



(51) International Patent Classification:

C07D 413/06 (2006.01) A61P 25/30 (2006.01)
 A61K 31/553 (2006.01) A61P 25/32 (2006.01)
 C07D 267/12 (2006.01) A61P 25/34 (2006.01)
 C07D 267/14 (2006.01) A61P 25/36 (2006.01)
 A61P 25/18 (2006.01) A61P 27/16 (2006.01)

(21) International Application Number:

PCT/JP2017/024276

(22) International Filing Date:

23 June 2017 (23.06.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1610956.3 23 June 2016 (23.06.2016) GB

Published:

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

(71) Applicant: TAKEDA PHARMACEUTICAL COMPANY LIMITED [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka, 5410045 (JP).

(72) Inventors: MACK, Stephen; c/o Takeda Cambridge Limited, 418 Cambridge Science Park, Milton Road, Cambridge CB4 0PA (GB). TEALL, Martin; c/o Takeda Cambridge Limited, 418 Cambridge Science Park, Milton Road, Cambridge CB4 0PA (GB). PARMAR, Alka; c/o Takeda Cambridge Limited, 418 Cambridge Science Park, Milton Road, Cambridge, CB4 0PA (GB).

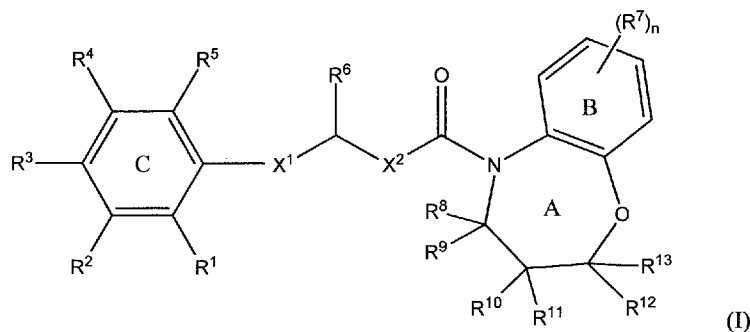
(74) Agent: TAKASHIMA, Hajime; Meiji Yasuda Seimei Osaka Midouji Bldg., 1-1, Fushimimachi 4-chome, Chuo-ku, Osaka-shi, Osaka, 5410044 (JP).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME,

MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

(54) Title: NOVEL COMPOUNDS



(57) Abstract: The present invention provides compounds of formula (I) and pharmaceutically acceptable salts thereof, wherein n, X¹, X², R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are as defined in the specification, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

DESCRIPTION

Title of Invention: NOVEL COMPOUNDS

The present invention relates to benzoxazepine derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy, particularly for use
5 in treating disorders associated with changes in one or both of the glutamatergic and GABAergic signalling pathways regulated in full or in part by metabotropic glutamate receptor 7 (mGluR7).

L-Glutamate is the major neurotransmitter in the mammalian central nervous system and
10 activates both ionotropic and metabotropic glutamate receptors. L-Glutamate plays a central role in numerous physiological functions such as learning and memory (1), sensory perception, development of synaptic plasticity, motor control, respiration and regulation of cardiovascular function. Thus an imbalance in glutamatergic neurotransmission often underlies many neuropathological conditions.

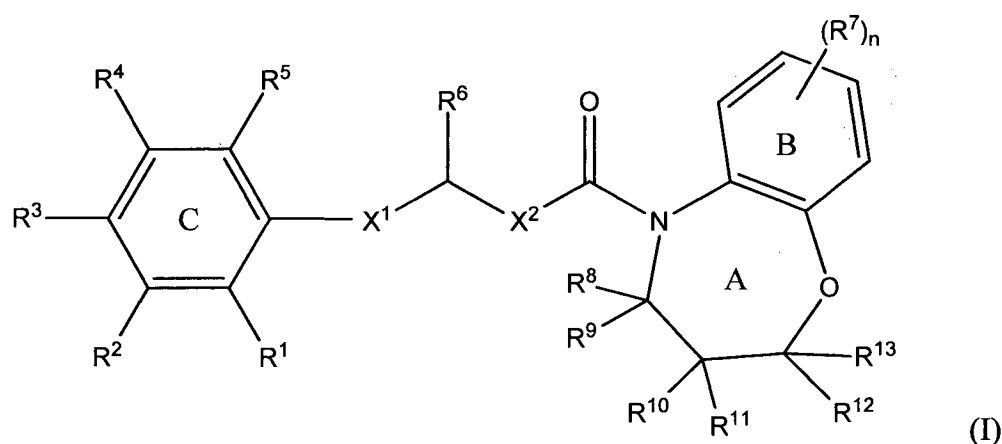
The metabotropic glutamate receptors are a family of G protein-coupled receptors that have been divided into three groups on the basis of sequence homology, putative signal transduction mechanisms and pharmacologic properties. Group I includes mGluR1 and mGluR5 and these receptors have been shown to activate phospholipase C. Group II
15 includes mGluR2 and mGluR3 whilst Group III includes mGluR4, mGluR6, mGluR7 and mGluR8. Group II and III receptors are linked to the inhibition of the cyclic AMP cascade but differ in their agonist selectivities.

mGluR7 is an inhibitory GPCR expressed pre-synaptically at the synaptic cleft on
25 GABAergic and glutamatergic neurons. Depending on the location it can inhibit or disinhibit synaptic activity and can therefore be seen as a modulator of neuronal function. Therefore, mGluR7 modulators would be expected to be useful in treating a wide variety of neurological and psychiatric disorders such as Parkinson's disease (2, 3); dementia associated with Parkinson's disease (3, 4); Alzheimer's disease (5); Huntington's Chorea
30 (6); amyotrophic lateral sclerosis and multiple sclerosis; bipolar disorder (6, 7); psychiatric diseases such as schizophrenia, post-traumatic stress disorder, anxiety disorders and depression (1, 4, 6, 8-11); and addiction. They may also be useful in treating age-related hearing loss/tinnitus (12).

There is a need for treatment of the above conditions and others described herein with compounds that are mGluR7 modulators. The present invention provides modulators of mGluR7.

5

In accordance with the present invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof



wherein

10 X^1 is absent or is $-\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)-$;

X^2 is $-\text{CH}_2-$, $-\text{CHF}-$, $-\text{CF}_2-$ or $-\text{CH}_2\text{CH}_2-$, provided that when X^1 is $-\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)-$, then X^2 is $-\text{CH}_2-$ only;

R^1 , R^2 , R^3 and R^4 each independently represent hydrogen, halogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl or C_1 - C_6 alkoxy;

15 either R^5 represents hydrogen, halogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl or C_1 - C_6 alkoxy and R^6 represents hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkylsulphonyl or $-\text{NR}^{14}\text{R}^{15}$, or

when X^1 is absent, R^5 and R^6 together form a linking group, $-\text{[CH}_2\text{]}_m-$, in which m is 2, 3 or 4, wherein up to two $-\text{[CH}_2\text{]}-$ moieties may be replaced by oxygen, NH or

20 $\text{N}(\text{COCH}_3)$ heteroatom moieties provided that if the linking group contains two heteroatom moieties then m is 3 or 4 and the heteroatom moieties are not situated adjacent one another;

n is 0, 1 or 2;

each R⁷ independently represents halogen, cyano, C₁-C₆ alkyl, C₃-C₆ cycloalkyl or C₁-C₆ alkoxy;

each of R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ independently represents hydrogen,

5 hydroxyl, cyano, halogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl or C₁-C₆ alkoxy; or,

alternatively,

(i) R⁸ and R⁹ together with the carbon atom to which they are attached form a saturated 3- to 6-membered carbocyclic ring; or

10 (ii) R¹⁰ and R¹¹ together with the carbon atom to which they are attached form a saturated 3- to 6-membered carbocyclic ring; or

(iii) R¹² and R¹³ together with the carbon atom to which they are attached form a saturated 3- to 6-membered carbocyclic ring; or

(iv) R⁹ and R¹⁰ together with the carbon atoms to which they are attached form a saturated 3- to 6-membered carbocyclic ring; or

15 (v) R⁸ and R¹² together form a methylene bridge,

provided that no more than one carbocyclic ring or methylene bridge according to (i) to (v) above can be present in ring A; and

either R¹⁴ and R¹⁵ each independently represent hydrogen or a C₁-C₆ alkyl, C₃-C₆ cycloalkylmethyl, C₁-C₆ alkylcarbonyl, C₃-C₆ cycloalkylcarbonyl or C₁-C₆

20 alkoxy carbonyl group, wherein each of the preceding groups is optionally substituted by at least one halogen atom, or

R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a saturated 4- to 6-membered heterocyclic ring optionally comprising a further ring heteroatom selected from nitrogen and oxygen, the heterocyclic ring being unsubstituted or
25 substituted by at least one substituent selected from halogen, oxo and C₁-C₃ alkyl.

In the context of the present specification, unless otherwise stated, an “alkyl” substituent group or an “alkyl” moiety in a substituent group (such as an alkoxy group) may be linear or branched.

- 5 Examples of C₁-C₆ alkyl groups/moieties include methyl, ethyl, propyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2--methyl-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, tert-butyl, n-pentyl, and n-hexyl.

10

A “cycloalkyl” substituent group or a “cycloalkyl” moiety in a substituent group refers to a saturated hydrocarbyl ring containing, for example, from 3 to 8 carbon atoms, examples of which include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

- 15 The term “oxo” refers to an oxygen atom doubly bonded to the carbon atom to which it is attached to form the carbonyl of a ketone or aldehyde.

The term “halogen” includes fluorine, chlorine, bromine and iodine.

- 20 When R¹⁴ and R¹⁵ form a saturated 4- to 6-membered heterocyclic ring which is substituted, it should be understood that the substituent(s) may be attached to any suitable ring atom.

- For the purposes of the present invention, where a combination of moieties is referred to as one group, for example, alkylsulphonyl or alkoxycarbonyl, the last mentioned moiety
25 contains the atom by which the group is attached to the rest of the molecule.

- When any chemical group or moiety in formula (I) is described as substituted, it will be appreciated that the number and nature of substituents will be selected so as to avoid
30 sterically undesirable combinations.

Further, it will be appreciated that the invention does not encompass any unstable ring or other structures (e.g. $>\text{NCH}_2\text{N}<$, $>\text{NCH}_2\text{O}-$ or aminal groupings of the type $>\text{C}(\text{NR}_a\text{R}_b)(\text{NR}_c\text{R}_d)$) or any O-O or S-S bonds.

- 5 X^1 is absent or is $-\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)-$ and X^2 is $-\text{CH}_2-$, $-\text{CHF}-$, $-\text{CF}_2-$ or $-\text{CH}_2\text{CH}_2-$, provided that when X^1 is $-\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)-$, then X^2 is $-\text{CH}_2-$ only. Consequently, when X^1 is absent, X^2 is $-\text{CH}_2-$, $-\text{CHF}-$, $-\text{CF}_2-$ or $-\text{CH}_2\text{CH}_2-$, and when X^1 is $-\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)-$, then X^2 is $-\text{CH}_2-$;
- 10 In one embodiment, X^1 is absent.

In another embodiment, X^2 is $-\text{CH}_2-$, $-\text{CF}_2-$ or $-\text{CH}_2\text{CH}_2-$.

In yet another embodiment, X^2 is $-\text{CH}_2-$.

15

In a still further embodiment, X^1 and X^2 have the following meanings:

X^1	X^2
absent	$-\text{CH}_2-$
absent	$-\text{CF}_2-$
absent	$-\text{CH}_2\text{CH}_2-$
$-\text{CH}(\text{CH}_3)-$	$-\text{CH}_2-$
$-\text{CH}_2-$	$-\text{CH}_2-$

- R^1 , R^2 , R^3 and R^4 each independently represent hydrogen, halogen (e.g. fluorine, chlorine or bromine), C_1 - C_6 , or C_1 - C_4 , or C_1 - C_2 alkyl, C_3 - C_6 , or C_4 - C_6 , or C_5 - C_6 cycloalkyl or C_1 - C_6 , or C_1 - C_4 , or C_1 - C_2 alkoxy.
- 20

In one embodiment, R^1 , R^2 , R^3 and R^4 each independently represent hydrogen, halogen (e.g. fluorine, chlorine or bromine), C_1 - C_4 , or C_1 - C_3 , or C_1 - C_2 alkyl (e.g. methyl), cyclopropyl or C_1 - C_4 , or C_1 - C_3 , or C_1 - C_2 alkoxy (e.g. methoxy).

