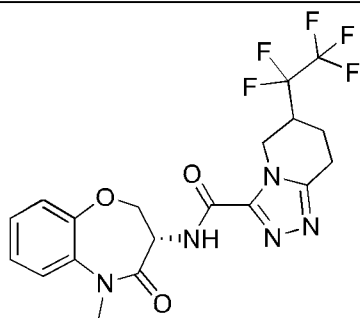
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide



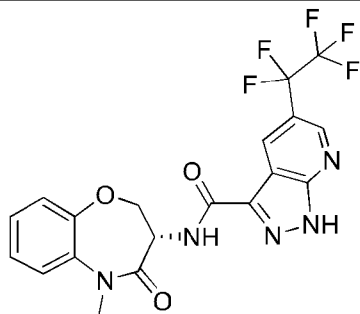
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(perfluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxamide



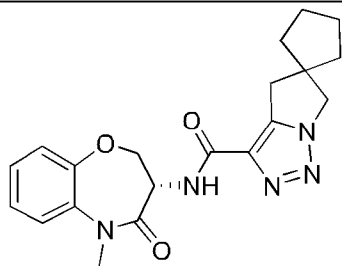
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-1H-indazole-3-carboxamide



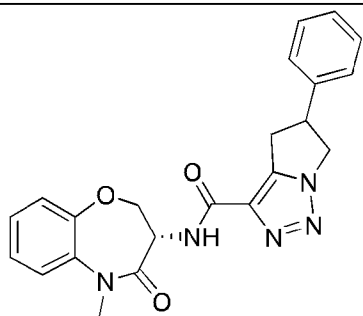
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(perfluoroethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide



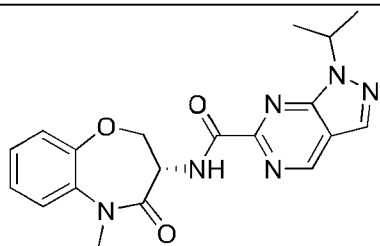
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(perfluoroethyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxamide



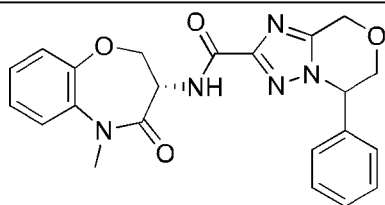
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4'H,6'H-spiro[cyclopentane-1,5'-pyrrolo[1,2-c][1,2,3]triazole]-3'-carboxamide



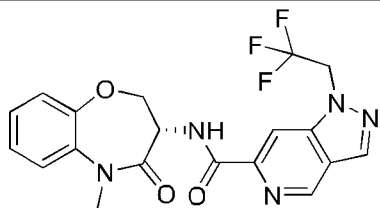
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-phenyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole-3-carboxamide



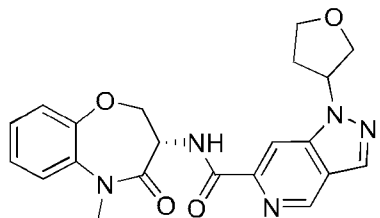
(S)-1-isopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-carboxamide



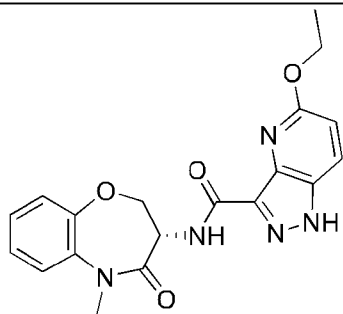
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-phenyl-5,6-dihydro-8H-[1,2,4]triazolo[5,1-c][1,4]oxazine-2-carboxamide



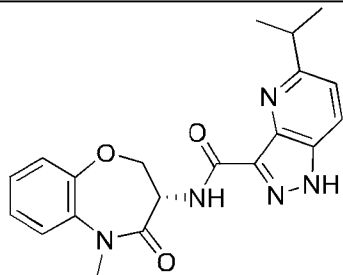
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1-(2,2,2-trifluoroethyl)pyrazolo[4,3-c]pyridine-6-carboxamide



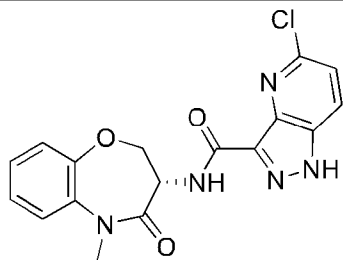
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]pyridine-6-carboxamide



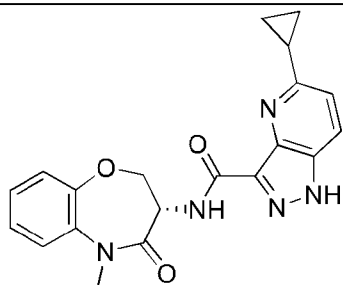
(S)-5-ethoxy-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[4,3-b]pyridine-3-carboxamide



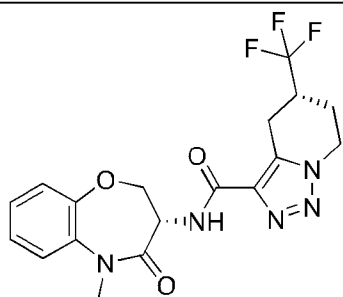
(S)-5-isopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[4,3-b]pyridine-3-carboxamide



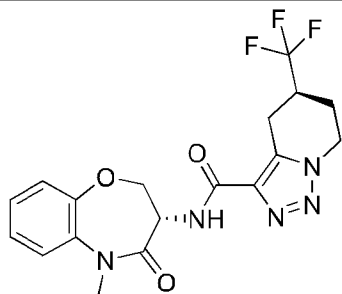
(S)-5-chloro-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[4,3-b]pyridine-3-carboxamide



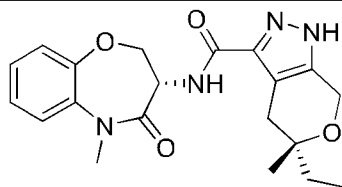
(S)-5-cyclopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[4,3-b]pyridine-3-carboxamide



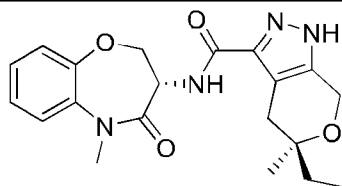
(R)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide



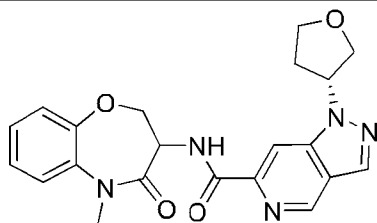
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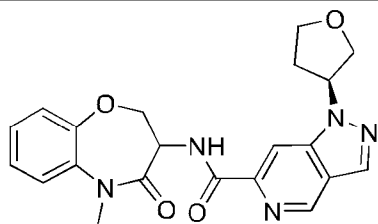
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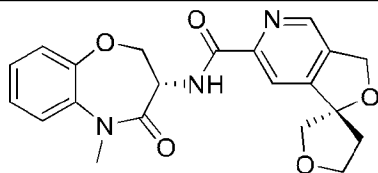
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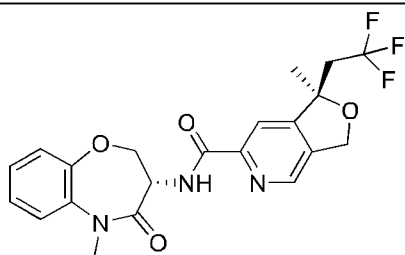
N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1-((R)-tetrahydrofuran-3-yl)-1H-pyrazolo[4,3-c]pyridine-6-carboxamide



