

TRICYCLIC COMPOUNDS, PREPARATION THEREOF AND THERAPEUTIC
USES AS ERK5 INHIBITORS

Compounds are provided which can inhibit ERK5. Also provided are pharmaceutical compositions and medical uses of the same, including the use in treating or preventing conditions such as cancers.

SUMMARY

The mitogen-activated protein kinase (MAPK) cascade is a highly-conserved cellular pathway which transmits signals from the cell surface to the nucleus. The pathway plays an important role in cell proliferation, differentiation, and migration and it is well known to be involved in the development of cancer. Proteins in the pathway include the extracellular signal-regulated kinase (ERK) proteins; among those, ERK5 (expressed from the *MAPK7* gene) plays an important role in cell proliferation, as well as epithelial development and neural differentiation (see, e.g., Nishimoto *et al.*, EMBO Reports (2006) 7(8):782-786). ERK5 is unique among the ERK proteins, having a large C-terminal domain which contains a transcriptional activation domain (TAD) as well as a nuclear localization signal and two proline-rich regions (see, e.g., Guo *et al.*, Exp Ther Med. (2020) 19:1997-2007). Autophosphorylation of the TAD is required for transcriptional activation (see, e.g., Morimoto *et al.*, J Biol Chem. (2007) 282(49):35449-35456).

ERK5 plays an important role in controlling cell proliferation and cell cycle progression, for example via direct or indirect phosphorylation of MEF2C, cMYC, SGK1, RSK, FOS, and FRA1 among others (see, e.g., Paudel *et al.*, Int J Mol Sci. (2021) 22:7594-7614; Terasawa *et al.*, Genes to Cells (2003) 8(3):263-273). The involvement of ERK5 in numerous biological pathways means that its activity is associated with many aspects of cancer progression, including tumour angiogenesis, metastasis, inflammation, sustained proliferation, and evasion of growth suppression. It therefore presents an attractive target for modulating disease pathology and treatment in a wide range of conditions. In previous studies, ERK5 inhibition or down-regulation has been shown to block tumorigenesis in murine leukaemia cells, reduce growth of chronic myeloid leukaemia cells, inhibit growth of breast cancer and multiple myeloma cells, suppress colon cancer cell proliferation, and have to have an impact on renal cell carcinoma, mesothelioma, adenocarcinoma, neuroblastoma and hepatocellular carcinoma cell growth or survival, among others (see, e.g., Stecca *et al.*, Int J Mol Sci. (2019) 20:1426-1446).

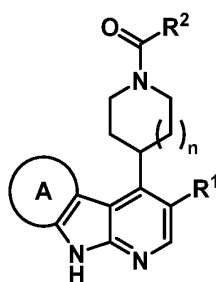
ERK5 inhibition thus represents a promising approach to tackle a broad range of cancers. Several ERK5 inhibitors have been developed and some are under clinical review. For

example, WO 2019/170543 (Bayer AG and Bayer Pharma AG) discloses compounds which are said to be active as ERK5 inhibitors in the μM to nM concentration range.

Despite recent progress in cancer treatment with the development of targeted therapies and immunotherapies, not all cancer patients can be offered an efficient therapeutic solution.

- 5 There is therefore a need to identify and develop new drugs. The present disclosure seeks to address this need by providing novel compounds for use as ERK5 inhibitors and for the treatment of ERK5 related diseases and conditions.

Accordingly, a first aspect provides a compound, being of Formula (I)



Formula (I)

- 10 or a pharmaceutically acceptable salt thereof, wherein:

ring A is (C₅-C₈)cycloalkane, (C₆-C₈)cycloalkene, or 5- to 8-membered heterocycloalkane, wherein ring A is optionally substituted with one or more occurrences of R^A,

wherein R^A at each occurrence is:

- 15 (a) independently selected from -D, halo, -OH, oxo, =N-OH, -NHR['], -CN, -C(O)R^{''}, -(C₁-C₃)alkyl, -O(C₁-C₃)alkyl, -(C₃-C₆)cycloalkyl, and 3- to 6-membered heterocycloalkyl, wherein each occurrence of -(C₁-C₃)alkyl is optionally substituted with one or more groups selected from halo and -OH,

- 20 wherein each R['] is selected from -H, -(C₁-C₃)alkyl optionally substituted with one or more halo, -(C₃-C₄)cycloalkyl, and 3- to 4-membered heterocycloalkyl,

wherein each R^{''} is selected from -OH, -O(C₁-C₃)alkyl, and -(C₁-C₃)alkyl (e.g. -CH₃); and/or

- 25 (b) taken together with another occurrence of R^A and the intervening atom(s) to form a (C₄-C₇)cycloalkyl or 4- to 7-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring and said cycloalkyl ring are optionally substituted by one or more groups selected from oxo, -C(O)OH, -C(O)N((C₁-C₃)alkyl)₂, and -(C₁-C₃)alkyl;

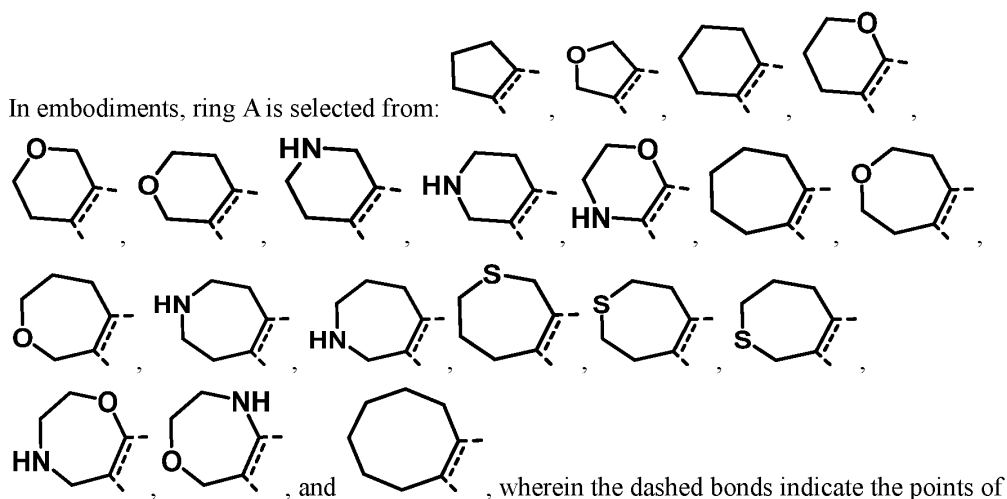
R^1 is selected from -H, and halo (e.g., -F);

R^2 is $-(C_6-C_{10})$ aryl, wherein R^2 is substituted with one, or two occurrences of R^B , wherein each R^B is independently selected from halo, -OH, -NH₂, -SF₅, $-(C_1-C_3)$ alkyl, and $-O(C_1-C_3)$ alkyl, wherein each occurrence of $-(C_1-C_3)$ alkyl and $-O(C_1-C_3)$ alkyl is optionally substituted by one or more halo; and

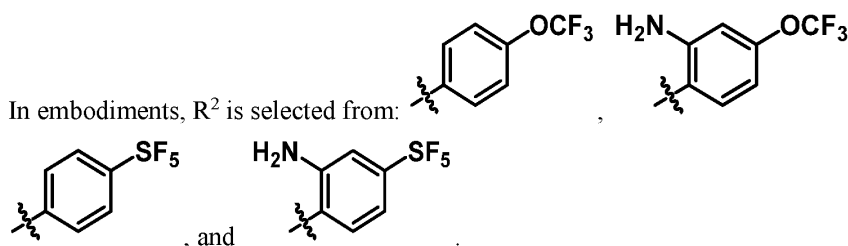
n is 0, 1, or 2,

with the proviso that when R^2 is 4-(pentafluorosulfanyl)phenyl, R^1 is -H, and n is 1, then ring A is not unsubstituted cyclopentane.

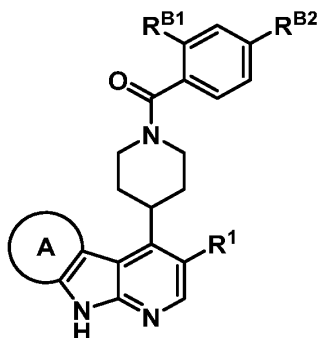
In embodiments, ring A is selected from cyclopentane, cyclohexane, cycloheptane, cyclooctane, tetrahydrofuran, tetrahydropyran, piperidine, morpholine, oxepane, azepane, 1,4-oxazepane, and thiepane, wherein ring A is optionally substituted with one or more occurrences of R^A as defined hereinbefore.



wherein the dashed bonds indicate the points of fusion to the pyrrole ring, wherein ring A is optionally substituted by one or more occurrences of R^A as defined hereinbefore.



Another aspect provides a compound, being of Formula (II)



Formula (II)

or a pharmaceutically acceptable salt thereof, wherein:

ring A is (C₅-C₈)cycloalkane or 6- to 7-membered heterocycloalkane, wherein ring A is optionally substituted with one or more occurrences of R^A,

5 wherein R^A at each occurrence is:

(a) independently selected from -OH, oxo, -NHR', -C(O)CH₃, -(C₁-C₃)alkyl, and -O(C₁-C₃)alkyl,

10 wherein each R' is selected from -(C₁-C₃)alkyl optionally substituted with one or more halo, -(C₃-C₄)cycloalkyl, and 3- to 4-membered heterocycloalkyl; or

(b) taken together with another occurrence of R^A and the intervening atom(s) to form a (C₅-C₇)cycloalkyl or 4- to 6-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is optionally substituted by oxo;

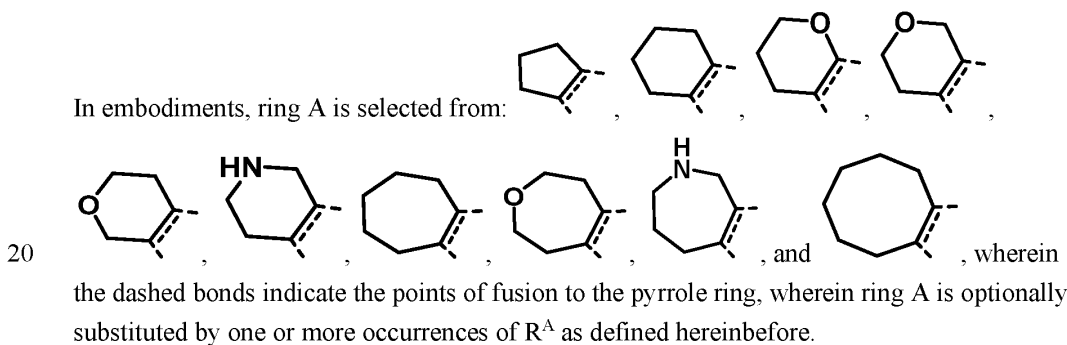
R¹ is selected from -H, and -F;

15 R^{B1} is selected from -H, and -NH₂; and

R^{B2} is selected from -OCF₃, and -SF₅,

with the proviso that when R^{B1} is -H, R^{B2} is -SF₅, and R¹ is -H, then ring A is not unsubstituted cyclopentane.

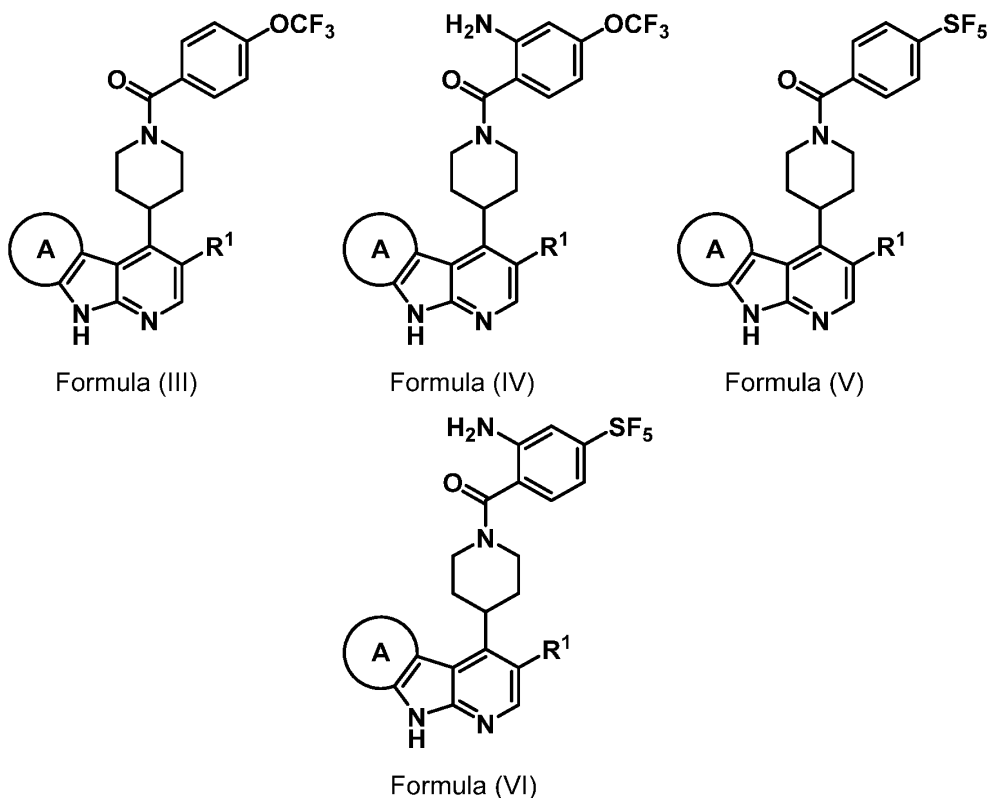
In embodiments, ring A is selected from:



In embodiments, R^{B2} is -OCF₃.

In embodiments, R^1 is -F.

Another aspect provides a compound, being of Formula (III), Formula (IV), Formula (V), or Formula (VI):



5

or a pharmaceutically acceptable salt thereof, wherein ring A and R^1 are as defined hereinbefore, with the proviso that when the compound is a compound of Formula (V) and R^1 is -H, then ring A is not unsubstituted cyclopentane.

A further aspect provides a compound selected from the group consisting of:

- 10
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12R)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-7-hydroxy-6,7,8,9-
 - 15 tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone;
 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-fluoro-5-oxa-8,10-diazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),10,12-tetraen-13-yl)-1-piperidyl]methanone;
 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-oxetane]-4-yl)-1-piperidyl]methanone;

- [4-[(12R)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(12S)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 5 - (rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone;
- 10 - (6R)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
- (6S)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
- 15 - [4-[(3R,8R)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(3S,8S)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(2S, 7S)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-
- 20 1(9),10,12,14-tetraen-11-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(2R, 7R)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone;
- 25 - 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-13-methyl-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13R)-4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13S)-4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- 30 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-6,8-diazatricyclo[7.6.0.02,7]pentadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6R)-3-fluoro-6-(1-hydroxy-1-methylethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 35 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6S)-3-fluoro-6-(1-hydroxy-1-methylethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methylethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;

- (7R)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile;
- (7S)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile;
- 5 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-1'-methyl-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6E)-3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6Z)-3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 10 - [4-[(5R)-3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(5S)-3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 15 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7E)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7Z)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12E)-4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 20 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12Z)-4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
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- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(5R)-3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(5S)-3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 30 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(3R,8R)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.0.3,8.0.11,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone;
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- 35 -

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2R,7R)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone;
- 5 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2S,7S)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone;
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- [4-[(6R)-3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 15 - [4-[(6S)-3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6R)-3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
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- 20 - [4-[(12R)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(12S)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 25 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7R)-3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7S)-3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 1-[4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-yl]methanone;
- 30 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13R)-4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13S)-4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 35 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;

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- 4-fluoro-11,11-dimethyl-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one;
- [4-[(6R)-6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 10 - [4-[(6S)-6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6R)-3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 15 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6S)-3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [4-[(7E)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(7Z)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 20 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(11R,15S)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(11S,15R)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 25 - (6R)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
- (6S)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
- 30 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12R)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- 35 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12R)-12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone; and

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone,

and the pharmaceutically acceptable salts thereof.

- 5 A further aspect provides a pharmaceutical composition comprising the compound defined hereinbefore and at least one pharmaceutically acceptable excipient or carrier.

A further aspect provides a compound, or a pharmaceutical composition, as defined hereinbefore for use in therapy.

- A further aspect provides a compound, or a pharmaceutical composition, as defined
10 hereinbefore for use in the treatment or prevention of cancer.

In embodiments, the cancer is characterized by increased *MAPK7* expression and/or increased ERK5 activity.

- In embodiments, the cancer is selected from leukaemia, breast cancer, multiple myeloma, colon cancer, colorectal cancer, lung cancer, pancreatic cancer, renal cell carcinoma,
15 mesothelioma, adenocarcinoma, neuroblastoma, melanoma, and hepatocellular carcinoma.

DETAILED DESCRIPTION

- Although specific embodiments of the present disclosure will now be described with reference to the description and examples, it should be understood that such embodiments are
20 by way of example only and merely illustrative of but a small number of the many possible specific embodiments which can represent applications of the principles of the present disclosure. Various changes and modifications will be obvious to those of skill in the art given the benefit of the present disclosure and are deemed to be within the spirit and scope of the present disclosure as further defined in the appended claims.

25 Definitions

- Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, exemplary methods, devices,
30 and materials are now described. All technical and patent publications cited herein are incorporated herein by reference in their entirety.

- The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of chemical synthesis, tissue culture, immunology, molecular biology, microbiology, cell biology, recombinant DNA, etc., which are within the skill of the art. See, e.g., Michael R. Green and Joseph Sambrook, *Molecular Cloning* (4th ed., Cold Spring Harbor Laboratory Press 2012); the series Ausubel *et al.* eds. (2007) *Current Protocols in Molecular Biology*; the series *Methods in Enzymology* (Academic Press, Inc., N.Y.); MacPherson *et al.* (1991) *PCR 1: A Practical Approach* (IRL Press at Oxford University Press); MacPherson *et al.* (1995) *PCR 2: A Practical Approach*; Harlow and Lane eds. (1999) *Antibodies, A Laboratory Manual*; Freshney (2005) *Culture of Animal Cells: A Manual of Basic Technique*, 5th edition; Gait ed. (1984) *Oligonucleotide Synthesis*; U.S. Patent No. 4,683,195; Hames and Higgins eds. (1984) *Nucleic Acid Hybridization*; Anderson (1999) *Nucleic Acid Hybridization*; Hames and Higgins eds. (1984) *Transcription and Translation: Immobilized Cells and Enzymes* (IRL Press (1986)); Perbal (1984) *A Practical Guide to Molecular Cloning*; Miller and Calos eds. (1987) *Gene Transfer Vectors for Mammalian Cells* (Cold Spring Harbor Laboratory); Makrides ed. (2003) *Gene Transfer and Expression in Mammalian Cells*; Mayer and Walker eds. (1987) *Immunochemical Methods in Cell and Molecular Biology* (Academic Press, London); Herzenberg *et al.* eds (1996) *Weir's Handbook of Experimental Immunology*; *Manipulating the Mouse Embryo: A Laboratory Manual*, 3rd edition (Cold Spring Harbor Laboratory Press (2002)); Sohail (ed.) (2004) *Gene Silencing by RNA Interference: Technology and Application* (CRC Press).

- All numerical designations, e.g., pH, temperature, time, concentration, molecular weight, etc., including ranges, are approximations which are varied (+) or (-) by increments of, e.g., 0.1 or 1.0, where appropriate. It is to be understood, although not always explicitly stated, that all numerical designations are preceded by the term “about”, which is used to denote a conventional level of variability. For example, a numerical designation which is “about” a given value may vary by $\pm 10\%$ of said value; alternatively, the variation may be $\pm 5\%$, $\pm 2\%$, or $\pm 1\%$ of the value. It also is to be understood, although not always explicitly stated, that the reagents described herein are merely exemplary and that equivalents of such are known in the art.

- As used in the specification and claims, the singular forms “a”, “an”, and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a cell” includes a plurality of cells, including mixtures thereof. Unless specifically stated or obvious from context, as used herein, the term “or” is understood to be inclusive. The term “including” is used herein to mean, and is used interchangeably with, the phrase “including but not limited to”.

As used herein, the term “comprising” or “comprises” is intended to mean that the compositions and methods include the recited elements, without excluding other elements.

“Consisting essentially of” when used to define compositions and methods, shall mean excluding other elements of any essential significance for the stated purpose. Thus, a composition consisting essentially of the elements as defined herein would not exclude trace contaminants from the isolation and purification method and pharmaceutically acceptable carriers, such as phosphate buffered saline, preservatives, and the like. “Consisting of” shall mean excluding more than trace elements of other ingredients and substantial method steps for administering the compositions of this disclosure or process steps to produce a composition or achieve an intended result. Embodiments defined by each of these transition terms are within the scope of this disclosure. Use of the term “comprising” herein is intended to encompass, and to disclose, the corresponding statements in which the term “comprising” is replaced by “consisting essentially of” or “consisting of”.

A “subject,” “individual”, or “patient” is used interchangeably herein, and refers to a vertebrate, such as a mammal. Mammals include, but are not limited to, rodents, farm animals, sport animals, pets, and primates; for example murines, rats, rabbit, simians, bovines, ovines, porcines, canines, felines, equines, and humans. In a particular embodiment, the mammal is a human.

“Administering” is defined herein as a means of providing an agent or a composition containing the agent to a subject in a manner that results in the agent being contacted with (e.g., being inside) the subject’s body. Such an administration can be by any route including, without limitation, oral, transdermal (e.g., by the vagina, rectum, or oral mucosa), by injection (e.g., subcutaneous, intravenous, parenteral, intraperitoneal, or into the central nervous system), or by inhalation (e.g., oral or nasal). Administration may also involve providing a substance or composition to a part of the surface of the subject’s body, for example by topical administration to the skin. Pharmaceutical preparations are, of course, given by forms suitable for each administration route.

“Treating” or “treatment” of a disease includes: (1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a patient that may be predisposed to the disease but does not yet experience or display symptoms of the disease; (2) inhibiting the disease, i.e. arresting or reducing the development of the disease or its clinical symptoms; and/or (3) relieving the disease, i.e. causing regression of the disease or its clinical symptoms.

The term “suffering” as it relates to the term “treatment” refers to a patient or individual who has been diagnosed with or is predisposed to the disease. A patient may also be referred to being “at risk of suffering” from a disease because of a history of disease in their family lineage or because of the presence of genetic mutations associated with the disease. A patient at risk of a disease has not yet developed all or some of the characteristic pathologies of the disease.

An "effective amount" or "therapeutically effective amount" is an amount sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications, or dosages. Such delivery is dependent on a number of variables including the time period for which the individual dosage unit is to be used, the bioavailability of the therapeutic agent, the route of administration, etc. It is understood, however, that specific dose levels of the therapeutic agents of the present disclosure for any particular subject depends upon a variety of factors including, for example, the activity of the specific compound employed, the age, body weight, general health, sex, and diet of the subject, the time of administration, the rate of excretion, the drug combination, the severity of the particular disorder being treated and the form of administration. Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from *in vitro* and/or *in vivo* tests initially can provide useful guidance on the proper doses for patient administration. In general, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with the concentrations found to be effective *in vitro*. Determination of these parameters is well within the skill of the art. These considerations, as well as effective formulations and administration procedures are well known in the art and are described in standard textbooks. Consistent with this definition, as used herein, the term "therapeutically effective amount" is an amount sufficient to treat (e.g., improve) one or more symptoms associated with the condition. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein.

As used herein, the terms "increased" and "elevated" are used interchangeably and encompass any measurable increase in a biological function and/or a biological activity and/or a concentration. For example, an increase can be by at least about 10%, e.g. at least about 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, such as at least about 95%, 96%, 97%, 98%, 99%, or 100%. Thus, an increase can be by at least about 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, or 10-fold, such as at least about 20-fold, 25-fold, 50-fold, 100-fold, or higher, relative to a control or baseline amount or function, or activity, or concentration.

As used herein, the terms "increased expression" and/or "increased activity" of a substance, such as ERK5, in a sample or cancer or patient, typically refers to an increase in the amount of the substance (e.g., of the *MAPK7* gene product or ERK5 protein), although it may also denote an increase in the biological activity of the substance (e.g., constitutive activation of phosphorylation and/or reduced discrimination of phosphorylation sites of ERK5). For example, an increase can be by an amount of about 5%, e.g., about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, such as about 96%, 97%, 98%, 99%, or 100%. Thus, the increase can be about 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, or 10-fold, such as about 20-fold, 25-fold, 50-fold, 100-

fold, or higher, relative to the amount (or activity) of the substance, such as ERK5, in a control sample or control samples, such as an individual or group of individuals who are not suffering from the disease or disorder (e.g. cancer) or an internal control, as determined by techniques known in the art. A subject can also be determined to have an "increased expression" or "increased activity" of ERK5 if the expression and/or activity of ERK5 is increased by one standard deviation, two standard deviations, three standard deviations, four standard deviations, five standard deviations, or more, relative to the mean (average) or median amount of ERK5 in a control group of samples or a baseline group of samples or a retrospective analysis of patient samples. As practiced in the art, such control or baseline expression levels can be previously determined, or measured prior to the measurement in the sample or cancer or subject, or can be obtained from a database of such control samples.

As used herein, the term "pharmaceutically acceptable excipient" encompasses any of the standard pharmaceutical excipients, for example as described in Remington's Pharmaceutical Sciences (20th ed., Mack Publishing Co. 2000). Such excipients include carriers such as a phosphate buffered saline solution, water, and emulsions, such as an oil/water or water/oil emulsion, and various types of wetting agents. Pharmaceutical compositions also can include stabilizers, preservatives, adjuvants, fillers, binders, lubricants, and the like.

As used herein, the term "alkyl" means a saturated linear or branched free radical consisting essentially of carbon atoms and a corresponding number of hydrogen atoms. Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, etc. Other alkyl groups will be readily apparent to those of skill in the art given the benefit of the present disclosure. The terms "(C₁-C₃)alkyl", "(C₁-C₆)alkyl", etc., have equivalent meanings, i.e., a saturated linear or branched free radical consisting essentially of 1 to 3 (or 1 to 6) carbon atoms and a corresponding number of hydrogen atoms. The definition of "alkyl" also applies in the context of other groups which comprise alkyl groups, such as "-O(C₁-C₃)alkyl". The term "haloalkyl" means an alkyl group which is substituted by one or more halogens. Exemplary haloalkyl groups include trifluoromethyl, trifluoroethyl, difluoroethyl, pentafluoroethyl, chloromethyl, etc. One or more carbon atoms in the backbone of the alkyl group may be substituted by (or bonded to) a heteroatom by a multiple bond (e.g., a double bond); for example, a carbon atom of the alkyl group may be bonded to oxygen via a double bond (i.e., substituted by oxo to provide a carbonyl function). The presence of such a substituent does not prevent the carbon backbone of the free radical being considered as an alkyl group.

As used herein, the term "cyclic group" means a saturated, partially or fully unsaturated, or aromatic group having at least 3 to 10 atoms (i.e., ring atoms) that form a ring. Where a cyclic group is defined as having a certain number of members, the term "members", "membered" and the like is used to denote the number of ring atoms in said cyclic group. For example, a 5-membered cyclic group (e.g., a 5-membered heterocyclic group) contains 5 ring

- atoms. It will be appreciated that a cyclic group may be part of a larger cyclic system; for example, bicyclo[4.3.0]nonane comprises two carbocyclic groups, namely a cyclohexane group and a cyclopentane group, which are fused to form the carbocyclic system which makes up the molecule. The term “cyclic group” is intended to encompass both carbocyclic groups as well as heterocyclic groups. The term “carbocyclic” refers to a group having at least 3 to 9 carbon atoms that form a ring. The term “heterocyclic” refers to a group having at least 3 to 10 atoms that form a ring, wherein at least 1 to 9 of said ring atoms are carbon and the remaining at least 1 to 9 ring atom(s) (i.e., hetero ring atom(s)) are selected independently from the group consisting of nitrogen, sulphur, and oxygen.
- 10 The term “spiro” or “spirocyclic” as used herein in relation to cyclic groups denotes that a first cyclic group within a multicyclic system is attached to a second cyclic group within said multicyclic system, wherein the ring atoms of said first cyclic group and the ring atoms of said second cyclic group have only one atom in common, i.e., said first and second cyclic groups share only one common ring atom. For example, the spiro[5.5]undecanyl group
- 15 comprises two cyclohexyl rings which have a single carbon ring atom in common.

- The term “fused” as used herein in relation to cyclic groups denotes that a first cyclic group within a multicyclic system is attached to a second cyclic group within said multicyclic system, wherein the ring atoms of said first cyclic group and the ring atoms of said second cyclic group have two adjacent atoms in common, i.e., said first and second cyclic groups share two common ring atoms. For example, the bicyclo[4.4.0]decanyl group comprises two cyclohexyl rings which have two adjacent carbon ring atoms in common.
- 20

- The term “bridged” as used herein in relation to cyclic groups denotes that a first cyclic group within a multicyclic system is attached to a second cyclic group within said multicyclic system, wherein the ring atoms of said first cyclic group and the ring atoms of said second cyclic group have more than two adjacent atoms in common, i.e., said first and second cyclic groups share three or more common ring atoms. For example, the bicyclo[3.3.1]nonanyl group comprises two cyclohexyl rings which have three adjacent carbon ring atoms in common.
- 25

- Within the structural formulae described herein, any ring system (including any spiro, fused, or bridged ring system) may be connected to other parts of a molecule through any atom having suitable valency. For example, a bicyclic ring may be connected to another part of the molecule through a ring atom (e.g., a secondary carbon atom or heteroatom such as N), or a bridgehead (e.g., a tertiary carbon atom). Spiro, fused, and bridged rings may be fully unsaturated, partially unsaturated, or fully saturated, and may have aromatic character in one or more of their constituent rings.
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As used herein, the term “cycloalkane” means a saturated cyclic group having at least 3 to 9 carbon atoms (i.e., ring atoms) that form a ring moiety, wherein the cycloalkane moiety is fused to another cyclic group. Cycloalkane moieties described herein (e.g., ring A of Formula (I)) are typically fused to aromatic rings (e.g., the pyrrole ring depicted in Formula (I)) through common carbon atoms. The presence of unsaturation (e.g., a bond having aromatic character) in the fused portion does not prevent the cyclic group being considered as a cycloalkane moiety. The term “(C₅-C₈)cycloalkane” means a saturated cyclic group which contains a total of 5, 6, 7, or 8 ring carbon atoms, wherein the cycloalkane moiety is fused to another cyclic group. One or more ring atoms of the cycloalkane group may be substituted by (i.e., bonded to) a heteroatom by a double bond (e.g., cycloalkane substituted by oxo). The presence of such a substituent does not prevent the cyclic group being considered as a cycloalkane moiety. Exemplary cycloalkane moieties include cyclopentane, cyclohexane, cycloheptane, and cyclooctane.

As used herein, the term “cycloalkene” means an unsaturated cyclic group having at least 5 to 9 carbon atoms (i.e., ring atoms) that form a ring moiety, wherein the cycloalkene moiety is fused to another cyclic group. Cycloalkene moieties described herein (e.g., ring A of Formula (I)) are typically fused to aromatic rings (e.g., the pyrrole ring depicted in Formula (I)) through common carbon atoms. The presence of unsaturation (e.g., a bond having aromatic character) in the fused portion is not determinative in considering the cyclic group as a cycloalkene moiety. For the avoidance of doubt, in addition to the bond having unsaturated character in the fused portion, the cycloalkene ring also has additional unsaturation. The term “(C₆-C₈)cycloalkene” means an unsaturated cyclic group which contains a total of 6, 7, or 8 ring carbon atoms, wherein the cycloalkene moiety is fused to another cyclic group. One or more ring atoms of the cycloalkene group may be substituted by (i.e., bonded to) a heteroatom by a double bond (e.g., cycloalkene substituted by oxo). The presence of such a substituent does not prevent the cyclic group being considered as a cycloalkene moiety. An exemplary cycloalkene moiety is cycloheptene.

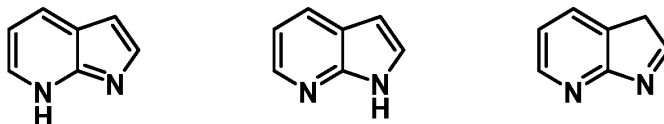
As used herein, the term “cycloalkyl” means a saturated cyclic group (e.g., a saturated free radical) having at least 3 to 9 carbon atoms (i.e., ring atoms) that form a ring. A cycloalkyl group may be a cycloalkyl ring, in which the ring is connected to another cyclic group in a spiro, fused, or bridged configuration, or it may be a cycloalkyl substituent, in which the ring is connected by one exocyclic bond to another atom. For example, a cycloheptane moiety may be substituted by two substituents which taken together form a bridgehead, such that the cycloheptane and the substituents taken together form a bicyclo[3.2.1]octane. The term “(C₄-C₇)cycloalkyl” denotes that the cycloalkyl group contains a total of 4, 5, 6, or 7 carbon atoms in the ring portion of the group, for example cyclohexyl (having 6 ring carbon atoms). One or more ring atoms of the cycloalkyl group may be substituted by (i.e., bonded to) a heteroatom by a double bond (e.g., cycloalkyl substituted by oxo). The presence of such a substituent

does not prevent the cyclic group being considered as a cycloalkyl group. Cycloalkyl groups may be monocyclic or multicyclic (e.g., bicyclic). In embodiments, the cycloalkyl group is monocyclic. Exemplary cycloalkyl groups include cyclopropyl, cyclopentyl, cyclohexyl, and cycloheptyl.

- 5 As used herein, the term “aryl” means an aromatic free radical having at least 6 carbon atoms (i.e., ring atoms) that form a ring. It will be appreciated that the aryl group may be monocyclic or multicyclic (e.g., fused). Examples of aryl groups include phenyl and naphthalenyl. The term “(C₆-C₁₀)aryl” denotes that the aryl group contains from 6 to 10 carbon atoms in the ring portion of the group. In embodiments, (C₆-C₁₀)aryl is phenyl.
- 10 As used herein, the term “heterocycloalkane” means a saturated cyclic group having at least 3 to 10 atoms (i.e., ring atoms) that form a ring moiety, wherein at least 1 to 9 of said ring atoms are carbon and the remaining at least 1 to 9 ring atom(s) (i.e., hetero ring atom(s)) are selected independently from the group consisting of nitrogen, sulphur, and oxygen, wherein the heterocycloalkane moiety is fused to another cyclic group. Heterocycloalkane moieties described herein (e.g., ring A of Formula (I)) are typically fused to aromatic rings (e.g., the pyrrole ring depicted in Formula (I)) through common carbon atoms. The presence of unsaturation (e.g., a bond having aromatic character) in the fused portion does not prevent the cyclic group being considered as a heterocycloalkane moiety. In embodiments, the hetero ring atom(s) are selected independently from the group consisting of nitrogen and oxygen.
- 15 Where a heterocycloalkane moiety is described as being “X- to Y-membered” (where X and Y are integers), this means that the heterocycloalkane moiety contains a total number of ring atoms from X to Y. For example, the term “5- to 8-membered heterocycloalkane” means a saturated cyclic group which contains a total of 5, 6, 7, or 8 ring atoms, of which one or more is a hetero ring atom, wherein the heterocycloalkane moiety is fused to another cyclic group.
- 20 One or more ring atoms of the heterocycloalkane group may be substituted by (i.e., bonded to) a heteroatom by a double bond (e.g., heterocycloalkane substituted by oxo), but the heteroatom does not form part of the ring and is excluded from the number of ring atoms. Such substituents (e.g., oxo groups) are typically located adjacent to a heteroatom (e.g., in the case of 2-oxepanone, also known as caprolactone, or 2-azepanone, also known as caprolactam). Any ring sulphur atom may optionally carry one or more pendant (i.e., non-
- 25 ring) oxygen atoms, as found in, e.g., a sulfolanyl group. The presence of any such substituents do not prevent the cyclic group being considered as a heterocycloalkane moiety. Exemplary heterocycloalkane moieties include tetrahydropyran, piperidine, oxepane, and azepane.
- 30 As used herein, the term “heterocycloalkyl” means a saturated cyclic group (e.g. a saturated free radical) having at least 3 to 10 atoms (i.e., ring atoms) that form a ring, wherein at least 1 to 9 of said ring atoms are carbon and the remaining at least 1 to 9 ring atom(s) (i.e., hetero

- ring atom(s)) are selected independently from the group consisting of nitrogen, sulphur, and oxygen. A heterocycloalkyl group may be a heterocycloalkyl ring, in which the ring is connected to another cyclic group in a spiro, fused, or bridged configuration, or it may be a heterocycloalkyl substituent, in which the ring is connected by one exocyclic bond to another
- 5 atom. In embodiments, the hetero ring atom(s) are selected independently from the group consisting of nitrogen and oxygen. Where a heterocycloalkyl group is described as being “X- to Y-membered” (where X and Y are integers), this means that the heterocycloalkyl group contains a total number of ring atoms from X to Y. For example, the term “4- to 7-membered heterocycloalkyl” means a saturated cyclic group which contains a total of 4, 5, 6, or 7 ring
- 10 atoms, of which one or more is a hetero ring atom, for example tetrahydropyranyl (6 ring atoms). Heterocycloalkyl groups may have oxo substituents, typically adjacent to a heteroatom (e.g., 2-oxopyrrolidinyl), but the oxygen atom of the oxo group does not form part of the ring and is excluded from the number of ring atoms. The presence of such a substituent does not prevent the cyclic group being considered as a heterocycloalkyl group.
- 15 Any ring sulphur atom may optionally carry one or more pendant (i.e., non-ring) oxygen atoms, as found in, e.g., a sulfolanyl group. Heterocycloalkyl groups may be monocyclic or multicyclic (e.g., bicyclic). In embodiments, the heterocycloalkyl group is monocyclic. Exemplary heterocycloalkyl groups include oxetanyl, tetrahydrofuranyl, piperidinyl, and morpholinyl.
- 20 As used herein, the terms “halo” and “halogen” mean fluorine, chlorine, bromine, or iodine. These terms are used interchangeably and may refer to a halogen free radical group or to a halogen atom as such. Those of skill in the art will readily be able to ascertain the identification of which in view of the context in which this term is used in the present disclosure. In embodiments, the halogen is fluorine.
- 25 As used herein, the term “CN” means a free radical having a carbon atom linked to a nitrogen atom via a triple bond. The CN radical is attached via its carbon atom.
- As used herein, the term “oxo” means a free radical wherein an oxygen atom is connected to the atom bearing this radical via a double bond. For example, where a carbon atom carries an oxo radical it forms a carbon-oxygen double bond. It will be appreciated that not all atoms
- 30 within a given structure can be substituted by oxo, and that this will depend on the free valency of the atom to be substituted.
- The compounds of the present disclosure are described, *inter alia*, by way of structural formulae. It will be appreciated that these formulae typically show only one form (e.g., resonance form, tautomeric form, etc.) of the compound, whereas certain compounds may
- 35 exist in more than one such form. This will be readily apparent to the skilled reader. The present disclosure includes all possible tautomers of the compounds characterised by the

structural formulae herein, including as single tautomers, or as any mixture of tautomers in any ratio. For example, a pyrrolopyridine moiety (as shown, e.g., in Formula (I), and which may be referred to as 1H-pyrrolo[2,3-b]pyridine or 7-azaindole) may be illustrated by any of the below tautomeric forms, which are used interchangeably throughout this description:



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It will also be appreciated that certain of the present compounds may exist in one or more isomeric (e.g., stereoisomeric) forms. The present disclosure includes all possible stereoisomers, enantiomers, diastereomers, etc. of the compounds described hereinbefore and below, as well as cis- and trans- forms and conformers of the same. The purification and the separation of isomers may be accomplished by methods described hereinafter, as well as by techniques known in the art. For example, optical isomers of the compounds can be obtained by resolution of the racemic mixture of diastereoisomeric salts thereof (e.g., using an optically active acid or base, or by the formation of covalent diastereomers). A different process for separation of optical isomers involves the use of chiral chromatography (e.g., HPLC columns using a chiral phase), with or without conventional derivatization. Enzymatic separation, with or without derivatisation, may also be useful, and optically active compounds of the present disclosure can likewise be obtained by chiral syntheses utilizing optically active starting materials. The present disclosure includes all possible stereoisomers of the compounds described herein as single stereoisomers, or as any mixture of said stereoisomers, e.g. (R)- or (S)- isomers, in any ratio.

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The compounds of the disclosure may exist in the form of free acids or bases, or may exist as addition salts with suitable acids or bases. Methods for forming salts are described below and are also known in the art (see, e.g., Berge *et al.*, J Pharm Sci. (1977) 66:1-19).

As used herein, the term “pharmaceutically acceptable” when used in connection with salts means a salt of a currently disclosed compound that may be administered without any resultant substantial undesirable biological effect(s) or any resultant deleterious interaction(s) with any other component of a pharmaceutical composition in which it may be contained.

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A group defined as “optionally substituted” may be either unsubstituted, or substituted with one or more substituents, e.g. 1, 2, 3, 4, 5, 6, or more substituents. In embodiments, a substituted group has 1 to 4 substituents, e.g. 1, 2, or 3 substituents. In embodiments, a substituted group has 1 or 2 substituents. In embodiments, a substituted group has 3 substituents.

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The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable or aspect herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

- 5 Compositions and methods provided herein may be combined with one or more of any of the other compositions and methods provided herein.

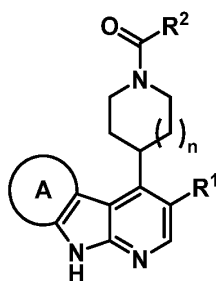
The following abbreviations and empirical formulae are used herein:

	Ac	acetyl
	AE	ethyl acetate
10	ATP	adenosine triphosphate
	Boc/BOC	tert-butyloxy carbonyl
	DABCO	1,4-diazabicyclo[2.2.2]octane
	DAD	diode-array detection
	DCM	dichloromethane
15	DIBAL-H	diisobutylaluminium hydride
	DIPEA	diisopropylethylamine
	DMA	dimethylacetamide
	DMF	N,N-dimethylformamide
	DMSO	dimethyl sulfoxide
20	4EBP1	eukaryotic translation initiation factor 4E-binding protein 1
	EDC/EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
	ERK	extracellular signal-regulated kinase
	ESI	electrospray ionisation
	EtOAc/AcOEt	ethyl acetate
25	FRET	Forster resonance energy transfer
	HATU	hexafluorophosphate azabenzotriazole tetramethyl uronium
	HOBt	hydroxybenzotriazole
	HPLC	high performance liquid chromatography
	LC	liquid chromatography
30	LC/MS	liquid chromatography / mass spectrometry
	LDA	lithium di-isopropylamide
	MAPK	mitogen-activated protein kinase
	MS	mass spectrometry
	MTBE	methyl tert-butyl ether
35	NBS	N-bromosuccinimide
	NCS	N-chlorosuccinimide
	NIS	N-iodosuccinimide

	NMP	N-methyl-2-pyrrolidone
	Pd/C	palladium on carbon
	PdCl ₂ (dppf)	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
	PE	petroleum ether
5	PIFA	[bis(trifluoroacetoxy)iodo]benzene
	Pin	2,3-dimethyl-2,3-butanediolate
	PTFE	poly(tetrafluoroethylene)
	rac	racemic mixture
	RPMI	Roswell Park Memorial Institute medium
10	SEM	2-trimethylsilylethoxymethyl
	SFC	supercritical fluid chromatography
	SGC	silica gel chromatography
	TAD	transcriptional activation domain
	TATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium
15		3-oxide tetrafluoroborate
	TBS	tert-butyldimethylsilyl
	TBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
	TEA	triethylamine
20	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	TosMIC	toluenesulfonylmethyl isocyanide
	TPP	5,10,15,20-tetraphenyl-21H,23H-porphyrin / meso- tetraphenylporphyrin
25	Ts	4-toluenesulfonyl (tosyl)
	UPLC	ultra-high performance liquid chromatography
	UV	ultraviolet

Compounds

In a first aspect the present disclosure provides a compound being of Formula (I)



Formula (I)

30

or a pharmaceutically acceptable salt thereof, wherein:

ring A is (C₅-C₈)cycloalkane, (C₆-C₈)cycloalkene, or 5- to 8-membered heterocycloalkane, wherein ring A is optionally substituted with one or more occurrences of R^A,

5 wherein R^A at each occurrence is:

(a) independently selected from -D, halo, -OH, oxo, =N-OH, -NHR', -CN, -C(O)R'', -(C₁-C₃)alkyl, -O(C₁-C₃)alkyl, -(C₃-C₆)cycloalkyl, and 3- to 6-membered heterocycloalkyl, wherein each occurrence of -(C₁-C₃)alkyl is optionally substituted with one or more groups selected from halo and -OH,

10 wherein each R' is selected from -H, -(C₁-C₃)alkyl optionally substituted with one or more halo, -(C₃-C₄)cycloalkyl, and 3- to 4-membered heterocycloalkyl,

15 wherein each R'' is selected from -OH, -O(C₁-C₃)alkyl, and -(C₁-C₃)alkyl (e.g. -CH₃); and/or

(b) taken together with another occurrence of R^A and the intervening atom(s) to form a (C₄-C₇)cycloalkyl or 4- to 7-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring and said cycloalkyl ring are optionally substituted by one or more groups selected from oxo, -C(O)OH, -C(O)N((C₁-C₃)alkyl)₂, and -(C₁-C₃)alkyl;

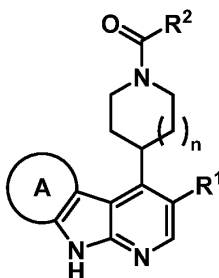
20 **R¹** is selected from -H, and halo (e.g., -F);

R² is -(C₆-C₁₀)aryl, wherein R² is substituted with one, or two occurrences of R^B, wherein each R^B is independently selected from halo, -OH, -NH₂, -SF₅, -(C₁-C₃)alkyl, and -O(C₁-C₃)alkyl, wherein each occurrence of -(C₁-C₃)alkyl and -O(C₁-C₃)alkyl is optionally substituted by one or more halo; and

25 **n** is 0, 1, or 2,

with the proviso that when R² is 4-(pentafluorosulfanyl)phenyl, R¹ is -H, and n is 1, then ring A is not unsubstituted cyclopentane.

In another aspect the present disclosure provides a compound being of Formula (I)



Formula (I)

30

or a pharmaceutically acceptable salt thereof, wherein:

ring A is (C₅-C₈)cycloalkane or 5- to 8-membered heterocycloalkane, wherein ring A is optionally substituted with one or more occurrences of R^A,

wherein R^A at each occurrence is:

- 5 (a) independently selected from halo, -OH, oxo, -NHR['], -CN, -C(O)R^{''}, -(C₁-C₃)alkyl, -O(C₁-C₃)alkyl, -(C₃-C₆)cycloalkyl, and 3- to 6-membered heterocycloalkyl, wherein each occurrence of -(C₁-C₃)alkyl is optionally substituted with one or more halo or -OH,
- 10 wherein each R['] is selected from -H, -(C₁-C₃)alkyl optionally substituted with one or more halo, -(C₃-C₄)cycloalkyl, and 3- to 4-membered heterocycloalkyl,
- wherein each R^{''} is selected from -OH and -CH₃; and/or
- (b) taken together with another occurrence of R^A and the intervening atom(s) to form a (C₄-C₇)cycloalkyl or 4- to 7-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is optionally substituted by oxo;
- 15 **R¹** is selected from -H, and halo (e.g., -F);
- R²** is -(C₆-C₁₀)aryl, wherein R² is substituted with one, or two occurrences of R^B, wherein each R^B is independently selected from halo, -OH, -NH₂, -SF₅,
- 20 -(C₁-C₃)alkyl, -O(C₁-C₃)alkyl, wherein each occurrence of -(C₁-C₃)alkyl and -O(C₁-C₃)alkyl is optionally substituted by one or more halo; and
- n** is 0, 1, or 2,
- with the proviso that when R² is 4-(pentafluorosulfanyl)phenyl, R¹ is -H, and n is 1, then ring A is not unsubstituted cyclopentane.

- 25 When one occurrence of R^A is taken together with another occurrence of R^A to form a (C₄-C₇)cycloalkyl or 4- to 7-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring and said cycloalkyl ring are optionally substituted by one or more groups selected from oxo, -C(O)OH, -C(O)N((C₁-C₃)alkyl)₂, and -(C₁-C₃)alkyl, then the (C₄-C₇)cycloalkyl or 4- to 7-membered heterocycloalkyl ring may be bonded to ring A in a spiro, fused, or bridged
- 30 configuration. In embodiments, one occurrence of R^A is taken together with another occurrence of R^A to form a (C₄-C₇)cycloalkyl or 4- to 7-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring and said cycloalkyl ring are substituted by one or more groups selected from oxo, -C(O)OH, -C(O)N((C₁-C₃)alkyl)₂, and -(C₁-C₃)alkyl, and wherein the (C₄-C₇)cycloalkyl or 4- to 7-membered heterocycloalkyl ring is bonded to ring A in a
- 35 spiro configuration.

When one occurrence of R^A is taken together with another occurrence of R^A to form a (C₄-C₇)cycloalkyl or 4- to 7-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring

is optionally substituted by oxo, the (C₄-C₇)cycloalkyl or 4- to 7-membered heterocycloalkyl ring may be bonded to ring A in a spiro, fused, or bridged configuration.

In embodiments, ring A is (C₅-C₈)cycloalkane or 5- to 7-membered heterocycloalkane, wherein ring A is optionally substituted with one or more occurrences of R^A as defined
5 herein.

In embodiments, ring A is (C₅-C₈)cycloalkane, wherein ring A is optionally substituted with one or more occurrences of R^A as defined herein. In embodiments, ring A is cyclopentane, cyclohexane, cycloheptane, or cyclooctane, wherein ring A is optionally substituted with one or more occurrences of R^A. In embodiments, ring A is (C₅-C₇)cycloalkane, wherein ring A is
10 optionally substituted with one or more occurrences of R^A. In embodiments, ring A is cyclopentane, cyclohexane, or cycloheptane, wherein ring A is optionally substituted with one or more occurrences of R^A.

In embodiments, ring A is (C₅-C₆)cycloalkane, wherein ring A is substituted by one or more occurrences of R^A as defined herein. In embodiments, ring A is (C₅-C₆)cycloalkane, wherein
15 ring A is substituted by one, or two occurrences of R^A as defined herein. In embodiments, ring A is (C₅-C₆)cycloalkane substituted with two occurrences of R^A, wherein the two occurrences of R^A are taken together with the intervening carbon atom(s) to form a 4- to 6-membered heterocycloalkyl ring.

In embodiments, ring A is (C₆-C₈)cycloalkene, wherein ring A is optionally substituted with one or more occurrences of R^A as defined herein. In embodiments, ring A is cycloheptene,
20 e.g. unsubstituted cycloheptene.

In embodiments, ring A is 5- to 8-membered heterocycloalkane, wherein ring A is optionally substituted with one or more occurrences of R^A as defined herein. In embodiments, ring A is 5- to 7-membered heterocycloalkane, wherein ring A is optionally substituted with one or
25 more occurrences of R^A as defined herein. In embodiments, ring A is 6- to 7-membered heterocycloalkane, wherein ring A is optionally substituted with one or more occurrences of R^A as defined herein.

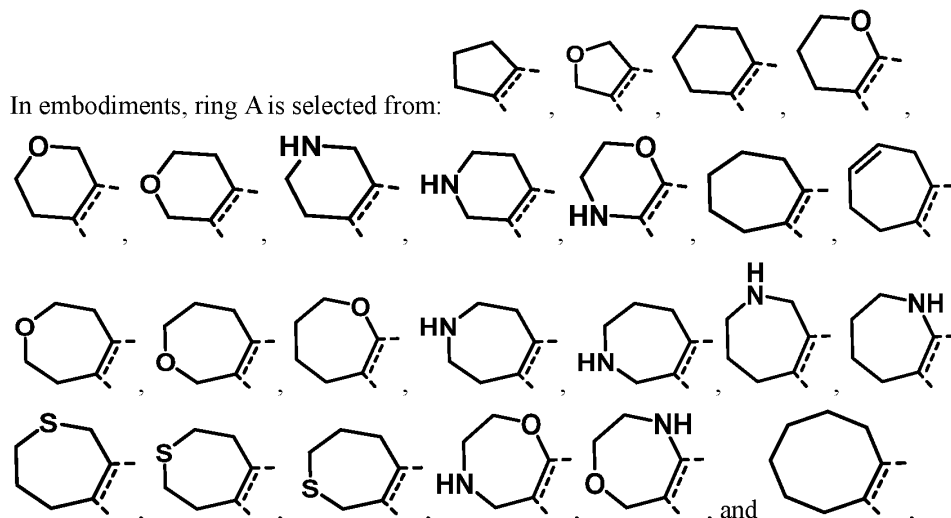
In embodiments, the heterocycloalkane contains two heteroatoms (e.g. independently selected from a nitrogen, oxygen or sulfur atom) within its ring. In embodiments, the
30 heterocycloalkane contains two heteroatoms (e.g. independently selected from a nitrogen or oxygen or sulfur atom) within its ring. In embodiments, the heterocycloalkane contains two heteroatoms within its ring, wherein one of the heteroatoms is a nitrogen atom and the other is selected from oxygen and sulfur. In embodiments, the first heteroatom is nitrogen and the second heteroatom is oxygen. In embodiments, the heterocycloalkane contains one
35 heteroatom within its ring, wherein the heteroatom is selected from a nitrogen atom, an

oxygen atom and a sulfur atom. In embodiments, the heterocycloalkane contains one heteroatom (e.g. a nitrogen or oxygen atom) within its ring.

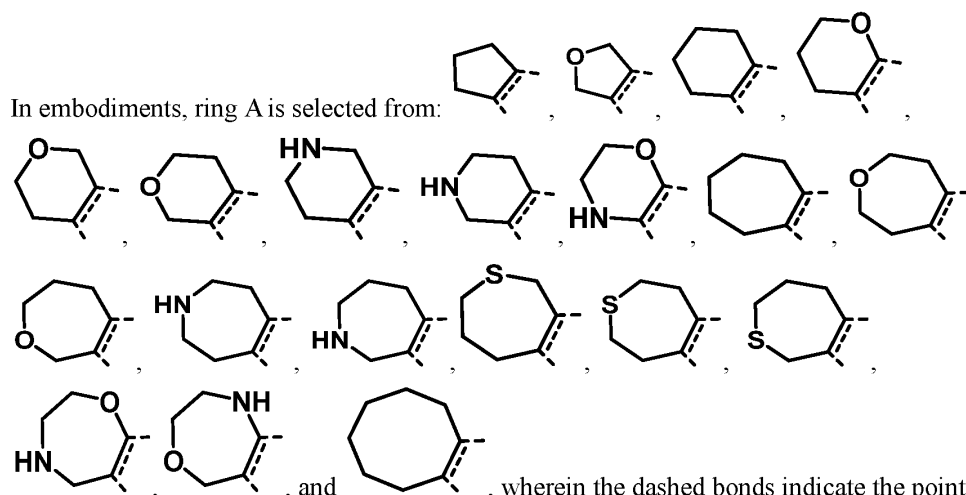
In embodiments, the heterocycloalkane contains one heteroatom within its ring, wherein the heteroatom is a nitrogen atom, and the heterocycloalkane comprises an R^A substituent which is selected from halo, -OH, oxo, -C(O)R'', -(C₁-C₃)alkyl, -(C₃-C₆)cycloalkyl, and 3- to 6-membered heterocycloalkyl, wherein each occurrence of -(C₁-C₃)alkyl is optionally substituted with one or more groups selected from halo, wherein each R'' is selected from -(C₁-C₃)alkyl (e.g. -CH₃). In embodiments, the R^A substituent is bonded to the nitrogen atom within the heterocycloalkane ring. In embodiments, said R^A substituent is selected from -CH₃, -CH₂CF₃, cyclopropyl, and oxetanyl (e.g., -oxetan-3-yl).

In embodiments, the heterocycloalkane comprises an R^A substituent which is oxo. In embodiments, the heterocycloalkane contains one heteroatom (e.g. a nitrogen or oxygen atom) within its ring, and the heterocycloalkane comprises an R^A substituent which is oxo, wherein the oxo is bonded to a carbon atom adjacent to the heteroatom (e.g. adjacent to the nitrogen or oxygen atom). In embodiments, the heterocycloalkane comprises a sulfur atom within its ring, and the heterocycloalkane comprises two R^A substituents which are oxo, wherein the oxo substituents are both bonded to the sulfur atom (i.e. to form a cyclic sulfone group). In embodiments, the heterocycloalkane contains two heteroatoms within its ring (e.g. wherein the two heteroatoms are bonded to each other), wherein one heteroatom is a sulfur atom and the other heteroatom is a nitrogen atom, and the heterocycloalkane comprises two R^A substituents which are oxo, wherein the oxo substituents are both bonded to the sulfur atom (i.e. to form a cyclic sulfonamide group).

In embodiments, ring A is selected from cyclopentane, cyclohexane, cycloheptane, cyclooctane, cycloheptene, tetrahydrofuran, tetrahydropyran, piperidine, morpholine, oxepane, azepane, 1,4-oxazepane, and thiepane, wherein ring A is optionally substituted with one or more occurrences of R^A as defined herein. In embodiments, ring A is selected from cyclopentane, cyclohexane, cycloheptane, cyclooctane, tetrahydrofuran, tetrahydropyran, piperidine, morpholine, oxepane, azepane, 1,4-oxazepane, and thiepane, wherein ring A is optionally substituted with one or more occurrences of R^A as defined herein. In embodiments, ring A is cyclohexane substituted with one or more occurrences of R^A as defined herein. In embodiments, ring A is cycloheptane substituted with one or more occurrences of R^A as defined herein. In embodiments, ring A is cyclooctane substituted with one or more occurrences of R^A as defined herein. In embodiments, ring A is oxepane substituted with one or more occurrences of R^A as defined herein. In embodiments, ring A is azepane substituted with one or more occurrences of R^A as defined herein.



- 5 wherein the dashed bonds indicate the points of fusion to the pyrrole ring, wherein ring A is optionally substituted by one or more occurrences of R^A as defined herein.



- 10 wherein the dashed bonds indicate the points of fusion to the pyrrole ring, wherein ring A is optionally substituted by one or more occurrences of R^A as defined herein.

In embodiments, ring A is substituted with one or more occurrences of R^A , wherein R^A at each occurrence is independently selected from -D, halo, -OH, oxo, =N-

- 15 OH, -NHR', -CN, -C(O)R'', -(C₁-C₃)alkyl, -O(C₁-C₃)alkyl, -(C₃-C₆)cycloalkyl, and 3- to 6-membered heterocycloalkyl; wherein each occurrence of -(C₁-C₃)alkyl is optionally substituted with one or more groups selected from halo and -OH; wherein each R' is selected from -H, -(C₁-C₃)alkyl optionally substituted with one or more halo, -(C₃-C₄)cycloalkyl, and

3- to 4-membered heterocycloalkyl; and wherein each R'' is selected from -OH, -O(C₁-C₃)alkyl, and -(C₁-C₃)alkyl (e.g. -CH₃).

- In embodiments, ring A is substituted with one or more occurrences of R^A, wherein R^A at each occurrence is independently selected from halo, -OH, oxo, -NHR', -CN, -C(O)R'', -(C₁-C₃)alkyl, -O(C₁-C₃)alkyl, -(C₃-C₆)cycloalkyl, and 3- to 6-membered heterocycloalkyl; wherein each occurrence of -(C₁-C₃)alkyl is optionally substituted with one or more halo or -OH; wherein each R' is selected from -H, -(C₁-C₃)alkyl optionally substituted with one or more halo, -(C₃-C₄)cycloalkyl, and 3- to 4-membered heterocycloalkyl; and wherein each R'' is selected from -OH and -CH₃.
- 10 In embodiments, ring A is substituted with one or more occurrences of R^A, wherein R^A at each occurrence is independently selected from -D, halo (e.g., F), -OH, oxo, =N-OH, -NHR', -CN, -C(O)R'', -CH₃, -CF₃, -CH₂CF₃, -CH₂OH, -C(CH₃)₂CH₂OH, -OCH₃, -cyclopropyl, oxetanyl (e.g., oxetan-3-yl), and morpholinyl (e.g., 4-morpholinyl); wherein each R' is selected from -H, -CH₂CH₂F, cyclopropyl, and oxetanyl (e.g., oxetan-3-yl); and wherein each R'' is selected from -OH, -OCH₃, and -CH₃.

In embodiments, ring A is (C₆-C₇)cycloalkane, wherein ring A is substituted by one occurrence of R^A, wherein R^A is =N-OH (i.e., an oxime). In embodiments, the oxime is a mixture of E and Z isomers. In embodiments, the oxime is an E oxime. In other embodiments, the oxime is a Z oxime.

- 20 In embodiments, ring A is substituted with one or more occurrences of R^A, wherein R^A at each occurrence is independently selected from halo, -OH, oxo, -NHR', -CN, -C(O)R'', -CH₃, -CF₃, -CH₂CF₃, -CH₂OH, -OCH₃, -cyclopropyl, and -oxetanyl (e.g., -oxetan-3-yl); wherein each R' is selected from -H, -CH₂CH₂F, -cyclopropyl, and -oxetanyl (e.g., -oxetan-3-yl); and wherein each R'' is selected from -OH and -CH₃.
- 25 In other embodiments, ring A is substituted with two occurrences of R^A, wherein R^A at one occurrence is taken together with the other occurrence of R^A and the intervening atom(s) to form a (C₄-C₇)cycloalkyl or 4- to 7-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring and said cycloalkyl ring are optionally substituted by one or more groups selected from oxo, -C(O)OH, -C(O)N((C₁-C₃)alkyl)₂, and -(C₁-C₃)alkyl. In
- 30 In embodiments, ring A is substituted with two occurrences of R^A, wherein R^A at one occurrence is taken together with the other occurrence of R^A and the intervening atom(s) to form a (C₄-C₇)cycloalkyl or 4- to 7-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is optionally substituted by oxo. The (C₄-C₇)cycloalkyl or 4- to 7-membered heterocycloalkyl ring may be connected to ring A in a spiro, fused, or bridged
- 35 configuration.

In embodiments, ring A is substituted with two occurrences of R^A , wherein R^A at one occurrence is taken together with the other occurrence of R^A and the intervening atom(s) to form a 4- to 7-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is optionally substituted by one or more groups selected from oxo, -C(O)OH, -C(O)N((C₁-C₃)alkyl)₂, and -(C₁-C₃)alkyl. In embodiments, ring A is substituted with two occurrences of R^A , wherein R^A at one occurrence is taken together with the other occurrence of R^A and the intervening atom(s) to form a 4- to 7-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is optionally substituted by oxo. In embodiments, the (C₄-C₇)cycloalkyl or 4- to 7-membered heterocycloalkyl ring is connected to ring A in a spiro, or fused configuration. In embodiments, ring A is substituted with two occurrences of R^A , wherein R^A at one occurrence is taken together with the other occurrence of R^A and the intervening atom(s) to form a 4- to 7-membered heterocycloalkyl ring, wherein the 4- to 7-membered heterocycloalkyl ring is connected to ring A in a spiro, or fused configuration, and wherein said heterocycloalkyl ring is optionally substituted by one or more groups selected from oxo, -C(O)OH, -C(O)N((C₁-C₃)alkyl)₂, and -(C₁-C₃)alkyl. In embodiments, ring A is substituted with two occurrences of R^A , wherein R^A at one occurrence is taken together with the other occurrence of R^A and the intervening atom(s) to form a 4- to 7-membered heterocycloalkyl ring, wherein the 4- to 7-membered heterocycloalkyl ring is connected to ring A in a spiro, or fused configuration, and wherein said heterocycloalkyl ring is optionally substituted by oxo.

In other embodiments, ring A is substituted with two occurrences of R^A , wherein R^A at one occurrence is taken together with the other occurrence of R^A and the intervening atoms to form a (C₄-C₇)cycloalkyl ring, wherein the (C₄-C₇)cycloalkyl ring is connected to ring A in a bridged configuration. In embodiments, the (C₄-C₇)cycloalkyl ring is substituted with one or more -OH groups.

In embodiments, ring A is substituted with two occurrences of R^A , wherein R^A at one occurrence is taken together with the other occurrence of R^A and the intervening atom(s) to form a (C₅-C₇)cycloalkyl or 4- to 6-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring and said cycloalkyl ring are optionally substituted by one or more groups selected from oxo, -C(O)OH, -C(O)N((C₁-C₃)alkyl)₂, and -(C₁-C₃)alkyl. In embodiments, ring A is substituted with two occurrences of R^A , wherein R^A at each occurrence is taken together with the other occurrence of R^A and the intervening atom(s) to form a (C₅-C₇)cycloalkyl or 4- to 6-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is optionally substituted by oxo. In embodiments, the (C₅-C₇)cycloalkyl or 4- to 6-membered heterocycloalkyl ring is connected to ring A in a spiro, fused, or bridged configuration. In embodiments, ring A is substituted with two occurrences of R^A , wherein R^A at one occurrence is taken together with the other occurrence of R^A and the intervening atom(s) to form a 4- to 6-membered heterocycloalkyl ring, and wherein said heterocycloalkyl

- ring is optionally substituted by one or more groups selected from oxo, -C(O)OH, -C(O)N((C₁-C₃)alkyl)₂, and -(C₁-C₃)alkyl. In embodiments, ring A is substituted with two occurrences of R^A, wherein R^A at one occurrence is taken together with the other occurrence of R^A and the intervening atom(s) to form a 4- to 6-membered
- 5 heterocycloalkyl ring, and wherein said heterocycloalkyl ring is optionally substituted by oxo. In embodiments, the (C₅-C₇)cycloalkyl or 4- to 6-membered heterocycloalkyl ring is connected to ring A in a spiro, or fused configuration. In embodiments, ring A is substituted with two occurrences of R^A, wherein R^A at one occurrence is taken together with the other occurrence of R^A and the intervening atom(s) to form a 4- to 6-membered heterocycloalkyl
- 10 ring, wherein the 4- to 6-membered heterocycloalkyl ring is connected to ring A in a spiro, or fused configuration, and wherein said heterocycloalkyl ring is optionally substituted by one or more groups selected from oxo, -C(O)OH, -C(O)N((C₁-C₃)alkyl)₂, and -(C₁-C₃)alkyl. In embodiments, ring A is substituted with two occurrences of R^A, wherein R^A at one occurrence is taken together with the other occurrence of R^A and the intervening atom(s) to
- 15 form a 4- to 6-membered heterocycloalkyl ring, wherein the 4- to 6-membered heterocycloalkyl ring is connected to ring A in a spiro, or fused configuration, and wherein said heterocycloalkyl ring is optionally substituted by oxo. In embodiments, the heterocycloalkyl ring is selected from oxetanyl, azetidiny optionally substituted by methyl (e.g., N-methylazetidiny), tetrahydrofuranyl, dioxolanyl, pyrrolidinyl optionally substituted
- 20 by oxo (e.g., 2-pyrrolidinonyl), tetrahydropyranyl, piperidinyl, and morpholinyl. In embodiments, the heterocycloalkyl ring is selected from oxetanyl, azetidiny, tetrahydrofuranyl, dioxolanyl, pyrrolidinyl optionally substituted by oxo (e.g., 2-pyrrolidinonyl), tetrahydropyranyl, piperidinyl, and morpholinyl.
- In other embodiments, ring A is substituted with two occurrences of R^A, wherein R^A at one
- 25 occurrence is taken together with the other occurrence of R^A and the intervening atoms to form a (C₅-C₇)cycloalkyl ring, wherein the (C₅-C₇)cycloalkyl ring is connected to ring A in a bridged configuration. In embodiments, ring A is substituted with two occurrences of R^A, wherein R^A at one occurrence is taken together with the other occurrence of R^A and the intervening atom(s) to form a (C₄-C₇)cycloalkyl ring, wherein said (C₄-C₇)cycloalkyl ring is
- 30 optionally substituted by one or more groups selected from oxo, -C(O)OH, -C(O)N((C₁-C₃)alkyl)₂, and -(C₁-C₃)alkyl. In embodiments, ring A is substituted with two occurrences of R^A, wherein R^A at one occurrence is taken together with the other occurrence of R^A and the intervening atom(s) to form a (C₄-C₇)cycloalkyl ring, wherein said (C₄-C₇)cycloalkyl ring is optionally substituted by one or more groups selected from oxo, -C(O)OH, and -C(O)N((C₁-C₃)alkyl)₂. In embodiments, the (C₄-C₇)cycloalkyl ring is selected from cyclobutyl optionally substituted by oxo (e.g., cyclobutan-2-onyl), -C(O)OH, and -C(O)N(CH₃)₂. In embodiments,
- 35 ring A is substituted with two occurrences of R^A, wherein R^A at one occurrence is taken together with the other occurrence of R^A and the intervening atom(s) to form a (C₄-

C₇)cycloalkyl ring, wherein said (C₄-C₇)cycloalkyl ring is connected to ring A in a spiro, bridged, or fused configuration, and wherein said cycloalkyl ring is optionally substituted by one or more groups selected from oxo, -C(O)OH, and -C(O)N((C₁-C₃)alkyl)₂.

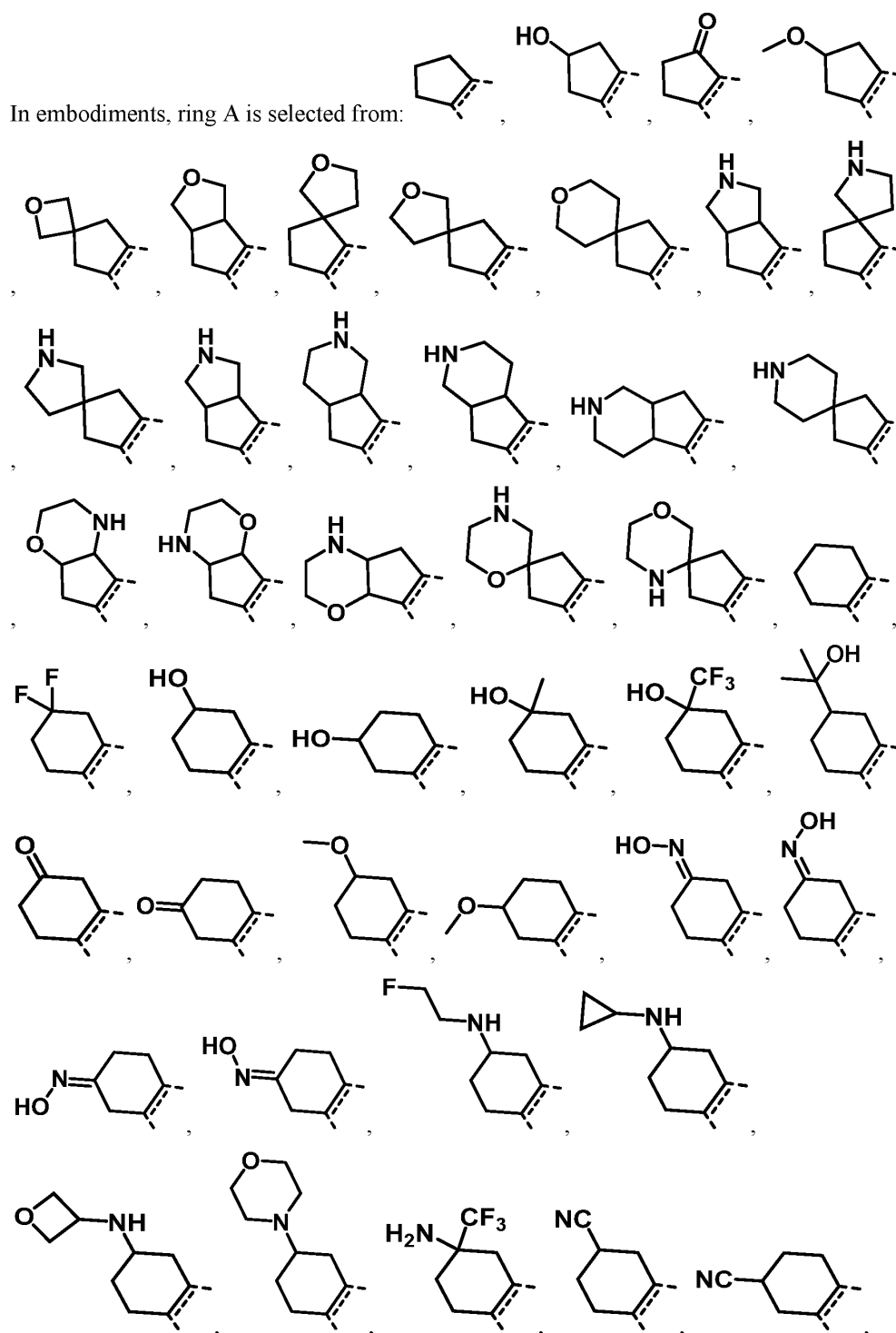
- In embodiments, ring A is unsubstituted. In embodiments, ring A is unsubstituted (C₆-C₈)cycloalkane. In embodiments, ring A is unsubstituted cyclohexane. In embodiments, ring A is unsubstituted cycloheptane. In embodiments, ring A is unsubstituted cyclooctane. In embodiments, ring A is unsubstituted 7-membered cycloalkene. In embodiments, ring A is unsubstituted 5- to 7-membered heterocycloalkane. In embodiments, ring A is unsubstituted 5-membered heterocycloalkane. In embodiments, ring A is unsubstituted 6-membered heterocycloalkane. In embodiments, ring A is unsubstituted 7-membered heterocycloalkane.

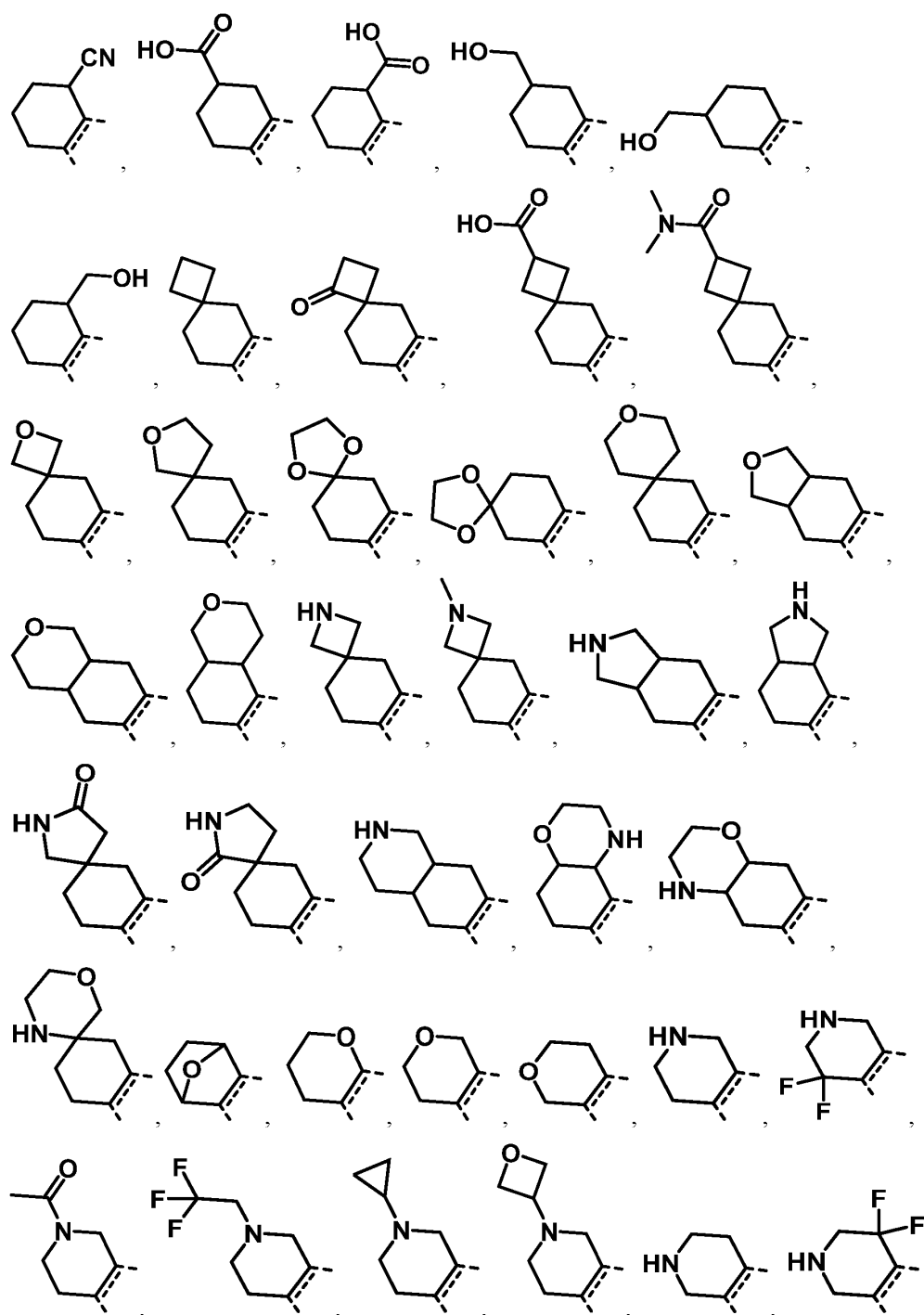
- In other embodiments, ring A is substituted with one, two, or three occurrences of R^A as defined herein. In embodiments, ring A is substituted with one, or two occurrences of R^A as defined herein. In embodiments, ring A is substituted with one occurrence of R^A. In embodiments, ring A is substituted with two occurrences of R^A. In embodiments, ring A is substituted with three occurrences of R^A.

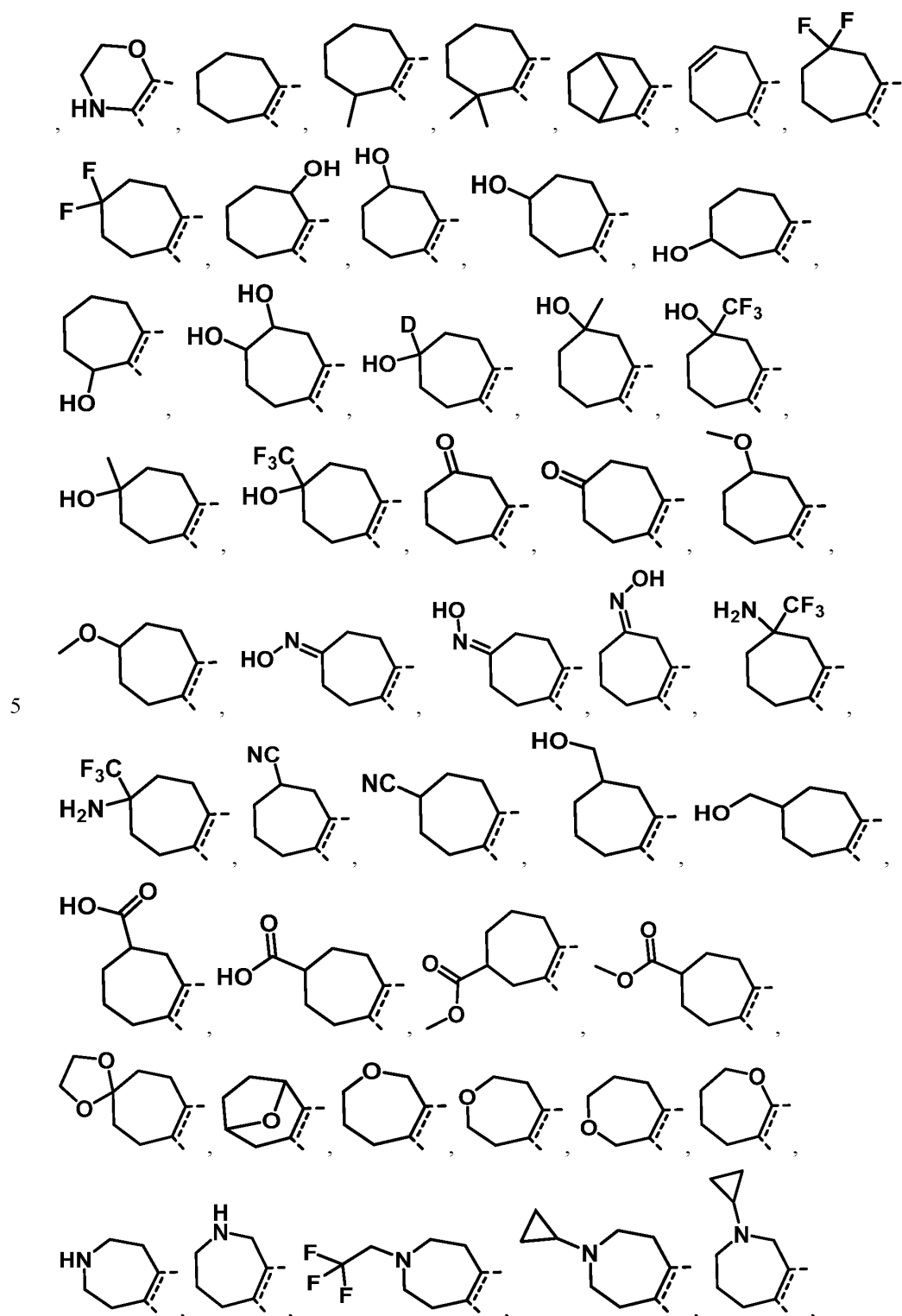
- In embodiments, each occurrence of -(C₁-C₃)alkyl for the group R^A is optionally substituted by one or more -OH groups, e.g. is independently selected from -CH₂OH and -C(CH₃)₂OH. In embodiments, each occurrence of -(C₁-C₃)alkyl for the group R^A is independently methyl or ethyl, optionally substituted by one or more halo or -OH. In embodiments, each occurrence of -(C₁-C₃)alkyl optionally substituted by one or more halo for the group R^A is independently selected from -CH₃, -CF₃, and -CH₂CF₃.

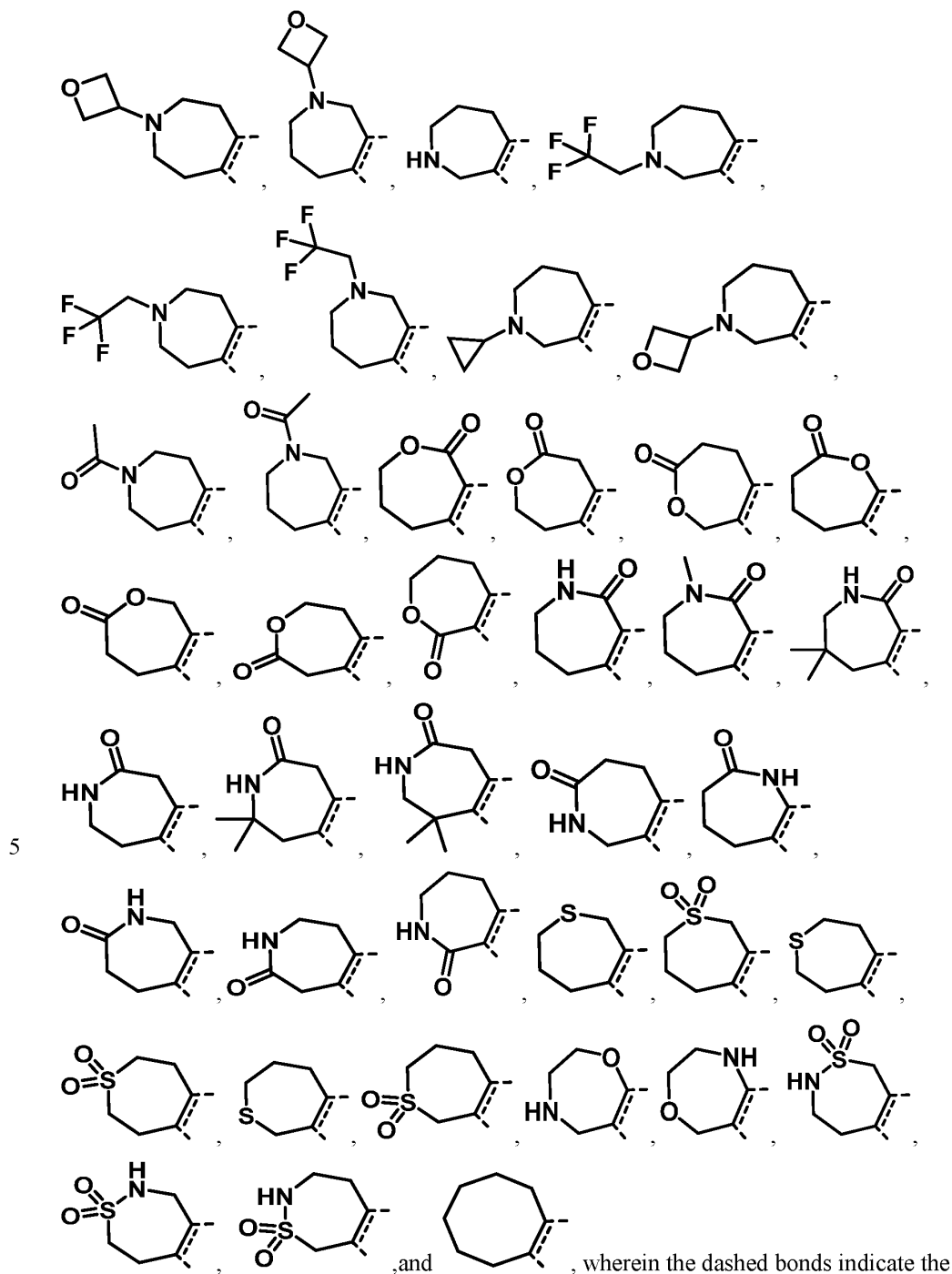
In embodiments, each occurrence of 3- to 6-membered heterocycloalkyl for the group R^A is independently morpholinyl (e.g., 4-morpholinyl).

- In embodiments, each occurrence of -(C₁-C₃)alkyl for the group R['] is independently ethyl optionally substituted by one or more halo. In embodiments, each occurrence of -(C₁-C₃)alkyl optionally substituted by one or more halo for the group R['] is independently -CH₂CH₂F. In embodiments, each occurrence of -(C₃-C₄)cycloalkyl for the group R['] is independently -cyclopropyl. In embodiments, each occurrence of 3- to 4-membered heterocycloalkyl for the group R['] is independently -oxetanyl (e.g., -oxetan-3-yl).
- In embodiments, each occurrence of -O(C₁-C₃)alkyl for the group R^{''} is independently -OCH₃. In embodiments, each occurrence of -(C₁-C₃)alkyl for the group R^{''} is independently -CH₃.

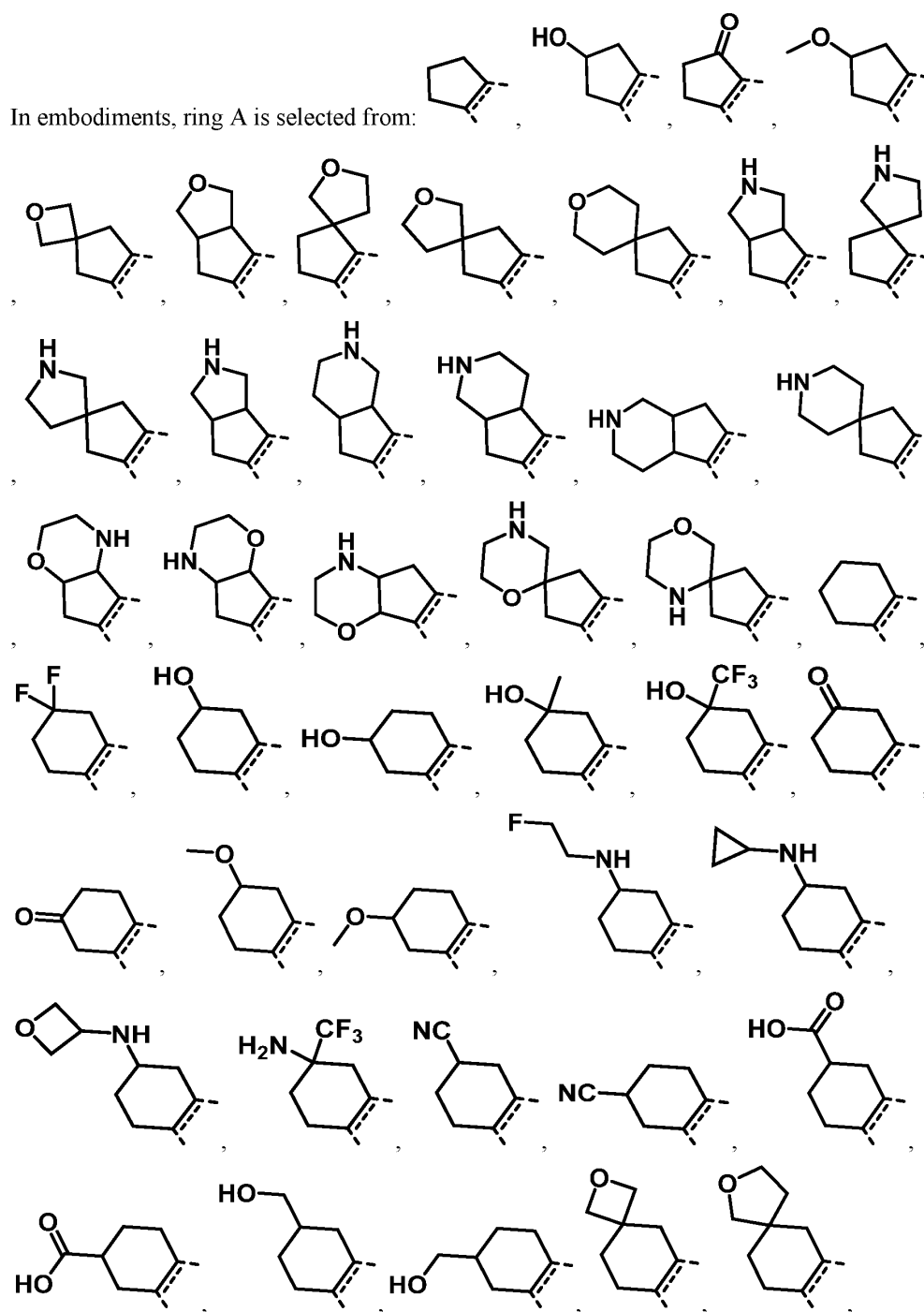


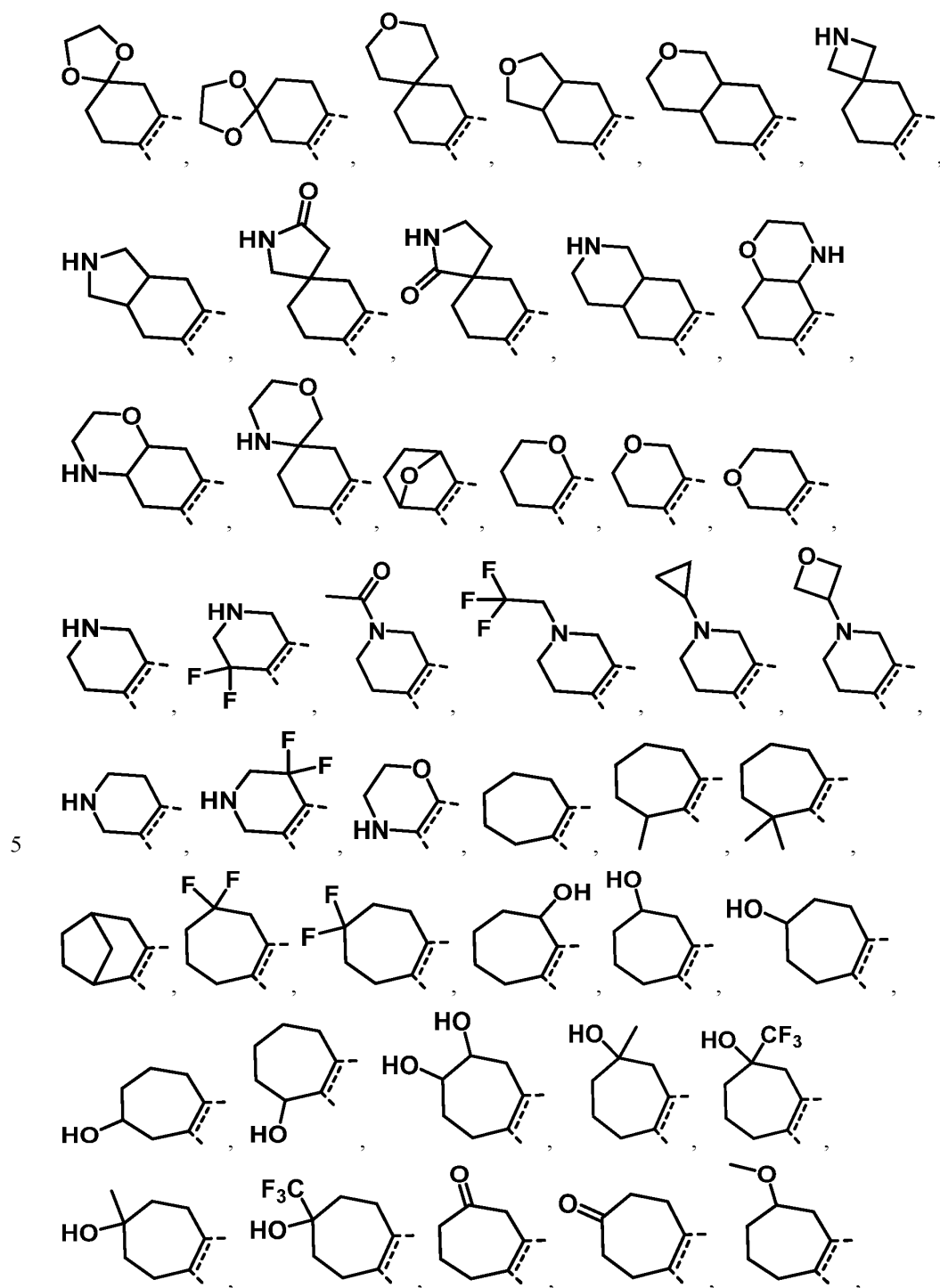


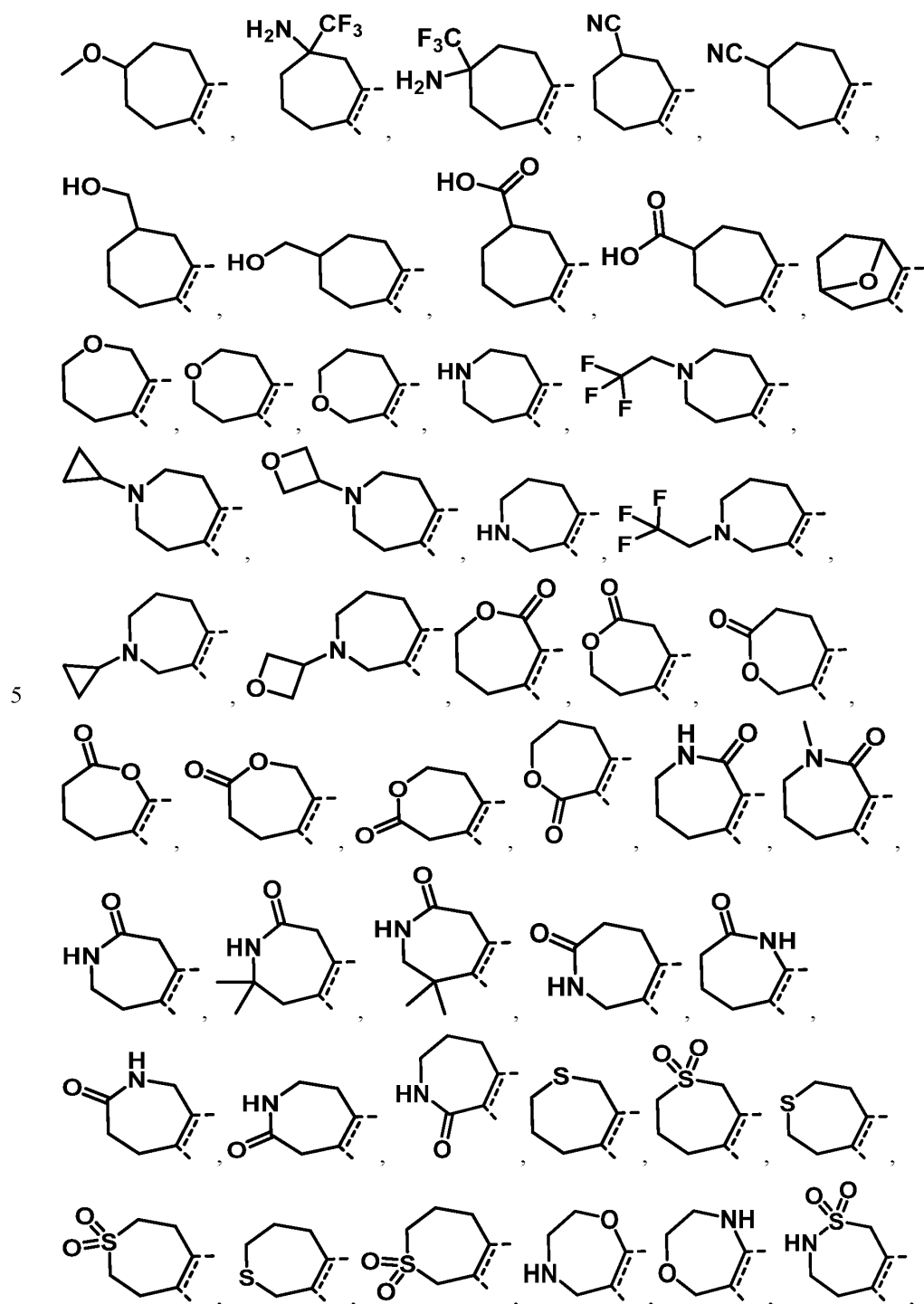


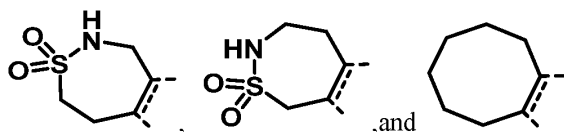


points of fusion to the pyrrole ring. These structures depict ring A and the one or more occurrences of R^A, in the event that ring A is substituted.