5

In another embodiment, R^1 , R^2 , R^3 and R^4 each independently represent hydrogen, fluorine, chlorine, methyl or methoxy.

In a further embodiment, R^1 represents hydrogen, fluorine, chlorine, methyl or methoxy and R^2 , R^3 and R^4 each represent hydrogen.

10

In a still further embodiment, R^3 represents hydrogen, fluorine, chlorine, methyl or methoxy and R^1 , R^2 and R^4 each represent hydrogen.

According to one aspect of the invention, R^5 represents hydrogen, halogen (e.g. fluorine, chlorine or bromine), C_1 - C_6 , or C_1 - C_4 , or C_1 - C_2 alkyl, C_3 - C_6 , or C_4 - C_6 , or C_5 - C_6 cycloalkyl or C_1 - C_6 , or C_1 - C_4 , or C_1 - C_2 alkoxy and R^6 represents hydrogen, C_1 - C_6 , or C_1 - C_4 , or C_1 - C_2 alkyl, C_3 - C_6 , or C_4 - C_6 , or C_5 - C_6 cycloalkyl, C_1 - C_6 , or C_1 - C_4 , or C_1 - C_2 alkylsulphonyl or $NR^{14}R^{15}$.

20

In one embodiment, R^5 represents hydrogen, halogen (e.g. fluorine, chlorine or bromine), C_1 - C_4 , or C_1 - C_3 , or C_1 - C_2 alkyl, cyclopropyl or C_1 - C_4 , or C_1 - C_3 , or C_1 - C_2 alkoxy.

In another embodiment, R^5 represents hydrogen, fluorine, chlorine, bromine, C_1 - C_2 alkyl, cyclopropyl or C_1 - C_2 alkoxy.

25

In still another embodiment, R⁵ represents hydrogen, fluorine, chlorine, bromine, cyclopropyl, methyl or methoxy.

In yet another embodiment, R¹, R², R³, R⁴ and R⁵ each independently represent hydrogen or halogen.

In one embodiment, R⁶ represents hydrogen, C₁-C₄, or C₁-C₃, or C₁-C₂ alkyl, cyclopropyl, C₁-C₄, or C₁-C₃, or C₁-C₂ alkylsulphonyl or NR¹⁴R¹⁵.

In another embodiment, R⁶ represents hydrogen, C₁-C₂ alkyl or NR¹⁴R¹⁵.

In a further embodiment, R⁶ represents NR¹⁴R¹⁵.

R¹⁴ and R¹⁵ each independently represent hydrogen or a C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl, C₃-C₆, or C₄-C₆, or C₅-C₆ cycloalkylmethyl, C₁-C₆, or C₁-C₄, or C₁-C₂ alkylcarbonyl, C₃-C₆, or C₄-C₆, or C₅-C₆ cycloalkylcarbonyl or C₁-C₆, or C₁-C₄, or C₁-C₂ alkoxy carbonyl group, wherein each of the preceding groups is optionally substituted by at least one halogen (such as fluorine, chlorine or bromine) atom (e.g. one, two, three, four or five halogen atoms), or R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a saturated 4-, 5- or 6-membered heterocyclic ring optionally comprising a further ring heteroatom selected from nitrogen and oxygen, the heterocyclic ring being unsubstituted or substituted by at least one substituent (e.g. one, two or three substituents independently) selected from halogen (e.g. fluorine, chlorine or bromine), oxo and C₁-C₃ alkyl (e.g. methyl or ethyl).

In one embodiment, R¹⁴ and R¹⁵ each independently represent hydrogen or a C₁-C₄, or C₁-C₃, or C₁-C₂ alkyl, cyclopropylmethyl, C₁-C₄, or C₁-C₃, or C₁-C₂ alkylcarbonyl, cyclopropylcarbonyl or C₁-C₄, or C₁-C₃, or C₁-C₂ alkoxy carbonyl group, wherein each of

the preceding groups is optionally substituted by one to five, or one to three, halogen, particularly fluorine, atoms.

In another embodiment, R¹⁴ and R¹⁵ each independently represent hydrogen or a
5 C₁-C₂ alkyl, cyclopropylmethyl, C₁-C₃ alkylcarbonyl, cyclopropylcarbonyl or C₁-C₄ alkoxy carbonyl group, wherein each of the preceding groups is optionally substituted by one to five, or one to three, halogen, particularly fluorine, atoms.

In yet another embodiment, R¹⁴ and R¹⁵ each independently represent hydrogen or a
10 C₁-C₂ alkyl, cyclopropylmethyl, C₁-C₃ alkylcarbonyl, cyclopropylcarbonyl or C₁-C₄ alkoxy carbonyl group, wherein the C₁-C₂ alkyl and C₁-C₃ alkylcarbonyl groups are optionally substituted by one to three halogen, particularly fluorine, atoms.

In still another embodiment, R¹⁴ and R¹⁵ together with the nitrogen atom to which they
15 are attached form a saturated 5-membered heterocyclic ring optionally comprising a further ring heteroatom selected from nitrogen and oxygen, the heterocyclic ring being unsubstituted or substituted by at least one substituent (e.g. one, two or three substituents independently) selected from fluorine, chlorine, oxo, methyl and ethyl.

20 In a particular embodiment of the invention, -NR¹⁴R¹⁵ represents any one of the following moieties or is selected from a group containing any two or more of such moieties:

- (i) -NH₂
- (ii) -NHCH₃
- (iii) -N(CH₃)₂
- 25 (iv) -NHC₂H₅
- (v) -NHCH₂CHF₂
- (vi) -NH(cyclopropylmethyl)
- (vii) -NHC(O)CH₃

- (viii) -NHC(O)CF₃
- (ix) -NHC(O)C₂H₅
- (x) -NHC(O)CH(CH₃)₂
- (xi) -NHC(O)cyclopropyl
- 5 (xii) -NHC(O)(*tert*-butoxy)
- (xiii) pyrrolidin-2-one.

In a particular embodiment of the invention, R¹ to R⁶ have the following meanings where -NR¹⁴R¹⁵ is as defined above:

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
H	H	H	H	H	-NR ¹⁴ R ¹⁵
H	H	F	H	H	-NR ¹⁴ R ¹⁵
H	H	H	H	F	-NR ¹⁴ R ¹⁵
F	H	H	H	H	-NR ¹⁴ R ¹⁵
CH ₃	H	H	H	H	-NR ¹⁴ R ¹⁵
H	H	H	H	CH ₃	-NR ¹⁴ R ¹⁵
-OCH ₃	H	H	H	H	-NR ¹⁴ R ¹⁵
H	H	H	H	-OCH ₃	-NR ¹⁴ R ¹⁵
Cl	H	H	H	H	-NR ¹⁴ R ¹⁵
H	H	H	H	Cl	-NR ¹⁴ R ¹⁵
H	H	H	H	Br	-NR ¹⁴ R ¹⁵
H	H	H	H	cyclopropyl	-NR ¹⁴ R ¹⁵
H	H	H	H	H	CH ₃
H	H	H	H	H	H
CH ₃	H	H	H	H	H
H	H	H	H	CH ₃	H

According to a second aspect of the invention, when X^1 is absent, R^5 and R^6 together form a linking group, $-[CH_2]_m-$, in which m is 2, 3 or 4, wherein up to two $-[CH_2]-$ moieties may be replaced by oxygen, NH or $N(COCH_3)$ heteroatom moieties provided that if the linking group contains two heteroatom moieties then m is 3 or 4 and the heteroatom moieties are not situated adjacent one another. Examples of such linking groups include: $-CH_2CH_2NH-$, $CH_2CH_2N(COCH_3)-$, $-NHCH_2CH_2-$, $-N(COCH_3)CH_2CH_2-$, $-CH_2NHCH_2-$, $-CH_2N(COCH_3)CH_2-$, $-OCH_2CH_2NH-$ or $-NHCH_2CH_2O-$.

Each R^7 independently represents halogen (e.g. fluorine, chlorine or bromine), cyano, C_1-C_6 , or C_1-C_4 , or C_1-C_2 alkyl, C_3-C_6 , or C_4-C_6 , or C_5-C_6 cycloalkyl or C_1-C_6 , or C_1-C_4 , or C_1-C_2 alkoxy.

In an embodiment of the invention, each R^7 independently represents halogen (e.g. fluorine, chlorine or bromine), cyano, C_1-C_4 , or C_1-C_3 , or C_1-C_2 alkyl (e.g. methyl), cyclopropyl or C_1-C_4 , or C_1-C_3 , or C_1-C_2 alkoxy (e.g. methoxy).

In another embodiment, each R^7 independently represents fluorine, chlorine, methyl or methoxy.

In yet another embodiment, n is 1 and R^7 represents a halogen atom, particularly a fluorine atom.

In still another embodiment, n is 0.

According to an aspect of the present invention, R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} each independently represent hydrogen, hydroxyl, cyano, halogen (e.g. fluorine, chlorine or

bromine), C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl, C₃-C₆, or C₄-C₆, or C₅-C₆ cycloalkyl or C₁-C₆, or C₁-C₄, or C₁-C₂ alkoxy.

In one embodiment, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ each independently represent hydrogen,
 5 hydroxyl, cyano, halogen (e.g. fluorine, chlorine or bromine), C₁-C₄, or C₁-C₃, or C₁-C₂ alkyl, cyclopropyl or C₁-C₄, or C₁-C₃, or C₁-C₂ alkoxy.

In another embodiment, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ each independently represent
 hydrogen, hydroxyl, halogen (e.g. fluorine or chlorine), C₁-C₂ alkyl, cyclopropyl or
 10 C₁-C₂ alkoxy.

In a further embodiment, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ each independently represent
 hydrogen, hydroxyl, fluorine, methyl or methoxy.

15 Particular values of R⁸ to R¹³ are shown in the following table:

R ⁸	R ⁹	R ¹⁰	R ¹¹	R ¹²	R ¹³
H	H	H	H	H	H
H	H	CH ₃	OH	H	H
H	H	OH	CH ₃	H	H
H	H	H	OCH ₃	H	H
H	H	OCH ₃	H	H	H
H	H	F	F	H	H
H	H	H	F	H	H
H	H	F	H	H	H
CH ₃	H	H	H	H	H

According to a second aspect of the invention, R^8 and R^9 together with the carbon atom to which they are attached form a saturated 3- to 6-membered carbocyclic ring and R^{10} to R^{13} are as defined above.

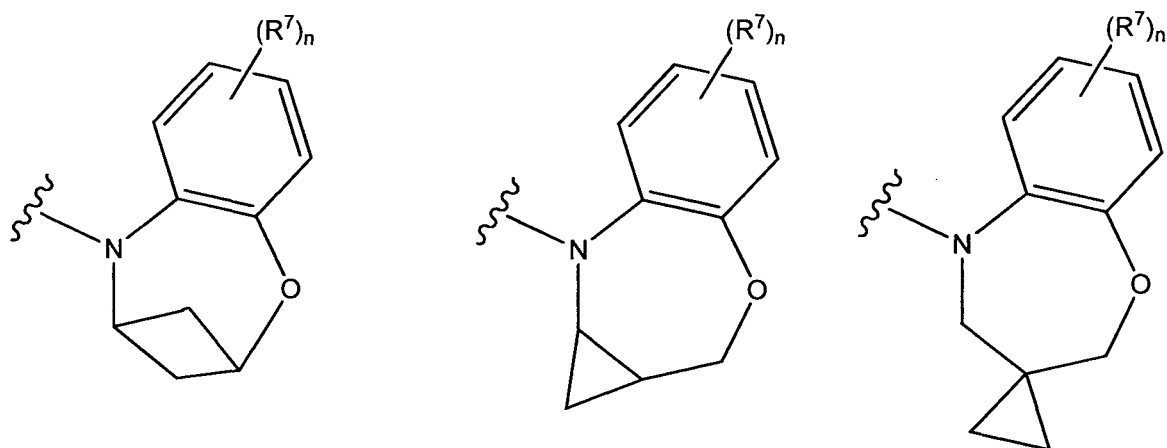
- 5 According to a third aspect of the invention, R^{10} and R^{11} together with the carbon atom to which they are attached form a saturated 3- to 6-membered carbocyclic ring and R^8 , R^9 , R^{12} and R^{13} are as defined above.

- 10 According to a fourth aspect of the invention, R^{12} and R^{13} together with the carbon atom to which they are attached form a saturated 3- to 6-membered carbocyclic ring and R^8 to R^{11} are as defined above.