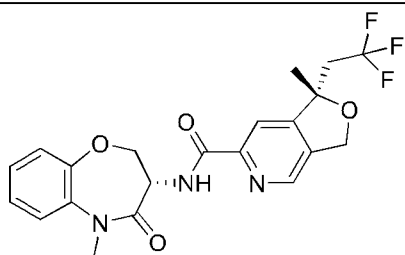
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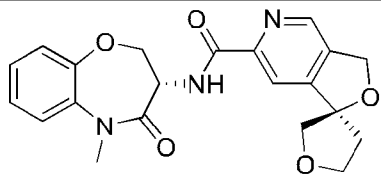
(S)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5-dihydro-2H,3'H-spiro[furan-3,1'-furo[3,4-c]pyridine]-6'-carboxamide



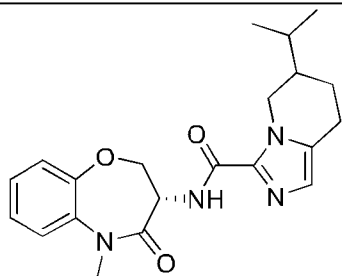
(R)-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1-(2,2,2-trifluoroethyl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide



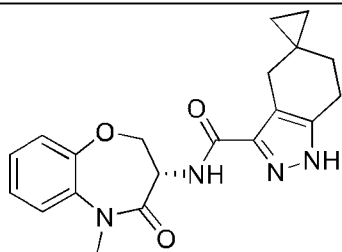
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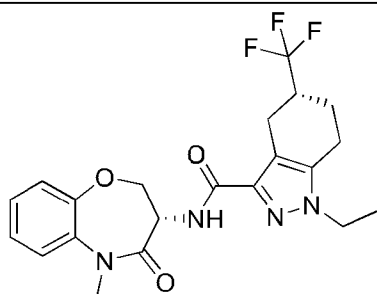
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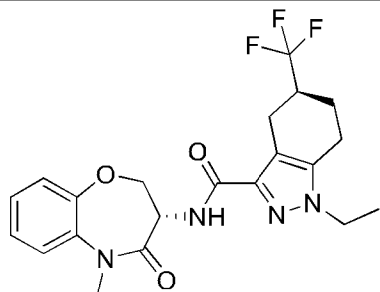
6-isopropyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide



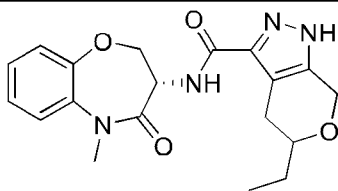
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1',4',6',7'-tetrahydrospiro[cyclopropane-1,5'-indazole]-3'-carboxamide



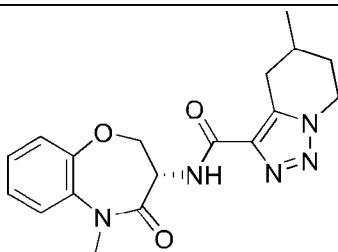
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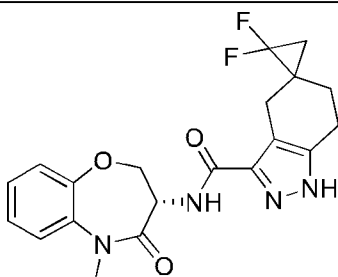
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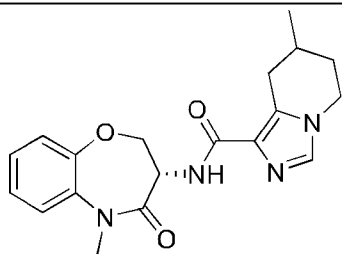
5-ethyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide



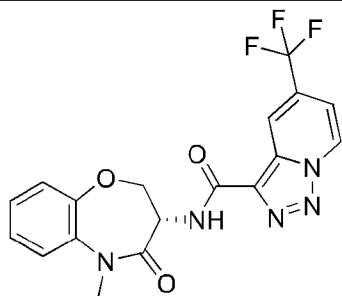
5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide



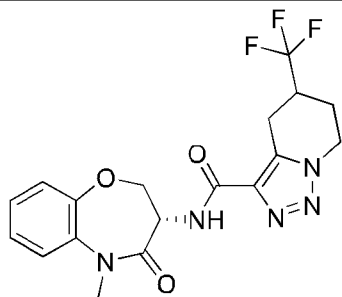
2,2-difluoro-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1',4',6',7'-tetrahydrospiro[cyclopropane-1,5'-indazole]-3'-carboxamide



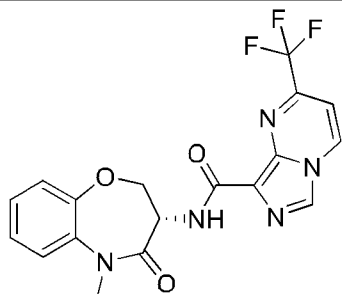
7-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-1-carboxamide



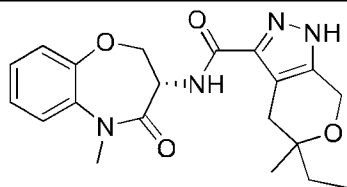
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide



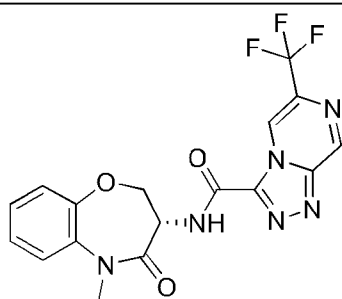
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide



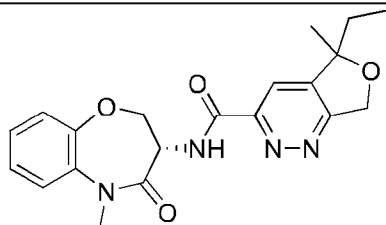
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-2-(trifluoromethyl)imidazo[1,5-a]pyrimidine-8-carboxamide



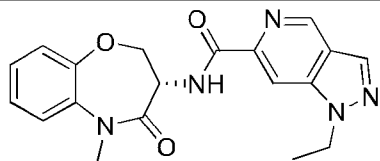
5-ethyl-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide



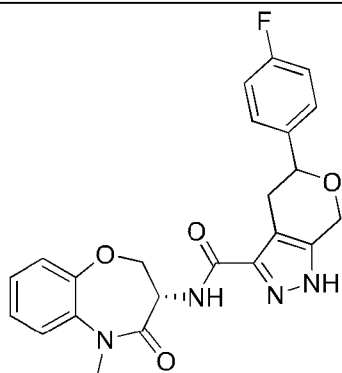
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyrazine-3-carboxamide



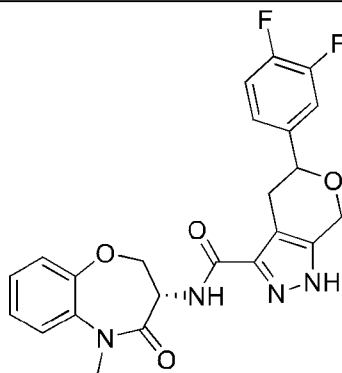
5-ethyl-5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,7-dihydrofuro[3,4-c]pyridazine-3-carboxamide



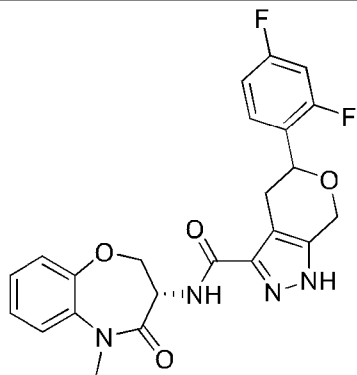
(S)-1-ethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[4,3-c]pyridine-6-carboxamide



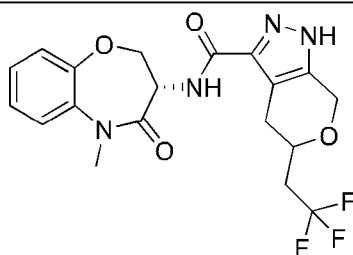
5-(4-fluorophenyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide



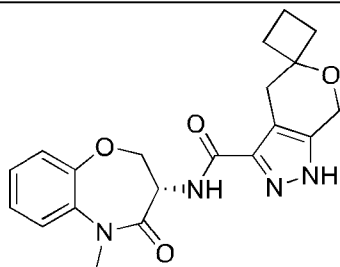
5-(3,4-difluorophenyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide



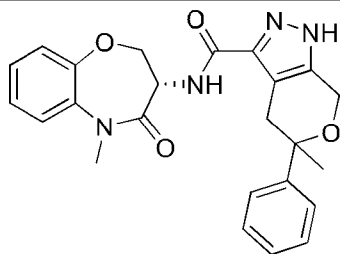
5-(2,4-difluorophenyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide



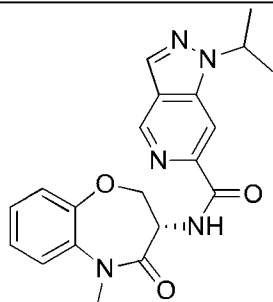
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(2,2,2-trifluoroethyl)-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide



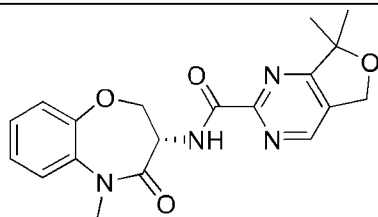
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4',7'-dihydro-1'H-spiro[cyclobutane-1,5'-pyrano[3,4-c]pyrazole]-3'-carboxamide



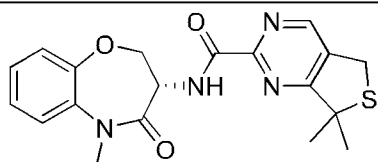
5-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-phenyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxamide



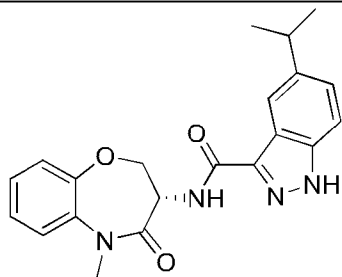
(S)-1-isopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[4,3-c]pyridine-6-carboxamide



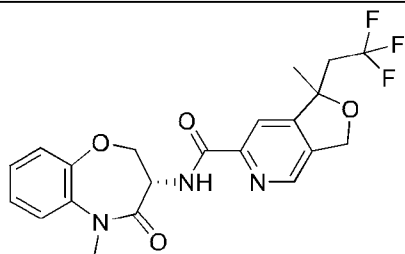
(S)-7,7-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxamide



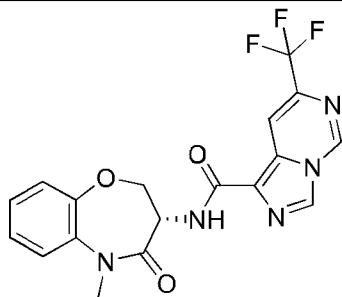
(S)-7,7-dimethyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,7-dihydrothieno[3,4-d]pyrimidine-2-carboxamide



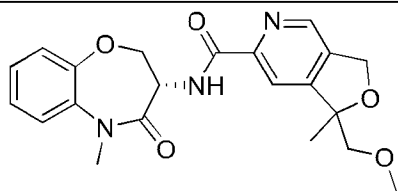
(S)-5-isopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-indazole-3-carboxamide



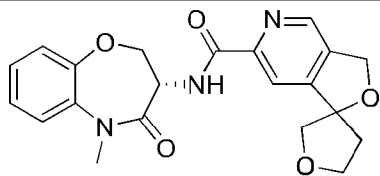
1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1-(2,2,2-trifluoroethyl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide



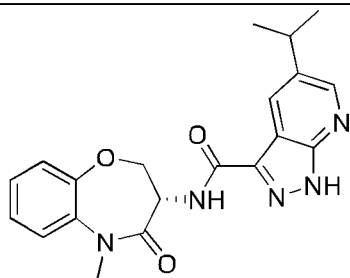
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-7-(trifluoromethyl)imidazo[1,5-c]pyrimidine-1-carboxamide



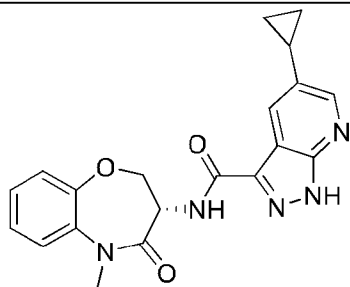
1-(methoxymethyl)-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide



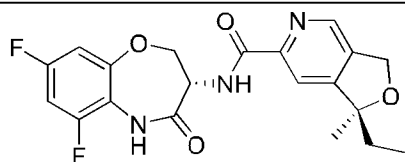
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5-dihydro-2H,3'H-spiro[furan-3,1'-furo[3,4-c]pyridine]-6'-carboxamide



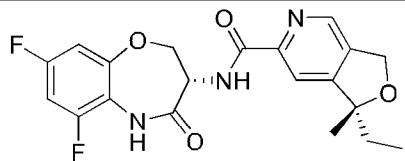
(S)-5-isopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[3,4-b]pyridine-3-carboxamide



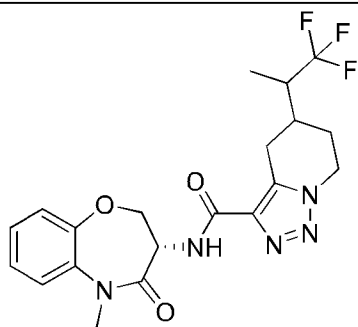
(S)-5-cyclopropyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazolo[3,4-b]pyridine-3-carboxamide



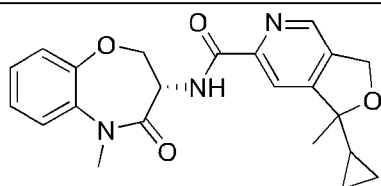
(S)-N-((S)-6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide



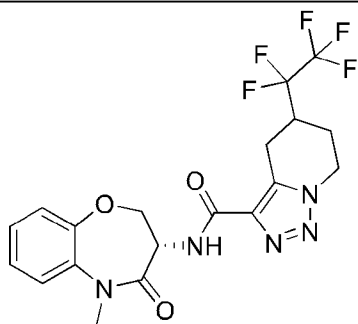
(R)-N-((S)-6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1-ethyl-1-methyl-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide



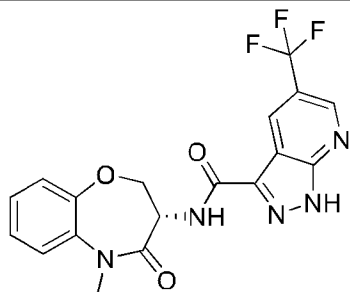
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(1,1,1-trifluoropropan-2-yl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide



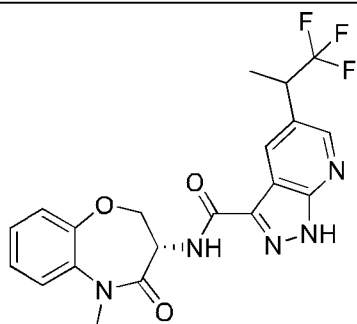
1-cyclopropyl-1-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1,3-dihydrofuro[3,4-c]pyridine-6-carboxamide



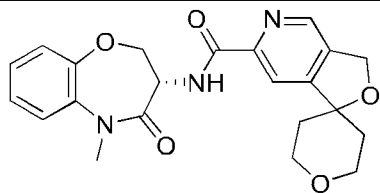
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(perfluoroethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-3-carboxamide



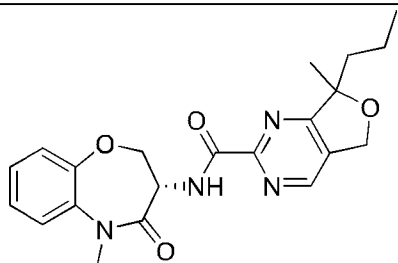
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxamide



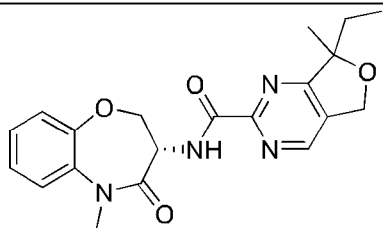
N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5-(1,1,1-trifluoropropan-2-yl)-1H-pyrazolo[3,4-b]pyridine-3-carboxamide



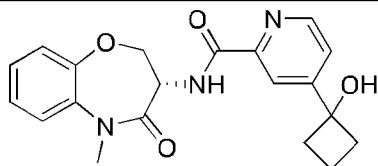
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-2',3',5',6'-tetrahydro-3H-spiro[furo[3,4-c]pyridine-1,4'-pyran]-6-carboxamide



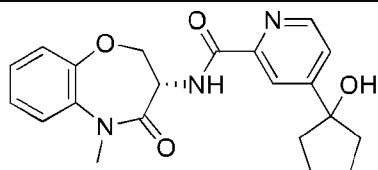
7-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-7-propyl-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxamide



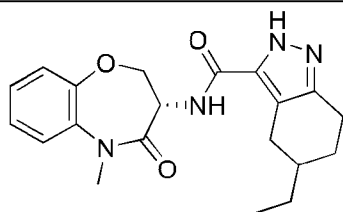
7-ethyl-7-methyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxamide



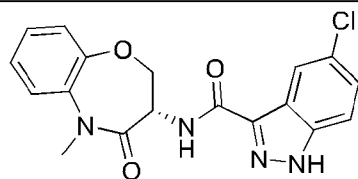
(S)-4-(1-hydroxycyclobutyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)picolinamide



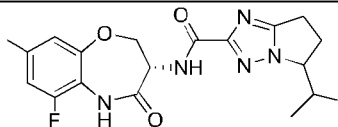
(S)-4-(1-hydroxycyclopentyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)picolinamide



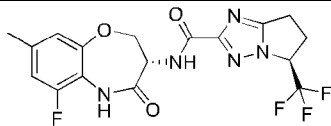
5-ethyl-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide



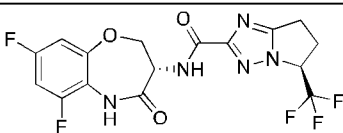
(S)-5-chloro-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-indazole-3-carboxamide



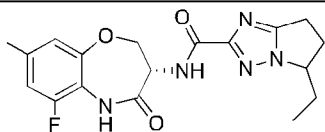
N-[(3S)-6-fluoro-8-methyl-4-oxo-3,5-dihydro-2H-1,5-benzoxazepin-3-yl]-5-isopropyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



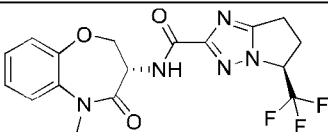
(5S)-N-[(3S)-6-fluoro-8-methyl-4-oxo-3,5-dihydro-2H-1,5-benzoxazepin-3-yl]-5-(trifluoromethyl)-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



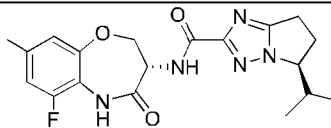
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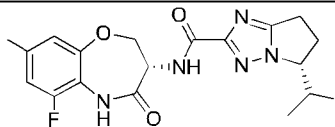
5-ethyl-N-[(3S)-6-fluoro-8-methyl-4-oxo-3,5-dihydro-2H-1,5-benzoxazepin-3-yl]-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



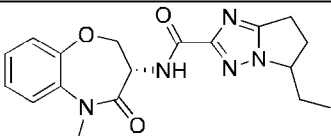
(5S)-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5-(trifluoromethyl)-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



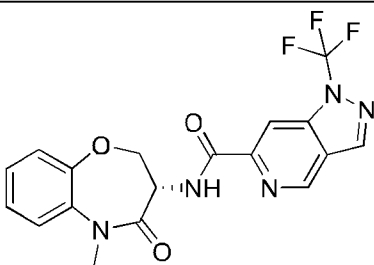
(5S)-5-isopropyl-N-[(3S)-6-fluoro-8-methyl-4-oxo-3,5-dihydro-2H-1,5-benzoxazepin-3-yl]-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



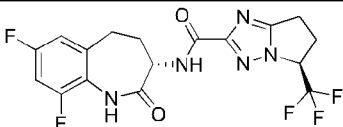
(5R)-5-isopropyl-N-[(3S)-6-fluoro-8-methyl-4-oxo-3,5-dihydro-2H-1,5-benzoxazepin-3-yl]-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



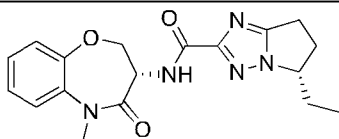
5-ethyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



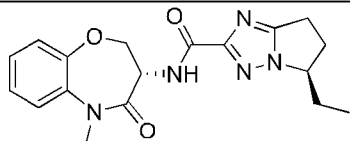
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1-(trifluoromethyl)-1H-pyrazolo[4,3-c]pyridine-6-carboxamide



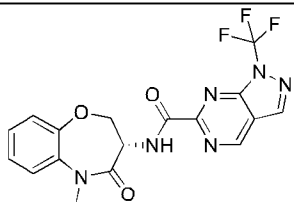
(5S)-N-[(3S)-7,9-difluoro-2-oxo-1,3,4,5-tetrahydro-1-benzazepin-3-yl]-5-(trifluoromethyl)-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



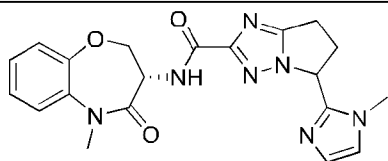
(5S)-5-ethyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



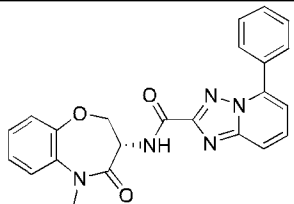
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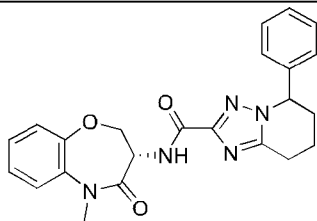
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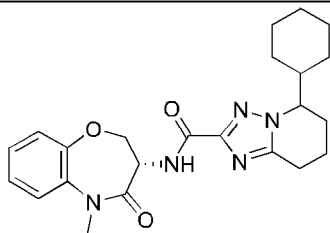
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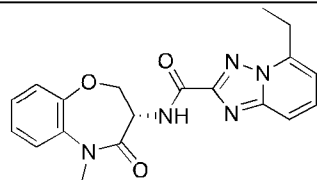
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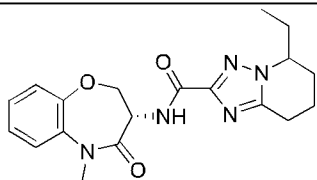
5-phenyl-N-[rac-(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-2-carboxamide