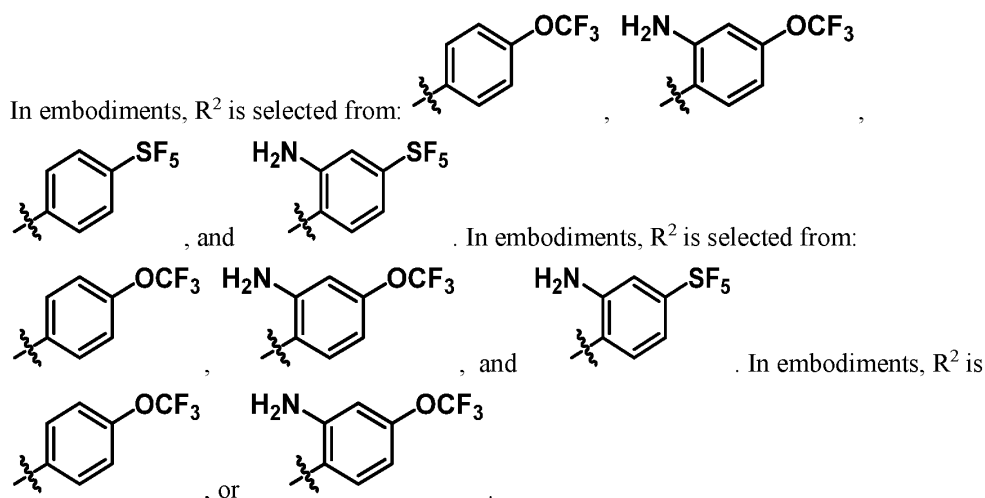
, wherein the dashed bonds indicate the points of fusion to the pyrrole ring. These structures depict ring A and the one or more occurrences of R^A , in the event that ring A is substituted.

In embodiments, R^1 is -H. In embodiments, R^1 is halo. In embodiments, R^1 is -F.

- 5 In embodiments, R^2 is $-(C_6-C_{10})$ aryl substituted with one, or two occurrences of R^B as defined herein. In embodiments, R^2 is $-(C_6-C_{10})$ aryl substituted with one occurrence of R^B . In embodiments, R^2 is $-(C_6-C_{10})$ aryl substituted with two occurrences of R^B . In embodiments, R^2 is phenyl substituted with one, or two occurrences of R^B as defined herein. In embodiments, R^2 is phenyl substituted with one occurrence of R^B . In embodiments, R^2 is phenyl substituted with two occurrences of R^B .

- In embodiments, each R^B is independently selected from halo (e.g., -F), -OH, -NH₂, -SF₅, and -O(C₁-C₃)alkyl optionally substituted by one or more halo (e.g., -F). In embodiments, each R^B is independently selected from halo (e.g., -F), -OH, -NH₂, and -O(C₁-C₃)alkyl optionally substituted by one or more halo (e.g., -F). In embodiments, each R^B is independently selected from -NH₂, -SF₅, and -O(C₁-C₃)alkyl optionally substituted by one or more halo (e.g., -F). In embodiments, each occurrence of -O(C₁-C₃)alkyl for the group R^B is independently -O(methyl) optionally substituted by one or more halo. In embodiments, each occurrence of -O(C₁-C₃)alkyl optionally substituted by one or more halo for the group R^B is independently -OCF₃. In embodiments, each R^B is independently selected from -NH₂, -SF₅, and -OCF₃. In embodiments, each R^B is independently selected from -NH₂, and -OCF₃.

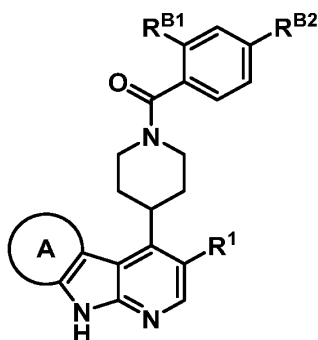
- In embodiments, R^2 is $-(C_6-C_{10})$ aryl substituted with one, or two occurrences of R^B , wherein each R^B is independently selected from -NH₂, -SF₅, and -OCF₃. In embodiments, R^2 is $-(C_6-C_{10})$ aryl substituted with one, or two occurrences of R^B , wherein each R^B is independently selected from -NH₂, and -OCF₃. In embodiments, R^2 is phenyl substituted with one, or two occurrences of R^B , wherein each R^B is independently selected from -NH₂, -SF₅, and -OCF₃. In embodiments, R^2 is phenyl substituted with one, or two occurrences of R^B , wherein each R^B is independently selected from -NH₂, and -OCF₃. In embodiments, R^2 is phenyl substituted with two occurrences of R^B , wherein one occurrence of R^B is -NH₂, and the other occurrence of R^B is selected from -SF₅ and -OCF₃. In embodiments, R^2 is phenyl substituted with two occurrences of R^B , wherein one occurrence of R^B is -NH₂, and the other occurrence of R^B is -OCF₃. In embodiments, R^2 is phenyl substituted with one occurrence of R^B , wherein R^B is -OCF₃.



- 5 In embodiments, n is 0 or 1. In embodiments, n is 1 or 2. In embodiments, n is 0. In embodiments, n is 1. In embodiments, n is 2.

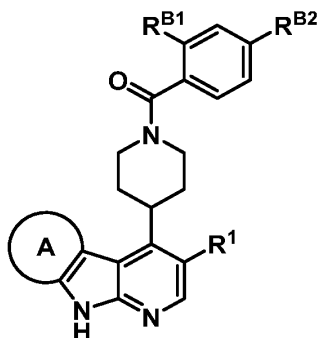
In embodiments, R^1 is -F and n is 1.

In embodiments, the compound is a compound of Formula (II)



Formula (II)

- 10 or a pharmaceutically acceptable salt thereof, wherein **ring A** and R^1 are as defined herein, R^{B1} is selected from -H and R^B as defined herein, and R^{B2} is selected from R^B as defined herein. In embodiments, R^{B1} is selected from -H and -NH₂. In embodiments, R^{B2} is selected from -OCF₃, and -SF₅ (e.g. -OCF₃). In embodiments, R^{B1} is selected from -H and -NH₂, and R^{B2} is -OCF₃.
- 15 In embodiments, the compound is a compound of Formula (II)



Formula (II)

or a pharmaceutically acceptable salt thereof, wherein:

ring A is (C₅-C₈)cycloalkane or 6- to 7-membered heterocycloalkane, wherein ring A is optionally substituted with one or more occurrences of R^A,

5 wherein $\mathbf{R}^A$ at each occurrence is:

(a) independently selected from -OH, oxo, -NHR', -C(O)CH₃, -(C₁-C₃)alkyl, and -O(C₁-C₃)alkyl,

wherein each **R'** is selected from -(C₁-C₃)alkyl optionally substituted with one or more halo, -(C₃-C₄)cycloalkyl, and 3- to 4-membered heterocycloalkyl; or

(b) taken together with another occurrence of R^A and the intervening atom(s) to form a (C₅-C₇)cycloalkyl or 4- to 6-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is optionally substituted by oxo;

R¹ is selected from -H, and -F;

15 **R^{B1}** is selected from -H, and -NH₂; and

R^{B2} is selected from -OCF₃, and -SF₅.

with the proviso that when R^{B1} is -H, R^{B2} is -SF₅, and R¹ is -H, then ring A is not unsubstituted cyclopentane.

In embodiments, ring A is (C₅-C₈)cycloalkane or 6- to 7-membered heterocycloalkane, wherein ring A is optionally substituted with one or two occurrences of R^A as defined herein.

In embodiments, ring A is selected from cyclopentane, cyclohexane, cycloheptane, cyclooctane, tetrahydropyran, piperidine, oxepane, and azepane, wherein ring A is optionally substituted with one or more occurrences (e.g., one or two occurrences) of R^A as defined herein.

occurrence of R^A and the intervening atom(s) to form a (C₅-C₇)cycloalkyl or 4- to 6-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is optionally substituted by oxo. The (C₅-C₇)cycloalkyl or 4- to 6-membered heterocycloalkyl ring may be bonded to ring A in a spiro, fused, or bridged configuration.

- 5 In embodiments, ring A is substituted with two occurrences of R^A which are taken together with the intervening atom(s) to form a 4- to 6-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is optionally substituted by oxo. The 4- to 6-membered heterocycloalkyl ring may be bonded to ring A in a spiro, fused, or bridged configuration. In
 10 In embodiments, ring A is substituted with two occurrences of R^A which are taken together with the intervening atom(s) to form a 4- to 6-membered heterocycloalkyl ring, wherein the 4- to 6-membered heterocycloalkyl ring is bonded to ring A in a spiro, or fused configuration, and wherein said heterocycloalkyl ring is optionally substituted by oxo. In embodiments, the 4- to 6-membered heterocycloalkyl ring comprises one or two ring heteroatoms independently selected from O and N. In embodiments, the 4- to 6-membered heterocycloalkyl ring is
 15 selected from oxetanyl, azetidiny, tetrahydrofuranyl, dioxolanyl, pyrrolidinyl optionally substituted by oxo (e.g., 2-pyrrolidinonyl), tetrahydropyranyl, and piperidinyl.

In embodiments, ring A is substituted with two occurrences of R^A which are taken together with the intervening atom(s) to form a (C₅-C₇)cycloalkyl ring, wherein the (C₅-C₇)cycloalkyl ring is bonded to ring A in a bridged configuration.

- 20 In embodiments, each occurrence of -(C₁-C₃)alkyl for the group R^A is independently -CH₃. In embodiments, each occurrence of -O(C₁-C₃)alkyl for the group R^A is independently -OCH₃.

In embodiments, each occurrence of -(C₁-C₃)alkyl for the group R' is independently ethyl, optionally substituted by one or more halo. In embodiments, each said occurrence of -(C₁-C₃)alkyl for the group R' is independently -CH₂CH₂F.

- 25 In embodiments, each occurrence of -(C₃-C₄)cycloalkyl for the group R' is independently -cyclopropyl. In embodiments, each occurrence of 3- to 4-membered heterocycloalkyl for the group R' is independently -oxetanyl (e.g., -oxetan-3-yl).

In embodiments, the compound is a compound of Formula (II) or a pharmaceutically acceptable salt thereof, wherein:

- 30 **ring A** is (C₅-C₈)cycloalkane or 6- to 7-membered heterocycloalkane, wherein ring A is optionally substituted with one or two occurrences of R^A ,
 wherein R^A at each occurrence is:
 (a) independently selected from -OH, oxo, -NHR', -C(O)CH₃, -CH₃,
 and -OCH₃,

wherein each **R'** is selected from -CH₂CH₂F, -cyclopropyl, and -oxetanyl (e.g., -oxetan-3-yl); or

(b) taken together with another occurrence of R^A and the intervening atom(s) to form a (C₅-C₇)cycloalkyl or 4- to 6-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is optionally substituted by oxo;

R¹ is selected from -H, and -F;

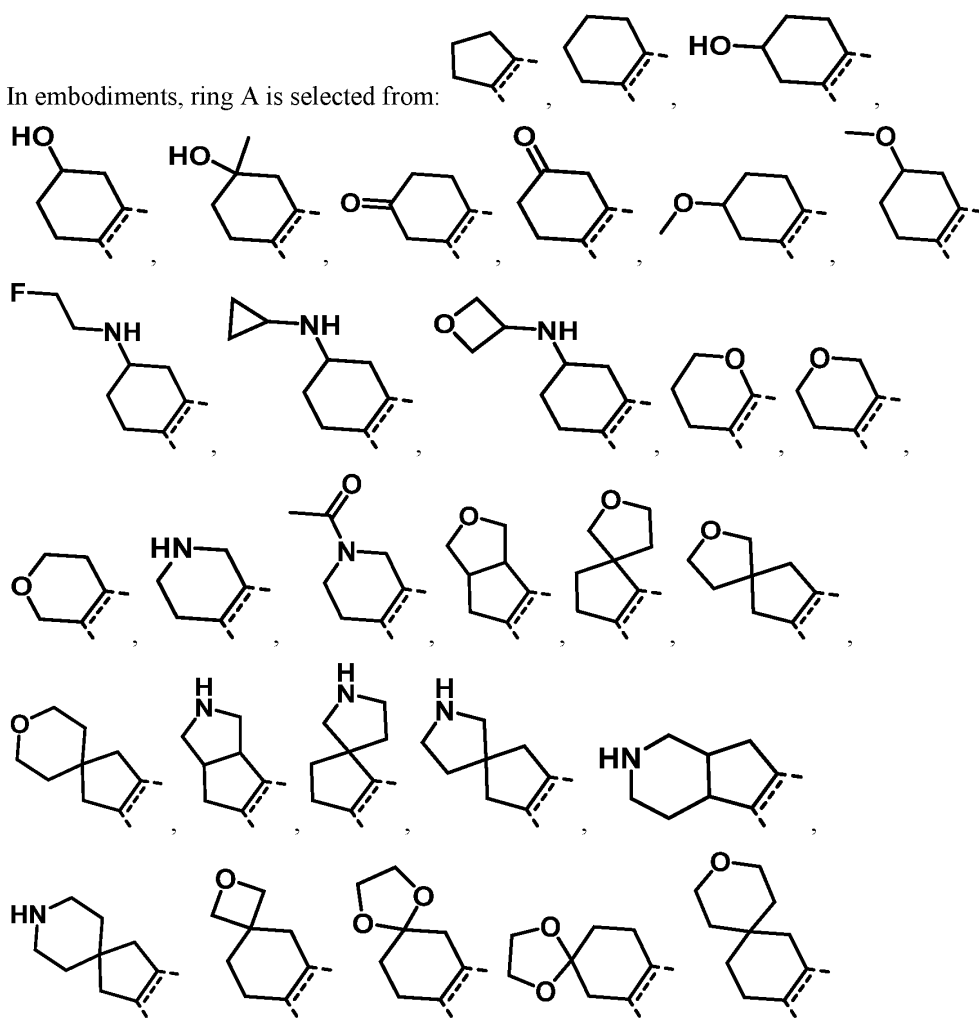
R^{B1} is selected from -H, and -NH₂; and

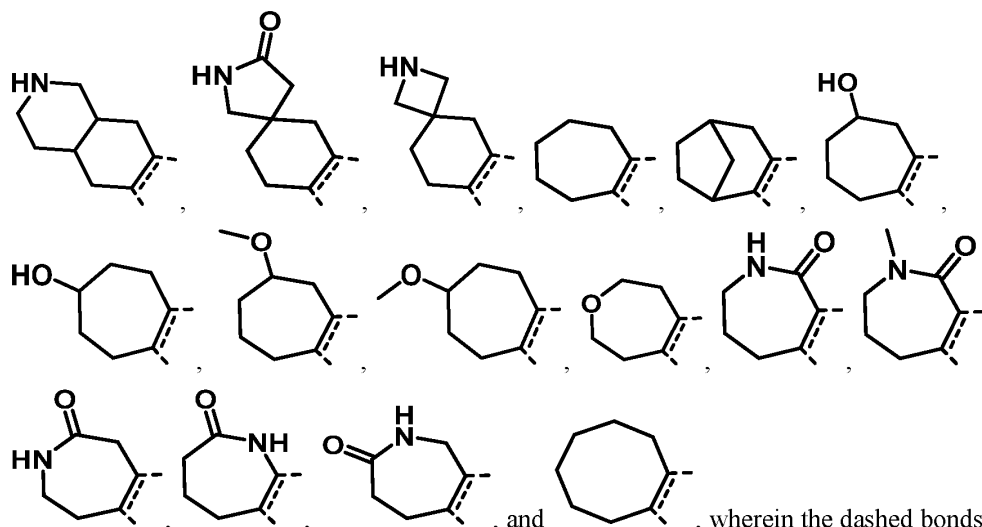
R^{B2} is selected from -OCF₃, and -SF₅,

with the proviso that when R^{B1} is -H, R^{B2} is -SF₅, and R^1 is -H, then ring A is not

10 unsubstituted cyclopentane.

In embodiments, ring A is selected from:





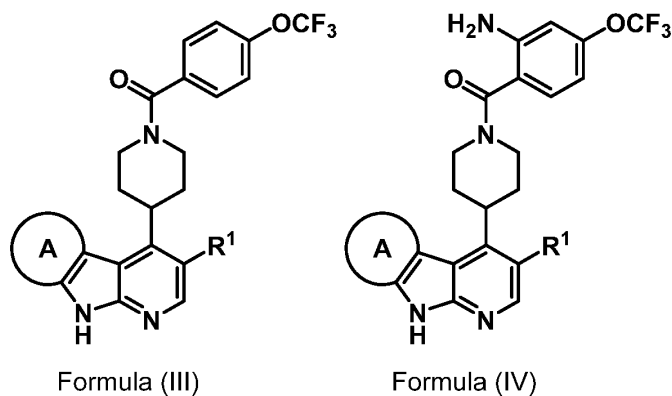
indicate the points of fusion to the pyrrole ring. These structures depict ring A and the one or more occurrences of R^A, in the event that ring A is substituted.

In embodiments, R^1 is -F.

In embodiments, R^{B1} is -H. In other embodiments, R^{B1} is -NH₂.

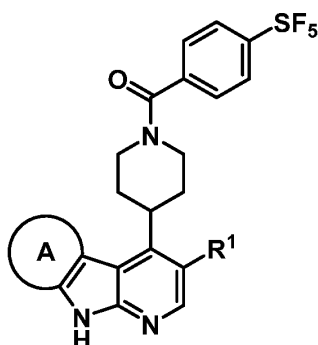
In embodiments, R^{B2} is $-OCF_3$. In embodiments, R^{B1} is $-H$, and R^{B2} is $-OCF_3$. In other embodiments, R^{B1} is $-NH_2$, and R^{B2} is $-OCF_3$. In embodiments, R^{B1} is $-NH_2$ and R^{B2} is $-SF_5$.

10 In embodiments, the compound is a compound of Formula (III) or Formula (IV)



or a pharmaceutically acceptable salt thereof, wherein ring A and R¹ are as defined herein. In embodiments, the compound is a compound of Formula (III), or a pharmaceutically acceptable salt thereof. In other embodiments, the compound is a compound of Formula (IV), or a pharmaceutically acceptable salt thereof. In embodiments, R¹ is -H. In embodiments, R¹ is -F.

In embodiments, the compound is a compound of Formula (V)

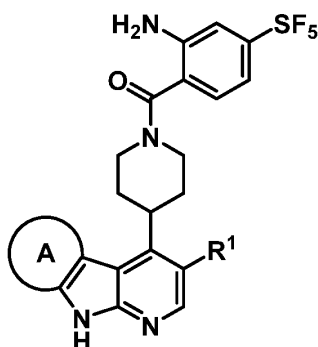


Formula (V)

or a pharmaceutically acceptable salt thereof, wherein ring A and R¹ are as defined herein, with the proviso that when R¹ is -H, then ring A is not unsubstituted cyclopentane. In

- 5 embodiments, R¹ is -H. In embodiments, R¹ is -F.

In embodiments, the compound is a compound of Formula (VI)



Formula (VI)

or a pharmaceutically acceptable salt thereof, wherein ring A and R¹ are as defined herein. In embodiments, R¹ is -H. In embodiments, R¹ is -F.

- 10 In embodiments, the compound is selected from the group consisting of:
- [4-[3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
 - [4-(3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

15 -

 - 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,14-triazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-13-one;
 - trans-[4-[13-fluoro-6,15,17-triazatetracyclo[8.7.0.0.3,8.0.11,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- trans-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.0.1.1,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- trans-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.0.1.1,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 5 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 10 - [4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.0.2,6]dodeca-1(8),2(6),9,11-tetraene-4,4'-piperidine]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-oxetane]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone;
- 15 - [4-(3-fluoro-5,6,8,9-tetrahydropyrido[2,3-b]indole-7,2'-dioxolan]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,6,8,9-tetrahydropyrido[2,3-b]indol-7-one;
- 20 - [4-(3-fluoro-6-hydroxy-6-methyl-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[11-fluorospiro[7,9-diazatricyclo[6.4.0.0.2,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl]-1-piperidyl]methanone;
- 25 - 1-[12-fluoro-13-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4,8,10-triazatricyclo[7.4.0.0.2,7]trideca-1(9),2(7),10,12-tetraen-4-yl]ethanone;
- [4-[11-fluorospiro[7,9-diazatricyclo[6.4.0.0.2,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 - [4-[3-fluoro-6-(oxetan-3-ylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-fluoro-3-oxa-8,10-diazatricyclo[7.4.0.0.2,7]trideca-1(13),2(7),9,11-tetraen-13-yl)-1-piperidyl]methanone;
- 35 - [4-(12-fluoro-3-oxa-8,10-diazatricyclo[7.4.0.0.2,7]trideca-1(13),2(7),9,11-tetraen-13-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- cis-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.0.1.1,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- cis-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-fluoro-5-oxa-8,10-diazatricyclo[7.4.0.02,7]trideca-1(9),2(7),10,12-tetraen-13-yl)-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-oxetane]-4-yl)-1-piperidyl]methanone;
- 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one;
- 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-one;
- [4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- cis-[4-[4-fluoro-6,8,13-triazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-one;
- 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one;
- [4-(3-fluoro-7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-tetrahydropyran]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-tetrahydropyran]-4-yl)-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,4'-tetrahydropyran]-12-yl)-1-piperidyl]methanone;
- [4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone;
- [4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,4'-tetrahydropyran]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,3'-pyrrolidine]-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,6,8,9-tetrahydropyrido[2,3-b]indol-7-one;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-5,6,8,9-tetrahydrospiro[pyrido[2,3-b]indole-7,2'-[1,3]dioxolan]-4-yl)-1-piperidyl]methanone;
- 5 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-3,3'-tetrahydrofuran]-12-yl)-1-piperidyl]methanone;
- [4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-3,3'-tetrahydrofuran]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 10 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone;
- [4-(3-fluoro-5,7,8,9-tetrahydrospiro[pyrido[2,3-b]indole-6,2'-[1,3]dioxolan]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 15 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-6-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone;
- [4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-3,3'-pyrrolidine]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 20 - [4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-(3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one;
- 25 - [4-(3-fluoro-6-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 - [4-(12-fluoro-4,8,10-triazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one;
- 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one;
- 35 - 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one;

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-fluoro-4-oxa-8,10-diazatricyclo[7.4.0.02,7]trideca-1(9),2(7),10,12-tetraen-13-yl)-1-piperidyl]methanone;
- 5 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-(7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraen-12-yl)-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraen-12-yl)-1-piperidyl]methanone;
- 10 - [4-(7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraen-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone;
- 15 - [4-(7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-(12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
- 20 - trans-[4-[13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-(12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 25 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone;
- 30 - 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-13-methyl-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- 35 and
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-6,8-diazatricyclo[7.6.0.02,7]pentadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone,

and the pharmaceutically acceptable salts thereof.

In embodiments, the compound is selected from the group consisting of:

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 5 - 3-fluoro-N,N-dimethyl-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxamide;
- 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxylic acid;
- 10 - methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate;
- methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate;
- [4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 15 - 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid;
- 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid;
- [4-(4'-fluorospiro[1,3-dioxolane-2,12'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene]-3'-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 20 - [4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 25 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-(4-fluoro-14-oxa-6,8,11-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 - [4-[(trans)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 35 - [4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,2'-cyclobutane]-1'-one;

- 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile;
- 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile;
- 5 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-1'-methyl-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 10 - 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile;
- 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile;
- [4-(3-fluoro-1'-methyl-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 15 - 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid;
- [4-[4-fluoro-12-(oxetan-3-yl)-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]methanone;
- 20 - [4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[4-fluoro-13-(oxetan-3-yl)-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 25 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [4-(12-cyclopropyl-4-fluoro-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid;
- 30 - [4-(13-cyclopropyl-4-fluoro-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 35 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [4-(3-fluoro-6-morpholino-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [4-(4-fluoro-12,12-dioxo-12 λ ⁶-thia-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 5 - [4-(4-fluoro-13,13-dioxo-13 λ ⁶-thia-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.0^{3,8}.0^{11,16}]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone;
- 10 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.0^{2,7}.0^{10,15}]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.0^{2,7}.0^{10,15}]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone;
- 15 - [4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 20 - 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile;
- [4-[3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 25 - [4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 1-[4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,12-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-12-yl]ethanone;
- 30 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 1-[4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-13-yl]ethanone;
- [4-[4-fluoro-12-(2,2,2-trifluoroethyl)-6,8,12-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 35 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,1'-cyclobutane]-4-yl)-1-piperidyl]methanone;

- [4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,1'-cyclobutane]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[4-fluoro-13-(2,2,2-trifluoroethyl)-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 5 - [4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone;
- 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]methanone;
- 10 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone;
- 15 - 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one;
- [4-[3-fluoro-7-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 20 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 25 - [4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-(4-fluoro-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-(4-fluoro-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 - 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one;
- [4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 35 - 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;

- [4-[(cis)-14-fluoro-4,10,12-triazatetracyclo[7.7.0.02,6.011,16]hexadeca-1(9),11,13,15-tetraen-15-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 5 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone;
- 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-one;
- 10 - 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile;
- 1-[13-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-12-fluoro-4,8,10-triazatricyclo[7.4.0.02,7]trideca-1(9),2(7),10,12-tetraen-4-yl]ethanone;
- 4-fluoro-11,11-dimethyl-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one;
- 15 - 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-12-one;
- 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one;
- 20 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone;
- 25 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone;
- [2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 30 - [4-[6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-11,11-dimethyl-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one;
- 35 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-14-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone;
- [4-(4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- [2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 5 - 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,11-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-one;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl)-1-piperidyl]methanone;
- [4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 10 - [4-[3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone;
- 15 - 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-11-one;
- [4-[3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone;
- 20 - [4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 25 - [4-(4-fluoro-6,8,13-triazatetracyclo[7.7.0.02,7.011,15]hexadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
- [4-(14-fluoro-4,10,12-triazatetracyclo[7.7.0.02,6.011,16]hexadeca-1(9),11,13,15-tetraen-15-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 - 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
- [4-[6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 35 - [4-[(cis)-7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone;
- 5 - [4-[12-fluoro-4-(2,2,2-trifluoroethyl)-4,8,10-triazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3,6,6-trifluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-fluoro-4-(2,2,2-trifluoroethyl)-4,8,10-triazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl]-1-piperidyl]methanone;
- 10 - [4-(12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(trans)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 15 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-11-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone;
- 20 - [4-[(cis)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
- 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
- 25 - [4-[4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- 4-fluoro-13-methyl-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one;
- [4-(trifluoromethoxy)phenyl]-[4-(3,6,6-trifluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone;
- 35 - 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8,14-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one;

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl)-1-piperidyl]methanone;
- [4-(7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 5 - [4-[3-fluoro-6-(oxetan-3-ylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 10 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone;
- [4-(3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 15 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl)-1-piperidyl]methanone;
- [4-[(cis)-4-fluoro-6,8,13-triazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 20 - [4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,3'-pyrrolidine]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 25 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone;
- [4-(4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5,12-pentaen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-(4-fluoro-6,8-diazatricyclo[7.6.0.02,7]pentadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone;
- 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carbonitrile;
- 35 - 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-13-carbonitrile;
- 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carbonitrile; and

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone, and the pharmaceutically acceptable salts thereof.

In embodiments where the compound has enantiomeric forms (e.g., where the compound has a chiral centre, such as a chiral carbon atom), the compound is present as a racemic mixture of enantiomers. In embodiments where the compound has a chiral centre (e.g., a chiral carbon atom), the compound is present as the (R) isomer. In other embodiments where the compound has a chiral centre (e.g., a chiral carbon atom), the compound is present as the (S) isomer.

Thus, in embodiments the compound is selected from the group consisting of:

- 10 - (rac)-[4-[3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(6R)-3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(6S)-3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 15 - (rac)-[4-(3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-trans-[4-[13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 20 - (rac)-trans-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-trans-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 25 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12R)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 30 - (rac)-2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone (rac)-[4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 35 - [4-[(6R)-6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(6S)-6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- (rac)-[4-(3-fluoro-6-hydroxy-6-methyl-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl]-1-piperidyl]methanone;
- 5 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(4R)-11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl]-1-piperidyl]methanone;
- 10 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(4S)-11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl]-1-piperidyl]methanone;
- (rac)-[4-[11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(4R)-11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 15 - [4-[(4S)-11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[4-[3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 20 - (rac)-[4-[3-fluoro-6-(oxetan-3-ylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-cis-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-cis-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 25 - (rac)-[4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(6R)-3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 - [4-[(6S)-3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-cis-[4-[4-fluoro-6,8,13-triazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 35 - [4-[(11S, 15S)-4-fluoro-6,8,13-triazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(11R, 15R)-4-fluoro-6,8,13-triazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- (rac)-[4-(3-fluoro-7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 5 - [4-[(12R)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(12S)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 10 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone;
- (rac)-[4-[11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,3'-pyrrolidine]-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 15 - [4-[(4R)-11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,3'-pyrrolidine]-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(4S)-11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,3'-pyrrolidine]-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 20 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-3,3'-tetrahydrofuran]-12-yl)-1-piperidyl]methanone;
- (rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-3,3'-tetrahydrofuran]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone;
- 25 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-6-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone;
- (rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-3,3'-pyrrolidine]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 - (rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[4-(3-fluoro-6-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 35 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7R)-7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7S)-7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
 - (rac)-[4-(7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
 - 5 - (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
 - (6R)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
 - (6S)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
 - 10 - (rac)-trans-[4-[13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
 - [4-[(3R, 8R)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
 - 15 - [4-[(3S, 8S)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
 - (rac)-[4-(12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone;
 - 20 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(1R,12S)-7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone;
 - 25 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(1S,12R)-7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone;
 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
 - 30 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13S)-4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13R)-4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
 - 35 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12R)-4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- and

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraene-3-yl]-1-piperidyl]methanone, and the pharmaceutically acceptable salts thereof.

In embodiments, the compound is selected from the group consisting of:

- 5 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6R)-3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6S)-3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 10 - (rac)-3-fluoro-N,N-dimethyl-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxamide;
- (trans)-3-fluoro-N,N-dimethyl-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxamide;
- 15 - (cis)-3-fluoro-N,N-dimethyl-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxamide;
- 20 - (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxylic acid;
- (trans)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxylic acid;
- (cis)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxylic acid;
- 25 - (rac)-methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate;
- methyl (11R)-3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate;
- 30 - (rac)-methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate;
- methyl (12R)-3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate;
- methyl (11S)-3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate;
- 35 - methyl (12S)-3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate;

- (rac)-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(6R)-3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 5 - [4-[(6S)-3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid;
- (6R)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid;
- 10 - (6S)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid;
- (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid;
- 15 - (6R)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid;
- (6S)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid;
- [4-[(12E/Z)-4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 20 - [4-[(12Z)-4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(12E)-4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 25 - [4-[(13E/Z)-4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(13Z)-4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(13E)-4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 - (rac)-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[4-[(trans)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 35 - [4-[(3R,8S)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- [4-[(2S,7R)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(2R,7S)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 5 - (rac)-[4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(3S,8R)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 10 - [4-[(2S,7S)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(2R,7R)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,2'-cyclobutane]-1'-one;
- 15 - (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile;
- (7R)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile;
- (7S)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile;
- 20 - (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile;
- (5R)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile;
- 25 - (5S)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6E/Z)-3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6E)-3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 30 - (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile;
- (7R)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile;
- 35 - (7S)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile;
- (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile;

- (5R)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile;
- (5S)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile;
- 5 - (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid;
- (5R)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid;
- (5S)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid;
- 10 - (rac)-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(5R)-3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone; [4-[(5S)-3-fluoro-5-
- 15 - (hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7E/Z)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7Z)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 20 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7E)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid;
- 25 - (7R)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid;
- (7S)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12E/Z)-4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 30 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12Z)-4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12E)-4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 35 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13E/Z)-4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13E)-4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13Z)-4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- (rac)-[4-(3-fluoro-6-morpholino-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 5 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(5R)-3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(5S)-3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 10 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6Z)-3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone;
- 15 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(3S,8S)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(3R,8R)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone;
- 20 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone;
- 25 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2R,7R)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2S,7S)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone;
- 30 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2S,7R)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone;
- 35

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2R,7S)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone;
- (rac)-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(6R)-3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(6S)-3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6R)-3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6S)-3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile;
- 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-(6R)-carbonitrile;
- 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-(6S)-carbonitrile;
- [4-[(6E/Z)-3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(6Z)-3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(6E)-3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[3-fluoro-(7R)-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[3-fluoro-(7S)-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(12R)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- [4-[(12S)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 5 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7R)-3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7S)-3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 10 - (rac)-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone;
- [4-[(12R)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone;
- [4-[(12S)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone;
- 15 - (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(4R)-3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]methanone;
- 20 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(4S)-3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 25 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13R)-4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13S)-4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone;
- 30 - (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one;
- (6R)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one;
- 35 - (6S)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one;
- (rac)-[4-[3-fluoro-7-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- (rac)-[4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(6R)-3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 5 - [4-[(6S)-3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 10 - (rac)-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one;
- 15 - (6R)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one;
- (6S)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one;
- (rac)-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 20 - (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 25 - (rac)-[4-[(cis)-14-fluoro-4,10,12-triazatetracyclo[7.7.0.02,6.011,16]hexadeca-1(9),11,13,15-tetraen-15-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(11R,16R)-14-fluoro-4,10,12-triazatetracyclo[7.7.0.02,6.011,16]hexadeca-1(9),11,13,15-tetraen-15-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(11S,16S)-14-fluoro-4,10,12-triazatetracyclo[7.7.0.02,6.011,16]hexadeca-1(9),11,13,15-tetraen-15-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 - (rac)-[4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(13R)-4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 35 - [4-[(13S)-4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone;
- 5 - (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile;
- 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-12-one;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone;
- 10 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2R,7R)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone;
- 15 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(3S,8S)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone;
- 20 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2R,7S)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone;
- 25 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2S,7R)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(3R,8R)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone;
- 30 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2S,7S)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone;
- 35 - (rac)-[2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-[(12R)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;

- [2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-[(12S)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- (rac)-[4-[6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 5 - [4-[(6R)-6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(6S)-6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[4-(4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 10 - (rac)-[2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 15 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6R)-3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6S)-3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl)-1-piperidyl]methanone;
- 20 - (rac)-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(7E/Z)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 25 - [4-[(7E)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(7Z)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone;
- 30 - (rac)-[4-[3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(6R)-3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 35 - [4-[(6S)-3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone;

- (rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 5 [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(11R,15S)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(11S,15R)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 10 [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(11S,15R)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- (rac)-[4-(4-fluoro-6,8,13-triazatetracyclo[7.7.0.02,7.011,15]hexadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[4-(14-fluoro-4,10,12-triazatetracyclo[7.7.0.02,6.011,16]hexadeca-1(9),11,13,15-tetraen-15-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 15 (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
- (6R)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
- 20 (6S)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
- (rac)-[4-[6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[4-[3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 25 (rac)-[4-[(cis)-7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(1R,12R)-7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 [4-[(1S,12S)-7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone;
- 35 [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(1R,12R)-7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone;

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(1S,12S)-7-fluoro-3,5-diazatetracyclo[10.2.1.0²,10.0⁴,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone;
- 5 - (rac)-[4-(12-fluoro-5,14,16-triazatetracyclo[7.7.0.0²,7.0¹⁰,15]hexadeca-1(9),10,12,14-tetraen-11-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[4-[(trans)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0²,7.0¹¹,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(11R,15S)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0²,7.0¹¹,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 10 - [4-[(11S,15R)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0²,7.0¹¹,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0²,7.0¹¹,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 15 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(11R,15R)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0²,7.0¹¹,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- (rac)-[4-[(cis)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0²,7.0¹¹,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 20 - [4-[(11R,15R)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0²,7.0¹¹,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(11S,15S)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0²,7.0¹¹,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 25 - (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
- (rac)-[4-[4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.0²,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 - [4-[(12R)-4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.0²,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(12S)-4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.0²,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 35 - (rac)-[4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.0²,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(13R)-4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.0²,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- [4-[(13S)-4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- 5 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13R)-4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13S)-4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- 10 - [4-[(11S,15S)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl)-1-piperidyl]methanone;
- (rac)-[4-(7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 15 - (rac)-[4-[3-fluoro-6-(oxetan-3-ylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(6R)-3-fluoro-6-(oxetan-3-ylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 20 - [4-[(6S)-3-fluoro-6-(oxetan-3-ylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone;
- 25 - (rac)-[4-(3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl)-1-piperidyl]methanone;
- (rac)-[4-[(cis)-4-fluoro-6,8,13-triazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 35 - (rac)-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- (rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,3'-pyrrolidine]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- 5 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12R)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- (rac)-4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-
- 10 diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carbonitrile;
- (rac)-3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-
- diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-13-carbonitrile;
- (rac)-3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-
- diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carbonitrile;
- 15 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12R)-12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone; and
- 20 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone,

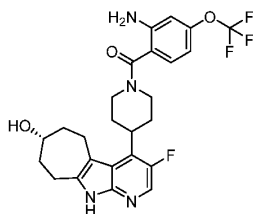
and the pharmaceutically acceptable salts thereof.

- In embodiments, the compound is selected from the compounds produced in Examples 1 to
- 25 294 (i.e., from the group consisting of Compounds 1-294), and the pharmaceutically acceptable salts thereof. In other embodiments, the compound is selected from the compounds obtainable by the synthetic methods described in any one of Examples 1 to 294 (i.e., the methods for synthesising Compounds 1-294), and the pharmaceutically acceptable salts thereof. In embodiments, the compound is selected from the compounds produced in
- 30 Examples 1 to 90 (i.e., from the group consisting of Compounds 1-90), and the pharmaceutically acceptable salts thereof. In other embodiments, the compound is selected from the compounds obtainable by the synthetic methods described in any one of Examples 1 to 90 (i.e., the methods for synthesising Compounds 1-90), and the pharmaceutically acceptable salts thereof. In embodiments, the compound is selected from the compounds
- 35 produced in Examples 91 to 294 (i.e., from the group consisting of Compounds 91 to 294), and the pharmaceutically acceptable salts thereof. In other embodiments, the compound is selected from the compounds obtainable by the synthetic methods described in any one of

Examples 91 to 294 (i.e., the methods for synthesising Compounds 91 to 294), and the pharmaceutically acceptable salts thereof.

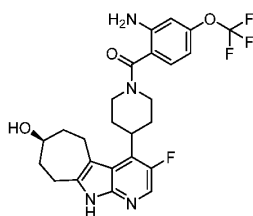
- In embodiments, the compound is selected from the compounds produced in any one of Examples 8, 9, 14, 29, 30, 44, 59, 67, 68, 79, 81, 83, 85, 86, 87, 90, 91, 111, 122, 125, 126, 136, 137, 139, 144, 145, 146, 147, 149, 150, 154, 155, 156, 159, 160, 161, 168, 171, 172, 173, 183, 184, 185, 191, 192, 204, 210, 222, 227, 228, 233, 240, 245, 288, 289, 293, and 294 (i.e., from the group consisting of Compounds 8, 9, 14, 29, 30, 44, 59, 67, 68, 79, 81, 83, 85, 86, 87, 90, 91, 111, 122, 125, 126, 136, 137, 139, 144, 145, 146, 147, 149, 150, 154, 155, 156, 159, 160, 161, 168, 171, 172, 173, 183, 184, 185, 191, 192, 204, 210, 222, 227, 228, 233, 240, 245, 288, 289, 293, and 294, and the pharmaceutically acceptable salts thereof).

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12R)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone



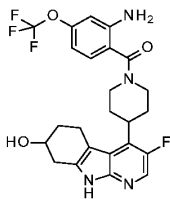
- or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone



- or a pharmaceutically acceptable salt thereof.

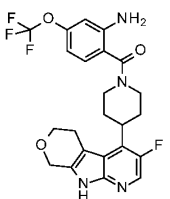
In an embodiment, the compound is (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone



or a pharmaceutically acceptable salt thereof.

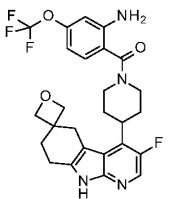
In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-fluoro-5-oxa-8,10-diazatricyclo[7.4.0.0.2,7]trideca-1(9),2(7),10,12-tetraen-13-yl)-1-

5 piperidyl]methanone



or a pharmaceutically acceptable salt thereof.

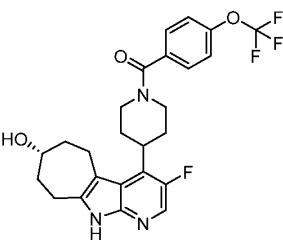
In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-oxetane]-4-yl)-1-piperidyl]methanone



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or a pharmaceutically acceptable salt thereof.

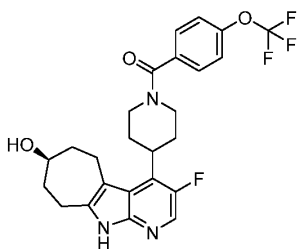
In an embodiment, the compound is [4-[(12R)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



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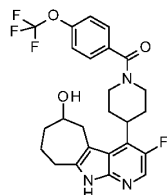
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [4-[(12S)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



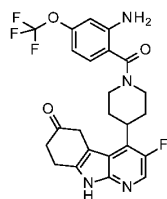
- 5 or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is (rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



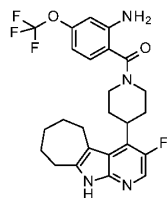
- 10 or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one



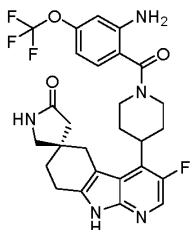
or a pharmaceutically acceptable salt thereof.

- 15 In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone



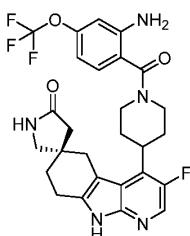
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is (6R)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one



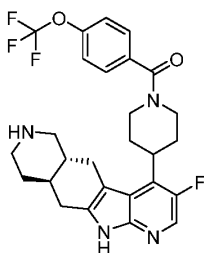
or a pharmaceutically acceptable salt thereof.

- 5 In an embodiment, the compound is (6S)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one



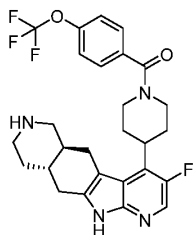
or a pharmaceutically acceptable salt thereof.

- 10 In an embodiment, the compound is [4-[(3R,8R)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.0.3,8.0.11,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



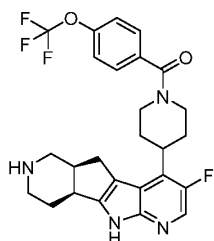
or a pharmaceutically acceptable salt thereof.

- 15 In an embodiment, the compound is [4-[(3S,8S)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.0.3,8.0.11,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



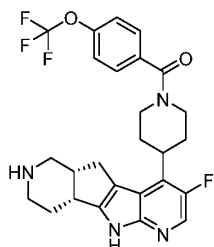
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [4-((2S,7S)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.0.2,7.0.10,15]hexadeca-1(9),10,12,14-tetraen-11-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



or a pharmaceutically acceptable salt thereof.

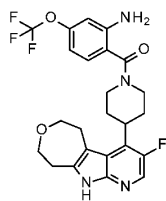
In an embodiment, the compound is [4-((2R,7R)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.0.2,7.0.10,15]hexadeca-1(9),10,12,14-tetraen-11-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



or a pharmaceutically acceptable salt thereof.

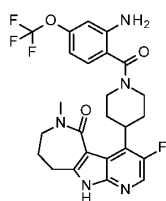
In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-oxa-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone

15



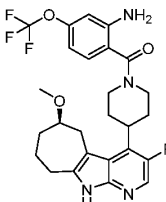
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-13-methyl-6,8,13-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-14-one



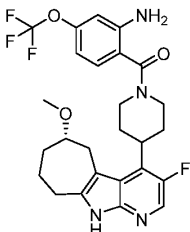
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13R)-4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone



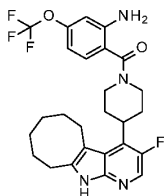
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13S)-4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone



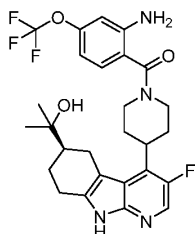
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-6,8-diazatricyclo[7.6.0.0^{2,7}]pentadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone



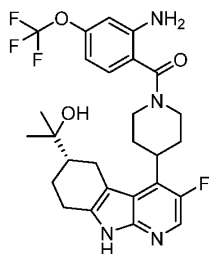
or a pharmaceutically acceptable salt thereof.

- 5 In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6R)-3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



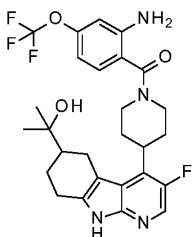
or a pharmaceutically acceptable salt thereof.

- 10 In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6S)-3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



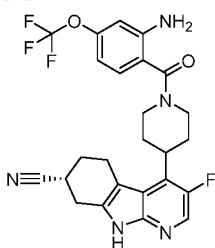
or a pharmaceutically acceptable salt thereof.

- 15 In an embodiment, the compound is (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



or a pharmaceutically acceptable salt thereof.

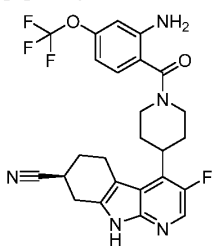
In an embodiment, the compound is (7R)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile



5

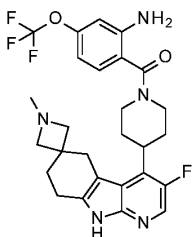
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is (7S)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile



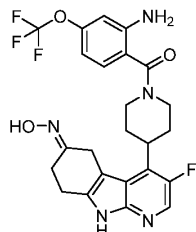
10 or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-1'-methyl-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]methanone



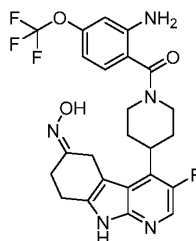
15 or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6E)-3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



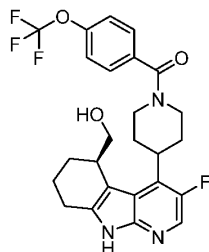
or a pharmaceutically acceptable salt thereof.

- 5 In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6Z)-3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



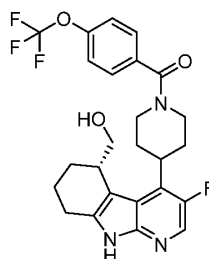
or a pharmaceutically acceptable salt thereof.

- 10 In an embodiment, the compound is [4-[(5R)-3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



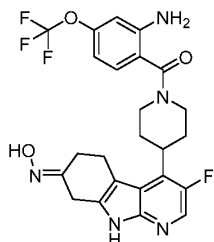
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [4-[(5S)-3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



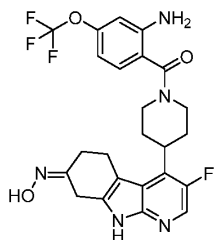
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7E)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



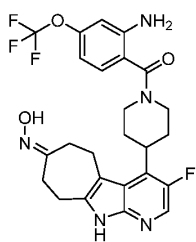
- 5 or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7Z)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



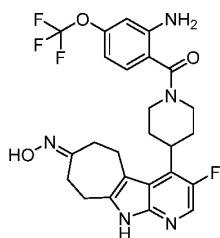
or a pharmaceutically acceptable salt thereof.

- 10 In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12E)-4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone



or a pharmaceutically acceptable salt thereof.

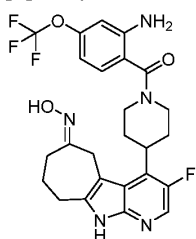
- 15 In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12Z)-4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone



or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13E)-4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone

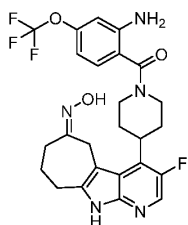
5



or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13Z)-4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone

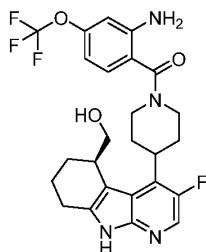
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or a pharmaceutically acceptable salt thereof.

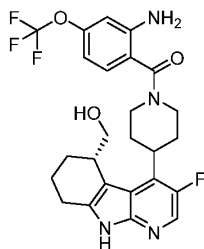
In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(5R)-3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone

15



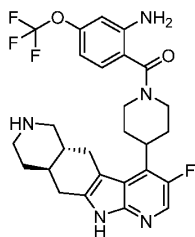
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(5S)-3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



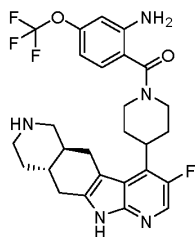
5 or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(3R,8R)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone



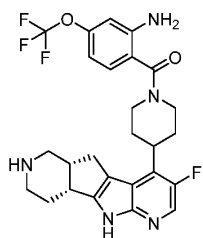
10 or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(3S,8S))-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone



15 or a pharmaceutically acceptable salt thereof.

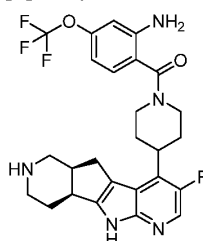
In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2R,7R)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone



or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2S,7S)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.0.2,7.0.10,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone

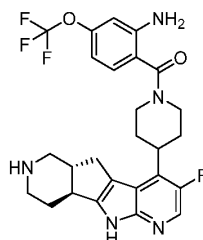
5



or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2S,7R)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.0.2,7.0.10,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone

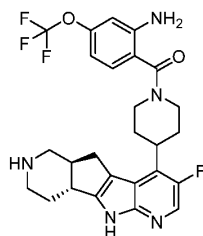
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or a pharmaceutically acceptable salt thereof.

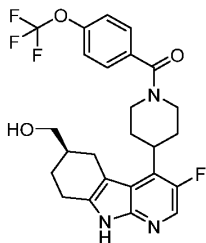
In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2R,7S)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.0.2,7.0.10,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone

15



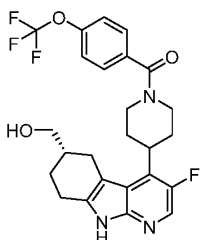
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [4-[(6R)-3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



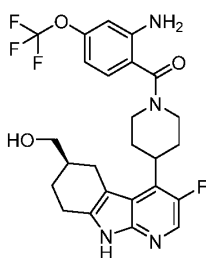
- 5 or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [4-[(6S)-3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



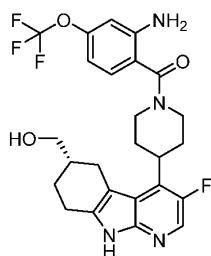
or a pharmaceutically acceptable salt thereof.

- 10 In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6R)-3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



or a pharmaceutically acceptable salt thereof.

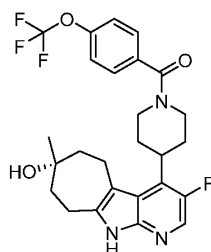
- 15 In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6S)-3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [4-[(12R)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-

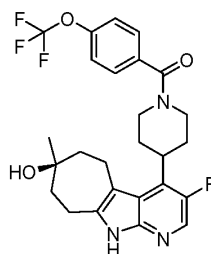
5 (trifluoromethoxy)phenyl]methanone



or a pharmaceutically acceptable salt thereof.

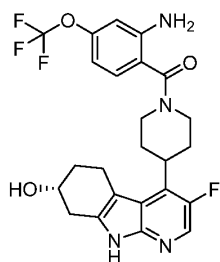
In an embodiment, the compound is [4-[(12S)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-

10 (trifluoromethoxy)phenyl]methanone



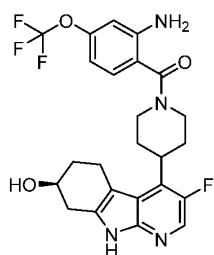
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7R)-3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



or a pharmaceutically acceptable salt thereof.

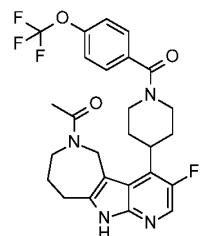
In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7S)-3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



5

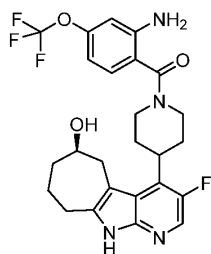
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is 1-[4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-13-yl]ethanone



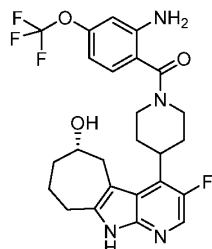
10 or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13R)-4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone



or a pharmaceutically acceptable salt thereof.

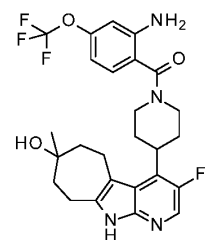
In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13S)-4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone



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or a pharmaceutically acceptable salt thereof.

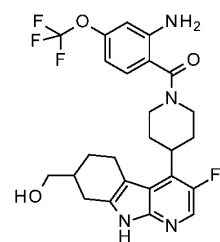
In an embodiment, the compound is (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone



10

or a pharmaceutically acceptable salt thereof.

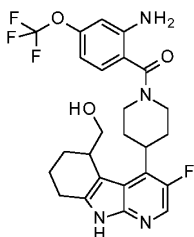
In an embodiment, the compound is (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



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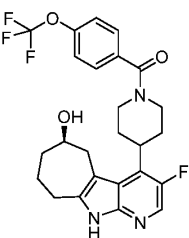
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



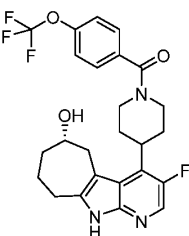
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [4-[(13R)-4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



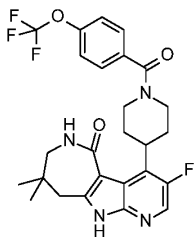
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [4-[(13S)-4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



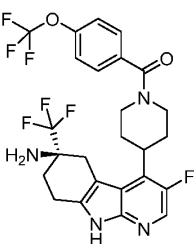
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is 4-fluoro-11,11-dimethyl-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-14-one



or a pharmaceutically acceptable salt thereof.

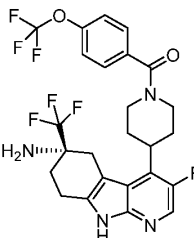
In an embodiment, the compound is [4-[(6R)-6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



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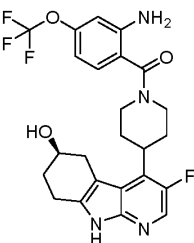
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [4-[(6S)-6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



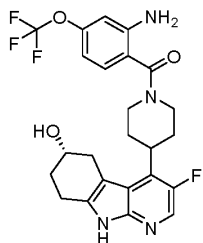
10 or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6R)-3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



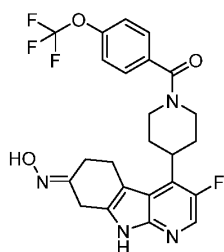
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6S)-3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



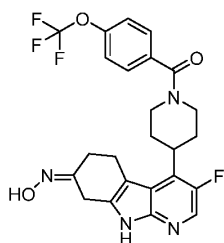
or a pharmaceutically acceptable salt thereof.

- 5 In an embodiment, the compound is [4-[(7E)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



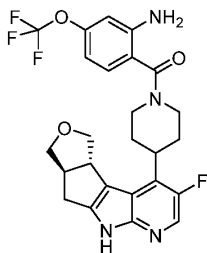
or a pharmaceutically acceptable salt thereof.

- 10 In an embodiment, the compound is [4-[(7Z)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



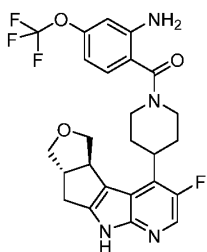
or a pharmaceutically acceptable salt thereof.

- 15 In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(11R,15S)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.0.11,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone



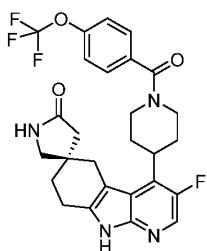
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(11S,15R)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone



or a pharmaceutically acceptable salt thereof.

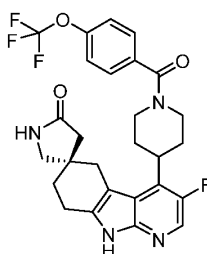
In an embodiment, the compound is (6R)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one



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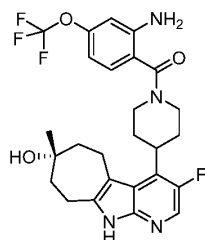
or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is (6S)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one



or a pharmaceutically acceptable salt thereof.

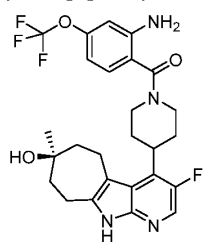
In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12R)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone



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or a pharmaceutically acceptable salt thereof.

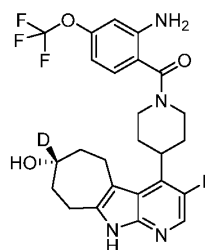
In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone



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or a pharmaceutically acceptable salt thereof.

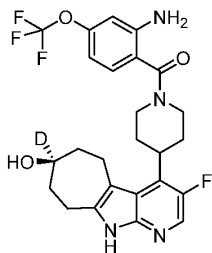
In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12R)-12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone



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or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound is [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone



or a pharmaceutically acceptable salt thereof.

In embodiments, the compound of the disclosure is characterised according to its inhibitory activity against ERK5, e.g., as measured according to the cell-based assay or cell-free assay described in the examples below. In embodiments, the compound has an IC_{50} value of less than about 10 μM against ERK5 (e.g., when measured according to the cell-free assay described below). In embodiments, the compound has an IC_{50} value of less than about 5 μM , e.g., less than about 2 μM , 1 μM , 0.5 μM , 0.2 μM , 100 nM, or 50 nM against ERK5 (e.g., when measured according to the cell-free assay described below). In embodiments, the compound has an IC_{50} value of less than about 10 μM against ERK5 when measured according to the cell-free assay described below. In embodiments, the compound has an IC_{50} value of less than about 5 μM , e.g., less than about 2 μM , 1 μM , 0.5 μM , 0.2 μM , 100 nM, or 50 nM against ERK5 when measured according to the cell-free assay described below. In embodiments, the compound has an IC_{50} value of less than about 10 μM against ERK5 when measured according to the cell-based assay described below. In embodiments, the compound has an IC_{50} value of less than about 5 μM , e.g., less than about 2 μM , 1 μM , 0.5 μM , 0.2 μM , 100 nM, or 50 nM against ERK5 when measured according to the cell-based assay described below.

In embodiments, the compound is selected from the compound of Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269,

270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, and 294. In other embodiments, the compound is selected from the compound of Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, and 294. In other embodiments, the compound is selected from the compound of Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, and 294. In other embodiments, the compound is selected from the compound of Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 73, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 96, 97, 98, 99, 100, 101, 102, 103, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 136, 137, 138, 139,

140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 5 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, and 294. In other embodiments, the compound is
10 selected from the compound of Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 73, 75, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 97, 98, 100, 101, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124,
15 125, 126, 127, 128, 129, 130, 131, 133, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 166, 167, 168, 169, 170, 171, 172, 173, 175, 177, 178, 179, 181, 182, 183, 184, 185, 186, 188, 189, 190, 191, 192, 193, 194, 195, 196, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 222, 223, 224, 225, 226,
20 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, and 294. In other embodiments, the
compound is selected from the compound of Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14,
25 16, 17, 18, 19, 20, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 37, 38, 39, 41, 43, 44, 45, 46, 48, 50, 52, 53, 54, 55, 57, 58, 59, 60, 61, 63, 65, 66, 67, 68, 69, 75, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 97, 98, 100, 101, 107, 108, 109, 110, 111, 112, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 128, 129, 131, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 153, 154, 155, 156, 157, 158,
30 159, 160, 161, 162, 166, 167, 168, 169, 170, 171, 172, 173, 178, 179, 181, 182, 183, 184, 185, 186, 188, 190, 191, 192, 193, 194, 195, 196, 198, 199, 200, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 222, 223, 224, 225, 226, 227, 228, 230, 231, 232, 233, 234, 236, 238, 239, 240, 241, 242, 243, 245, 246, 247, 249, 250, 252, 253, 254, 255, 256, 257, 258, 260, 262, 263, 264, 266, 267, 269, 270, 271,
35 272, 273, 274, 275, 276, 277, 278, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, and 294. In other embodiments, the compound is selected from the compound
of Examples 2, 3, 4, 5, 7, 8, 9, 13, 14, 16, 17, 18, 20, 23, 24, 25, 28, 29, 30, 31, 32, 33, 35, 38, 39, 41, 43, 44, 46, 50, 52, 53, 54, 55, 57, 58, 59, 61, 63, 65, 66, 67, 68, 69, 75, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 100, 108, 109, 110, 111, 112, 114, 115, 117, 118, 120,

121, 122, 123, 124, 125, 126, 128, 129, 131, 136, 137, 138, 139, 140, 141, 143, 144, 145, 146, 147, 148, 149, 150, 151, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 166, 167, 168, 169, 170, 171, 172, 173, 178, 179, 181, 182, 183, 184, 185, 186, 188, 191, 192, 193, 194, 196, 198, 199, 200, 202, 203, 204, 205, 206, 207, 209, 210, 211, 212, 213, 214, 215, 5 216, 217, 218, 219, 220, 223, 225, 226, 227, 228, 230, 232, 233, 234, 239, 240, 241, 242, 243, 245, 249, 250, 252, 254, 257, 258, 260, 262, 267, 269, 271, 272, 273, 274, 275, 276, 277, 278, 282, 286, 287, 288, 289, 290, 291, 292, 293, and 294.

In embodiments, the compound is selected from the compound of Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 10 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 108, 109, 110, 111, 112, 113, 114, 115, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 15 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 238, 239, 240, 241, 20 242, 243, 244, 245, 246, 247, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, and 287. In other embodiments, the compound is selected from the compound of Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 25 46, 48, 49, 50, 51, 52, 54, 55, 56, 57, 58, 59, 61, 62, 63, 64, 65, 66, 67, 68, 69, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 108, 109, 110, 111, 112, 113, 114, 115, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 30 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 249, 252, 253, 254, 255, 256, 257, 35 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, and 287. In other embodiments, the compound is selected from the compound of Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41,

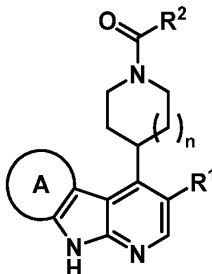
42, 43, 44, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 61, 62, 63, 64, 65, 66, 67, 68, 69, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 99, 100, 101, 102, 103, 104, 105, 106, 108, 109, 110, 111, 112, 113, 114, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 178, 179, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 249, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 280, 281, 282, 283, 284, 285, and 287. In other embodiments, the compound is selected from the compound of Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 20, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 40, 41, 42, 43, 44, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 61, 62, 63, 64, 65, 66, 67, 68, 69, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 96, 97, 99, 100, 101, 102, 103, 104, 105, 106, 108, 109, 110, 111, 112, 113, 114, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 134, 135, 136, 137, 138, 139, 140, 141, 142, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 178, 179, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 249, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 280, 281, 282, 283, 285, and 287. In other embodiments, the compound is selected from the compound of Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 20, 23, 24, 27, 28, 29, 30, 31, 32, 33, 34, 35, 37, 38, 41, 43, 44, 46, 48, 49, 52, 54, 55, 57, 58, 59, 61, 63, 64, 65, 66, 67, 68, 69, 75, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 97, 101, 102, 103, 104, 105, 106, 108, 109, 110, 111, 112, 113, 114, 117, 118, 120, 121, 122, 123, 124, 125, 126, 128, 129, 131, 134, 135, 136, 137, 138, 139, 140, 141, 144, 145, 146, 147, 148, 149, 150, 151, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 170, 171, 172, 173, 178, 181, 182, 183, 184, 185, 186, 188, 191, 192, 193, 194, 195, 196, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 216, 217, 218, 219, 220, 223, 225, 226, 227, 228, 231, 232, 233, 234, 240, 241, 242, 243, 245, 246, 247, 249, 252, 254, 255, 256, 257, 258, 259, 260, 261, 262, 267, 269, 271, 272, 274, 275, 276, 277, 278, 281, 282, 283, 285, and 287. In other embodiments, the compound is selected from the compound of Examples 1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 14, 17, 20, 23, 24, 30, 31, 32, 33, 34, 35, 38, 43, 44, 46, 48, 54, 58, 59, 61, 63, 65, 66, 67, 75, 78, 79, 80, 81, 82, 83, 85, 86, 87, and 90, 91, 92, 101, 102, 103, 104, 105, 106, 108, 109, 110, 111,

- 112, 113, 117, 118, 122, 123, 124, 125, 126, 129, 131, 134, 135, 136, 137, 139, 140, 144, 145, 146, 147, 148, 149, 150, 151, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 164, 165, 166, 167, 168, 170, 171, 172, 173, 181, 183, 184, 185, 186, 188, 191, 192, 193, 194, 196, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 212, 218, 223, 225, 226, 227, 228, 232, 233, 240, 241, 242, 243, 245, 252, 254, 255, 256, 257, 258, 259, 260, 261, 262, 269, 271, 274, 275, 276, 277, 278, 281, 282, 283, 285. In other embodiments, the compound is selected from the compound of Examples 2, 3, 5, 7, 8, 9, 14, 23, 30, 31, 32, 33, 34, 35, 38, 44, 46, 48, 54, 58, 59, 63, 65, 66, and 67, 78, 79, 80, 81, 82, 83, 85, 86, 90, 103, 105, 106, 109, 110, 111, 118, 122, 123, 125, 126, 129, 131, 134, 135, 136, 137, 139, 140, 144, 145, 146, 147, 149, 150, 153, 154, 155, 156, 157, 160, 161, 166, 167, 168, 171, 172, 173, 183, 184, 185, 186, 188, 191, 192, 193, 194, 196, 200, 202, 203, 204, 205, 206, 207, 209, 210, 218, 223, 227, 228, 233, 240, 242, 243, 245, 254, 255, 256, 257, 260, 262, 271, 274, 277, 281, 282, and 283.

Processes for producing Compounds of the disclosure and Intermediate Compounds

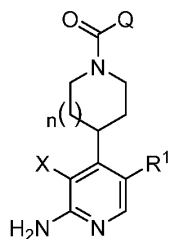
- 15 The present disclosure also provides processes for the preparation of compounds as described herein, and intermediates for use in the preparation of said compounds.

Accordingly, provided is a process for the preparation of a compound of Formula (I) as defined herein



Formula (I)

- 20 or a pharmaceutically acceptable salt thereof, wherein the process comprises reacting a compound of Formula HE

**HE**

with a compound of Formula J

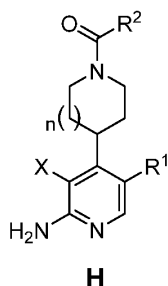
**J**

wherein:

- 5 Q is either a group R^2 as defined herein (or a protected version of the same), or taken together with the adjacent carbonyl is an amine protecting group, and wherein ring A, R^1 , and n are as defined herein, and X is a halogen (e.g. I, Br or Cl).

In embodiments, R^1 is F.

- In embodiments, the process comprises a chiral separation step (e.g., to isolate one stereoisomer from a mixture of stereoisomers). In embodiments, the process comprises a regioisomer separation step (e.g., to isolate one regioisomer from a mixture of regioisomers). In embodiments, the process comprises a step in which an E (or cis) isomer is separated from a mixture of E and Z isomers. In embodiments, the process comprises a step in which a Z (or trans) isomer is separated from a mixture of E and Z isomers. A person of ordinary skill in the art will be aware of many chiral, stereoisomer, and regioisomer separation methods, for example those illustrated herein.
- 10 In embodiments, Q is a protected version of a group R^2 as defined herein. In embodiments, Q is a phenyl group having a protected amine substituent, optionally alongside other substituents (e.g. a group $-OCF_3$).
- 15 In embodiments, Q is a group R^2 as defined herein. Accordingly, in embodiments the compound of Formula HE is a compound of Formula H

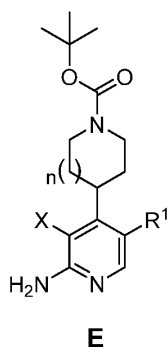


wherein R^1 , R^2 , n , and X are as defined herein.

In embodiments, the process of reacting Compound H with Compound J comprises the use of a Pd catalyst. In embodiments, the process comprises the use of a Pd catalyst, a base, and a solvent. A person of ordinary skill in the art will appreciate that references to “a Pd catalyst” include a Pd catalyst / ligand. In embodiments, the Pd catalyst is bis(tri-tert-butylphosphine)palladium (0). In embodiments, the base is 1,4-diazabicyclo[2.2.2]octane. In embodiments, the solvent is DMF. Thus, in embodiments the process comprises the use of bis(tri-tert-butylphosphine)palladium (0) as catalyst, 1,4-diazabicyclo[2.2.2]octane as a base, and DMF a solvent.

In embodiments, the process comprises one or more of the steps shown in Scheme 1. In embodiments, the process comprises all of the steps shown in Scheme 1. In embodiments, the process comprises Step 6 of Scheme 1. In embodiments, the process comprises one or more of the steps of Method A. In embodiments, the process is substantially as described in Method A. In embodiments, the process comprises one or more of the steps of Method D. In embodiments, the process is substantially as described in Method D.

In embodiments, Q taken together with the adjacent carbonyl is an amine protecting group (e.g., Boc). Accordingly, in embodiments the compound of Formula HE is a compound of Formula E



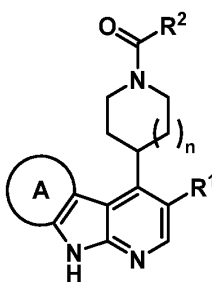
wherein R^1 , n , and X are as defined herein.

In embodiments, the process of reacting Compound E with Compound J comprises the use of a Pd catalyst. In embodiments, the process comprises the use of a Pd catalyst, a base, and a solvent. A person of ordinary skill in the art will appreciate that references to “a Pd catalyst” include a Pd catalyst / ligand. In embodiments, the Pd catalyst is bis(tri-tert-

- 5 butylphosphine)palladium (0). In embodiments, the base is 1,4-diazabicyclo[2.2.2]octane. In embodiments, the solvent is DMF. Thus, in embodiments the process comprises the use of bis(tri-tert-butylphosphine)palladium (0) as catalyst, 1,4-diazabicyclo[2.2.2]octane as a base, and DMF a solvent.

- In embodiments, the process comprises one or more of the steps shown in Scheme 3. In
10 embodiments, the process comprises Step 1 of Scheme 3. In embodiments, the process comprises one or more of the steps of Method E. In embodiments, the process is substantially as described in Method E.

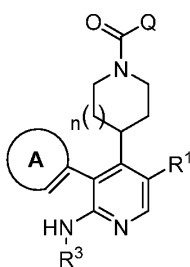
In another aspect, the disclosure provides a process for the preparation of a compound of Formula (I) as defined herein



Formula (I)

15

or a pharmaceutically acceptable salt thereof, wherein the process comprises the intramolecular cyclisation of a compound of Formula MP



MP

wherein:

- 20 Q is either a group R² as defined herein (or a protected version of the same), or taken together with the adjacent carbonyl is an amine protecting group; and
R³ is selected from H and a nitrogen-compatible leaving group (e.g., Ts),

and wherein ring A, R^1 , and n are as defined herein.

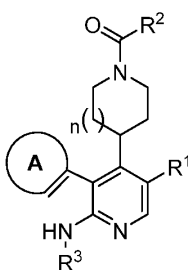
In embodiments, R^3 is H. In embodiments, R^3 is Ts. In embodiments, R^1 is F.

In embodiments, the process comprises a chiral separation step (e.g., to isolate one stereoisomer from a mixture of stereoisomers). In embodiments, the process comprises a regioisomer separation step (e.g., to isolate one regioisomer from a mixture of regioisomers). In embodiments, the process comprises a step in which an E (or cis) isomer is separated from a mixture of E and Z isomers. In embodiments, the process comprises a step in which a Z (or trans) isomer is separated from a mixture of E and Z isomers. A person of ordinary skill in the art will be aware of many chiral, stereoisomer, and regioisomer separation methods, for example those illustrated herein.

In embodiments, the intramolecular cyclisation of the compound of Formula MP comprises the use of a hypervalent iodine reagent and optionally a solvent. In embodiments, the hypervalent iodine reagent is PIFA. In embodiments, the solvent is THF. In embodiments, the intramolecular cyclisation of the compound of Formula MP comprises the use of PIFA and THF.

In embodiments, Q is a protected version of a group R^2 as defined herein. In embodiments, Q is a phenyl group having a protected amine substituent, optionally alongside other substituents (e.g. a group $-OCF_3$).

In embodiments, Q is a group R^2 as defined herein. Accordingly, in embodiments the compound of Formula MP is a compound of Formula M1



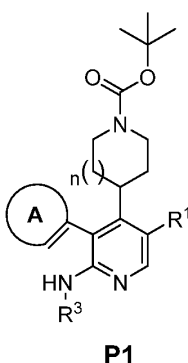
M1

wherein ring A, R^1 , R^2 , R^3 , and n are as defined herein. In embodiments, R^3 is H (i.e. the compound is Compound M as defined herein). In other embodiments, R^3 is Ts (i.e. the compound is Compound M' as defined herein).

In embodiments, the intramolecular cyclisation comprises the use of a silver (I) salt and optionally a solvent. In embodiments, the silver (I) salt is Ag_2CO_3 . In embodiments, the solvent is THF. In embodiments, the intramolecular cyclisation comprises the use of Ag_2CO_3 and THF.

In embodiments, the process comprises one or more of the steps shown in Scheme 2. In
embodiments, the process comprises all of the steps shown in Scheme 2. In embodiments, the
process comprises Step 2 of Scheme 2. In embodiments, the process comprises one or more
of the steps shown in Scheme 2A. In embodiments, the process comprises all of the steps
5 shown in Scheme 2A. In embodiments, the process comprises Step 3 of Scheme 2A. In
embodiments, the process comprises one or more of the steps of Method C. In embodiments,
the process is substantially as described in Method C.

In embodiments, Q taken together with the adjacent carbonyl is an amine protecting group
(e.g., Boc). Accordingly, in embodiments the compound of Formula MP is a compound of
10 Formula P1



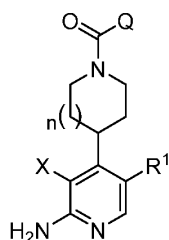
wherein ring A, R^1 , R^3 , and n are as defined herein. In embodiments, R^3 is H (i.e. the
compound is Compound P as defined herein). In other embodiments, R^3 is Ts (i.e. the
compound is Compound P' as defined herein).

15 In embodiments, the process comprises one or more of the steps shown in Scheme 4. In
embodiments, the process comprises all of the steps shown in Scheme 4. In embodiments, the
process comprises Step 3 of Scheme 4. In embodiments, the process comprises one or more
of the steps of Method F. In embodiments, the process is substantially as described in Method
F. In embodiments, the process comprises all of the steps of Method F apart from the steps of
20 N-tosylation and de-tosylation.

In embodiments, the compound prepared by the processes defined herein is selected from a
compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (V) or Formula
(VI) as defined herein, and the pharmaceutically acceptable salts thereof.

The present disclosure is also directed to intermediates useful in the preparation of the
25 compounds of the disclosure. A person of ordinary skill in the art will appreciate that the
processes described herein in the context of preparing compounds of the disclosure can be
used to provide such intermediates.

Viewed from this aspect, the disclosure provides a compound of Formula HE



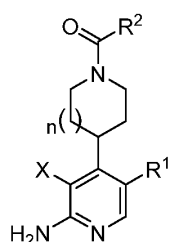
HE

or a pharmaceutically acceptable salt thereof, wherein R^1 and n are as defined herein, and wherein:

- 5 Q is either a group R^2 as defined herein (or a protected version of the same), or taken together with the adjacent carbonyl is an amine protecting group (e.g. Boc); and
 X is a halogen (e.g. I, Br, Cl).

In embodiments, R^1 is F.

In embodiments, the compound is a compound of Formula H

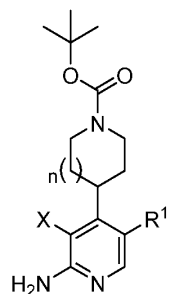


H

10

or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , n , and X are as defined herein.

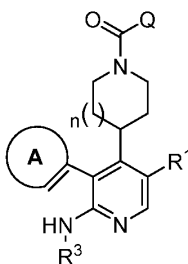
In other embodiments, the compound is a compound of Formula E



E

or a pharmaceutically acceptable salt thereof, wherein R^1 , n , and X are as defined herein.

The disclosure also provides a compound of Formula MP



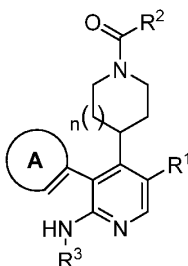
MP

or a pharmaceutically acceptable salt thereof, wherein ring A, R^1 , and n are as defined herein,
5 and wherein:

Q is either a group R^2 as defined herein (or a protected version of the same), or taken together with the adjacent carbonyl is an amine protecting group (e.g., Boc); and
 R^3 is selected from H and a nitrogen-compatible leaving group (e.g., Ts).

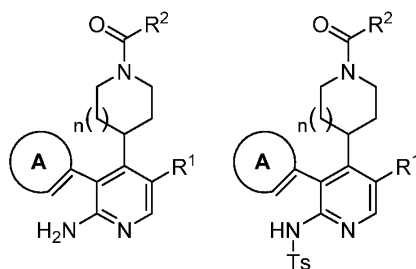
In embodiments, R^3 is H. In other embodiments, R^3 is Ts. In embodiments, R^1 is F.

10 In embodiments, the compound is a compound of Formula M1



M1

or a pharmaceutically acceptable salt thereof, wherein ring A, R^1 , R^2 , R^3 , and n are as defined herein. In embodiments, the compound is a compound of Formula M or Formula M'

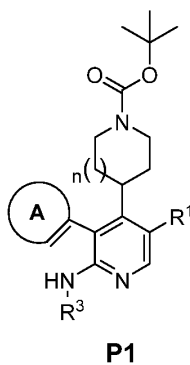


M

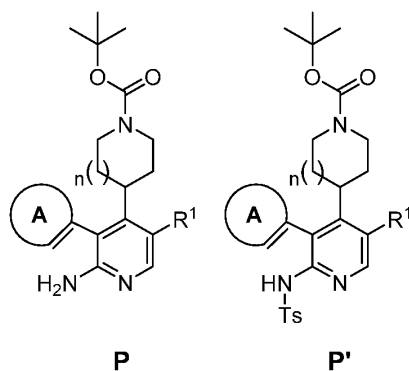
M'

or a pharmaceutically acceptable salt thereof, wherein ring A, R^1 , R^2 , and n are as defined herein.

In embodiments, the compound is a compound of Formula P1



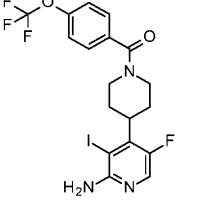
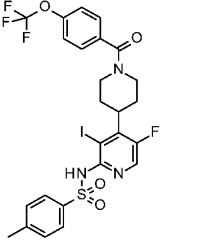
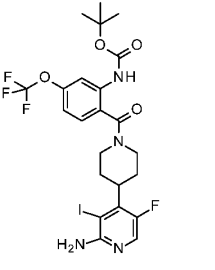
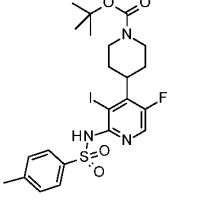
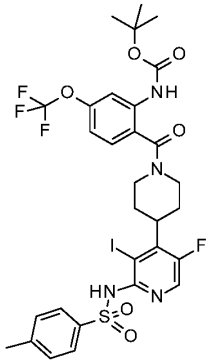
- 5 or a pharmaceutically acceptable salt thereof, wherein ring A, R^1 , R^3 , and n are as defined herein. In embodiments, the compound is a compound of Formula P or Formula P'

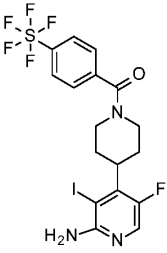
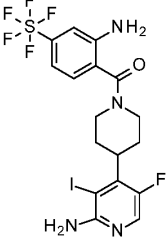


or a pharmaceutically acceptable salt thereof, wherein ring A, R^1 , and n are as defined herein.

In embodiments, the compound is selected from:

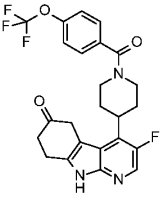
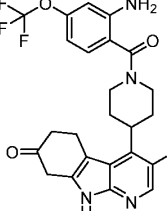
	tert-butyl 4-(2-amino-5-fluoro-3-iodo-4-pyridyl)piperidine-1-carboxylate
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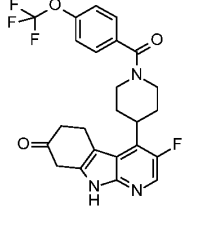
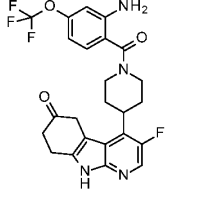
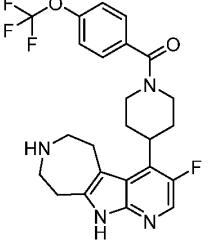
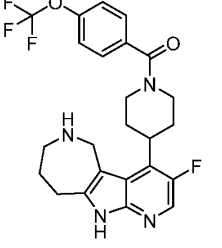
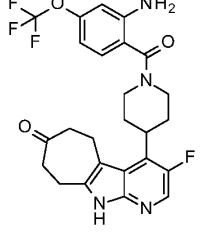
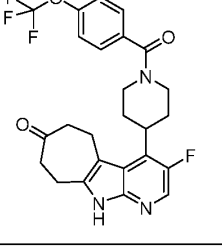
	[4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
	N-[5-fluoro-3-iodo-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-2-pyridyl]-4-methyl-benzenesulfonamide
	tert-butyl N-[2-[4-(2-amino-5-fluoro-3-iodo-4-pyridyl)piperidine-1-carbonyl]-5-(trifluoromethoxy)phenyl]carbamate
	tert-butyl 4-[5-fluoro-3-iodo-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carboxylate
	tert-butyl N-[2-[4-[5-fluoro-3-iodo-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carbonyl]-5-(trifluoromethoxy)phenyl]carbamate

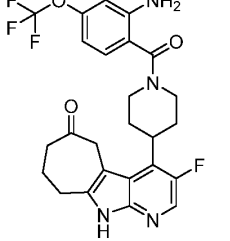
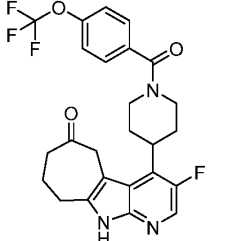
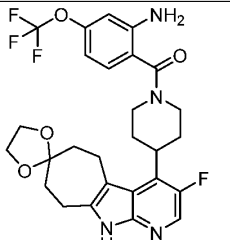
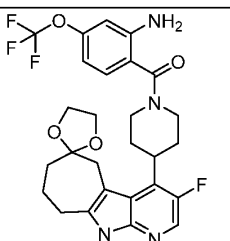
	[4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[4-(pentafluoro-λ ⁶ -sulfanyl)phenyl]methanone
	[4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[2-amino-4-(pentafluoro-λ ⁶ -sulfanyl)phenyl]methanone

and the pharmaceutically acceptable salts thereof.

- It will be appreciated that compounds of the disclosure can act as precursors or intermediates to other compounds of the disclosure. For example, compounds bearing a ketone on ring A
- 5 may be used as precursors of compounds which carry alkyl groups, hydroxyl groups and/or other groups at the ketone position. The present disclosure thus provides the following compounds which may be useful as intermediates or precursors in the preparation of compounds as disclosed herein:

	3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one
	4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,6,8,9-tetrahydropyrido[2,3-b]indol-7-one

	3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,6,8,9-tetrahydropyrido[2,3-b]indol-7-one
	4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one
	[4-(4-fluoro-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
	[4-(4-fluoro-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
	3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-12-one
	4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-12-one

	3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-13-one
	4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one
	[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4'-fluorospiro[1,3-dioxolane-2,12'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraene]-3'-yl)-1-piperidyl]methanone
	[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4'-fluorospiro[1,3-dioxolane-2,13'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraene]-3'-yl)-1-piperidyl]methanone

and the pharmaceutically acceptable salts thereof.

Pharmaceutical Compositions

The present disclosure provides a pharmaceutical composition comprising a compound described herein (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof), and at least one pharmaceutically acceptable excipient or carrier.

In embodiments, the pharmaceutical composition comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (II) or a pharmaceutically acceptable salt thereof. In 10
embodiments, the pharmaceutical composition comprises a compound of Formula (III) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition

comprises a compound of Formula (IV) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (V) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (VI) or a pharmaceutically acceptable salt thereof.

- 5 The pharmaceutical compositions of the disclosure may be formulated for administration in solid or liquid form, e.g., using conventional carriers or excipients. Compositions may be adapted for, e.g., oral administration (e.g., as a solution, suspension, tablet, or capsule), parenteral administration (e.g., as a solution, dispersion, suspension, or emulsion, or as a dry powder for reconstitution), or topical application (e.g., as a cream, ointment, patch, or spray
10 to be applied to the skin) using techniques known in the art.

Medical Uses

Compounds of the present disclosure act as inhibitors of ERK5, which gives them utility in the treatment of ERK5-associated disorders and conditions. In particular, compounds of the disclosure are useful in the treatment of cancers.

- 15 Viewed from this aspect, the disclosure provides a method of treatment comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof). In a related aspect, the disclosure provides the use of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof) in the
20 manufacture of a medicament. In a further related aspect, the disclosure provides a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof) for use in therapy.

- Compounds of the present disclosure are useful for treating or preventing: diseases or deleterious conditions in which ERK5, or a variant or mutant thereof, is known to play a role;
25 diseases or disorders associated with increased *MAPK7* (i.e., ERK5 gene) expression and/or increased ERK5 activity; and diseases or disorders in which inhibition or antagonism of ERK5 activity is beneficial.

- In one aspect, the present disclosure provides a method of treating or preventing a disease or disorder mediated by ERK5, or a disease or disorder in which ERK5 is implicated, in a
30 subject in need thereof, the method comprising administering to the subject an effective amount of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof). In a related aspect, the disclosure provides the use of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for the treatment or prevention of
35 a disease or disorder mediated by ERK5, or a disease or disorder in which ERK5 is

implicated. In a further related aspect, the disclosure provides a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof) for use in the treatment or prevention of a disease or disorder mediated by ERK5, or a disease or disorder in which ERK5 is implicated.

- 5 In another aspect, the present disclosure provides a method of treating or preventing a disease or disorder associated with ERK5 (e.g., cancer) in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof). In a related aspect, the disclosure provides the use of a compound of the disclosure (e.g., a compound of
- 10 Formula (I) or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for the treatment or prevention of a disease or disorder associated with ERK5 (e.g., cancer). In a further related aspect, the disclosure provides a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof) for use in the treatment or prevention of a disease or disorder associated with ERK5 (e.g.,
- 15 cancer).

- In another aspect, the present disclosure provides a method of treating or preventing cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof). In a related aspect, the disclosure provides the use
- 20 of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for the treatment or prevention of cancer. In a further related aspect, the disclosure provides a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof) for use in the treatment or prevention of cancer.

- 25 In embodiments, the compound reduces angiogenesis, reduces or prevents metastasis, reduces inflammation, blocks tumorigenesis (e.g., in part or completely), reduces evasion of growth suppression, reduces or inhibits growth of cancerous or pre-cancerous cells, suppresses proliferation of cancerous or pre-cancerous cells, and/or reduces the survival of cancerous or pre-cancerous cells.
- 30 In embodiments, the cancer is characterized by increased *MAPK7* (i.e., ERK5 gene) expression and/or increased ERK5 activity. In embodiments, the cancer has elevated ERK5 activity. In embodiments, the cancer overexpresses ERK5. In embodiments, the cancer is characterised by *MAPK7* genomic amplification and/or constitutively active ERK5 signalling. In embodiments, the cancer has genomically amplified ERK5. In embodiments, the cancer
- 35 has constitutively active ERK5 signalling.

In embodiments, the cancer is a solid tumour (e.g., a melanoma, carcinoma, or blastoma). In other embodiments, the cancer is leukaemia (e.g., chronic lymphocytic leukaemia, CLL; acute myelogenous leukaemia, AML; or chronic myelogenous leukaemia, CML).

5 In embodiments, the cancer is a primary tumour. In other embodiments, the cancer is a secondary tumour (e.g., a metastatic tumour).

In embodiments, the cancer is selected from breast cancer (e.g., ductal breast carcinoma, or breast adenocarcinoma), liver cancer, kidney cancer (e.g., hepatocellular carcinoma), prostate cancer, colorectal cancer (CRC), lung cancer (e.g., non-small cell lung cancer, NSCLC; lung adenocarcinoma; or lung squamous cell carcinoma), pancreatic cancer (e.g.,
10 adenocarcinoma), ovarian cancer, brain cancer (e.g., glioblastoma), cervical cancer (e.g., adenocarcinoma), gastric cancer, skin cancer (e.g., melanoma), bile duct cancer (e.g., cholangiocarcinoma), nervous system cancer (e.g., neuroblastoma), and melanoma.