- 15 According to a fifth aspect of the invention, R^9 and R^{10} together with the carbon atoms to which they are attached form a saturated 3- to 6-membered carbocyclic ring and R^8 , R^{11} , R^{12} and R^{13} are as defined above.

According to a sixth aspect of the invention, R^8 and R^{12} together form a methylene bridge and R^9 , R^{10} , R^{11} and R^{13} are as defined above.

- 20 Examples of bicyclic ring systems (AB) according to the above-mentioned second to sixth aspects of the invention include the following structures:



In a preferred embodiment of the invention, the compounds of formula (I) are those in which:

5 X^1 is absent or is $-CH_2-$ or $-CH(CH_3)-$;

X^2 is $-CH_2-$, $-CF_2-$ or $-CH_2CH_2-$;

R^1 , R^2 , R^3 and R^4 each independently represent hydrogen, fluorine, chlorine, methyl or methoxy;

either R^5 represents hydrogen, fluorine, chlorine, bromine, cyclopropyl, methyl or
10 methoxy and R^6 represents hydrogen, methyl or $-NR^{14}R^{15}$, or

when X^1 is absent, R^5 and R^6 together form a linking group, $-[CH_2]_m-$, in which m
is 2, 3 or 4, wherein up to two $-[CH_2]-$ moieties may be replaced by oxygen, NH or
N(COCH₃) heteroatom moieties provided that if the linking group contains two
heteroatom moieties then m is 3 or 4 and the heteroatom moieties are not situated adjacent
15 one another;

n is 0 or 1;

R^7 represents halogen, methyl or methoxy;

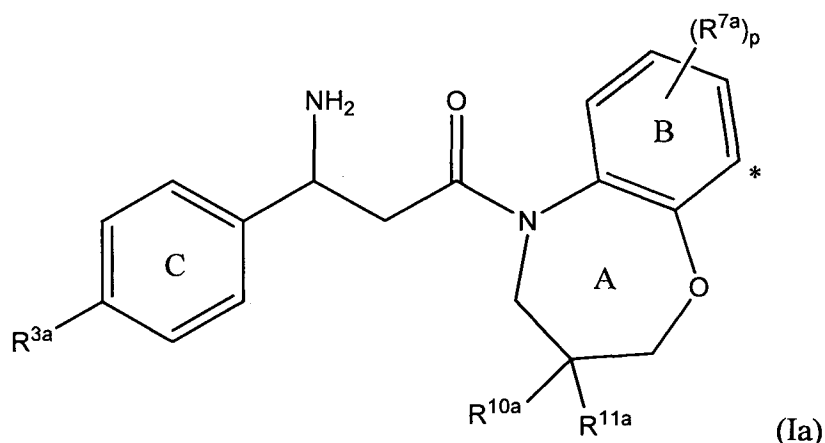
each of R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} independently represents hydrogen,
hydroxyl, fluorine, methyl or methoxy or, alternatively, either R^{10} and R^{11} together with
20 the carbon atom to which they are attached form a saturated 3- to 6-membered carbocyclic
ring, or R^8 and R^{12} together form a methylene bridge; and

either R^{14} and R^{15} each independently represent hydrogen or a C₁-C₂ alkyl, cyclopropylmethyl, C₁-C₃ alkylcarbonyl, cyclopropylcarbonyl or C₁-C₄ alkoxy carbonyl group, wherein each of the preceding groups is optionally substituted by at least one halogen atom, or

R^{14} and R^{15} together with the nitrogen atom to which they are attached form a saturated 5-membered heterocyclic ring, the heterocyclic ring being unsubstituted or substituted by at least one substituent selected from halogen, oxo and C₁-C₃ alkyl.

In another preferred embodiment, there is provided a subset of compounds of formula (I)

as represented by formula (Ia)



in which

R^{3a} is hydrogen or fluorine;

p is 0 or 1;

R^{7a} is fluorine;

R^{10a} is hydrogen or fluorine; and

R^{11a} is hydrogen or fluorine.

According to one aspect, the compounds of formula (Ia) contain a single fluorine

substituent. If R^{7a} is a fluorine substituent, it is preferably attached to the 9-position of the bicyclic ring structure AB (which is shown marked with an asterisk in formula (Ia) above).

According to another aspect, the compounds of formula (Ia) contain two fluorine substituents as R^{10a} and R^{11a}.

Examples of compounds of the invention include:

- 5 N-[3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]acetamide;
(3R)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;
(3S)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;
(3S)-3-amino-1-(8-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;
10 (3S)-3-amino-3-(4-fluorophenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;
(3S)-3-amino-3-(2-fluorophenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;
(3S)-3-(methylamino)-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;
15 (3S)-3-(dimethylamino)-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;
(3S)-3-amino-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;
20 (3S)-3-amino-3-(2-methylphenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;
(3S)-3-amino-3-(2-methoxyphenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;
(3S)-3-amino-3-(2-chlorophenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;
25 (3S)-3-(ethylamino)-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;
(3S)-3-[(cyclopropylmethyl)amino]-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;
30 1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-2-(1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-one;

(3S)-1-(3-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(methylamino)-3-phenylpropan-1-one;

N-[(1S)-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]propanamide;

5 N-[(1S)-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]cyclopropanecarboxamide;

2-methyl-N-[(1S)-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]propanamide;

10 2,2,2-trifluoro-N-[(1S)-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]acetamide;

N-[(1S)-1-(2-methylphenyl)-3-oxo-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]acetamide;

N-[(1S)-1-(2-chlorophenyl)-3-oxo-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]acetamide;

15 1-[(1S)-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]pyrrolidin-2-one;

(3S)-3-amino-1-(6-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;

20 (3S)-3-amino-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(4-fluorophenyl)propan-1-one;

1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-2-(1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-one;

(3S)-3-amino-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(2-fluorophenyl)propan-1-one;

25 (3S)-3-[(2,2-difluoroethyl)amino]-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-amino-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(2-methylphenyl)propan-1-one;

30 (3S)-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(methylamino)-3-phenylpropan-1-one;

tert-butyl N-[2,2-difluoro-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]carbamate;

3-amino-2,2-difluoro-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-amino-1-(3-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;

5 (3S)-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)butan-1-one;

1-(3-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(2-methylphenyl)propan-1-one;

4-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)pentan-1-one;

3-(2-methylphenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

10 (3R)-3-amino-4-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)butan-1-one;

(3S)-3-amino-4-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)butan-1-one;

4-amino-4-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)butan-1-one;

1-(3-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(2-methylphenyl)propan-1-one;

15 1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-2-(1,2,3,4-tetrahydroisoquinolin-4-yl)ethan-1-one;

(3S)-3-amino-3-(2-chlorophenyl)-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-amino-1-(3,3-difluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;

20 (3S)-3-amino-1-(7-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;

2-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)ethan-1-one;

25 (3S)-3-amino-1-(3-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;

2-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)ethan-1-one;

(3S)-amino-1-{3,4-dihydro-2,4-methanobenzo[b][1,4]oxazepin-5-yl}-3-phenylpropan-1-one

30 (3S)-3-amino-1-[(4S)-9-fluoro-4-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl]-3-phenylpropan-1-one;

(3S)-3-amino-1-(9-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;

(3S)-3-amino-1-(9-chloro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;

5 (3S)-3-amino-1-[(4R)-9-fluoro-4-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl]-3-phenylpropan-1-one;

(3S)-3-amino-1-{4,5-dihydro-2H-spiro[1,5-benzoxazepine-3,1'-cyclopropane]-5-yl}-3-phenylpropan-1-one;

10 (3S)-3-amino-1-(9-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;

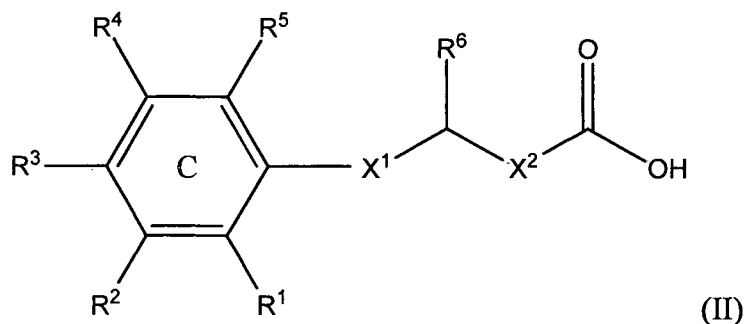
(3S)-3-amino-3-(2-bromophenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-amino-3-(2-cyclopropylphenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one; and enantiomers, diastereoisomers and mixtures thereof; and

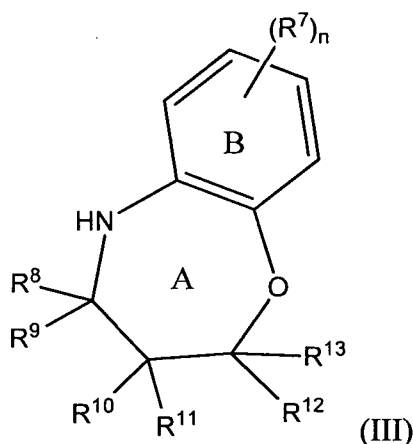
15 pharmaceutically acceptable salts of any of the foregoing.

It should be noted that each of the chemical compounds listed above represents a particular and independent aspect of the invention.

20 The present invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined above which comprises reacting a compound of formula (II), or a salt (e.g. hydrochloride salt) thereof,



25 in which X¹, X², R¹, R², R³, R⁴, R⁵ and R⁶ are as defined in formula (I) above, with a compound of formula (III), or a salt (e.g. hydrochloride salt) thereof,



in which n , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} are as defined in formula (I) above;

and optionally thereafter carrying out one or more of the following procedures:

- 5 • converting a compound of formula (I) into another compound of formula (I)
- removing any protecting groups
- forming a pharmaceutically acceptable salt.

The above process may conveniently be carried out by combining the carboxylic acid of
 10 formula (II) with the amine of formula (III) in the presence of a coupling reagent such as
 (1) EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) and HOAt (7-aza-1-
 hydroxybenzotriazole) with triethylamine in dichloromethane at room temperature to 60°C,
 or

(2) HATU (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid
 15 hexafluorophosphate) with triethylamine in dichloromethane at room temperature to 60°C;
 or

(3) HATU with *N,N*-diisopropylethylamine in dimethylformamide at room temperature to
 60°C; or

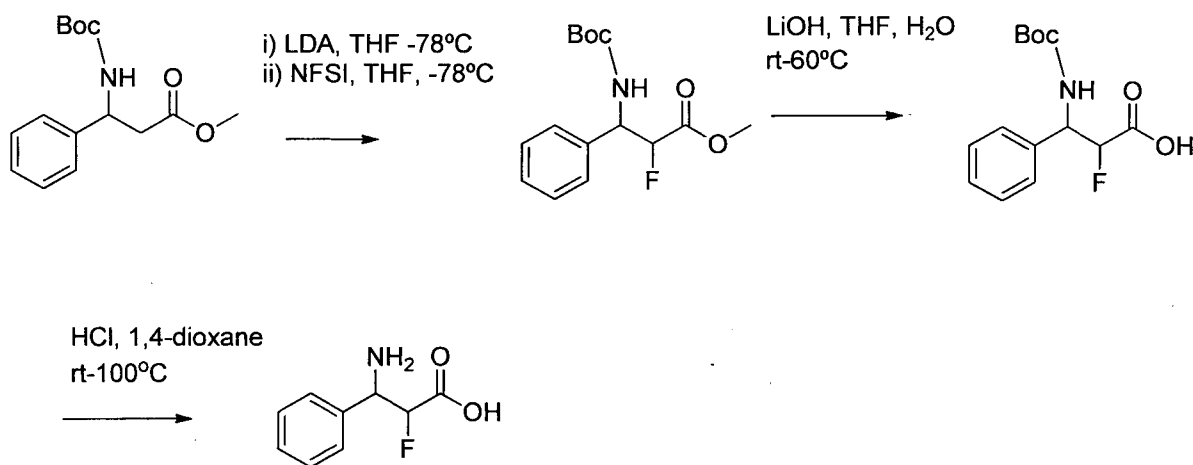
(4) Propylphosphonic anhydride with triethylamine in dichloromethane at room
 20 temperature to 60°C;

followed, if necessary, to remove any protecting groups (e.g. a tert-butyloxycarbonyl group
 if R^6 is a $-NR^{14}R^{15}$ group such as $-NH_2$), by reaction with hydrochloric acid in an organic
 solvent, e.g. a polar solvent such as 1,4-dioxane, at a temperature in the range from, for
 example, room temperature to 100°C.