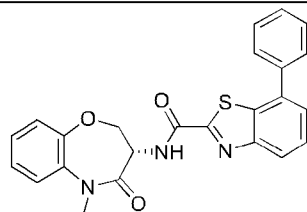
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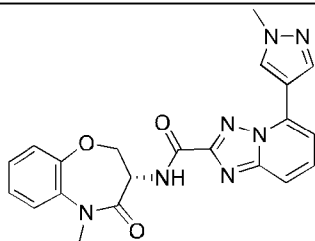
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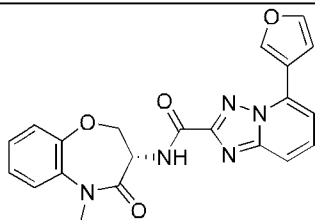
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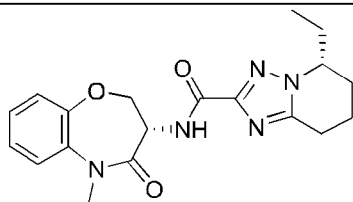
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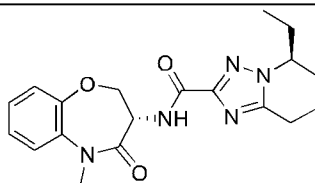
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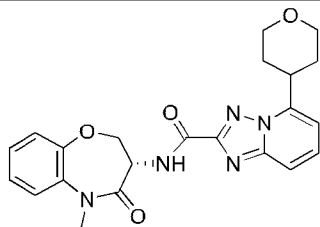
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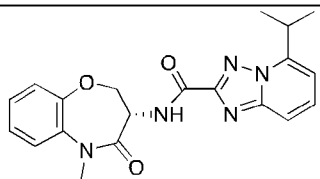
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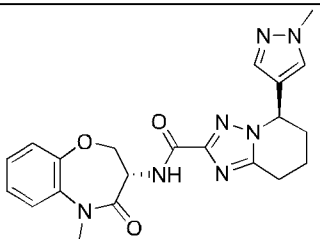
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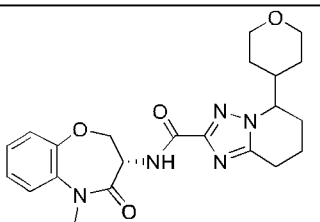
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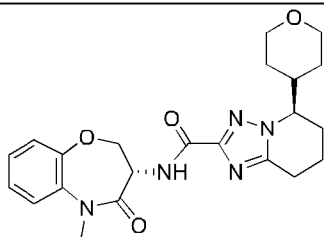
5-isopropyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-[1,2,4]triazolo[1,5-a]pyridine-2-carboxamide



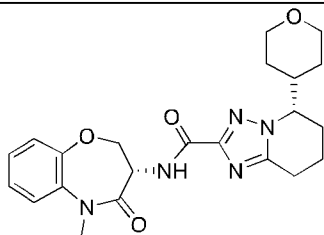
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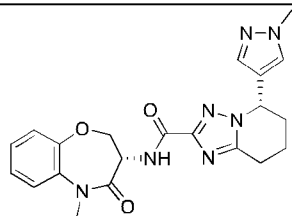
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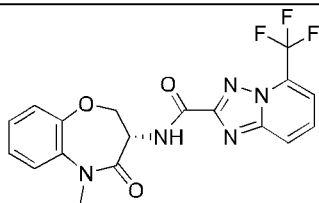
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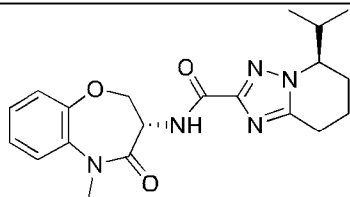
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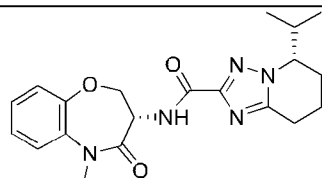
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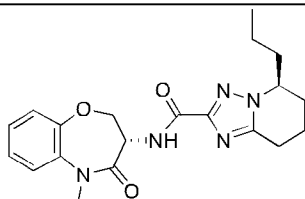
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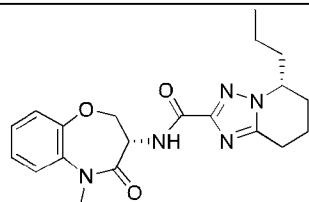
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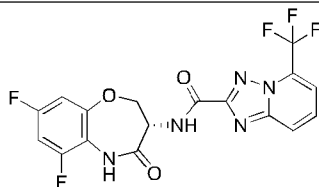
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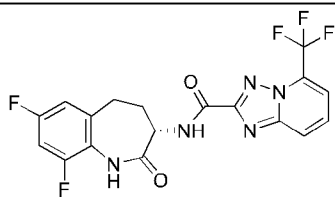
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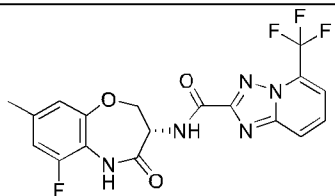
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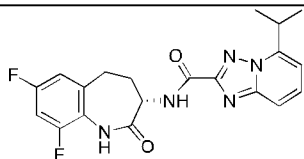
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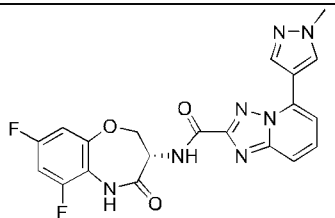
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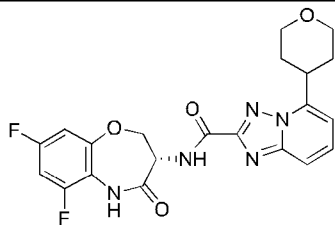
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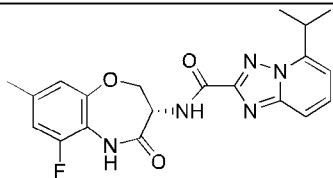
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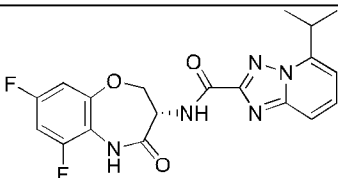
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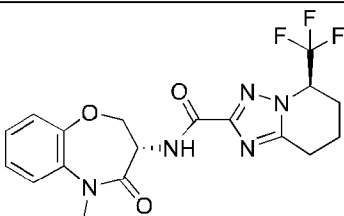
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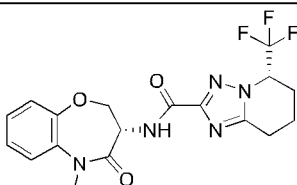
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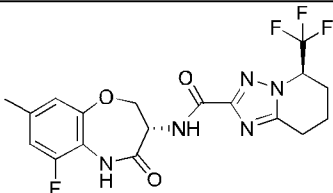
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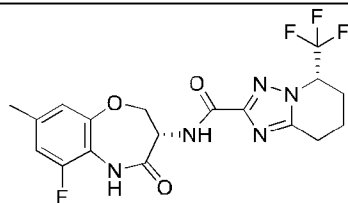
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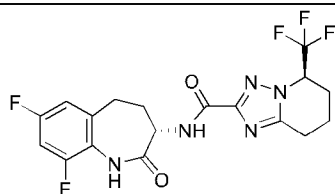
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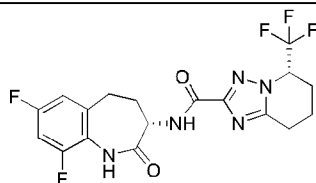
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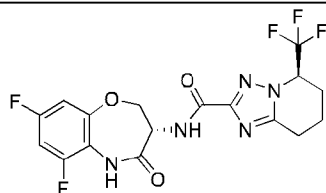
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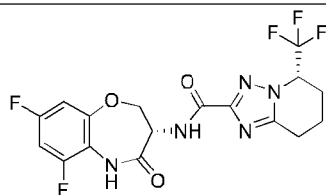
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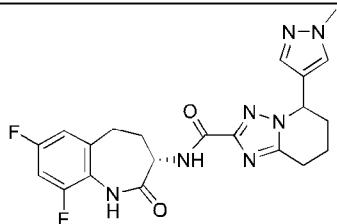
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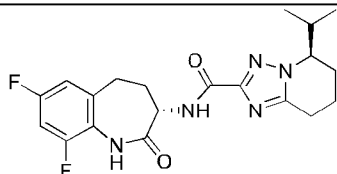
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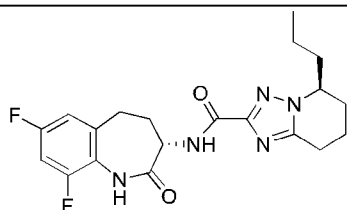
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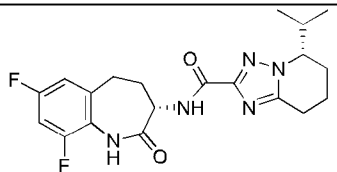
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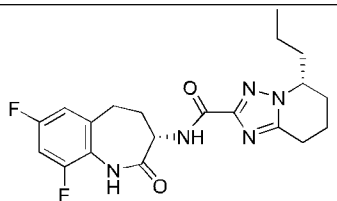
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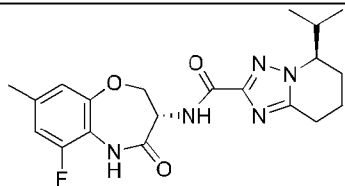
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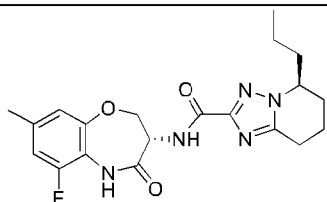
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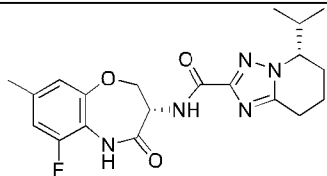
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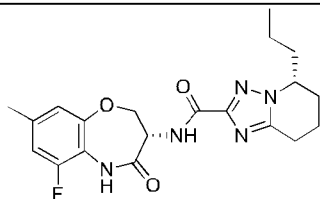
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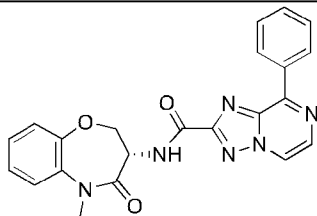
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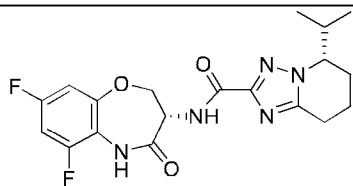
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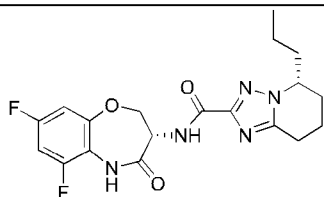
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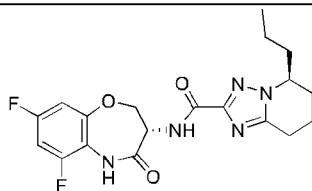
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-8-phenyl-[1,2,4]triazolo[1,5-a]pyrazine-2-carboxamide