In embodiments, the cancer is selected from leukaemia (e.g., acute leukaemia, acute lymphocytic leukaemia, acute myelocytic leukaemia, acute myeloblastic leukaemia, acute
15 promyelocytic leukaemia, acute myelomonocytic leukaemia, acute monocytic leukaemia, acute erythroleukemia, chronic leukaemia, chronic myelocytic leukaemia, or chronic lymphocytic leukaemia), polycythaemia vera, lymphoma (e.g., Hodgkin's disease or non-Hodgkin's disease), Waldenström macroglobulinemia, and multiple myeloma.

In embodiments, the cancer is selected from leukaemia (e.g., chronic myeloid leukaemia),
20 breast cancer, multiple myeloma, colon cancer, colorectal cancer, lung cancer, pancreatic cancer, renal cell carcinoma, mesothelioma, adenocarcinoma, neuroblastoma, melanoma, and hepatocellular carcinoma.

In another aspect, the disclosure provides a method of inhibiting ERK5 activity, the method comprising contacting ERK5 (e.g., a cell comprising ERK5) with a compound of the present
25 disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof). In embodiments, the method is an *in vitro* or *ex vivo* method. In other embodiments the method is an *in vivo* method. In a related aspect, the disclosure provides an *in vitro* method of inhibiting ERK5 activity in a cell, the method comprising contacting the cell with a compound of the present disclosure (e.g., a compound of Formula (I) or a pharmaceutically
30 acceptable salt thereof).

Compounds of the present disclosure (e.g., compounds of Formula (I)) and the pharmaceutically acceptable salts thereof may be administered as pharmaceutical compositions, which may optionally comprise one or more pharmaceutically acceptable excipients.

It will be appreciated that the methods and treatments of the various aspects of this disclosure may be effected by administering to a subject an effective amount of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof), in the form of a pharmaceutical composition, which may optionally comprise one or more
 5 pharmaceutically acceptable excipients, as described herein.

The compounds of the disclosure may be used alone (e.g., as a monotherapy) or in combination with one or more cancer therapies.

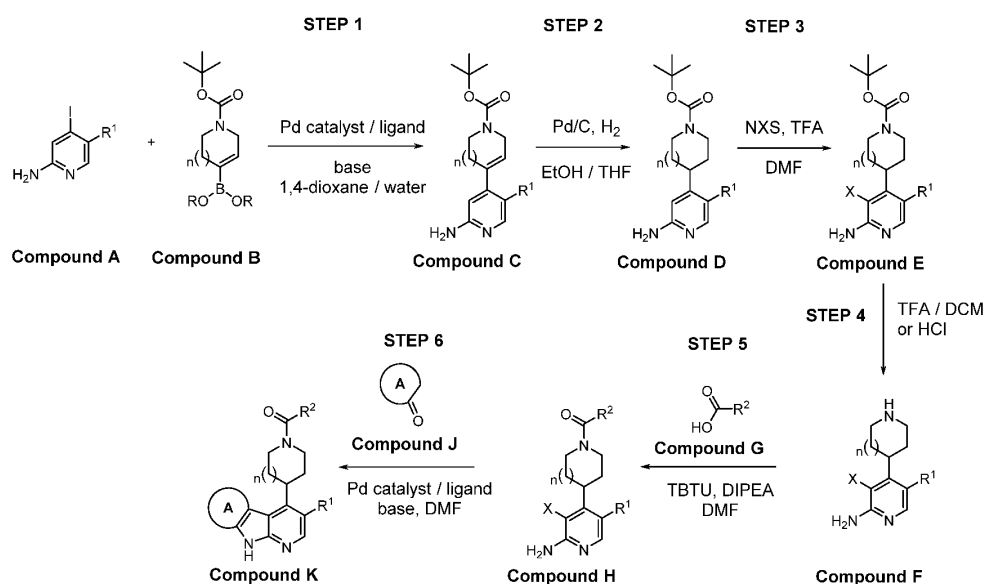
Having been generally described herein, the follow non-limiting examples are provided to further illustrate this disclosure.

10

EXAMPLES

General synthetic schemes

The following scheme, Scheme 1, illustrates an exemplary way of preparing compounds in accordance with the present disclosure and examples (e.g. compounds of Formula (I)):



15

SCHEME 1

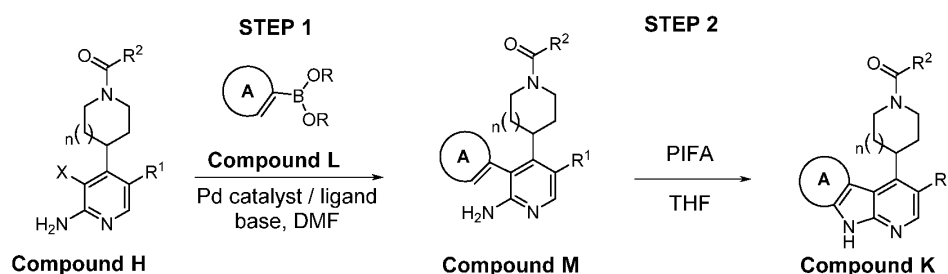
According to Scheme 1 (in which ring A, R¹, R², and n may be, e.g., as described above), Compound C can be obtained in STEP 1 by Suzuki coupling between Compound A and Compound B (in which -B(OR)₂ is a boronate group such as -B(Pin)) using a palladium catalyst such as PdCl₂(dppf).CH₂Cl₂ in the presence of a base such as potassium phosphate
 20

tribasic. Compound C can be reduced in STEP 2 to Compound D by hydrogenation with a catalyst such as Pd/C under hydrogen pressure (H_2) around 5 bars at 40 °C, for example.

Compound D can then be converted to Compound E (in which X may be I, Br, or Cl) in STEP 3 by halogenation with NIS, NBS, or NCS (i.e. X = I, Br, or Cl) for example.

- 5 Compound E can be N-deprotected in STEP 4 by using HCl or TFA to give Compound F. Compound H can then be prepared in STEP 5 by reaction of Compound F with carboxylic acid Compound G, using conditions known by the person skilled in the art such as TBTU in a solvent like DMF in presence of a base such as DIPEA. Compound H, in the presence of Compound J, can be then converted into Compound K in STEP 6 using a palladium catalyst such as $Pd(t-Bu_3P)_2$ in the presence of a base such as DABCO.
- 10

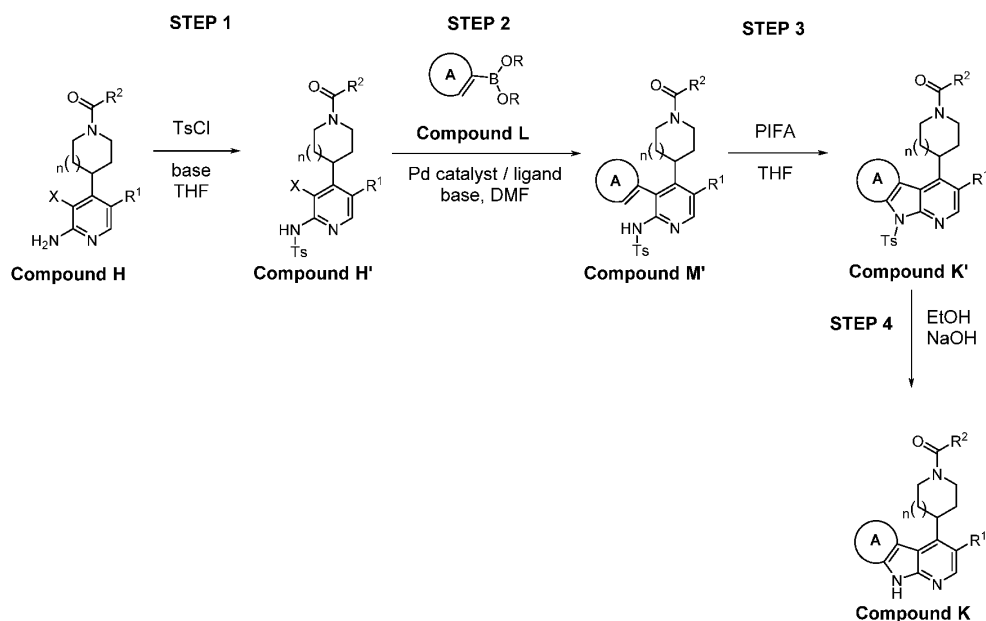
The following scheme, Scheme 2, illustrates an alternative way of preparing Compound K from Compound H:



SCHEME 2

- 15 According to Scheme 2 (in which ring A, R^1 , R^2 , and n may be, e.g., as described above), Compound M can be obtained by Suzuki coupling between Compound H (in which X may be I, Br, or Cl) and Compound L (in which $-B(OR)_2$ is a boronate group such as $-B(Pin)$) in STEP 1 using a palladium catalyst such as $PdCl_2(dppf) \cdot CH_2Cl_2$ in the presence of a base such as potassium carbonate, for example. Compound K can then be obtained directly from
- 20 Compound M in the in the presence of a hypervalent iodine(III) reagent such as PIFA in STEP 2.

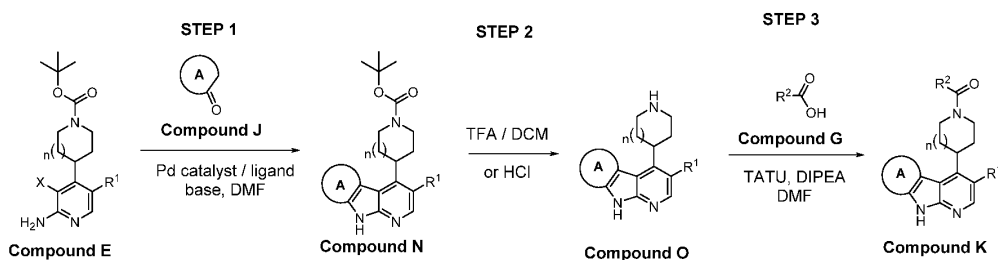
In some cases, Compound K can be prepared from Compound H via N-protected compounds according to the following scheme, Scheme 2A:



SCHEME 2A

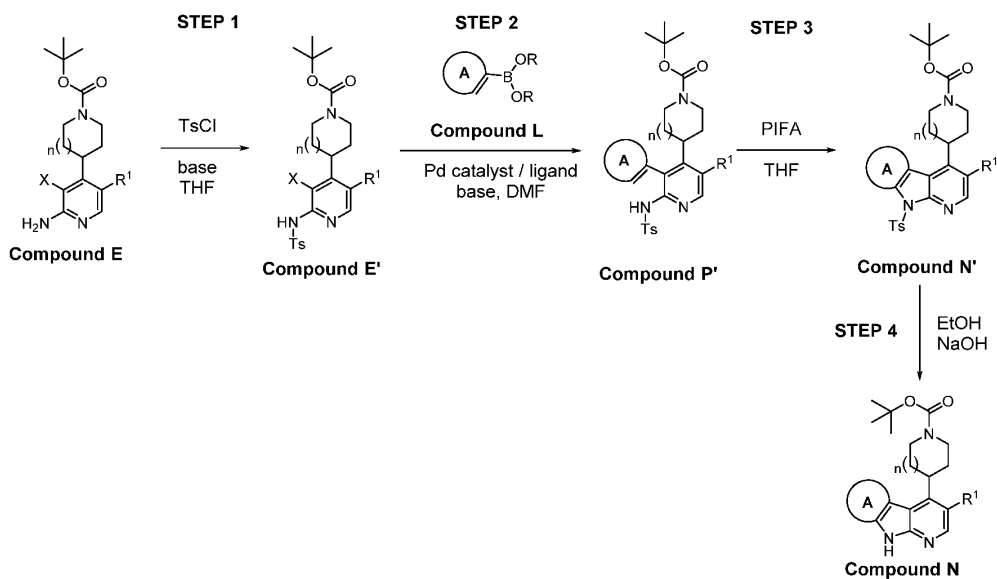
- According to Scheme 2A (in which ring A, R¹, R², and n may be, e.g., as described above), Compound H' (in which X may be I, Br, or Cl) can be obtained in STEP 1 by tosylation of
- 5 Compound H with tosyl chloride using a base such as sodium hydride, for example.
- Compound H' can then be transformed, in the presence of Compound L (in which -B(OR)₂ is a boronate group such as -B(Pin)), into Compound M' in STEP 2 by Suzuki coupling using a palladium catalyst such as PdCl₂(dppf).CH₂Cl₂ in the presence of a base such as potassium carbonate, for example. Compound K' can be obtained in STEP 3 from Compound M' in the
- 10 presence of a hypervalent iodine(III) reagent such as PIFA. Compound K' can be N-deprotected in STEP 4 by using sodium hydroxide in EtOH for example, to give Compound K.

The following scheme, Scheme 3, illustrates an alternative way of preparing Compound K from Compound E:



SCHEME 3

- According to Scheme 3 (in which ring A, R^1 , R^2 , and n may be, e.g., as described above), Compound N can be obtained from Compound E (in which X may be I, Br, or Cl) in STEP 1 in the presence of Compound J, using a palladium catalyst such as $\text{Pd}(\text{t-Bu}_3\text{P})_2$ in the presence of a base such as DABCO. Compound N can be N-deprotected in STEP 2, by using HCl or TFA to give Compound O. Compound K can then be prepared from Compound O in STEP 3 with carboxylic acid Compound G, using conditions known by the person skilled in the art such as TATU in a solvent like DMF in presence of a base such as DIPEA.
- 10 The following scheme, Scheme 4, illustrates an alternative way of preparing Compound N from Compound E:



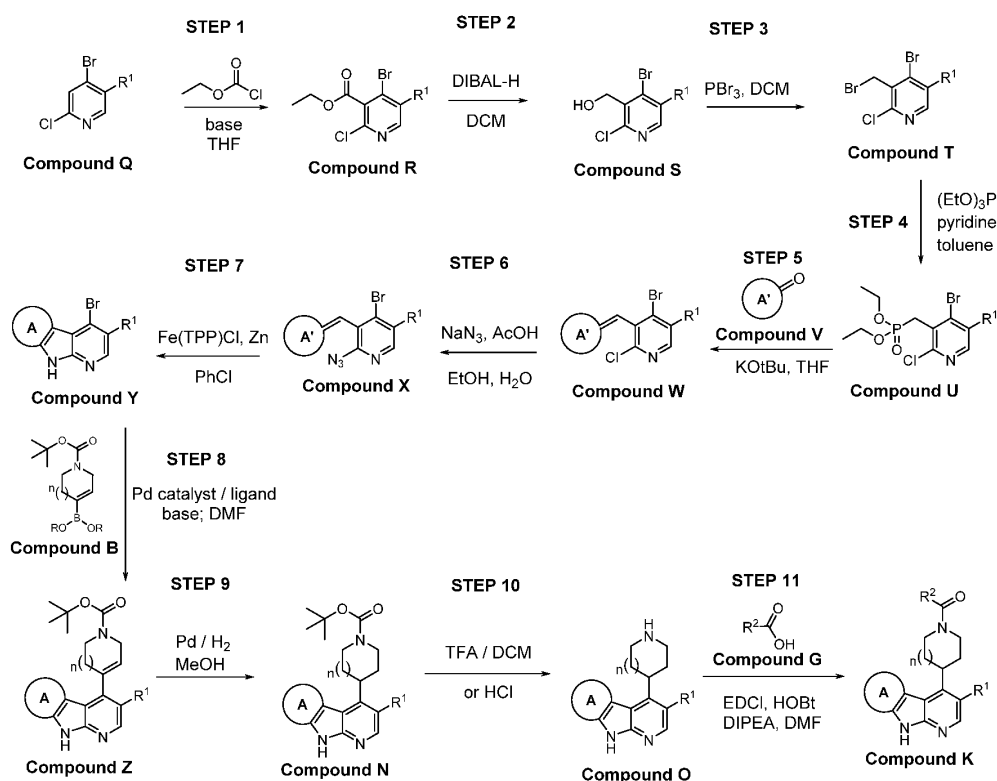
SCHEME 4

- According to Scheme 4 (in which ring A, R^1 , and n may be, e.g., as described above), Compound E' can be obtained in STEP 1 by tosylation of Compound E (in which X may be I, Br, or Cl) with tosyl chloride using a base such as sodium hydride, for example. Compound E' can then be transformed into Compound P', by Suzuki coupling with Compound L using a

palladium catalyst such as $\text{PdCl}_2(\text{dppf})$, CH_2Cl_2 in the presence of a base such as potassium carbonate, for example. Compound N' can be obtained in STEP 3 from Compound P' in the presence of a hypervalent iodine(III) reagent such as PIFA. Compound N' can be N-detosylated in STEP 4 by using sodium hydroxide in EtOH for example, to give Compound

5 N.

The following scheme, Scheme 5, illustrates a further exemplary way of preparing Compound K via Compound N:

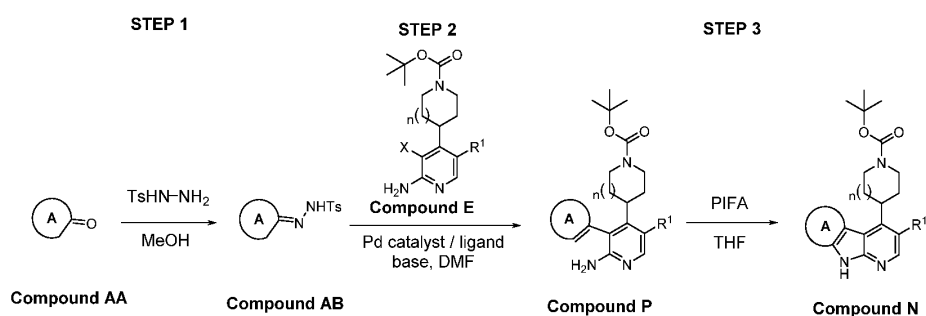


SCHEME 5

- 10 According to Scheme 5 (in which ring A, R^1 , R^2 , and n may be, e.g., as described above), Compound R can be obtained in STEP 1 by acylation of Compound Q in the presence of a base such as LDA. Compound R can be transformed in STEP 2 to Compound S by reduction with a hydride source such as DIBAL-H, for example. Compound S can then be converted to Compound T in STEP 3 by reaction with PBr_3 . Compound U can be obtained in STEP 4 from
- 15 Compound T in the presence of triethylphosphite. Compound U is transformed in STEP 5 to Compound W in the presence of Compound V (in which ring A' is a precursor to ring A, e.g. having one fewer ring carbon atoms than ring A) and a base such as potassium tert-butoxide. Nucleophilic aromatic substitution of Compound W with sodium azide gives Compound X in

- STEP 6. Compound X is then transformed into Compound Y in the presence of an iron catalyst and zinc powder in STEP 7; during STEP 7, ring A' in Compound X undergoes rearrangement to furnish ring A in Compound Y. Suzuki coupling reaction of Compound Y with Compound B (in which -B(OR)₂ is a boronate group such as -B(Pin)) in STEP 8, using a
- 5 palladium catalyst such as PdCl₂(dppf).CH₂Cl₂ in the presence of a base such as sodium carbonate, furnishes Compound Z. Compound Z can be reduced in STEP 9 to Compound N by hydrogenation with a catalyst such as Pd/C under hydrogen pressure (H₂) around 1 bar, for example. Compound N can be N-deprotected in STEP 10 using HCl or TFA to give Compound O. Compound K can then be prepared from Compound O in STEP 11 by reaction
- 10 with carboxylic acid Compound G, using conditions known by the person skilled in the art such as EDCI and HOBT in a solvent like DMF in presence of a base such as DIPEA.

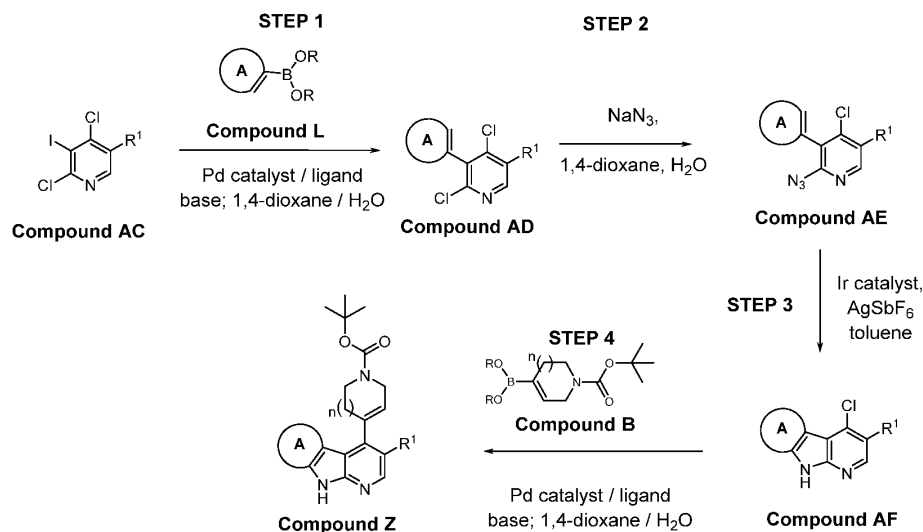
The following scheme, Scheme 6, illustrates an alternative way of preparing Compound N:



SCHEME 6

- 15 According to Scheme 6 (in which ring A, R¹, and n may be, e.g., as described above), Compound AB can be obtained in STEP 1 by condensation of Compound AA with p-toluenesulfonyl hydrazide. Compound P can be obtained in STEP 2 by Barluenga-Valdés cross coupling reaction with Compound E (in which X may be I, Br, or Cl) and Compound AB, using a palladium catalyst such as Pd(OAc)₂ and phosphonium ligand such as tri-tert-
- 20 butylphosphonium tetrafluoroborate in the presence of a base such as potassium carbonate. Compound N can be obtained in STEP 3 from Compound P in the presence of a hypervalent iodine(III) reagent such as PIFA.

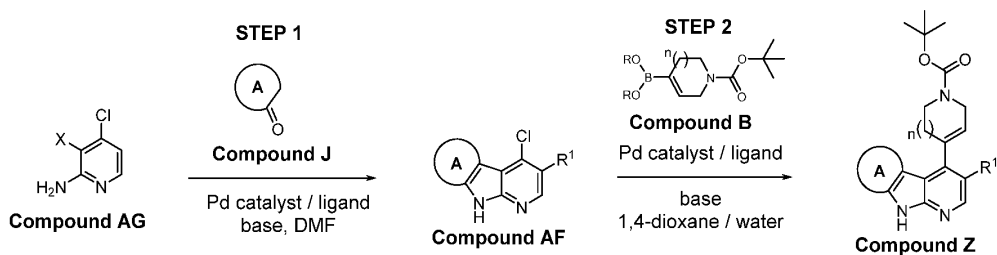
The following scheme, Scheme 7, illustrates an alternative way of preparing Compound Z:



SCHEME 7

- According to Scheme 7 (in which ring A, R¹, and n may be, e.g., as described above), Compound AD can be obtained in STEP 1 by Suzuki coupling reaction of Compound AC with Compound L, using a palladium catalyst such as PdCl₂(dppf) in the presence of a base such as sodium carbonate. Nucleophilic aromatic substitution reaction of Compound AD with sodium azide gives Compound AE in STEP 2. Compound AE is then transformed into Compound AF in the presence of an iridium catalyst and AgSbF₆ in STEP 3. Compound Z can be obtained in STEP 4 by Suzuki coupling reaction of Compound AF with Compound B (in which -B(OR)₂ is a boronate group such as -B(Pin)), using a palladium catalyst such as Pd(t-Bu₃P)₂ in the presence of a base such as potassium carbonate tribasic.

The following scheme, Scheme 8, illustrates an alternative way of preparing Compound Z:



SCHEME 8

- According to Scheme 8 (in which ring A, R¹, and n may be, e.g., as described above), Compound AF can be obtained in STEP 1 from Compound AG (in which X may be I, Br, or Cl) and Compound J, using a palladium catalyst such as Pd(Pt-Bu₃)₂ in the presence of a base

such as DABCO. Compound AF can then be transformed in STEP 2, in the presence of Compound B (in which $-B(OR)_2$ is a boronate group such as $-B(Pin)$), into Compound Z by Suzuki coupling using a palladium catalyst such as $PdCl_2(dppf).CH_2Cl_2$ in the presence of a base such as cesium carbonate, for example.

- 5 Where necessary in the aforementioned transformations, protecting groups may be used, e.g., on free $-NH_2$ substituents of R^2 or of ring A. Suitable protection strategies will be apparent to a person of skill in the art in view of the present disclosure. For example, compounds of the disclosure (e.g., compounds of Formula (I)) in which R^2 is $-(C_6-C_{10})$ aryl substituted with $-NH_2$, can be prepared from the corresponding $-NHBOC$ compound, which can be
- 10 prepared by a method analogous to the above schemes and N-deprotected using conditions described herein or otherwise known to the skilled person. Compounds of the disclosure (e.g., compounds of Formula (I)) in which ring A is a heterocycloalkane comprising at least one nitrogen ring atom can be prepared from the corresponding N-protected (e.g. NBOC) compound, which can be N-deprotected. Compounds in which ring A is substituted with $-OH$
- 15 or $-NH_2$, can be prepared from the corresponding O-protected or N-protected compound, which can be prepared by methods analogous to the above schemes and O-deprotected or N-deprotected using conditions described herein or otherwise known to the skilled person. Compounds in which ring A is substituted with oxo (e.g. rings comprising a carbonyl, i.e. $-(C=O)-$, group) can be prepared from a corresponding acetal compound (e.g. $-(O-CH_2CH_2-O)-$), which can be prepared by a method analogous to the above schemes and
- 20 revealed by exposure to, e.g., acidic reaction conditions.

- Certain compounds of the disclosure may carry substituents which are capable of undergoing further transformation to prepare additional compounds in accordance with the disclosure (e.g. compounds of Formula (I)). For example, compounds obtainable, e.g., according to the
- 25 above schemes (such as, e.g., Compound K) in which ring A is substituted with oxo (e.g. rings comprising a carbonyl, i.e. $-(C=O)-$, group), can be submitted to chemical transformations such as: (1) nucleophilic addition; (2) reductive amination; and (3) reduction with hydride reagents; to give the corresponding compounds of the disclosure (e.g. compounds of Formula (I)) in which, e.g.: (1) ring A is substituted with $-OH$, and a further substituent (e.g. selected from $-(C_1-C_3)$ alkyl optionally substituted with one or more halo or $-OH$, $-(C_3-C_6)$ cycloalkyl, 3- to 6-membered heterocycloalkyl, $-O(C_1-C_3)$ alkyl and $-CN$);
- 30 (2) ring A is substituted with $-NHR'$, in which R' may be, e.g., as described above; and (3) ring A is substituted with $-OH$.

- Compounds which possess one or more stereogenic centers can be purified, e.g. using chiral
- 35 separation techniques such as chiral HPLC or SFC, to obtain separate isomers.

Experimental techniques

¹H NMR Spectra at 400 and 500 MHz were performed on a Bruker Avance DRX-400 and Bruker Avance DPX-500 spectrometer, respectively, with the chemical shifts (δ in ppm) in the solvent dimethyl sulfoxide-d₆ (DMSO-d₆) referenced at 2.5 ppm at the quoted

- 5 temperatures. Coupling constants (J) are given in Hertz.

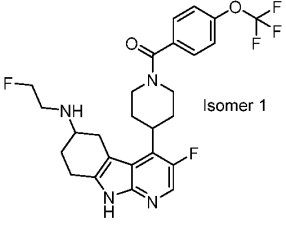
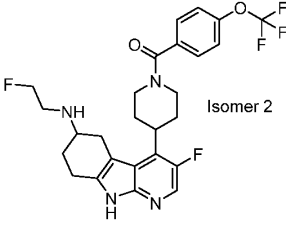
The liquid chromatography/mass spectra (LC/MS) were obtained on a UPLC Acquity Waters instrument, light scattering detector Sedere and SQD Waters mass spectrometer using UV detection DAD 210<I>400 nm and column Acquity UPLC CSH C18 1.7 μ m, dimension 2.1x50 mm, mobile phase H₂O + 0.1% HCO₂H / CH₃CN + 0.1% HCO₂H.

- 10 All synthetic reactions were performed under an inert atmosphere, unless otherwise stated. In the following examples, when the source of the starting products is not specified, it should be understood that said products are known compounds (e.g., commercially available compounds from suppliers such as Sigma-Aldrich).

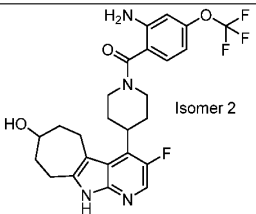
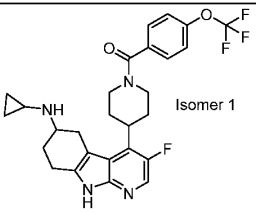
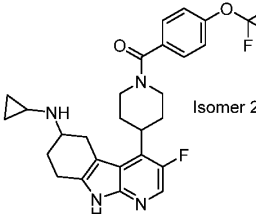
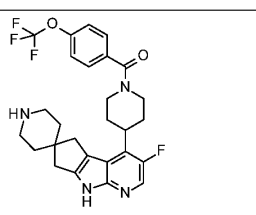
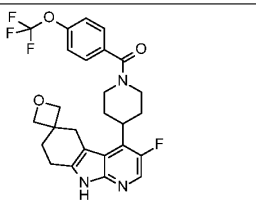
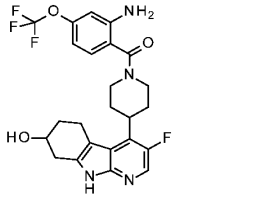
Examples 1 to 294 – Compounds

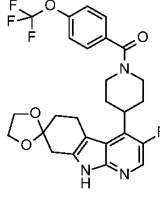
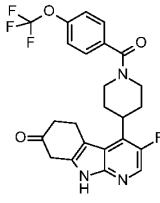
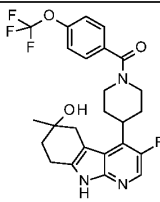
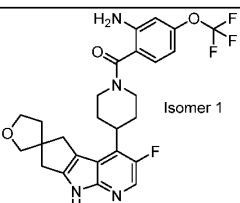
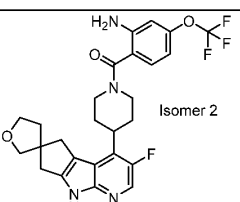
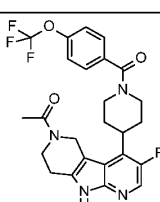
- 15 Tables 1a and 1b below list specific compounds of the present disclosure along with their name and structure (Table 1a), as well as their methods of preparation and characterization by NMR and LC/MS (Table 1b).

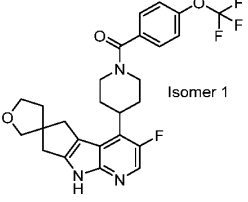
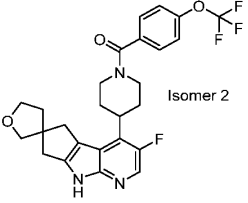
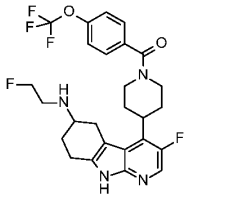
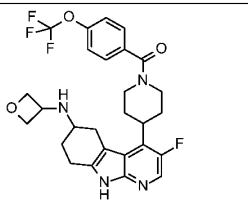
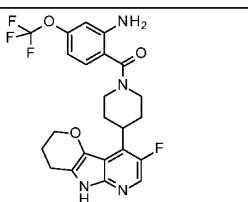
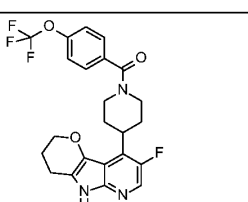
Table 1a:

Example No.	Structure	Name
1	 Isomer 1	[4-[3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
2	 Isomer 2	[4-[3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2

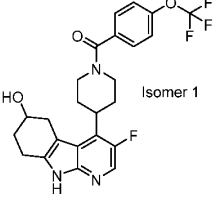
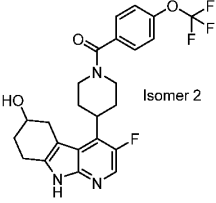
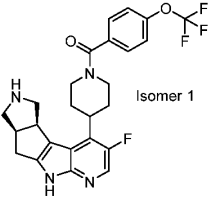
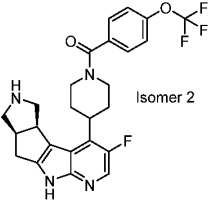
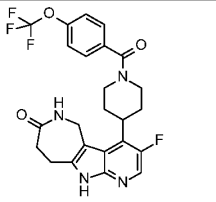
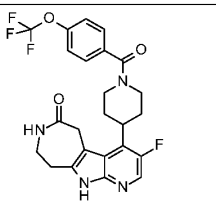
Example No.	Structure	Name
3		(rac)-[4-(3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
4		4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,14-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one
5		(rac)-trans-[4-[13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
6		(rac)-trans-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
7		(rac)-trans-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone
8		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 1

Example No.	Structure	Name
9	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 2
10	 Isomer 1	[4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
11	 Isomer 2	[4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
12		[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,4'-piperidine]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
13		[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-oxetane]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
14		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone

Example No.	Structure	Name
15		[4-(3-fluoro-5,6,8,9-tetrahydrospiro[pyrido[2,3-b]indole-7,2'-dioxolan]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
16		3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,6,8,9-tetrahydropyrido[2,3-b]indol-7-one
17		(rac)-[4-(3-fluoro-6-hydroxy-6-methyl-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
18		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl]-1-piperidyl]methanone, Isomer 1
19		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl]-1-piperidyl]methanone, Isomer 2
20		1-[12-fluoro-13-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4,8,10-triazatricyclo[7.4.0.02,7]trideca-1(9),2(7),10,12-tetraen-4-yl]ethanone

Example No.	Structure	Name
21	 Isomer 1	[4-[11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
22	 Isomer 2	[4-[11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
23		(rac)-[4-[3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
24		(rac)-[4-[3-fluoro-6-(oxetan-3-ylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
25		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-fluoro-3-oxa-8,10-diazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl)-1-piperidyl]methanone
26		[4-(12-fluoro-3-oxa-8,10-diazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

Example No.	Structure	Name
27		(rac)-cis-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
28		(rac)-cis-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone
29		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-fluoro-5-oxa-8,10-diazatricyclo[7.4.0.02,7]trideca-1(9),2(7),10,12-tetraen-13-yl)-1-piperidyl]methanone
30		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-oxetane]-4-yl)-1-piperidyl]methanone
31		3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one
32		3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-one

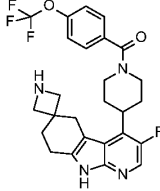
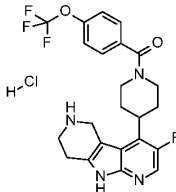
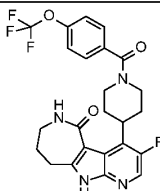
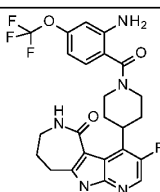
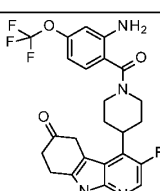
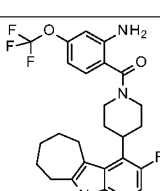
Example No.	Structure	Name
33	 Isomer 1	[4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
34	 Isomer 2	[4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
35	 Isomer 1	cis-[4-[4-fluoro-6,8,13-triazatetracyclo[7.6.0.0.2,7.0.11,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
36	 Isomer 2	cis-[4-[4-fluoro-6,8,13-triazatetracyclo[7.6.0.0.2,7.0.11,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
37		4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-12-one
38		4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,12-triazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-13-one

Example No.	Structure	Name
39		(rac)-[4-(3-fluoro-7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
40		[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-tetrahydropyran]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
41		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-tetrahydropyran]-4-yl)-1-piperidyl]methanone
42		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,4'-tetrahydropyran]-12-yl)-1-piperidyl]methanone
43		[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
44		[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2

Example No.	Structure	Name
45		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone
46		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone
47		[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,4'-tetrahydropyran]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
48		[4-[11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,3'-pyrrolidine]-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
49		[4-[11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,3'-pyrrolidine]-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
50		4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,6,8,9-tetrahydropyrido[2,3-b]indol-7-one

Example No.	Structure	Name
51		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-5,6,8,9-tetrahydrospiro[pyrido[2,3-b]indole-7,2'-[1,3]dioxolan]-4-yl)-1-piperidyl]methanone
52		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-3,3'-tetrahydrofuran]-12-yl)-1-piperidyl]methanone
53		(rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-3,3'-tetrahydrofuran]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
54		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone
55		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone
56		[4-(3-fluoro-5,7,8,9-tetrahydrospiro[pyrido[2,3-b]indole-6,2'-[1,3]dioxolan]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

Example No.	Structure	Name
57		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-6-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone
58		(rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-3,3'-pyrrolidine]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
59		(rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
60		[4-(3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
61		3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one
62		(rac)-[4-(3-fluoro-6-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

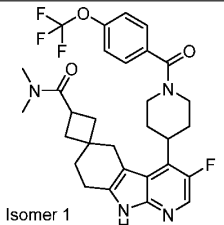
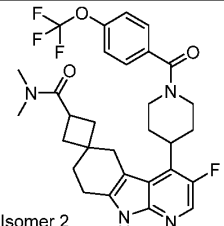
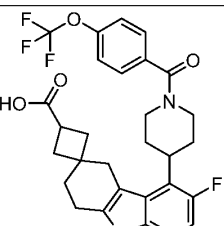
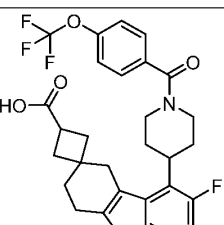
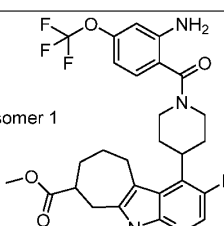
Example No.	Structure	Name
63		[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
64		[4-(12-fluoro-4,8,10-triazatricyclo[7.4.0.0.2,7]trideca-1(13),2(7),9,11-tetraen-13-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, hydrochloride
65		4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-14-one
66		3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8,13-triazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-14-one
67		4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one
68		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone

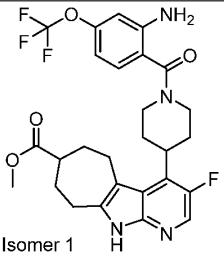
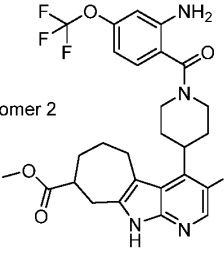
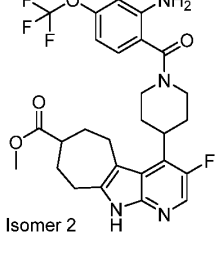
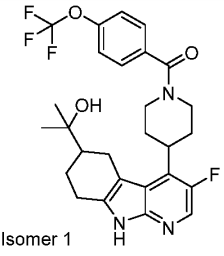
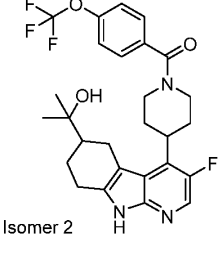
Example No.	Structure	Name
69		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-fluoro-4-oxa-8,10-diazatricyclo[7.4.0.02,7]trideca-1(9),2(7),10,12-tetraen-13-yl)-1-piperidyl]methanone
70		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 1
71		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 2
72		[2-amino-4-(pentafluoro-λ⁶-sulfanyl)phenyl]-[4-(7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraen-12-yl)-1-piperidyl]methanone
73		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraen-12-yl)-1-piperidyl]methanone
74		[4-(7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraen-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

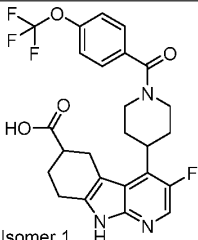
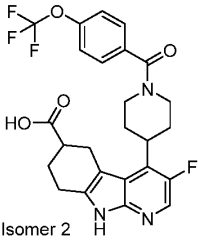
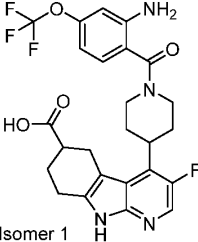
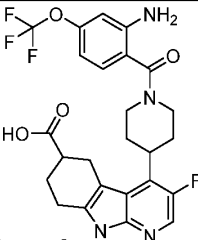
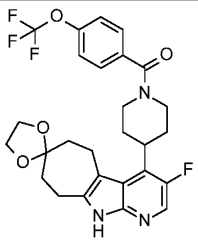
Example No.	Structure	Name
75		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone
76		(rac)-[4-(7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
77		[4-(12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
78		4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one, Isomer 1
79		4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one, Isomer 2
80		trans-[4-[13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1

Example No.	Structure	Name
81		trans-[4-[13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
82		[4-(12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
83		[4-(12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
84		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone, Isomer 1
85		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone
86		3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-13-methyl-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one

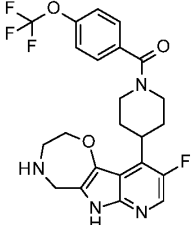
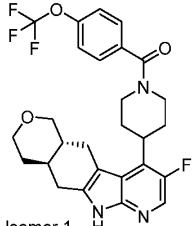
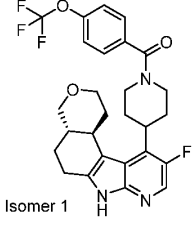
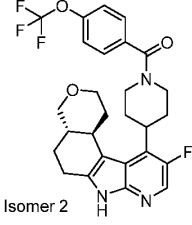
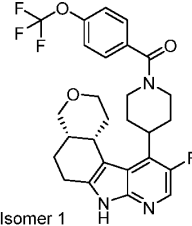
Example No.	Structure	Name
87		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone, Isomer 2
88		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone, Isomer 1
89		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone, Isomer 2
90		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-6,8-diazatricyclo[7.6.0.02,7]pentadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone
91		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 1
92		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 2

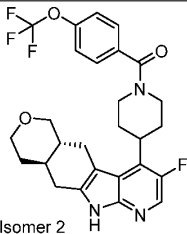
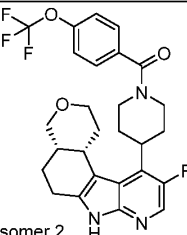
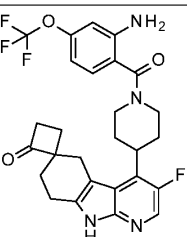
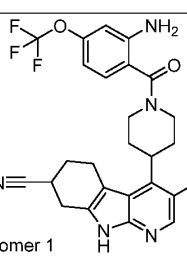
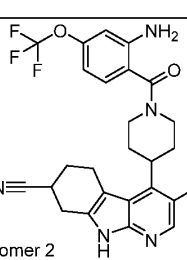
Example No.	Structure	Name
93	 Isomer 1	3-fluoro-N,N-dimethyl-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxamide, Isomer 1
94	 Isomer 2	3-fluoro-N,N-dimethyl-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxamide, Isomer 2
95	 Isomer 1	3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxylic acid, Isomer 1
96	 Isomer 2	3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxylic acid, Isomer 2
97	 Isomer 1	methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate, Isomer 1

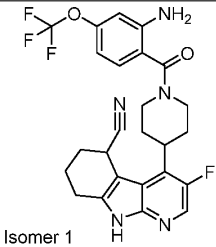
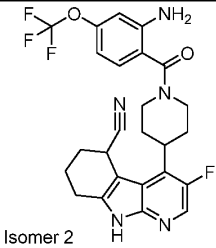
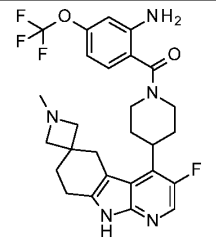
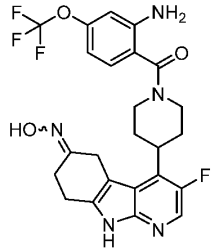
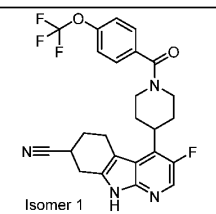
Example No.	Structure	Name
98	 Isomer 1	methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate, Isomer 1
99	 Isomer 2	methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate, Isomer 2
100	 Isomer 2	methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate, Isomer 2
101	 Isomer 1	[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
102	 Isomer 2	[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2

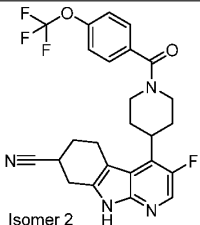
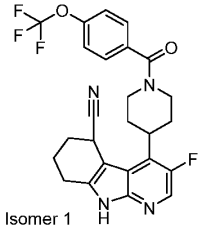
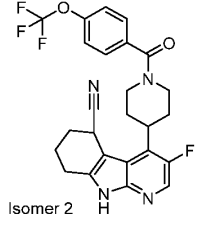
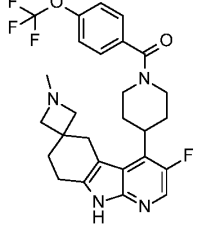
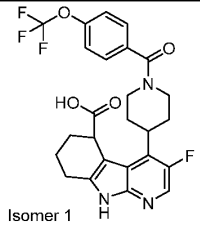
Example No.	Structure	Name
103	 Isomer 1	3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid, Isomer 1
104	 Isomer 2	3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid, Isomer 2
105	 Isomer 1	4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid, Isomer 1
106	 Isomer 2	4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid, Isomer 2
107		[4-(4'-fluorospiro[1,3-dioxolane-2,12'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene]-3'-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

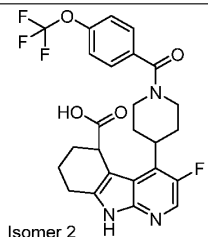
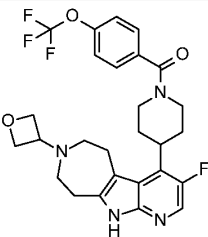
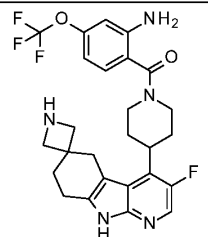
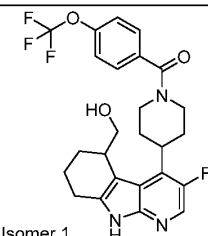
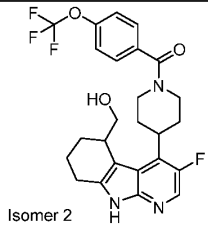
Example No.	Structure	Name
108	Isomer 1	[4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
109	Isomer 2	[4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
110	Isomer 1	[4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
111		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone
112		(rac)-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

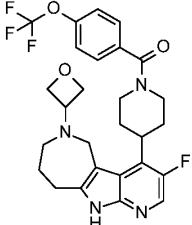
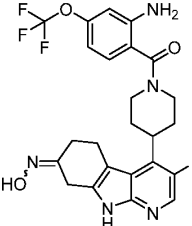
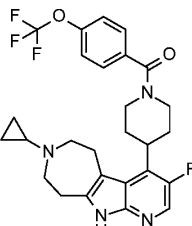
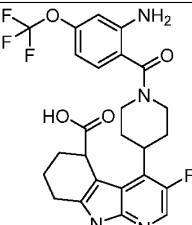
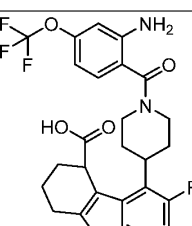
Example No.	Structure	Name
113		[4-(4-fluoro-14-oxa-6,8,11-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
114		[4-[(trans)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
115		[4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
116		[4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
117		[4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1

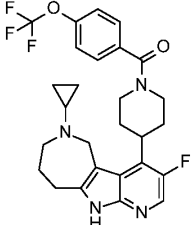
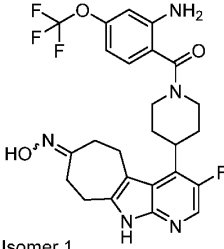
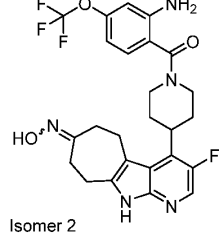
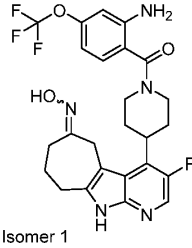
Example No.	Structure	Name
118	 Isomer 2	[4-[(trans)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.0.3,8.0]heptadec-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
119	 Isomer 2	[4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.0.2,7.0]heptadec-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
120		(rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,2'-cyclobutane]-1'-one
121	 Isomer 1	4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile, Isomer 1
122	 Isomer 2	4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile, Isomer 2

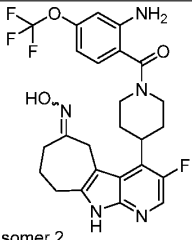
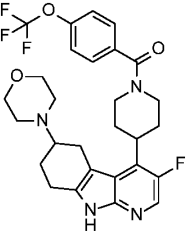
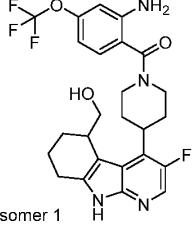
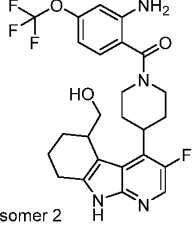
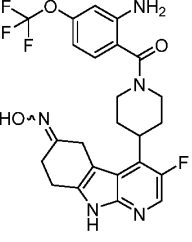
Example No.	Structure	Name
123	 Isomer 1	4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile, Isomer 1
124	 Isomer 2	4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile, Isomer 2
125		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-1'-methyl-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]methanone
126	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 1
127	 Isomer 1	3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile, Isomer 1

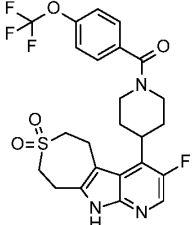
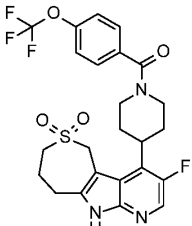
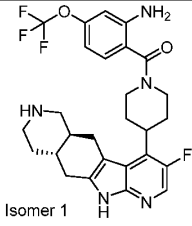
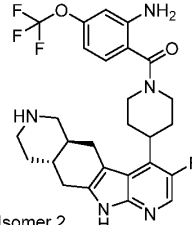
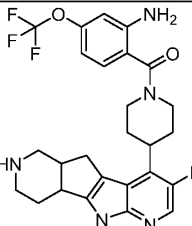
Example No.	Structure	Name
128	 Isomer 2	3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile, Isomer 2
129	 Isomer 1	3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile, Isomer 1
130	 Isomer 2	3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile, Isomer 2
131	 Isomer 1	[4-(3-fluoro-1'-methyl-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
132	 Isomer 1	3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid, Isomer 1

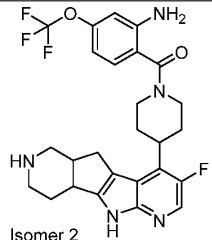
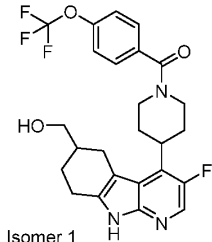
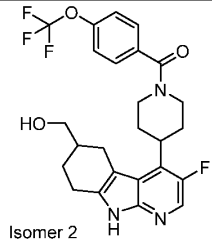
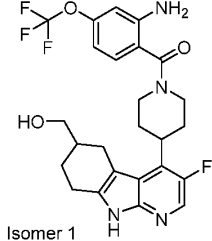
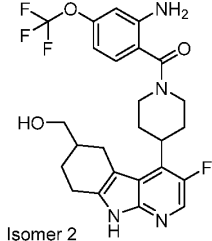
Example No.	Structure	Name
133	 Isomer 2	3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid, Isomer 2
134		[4-[4-fluoro-12-(oxetan-3-yl)-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
135		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]methanone
136	 Isomer 1	[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
137	 Isomer 2	[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2

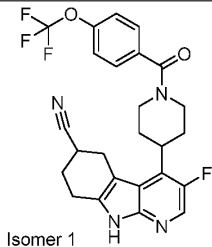
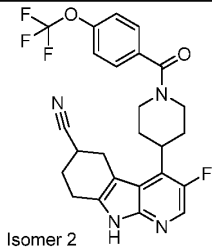
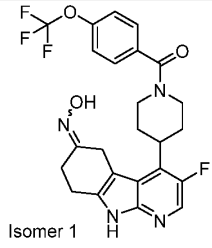
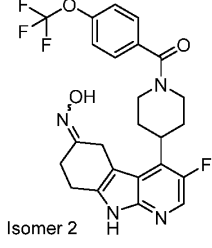
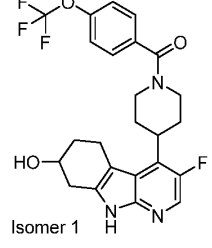
Example No.	Structure	Name
138		[4-[4-fluoro-13-(oxetan-3-yl)-6,8,13-triazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
139	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 1
140		[4-(12-cyclopropyl-4-fluoro-6,8,12-triazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
141	 Isomer 1	4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid, Isomer 1
142	 Isomer 2	4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid, Isomer 2

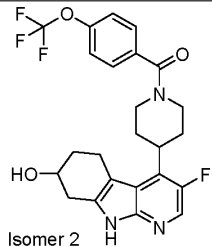
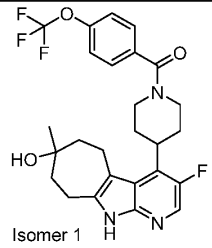
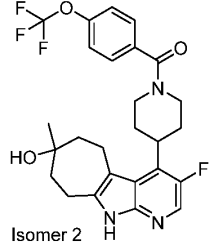
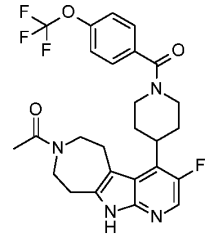
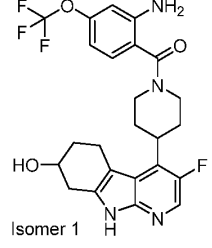
Example No.	Structure	Name
143		[4-(13-cyclopropyl-4-fluoro-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
144	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 1
145	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 2
146	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 1

Example No.	Structure	Name
147	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 2
148		(rac)-[4-(3-fluoro-6-morpholino-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
149	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 1
150	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 2
151	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 2

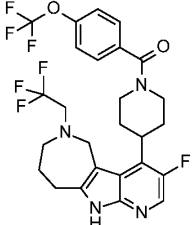
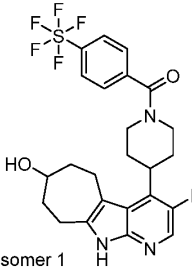
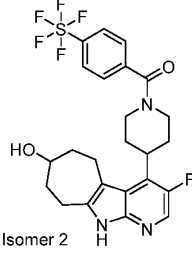
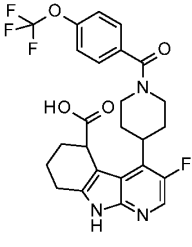
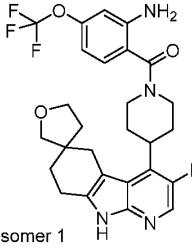
Example No.	Structure	Name
152		[4-(4-fluoro-12,12-dioxo-12 λ^6 -thia-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
153		[4-(4-fluoro-13,13-dioxo-13 λ^6 -thia-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
154	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone, Isomer 1
155	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone, Isomer 2
156	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone, Isomer 1

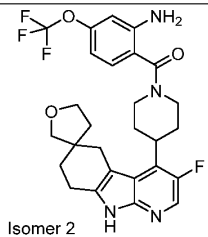
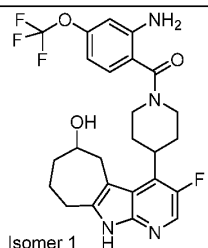
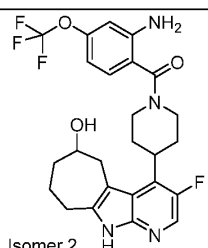
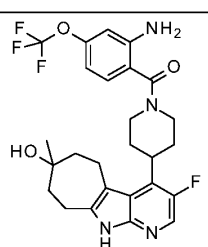
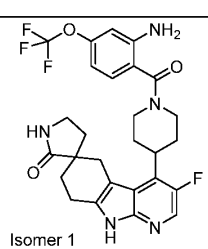
Example No.	Structure	Name
157	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-fluoro-5,14,16-triazatetracyclo[7.7.0.0.2,7.0.10,15]hexadecan-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone, Isomer 2
158	 Isomer 1	[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
159	 Isomer 2	[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
160	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 1
161	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 2

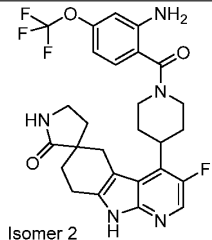
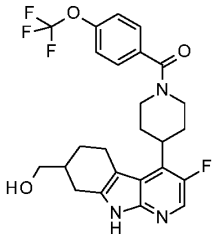
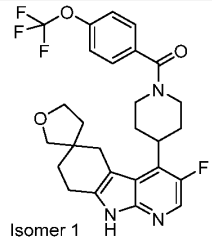
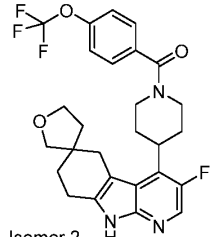
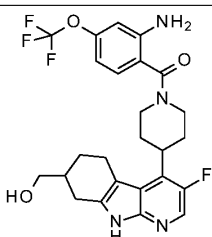
Example No.	Structure	Name
162	 Isomer 1	3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile, Isomer 1
163	 Isomer 2	3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile, Isomer 2
164	 Isomer 1	[4-[3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
165	 Isomer 2	[4-[3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
166	 Isomer 1	[4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1

Example No.	Structure	Name
167	 Isomer 2	[4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
168	 Isomer 1	[4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
169	 Isomer 2	[4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
170		1-[4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,12-triazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-12-yl]ethanone
171	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 1

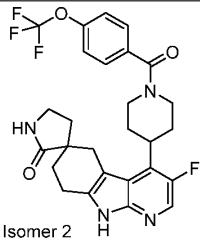
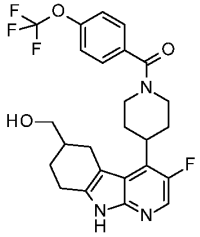
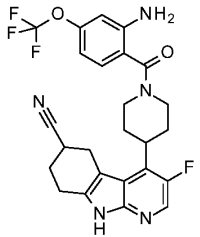
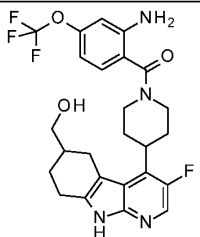
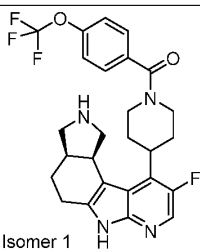
Example No.	Structure	Name
172	Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 2
173		1-[4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-yl]ethanone
174		[4-[4-fluoro-12-(2,2,2-trifluoroethyl)-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
175		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,1'-cyclobutane]-4-yl)-1-piperidyl]methanone
176		[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,1'-cyclobutane]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

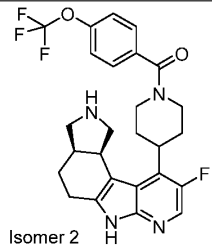
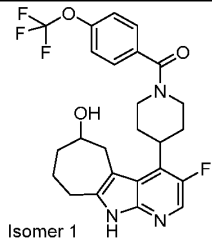
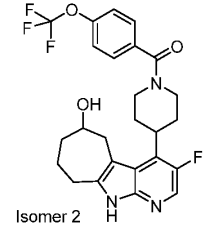
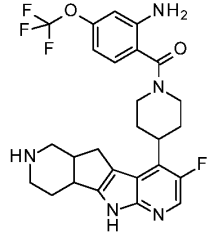
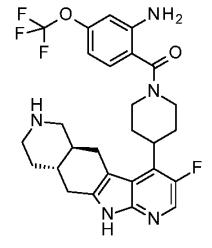
Example No.	Structure	Name
177		[4-[4-fluoro-13-(2,2,2-trifluoroethyl)-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
178	 Isomer 1	[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(pentafluoro-λ ⁶ -sulfanyl)phenyl]methanone, Isomer 1
179	 Isomer 2	[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(pentafluoro-λ ⁶ -sulfanyl)phenyl]methanone, Isomer 2
180		(rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid
181	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]methanone, Isomer 1

Example No.	Structure	Name
182	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]methanone, Isomer 2
183	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 1
184	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 2
185	 Isomer 2	(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone
186	 Isomer 1	4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one, Isomer 1

Example No.	Structure	Name
187	 Isomer 2	4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one, Isomer 2
188		(rac)-[4-[3-fluoro-7-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
189	 Isomer 1	[4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
190	 Isomer 2	[4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
191		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone

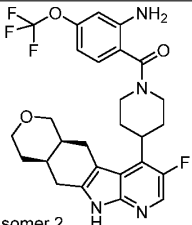
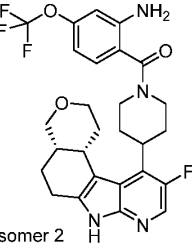
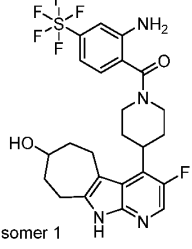
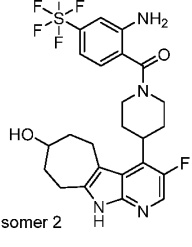
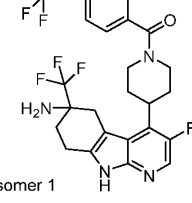
Example No.	Structure	Name
192		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone
193		(rac)-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
194		[4-(4-fluoro-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
195		[4-(4-fluoro-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
196		3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one, Isomer 1

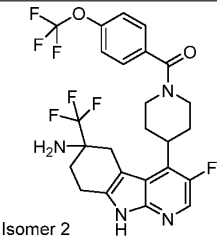
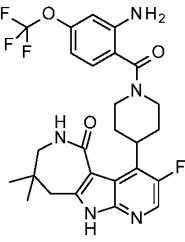
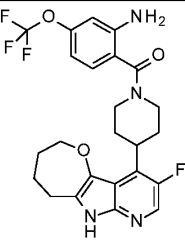
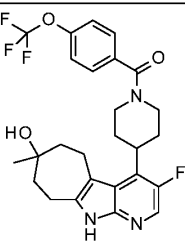
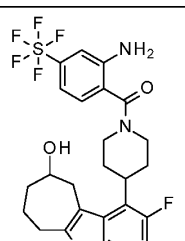
Example No.	Structure	Name
197	 Isomer 2	3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one, Isomer 2
198		(rac)-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
199		(rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile
200		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone
201	 Isomer 1	[4-[(cis)-14-fluoro-4,10,12-triazatetracyclo[7.7.0.0.2,6.0.11,16]hexadecatrien-1(9),11,13,15-tetraen-15-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1

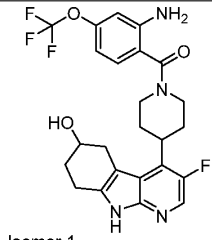
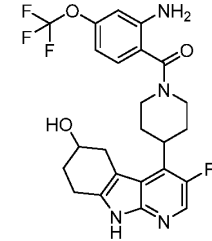
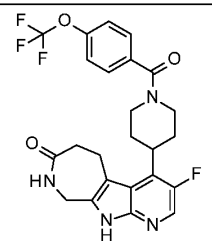
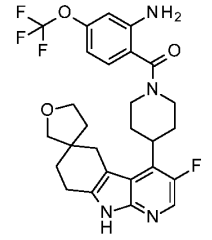
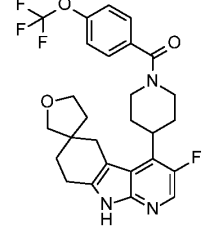
Example No.	Structure	Name
202	 Isomer 2	[4-[(cis)-14-fluoro-4,10,12-triazatetracyclo[7.7.0.0.2,6.0]11,16]hexadeca-1(9),11,13,15-tetraen-15-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
203	 Isomer 1	[4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
204	 Isomer 2	[4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
205		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-fluoro-5,14,16-triazatetracyclo[7.7.0.0.2,7.0]10,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone
206		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.0.3,8.0]11,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone

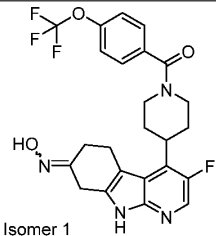
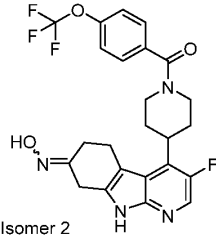
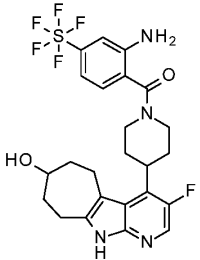
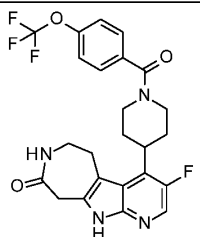
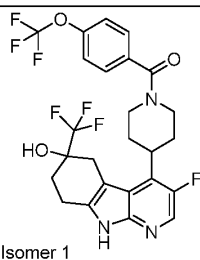
Example No.	Structure	Name
207		3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-one
208		(rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile
209		1-[13-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-12-fluoro-4,8,10-triazatricyclo[7.4.0.02,7]trideca-1(9),2(7),10,12-tetraen-4-yl]ethanone
210		4-fluoro-11,11-dimethyl-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one
211		4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-12-one

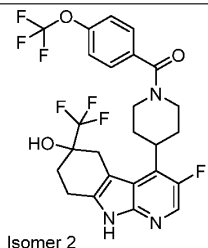
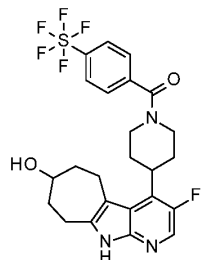
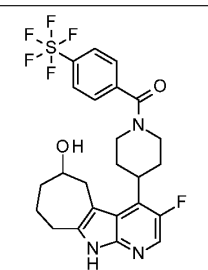
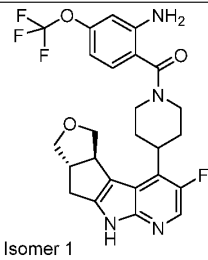
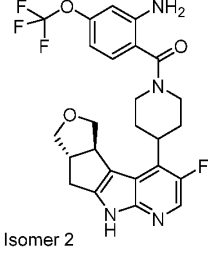
Example No.	Structure	Name
212		4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one
213		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone, Isomer 1
214		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone, Isomer 1
215		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone, Isomer 1
216		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone, Isomer 2

Example No.	Structure	Name
217	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone, Isomer 2
218	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone, Isomer 2
219	 Isomer 1	[2-amino-4-(pentafluoro-λ ⁶ -sulfanyl)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 1
220	 Isomer 2	[2-amino-4-(pentafluoro-λ ⁶ -sulfanyl)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 2
221	 Isomer 1	[4-[6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1

Example No.	Structure	Name
222	 Isomer 2	[4-[6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
223		3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-11,11-dimethyl-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one
224		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-14-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone
225		(rac)-[4-(4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
226		(rac)-[2-amino-4-(pentafluoro-λ ⁶ -sulfanyl)phenyl]-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone

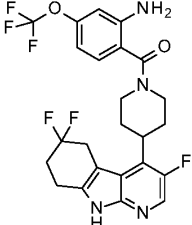
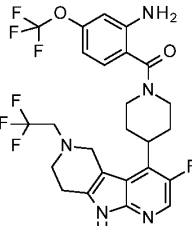
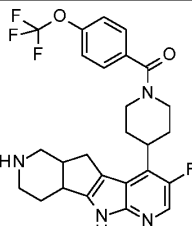
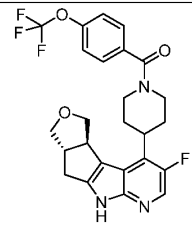
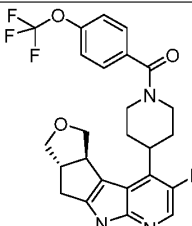
Example No.	Structure	Name
227	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 1
228	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 2
229		4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,11-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-one
230		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl)-1-piperidyl]methanone
231		(rac)-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

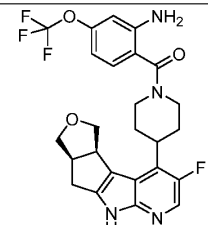
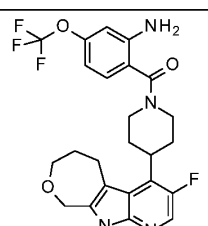
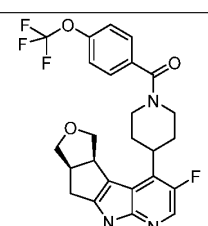
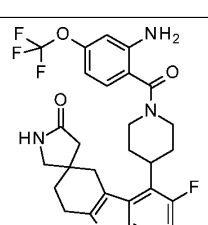
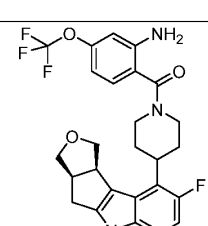
Example No.	Structure	Name
232	 Isomer 1	[4-[3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
233	 Isomer 2	[4-[3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
234		(rac)-[2-amino-4-(pentafluoro-λ ⁶ -sulfonyl)phenyl]-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone
235		4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,12-triazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-11-one
236	 Isomer 1	[4-[3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1

Example No.	Structure	Name
237	 Isomer 2	[4-[3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
238		(rac)-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0 ^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(pentafluoro-λ ⁶ -sulfanyl)phenyl]methanone
239		(rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0 ^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(pentafluoro-λ ⁶ -sulfanyl)phenyl]methanone
240	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0 ^{2,7} ,7.0 ^{11,15}]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 1
241	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0 ^{2,7} ,7.0 ^{11,15}]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 2

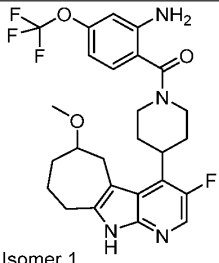
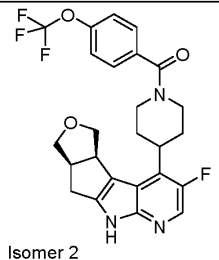
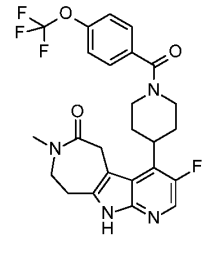
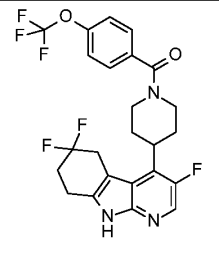
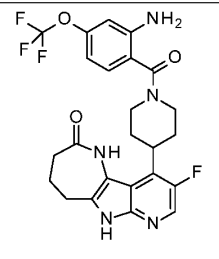
Example No.	Structure	Name
242		(rac)-[4-(4-fluoro-6,8,13-triazatetracyclo[7.7.0.02,7.011,15]hexadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
243		(rac)-[4-(14-fluoro-4,10,12-triazatetracyclo[7.7.0.02,6.011,16]hexadeca-1(9),11,13,15-tetraen-15-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
244		3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one, Isomer 1
245		3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one, Isomer 2
246		(rac)-[4-[6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

Example No.	Structure	Name
247		(rac)-[4-[3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
248		[4-[(cis)-7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
249		[4-[(cis)-7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
250		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone, Isomer 1
251		[4-[12-fluoro-4-(2,2,2-trifluoroethyl)-4,8,10-triazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

Example No.	Structure	Name
252		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3,6,6-trifluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone
253		[2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-fluoro-4-(2,2,2-trifluoroethyl)-4,8,10-triazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl]-1-piperidyl]methanone
254		(rac)-[4-(12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
255	 Isomer 1	[4-[(trans)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
256	 Isomer 2	[4-[(trans)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2

Example No.	Structure	Name
257	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.0.1.1,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 1
258		[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-11-oxa-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone
259	 Isomer 1	[4-[(cis)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.0.1.1,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
260		(rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one
261	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.0.1.1,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 2

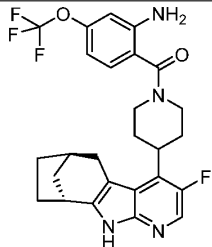
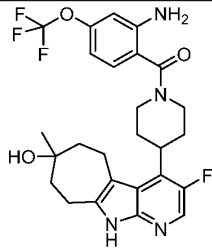
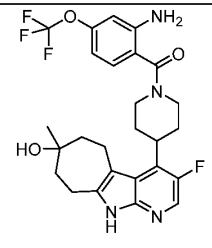
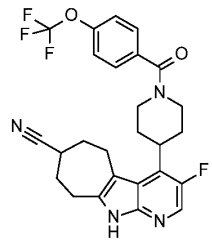
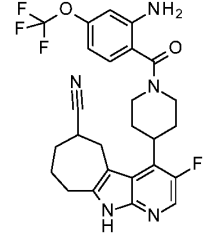
Example No.	Structure	Name
262		(rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one
263		[4-[4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
264		[4-[4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
265		[4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
266		[4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2

Example No.	Structure	Name
267	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone, Isomer 1
268	 Isomer 2	[4-[(cis)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
269	 Isomer 3	4-fluoro-13-methyl-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one
270	 Isomer 4	[4-(trifluoromethoxy)phenyl]-[4-(3,6,6-trifluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone
271	 Isomer 5	3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8,14-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one

Example No.	Structure	Name
272		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl)-1-piperidyl]methanone
273		(rac)-[4-(7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
274		[4-[3-fluoro-6-(oxetan-3-ylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1
275		[4-[3-fluoro-6-(oxetan-3-ylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2
276		(rac)-[4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

Example No.	Structure	Name
277		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone
278		(rac)-[4-(3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
279		(rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
280		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl)-1-piperidyl]methanone
281		(rac)-[4-[(cis)-4-fluoro-6,8,13-triazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

Example No.	Structure	Name
282		(rac)-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
283		(rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,3'-pyrrolidine]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
284		(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone
285		[4-(4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5,12-pentaen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
286		[4-(4-fluoro-6,8-diazatricyclo[7.6.0.02,7]pentadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

Example No.	Structure	Name
287	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-7-fluoro-3,5-diazatetracyclo[10.2.1.0.2,10.0.4,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone, Isomer 2
288	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone, Isomer 1
289	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone, Isomer 2
290		(rac)-4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraene-12-carbonitrile
291		(rac)-3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraene-13-carbonitrile

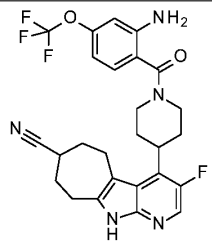
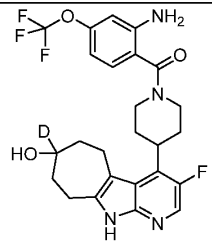
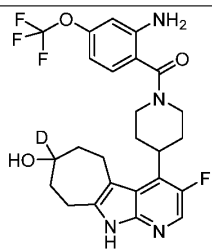
Example No.	Structure	Name
292		(rac)-3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraene-12-carbonitrile
293	 Isomer 1	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone, Isomer 1
294	 Isomer 2	[2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone, Isomer 2

Table 1b:

Example No.	Preparation Method	NMR	MASS: LC/MS (m/z, [M+H] ⁺)
1	A + Ketal deprotection +reductive amination + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.60 - 1.71 (m, 1 H) 1.72 - 1.92 (m, 3 H) 1.96 - 2.10 (m, 3 H) 2.63 (dd, <i>J</i> =14.1, 7.4 Hz, 1 H) 2.70 - 2.86 (m, 2 H) 2.97 - 3.20 (m, 6 H) 3.49 - 3.61 (m, 1 H) 4.10 - 4.32 (m, 2 H) 4.50 (dt, <i>J</i> =47.7, 5.3 Hz, 2 H) 7.41 (br d, <i>J</i> =8.4 Hz, 2 H) 7.57 (d, <i>J</i> =8.4 Hz, 2 H) 7.91 (d, <i>J</i> =4.3 Hz, 1 H) 10.97 (br s, 1 H)	523

2	A + ketal deprotection + reductive amination + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.61 - 1.71 (m, 1 H) 1.73 - 1.93 (m, 3 H) 1.96 - 2.10 (m, 3 H) 2.63 (dd, <i>J</i> =14.1, 7.4 Hz, 1 H) 2.69 - 2.85 (m, 2 H) 2.97 - 3.21 (m, 6 H) 3.49 - 3.61 (m, 1 H) 4.08 - 4.30 (m, 2 H) 4.50 (dt, <i>J</i> =47.7, 5.3 Hz, 2 H) 7.41 (d, <i>J</i> =8.4 Hz, 2 H) 7.57 (br d, <i>J</i> =8.4 Hz, 2 H) 7.91 (d, <i>J</i> =4.3 Hz, 1 H) 10.97 (br s, 1 H)	523
3	C	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.74 - 1.89 (m, 3 H), 1.95 - 2.08 (m, 3 H), 2.63 (dd, <i>J</i> =7.4 and 16.6 Hz, 1 H), 2.82 - 2.92 (m, 1 H), 2.98 - 3.03 (m partially hidden, 2 H), 3.10 (br t, <i>J</i> =12.7 Hz, 2 H), 3.52 - 3.61 (m, 1 H), 4.02 - 4.10 (m, 1 H), 4.11 - 4.29 (m, 2 H), 4.50 (br d, <i>J</i> =4.0 Hz, 1 H), 7.41 (br d, <i>J</i> =8.4 Hz, 2 H), 7.56 (br d, <i>J</i> =8.4 Hz, 2 H), 7.90 (d, <i>J</i> =4.3 Hz, 1 H), 10.94 (br s, 1 H)	478
4	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.86 (br d, <i>J</i> =12.7 Hz, 2 H), 1.91 - 2.05 (m, 2 H), 2.17 - 2.30 (m, 4 H), 2.87 - 2.91 (m partially hidden, 2 H), 3.06 (t, <i>J</i> =12.7 Hz, 2 H), 3.65 - 3.75 (m, 1 H), 4.08 - 4.22 (m, 2 H), 7.38 (br d, <i>J</i> =8.4 Hz, 2 H), 7.55 (br d, <i>J</i> =8.4 Hz, 2 H), 7.97 (d, <i>J</i> =4.3 Hz, 1 H), 8.73 (br s, 1 H), 11.22 - 11.39 (m, 1 H)	491
5	A + N-BOC deprotection	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.25 - 1.37 (m, 1 H), 1.52 - 1.63 (m, 2 H), 1.76 - 1.92 (m, 3 H), 1.95 - 2.09 (m, 2 H), 2.35 - 2.45 (m, 3 H), 2.60 (td, <i>J</i> =2.5 and 12.2 Hz, 1 H), 2.73 - 2.82 (m, 1 H), 2.87 - 2.94 (m partially hidden, 2 H), 3.00 - 3.18 (m, 3 H), 3.46 - 3.60 (m, 1 H), 4.07 - 4.28 (m, 2 H), 7.41 (br d, <i>J</i> =8.4 Hz, 2 H), 7.56 (br d, <i>J</i> =8.4 Hz, 2 H), 7.90 (d, <i>J</i> =4.3 Hz, 1 H), 10.95 (br s, 1 H)	517
6	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.79 - 1.90 (m, 2 H) 1.90 - 2.05 (m, 2 H) 2.62 - 2.79 (m, 2 H) 2.97 - 3.24 (m, 4 H) 3.25 - 3.33 (m, 1 H) 3.62 - 3.74 (m, 2 H) 3.94 (t, <i>J</i> =6.4 Hz, 1 H) 4.16 - 4.33 (m, 2 H) 4.29 (br t, <i>J</i> =6.4 Hz, 1 H) 7.43 (br d, <i>J</i> =8.4 Hz, 2 H) 7.58 (br d, <i>J</i> =8.4 Hz, 2 H) 7.98 (d, <i>J</i> =3.6 Hz, 1 H) 11.51 (br s, 1 H)	490

7	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.80 - 1.90 (m, 2 H) 1.91 - 2.05 (m, 2 H) 2.63 - 2.79 (m, 2 H) 2.97 - 3.19 (m, 4 H) 3.23 - 3.33 (m, 1 H) 3.61 - 3.73 (m, 2 H) 3.94 (t, <i>J</i> =6.4 Hz, 1 H) 4.18 - 4.28 (m, 2 H) 4.30 (t, <i>J</i> =6.4 Hz, 1 H) 5.39 (br s, 2 H) 6.52 (br d, <i>J</i> =8.4 Hz, 1 H) 6.71 (br s, 1 H) 7.16 (d, <i>J</i> =8.4 Hz, 1 H) 7.97 (d, <i>J</i> =3.6 Hz, 1 H) 11.50 (br s, 1 H)	505
8	D + OTBS deprotection + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.60 - 1.74 (m, 2 H), 1.86 (br d, <i>J</i> =12.7 Hz, 2 H), 1.98 - 2.11 (m, 4 H), 2.61 - 2.79 (m, 2 H), 2.97 - 3.01 (m partially hidden, 1 H), 3.04 - 3.20 (m, 3 H), 3.62 - 3.75 (m, 1 H), 3.87 - 3.97 (m, 1 H), 4.19 (br d, <i>J</i> =12.7 Hz, 2 H), 4.24 (br d, <i>J</i> =4.3 Hz, 1 H), 5.35 (br s, 2 H), 6.51 (br d, <i>J</i> =8.4 Hz, 1 H), 6.70 (br s, 1 H), 7.13 (d, <i>J</i> =8.4 Hz, 1 H), 7.89 (d, <i>J</i> =4.3 Hz, 1 H), 11.01 (br s, 1 H)	507
9	D + OTBS deprotection + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.59 - 1.75 (m, 2 H), 1.86 (br d, <i>J</i> =12.7 Hz, 2 H), 1.98 - 2.12 (m, 4 H), 2.61 - 2.79 (m, 2 H), 2.97 - 3.00 (m partially hidden, 1 H), 3.04 - 3.20 (m, 3 H), 3.62 - 3.74 (m, 1 H), 3.88 - 3.96 (m, 1 H), 4.19 (br d, <i>J</i> =12.7 Hz, 2 H), 4.24 (br d, <i>J</i> =4.3 Hz, 1 H), 5.35 (br s, 2 H), 6.51 (br d, <i>J</i> =8.4 Hz, 1 H), 6.70 (br s, 1 H), 7.13 (d, <i>J</i> =8.4 Hz, 1 H), 7.89 (d, <i>J</i> =4.3 Hz, 1 H), 11.02 (br s, 1 H)	507
10	A+ ketal deprotection + reductive amination + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 0.23 - 0.32 (m, 2 H) 0.38 - 0.46 (m, 2 H) 1.59 - 1.73 (m, 1 H) 1.85 (br t, <i>J</i> =12.7 Hz, 2 H) 1.93 - 2.13 (m, 4 H) 2.21 (tt, <i>J</i> =6.7, 3.5 Hz, 1 H) 2.60 - 2.68 (m, 1 H) 2.68 - 2.79 (m, 2 H) 3.00 - 3.11 (m, 3 H) 3.17 (dd, <i>J</i> =14.4, 5.2 Hz, 1 H) 3.49 - 3.61 (m, 1 H) 4.10 - 4.29 (m, 2 H) 7.39 (d, <i>J</i> =8.4 Hz, 2 H) 7.54 (d, <i>J</i> =8.4 Hz, 2 H) 7.88 (d, <i>J</i> =4.3 Hz, 1 H) 10.93 (br s, 1 H)	517
11	A+ ketal deprotection + reductive amination + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 0.24 - 0.31 (m, 2 H) 0.38 - 0.46 (m, 2 H) 1.60 - 1.73 (m, 1 H) 1.85 (br t, <i>J</i> =12.7 Hz, 2 H) 1.93 - 2.17 (m, 4 H) 2.21 (tt, <i>J</i> =6.7, 3.5 Hz, 1 H) 2.61 - 2.69 (m, 1 H) 2.69 - 2.85 (m, 2 H) 3.00 - 3.12 (m, 3 H) 3.17 (dd, <i>J</i> =14.4, 5.2 Hz, 1 H) 3.48 - 3.61 (m, 1 H) 4.08 - 4.26 (m, 2 H) 7.39 (d, <i>J</i> =8.4 Hz, 2 H) 7.54 (d, <i>J</i> =8.4 Hz, 2 H) 7.88 (d, <i>J</i> =4.3 Hz, 1 H) 10.93 (br s, 1 H)	517

12	A+ NBOC deprotection	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.67 (t, <i>J</i> =5.4 Hz, 4 H) 1.82 (br d, <i>J</i> =12.7 Hz, 2 H) 1.91 - 2.05 (m, 2 H) 2.77 (s, 2 H) 2.78 - 2.91 (m, 4 H) 2.83 (br s, 2 H) 3.13 (br t, <i>J</i> =12.7 Hz, 2 H) 3.32 - 3.48 (m, 1 H) 4.10 - 4.33 (m, 2 H) 7.43 (br d, <i>J</i> =8.4 Hz, 2 H) 7.58 (d, <i>J</i> =8.4 Hz, 2 H) 7.91 (d, <i>J</i> =3.4 Hz, 1 H) 11.02 - 11.21 (m, 1 H)	517
13	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.87 - 1.94 (m, 2 H) 1.99 - 2.10 (m, 2 H) 2.13 (t, <i>J</i> =6.3 Hz, 2 H) 2.80 (t, <i>J</i> =6.3 Hz, 2 H) 3.13 - 3.20 (m, 2 H) 3.20 (s, 2 H) 3.54 - 3.64 (m, 1 H) 4.13 - 4.31 (m, 2 H) 4.40 (d, <i>J</i> =5.6 Hz, 2 H) 4.45 (d, <i>J</i> =5.6 Hz, 2 H) 7.42 (d, <i>J</i> =8.4 Hz, 2 H) 7.58 (d, <i>J</i> =8.4 Hz, 2 H) 7.92 (d, <i>J</i> =4.3 Hz, 1 H) 11.03 (br s, 1 H)	504
14	C + OTBS deprotection	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.71 - 1.87 (m, 3 H), 1.93 - 2.07 (m, 3 H), 2.60 (dd, <i>J</i> =7.4 and 16.6 Hz, 1 H), 2.80 - 2.88 (m, 1 H), 2.94 - 3.01 (m partially hidden, 2 H), 3.06 (br t, <i>J</i> =12.7 Hz, 2 H), 3.47 - 3.56 (m, 1 H), 3.98 - 4.07 (m, 1 H), 4.16 (br d, <i>J</i> =12.7 Hz, 2 H), 4.47 (d, <i>J</i> =4.0 Hz, 1 H), 5.33 (br s, 2 H), 6.49 (br d, <i>J</i> =8.4 Hz, 1 H), 6.68 (br s, 1 H), 7.11 (d, <i>J</i> =8.4 Hz, 1 H), 7.87 (d, <i>J</i> =4.3 Hz, 1 H), 10.90 (br s, 1 H)	493
15	B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.86 (br d, <i>J</i> =12.7 Hz, 2 H), 1.94 - 2.09 (m, 4 H), 2.93 (br s partially hidden, 2 H), 2.98 - 3.02 (m partially hidden, 2 H), 3.05 - 3.16 (m, 2 H), 3.50 - 3.60 (m, 1 H), 3.98 (br s, 4 H), 4.09 - 4.28 (m, 2 H), 7.41 (d, <i>J</i> =7.7 Hz, 2 H), 7.56 (d, <i>J</i> =7.7 Hz, 2 H), 7.93 (d, <i>J</i> =4.3 Hz, 1 H), 10.97 - 11.03 (m, 1 H)	520
16	B + Ketal deprotection	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.87 (br d, <i>J</i> =12.7 Hz, 2 H) 1.93 - 2.08 (m, 2 H) 2.71 (t, <i>J</i> =6.8 Hz, 2 H) 3.09 (br t, <i>J</i> =12.7 Hz, 2 H) 3.25 (t, <i>J</i> =6.8 Hz, 2 H) 3.48 - 3.58 (m, 1 H) 3.62 (s, 2 H) 4.11 - 4.24 (m, 2 H) 7.39 (br d, <i>J</i> =8.4 Hz, 2 H) 7.54 (d, <i>J</i> =8.4 Hz, 2 H) 7.97 (d, <i>J</i> =4.3 Hz, 1 H) 11.11 - 11.20 (m, 1 H)	476
17	A + ketal deprotection + MeMgBr addition	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.31 (s, 3 H) 1.71 - 1.80 (m, 1 H) 1.80 - 1.90 (m, 3 H) 1.97 - 2.10 (m, 2 H) 2.62 - 2.70 (m, 1 H) 2.83 - 2.93 (m, 1 H) 2.89 (s, 2 H) 3.05 - 3.15 (m, 2 H) 3.47 - 3.58 (m, 1 H) 4.07 (br s, 1 H) 4.14 - 4.29 (m, 2 H) 7.41 (br d, <i>J</i> =8.4 Hz, 2 H) 7.57 (br d, <i>J</i> =8.4 Hz, 2 H) 7.90 (d, <i>J</i> =4.3 Hz, 1 H) 10.91 - 11.00 (m, 1 H)	492

18	D + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.82 (br d, J=12.7 Hz, 2 H), 1.89 - 2.03 (m, 2 H), 2.09 (t, J=7.1 Hz, 2 H), 2.95 - 3.05 (m partially hidden, 4 H), 3.10 (br t, J=12.7 Hz, 2 H), 3.29 - 3.44 (m, 1 H), 3.71 (s, 2 H), 3.86 - 3.95 (m, 2 H), 4.14 - 4.26 (m, 2 H), 5.37 (br s, 2 H), 6.51 (br d, J=8.4 Hz, 1 H), 6.71 (br s, 1 H), 7.15 (d, J=8.4 Hz, 1 H), 7.93 (d, J=3.3 Hz, 1 H), 11.20 (br s, 1 H)	519
19	D + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.82 (br d, J=12.7 Hz, 2 H), 1.90 - 2.03 (m, 2 H), 2.09 (t, J=7.1 Hz, 2 H), 2.95 - 3.05 (m partially hidden, 4 H), 3.10 (br t, J=12.7 Hz, 2 H), 3.29 - 3.42 (m, 1 H), 3.71 (s, 2 H), 3.86 - 3.95 (m, 2 H), 4.14 - 4.26 (m, 2 H), 5.37 (br s, 2 H), 6.51 (br d, J=8.4 Hz, 1 H), 6.71 (br s, 1 H), 7.15 (d, J=8.4 Hz, 1 H), 7.93 (d, J=3.3 Hz, 1 H), 11.20 (br s, 1 H)	519
20	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.89 (br d, J=12.7 Hz, 2 H), 1.95 - 2.08 (m, 2 H), 2.13 (s, 3 H), 2.79 - 2.86 (m partially hidden, 2 H), 3.10 (br t, J=12.7 Hz, 2 H), 3.21 - 3.32 (m, 1 H), 3.80 (t, J=5.6 Hz, 2 H), 4.12 - 4.27 (m, 2 H), 4.82 (br s, 2 H), 7.39 (br d, J=8.4 Hz, 2 H), 7.56 (br d, J=8.4 Hz, 2 H), 7.96 (d, J=4.3 Hz, 1 H), 11.20 - 11.29 (m, 1 H)	505
21	A + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.83 (br d, J=12.7 Hz, 2 H), 1.89 - 2.04 (m, 2 H), 2.09 (t, J=7.1 Hz, 2 H), 2.95 - 2.97 (m partially hidden, 2 H), 2.98 - 3.06 (m, 2 H), 3.12 (br t, J=12.7 Hz, 2 H), 3.34 - 3.45 (m, 1 H), 3.67 - 3.75 (m, 2 H), 3.86 - 3.97 (m, 2 H), 4.10 - 4.32 (m, 2 H), 7.41 (br d, J=8.4 Hz, 2 H), 7.57 (br d, J=8.4 Hz, 2 H), 7.93 (d, J=3.3 Hz, 1 H), 11.21 (br s, 1 H)	504
22	A + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.83 (br d, J=12.7 Hz, 2 H), 1.90 - 2.04 (m, 2 H), 2.09 (t, J=7.1 Hz, 2 H), 2.95 - 2.97 (m partially hidden, 2 H), 2.98 - 3.07 (m, 2 H), 3.12 (br t, J=12.7 Hz, 2 H), 3.34 - 3.43 (m, 1 H), 3.69 - 3.74 (m, 2 H), 3.87 - 3.96 (m, 2 H), 4.06 - 4.33 (m, 2 H), 7.41 (br d, J=8.4 Hz, 2 H), 7.57 (br d, J=8.4 Hz, 2 H), 7.93 (br d, J=3.3 Hz, 1 H), 11.21 (br s, 1 H)	504