Compounds of formulae (II) and (III) are known compounds or may be prepared according to processes known in the art. For example, compounds of formula (II) in which R^1 to R^5 are each hydrogen, X^1 is absent, X^2 is $-\text{CHF}-$ and R^6 is $-\text{NH}_2$ may be prepared as shown in the following reaction scheme 1:

5

Scheme 1



in which the abbreviations used have the following meanings:

10 Boc : *tert*-butoxycarbonyl (a protecting group)

LDA : lithium diisopropylamide

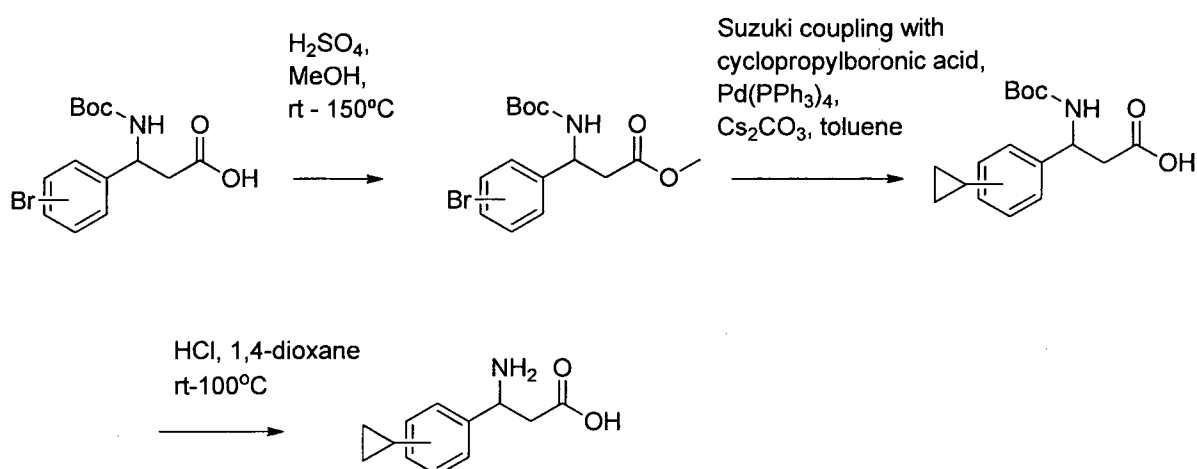
THF : tetrahydrofuran

NFSI : N-Fluorobenzenesulfonimide

15 Compounds of formula (II) in which one of R^1 to R^5 is a C_3 - C_6 cycloalkyl, e.g.

cyclopropyl, group and the remainder are hydrogen, X^1 is absent, X^2 is $-\text{CH}_2-$ and R^6 is $-\text{NH}_2$ may be prepared as shown in the following reaction scheme 2:

Scheme 2



in which the abbreviations used have the following meanings:

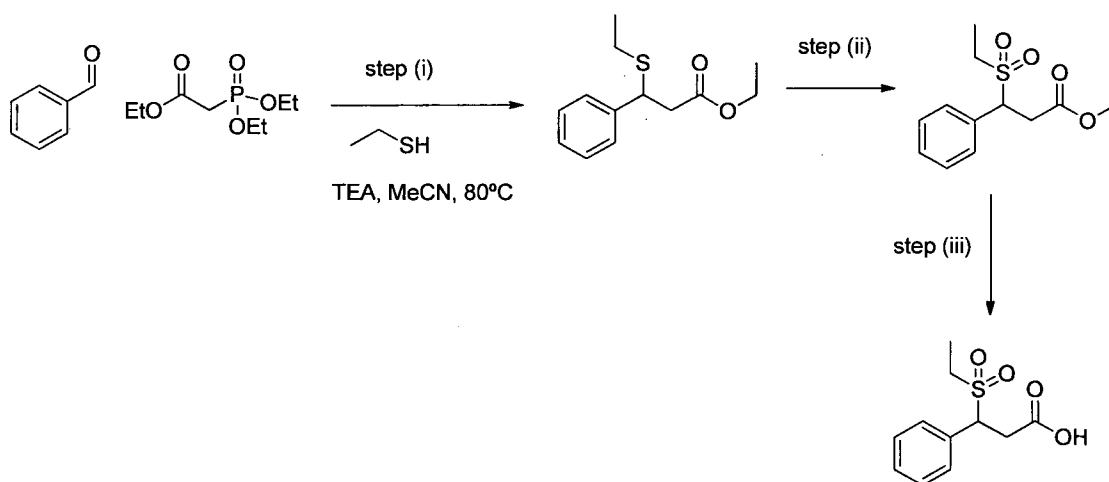
Boc : *tert*-butoxycarbonyl (a protecting group)

5 MeOH : methanol

Compounds of formula (II) in which R^1 to R^5 are each hydrogen, X^1 is absent, X^2 is $-\text{CH}_2-$ and R^6 is C_1 - C_6 alkylsulphonyl (e.g. ethyl sulphonyl) may be prepared as shown in the following reaction scheme 3:

10

Scheme 3

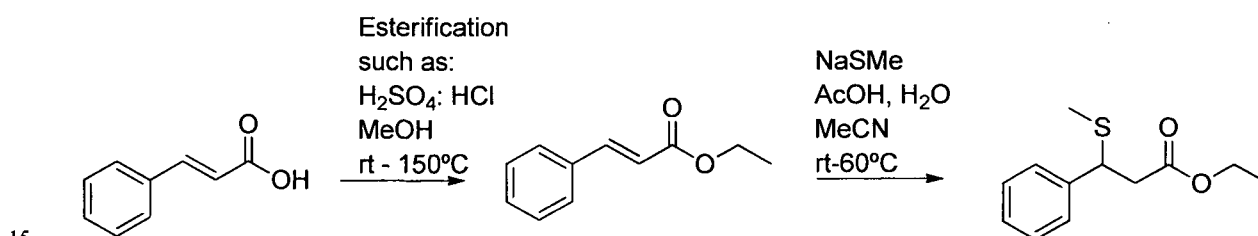


Step (i) is analogous to methods described in the journal article by S. Has-Becker et al.,
 15 *Synlett* 2001, No. 9, 1395-1398. TEA denotes trimethylamine and MeCN denotes acetonitrile.

Step (ii) is an oxidation reaction which may conveniently be carried out using 3-chlorobenzenecarboxoperoxoic acid (mCPBA) in an organic solvent such as dichloromethane at a temperature in the range of from room temperature to 60°C.

5 Step (iii) is a hydrolysis reaction which may conveniently be carried out in the presence of a base such as lithium hydroxide in a polar solvent, e.g. a mixture of water and tetrahydrofuran, at a pressure of 8 bar (800 kPa) and at a temperature in the range of from room temperature to 60°C.

10 As an alternative, a compound of formula (II) in which R^1 to R^5 are each hydrogen, X^1 is absent, X^2 is $-CH_2-$ and R^6 is methyl sulphonyl may be prepared as shown in reaction scheme 3 except that step (i) is replaced as follows (see methods described in US 2010/0048939 in the name of Dow Agrosiences LLC):



in which the abbreviations used have the following meanings:

MeOH: methanol

AcOH: acetic acid (ethanoic acid)

NaSMe: sodium methanethiolate

20 MeCN: acetonitrile

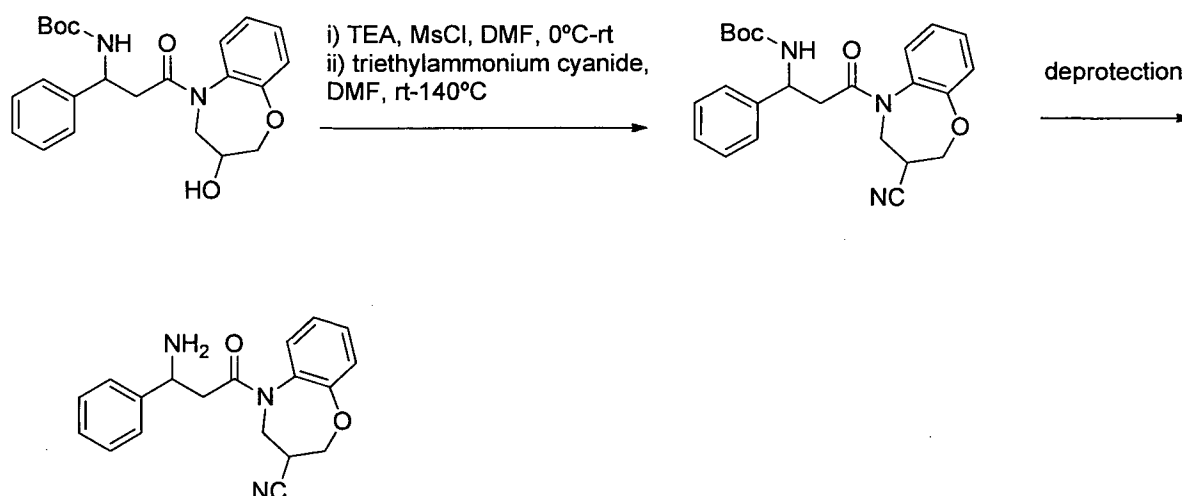
In one embodiment, a compound of formula (I) may be converted into another compound of formula (I). For example, a compound of formula (I) in which R^7 represents a halogen atom may be converted to a corresponding compound of formula (I) in which R^7

25 represents a C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl group by reacting the former with a boronic acid derivative such as R^{7a} -B(OH) $_2$, R^{7a} -B(pinacole ester) or R^{7a} -BF $_3$ -K $^+$ where R^{7a} represents the replacement R^7 bonded to the boron atom via a carbon-boron bond, in the

presence of a base such as potassium carbonate, caesium carbonate or potassium phosphate, and a metal catalyst such as Pd(0), typically where the metal catalyst is in the form of a transition metal complex such as tetrakis(triphenylphosphine) palladium or di-tert-butyl[dichloro({di-tert-butyl[4-(dimethylamino)phenyl]-phosphonium})palladio][4-(dimethylamino)phenyl] phosphonium. A solvent such as a dioxane/water mixture may be used and the reaction mixture is typically heated, e.g. to around 100-160°C under conventional heating or microwave irradiation.

Further, a compound of formula (I) in which R⁷ represents a halogen atom may be converted to a corresponding compound of formula (I) in which R⁷ represents a C₁-C₆ alkoxy group by reacting the former with the desired alcohol in the presence of a base such as sodium hydride and a solvent such as anhydrous tetrahydrofuran. The reaction mixture is typically heated, e.g. to around 60-120°C under conventional heating or microwave irradiation.

Still further, a compound of formula (I) in which R¹⁰ represents a hydroxyl group may be converted to a corresponding compound of formula (I) in which R¹⁰ represents a cyano group according to methods described in US 2002/0188124 in the name of Fukami et al. (Banyu Pharmaceutical Co. Ltd.), for example,



in which the abbreviations used have the following meanings and the deprotection

reaction is carried out according to procedures known in the art, for example, as described in Scheme 1 above:

TEA: trimethylamine

MsCl: methanesulphonyl chloride

5 DMF: dimethylformamide

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as phenol, hydroxyl or amino groups in the reagents may need to be protected by protecting groups. Thus, the preparation of the
10 compounds of formula (I) may involve, at an appropriate stage, the introduction and/or removal of one or more protecting groups.

The protection and deprotection of functional groups is described, for example, in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973);
15 'Greene's Protective Groups in Organic Synthesis', 4th edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (2007); and 'Protecting Groups', 3rd edition, P. J. Kocienski, Thieme (2005).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable
20 salt thereof, preferably an acid addition salt such as a formate, hemi-formate, hydrochloride, hydrobromide, benzenesulphonate (besylate), saccharin (e.g. monosaccharin), trifluoroacetate, sulphate, nitrate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, valerate, propanoate, butanoate, malonate, oxalate, 1-hydroxy-2-naphthoate (xinafoate), methanesulphonate or *p*-toluenesulphonate salt.
25 In one embodiment of the invention, the compounds of formula (I) are in the form of a hydrochloride salt.

In one aspect of the invention, compounds of formula (I) may bear one or more radiolabels. Such radiolabels may be introduced by using radiolabel-containing reagents in the
30 synthesis of the compounds of formula (I), or may be introduced by coupling the compounds of formula (I) to chelating moieties capable of binding to a radioactive metal atom. Such radiolabeled versions of the compounds may be used, for example, in diagnostic imaging studies.