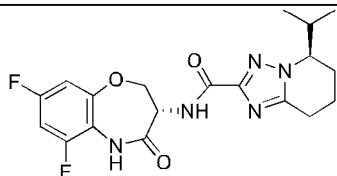
(5S)-N-[(3S)-6,8-difluoro-4-oxo-3,5-dihydro-2H-1,5-benzoxazepin-3-yl]-5-isopropyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-2-carboxamide



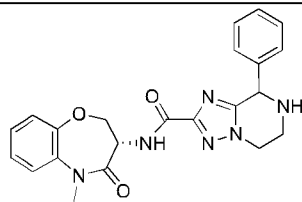
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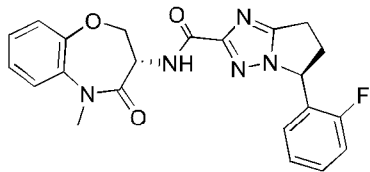
(5S)-N-[(3S)-6,8-difluoro-4-oxo-3,5-dihydro-2H-1,5-benzoxazepin-3-yl]-5-propyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-2-carboxamide



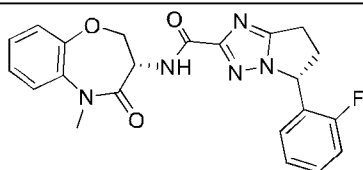
(5R)-N-[(3S)-6,8-difluoro-4-oxo-3,5-dihydro-2H-1,5-benzoxazepin-3-yl]-5-isopropyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-2-carboxamide



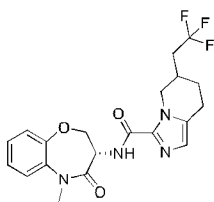
8-phenyl-N-[rac-(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine-2-carboxamide



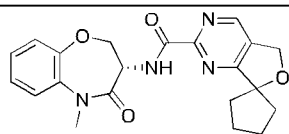
(S)-5-(2-fluorophenyl)-N-((S)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



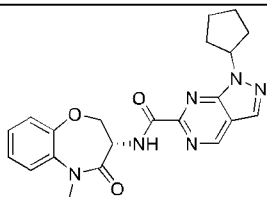
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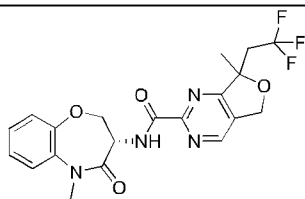
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-6-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-3-carboxamide



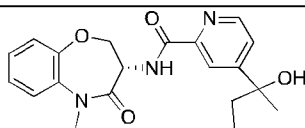
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]spiro[5H-furo[3,4-d]pyrimidine-7,1'-cyclopentane]-2-carboxamide



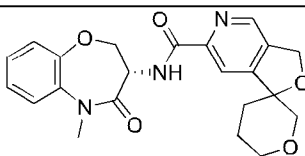
1-cyclopentyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]pyrazolo[3,4-d]pyrimidine-6-carboxamide



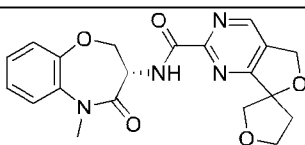
7-methyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-7-(2,2,2-trifluoroethyl)-5H-furo[3,4-d]pyrimidine-2-carboxamide



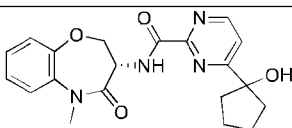
4-(1-hydroxy-1-methyl-propyl)-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]pyridine-2-carboxamide



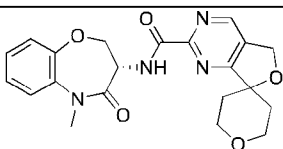
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]spiro[3H-furo[3,4-c]pyridine-1,3'-tetrahydropyran]-6-carboxamide



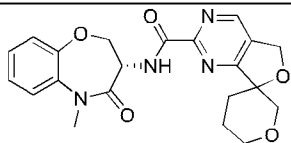
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]spiro[5H-furo[3,4-d]pyrimidine-7,3'-tetrahydrofuran]-2-carboxamide



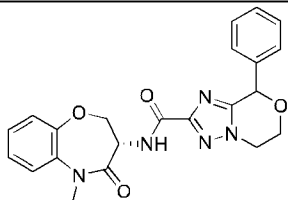
4-(1-hydroxycyclopentyl)-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]pyrimidine-2-carboxamide



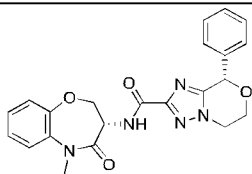
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]spiro[5H-furo[3,4-d]pyrimidine-7,4'-tetrahydropyran]-2-carboxamide



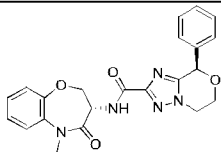
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]spiro[5H-furo[3,4-d]pyrimidine-7,3'-tetrahydropyran]-2-carboxamide



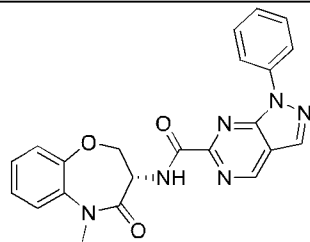
8-phenyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazine-2-carboxamide



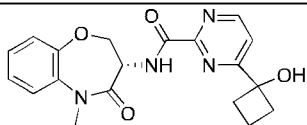
(8S)-8-phenyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazine-2-carboxamide



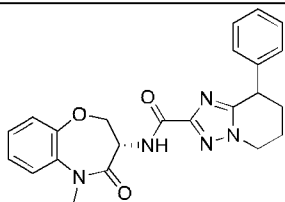
(8R)-8-phenyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazine-2-carboxamide