23	A + ketal deprotection + reductive amination	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.58 - 1.70 (m, 1 H) 1.72 - 1.90 (m, 3 H) 1.96 - 2.07 (m, 3 H) 2.61 (dd, <i>J</i> =14.1, 7.4 Hz, 1 H) 2.69 - 2.85 (m, 2 H) 2.94 - 3.18 (m, 6 H) 3.47 - 3.61 (m, 1 H) 4.05 - 4.29 (m, 2 H) 4.48 (dt, <i>J</i> =47.7, 5.3 Hz, 2 H) 7.39 (br d, <i>J</i> =8.4 Hz, 2 H) 7.54 (br d, <i>J</i> =8.4 Hz, 2 H) 7.88 (d, <i>J</i> =4.3 Hz, 1 H) 10.95 (br s, 1 H)	523
24	A + ketal deprotection + reductive amination	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.56 - 1.69 (m, 1 H) 1.79 - 2.09 (m, 5 H) 2.27 - 2.37 (m, 1 H) 2.54 - 2.64 (m, 2 H) 2.69 - 2.83 (m, 2 H) 3.00 - 3.14 (m, 3 H) 3.41 - 3.60 (m, 1 H) 4.07 - 4.16 (m, 1 H) 4.15 - 4.28 (m, 2 H) 4.35 - 4.41 (m, 2 H) 4.70 (t, <i>J</i> =6.2 Hz, 2 H) 7.41 (br d, <i>J</i> =8.4 Hz, 2 H) 7.57 (d, <i>J</i> =8.4 Hz, 2 H) 7.90 (d, <i>J</i> =4.3 Hz, 1 H) 10.96 (br s, 1 H)	533
25	E	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.73 (br d, <i>J</i> =12.7 Hz, 2 H) 2.03 - 2.11 (m, 2 H) 2.12 - 2.24 (m, 2 H) 2.80 (t, <i>J</i> =6.5 Hz, 2 H) 2.99 - 3.08 (m, 2 H) 3.52 - 3.61 (m, 1 H) 4.14 - 4.24 (m, 4 H) 5.35 (br s, 2 H) 6.52 (br d, <i>J</i> =8.4 Hz, 1 H) 6.70 (br s, 1 H) 7.15 (d, <i>J</i> =8.4 Hz, 1 H) 7.93 (d, <i>J</i> =3.4 Hz, 1 H) 10.74 (br s, 1 H)	479
26	E	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.71 (br d, <i>J</i> =12.7 Hz, 2 H) 2.01 - 2.10 (m, 2 H) 2.10 - 2.22 (m, 2 H) 2.79 (t, <i>J</i> =6.5 Hz, 2 H) 2.99 - 3.11 (m, 2 H) 3.52 - 3.63 (m, 1 H) 4.06 - 4.27 (m, 4 H) 7.40 (br d, <i>J</i> =8.4 Hz, 2 H) 7.54 (br d, <i>J</i> =8.4 Hz, 2 H) 7.92 (d, <i>J</i> =3.4 Hz, 1 H) 10.73 (br s, 1 H)	464
27	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.80 - 1.91 (m, 2 H) 1.93 - 2.09 (m, 2 H) 2.67 - 2.75 (m, 1 H) 3.01 - 3.21 (m, 4 H) 3.46 - 3.61 (m, 3 H) 3.91 - 4.02 (m, 2 H) 4.06 - 4.12 (m, 1 H) 4.14 - 4.30 (m, 2 H) 7.42 (br d, <i>J</i> =8.4 Hz, 2 H) 7.56 (br d, <i>J</i> =8.4 Hz, 2 H) 7.93 (d, <i>J</i> =3.8 Hz, 1 H) 11.17 (br s, 1 H)	490
28	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.80 - 1.90 (m, 2 H) 1.92 - 2.08 (m, 2 H) 2.67 - 2.75 (m, 1 H) 2.99 - 3.22 (m, 4 H) 3.46 - 3.61 (m, 3 H) 3.90 - 4.01 (m, 2 H) 4.06 - 4.12 (m, 1 H) 4.15 - 4.28 (m, 2 H) 5.36 (br s, 2 H) 6.51 (br d, <i>J</i> =8.4 Hz, 1 H) 6.71 (br s, 1 H) 7.14 (d, <i>J</i> =8.4 Hz, 1 H) 7.92 (d, <i>J</i> =3.8 Hz, 1 H) 11.16 (br s, 1 H)	505

29	C + NHBOC deprotection	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.85 (br d, <i>J</i> =12.7 Hz, 2 H), 1.92 - 2.06 (m, 2 H), 2.93 - 2.95 (m partially hidden, 2 H), 3.01 - 3.11 (m, 2 H), 3.39 - 3.49 (m, 1 H), 3.94 (t, <i>J</i> =5.6 Hz, 2 H), 4.17 (br d, <i>J</i> =12.7 Hz, 2 H), 4.71 (br s, 2 H), 5.33 (br s, 2 H), 6.49 (br d, <i>J</i> =8.4 Hz, 1 H), 6.68 (br s, 1 H), 7.11 (d, <i>J</i> =8.4 Hz, 1 H), 7.94 (d, <i>J</i> =4.3 Hz, 1 H), 11.01 - 11.12 (m, 1 H)	479
30	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.87 (br d, <i>J</i> =12.7 Hz, 2 H) 1.95 - 2.08 (m, 2 H) 2.10 (t, <i>J</i> =6.3 Hz, 2 H) 2.77 (t, <i>J</i> =6.3 Hz, 2 H) 3.13 (br t, <i>J</i> =12.7 Hz, 2 H) 3.18 (s, 2 H) 3.49 - 3.60 (m, 1 H) 4.19 (br d, <i>J</i> =12.7 Hz, 2 H) 4.38 (d, <i>J</i> =5.6 Hz, 2 H) 4.43 (d, <i>J</i> =5.6 Hz, 2 H) 5.34 (br s, 2 H) 6.49 (br d, <i>J</i> =8.4 Hz, 1 H) 6.69 (br s, 1 H) 7.13 (d, <i>J</i> =8.4 Hz, 1 H) 7.89 (d, <i>J</i> =4.3 Hz, 1 H) 11.00 (br s, 1 H)	519
31	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.88 (br d, <i>J</i> =12.7 Hz, 2 H) 1.98 - 2.13 (m, 2 H) 2.93 - 2.95 (m hidden, 2 H) 3.09 (br t, <i>J</i> =12.7 Hz, 2 H) 3.54 (br q, <i>J</i> =5.8 Hz, 2 H) 3.57 - 3.66 (m, 1 H) 3.91 (s, 2 H) 4.19 (br d, <i>J</i> =12.7 Hz, 2 H) 5.34 (br s, 2 H) 6.48 (br d, <i>J</i> =8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.14 (d, <i>J</i> =8.4 Hz, 1 H) 7.35 (br t, <i>J</i> =5.8 Hz, 1 H) 7.93 (d, <i>J</i> =4.3 Hz, 1 H) 11.22 (br s, 1 H)	506
32	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.87 (br d, <i>J</i> =12.7 Hz, 2 H) 1.97 - 2.09 (m, 2 H) 2.75 (br t, <i>J</i> =6.5 Hz, 2 H) 3.01 (t, <i>J</i> =6.5 Hz, 2 H) 3.08 (br t, <i>J</i> =12.7 Hz, 2 H) 3.35 - 3.43 (m, 1 H) 4.17 (br d, <i>J</i> =12.7 Hz, 2 H) 4.55 (d, <i>J</i> =5.8 Hz, 2 H) 5.34 (br s, 2 H) 6.49 (br d, <i>J</i> =8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.12 (d, <i>J</i> =8.4 Hz, 1 H) 7.51 (br t, <i>J</i> =5.8 Hz, 1 H) 7.93 (d, <i>J</i> =4.3 Hz, 1 H) 11.23 (br s, 1 H)	506
33	A + ketal deprotection + Reduction + Chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.73 - 1.88 (m, 3 H), 1.92 - 2.08 (m, 3 H), 2.65 - 2.86 (m, 3 H), 3.07 (br t, <i>J</i> =12.7 Hz, 2 H), 3.14 (br dd, <i>J</i> =5.1 and 15.4 Hz, 1 H), 3.46 - 3.58 (m, 1 H), 3.96 - 4.10 (m, 1 H), 4.11 - 4.25 (m, 2 H), 4.41 (d, <i>J</i> =4.0 Hz, 1 H), 7.39 (br d, <i>J</i> =8.4 Hz, 2 H), 7.55 (d, <i>J</i> =8.4 Hz, 2 H), 7.88 (d, <i>J</i> =4.3 Hz, 1 H), 10.94 (br s, 1 H)	478

34	A + ketal deprotection + reduction + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.73 - 1.88 (m, 3 H), 1.92 - 2.08 (m, 3 H), 2.65 - 2.86 (m, 3 H), 3.07 (br t, J=12.7 Hz, 2 H), 3.14 (br dd, J=5.1 and 15.4 Hz, 1 H), 3.47 - 3.58 (m, 1 H), 3.97 - 4.09 (m, 1 H), 4.10 - 4.27 (m, 2 H), 4.38 - 4.46 (m, 1 H), 7.39 (br d, J=8.4 Hz, 2 H), 7.55 (d, J=8.4 Hz, 2 H), 7.88 (d, J=4.3 Hz, 1 H), 10.96 (br s, 1 H)	478
35	A + NBOC deprotection + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.80 - 1.91 (m, 2 H) 1.95 - 2.11 (m, 2 H) 2.12 - 2.27 (m, 1 H) 2.60 - 2.72 (m, 3 H) 2.99 - 3.17 (m, 4 H) 3.18 - 3.41 (m, 3 H) 3.69 - 3.80 (m, 1 H) 4.12 - 4.36 (m, 2 H) 7.41 (br d, J=8.4 Hz, 2 H) 7.57 (br d, J=8.4 Hz, 2 H) 7.90 (d, J=4.0 Hz, 1 H) 11.00 - 11.14 (m, 1 H)	489
36	A + NBOC deprotection + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.80 - 1.91 (m, 2 H) 1.95 - 2.11 (m, 2 H) 2.11 - 2.28 (m, 1 H) 2.60 - 2.71 (m, 3 H) 2.99 - 3.17 (m, 4 H) 3.18 - 3.41 (m, 3 H) 3.70 - 3.80 (m, 1 H) 4.12 - 4.35 (m, 2 H) 7.41 (br d, J=8.4 Hz, 2 H) 7.57 (br d, J=8.4 Hz, 2 H) 7.90 (d, J=4.0 Hz, 1 H) 11.00 - 11.14 (m, 1 H)	489
37	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.88 (br d, J=12.7 Hz, 2 H) 1.96 - 2.10 (m, 2 H) 2.75 (br t, J=6.5 Hz, 2 H) 3.01 (br t, J=6.5 Hz, 2 H) 3.09 (br t, J=12.7 Hz, 2 H) 3.36 - 3.47 (m, 1 H) 4.08 - 4.28 (m, 2 H) 4.56 (d, J=5.8 Hz, 2 H) 7.40 (br d, J=8.4 Hz, 2 H) 7.51 (br t, J=5.8 Hz, 1 H) 7.55 (d, J=8.4 Hz, 2 H) 7.94 (d, J=4.3 Hz, 1 H) 11.26 (br s, 1 H)	491
38	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.88 (br d, J=12.7 Hz, 2 H), 2.01 - 2.14 (m, 2 H), 2.90 - 2.93 (m hidden, 2 H), 3.11 (br t, J=12.7 Hz, 2 H), 3.54 (br q, J=5.8 Hz, 2 H), 3.58 - 3.69 (m, 1 H), 3.92 (s, 2 H), 4.08 - 4.28 (m, 2 H), 7.32 - 7.38 (m, 1 H), 7.39 (br d, J=8.4 Hz, 2 H), 7.57 (br d, J=8.4 Hz, 2 H), 7.95 (d, J=4.3 Hz, 1 H), 11.24 (br s, 1 H)	491
39	C	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.79 - 1.94 (m, 3 H), 1.94 - 2.09 (m, 3 H), 2.65 - 2.73 (m, 1 H), 2.80 - 2.90 (m, 1 H), 2.96 - 3.14 (m partially hidden, 4 H), 3.34 (s, 3 H), 3.48 - 3.58 (m, 1 H), 3.70 - 3.76 (m, 1 H), 4.05 - 4.29 (m, 2 H), 7.39 (br d, J=8.4 Hz, 2 H), 7.54 (d, J=8.4 Hz, 2 H), 7.90 (d, J=4.3 Hz, 1 H), 10.97 (br s, 1 H)	492

40	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.48 - 1.57 (m, 4 H) 1.80 (t, <i>J</i> =6.5 Hz, 2 H) 1.88 (br d, <i>J</i> =12.7 Hz, 2 H) 1.98 - 2.10 (m, 2 H) 2.73 (t, <i>J</i> =6.5 Hz, 2 H) 2.82 (s, 2 H) 3.13 (br t, <i>J</i> =12.7 Hz, 2 H) 3.54 - 3.62 (m, 1 H) 3.63 - 3.69 (m, 4 H) 4.10 - 4.34 (m, 2 H) 7.42 (br d, <i>J</i> =8.4 Hz, 2 H) 7.57 (br d, <i>J</i> =8.4 Hz, 2 H) 7.91 (d, <i>J</i> =4.3 Hz, 1 H) 11.00 (br s, 1 H)	532
41	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.47 - 1.58 (m, 4 H) 1.80 (t, <i>J</i> =6.5 Hz, 2 H) 1.87 (br d, <i>J</i> =12.7 Hz, 2 H) 1.95 - 2.12 (m, 2 H) 2.73 (t, <i>J</i> =6.5 Hz, 2 H) 2.82 (s, 2 H) 3.11 (br t, <i>J</i> =12.7 Hz, 2 H) 3.51 - 3.61 (m, 1 H) 3.61 - 3.72 (m, 4 H) 4.21 (br d, <i>J</i> =12.7 Hz, 2 H) 5.36 (br s, 2 H) 6.51 (br d, <i>J</i> =8.4 Hz, 1 H) 6.71 (br s, 1 H) 7.15 (d, <i>J</i> =8.4 Hz, 1 H) 7.90 (d, <i>J</i> =4.3 Hz, 1 H) 10.98 (br s, 1 H)	547
42	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.69 - 1.77 (m, 4 H) 1.82 (br d, <i>J</i> =12.7 Hz, 2 H) 1.90 - 2.03 (m, 2 H) 2.83 (s, 2 H) 2.87 (s, 2 H) 3.11 (br t, <i>J</i> =12.7 Hz, 2 H) 3.31 - 3.43 (m, 1 H) 3.63 - 3.76 (m, 4 H) 4.21 (br d, <i>J</i> =12.7 Hz, 2 H) 5.41 (br s, 2 H) 6.52 (br d, <i>J</i> =8.4 Hz, 1 H) 6.72 (br s, 1 H) 7.16 (d, <i>J</i> =8.4 Hz, 1 H) 7.91 (d, <i>J</i> =3.4 Hz, 1 H) 11.16 (br s, 1 H)	533
43	A + OTBS deprotection + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.59 - 1.72 (m, 2 H), 1.84 (br d, <i>J</i> =12.7 Hz, 2 H), 1.96 - 2.10 (m, 4 H), 2.60 - 2.78 (m, 2 H), 2.93 - 3.00 (m partially hidden, 1 H), 3.05 - 3.19 (m, 3 H), 3.63 - 3.73 (m, 1 H), 3.85 - 3.95 (m, 1 H), 4.08 - 4.30 (m, 3 H), 7.39 (br d, <i>J</i> =8.4 Hz, 2 H), 7.54 (br d, <i>J</i> =8.4 Hz, 2 H), 7.88 (d, <i>J</i> =4.3 Hz, 1 H), 11.00 (br s, 1 H)	492
44	A + OTBS deprotection + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.58 - 1.72 (m, 2 H), 1.84 (br d, <i>J</i> =12.7 Hz, 2 H), 1.96 - 2.09 (m, 4 H), 2.60 - 2.77 (m, 2 H), 2.94 - 2.99 (m partially hidden, 1 H), 3.04 - 3.20 (m, 3 H), 3.62 - 3.73 (m, 1 H), 3.84 - 3.95 (m, 1 H), 4.07 - 4.30 (m, 3 H), 7.39 (br d, <i>J</i> =8.4 Hz, 2 H), 7.54 (d, <i>J</i> =8.4 Hz, 2 H), 7.88 (d, <i>J</i> =4.3 Hz, 1 H), 11.00 (br s, 1 H)	492

45	C + NHBOC deprotection	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.81 - 1.95 (m, 3 H) 1.96 - 2.10 (m, 3 H) 2.67 - 2.74 (m, 1 H) 2.83 - 2.90 (m partially hidden, 1 H) 3.01 - 3.14 (m partially hidden, 4 H) 3.36 (s, 3 H) 3.47 - 3.59 (m, 1 H) 3.71 - 3.80 (m, 1 H) 4.14 - 4.23 (m, 2 H) 5.36 (br s, 2 H) 6.51 (br d, J=8.4 Hz, 1 H) 6.70 (br s, 1 H) 7.13 (br d, J=8.4 Hz, 1 H) 7.91 (br s, 1 H) 10.98 (br s, 1 H)	507
46	D + OTBS deprotection	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.54 - 1.76 (m, 2 H), 1.85 - 1.95 (m, 3 H), 1.99 - 2.16 (m, 3 H), 2.71 - 2.90 (m, 2 H), 2.90 - 2.97 (m partially hidden, 1 H), 3.04 - 3.18 (m, 2 H), 3.25 - 3.34 (m, 1 H), 3.67 - 3.77 (m, 2 H), 4.20 (br d, J=12.7 Hz, 2 H), 4.28 (d, J=3.9 Hz, 1 H), 5.35 (br s, 2 H), 6.51 (br d, J=8.4 Hz, 1 H), 6.70 (br s, 1 H), 7.15 (d, J=8.4 Hz, 1 H), 7.89 (d, J=4.3 Hz, 1 H), 11.05 (br s, 1 H)	507
47	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.69 - 1.78 (m, 4 H) 1.83 (br d, J=12.7 Hz, 2 H) 1.93 - 2.05 (m, 2 H) 2.83 (s, 2 H) 2.89 (s, 2 H) 3.14 (br t, J=12.7 Hz, 2 H) 3.33 - 3.46 (m, 1 H) 3.64 - 3.76 (m, 4 H) 4.08 - 4.32 (m, 2 H) 7.42 (br d, J=8.4 Hz, 2 H) 7.58 (br d, J=8.4 Hz, 2 H) 7.92 (d, J=3.4 Hz, 1 H) 11.07 - 11.23 (m, 1 H)	518
48	A + NBOC deprotection + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.82 (br d, J=12.7 Hz, 2 H), 1.89 (t, J=7.0 Hz, 2 H), 1.92 - 2.03 (m, 2 H), 2.84 - 2.92 (m partially hidden, 6 H), 2.98 - 3.02 (m partially hidden, 2 H), 3.06 - 3.17 (m, 2 H), 3.34 - 3.43 (m, 1 H), 4.11 - 4.32 (m, 2 H), 7.42 (br d, J=8.4 Hz, 2 H), 7.58 (br d, J=8.4 Hz, 2 H), 7.92 (d, J=3.5 Hz, 1 H), 11.06 - 11.25 (m, 1 H)	503
49	A + NBOC deprotection + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.82 (br d, J=12.7 Hz, 2 H), 1.89 (t, J=7.0 Hz, 2 H), 1.91 - 2.03 (m, 2 H), 2.83 - 2.91 (m partially hidden, 6 H), 2.98 - 3.02 (m partially hidden, 2 H), 3.07 - 3.17 (m, 2 H), 3.33 - 3.44 (m, 1 H), 4.11 - 4.31 (m, 2 H), 7.42 (br d, J=8.4 Hz, 2 H), 7.58 (br d, J=8.4 Hz, 2 H), 7.92 (d, J=3.5 Hz, 1 H), 11.04 - 11.27 (m, 1 H)	503

50	F	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.86 (br d, <i>J</i> =12.7 Hz, 2 H) 1.94 - 2.07 (m, 2 H) 2.71 (t, <i>J</i> =6.8 Hz, 2 H) 3.08 (br t, <i>J</i> =12.7 Hz, 2 H) 3.25 (br t, <i>J</i> =6.8 Hz, 2 H) 3.47 - 3.56 (m, 1 H) 3.62 (s, 2 H) 4.17 (br d, <i>J</i> =12.7 Hz, 2 H) 5.34 (br s, 2 H) 6.49 (br d, <i>J</i> =8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.11 (d, <i>J</i> =8.4 Hz, 1 H) 7.96 (d, <i>J</i> =4.3 Hz, 1 H) 11.16 (br s, 1 H)	491
51	F	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.83 (br d, <i>J</i> =12.7 Hz, 2 H), 1.95 (br t, <i>J</i> =6.3 Hz, 2 H), 1.96 - 2.06 (m, 2 H), 2.91 (s partially hidden, 2 H), 2.98 (br t partially hidden, <i>J</i> =6.3 Hz, 2 H), 3.03 - 3.09 (m partially hidden, 2 H), 3.46 - 3.55 (m, 1 H), 3.96 (s, 4 H), 4.17 (br d, <i>J</i> =12.7 Hz, 2 H), 6.49 (br d, <i>J</i> =8.4 Hz, 1 H), 6.68 (br s, 1 H), 7.11 (d, <i>J</i> =8.4 Hz, 1 H), 7.90 (d, <i>J</i> =4.3 Hz, 1 H), 10.98 (br s, 1 H)	535
52	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.76 - 1.86 (m, 3 H) 1.99 - 2.19 (m, 5 H) 2.86 - 2.89 (m partially hidden, 2 H) 2.95 - 3.03 (m partially hidden, 2 H) 3.32 - 3.39 (m, 1 H) 3.67 (d, <i>J</i> =9.0 Hz, 1 H) 3.76 - 3.82 (m, 1 H) 3.99 (d, <i>J</i> =9.0 Hz, 1 H) 4.11 - 4.21 (m, 3 H) 5.33 (br s, 2 H) 6.49 (br d, <i>J</i> =8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.12 (d, <i>J</i> =8.4 Hz, 1 H) 7.90 (d, <i>J</i> =3.8 Hz, 1 H) 11.21 (br s, 1 H)	519
53	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.77 - 1.89 (m, 3 H), 1.95 - 2.21 (m, 5 H), 2.87 - 2.90 (m partially hidden, 2 H), 2.95 - 3.05 (m partially hidden, 2 H), 3.33 - 3.45 (m, 1 H), 3.67 (d, <i>J</i> =9.0 Hz, 1 H), 3.75 - 3.83 (m, 1 H), 4.00 (d, <i>J</i> =9.0 Hz, 1 H), 4.10 - 4.26 (m, 3 H), 7.39 (br d, <i>J</i> =8.4 Hz, 2 H), 7.54 (d, <i>J</i> =8.4 Hz, 2 H), 7.91 (d, <i>J</i> =3.8 Hz, 1 H), 11.18 - 11.27 (m, 1 H)	504
54	E + reduction of the ketone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.76 - 1.90 (m, 3 H), 1.94 - 2.10 (m, 3 H), 2.69 - 2.88 (m, 3 H), 3.07 (br t, <i>J</i> =12.7 Hz, 2 H), 3.15 (dd, <i>J</i> =5.1 and 15.4 Hz, 1 H), 3.45 - 3.58 (m, 1 H), 4.00 - 4.10 (m, 1 H), 4.20 (br d, <i>J</i> =12.7 Hz, 2 H), 4.44 (d, <i>J</i> =4.0 Hz, 1 H), 5.35 (br s, 2 H), 6.51 (br d, <i>J</i> =8.4 Hz, 1 H), 6.70 (br s, 1 H), 7.14 (d, <i>J</i> =8.4 Hz, 1 H), 7.89 (d, <i>J</i> =4.3 Hz, 1 H), 10.96 (br s, 1 H)	493

55	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.78 - 1.87 (m, 6 H) 1.93 - 2.06 (m, 2 H) 2.67 - 2.73 (m, 2 H) 2.83 - 2.88 (m, 2 H) 3.05 (br t, <i>J</i> =12.7 Hz, 2 H) 3.47 - 3.56 (m, 1 H) 4.17 (br d, <i>J</i> =12.7 Hz, 2 H) 5.33 (br s, 2 H) 6.49 (br d, <i>J</i> =8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.11 (d, <i>J</i> =8.4 Hz, 1 H) 7.87 (d, <i>J</i> =4.3 Hz, 1 H) 10.91 (br s, 1 H)	477
56	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.83 (br d, <i>J</i> =12.7 Hz, 2 H) 1.94 (br t, <i>J</i> =6.5 Hz, 2 H) 1.95 - 2.06 (m, 2 H) 2.83 (br t, <i>J</i> =6.5 Hz, 2 H) 3.04 (s, 2 H) 3.09 (br t, <i>J</i> =12.7 Hz, 2 H) 3.38 - 3.47 (m, 1 H) 3.94 - 4.02 (m, 4 H) 4.09 - 4.22 (m, 2 H) 7.39 (br d, <i>J</i> =8.4 Hz, 2 H) 7.54 (d, <i>J</i> =8.4 Hz, 2 H) 7.90 (d, <i>J</i> =4.3 Hz, 1 H) 11.05 (br s, 1 H)	520
57	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.80 - 1.90 (m, 3 H) 1.93 - 2.08 (m, 3 H) 2.67 - 2.86 (m, 3 H) 3.07 (br t, <i>J</i> =12.7 Hz, 2 H) 3.18 (dd, <i>J</i> =15.4, 5.1 Hz, 1 H) 3.36 (s, 3 H) 3.44 - 3.54 (m, 1 H) 3.67 - 3.76 (m, 1 H) 4.17 (br d, <i>J</i> =12.7 Hz, 2 H) 5.33 (br s, 2 H) 6.49 (br d, <i>J</i> =8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.12 (d, <i>J</i> =8.4 Hz, 1 H) 7.88 (d, <i>J</i> =4.3 Hz, 1 H) 10.97 (br s, 1 H)	507
58	A + NBOC deprotection	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.78 - 1.92 (m, 3 H), 1.99 - 2.13 (m, 3 H), 2.33 - 2.48 (m, 2 H), 2.84 - 2.89 (m, 2 H), 2.91 - 2.94 (m partially hidden, 1 H), 2.99 - 3.19 (m, 5 H), 3.54 - 3.65 (m, 1 H), 4.09 - 4.31 (m, 2 H), 7.41 (br d, <i>J</i> =8.4 Hz, 2 H), 7.56 (br d, <i>J</i> =8.4 Hz, 2 H), 7.91 (d, <i>J</i> =4.0 Hz, 1 H), 11.08 - 11.25 (m, 1 H)	503
59	A + NBOC deprotection	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 30°C) δ ppm 1.47 - 1.58 (m, 1 H) 1.60 - 1.71 (m, 1 H) 1.74 - 2.18 (m, 6 H) 2.64 - 2.75 (m, 1 H) 2.77 - 2.90 (m, 2 H) 2.91 - 3.27 (m, 2 H) 3.25 - 3.29 (m, 1 H) 3.57 - 3.65 (m, 1 H) 3.66 - 3.77 (m, 2 H) 4.56 - 4.80 (m, 2 H) 7.46 (br d, <i>J</i> =8.4 Hz, 2 H) 7.59 (br d, <i>J</i> =8.4 Hz, 2 H) 7.93 (d, <i>J</i> =4.3 Hz, 1 H) 11.43 (br s, 1 H)	492
60	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.81 - 1.89 (m, 6 H), 1.96 - 2.10 (m, 2 H), 2.70 - 2.75 (m, 2 H), 2.86 - 2.90 (m partially hidden, 2 H), 3.09 (br t, <i>J</i> =12.7 Hz, 2 H), 3.50 - 3.63 (m, 1 H), 4.09 - 4.29 (m, 2 H), 7.41 (br d, <i>J</i> =8.4 Hz, 2 H), 7.56 (br d, <i>J</i> =8.4 Hz, 2 H), 7.90 (d, <i>J</i> =4.3 Hz, 1 H), 10.94 (br s, 1 H)	462

61	A + ketal deprotection	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.85 (br d, <i>J</i> =12.7 Hz, 2 H) 1.93 - 2.06 (m, 2 H) 2.71 (t, <i>J</i> =6.8 Hz, 2 H) 3.05 - 3.18 (m, 4 H) 3.34 - 3.43 (m, 1 H) 3.75 (s, 2 H) 4.08 - 4.25 (m, 2 H) 7.39 (br d, <i>J</i> =8.4 Hz, 2 H) 7.54 (br d, <i>J</i> =8.4 Hz, 2 H) 7.96 (d, <i>J</i> =4.3 Hz, 1 H) 11.28 (br s, 1 H)	476
62	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 30°C) δ ppm 1.68 - 2.12 (m, 6 H) 2.70 - 2.85 (m, 3 H) 2.86 - 3.21 (m, 2 H) 3.13 - 3.22 (m, 1 H) 3.35 (br s, 3 H) 3.45 - 3.53 (m, 1 H) 3.59 - 3.79 (m, 2 H) 4.52 - 4.77 (m, 1 H) 7.45 (br d, <i>J</i> =8.4 Hz, 2 H) 7.57 (br d, <i>J</i> =8.4 Hz, 2 H) 7.94 (d, <i>J</i> =4.3 Hz, 1 H) 11.34 (s, 1 H)	492
63	A + NBOC deprotection	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.88 (br d, <i>J</i> =12.7 Hz, 2 H) 1.94 - 2.12 (m, 4 H) 2.77 (br t, <i>J</i> =6.1 Hz, 2 H) 3.06 (br s partially hidden, 2 H) 3.09 - 3.18 (m, 2 H) 3.30 - 3.36 (m, 2 H) 3.36 - 3.44 (m, 2 H) 3.52 - 3.63 (m, 1 H) 4.12 - 4.28 (m, 2 H) 7.41 (br d, <i>J</i> =8.4 Hz, 2 H) 7.57 (br d, <i>J</i> =8.4 Hz, 2 H) 7.90 (d, <i>J</i> =4.3 Hz, 1 H) 10.54 - 11.50 (m, 1 H)	503
64	A + NBOC deprotection	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.89 (br d, <i>J</i> =12.7 Hz, 2 H) 1.97 - 2.09 (m, 2 H) 3.11 - 3.20 (m, 5 H) 3.47 (br t, <i>J</i> =6.1 Hz, 2 H) 4.12 - 4.29 (m, 2 H) 4.52 (br s, 2 H) 7.42 (br d, <i>J</i> =8.4 Hz, 2 H) 7.57 (br d, <i>J</i> =8.4 Hz, 2 H) 8.06 (d, <i>J</i> =4.3 Hz, 1 H) 9.41 - 9.57 (m, 2 H) 11.57 (br s, 1 H)	463
65	E	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 30°C) δ ppm 1.69 - 2.02 (m, 6 H), 2.69 - 2.87 (m, 1 H), 2.95 (t, <i>J</i> =7.4 Hz, 2 H), 2.99 - 3.13 (m, 1 H), 3.11 - 3.20 (m, 2 H), 3.57 - 3.78 (m, 1 H), 4.05 - 4.16 (m, 1 H), 4.53 - 4.75 (m, 1 H), 7.45 (br d, <i>J</i> =8.4 Hz, 2 H), 7.57 (br d, <i>J</i> =8.4 Hz, 2 H), 7.78 (t, <i>J</i> =6.1 Hz, 1 H), 8.10 (d, <i>J</i> =4.0 Hz, 1 H), 12.14 (br s, 1 H)	491
66	E	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.84 (br d, <i>J</i> =12.7 Hz, 2 H), 1.94 - 2.06 (m, 4 H), 2.97 - 3.02 (m partially hidden, 4 H), 3.19 (q, <i>J</i> =6.2 Hz, 2 H), 4.11 - 4.22 (m, 3 H), 5.34 (br s, 2 H), 6.50 (br d, <i>J</i> =8.4 Hz, 1 H), 6.69 (br s, 1 H), 7.13 (d, <i>J</i> =8.4 Hz, 1 H), 7.37 - 7.41 (m, 1 H), 8.05 (d, <i>J</i> =4.3 Hz, 1 H), 11.69 - 11.92 (m, 1 H)	506

67	E	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 30°C) δ ppm 1.83 (br d, <i>J</i> =12.7 Hz, 2 H), 1.88 - 2.00 (m, 2 H), 2.71 (t, <i>J</i> =6.8 Hz, 2 H), 3.02 - 3.16 (m, 2 H), 3.10 (br t, <i>J</i> =6.8 Hz, 2 H), 3.31 - 3.38 (m partially hidden, 1 H), 3.77 (s, 2 H), 3.83 - 4.57 (m, 2 H), 5.57 (br s, 2 H), 6.50 (br d, <i>J</i> =8.4 Hz, 1 H), 6.66 (br s, 1 H), 7.12 (d, <i>J</i> =8.4 Hz, 1 H), 8.00 (d, <i>J</i> =4.3 Hz, 1 H), 11.61 (br s, 1 H)	491
68	E	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.72 - 1.90 (m, 8 H) 1.96 - 2.12 (m, 2 H) 2.82 - 2.89 (m, 2 H) 2.97 - 3.03 (m, 2 H) 3.09 (br t, <i>J</i> =12.7 Hz, 2 H) 3.63 - 3.72 (m, 1 H) 4.19 (br d, <i>J</i> =12.7 Hz, 2 H) 5.35 (br s, 2 H) 6.51 (br d, <i>J</i> =8.4 Hz, 1 H) 6.70 (br s, 1 H) 7.13 (d, <i>J</i> =8.4 Hz, 1 H) 7.89 (d, <i>J</i> =4.3 Hz, 1 H) 10.95 - 11.06 (m, 1 H)	491
69	E	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.85 (br d, <i>J</i> =12.7 Hz, 2 H), 1.92 - 2.05 (m, 2 H), 2.83 (br t, <i>J</i> =5.6 Hz, 2 H), 2.98 - 3.04 (m partially hidden, 1 H), 3.04 - 3.13 (m, 2 H), 3.96 (t, <i>J</i> =5.6 Hz, 2 H), 4.18 (br d, <i>J</i> =12.7 Hz, 2 H), 4.96 (br s, 2 H), 5.35 (br s, 2 H), 6.51 (br d, <i>J</i> =8.4 Hz, 1 H), 6.70 (br s, 1 H), 7.13 (d, <i>J</i> =8.4 Hz, 1 H), 7.96 (d, <i>J</i> =4.3 Hz, 1 H), 11.20 - 11.27 (m, 1 H)	479
70	G	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.66 - 1.80 (m, 2 H) 1.80 - 1.93 (m, 3 H) 2.00 - 2.10 (m, 1 H) 2.67 (dd, <i>J</i> =16.4, 6.7 Hz, 1 H) 2.81 - 2.89 (m, 1 H) 2.96 - 3.12 (m, 4 H) 3.34 (s, 3 H) 3.35 - 3.46 (m, 1 H) 3.69 - 3.76 (m, 1 H) 4.17 (br d, <i>J</i> =12.7 Hz, 2 H) 5.34 (br s, 2 H) 6.48 (br d, <i>J</i> =8.4 Hz, 1 H) 6.67 (br s, 1 H) 6.82 (d, <i>J</i> =5.1 Hz, 1 H) 7.14 (d, <i>J</i> =8.4 Hz, 1 H) 7.97 (d, <i>J</i> =5.1 Hz, 1 H) 10.79 (br s, 1 H)	489
71	G	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.65 - 1.79 (m, 2 H) 1.80 - 1.92 (m, 3 H) 2.01 - 2.09 (m, 1 H) 2.67 (dd, <i>J</i> =16.4, 6.7 Hz, 1 H) 2.81 - 2.89 (m, 1 H) 2.95 - 3.11 (m, 4 H) 3.34 (s, 3 H) 3.35 - 3.45 (m, 1 H) 3.69 - 3.76 (m, 1 H) 4.17 (br d, <i>J</i> =12.7 Hz, 2 H) 5.34 (br s, 2 H) 6.48 (br d, <i>J</i> =8.4 Hz, 1 H) 6.67 (br s, 1 H) 6.82 (d, <i>J</i> =5.1 Hz, 1 H) 7.14 (d, <i>J</i> =8.4 Hz, 1 H) 7.97 (d, <i>J</i> =5.1 Hz, 1 H) 10.79 (br s, 1 H)	489

72	H	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.68 - 1.82 (m, 2 H), 1.87 (br d, J=12.7 Hz, 2 H), 2.40 - 2.45 (m partially hidden, 2 H), 2.84 (t, J=7.3 Hz, 2 H), 2.88 - 2.92 (m partially hidden, 2 H), 3.09 (td, J=2.8 and 12.7 Hz, 2 H), 3.14 - 3.23 (m, 1 H), 4.04 - 4.22 (m, 2 H), 5.45 (br s, 2 H), 6.82 (d, J=5.0 Hz, 1 H), 7.00 (dd, J=2.3 and 8.4 Hz, 1 H), 7.22 (d, J=8.4 Hz, 1 H), 7.26 (d, J=2.3 Hz, 1 H), 7.96 (d, J=5.0 Hz, 1 H), 10.89 - 10.99 (m, 1 H)	487
73	H	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.68 - 1.80 (m, 2 H), 1.87 (br d, J=12.7 Hz, 2 H), 2.39 - 2.46 (m partially hidden, 2 H), 2.84 (t, J=7.3 Hz, 2 H), 2.88 - 2.92 (m partially hidden, 2 H), 3.07 (td, J=2.8 and 12.7 Hz, 2 H), 3.14 - 3.24 (m, 1 H), 4.17 (br d, J=12.7 Hz, 2 H), 5.34 (br s, 2 H), 6.48 (br d, J=8.4 Hz, 1 H), 6.68 (br s, 1 H), 6.82 (d, J=5.0 Hz, 1 H), 7.13 (d, J=8.4 Hz, 1 H), 7.96 (d, J=5.0 Hz, 1 H), 10.90 - 11.00 (m, 1 H)	445
74	H	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.68 - 1.81 (m, 2 H), 1.87 (br d, J=12.7 Hz, 2 H), 2.40 - 2.46 (m partially hidden, 2 H), 2.84 (t, J=7.3 Hz, 2 H), 2.88 - 2.92 (m partially hidden, 2 H), 3.10 (br t, J=12.7 Hz, 2 H), 3.16 - 3.25 (m, 1 H), 4.06 - 4.27 (m, 2 H), 6.84 (d, J=5.0 Hz, 1 H), 7.38 (br d, J=8.4 Hz, 2 H), 7.56 (br d, J=8.4 Hz, 2 H), 7.97 (d, J=5.0 Hz, 1 H), 10.88 - 11.03 (m, 1 H)	430
75	I	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.35 (s, 1H), 8.01 (d, J=4.8 Hz, 1H), 7.13 (d, J=8.4 Hz, 1H), 6.85 (d, J=5.2 Hz, 1H), 6.65 (s, 1H), 5.59 (s, 2H), 5.05-3.58 (m, 6H), 3.49-3.43 (m, 1H), 3.09-2.97 (m, 6H), 1.88-1.82 (m, 2H) 1.71-1.68 (m, 2H) ppm.	475.1 (ESI)
76	G	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 11.18 (s, 1H), 7.99 (d, J = 5.0 Hz, 1H), 7.60 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 6.89 (d, J = 5.0 Hz, 1H), 4.66 (s, 1H), 3.68 (d, J = 37.3 Hz, 2H), 3.41 (t, J = 11.6 Hz, 1H), 3.33 (s, 3H), 3.26 (s, 1H), 3.08 - 2.81 (m, 4H), 2.65 (dd, J = 16.2, 6.4 Hz, 1H), 2.09 - 2.01 (m, 1H), 1.95 - 1.66 (m, 5H).	474.1 (ESI)

77	I	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 11.36 (s, 1H), 8.02 (d, J=5.0 Hz, 1H), 7.60-7.44 (m, 4H), 6.89 (d, J=5.0 Hz, 1H), 4.70-4.62 (m, 1H), 3.86-3.80 (m, 4H), 3.69-3.61 (m, 1H), 3.53-3.49 (m, 1H), 3.34-3.24 (m, 1H), 3.10-3.05 (m, 2H), 3.02-2.92 (m, 3H), 2.00-1.65 (m, 4H) ppm.	460.1 (ESI)
78	D + Chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.82 - 1.93 (m, 4 H), 1.93 - 2.07 (m, 2 H), 2.08 - 2.24 (m, 2 H), 2.81 (br t, J=6.3 Hz, 2 H), 2.90 - 2.99 (m partially hidden, 2 H), 3.03 - 3.22 (m, 4 H), 3.43 - 3.56 (m, 1 H), 4.18 (br d, J=12.7 Hz, 2 H), 5.35 (br s, 2 H), 6.51 (br d, J=8.4 Hz, 1 H), 6.70 (br s, 1 H), 7.09 - 7.18 (m, 2 H), 7.91 (d, J=4.3 Hz, 1 H), 11.05 (br s, 1 H)	546
79	D + Chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.82 - 1.93 (m, 4 H), 1.93 - 2.07 (m, 2 H), 2.08 - 2.24 (m, 2 H), 2.81 (br t, J=6.3 Hz, 2 H), 2.90 - 2.99 (m partially hidden, 2 H), 3.03 - 3.22 (m, 4 H), 3.43 - 3.56 (m, 1 H), 4.18 (br d, J=12.7 Hz, 2 H), 5.35 (br s, 2 H), 6.51 (br d, J=8.4 Hz, 1 H), 6.70 (br s, 1 H), 7.09 - 7.18 (m, 2 H), 7.91 (d, J=4.3 Hz, 1 H), 11.05 (br s, 1 H)	546
80	A + N-Boc deprotection + Chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.26 - 1.34 (m, 1 H), 1.50 - 1.60 (m, 2 H), 1.74 - 1.90 (m, 3 H), 1.93 - 2.07 (m, 2 H), 2.32 - 2.42 (m, 3 H), 2.56 (td, J=2.5 and 12.2 Hz, 1 H), 2.71 - 2.79 (m, 1 H), 2.85 - 2.96 (m partially hidden, 2 H), 3.00 - 3.17 (m, 3 H), 3.46 - 3.57 (m, 1 H), 4.08 - 4.27 (m, 2 H), 7.40 (br d, J=8.4 Hz, 2 H), 7.54 (br d, J=8.4 Hz, 2 H), 7.88 (d, J=4.3 Hz, 1 H), 10.93 (br s, 1 H)	517
81	A + N-Boc deprotection + Chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.28 - 1.35 (m, 1 H), 1.52 - 1.62 (m, 2 H), 1.75 - 1.91 (m, 3 H), 1.93 - 2.08 (m, 2 H), 2.34 - 2.42 (m, 3 H), 2.59 (td, J=2.5 and 12.2 Hz, 1 H), 2.72 - 2.80 (m, 1 H), 2.86 - 2.91 (m partially hidden, 2 H), 2.98 - 3.17 (m, 3 H), 3.45 - 3.57 (m, 1 H), 4.08 - 4.26 (m, 2 H), 7.39 (br d, J=8.4 Hz, 2 H), 7.54 (br d, J=8.4 Hz, 2 H), 7.88 (d, J=4.3 Hz, 1 H), 10.93 (br s, 1 H)	517

82	A + N-BOC deprotection + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.61 - 1.70 (m, 1 H), 1.75 - 2.07 (m, 6 H), 2.59 (br t, J=5.7 Hz, 2 H), 2.62 - 2.75 (m, 3 H), 2.85 - 2.98 (m partially hidden, 2 H), 3.09 (br t, J=12.7 Hz, 2 H), 3.22 (q, J=6.4 Hz, 1 H), 3.34 - 3.44 (m, 1 H), 4.10 - 4.29 (m, 2 H), 7.40 (d, J=8.4 Hz, 2 H), 7.54 (br d, J=8.4 Hz, 2 H), 7.89 (d, J=3.4 Hz, 1 H), 11.22 (br s, 1 H)	503
83	A + N-BOC deprotection + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.61 - 1.71 (m, 1 H), 1.75 - 2.08 (m, 6 H), 2.59 (br t, J=5.7 Hz, 2 H), 2.62 - 2.75 (m, 3 H), 2.85 - 2.98 (m partially hidden, 2 H), 3.09 (br t, J=12.7 Hz, 2 H), 3.22 (q, J=6.4 Hz, 1 H), 3.34 - 3.44 (m, 1 H), 4.10 - 4.30 (m, 2 H), 7.40 (br d, J=8.4 Hz, 2 H), 7.54 (br d, J=8.4 Hz, 2 H), 7.90 (d, J=3.4 Hz, 1 H), 11.22 (br s, 1 H)	503
84	D + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.39 - 1.49 (m, 1 H), 1.67 - 2.05 (m, 9 H), 2.61 - 2.71 (m, 2 H), 3.04 (t, J=12.7 Hz, 2 H), 3.09 - 3.17 (m, 2 H), 3.36 - 3.45 (m, 1 H), 4.16 (br d, J=12.7 Hz, 2 H), 5.33 (br s, 2 H), 6.49 (br d, J=8.4 Hz, 1 H), 6.68 (br s, 1 H), 7.11 (br d, J=8.4 Hz, 1 H), 7.85 (br d, J=3.4 Hz, 1 H), 10.95 (br s, 1 H)	503
85	F (without N-Tosylation / N-deTosylation steps)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.83 (br d, J=12.7 Hz, 2 H), 1.95 - 2.08 (m, 2 H), 2.98 - 3.15 (m, 6 H), 3.56 - 3.66 (m, 1 H), 3.84 (br t, J=5.0 Hz, 2 H), 3.88 (br t, J=5.0 Hz, 2 H), 4.15 (br d, J=12.7 Hz, 2 H), 5.32 (br s, 2 H), 6.49 (br d, J=8.4 Hz, 1 H), 6.68 (br s, 1 H), 7.10 (d, J=8.4 Hz, 1 H), 7.91 (d, J=4.3 Hz, 1 H), 11.10 (br s, 1 H)	493
86	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.82 (br d, J=12.7 Hz, 2 H), 1.92 - 2.05 (m, 2 H), 2.05 - 2.13 (m, 2 H), 2.89 - 2.99 (m partially hidden, 4 H), 3.08 (s, 3 H), 3.40 (t, J=6.1 Hz, 2 H), 3.98 - 4.07 (m, 1 H), 4.13 (br d, J=12.7 Hz, 2 H), 5.32 (br s, 2 H), 6.48 (br d, J=8.4 Hz, 1 H), 6.67 (br s, 1 H), 7.12 (d, J=8.4 Hz, 1 H), 8.02 (d, J=4.3 Hz, 1 H), 11.66 - 11.80 (m, 1 H)	520

87	D + Chiral Separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.57 - 1.69 (m, 1 H), 1.71 - 1.82 (m, 1 H), 1.85 - 1.96 (m, 3 H), 2.00 - 2.18 (m, 3 H), 2.75 - 2.88 (m, 2 H), 2.96 - 3.01 (m partially hidden, 1 H), 3.02 - 3.13 (m, 2 H), 3.31 (s, 3 H), 3.32 - 3.42 (m, 2 H), 3.66 - 3.76 (m, 1 H), 4.21 (br d, J=12.7 Hz, 2 H), 5.35 (br s, 2 H), 6.50 (br d, J=8.4 Hz, 1 H), 6.70 (br s, 1 H), 7.14 (d, J=8.4 Hz, 1 H), 7.90 (d, J=4.3 Hz, 1 H), 11.09 (br s, 1 H)	521
88	D + Chiral Separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.72 - 1.90 (m, 4 H), 1.98 - 2.13 (m, 4 H), 2.64 - 2.73 (m, 1 H), 2.75 - 2.85 (m, 1 H), 2.92 - 2.98 (m partially hidden, 1 H), 3.03 - 3.19 (m, 3 H), 3.33 (s, 3 H), 3.54 - 3.61 (m, 1 H), 3.61 - 3.71 (m, 1 H), 4.19 (br d, J=12.7 Hz, 2 H), 5.36 (br s, 2 H), 6.51 (br d, J=8.4 Hz, 1 H), 6.70 (br s, 1 H), 7.13 (d, J=8.4 Hz, 1 H), 7.89 (d, J=4.3 Hz, 1 H), 11.03 (br s, 1 H)	521
89	D + Chiral Separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.71 - 1.88 (m, 4 H), 1.95 - 2.10 (m, 4 H), 2.62 - 2.71 (m, 1 H), 2.73 - 2.83 (m, 1 H), 2.89 - 2.98 (m partially hidden, 1 H), 3.02 - 3.15 (m, 3 H), 3.31 (s, 3 H), 3.51 - 3.59 (m, 1 H), 3.59 - 3.69 (m, 1 H), 4.17 (br d, J=12.7 Hz, 2 H), 5.33 (br s, 2 H), 6.49 (br d, J=8.4 Hz, 1 H), 6.68 (br s, 1 H), 7.11 (d, J=8.4 Hz, 1 H), 7.87 (d, J=4.3 Hz, 1 H), 11.00 (br s, 1 H)	521
90	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.26 - 1.36 (m, 2 H), 1.43 - 1.52 (m, 2 H), 1.63 - 1.75 (m, 4 H), 1.84 (br d, J=12.7 Hz, 2 H), 1.99 - 2.12 (m, 2 H), 2.79 - 2.86 (m, 2 H), 2.91 - 2.96 (m partially hidden, 2 H), 3.01 - 3.10 (m, 2 H), 3.49 - 3.64 (m, 1 H), 4.21 (br d, J=12.7 Hz, 2 H), 5.35 (br s, 2 H), 6.51 (br d, J=8.4 Hz, 1 H), 6.70 (br s, 1 H), 7.13 (br d, J=8.4 Hz, 1 H), 7.89 - 7.92 (m, 1 H), 11.02 (br s, 1 H)	505
91	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 100°C) δ ppm 1.15 - 1.24 (m, 6 H) 1.44 (qd, J=12.2, 5.4 Hz, 1 H) 1.62 - 1.77 (m, 1 H) 1.79 - 1.90 (m, 2 H) 1.92 - 2.20 (m, 3 H) 2.52 - 2.83 (m, 3 H) 2.86 - 3.13 (m partially hidden, 3 H) 3.47 - 3.61 (m, 1 H) 3.83 (s, 1 H) 4.19 (br d, J=12.5 Hz, 2 H) 5.34 (br s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 10.90 (br s, 1 H)	535

92	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.14 - 1.23 (m, 6 H) 1.44 (qd, J=12.2, 5.5 Hz, 1 H) 1.64 - 1.75 (m, 1 H) 1.79 - 1.90 (m, 2 H) 1.92 - 2.19 (m, 3 H) 2.54 - 2.84 (m, 3 H) 2.89 - 3.11 (m partially hidden, 3 H) 3.47 - 3.61 (m, 1 H) 3.83 (s, 1 H) 4.19 (br d, J=12.9 Hz, 2 H) 5.34 (br s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 10.90 (br s, 1 H)	535
93	SCHEME 1 + cis/trans separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.77 (t, J=6.3 Hz, 2 H) 1.88 (br d, J=12.0 Hz, 2 H) 1.96 - 2.16 (m, 6 H) 2.70 (br t, J=6.3 Hz, 2 H) 2.85 (s, 6 H) 2.98 (s, 2 H) 3.14 (br t, J=12.8 Hz, 2 H) 3.38 (quin, J=8.5 Hz, 1 H) 3.52 - 3.62 (m, 1 H) 4.08 - 4.34 (m, 2 H) 7.40 (br d, J=8.5 Hz, 2 H) 7.55 (d, J=8.5 Hz, 2 H) 7.89 (d, J=4.0 Hz, 1 H) 10.95 (br s, 1 H)	573.5
94	SCHEME 1 + cis/trans separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.80 - 1.87 (m, 2 H) 1.90 (t, J=6.4 Hz, 2 H) 1.93 - 2.17 (m, 6 H) 2.76 (br t, J=6.4 Hz, 2 H) 2.84 (br s, 6 H) 2.85 (br s, 2 H) 3.09 (br t, J=12.6 Hz, 2 H) 3.23 - 3.35 (m, 1 H) 3.45 - 3.55 (m, 1 H) 4.08 - 4.33 (m, 2 H) 7.40 (br d, J=8.8 Hz, 2 H) 7.55 (d, J=8.8 Hz, 2 H) 7.88 (d, J=4.1 Hz, 1 H) 10.95 (br s, 1 H)	573
95	SCHEME 1 + cis/trans separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.81 (br t, J=6.2 Hz, 2 H) 1.87 (br d, J=11.6 Hz, 2 H) 1.94 - 2.18 (m, 6 H) 2.70 (br t, J=6.2 Hz, 2 H) 2.96 (s partially hidden, 2 H) 3.05 - 3.48 (m, 3 H) 3.49 - 3.62 (m, 1 H) 4.09 - 4.33 (m, 2 H) 7.40 (br d, J=8.5 Hz, 2 H) 7.55 (d, J=8.5 Hz, 2 H) 7.89 (d, J=4.0 Hz, 1 H) 10.95 (br s, 1 H)	546
96	SCHEME 1 + cis/trans separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.80 - 1.91 (m, 4 H) 1.94 - 2.08 (m, 4 H) 2.08 - 2.19 (m, 2 H) 2.75 (br t, J=6.1 Hz, 2 H) 2.90 (s, 2 H) 2.92 - 3.23 (m partially hidden, 3 H) 3.46 - 3.58 (m, 1 H) 4.08 - 4.32 (m, 2 H) 7.40 (d, J=8.6 Hz, 2 H) 7.55 (d, J=8.6 Hz, 2 H) 7.88 (d, J=4.1 Hz, 1 H) 10.96 (br s, 1 H)	546
97	SCHEME 6 + STEP 2&3 (TBTU) of SCHEME 3 + Regio & Chiral Separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.66 - 1.78 (m, 1 H) 1.83 (br d, J=12.4 Hz, 2 H) 1.87 - 2.09 (m, 4 H) 2.09 - 2.20 (m, 1 H) 2.72 - 2.83 (m, 1 H) 2.87 - 2.99 (m partially hidden, 1 H) 3.00 - 3.23 (m, 5 H) 3.56 - 3.70 (m, 1 H) 3.62 (s, 3 H) 4.16 (br d, J=12.9 Hz, 2 H) 5.34 (br s, 2 H) 6.45 - 6.53 (m, 1 H) 6.68 (br s, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.87 - 7.96 (m, 1 H) 11.09 (br s, 1 H)	549

98	SCHEME 6 + STEP 2&3 (TBTU) of SCHEME 3 + Regio & Chiral Separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.77 - 2.22 (m, 8 H) 2.75 - 3.02 (m partially hidden, 4 H) 3.08 (br t, J=12.8 Hz, 2 H) 3.13 - 3.27 (m, 1 H) 3.52 - 3.73 (m, 1 H) 3.64 (s, 3 H) 4.16 (br d, J=12.3 Hz, 2 H) 5.34 (br s, 2 H) 6.49 (br d, J=7.9 Hz, 1 H) 6.68 (br s, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.88 (d, J=3.9 Hz, 1 H) 11.04 (br s, 1 H)	549
99	SCHEME 6 + STEP 2&3 (TBTU) of SCHEME 3 + Regio & Chiral Separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.65 - 1.78 (m, 1 H) 1.83 (br d, J=12.3 Hz, 2 H) 1.88 - 2.09 (m, 4 H) 2.09 - 2.21 (m, 1 H) 2.77 (tt, J=8.7, 4.5 Hz, 1 H) 2.87 - 2.98 (m partially hidden, 1 H) 3.00 - 3.23 (m, 5 H) 3.56 - 3.70 (m, 1 H) 3.62 (s, 3 H) 4.16 (br d, J=12.8 Hz, 2 H) 5.34 (s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.89 (d, J=4.1 Hz, 1 H) 11.09 (br s, 1 H)	549
100	SCHEME 6 + STEP 2&3 (TBTU) of SCHEME 3 + Regio & Chiral Separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.76 - 2.23 (m, 8 H) 2.76 - 3.02 (m partially hidden, 4 H) 3.07 (br t, J=12.5 Hz, 2 H) 3.17 (br dd, J=15.8, 6.9 Hz, 1 H) 3.57 - 3.72 (m, 1 H) 3.64 (s, 3 H) 4.16 (br d, J=13.0 Hz, 2 H) 5.34 (s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.88 (d, J=4.1 Hz, 1 H) 11.04 (br s, 1 H)	549
101	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.16 - 1.25 (m, 6 H) 1.44 (qd, J=12.2, 5.6 Hz, 1 H) 1.63 - 1.76 (m, 1 H) 1.79 - 1.91 (m, 2 H) 1.93 - 2.21 (m, 3 H) 2.54 - 2.84 (m, 3 H) 2.87 - 3.14 (m partially hidden, 3 H) 3.50 - 3.65 (m, 1 H) 3.83 (s, 1 H) 4.08 - 4.31 (m, 2 H) 7.39 (br d, J=8.8 Hz, 2 H) 7.55 (br d, J=8.8 Hz, 2 H) 7.88 (d, J=4.3 Hz, 1 H) 10.92 (br s, 1 H)	520
102	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.12 - 1.27 (m, 6 H) 1.44 (qd, J=12.2, 5.4 Hz, 1 H) 1.63 - 1.76 (m, 1 H) 1.80 - 1.91 (m, 2 H) 1.93 - 2.23 (m, 3 H) 2.54 - 2.88 (m, 3 H) 2.89 - 3.15 (m partially hidden, 3 H) 3.49 - 3.68 (m, 1 H) 3.83 (s, 1 H) 4.09 - 4.36 (m, 2 H) 7.39 (d, J=8.6 Hz, 2 H) 7.55 (d, J=8.6 Hz, 2 H) 7.88 (d, J=4.1 Hz, 1 H) 10.91 (br s, 1 H)	520
103	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.80 - 1.94 (m, 3 H) 1.94 - 2.09 (m, 2 H) 2.10 - 2.23 (m, 1 H) 2.68 - 3.26 (m partially hidden, 7 H) 3.46 - 3.57 (m, 1 H) 4.05 - 4.29 (m, 2 H) 7.39 (br d, J=8.4 Hz, 2 H) 7.55 (br d, J=8.4 Hz, 2 H) 7.91 (br d, J=3.8 Hz, 1 H) 11.02 (br s, 1 H)	506

104	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.78 - 1.94 (m, 3 H) 1.94 - 2.09 (m, 2 H) 2.10 - 2.21 (m, 1 H) 2.59 - 3.31 (m partially hidden, 7 H) 3.52 (br t, J=11.9 Hz, 1 H) 4.09 - 4.28 (m, 2 H) 7.38 (br d, J=8.6 Hz, 2 H) 7.54 (d, J=8.6 Hz, 2 H) 7.90 (d, J=4.1 Hz, 1 H) 10.85 - 11.17 (m, 1 H)	506
105	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.77 - 1.92 (m, 3 H) 1.93 - 2.07 (m, 2 H) 2.09 - 2.23 (m, 1 H) 2.58 - 3.43 (m partially hidden, 7 H) 3.45 - 3.58 (m, 1 H) 4.17 (br d, J=9.6 Hz, 2 H) 5.23 - 5.48 (m, 2 H) 6.48 (br d, J=8.0 Hz, 1 H) 6.67 (br s, 1 H) 7.12 (d, J=8.0 Hz, 1 H) 7.88 (br d, J=3.6 Hz, 1 H) 10.96 (br s, 1 H)	521
106	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.76 - 1.91 (m, 3 H) 1.93 - 2.07 (m, 2 H) 2.10 - 2.20 (m, 1 H) 2.64 - 2.81 (m, 1 H) 2.88 - 3.43 (m partially hidden, 6 H) 3.46 - 3.58 (m, 1 H) 4.17 (br d, J=11.8 Hz, 2 H) 5.33 (br s, 2 H) 6.48 (br dd, J=8.4, 1.1 Hz, 1 H) 6.67 (d, J=1.1 Hz, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.88 (d, J=4.1 Hz, 1 H) 10.98 (br s, 1 H)	521
107	SCHEME 1 + Acetal deprotection + oxime formation + regio and cis/trans separation (Example 107 is a side product)	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.85 (br d, J=12.3 Hz, 2 H) 1.89 - 2.09 (m, 6 H) 2.79 - 2.85 (m, 2 H) 2.95 - 3.01 (m, 2 H) 3.10 (br t, J=12.6 Hz, 2 H) 3.58 - 3.72 (m, 1 H) 3.93 (s, 4 H) 4.04 - 4.35 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.53 (br d, J=8.6 Hz, 2 H) 7.89 (d, J=4.1 Hz, 1 H) 11.06 (br s, 1 H)	534
108	SCHEME 1 + Acetal deprotection + oxime formation + regio and cis/trans separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.84 (br d, J=12.6 Hz, 2 H) 1.95 - 2.11 (m, 2 H) 2.60 - 2.68 (m, 2 H) 2.80 - 2.87 (m, 2 H) 2.97 - 3.02 (m, 2 H) 3.05 - 3.20 (m, 4 H) 3.61 - 3.73 (m, 1 H) 4.00 - 4.39 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.91 (d, J=4.1 Hz, 1 H) 9.96 (s, 1 H) 11.06 (br d, J=1.0 Hz, 1 H)	505
109	SCHEME 1 + Acetal deprotection + oxime formation + regio and cis/trans separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.83 (br d, J=12.0 Hz, 2 H) 1.94 - 2.10 (m, 2 H) 2.73 - 2.81 (m, 4 H) 2.98 - 3.21 (m, 6 H) 3.56 - 3.68 (m, 1 H) 4.04 - 4.29 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.53 (br d, J=8.6 Hz, 2 H) 7.92 (d, J=4.3 Hz, 1 H) 9.99 (s, 1 H) 11.02 (br s, 1 H)	505

110	SCHEME 1 + Acetal deprotection + oxime formation + regio and cis/trans separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.85 - 1.97 (m, 4 H) 1.98 - 2.12 (m, 2 H) 2.46 - 2.55 (m partially hidden, 2 H) 2.87 - 2.92 (m partially hidden, 2 H) 3.07 (br t, J=12.3 Hz, 2 H) 3.83 - 4.03 (m, 1 H) 3.95 (s, 2 H) 4.06 - 4.33 (m, 2 H) 7.39 (br d, J=8.5 Hz, 2 H) 7.54 (br d, J=8.5 Hz, 2 H) 7.91 (d, J=4.1 Hz, 1 H) 9.99 (s, 1 H) 11.15 (br s, 1 H)	505
111	SCHEME 1 (then chiral separation to give Examples 91 and 92)	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.15 - 1.22 (m, 6 H) 1.44 (qd, J=12.2, 5.5 Hz, 1 H) 1.64 - 1.75 (m, 1 H) 1.80 - 1.90 (m, 2 H) 1.92 - 2.20 (m, 3 H) 2.54 - 2.83 (m, 3 H) 2.94 - 3.11 (m, 3 H) 3.54 (tt, J=12.0, 3.2 Hz, 1 H) 3.83 (s, 1 H) 4.19 (br d, J=12.8 Hz, 2 H) 5.34 (s, 2 H) 6.49 (dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 10.91 (br s, 1 H)	535
112	SCHEME 1 (then chiral separation to give Examples 101 and 102)	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.19 - 1.22 (m, 6 H) 1.44 (qd, J=12.2, 5.6 Hz, 1 H) 1.65 - 1.76 (m, 1 H) 1.81 - 1.90 (m, 2 H) 1.92 - 2.18 (m, 3 H) 2.54 - 2.84 (m, 3 H) 2.94 - 3.12 (m, 3 H) 3.52 - 3.62 (m, 1 H) 3.83 (s, 1 H) 4.06 - 4.38 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.55 (br d, J=8.6 Hz, 2 H) 7.88 (d, J=4.1 Hz, 1 H) 10.92 (br s, 1 H)	520
113	SCHEME 1 + debo	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.73 (br d, J=10.8 Hz, 2 H) 2.15 (br qd, J=12.3, 4.3 Hz, 2 H) 3.06 (br t, J=12.2 Hz, 2 H) 3.19 - 3.24 (m, 2 H) 3.69 (tt, J=12.2, 3.9 Hz, 1 H) 4.02 (s, 2 H) 4.05 - 4.09 (m, 2 H) 4.09 - 4.33 (m, 2 H) 7.40 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.97 (d, J=3.4 Hz, 1 H) 10.92 (br s, 1 H)	479
114	SCHEME 1 + regio and chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.37 - 1.47 (m, 1 H) 1.51 - 1.64 (m, 1 H) 1.85 (br d, J=12.1 Hz, 2 H) 1.92 - 2.12 (m, 3 H) 2.20 - 2.30 (m, 1 H) 2.52 - 2.63 (m, 1 H) 2.81 - 3.18 (m partially hidden, 5 H) 3.45 (td, J=10.8, 2.9 Hz, 1 H) 3.51 - 3.65 (m, 2 H) 3.73 (dd, J=11.1, 3.1 Hz, 1 H) 3.85 (dt, J=11.2, 3.7 Hz, 1 H) 4.08 - 4.32 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.89 (d, J=4.1 Hz, 1 H) 10.95 (br s, 1 H)	518

115	SCHEME 1 + regio and chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.39 - 1.57 (m, 1 H) 1.64 - 1.91 (m, 5 H) 1.92 - 2.08 (m, 2 H) 2.26 - 2.51 (m partially hidden, 2 H) 2.73 - 2.90 (m, 2 H) 3.00 - 3.13 (m, 2 H) 3.17 (br t, J=10.5 Hz, 1 H) 3.36 - 3.57 (m, 2 H) 3.92 (dd, J=11.3, 4.0 Hz, 1 H) 3.99 (dd, J=11.3, 3.1 Hz, 1 H) 4.05 - 4.31 (m, 2 H) 7.39 (br d, J=8.5 Hz, 2 H) 7.53 (br d, J=8.5 Hz, 2 H) 7.89 (d, J=4.0 Hz, 1 H) 11.00 (br s, 1 H)	518
116	SCHEME 1 + regio and chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.40 - 1.54 (m, 1 H) 1.63 - 1.91 (m, 5 H) 1.92 - 2.09 (m, 2 H) 2.27 - 2.48 (m, 2 H) 2.74 - 2.90 (m, 2 H) 3.06 (q, J=12.7 Hz, 2 H) 3.17 (br t, J=10.6 Hz, 1 H) 3.34 - 3.55 (m, 2 H) 3.92 (dd, J=11.3, 4.3 Hz, 1 H) 3.99 (dd, J=11.1, 3.2 Hz, 1 H) 4.07 - 4.31 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.53 (br d, J=8.6 Hz, 2 H) 7.89 (d, J=4.1 Hz, 1 H) 10.99 (br s, 1 H)	518
117	SCHEME 1 + regio and chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.66 - 1.78 (m, 3 H) 1.79 - 1.90 (m, 3 H) 1.93 - 2.16 (m, 2 H) 2.16 - 2.35 (m, 1 H) 2.68 - 3.04 (m partially hidden, 3 H) 3.11 (br t, J=12.2 Hz, 1 H) 3.16 - 3.25 (m, 1 H) 3.32 - 3.43 (m, 1 H) 3.51 (td, J=10.6, 4.6 Hz, 1 H) 3.69 - 3.78 (m, 1 H) 3.80 - 3.92 (m, 2 H) 4.08 - 4.34 (m, 2 H) 7.40 (br d, J=8.8 Hz, 2 H) 7.55 (br d, J=8.8 Hz, 2 H) 7.90 (d, J=4.3 Hz, 1 H) 11.01 (br s, 1 H)	518
118	SCHEME 1 + regio and chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.41 (br dd, J=13.5, 3.1 Hz, 1 H) 1.50 - 1.66 (m, 1 H) 1.86 (br d, J=12.3 Hz, 2 H) 1.92 - 2.13 (m, 3 H) 2.19 - 2.34 (m, 1 H) 2.57 (br d, J=17.8 Hz, 1 H) 2.78 - 3.21 (m partially hidden, 5 H) 3.45 (td, J=10.8, 2.6 Hz, 1 H) 3.51 - 3.66 (m, 2 H) 3.73 (dd, J=11.2, 2.9 Hz, 1 H) 3.85 (dt, J=11.0, 3.4 Hz, 1 H) 4.08 - 4.29 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.89 (br d, J=4.0 Hz, 1 H) 10.94 (br s, 1 H)	518
119	SCHEME 1 + regio and chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.63 - 1.78 (m, 3 H) 1.78 - 1.90 (m, 3 H) 1.92 - 2.16 (m, 2 H) 2.16 - 2.33 (m, 1 H) 2.70 - 3.04 (m partially hidden, 3 H) 3.11 (br t, J=12.8 Hz, 1 H) 3.16 - 3.26 (m, 1 H) 3.38 (br t, J=12.1 Hz, 1 H) 3.46 - 3.57 (m, 1 H) 3.70 - 3.79 (m, 1 H) 3.80 - 3.95 (m, 2 H) 4.08 - 4.42 (m, 2 H) 7.40 (br d, J=8.6 Hz, 2 H) 7.55 (br d, J=8.6 Hz, 2 H) 7.90 (d, J=4.0 Hz, 1 H) 11.01 (br s, 1 H)	518

120	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.77 - 2.09 (m, 8 H) 2.81 (br t, J=6.3 Hz, 2 H) 2.87 - 3.20 (m, 6 H) 3.39 - 3.53 (m, 1 H) 4.15 (br d, J=12.0 Hz, 2 H) 5.33 (s, 2 H) 6.49 (br dd, J=8.4, 1.0 Hz, 1 H) 6.68 (br d, J=1.0 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.90 (d, J=4.1 Hz, 1 H) 11.04 (br s, 1 H)	531
121	SCHEME 1 + regio and chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.76 - 1.90 (m, 2 H) 1.92 - 2.23 (m, 4 H) 2.87 - 3.22 (m partially hidden, 6 H) 3.29 - 3.40 (m, 1 H) 3.49 (tt, J=12.0, 3.3 Hz, 1 H) 4.17 (br d, J=13.0 Hz, 2 H) 5.34 (s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.94 (d, J=4.1 Hz, 1 H) 11.13 (br s, 1 H)	502
122	SCHEME 1 + regio and chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.76 - 1.90 (m, 2 H) 1.92 - 2.23 (m, 4 H) 2.87 - 3.22 (m partially hidden, 6 H) 3.29 - 3.40 (m, 1 H) 3.49 (tt, J=12.0, 3.3 Hz, 1 H) 4.17 (br d, J=13.0 Hz, 2 H) 5.34 (s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.94 (d, J=4.1 Hz, 1 H) 11.13 (br s, 1 H)	502
123	SCHEME 1 + regio and chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.83 - 2.14 (m, 7 H) 2.19 - 2.27 (m, 1 H) 2.69 - 2.87 (m, 2 H) 3.07 (br t, J=12.4 Hz, 1 H) 3.16 (br t, J=12.8 Hz, 1 H) 3.38 - 3.55 (m, 1 H) 4.17 (br t, J=11.6 Hz, 2 H) 4.53 - 4.64 (m, 1 H) 5.35 (br s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.98 (d, J=4.1 Hz, 1 H) 11.39 (br s, 1 H)	502
124	SCHEME 1 + regio and chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.83 - 2.14 (m, 7 H) 2.19 - 2.27 (m, 1 H) 2.69 - 2.87 (m, 2 H) 3.07 (br t, J=12.4 Hz, 1 H) 3.16 (br t, J=12.8 Hz, 1 H) 3.38 - 3.55 (m, 1 H) 4.17 (br t, J=11.6 Hz, 2 H) 4.53 - 4.64 (m, 1 H) 5.35 (br s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.98 (d, J=4.1 Hz, 1 H) 11.39 (br s, 1 H)	502
125	SCHEME 1 + deboc + reductive amination	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.85 (br d, J=11.6 Hz, 2 H) 1.92 - 2.09 (m, 4 H) 2.27 (s, 3 H) 2.73 (t, J=6.3 Hz, 2 H) 2.97 - 3.01 (m, 2 H) 3.01 - 3.19 (m partially hidden, 6 H) 3.45 - 3.56 (m, 1 H) 4.18 (br d, J=12.8 Hz, 2 H) 5.35 (br s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br s, 1 H) 7.14 (d, J=8.4 Hz, 1 H) 7.88 (d, J=4.1 Hz, 1 H) 10.88 - 11.03 (m, 1 H)	532

126	SCHEME 1 + acetal deprotection + oxime formation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.88 (br d, J=12.3 Hz, 2 H) 1.96 - 2.11 (m, 2 H) 2.83 - 2.91 (m, 4 H) 3.12 (br t, J=12.5 Hz, 2 H) 3.41 - 3.54 (m, 1 H) 3.69 (s, 2 H) 4.20 (br d, J=11.9 Hz, 2 H) 5.36 (br s, 2 H) 6.52 (m, 1 H) 6.71 (br s, 1 H) 7.15 (d, J=8.4 Hz, 1 H) 7.96 (br d, J=3.8 Hz, 1 H) 10.15 (s, 1 H) 11.17 (br s, 1 H)	506
127	SCHEME 1 + regio and chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.80 - 1.91 (m, 2 H) 1.93 - 2.20 (m, 4 H) 2.97 - 3.04 (m, 3 H) 3.04 - 3.17 (m, 3 H) 3.32 - 3.41 (m, 1 H) 3.51 (tt, J=12.1, 3.3 Hz, 1 H) 4.05 - 4.31 (m, 2 H) 7.39 (br d, J=8.5 Hz, 2 H) 7.54 (br d, J=8.5 Hz, 2 H) 7.95 (d, J=4.1 Hz, 1 H) 11.08 - 11.21 (m, 1 H)	487
128	SCHEME 1 + regio and chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.79 - 1.91 (m, 2 H) 1.93 - 2.08 (m, 2 H) 2.09 - 2.18 (m, 2 H) 2.91 - 3.04 (m partially hidden, 3 H) 3.04 - 3.18 (m, 3 H) 3.31 - 3.40 (m, 1 H) 3.47 - 3.57 (m, 1 H) 4.09 - 4.29 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.95 (d, J=4.1 Hz, 1 H) 11.07 - 11.24 (m, 1 H)	487
129	SCHEME 1 + regio and chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.82 - 2.14 (m, 7 H) 2.18 - 2.28 (m, 1 H) 2.69 - 2.86 (m, 2 H) 3.03 - 3.13 (m, 1 H) 3.18 (br t, J=12.7 Hz, 1 H) 3.50 (tt, J=11.8, 3.5 Hz, 1 H) 4.11 - 4.29 (m, 2 H) 4.56 - 4.61 (m, 1 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.55 (br d, J=8.6 Hz, 2 H) 8.00 (d, J=4.3 Hz, 1 H) 11.40 (br s, 1 H)	487
130	SCHEME 1 + regio and chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.82 - 2.15 (m, 7 H) 2.19 - 2.28 (m, 1 H) 2.69 - 2.87 (m, 2 H) 3.03 - 3.13 (m, 1 H) 3.18 (br t, J=12.9 Hz, 1 H) 3.50 (ddd, J=11.8, 8.3, 3.8 Hz, 1 H) 4.08 - 4.29 (m, 2 H) 4.56 - 4.61 (m, 1 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.55 (d, J=8.6 Hz, 2 H) 8.00 (d, J=4.1 Hz, 1 H) 11.40 (br s, 1 H)	487

131	SCHEME 1 + Boc deprotection + reductive amination + NaOH to remove CH ₂ OH on the pyrrole (6/4 mixture with the desired compound)	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.85 (br d, J=11.4 Hz, 2 H) 1.92 - 2.09 (m, 4 H) 2.27 (s, 3 H) 2.74 (t, J=6.3 Hz, 2 H) 2.93 (s, 2 H) 2.98 - 3.01 (m, 2 H) 3.03 - 3.06 (m partially hidden, 2 H) 3.11 (br t, J=12.6 Hz, 2 H) 3.53 (tt, J=12.0, 3.6 Hz, 1 H) 4.05 - 4.36 (m, 2 H) 7.39 (br d, J=8.8 Hz, 2 H) 7.56 (br d, J=8.8 Hz, 2 H) 7.89 (d, J=4.1 Hz, 1 H) 10.98 (br s, 1 H)	517
132	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.67 - 2.08 (m, 7 H) 2.09 - 2.20 (m, 1 H) 2.68 - 2.78 (m, 2 H) 2.78 - 3.25 (m partially hidden, 2 H) 3.33 - 3.48 (m, 1 H) 3.94 - 4.03 (m, 1 H) 4.05 - 4.36 (m, 2 H) 7.39 (br d, J=8.5 Hz, 2 H) 7.53 (br d, J=8.5 Hz, 2 H) 7.91 (d, J=4.1 Hz, 1 H) 11.07 (br s, 1 H)	506
133	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.67 - 2.08 (m, 7 H) 2.09 - 2.20 (m, 1 H) 2.68 - 2.78 (m, 2 H) 2.78 - 3.25 (m partially hidden, 2 H) 3.33 - 3.48 (m, 1 H) 3.94 - 4.03 (m, 1 H) 4.05 - 4.36 (m, 2 H) 7.39 (br d, J=8.5 Hz, 2 H) 7.53 (br d, J=8.5 Hz, 2 H) 7.91 (d, J=4.1 Hz, 1 H) 11.07 (br s, 1 H)	506.3
134	SCHEME 1 + boc deprotection + reductive amination	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.84 (br d, J=13.3 Hz, 2 H) 1.93 - 2.13 (m, 2 H) 2.61 - 2.77 (m, 4 H) 2.87 - 3.00 (m hidden, 2 H) 3.02 - 3.15 (m, 4 H) 3.65 (ddd, J=11.9, 8.5, 3.8 Hz, 1 H) 3.83 (quin, J=6.5 Hz, 1 H) 4.03 - 4.29 (m, 2 H) 4.48 (t, J=6.1 Hz, 2 H) 4.57 (t, J=6.1 Hz, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.53 (br d, J=8.6 Hz, 2 H) 7.90 (d, J=4.3 Hz, 1 H) 11.06 (br s, 1 H)	533.5
135	SCHEME 1 + boc deprotecton	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.87 (br d, J=11.3 Hz, 2 H) 1.95 - 2.10 (m, 4 H) 2.76 (br t, J=6.3 Hz, 2 H) 3.04 - 3.17 (m, 2 H) 3.10 (s, 2 H) 3.39 - 3.45 (m, 2 H) 3.46 - 3.59 (m, 3 H) 4.19 (br d, J=13.0 Hz, 2 H) 5.36 (br s, 2 H) 6.47 - 6.52 (m, 1 H) 6.69 (br s, 1 H) 7.13 (d, J=8.4 Hz, 1 H) 7.89 (d, J=4.1 Hz, 1 H) 10.99 (br s, 1 H)	518

136	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.66 (tt, J=13.2, 4.0 Hz, 1 H) 1.73 - 2.16 (m, 6 H) 2.20 (br d, J=13.0 Hz, 1 H) 2.62 - 2.77 (m, 2 H) 3.04 - 3.20 (m, 3 H) 3.40 - 3.50 (m, 1 H) 3.51 - 3.61 (m, 1 H) 3.65 (br d, J=10.9 Hz, 1 H) 3.99 - 4.33 (m, 2 H) 4.35 - 4.46 (m, 1 H) 7.39 (br d, J=8.3 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.89 (d, J=4.1 Hz, 1 H) 10.97 (br s, 1 H)	492
137	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.66 (tt, J=13.2, 4.0 Hz, 1 H) 1.73 - 2.16 (m, 6 H) 2.20 (br d, J=13.0 Hz, 1 H) 2.62 - 2.77 (m, 2 H) 3.04 - 3.20 (m, 3 H) 3.40 - 3.50 (m, 1 H) 3.51 - 3.61 (m, 1 H) 3.65 (br d, J=10.9 Hz, 1 H) 3.99 - 4.33 (m, 2 H) 4.35 - 4.46 (m, 1 H) 7.39 (br d, J=8.3 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.89 (d, J=4.1 Hz, 1 H) 10.97 (br s, 1 H)	492
138	SCHEME 1 + boc deprotection + reductive amination	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.76 - 1.88 (m, 4 H) 1.97 - 2.10 (m, 2 H) 2.76 - 2.81 (m, 2 H) 2.87 - 2.96 (m partially hidden, 2 H) 3.04 (br t, J=12.6 Hz, 2 H) 3.34 - 3.44 (m, 1 H) 3.80 - 3.90 (m, 1 H) 3.90 (s, 2 H) 4.56 (t, J=6.1 Hz, 2 H) 4.47 (t, J=6.1 Hz, 2 H) 4.53 - 4.59 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.91 (d, J=4.3 Hz, 1 H) 11.19 (br s, 1 H)	533
139	SCHEME 2A (silver carbonate instead of PIFA in step 3) + oxime formation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.85 (br d, J=12.8 Hz, 2 H) 1.93 - 2.08 (m, 2 H) 2.60 (t, J=6.4 Hz, 2 H) 3.00 - 3.16 (m, 4 H) 3.45 - 3.58 (m, 1 H) 3.73 (s, 2 H) 4.10 - 4.23 (m, 2 H) 5.34 (s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.92 (d, J=4.1 Hz, 1 H) 10.27 (s, 1 H) 11.13 (br s, 1 H)	506
140	SCHEME 1 + boc deprotection + reductive amination	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 0.35 - 0.42 (m, 2 H) 0.46 - 0.53 (m, 2 H) 1.84 (br d, J=11.9 Hz, 2 H) 1.95 - 2.13 (m, 3 H) 2.89 - 2.99 (m partially hidden, 4 H) 2.99 - 3.19 (m, 6 H) 3.67 (tt, J=12.0, 3.5 Hz, 1 H) 4.07 - 4.28 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.89 (d, J=4.1 Hz, 1 H) 11.04 (br s, 1 H)	617

141	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.67 - 2.07 (m, 7 H) 2.09 - 2.19 (m, 1 H) 2.67 - 2.77 (m, 2 H) 2.79 - 3.20 (m partially hidden, 2 H) 3.29 - 3.42 (m, 1 H) 4.00 (dd, J=5.7, 3.7 Hz, 1 H) 4.14 (br d, J=12.5 Hz, 2 H) 5.33 (br s, 2 H) 6.49 (dd, J=8.4, 1.1 Hz, 1 H) 6.68 (d, J=1.1 Hz, 1 H) 7.10 (d, J=8.4 Hz, 1 H) 7.90 (d, J=4.1 Hz, 1 H) 11.07 (br s, 1 H)	521
142	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.67 - 2.07 (m, 7 H) 2.09 - 2.19 (m, 1 H) 2.67 - 2.77 (m, 2 H) 2.79 - 3.20 (m partially hidden, 2 H) 3.29 - 3.42 (m, 1 H) 4.00 (dd, J=5.7, 3.7 Hz, 1 H) 4.14 (br d, J=12.5 Hz, 2 H) 5.33 (br s, 2 H) 6.49 (dd, J=8.4, 1.1 Hz, 1 H) 6.68 (d, J=1.1 Hz, 1 H) 7.10 (d, J=8.4 Hz, 1 H) 7.90 (d, J=4.1 Hz, 1 H) 11.07 (br s, 1 H)	521
143	SCHEME 1 + boc deprotection + reductive amination	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 0.32 - 0.46 (m, 4 H) 1.73 - 1.83 (m, 2 H) 1.87 (br d, J=12.5 Hz, 2 H) 1.92 - 1.99 (m, 1 H) 2.00 - 2.13 (m, 2 H) 2.87 - 2.92 (m, 2 H) 3.03 - 3.14 (m, 4 H) 3.54 - 3.69 (m, 1 H) 4.09 - 4.34 (m, 2 H) 4.17 (s, 2 H) 7.40 (br d, J=8.4 Hz, 2 H) 7.55 (br d, J=8.6 Hz, 2 H) 7.89 (d, J=4.3 Hz, 1 H) 11.18 (br s, 1 H)	517
144	SCHEME 1 + acetal deprotection + oxime formation + regio & Z/E separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.84 (br d, J=12.5 Hz, 2 H) 1.94 - 2.13 (m, 2 H) 2.57 - 2.72 (m, 2 H) 2.78 - 2.88 (m, 2 H) 2.96 - 3.22 (m, 6 H) 3.55 - 3.72 (m, 1 H) 4.16 (br d, J=12.5 Hz, 2 H) 5.34 (s, 2 H) 6.42 - 6.56 (m, 1 H) 6.68 (s, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.90 (d, J=4.1 Hz, 1 H) 9.96 (s, 1 H) 11.06 (br s, 1 H)	520
145	SCHEME 1 + acetal deprotection + oxime formation + regio & Z/E separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.82 (br d, J=12.4 Hz, 2 H) 2.01 (q, J=12.2 Hz, 2 H) 2.70 - 2.86 (m, 4 H) 2.97 - 3.23 (m, 6 H) 3.53 - 3.68 (m, 1 H) 4.15 (br d, J=12.9 Hz, 2 H) 5.33 (s, 2 H) 6.49 (dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br s, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.91 (d, J=4.3 Hz, 1 H) 9.98 (br s, 1 H) 11.01 (br s, 1 H)	520
146	SCHEME 1 + acetal deprotection + oxime formation + regio & Z/E separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.89 (br d, J=12.1 Hz, 2 H) 1.95 - 2.14 (m, 4 H) 2.67 (t, J=6.4 Hz, 2 H) 2.83 - 2.90 (m, 2 H) 3.07 (br t, J=12.7 Hz, 2 H) 3.63 (ddd, J=12.0, 8.8, 3.6 Hz, 1 H) 3.82 (s, 2 H) 4.18 (br d, J=12.6 Hz, 2 H) 5.34 (s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.91 (d, J=4.3 Hz, 1 H) 9.95 (s, 1 H) 11.10 (br s, 1 H)	520

147	SCHEME 1 + acetal deprotection + oxime formation + regio & Z/E separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.83 - 1.95 (m, 4 H) 1.96 - 2.15 (m, 2 H) 2.44 - 2.55 (m partially hidden, 2 H) 2.86 - 2.92 (m, 2 H) 3.05 (br t, J=12.6 Hz, 2 H) 3.82 - 3.98 (m, 3 H) 4.18 (br d, J=12.9 Hz, 2 H) 5.33 (br s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.89 (d, J=4.1 Hz, 1 H) 9.99 (s, 1 H) 11.14 (br s, 1 H)	520
148	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.61 - 1.77 (m, 1 H) 1.80 - 1.91 (m, 2 H) 1.94 - 2.16 (m, 3 H) 2.53 - 2.70 (m, 4 H) 2.69 - 3.18 (m partially hidden, 7 H) 3.46 - 3.60 (m, 1 H) 3.62 (t, J=4.6 Hz, 4 H) 4.07 - 4.34 (m, 2 H) 7.39 (br d, J=8.8 Hz, 2 H) 7.56 (br d, J=8.8 Hz, 2 H) 7.89 (d, J=4.1 Hz, 1 H) 10.90 - 11.12 (m, 1 H)	547
149	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.60 - 1.72 (m, 1 H) 1.73 - 2.24 (m, 7 H) 2.59 - 2.77 (m, 2 H) 3.02 - 3.22 (m, 3 H) 3.44 (td, J=10.0, 4.6 Hz, 1 H) 3.54 (br t, J=11.9 Hz, 1 H) 3.60 - 3.70 (m, 1 H) 4.17 (br t, J=13.5 Hz, 2 H) 4.36 - 4.44 (m, 1 H) 5.33 (s, 2 H) 6.44 - 6.54 (m, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.88 (d, J=4.1 Hz, 1 H) 10.97 (br s, 1 H)	507
150	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.60 - 1.72 (m, 1 H) 1.73 - 2.24 (m, 7 H) 2.59 - 2.77 (m, 2 H) 3.02 - 3.22 (m, 3 H) 3.44 (td, J=10.0, 4.6 Hz, 1 H) 3.54 (br t, J=11.9 Hz, 1 H) 3.60 - 3.70 (m, 1 H) 4.17 (br t, J=13.5 Hz, 2 H) 4.36 - 4.44 (m, 1 H) 5.33 (s, 2 H) 6.44 - 6.54 (m, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.88 (d, J=4.1 Hz, 1 H) 10.97 (br s, 1 H)	507
151	SCHEME 1 + acetal deprotection + oxime formation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.83 - 1.91 (m, 2 H) 1.94 - 2.08 (m, 2 H) 2.61 (t, J=6.6 Hz, 2 H) 2.89 (br t, J=6.6 Hz, 2 H) 3.05 (br t, J=12.6 Hz, 2 H) 3.43 - 3.54 (m, 1 H) 3.86 (s, 2 H) 4.19 (br d, J=13.1 Hz, 2 H) 5.34 (s, 2 H) 6.48 (br dd, J=8.4, 1.0 Hz, 1 H) 6.67 (br d, J=1.0 Hz, 1 H) 7.13 (d, J=8.4 Hz, 1 H) 7.93 (d, J=4.1 Hz, 1 H) 10.25 (s, 1 H) 11.14 (br s, 1 H)	506
152	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.87 (br d, J=11.4 Hz, 2 H) 1.96 - 2.10 (m, 2 H) 3.06 - 3.40 (m, 10 H) 3.59 - 3.70 (m, 1 H) 4.08 - 4.30 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.99 (d, J=4.3 Hz, 1 H) 11.42 (br s, 1 H)	526

153	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.86 - 1.96 (m, 2 H) 1.96 - 2.09 (m, 2 H) 2.10 - 2.19 (m, 2 H) 3.06 - 3.20 (m, 4 H) 3.33 - 3.42 (m, 2 H) 3.57 (tt, J=11.9, 3.6 Hz, 1 H) 4.07 - 4.25 (m, 2 H) 4.74 (s, 2 H) 7.38 (d, J=8.6 Hz, 2 H) 7.55 (br d, J=8.6 Hz, 2 H) 8.00 (d, J=4.1 Hz, 1 H) 11.60 (br s, 1 H)	526
154	SCHEME 1 + boc deprotection + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.20 - 1.38 (m, 1 H) 1.48 - 1.63 (m, 2 H) 1.72 - 1.90 (m, 3 H) 1.91 - 2.09 (m, 2 H) 2.31 - 2.42 (m, 3 H) 2.56 (td, J=12.2, 2.3 Hz, 1 H) 2.75 (br dd, J=16.6, 3.3 Hz, 1 H) 2.81 - 3.23 (m partially hidden, 5 H) 3.42 - 3.56 (m, 1 H) 4.16 (br d, J=12.9 Hz, 2 H) 5.34 (br s, 2 H) 6.34 - 6.56 (m, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 10.92 (br s, 1 H)	532
155	SCHEME 1 + boc deprotection + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.20 - 1.38 (m, 1 H) 1.48 - 1.63 (m, 2 H) 1.72 - 1.90 (m, 3 H) 1.91 - 2.09 (m, 2 H) 2.31 - 2.42 (m, 3 H) 2.56 (td, J=12.2, 2.3 Hz, 1 H) 2.75 (br dd, J=16.6, 3.3 Hz, 1 H) 2.81 - 3.23 (m partially hidden, 5 H) 3.42 - 3.56 (m, 1 H) 4.16 (br d, J=12.9 Hz, 2 H) 5.34 (br s, 2 H) 6.34 - 6.56 (m, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 10.92 (br s, 1 H)	532
156	SCHEME 1 + boc deprotection + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.59 - 1.71 (m, 1 H) 1.73 - 2.05 (m, 5 H) 2.54 - 2.79 (m, 5 H) 2.81 - 3.01 (m partially hidden, 2 H) 3.07 (br t, J=13.0 Hz, 2 H) 3.16 - 3.25 (m, 1 H) 3.37 (tt, J=12.1, 3.8 Hz, 1 H) 4.12 - 4.27 (m, 2 H) 5.37 (s, 2 H) 6.49 (dd, J=8.4, 1.1 Hz, 1 H) 6.69 (br d, J=1.1 Hz, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.89 (d, J=3.3 Hz, 1 H) 11.23 (br s, 1 H)	518
157	SCHEME 1 + boc deprotection + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.58 - 1.70 (m, 1 H) 1.71 - 2.08 (m, 5 H) 2.53 - 2.77 (m, 5 H) 2.78 - 3.00 (m partially hidden, 2 H) 3.07 (br t, J=12.9 Hz, 2 H) 3.16 - 3.27 (m, 1 H) 3.37 (tt, J=12.2, 3.9 Hz, 1 H) 4.11 - 4.27 (m, 2 H) 5.37 (s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.69 (br s, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.89 (d, J=3.4 Hz, 1 H) 11.22 (br s, 1 H)	518

158	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.45 - 1.57 (m, 1 H) 1.78 - 2.10 (m, 6 H) 2.50 - 2.57 (m partially hidden, 1 H) 2.66 - 2.81 (m, 2 H) 2.90 - 3.00 (m partially hidden, 1 H) 3.01 - 3.13 (m, 2 H) 3.43 - 3.61 (m, 3 H) 4.07 - 4.28 (m, 3 H) 7.39 (br d, J=8.5 Hz, 2 H) 7.54 (br d, J=8.5 Hz, 2 H) 7.88 (d, J=4.3 Hz, 1 H) 10.93 (br s, 1 H)	492
159	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.45 - 1.57 (m, 1 H) 1.78 - 2.10 (m, 6 H) 2.50 - 2.57 (m partially hidden, 1 H) 2.66 - 2.81 (m, 2 H) 2.90 - 3.00 (m partially hidden, 1 H) 3.01 - 3.13 (m, 2 H) 3.43 - 3.61 (m, 3 H) 4.07 - 4.28 (m, 3 H) 7.39 (br d, J=8.5 Hz, 2 H) 7.54 (br d, J=8.5 Hz, 2 H) 7.88 (d, J=4.3 Hz, 1 H) 10.93 (br s, 1 H)	492
160	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.77 (br d, J=12.3 Hz, 2 H) 1.90 - 2.05 (m, 2 H) 2.97 - 3.08 (m, 2 H) 3.07 (s, 6 H) 3.41 - 3.52 (m, 1 H) 4.05 - 4.33 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.53 (br d, J=8.6 Hz, 2 H) 7.96 (d, J=2.6 Hz, 1 H) 8.23 (br s, 1 H)	507
161	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.44 - 1.57 (m, 1 H) 1.77 - 2.09 (m, 6 H) 2.45 - 2.59 (m partially hidden, 1 H) 2.64 - 2.81 (m, 2 H) 2.89 - 3.12 (m partially hidden, 3 H) 3.42 - 3.60 (m, 3 H) 4.13 - 4.23 (m, 3 H) 5.34 (s, 2 H) 6.49 (dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 10.93 (br s, 1 H)	507
162	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.81 - 1.91 (m, 2 H) 1.93 - 2.20 (m, 4 H) 2.85 (br t, J=6.1 Hz, 2 H) 3.06 - 3.19 (m, 3 H) 3.23 - 3.36 (m, 2 H) 3.45 (ddd, J=11.9, 8.3, 3.8 Hz, 1 H) 4.05 - 4.32 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.94 (d, J=4.1 Hz, 1 H) 11.17 (br s, 1 H)	487
163	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.81 - 1.91 (m, 2 H) 1.93 - 2.20 (m, 4 H) 2.85 (br t, J=6.1 Hz, 2 H) 3.06 - 3.19 (m, 3 H) 3.23 - 3.36 (m, 2 H) 3.45 (ddd, J=11.9, 8.3, 3.8 Hz, 1 H) 4.05 - 4.32 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.94 (d, J=4.1 Hz, 1 H) 11.17 (br s, 1 H)	487