Unless stated otherwise, any atom specified herein may also be an isotope of said atom. For example, the term “hydrogen” encompasses ^1H , ^2H and ^3H . Similarly carbon atoms are to be understood to include ^{12}C , ^{13}C and ^{14}C , nitrogen atoms are to be understood to include ^{14}N and ^{15}N , and oxygen atoms are to be understood to include ^{16}O , ^{17}O and ^{18}O .

In a further aspect of the invention, compounds of formula (I) may be isotopically labelled. As used herein, an “isotopically labelled” compound is one in which the abundance of a particular nuclide at a particular atomic position within the molecule is increased above the level at which it occurs in nature.

Compounds of formula (I) and their salts may be in the form of hydrates or solvates which form an aspect of the present invention. Such solvates may be formed with common organic solvents, including but not limited to, alcoholic solvents e.g. methanol, ethanol or isopropanol.

Where compounds of formula (I) are capable of existing in stereoisomeric forms, it will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also forms an aspect of the present invention. Enantiomerically pure forms are particularly desired. “Enantiomerically pure” denotes the presence of at least 75%w, in particular at least 90%w and, more particularly, at least 95%w of one of the two possible enantiomers of a compound.

Compounds of formula (I) and their salts may be amorphous or in a polymorphic form or a mixture of any of these, each of which forms an aspect of the present invention.

The compounds of formula (I) and their pharmaceutically acceptable salts have activity as pharmaceuticals and may be used in treating conditions or disorders associated with changes in one or both of the glutamatergic and GABAergic signalling pathways regulated in full or in part by metabotropic glutamate receptor 7.

Thus, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined for use in therapy, in particular for the treatment of conditions associated with metabotropic glutamate receptor 7.

- 5 The present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined for the preparation of a medicament for the treatment of conditions associated with metabotropic glutamate receptor 7.
- 10 The present invention still further provides a method of treating a condition associated with metabotropic glutamate receptor 7 which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.
- 15 In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have
20 suffered a previous episode of, or are otherwise considered to be at increased risk of, the disorder or condition in question. Persons at risk of developing a particular disorder or condition generally include those having a family history of the disorder or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disorder or condition or those in the prodromal phase of a
25 disorder.

The terms "treat", "treatment" and "treating" include improvement of the conditions described herein. The terms "treat", "treatment" and "treating" include all processes providing slowing, interrupting, arresting, controlling, or stopping of the state or
30 progression of the conditions described herein, but does not necessarily indicate a total elimination of all symptoms or a cure of the condition. The terms "treat", "treatment," and "treating" are intended to include therapeutic as well as prophylactic treatment of such conditions.

As used herein the terms “condition,” “disorder,” and “disease” relate to any unhealthy or abnormal state. The term “conditions associated with metabotropic glutamate receptor 7” includes conditions, disorders and diseases in which the modulation of mGluR7 may
5 provide a therapeutic benefit, examples of which include:

(1) **Nervous system disorders:** Parkinson’s disease, including dementia associated with Parkinson’s disease; Alzheimer’s disease; Huntington’s Chorea; amyotrophic lateral sclerosis; multiple sclerosis; bipolar disorder; and psychiatric disorders such as
10 schizophrenia, post-traumatic stress disorder, anxiety disorders and depression (e.g. major depressive disorder);

(2) **Addiction disorders:** alcohol, drug or nicotine addiction;

(3) **Hearing disorders:** hearing loss and/or tinnitus caused by age, noise or trauma; and

(4) **Others:** idiopathic autism; severe neonatal encephalopathy; autism spectrum

15 disorder (ASD); X-linked intellectual disability (also known as X-linked mental retardation); epilepsy; cerebral ischemias; eye disorders; and pain (e.g. inflammatory pain or neuropathic pain).

Schizophrenia is a debilitating psychiatric disorder characterised by a combination of
20 negative symptoms (such as social withdrawal, anhedonia, avolition and apathy) and positive symptoms (including hallucinations, delusions and paranoia) as well as marked cognitive deficits (such as impairment of executive function). The executive function (EF) has been defined as “a set of abilities, which allows us to invoke voluntary control of our behavioral responses. These functions enable human beings to develop and carry out plans,
25 make up analogies, obey social rules, solve problems, adapt to unexpected circumstances, do many tasks simultaneously, and locate episodes in time and place. EF includes divided attention and sustained attention, working memory (WM), set-shifting, flexibility, planning, and the regulation of goal directed behavior and can be defined as a brain function underlying the human faculty to act or think not only in reaction to external events but also
30 in relation with internal goals and states” (Orellana G. and Slachevsky A., 2013. Executive Functioning in Schizophrenia. *Front. Psychiatry*, 4, 35).

Accordingly, the present invention also provides a method of treating a negative symptom, a positive symptom and/or a cognitive deficit associated with a psychiatric disorder, especially schizophrenia, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. For example, the daily dosage of the compound of the invention, if inhaled, may be in the range from 0.05 micrograms per kilogram body weight ($\mu\text{g/kg}$) to 100 micrograms per kilogram body weight ($\mu\text{g/kg}$). Alternatively, if the compound is administered orally, then the daily dosage of the compound of the invention may be in the range from 0.01 micrograms per kilogram body weight ($\mu\text{g/kg}$) to 100 milligrams per kilogram body weight (mg/kg).

The compounds of formula (I) and pharmaceutically acceptable salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

Therefore the present invention further provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention still further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceutics - The Science of Dosage Form Design", M. E. Aulton, Churchill Livingstone, 1988.

Pharmaceutically acceptable adjuvants, diluents or carriers that may be used in the pharmaceutical compositions of the invention are those conventionally employed in the field of pharmaceutical formulation, and include, but are not limited to, sugars, sugar alcohols, starches, ion exchangers, alumina, aluminium stearate, lecithin, serum proteins
5 such as human serum albumin, buffer substances such as phosphates, glycerine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes such as protamine sulphate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium
10 carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The pharmaceutical compositions of the present invention may be administered orally, parenterally, by inhalation spray, rectally, nasally, buccally, vaginally or via an implanted
15 reservoir. Oral administration is preferred. The pharmaceutical compositions of the invention may contain any conventional non-toxic pharmaceutically acceptable adjuvants, diluents or carriers. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

20

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. The suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable
25 preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable diluents and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland
30 fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically acceptable oils, such as olive oil or castor oil, especially in their

polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, powders, granules, and aqueous suspensions and solutions. These dosage forms are prepared according to techniques well-known in the art of pharmaceutical formulation. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavouring and/or colouring agents may be added.

The pharmaceutical compositions of the invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active ingredient. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilising or dispersing agents known in the art.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The compounds of the invention (that is, compounds of formula (I) and pharmaceutically acceptable salts thereof) may also be administered in conjunction with other compounds used for the treatment of the above conditions.

5 The invention therefore further relates to combination therapies wherein a compound of the invention or a pharmaceutical composition or formulation comprising a compound of the invention is administered with another therapeutic agent or agents for the treatment of one or more of the conditions previously indicated. Such therapeutic agents may be selected from the following:

10

(i) **anti-addiction drugs** including, for example, acamprosate, disulfiram, naltrexone and nalmefene for alcohol dependency, and gabapentin, modafinil, topiramate, vigabatrin and baclofen for drug, particularly cocaine, addiction;

15

(ii) **antidepressants** such as amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin duloxetine, elzasonan, escitalopram, fluvoxamine, fluoxetine, gepirone, imipramine, ipsapirone, maprotiline, nortriptyline, nefazodone, paroxetine, phenelzine, protriptyline, reboxetine, robaizotan, sertraline, sibutramine, tianeptine, thionisoxetine, tranlycypromaine, trazodone, trimipramine, venlafaxine, vortioxetine and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

20

(iii) **antipsychotics** including, for example, amisulpride, aripiprazole, asenapine, benzisoxidil, bifeprunox, brexpiprazole, carbamazepine, cariprazine, clozapine, chlorpromazine, debenzapine, divalproex, duloxetine, eszopiclone, fluphenazine, haloperidol, iloperidone, lamotrigine, loxapine, lurasidone, mesoridazine, olanzapine, paliperidone, perlapine, perphenazine, phenothiazine, phenylbutylpiperidine, pimozide, prochlorperazine, quetiapine, risperidone, sertindole, sulpiride, suproclon, suriclone, thioridazine, trifluoperazine, trimetozine, valproate, valproic acid, zopiclone, zotepine, zicronapine, ziprasidone, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

30

(iv) **anxiolytics** including, for example, alnespirone, azapirones, benzodiazepines,

barbiturates, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof. Example anxiolytics include adinazolam, alprazolam, balezepam, bentazepam, bromazepam, brotizolam, buspirone, clonazepam, clorazepate, chlordiazepoxide, cyprazepam, diazepam, diphenhydramine, estazolam, fenobam, flunitrazepam, flurazepam, fosazepam, lorazepam, lormetazepam, meprobamate, midazolam, nitrazepam, oxazepam, prazepam, prazosin, quazepam, reclazepam, tracazolate, trepipam, temazepam, triazolam, uldazepam, and zolazepam; and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(v) **anticonvulsants** including, for example, carbamazepine, valproate, lamotrigine, levetiracetam and gabapentin, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(vi) **Alzheimer's therapies** including, for example, donepezil, galantamine, memantine, rivastigmine, tacrine, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(vii) **Parkinson's therapies** including, for example, L-dopa, ropinirole, pramipexole, monoamine oxidase type B (MAO-B) inhibitors such as deprenyl, selegiline and rasagiline, catechol-O-methyl transferase (COMT) inhibitors such as entacapone or tolcapone, adenosine A-2 inhibitors, dopamine re-uptake inhibitors, NMDA antagonists, Nicotine agonists, and Dopamine agonists and inhibitors of neuronal nitric oxide synthase, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(viii) **migraine therapies** including, for example, almotriptan, amantadine, botulinum toxin A, bromocriptine, butalbital, cabergoline, dichloralphenazone, dihydroergotamine, eletriptan, frovatriptan, lisuride, naratriptan, pergolide, pramipexole, rizatriptan, ropinirole, sumatriptan, topiramate, zolmitriptan, and zomitriptan, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

30

(ix) **stroke therapies** including, for example, abciximab, activase, citicoline, desmoteplase, , and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(x) **urinary incontinence therapies** including, for example, darafenacin, duloxetine, falvoxate, mirabegron, oxybutynin, propiverine, robalzotan, solifenacin, and tolterodine, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

5

(xi) **neuropathic pain therapies** including, for example, capsaicin, gabapentin, lidoderm, and pregabalin, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

10 (xii) **nociceptive pain therapies** such as celecoxib, etoricoxib, lumiracoxib, rofecoxib, valdecoxib, diclofenac, loxoprofen, naproxen, and paracetamol, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(xiii) **insomnia therapies** including, for example, allobarbital, alonimid, amobarbital,
15 benzoctamine, butabarbital, capuride, chloral, cloperidone, clorethate, dexclamol, ethchlorvynol, eszopiclone, etomidate, glutethimide, halazepam, hydroxyzine, lorediplon, mecloqualone, melatonin, mephobarbital, methaqualone, midaflur, nisobamate, pentobarbital, phenobarbital, propofol, ralmeteon, roletamide, suvorexant, triclofos, secobarbital, zaleplon, and zolpidem, zopiclone and equivalents and pharmaceutically
20 active isomer(s) and/or metabolite(s) thereof;

(xiv) **mood stabilizers** including, for example, carbamazepine, divalproex, gabapentin, lamotrigine, lithium, olanzapine, quetiapine, valproate, valproic acid, and verapamil, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

25

(xv) 5HT1B ligands such as, for example, compounds disclosed in WO 99/05134 and WO 02/08212;

(xvi) mGluR2 agonists;

30

(xvii) alpha 7 nicotinic agonists such as, for example, compounds disclosed in WO 96/006098, WO 97/030998, WO 99/003859, WO 00/042044, WO 01/029034, WO 01/60821, WO 01/36417, WO 02/096912, WO 03/087102, WO 03/087103,

WO 03/087104, WO 2004/016617, WO 2004/016616, and WO 2004/019947;

(xviii) chemokine receptor CCRI inhibitors; and

- 5 (xix) delta opioid agonists such as, for example, compounds disclosed in WO 97/23466 and WO 02/094794.

Such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent within approved dosage
10 ranges.

The present invention will now be further explained by reference to the following illustrative examples, in which the starting materials and reagents used are available from commercial suppliers or prepared via literature procedures.