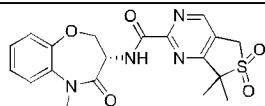
1-phenyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]pyrazolo[3,4-d]pyrimidine-6-carboxamide



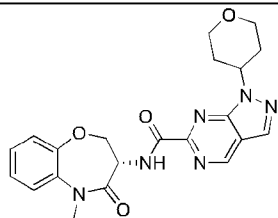
4-(1-hydroxycyclobutyl)-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]pyrimidine-2-carboxamide



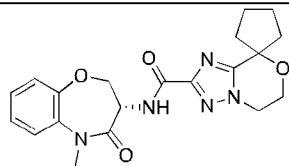
8-phenyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-2-carboxamide



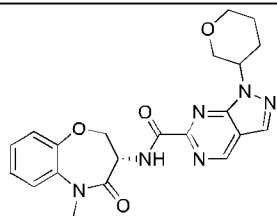
7,7-dimethyl-6,6-dioxo-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5H-thieno[3,4-d]pyrimidine-2-carboxamide



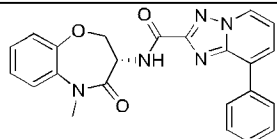
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1-tetrahydropyran-4-yl-pyrazolo[3,4-d]pyrimidine-6-carboxamide



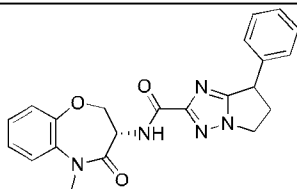
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]spiro[5,6-dihydro-[1,2,4]triazolo[5,1-c][1,4]oxazine-8,1'-cyclopentane]-2-carboxamide



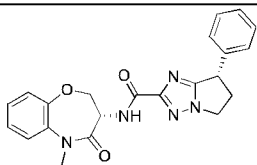
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-1-tetrahydropyran-3-yl-pyrazolo[3,4-d]pyrimidine-6-carboxamide



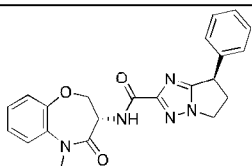
8-phenyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-[1,2,4]triazolo[1,5-a]pyridine-2-carboxamide



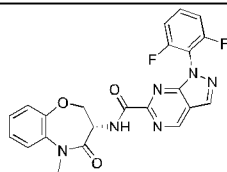
7-phenyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



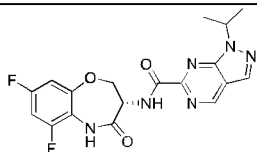
(7S)-7-phenyl-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



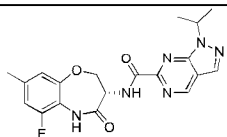
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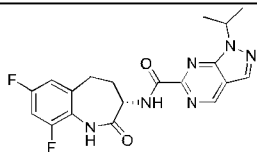
1-(2,6-difluorophenyl)-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]pyrazolo[3,4-d]pyrimidine-6-carboxamide



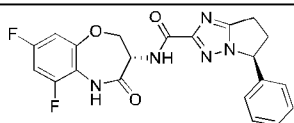
1-isopropyl-N-[(3S)-6,8-difluoro-4-oxo-3,5-dihydro-2H-1,5-benzoxazepin-3-yl]pyrazolo[3,4-d]pyrimidine-6-carboxamide



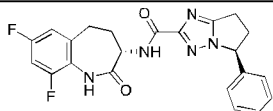
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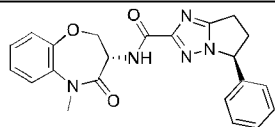
1-isopropyl-N-[(3S)-7,9-difluoro-2-oxo-1,3,4,5-tetrahydro-1-benzazepin-3-yl]pyrazolo[3,4-d]pyrimidine-6-carboxamide



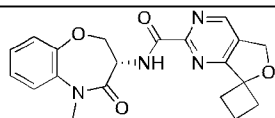
(5S)-5-phenyl-N-[(3S)-6,8-difluoro-4-oxo-3,5-dihydro-2H-1,5-benzoxazepin-3-yl]-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



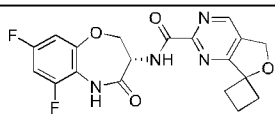
(5S)-5-phenyl-N-[(3S)-7,9-difluoro-2-oxo-1,3,4,5-tetrahydro-1-benzazepin-3-yl]-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



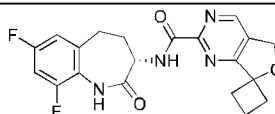
rac-(5S)-5-phenyl-N-[rac-(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



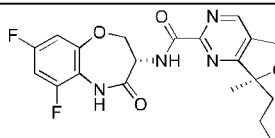
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]spiro[5H-furo[3,4-d]pyrimidine-7,1'-cyclobutane]-2-carboxamide



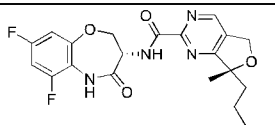
N-[(3S)-6,8-difluoro-4-oxo-3,5-dihydro-2H-1,5-benzoxazepin-3-yl]spiro[5H-furo[3,4-d]pyrimidine-7,1'-cyclobutane]-2-carboxamide



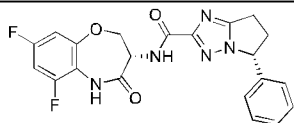
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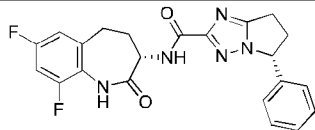
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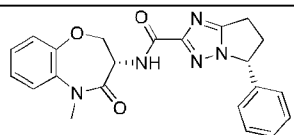
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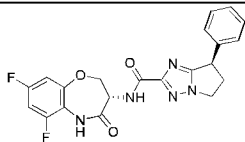
(5R)-5-phenyl-N-[(3S)-6,8-difluoro-4-oxo-3,5-dihydro-2H-1,5-benzoxazepin-3-yl]-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



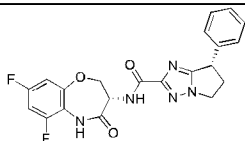
(5R)-5-phenyl-N-[(3S)-7,9-difluoro-2-oxo-1,3,4,5-tetrahydro-1-benzazepin-3-yl]-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



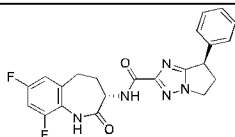
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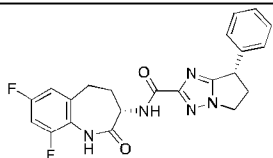
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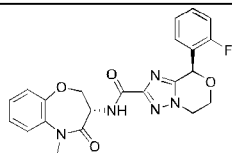
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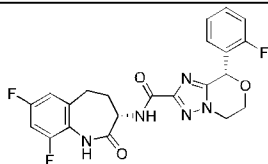
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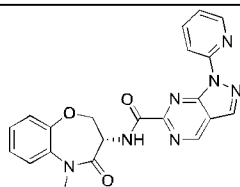
(7S)-7-phenyl-N-[(3S)-7,9-difluoro-2-oxo-1,3,4,5-tetrahydro-1-benzazepin-3-yl]-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



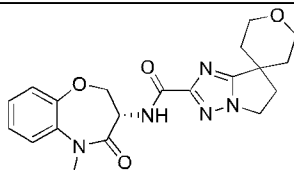
(8R)-8-(2-fluorophenyl)-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazine-2-carboxamide



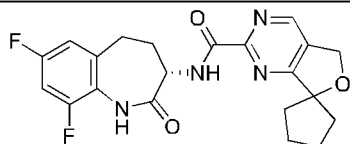
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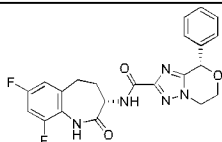
1-(2-pyridyl)-N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]pyrazolo[3,4-d]pyrimidine-6-carboxamide



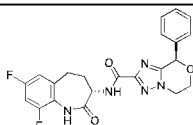
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]spiro[5,6-dihydropyrrolo[1,2-b][1,2,4]triazole-7,4'-tetrahydropyran]-2-carboxamide