164	SCHEME 1 + acetal deprotection + oxime formation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.84 - 1.91 (m, 2 H) 1.96 - 2.10 (m, 2 H) 2.61 (t, J=6.6 Hz, 2 H) 2.89 (t, J=6.6 Hz, 2 H) 3.06 (br t, J=12.5 Hz, 2 H) 3.45 - 3.57 (m, 1 H) 3.86 (s, 2 H) 4.10 - 4.29 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.56 (br d, J=8.6 Hz, 2 H) 7.94 (d, J=4.1 Hz, 1 H) 10.26 (s, 1 H) 11.15 (br s, 1 H)	491
165	SCHEME 1 + acetal deprotection + oxime formation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.86 (br d, J=11.1 Hz, 2 H) 1.95 - 2.08 (m, 2 H) 2.81 - 2.90 (m, 4 H) 3.11 (br t, J=12.8 Hz, 2 H) 3.43 - 3.53 (m, 1 H) 3.66 (s, 2 H) 4.09 - 4.32 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.55 (br d, J=8.6 Hz, 2 H) 7.94 (d, J=4.1 Hz, 1 H) 10.12 (s, 1 H) 11.15 (br s, 1 H)	491
166	SCHEME 2A (silver carbonate instead of PIFA in step 3) + OTBS deprotection + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.72 - 1.89 (m, 3 H) 1.94 - 2.08 (m, 3 H) 2.60 (br dd, J=16.7, 7.1 Hz, 1 H) 2.79 - 2.89 (m, 1 H) 2.90 - 3.02 (m partially hidden, 2 H) 3.08 (br t, J=12.6 Hz, 2 H) 3.49 - 3.59 (m, 1 H) 3.99 - 4.08 (m, 1 H) 4.08 - 4.28 (m, 2 H) 4.49 (br d, J=3.8 Hz, 1 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.88 (d, J=4.3 Hz, 1 H) 10.93 (br s, 1 H)	478
167	SCHEME 2A (silver carbonate instead of PIFA in step 3) + OTBS deprotection + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.72 - 1.89 (m, 3 H) 1.94 - 2.08 (m, 3 H) 2.60 (br dd, J=16.7, 7.1 Hz, 1 H) 2.79 - 2.89 (m, 1 H) 2.90 - 3.02 (m partially hidden, 2 H) 3.08 (br t, J=12.6 Hz, 2 H) 3.49 - 3.59 (m, 1 H) 3.99 - 4.08 (m, 1 H) 4.08 - 4.28 (m, 2 H) 4.49 (br d, J=3.8 Hz, 1 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.88 (d, J=4.3 Hz, 1 H) 10.93 (br s, 1 H)	478
168	SCHEME 1 + acetal deprotection + MeMgBr addition + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.23 (s, 3 H) 1.66 - 1.93 (m, 6 H) 1.95 - 2.12 (m, 2 H) 2.57 - 2.71 (m, 1 H) 2.76 - 2.87 (m, 1 H) 2.89 - 3.18 (m partially hidden, 4 H) 3.67 (tt, J=12.1, 3.4 Hz, 1 H) 3.98 (s, 1 H) 4.05 - 4.31 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.87 (d, J=4.3 Hz, 1 H) 10.97 (br s, 1 H)	506
169	SCHEME 1 + acetal deprotection + MeMgBr addition + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.23 (s, 3 H) 1.66 - 1.93 (m, 6 H) 1.95 - 2.12 (m, 2 H) 2.57 - 2.71 (m, 1 H) 2.76 - 2.87 (m, 1 H) 2.89 - 3.18 (m partially hidden, 4 H) 3.67 (tt, J=12.1, 3.4 Hz, 1 H) 3.98 (s, 1 H) 4.05 - 4.31 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.87 (d, J=4.3 Hz, 1 H) 10.97 (br s, 1 H)	506

170	SCHEME 1 + boc deprotection + N- acetylation	¹ H NMR (400 MHz, DMSO-d ₆ , 120°C) δ ppm 1.84 (br d, J=12.9 Hz, 2 H) 1.96 - 2.13 (m, 2 H) 2.06 (s, 3 H) 3.01 - 3.23 (m, 6 H) 3.58 - 3.68 (m, 1 H) 3.73 (t, J=5.9 Hz, 2 H) 3.78 - 3.86 (m, 2 H) 4.16 (br d, J=12.4 Hz, 2 H) 7.38 (br d, J=8.6 Hz, 2 H) 7.53 (br d, J=8.6 Hz, 2 H) 7.92 (d, J=4.3 Hz, 1 H) 11.02 (br s, 1 H)	519
171	SCHEME 2A (silver carbonate instead of PIFA in step 3) + OTBS deprotection + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.71 - 1.89 (m, 3 H) 1.92 - 2.07 (m, 3 H) 2.60 (br dd, J=16.6, 7.1 Hz, 1 H) 2.77 - 3.01 (m partially hidden, 3 H) 3.02 - 3.13 (m, 2 H) 3.52 (ddd, J=12.3, 8.9, 3.3 Hz, 1 H) 3.99 - 4.08 (m, 1 H) 4.17 (br d, J=13.3 Hz, 2 H) 4.48 (d, J=4.0 Hz, 1 H) 5.34 (br s, 2 H) 6.45 - 6.52 (m, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 10.92 (br s, 1 H)	493
172	SCHEME 2A (silver carbonate instead of PIFA in step 3) + OTBS deprotection + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.71 - 1.89 (m, 3 H) 1.93 - 2.06 (m, 3 H) 2.60 (br dd, J=16.5, 7.1 Hz, 1 H) 2.77 - 3.01 (m partially hidden, 3 H) 3.06 (br t, J=12.9 Hz, 2 H) 3.45 - 3.57 (m, 1 H) 3.97 - 4.09 (m, 1 H) 4.17 (br d, J=12.5 Hz, 2 H) 4.49 (br d, J=2.9 Hz, 1 H) 5.34 (br s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 10.92 (br s, 1 H)	493
173	SCHEME 1 + boc deprotection + N- acetylation	¹ H NMR (400 MHz, DMSO-d ₆ , 120°C) δ ppm 1.81 - 2.14 (m, 6 H) 1.99 (s, 3 H) 2.85 - 3.03 (m, 2 H) 3.13 (br t, J=12.0 Hz, 2 H) 3.67 - 3.92 (m, 3 H) 4.13 - 4.25 (m, 2 H) 4.84 (s, 2 H) 7.37 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.91 (br d, J=3.9 Hz, 1 H) 11.14 (br d, J=1.4 Hz, 1 H)	519
174	SCHEME 1 + boc deprotection + N- alkylation with F ₃ C- CH ₂ -OTf	¹ H NMR (400 MHz, DMSO-d ₆ , 120°C) δ ppm 1.81 - 1.88 (m, 2 H) 1.93 - 2.12 (m, 2 H) 2.89 - 3.21 (m, 10 H) 3.40 (q, J=10.0 Hz, 2 H) 3.59 - 3.71 (m, 1 H) 4.09 - 4.24 (m, 2 H) 7.37 (br d, J=8.6 Hz, 2 H) 7.53 (br d, J=8.6 Hz, 2 H) 7.89 (d, J=4.1 Hz, 1 H) 10.96 (br s, 1 H)	559
175	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.75 - 2.11 (m, 12 H) 2.72 (t, J=6.3 Hz, 2 H) 2.91 (br s, 2 H) 3.10 (br t, J=12.7 Hz, 2 H) 3.53 (tt, J=12.2, 3.4 Hz, 1 H) 4.19 (br d, J=12.9 Hz, 2 H) 5.35 (br s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.69 (br d, J=1.1 Hz, 1 H) 7.13 (d, J=8.4 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 10.92 (br s, 1 H)	517

176	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.77 - 2.11 (m, 12 H) 2.72 (t, J=6.3 Hz, 2 H) 2.91 (s, 2 H) 3.12 (br t, J=12.7 Hz, 2 H) 3.55 (tt, J=12.1, 3.5 Hz, 1 H) 4.09 - 4.39 (m, 2 H) 7.40 (br d, J=8.6 Hz, 2 H) 7.55 (br d, J=8.6 Hz, 2 H) 7.88 (d, J=4.1 Hz, 1 H) 10.93 (br s, 1 H)	502
177	SCHEME 1 + boc deprotection + N- alkylation with F3C- CH ₂ -OTf	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.75 - 1.88 (m, 4 H) 1.97 - 2.11 (m, 2 H) 2.88 - 3.10 (m partially hidden, 4 H) 3.13 - 3.28 (m, 4 H) 3.38 - 3.47 (m, 1 H) 4.07 - 4.24 (m, 2 H) 4.25 (s, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.92 (d, J=4.3 Hz, 1 H) 11.27 (br d, J=1.0 Hz, 1 H)	559
178	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.56 - 1.74 (m, 2 H) 1.85 (br d, J=12.4 Hz, 2 H) 1.95 - 2.13 (m, 4 H) 2.57 - 2.80 (m, 2 H) 2.89 - 3.00 (m partially hidden, 1 H) 3.04 - 3.24 (m, 3 H) 3.68 (tt, J=12.1, 3.6 Hz, 1 H) 3.90 (tq, J=7.8, 3.8 Hz, 1 H) 3.95 - 4.28 (m, 2 H) 4.24 (d, J=4.1 Hz, 1 H) 7.62 (br d, J=8.8 Hz, 2 H) 7.89 (br d, J=3.9 Hz, 1 H) 7.95 (br d, J=8.8 Hz, 2 H) 11.02 (br s, 1 H)	534
179	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.57 - 1.75 (m, 2 H) 1.80 - 1.90 (m, 2 H) 1.94 - 2.11 (m, 4 H) 2.58 - 2.80 (m, 2 H) 2.88 - 3.00 (m partially hidden, 1 H) 3.05 - 3.23 (m, 3 H) 3.61 - 3.76 (m, 1 H) 3.85 - 3.94 (m, 1 H) 3.98 - 4.33 (m, 3 H) 7.62 (br d, J=8.6 Hz, 2 H) 7.88 (br s, 1 H) 7.95 (br d, J=8.6 Hz, 2 H) 10.93 - 11.10 (m, 1 H)	534
180	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.70 - 2.08 (m, 7 H) 2.09 - 2.19 (m, 1 H) 2.67 - 2.81 (m, 2 H) 2.92 - 3.09 (m partially hidden, 2 H) 3.32 - 3.42 (m, 1 H) 4.01 (dd, J=5.9, 3.6 Hz, 1 H) 4.06 - 4.29 (m, 2 H) 7.39 (br d, J=8.8 Hz, 2 H) 7.53 (br d, J=8.8 Hz, 2 H) 7.91 (d, J=4.1 Hz, 1 H) 11.09 (br s, 1 H) 11.81 - 12.13 (m, 1 H)	506
181	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.66 - 1.89 (m, 6 H) 1.91 - 2.07 (m, 2 H) 2.68 - 2.82 (m, 2 H) 2.86 (br s, 2 H) 3.06 (br t, J=12.1 Hz, 2 H) 3.40 - 3.61 (m, 3 H) 3.76 - 3.89 (m, 2 H) 4.17 (br d, J=13.0 Hz, 2 H) 5.34 (br s, 2 H) 6.43 - 6.55 (m, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.89 (d, J=4.3 Hz, 1 H) 11.02 (br s, 1 H)	533

182	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.69 - 1.89 (m, 6 H) 1.93 - 2.06 (m, 2 H) 2.69 - 2.83 (m, 2 H) 2.86 (br s, 2 H) 3.06 (br t, J=12.1 Hz, 2 H) 3.40 - 3.60 (m, 3 H) 3.77 - 3.90 (m, 2 H) 4.17 (br d, J=13.0 Hz, 2 H) 5.34 (br s, 2 H) 6.43 - 6.54 (m, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.89 (d, J=4.1 Hz, 1 H) 11.00 (br s, 1 H)	533
183	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.49 - 1.77 (m, 2 H) 1.80 - 1.95 (m, 3 H) 1.95 - 2.17 (m, 3 H) 2.67 - 2.98 (m partially hidden, 3 H) 3.08 (q, J=13.2 Hz, 2 H) 3.27 (br d, J=14.6 Hz, 1 H) 3.61 - 3.79 (m, 2 H) 4.18 (br d, J=12.6 Hz, 2 H) 4.28 (br d, J=3.8 Hz, 1 H) 5.34 (s, 2 H) 6.44 - 6.53 (m, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.13 (d, J=8.4 Hz, 1 H) 7.87 (d, J=4.3 Hz, 1 H) 11.03 (br s, 1 H)	507
184	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.49 - 1.77 (m, 2 H) 1.80 - 1.95 (m, 3 H) 1.95 - 2.17 (m, 3 H) 2.67 - 2.98 (m partially hidden, 3 H) 3.08 (q, J=13.2 Hz, 2 H) 3.27 (br d, J=14.6 Hz, 1 H) 3.61 - 3.79 (m, 2 H) 4.18 (br d, J=12.6 Hz, 2 H) 4.28 (br d, J=3.8 Hz, 1 H) 5.34 (s, 2 H) 6.44 - 6.53 (m, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.13 (d, J=8.4 Hz, 1 H) 7.87 (d, J=4.3 Hz, 1 H) 11.03 (br s, 1 H)	507
185	SCHEME 1 + acetal deprotection + MeMgBr addition	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.23 (s, 3 H) 1.69 - 1.92 (m, 6 H) 1.95 - 2.10 (m, 2 H) 2.57 - 2.68 (m, 1 H) 2.81 (br dd, J=15.9, 8.9 Hz, 1 H) 2.88 - 3.02 (m, 1 H) 3.03 - 3.13 (m, 3 H) 3.56 - 3.74 (m, 1 H) 3.97 (s, 1 H) 4.16 (br d, J=12.9 Hz, 2 H) 5.34 (s, 2 H) 6.49 (dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.86 (d, J=4.1 Hz, 1 H) 10.95 (br s, 1 H)	521
186	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.66 - 1.75 (m, 1 H) 1.76 - 2.10 (m, 7 H) 2.73 (br d, J=15.5 Hz, 1 H) 2.71 - 2.88 (m, 2 H) 3.01 (br d, J=15.5 Hz, 1 H) 3.00 - 3.12 (m, 2 H) 3.24 (t, J=6.8 Hz, 2 H) 3.44 (ddd, J=12.1, 8.7, 3.3 Hz, 1 H) 4.09 - 4.23 (m, 2 H) 5.32 (br s, 2 H) 6.39 - 6.52 (m, 1 H) 6.67 (br d, J=1.0 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.24 (br s, 1 H) 7.89 (d, J=4.1 Hz, 1 H) 11.03 (br s, 1 H)	546

187	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.66 - 1.75 (m, 1 H) 1.76 - 2.10 (m, 7 H) 2.73 (br d, J=15.5 Hz, 1 H) 2.71 - 2.88 (m, 2 H) 3.01 (br d, J=15.5 Hz, 1 H) 3.00 - 3.12 (m, 2 H) 3.24 (t, J=6.8 Hz, 2 H) 3.44 (ddd, J=12.1, 8.7, 3.3 Hz, 1 H) 4.09 - 4.23 (m, 2 H) 5.32 (br s, 2 H) 6.39 - 6.52 (m, 1 H) 6.67 (br d, J=1.0 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.24 (br s, 1 H) 7.89 (d, J=4.1 Hz, 1 H) 11.03 (br s, 1 H)	546
188	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.45 - 1.58 (m, 1 H) 1.78 - 2.08 (m, 6 H) 2.39 - 2.51 (m partially hidden, 1 H) 2.74 - 2.87 (m, 2 H) 2.91 - 2.99 (m partially hidden, 1 H) 3.00 - 3.19 (m, 2 H) 3.40 - 3.60 (m, 3 H) 4.08 - 4.26 (m, 2 H) 4.21 (br t, J=5.3 Hz, 1 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.88 (d, J=4.1 Hz, 1 H) 10.95 (br s, 1 H)	492
189	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.71 - 1.89 (m, 6 H) 1.94 - 2.07 (m, 2 H) 2.70 - 2.83 (m, 2 H) 2.86 (s, 2 H) 3.08 (br t, J=12.4 Hz, 2 H) 3.46 - 3.59 (m, 3 H) 3.78 - 3.88 (m, 2 H) 4.06 - 4.33 (m, 2 H) 7.39 (br d, J=8.5 Hz, 2 H) 7.54 (br d, J=8.5 Hz, 2 H) 7.90 (d, J=4.1 Hz, 1 H) 10.93 - 11.10 (br s, 1 H)	518
190	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.71 - 1.89 (m, 6 H) 1.94 - 2.07 (m, 2 H) 2.70 - 2.83 (m, 2 H) 2.86 (s, 2 H) 3.08 (br t, J=12.4 Hz, 2 H) 3.46 - 3.59 (m, 3 H) 3.78 - 3.88 (m, 2 H) 4.06 - 4.33 (m, 2 H) 7.39 (br d, J=8.5 Hz, 2 H) 7.54 (br d, J=8.5 Hz, 2 H) 7.90 (d, J=4.1 Hz, 1 H) 10.93 - 11.10 (br s, 1 H)	518
191	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.44 - 1.58 (m, 1 H) 1.77 - 1.88 (m, 2 H) 1.89 - 2.07 (m, 4 H) 2.39 - 2.50 (m partially hidden, 1 H) 2.75 - 2.87 (m, 2 H) 2.90 - 2.99 (m partially hidden, 1 H) 3.00 - 3.13 (m, 2 H) 3.40 - 3.57 (m, 3 H) 4.11 - 4.25 (m, 3 H) 5.34 (br s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 10.94 (br s, 1 H)	507

192	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.66 (tt, J=13.3, 4.0 Hz, 1 H) 1.73 - 2.26 (m, 7 H) 2.60 - 2.76 (m, 2 H) 3.01 - 3.20 (m, 3 H) 3.44 (td, J=10.1, 5.8 Hz, 1 H) 3.50 - 3.59 (m, 1 H) 3.65 (dt, J=10.7, 3.8 Hz, 1 H) 4.17 (br t, J=13.6 Hz, 2 H) 4.40 (t, J=5.0 Hz, 1 H) 5.33 (br s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.69 (br d, J=1.1 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.88 (d, J=4.1 Hz, 1 H) 10.97 (br s, 1 H)	507
193	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.61 - 1.72 (m, 1 H) 1.74 - 2.26 (m, 7 H) 2.61 - 2.77 (m, 2 H) 3.05 - 3.20 (m, 3 H) 3.44 (td, J=10.1, 5.8 Hz, 1 H) 3.56 (br t, J=11.9 Hz, 1 H) 3.62 - 3.68 (m, 1 H) 4.07 - 4.32 (m, 2 H) 4.40 (t, J=5.0 Hz, 1 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.89 (d, J=4.1 Hz, 1 H) 10.98 (br s, 1 H)	492
194	SCHEME 1 + N-boc deprotection	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.83 (br d, J=12.0 Hz, 2 H) 1.96 - 2.09 (m, 2 H) 2.83 - 3.15 (m partially hidden, 10 H) 3.67 (tt, J=12.0, 3.6 Hz, 1 H) 4.08 - 4.29 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.53 (br d, J=8.6 Hz, 2 H) 7.89 (d, J=4.3 Hz, 1 H) 11.01 (br s, 1 H)	477
195	SCHEME 1 + N-boc deprotection	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.77 - 1.91 (m, 4 H) 1.95 - 2.10 (m, 2 H) 2.86 - 2.98 (m partially hidden, 2 H) 2.99 - 3.16 (m, 4 H) 3.41 - 3.53 (m, 1 H) 4.07 - 4.28 (m, 2 H) 4.13 (s, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.88 (d, J=4.1 Hz, 1 H) 11.04 (br s, 1 H)	477
196	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.66 - 1.75 (m, 1 H) 1.78 - 2.09 (m, 7 H) 2.74 (br d, J=14.8 Hz, 1 H) 2.75 - 2.88 (m, 2 H) 3.01 (br d, J=14.8 Hz, 1 H) 3.01 - 3.14 (m, 2 H) 3.24 (t, J=6.8 Hz, 2 H) 3.40 - 3.54 (m, 1 H) 4.04 - 4.31 (m, 2 H) 7.25 (br s, 1 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.53 (br d, J=8.6 Hz, 2 H) 7.90 (d, J=4.0 Hz, 1 H) 10.95 - 11.11 (br s, 1 H)	531
197	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.66 - 1.75 (m, 1 H) 1.78 - 2.09 (m, 7 H) 2.74 (br d, J=14.8 Hz, 1 H) 2.75 - 2.88 (m, 2 H) 3.01 (br d, J=14.8 Hz, 1 H) 3.01 - 3.14 (m, 2 H) 3.24 (t, J=6.8 Hz, 2 H) 3.40 - 3.54 (m, 1 H) 4.04 - 4.31 (m, 2 H) 7.25 (br s, 1 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.53 (br d, J=8.6 Hz, 2 H) 7.90 (d, J=4.0 Hz, 1 H) 10.95 - 11.11 (br s, 1 H)	531

198	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.44 - 1.60 (m, 1 H) 1.77 - 2.12 (m, 6 H) 2.41 - 2.58 (m partially hidden, 1 H) 2.66 - 2.80 (m, 2 H) 2.85 - 3.17 (m partially hidden, 3 H) 3.39 - 3.63 (m, 3 H) 4.06 - 4.29 (m, 3 H) 7.39 (br d, J=8.5 Hz, 2 H) 7.54 (br d, J=8.5 Hz, 2 H) 7.88 (d, J=4.1 Hz, 1 H) 10.94 (br s, 1 H)	492
199	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.85 (br d, J=12.4 Hz, 2 H) 1.92 - 2.20 (m, 4 H) 2.85 (t, J=6.2 Hz, 2 H) 3.04 - 3.18 (m, 3 H) 3.23 - 3.36 (m, 2 H) 3.42 (tt, J=12.0, 3.6 Hz, 1 H) 4.16 (br d, J=12.5 Hz, 2 H) 5.35 (s, 2 H) 6.44 - 6.54 (m, 1 H) 6.64 - 6.74 (m, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.93 (d, J=4.3 Hz, 1 H) 11.17 (br s, 1 H)	502
200	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.44 - 1.58 (m, 1 H) 1.75 - 2.11 (m, 6 H) 2.43 - 2.60 (m partially hidden, 1 H) 2.66 - 2.80 (m, 2 H) 2.88 - 3.14 (m partially hidden, 3 H) 3.41 - 3.60 (m, 3 H) 4.12 - 4.24 (m, 3 H) 5.33 (s, 2 H) 6.45 - 6.53 (m, 1 H) 6.68 (br s, 1 H) 7.12 (d, J=8.3 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 10.92 (br s, 1 H)	507
201	SCHEME 1 + boc deprotection + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.72 - 1.89 (m, 4 H) 1.93 - 2.15 (m, 2 H) 2.34 - 2.50 (m partially hidden, 1 H) 2.58 - 2.78 (m, 4 H) 2.99 - 3.20 (m, 3 H) 3.26 - 3.44 (m, 2 H) 3.42 - 3.59 (m, 1 H) 4.04 - 4.35 (m, 2 H) 7.40 (br d, J=8.8 Hz, 2 H) 7.54 (br d, J=8.8 Hz, 2 H) 7.90 (d, J=4.1 Hz, 1 H) 10.92 - 11.11 (m, 1 H)	503
202	SCHEME 1 + boc deprotection + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.73 - 1.89 (m, 4 H) 1.94 - 2.16 (m, 2 H) 2.35 - 2.50 (m partially hidden, 1 H) 2.58 - 2.78 (m, 4 H) 2.99 - 3.19 (m, 3 H) 3.28 - 3.42 (m, 2 H) 3.43 - 3.54 (m, 1 H) 4.07 - 4.32 (m, 2 H) 7.39 (br d, J=8.8 Hz, 2 H) 7.54 (br d, J=8.8 Hz, 2 H) 7.90 (d, J=4.1 Hz, 1 H) 10.92 - 11.09 (m, 1 H)	503
203	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.50 - 1.63 (m, 1 H) 1.69 (dtd, J=13.1, 9.6, 9.6, 3.2 Hz, 1 H) 1.82 - 1.95 (m, 3 H) 1.98 - 2.15 (m, 3 H) 2.68 - 2.78 (m, 1 H) 2.78 - 3.00 (m partially hidden, 2 H) 3.04 - 3.17 (m, 2 H) 3.27 (br d, J=14.9 Hz, 1 H) 3.65 - 3.78 (m, 2 H) 4.09 - 4.26 (m, 2 H) 4.27 (br d, J=2.6 Hz, 1 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.56 (br d, J=8.6 Hz, 2 H) 7.88 (d, J=4.3 Hz, 1 H) 11.05 (br s, 1 H)	492

204	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.50 - 1.63 (m, 1 H) 1.69 (dtd, J=13.1, 9.6, 9.6, 3.2 Hz, 1 H) 1.82 - 1.95 (m, 3 H) 1.98 - 2.15 (m, 3 H) 2.68 - 2.78 (m, 1 H) 2.78 - 3.00 (m partially hidden, 2 H) 3.04 - 3.17 (m, 2 H) 3.27 (br d, J=14.9 Hz, 1 H) 3.65 - 3.78 (m, 2 H) 4.09 - 4.26 (m, 2 H) 4.27 (br d, J=2.6 Hz, 1 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.56 (br d, J=8.6 Hz, 2 H) 7.88 (d, J=4.3 Hz, 1 H) 11.05 (br s, 1 H)	492
205	SCHEME 1 + boc deprotection	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.60 - 1.71 (m, 1 H) 1.75 - 2.06 (m, 6 H) 2.53 - 2.76 (m, 5 H) 2.82 - 2.99 (m partially hidden, 2 H) 3.07 (br t, J=12.9 Hz, 2 H) 3.21 (q, J=6.3 Hz, 1 H) 3.37 (tt, J=12.2, 3.7 Hz, 1 H) 4.14 - 4.25 (m, 2 H) 5.37 (br s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.69 (br s, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.89 (d, J=3.4 Hz, 1 H) 11.22 (br s, 1 H)	518
206	SCHEME 1 + boc deprotection	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.21 - 1.35 (m, 1 H) 1.46 - 1.64 (m, 2 H) 1.71 - 1.91 (m, 3 H) 1.91 - 2.22 (m, 3 H) 2.31 - 2.43 (m, 3 H) 2.57 (td, J=12.3, 2.4 Hz, 1 H) 2.75 (br dd, J=16.6, 3.3 Hz, 1 H) 2.83 - 2.95 (m partially hidden, 1 H) 2.96 - 3.17 (m, 4 H) 3.49 (ddd, J=12.1, 8.6, 3.8 Hz, 1 H) 4.16 (br d, J=12.4 Hz, 2 H) 5.34 (br s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br s, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 10.93 (br s, 1 H)	532
207	SCHEME 1 + acetal deprotection	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.83 (br d, J=12.3 Hz, 2 H) 1.94 - 2.09 (m, 2 H) 2.68 - 2.76 (m, 2 H) 2.83 - 3.00 (m partially hidden, 2 H) 3.02 - 3.16 (m, 4 H) 3.18 - 3.23 (m, 2 H) 3.50 - 3.66 (m, 1 H) 4.15 (br d, J=12.8 Hz, 2 H) 5.33 (br s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.93 (d, J=4.3 Hz, 1 H) 11.13 (br s, 1 H)	505
208	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.81 - 1.90 (m, 2 H) 1.93 - 2.20 (m, 4 H) 2.85 (t, J=6.3 Hz, 2 H) 3.05 - 3.22 (m, 3 H) 3.24 - 3.37 (m, 2 H) 3.45 (tt, J=11.9, 3.5 Hz, 1 H) 4.08 - 4.31 (m, 2 H) 7.39 (br d, J=8.8 Hz, 2 H) 7.54 (br d, J=8.8 Hz, 2 H) 7.94 (d, J=4.3 Hz, 1 H) 11.17 (br s, 1 H)	487

209	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.87 - 1.95 (m, 2 H) 2.04 (br q, J=11.6 Hz, 2 H) 2.16 (s, 3 H) 2.80 - 3.18 (m partially hidden, 4 H) 3.21 - 3.36 (m, 1 H) 3.83 (br t, J=5.7 Hz, 2 H) 4.22 (br d, J=13.1 Hz, 2 H) 4.85 (s, 2 H) 5.38 (br s, 2 H) 6.53 (br dd, J=8.4, 1.0 Hz, 1 H) 6.72 (br d, J=1.0 Hz, 1 H) 7.17 (d, J=8.4 Hz, 1 H) 7.99 (d, J=4.1 Hz, 1 H) 11.29 (br s, 1 H)	520
210	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.00 (s, 6 H) 1.83 (br d, J=10.9 Hz, 2 H) 1.92 - 2.06 (m, 2 H) 2.67 (s, 2 H) 2.80 (d, J=5.9 Hz, 2 H) 2.89 - 3.05 (m partially hidden, 2 H) 4.06 - 4.27 (m, 3 H) 7.38 (br d, J=8.6 Hz, 2 H) 7.51 - 7.61 (m, 1 H) 7.54 (br d, J=8.6 Hz, 2 H) 8.04 (d, J=4.1 Hz, 1 H) 11.90 (br d, J=2.1 Hz, 1 H)	519
211	SCHEME 1 + acetal deprotection	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.87 (br d, J=12.0 Hz, 2 H) 1.98 - 2.11 (m, 2 H) 2.71 - 2.77 (m, 2 H) 2.90 - 2.99 (m partially hidden, 2 H) 3.06 - 3.20 (m, 4 H) 3.21 - 3.28 (m, 2 H) 3.59 - 3.70 (m, 1 H) 4.08 - 4.32 (m, 2 H) 7.42 (br d, J=8.8 Hz, 2 H) 7.56 (br d, J=8.8 Hz, 2 H) 7.97 (d, J=4.3 Hz, 1 H) 11.17 (br s, 1 H)	490
212	SCHEME 1 + acetal deprotection	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.90 (br d, J=12.1 Hz, 2 H) 1.99 - 2.20 (m, 4 H) 2.62 - 2.67 (m, 2 H) 2.92 - 3.03 (m partially hidden, 2 H) 3.13 (br t, J=12.5 Hz, 2 H) 3.63 (tt, J=12.0, 3.3 Hz, 1 H) 4.02 (s, 2 H) 4.11 - 4.36 (m, 2 H) 7.42 (br d, J=8.6 Hz, 2 H) 7.58 (br d, J=8.6 Hz, 2 H) 7.98 (d, J=4.1 Hz, 1 H) 11.31 (br s, 1 H)	490
213	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.61 - 2.35 (m, 9 H) 2.76 - 2.86 (m, 2 H) 2.87 - 2.99 (m partially hidden, 1 H) 3.09 (br t, J=12.6 Hz, 1 H) 3.15 - 3.25 (m, 1 H) 3.30 - 3.41 (m, 1 H) 3.45 - 3.57 (m, 1 H) 3.70 - 3.79 (m, 1 H) 3.79 - 3.94 (m, 2 H) 4.20 (br t, J=12.9 Hz, 2 H) 5.35 (br s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.89 (d, J=4.0 Hz, 1 H) 11.00 (br s, 1 H)	533

214	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.37 - 1.46 (m, 1 H) 1.51 - 1.64 (m, 1 H) 1.85 (br d, J=12.3 Hz, 2 H) 1.91 - 2.13 (m, 3 H) 2.18 - 2.29 (m, 1 H) 2.53 - 2.61 (m, 1 H) 2.83 - 3.16 (m partially hidden, 5 H) 3.45 (td, J=10.8, 2.9 Hz, 1 H) 3.49 - 3.58 (m, 1 H) 3.59 (dd, J=11.3, 2.5 Hz, 1 H) 3.73 (dd, J=11.3, 3.1 Hz, 1 H) 3.85 (dt, J=11.2, 3.7 Hz, 1 H) 4.11 - 4.25 (m, 2 H) 5.34 (s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.88 (d, J=4.1 Hz, 1 H) 10.94 (br s, 1 H)	533
215	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.40 - 1.54 (m, 1 H) 1.63 - 1.89 (m, 5 H) 1.91 - 2.11 (m partially hidden, 2 H) 2.27 - 2.58 (m, 2 H) 2.70 - 2.90 (m, 2 H) 3.05 (q, J=12.6 Hz, 2 H) 3.13 - 3.24 (m, 1 H) 3.33 - 3.54 (m, 2 H) 3.92 (dd, J=11.2, 4.2 Hz, 1 H) 3.99 (dd, J=11.0, 3.1 Hz, 1 H) 4.16 (br d, J=12.6 Hz, 2 H) 5.33 (s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.88 (d, J=4.1 Hz, 1 H) 10.98 (br s, 1 H)	533
216	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.40 - 1.54 (m, 1 H) 1.63 - 1.89 (m, 5 H) 1.91 - 2.11 (m partially hidden, 2 H) 2.27 - 2.58 (m, 2 H) 2.70 - 2.90 (m, 2 H) 3.05 (q, J=12.6 Hz, 2 H) 3.13 - 3.24 (m, 1 H) 3.33 - 3.54 (m, 2 H) 3.92 (dd, J=11.2, 4.2 Hz, 1 H) 3.99 (dd, J=11.0, 3.1 Hz, 1 H) 4.16 (br d, J=12.6 Hz, 2 H) 5.33 (s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.88 (d, J=4.1 Hz, 1 H) 10.98 (br s, 1 H)	533
217	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.37 - 1.46 (m, 1 H) 1.51 - 1.64 (m, 1 H) 1.85 (br d, J=12.3 Hz, 2 H) 1.91 - 2.13 (m, 3 H) 2.18 - 2.29 (m, 1 H) 2.53 - 2.61 (m, 1 H) 2.83 - 3.16 (m partially hidden, 5 H) 3.45 (td, J=10.8, 2.9 Hz, 1 H) 3.49 - 3.58 (m, 1 H) 3.59 (dd, J=11.3, 2.5 Hz, 1 H) 3.73 (dd, J=11.3, 3.1 Hz, 1 H) 3.85 (dt, J=11.2, 3.7 Hz, 1 H) 4.11 - 4.25 (m, 2 H) 5.34 (s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.88 (d, J=4.1 Hz, 1 H) 10.94 (br s, 1 H)	533

218	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.63 - 2.35 (m, 9 H) 2.76 - 2.85 (m, 2 H) 2.87 - 3.00 (m partially hidden, 1 H) 3.09 (br t, J=12.9 Hz, 1 H) 3.19 (dt, J=10.1, 5.1 Hz, 1 H) 3.31 - 3.42 (m, 1 H) 3.51 (td, J=10.9, 4.3 Hz, 1 H) 3.70 - 3.78 (m, 1 H) 3.79 - 3.94 (m, 2 H) 4.20 (br t, J=13.0 Hz, 2 H) 5.35 (s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.89 (d, J=4.1 Hz, 1 H) 11.00 (br s, 1 H)	533
219	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.54 - 1.74 (m, 2 H) 1.85 (br d, J=13.0 Hz, 2 H) 1.94 - 2.14 (m, 4 H) 2.58 - 2.79 (m, 2 H) 2.88 - 3.01 (m partially hidden, 1 H) 3.03 - 3.20 (m, 3 H) 3.59 - 3.73 (m, 1 H) 3.84 - 3.96 (m, 1 H) 4.06 - 4.20 (m, 2 H) 4.23 (d, J=4.0 Hz, 1 H) 5.44 (s, 2 H) 7.01 (dd, J=8.5, 2.3 Hz, 1 H) 7.20 (d, J=8.5 Hz, 1 H) 7.27 (d, J=2.3 Hz, 1 H) 7.87 (d, J=4.3 Hz, 1 H) 10.88 - 11.06 (m, 1 H)	549
220	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.58 - 1.74 (m, 2 H) 1.85 (br d, J=13.1 Hz, 2 H) 1.96 - 2.11 (m, 4 H) 2.58 - 2.79 (m, 2 H) 2.89 - 3.01 (m partially hidden, 1 H) 3.04 - 3.20 (m, 3 H) 3.60 - 3.71 (m, 1 H) 3.85 - 3.94 (m, 1 H) 4.08 - 4.20 (m, 2 H) 4.23 (br d, J=4.3 Hz, 1 H) 5.44 (s, 2 H) 7.01 (dd, J=8.4, 2.1 Hz, 1 H) 7.20 (br d, J=8.4 Hz, 1 H) 7.27 (d, J=2.1 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 11.00 (br s, 1 H)	549
221	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.79 - 2.10 (m, 8 H) 2.70 - 2.80 (m, 1 H) 2.88 (br d, J=15.3 Hz, 1 H) 2.92 - 3.08 (m partially hidden, 3 H) 3.11 (br d, J=15.3 Hz, 1 H) 3.42 (tt, J=11.7, 3.7 Hz, 1 H) 4.05 - 4.31 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.55 (br d, J=8.6 Hz, 2 H) 7.92 (d, J=4.1 Hz, 1 H) 11.02 - 11.15 (br s, 1 H)	545
222	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.77 - 2.09 (m, 8 H) 2.70 - 2.80 (m, 1 H) 2.88 (d, J=15.4 Hz, 1 H) 2.91 - 3.08 (m partially hidden, 3 H) 3.11 (br d, J=15.4 Hz, 1 H) 3.42 (tt, J=11.9, 3.9 Hz, 1 H) 4.05 - 4.34 (m, 2 H) 7.39 (br d, J=8.8 Hz, 2 H) 7.55 (br d, J=8.8 Hz, 2 H) 7.92 (d, J=4.3 Hz, 1 H) 11.05 - 11.20 (br s, 1 H)	545

223	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 0.99 (s, 6 H) 1.82 (br d, J=10.5 Hz, 2 H) 1.92 - 2.08 (m, 2 H) 2.67 (s, 2 H) 2.80 (d, J=6.0 Hz, 2 H) 2.87 - 3.08 (m partially hidden, 2 H) 4.01 - 4.28 (m, 3 H) 5.33 (s, 2 H) 6.40 - 6.52 (m, 1 H) 6.67 (br d, J=1.1 Hz, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.55 (br t, J=5.8 Hz, 1 H) 8.04 (d, J=4.0 Hz, 1 H) 11.91 (br s, 1 H)	534
224	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.65 - 1.83 (m, 4 H) 1.92 - 2.03 (m, 2 H) 2.07 - 2.22 (m, 2 H) 2.80 - 2.88 (m, 2 H) 2.98 - 3.12 (m, 2 H) 3.67 (tt, J=12.2, 3.8 Hz, 1 H) 3.95 - 4.04 (m, 2 H) 4.18 (br d, J=12.6 Hz, 2 H) 5.35 (s, 2 H) 6.49 (br dd, J=8.4, 1.1 Hz, 1 H) 6.68 (br d, J=1.0 Hz, 1 H) 7.13 (d, J=8.4 Hz, 1 H) 7.91 (d, J=3.4 Hz, 1 H) 10.81 (br s, 1 H)	493
225	SCHEME 1 + acetal deprotection + MeMgBr addition	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.23 (s, 3 H) 1.68 - 1.93 (m, 6 H) 1.96 - 2.11 (m, 2 H) 2.58 - 2.67 (m, 1 H) 2.82 (br dd, J=15.4, 8.4 Hz, 1 H) 2.90 - 3.01 (m partially hidden, 1 H) 3.02 - 3.16 (m, 3 H) 3.61 - 3.72 (m, 1 H) 3.97 (s, 1 H) 4.07 - 4.29 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.87 (d, J=4.1 Hz, 1 H) 10.96 (br s, 1 H)	506
226	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.50 - 1.75 (m, 2 H) 1.82 - 1.94 (m, 3 H) 1.96 - 2.15 (m, 3 H) 2.68 - 2.78 (m, 1 H) 2.79 - 2.97 (m partially hidden, 2 H) 3.02 - 3.18 (m, 2 H) 3.27 (br d, J=15.3 Hz, 1 H) 3.64 - 3.76 (m, 2 H) 4.11 - 4.20 (m, 2 H) 4.28 (br d, J=3.4 Hz, 1 H) 5.45 (br s, 2 H) 7.01 (dd, J=8.4, 2.1 Hz, 1 H) 7.22 (br d, J=8.4 Hz, 1 H) 7.27 (d, J=2.1 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 11.04 (br s, 1 H)	549
227	SCHEME 1 + OTBS deprotection + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.71 - 1.89 (m, 3 H) 1.91 - 2.09 (m, 3 H) 2.66 - 2.88 (m, 3 H) 3.00 - 3.10 (m, 2 H) 3.13 (br dd, J=14.9, 5.0 Hz, 1 H) 3.44 - 3.56 (m, 1 H) 3.93 - 4.10 (m, 1 H) 4.18 (br d, J=12.4 Hz, 2 H) 4.42 (br d, J=3.3 Hz, 1 H) 5.34 (br s, 2 H) 6.41 - 6.54 (m, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 10.79 - 11.09 (br s, 1 H)	493

228	SCHEME 1 + OTBS deprotection + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.72 - 1.89 (m, 3 H) 1.90 - 2.09 (m, 3 H) 2.66 - 2.88 (m, 3 H) 3.05 (br t, J=12.8 Hz, 2 H) 3.13 (dd, J=14.9, 4.9 Hz, 1 H) 3.50 (tt, J=12.1, 3.3 Hz, 1 H) 3.98 - 4.07 (m, 1 H) 4.18 (br d, J=12.9 Hz, 2 H) 4.42 (br d, J=2.5 Hz, 1 H) 5.34 (br s, 2 H) 6.43 - 6.53 (m, 1 H) 6.68 (br d, J=1.1 Hz, 1 H) 7.12 (d, J=8.3 Hz, 1 H) 7.87 (d, J=4.3 Hz, 1 H) 10.95 (br s, 1 H)	493
229	SCHEME 2A + acetal deprotection + oxime formation + Beckmann rearrangement	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.84 (br d, J=12.0 Hz, 2 H) 1.93 - 2.10 (m, 2 H) 2.75 - 2.84 (m, 2 H) 3.03 - 3.22 (m, 4 H) 3.50 - 3.67 (m, 1 H) 4.06 - 4.28 (m, 2 H) 4.38 (br d, J=5.1 Hz, 2 H) 7.39 (br d, J=8.1 Hz, 2 H) 7.53 (br d, J=8.5 Hz, 2 H) 7.60 - 7.72 (m, 1 H) 7.97 (d, J=4.0 Hz, 1 H) 11.19 (br s, 1 H)	491
230	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.71 - 1.89 (m, 6 H) 1.92 - 2.12 (m, 2 H) 2.69 - 2.83 (m, 2 H) 2.86 (br s, 2 H) 3.06 (br t, J=12.1 Hz, 2 H) 3.44 - 3.60 (m, 3 H) 3.76 - 3.90 (m, 2 H) 4.17 (br d, J=12.6 Hz, 2 H) 5.34 (br s, 2 H) 6.45 - 6.53 (m, 1 H) 6.68 (br d, J=1.3 Hz, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.89 (d, J=4.1 Hz, 1 H) 11.00 (br s, 1 H)	533
231	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.71 - 1.90 (m, 6 H) 1.94 - 2.09 (m, 2 H) 2.70 - 2.83 (m, 2 H) 2.86 (br s, 2 H) 3.08 (br t, J=12.4 Hz, 2 H) 3.46 - 3.60 (m, 3 H) 3.78 - 3.90 (m, 2 H) 4.06 - 4.31 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.90 (d, J=4.1 Hz, 1 H) 11.01 (br s, 1 H)	518
232	SCHEME 2A + acetal deprotection + oxime formation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.85 (br d, J=12.6 Hz, 2 H) 1.93 - 2.08 (m, 2 H) 2.79 - 2.88 (m, 2 H) 2.99 - 3.18 (m, 4 H) 3.43 - 3.61 (m, 3 H) 4.06 - 4.30 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.93 (d, J=4.0 Hz, 1 H) 10.16 (s, 1 H) 11.13 (br s, 1 H)	491
233	SCHEME 2A + acetal deprotection + oxime formation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.85 (br d, J=12.1 Hz, 2 H) 1.93 - 2.09 (m, 2 H) 2.60 (t, J=6.4 Hz, 2 H) 3.00 - 3.14 (m, 4 H) 3.46 - 3.61 (m, 1 H) 3.74 (s, 2 H) 4.05 - 4.34 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.54 (br d, J=8.6 Hz, 2 H) 7.93 (d, J=4.1 Hz, 1 H) 10.27 (s, 1 H) 11.13 (br s, 1 H)	491

234	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.57 - 1.74 (m, 2 H) 1.85 (br d, J=13.0 Hz, 2 H) 1.95 - 2.11 (m, 4 H) 2.58 - 2.78 (m, 2 H) 2.87 - 3.00 (m partially hidden, 1 H) 3.03 - 3.20 (m, 3 H) 3.60 - 3.72 (m, 1 H) 3.84 - 3.95 (m, 1 H) 4.08 - 4.20 (m, 2 H) 4.23 (d, J=4.1 Hz, 1 H) 5.45 (br s, 2 H) 7.01 (dd, J=8.4, 2.1 Hz, 1 H) 7.20 (br d, J=8.4 Hz, 1 H) 7.27 (d, J=2.1 Hz, 1 H) 7.87 (d, J=4.1 Hz, 1 H) 11.00 (br s, 1 H)	549
235	SCHEME 2A + acetal deprotection + oxime formation + Beckmann rearrangement	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.81 - 1.89 (m, 2 H) 1.94 - 2.09 (m, 2 H) 3.01 - 3.16 (m partially hidden, 4 H) 3.51 - 3.62 (m, 3 H) 3.81 (br s, 2 H) 4.03 - 4.33 (m, 2 H) 7.39 (br d, J=8.6 Hz, 2 H) 7.46 (br t, J=6.3 Hz, 1 H) 7.53 (br d, J=8.6 Hz, 2 H) 7.95 (d, J=4.3 Hz, 1 H) 11.16 (br s, 1 H)	491
236	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.79 - 2.12 (m, 6 H) 2.73 - 2.83 (m, 1 H) 2.85 - 2.91 (m partially hidden, 1 H) 2.97 - 3.11 (m, 3 H) 3.12 - 3.20 (m, 1 H) 3.36 - 3.45 (m, 1 H) 4.10 - 4.29 (m, 2 H) 5.65 (br s, 1 H) 7.39 (br d, J=8.4 Hz, 2 H) 7.55 (br d, J=8.4 Hz, 2 H) 7.93 (d, J=4.3 Hz, 1 H) 11.13 (br s, 1 H)	546
237	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.78 - 2.13 (m, 6 H) 2.73 - 2.83 (m, 1 H) 2.85 - 2.90 (m partially hidden, 1 H) 2.96 - 3.11 (m, 3 H) 3.12 - 3.19 (m, 1 H) 3.35 - 3.45 (m, 1 H) 4.09 - 4.29 (m, 2 H) 5.65 (br s, 1 H) 7.39 (br d, J=8.4 Hz, 2 H) 7.55 (br d, J=8.4 Hz, 2 H) 7.93 (d, J=4.3 Hz, 1 H) 11.13 (br s, 1 H)	546
238	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.57 - 1.72 (m, 2 H) 1.85 (br d, J=12.7 Hz, 2 H) 1.96 - 2.12 (m, 4 H) 2.58 - 2.78 (m, 2 H) 2.93 - 3.00 (m partially hidden, 1 H) 3.06 - 3.20 (m, 3 H) 3.64 - 3.73 (m, 1 H) 3.85 - 3.94 (m, 1 H) 3.95 - 4.40 (m, 2 H) 4.22 (d, J=4.1 Hz, 1 H) 7.62 (br d, J=8.4 Hz, 2 H) 7.88 (d, J=4.3 Hz, 1 H) 7.95 (br d, J=8.4 Hz, 2 H) 11.00 (br s, 1 H)	534

239	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.52 - 1.75 (m, 2 H) 1.81 - 1.95 (m, 3 H) 1.99 - 2.13 (m, 3 H) 2.70 - 2.88 (m, 2 H) 2.88 - 2.95 (m partially hidden, 1 H) 3.03 - 3.18 (m, 2 H) 3.23 - 3.31 (m, 1 H) 3.64 - 3.78 (m, 2 H) 3.96 - 4.33 (m, 2 H) 4.26 (d, J=4.1 Hz, 1 H) 7.65 (br d, J=8.4 Hz, 2 H) 7.88 (d, J=4.3 Hz, 1 H) 7.94 (br d, J=8.4 Hz, 2 H) 11.04 (br s, 1 H)	534
240	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.76 - 1.85 (m, 2 H) 1.88 - 2.01 (m, 2 H) 2.57 - 2.77 (m, 2 H) 2.94 - 3.16 (m partially hidden, 4 H) 3.20 - 3.29 (m, 1 H) 3.58 - 3.69 (m, 2 H) 3.90 (t, J=6.4 Hz, 1 H) 4.13 - 4.24 (m, 2 H) 4.26 (t, J=6.4 Hz, 1 H) 5.35 (br s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.93 (d, J=3.6 Hz, 1 H) 11.46 (br s, 1 H)	505
241	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.76 - 1.85 (m, 2 H) 1.86 - 2.01 (m, 2 H) 2.58 - 2.76 (m, 2 H) 2.94 - 3.17 (m partially hidden, 4 H) 3.21 - 3.29 (m, 1 H) 3.57 - 3.69 (m, 2 H) 3.90 (t, J=6.4 Hz, 1 H) 4.13 - 4.24 (m, 2 H) 4.26 (t, J=6.4 Hz, 1 H) 5.35 (br s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.93 (d, J=3.6 Hz, 1 H) 11.47 (br s, 1 H)	505
242	SCHEME 1 + boc deprotection	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.86 (br d, J=12.7 Hz, 2 H) 1.97 - 2.10 (m, 2 H) 2.11 - 2.32 (m, 1 H) 2.40 - 2.48 (m, 2 H) 2.60 - 2.69 (m, 3 H) 2.77 - 2.92 (m partially hidden, 2 H) 3.02 - 3.17 (m, 5 H) 3.53 - 3.64 (m, 1 H) 4.10 - 4.27 (m, 2 H) 7.41 (br d, J=8.4 Hz, 2 H) 7.56 (br d, J=8.4 Hz, 2 H) 7.90 (d, J=4.3 Hz, 1 H) 10.90 - 11.04 (m, 1 H)	503
243	SCHEME 1 + boc deprotection	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.81 - 1.97 (m, 4 H), 2.03 - 2.23 (m, 2 H), 2.28 - 2.46 (m, 1 H), 2.47 - 2.53 (m, 1 H), 2.67 - 2.75 (m, 1 H), 2.75 - 2.83 (m, 3 H), 3.09 - 3.25 (m, 3 H), 3.39 - 3.51 (m, 2 H), 3.52 - 3.61 (m, 1 H), 4.15 - 4.38 (m, 2 H), 7.48 (d, J=8.4 Hz, 2 H), 7.63 (br d, J=8.4 Hz, 2 H), 7.99 (d, J=4.3 Hz, 1 H), 11.00 - 11.17 (m, 1 H)	503

244	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.79 - 1.91 (m, 4 H) 1.94 - 2.06 (m, 2 H) 2.06 - 2.21 (m, 2 H) 2.79 (t, J=6.5 Hz, 2 H) 2.88 - 2.99 (m partially hidden, 2 H) 3.03 - 3.20 (m, 4 H) 3.44 - 3.55 (m, 1 H) 4.07 - 4.26 (m, 2 H) 7.13 (br s, 1 H) 7.39 (br d, J=8.4 Hz, 2 H) 7.54 (br d, J=8.4 Hz, 2 H) 7.90 (d, J=4.3 Hz, 1 H) 11.03 (br s, 1 H)	531
245	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.79 - 1.92 (m, 4 H) 1.93 - 2.07 (m, 2 H) 2.07 - 2.21 (m, 2 H) 2.80 (t, J=6.5 Hz, 2 H) 2.88 - 2.98 (m partially hidden, 2 H) 3.03 - 3.20 (m, 4 H) 3.45 - 3.55 (m, 1 H) 4.08 - 4.25 (m, 2 H) 7.13 (br s, 1 H) 7.39 (br d, J=8.4 Hz, 2 H) 7.54 (br d, J=8.4 Hz, 2 H) 7.90 (d, J=4.3 Hz, 1 H) 11.02 (br s, 1 H)	531
246	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.82 - 2.12 (m, 8 H) 2.72 - 2.82 (m, 1 H) 2.87 - 2.92 (m partially hidden, 1 H) 2.96 - 3.00 (m partially hidden, 1 H) 3.00 - 3.17 (m, 3 H) 3.38 - 3.50 (m, 1 H) 4.10 - 4.32 (m, 2 H) 7.41 (br d, J=8.4 Hz, 2 H) 7.57 (br d, J=8.4 Hz, 2 H) 7.94 (d, J=4.3 Hz, 1 H) 11.11 (br s, 1 H)	545
247	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.81 - 2.15 (m, 6 H) 2.76 - 2.85 (m, 1 H) 2.87 - 3.00 (m partially hidden, 1 H) 3.00 - 3.11 (m, 2 H) 3.10 (br d, J=16.0 Hz, 1 H) 3.19 (br d, J=16.0 Hz, 1 H) 3.43 (ddd, J=11.7, 8.4, 3.8 Hz, 1 H) 4.12 - 4.35 (m, 2 H) 5.67 (s, 1 H) 7.42 (br d, J=8.6 Hz, 2 H) 7.58 (br d, J=8.6 Hz, 2 H) 7.95 (d, J=4.1 Hz, 1 H) 11.15 (br s, 1 H)	546
248	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.39 - 1.51 (m, 1 H), 1.69 - 2.07 (m, 9 H), 2.63 - 2.72 (m, 2 H), 3.00 - 3.18 (m, 4 H), 3.38 - 3.49 (m, 1 H), 4.07 - 4.29 (m, 2 H), 7.39 (br d, J=8.4 Hz, 2 H), 7.53 (br d, J=8.4 Hz, 2 H), 7.86 (d, J=4.1 Hz, 1 H), 10.96 (br s, 1 H)	488
249	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.41 - 1.51 (m, 1 H), 1.70 - 2.10 (m, 9 H), 2.65 - 2.73 (m, 2 H), 3.01 - 3.19 (m, 4 H), 3.39 - 3.50 (m, 1 H), 4.07 - 4.31 (m, 2 H), 7.41 (br d, J=8.4 Hz, 2 H), 7.55 (br d, J=8.4 Hz, 2 H), 7.88 (d, J=4.1 Hz, 1 H), 10.98 (br s, 1 H)	488

250	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.38 - 1.51 (m, 1 H), 1.68 - 2.08 (m, 9 H), 2.62 - 2.71 (m, 2 H), 2.99 - 3.17 (m, 4 H), 3.35 - 3.46 (m, 1 H), 4.10 - 4.21 (m, 2 H), 5.33 (br s, 2 H), 6.49 (br d, J=8.4 Hz, 1 H), 6.68 (br s, 1 H), 7.11 (d, J=8.4 Hz, 1 H), 7.85 (d, J=4.1 Hz, 1 H), 10.95 (br s, 1 H)	503
251	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.84 - 1.91 (m, 2 H) 1.95 - 2.11 (m, 2 H) 2.82 - 2.88 (m, 2 H) 3.03 - 3.16 (m, 4 H) 3.23 (tt, J=12.1, 3.5 Hz, 1 H) 3.44 (q, J=10.1 Hz, 2 H) 4.09 (s, 2 H) 4.14 - 4.32 (m, 2 H) 7.42 (br d, J=8.6 Hz, 2 H) 7.57 (br d, J=8.6 Hz, 2 H) 7.96 (d, J=4.1 Hz, 1 H) 11.17 (br s, 1 H)	545
252	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.84 (br d, J=12.7 Hz, 2 H) 1.93 - 2.06 (m, 2 H) 2.27 - 2.36 (m, 2 H) 2.92 - 2.96 (m partially hidden, 2 H) 3.06 - 3.16 (m, 2 H) 3.30 - 3.39 (m, 1 H) 3.44 (br t, J=14.5 Hz, 2 H) 4.16 (br d, J=12.7 Hz, 2 H) 5.33 (s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.95 (d, J=4.3 Hz, 1 H) 11.25 (br s, 1 H)	513
253	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.87 (br d, J=12.7 Hz, 2 H) 1.96 - 2.08 (m, 2 H) 2.85 (br t, J=5.6 Hz, 2 H) 3.02 - 3.13 (m, 4 H) 3.15 - 3.26 (m, 1 H) 3.45 (q, J=10.1 Hz, 2 H) 4.10 (br s, 2 H) 4.21 (br d, J=12.7 Hz, 2 H) 5.37 (br s, 2 H) 6.52 (br d, J=8.4 Hz, 1 H) 6.72 (br s, 1 H) 7.15 (d, J=8.4 Hz, 1 H) 7.95 (d, J=4.3 Hz, 1 H) 11.17 (br s, 1 H)	560
254	SCHEME 1 + boc deprotection	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.62 - 1.74 (m, 1 H) 1.78 - 2.11 (m, 5 H) 2.55 - 2.81 (m, 5 H) 2.85 - 3.04 (m partially hidden, 2 H) 3.12 (br t, J=12.7 Hz, 2 H) 3.25 (q, J=6.4 Hz, 1 H) 3.42 (tt, J=12.2, 3.9 Hz, 1 H) 4.14 - 4.35 (m, 2 H) 7.43 (br d, J=8.6 Hz, 2 H) 7.57 (br d, J=8.6 Hz, 2 H) 7.92 (d, J=3.4 Hz, 1 H) 11.25 (br s, 1 H)	503
255	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.77 - 1.88 (m, 2 H) 1.88 - 2.05 (m, 2 H) 2.61 - 2.78 (m, 2 H) 2.96 - 3.31 (m partially hidden, 5 H) 3.61 - 3.72 (m, 2 H) 3.93 (t, J=6.4 Hz, 1 H) 4.12 - 4.33 (m, 2 H) 4.28 (t, J=6.4 Hz, 1 H) 7.42 (br d, J=8.4 Hz, 2 H) 7.57 (br d, J=8.4 Hz, 2 H) 7.96 (d, J=3.6 Hz, 1 H) 11.50 (br s, 1 H)	490

256	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.76 - 1.86 (m, 2 H) 1.86 - 2.02 (m, 2 H) 2.59 - 2.75 (m, 2 H) 2.93 - 3.31 (m partially hidden, 5 H) 3.58 - 3.70 (m, 2 H) 3.91 (t, J=6.4 Hz, 1 H) 4.10 - 4.32 (m, 2 H) 4.26 (t, J=6.4 Hz, 1 H) 7.40 (br d, J=8.4 Hz, 2 H) 7.54 (br d, J=8.4 Hz, 2 H) 7.94 (d, J=3.6 Hz, 1 H) 11.47 (br s, 1 H)	490
257	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.77 - 1.89 (m, 2 H) 1.91 - 2.06 (m, 2 H) 2.65 - 2.74 (m, 1 H) 2.97 - 3.19 (m, 4 H) 3.43 - 3.59 (m, 3 H) 3.87 - 4.01 (m, 2 H) 4.03 - 4.10 (m, 1 H) 4.12 - 4.25 (m, 2 H) 5.34 (br s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.90 (d, J=3.8 Hz, 1 H) 11.14 (br s, 1 H)	505
258	SCHEME 6 + boc deprotection + couplage peptidique partie nord avec TBTU	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.85 (br d, J=12.7 Hz, 2 H) 1.96 - 2.09 (m, 4 H) 3.03 - 3.13 (m, 4 H) 3.60 - 3.69 (m, 1 H) 3.91 - 3.97 (m, 2 H) 4.17 (br d, J=12.7 Hz, 2 H) 4.71 (s, 2 H) 5.33 (br s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.11 (d, J=8.4 Hz, 1 H) 7.94 (d, J=4.1 Hz, 1 H) 11.07 - 11.17 (m, 1 H)	493
259	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.78 - 1.89 (m, 2 H) 1.90 - 2.07 (m, 2 H) 2.66 - 2.73 (m, 1 H) 2.98 - 3.19 (m, 4 H) 3.44 - 3.58 (m, 3 H) 3.88 - 4.00 (m, 2 H) 4.03 - 4.11 (m, 1 H) 4.12 - 4.28 (m, 2 H) 7.39 (br d, J=8.4 Hz, 2 H) 7.54 (br d, J=8.4 Hz, 2 H) 7.91 (d, J=3.8 Hz, 1 H) 11.15 (br s, 1 H)	490
260	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.77 - 1.95 (m, 4 H) 1.95 - 2.25 (m, 4 H) 2.82 (br t, J=6.3 Hz, 2 H) 2.89 - 3.02 (m partially hidden, 2 H) 3.03 - 3.26 (m, 4 H) 3.42 - 3.59 (m, 1 H) 4.19 (br d, J=12.8 Hz, 2 H) 5.36 (s, 2 H) 6.52 (br dd, J=8.3, 1.0 Hz, 1 H) 6.71 (br s, 1 H) 7.10 - 7.20 (m, 2 H) 7.92 (d, J=4.1 Hz, 1 H) 11.04 (br s, 1 H)	546
261	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.78 - 1.88 (m, 2 H) 1.90 - 2.06 (m, 2 H) 2.65 - 2.73 (m, 1 H) 2.97 - 3.19 (m, 4 H) 3.44 - 3.59 (m, 3 H) 3.88 - 3.99 (m, 2 H) 4.03 - 4.10 (m, 1 H) 4.13 - 4.26 (m, 2 H) 5.34 (br s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.90 (d, J=3.8 Hz, 1 H) 11.13 (br s, 1 H)	505

262	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.82 - 1.95 (m, 4 H) 1.96 - 2.28 (m, 4 H) 2.82 (br t, J=6.3 Hz, 2 H) 2.90 - 3.02 (m partially hidden, 2 H) 3.05 - 3.25 (m, 4 H) 3.47 - 3.58 (m, 1 H) 4.08 - 4.37 (m, 2 H) 7.15 (br s, 1 H) 7.42 (br d, J=8.6 Hz, 2 H) 7.56 (br d, J=8.6 Hz, 2 H) 7.93 (d, J=4.1 Hz, 1 H) 11.05 (br s, 1 H)	531
263	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.71 - 1.90 (m, 4 H) 1.96 - 2.12 (m, 4 H) 2.62 - 2.72 (m, 1 H) 2.73 - 2.83 (m, 1 H) 2.94 - 2.98 (m partially hidden, 1 H) 3.04 - 3.17 (m, 3 H) 3.31 (s, 3 H) 3.52 - 3.61 (m, 1 H) 3.61 - 3.72 (m, 1 H) 4.06 - 4.29 (m, 2 H) 7.39 (br d, J=8.4 Hz, 2 H) 7.54 (br d, J=8.4 Hz, 2 H) 7.88 (d, J=4.3 Hz, 1 H) 11.01 (br s, 1 H)	506
264	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.73 - 1.92 (m, 4 H) 1.99 - 2.13 (m, 4 H) 2.64 - 2.73 (m, 1 H) 2.76 - 2.87 (m, 1 H) 2.96 - 3.01 (m partially hidden, 1 H) 3.06 - 3.19 (m, 3 H) 3.34 (s, 3 H) 3.54 - 3.64 (m, 1 H) 3.64 - 3.75 (m, 1 H) 4.09 - 4.31 (m, 2 H) 7.42 (br d, J=8.4 Hz, 2 H) 7.56 (br d, J=8.4 Hz, 2 H) 7.91 (d, J=4.3 Hz, 1 H) 11.04 (br s, 1 H)	506
265	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.54 - 1.67 (m, 1 H) 1.70 - 1.81 (m, 1 H) 1.83 - 1.93 (m, 3 H) 1.99 - 2.16 (m, 3 H) 2.73 - 2.88 (m, 2 H) 2.94 - 3.00 (m partially hidden, 1 H) 3.00 - 3.12 (m, 2 H) 3.29 (s, 3 H) 3.31 - 3.40 (m, 2 H) 3.67 - 3.76 (m, 1 H) 4.10 - 4.29 (m, 2 H) 7.39 (br d, J=8.4 Hz, 2 H) 7.55 (br d, J=8.4 Hz, 2 H) 7.90 (d, J=4.3 Hz, 1 H) 11.09 (br s, 1 H)	506
266	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.55 - 1.67 (m, 1 H) 1.70 - 1.81 (m, 1 H) 1.83 - 1.94 (m, 3 H) 1.99 - 2.16 (m, 3 H) 2.73 - 2.88 (m, 2 H) 2.95 - 2.99 (m partially hidden, 1 H) 3.02 - 3.12 (m, 2 H) 3.29 (s, 3 H) 3.30 - 3.40 (m, 2 H) 3.67 - 3.76 (m, 1 H) 4.11 - 4.31 (m, 2 H) 7.39 (br d, J=8.4 Hz, 2 H) 7.55 (br d, J=8.4 Hz, 2 H) 7.90 (d, J=4.3 Hz, 1 H) 11.09 (br s, 1 H)	506

267	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.54 - 1.67 (m, 1 H) 1.69 - 1.80 (m, 1 H) 1.83 - 1.94 (m, 3 H) 1.98 - 2.16 (m, 3 H) 2.73 - 2.89 (m, 2 H) 2.94 - 3.00 (m partially hidden, 1 H) 3.00 - 3.12 (m, 2 H) 3.26 - 3.42 (m, 2 H) 3.30 (s, 3 H) 3.65 - 3.74 (m, 1 H) 4.19 (br d, J=12.7 Hz, 2 H) 5.34 (br s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.88 (d, J=4.3 Hz, 1 H) 11.07 (br s, 1 H)	521
268	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.78 - 1.89 (m, 2 H) 1.91 - 2.07 (m, 2 H) 2.66 - 2.73 (m, 1 H) 2.98 - 3.20 (m, 4 H) 3.44 - 3.60 (m, 3 H) 3.89 - 4.00 (m, 2 H) 4.03 - 4.10 (m, 1 H) 4.11 - 4.28 (m, 2 H) 7.39 (br d, J=8.4 Hz, 2 H) 7.54 (br d, J=8.4 Hz, 2 H) 7.91 (d, J=3.8 Hz, 1 H) 11.14 (br s, 1 H)	490
269	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.83 (br d, J=12.7 Hz, 2 H) 1.93 - 2.05 (m, 2 H) 2.05 - 2.14 (m, 2 H) 2.89 - 3.01 (m partially hidden, 4 H) 3.08 (s, 3 H) 3.40 (t, J=6.1 Hz, 2 H) 4.00 - 4.09 (m, 1 H) 4.09 - 4.28 (m, 2 H) 7.38 (br d, J=8.4 Hz, 2 H) 7.54 (br d, J=8.4 Hz, 2 H) 8.03 (d, J=4.1 Hz, 1 H) 11.62 - 11.87 (m, 1 H)	505
270	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.85 (br d, J=12.7 Hz, 2 H) 1.93 - 2.07 (m, 2 H) 2.26 - 2.37 (m, 2 H) 2.90 - 2.96 (m partially hidden, 2 H) 3.13 (br t, J=12.7 Hz, 2 H) 3.32 - 3.41 (m, 1 H) 3.39 - 3.50 (m, 2 H) 4.04 - 4.28 (m, 2 H) 7.39 (br d, J=8.4 Hz, 2 H) 7.54 (br d, J=8.4 Hz, 2 H) 7.96 (d, J=4.3 Hz, 1 H) 11.16 - 11.35 (m, 1 H)	498
271	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.81 - 1.89 (m, 2 H) 1.90 - 2.03 (m, 2 H) 2.17 - 2.29 (m, 4 H) 2.88 - 2.91 (m partially hidden, 2 H) 3.05 (br t, J=12.7 Hz, 2 H) 3.62 - 3.72 (m, 1 H) 4.14 (br d, J=12.7 Hz, 2 H) 5.32 (br s, 2 H) 6.48 (br d, J=8.4 Hz, 1 H) 6.67 (br s, 1 H) 7.12 (d, J=8.4 Hz, 1 H) 7.96 (d, J=4.3 Hz, 1 H) 8.70 (br s, 1 H) 11.30 (br s, 1 H)	506
272	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.40 - 1.53 (m, 1 H) 1.71 - 2.10 (m, 9 H) 2.63 - 2.77 (m, 2 H) 3.00 - 3.20 (m, 4 H) 3.44 (tt, J=12.1, 3.5 Hz, 1 H) 4.20 (br d, J=12.8 Hz, 2 H) 5.36 (s, 2 H) 6.47 - 6.56 (m, 1 H) 6.72 (br s, 1 H) 7.14 (d, J=8.4 Hz, 1 H) 7.88 (d, J=4.1 Hz, 1 H) 10.98 (br s, 1 H)	503

273	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.40 - 1.53 (m, 1 H) 1.71 - 2.11 (m, 9 H) 2.62 - 2.76 (m, 2 H) 3.01 - 3.22 (m, 4 H) 3.38 - 3.51 (m, 1 H) 4.01 - 4.39 (m, 2 H) 7.42 (br d, J=8.6 Hz, 2 H) 7.56 (br d, J=8.6 Hz, 2 H) 7.89 (d, J=4.1 Hz, 1 H) 10.97 (br s, 1 H)	488
274	SCHEME 1 +acetal deprotection + reductive amination + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.54 - 1.67 (m, 1 H) 1.75 - 2.12 (m, 5 H) 2.54 - 2.60 (m, 1 H) 2.69 - 2.82 (m, 2 H) 2.93 - 2.95 (m partially hidden, 1 H) 3.00 - 3.14 (m, 3 H) 3.45 - 3.56 (m, 1 H) 4.03 - 4.13 (m, 1 H) 4.14 - 4.30 (m, 2 H) 4.36 (td, J=6.2, 2.3 Hz, 2 H) 4.68 (t, J=6.6 Hz, 2 H) 7.39 (br d, J=8.4 Hz, 2 H) 7.55 (br d, J=8.4 Hz, 2 H) 7.88 (d, J=4.1 Hz, 1 H) 10.95 (br s, 1 H)	533
275	SCHEME 1 +acetal deprotection + reductive amination + chiral separatoin	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.55 - 1.66 (m, 1 H) 1.77 - 2.09 (m, 5 H) 2.23 - 2.40 (m, 1 H) 2.54 - 2.61 (m, 1 H) 2.68 - 2.82 (m, 2 H) 2.93 - 2.98 (m partially hidden, 1 H) 3.01 - 3.14 (m, 3 H) 3.45 - 3.57 (m, 1 H) 4.05 - 4.14 (m, 1 H) 4.14 - 4.28 (m, 2 H) 4.36 (td, J=6.2, 2.3 Hz, 2 H) 4.69 (t, J=6.6 Hz, 2 H) 7.39 (br d, J=8.4 Hz, 2 H) 7.55 (br d, J=8.4 Hz, 2 H) 7.88 (d, J=4.1 Hz, 1 H) 10.94 (br s, 1 H)	533
276	SCHEME 1 +acetal deprotection + reductive amination	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 0.19 - 0.33 (m, 2 H) 0.37 - 0.49 (m, 2 H) 1.60 - 1.73 (m, 1 H) 1.79 - 1.92 (m, 2 H) 1.94 - 2.16 (m, 3 H) 2.21 (tt, J=6.7, 3.5 Hz, 1 H) 2.60 - 2.84 (m, 3 H) 3.00 - 3.12 (m, 3 H) 3.17 (dd, J=14.7, 4.8 Hz, 1 H) 3.47 - 3.62 (m, 1 H) 4.06 - 4.29 (m, 2 H) 7.39 (br d, J=8.5 Hz, 2 H) 7.54 (br d, J=8.5 Hz, 2 H) 7.88 (d, J=4.1 Hz, 1 H) 10.93 (br s, 1 H)	517
277	SCHEME 1 + OTBS deprotection	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.59 - 1.78 (m, 2 H) 1.81 - 1.95 (m, 2 H) 1.98 - 2.14 (m, 4 H) 2.61 - 2.86 (m, 2 H) 2.92 - 3.04 (m partially hidden, 1 H) 3.05 - 3.27 (m, 3 H) 3.62 - 3.78 (m, 1 H) 3.87 - 3.98 (m, 1 H) 4.20 (br d, J=12.0 Hz, 2 H) 4.24 (br d, J=3.6 Hz, 1 H) 5.36 (br s, 2 H) 6.49 - 6.55 (m, 1 H) 6.68 - 6.73 (m, 1 H) 7.14 (d, J=8.4 Hz, 1 H) 7.89 (d, J=4.1 Hz, 1 H) 11.02 (br s, 1 H)	507
278	SCHEME 1 +acetal deprotection + ketone reduction	¹ H NMR (400 MHz, DMSO-d ₆ , 30°C) δ ppm 1.69 - 2.11 (m, 6 H) 2.65 - 2.84 (m, 3 H) 2.84 - 3.23 (m, 3 H) 3.46 - 3.56 (m, 1 H) 3.56 - 3.90 (m, 1 H) 3.96 - 4.06 (m, 1 H) 4.48 - 4.82 (m, 1 H) 4.84 (d, J=4.0 Hz, 1 H) 7.46 (br d, J=8.8 Hz, 2 H) 7.58 (br d, J=8.8 Hz, 2 H) 7.94 (d, J=4.0 Hz, 1 H) 11.32 (s, 1 H)	478

279	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.80 (br d, J=12.5 Hz, 2 H) 1.87 - 2.03 (m, 2 H) 2.07 (t, J=7.1 Hz, 2 H) 2.90 - 3.03 (m partially hidden, 4 H) 3.04 - 3.19 (m, 2 H) 3.37 (tt, J=12.1, 3.7 Hz, 1 H) 3.63 - 3.75 (m, 2 H) 3.85 - 3.95 (m, 2 H) 4.03 - 4.34 (m, 2 H) 7.40 (br d, J=8.8 Hz, 2 H) 7.55 (br d, J=8.8 Hz, 2 H) 7.91 (d, J=3.4 Hz, 1 H) 11.18 (br s, 1 H)	504
280	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.80 (br d, J=12.8 Hz, 2 H) 1.87 - 2.01 (m, 2 H) 2.06 (t, J=7.1 Hz, 2 H) 2.85 - 3.02 (m partially hidden, 4 H) 3.08 (br t, J=12.8 Hz, 2 H) 3.34 (tt, J=12.2, 3.9 Hz, 1 H) 3.68 (s, 2 H) 3.81 - 3.98 (m, 2 H) 4.10 - 4.25 (m, 2 H) 5.35 (br s, 2 H) 6.49 (br dd, J=8.4, 1.0 Hz, 1 H) 6.69 (br d, J=1.0 Hz, 1 H) 7.13 (d, J=8.4 Hz, 1 H) 7.90 (d, J=3.4 Hz, 1 H) 11.17 (br s, 1 H)	519
281	SCHEME 1 + boc deprotection	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.81 - 1.91 (m, 2 H) 1.95 - 2.13 (m, 2 H) 2.14 - 2.32 (m, 1 H) 2.60 - 2.73 (m, 3 H) 3.00 - 3.17 (m, 4 H) 3.19 - 3.41 (m, 3 H) 3.72 - 3.79 (m, 1 H) 4.14 - 4.35 (m, 2 H) 7.42 (br d, J=8.6 Hz, 2 H) 7.57 (br d, J=8.6 Hz, 2 H) 7.91 (d, J=3.9 Hz, 1 H) 11.07 (br s, 1 H)	489
282	SCHEME 1 + OTBS deprotection	¹ H NMR (400 MHz, DMSO-d ₆ , 30°C) δ ppm 1.48 - 1.70 (m, 2 H) 1.72 - 2.15 (m, 6 H) 2.57 - 2.77 (m, 2 H) 2.83 - 3.44 (m partially hidden, 4 H) 3.53 - 3.81 (m, 2 H) 3.83 - 3.99 (m, 1 H) 4.47 - 4.85 (m, 1 H) 4.63 (d, J=4.1 Hz, 1 H) 7.47 (br d, J=8.6 Hz, 2 H) 7.57 (br d, J=8.6 Hz, 2 H) 7.93 (d, J=4.1 Hz, 1 H) 11.38 (br s, 1 H)	492
283	SCHEME 1 + boc deprotection	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.84 (br d, J=12.8 Hz, 2 H) 1.90 - 2.09 (m, 4 H) 2.73 - 3.24 (m, 10 H) 3.33 - 3.47 (m, 1 H) 4.04 - 4.49 (m, 2 H) 7.42 (br d, J=8.6 Hz, 2 H) 7.58 (br d, J=8.6 Hz, 2 H) 7.93 (d, J=3.4 Hz, 1 H) 11.19 (br s, 1 H)	503
284	SCHEME 7	¹ H NMR (500 MHz, DMSO) δ 11.17 (s, 1H), 7.98 (d, J = 5.0 Hz, 1H), 7.15 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 5.0 Hz, 1H), 6.65 (s, 1H), 6.49 (d, J = 9.0 Hz, 1H), 5.59 (d, J = 8.8 Hz, 2H), 3.72 (d, J = 5.3 Hz, 1H), 3.38 (t, J = 11.8 Hz, 1H), 3.33 (s, 3H), 3.32 - 3.25 (m, 2H), 3.24 - 2.79 (m, 5H), 2.65 (dd, J = 16.5, 6.4 Hz, 1H), 2.05 (dd, J = 13.6, 7.8 Hz, 1H), 1.89 - 1.78 (m, 3H), 1.71 (s, 2H)	489.1

285	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.81 - 1.90 (m, 2 H) 1.95 - 2.11 (m, 2 H) 2.36 - 2.43 (m, 2 H) 2.90 - 2.93 (partially hidden m, 2 H) 3.11 (br t, J=12.5 Hz, 2 H) 3.67 (tt, J=11.8, 3.5 Hz, 1 H) 3.73 - 3.79 (m, 2 H) 4.03 - 4.31 (m, 2 H) 5.82 - 5.91 (m, 2 H) 7.39 (br d, J=8.4 Hz, 2 H) 7.54 (br d, J=8.4 Hz, 2 H) 7.90 (d, J=4.3 Hz, 1 H) 10.97 - 11.06 (m, 1 H)	474
286	SCHEME 1	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.25 - 1.40 (m, 2 H) 1.44 - 1.55 (m, 2 H) 1.62 - 1.80 (m, 4 H) 1.81 - 1.93 (m, 2 H) 1.98 - 2.19 (m, 2 H) 2.80 - 2.89 (m, 2 H) 2.91 - 3.00 (partially hidden m, 2 H) 3.09 (br t, J=12.8 Hz, 2 H) 3.61 (tt, J=12.2, 3.5 Hz, 1 H) 4.13 - 4.36 (m, 2 H) 7.42 (br d, J=8.5 Hz, 2 H) 7.58 (br d, J=8.5 Hz, 2 H) 7.93 (d, J=4.3 Hz, 1 H) 10.98 - 11.11 (m, 1 H)	490
287	SCHEME 1 + chiral separation	¹ H NMR (400 MHz, DMSO-d ₆ , 100°C) δ ppm 1.39 - 1.49 (m, 1 H) 1.67 - 2.05 (m, 9 H) 2.61 - 2.71 (m, 2 H) 2.98 - 3.09 (m, 2 H) 3.09 - 3.17 (m, 2 H) 3.36 - 3.45 (m, 1 H) 4.16 (br d, J=12.7 Hz, 2 H) 5.33 (br s, 2 H) 6.49 (br d, J=8.4 Hz, 1 H) 6.68 (br s, 1 H) 7.11 (br d, J=8.4 Hz, 1 H) 7.85 (br d, J=3.4 Hz, 1 H) 10.95 (br s, 1 H)	503
288	Scheme 1 + 3 additional steps: 1) acetal deprotection (see step 2 of Examples 144-147); 2) MeMgBr addition; 3) chiral separation	¹ H NMR (400 MHz, DMSO-d ₆) δ (ppm): 11.31 (s, 1H), 7.90 (d, J = 4.1 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 6.66 (s, 1H), 6.50 (d, J = 8.2 Hz, 1H), 5.58 (s, 2H), 4.37 (s, 1H), 4.10 (br s, 1H), 3.67 - 3.54 (m, 1H), 3.16 - 2.86 (m, 4H), 2.86 - 2.75 (m, 1H), 2.64 - 2.56 (m, 1H), 2.04 - 1.67 (m, 9H), 1.22 (s, 3H).	521.3
289	Scheme 1 + 3 additional steps: 1) acetal deprotection (see step 2 of Examples 144-147); 2) MeMgBr addition; 3) chiral separation	¹ H NMR (400 MHz, DMSO-d ₆) δ (ppm): 11.32 (s, 1H), 7.91 (d, J = 4.1 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 6.68 - 6.65 (m, 1H), 6.53 - 6.48 (m, 1H), 5.59 (s, 2H), 4.39 (s, 1H), 4.16 (s, 1H), 3.67 - 3.57 (m, 1H), 3.14 - 2.90 (m, 4H), 2.86 - 2.77 (m, 1H), 2.65 - 2.57 (m, 1H), 2.07 - 1.67 (m, 9H), 1.22 (s, 3H)	521.3

290	Method A	¹ H NMR (400 MHz, DMSO-d ₆) δ (ppm) 11.49 (s, 1H), 7.96 (d, <i>J</i> = 4.1 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.49 – 7.43 (m, 2H), 4.64 (br s, 1H), 3.74 – 3.56 (m, 2H), 3.43 – 3.36 (m, 1H), 3.11 – 3.04 (m, 2H), 3.00 – 2.84 (m, 3H), 2.11 – 1.74 (m, 9H).	501.2
291	Method D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ (ppm) 11.63 (s, 1H), 7.97 (d, <i>J</i> = 4.1 Hz, 1H), 7.13 (d, <i>J</i> = 8.4 Hz, 1H), 6.68 – 6.65 (m, 1H), 6.53 – 6.48 (m, 1H), 5.60 (s, 2H), 4.15 (br s, 1H), 3.66 – 3.56 (m, 1H), 3.48 – 3.39 (m, 1H), 3.38 – 3.33 (m, 1H), 3.20 – 3.02 (m, 3H), 2.92 – 2.78 (m, 2H), 2.21 – 1.78 (m, 8H), 1.71 – 1.59 (m, 1H).	516.2
292	Method D	¹ H NMR (400 MHz, DMSO-d ₆) δ (ppm) 11.49 (s, 1H), 7.95 (d, <i>J</i> = 4.1 Hz, 1H), 7.12 (d, <i>J</i> = 8.4 Hz, 1H), 6.70 – 6.64 (m, 1H), 6.55 – 6.47 (m, 1H), 5.59 (s, 2H), 4.03 (br s, 1H), 3.69 – 3.55 (m, 1H), 3.43 – 3.35 (m, 1H), 3.25 – 2.98 (m, 4H), 2.98 – 2.83 (m, 2H), 2.17 – 1.89 (m, 6H), 1.89 – 1.72 (m, 2H). One proton under the DMSO peak.	516.2
293	Scheme 1 + 3 additional steps: 1) acetal deprotection (see step 2 of Examples 144-147); 2) NaBD ₄ addition; & 3) chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ (ppm): 11.38 (s, 1H), 7.91 (d, <i>J</i> = 4.0 Hz, 1H), 7.12 (d, <i>J</i> = 8.4 Hz, 1H), 6.69 – 6.64 (m, 1H), 6.55 – 6.47 (m, 1H), 5.59 (s, 2H), 4.61 (s, 1H), 4.43 – 3.84 (br s, 1H), 3.69 – 3.58 (m, 1H), 3.17 – 2.99 (m, 3H), 2.94 – 2.84 (m, 1H), 2.77 – 2.68 (m, 1H), 2.68 – 2.57 (m, 1H), 2.06 – 1.94 (m, 4H), 1.88 – 1.78 (m, 2H), 1.67 – 1.53 (m, 2H). One proton under the DMSO peak.	508.2
294	Scheme 1 + 3 additional steps: 1) acetal deprotection (see step 2 of Examples 144-147); 2) NaBD ₄ addition; & 3) chiral separation	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ (ppm): 11.38 (s, 1H), 7.92 (d, <i>J</i> = 4.0 Hz, 1H), 7.12 (d, <i>J</i> = 8.4 Hz, 1H), 6.69 – 6.64 (m, 1H), 6.55 – 6.48 (m, 1H), 5.59 (s, 2H), 4.61 (s, 1H), 4.43 – 3.92 (br s, 1H), 3.70 – 3.58 (m, 1H), 3.20 – 2.99 (m, 3H), 2.94 – 2.84 (m, 1H), 2.77 – 2.68 (m, 1H), 2.66 – 2.58 (m, 1H), 2.07 – 1.95 (m, 4H), 1.84 (s, 2H), 1.67 – 1.53 (m, 2H). One proton under the DMSO peak.	508.2

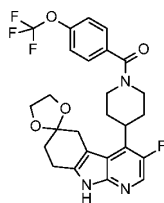
Preparation Methods

- Compounds of the disclosure can be prepared according to Methods A to J below (see also Table 1b above). Each of those synthetic methods is illustrated by reference to the preparation of one or more specific compounds of the disclosure. The skilled person will appreciate how features of the various synthetic steps (e.g., reactants, reagents, and conditions) shown in the illustrative examples may be adapted when preparing other compounds in accordance with the disclosure, in particular in light of the general synthetic schemes provided above.

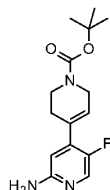
METHOD A

- 10 Method A is illustrated by the preparation of Example 56. Method A contains steps which are found, e.g., in Scheme 1 above.

Example 56: [4-(3-fluoro-5,7,8,9-tetrahydrospiro[pyrido[2,3-b]indole-6,2'-[1,3]dioxolan]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



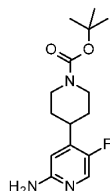
- 15 **STEP 1:** tert-butyl 4-(2-amino-5-fluoro-4-pyridyl)-3,6-dihydro-2H-pyridine-1-carboxylate



- To a solution of 5-fluoro-4-iodopyridin-2-amine (20 g, 84.03 mmol) in 1,4-dioxane (1 L) and water (110 mL) at room temperature, were added N-BOC-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (31.18 g, 100.84 mmol) and potassium phosphate tribasic (53.512 g, 252.1 mmol). Then, the whole mixture was bubbled with argon for 15 minutes. 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (3.43 g, 4.2 mmol) was then added and the whole mixture was refluxed under argon atmosphere for 12 hours. After 12 hours, the reaction mixture was cooled down to room temperature, 250 mL of ethyl acetate and 250 mL of water, were added to the reaction mixture. The organic layer was then washed twice with water (2x250 mL), twice with brine (2x250 mL), dried over

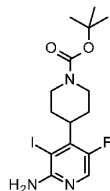
magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 800 g) eluting with a 75/25 mixture of heptane / ethyl acetate to give 17.93 g (72.7% yield) of tert-butyl 4-(2-amino-5-fluoro-4-pyridyl)-3,6-dihydro-2H-pyridine-1-carboxylate as a solid. LC/MS (m/z, M+H): calc. 294.2, found 294.2.

5 **STEP 2:** tert-butyl 4-(2-amino-5-fluoro-4-pyridyl)piperidine-1-carboxylate



To a solution of tert-butyl 4-(2-amino-5-fluoro-4-pyridyl)-3,6-dihydro-2H-pyridine-1-carboxylate (13 g, 44.3 mmol) in THF (47 mL) and EtOH (135 mL) was added Pd/C (10% wet, 2.36 g, 2.22 mmol). The whole mixture was then submitted to hydrogenation with 5 bars of H₂ at 40 °C for 1.5 hours. The whole mixture was then cooled down to room temperature, filtered on clarcel, washed with EtOH (50 mL), THF (40 mL). The resulting filtrate was concentrated in vacuo to give a light brown solid. This latter was then triturated in pentane (100 mL), filtered and dried under vacuum for 12 hours to give 12.68 g (96.9% yield) of tert-butyl 4-(2-amino-5-fluoro-4-pyridyl)piperidine-1-carboxylate as a light brown solid. LC/MS (m/z, M+H): calc. 296.2, found 296.4.

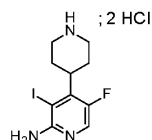
STEP 3: tert-butyl 4-(2-amino-5-fluoro-3-iodo-4-pyridyl)piperidine-1-carboxylate



To a solution of tert-butyl 4-(2-amino-5-fluoro-4-pyridyl)piperidine-1-carboxylate (14.5 g, 49.1 mmol) in solution with DMF (290 mL) was added portionwise NIS (33.1 g, 147 mmol) followed by TFA (22.7 mL, 295 mmol) and the resulting mixture was stirred at room temperature for 48 hours. After 48 hours, the whole mixture was poured in 1.8 L of an aqueous saturated solution of NaHSO₃. 600 mL of ethyl acetate were then added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2x600 mL). The combined organic layers were then washed with water (500 mL), brine (300 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 330 g) eluting with a 95/5 to 60/40 mixture of

heptane/ethyl acetate to give 13.1 g (63.5% yield) of tert-butyl 4-(2-amino-5-fluoro-3-iodo-4-pyridyl)piperidine-1-carboxylate as a light pink solid. LC/MS (m/z, M+H): calc. 422.1, found 422.3.

STEP 4: 5-fluoro-3-iodo-4-(4-piperidyl)pyridin-2-amine, dihydrochloride

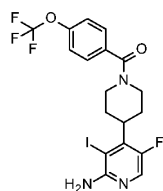


5

Tert-butyl 4-(2-amino-5-fluoro-3-iodo-4-pyridyl)piperidine-1-carboxylate (1.14 g, 2.71 mmol) was dissolved in 10 mL of a 5/6 M HCl solution in isopropanol and stirred for 4 hours at room temperature. After 4 hours, the whole mixture was concentrated to dryness to give 1.07 g (100% yield) of 5-fluoro-3-iodo-4-(4-piperidyl)pyridin-2-amine, dihydrochloride as a solid. LC/MS (m/z, M+ -2 HCl): calc. 321.0, found 321.0.

10

STEP 5: [4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



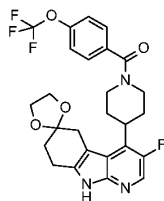
To a solution of 5-fluoro-3-iodo-4-(4-piperidyl)pyridin-2-amine, dihydrochloride (9.35 g, 23.7 mmol) in DMF (95 mL), was added 4-(trifluoromethoxy)benzoic acid (4.89 g, 23.7 mmol) followed by 16.5 mL of DIPEA (94.9 mmol) and TBTU (8.38 g, 26.1 mmol) portionwise. The whole mixture was stirred for 60 minutes. After 60 minutes, ethyl acetate and water were added to the mixture. The organic layer was then washed with a saturated aqueous solution of NaHCO₃, with brine three times, and the combined aqueous layers were extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting orange residue was triturated in diisopropyl ether, filtered, to give 11.232 g (93% yield) of [4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a pale brown solid. LC/MS (m/z, M+): calc. 509.0, found 509.0.

15

20

STEP 6: [4-(3-fluoro-5,7,8,9-tetrahydrospiro[pyrido[2,3-b]indole-6,2'-[1,3]dioxolan]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

25

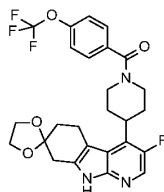


- Under argon atmosphere, to a solution of [4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (590 mg, 1.16 mmol) in DMF (2.5 mL), were successively added 1,4-diazabicyclo[2.2.2]octane (384 mg, 3.42 mmol), 1,4-
- 5 dioxaspiro[4.5]decan-8-one (310 mg, 1.98 mmol) and a solution of bis(tri-tert-butylphosphine)palladium(0) (29 mg, 0.056 mmol) in DMF (2 mL). The whole mixture was then stirred at 170 °C (bath temperature), DMF (3 mL) was added, and the mixture was stirred at this temperature for 12 hours, followed by 24 hours at room temperature. The reaction was then diluted with ethyl acetate, washed 3 times with water and the combined
- 10 aqueous layers were extracted with ethyl acetate. The combined organic layers were then washed with water, dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was then purified by flash chromatography on silica gel (SiO₂ 120 g) eluting with a 50/50 to 0/100 mixture of heptane / ethyl acetate to give 439 mg (72.9% yield) of [4-(3-fluoro-5,7,8,9-tetrahydrospiro[pyrido[2,3-b]indole-6,2'-[1,3]dioxolan]-4-yl)-1-piperidyl]-
- 15 [4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M+H): calc. 520.2, found 520.4.

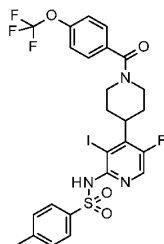
METHOD B

Method B is illustrated by the preparation of Example 15. Method B contains steps which are found, e.g., in Scheme 2A above.