15

Nuclear magnetic resonance (NMR) spectra were recorded at 400 MHz or 300 MHz as stated and at 300.3K, 298.2K or 293K unless otherwise stated; the chemical shifts (δ) are reported in parts per million. Spectra were recorded using a Bruker (trade mark) 400 AVANCE instrument fitted with a 5mm BBFO probe with instrument controlled by Bruker
20 TopSpin 2.1 software, or by a Bruker 400 AVANCE-III HD instrument fitted with a 5mm BBFO smart probe or a 5mm BBFO probe with instrument controlled by Bruker TopSpin 3.2 software, or by a Bruker 400 AVANCE-III instrument fitted with a 5mm BBFO probe with instrument controlled by Bruker Topspin 3.0 software or by a Bruker 300MHz AVANCE II instrument fitted with a 5mm DUL probe with instrument controlled by
25 Bruker TopSpin 1.3 software, or 5mm BBFO probe controlled by Bruker Topspin 3.2 software.

Purity was assessed using one or more of the following:

- Ultra Performance Liquid Chromatography (UPLC) with UV (photodiode array)
30 detection over a wide range of wavelengths, normally 220-450 nm, using a Waters (trade mark) Acquity UPLC system equipped with Acquity UPLC BEH, HSS or HSS T3 C18 columns (2.1mm id x 50mm long) operated at 50 or 60 °C. Mobile phases typically consisted of acetonitrile mixed with water containing either 0.1%

formic acid, 0.1% TFA or 0.025% ammonia. Mass spectra were recorded with a Waters SQD single quadrupole mass spectrometer using atmospheric pressure ionisation.

- UPLC with UV (photodiode array) detection over a wide range of wavelengths, normally 220 – 450 nm, using Shimadzu (trade mark) Nexera X2 UPLC controlled by Lab Solution software equipped with Acquity UPLC BEH, HSS or HSS T3 C18 columns (2.1mm id x 50mm long) operated at 50 °C. Mobile phases typically consisted of acetonitrile mixed with water containing either 0.1% formic acid, 0.1% TFA or 0.025% ammonia. Mass spectra were recorded with a Shimadzu single quadrupole mass spectrometer using DUIS ionisation.

Compounds were purified using normal phase chromatography on silica, using Biotage (trade mark) KP-Sil cartridges, Interchim (trade mark) PuriFlash cartridges or Kinesis (trade mark) Telos silica cartridges, or on basic silica using Biotage KP-NH cartridges, or by reverse phase chromatographic methods using Biotage KP-C18-HS cartridges or by Biotage Isolute SCX-2 or Phenomenex (trade mark) Strata ABW catch-release cartridges, or by preparative high performance liquid chromatography (HPLC).

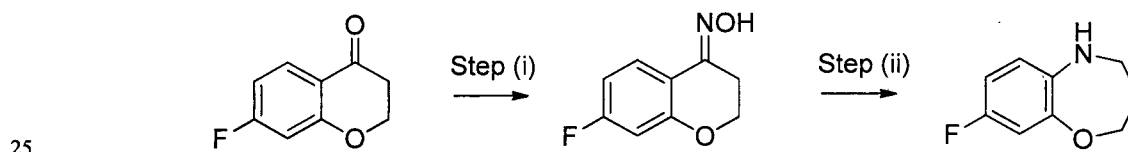
Preparative HPLC was performed using Agilent Technologies (trade mark) 1100 Series system or a Waters autopurification LC/MS system typically using Waters 19 mm id x 250 mm long C18 columns such as XBridge (trade mark) or SunFire (trade mark) 5 µm materials at room temperature. Mobile phases typically consisted of acetonitrile mixed with water containing either 0.1% formic acid or 0.1% ammonia, unless otherwise stated.

Super Critical Fluid Chromatography (SFC) chiral separations were performed on a Waters prep30/MS system, using a flow rate of 30 mL/min, temperature of 40 °C and a pressure of 100 bar. Mobile phases typically consisted of supercritical CO₂ and a polar solvent such as methanol, ethanol or isopropanol. Column type and eluent are detailed for individual examples.

‘Room temperature’, as used in the present specification, means a temperature in the range from about 18 °C to about 25 °C.

Abbreviations

	DAST:	Diethylaminosulfur trifluoride
	DCM:	Dichloromethane
	DIAD:	Diisopropyl azodicarboxylate
5	DIBAL-H:	Diisobutylaluminium hydride
	DIPEA:	<i>N,N</i> -Diisopropylethylamine
	DMF:	Dimethylformamide
	DMP:	Dess-Martin Periodinane
	EtOAc:	Ethyl acetate
10	h:	hour
	HATU:	1-[Bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxid hexafluorophosphate
	HPLC:	High-Performance Liquid Chromatography
	MeCN:	Acetonitrile
15	MeOH:	Methanol
	min:	minute
	Pd ₂ (dba) ₃ :	Tris(dibenzylideneacetone)dipalladium(0)
	TEA:	Triethylamine
	THF:	Tetrahydrofuran
20	TFAA:	Trifluoroacetic anhydride
	T3P:	Propylphosphonic Anhydride

1. Intermediates**Intermediate 1: 8-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepine****Step (i): *N*-(7-fluoro-3,4-dihydro-2*H*-1-benzopyran-4-ylidene)hydroxylamine**

7-Fluorochroman-4-one (10.0 g, 60.2 mmol) and hydroxylamine hydrochloride (4.60 g, 66.2 mmol) were dissolved in anhydrous methanol (100 mL) and cooled to 0 °C. TEA (10.1 mL, 72.2 mmol) was added drop wise. The reaction mixture was warmed to room temperature and refluxed for 2h. The reaction mixture was cooled to room temperature,

30

then cooled to 0 °C in an ice-bath before quenching it with water (200 mL). The reaction mixture was stirred at 0 °C for 30 min. The solid was filtered, washed with water and dried in a vacuum oven at 50 °C overnight to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 2.99 (t, *J* = 6.27 Hz, 2 H), 4.27 (t, *J* = 6.13 Hz, 2 H),
5 6.54 - 6.71 (m, 2 H), 7.75 - 7.88 (m, 1 H), 8.14 (s, 1 H)

MS ES⁺: 182

Step (ii): 8-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepine

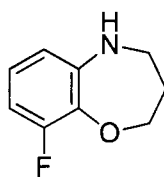
N-(7-fluoro-3,4-dihydro-2H-1-benzopyran-4-ylidene)hydroxylamine (7.60 g, 41.9 mmol)
10 was dissolved in DCM (450 mL) and the solution was cooled to 0 to -5 °C. DIBAL-H (1M solution in cyclohexane, 252 mL, 252 mmol) was added drop wise at 0 to -5 °C over 5 min and the reaction mixture was warmed to room temperature and stirred for 2h. The reaction mixture was cooled again to 0 °C, and sodium fluoride (50.40 g, 1.20 mol) was added followed by the careful addition of water (19 mL). The reaction mixture was stirred at 0 °C
15 for 30 min. The mixture was filtered through a pad of celite and was washed with EtOAc.

The filtrates were evaporated *in vacuo*. The crude product was purified by flash chromatography (10-20% EtOAc in hexanes on silica) to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.90 - 2.07 (m, 2 H), 3.05 - 3.23 (m, 2 H), 3.28 - 3.82 (m, 1 H), 3.98 - 4.14 (m, 2 H), 6.53 - 6.73 (m, 3 H)

20 MS ES⁺: 168

Intermediate 2: 9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepine

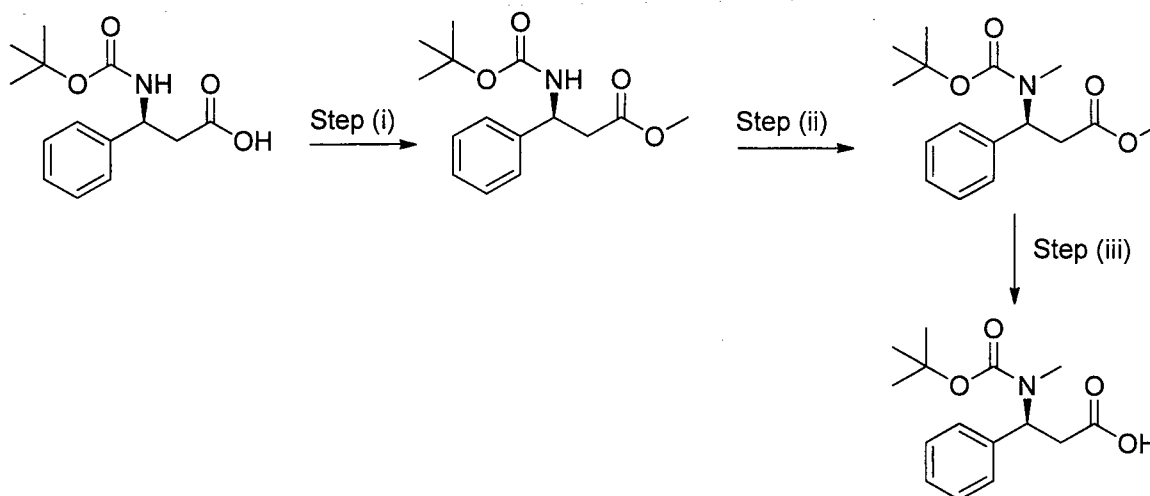


Prepared as described for **Intermediate 1** using 8-Fluorochroman-4-one (9.50 g, 57.2
25 mmol) to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.96 - 2.10 (m, 2 H), 3.19 - 3.31 (m, 2 H), 3.84 (br. s., 1 H), 4.09 - 4.20 (m, 2 H), 6.42 - 6.52 (m, 1 H), 6.54 - 6.65 (m, 1 H), 6.70 - 6.81 (m, 1 H)

MS ES⁺: 168

Intermediate 3: (3S)-3-[[*tert*-butoxy)carbonyl](methyl)amino]-3-phenylpropanoic acid



Step (i): methyl (3S)-3-[[*tert*-butoxy)carbonyl]amino]-3-phenylpropanoate

- 5 Methyl iodide (2.95 mL, 47.1 mmol) was added to a suspension of (3S)-3-[[*tert*-butoxy)carbonyl]amino]-3-phenylpropanoic (2.5 g, 9.42 mmol) and K₂CO₃ (2.60 g, 18.9 mmol) in DMF (50 mL) at room temperature. The mixture was heated at 80 °C under nitrogen for 24h. The mixture was concentrated *in vacuo* to remove most of the DMF and the residue was partitioned between water and EtOAc. The organic phase was dried
- 10 (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash chromatography (20-30% [1:1 EtOAc:THF] in petroleum ether on silica) to afford the title compound.
- ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.36 (s, 9 H), 2.60 - 2.83 (m, 2 H), 3.56 (s, 3 H), 4.81 - 5.06 (m, 1 H), 7.16 - 7.26 (m, 1 H), 7.28 - 7.36 (m, 4 H), 7.42 - 7.53 (m, 1 H)

15 **Step (ii): methyl (3S)-3-[[*tert*-butoxy)carbonyl](methyl)amino]-3-phenylpropanoate**