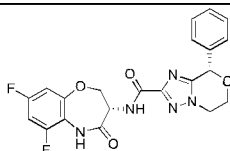
N-[(3S)-7,9-difluoro-2-oxo-1,3,4,5-tetrahydro-1-benzazepin-3-yl]spiro[5H-furo[3,4-d]pyrimidine-7,1'-cyclopentane]-2-carboxamide



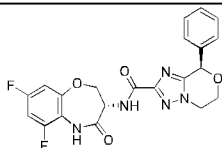
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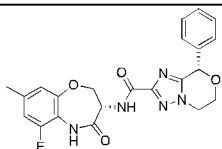
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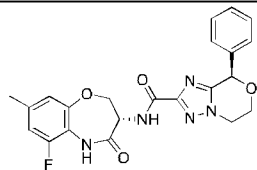
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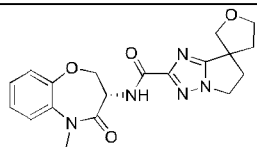
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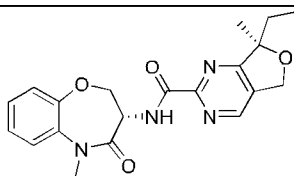
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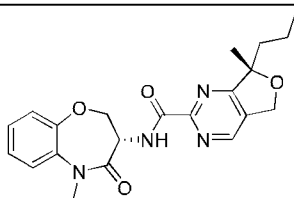
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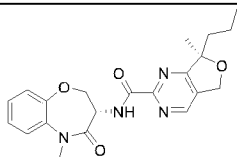
N-[(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]spiro[5,6-dihydropyrrolo[1,2-b][1,2,4]triazole-7,3'-tetrahydrofuran]-2-carboxamide



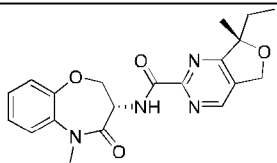
(7R)-7-ethyl-7-methyl-N-[rac-(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5H-furo[3,4-d]pyrimidine-2-carboxamide



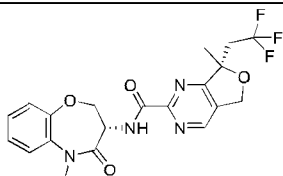
(7S)-7-methyl-7-propyl-N-[rac-(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5H-furo[3,4-d]pyrimidine-2-carboxamide



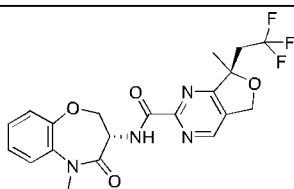
rac-(7R)-7-methyl-7-propyl-N-[rac-(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5H-furo[3,4-d]pyrimidine-2-carboxamide



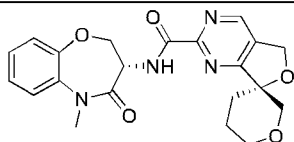
rac-(7S)-7-ethyl-7-methyl-N-[rac-(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-5H-furo[3,4-d]pyrimidine-2-carboxamide



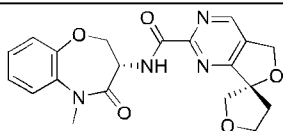
rac-(7S)-7-methyl-N-[rac-(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-7-(2,2,2-trifluoroethyl)-5H-furo[3,4-d]pyrimidine-2-carboxamide



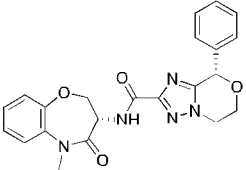
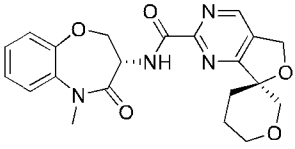
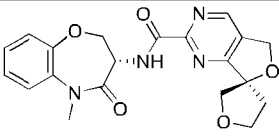
rac-(7R)-7-methyl-N-[rac-(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-7-(2,2,2-trifluoroethyl)-5H-furo[3,4-d]pyrimidine-2-carboxamide



rac-(7R)-N-[rac-(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]spiro[5H-furo[3,4-d]pyrimidine-7,3'-tetrahydropyran]-2-carboxamide



rac-(7S)-N-[rac-(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]spiro[5H-furo[3,4-d]pyrimidine-7,3'-tetrahydrofuran]-2-carboxamide

 rac-(8S)-8-phenyl-N-[rac-(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazine-2-carboxamide
 rac-(7S)-N-[rac-(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]spiro[5H-furo[3,4-d]pyrimidine-7,3'-tetrahydropyran]-2-carboxamide or
 rac-(7R)-N-[rac-(3S)-5-methyl-4-oxo-2,3-dihydro-1,5-benzoxazepin-3-yl]spiro[5H-furo[3,4-d]pyrimidine-7,3'-tetrahydrofuran]-2-carboxamide;
or a pharmaceutically acceptable salt thereof.

16. The compound or salt according to claim 15, wherein the compound has a K_i in the RIP1 kinase inhibitory assay of less than or equal to 0.1 μM .

5 17. A compound as defined in any one of claims 1-16, or a pharmaceutically acceptable salt thereof, for use as a therapeutically active substance.

18. A pharmaceutical composition comprising: a compound as defined in any one of claims 1-16, or a pharmaceutically acceptable salt thereof; and a therapeutically inert carrier.

10

19. A use of a compound as defined in any one of claims 1-16, or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of a disease or disorder selected from the group consisting of inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia-reperfusion injury of kidney,

liver or lungs, cisplatin-induced kidney injury, sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa, retinal degeneration, chronic kidney disease, acute respiratory distress syndrome (ARDS), and chronic obstructive pulmonary disease (COPD).

5 20. A use of a compound as defined in any one of claims 1-16, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder selected from the group consisting of inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia-reperfusion injury of kidney, liver or lung, cisplatin-induced kidney injury, sepsis, systemic
10 inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa, retinal degeneration, chronic kidney disease, acute respiratory distress syndrome (ARDS), and chronic obstructive pulmonary disease (COPD).

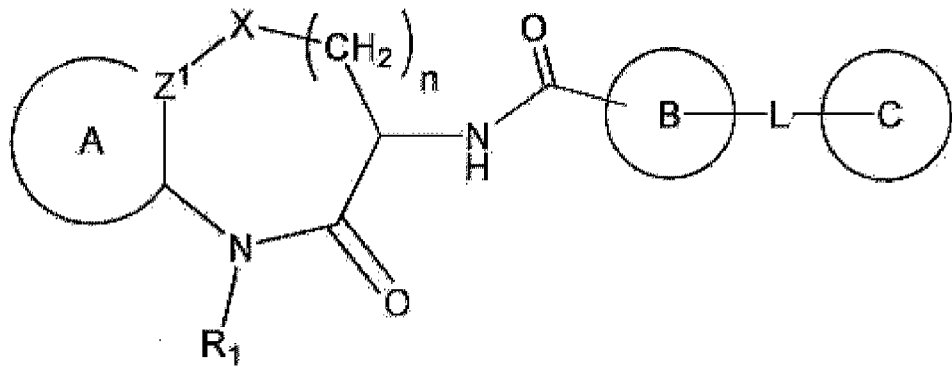
15 21. The use according to claim 19 or 20, wherein the disease or disorder is inflammatory bowel disease (IBD).

22. The use according to any one of claims 19-21, for said treatment.

20 23. A compound according to any one of claims 1-16, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of a disease or disorder selected from the group consisting of inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia-reperfusion injury of kidney, liver or lung, cisplatin-induced kidney injury, sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa, retinal degeneration, chronic kidney disease, acute respiratory
25 distress syndrome (ARDS), and chronic obstructive pulmonary disease (COPD).

24. The compound or salt for use according to claim 23, wherein the disease or disorder is inflammatory bowel disease (IBD).

30 25. The compound or salt for use according to claim 23 or 24, for said treatment.



(I)