- 20 **Example 15:** [4-(3-fluoro-5,6,8,9-tetrahydrospiro[pyrido[2,3-b]indole-7,2'-dioxolan]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

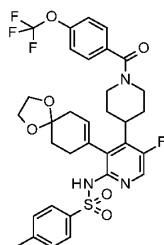


STEP 1: N-[5-fluoro-3-iodo-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-2-pyridyl]-4-methyl-benzenesulfonamide



At 0 °C, under argon atmosphere, to a solution of [4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (described in STEP 5 of Example 56) (1120 mg, 2.2 mmol) in THF (15 mL) was added sodium hydride (60% dispersion in oil, 176 mg, 4.4 mmol) and the resulting mixture was stirred at 0 °C, for 30 minutes. After 30 minutes, para-toluenesulfonyl chloride (503 mg, 2.64 mmol) was added and the resulting reaction mixture was stirred for 48 hours at room temperature. After 48 hours, the reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was then purified by flash chromatography on silica gel (SiO₂ 70 g) eluting with a 100/0 to 0/100 mixture of DCM / [heptane/ethyl acetate 50/50] to give 290 mg (20% yield) of N-[5-fluoro-3-iodo-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-2-pyridyl]-4-methyl-benzenesulfonamide as a white solid. LC/MS (m/z, M+H): calc. 664.0, found 664.1.

STEP 2: N-[3-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-5-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-2-pyridyl]-4-methyl-benzenesulfonamide

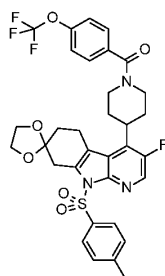


In a 2-5 mL microwave vial, to a solution of N-[5-fluoro-3-iodo-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-2-pyridyl]-4-methyl-benzenesulfonamide (290 mg, 0.44 mmol) in DMF (2.5 mL) and water (1.25 mL), bubbled with argon, were successively added potassium carbonate (242 mg, 1.75 mmol), dichlorobis(triphenylphosphine)palladium(II) (31 mg, 0.044 mmol) and 4,4,5,5-tetramethyl-2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1,3,2-dioxaborolane (140 mg, 0.52 mmol). The vial was sealed and submitted to microwave irradiation at 80 °C for 45 minutes. After 45 minutes, the reaction mixture was cooled down to room temperature, the vial was opened, the reaction mixture diluted with ethyl acetate and an aqueous saturated solution of NaHCO₃. The organic

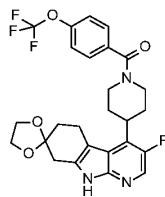
layer was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was then purified by flash chromatography on silica gel (SiO₂ 25 g) eluting with a 100/0 to 0/100 mixture of DCM / [heptane/ethyl acetate 50/50] to give 255 mg (86% yield) of N-[3-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-5-fluoro-4-[1-[4-

- 5 (trifluoromethoxy)benzoyl]-4-piperidyl]-2-pyridyl]-4-methyl-benzenesulfonamide as a white solid. LC/MS (m/z, M+H): calc. 676.2, found 676.3.

STEP 3: [4-[3'-fluoro-9'-(p-tolylsulfonyl)spiro[1,3-dioxolane-2,7'-6,8-dihydro-5H-pyrido[2,3-b]indole]-4'-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



- 10 At room temperature, under argon atmosphere, to a solution of N-[3-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-5-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-2-pyridyl]-4-methyl-benzenesulfonamide (255 mg, 0.38 mmol) in THF (1.3 mL) and some drops of acetonitrile. The reaction mixture was heated at 50 °C for complete dissolution, then cooled down to room temperature and a solution of [bis(trifluoroacetoxy)iodo]benzene (125 µL, 0.57 mmol) in
- 15 THF (1.3 mL) was slowly added and the resulting reaction mixture was stirred at room temperature for 45 minutes. After 45 minutes, the whole mixture was concentrated in vacuo, and the resulting residue was poured in an aqueous saturated solution of NaHCO₃, extracted three times with DCM. The combined organic layers were then dried over magnesium sulfate; filtered and concentrated. The resulting residue was purified by flash chromatography
- 20 on silica gel (SiO₂ 25 g) eluting with a mixture of Heptane / [heptane/AcOEt 50/50] from 100/0 to 0/100, to give 167 mg (65% yield) of [4-[3'-fluoro-9'-(p-tolylsulfonyl)spiro[1,3-dioxolane-2,7'-6,8-dihydro-5H-pyrido[2,3-b]indole]-4'-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 674.2, found 674.3.
- 25 **STEP 4:** [4-(3-fluoro-5,6,8,9-tetrahydrospiro[pyrido[2,3-b]indole-7,2'-dioxolan]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

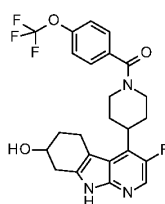


- At room temperature, under argon atmosphere, to a solution of 4-[3'-fluoro-9'-(p-tolylsulfonyl)spiro[1,3-dioxolane-2,7'-6,8-dihydro-5H-pyrido[2,3-b]indole]-4'-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (167 mg, 0.25 mmol) in ethanol (0.5 mL) was added sodium hydroxide (30 mg, 0.74 mmol). The resulting mixture was then stirred at 80 °C for 45 minutes. After 45 minutes, the whole mixture was cooled down to room temperature, concentrated to dryness, diluted with AcOEt and water. The aqueous layer was extracted three times with AcOEt, and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 4 g) eluting with a mixture of DCM / [DCM/MeOH 90/10] from 100/0 to 0/100, to give 88 mg (68% yield) of [4-(3-fluoro-5,6,8,9-tetrahydrospiro[pyrido[2,3-b]indole-7,2'-dioxolan]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M⁺): calc. 519.2, found 519.0.

15 **METHOD C**

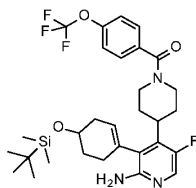
Method C is illustrated by the preparation of Examples 3, 4, 5, and 6. Method C contains steps which are found, e.g., in Scheme 2 above.

Example 3: (rac)-[4-(3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



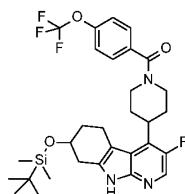
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STEP 1: (rac)-[4-[2-amino-3-[4-[tert-butyl(dimethyl)silyl]oxycyclohexen-1-yl]-5-fluoro-4-pyridyl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



- In a 10-20 mL microwave vial, a solution of [4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (500 mg, 0.98 mmol, prepared as described in step 5 of Example 56) in DMF / water (6 mL / 3 mL) was bubbled with argon for 5 minutes. Then, were successively added potassium carbonate (543 mg, 3.93 mmol), dichlorobis(triphenylphosphine)palladium(II) (69 mg, 0.098 mmol) and (rac)-tert-butyl(dimethyl)[(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)oxy]silane (399 mg, 1.18 mmol). The vial was sealed and submitted to microwaves for 60 minutes at 80 °C. After 60 minutes, the reaction mixture was cooled down to room temperature, the diluted with ethyl acetate and a saturated aqueous solution of NaHCO₃. The organic layer was then washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography (SiO₂ 70 g) eluting with a mixture of Heptane / [Heptane/AcOEt/MeOH 85/10/5] from a 100 / 0 to 0 / 100 ratio, to give 415 mg (71 % yield) of (rac)-[4-[2-amino-3-[4-[tert-butyl(dimethyl)silyl]oxycyclohexen-1-yl]-5-fluoro-4-pyridyl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a pale brown solid. LC/MS (m/z, M+H): calc. 594.3, found 594.4.

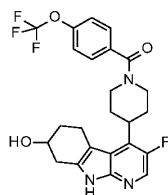
STEP 2: (rac)-[4-[7-[tert-butyl(dimethyl)silyl]oxy-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



- (rac)-[4-[7-[tert-butyl(dimethyl)silyl]oxy-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone was prepared following the protocol described in STEP 3 of Example 15, using 415 mg (0.7 mmol) of (rac)-[4-[2-amino-3-[4-[tert-butyl(dimethyl)silyl]oxycyclohexen-1-yl]-5-fluoro-4-pyridyl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone to give 100 mg (21% yield) of (rac)-[4-[7-[tert-butyl(dimethyl)silyl]oxy-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 592.2, found 592.3.

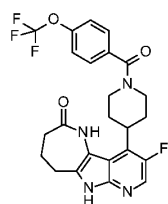
STEP 3: (rac)-[4-(3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-

piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



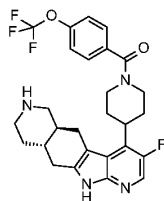
- To a solution of (rac)-[4-[7-[tert-butyl(dimethyl)silyl]oxy-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (100 mg, 0.17 mmol) in Methanol / DCM (1 mL / 1 mL), was added 0.42 mL of a 4 N solution of HCl in dioxane (0.17 mmol). The resulting mixture was stirred at room temperature for 12 hours, then concentrated to dryness and the resulting residue was purified by flash chromatography on silica gel (SiO₂ 9 g) eluting with a mixture of DCM / [DCM/MeOH (NH₃ 7N) 90 / 10] from 100 / 0 to 0/100, to give 55 mg (68% yield) of (rac)-[4-(3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 478.2, found 478.2.

Example 4: 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,14-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-13-one

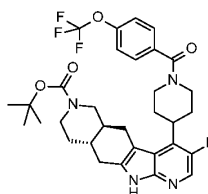


- 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,14-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-13-one was prepared following the protocol described in step 6 of example 56 using [4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (100 mg, 0.19 mmol, described in step 5 of Example 56) and azepane-2,6-dione (83 mg, 0.59 mmol) to give 20 mg (20% yield) of 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,14-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-13-one as a white solid. LC/MS (m/z, M+H): calc. 491.4, found 491.2.

Example 5: (rac)-trans-[4-[13-fluoro-6,15,17-triazatetracyclo[8.7.0.0^{3,8}.0^{11,16}]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

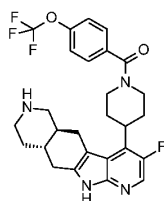


STEP 1: (rac)-trans-tert-butyl (13-fluoro-12-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,15,17-triazatetracyclo[8.7.0.0.3,8.0.11,16]heptadeca-1(10),11,13,15-tetraene-6-carboxylate



- 5 (rac)-trans-tert-butyl- 13-fluoro-12-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,15,17-triazatetracyclo[8.7.0.0.3,8.0.11,16]heptadeca-1(10),11,13,15-tetraene-6-carboxylate was prepared following the protocol described in step 6 of Example 56 using [4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (350 mg, 0.69 mmol, described in step 5 of Example 56) and (rac)-trans-N-Boc-octahydroisquinolin-6-one
- 10 (522 mg, 2.06 mmol) to give 258 mg (55% yield) of (rac)-trans-tert-butyl (13-fluoro-12-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,15,17-triazatetracyclo[8.7.0.0.3,8.0.11,16]heptadeca-1(10),11,13,15-tetraene-6-carboxylate as a white solid. LC/MS (m/z, M+H): calc. 617.6, found 617.4.

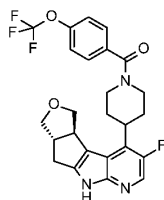
STEP 2: (rac)-trans-[4-[13-fluoro-6,15,17-triazatetracyclo[8.7.0.0.3,8.0.11,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



- To a solution of (rac)-trans-tert-butyl (13-fluoro-12-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,15,17-triazatetracyclo[8.7.0.0.3,8.0.11,16]heptadeca-1(10),11,13,15-tetraene-6-carboxylate (265 mg, 0.43 mmol) in MeOH (2 mL), was added a 4 N HCl solution in dioxane
- 20 (1.07 mL, 4.3 mmol). The resulting mixture was stirred at room temperature for 4 hours, then concentrated to dryness, diluted with 2 mL of a 7 N solution of NH₃ in MeOH. Silica gel was added to the mixture which was concentrated and the resulting residue was purified by flash chromatography on silica gel (SiO₂ 12 g) eluting with DCM / MeOH / NH₄OH 90/10/1, to give 212 mg (95% yield) of (rac)-trans-[4-[13-fluoro-6,15,17-
- 25 triazatetracyclo[8.7.0.0.3,8.0.11,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-

(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z , M^+): calc. 517.2, found 517.0.

Example 6: (rac)-trans-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.0.11,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



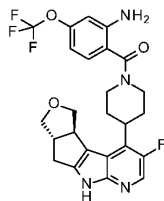
5

(rac)-trans-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.0.11,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone was prepared following the protocol described in step 6 of Example 56 using [4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (300 mg, 0.59 mmol, described in step 10 5 of Example 56) and trans-hexahydro-1H-cyclopenta[c]furan-5-one (223 mg, 1.77 mmol) to give 166 mg (57% yield) of (rac)-trans-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.0.11,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a grey solid. LC/MS (m/z , M^+): calc. 489.2, found 489.0.

15 **METHOD D**

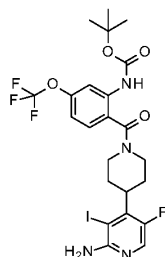
Method D is illustrated by the preparation of Examples 7, 46, 8, and 9. Method D contains steps which are found, e.g., in Scheme 1 above.

Example 7: (rac)-trans-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.0.11,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone



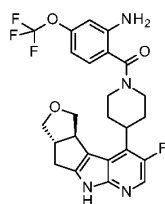
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STEP 1: tert-butyl N-[2-[4-(2-amino-5-fluoro-3-iodo-4-pyridyl)piperidine-1-carbonyl]-5-(trifluoromethoxy)phenyl]carbamate



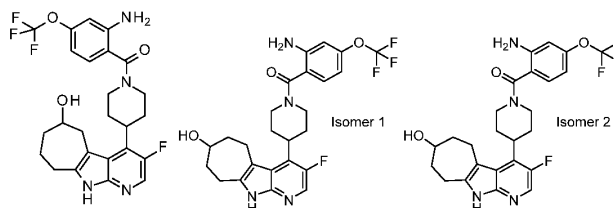
tert-butyl N-[2-[4-(2-amino-5-fluoro-3-iodo-4-pyridyl)piperidine-1-carbonyl]-5-(trifluoromethoxy)phenyl]carbamate was prepared following the protocol described in step 5 of example 56 using 5-fluoro-3-iodo-4-(4-piperidyl)pyridin-2-amine, dihydrochloride (9.35 g, 23.7 mmol, described in step 4 of Example 56) and 2-(tert-butoxycarbonylamino)-4-(trifluoromethoxy)benzoic acid (7.62 g, 23.7 mmol) to give 13.207 g (89% yield) of tert-butyl N-[2-[4-(2-amino-5-fluoro-3-iodo-4-pyridyl)piperidine-1-carbonyl]-5-(trifluoromethoxy)phenyl]carbamate as pale brown solid. LC/MS (m/z, M⁺): calc. 624.1, found 624.0.

10 **STEP 2:** (rac)-trans-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0^{2,7}.1^{1,15}]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone

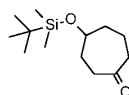


(rac)-trans-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0^{2,7}.1^{1,15}]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone was prepared following the protocol described in step 6 of Example 56 using tert-butyl N-[2-[4-(2-amino-5-fluoro-3-iodo-4-pyridyl)piperidine-1-carbonyl]-5-(trifluoromethoxy)phenyl]carbamate (350 mg, 0.56 mmol) and (rac)-trans-hexahydro-1H-cyclopenta[c]furan-5-one (212 mg, 1.68 mmol) to give 125 mg (44% yield) of (rac)-trans-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0^{2,7}.1^{1,15}]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone as a pale brown solid. LC/MS (m/z, M⁺): calc. 504.2, found 504.0.

Examples 46, 8 & 9: (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone, and [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomers 1 & 2

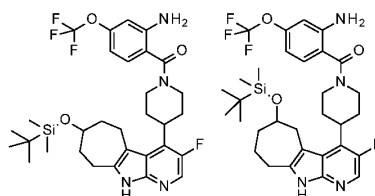


STEP 1: (rac)-4-[tert-butyl(dimethyl)silyl]oxycycloheptanone



- To a solution of (rac)-4-hydroxycycloheptanone (527 mg, 4.1 mmol) in DCM (14 mL) were
 5 added tert-butyldimethylchlorosilane (682 mg, 4.52 mmol) and imidazole (420 mg, 6.17 mmol) and the resulting mixture was stirred at room temperature for one hour. After one hour, tert-butyldimethylchlorosilane (158 mg, 1.26 mmol) and imidazole (126 mg, 1.85 mmol) were added and the resulting mixture was stirred for two additional hours, then
 10 filtered and the resulting filtrate was concentrated in vacuo. The thus obtained residue was diluted with AcOEt, washed with a saturated aqueous solution of NaHCO₃, dried over sodium sulfate, filtered and concentrated in vacuo. The resulting colorless oil was then purified by flash chromatography on silica gel (SiO₂ 40 g) eluting with AcOEt / Heptane 5 / 95 to give 852 mg (85% yield) of (rac)-4-[tert-butyl(dimethyl)silyl]oxycycloheptanone as a colorless oil.

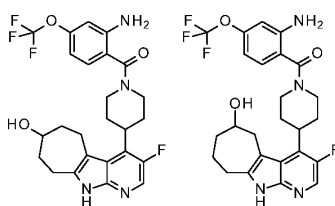
- STEP 2:** (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-[tert-butyl(dimethyl)silyl]oxy-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone and (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[13-[tert-butyl(dimethyl)silyl]oxy-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone



- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-[tert-butyl(dimethyl)silyl]oxy-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone and (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[13-[tert-butyl(dimethyl)silyl]oxy-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone were prepared following the protocol described in step 6 of Example 56 using tert-butyl N-[2-[4-(2-amino-5-fluoro-3-iodo-4-pyridyl)piperidine-1-carbonyl]-5-(trifluoromethoxy)phenyl]carbamate (350 mg, 0.5 mmol, described in step 1 of Example 7) and 4-[tert-butyl(dimethyl)silyl]oxycycloheptanone (367 mg, 1.61 mmol) to give 153 mg

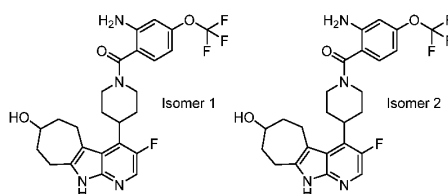
(42% yield) of a 75/25 mixture of respectively (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-[tert-butyl(dimethyl)silyl]oxy-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone and (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[13-[tert-butyl(dimethyl)silyl]oxy-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone. LC/MS (m/z, M⁺): calc. 621.3, found 621.5.

STEP 3: (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone and (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone



(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone and (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone were prepared following the protocol described in step 2 of Example 5 using 150 mg (0.24 mmol) of the mixture of the two regioisomers described in the previous step, to give, after flash chromatography on silica gel (SiO₂ 12 g) eluting with DCM / MeOH / NH₄OH 96 / 4 / 0.4: 71 mg (58% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone as pale brown solid. LC/MS (m/z, M⁺): calc. 506.5, found 506.0; and 24 mg (20% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone (Example 17) as a pale brown solid. LC/MS (m/z, M⁺): calc. 506.2, found 506.0.

STEP 4: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomers 1 & 2. (Examples 8 & 9)

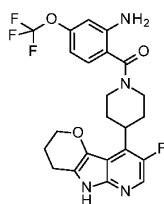


Chiral separation of ((rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone (63 mg, 0.12 mmol) was performed using a Chiralpak AD-H column (5 μ m, 250x30 mm), eluting with (Heptane 70/EtOH 30)+0.1% TEA (flow rate 40 mL / min, UV detection at 254 nm) to give: 17 mg (27% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 1. LC/MS (m/z, M+H): calc. 507.2, found 507.4; and 7 mg (11% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone, Isomer 2. LC/MS (m/z, M+H): calc. 507.2, found 507.4.

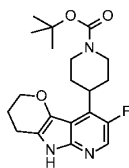
METHOD E

Method E is illustrated by the preparation of Example 25. Method E contains steps which are found, e.g., in Scheme 3 above.

Example 25: [2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-fluoro-3-oxa-8,10-diazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl)-1-piperidyl]methanone



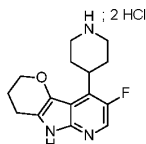
STEP 1: tert-butyl 4-(12-fluoro-3-oxa-8,10-diazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl)piperidine-1-carboxylate



In a 2-5 mL microwave vial, to a solution of tert-butyl 4-(2-amino-5-fluoro-3-iodo-4-pyridyl)piperidine-1-carboxylate (300 mg, 0.71 mmol, described in step 3 of Example 56) in DMF (6 mL) was added 1,4-diazabicyclo[2.2.2]octane (240 mg, 2.14 mmol) and tetrahydropyran-3-one (107 mg, 1.07 mmol) and the resulting mixture was bubbled with argon for 2 minutes. Then, bis(tri-tert-butylphosphine)palladium (0) (24 mg, 0.04 mmol) was added and the resulting mixture was submitted to microwaves at 160 °C, for 3 hours (2x90minutes). After 3 hours, the reaction mixture was concentrated to dryness, and the

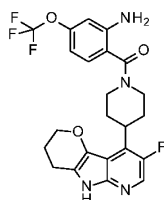
resulting residue was purified by flash chromatography on silica gel (SiO₂ 30 g) eluting with Heptane / AcOEt 7 / 3 to give 169 mg (63% yield) of tert-butyl 4-(12-fluoro-3-oxa-8,10-diazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl)piperidine-1-carboxylate as a solid. LC/MS (m/z, M⁺): calc. 375.4, found 375.0.

- 5 **STEP 2:** 12-fluoro-13-(4-piperidyl)-3-oxa-8,10-diazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraene, dihydrochloride



- To a solution of tert-butyl 4-(12-fluoro-3-oxa-8,10-diazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl)piperidine-1-carboxylate (169 mg, 0.45 mmol) in MeOH (2 mL), was added a 4 N solution of HCl in dioxane (2 mL, 8 mmol) and the resulting mixture was stirred at room temperature for 24 hours, then concentrated to dryness, to give 157 mg (100% yield) of 12-fluoro-13-(4-piperidyl)-3-oxa-8,10-diazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraene, dihydrochloride. LC/MS (m/z, M+H -2HCl): calc. 276.3, found 276.3.

- 15 **STEP 3:** [2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-fluoro-3-oxa-8,10-diazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl)-1-piperidyl]methanone



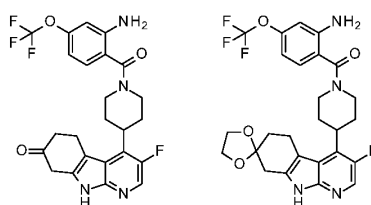
- Under argon atmosphere, to a solution of 12-fluoro-13-(4-piperidyl)-3-oxa-8,10-diazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraene, dihydrochloride (80 mg, 0.22 mmol) in DMF (2 mL) was added N,N-diisopropylethylamine (0.25 mL, 1.45 mmol) and the resulting mixture was stirred at room temperature for 30 minutes. Then, were successively added 2-amino-4-(trifluoromethoxy)benzoic acid (68 mg, 0.30 mmol) and TATU (99 mg, 0.3 mmol) and the whole mixture was stirred at room temperature for 90 minutes. After 90 minutes, the resulting mixture was diluted with AcOEt and water. The organic layer was then dried over magnesium sulfate, filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 20 g) eluting with DCM / [DCM/MeOH/NH₄OH 90/10/4] 90/10, to give 10 mg (9% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-

fluoro-3-oxa-8,10-diazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),9,11-tetraen-13-yl)-1-piperidyl]methanone as a solid. LC/MS (m/z, M+H): calc. 479.2, found 479.3.

METHOD F

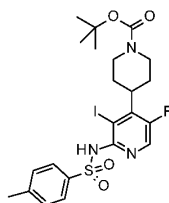
Method F is illustrated by the preparation of Examples 50 and 51. Method F contains steps which are found, e.g., in Scheme 4 above.

Examples 50 & 51: 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,6,8,9-tetrahydropyrido[2,3-b]indol-7-one, and [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-5,6,8,9-tetrahydrospiro[pyrido[2,3-b]indole-7,2'-[1,3]dioxolan]-4-yl)-1-piperidyl]methanone



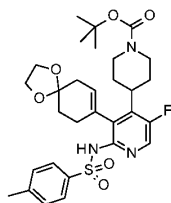
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STEP 1: tert-butyl 4-[5-fluoro-3-iodo-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carboxylate

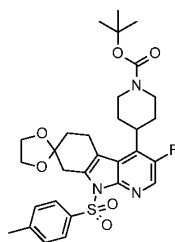


tert-butyl 4-[5-fluoro-3-iodo-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carboxylate was prepared following the protocol described in step 1 of example 15 using tert-butyl 4-(2-amino-5-fluoro-3-iodo-4-pyridyl)piperidine-1-carboxylate (1000 mg, 2.37 mmol, described in step 3 of Example 56) to give 438 mg (32% yield) of tert-butyl 4-[5-fluoro-3-iodo-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carboxylate as a white solid. LC/MS (m/z, M+H): calc. 576.1, found 576.2.

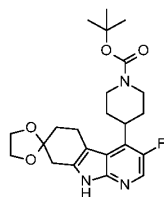
STEP 2: tert-butyl 4-[3-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-5-fluoro-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carboxylate



- tert-butyl 4-[3-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-5-fluoro-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carboxylate was prepared following the protocol described in step 2 of Example 15 using tert-butyl 4-[5-fluoro-3-iodo-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carboxylate (435 mg, 0.76 mmol) and 4,4,5,5-tetramethyl-2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1,3,2-dioxaborolane (241 mg, 0.91 mmol) to give 425 mg (95 % yield) of tert-butyl 4-[3-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-5-fluoro-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carboxylate as a pale yellow solid. LC/MS (m/z, M+H): calc. 588.2, found 588.4.
- 10 **STEP 3:** tert-butyl 4-[3'-fluoro-9'-(p-tolylsulfonyl)spiro[1,3-dioxolane-2,7'-6,8-dihydro-5H-pyrido[2,3-b]indole]-4'-yl]piperidine-1-carboxylate

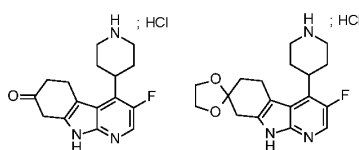


- tert-butyl 4-[3'-fluoro-9'-(p-tolylsulfonyl)spiro[1,3-dioxolane-2,7'-6,8-dihydro-5H-pyrido[2,3-b]indole]-4'-yl]piperidine-1-carboxylate was prepared following the protocol described in step 3 of Example 15 using tert-butyl 4-[3-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-5-fluoro-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carboxylate (530 mg, 0.9 mmol) to give 350 mg (66% yield) of tert-butyl 4-[3'-fluoro-9'-(p-tolylsulfonyl)spiro[1,3-dioxolane-2,7'-6,8-dihydro-5H-pyrido[2,3-b]indole]-4'-yl]piperidine-1-carboxylate as a white solid. LC/MS (m/z, M+H): calc. 586.2, found 586.3.
- 20 **STEP 4:** tert-butyl 4-(3'-fluorospiro[1,3-dioxolane-2,7'-5,6,8,9-tetrahydropyrido[2,3-b]indole]-4'-yl)piperidine-1-carboxylate



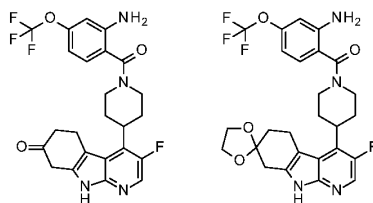
tert-butyl 4-(3'-fluorospiro[1,3-dioxolane-2,7'-5,6,8,9-tetrahydropyrido[2,3-b]indole]-4'-yl)piperidine-1-carboxylate was prepared following the protocol described in step 4 of example 15 using tert-butyl 4-[3'-fluoro-9'-(p-tolylsulfonyl)spiro[1,3-dioxolane-2,7'-6,8-dihydro-5H-pyrido[2,3-b]indole]-4'-yl]piperidine-1-carboxylate (150 mg, 0.26 mmol) to give 105 mg (95% yield) of tert-butyl 4-(3'-fluorospiro[1,3-dioxolane-2,7'-5,6,8,9-tetrahydropyrido[2,3-b]indole]-4'-yl)piperidine-1-carboxylate as a white solid. LC/MS (m/z, M+H): calc. 432.2, found 432.4.

STEP 5: Mixture of 3-fluoro-4-(4-piperidyl)-5,6,8,9-tetrahydropyrido[2,3-b]indol-7-one, hydrochloride and 3'-fluoro-4'-(4-piperidyl)spiro[1,3-dioxolane-2,7'-5,6,8,9-tetrahydropyrido[2,3-b]indole], hydrochloride



At room temperature, to a solution of 4-(3'-fluorospiro[1,3-dioxolane-2,7'-5,6,8,9-tetrahydropyrido[2,3-b]indole]-4'-yl)piperidine-1-carboxylate (105 mg, 0.24 mmol) in THF (0.5 mL) was added fuming HCl (0.06 mL, 0.73 mmol) and the resulting mixture was stirred at room temperature for 16 hours. After 16 hours, fuming HCl (0.06 mL, 0.73 mmol) was added and the resulting mixture was stirred at room temperature for 3 additional hours, then filtered and the resulting filtrate was concentrated to dryness to give 60 mg of a mixture of crude 3-fluoro-4-(4-piperidyl)-5,6,8,9-tetrahydropyrido[2,3-b]indol-7-one, hydrochloride and 3'-fluoro-4'-(4-piperidyl)spiro[1,3-dioxolane-2,7'-5,6,8,9-tetrahydropyrido[2,3-b]indole], hydrochloride as a yellow solid. Respectively, LC/MS (m/z, M+H -HCl): calc. 288.1, found 288.2 and LC/MS (m/z, M+H -HCl): calc. 332.2, found 332.2.

STEP 6: 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,6,8,9-tetrahydropyrido[2,3-b]indol-7-one and [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-5,6,8,9-tetrahydrospiro[pyrido[2,3-b]indole-7,2'-[1,3]dioxolan]-4-yl)-1-piperidyl]methanone

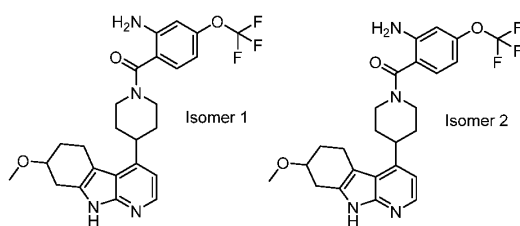


- 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,6,8,9-tetrahydropyrido[2,3-b]indole-7-one and [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3'-fluorospiro[1,3-dioxolane-2,7'-5,6,8,9-tetrahydropyrido[2,3-b]indole]-4'-yl)-1-piperidyl]methanone were prepared following the protocol described in step 3 of Example 25 using 60 mg of the crude previous mixture, 2-amino-4-(trifluoromethoxy)benzoic acid (42 mg, 0.19 mmol) and triethylamine (0.13 mL, 0.93 mmol) instead of DIPEA to give, after flash chromatography on silica gel (SiO₂ 12 g), eluting with Heptane / [DCM/MeOH 95/5] from 100/0 to 0/100:
- 15 15 mg (16% yield) of 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,6,8,9-tetrahydropyrido[2,3-b]indole-7-one as a white solid. LC/MS (m/z, M+H): calc. 491.2, found 491.3; and
- 8 mg (8% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-5,6,8,9-tetrahydrospiro[pyrido[2,3-b]indole-7,2'-[1,3]dioxolan]-4-yl)-1-piperidyl]methanone as a
- 15 white solid. LC/MS (m/z, M+H): calc. 535.2, found 535.3

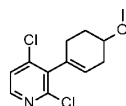
METHOD G

Method G is illustrated by the preparation of Examples 70 and 71. Method G contains steps which are found, e.g., in Scheme 7 above.

- Examples 70 and 71:** [2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomers 1 & 2

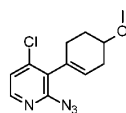


STEP 1: 2,4-dichloro-3-(4-methoxycyclohexen-1-yl)pyridine



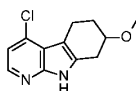
A mixture of 2,4-dichloropyridine (3.45 g, 12.59 mmol), 2-(4-methoxycyclohexen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3 g, 12.59 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (107 mg, 0.15 mmol), sodium bicarbonate (4.01 g, 37.8 mmol) in 1,4-dioxane (50 mL) and water (10 mL) was stirred at 80 °C for 3 hours under nitrogen atmosphere. After 3 hours, the mixture was diluted with water (150 mL), and extracted with ethyl acetate (3x100 mL). The organic layers were combined and washed with brine (2x100 mL), dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by silica gel flash chromatography (0-15% ethyl acetate in petroleum ether) to give 2.9 g (89% yield) of the target product as a yellow solid. LCMS; ESI m/z 258 (M + H)⁺.

10 **STEP 2:** 2-azido-4-chloro-3-(4-methoxycyclohexen-1-yl)pyridine



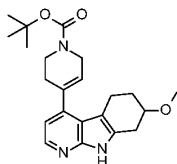
A mixture of 2,4-dichloro-3-(4-methoxycyclohexen-1-yl)pyridine (2.9 g, 11.2 mmol), sodium azide (1.46 g, 22.46 mmol) in water (20 mL), ethanol (10 mL) and acetic acid (5 mL) was stirred at 110 °C for 18 hours under nitrogen atmosphere. After 18 hours, the mixture was diluted with water (150 mL), and extracted with ethyl acetate (3x100 mL). The organic layers were combined and washed with brine (2x100 mL), dried over Na₂SO₄, filtered and concentrated to dryness. The resulting residue was purified by silica gel flash chromatography (0-40% ethyl acetate in petroleum ether) to give 0.98 g (33% yield) of the target product as a yellow solid. LCMS: ESI m/z 265.1 (M + H)⁺.

20 **STEP 3:** (rac)-4-chloro-7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole

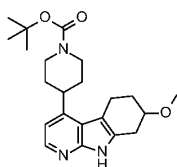


A mixture of 2-azido-4-chloro-3-(4-methoxycyclohexen-1-yl)pyridine (0.980 g, 3.7 mmol), Silver hexafluoroantimonate (V) (0.763 g, 2.22 mmol), dichloro(pentamethylcyclopentadienyl)iridium(III) dimer (0.885 g, 1.11 mmol) in toluene (15 mL) was stirred at 130 °C for 72 hours under argon atmosphere. After 72 hours, the mixture was diluted with water (50 mL), and extracted with dichloromethane (3x50 mL). The organic layers were combined and washed with brine (2x50 mL), dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by silica gel flash chromatography (0-95% ethyl acetate in petroleum ether) to give 0.55 g (63% yield) of (rac)-4-chloro-7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole as a yellow oil. LCMS: ESI m/z 237.1 (M + H)⁺.

STEP 4: (rac)-tert-butyl 4-(7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-3,6-dihydro-2H-pyridine-1-carboxylate

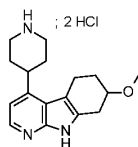


- A mixture of (rac)-4-chloro-7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole (0.550 g, 2.32 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (0.718 g, 2.32 mmol), bis(tri-tert-butylphosphine) palladium(0) (59 mg, 0.12 mmol), tripotassium phosphate (1.480 g, 6.97 mmol) in 1,4-dioxane (20 mL) and water (4 mL) was stirred at 100 °C for 16 hours under argon atmosphere. After 16 hours, the mixture was diluted with water (100 mL), and extracted with ethyl acetate (3x50 mL). The organic layers were combined and washed with brine (2x50 mL), dried over Na₂SO₄, filtered and concentrated and the residue was purified by silica gel flash chromatography (0-35% ethyl acetate in petroleum ether) to give 0.6 g (67% yield) of (rac)-tert-butyl 4-(7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-3,6-dihydro-2H-pyridine-1-carboxylate as a yellow oil. LCMS: ESI m/z 384.1 (M + H)⁺.
- STEP 5:** (rac)-tert-butyl 4-(7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)piperidine-1-carboxylate



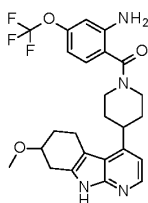
- A mixture of (rac)-tert-butyl 4-[5-(2,5-dihydrofuran-3-yl)-1-(2-trimethylsilylethoxymethyl)pyrazolo[3,4-b]pyridine-3-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (0.637 g, 1.28 mmol), 5% Pd/C (0.5 g) and Pd(OH)₂/C 20%(0.5 g) in methanol (80 mL) was stirred at room temperature for 96 hours under 1 atmosphere of H₂. After 96 hours, the mixture was filtered and concentrated. The resulting residue was purified by preparative HPLC to give 237 mg (39% yield) of (rac)-tert-butyl 4-(7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)piperidine-1-carboxylate as a white solid. LCMS: ESI m/z 386.1 (M + H)⁺.

STEP 6: (rac)-7-methoxy-4-(4-piperidyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole, hydrochloride



To a solution of (rac)-tert-butyl 4-(7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)piperidine-1-carboxylate (117 mg, 0.3 mmol) in MeOH (2 mL), at room temperature, was added 1.14 ml of a 4 N HCl solution in dioxane (4.55 mmol) and the resulting mixture was stirred at room temperature for 1 hour, concentrated to dryness to give 108 mg (100% yield) of (rac)-7-methoxy-4-(4-piperidyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole, hydrochloride as a yellow solid. LC/MS (m/z, M+H- 2HCl): calc. 286.2, found 286.1.

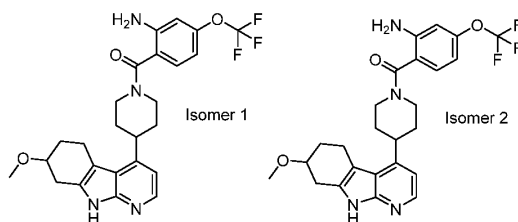
STEP 7: (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



10

(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone was prepared following the protocol described in step 5 of Example 56 using (rac)-7-methoxy-4-(4-piperidyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole, hydrochloride (108 mg, 0.3 mmol) and 2-amino-4-(trifluoromethoxy)benzoic acid (70 mg, 0.32 mmol) to give 126 mg (85% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone as a pale brown solid. LC/MS (m/z, M+H): calc. 489.2, found 489.2.

STEP 8: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomers 1 & 2

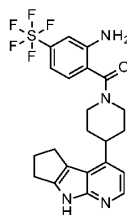


Chiral separation of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone (123 mg, 0.25 mmol) was performed using a Chiralcel OD-I column (20 μ m, 350x76.5 mm), eluting with (Heptane 60%/ EtOH 40%)+0.1%TEA (flow rate 400 mL / min, UV detection at 265 nm) to give 52 mg (42% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 1. LC/MS (m/z, M+H): calc. 489.2, found 489.4; and 59 mg (48% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, Isomer 2. LC/MS (m/z, M+H): calc. 489.2, found 489.4.

10 **METHOD H**

Method H is illustrated by the preparation of Example 72. Method H contains steps which are found, e.g., in Scheme 8 above.

Example 72: [2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-(7,9-diazatricyclo[6.4.0.0^{2,6}]dodeca-1(12),2(6),8,10-tetraen-12-yl)-1-piperidyl]methanone

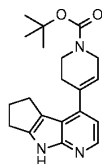


STEP 1: 12-chloro-7,9-diazatricyclo[6.4.0.0^{2,6}]dodeca-1(12),2(6),8,10-tetraene



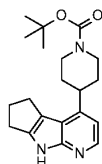
In a 10-20 mL microwave vial, to a solution of 4-chloro-3-iodopyridin-2-amine (500 mg, 1.87 mmol) in DMF (10 mL) was added cyclopentanone (495 mg, 5.6 mmol), 1,4-diazabicyclo[2.2.2]octane (661 mg, 5.6 mmol) and bis(tri-tert-butylphosphine)palladium (0) (97 mg, 0.19 mmol) and the whole mixture was bubbled with argon for 10 minutes, then submitted to microwave at 165 °C for 130 minutes. After 130 minutes, the reaction mixture was diluted with ethyl acetate, filtered and the resulting filtrate was washed three times with water, with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 20 g) eluting with Heptane / AcOEt 85/15 to give 84 mg (23% yield) of 12-chloro-7,9-diazatricyclo[6.4.0.0^{2,6}]dodeca-1(12),2(6),8,10-tetraene as a white solid. LC/MS (m/z, M+H): calc. 193.0, found 192.9.

STEP 2: tert-butyl 4-(7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraen-12-yl)-3,6-dihydro-2H-pyridine-1-carboxylate



- In a 2-5 mL microwave vial, to a solution of 12-chloro-7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene (120 mg, 0.53 mmol) in dioxane (4.5 mL) and water (0.4 mL) was added cesium carbonate (431 mg, 1.32 mmol), Pd(dppf)Cl₂.DCM (43 mg, 0.05 mmol) and N-BOC-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (275 mg, 0.85 mmol) and the whole mixture was bubbled with argon for 10 minutes and submitted to microwave at 160 °C for 50 minutes. After 50 minutes, additional Pd(dppf)Cl₂.DCM (20 mg, 0.02 mmol) and N-BOC-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (100 mg, 0.3 mmol) were added and the reaction mixture was submitted to microwave 40 additional minutes at 160 °C, then diluted with DCM, washed with brine, dried over magnesium sulfate, filtered and concentrated. The resulting residue was purified by flash chromatography in silica gel (SiO₂ 80 mg) eluting with Heptane / AcOEt 60 /40 to 50 /50 to give 113 mg (63% yield) of tert-butyl 4-(7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraen-12-yl)-3,6-dihydro-2H-pyridine-1-carboxylate as a white solid. LC/MS (m/z, M+H): calc. 340.2, found 340.2.

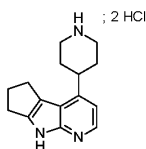
STEP 3: tert-butyl 4-(7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraen-12-yl)piperidine-1-carboxylate



- To a solution of tert-butyl 4-(7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraen-12-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (267 mg, 0.79 mmol) in EtOH (10 mL) was added ammonium formate (77 mg, 1.23 mmol) and Pd/C (10%) (126 mg, 0.12 mmol) and the resulting mixture was stirred 2 hours under reflux followed by 12 hours at room temperature. Then, ammonium formate (400 mg, 6.4 mmol) and Pd/C (10%) (59 mg, 0.06 mmol) were added and the resulting mixture was refluxed for one additional hour, then cooled down to room temperature, filtered, and the resulting filtrate was concentrated, diluted with AcOEt, washed with water, brine, dried over magnesium sulfate, filtered and concentrated to dryness to give 240 mg (89% yield) of tert-butyl 4-(7,9-diazatricyclo[6.4.0.02,6]dodeca-

1(12),2(6),8,10-tetraen-12-yl)piperidine-1-carboxylate as a white foam. LC/MS (m/z, M+H): calc. 342.2, found 342.3.

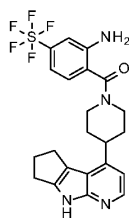
STEP 4: 12-(4-piperidyl)-7,9-diazatricyclo[6.4.0.0^{2,6}]dodeca-1(12),2(6),8,10-tetraene, dihydrochloride



5

To a solution of tert-butyl 4-(7,9-diazatricyclo[6.4.0.0^{2,6}]dodeca-1(12),2(6),8,10-tetraen-12-yl)piperidine-1-carboxylate (234 mg, 0.68 mmol) in MeOH / DCM (3 mL / 0.5 mL) was added dropwise a 5/6 M HCl solution in i-PrOH (1.37 mL, 6.85 mmol) and the resulting mixture was stirred at room temperature for 4 hours. After 4 hours, a 5/6 M HCl solution in i-PrOH (1.37 mL, 6.85 mmol) was added and the resulting mixture was stirred at room temperature for 1 additional hour, concentrated to dryness, 1 mL of MeOH was added followed by a 5/6 M HCl solution in i-PrOH (1.37 mL, 6.85 mmol) and the reaction mixture was stirred for 2 hours at room temperature, concentrated, diluted with MeOH and concentrated to dryness three times. The resulting residue was triturated in Et₂O, filtered to give 202 mg (94% yield) of 12-(4-piperidyl)-7,9-diazatricyclo[6.4.0.0^{2,6}]dodeca-1(12),2(6),8,10-tetraene, dihydrochloride as a white solid. LC/MS (m/z, M+H -2HCl): calc. 242.2, found 242.2.

STEP 5: [2-amino-4-(pentafluoro-λ⁶-sulfanyl)phenyl]-[4-(7,9-diazatricyclo[6.4.0.0^{2,6}]dodeca-1(12),2(6),8,10-tetraen-12-yl)-1-piperidyl]methanone



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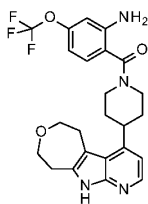
[2-amino-4-(pentafluoro-λ⁶-sulfanyl)phenyl]-[4-(7,9-diazatricyclo[6.4.0.0^{2,6}]dodeca-1(12),2(6),8,10-tetraen-12-yl)-1-piperidyl]methanone was prepared following the protocol described in step 3 of Example 25 using 12-(4-piperidyl)-7,9-diazatricyclo[6.4.0.0^{2,6}]dodeca-1(12),2(6),8,10-tetraene, dihydrochloride (57 mg, 0.18 mmol) and 2-amino-4-(pentafluoro-λ⁶-sulfanyl)benzoic acid (50 mg, 0.18 mmol) to give 60 mg (68% yield) of [2-amino-4-(pentafluoro-λ⁶-sulfanyl)phenyl]-[4-(7,9-

diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraen-12-yl)-1-piperidyl]methanone as a solid. LC/MS (m/z, M+H): calc. 487.2, found 487.1.

METHOD I

Method I is illustrated by the preparation of Example 75. Method I contains steps which are found, e.g., in Scheme 5 above.

Example 75: [2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone



STEP 1: (4-bromo-2-chloro-3-pyridyl)methanol



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To a solution of ethyl 4-bromo-2-chloro-pyridine-3-carboxylate (10 g, 37.8 mmol) in anhydrous dichloromethane (100 mL) at -78 °C under nitrogen atmosphere was added DIBAL-H (1.0 M solution in hexane, 83.2 mmol, 83.2 mL) dropwise in 30 minutes. The reaction mixture was then stirred for 3 hours at -78 °C, warmed to room temperature and stirred for 16 hours, then quenched with methanol (5 ml). The resulting mixture was treated with concentrated aqueous potassium sodium tartrate (200 mL) and stirred for 2 hours. The layers were separated and the aqueous layer extracted with dichloromethane (3×100 mL). The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to give the crude product which was purified by silica gel chromatography (5% MeOH in DCM) to give 6.68 g (78% yield) of (4-bromo-2-chloro-3-pyridyl)methanol as a white solid. LCMS: ESI m/z 224.1 (M+H)⁺.

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STEP 2: 4-bromo-3-(bromomethyl)-2-chloro-pyridine

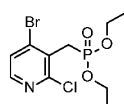


A solution of (4-bromo-2-chloro-3-pyridyl)methanol (6.68 g, 29.6 mmol) in dichloromethane (70 mL) was cooled to 0 °C and treated with tribromophosphane (16 g, 59.3 mmol). The

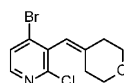
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- reaction was then allowed to warm to 20 °C and was stirred for 12 hours. The mixture was poured into ice-cold water (80 mL) and neutralized with a saturated aqueous solution of NaHCO₃. The resulting mixture was extracted with dichloromethane (2×100 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to give 8.45 g (99% yield) of 4-bromo-3-(bromomethyl)-2-chloro-pyridine as a white solid. LCMS: ESI m/z 285.8 (M+H) ⁺.

STEP 3: 4-bromo-2-chloro-3-(diethoxyphosphorylmethyl)pyridine

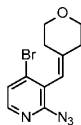


- A mixture of 4-bromo-3-(bromomethyl)-2-chloro-pyridine (8.45 g, 29.3 mmol) and triethyl phosphite (7.3 g, 44 mmol) in toluene (50 mL) was stirred at 130 °C for 16 hours. After completion, the reaction mixture was cooled down to room temperature, concentrated and the resulting residue was purified by silica-gel column chromatography (0-50% EtOAc in PE) to give 8.44 g (79% yield) of 4-bromo-2-chloro-3-(diethoxyphosphorylmethyl)pyridine as a colorless oil. LCMS: ESI m/z 344.0 (M+H) ⁺.
- STEP 4:** 4-bromo-2-chloro-3-(tetrahydropyran-4-ylidenemethyl)pyridine



- To a solution of 4-bromo-2-chloro-3-(diethoxyphosphorylmethyl)pyridine (8.44 g, 23.3 mmol) in anhydrous THF (80 mL) under argon atmosphere was added at -78 °C, potassium-2-methylpropan-2-olate (3.13 g, 27.9 mmol) and the resulting mixture was warmed up to room temperature and stirred for 2 hours. Then, at -78 °C, a solution of tetrahydropyran-4-one (2.80 g, 27.9 mmol) in 20 mL dry THF was added very slowly and the resulting reaction mixture was stirred for 16 hours at room temperature. After completion, reaction mixture was quenched with very slow addition of water (150 mL), extracted with ethyl acetate (3×100 mL). The organic layers were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give a crude oil which was purified by silica-gel column chromatography (0-20% EtOAc in PE) to give 2.3 g (32% yield) of 4-bromo-2-chloro-3-(tetrahydropyran-4-ylidenemethyl)pyridine as a white solid. LCMS: ESI m/z 290.0 (M+H) ⁺.

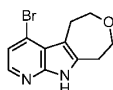
STEP 5: 2-azido-4-bromo-3-(tetrahydropyran-4-ylidenemethyl)pyridine



4-bromo-2-chloro-3-(tetrahydropyran-4-ylidenemethyl)pyridine (2.30 g, 7.48 mmol) and sodium azide (0.972 g, 15 mmol) were solubilized in water (16 mL), ethanol (8 mL) and acetic acid (4.00 mL) in a tank. The reaction mixture was then stirred at 120 °C for 16 hours.

- 5 After 16 hours, the reaction mixture was poured into water (30 mL), neutralized with a saturated aqueous solution of NaHCO₃, extracted with dichloromethane (3×50 mL). The organic layers were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give a crude oil which was purified by silica-gel column chromatography (0-25% EtOAc in PE) to give 780 mg (35% yield) of 2-azido-4-bromo-3-(tetrahydropyran-4-ylidenemethyl)pyridine as a white solid. LCMS: ESI m/z 295.0 (M+H) +.
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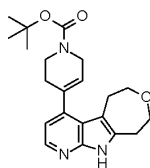
STEP 6: 3-bromo-12-oxa-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraene



A solution of iron tetraphenylporphyrin chloride (93 mg, 0.13 mmol) and zinc (17 mg, 0.26 mmol) in chlorobenzene (10 mL) was stirred at 130 °C under argon atmosphere for 2 hours.

- 15 This solution was then added to 2-azido-4-bromo-3-(tetrahydropyran-4-ylidenemethyl)pyridine (780 mg, 2.64 mmol), and the resulting mixture was stirred for 16 hours under the same conditions. After 16 hours, the resulting mixture was concentrated under vacuum and purified by silica-gel column chromatography (0-2% DCM in MeOH) to give 630 mg (89% yield) of 3-bromo-12-oxa-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-
- 20 1(9),2,4,6-tetraene as a yellow solid. LCMS: ESI m/z 267.0 (M+H) +.

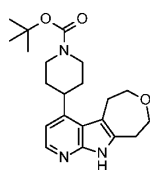
STEP 7: tert-butyl 4-(12-oxa-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylate



- A solution of 3-bromo-12-oxa-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraene (630 mg, 2.36 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (1.09 g, 3.54 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (173 mg, 0.24 mmol) and disodium
- 25

carbonate (750 mg, 7.1 mmol) in 1,4-dioxane (12 mL) and water (3 mL) was stirred at 80 °C for 3 hours under nitrogen atmosphere. After 3 hours, the resulting mixture was treated with water (20 mL), extracted with ethyl acetate (3×30 mL). The organic layers were combined, concentrated to give a crude oil which was purified by reverse phase passing column (5%-35% MeCN in water, 0.01% TFA) to give 630 mg (65% yield) of tert-butyl 4-(12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylate as a light yellow solid. LCMS: ESI m/z 370.1 (M+H) +.

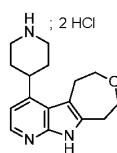
STEP 8: tert-butyl 4-(12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)piperidine-1-carboxylate



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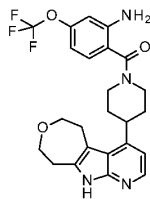
To a solution of tert-butyl 4-(12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (630 mg, 1.54 mmol) in methanol (20 mL) was added Pd on carbon (20 wt %, 130 mg). The mixture was stirred for 2 weeks at room temperature under one atmosphere of H₂. The reaction mixture was then filtered through diatomaceous earth, and the filtrate was concentrated to get a yellow oil which was purified by preparative HPLC (5% to 95% MeCN in Water, 10 mM NH₄HCO₃) to give tert-butyl 238 mg (41% yield) of 4-(12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)piperidine-1-carboxylate as a white solid. LCMS: ESI m/z 372.1 (M+H) +.

STEP 9: 3-(4-piperidyl)-12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraene dihydrochloride



3-(4-piperidyl)-12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraene dihydrochloride was prepared following the protocol described in step 2 of Example 25 to give 218 mg (99% yield) of 3-(4-piperidyl)-12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraene dihydrochloride as a yellow solid. LC/MS (m/z, M+H -2HCl): calc. 272.2, found 272.2.

STEP 10: [2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone

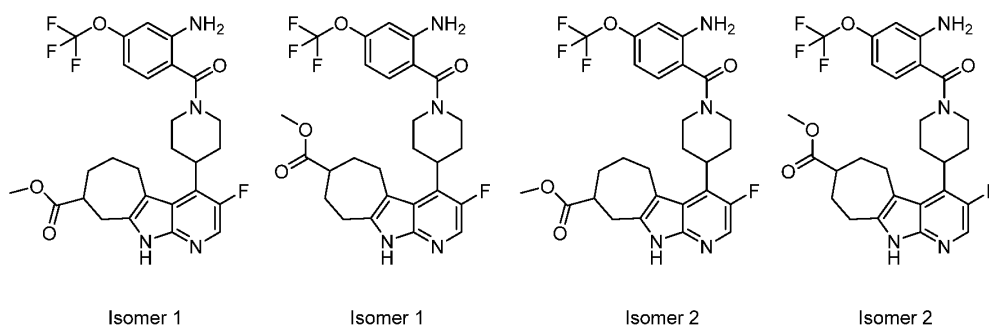


- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-oxa-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraene-3-yl)-1-piperidyl]methanone was prepared following the protocol described in step 5 of Example 56 using 3-(4-piperidyl)-12-oxa-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraene dihydrochloride (200 mg, 0.58 mmol) and 2-amino-4-(trifluoromethoxy)benzoic acid (134 mg, 0.61 mmol) to give 250 mg (81% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-oxa-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraene-3-yl)-1-piperidyl]methanone as a pale brown solid. LC/MS (m/z, M+H): calc. 475.2, found 475.1.

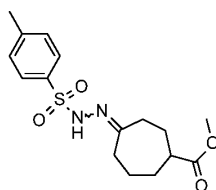
10 **METHOD J**

Method J is illustrated by the preparation of Examples 97, 98, 99 & 100. Method J contains steps which are found, e.g., in Scheme 6 above.

- Examples 97, 98, 99 & 100:** methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate isomer 1, methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate isomer 1, methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate isomer 2, and methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate isomer 2.

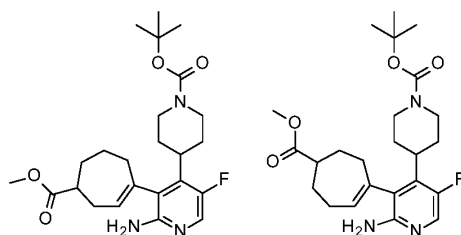


STEP 1: methyl 4-(p-tolylsulfonylhydrazono)cycloheptanecarboxylate



To a solution of methyl 4-oxocycloheptane carboxylate (1 g, 5.87 mmol) in methanol (20 mL) was added 4-methylbenzenesulfonylhydrazide (1.1g, 5.9 mmol) and the resulting reaction mixture was stirred at room temperature for 2.5 hours, then concentrated in vacuo to give a white residue which was triturated in MTBE, filtered to give 1.71 g (86% yield) of methyl 4-(p-tolylsulfonylhydrazono)cycloheptanecarboxylate which was engaged in the next step without further purification. LC/MS (m/z, M+H): calc. 339.1, found 339.1.

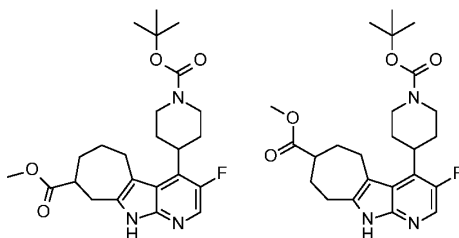
STEP 2: tert-butyl 4-[2-amino-5-fluoro-3-(4-methoxycarbonylcyclohepten-1-yl)-4-pyridyl]piperidine-1-carboxylate and tert-butyl 4-[2-amino-5-fluoro-3-(5-methoxycarbonylcyclohepten-1-yl)-4-pyridyl]piperidine-1-carboxylate



A solution of palladium acetate (25 mg, 0.11 mmol), potassium carbonate (900 mg, 6.5 mmol), tri-tert-butylphosphonium tetrafluoroborate (85 mg, 0.29 mmol) in DMF (3 mL) was bubbled with argon for 2 minutes and then, tert-butyl 4-(2-amino-5-fluoro-3-iodo-4-pyridyl)piperidine-1-carboxylate (prepared in step 3 of example 56 (Method A), 915 mg, 2.17 mmol). The whole mixture was then stirred at 110 °C, and methyl 4-(p-tolylsulfonylhydrazono)cycloheptanecarboxylate (880 mg, 2.60 mmol) was added. The resulting reaction mixture was stirred at 110 °C for 1.5 hrs and then 4-(p-tolylsulfonylhydrazono)cycloheptanecarboxylate (880 mg, 2.60 mmol) was added again, and the resulting reaction mixture was stirred at 110 °C, for 4 additional hours, then cooled down to room temperature, diluted with AE (50 mL) and water (50 mL). The aqueous layer was extracted with AE (50 mL) and the combined organic layers were dried over sodium sulfate, filtered, concentrated and the resulting residue was purified by flash chromatography (SiO₂ 24 g) eluting with CycloHexane / AE 6/4 to 4/6 to give 617 mg (50% yield) of a mixture of tert-butyl 4-[2-amino-5-fluoro-3-(4-methoxycarbonylcyclohepten-1-yl)-4-pyridyl]piperidine-1-carboxylate and tert-butyl 4-[2-amino-5-fluoro-3-(5-methoxycarbonylcyclohepten-1-yl)-4-

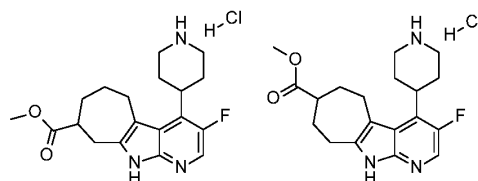
pyridyl]piperidine-1-carboxylate as a white solid which was engaged in the next step. LC/MS (m/z, M+H): calc. 448.2, found 448.3.

STEP 3: methyl 3-(1-tert-butoxycarbonyl-4-piperidyl)-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate & methyl 3-(1-tert-butoxycarbonyl-4-piperidyl)-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate



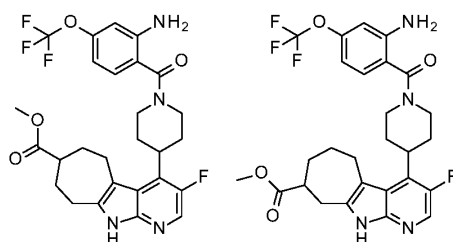
To a solution of the above-mentioned mixture of 4-[2-amino-5-fluoro-3-(4-methoxycarbonylcyclohepten-1-yl)-4-pyridyl]piperidine-1-carboxylate and tert-butyl 4-[2-amino-5-fluoro-3-(5-methoxycarbonylcyclohepten-1-yl)-4-pyridyl]piperidine-1-carboxylate (610 mg, 1.36 mmol) in THF (5 mL) was added at 5 °C, dropwise, a solution of [bis(trifluoroacetoxy)iodo]benzene (720 mg, 1.67 mmol) in THF (5 mL) and the resulting mixture was warmed up to room temperature and stirred for 3 hours. Then, 200 additional mg of [bis(trifluoroacetoxy)iodo]benzene (0.46 mmol) were added and the resulting reaction mixture was stirred overnight at room temperature, then, diluted with AE (50 mL) and an aqueous saturated solution of NaHCO₃ (50 mL). The aqueous layer was extracted with AE (50 mL) and the combined organic layers were dried over sodium sulfate, filtered, concentrated and the resulting residue was purified by flash chromatography (SiO₂ 24 g) eluting with DCM / [DCM/MeOH 95/5] from 100/0 to 0/100 to give 151 mg (19% yield) of a mixture of methyl 3-(1-tert-butoxycarbonyl-4-piperidyl)-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate & methyl 3-(1-tert-butoxycarbonyl-4-piperidyl)-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate as an orange solid which was engaged in the next step. LC/MS (m/z, M+H): calc. 446.2, found 446.2.

STEP 4: methyl 4-fluoro-3-(4-piperidyl)-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate hydrochloride & methyl 4-fluoro-3-(4-piperidyl)-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate hydrochloride



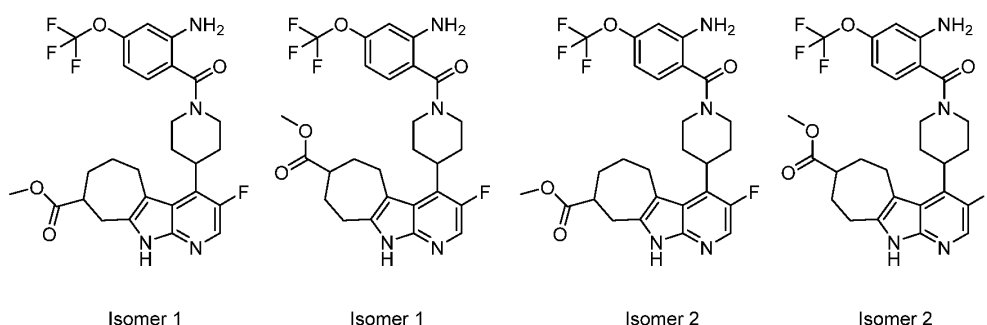
The title compounds were prepared following the protocol described in step 2 of example 25 to give 132 mg (100% yield) of a crude mixture of methyl 4-fluoro-3-(4-piperidyl)-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate hydrochloride & methyl 4-fluoro-3-(4-piperidyl)-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate hydrochloride as a yellow solid which was engaged in the next step.

STEP 5: methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate & methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate



To the above-mentioned mixture of 4-fluoro-3-(4-piperidyl)-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate hydrochloride & methyl 4-fluoro-3-(4-piperidyl)-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate hydrochloride (132 mg, 0.35 mmol) in solution in DMF (5 mL), was added triethylamine (0.3 mL, 2.15 mmol) followed by 2-amino-4-trifluoromethoxybenzoic acid (90 mg, 0.41 mmol) and TBTU (160 mg, 0.5 mmol) and the resulting reaction mixture was stirred at room temperature for 2 hours, diluted with AE (50 mL) and water (50 mL). The aqueous layer was extracted with AE (50 mL) and the combined organic layers were dried over sodium sulfate, filtered, concentrated. The resulting residue was purified by flash chromatography (SiO₂ 12 g) eluting with DCM / [DCM/MeOH 95/5] from 100/0 to 0/100 to give 135 mg (53% yield) of a mixture of methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate & methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate as a yellow solid which was engaged in the next step. LC/MS (m/z, M+H): calc. 549.2, found 549.2.

STEP 6: methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate isomer 1 and isomer 2, and methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate isomer 1 and isomer 2.



STEP 6 of examples 97, 98, 99 & 100 was performed as followed:

General Chiral Separation Method CS#3: Chiral separation of the above-mentioned mixture (199 mg), using a chiralpak AD-H column (5 μ m, 250x30 mm), eluting with (CO₂ 80%, MeOH+0.1% TEA 20%), flow rate 110 mL / min, UV detection at 230 nm) gave:

26 mg (13% yield) of methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 549.2, found 549.3.

30 mg (15% yield) of methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 549.2, found 549.3.

31 mg (15% yield) of methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 549.2, found 549.4.

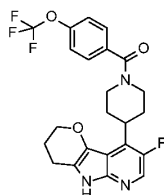
28 mg (14% yield) of methyl 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 549.2, found 549.3.

Specific synthetic examples

The following examples illustrate further methods of preparing compounds of the disclosure, e.g., compounds preparable from other compounds of the disclosure which carry substituents which are capable of undergoing further transformation. The skilled person will appreciate

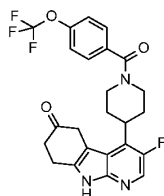
how features of the various synthetic steps (e.g., reactants, reagents, and conditions) shown in the below examples may be adapted when preparing other compounds in accordance with the disclosure, in particular in light of the general synthetic schemes provided above.

- Example 26:** [4-(12-fluoro-3-oxa-8,10-diazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),9,11-tetraen-13-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



- [4-(12-fluoro-3-oxa-8,10-diazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),9,11-tetraen-13-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone was prepared following the protocol described in step 3 of Example 25 using 12-fluoro-13-(4-piperidyl)-3-oxa-8,10-diazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),9,11-tetraene dihydrochloride (80 mg, 0.22 mmol) and 4-(trifluoromethoxy)benzoic acid (63 mg, 0.3 mmol) to give 30 mg (28% yield) of [4-(12-fluoro-3-oxa-8,10-diazatricyclo[7.4.0.0^{2,7}]trideca-1(13),2(7),9,11-tetraen-13-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M+H): calc. 464.4, found 464.3

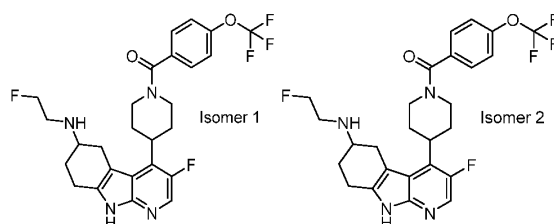
- Example 61:** 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one



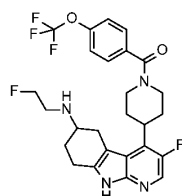
- At room temperature, to a solution of [4-(3'-fluorospiro[1,3-dioxolane-2,6'-5,7,8,9-tetrahydropyrido[2,3-b]indole]-4'-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (Example 56) (400 mg, 0.77 mmol) in DCM (4 mL) was added TFA (4 mL) and the reaction mixture was stirred for 12 hours. After 12 hours, the reaction mixture was diluted with DCM, washed twice with an aqueous saturated solution of NaHCO₃. The combined aqueous layers were extracted with DCM. The combined organic layers were then dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was diluted again with DCM, washed twice with an aqueous saturated solution of NaHCO₃. The combined aqueous layers were extracted with DCM. The combined organic layers were then dried over

magnesium sulfate, filtered and concentrated in vacuo to give 348 mg (95% yield) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one as a solid. LC/MS (m/z, M⁺): calc. 475.2, found 475.0.

Examples 1 & 2: [4-[3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomers 1 & 2

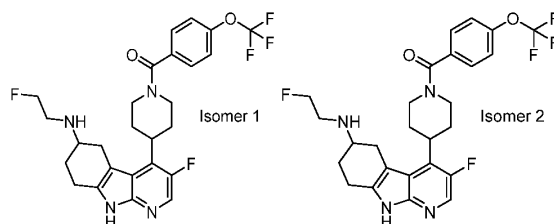


STEP 1 (Example 23): (rac)-[4-[3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



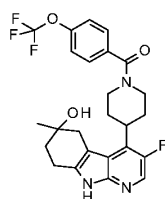
- At room temperature, under argon atmosphere, to a solution of 2-fluoroethylamine hydrochloride (51 mg, 0.51 mmol) in DCM (4 mL) was added DIPEA (0.17 mL, 0.99 mmol) and the resulting mixture was stirred for 20 minutes. Then, 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one (Example 61) (120 mg, 0.25 mmol) in solution in DCM (5 mL) was added followed by 58 μ L of acetic acid (1.01 mmol) and sodium triacetoxyborohydride (90 mg, 0.42 mmol). The whole mixture was stirred for 2.5 hours, then diluted with DCM and water. The aqueous layer was basified to pH 12 with a 10 N solution of NaOH, extracted twice with DCM. The combined organic layers were then washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was then purified by flash chromatography on silica gel (SiO₂ 12 g) eluting with a 94/6 to 90/10 mixture of DCM / MeOH to give 93 mg (70% yield) of (rac)-[4-[3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M⁺H): calc. 523.2, found 523.4.

STEP 2: [4-[3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomers 1 & 2



- Chiral separation of (rac)-[4-[3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (80 mg, 0.15 mmol) was performed using a Chiralpak AS column (5 μ m, 250x30 mm), eluting with (CO₂ 80%/ MeOH+0.1%TEA 20%) (flow rate 120 mL / min, UV detection at 230 nm) to give 30 mg (37.5% yield) of [4-[3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1. LC/MS (m/z, M+H): calc. 523.2, found 523.4; and 36 mg (45% yield) of [4-[3-fluoro-6-(2-fluoroethylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2. LC/MS (m/z, M+H): calc. 523.2, found 523.4.

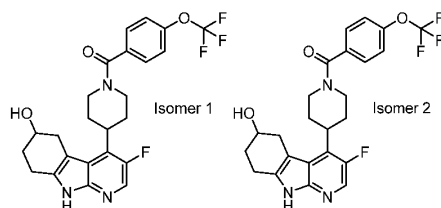
Example 17: (rac)-[4-(3-fluoro-6-hydroxy-6-methyl-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



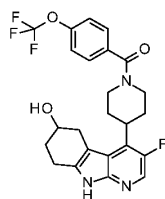
- At 0 °C, under argon atmosphere, to a solution of methylmagnesium bromide (157 μ L of a 1 M solution in THF, 0.157 mmol) in THF (1 mL), were successively added diethylene glycol diethyl ether (40 μ L, 0.2 mmol) and tetrabutylammonium chloride (29 mg, 0.1 mmol) and the resulting mixture was stirred at room temperature for 30 minutes. Then, 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one (Example 61) (50 mg, 0.1 mmol) in solution in THF (1 mL) was added and the resulting mixture was stirred for 3 additional hours. After 3 hours, methylmagnesium bromide (300 μ L of a 1 M solution in THF, 0.3 mmol) was added and the resulting mixture was stirred for 1 hour. After 1 hour, methylmagnesium bromide (200 μ L of a 1 M solution in THF, 0.2 mmol) was added and the resulting mixture was stirred for 12 hours. After 12 hours, at 0 °C, to the reaction mixture were added an aqueous saturated solution of ammonium chloride and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were then dried over magnesium sulfate, filtered and concentrated in vacuo. The

resulting residue was then purified by flash chromatography on silica gel (SiO₂ 12 g) eluting with a 98/2 to 95/5 mixture of DCM / MeOH to give 17 mg (33% yield) of (rac)-[4-(3-fluoro-6-hydroxy-6-methyl-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M+H): calc. 492.2, found 492.4.

Examples 33 & 34: [4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomers 1 & 2

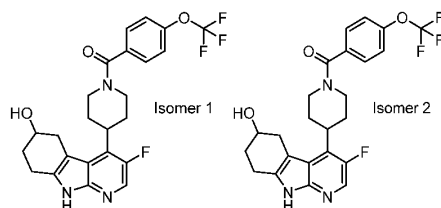


STEP 1: (rac)-[4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



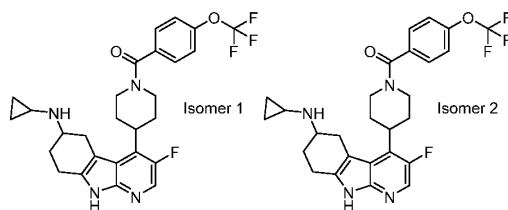
At 0 °C, under argon atmosphere, to a solution of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one (Example 61) (83 mg, 0.17 mmol) in solution in MeOH (2.5 mL) was added sodium borohydride (7.2 mg, 0.19 mmol) and the reaction mixture was stirred for 30 minutes. After 30 minutes, to the reaction mixture were added an aqueous saturated solution of ammonium chloride and ethyl acetate. The organic layer was washed twice with water and the combined aqueous layers were extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The resulting residue was then purified by flash chromatography on silica gel (SiO₂ 12 g) eluting with ethyl acetate to give 53 mg (63% yield) of (rac)-[4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M+H): calc. 478.2, found 478.4.

STEP 2: [4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomers 1 & 2

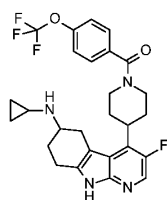


Chiral separation of (rac)-[4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (47 mg, 0.1 mmol) was performed using an i-Cellulose-5 column (5 μ m, 250x30 mm), eluting with (CO₂ 75%/ EtOH+0.1%TEA 25%) (flow rate 120 mL / min, UV detection at 230 nm) to give 17.6 mg (37% yield) of [4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1. LC/MS (m/z, M+H): calc. 478.2, found 478.4; and 11.8 mg (25% yield) of [4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2. LC/MS (m/z, M+H): calc. 478.2, found 478.4.

Examples 10 & 11: [4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomers 1 & 2



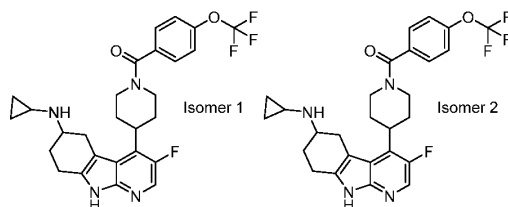
STEP 1: (rac)-[4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



(rac)-[4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone was prepared following the protocol described in STEP 1 of Examples 1 & 2 using 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one (60.6 mg, 0.13 mmol) and cyclopropylamine (8.7 μ L, 0.13 mmol) and without the use of DIPEA, to give 34 mg (51% yield) of (rac)-[4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-

4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M+H):
calc. 517.2, found 517.4.

STEP 2: [4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomers 1 & 2.

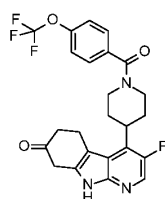


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Chiral separation of rac)-[4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone was performed following the protocol described in STEP 2 of Examples 1 & 2 to give 37.5 mg (42% yield) of [4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 1. LC/MS (m/z, M+H): calc. 517.2, found 517.4; and 39.1 mg (43% yield) of [4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, Isomer 2. LC/MS (m/z, M+H): calc. 517.2, found 517.4.

Example 16: 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,6,8,9-tetrahydropyrido[2,3-b]indol-7-one

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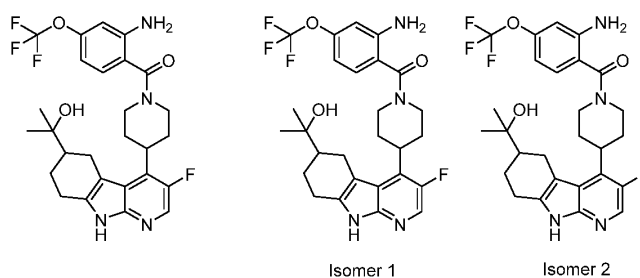
At room temperature, to a solution of [4-(3'-fluorospiro[1,3-dioxolane-2,7'-5,6,8,9-tetrahydropyrido[2,3-b]indole]-4'-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (80 mg, 0.15 mmol, described in step 4 of example 15) in DCM (1 mL) was added 1 mL of TFA (13.1 mmol) and the resulting mixture was stirred for 16 hours at room temperature. A yellow precipitate appeared. After 16 hours, the reaction mixture was diluted with DCM, and basified with a saturated aqueous solution of NaHCO₃ (added dropwise). The aqueous layer was then extracted three times with DCM, and the combined organic layers were then washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 12 g) eluting with a mixture of DCM / [DCM/MeOH 90/10] from 100/0 to 0/100, to give 57 mg (77% yield) of 3-fluoro-

20

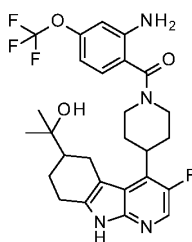
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4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,6,8,9-tetrahydropyrido[2,3-b]indol-7-one as a white solid. LC/MS (m/z, M+H): calc. 476.2, found 476.2.

- Examples 111, 91 & 92:** (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, and [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 1 and isomer 2

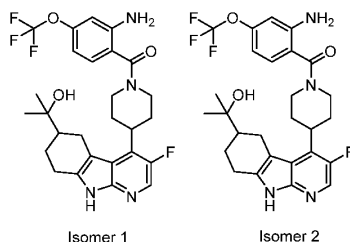


- 10 **STEP 1 (example 111):** (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



- Example 111 was prepared following the general method D using 4-(1-hydroxy-1-methyl-ethyl)cyclohexanone (262 mg, 1.68 mmol) in step 2, to give 135 mg (45% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 535.2, found 535.3.

- STEP 2 (examples 91 & 92):** [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 1 and isomer 2

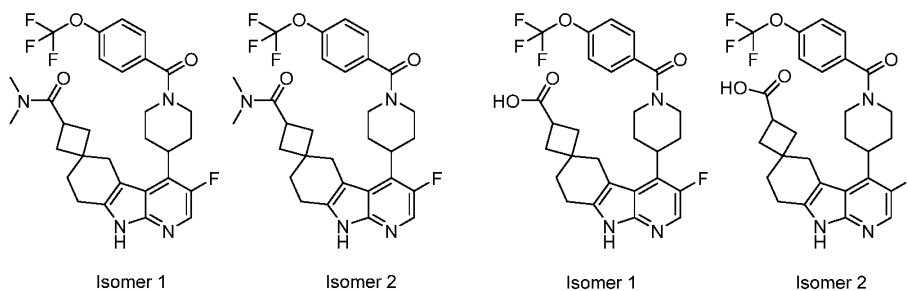


STEP 2 of examples 111, 91 & 92 was performed as followed:

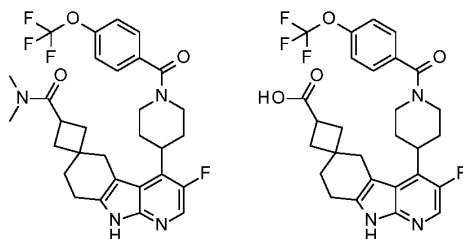
- General Chiral Separation Method CS#1:** Chiral separation of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone (50 mg, 0.09 mmol), using a Chiralpak AS-H column (5 μ m, 250x30 mm), eluting with ((EtOH+0.1% TEA) 30%, CO₂ 70%), flow rate 110 mL / min, UV detection at 230 nm) gave 20 mg (40% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 535.2, found 535.4.

And 23 mg (46% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 535.2, found 535.4.

- Examples 93, 94, 95 & 96:** 3-fluoro-N,N-dimethyl-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxamide isomer 1 and isomer 2, 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxylic acid isomer 1 and isomer 2.

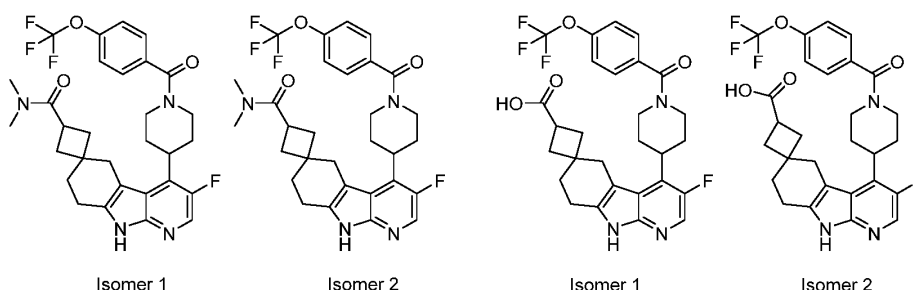


- STEP 1:** 3-fluoro-N,N-dimethyl-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxamide and 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxylic acid



3-fluoro-N,N-dimethyl-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxamide and 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxylic acid were prepared following general method A using 7-oxospiro[3.5]nonane-2-carboxylic acid (214 mg, 1.18 mmol) in step 6, to give 189 mg of a crude mixture of 3-fluoro-N,N-dimethyl-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxamide and 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxylic acid which was engaged in the next step.

STEP 2: 3-fluoro-N,N-dimethyl-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxamide isomer 1 and isomer 2, 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxylic acid isomer 1 and isomer 2.



STEP 2 of examples 93, 94, 95 & 96 was performed as followed:

General Chiral Separation Method CS#2: Chiral separation of the above-mentioned mixture (186 mg), using a chiralpak IC column (5 μ m, 250x30 mm), eluting with (CO₂ 55%, MeOH+0.1% TEA 45%), flow rate 110 mL / min, UV detection at 230 nm) gave:

21 mg (9% yield on the two steps) of 3-fluoro-N,N-dimethyl-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-

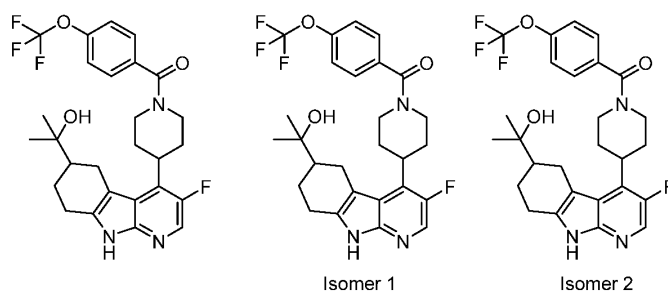
cyclobutane]-1'-carboxamide isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 573.2, found 573.5.

17 mg (8% yield on the two steps) of 3-fluoro-N,N-dimethyl-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxamide isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 573.2, found 573.4.

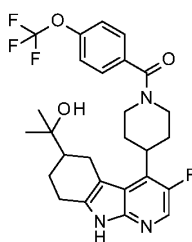
52 mg (24% yield on the two steps) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxylic acid isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 546.5, found 546.3.

40 mg (19% yield on the two steps) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-cyclobutane]-1'-carboxylic acid isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 546.5, found 546.3.

Examples 112, 101 & 102: (rac)-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, [4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2.



STEP 1 (example 112): (rac)-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

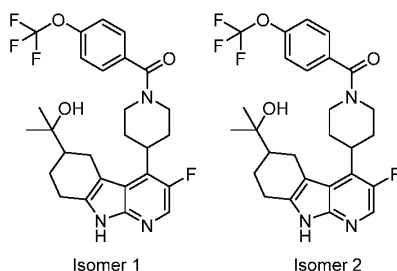


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Example 112 was prepared following the general method A using 4-(1-hydroxy-1-methyl-ethyl)cyclohexanone (276 mg, 1.77 mmol) in step 6, to give 237 mg (77% yield) of (rac)-[4-

[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 520.2, found 520.2.

- STEP 2 (examples 101 & 102):** [4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2.

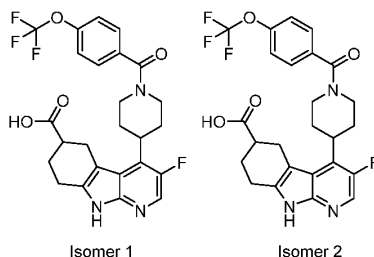


STEP 2 of examples 112, 101 & 102 was performed as followed:

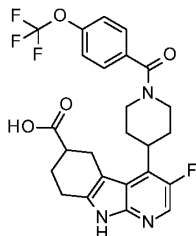
- General Chiral Separation Method CS#4:** Chiral separation of (rac)-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (212 mg, 0.41 mmol), was performed using a Chiralpak AY column (20 μ m, 350x76.5 mm), eluting with ((EtOH+0.1% TEA) 10%, heptane 90%), flow rate 400 mL / min, UV detection at 254 nm) gave 88 mg (41% yield) of [4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 520.2, found 520.3.

And 92 mg (43% yield) of [4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 520.2, found 520.3.

- Examples 103 & 104:** 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid isomer 1 and isomer 2.

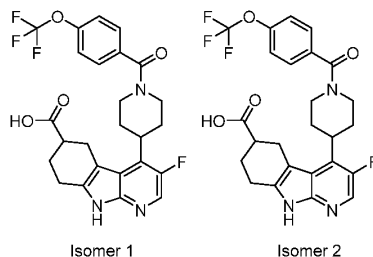


STEP 1: (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid



- 5 Step 1 of examples 103 & 104 was performed following the general method A using 4-oxocyclohexanecarboxylic acid (54 mg, 0.38 mmol) in step 6, to give 89 mg (60% yield) of (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid. LC/MS (m/z, M+H): calc. 506.2, found 506.3.

STEP 2: 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid isomer 1 and isomer 2.

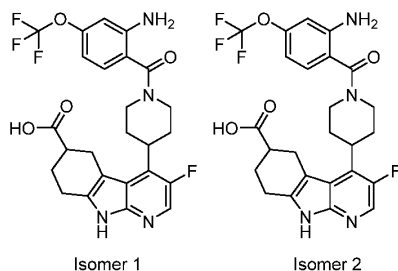


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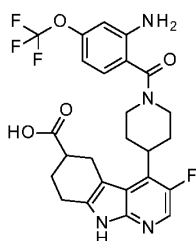
Step 2 of examples 103 & 104 was performed following the general chiral separation method CS#3 to give 9 mg (10% yield) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 506.2, found 506.3.

- 15 And 7 mg (8% yield) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 506.2, found 506.3.

Examples 105 & 106: 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid isomer 1 & isomer 2.

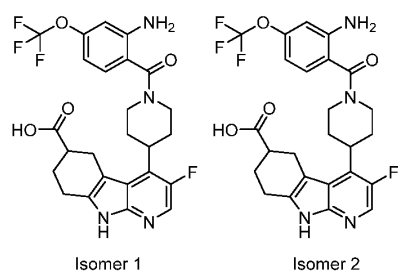


STEP 1: (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid



- 5 Step 1 of examples 105 & 106 was performed following the general method D using 4-oxocyclohexanecarboxylic acid (44 mg, 0.31 mmol) in step 2, to give 118 mg (94% yield) of (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid. LC/MS (m/z, M+H): calc. 521.2, found 521.3.

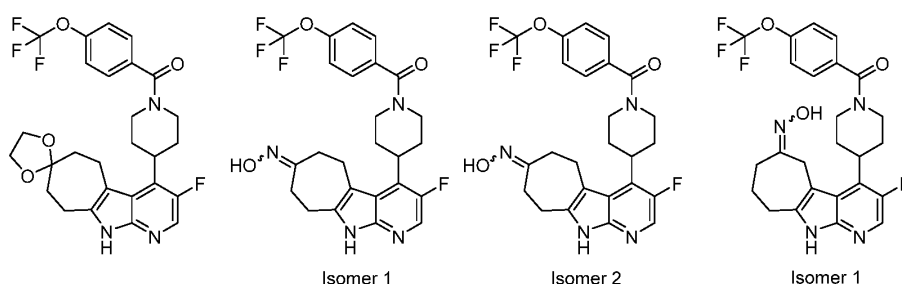
- STEP 2:** 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid isomer 1 & isomer 2.
- 10



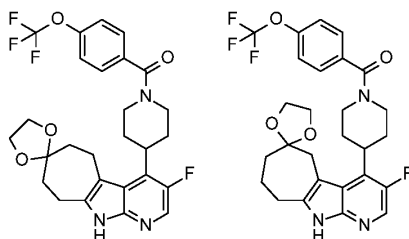
- Step 2 of examples 105 & 106 was performed following the general chiral separation method CS#3 to give 7 mg (6% yield) of: 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 521.2, found 521.3.
- 15

And 7 mg (6% yield) of 3: 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carboxylic acid isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 521.2, found 521.3.

- Examples 107, 108, 109 & 110:** [4-(4'-fluorospiro[1,3-dioxolane-2,12'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene]-3'-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, [4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomers 1 and 2, and [4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomer 1.

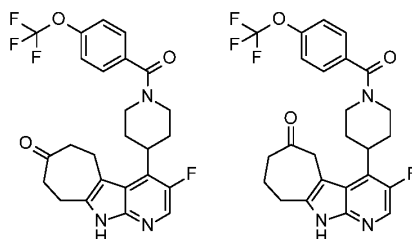


- STEP 1:** [4-(4'-fluorospiro[1,3-dioxolane-2,12'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene]-3'-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone and [4-(4'-fluorospiro[1,3-dioxolane-2,13'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene]-3'-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone.



- Step 1 of examples 107, 108, 109 & 110 was performed following the general method A using 1,4-dioxaspiro[4.6]undecan-8-one (500 mg, 3 mmol) in step 6, to give 250 mg (50% yield) of a 77/23 mixture of 4-(4'-fluorospiro[1,3-dioxolane-2,12'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene]-3'-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone and [4-(4'-fluorospiro[1,3-dioxolane-2,13'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene]-3'-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid which was engaged in the next step. LC/MS (m/z, M+H): calc. 534.2, found 534.3.

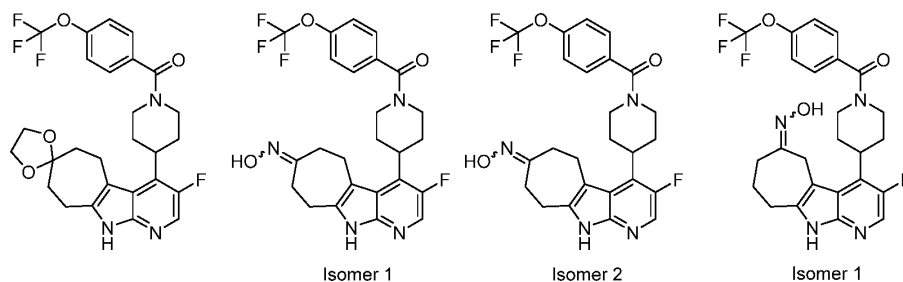
STEP 2: 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-12-one and 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one



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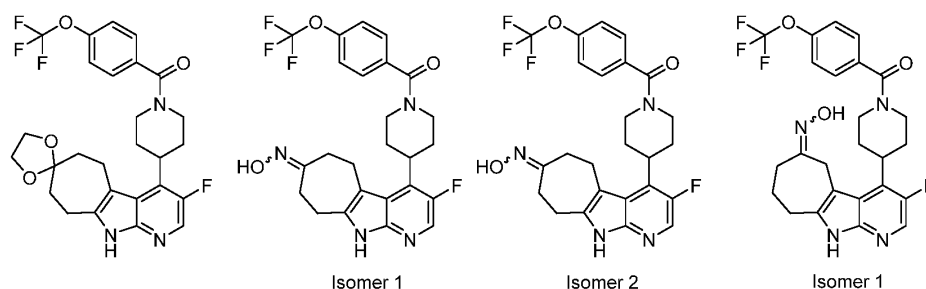
To a solution of the abovementioned mixture of 4-(4'-fluorospiro[1,3-dioxolane-2,12'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene]-3'-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone and [4-(4'-fluorospiro[1,3-dioxolane-2,13'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene]-3'-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (195 mg, 0.36 mmol) in DCM (2 mL), was added at room temperature, dropwise, 2 mL of TFA. The resulting reaction mixture was then stirred at room temperature for 16 hours, diluted with DCM and water, and a saturated aqueous solution of NaHCO₃ was slowly added until pH = 8. Then, the whole was transferred in a separating funnel, and the aqueous layer was extracted three times with DCM. The combined organic layers were then washed with a saturated aqueous solution of NaCl, dried over Na₂SO₄, filtered and concentrated to give 178 mg (100% yield) of a crude mixture of 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-12-one and 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one as a yellow solid which was engaged in the next step without further purification. LC/MS (m/z, M+H): calc. 490.2, found 490.3.

STEP 3: [4-(4'-fluorospiro[1,3-dioxolane-2,12'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene]-3'-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, [4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomers 1 and 2, and [4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomer 1.



To a solution of the abovementioned crude mixture of 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-12-one and 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one (225 mg, 0.46 mmol) in EtOH (2 mL), were added a solution of hydroxylamine (64 mg, 0.92 mmol) in water (1 mL) and sodium acetate (124 mg, 1.52 mol) and the resulting mixture was then stirred at 80 °C for 1 hour. Then, the reaction mixture was cooled down to room temperature, concentrated to dryness and the resulting residue was diluted with water and AE. The aqueous layer was extracted three times with AE and the combined organic layers were washed with water, with a saturated aqueous solution of NaHCO₃, dried over sodium sulfate, filtered and concentrated to dryness. The resulting crude residue was engaged in the next step.

STEP 4: [4-(4'-fluorospiro[1,3-dioxolane-2,12'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene]-3'-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, [4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomers 1 and 2, and [4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomer 1.



STEP 4 of examples 107, 108, 109 & 110 was performed as followed:

General Chiral Separation Method CS#5: Chiral separation of the abovementioned crude mixture (330 mg, 0.65 mmol), was performed using a Lux Cellulose-4 column (5 µm,

30x250 mm), eluting with (EtOH 12%, heptane 88%) + 0.1% TEA, flow rate 45 mL / min, UV detection at 280 nm) and gave:

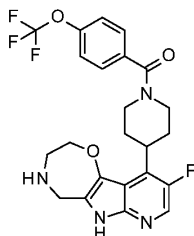
38 mg (11% yield) of [4-(4'-fluorospiro[1,3-dioxolane-2,12'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene]-3'-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (unreacted in step 2) as a white solid. LC/MS (m/z, M+H): calc. 534.2, found 534.3.

28 mg (8% yield) of [4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (Z/E configuration unknown) isomer 1 as a yellow solid. LC/MS (m/z, M+H): calc. 505.2, found 505.3.

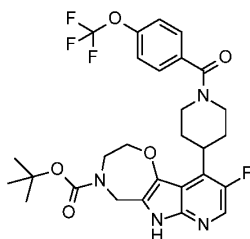
99 mg (30% yield) of [4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (Z/E configuration unknown) isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 505.2, found 505.3.

8 mg (2% yield) of [4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (Z/E configuration unknown) isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 505.2, found 505.3.