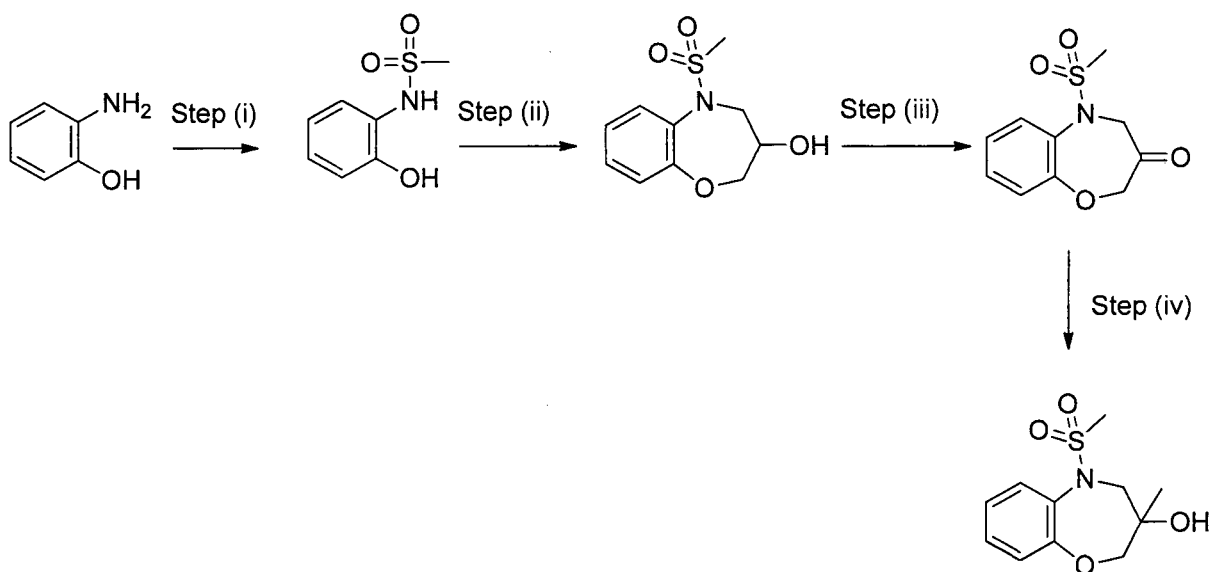
- Sodium hydride (60% dispersion in mineral oil, 0.134 g, 3.35 mmol) was added to a solution of methyl (3S)-3-[[*tert*-butoxy)carbonyl]amino]-3-phenylpropanoate (0.850 g, 3.04 mmol) in DMF (15 mL) and stirred for 30 min. The reaction was cooled to 0 °C and methyl iodide (0.228 mL, 3.65 mmol) was added and the reaction was stirred at room
- 20 temperature for 2h. The reaction mixture was partitioned between EtOAc and water. The aqueous was further extracted with EtOAc and the combined organics then washed with brine. The organic phase was passed through a phase separator and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-50% EtOAc in petroleum ether on silica) to afford the title compound.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.37 - 1.45 (m, 9 H), 2.55 (s, 3 H), 2.87 - 3.17 (m, 2 H), 3.60 (s, 3 H), 5.44 - 5.72 (m, 1 H), 7.26 - 7.33 (m, 3 H), 7.33 - 7.41 (m, 2 H)

Step (iii): (3S)-3-[[*tert*-butoxy)carbonyl](methyl)amino]-3-phenylpropanoic acid

- LiOH (453 mg, 18.9 mmol) was added to a stirred solution of methyl (3S)-3-[[*tert*-butoxy)carbonyl](methyl)amino]-3-phenylpropanoate (0.555 g, 1.89 mmol) in dioxane (5 mL) and water (5 mL) and the mixture was stirred for 3h at room temperature. The reaction mixture was acidified with 2M HCl to pH~5 and extracted with EtOAc. The organic phase was dried (MgSO_4) and concentrated *in vacuo* to afford the title compound.
- ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.32 - 1.48 (m, 9 H), 2.57 (s, 3 H), 2.74 - 2.89 (m, 1 H), 2.93 - 3.07 (m, 1 H), 5.43 - 5.68 (m, 1 H), 7.25 - 7.32 (m, 3 H), 7.33 - 7.41 (m, 2 H), 12.22 - 12.41 (m, 1 H)

Intermediate 4: 5-methanesulfonyl-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-ol



Step (i): N-(2-hydroxyphenyl)methanesulfonamide

- A solution of methanesulphonyl chloride (14.3 mL, 183 mmol) in DCM (20 mL) was added drop wise over *ca.* 5 min to a solution of 2-aminophenol (20 g, 183 mmol) and pyridine (44.5 mL, 550 mmol) in DCM (100 mL). The mixture was stirred at 0 °C for 5 min and allowed to warm to room temperature for 1h. The mixture was concentrated *in vacuo*. The residue was partitioned between water and EtOAc, HCl (2M) was added until the aqueous pH ~ 1. The organic phase was separated, washed with water and brine, dried

(MgSO₄) and concentrated *in vacuo*. The residue was triturated with ether, filtered and dried to afford the title compound.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 2.94 (s, 3 H), 6.73 - 6.82 (m, 1 H), 6.85 - 6.91 (m, 1 H), 6.99 - 7.09 (m, 1 H), 7.15 - 7.22 (m, 1 H), 8.66 (br. s, 1 H), 9.74 (br. s, 1 H)

5

Step (ii): 5-(Methylsulfonyl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ol

N-(2-Hydroxyphenyl)methanesulfonamide (85.00 g, 0.46 mol) was dissolved in ethanol (275 mL). A solution of sodium ethoxide (21% solution in ethanol) (173 mL, 0.47 mol) in ethanol (275 mL) was added. More ethanol (200 mL) was added and the reaction was

10 stirred under nitrogen for 30 min. The solvent was concentrated *in vacuo*, and azeotroped with THF (200 mL). The residue was dissolved in DMF (680 mL). (±)-Epichlorohydrin (35.5 mL, 0.46 mol) was added and the mixture was heated to 90 °C for 7h and stirred at room temperature overnight. Half the amount of DMF was concentrated *in vacuo* and the remaining solution was partitioned between EtOAc and water. The organic layer was
15 separated and the aqueous layer was further extracted with EtOAc. The combined organics were washed with brine and water. The organic layer was dried (Na₂SO₄), filtered through a pad of celite and the filtrate was concentrated *in vacuo*. The resulting residue was triturated in ethanol (170 mL) for 15 min. The solid was collected upon filtration, washed with cold ethanol and dried in the vacuum oven at 40 °C to afford the title compound.

20 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.11 (s, 3 H), 3.43 - 3.57 (m, 1 H), 3.57 - 3.87 (m, 2 H), 3.93 - 4.10 (m, 2 H), 5.45 - 5.53 (m, 1 H), 7.08 - 7.16 (m, 2 H), 7.24 - 7.34 (m, 1 H), 7.36 - 7.43 (m, 1 H)

MS ES⁺: 244

25 **Step (iii): 5-methanesulfonyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-one**

DMP (17.4 g, 41.0 mmol) was added to a suspension of 5-(methylsulfonyl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ol (5 g, 20.6 mmol) in DCM (200 mL) under nitrogen.

The reaction was stirred at room temperature for 18h. The reaction was quenched with saturated aqueous sodium thiosulfate, with vigorous stirring for 15 min. The phases were

30 separated and the organic was washed 3 times with saturated aqueous sodium bicarbonate then brine, dried (phase separator) and concentrated *in vacuo* to afford the title product

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.39 (s, 3 H), 4.52 (s, 2 H), 4.71 (s, 2 H), 7.07 - 7.15 (m, 2 H), 7.24 - 7.34 (m, 1 H), 7.41 - 7.51 (m, 1 H)

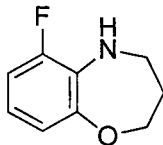
MS ES⁺: 242

Step (iv): 5-methanesulfonyl-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-

olMethylmagnesium bromide (3M in diethyl ether) (8.29 mL, 24.87 mmol) was added to
5 suspension of 5-methanesulfonyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-one (2 g, 8.29
mmol) in THF (40 mL) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 3h, then
allowed to warm to room temperature and stirred for 18h. The reaction was quenched by
cautious addition of saturated aqueous NH₄Cl solution, extracted 3 times with EtOAc,
dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash
10 chromatography (0-75% EtOAc in petroleum ether on silica). The material was loaded
onto a cation exchange cartridge, washing with methanol and eluting with 2M ammonia in
methanol solution and concentrated *in vacuo* to afford the title compound.

MS ES⁺: 258

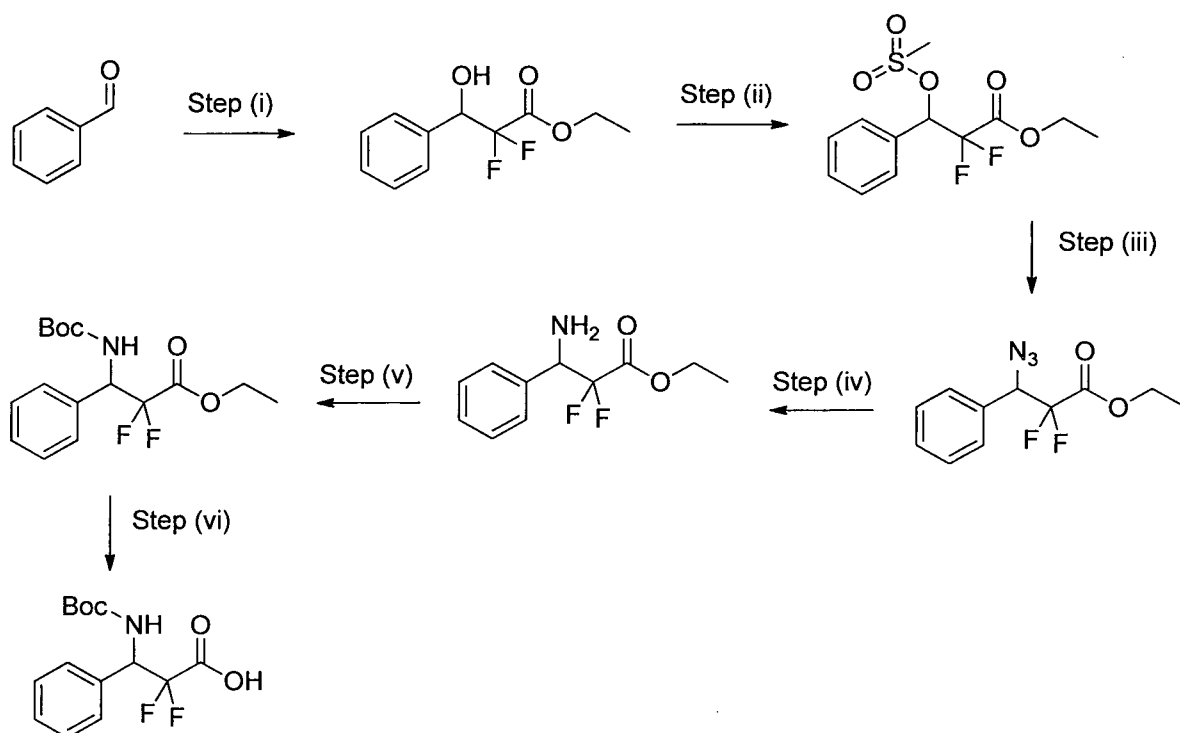
15 **Intermediate 5: 6-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepine**



Prepared as described for **Intermediate 1** using 5-Fluorochroman-4-one (2.00 g, 12.0
mmol) to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.96 - 2.11 (m, 2 H), 3.21 - 3.36 (m, 2 H), 4.02 - 4.20
20 (m, 3 H), 6.57 - 6.80 (m, 3 H)

**Intermediate 6: 3-{[(*tert*-butoxy)carbonyl]amino}-2,2-difluoro-3-phenylpropanoic
acid**



Step (i): ethyl 2,2-difluoro-3-hydroxy-3-phenylpropanoate

Zinc (8.87 g, 136 mmol) was added to a refluxing solution of THF (250 mL) under nitrogen. Ethyl 2-bromo-2,2-difluoroacetate (18.00 mL, 136 mmol) and benzaldehyde (11.49 mL, 113 mmol) were added sequentially. The reaction was heated to reflux for 15 min then cooled to room temperature. The reaction was poured into a mixture of EtOAc, aqueous sodium hydrogen sulfate and aqueous sodium bicarbonate. The mixture was stirred for 15 min. The layers were separated and the aqueous was extracted with more EtOAc. The organics were combined, dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-50% EtOAc in petroleum ether on silica) to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.31 (t, *J* = 7.15 Hz, 3 H), 2.65 - 2.73 (m, 1 H), 4.33 (q, *J* = 7.15 Hz, 2 H), 5.20 (s, 1 H), 7.37 - 7.52 (m, 5 H)

Step (ii): ethyl 2,2-difluoro-3-(methanesulfonyloxy)-3-phenylpropanoate

A solution of methanesulfonyl chloride (4.86 mL, 62.3 mmol) was added drop wise to a solution of ethyl 2,2-difluoro-3-hydroxy-3-phenylpropanoate (12.0 g, 48.0 mmol) and TEA (8.69 mL, 62.3 mmol) in DCM (200 mL) under nitrogen. The reaction was stirred at room temperature for 2 hours. The mixture was washed with 10% HCl, water, sodium

bicarbonate and brine, dried (MgSO₄) and concentrated *in vacuo* to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.33 (t, *J* = 7.20 Hz, 3 H), 2.91 (s, 3 H), 4.35 (q, *J* = 7.15 Hz, 2 H), 5.92 - 6.03 (m, 1 H), 7.44 - 7.58 (m, 5 H)

5

Step (iii): ethyl 3-azido-2,2-difluoro-3-phenylpropanoate

Sodium azide (5.53 g, 85 mmol) was added to a solution of ethyl 2,2-difluoro-3-(methylsulfonyloxy)-3-phenylpropanoate (13.8 g, 42.5 mmol) and tetrabutylammonium bromide (0.137 g, 0.43 mmol) in DMF (130 mL) under nitrogen. The reaction was heated to 65 °C for 48h. The reaction was cooled to room temperature. Water was added to quench the reaction. The mixture was diluted with EtOAc, washed three times with water, dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-50% EtOAc in petroleum ether on silica). The crude product was further purified by flash chromatography (0-50% EtOAc in petroleum ether on silica) to afford the title compound.