Example 113: [4-(4-fluoro-14-oxa-6,8,11-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

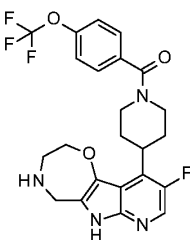


STEP 1: tert-butyl 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-14-oxa-6,8,11-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate

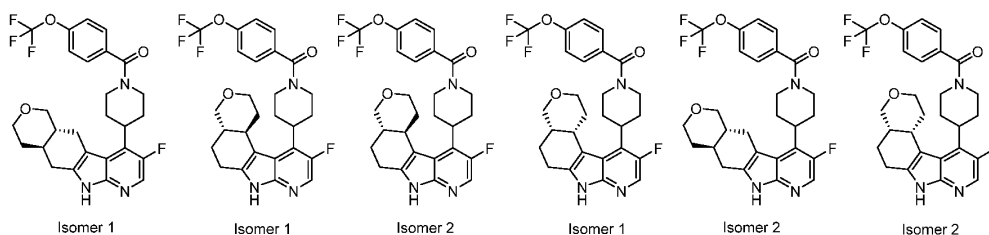


- Step 1 of example 113 was performed following the general method A using tert-butyl 6-oxo-1,4-oxazepane-4-carboxylate (507 mg, 2.36 mmol) in step 6, to give 20 mg (4% yield) of tert-butyl 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-14-oxa-6,8,11-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-11-carboxylate as a solid. LC/MS (m/z, M+H): calc. 579.2, found 579.4.

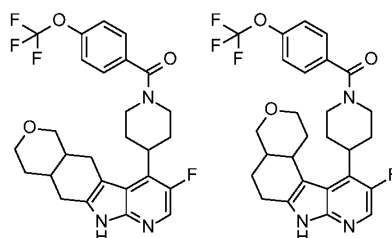
STEP 2: [4-(4-fluoro-14-oxa-6,8,11-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



- Step 2 of example 113 was performed following step 2 of the general method E (example 25) with a basic work up (aqueous saturated solution of NaHCO_3 to release HCl), to give 17 mg (100% yield) of [4-(4-fluoro-14-oxa-6,8,11-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M+H): calc. 479.2, found 479.3.
- Examples 114, 115, 116, 117, 118 & 119:** [4-[(trans)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomers 1 and 2, [4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomers 1 and 2, and [4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomers 1 and 2.

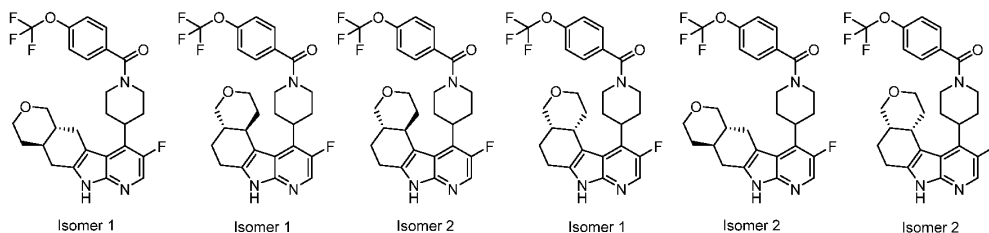


STEP 1: [4-(13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone & [4-(15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone.



Step 1 of examples 114, 115, 116, 117, 118 & 119 was performed following the general method A using 1,3,4,4a,5,7,8,8a-octahydroisochromen-6-one (272 mg, 1.77 mmol) in step 6, to give 122 mg (40% yield) of a mixture of 4-(13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone & [4-(15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid which was engaged in the next step for chiral separation.. LC/MS (m/z, M+H): calc. 518.2, found 518.3.

STEP 2: [4-[(trans)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1, [4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1, [4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2, [4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1, [4-[(trans)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 and [4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2.



Step 2 of examples 114, 115, 116, 117, 118 & 119 was performed following General Chiral Separation Method CS#3 (twice) to give:

8 mg (7% yield) of [4-[(trans)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 518.2, found 518.3.

16 mg (16% yield) of [4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 518.2, found 518.3.

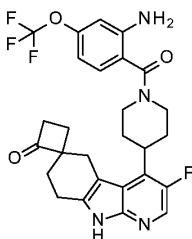
10 mg (9% yield) of [4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 518.2, found 518.3.

12 mg (10% yield) of [4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 518.2, found 518.3.

10 mg (9% yield) of [4-[(trans)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 518.2, found 518.3.

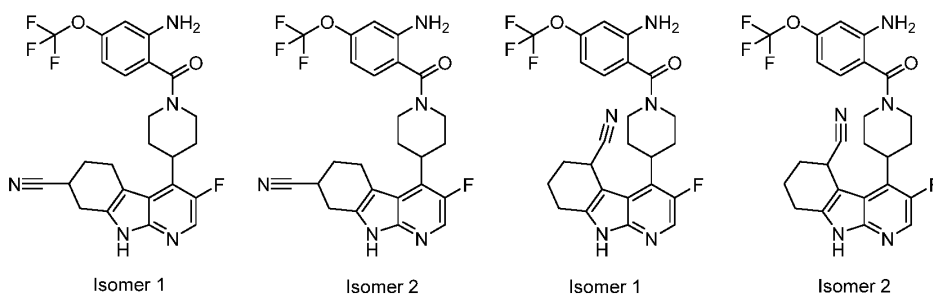
11 mg (10% yield) of [4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 518.2, found 518.3.

Example 120: (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,2'-cyclobutane]-1'-one

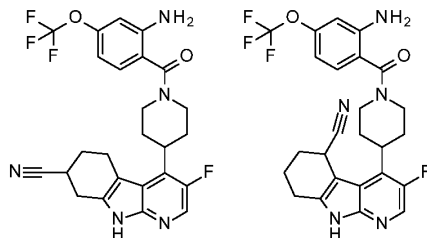


Example 120 was prepared following the protocol described in general method D, using spiro[3.5]nonane-3,7-dione (192 mg, 1.26 mmol) and Pd(OAc)₂ (4.5 mg, 0.02 mmol) instead of Pd[P(t-Bu)₃]₂ to give 60 mg (28% yield) of (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,2'-cyclobutane]-1'-one as a white solid. LC/MS (m/z, M+H): calc. 531.2, found 531.4.

Examples 121, 122, 123 & 124: 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile isomer 1 and isomer 2, 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile isomer 1 and isomer 2.

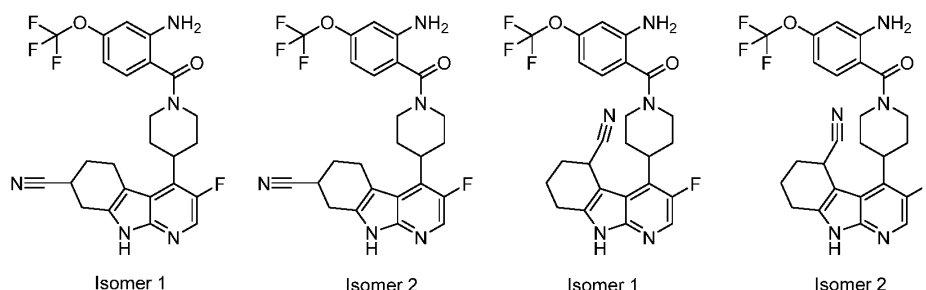


STEP 1: (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile & (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile.



Step 1 of examples 121, 122, 123 & 124 was performed following the general method D using 3-oxocyclohexanecarbonitrile (237 mg, 1.92 mmol) in step 2, to give 147 mg (46% yield) of a mixture of (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile & (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile as a solid which was engaged in the next step for chiral separation. LC/MS (m/z, M+H): calc. 502.2, found 502.2.

STEP 2: 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile isomer 1 and isomer 2, 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile isomer 1 & isomer 2.



Regioisomers separation of examples 121, 122, 123 & 124 was performed as followed:

General Chiral Separation Method CS#6: regioisomers separation of a mixture of (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile & (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile (144 mg, 0.14 mmol), was performed using a IC column (20 μ m, 350x80 mm), eluting with (EtOH 20%, n-heptane 80%)+0.1% TEA, flow rate 400 mL / min, UV detection at 254 nm)

Then, each couple of enantiomers was separated using the general chiral separation method CS#3 to give:

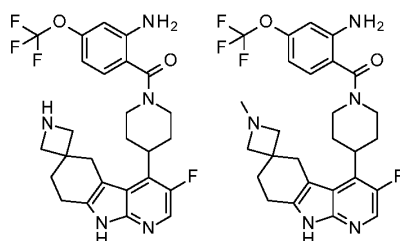
27 mg (19% yield) of 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 502.2, found 502.4.

26 mg (18% yield) of 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 502.2, found 502.3.

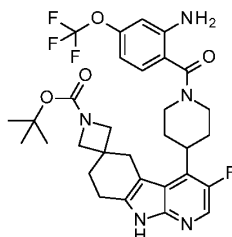
16 mg (11% yield) of 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile Isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 502.2, found 502.3.

18 mg (12% yield) of 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 502.2, found 502.3.

Examples 135 & 125: [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]methanone & [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-1'-methyl-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]methanone

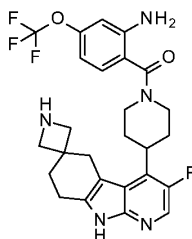


STEP 1: tert-butyl 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-1'-carboxylate



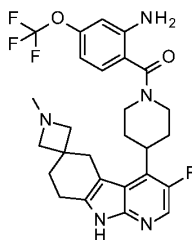
Step 1 of examples 135 & 125 was performed following the general method D using tert-butyl 7-oxo-2-azaspiro[3.5]nonane-2-carboxylate (335 mg, 1.40 mmol) in step 2, to give 154 mg (42% yield) of tert-butyl 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-1'-carboxylate as a yellow solid. LC/MS (m/z, M+H): calc. 618.3, found 618.4.

STEP 2 (example 135): [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]methanone



To a solution of tert-butyl 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-
 spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-1'-carboxylate (151 mg, 0.24
 mmol) in MeOH (2 mL) and DCM (1 mL) was added a 4N solution of HCl in 1,4-dioxane
 5 (0.61 mL, 2.44 mmol) and the resulting reaction mixture was stirred at room temperature for 2
 hours. Then, the whole was concentrated to dryness and the resulting residue was purified on
 silica gel (SiO₂ 4 g) eluting with DCM / MeOH / NH₄OH to give 108 mg (85% yield) of [2-
 amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-
 6,3'-azetidine]-4-yl)-1-piperidyl]methanone as pale brown solid. LC/MS (m/z, M+H): calc.
 10 518.2, found 518.3.

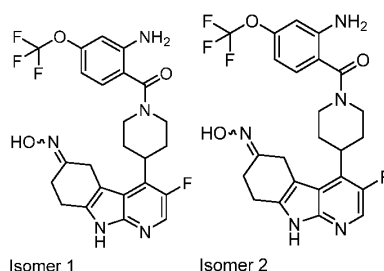
STEP 3 (example 125): [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-1'-methyl-
 spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]methanone



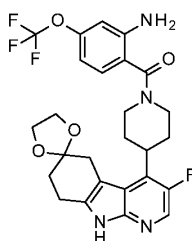
To a solution of [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-
 15 tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]methanone (95 mg, 0.18
 mmol) in DCM (4 mL) was added formaldehyde (16 mg, 0.20 mmol) and the resulting mixture
 was stirred for 15 minutes. Then, NaBH(OAc)₃ (77 mg, 0.37 mmol) was added and the
 resulting reaction mixture was stirred at room temperature for 4 hours, then, 2 mL of a 1N
 solution of NaOH was added, and the mixture was stirred for 15 additional minutes, filtered on
 20 a PTFE cartridge. The oily residue was diluted in 2 mL of MeOH and 0.5 mL of a 2N solution
 of NaOH was added followed by few drops of ethylenediamine and the whole mixture was
 stirred at room temperature for 1.5 hours, then the MeOH was concentrated, the mixture diluted
 with AE, washed with water. The organic layer was dried over sodium sulfate, filtered and
 concentrated. The resulting residue was purified on silica gel (SiO₂ 12 g) eluting with DCM /
 25 MeOH / NH₄OH 92 / 8 / 0.8 to give 66 mg (68% yield) of [2-amino-4-

(trifluoromethoxy)phenyl]-[4-(3-fluoro-1'-methyl-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]methanone as a white solid. LC/MS (m/z , $M+H$): calc. 532.2, found 532.3.

Examples 126 & 151: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone Isomer 1 & 2.

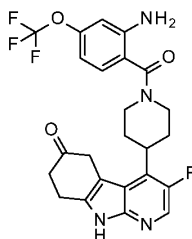


STEP 1: [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3'-fluorospiro[1,3-dioxolane-2,6'-5,7,8,9-tetrahydropyrido[2,3-b]indole]-4'-yl)-1-piperidyl]methanone



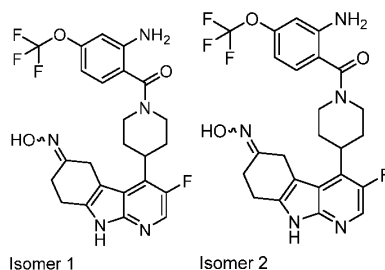
- 10 Step 1 of example 126 was performed following the general method D using 1,4-dioxaspiro[4.5]decan-8-one (472 mg, 3.02 mmol) and $\text{Pd}(\text{OAc})_2$ (11 mg, 0.05 mmol) instead of $\text{Pd}(\text{P}(\text{t-Bu})_3)_2$ in step 2, to give 230 mg (45% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3'-fluorospiro[1,3-dioxolane-2,6'-5,7,8,9-tetrahydropyrido[2,3-b]indole]-4'-yl)-1-piperidyl]methanone as a white solid. LC/MS (m/z , $M+H$): calc. 535.2,
- 15 found 535.2.

STEP 2: 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one



To a solution of [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3'-fluorospiro[1,3-dioxolane-2,6'-5,7,8,9-tetrahydropyrido[2,3-b]indole]-4'-yl)-1-piperidyl]methanone (230 mg, 0.43 mmol) in DCM (2.5 mL) was added TFA (2.5 mL) and the resulting reaction mixture was stirred at room temperature for 12 hours. Then, the whole mixture was diluted in DCM and then poured into a saturated aqueous solution of NaHCO₃. Then, the whole was extracted three times with DCM and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 15 g) eluting with DCM / [AE/ n-heptane / MeOH 85 / 10 / 5] 100/0 to 0/100 to give 165 mg (78% yield) of 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one as a pale brown solid. LC/MS (m/z, M+H): calc. 491.2, found 491.2.

STEP 3: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone Isomer 1 & 2.

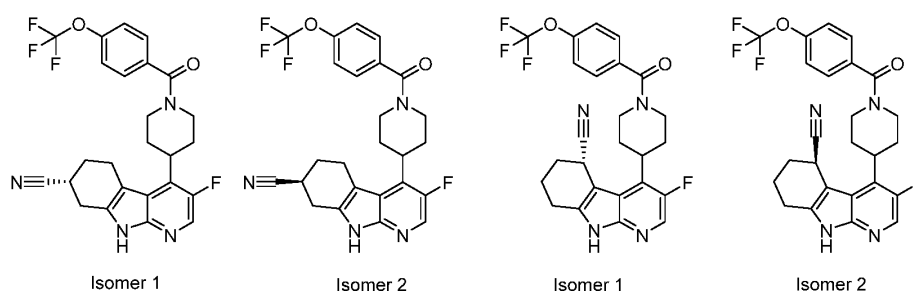


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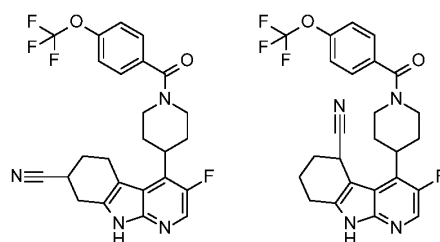
To a solution of 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one (165 mg, 0.34 mmol) in EtOH (1 mL) was added a solution of hydroxylamine hydrochloride (47 mg, 0.64 mmol) in water (0.5 mL) and a solution of sodium acetate (91 mg, 1.11 mmol) in water (0.5 mL). The resulting mixture was then stirred at 80 °C for 1 hour, then cool down to room temperature, concentrated to dryness and the resulting residue was purified by flash chromatography on silica gel (SiO₂ 4 g) eluting with DCM / [AE/ n-heptane / MeOH 85 / 10 / 5] 100/0 to 0/100 to give to give 7 mg (4%) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone Isomer 1 as a pale brown solid. LC/MS (m/z, M+H): calc. 506.2, found 506.3. And 85 mg (50% yield) of [2-amino-4-

(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone Isomer 2 as a pale brown solid. LC/MS (m/z, M+H): calc. 506.2, found 506.3.

Examples 127, 128, 129 & 130: 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile isomer 1 and isomer 2, 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile Isomer 1 and Isomer 2.

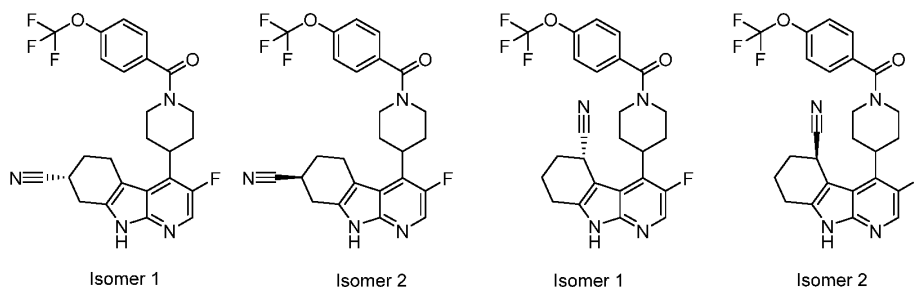


STEP 1: (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile and (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile



Step 1 of examples 127, 128, 129 & 130 was performed following the general method A using 3-oxocyclohexanecarbonitrile (254 mg, 2.06 mmol) in step 6, to give 236 mg (70% yield) of a 53/47 mixture of (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile and (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile as a yellow solid. LC/MS (m/z, M+H): calc. 487.2, found 487.2.

STEP 2: 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile isomer 1 and isomer 2, 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile isomer 1 & isomer 2.



Regioisomers and enantiomers separation of examples 127, 128, 129 & 130 was performed as followed:

- General Chiral Separation Method CS#7:** Chiral separation of the above-mentioned mixture (233 mg), using a chiralpak IC column (20 μ m, 350x76.5 mm), eluting with (n-heptane 80%, Ethanol 20%)+ 0.1% TEA, flow rate 400 mL / min, UV detection at 254 nm) gave the two couples of regioisomers which were then engaged in the following chiral separations :

Chiral separation of the first couple (100 mg) was performed using a chiralpak AS-H column (5 μ m, 250x30 mm), eluting with (CO₂ 60%, (MeOH+0.1%TEA) 40%), flow rate 110 mL / min, UV detection at 230 nm) gave

48mg (21% yield) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 487.2, found 487.3.

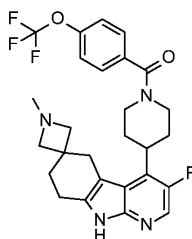
48mg (21% yield) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 487.2, found 487.3.

Chiral separation of the second couple (100 mg) was performed using a chiralpak AD-H column (5 μ m, 250x30 mm), eluting with (CO₂ 60%, (MeOH+0.1%TEA) 40%), flow rate 110 mL / min, UV detection at 230 nm) gave

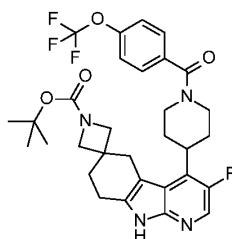
39 mg (17% yield) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 487.2, found 487.3.

38 mg (16% yield) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carbonitrile isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 487.2, found 487.3.

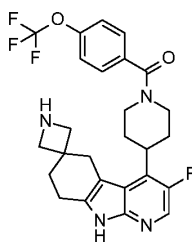
Example 131: [4-(3-fluoro-1'-methyl-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone.



STEP 1: tert-butyl 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-1'-carboxylate



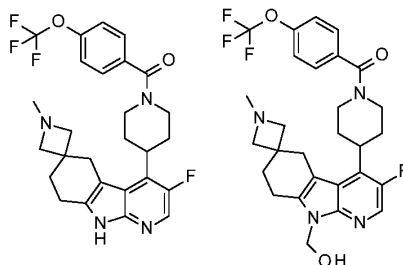
- 5 Step 1 of example 131 was performed following the general method A using tert-butyl 7-oxo-2-azaspiro[3.5]nonane-2-carboxylate (352 mg, 1.47 mmol) in step 6, to give 262 mg (74% yield) of tert-butyl 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-1'-carboxylate as a pale brown solid. LC/MS (m/z, M+H): calc. 603.2, found 603.4.
- 10 **STEP 2:** [4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



- Step 2 of example 131 was performed following the protocol described in step 2 of example 125 to give 195 mg (90% yield) of [4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a pale brown solid. LC/MS (m/z, M+H): calc. 503.2, found 503.3.
- 15

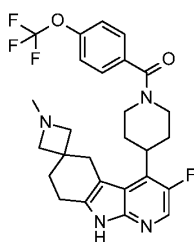
STEP 3: [4-(3-fluoro-1'-methyl-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone and [4-[3-fluoro-9-(hydroxymethyl)-

1'-methyl-spiro[7,8-dihydro-5H-pyrido[2,3-b]indole-6,3'-azetidine]-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone.



- To a solution of [of [4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (142 mg, 0.28 mmol) in DCM (5 mL) was added formaldehyde (25 mg, 0.31 mmol) and the resulting mixture was stirred for 15 minutes. Then, NaBH(OAc)₃ (119 mg, 0.56 mmol) was added and the resulting reaction mixture was stirred at room temperature for 1.5 hours, then, 2 mL of a 1N solution of NaOH was added, and the mixture was stirred for 15 additional minutes, filtered on a PTFE cartridge.
- The oily residue was purified on silica gel (SiO₂ 12 g) eluting with DCM / MeOH / NH₄OH 93 / 7 / 0.7 to give 157 mg (approx. 76% yield) of a 40/60 mixture of [[4-(3-fluoro-1'-methyl-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone and [4-[3-fluoro-9-(hydroxymethyl)-1'-methyl-spiro[7,8-dihydro-5H-pyrido[2,3-b]indole-6,3'-azetidine]-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a pale brown solid. LC/MS (m/z, M+H): calc. 517.2, found 517.3 and LC/MS (m/z, M+H): calc. 547.2, found 547.3.

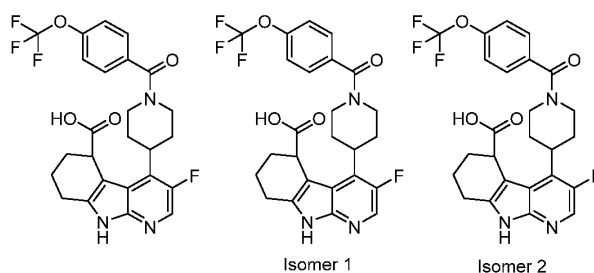
STEP 4: [4-(3-fluoro-1'-methyl-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



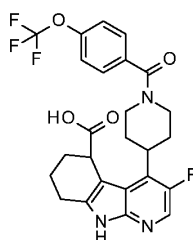
- To a solution of the abovementioned 40/60 mixture of [[4-(3-fluoro-1'-methyl-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone and [4-[3-fluoro-9-(hydroxymethyl)-1'-methyl-spiro[7,8-dihydro-5H-pyrido[2,3-b]indole-6,3'-azetidine]-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (154 mg) in MeOH (2 mL) was added a 2N solution of

NaOH (0.58 mL, 1.15 mmol) and the resulting reaction mixture was stirred at room temperature for 12 hours. Then, MeOH was concentrated and the resulting residue was diluted with AE, washed with water and the organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The resulting residue was then diluted in 2 mL of MeOH, and a 2N
 5 solution of NaOH (0.58 mL, 1.15 mmol) was added followed by 1 mL of THF and few drops of ethylenedimine and the resulting mixture was stirred at room temperature for 5 additional hours. Then, the whole mixture was concentrated, diluted with AE washed with water and the organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 12 g) eluting with DCM /
 10 MeOH / NH₄OH 93 / 7 / 0.7 to give 64 mg (43% yield) of [4-(3-fluoro-1'-methyl-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 517.2, found 517.3.

Examples 180, 132 & 133: (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-
 15 6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid, 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid isomer 1 & isomer 2.



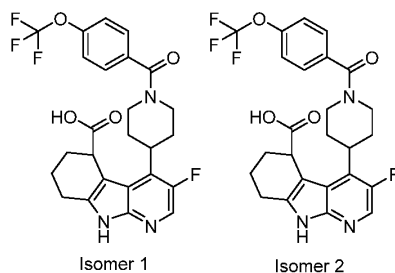
STEP 1 (example 180): (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-
 20 6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid



Step 1 of examples 180, 132 & 133 was performed following the general method A using 3-oxocyclohexanecarboxylic acid (293 mg, 2.06 mmol) in step 6, to give 244 mg (70% yield) of (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-

pyrido[2,3-b]indole-5-carboxylic acid as a white solid. LC/MS (m/z, M+H): calc. 506.2, found 506.2.

STEP 2 (examples 132 & 133): 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid isomer 1 & isomer 2.



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Step 2 of examples 180, 132 & 133 was performed following General Chiral Separation Method CS#3 to give:

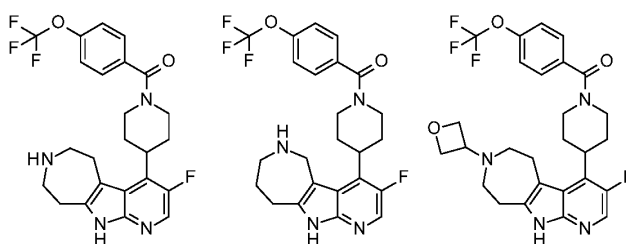
93 mg (44% yield) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 506.2, found 506.3.

10

90 mg (43% yield) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 506.2, found 506.3.

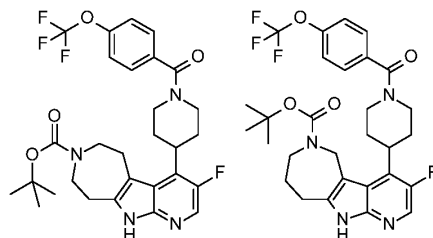
Examples 194, 195 & 134: [4-(4-fluoro-6,8,12-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, [4-(4-fluoro-6,8,13-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone & [4-[4-fluoro-12-(oxetan-3-yl)-6,8,12-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

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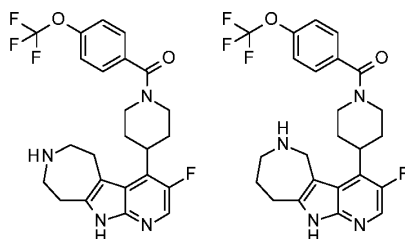
STEP 1 : tert-butyl 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,12-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate and tert-butyl 4-

fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-
 triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-13-carboxylate



- Step 1 of examples 194, 195 & 134 was performed following the general method A using tert-butyl 4-oxoazepane-1-carboxylate (1885 mg, 8.84 mmol) and Pd(OAc)₂ (33 mg, 0.15 mmol) instead of Pd(P(t-Bu)₃)₂ in step 6, to give 609 mg (35% yield) of a mixture of tert-butyl 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carboxylate and tert-butyl 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-13-carboxylate as a white solid. LC/MS (m/z, M+H): calc. 577.2, found 577.3.

- STEP 2 (examples 194 and 195):** [4-(4-fluoro-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone & [4-(4-fluoro-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

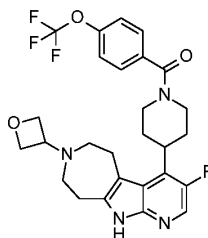


Step 2 of examples 194, 195 & 134 was performed following the protocol described in step 2 of example 125 to give:

- 202 mg (40% yield) of 4-(4-fluoro-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 477.2, found 477.2.

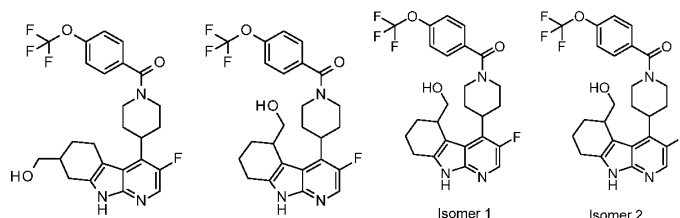
And 250 mg of [4-(4-fluoro-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 477.2, found 477.2.

STEP 3 (example 134): [4-[4-fluoro-12-(oxetan-3-yl)-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

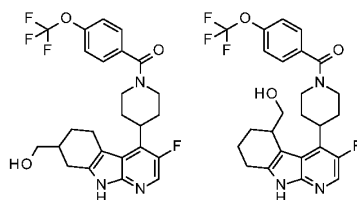


- 5 To a solution of [4-(4-fluoro-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (50 mg, 0.1 mmol) in DCM (8 mL) were successively added acetic acid (0.03 mL, 0.52 mmol) and 3-oxetanone (32 mg, 0.42 mmol). The resulting reaction mixture was stirred for 15 minutes at room temperature and NaBH(OAc)₃ (67 mg, 0.31 mmol) was added and the resulting mixture was stirred at room
- 10 temperature for 16 hours, then diluted with AE and poured onto an aqueous saturated solution of NaHCO₃. The aqueous layer was extracted with AE and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to dryness. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 4 g) eluting with DCM / [DCM/MeOH 90/10] 100/0 to 0/100 to give 44 mg (78% yield) of [4-[4-fluoro-12-(oxetan-3-yl)-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-
- 15 piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 533.2, found 533.5.

- Examples 188, 193, 136 & 137:** (rac)-[4-[3-fluoro-7-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, (rac)-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, [4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2
- 20



STEP 1 (examples 188 & 193): (rac)-[4-[3-fluoro-7-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, (rac)-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



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Step 1 of examples 188 & 193 was performed following the general method A using 3-(hydroxymethyl)cyclohexanone (264 mg, 2.06 mmol) in step 6, to give:

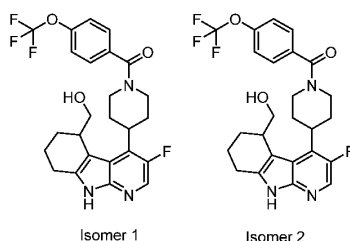
17 mg (5% yield) of (rac)-[4-[3-fluoro-7-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a pale brown solid.

10 LC/MS (m/z, M+H): calc. 492.2, found 492.3.

And 206 mg (61% yield) of (rac)-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 492.2, found 492.3.

STEP 2 (Examples 136 & 137): [4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2

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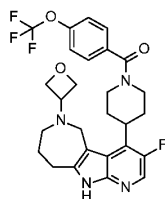
Step 2 of examples 188, 193, 136 & 137 was performed as followed: Chiral separation of (rac)-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (182 mg, 0.37 mmol) was realized using General Chiral Separation Method CS#4 to give:

20

76 mg (42% yield) of [4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 492.2, found 492.3.

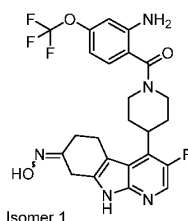
78 mg (43% yield) of [4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 492.2, found 492.3.

Example 138: [4-[4-fluoro-13-(oxetan-3-yl)-6,8,13-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



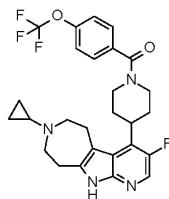
Example 138 was prepared following the protocol described in step 3 of examples 194, 195 & 134 using [4-(4-fluoro-6,8,13-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (described in step 2 of examples 194, 195 & 134, 50 mg, 0.1 mmol), to give 37 mg (66% yield) of [4-[4-fluoro-13-(oxetan-3-yl)-6,8,13-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 533.2, found 533.3.

Example 139: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone Isomer 1



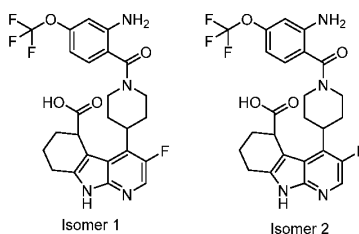
Example 139 prepared following the protocol described in step 3 of examples 126 & 151, using 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,6,8,9-tetrahydropyrido[2,3-b]indol-7-one (example 50, 45 mg, 0.09 mmol) to give 24 mg (52% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone Isomer 1 as a solid. LC/MS (m/z, M+H): calc. 506.2, found 506.1.

Example 140: [4-(12-cyclopropyl-4-fluoro-6,8,12-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

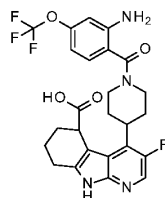


- To a solution of [4-(4-fluoro-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (example 194, 100 mg, 0.21 mmol) in THF (5 mL) and MeOH (1 mL) were successively added (1-ethoxycyclopropoxy)trimethylsilane (146 mg., 0.84 mmol), acetic acid (24 μ L, 0.42 mmol) and sodium cyanoborohydride (33 mg, 0.52 mmol). The resulting mixture was then stirred at 80 °C for 4 hours, then cooled down to room temperature, diluted with AE. The whole mixture was transferred in a separating funnel, washed with an aqueous saturated solution of NaHCO₃. The aqueous layer was extracted with AE and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated to dryness. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 12 g) eluting with DCM / [DCM / MeOH 9/1] from 100/0 to 0/100 and again on silica gel (SiO₂ 4 g) eluting with n-Heptane / [AE/ n-Heptane / MeOH 85/10/5] from 100/0 to 0/100 to give 77% (71% yield) of 4-(12-cyclopropyl-4-fluoro-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 517.2, found 517.3.

Examples 141 & 142: 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid isomer 1 & isomer 2

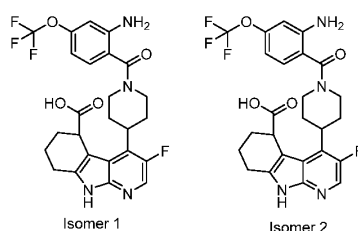


- STEP 1:** (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid



Step 1 of examples 141 & 142 was performed following the general method D using 3-oxocyclohexanecarboxylic acid (205 mg, 1.45 mmol) in step 2, to give 111 mg (33% yield) of (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid as a brown solid. LC/MS (m/z, M+H): calc. 521.2, found 521.2.

STEP 2: 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid isomer 1 & isomer 2

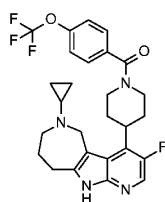


Step 2 of examples 141 & 142 was performed following General Chiral Separation Method CS#3 to give:

29 mg (27% yield) of 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 521.2, found 521.2.

28 mg (26% yield) of 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-5-carboxylic acid isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 521.2, found 521.2.

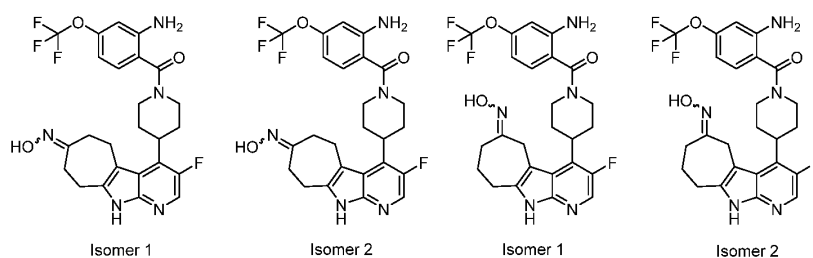
Example 143: [4-(13-cyclopropyl-4-fluoro-6,8,13-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



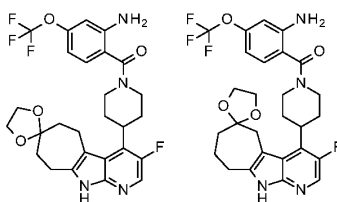
Example 143 was prepared following the protocol described for the preparation of example 140 using [4-(4-fluoro-6,8,13-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (example 195 (step 2 of examples 194, 195 & 134), 100 mg, 0.21 mmol) to give 40 mg (37% yield) of [4-(13-cyclopropyl-4-fluoro-6,8,13-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-

(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z , $M+H$): calc. 517.2, found 517.2.

- Examples 144, 145, 146 & 147:** [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone Isomers 1 and 2, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone Isomers 1 and 2.

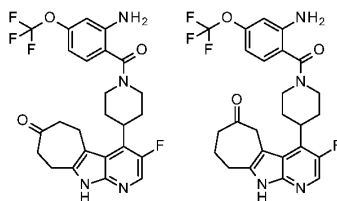


- STEP 1:** [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4'-fluorospiro[1,3-dioxolane-2,12'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraene]-3'-yl)-1-piperidyl]methanone & [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4'-fluorospiro[1,3-dioxolane-2,13'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraene]-3'-yl)-1-piperidyl]methanone



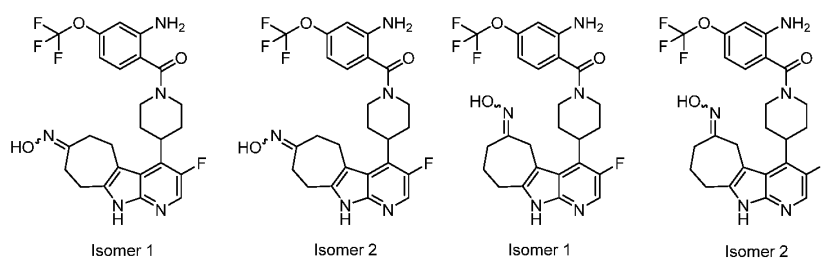
- Step 1 of examples 144, 145, 146 & 147 was performed following the general method D using 1,4-dioxaspiro[4.6]undecan-8-one (818 mg, 4.80 mmol) in step 2, to give 425 mg (48% yield) of a 76/24 mixture of [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4'-fluorospiro[1,3-dioxolane-2,12'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraene]-3'-yl)-1-piperidyl]methanone & [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4'-fluorospiro[1,3-dioxolane-2,13'-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraene]-3'-yl)-1-piperidyl]methanone as a pale brown solid. LC/MS (m/z , $M+H$): calc. 549.2, found 549.3.

STEP 2: 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-12-one & 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-13-one



- To a solution of the abovementioned 76/24 mixture of [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4'-fluorospiro[1,3-dioxolane-2,12'-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraene]-3'-yl)-1-piperidyl]methanone & [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4'-fluorospiro[1,3-dioxolane-2,13'-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraene]-3'-yl)-1-piperidyl]methanone (422 mg, 0.77 mmol) in DCM (4 mL) was added TFA (1.18 mL, 15.39 mmol) and the resulting reaction mixture was stirred at room temperature for 18 hours, then diluted with DCM (6 mL) and water (4 mL), and at 0 °C, under vigorous stirring, concentrated NaOH was added dropwise (1.54 mL, 16.15 mmol). After 10 additional minutes of stirring, DCM was concentrated and the resulting residue was diluted with AE and the whole was washed with a 2N solution of NaOH. The aqueous layer was extracted with AE and the combined organic layers were washed with a 2N solution of NaOH, dried over sodium sulfate, filtered and concentrated. The resulting residue was triturated in i-Pr₂O, filtered, to give 373 mg (96% yield) of a 78/22 mixture of 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-12-one & 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-13-one as a pale brown solid. LC/MS (m/z, M+H): calc. 505.2, found 505.3.

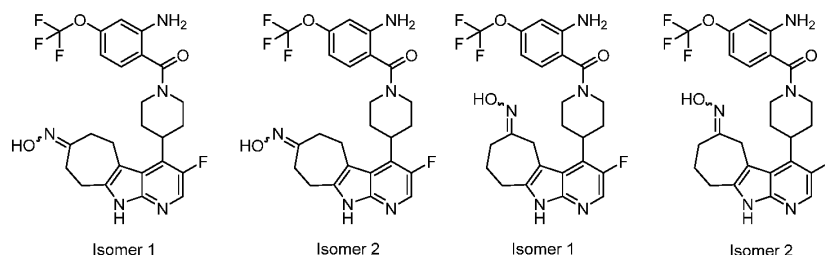
- STEP 3:** [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone Isomers 1 and 2, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone Isomers 1 and 2.



- To a solution of the abovementioned 78/22 mixture of 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-

- 1(9),2,4,6-tetraen-12-one & 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-13-one (320 mg, 0.63 mmol) in EtOH (3 mL) and water (3 mL) were added sodium acetate (172 mg, 2.09 mmol) and hydroxylamine hydrochloride (88 mg, 1.27 mmol) and the resulting reaction mixture was stirred for one hour at 80 °C, then cooled down to room temperature, diluted with AE and the whole was washed with an aqueous saturated solution of NaHCO₃, dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 25 g) eluting with DCM / MeOH / NH₄OH 95 / 5 / 0.5 to give 336 mg (88% yield) of a mixture of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone Isomers 1 and 2, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone Isomers 1 and 2 as a pale brown solid. LC/MS (m/z, M+H): calc. 520.2, found 520.2.

- STEP 4:** [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone Isomers 1 and 2, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone Isomers 1 and 2.



- The abovementioned mixture (333 mg, 0.64 mmol) was purified as followed:

General Chiral Separation Method CS#8: Separation of the abovementioned mixture was performed using a OD-I column (20 µm, 350x80 mm), eluting with (EtOH 25%, n-heptane 75%)+0.1% TEA, flow rate 400 mL / min, UV detection at 230 nm) to give:

- 64 mg (19% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone Isomer 1 as a solid. LC/MS (m/z, M+H): calc. 520.2, found 520.3.

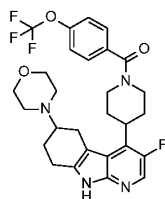
211 mg (63% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone Isomer 2 as a solid. LC/MS (m/z, M+H): calc. 520.2, found 520.3.

A third fraction with a mixture of the 2 remaining isomers was then purified following the General Chiral Separation Method CS#3 to give:

27 mg (8% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone Isomer 1 as a solid. LC/MS (m/z, M+H): calc. 520.2, found 520.3.

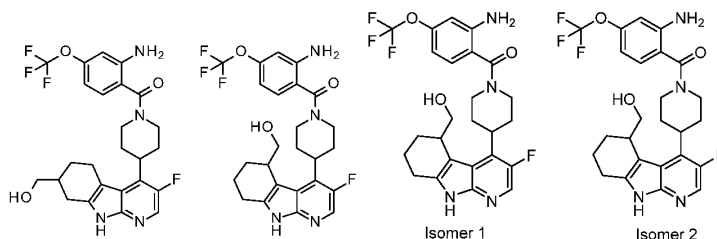
21 mg (6% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone Isomer 2 as a solid. LC/MS (m/z, M+H): calc. 520.2, found 520.3.

Example 148: (rac)-[4-(3-fluoro-6-morpholino-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



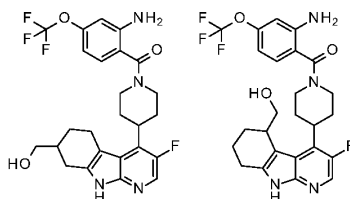
Example 148 was prepared following the general method A using 4-morpholinocyclohexanone (144 mg, 0.78 mmol) in step 6, to give 55 mg (26% yield) of (rac)-[4-(3-fluoro-6-morpholino-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M+H): calc. 547.2, found 547.2.

Examples 191, 192, 149 & 150: (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 1 & isomer 2



STEP 1 (Examples 191 & 192): (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone,

(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone

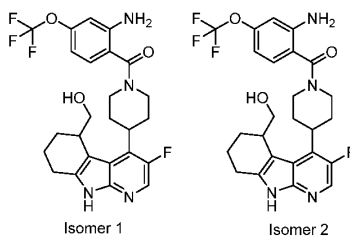


STEP 1 of examples 191, 192, 149 & 150 was prepared following the general method D using
 5 3-(hydroxymethyl)cyclohexanone (246 mg, 1.92 mmol) in step 2, to give:

18 mg (5% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone as a pale brown solid. LC/MS (m/z, M+H): calc. 507.2, found 507.3.

And 151 mg (46% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone as a
 10 pale brown solid. LC/MS (m/z, M+H): calc. 507.2, found 507.3.

STEP 2 (examples 149 & 150): [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone
 isomer 1 & isomer 2



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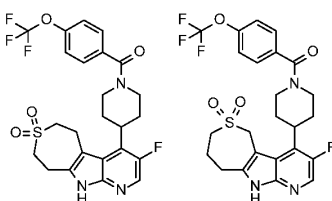
(rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone (133 mg, 0.26 mmol) was engaged in chiral separation as followed:

General Chiral Separation Method CS#9: Separation of the abovementioned mixture was
 20 performed using a chiralpak AD column (20 μ m, 350x76.5 mm), eluting with (EtOH 20%, n-heptane 80%)+0.1% TEA, flow rate 400 mL / min, UV detection at 280 nm) to give:

59 mg (44% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 507.2, found 507.2.

59 mg (44% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 507.2, found 507.2.

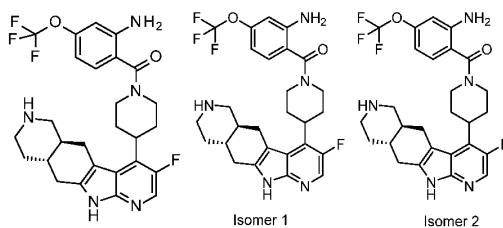
- Examples 152 & 153:** [4-(4-fluoro-12,12-dioxo-12 λ^6 -thia-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone & [4-(4-fluoro-13,13-dioxo-13 λ^6 -thia-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



- 10 Examples 152 & 153 were prepared following the general method A using 1 λ^6 -thiephane-1,1,4-trione (191 mg, 1.18 mmol) and Pd(OAc)₂ (4 mg, 0.02 mmol) instead of Pd(P(t-Bu)₃)₂ in step 6, to give 13 mg (6% yield) of [4-(4-fluoro-12,12-dioxo-12 λ^6 -thia-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 526.1, found 526.3,

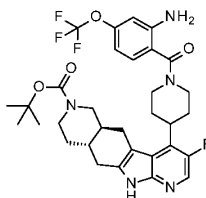
And 50 mg (24% yield) of [4-(4-fluoro-13,13-dioxo-13 λ^6 -thia-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 526.1, found 526.2.

- 20 **Examples 206, 154 and 155:** (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone isomer 1 and isomer 2.



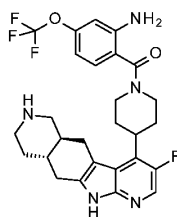
25

STEP 1: tert-butyl 12-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl](trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraene-6-carboxylate

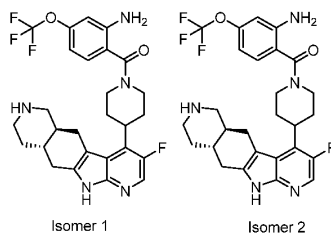


- 5 STEP 1 of examples 206, 154 & 155 was performed following the general method D using (rac)-trans-N-Boc-octahydroisoquinolin-6-one (426 mg, 1.68 mmol) and DMA (1.9 mL) instead of DMF as solvent in step 2, to give 130 mg (37% yield) of tert-butyl 12-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl](trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraene-6-carboxylate as a white solid. LC/MS (m/z, M+H): calc. 632.3, found 632.3.
- 10

STEP 2 (example 206): (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone



- 15 Step 2 of examples 206, 154 & 155 was performed following the protocol described in step 2 of example 125 to give 95 mg (88% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 532.2, found 532.3.
- 20 **STEP 3 (examples 154 & 155):** [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone isomer 1 and isomer 2.

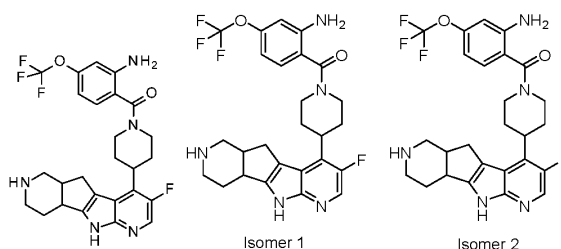


Step 3 of examples 206, 154 & 155 was performed following General Chiral Separation Method CS#5 to give:

- 30 mg (39% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone isomer 1 as a white solid. LC/MS (m/z , $M+H$): calc. 532.2, found 532.4.

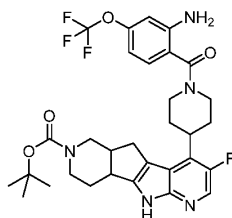
And 28 mg (36% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone isomer 2 as a white solid. LC/MS (m/z , $M+H$): calc. 532.2, found 532.3.

- 10 **Examples 205, 156 & 157:** (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans or cis)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone, and [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans or cis)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone isomer 1 & isomer 2.



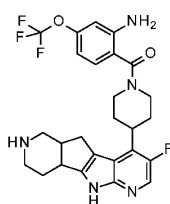
15

STEP 1: (rac)-tert-butyl 11-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-(trans or cis)12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraene-5-carboxylate



STEP 1 of examples 156 & 157 was performed following the general method D using (rac)-tert-butyl 5-oxo-3,4,4a,6,7,7a-hexahydro-1H-cyclopenta[c]pyridine-2-carboxylate (402 mg, 1.68 mmol) and DMA (1.9 mL) instead of DMF as solvent in step 2, to give 94 mg (27% yield) of (rac)-tert-butyl 11-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-(trans or cis)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.0.2,7.0.10,15]hexadeca-1(9),10,12,14-tetraene-5-carboxylate as a white solid. LC/MS (m/z, M+H): calc. 618.3, found 618.3.

STEP 2 (example 205): (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans or cis)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.0.2,7.0.10,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone

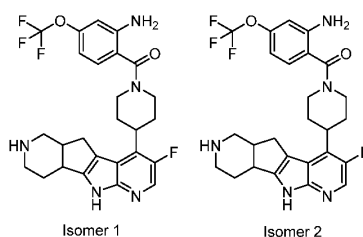


10

Step 2 of examples 205, 156 & 157 was performed following the protocol described in step 2 of example 125 to give 72 mg (94% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans or cis)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.0.2,7.0.10,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 518.2, found 518.3.

15

STEP 3 (examples 156 & 157): [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans or cis)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.0.2,7.0.10,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone isomer 1 & isomer 2.

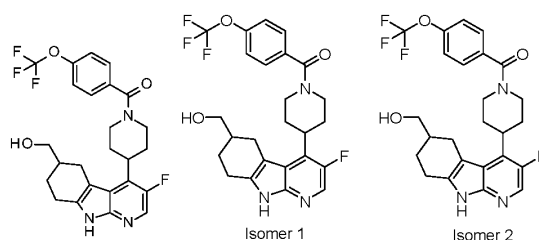


20 Step 3 of examples 205, 156 & 157 was performed following General Chiral Separation Method CS#1 to give:

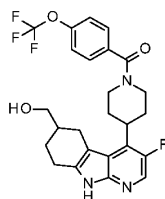
24 mg (38% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans or cis)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.0.2,7.0.10,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 518.2, found 518.4.

And 24 mg (38% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans or cis)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.0.2,7.0.10,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 518.2, found 518.3.

Examples 198, 158 & 159: (rac)-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, and [4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2.

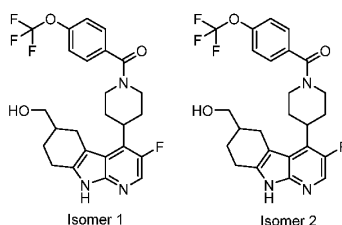


STEP 1 (example 198): (rac)-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



Step 1 of examples 198, 158 & 159 was performed following the general method A using 4-(hydroxymethyl)cyclohexanone (113 mg, 0.88 mmol) in step 6, to give 50 mg (34% yield) of (rac)-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 492.2, found 492.3.

STEP 2 (examples 158 & 159): [4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2.



20

Step 2 of examples 198, 158 & 159 was performed following General Chiral Separation Method CS#1 to give:

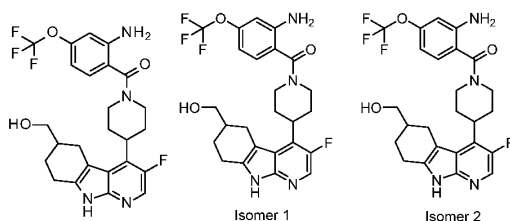
14 mg (41% yield) of [4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a white solid.

5 LC/MS (m/z, M+H): calc. 492.2, found 492.3.

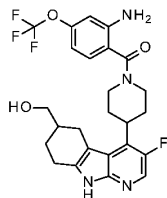
And 13 mg (38% yield) of [4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a white solid.

LC/MS (m/z, M+H): calc. 492.2, found 492.3.

Examples 200, 160 & 161: (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 1 & isomer 2.

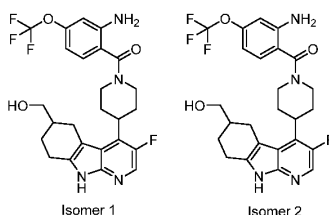


STEP 1 (example 200): (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



STEP 1 of examples 160 & 161 was performed following the general method D using 4-(hydroxymethyl)cyclohexanone (92 mg, 0.72 mmol) in step 2, to give 42 mg (34% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 507.2, found 507.3.

STEP 2 (examples 160 & 161): [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 1 & isomer 2.

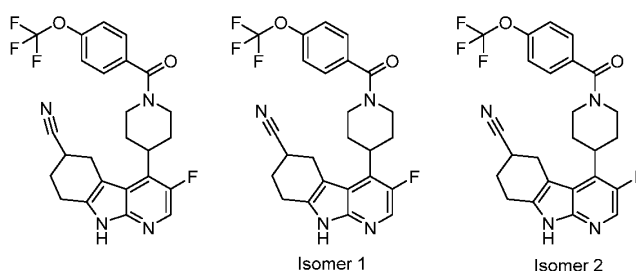


Step 2 of examples 200, 160 & 161 was performed following General Chiral Separation Method CS#3 to give:

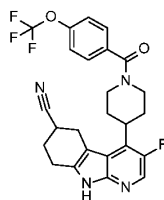
- 7 mg (23% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 507.2, found 507.3.

And 7 mg (23% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 507.2, found 507.3.

- 10 **Examples 208, 162 & 163:** (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile, 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile isomer 1 & isomer 2.



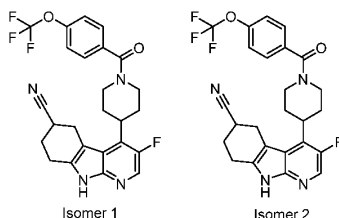
- 15 **STEP 1 (example 208):** (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile



Step 1 of examples 208, 162 & 163 was performed following the general method A using 4-oxocyclohexanecarbonitrile (47 mg, 0.38 mmol) in step 6, to give 85 mg (59% yield) of (rac)-

3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile as a white solid. LC/MS (m/z, M+H): calc. 487.2, found 487.3.

STEP 2 (examples 162 & 163): 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile isomer 1 & isomer 2.



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Step 2 of examples 200, 160 & 161 was performed following General Chiral Separation Method CS#3 to give:

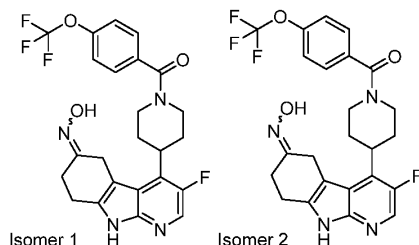
29 mg (38% yield) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 487.2, found 487.3.

10

And 28 mg (37% yield) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 487.2, found 487.3.

Examples 164 & 165: [4-[3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomers 1 and 2.

15



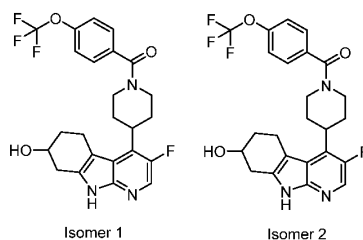
Examples 164 & 165 were prepared following the protocol described in step 3 of examples 126 & 151 using 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one (example 61, 220 mg, 0.46 mmol) to give :

80 mg (35%) of [4-[3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 491.2, found 491.3.

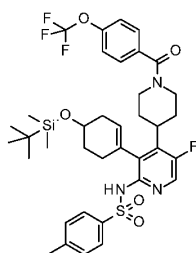
20

And 18 mg (8% yield) of [4-[3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomer 2 as a yellow solid. LC/MS (m/z , $M+H$): calc. 491.2, found 491.3.

Examples 166 & 167: [4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2.

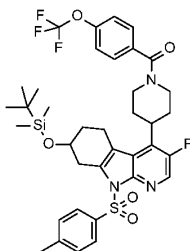


STEP 1: (rac)-N-[3-[4-[tert-butyl(dimethyl)silyl]oxycyclohexen-1-yl]-5-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-2-pyridyl]-4-methyl-benzenesulfonamide



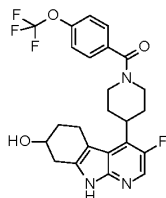
- 10 Step 1 of examples 166 & 167 was performed following the protocol described in step 2 of example 15 (Method B) using (rac)-tert-butyl(dimethyl)((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)oxy)silane (190 mg, 0.56 mmol) and tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.03 mmol) instead of dichlorobis(triphenylphosphine)palladium(II), and 1,4-dioxane (3 mL) instead of DMF, to give
- 15 275 mg (81% yield) of (rac)-N-[3-[4-[tert-butyl(dimethyl)silyl]oxycyclohexen-1-yl]-5-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-2-pyridyl]-4-methyl-benzenesulfonamide as a yellow solid. LC/MS (m/z , $M+H$): calc. 748.3, found 748.4.

STEP 2: [4-[7-[tert-butyl(dimethyl)silyl]oxy-3-fluoro-9-(p-tolylsulfonyl)-5,6,7,8-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



To a solution of N-[3-[4-[tert-butyl(dimethyl)silyl]oxycyclohexen-1-yl]-5-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-2-pyridyl]-4-methyl-benzenesulfonamide (270 mg, 0,361 mmol) in DMF (5 mL) was added silver carbonate (140 mg, 0.51 mmol) and the resulting mixture was stirred at 150 °C for 3 hours, then additional silver carbonate (140 mg, 0.51 mmol) was added and the resulting mixture was stirred at 150 °C for 12 additional hours. The whole mixture was then cooled down to room temperature, diluted with AE and water, filtered on clarcel. The aqueous layer was extracted with AE and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 12 g), eluting with cyclohexane / AE from 95 / 5 to 8 / 2 to give 89 mg (33% yield) of [4-[7-[tert-butyl(dimethyl)silyl]oxy-3-fluoro-9-(p-tolylsulfonyl)-5,6,7,8-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as an orange solid. LC/MS (m/z, M+H): calc. 746.3, found 746.3.

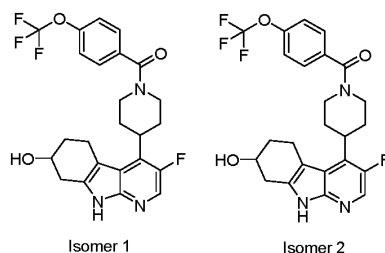
STEP 3: (rac)-[4-(3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



To a solution of [4-[7-[tert-butyl(dimethyl)silyl]oxy-3-fluoro-9-(p-tolylsulfonyl)-5,6,7,8-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (85 mg, 0,114 mmol) in EtOH (2 mL) was added a 10 N solution of NaOH (0.06 mL, 0.6 mmol) and the resulting mixture was stirred at 85 °C for one hour. After one hour, the reaction mixture was cooled down to 5 °C and a 4 M solution of HCl in 1,4-dioxane (0.45 mL, 1.8 mmol) was carefully added and the resulting mixture was then stirred at room temperature for 12 hours, then diluted with 50 mL of AE and 50 mL of an aqueous saturated solution of NaHCO₃. The aqueous layer was extracted with 50 mL of AE and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting residue was purified by flash

chromatography on silica gel (SiO₂ 12 g) eluting with DCM / [DCM/MeOH 95/5] 100/0 to 0/100 to give 32 mg (58% yield) of (rac)-[4-(3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 478.2, found 478.1.

- 5 **STEP 4:** [4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2.



Step 4 of examples 166 & 167 was performed following General Chiral Separation Method CS#3 to give:

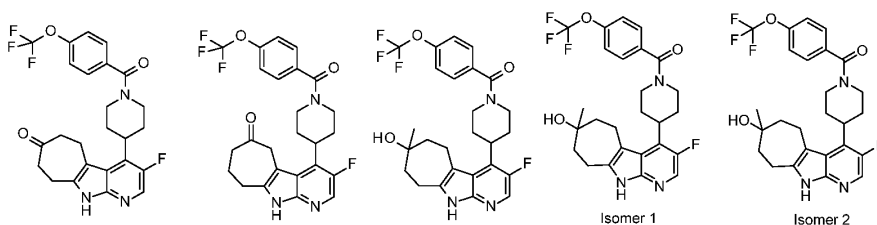
- 10 27 mg (39% yield) of 4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 478.2, found 478.3.

And 29 mg (42% yield) of 4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a white solid. LC/MS

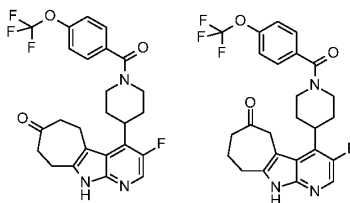
- 15 (m/z, M+H): calc. 478.2, found 478.3.

Examples 211, 212, 225, 168 & 169: 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-12-one, 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-13-one,

- 20 (rac)-[4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, [4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2



STEP 1 (examples 211 & 212): 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-12-one, 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one



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mixture of 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-12-one and 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one (96 mg, 0.2 mmol, previously obtained in step 2 of examples 107, 108, 109 & 110) was separated as followed:

10

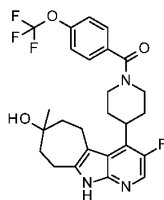
General Chiral Separation Method CS#10: Separation of the abovementioned mixture was performed using a Chiracel OJ-H column (5 μ m, 300x50 mm), eluting with (CO₂ 85%, (EtOH+0.1% TEA) 15%), flow rate 220 mL / min, UV detection at 230 nm) to give:

56 mg (58% yield) of 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-12-one as a solid. LC/MS (m/z, M+H): calc. 490.2, found 490.4.

15

17 mg (18% yield) of 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-13-one as a solid. LC/MS (m/z, M+H): calc. 490.2, found 490.4.

STEP 2 (Example 225): (rac)-[4-(4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

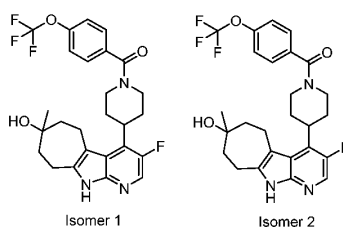


At 0 °C, under argon atmosphere, to a solution of methylmagnesium bromide (1 M solution in THF, 0.61 mL, 0.61 mmol) in THF (1 mL) were successively added diethylene glycol diethyl

25

ether (0.1 mL, 132 mg, 0.82 mmol) and tetrabutylammonium chloride (136 mg, 0.49 mmol) and the resulting mixture was stirred for 30 minutes at 0 °C. Then, a solution of 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-12-one (example 211, 200 mg, 0.41 mmol) in THF (5 mL) was added. The resulting mixture was stirred for one hour, and 0.65 mL of methyl magnesium bromide (0.65 mmol) were added followed by diethylene glycol diethyl ether (0.2 mL, 264 mg, 1.64 mmol) and tetrabutylammonium chloride (60 mg, 0.22 mmol) in 2 mL of THF. The resulting mixture was warmed up to room temperature, and 0.65 mL of methyl magnesium bromide (0.65 mmol) were added, the mixture was stirred for 12 hours, and 0.5 mL of methyl magnesium bromide (0.5 mmol) were added, the mixture was stirred for 5 hours, and 0.9 mL of methyl magnesium bromide (0.9 mmol) were added, the mixture was stirred for 12 hours. Then, at 0 °C, the reaction mixture was diluted with an aqueous saturated solution of NH₄Cl, and AE. The aqueous layer was extracted three times with AE and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 25 g), eluting with heptane / i-PrOH 80 / 20 then 70/30 to give 125 mg (60% yield) of (rac)-[4-(4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M+H): calc. 506.2, found 506.3.

STEP 3 (examples 168 & 169): [4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2



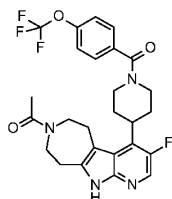
Step 3 of examples 211, 212, 225, 168 & 169 was performed following General Chiral Separation Method CS#8 to give:

47 mg (38% yield) of [4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 506.2, found 506.3.

And 41 mg (33% yield) of 4[4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-

(trifluoromethoxy)phenyl]methanone isomer 2 as a white solid. LC/MS (m/z , $M+H$): calc. 506.2, found 506.3.

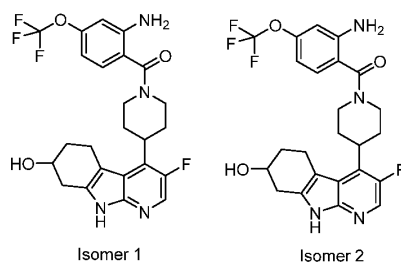
Example 170: 1-[4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-yl]ethenone



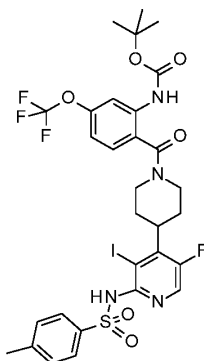
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Under argon atmosphere, to a solution of [4-(4-fluoro-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (example 194, prepared in step 2 of examples 194, 195 & 134, 87 mg, 0.18 mmol) in DCM (1 mL) were added N,N-Diisopropylethylamine (47 mg, 0.36 mmol) and acetyl chloride (29 mg, 0.37 mmol) and the resulting mixture was stirred at 0 °C for 30 minutes, then diluted with DCM and an aqueous saturated solution of NaHCO₃. The aqueous layers were extracted three times with DCM and the combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to dryness. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 12 g) eluting with DCM / [DCM/MeOH 90/10] from 100/0 to 0/100 to give 55 mg (58% yield) of 1-[4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-yl]ethenone as a white solid. LC/MS (m/z , $M+H$): calc. 519.2, found 519.4.

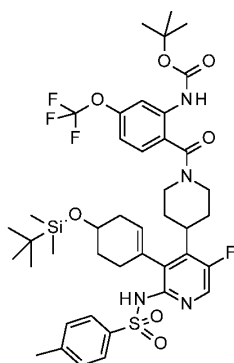
Examples 171 & 172: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 1 & isomer 2



STEP 1: tert-butyl N-[2-[4-[5-fluoro-3-iodo-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carbonyl]-5-(trifluoromethoxy)phenyl]carbamate

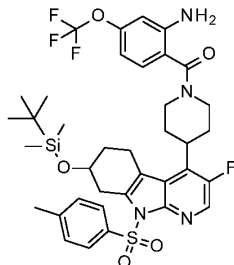


- To a solution of tert-butyl N-[2-[4-(2-amino-5-fluoro-3-iodo-4-pyridyl)piperidine-1-carbonyl]-5-(trifluoromethoxy)phenyl]carbamate (prepared in step 1 of example 7, 1 g, 1,6 mmol) in DCM/pyridine (3 mL / 3 mL) was added at 0 °C, portionwise, p-toluenesulfonic anhydride (630 mg, 1.93 mmol) and the resulting mixture was warmed up to room temperature and stirred for 3.5 hours. Then, p-toluenesulfonic anhydride (315 mg, 0.96 mmol) was added and the resulting mixture was stirred at room temperature for 12 additional hours, then diluted with 40 mL of DCM and with an aqueous saturated solution of NaHCO₃. The whole was filtered on a Radleys hydrophobic cartridge and the thus obtained substrate was concentrated to dryness. The resulting residue was diluted in THF/MeOH (10 mL/10 mL) and LiOH (300 mg, 12 mmol) was added and the resulting solution was stirred at room temperature for 2 hours, then concentrated in vacuo. The resulting orange gum was diluted with 100 mL of AE and with an aqueous saturated solution of NH₄Cl. The aqueous layer was extracted with AE (100 mL) and the combined organic layers were washed with an aqueous saturated solution of NH₄Cl (100 mL), dried over sodium sulfate, filtered and concentrated to dryness. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 40 g) eluting with cyclohexane / AE 8/2 to 6/4 to give 927 mg (74% yield) of tert-butyl N-[2-[4-[5-fluoro-3-iodo-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carbonyl]-5-(trifluoromethoxy)phenyl]carbamate as a yellow solid. LC/MS (m/z, M+H): calc. 779.1, found 779.1.
- STEP 2:** (rac)-tert-butyl N-[2-[4-[3-[4-[tert-butyl(dimethyl)silyl]oxycyclohexen-1-yl]-5-fluoro-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carbonyl]-5-(trifluoromethoxy)phenyl]carbamate



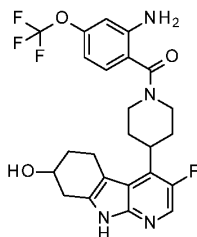
Step 2 of examples 171 & 172 was performed following the protocol described in Step 1 of examples 166 & 167 using tert-butyl N-[2-[4-[5-fluoro-3-iodo-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carbonyl]-5-(trifluoromethoxy)phenyl]carbamate (600 mg, 0.77 mmol) to give 538 mg (81% yield) of (rac)-tert-butyl N-[2-[4-[3-[4-[tert-butyl(dimethyl)silyl]oxycyclohexen-1-yl]-5-fluoro-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carbonyl]-5-(trifluoromethoxy)phenyl]carbamate as a yellow solid. LC/MS (m/z, M+H): calc. 863.3, found 863.3.

STEP 3: (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-[tert-butyl(dimethyl)silyl]oxy-3-fluoro-9-(p-tolylsulfonyl)-5,6,7,8-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



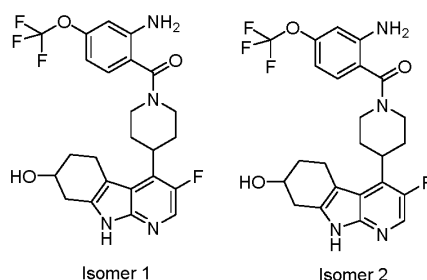
Step 3 of examples 171 & 172 was performed following the protocol described in step 2 of examples 166 & 167 using (rac)-tert-butyl N-[2-[4-[3-[4-[tert-butyl(dimethyl)silyl]oxycyclohexen-1-yl]-5-fluoro-2-(p-tolylsulfonylamino)-4-pyridyl]piperidine-1-carbonyl]-5-(trifluoromethoxy)phenyl]carbamate (535 mg, 0.62 mmol) to give 123 mg (70% purity, 18% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-[tert-butyl(dimethyl)silyl]oxy-3-fluoro-9-(p-tolylsulfonyl)-5,6,7,8-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone as a yellow solid. LC/MS (m/z, M+H): calc. 761.3, found 761.3.

STEP 4: (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone



Step 4 of examples 171 & 172 was performed following the protocol described in step 3 of examples 166 & 167, using (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[7-[tert-butyl(dimethyl)silyl]oxy-3-fluoro-9-(p-tolylsulfonyl)-5,6,7,8-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone (120 mg, 70% purity, 0.16 mmol) to give 38 mg (48% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 493.2, found 493.2.

STEP 5: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 1 & isomer 2

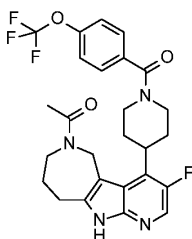


Step 5 of examples 171 & 172 was performed following General Chiral Separation Method CS#1 to give:

26 mg (45% yield) of 42-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 493.2, found 493.3.

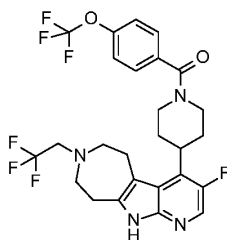
And 25 mg (43% yield) of 42-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 493.2, found 493.3.

Example 173: 1-[4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-13-yl]ethenone



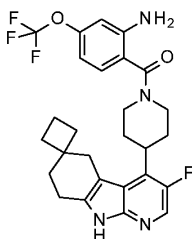
Example 173 was prepared following the protocol described for example 170, using [4-(4-fluoro-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (example 195, prepared in step 2 of examples 194, 195 and 134, 110 mg, 0.23 mmol) to give 50 mg (42% yield) of 1-[4-fluoro-3-[1-(4-(trifluoromethoxy)benzoyl)-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-yl]ethenone as a white solid. LC/MS (m/z, M+H): calc. 519.2, found 519.3.

Example 174: [4-[4-fluoro-12-(2,2,2-trifluoroethyl)-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



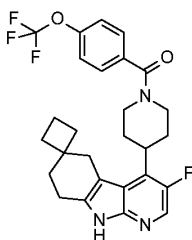
Example 174 was prepared following the protocol described for example 170, using [[4-(4-fluoro-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;hydrochloride (prepared in 2 steps: step 1 of examples 194, 195 & 134 where the two regio isomers were separated, and step 2 of examples 194, 195 & 134 on the chosen regioisomer without purification, 110 mg, 0.23 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (65 mg, 0.28 mmol) in acetonitrile (0.5 mL) to give 32 mg (56% yield) of [4-[4-fluoro-12-(2,2,2-trifluoroethyl)-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 559.2, found 559.4.

Example 175: [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,1'-cyclobutane]-4-yl)-1-piperidyl]methanone



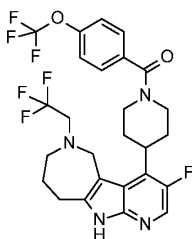
- Example 175 was prepared following the protocol described in Method D using spiro[3.5]nonan-7-one (166 mg, 1.2 mmol) in step 2 to give 100 mg (48% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,1'-cyclobutane]-4-yl)-1-piperidyl]methanone as a pale brown solid. LC/MS (m/z , $M+H$): calc. 517.2, found 517.4.

Example 176: [4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,1'-cyclobutane]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



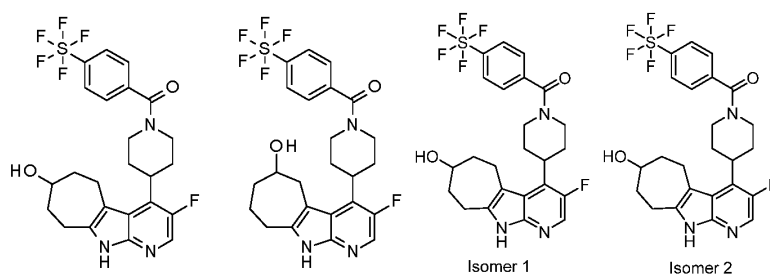
- Example 176 was prepared following the protocol described in Method A using spiro[3.5]nonan-7-one (162 mg, 1.18 mmol) in step 6 to give 132 mg (67% yield) of [4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,1'-cyclobutane]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a pale brown solid. LC/MS (m/z , $M+H$): calc. 502.2, found 502.4.

- Example 177:** [4-[4-fluoro-13-(2,2,2-trifluoroethyl)-6,8,13-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

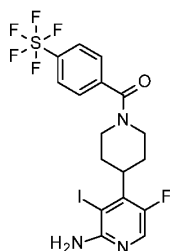


Example 177 was prepared following the protocol described for example 174 using [4-(4-fluoro-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;hydrochloride (72 mg, 0.14 mmol) and ,2,2-trifluoroethyl trifluoromethanesulfonate (65 mg, 0.28 mmol) to give 32 mg (41% yield) of 4-[4-fluoro-13-(2,2,2-trifluoroethyl)-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 559.2, found 559.3.

Examples 238, 239, 178 & 179: (rac)-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone , (rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone , [4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone isomer 1 & isomer 2

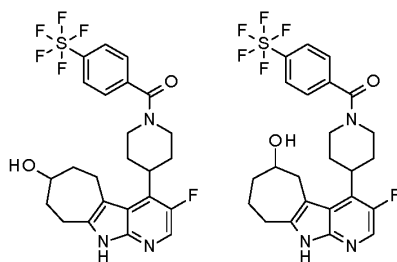


STEP 1: [4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone



Step 1 of examples 178 & 179 was performed using the protocol described in step 5 of example 56 using 4-(pentafluoro- λ^6 -sulfanyl)benzoic acid (1464 mg, 5.9 mmol) instead of 4-(trifluoromethoxy)benzoic acid to give 2891 mg (89% yield) of [4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone as a brown solid. LC/MS (m/z, M+H): calc. 552.0, found 552.1.

STEP 2 (examples 238 & 239): (rac)-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone, (rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone

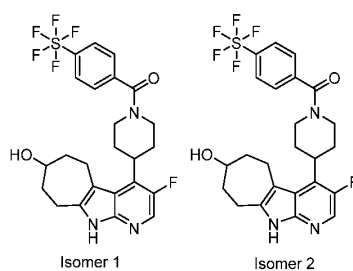


Step 2 of examples 238, 239, 178 & 179 was performed following the protocol described in step 6 of method A using 4-hydroxycycloheptanone (209 mg, 1.63 mmol) to give:

51 mg (17% yield) of (rac)-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone as a pale brown solid. LC/MS (m/z , $M+H$): calc. 534.2, found 534.3.

And 42 mg (14% yield) of (rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone as a pale brown solid. LC/MS (m/z , $M+H$): calc. 534.2, found 534.3.

STEP 3 (examples 178 & 179): [4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone isomer 1 & isomer 2

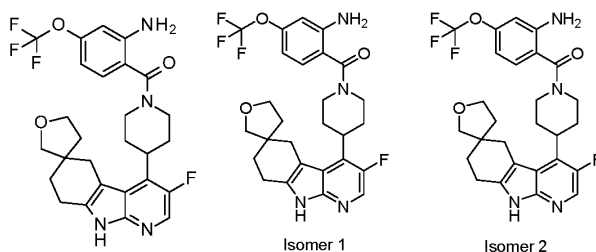


The two enantiomers of the above-obtained (rac)-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone (43 mg, 0.08 mmol) were separated following the general chiral separation method CS#1 to give:

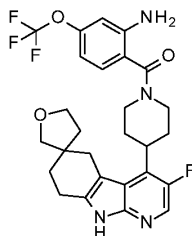
11 mg (25% yield) of [4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 534.2, found 534.3.

12 mg (28% yield) of [4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 534.2, found 534.3.

Examples 230, 181 & 182: (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]methanone, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]methanone isomer 1 & isomer 2

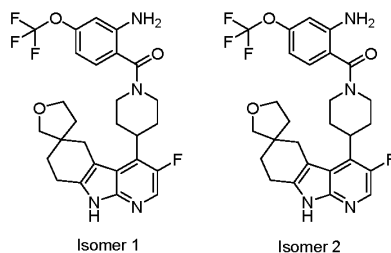


STEP 1 (example 230): (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]methanone



Step 1 of examples 230, 181 & 182 was performed following the protocol described in step 2 of method D using 2-oxaspiro[4.5]decan-8-one (259 mg, 1.68 mmol) to give 165 mg (55% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 533.2, found 533.4.

STEP 2 (examples 181 & 182): [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]methanone isomer 1 & isomer 2



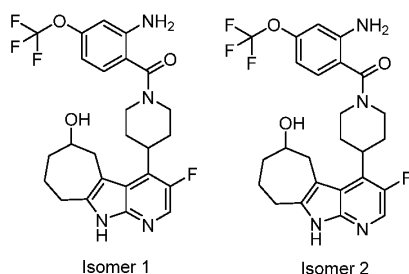
The abovementioned mixture (148 mg, 0.28 mmol) was purified as followed:

General Chiral Separation Method CS#11: Separation of the abovementioned mixture was performed using a chiralpak IF column (5 μ m, 30x250 mm), eluting with (EtOH 30%, n-heptane 70%)+0.1% TEA, flow rate 45 mL / min, UV detection at 280 nm) to give:

63 mg (42% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 533.2, found 533.4.

And 64 mg (43% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 533.2, found 533.4.

Examples 183 & 184: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone isomer 1 & isomer 2

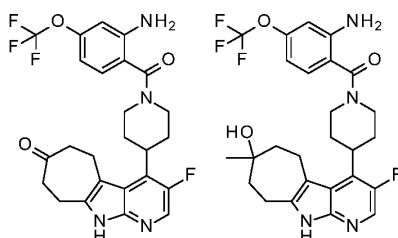


The two enantiomers from (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone (Example 46, 231 mg, 0.32 mmol) were separated following the **general chiral separation method CS#12** using a chiralcel OZ column (5 μ m, 30x250 mm), eluting with (EtOH 30%, n-heptane 70%)+0.1% TEA, flow rate 45 mL / min, UV detection at 280 nm) to give:

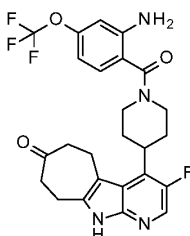
57 mg (25% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 507.2, found 507.4.

And 67 mg (29% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 507.2, found 507.4.

Examples 207 & 185: 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-one and (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone

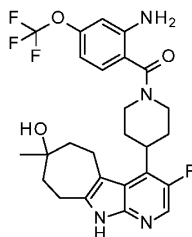


STEP 1 (example 207): 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-one



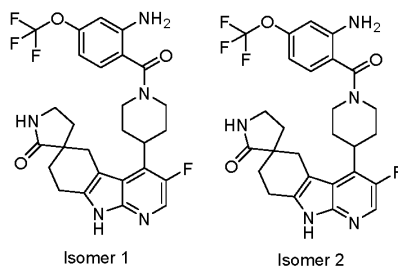
Step 1 of examples 207 & 185 was performed following the protocol described in step 2 of examples 144, 145, 146, 147 to give after purification by flash chromatography on silica gel (SiO₂ 220 g) eluting with n-heptane / isopropanol / NH₄OH 80/20/0.1 to 70/30/0.1, 105 mg (33% yield) of the isolated regioisomer 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-one as a solid. LC/MS (m/z, M+H): calc. 505.2, found 505.4.

STEP 2 (example 185): (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone

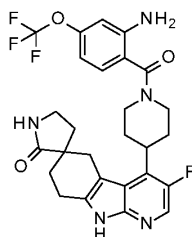


Step 2 of Examples 185 & 207 was performed following the protocol described in step 2 of examples 211, 212, 225, 168 & 169 to give 12 mg (19% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone as a solid. LC/MS (m/z, M+H): calc. 521.2, found 521.3.

Examples 186 & 187: 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one isomer 1 & isomer 2

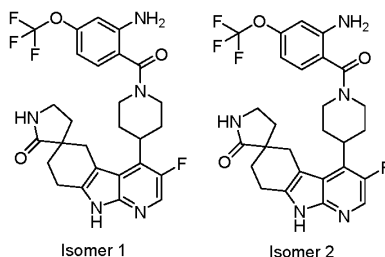


STEP 1: (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one



Step 1 of examples 186 & 187 was performed following the protocol described in step 2 of method D using 2-azaspiro[4.5]decane-1,8-dione (281 mg, 1.68 mmol) to give 105 mg (29% yield) of (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one as a white solid. LC/MS (m/z, M+H): calc. 546.2, found 546.2.

STEP 2: 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one isomer 1 & isomer 2



The two enantiomers of the above-obtained (rac)-4-[1-[2-amino-4-

- 5 (trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one (98 mg, 0.15 mmol) were separated following the general chiral separation method CS#9 to give:

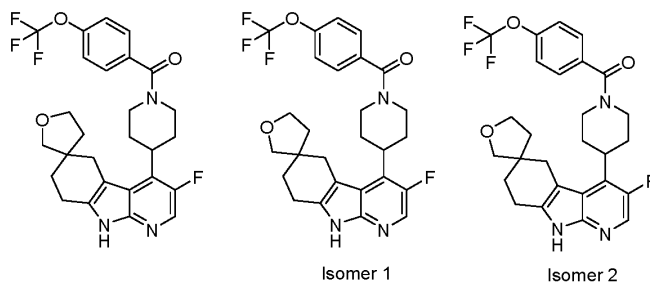
43 mg (44% yield) of 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one isomer 1 as a solid.

- 10 LC/MS (m/z, M+H): calc. 546.2, found 546.3.

40 mg (41% yield) of 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one isomer 2 as a solid.

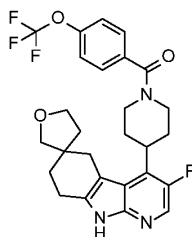
LC/MS (m/z, M+H): calc. 546.2, found 546.3.

Examples 231, 189 & 190: (rac)-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, [4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2



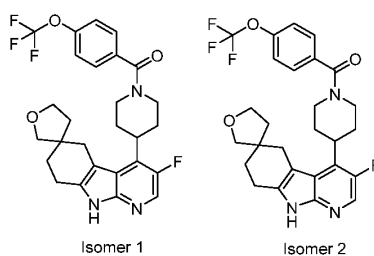
STEP 1 (example 231): (rac)-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

- 20

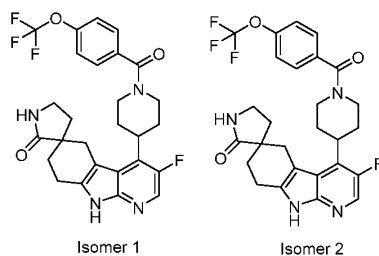


- Step 1 of examples 231, 189 & 190 was performed following the protocol described in step 6 of Method A using 2-oxaspiro[4.5]decan-8-one (272 mg, 1.76 mmol) to give 215 mg (70% yield) of (rac)-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 518.2, found 518.4.

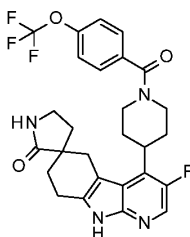
STEP 2: [4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2



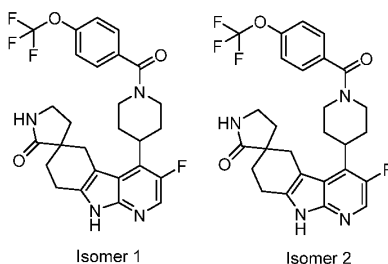
- The two enantiomers of the above-obtained (rac)-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (193 mg, 0.37 mmol) were separated following the general chiral separation method CS#12 to give:
- 35 mg (18% yield) of 4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 518.2, found 518.3.
- 30 mg (15% yield) of 4-[3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-tetrahydrofuran]-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 518.2, found 518.3.
- Examples 196 & 197:** 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one isomer 1 & isomer 2



STEP 1: (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one



- 5 Step 1 of examples 196 & 197 was performed following the protocol described in step 6 of method A using 2-azaspiro[4.5]decane-1,8-dione (295 mg, 1.77 mmol) to give 121 mg (34% yield) of (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one as a white solid. LC/MS (m/z, M+H): calc. 531.2, found 531.2.
- 10 **STEP 2:** 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one isomer 1 & isomer 2

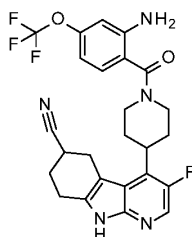


- The two enantiomers of the above-obtained (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one (115 mg, 0.19 mmol) were separated following the general chiral separation method CS#9 to give:
- 15

50 mg (43% yield) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one isomer 1 as a solid. LC/MS (m/z, M+H): calc. 531.2, found 531.4.

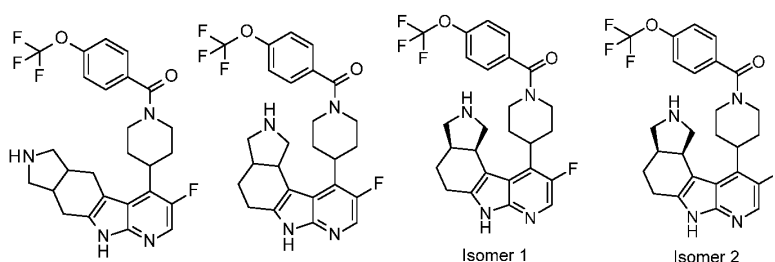
48 mg (42% yield) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-pyrrolidine]-2'-one isomer 2 as a solid. LC/MS (m/z, M+H): calc. 531.2, found 531.4.

Example 199: (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile



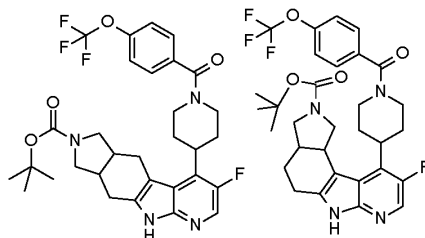
10 Example 199 was prepared following the protocol described in step 2 of method D using 4-oxocyclohexanecarbonitrile (38 mg, 0.31 mmol) to give 12 mg (10% yield) of (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-6-carbonitrile as a white solid. LC/MS (m/z, M+H): calc. 502.2, found 502.3.

Examples 242, 243, 201 & 202: (rac)-[4-(4-fluoro-6,8,13-triazatetracyclo[7.7.0.0.2,7.0.11,15]hexadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, (rac)-[4-(14-fluoro-4,10,12-triazatetracyclo[7.7.0.0.2,6.0.11,16]hexadeca-1(9),11,13,15-tetraen-15-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, [4-(cis)-14-fluoro-4,10,12-triazatetracyclo[7.7.0.0.2,6.0.11,16]hexadeca-1(9),11,13,15-tetraen-15-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2



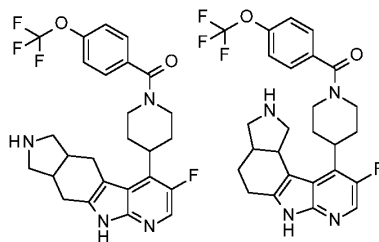
STEP 1: tert-butyl 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatetracyclo[7.7.0.0.2,7.0.11,15]hexadeca-1(9),2,4,6-tetraene-13-carboxylate and tert-butyl

14-fluoro-15-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4,10,12-triazatetracyclo[7.7.0.02,6.011,16]hexadeca-1(9),11,13,15-tetraene-4-carboxylate



- Step 1 of examples 242, 243, 201 & 202 was performed following the protocol described in step 6 of method A using tert-butyl (rac, cis)-6-oxo-3,3a,4,5,7,7a-hexahydro-1H-isoindole-2-carboxylate (564 mg, 2.36 mmol) to give 339 mg (72% yield) of a 1/1 mixture of tert-butyl 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatetracyclo[7.7.0.02,7.011,15]hexadeca-1(9),2,4,6-tetraene-13-carboxylate and tert-butyl 14-fluoro-15-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4,10,12-triazatetracyclo[7.7.0.02,6.011,16]hexadeca-1(9),11,13,15-tetraene-4-carboxylate as an orange foam. LC/MS (m/z, M+H): calc. 603.2, found 603.3.

- STEP 2 (examples 242 & 243):** (rac)-[4-(4-fluoro-6,8,13-triazatetracyclo[7.7.0.02,7.011,15]hexadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, (rac)-[4-(14-fluoro-4,10,12-triazatetracyclo[7.7.0.02,6.011,16]hexadeca-1(9),11,13,15-tetraen-15-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

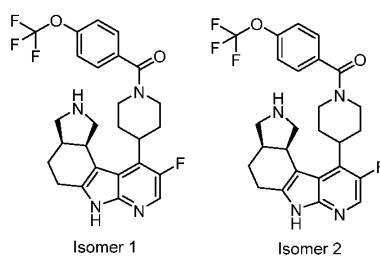


Step 2 of examples 242, 243, 201 & 202 was performed following the protocol described in step 2 of example 125 using MeOH as solvent (2 mL) to give :

- 139 mg (49% yield) of (rac)-[4-(4-fluoro-6,8,13-triazatetracyclo[7.7.0.02,7.011,15]hexadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a pale brown solid. LC/MS (m/z, M+H): calc. 503.2, found 503.4.

And 113 mg (40% yield) of (rac)-[4-(14-fluoro-4,10,12-triazatetracyclo[7.7.0.02,6.011,16]hexadeca-1(9),11,13,15-tetraen-15-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a pale brown solid. LC/MS (m/z, M+H): calc. 503.2, found 503.4.

- 5 **STEP 3 (examples 201 & 202:** [4-[(cis)-14-fluoro-4,10,12-triazatetracyclo[7.7.0.02,6.011,16]hexadeca-1(9),11,13,15-tetraen-15-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2

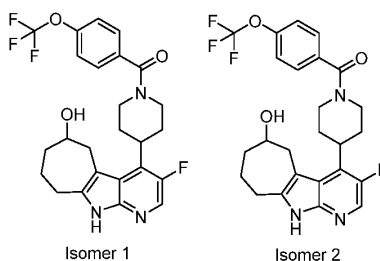


- The two enantiomers of the above-obtained (rac)-[4-(14-fluoro-4,10,12-triazatetracyclo[7.7.0.02,6.011,16]hexadeca-1(9),11,13,15-tetraen-15-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (99 mg, 0.2 mmol) were separated following the general chiral separation method CS#2 to give:

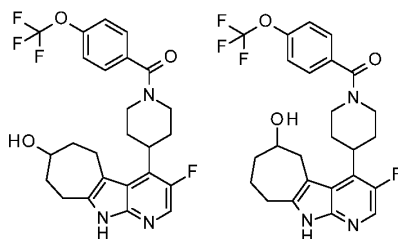
- 36 mg (36% yield) of [4-[(cis)-14-fluoro-4,10,12-triazatetracyclo[7.7.0.02,6.011,16]hexadeca-1(9),11,13,15-tetraen-15-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 503.2, found 503.3.

38 mg (38% yield) of [4-[(cis)-14-fluoro-4,10,12-triazatetracyclo[7.7.0.02,6.011,16]hexadeca-1(9),11,13,15-tetraen-15-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 503.2, found 503.3.

- Examples 203 & 204:** [4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2



STEP 1: (rac)-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone and (rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



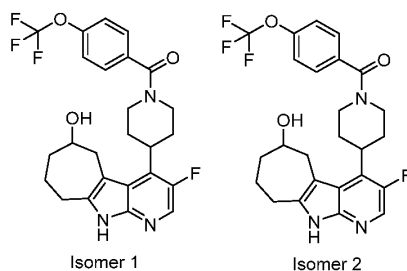
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Step 1 of examples 203 & 204 was performed following the protocol described in step 6 of method A using (rac)-4-hydroxycycloheptanone (755 mg, 5.89 mmol) to give after purification the 2 separated regioisomers:

244 mg (25% yield) of (rac)-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a pale brown solid. LC/MS (m/z, M+H): calc. 492.2, found 492.3.

And 181 mg (19% yield) of (rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a pale brown solid. LC/MS (m/z, M+H): calc. 492.2, found 492.3.

STEP 2: [4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2

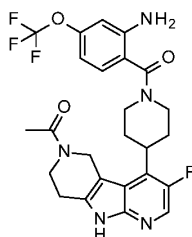


The two enantiomers of the above-obtained (rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (174 mg, 0.35 mmol) were separated following the general chiral separation method CS#9 to give:

75 mg (43% yield) of [4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 492.2, found 492.3.

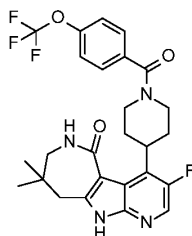
75 mg (43% yield) of [4-[4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 492.2, found 492.3.

Example 209: 1-[13-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-12-fluoro-4,8,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),10,12-tetraen-4-yl]ethenone



10 Example 209 was prepared following the protocol described in step 2 of method D using 1-acetyl-4-piperidone (91 mg, 0.65 mmol) to give 75 mg (67% yield) of 1-[13-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-12-fluoro-4,8,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),10,12-tetraen-4-yl]ethenone as a solid. LC/MS (m/z, M+H): calc. 520.2, found 520.3.

Example 210: 4-fluoro-11,11-dimethyl-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-14-one

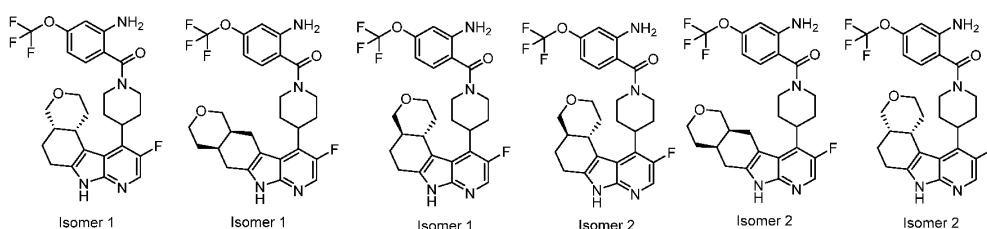


Example 210 was prepared following the protocol described in step 6 of method A using 6,6-dimethylazepane-2,4-dione (274 mg, 1.76 mmol) to give 64 mg (21% yield) of 4-fluoro-11,11-dimethyl-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-

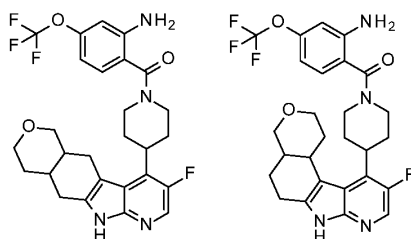
20 triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-14-one as a pale yellow solid. LC/MS (m/z, M+H): calc. 519.2, found 519.2.

Examples 213, 214, 215, 216, 217 & 218: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.0^{2,7},7^{0,12}]heptadeca-1(10),12,14,16-tetraen-16-

- yl]-1-piperidyl]methanone isomer 1, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone isomer 1, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone isomer 1, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone isomer 2, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone isomer 2 & [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone isomer 2

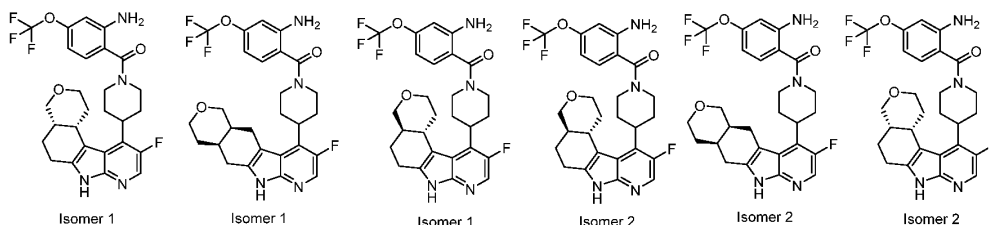


- STEP 1:** [2-amino-4-(trifluoromethoxy)phenyl]-[4-(13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl)-1-piperidyl]methanone and [2-amino-4-(trifluoromethoxy)phenyl]-[4-(15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl)-1-piperidyl]methanone



- Step 1 of examples 213, 214, 215, 216, 217 & 218 was performed following the protocol described in step 2 of method D using 1,3,4,4a,5,7,8,8a-octahydroisochromen-6-one (296 mg, 1.92 mmol) to give 148 mg (43% yield) of the mixture of the two regioisomers [2-amino-4-(trifluoromethoxy)phenyl]-[4-(13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl)-1-piperidyl]methanone and [2-amino-4-(trifluoromethoxy)phenyl]-[4-(15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl)-1-piperidyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 533.2, found 533.4.

- STEP 2:** 2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone isomer 1, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone isomer 1, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone isomer 1, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone isomer 2, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone isomer 2 & [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone isomer 2



- The isomers present in the above-mentioned mixture (141 mg, 0.26 mmol) were separated as followed: a first separation was performed using the general chiral separation method CS#9 to give two mixtures each containing three isomers. Each thus generated mixture was then separated using the following conditions: i-amylose-3 column (5 μ m, 250x30 mm), eluting with (CO₂ 65%, MeOH+0.1% TEA 35%), flow rate 115 mL / min, UV detection at 230 nm) to give:

12 mg (8% yield) of 2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 533.2, found 533.3.

- 19 mg (13% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 533.2, found 533.3.

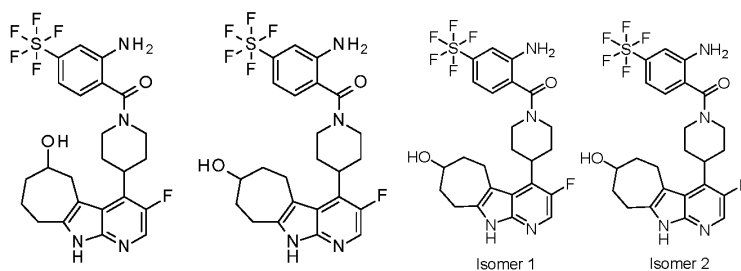
11 mg (8% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone isomer 1 as a white solid. LC/MS (m/z, M+H): calc. 533.2, found 533.4.

20 mg (14% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 533.2, found 533.4

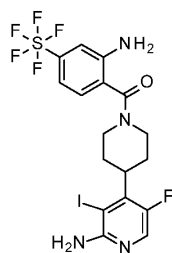
16 mg (11% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-13-fluoro-6-oxa-15,17-diazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 533.2, found 533.3.

10 mg (7% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-15-fluoro-5-oxa-11,13-diazatetracyclo[8.7.0.02,7.012,17]heptadeca-1(10),12,14,16-tetraen-16-yl]-1-piperidyl]methanone isomer 2 as a white solid. LC/MS (m/z, M+H): calc. 533.2, found 533.3.

- 10 **Examples 226, 234, 219 & 220:** (rac)-[2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone, (rac)-[2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone, [2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone isomer 1 & isomer 2



STEP 1: [4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone

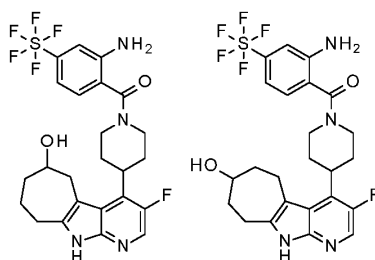


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Step 1 of examples 219 & 220 was performed using the protocol described in step 5 of example 56 using 2-amino-4-(pentafluoro- λ^6 -sulfanyl)benzoic acid (1553 mg, 5.9 mmol) instead of 4-(trifluoromethoxy)benzoic acid to give 3027 mg (87% yield) of [4-(2-amino-5-fluoro-3-iodo-

4-pyridyl)-1-piperidyl]-[2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone as a pale brown solid. LC/MS (m/z , $M+H$): calc. 567.0, found 567.1.

- STEP 2 (examples 226 & 234):** (rac)-[2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone, (rac)-[2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone

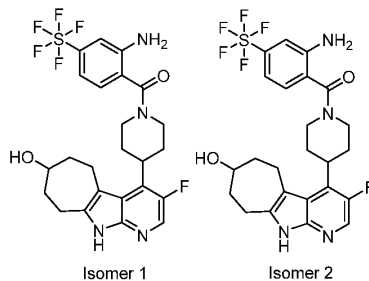


- Step 2 of examples 226, 234, 219 & 220 was performed following the protocol described in step 2 of method D using (rac)-4-hydroxycycloheptanone (325 mg, 2.54 mmol) and [4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]methanone (300 mg, 0.85 mmol) to give the separated racemic regioisomers:

- 22 mg (4% yield) of [2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone as a white solid. LC/MS (m/z , $M+H$): calc. 549.2, found 549.3.

And 65 mg (14% yield) of (rac)-[2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone as a pale brown solid. LC/MS (m/z , $M+H$): calc. 549.2, found 549.3.

- STEP 3 (examples 219 & 220):** [2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone isomer 1 & isomer 2



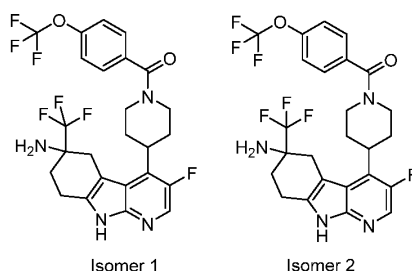
The two enantiomers of the above-obtained (rac)-[2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone (55 mg, 0.1 mmol) were separated following the general chiral separation method CS#3 to give:

- 5 20 mg (36% yield) of 2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 549.2, found 549.3

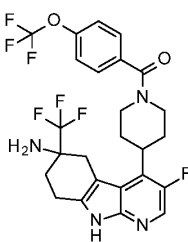
And 20 mg (36% yield) of 2-amino-4-(pentafluoro- λ^6 -sulfanyl)phenyl]-[4-[4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-

- 10 piperidyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 549.2, found 549.3.

Examples 221 & 222: [4-[6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2.

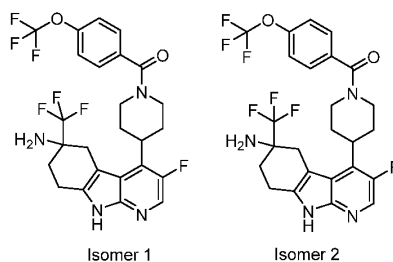


- STEP 1:** (rac)-[4-[6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone
- 15



- Step 1 of examples 221 & 222 was performed following the protocol described in step 6 of method A using 4-amino-4-(trifluoromethyl)cyclohexan-1-one hydrochloride (353 mg, 1.62 mmol) to give 167 mg (31% yield) of (rac)-[4-[6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M+H): calc. 545.2, found 545.3.
- 20

STEP 2: [4-[6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2.



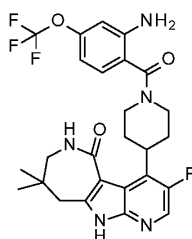
The abovementioned mixture (166 mg, 0.3 mmol) was purified as followed:

General Chiral Separation Method CS#13: Separation of the abovementioned mixture was performed using a chiralcel OD column (5 μ m, 30x250 mm), eluting with (EtOH 10%, n-heptane 90%)+0.1% TEA, flow rate 45 mL / min, UV detection at 265 nm) to give:

69 mg (41% yield) of [4-[6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 545.2, found 545.4.

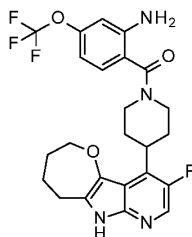
And 71 mg (43% yield) of [4-[6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 545.2, found 545.3.

Example 223: 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-11,11-dimethyl-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one



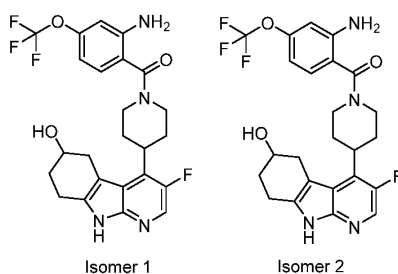
Example 223 was prepared following the protocol described in step 2 of method D using 6,6-dimethylazepane-2,4-dione (186 mg, 1.2 mmol) to give 40 mg (16% yield) of 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-11,11-dimethyl-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one as a yellow solid. LC/MS (m/z, M+H): calc. 534.2, found 534.2.

Example 224: [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-14-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone

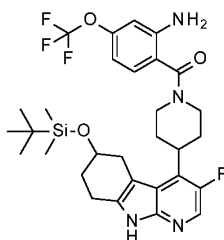


Example 224 was prepared following the protocol described in step 2 of method D using oxepan-3-one (45 mg, 0.39 mmol) and NMP (1.5 mL) as solvent to give 27 mg (23% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-14-oxa-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone as a orange solid. LC/MS (m/z, M+H): calc. 493.3, found 493.4.

Examples 227 & 228: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 1 & isomer 2.

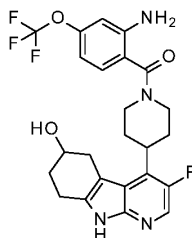


STEP 1: (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[6-[tert-butyl(dimethyl)silyl]oxy-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone



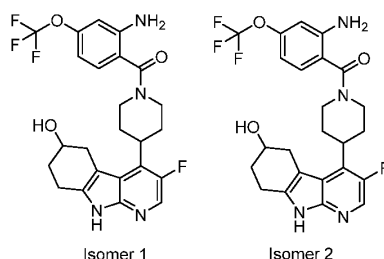
Step 1 of examples 227 & 228 was performed following the protocol described in step 2 of method D using 4-(tert-butyl(dimethyl)silyloxy)cyclohexanone (195 mg, 0.85 mmol) to give 128 mg (30% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[6-[tert-butyl(dimethyl)silyl]oxy-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone as an orange solid. LC/MS (m/z, M+H): calc. 607.3, found 607.4.

STEP 2: (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone



Step 2 of examples 227 & 228 was performed following the protocol described in step 3 of example 3 without DCM as cosolvent, to give 55 mg (54% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone as a pale brown solid. LC/MS (m/z, M+H): calc. 493.2, found 493.3.

STEP 3: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 1 & isomer 2.



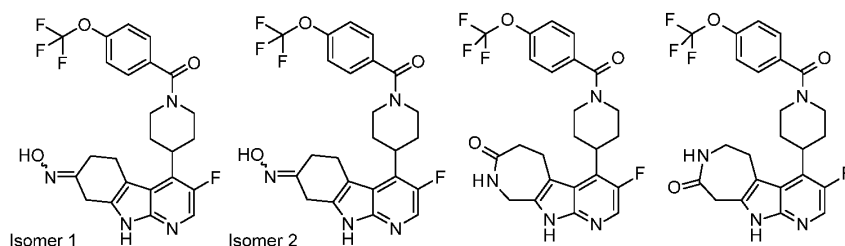
The abovementioned mixture (74 mg, 0.15 mmol) was purified as followed:

General Chiral Separation Method CS#14: Separation of the abovementioned mixture was performed using a Lux Amylose-1 column (5 μ m, 30x250 mm), eluting with (EtOH 15%, n-heptane 85%)+0.1% TEA, flow rate 45 mL / min, UV detection at 254 nm) to give:

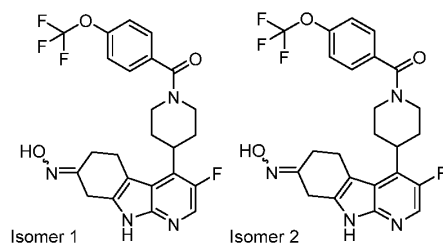
34 mg (46% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 493.2, found 493.3.

And 32 mg (42% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 493.2, found 493.3.

Examples 232, 233, 229 & 235: [4-[3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomers 1 and 2, 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,11-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-12-one & 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,12-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-11-one



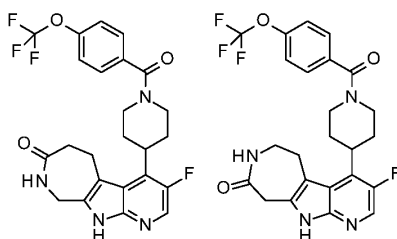
STEP 1 (examples 232 & 233): [4-[3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomers 1 and 2



- 10 At room temperature, to a solution of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,6,8,9-tetrahydropyrido[2,3-b]indol-7-one (example 16, 152 mg, 0.32 mmol) in EtOH (1 mL) was added a solution of hydroxylamine hydrochloride (44 mg, 0.64 mmol) in water (0.5 mL) and a solution of sodium acetate (86 mg, 1.06 mmol) in water (0.5 mL) and the resulting reaction mixture was stirred at 80 °C for 1 hour. After one hour, the whole was cooled
- 15 down to room temperature, and concentrated to dryness. The resulting residue was diluted with AE and water. The aqueous layer was extracted three times with AE and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to dryness. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 15g) eluting with DCM / [AE/n-heptane / MeOH 85 / 10 / 5] from 100 / 0 to 0 / 100 to give :
- 20 110 mg (70% yield) of [4-[3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomer 1 as a pale brown solid. LC/MS (m/z, M+H): calc. 491.2, found 491.3.

And 25 mg (16% yield) of [4-[3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone Isomer 2 as a solid. LC/MS (m/z, M+H): calc. 491.2, found 491.3.

- STEP 2 (examples 229 & 235):** 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,11-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-one & 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-11-one

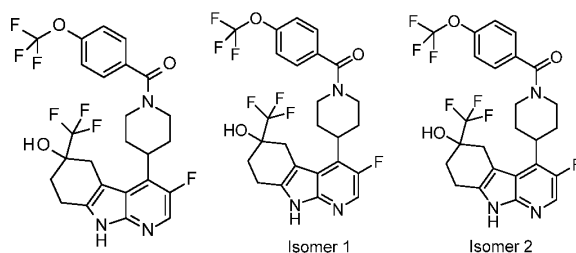


- At 0 °C, to a solution of [4-[(7Z)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (186 mg, 0.38 mmol) in acetonitrile (2 mL) was added phosphorus (V) oxychloride (70 µL, 0.76 mmol) and the resulting reaction mixture was stirred at 40 °C for one hour. After one hour, the reaction mixture was cooled down to room temperature, diluted with AE and water, and a saturated aqueous solution of NaHCO₃ was added to basic pH. The aqueous layer was then extracted three times with AE and the combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 12 g) eluting with DCM / [DCM/MeOH 9/1] from 100/0 to 0/100 to give:

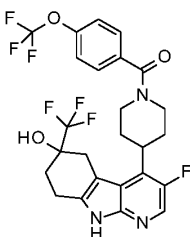
- 25 mg (13% yield) of 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-11-one as an orange solid. LC/MS (m/z, M+H): calc. 491.2, found 491.3.

And 7 mg (4% yield) of 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,11-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-one as a pale brown solid. LC/MS (m/z, M+H): calc. 491.2, found 491.3.

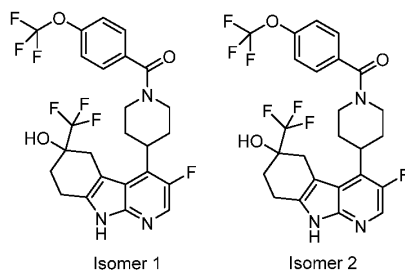
- Examples 247, 236 & 237:** (rac)-[4-[3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, [4-[3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2



STEP 1 (example 247): (rac)-[4-[3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



- 5 Step 1 of examples 236 & 237 was performed following the protocol described in step 6 of method A using 4-hydroxy-4-(trifluoromethyl)cyclohexan-1-one (58 mg, 0.32 mmol) to give 65 mg (61% yield) of (rac)-[4-[3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M+H): calc. 546.2, found 546.3.
- 10 **STEP 2 (examples 236 & 237):** [4-[3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2

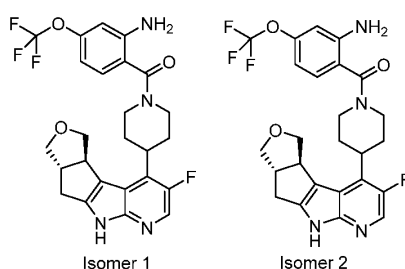


- The two enantiomers of the above-obtained (rac)-[4-[3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (53 mg, 0.1 mmol) were separated following the general chiral separation method CS#1 to give:
- 15

20 mg (38% yield) of [4-[3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 546.2, found 546.3.

And 30 mg (57% yield) of [4-[3-fluoro-6-hydroxy-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 546.2, found 546.3.

Examples 240 & 241: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.0.11,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone isomer 1 & isomer 2



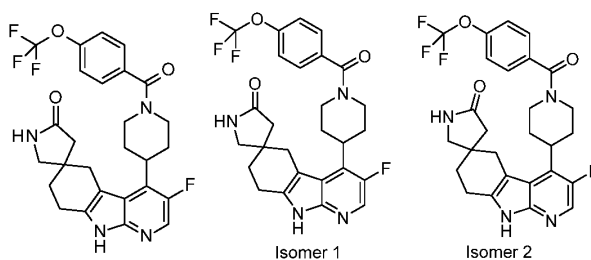
The two enantiomers of (rac)-trans-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.0.11,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone (example 7, 125 mg, 0.25 mmol) were purified as followed:

General Chiral Separation Method CS#15: Separation of the abovementioned mixture was performed using a chiralpak IE column (5 μ m, 4.6x250 mm), eluting with (EtOH 30%, n-heptane 70%)+0.1% TEA, flow rate 45 mL / min, UV detection at 254 nm) to give:

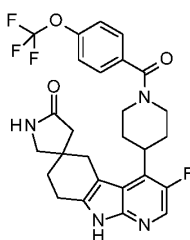
10 mg (8% yield) of [[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.0.11,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 505.2, found 505.3.

And 10 mg (8% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(trans)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.0.11,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 505.2, found 505.3.

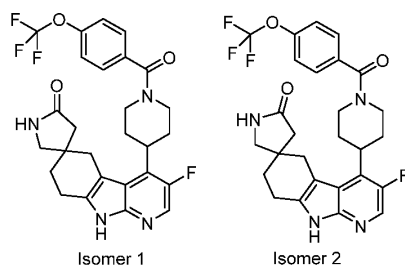
Examples 262, 244 & 245: (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one, 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one isomer 1 & isomer 2



STEP 1 (example 262): (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one



- 5 Step 1 of examples 262, 244 & 245 was performed following the protocol described in step 6 of method A using 2-azaspiro[4.5]decane-3,8-dione (295 mg, 1.77 mmol) to give 152 mg (49% yield) of (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one as a white solid. LC/MS (m/z, M+H): calc. 531.2, found 531.3.
- 10 **STEP 2 (examples 244 & 245):** 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one isomer 1 & isomer 2

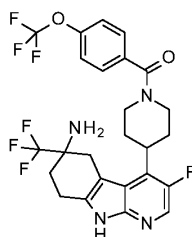


- The two enantiomers of the above-obtained (rac)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one (130 mg, 0.24 mmol) were separated following the general chiral separation method CS#8 to give:
- 15

56 mg (43% yield) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one isomer 1 as a solid. LC/MS (m/z, M+H): calc. 531.2, found 531.3.

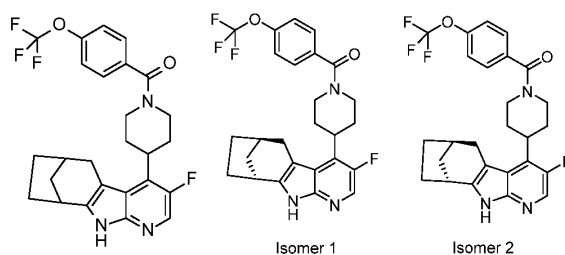
And 56 mg (43% yield) of 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one isomer 2 as a solid. LC/MS (m/z, M+H): calc. 531.2, found 531.3.

Example 246: (rac)-[4-[6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



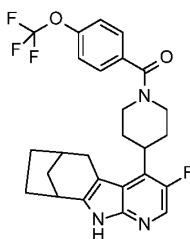
10 Example 246 was prepared following the protocol described in step 6 of method A using 4-amino-4-(trifluoromethyl)cyclohexan-1-one hydrochloride (36 mg, 0.17 mmol) to give 18 mg (30% yield) of (rac)-[4-[6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M+H): calc. 545.2, found 545.3.

15 **Examples 273, 248 & 249:** (rac)-[4-(7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone, [4-[(cis)-7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2



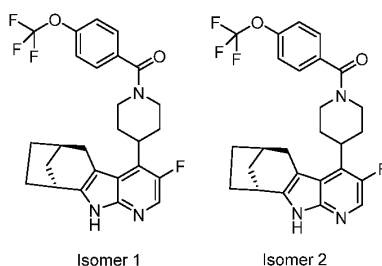
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STEP 1 (example 273): (rac)-[4-(7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



Step 1 of examples 273, 248 & 249 was performed following the protocol described in step 6 of method A using bicyclo[3.2.1]octan-2-one (183 mg, 1.47 mmol) to give 147 mg (51% yield) of (rac)-[4-(7-fluoro-3,5-diazatetracyclo[10.2.1.0.2,10.0.4,9]pentadeca-2(10),4,6,8-tetraen-8-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a pale brown solid. LC/MS (m/z, M+H): calc. 488.2, found 488.2.

STEP 2 (examples 248 & 249): [4-[(cis)-7-fluoro-3,5-diazatetracyclo[10.2.1.0.2,10.0.4,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2



10

The two isomers of the above-obtained (rac)-[4-(7-fluoro-3,5-diazatetracyclo[10.2.1.0.2,10.0.4,9]pentadeca-2(10),4,6,8-tetraen-8-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (91 mg, 0.19 mmol) were separated following the general chiral separation method CS#9 to give:

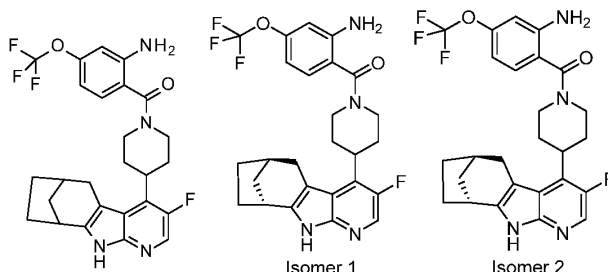
15 39 mg (43% yield) of [4-[(cis)-7-fluoro-3,5-diazatetracyclo[10.2.1.0.2,10.0.4,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 488.2, found 488.3.

And 39 mg (43% yield) of [4-[(cis)-7-fluoro-3,5-diazatetracyclo[10.2.1.0.2,10.0.4,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 488.2, found 488.3.

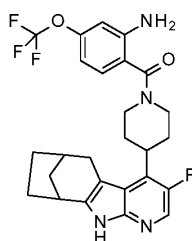
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Examples 272, 250 & 287: (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-7-fluoro-3,5-diazatetracyclo[10.2.1.0.2,10.0.4,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone, and [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-7-fluoro-3,5-

diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone
isomer 1 & isomer 2

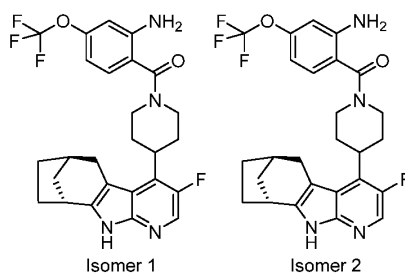


STEP 1 (example 272): (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-7-fluoro-3,5-
5 diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone



Step 1 of examples 272, 250 & 287 was performed following the protocol described in step 2
of method D using bicyclo[3.2.1]octan-2-one (209 mg, 1.68 mmol) to give 143 mg (51% yield)
of
10 (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-7-fluoro-3,5-
diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone
as a pale brown solid. LC/MS (m/z, M+H): calc. 503.2, found 503.2.

STEP 2 (examples 250 & 287): [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-7-fluoro-3,5-
diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone
isomer 1 & isomer 2



15

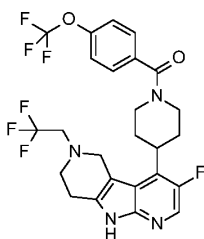
The two isomers of the above-obtained (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-
7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-

piperidyl]methanone (120 mg, 0.24 mmol) were separated following the general chiral separation method CS#9 to give:

54 mg (45% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 503.2, found 503.3.

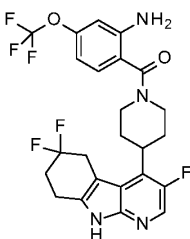
And 54 mg (45% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-7-fluoro-3,5-diazatetracyclo[10.2.1.02,10.04,9]pentadeca-2(10),4,6,8-tetraen-8-yl]-1-piperidyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 503.2, found 503.3.

Example 251: [4-[12-fluoro-4-(2,2,2-trifluoroethyl)-4,8,10-triazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



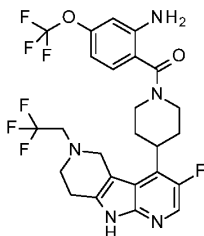
Example 251 was prepared following the protocol described in step 6 of method A using 1-(2,2,2-trifluoroethyl)piperidin-4-one (213 mg, 1.18 mmol) to give 118 mg (55% yield) of 4-[12-fluoro-4-(2,2,2-trifluoroethyl)-4,8,10-triazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 545.2, found 545.3.

Example 252: [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3,6,6-trifluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone



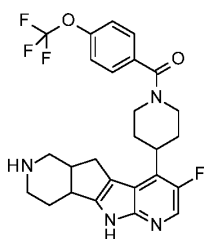
Example 252 was prepared following the protocol described in step 2 of method D using 4,4-difluorocyclohexanone (42 mg, 0.31 mmol) to give 17 mg (19% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3,6,6-trifluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone as a solid. LC/MS (m/z, M+H): calc. 513.2, found 513.3.

Example 253: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-fluoro-4-(2,2,2-trifluoroethyl)-4,8,10-triazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl]-1-piperidyl]methanone

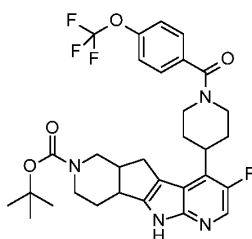


Example 253 was prepared following the protocol described in step 2 of method D using 1-(2,2,2-trifluoroethyl)piperidin-4-one (217 mg, 1.2 mmol) to give 73 mg (32% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-fluoro-4-(2,2,2-trifluoroethyl)-4,8,10-triazatricyclo[7.4.0.02,7]trideca-1(13),2(7),9,11-tetraen-13-yl]-1-piperidyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 560.2, found 560.3.

Example 254: (rac)-[4-(12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



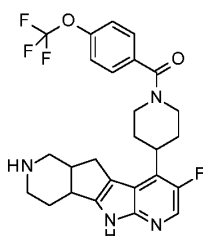
STEP 1: (rac)-tert-butyl 12-fluoro-11-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraene-5-carboxylate



Step 1 of example 254 was performed following the protocol described in step 6 of method A using tert-butyl 5-oxo-3,4,4a,6,7,7a-hexahydro-1H-cyclopenta[c]pyridine-2-carboxylate (493 mg, 2.06 mmol) to give 235 mg (49% yield) of (rac)-tert-butyl 12-fluoro-11-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,14,16-

triazatetracyclo[7.7.0.0.2,7.010,15]hexadeca-1(9),10,12,14-tetraene-5-carboxylate as a white solid. LC/MS (m/z, M+H): calc. 603.2, found 603.4.

STEP 2: (rac)-[4-(12-fluoro-5,14,16-triazatetracyclo[7.7.0.0.2,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



5

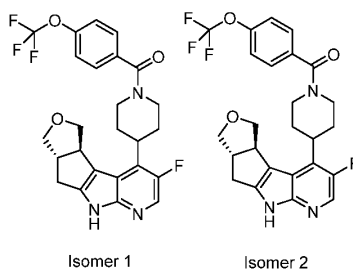
Step 2 of example 254 was performed following the protocol described in step 2 of example 125, without DCM as cosolvent, to give 181 mg (94% yield) of (rac)-[4-(12-fluoro-5,14,16-triazatetracyclo[7.7.0.0.2,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a pale brown solid. LC/MS (m/z, M+H): calc. 503.2, found 503.4.

10

Example 254 was then engaged in a chiral separation using the General chiral separation method CS#9 to furnish examples 82 & 83.

Examples 255 & 256: [4-[(trans)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2

15



The two enantiomers of (rac)-trans-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (example 6, 148 mg, 0.3 mmol) were separated following the general chiral separation method CS#15 to give:

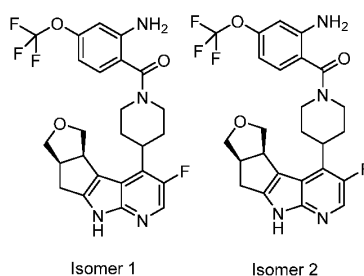
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56 mg (38% yield) of [[4-[(trans)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-

(trifluoromethoxy)phenyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 490.2, found 490.3.

And 57 mg (38% yield) of [4-[(trans)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 490.2, found 490.3.

Examples 257 & 261: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone isomer 1 & isomer 2



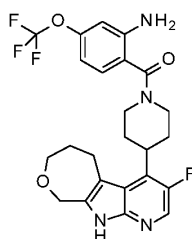
The two enantiomers of (rac)-cis-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone (example 28, 116 mg, 0.23 mmol) were separated following the general chiral separation method CS#8 to give:

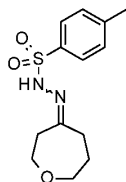
56 mg (48% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 505.2, found 505.3.

And 55 mg (47% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(cis)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-

piperidyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 505.2, found 505.3.

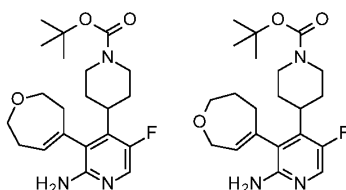
Example 258: [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-11-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone



STEP 1: 4-methyl-N-[oxepan-4-ylideneamino]benzenesulfonamide

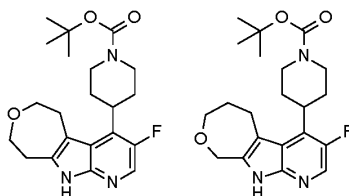
To a solution of oxepan-4-one (500 mg, 4.38 mmol) in MeOH (10 mL) was added portionwise 4-methylbenzene sulfonhydrazide (845 mg, 4.54 mmol) and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was then concentrated to dryness and the resulting residue was triturated in MTBE (10 mL), filtered to give 932 mg (75% yield) of 4-methyl-N-[oxepan-4-ylideneamino]benzenesulfonamide as a white solid. LC/MS (m/z, M+H): calc. 283.1, found 283.1.

STEP 2: tert-butyl 4-[2-amino-5-fluoro-3-(2,3,6,7-tetrahydrooxepin-4-yl)-4-pyridyl]piperidine-1-carboxylate & tert-butyl 4-[2-amino-5-fluoro-3-(2,3,4,7-tetrahydrooxepin-5-yl)-4-pyridyl]piperidine-1-carboxylate



A solution of palladium (II) acetate (25 mg, 0.11 mmol), potassium carbonate (750 mg, 5.43 mmol) and tri-tert-butylphosphonium tetrafluoroborate (70 mg, 0.24 mmol) in DMF (2.5 mL) was bubbled with argon for 2 minutes and tert-butyl 4-(2-amino-5-fluoro-3-iodo-4-pyridyl)piperidine-1-carboxylate (prepared in step 3 of example 56, 750 mg, 1.78 mmol) was added. The reaction mixture was then stirred at 110 °C and a solution of 4-methyl-N-[oxepan-4-ylideneamino]benzenesulfonamide (630 mg, 2.23 mmol) in DMF (2.5 mL) was added and the resulting reaction mixture was stirred at 110 °C under argon flux, for 5 hours. Then the reaction mixture was diluted with AE and water and the aqueous layer was extracted with AE. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 24 g) eluting with Cyclohexane / AE 80/20 to 0/100 to give 162 mg (23% yield) of a 1/1 mixture of tert-butyl 4-[2-amino-5-fluoro-3-(2,3,6,7-tetrahydrooxepin-4-yl)-4-pyridyl]piperidine-1-carboxylate & tert-butyl 4-[2-amino-5-fluoro-3-(2,3,4,7-tetrahydrooxepin-5-yl)-4-pyridyl]piperidine-1-carboxylate as a brown solid. LC/MS (m/z, M+H): calc. 392.2, found 392.3.

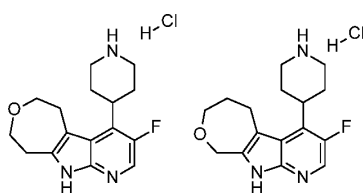
STEP 3: tert-butyl 4-(4-fluoro-12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)piperidine-1-carboxylate & tert-butyl 4-(4-fluoro-11-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)piperidine-1-carboxylate



- 5 To a solution of the above mentioned mixture of tert-butyl 4-[2-amino-5-fluoro-3-(2,3,6,7-tetrahydrooxepin-4-yl)-4-pyridyl]piperidine-1-carboxylate & tert-butyl 4-[2-amino-5-fluoro-3-(2,3,4,7-tetrahydrooxepin-5-yl)-4-pyridyl]piperidine-1-carboxylate (158 mg, 0.4 mmol) in THF (1 mL) was added a solution of [bis(trifluoroacetoxy)iodo]benzene (175 mg, 0.41 mmol) in THF (1 mL) and the resulting mixture was stirred at room temperature for 4.5 hours. Then,
- 10 the whole mixture was diluted with AE and with a saturated aqueous solution of NaHCO₃. The aqueous layer was extracted with AE and the combined organic layers were dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 12 g) eluting with DCM / [DCM/MeOH 95/5] 100/0 to 0/100 to give 80 mg (36% yield) of a 1/1 mixture of tert-butyl 4-(4-fluoro-12-oxa-6,8-
- 15 diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)piperidine-1-carboxylate & tert-butyl 4-(4-fluoro-11-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)piperidine-1-carboxylate as a brown wax. LC/MS (m/z, M+H): calc. 390.2, found 390.3.

STEP 4: 4-fluoro-3-(4-piperidyl)-12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraene;hydrochloride & 4-fluoro-3-(4-piperidyl)-11-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraene;hydrochloride

- 20

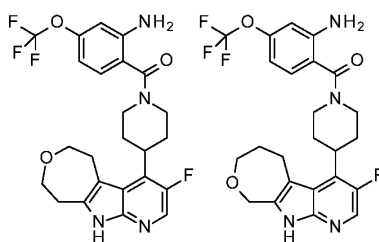


To a solution of the above mentioned 1/1 mixture of tert-butyl 4-(4-fluoro-12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)piperidine-1-carboxylate & tert-butyl 4-(4-fluoro-11-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)piperidine-1-carboxylate (78 mg, 0.2 mmol) in MeOH (2 mL) was added a 4 N solution of HCl in 1,4-dioxane (0.5 mL, 2 mmol) and the resulting reaction mixture was stirred at room temperature for 2.5 hours, then concentrated to dryness to give 73 mg (100% yield) of a crude

- 25

1/1 mixture of 4-fluoro-3-(4-piperidyl)-12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraene;hydrochloride & 4-fluoro-3-(4-piperidyl)-11-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraene;hydrochloride as a yellow wax which was engaged in the next step without further purification.

- 5 **STEP 5:** [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone & [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-11-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone

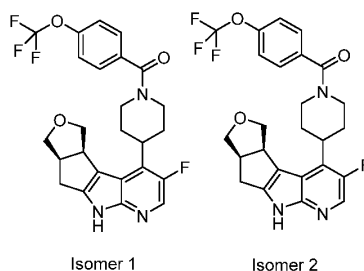


- 10 To a solution of the above mentioned 1/1 mixture of 4-fluoro-3-(4-piperidyl)-12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraene;hydrochloride & 4-fluoro-3-(4-piperidyl)-11-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraene;hydrochloride (73 mg, 0.2 mmol) in DMF (3 mL) was added triethylamine (0.17 mL, 1.22 mmol) followed by 2-amino-4-(trifluoromethoxy)benzoic acid (55 mg, 0.25 mmol) and TBTU (85 mg, 0.26 mmol)
- 15 and the resulting reaction mixture was stirred for 45 minutes, then diluted with AE and water. The aqueous layer was then extracted with AE and the combined organic layers were dried over sodium sulfate, filtered and concentrated to dryness. The resulting residue was purified by flash chromatography on silica gel (SiO₂ 12 g) eluting with cyclohexane / [AE/EtOH 3/1] 100/0 to 50/50 followed by a second purification to separate the regioisomers as follows:
- 20 DCPak SFC-B column (5 μM, 30x250nm) eluting with (90% CO₂, 10% MEOH/TEA), flow rate 120mL/min, UV detection at 230nm, to give:

33 mg (30% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone as a white powder. LC/MS (m/z, M+H): calc. 493.2, found 493.3.

- 25 And 18 mg (16% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-11-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone as a white powder. LC/MS (m/z, M+H): calc. 493.2, found 493.4.

Examples 259 & 268: [4-[(cis)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2



The two enantiomers of (rac)-cis-[4-[4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (example 27, 174 mg, 0.35 mmol) were separated

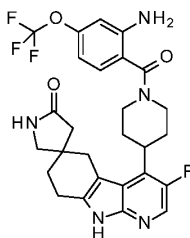
5 following the general chiral separation method CS#7 to give:

83 mg (48% yield) of [4-[(cis)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 490.2, found 490.3.

10 And 85 mg (49% yield) of [4-[(cis)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.0.2,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 490.2, found 490.3.

Example 260: (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one

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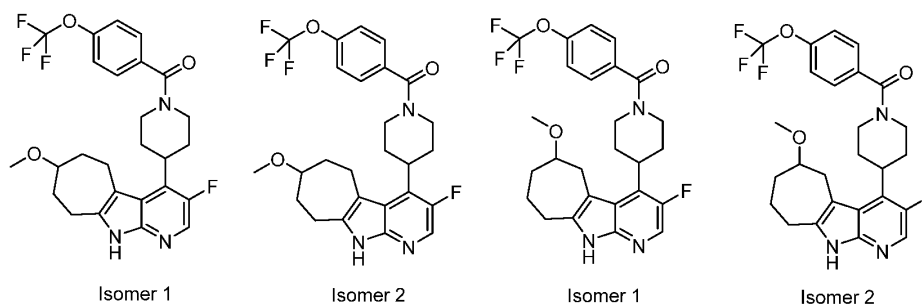
Example 260 was prepared following the protocol described in step 2 of method D using 2-azaspiro[4.5]decane-3,8-dione (281 mg, 1.68 mmol) to give 139 mg (45% yield) of (rac)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one as a white solid. LC/MS (m/z, M+H): calc. 546.2, found 546.4.

20

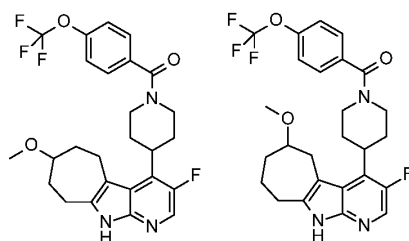
Example 260 was then engaged in a chiral separation using the General chiral separation method CS#16 (see below) to furnish examples 78 & 79.

General Chiral Separation Method CS#16: Separation of the abovementioned mixture was performed using a Phenomenex LUX I-cellulose 5 column (5 μ m, 30x250 mm), eluting with (EtOH 40%, n-heptane 60%)+0.1% TEA, flow rate 45 mL / min, UV detection at 254 nm.

- Examples 263, 264, 265 & 266:** [4-[4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 and isomer 2, [4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 and isomer 2

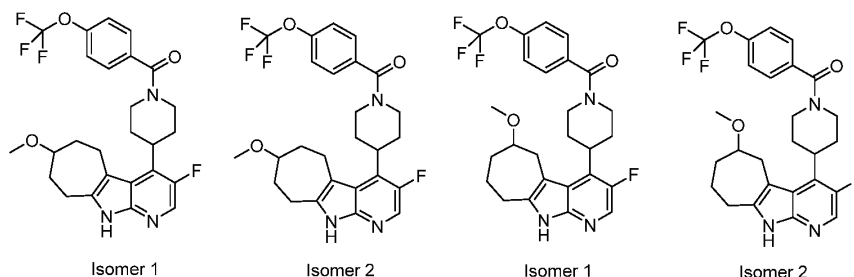


- STEP 1:** (rac)-[4-(4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone & (rac)-[4-(4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



- Step 1 of examples 263, 264, 265 & 266 was performed following the protocol described in step 6 of method A using 4-methoxycycloheptan-1-one (335 mg, 2.36 mmol) to give 170 mg (43% yield) of a 60/40 mixture of (rac)-[4-(4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone & (rac)-[4-(4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid, which was engaged in the next step. LC/MS (m/z, M+H): calc. 506.2, found 506.3.

STEP 2: [4-[4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 and isomer 2, [4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 and isomer 2



The above-mentioned mixture (161 mg, 0.32 mmol) were separated following the general chiral separation method CS#9 (followed by a purification using the general chiral separation method CS#14 for examples 265 & 266 which were not pure enough) to give:

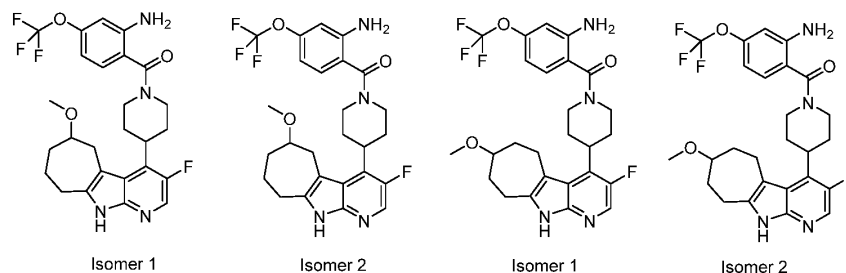
44 mg (27% yield) of [4-[4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 506.2, found 506.2.

43 mg (27% yield) of [4-[4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 506.2, found 506.2.

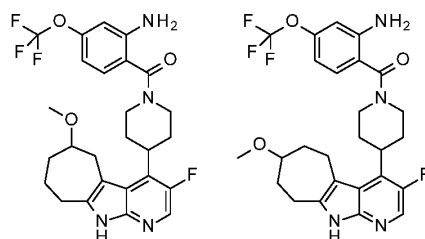
25 mg (15% yield) of [4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 506.2, found 506.4.

And 24 mg (15% yield) of [4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 506.2, found 506.4.

Examples 267, 87, 88, 89: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone isomer 1 and isomer 2, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone isomer 1 and isomer 2

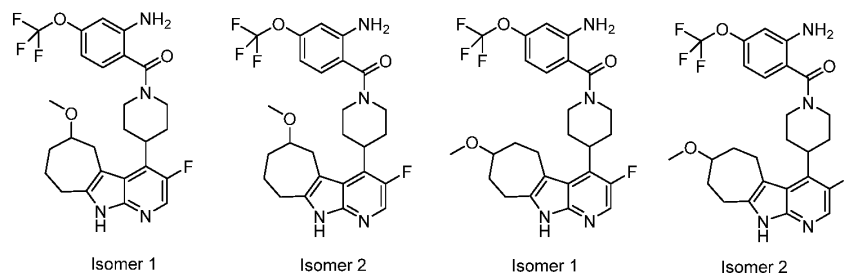


- STEP 1:** (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone, (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone



- Step 1 of examples 267, 87, 88, 89 was performed following the protocol described in step 2 of method D using 4-methoxycycloheptan-1-one (273 mg, 1.92 mmol) to give 117 mg (35% yield) of a 55/45 mixture of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone, (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone as a solid which was engaged in the next step. LC/MS (m/z, M+H): calc. 521.2, found 521.4.

- STEP 2:** [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone isomer 1 and isomer 2, [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone isomer 1 and isomer 2



The above-mentioned mixture (117 mg, 0.22 mmol) were separated following the general chiral separation method CS#9 (followed by a purification using the general chiral separation method CS#14 for the mixture of examples 291 & 292 which were not separated in the first method used) to give:

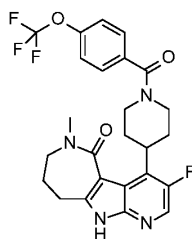
30 mg (26% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 521.2, found 521.2.

31 mg (26% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 521.2, found 521.2.

16 mg (14% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 521.2, found 521.3.

And 15 mg (13% yield) of [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-4-fluoro-12-methoxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 521.2, found 521.3.

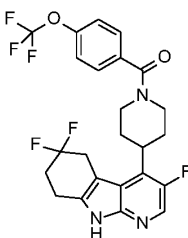
Example 269: 4-fluoro-13-methyl-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-14-one



Example 269 was prepared following the protocol described in step 6 of method A using 1-methylazepane-2,4-dione (166 mg, 1.18 mmol) to give 85 mg (43% yield) of 4-fluoro-13-methyl-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-

triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one as a white solid. LC/MS (m/z, M+H): calc. 505.2, found 505.3.

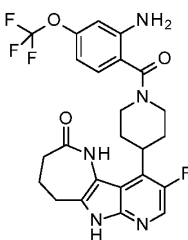
Example 270: [4-(trifluoromethoxy)phenyl]-[4-(3,6,6-trifluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone



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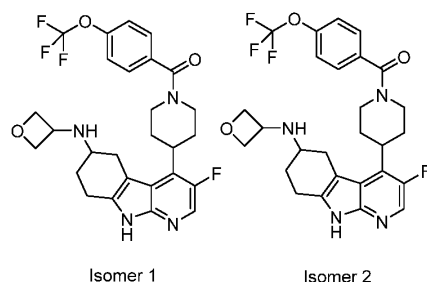
Example 270 was prepared following the protocol described in step 6 of method A using 4,4-difluorocyclohexanone (78 mg, 0.58 mmol) to give 11 mg (56% yield) of [4-(trifluoromethoxy)phenyl]-[4-(3,6,6-trifluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone as a solid. LC/MS (m/z, M+H): calc. 498.2, found 498.3.

10 **Example 271:** 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8,14-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one



15 Example 271 was prepared following the protocol described in step 2 of method D using azepane-2,6-dione (170 mg, 1.2 mmol) to give 25 mg (12% yield) of 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8,14-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-one as a white solid. LC/MS (m/z, M+H): calc. 506.2, found 506.3.

Examples 274 & 275: [4-[3-fluoro-6-(oxetan-3-ylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 & isomer 2

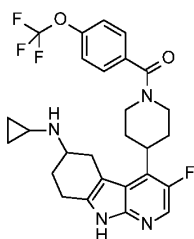


The two enantiomers of (rac)-[4-[3-fluoro-6-(oxetan-3-ylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (example 24, 100 mg, 0.19 mmol) were separated following the general chiral separation method CS#1 to give:

45 mg (45% yield) of [4-[3-fluoro-6-(oxetan-3-ylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 1 as a solid. LC/MS (m/z, M+H): calc. 533.2, found 533.2.

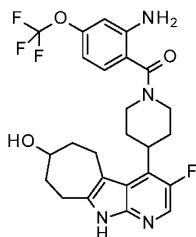
And 45 mg (45% yield) of [[4-[3-fluoro-6-(oxetan-3-ylamino)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone isomer 2 as a solid. LC/MS (m/z, M+H): calc. 533.2, found 533.2.

Example 276: (rac)-[4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



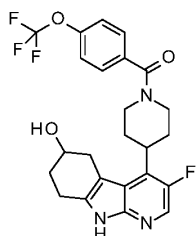
Example 276 was prepared following the protocol described in step 1 of examples 23, 1 & 2 using 3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one (example 61, 61 mg, 0.13 mmol) and cyclopropylamine (7.4 mg, 0.13 mmol) to give 34 mg (51% yield) of (rac)-[4-[6-(cyclopropylamino)-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M+H): calc. 517.2, found 517.4.

Example 277: (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone



The preparation of example 277 was described in step 3 of example 46, 8 & 9.

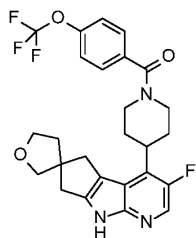
Example 278: (rac)-[4-(3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



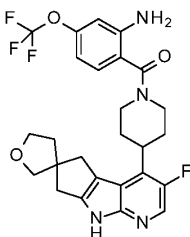
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The preparation of example 278 was described in step 1 of examples 33 & 34.

Example 279: (rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

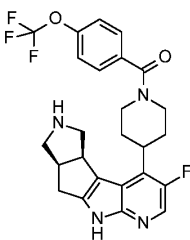


- 10 Example 279 was prepared following the protocol described in step 6 of method A using 2-oxaspiro[4.4]nonan-8-one (206 mg, 1.47 mmol) to give 100 mg (40% yield) of (rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as an orange solid. LC/MS (m/z , $M+H$): calc. 504.2, found 504.4.
- 15 **Example 280:** (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl)-1-piperidyl]methanone

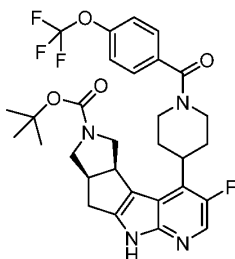


- Example 280 was prepared following the protocol described in step 2 of method D using 2-oxaspiro[4.4]nonan-8-one (242 mg, 1.73 mmol) to give 110 mg (37% yield) of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),9,11-tetraene-4,3'-tetrahydrofuran]-12-yl)-1-piperidyl]methanone as a solid. LC/MS (m/z, M+H): calc. 519.2, found 519.4.

Example 281: (rac)-[4-[(cis)-4-fluoro-6,8,13-triazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraene-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

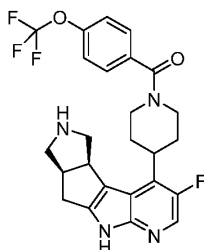


- 10 **STEP 1:** (rac)-tert-butyl 4-fluoro-3-[1-[4(cis)-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraene-13-carboxylate



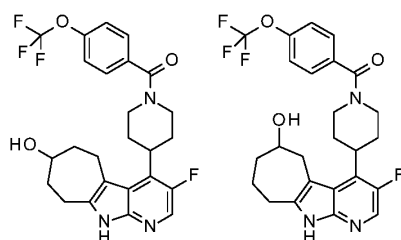
- Step 1 of example 281 was performed following the protocol described in step 6 of method A using tert-butyl (3aS,6aR)-5-oxo-1,3,3a,4,6,6a-hexahydrocyclopenta[c]pyrrole-2-carboxylate (331 mg, 1.47 mmol) to give 163 mg (47% yield) of (rac)-tert-butyl 4-fluoro-3-[1-[4(cis)-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraene-13-carboxylate as a yellow solid. LC/MS (m/z, M+H): calc. 589.2, found 589.4.

STEP 2: (rac)-[4-[(cis)-4-fluoro-6,8,13-triazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

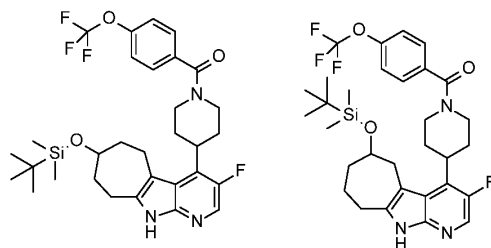


Step 2 of example 281 was performed following the protocol described in step 2 of example 125 without DCM as co-solvent to give 123 mg (93% yield) of (rac)-[4-[(cis)-4-fluoro-6,8,13-triazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z, M+H): calc. 489.2, found 489.4.

Examples 282 & 59: (rac)-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone & (rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

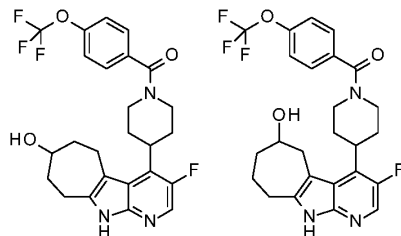


STEP 1: [4-[12-[tert-butyl(dimethyl)silyl]oxy-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone & [4-[13-[tert-butyl(dimethyl)silyl]oxy-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



- Step 1 of example 282 & 59 was performed following the protocol described in step 6 of method A using 4-[tert-butyl(dimethyl)silyl]oxycycloheptanone (described in step 1 of examples 46, 8, 9, 357 mg, 1.47 mmol) to give 159 mg (44% yield) of a 73/27 mixture of [4-[12-[tert-butyl(dimethyl)silyl]oxy-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone & [4-[13-[tert-butyl(dimethyl)silyl]oxy-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a pale brown solid. LC/MS (m/z, M+H): calc. 606.3, found 606.6.

- 10 **STEP 2:** (rac)-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone & (rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

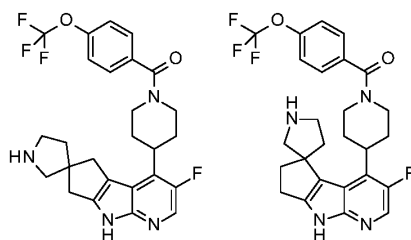


- 15 Step 2 of examples 282 & 59 was performed following the protocol described in step 3 of Examples 46, 8 & 9 to give :

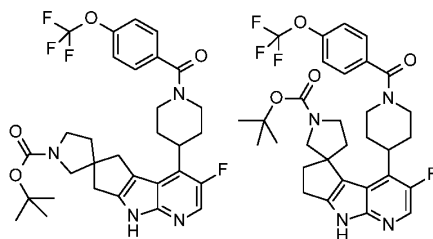
65 mg (51% yield) of (rac)-[4-(4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M+H): calc. 492.2, found 492.4.

- 20 And 24 mg (19% yield) of (rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M+H): calc. 492.2, found 492.4.

Examples 283 & 58: (rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,3'-pyrrolidine]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone & (rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-3,3'-pyrrolidine]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

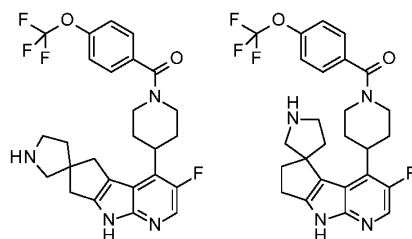


STEP 1: (rac)-tert-butyl 11-fluoro-12-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,3'-pyrrolidine]-1'-carboxylate & (rac)-tert-butyl 11-fluoro-12-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-3,3'-pyrrolidine]-1'-carboxylate



Step 1 of examples 283 & 58 was performed following the protocol described in step 6 of method A using (rac)-tert-butyl 8-oxo-2-azaspiro[4.4]nonane-2-carboxylate (352 mg, 1.47 mmol) to give 206 mg (52% yield) of a 80/20 mixture of (rac)-tert-butyl 11-fluoro-12-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,3'-pyrrolidine]-1'-carboxylate & (rac)-tert-butyl 11-fluoro-12-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-3,3'-pyrrolidine]-1'-carboxylate as a yellow solid. LC/MS (m/z, M+H): calc. 603.2, found 603.5.

STEP 2: (rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,3'-pyrrolidine]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone & (rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-3,3'-pyrrolidine]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

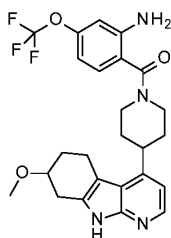


Step 2 of examples 283 & 58 was performed following the protocol described in step 2 of example 125 without DCM as co-solvent to give :

121 mg (79% yield) of (rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-4,3'-pyrrolidine]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a yellow solid. LC/MS (m/z , $M+H$): calc. 503.2, found 503.4.

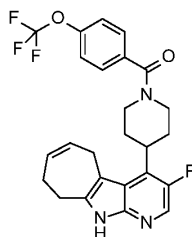
And 30 mg (20% yield) of (rac)-[4-(11-fluorospiro[7,9-diazatricyclo[6.4.0.02,6]dodeca-1(12),2(6),8,10-tetraene-3,3'-pyrrolidine]-12-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a white solid. LC/MS (m/z , $M+H$): calc. 503.2, found 503.5.

Example 284: (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone

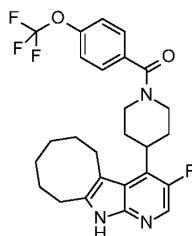


Example 284 was prepared following the protocols described in method G, steps 1 to 7, to give 23 mg of (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(7-methoxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone as a white solid. LC/MS (m/z , $M+H$): calc. 489.2, found 489.1.

Example 285: [4-(4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5,12-pentaen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone

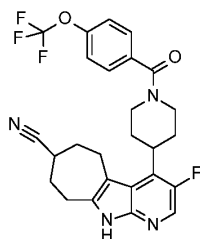


- In a 10-20 mL microwave vial, a solution of -[4-(2-amino-5-fluoro-3-iodo-4-pyridyl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone (see method A, 500 mg, 0.98 mmol), pyridinium para-toluenesulfonate (120 mg, 0.48 mmol), cycloheptene-5-one (342 mg, 2.95 mmol) and tetraethyl orthosilicate (240 μ L, 1.07 mmol) in 10 mL of pyridine was stirred at 160 °C for 1.5 hour. Then N-cyclohexyl-N-methylcyclohexanamine (330 μ L, 1.54 mmol) and tetrakis(triphenylphosphine)palladium (0) (120 mg, 0.1 mmol) in solution in 0.5 mL of pyridine were added and the resulting mixture was stirred under microwave irradiation at 160 °C for 6 hours followed by 12 hours at room temperature. Then, the whole mixture was concentrated and the resulting residue was purified by flash chromatography on silica gel (SiO₂ 120 g) eluting with n-Heptane / AE 90/10 to 50/50, followed by a second purification (SiO₂ 25 g) eluting with DCM / MeOH 100/0 to give 84 mg (18% yield) of [4-(4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5,12-pentaen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a solid. LC/MS (m/z, M+H): calc. 474.2, found 474.3.
- Example 286:** [4-(4-fluoro-6,8-diazatricyclo[7.6.0.0.2,7]pentadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone



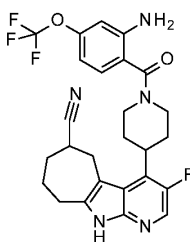
- Example 286 was prepared following the protocol described in step 6 of method A using cyclooctenone (148 mg, 1.18 mmol) to give 86 mg (45% yield) of [4-(4-fluoro-6,8-diazatricyclo[7.6.0.0.2,7]pentadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone as a pale brown solid. LC/MS (m/z, M+H): calc. 490.2, found 490.4.

Example 290: (rac)-4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraene-12-carbonitrile



To a microwave tube, under inert atmosphere, *t*-BuOK (55 mg, 0.49 mmol) was added to a solution of 4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2,4,6-tetraen-12-one (example 211, 100 mg, 0.20 mmol) and TosMIC (52 mg, 0.27 mmol) in a mixture of 1,2-dimethoxyethane (1 mL) and ethanol (35 μ L) at 0 $^{\circ}$ C. The resulting mixture was stirred at 0 $^{\circ}$ C for 1 hour and at room temperature for 3 hours. The reaction mixture was diluted with EtOAc (20 mL) and water (15 mL). The layers were separated. The aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by normal phase preparative LC (irregular SiOH, 15 μ m, 12 g interchim, solid loading (SiOH), mobile phase gradient: from DCM/EtOAc 90:10 to 20:80 to give (rac)-4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraene-12-carbonitrile (46 mg, 45% yield) as a white solid. LC/MS (*m/z*, *M*+*H*): calc. 501.2, found 501.2.

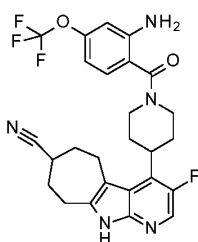
Example 291: (rac)-3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraene-13-carbonitrile



To a microwave tube, under inert atmosphere, *t*-BuOK (91 mg, 0.81 mmol) was added to a solution of 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.0.2,7]tetradeca-1(9),2(7),3,5-tetraen-13-one (isolated from step 2 of examples 144, 145, 146 & 147, 170 mg, 0.34 mmol) and TosMIC (86 mg, 0.44 mmol) in a mixture of 1,2-dimethoxyethane (1.7 mL) and ethanol (58 μ L) at 0 $^{\circ}$ C. The resulting mixture was stirred at 0 $^{\circ}$ C for 1 hour and at room temperature for 3 hours. The reaction mixture was diluted with EtOAc (80 mL) and water (60 mL). The layers were separated. The aqueous layer

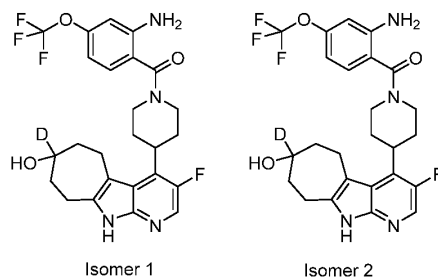
was extracted with EtOAc (80 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by normal phase preparative LC (irregular SiOH, 15 μm, 12 g interchim, solid loading (SiOH), mobile phase gradient: from DCM/EtOAc 90:10 to 10:90) to give (rac)-3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-13-carbonitrile (74 mg, 42% yield) as an off-white solid. LC/MS (m/z, M+H): calc. 516.2, found 516.2.

Example 292: (rac)-3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carbonitrile

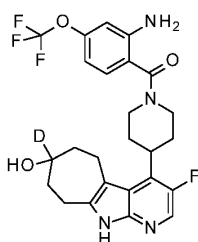


To a microwave tube, under inert atmosphere, t-BuOK (80 mg, 0.71 mmol) was added to a solution of 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-one (example 207, 150 mg, 0.3 mmol) and TosMIC (76 mg, 0.39 mmol) in a mixture of 1,2-dimethoxyethane (1.5 mL) and ethanol (51 μL) at 0 °C. The resulting mixture was stirred from 0 °C to room temperature for 5 hours. The reaction mixture was then diluted with EtOAc (50 mL) and water (50 mL). The layers were separated. The aqueous layer was extracted with EtOAc (25 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by normal phase preparative LC (irregular SiOH, 15 μm, 12 g interchim, solid loading (SiOH), mobile phase gradient: from DCM/EtOAc 80:20 to 20:80) to give (rac)-3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraene-12-carbonitrile (58 mg, 38%) as a white solid. LC/MS (m/z, M+H): calc. 516.2, found 516.2.

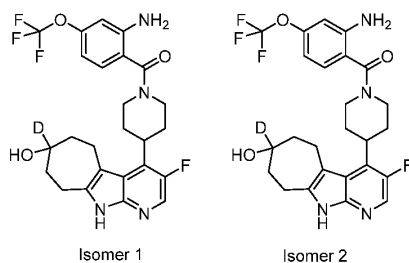
Examples 293 & 294: [2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone isomer 1 & isomer 2



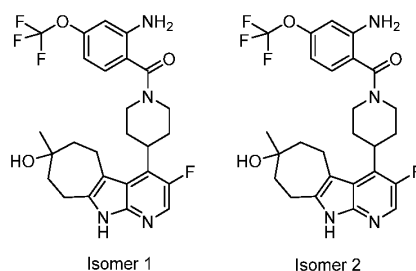
STEP 1: (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone



- 5 Sodium borodeuteride (15 mg, 0.357 mmol) was added to a solution of 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-12-one 1 (Example 207, 100 mg, 0.178 mmol) in methanol (5 mL) at 0 °C and under inert atmosphere. The resulting mixture was stirred from 0 °C to room temperature for 4 hours. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford crude (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone (95 mg, 95% yield) as a beige solid. LC/MS (m/z, M+H): calc. 508.2, found 508.2.
- 10
- 15 **STEP 2:** [2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone isomer 1 & isomer 2



- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone (89 mg) was separated by preparative chiral SFC (Stationary phase: Chiralpak AD-H 20 x 250 mm, Mobile phase: CO₂ / MeOH 70/30). The fractions containing enantiomers were combined and evaporated in vacuo to afford two fractions. The first fraction was dissolved in DCM (3 x 1 mL), dried under air overnight and then under high vacuum overnight to afford [2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone isomer 1 (26 mg, 28% yield) as an off-white solid. LC/MS (m/z, M+H): calc. 508.2, found 508.2.
- The second fraction was dissolved in DCM (3 x 1 mL), dried under air overnight and then under high vacuum overnight to afford [2-amino-4-(trifluoromethoxy)phenyl]-[4-[12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone isomer 2 (24 mg, 27% yield) as an off-white solid. LC/MS (m/z, M+H): calc. 508.2, found 508.2.
- Examples 288 & 289:** [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone isomer 1 & isomer 2



- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone (example 185, 100 mg, 0.18 mmol) was purified by preparative chiral SFC (Stationary phase: Chiralpak IC 20 x 250 mm, Mobile phase: CO₂ / EtOH 75/25). The fractions containing enantiomers were combined and evaporated in vacuo to afford two fractions. The first fraction was dissolved in DCM (3 x 1 mL), dried under air overnight and then under high vacuum overnight to afford [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone isomer 1 (17 mg, 17% yield) as an off-white solid. LC/MS (m/z, M+H): calc. 521.2, found 521.2.

- The second fraction was dissolved in DCM (3 x 1 mL), dried under air overnight and then under high vacuum overnight to afford [2-amino-4-(trifluoromethoxy)phenyl]-[4-[4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-

piperidyl]methanone isomer 2 (15 mg, 15% yield) as an off-white solid. LC/MS (m/z, M+H): calc. 521.2, found 521.2.

Example 295 – ERK5 inhibitory activity of compounds

- Two assays were performed to assess the ERK5 inhibitory activity of compounds of the Examples, a cell-based assay and a cell-free biochemical assay. Results of the assays are shown below in Table 2.

Inhibition of cellular ERK5 activity

- The renal cancer cell line SN12C was transduced by a lentivirus pGreenFire1 MEF2 EF1 Neo (ref TR030VA-N) from SBI using standard infection protocol. pGreenFire1 MEF2 EF1 Neo allows the expression of luciferase gene under the control of minimal promoter with MEF2 transcriptional response elements. Cells harboring the reporter construct were selected by geneticin treatment. The selected cells were then transposed by a piggyback based plasmid pCM4007 allowing the expression of constitutively activated MEK5DD under control of TREG3 promoter, a doxycycline regulated promoter. Transposed cells were selected by puromycin treatment. Upon doxycycline treatment (1 µg/ml) MEK5DD was expressed. MEK5DD activates ERK5 that phosphorylates MEF2C protein. Activated MEF2C protein can bind to its transcriptional response elements. Then the luciferase is expressed. In a 96-well plate (96F nuncleon ref137101 thermofisher), 50,000 cells were inoculated in 142.5 µl of RPMI medium containing 10% fetal calf serum, 1% glutamine, and 1 µg/ml doxycycline. After 24 hours, compounds were added in 7.5 µl culture medium (with 2% DMSO to give a final concentration of 0.1%) in order to obtain the desired concentration (0.3-10000 nM). The luciferase activity was measured using the Kit Bright Glo Luminescent Cell Assay Cat E2610 (Promega) according to the manufacturer's protocol. Luminescence was determined using 0.2 second reading/well using a Tecan SPARK. IC₅₀ values were calculated using XLFIT5 for Microsoft Excel using method 205. The IC₅₀ values represent the concentration of compound which inhibits the measurable luminescence signal by 50% as compared to DMSO-treated control cells.

Cell-free assay of ERK5 inhibition

- An assay was performed to measure the capacity of each compound to inhibit ERK5 enzymatic activity. Compound potency was evaluated by Time-Resolved Forster Resonance Energy Transfer (FRET system). The activated catalytic domain of protein ERK5 (CarnaBiosciences #04-146) was mixed at 4 nM with varying concentrations of compound and incubated for 30 minutes at room temperature. A mixture of 1 mM ATP and 1 µM biotinylated synthetic peptide was added (Biosyntan GmbH). This synthetic peptide represents amino acids 30-52 of Eukaryotic translation initiation factor 4E-binding protein 1 (see, e.g., the sequence under

- accession No. NP_004086.1) biotinylated at the N-terminus. After 30 minutes at 37°C, the peptide phosphorylation by ERK5 was measured by addition of FRET reagents consisting of 12.5 µg/ml Streptavidin-XL665, 1 nM Anti-P-4EBP1 antibody and 300ng/ml Anti-rabbit-K antibody. Following 90 minutes at room temperature fluorescent signals were read on the
- 5 Pherastar FSX multimod detector from BMG Labtech (Exc° 340 nm, Em1 620 nm, Em2 665 nm). The IC₅₀ values represent the concentration of compound which inhibits the measurable fluorescence signal by 50% as compared to the DMSO only control.

Table 2: Results of cell-based and cell-free assays

Compound (Example No.)	Cell-based assay (IC₅₀ in nM)	Cell-free assay (IC₅₀ in nM)
1	51	51
2	31	35
3	23	48
4	46	140
5	5	4
6	92	96
7	16	36
8	2	3
9	3	9
10	65	101
11	52	55
12	137	86
13	34	118
14	4	19
15	102	1042
16	22	193
17	30	89
18	29	854
19	66	631
20	19	67
21	174	5390
22	99	1144
23	19	40
24	25	78
25	31	244
26	100	475
27	51	167
28	17	104
29	18	114
30	15	42
31	2	7
32	40	38
33	28	23
34	53	44

Compound (Example No.)	Cell-based assay (IC ₅₀ in nM)	Cell-free assay (IC ₅₀ in nM)
35	22	23
36	492	477
37	75	197
38	12	17
39	47	577
40	118	357
41	22	112
42	116	498
43	11	81
44	9	30
45	53	1137
46	4	8
47	196	6264
48	53	13
49	170	101
50	13	267
51	105	1469
52	23	127
53	49	2887
54	5	26
55	32	109
56	269	1228
57	27	124
58	43	30
59	12	23
60	99	5527
61	22	72
62	185	318
63	45	23
64	135	137
65	18	26
66	5	8
67	7	32
68	13	185
69	15	185
70	124	2265
71	226	3741
72	4852	-
73	187	16491
74	850	>30000
75	28	96
76	205	374
77	122	113
78	63	23
79	5	2
80	13	8

Compound (Example No.)	Cell-based assay (IC ₅₀ in nM)	Cell-free assay (IC ₅₀ in nM)
81	3	2
82	18	20
83	1	<2
84	8	191
85	8	5
86	13	5
87	10	60
88	22	182
89	25	172
90	18	9
91	8	96
92	6	67
93	365	888
94	319	554
95	803	637
96	469	227
97	58	140
98	91	1986
99	265	416
100	13	313
101	54	91
102	202	87
103	204	41
104	986	65
105	1177	20
106	946	33
107	68	5062
108	12	76
109	6	36
110	15	36
111	6	15
112	19	83
113	118	71
114	17	191
115	22	1251
116	92	9383
117	42	91
118	28	41
119	54	311
120	5	157
121	25	125
122	11	33
123	2	5
124	12	99

Compound (Example No.)	Cell-based assay (IC ₅₀ in nM)	Cell-free assay (IC ₅₀ in nM)
125	7	3
126	4	31
127	111	330
128	27	124
129	3	22
130	111	203
131	6	18
132	210	637
133	116	745
134	238	47
135	895	5
136	17	41
137	26	28
138	44	199
139	3	3
140	2	34
141	49	104
142	54	201
143	19	501
144	1	21
145	0.8	23
146	1.5	24
147	1.4	9
148	23	84
149	1.2	13
150	1.6	8
151	22	52
152	104	263
153	14	7
154	2	<2
155	6.5	2
156	2	<2
157	29	14
158	15	72
159	9	53
160	9	17
161	5	25
162	40	52
163	209	154
164	>10000	96
165	>10000	59
166	12	45
167	17	45

Compound (Example No.)	Cell-based assay (IC ₅₀ in nM)	Cell-free assay (IC ₅₀ in nM)
168	3	40
169	13	218
170	16	68
171	8.5	17
172	6	12
173	9,5	45
174	204	>30000
175	135	>30000
176	456	>30000
177	193	2194
178	33	114
179	33	261
180	224	1485
181	13	74
182	29	198
183	3	7
184	1.5	3
185	5	49
186	33	14
187	319	303
188	15	30
189	159	323
190	88	320
191	3	11
192	5	9
193	26	46
194	16	13
195	92	110
196	40	25
197	493	1025
198	35	54
199	48	74
200	19	21
201	167	77
202	33	7
203	34	44
204	9	11
205	7	2
206	6	<2
207	4	30
208	66	91
209	10	14
210	2	9

Compound (Example No.)	Cell-based assay (IC ₅₀ in nM)	Cell-free assay (IC ₅₀ in nM)
211	14	120
212	12	56
213	18	281
214	30	242
215	32	237
216	16	115
217	11	114
218	13	47
219	49	171
220	39	102
221	414	2681
222	65	217
223	4	5
224	63	368
225	10	78
226	13	87
227	4	16
228	6	33
229	159	252
230	28	211
231	59	130
232	6	90
233	3	28
234	12	133
235	142	287
236	52	430
237	455	8193
238	95	217
239	48	200
240	6	25
241	22	62
242	34	9
243	28	34
244	134	216
245	6	13
246	63	112
247	55	147
248	103	>30000
249	16	170
250	48	3055
251	336	4757
252	15	79
253	83	282

Compound (Example No.)	Cell-based assay (IC ₅₀ in nM)	Cell-free assay (IC ₅₀ in nM)
254	2	4
255	63	27
256	65	41
257	33	40
258	23	50
259	111	53
260	16	6
261	102	61
262	16	24
263	59	314
264	66	458
265	107	277
266	71	387
267	21	192
268	180	356
269	44	69
270	95	297
271	29	42
272	13	159
273	40	399
274	44	43
275	44	87
276	38	55
277	2	4
278	32	59
279	248	1914
280	74	333
281	70	38
282	15	19
283	64	37
284	86	784
285	82	81
286	34	20842
287	8	191
288	9	-
289	8	-
290	5	-
291	4.3	-
292	1.4	-
293	0.6	-
294	2.1	-

“-” denotes that the values were not measured

The data in Table 2 indicate that the compounds synthesised are active in the micromolar or nanomolar concentration range in cell-based and/or cell-free systems. All of the compounds synthesised have an IC₅₀ value below 10 µM in at least one of the cell-based and cell-free assays.

5

* * * * *

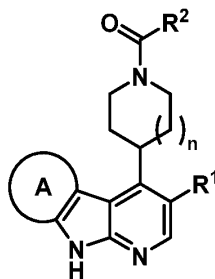
It is to be understood that while the disclosure has been described in conjunction with the above embodiments, that the foregoing description and examples are intended to illustrate and not limit the scope of the disclosure. Other aspects, advantages, and modifications within the scope of the disclosure will be apparent to those skilled in the art to which the disclosure
10 pertains.

In addition, where features or aspects are described in terms of Markush groups, those skilled in the art will recognize that such features or aspects are also thereby described in terms of any individual member or subgroup of members of the Markush group.

All publications, patent applications, patents, and other references mentioned herein are
15 expressly incorporated by reference in their entirety, to the same extent as if each were incorporated by reference individually. In case of conflict, the present specification, including definitions, will control.

CLAIMS

1. A compound, being of Formula (I)



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

5 **ring A** is (C₅-C₈)cycloalkane, (C₆-C₈)cycloalkene, or 5- to 8-membered heterocycloalkane, wherein ring A is optionally substituted with one or more occurrences of R^A,

wherein R^A at each occurrence is:

10 (a) independently selected from -D, halo, -OH, oxo, =N-OH, -NHR', -CN, -C(O)R'', -(C₁-C₃)alkyl, -O(C₁-C₃)alkyl, -(C₃-C₆)cycloalkyl, and 3- to 6-membered heterocycloalkyl, wherein each occurrence of -(C₁-C₃)alkyl is optionally substituted with one or more groups selected from halo and -OH,

15 wherein each R' is selected from -H, -(C₁-C₃)alkyl optionally substituted with one or more halo, -(C₃-C₄)cycloalkyl, and 3- to 4-membered heterocycloalkyl,

wherein each R'' is selected from -OH, -O(C₁-C₃)alkyl, and -(C₁-C₃)alkyl (e.g. -CH₃); and/or

20 (b) taken together with another occurrence of R^A and the intervening atom(s) to form a (C₄-C₇)cycloalkyl or 4- to 7-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring and said cycloalkyl ring are optionally substituted by one or more groups selected from oxo, -C(O)OH, -C(O)N((C₁-C₃)alkyl)₂, and -(C₁-C₃)alkyl;

R¹ is selected from -H, and halo (e.g., -F);

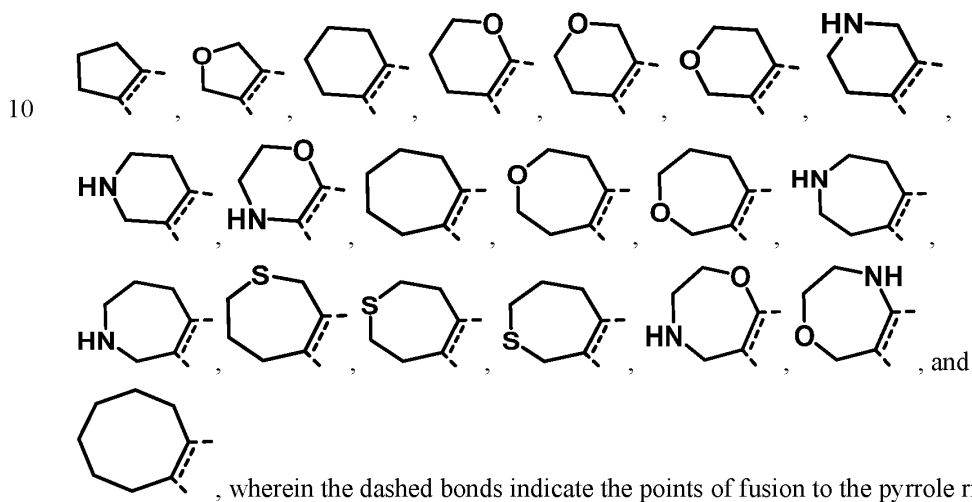
25 **R²** is -(C₆-C₁₀)aryl, wherein R² is substituted with one, or two occurrences of R^B, wherein each R^B is independently selected from halo, -OH, -NH₂, -SF₅, -(C₁-C₃)alkyl, and -O(C₁-C₃)alkyl, wherein each occurrence of -(C₁-C₃)alkyl and -O(C₁-C₃)alkyl is optionally substituted by one or more halo; and

n is 0, 1, or 2,

with the proviso that when R^2 is 4-(pentafluorosulfanyl)phenyl, R^1 is -H, and n is 1, then ring A is not unsubstituted cyclopentane.

2. The compound of claim 1, wherein ring A is selected from cyclopentane,
 5 cyclohexane, cycloheptane, cyclooctane, tetrahydrofuran, tetrahydropyran, piperidine, morpholine, oxepane, azepane, 1,4-oxazepane, and thiepane, wherein ring A is optionally substituted with one or more occurrences of R^A as defined in claim 1.

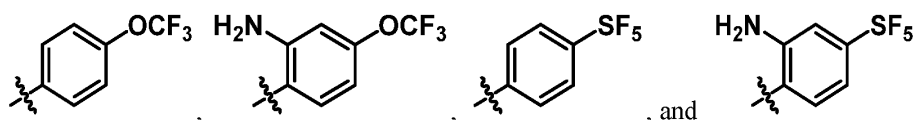
3. The compound of claim 1 or claim 2, wherein ring A is selected from:



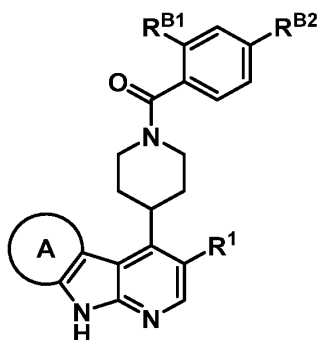
wherein ring A is optionally substituted by one or more occurrences of R^A as defined in claim

- 15 1.

4. The compound of any one of claims 1-3, wherein R^2 is selected from:



5. A compound, being of Formula (II)

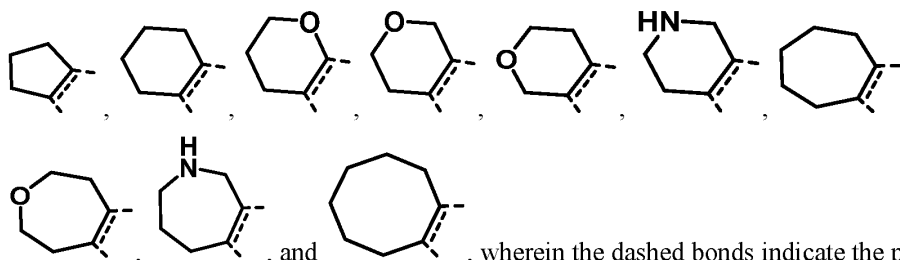


Formula (II)

or a pharmaceutically acceptable salt thereof, wherein:

- ring A** is (C₅-C₈)cycloalkane or 6- to 7-membered heterocycloalkane, wherein
- 5 ring A is optionally substituted with one or more occurrences of R^A,
 wherein R^A at each occurrence is:
- (a) independently selected from -OH, oxo, -NHR', -C(O)CH₃, -(C₁-C₃)alkyl, and -O(C₁-C₃)alkyl,
 wherein each R' is selected from -(C₁-C₃)alkyl optionally substituted
 10 with one or more halo, -(C₃-C₄)cycloalkyl, and 3- to 4-membered heterocycloalkyl; or
- (b) taken together with another occurrence of R^A and the intervening atom(s) to form a (C₅-C₇)cycloalkyl or 4- to 6-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is optionally substituted by oxo;
- 15 **R¹** is selected from -H, and -F;
R^{B1} is selected from -H, and -NH₂; and
R^{B2} is selected from -OCF₃, and -SF₅,
 with the proviso that when R^{B1} is -H, R^{B2} is -SF₅, and R¹ is -H, then ring A is not unsubstituted cyclopentane.

6. The compound of claim 5, wherein ring A is selected from:

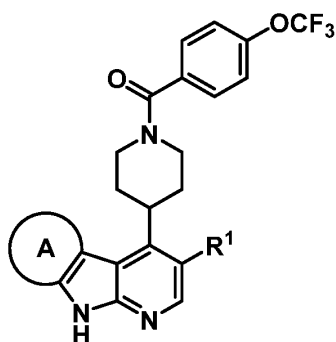


wherein the dashed bonds indicate the points of fusion to the pyrrole ring, wherein ring A is optionally substituted by one or more occurrences of R^A as defined in any one of the preceding claims.

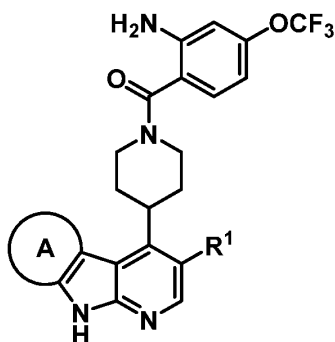
7. The compound of claim 5 or claim 6, wherein R^{B2} is $-\text{OCF}_3$.

8. The compound of any one of claims 1-7, wherein R^1 is $-\text{F}$.

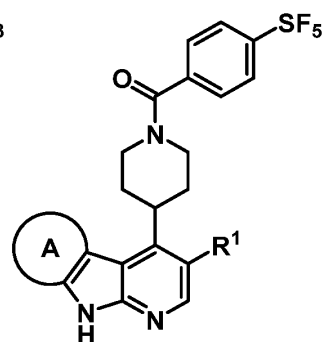
9. A compound, being of Formula (III), Formula (IV), Formula (V), or Formula (VI):



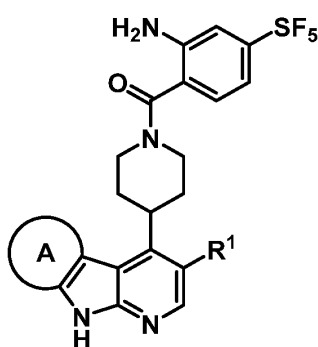
Formula (III)



Formula (IV)



Formula (V)



Formula (VI)

or a pharmaceutically acceptable salt thereof, wherein ring A and R¹ are as defined in any one of the preceding claims, with the proviso that when the compound is a compound of Formula (V) and R¹ is -H, then ring A is not unsubstituted cyclopentane.

- 5 10. A compound selected from the group consisting of:
 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12R)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
 - 10 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl)-1-piperidyl]methanone;
 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(12-fluoro-5-oxa-8,10-diazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),10,12-tetraen-13-yl)-1-piperidyl]methanone;
 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluorospiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-oxetane]-4-yl)-1-piperidyl]methanone;
 - 15 - [4-[(12R)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
 - [4-[(12S)-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
 - 20 - (rac)-[4-(4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
 - 4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-5,7,8,9-tetrahydropyrido[2,3-b]indol-6-one;
 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-6,8-diazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone;
 - 25 - (6R)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
 - (6S)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
 - 30 - [4-[(3R,8R)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.0^{3,8}.0^{11,16}]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
 - [4-[(3S,8S)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.0^{3,8}.0^{11,16}]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
 - [4-[(2S,7S)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.0^{2,7}.0^{10,15}]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
 - 35 - [4-[(2R,7R)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.0^{2,7}.0^{10,15}]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-oxa-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone;
- 3-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-4-fluoro-13-methyl-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one;
- 5 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13R)-4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13S)-4-fluoro-13-methoxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-6,8-
- 10 diazatricyclo[7.6.0.02,7]pentadeca-1(9),2,4,6-tetraen-3-yl)-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6R)-3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6S)-3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 15 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-6-(1-hydroxy-1-methyl-ethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- (7R)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile;
- (7S)-4-[1-[2-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]-3-fluoro-6,7,8,9-
- 20 tetrahydro-5H-pyrido[2,3-b]indole-7-carbonitrile;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-(3-fluoro-1'-methyl-spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,3'-azetidine]-4-yl)-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6E)-3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 25 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6Z)-3-fluoro-6-hydroxyimino-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [4-[(5R)-3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(5S)-3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7E)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7Z)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 35 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12E)-4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12Z)-4-fluoro-12-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13E)-4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13Z)-4-fluoro-13-hydroxyimino-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 5 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(5R)-3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(5S)-3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 10 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(3R,8R)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(3S,8S)-13-fluoro-6,15,17-triazatetracyclo[8.7.0.03,8.011,16]heptadeca-1(10),11,13,15-tetraen-12-yl]-1-piperidyl]methanone;
- 15 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2R,7R)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2S,7S)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone;
- 20 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2S,7R)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(2R,7S)-12-fluoro-5,14,16-triazatetracyclo[7.7.0.02,7.010,15]hexadeca-1(9),10,12,14-tetraen-11-yl]-1-piperidyl]methanone;
- 25 - [4-[(6R)-3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(6S)-3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 30 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6R)-3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6S)-3-fluoro-6-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 35 - [4-[(12R)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(12S)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7R)-3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(7S)-3-fluoro-7-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 5 - 1-[4-fluoro-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-13-yl]ethanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13R)-4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(13S)-4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
- 10 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-(4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl)-1-piperidyl]methanone;
- (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-7-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 15 - (rac)-[2-amino-4-(trifluoromethoxy)phenyl]-[4-[3-fluoro-5-(hydroxymethyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [4-[(13R)-4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(13S)-4-fluoro-13-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 20 - 4-fluoro-11,11-dimethyl-3-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]-6,8,13-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-14-one;
- [4-[(6R)-6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 25 - [4-[(6S)-6-amino-3-fluoro-6-(trifluoromethyl)-5,7,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6R)-3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(6S)-3-fluoro-6-hydroxy-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]indol-4-yl]-1-piperidyl]methanone;
- 30 - [4-[(7E)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- [4-[(7Z)-3-fluoro-7-hydroxyimino-5,6,8,9-tetrahydropyrido[2,3-b]indol-4-yl]-1-piperidyl]-[4-(trifluoromethoxy)phenyl]methanone;
- 35 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(11R,15S)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;

- [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(11S,15R)-4-fluoro-13-oxa-6,8-diazatetracyclo[7.6.0.02,7.011,15]pentadeca-1(9),2,4,6-tetraen-3-yl]-1-piperidyl]methanone;
 - (6R)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
 - (6S)-3-fluoro-4-[1-[4-(trifluoromethoxy)benzoyl]-4-piperidyl]spiro[5,7,8,9-tetrahydropyrido[2,3-b]indole-6,4'-pyrrolidine]-2'-one;
 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12R)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-4-fluoro-12-hydroxy-12-methyl-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone;
 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12R)-12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone; and
 - [2-amino-4-(trifluoromethoxy)phenyl]-[4-[(12S)-12-deuterio-4-fluoro-12-hydroxy-6,8-diazatricyclo[7.5.0.02,7]tetradeca-1(9),2(7),3,5-tetraen-3-yl]-1-piperidyl]methanone,
- and the pharmaceutically acceptable salts thereof.
11. A pharmaceutical composition comprising the compound of any one of claims 1-10 and at least one pharmaceutically acceptable excipient or carrier.
12. A compound according to any one of claims 1-10, or a pharmaceutical composition according to claim 11, for use in therapy.
13. A compound according to any one of claims 1-10, or a pharmaceutical composition according to claim 11, for use in the treatment or prevention of cancer.
14. The compound or pharmaceutical composition for use according to claim 13, wherein the cancer is characterized by increased *MAPK7* expression and/or increased ERK5 activity.
15. The compound or pharmaceutical composition for use according to claim 13 or claim 14, wherein the cancer is selected from leukaemia, breast cancer, multiple myeloma, colon cancer, colorectal cancer, lung cancer, pancreatic cancer, renal cell carcinoma, mesothelioma, adenocarcinoma, neuroblastoma, melanoma, and hepatocellular carcinoma.