10

¹H NMR (400 MHz, CDCl₃) δ ppm 1.31 (t, *J* = 7.15 Hz, 3 H), 4.33 (q, *J* = 7.15 Hz, 2 H), 5.01 - 5.16 (m, 1 H), 7.38 - 7.49 (m, 5 H)

Step (iv): ethyl 3-amino-2,2-difluoro-3-phenylpropanoate

10% Palladium on carbon (50% water) (1.06 g, 0.99 mmol) was added to a solution of ethyl 3-azido-2,2-difluoro-3-phenylpropanoate (2.53 g, 9.91 mmol) in EtOAc (45 mL) and the reaction was stirred under an atmosphere of hydrogen gas. The reaction was stirred at room temperature for 18h. The reaction was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc (45 mL) and 10% palladium on carbon (50% water) (1.06 g, 0.99 mmol) was added. The reaction was placed under vacuum then an atmosphere of hydrogen and stirred vigorously for 18h. The reaction was filtered through celite and washed with EtOAc and methanol. The filtrate was concentrated *in vacuo* to afford the title compound.

20

¹H NMR (400 MHz, CDCl₃) δ ppm 1.25 (t, *J* = 7.15 Hz, 3 H), 1.81 (br. s., 2 H), 4.26 (q, *J* = 7.15 Hz, 2 H), 4.42 - 4.57 (m, 1 H), 7.32 - 7.43 (m, 5 H)

25

MS ES⁺: 230

Step (v): ethyl 3-[[*tert*-butoxy]carbonyl]amino}-2,2-difluoro-3-phenylpropanoate

Di-*tert*-butyl dicarbonate (4.56 mL, 19.6 mmol) was added to a solution of ethyl 3-amino-2,2-difluoro-3-phenylpropanoate (2.25 g, 9.82 mmol) and sodium hydrogen carbonate (1.649 g, 19.6 mmol) in THF (10 mL) under nitrogen. The reaction was heated to 60 °C for 18h. Sodium hydrogen carbonate (0.5g) was added, followed by di-*tert*-butyl dicarbonate (1.35g) and the reaction was stirred at 60 °C for 30 min. The reaction was cooled to room temperature. The mixture was diluted with EtOAc, washed with water, 10% HCl, saturated sodium bicarbonate solution, and brine, dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-50% EtOAc in petroleum ether on silica) to afford the title compound.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.21 (t, *J* = 7.12 Hz, 3 H), 1.38 (s, 9 H), 4.14 - 4.36 (m, 2 H), 5.17 - 5.41 (m, 1 H), 7.28 - 7.55 (m, 5 H), 8.16 - 8.30 (m, 1 H)

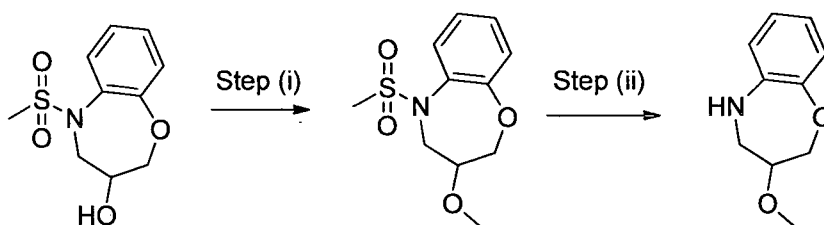
Step (vi): 3-{{{(*tert*-butoxy)carbonyl}amino)-2,2-difluoro-3-phenylpropanoic acid

LiOH (0.480 g, 20.0 mmol) was added to a suspension of ethyl 3-{{{(*tert*-butoxy)carbonyl}amino)-2,2-difluoro-3-phenylpropanoate (2.2 g, 6.68 mmol) in EtOH (10 mL) and water (5 mL). The reaction was stirred at room temperature for 30 min. The reaction was concentrated *in vacuo* and acidified with 1M HCl to pH1. The aqueous was extracted twice with EtOAc. The organics were combined, dried (MgSO₄) and concentrated *in vacuo* to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.38 (s, 9 H), 5.13 - 5.31 (m, 1 H), 7.27 - 7.50 (m, 5 H), 8.01 - 8.16 (m, 1 H)

MS ES⁺: 300

Intermediate 7: 3-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepine



Step (i): 3-methoxy-5-(methylsulfonyl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine

Methyl iodide (3.20 mL, 51.4 mmol) was added to a suspension of 5-(methylsulfonyl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ol (**Intermediate 4 step (ii)**, 5 g, 20.6 mmol) and silver oxide (23.81 g, 103 mmol) in MeCN (40 mL) and DMF (15 mL) in a sealed tube.

The reaction was covered in foil and stirred at room temperature overnight. The suspension

was filtered through celite and the filtrate was concentrated *in vacuo* to afford the title compound.

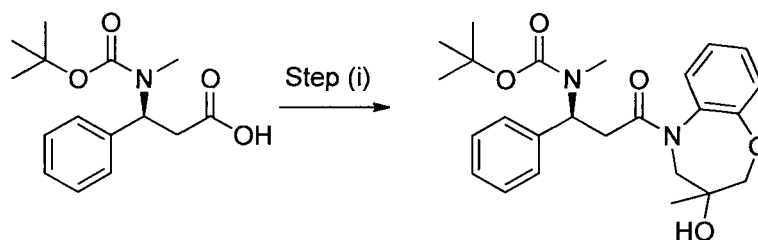
MS ES⁺: 258

5 **Step (ii): 3-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepine**

Bis(2-methoxyethoxy)aluminum(III) sodium hydride (60% in toluene, 1.848 mL, 5.83 mmol) was added to a solution of 3-methoxy-5-(methylsulfonyl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.3 g, 1.17 mmol) in toluene (3 mL) at room temperature and stirred for 18h. The reaction was quenched with sodium carbonate. The crude mixture was dissolved in methanol and loaded onto an SCX cartridge. The cartridge was washed with methanol and DCM, then eluted with 4M ammonia in methanol. The ammonia in methanol fractions were combined and concentrated *in vacuo* to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.13 - 3.23 (m, 1 H), 3.33 (s, 3 H), 3.35 - 3.44 (m, 1 H), 3.57 - 3.67 (m, 1 H), 4.02 - 4.11 (m, 1 H), 4.16 - 4.23 (m, 1 H), 5.36 - 5.43 (m, 1 H), 6.51 - 6.58 (m, 1 H), 6.64 - 6.76 (m, 3 H)

Intermediates 8 and 9: *tert*-butyl N-[(1*S*)-3-(3-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-oxo-1-phenylpropyl]-N-methylcarbamate



20

HATU (0.120 g, 0.32 mmol) was added to a solution of (*S*)-3-((*tert*-butoxycarbonyl)(methyl)amino)-3-phenylpropanoic acid (**Intermediate 3**, 0.084 g, 0.30 mmol) and DIPEA (0.058 mL, 0.33 mmol) in DMF (1 mL) at room temperature. The mixture was stirred for 5 min. 5-methanesulfonyl-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-3-ol (**Intermediate 4**, 0.054 g, 0.30 mmol) was added and the mixture was stirred until homogeneous and allowed to stand for 18h. The mixture was partitioned between water and EtOAc. The organic phase was concentrated *in vacuo*. The residue was purified by flash chromatography (20-50% EtOAc in petroleum ether on silica) to afford the two title compounds.

25

Intermediate 8: *tert*-butyl N-[(1*S*)-3-(3-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-oxo-1-phenylpropyl]-N-methylcarbamate

Fastest running stereoisomer

5 MS ES⁺: 441

Retention time: 1.52 min

Intermediate 9: *tert*-butyl N-[(1*S*)-3-(3-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-oxo-1-phenylpropyl]-N-methylcarbamate

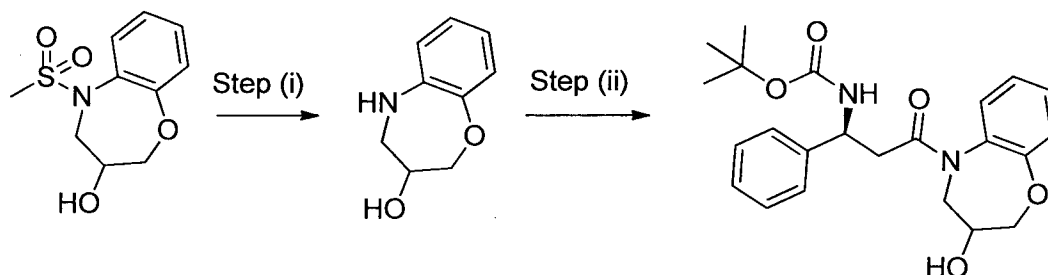
10 Slowest running stereoisomer

MS ES⁺: 441

Retention time: 1.53 min

Intermediate 10: (S)-*tert*-butyl (3-oxo-3-(3-oxo-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-1-phenylpropyl)carbamate (560 mg, 1.364 mmol)

15



Step (i): 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ol

Bis(2-methoxyethoxy)aluminum(III) sodium hydride (1.954 mL, 6.17 mmol) was added to a suspension of 5-(methylsulfonyl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ol

20 (**Intermediate 4 step (ii)**), 0.5 g, 2.055 mmol) in toluene (10 mL) under nitrogen. The

reaction was heated to 85 °C for 24h. The reaction was cooled to room temperature and quenched with sodium carbonate solution. The toluene was removed *in vacuo* and the

mixture was partitioned between EtOAc and sodium carbonate solution. The phases were separated and the aqueous was extracted three times with EtOAc. The combined organics

25 were dried (MgSO₄) and concentrated *in vacuo* to afford the title compound.

MS ES⁺: 166

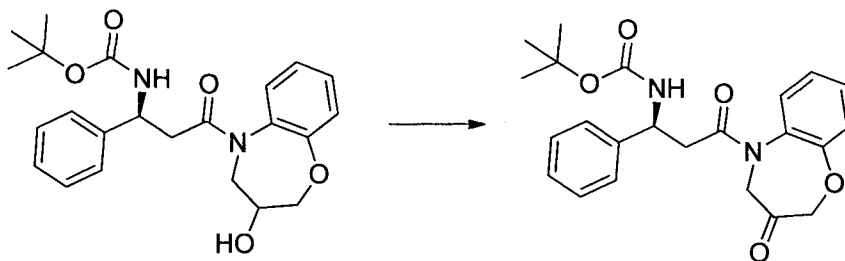
^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 2.95 - 3.08 (m, 1 H), 3.24 - 3.30 (m, 1 H), 3.74 - 3.94 (m, 2 H), 4.12 - 4.23 (m, 1 H), 4.91 - 5.01 (m, 1 H), 5.33 (br. s., 1 H), 6.51 - 6.61 (m, 1 H), 6.64 - 6.79 (m, 3 H)

5 **Step (ii): *tert*-butyl ((1*S*)-3-(3-hydroxy-3,4-dihydrobenzo[*b*][1,4]oxazepin-5(2*H*)-yl)-3-oxo-1-phenylpropyl)carbamate**

2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-ol (1.557 g, 9.42 mmol) was added to a solution of (3*S*)-3-[[*tert*-butoxy]carbonyl]amino]-3-phenylpropanoic (2.5 g, 9.42 mmol) and HATU (3.94 g, 10.37 mmol) and pyridine (0.838 mL, 10.37 mmol) in DMF (10 mL) under
10 nitrogen. The reaction was stirred at room temperature for 24h. HATU (3.94 g, 10.37 mmol) was added and the reaction was stirred at room temperature for 72h. The mixture was diluted with EtOAc, washed with saturated NaHCO_3 , water, and brine, dried (MgSO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-100% EtOAc in petroleum ether on silica) to afford the title compound.

15 MS ES^+ : 413

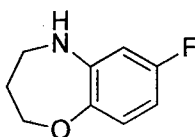
Intermediate 11: *tert*-butyl N-[(1*S*)-3-oxo-3-(3-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-1-phenylpropyl]carbamate



20 DMP (1.16 g, 2.74 mmol) was added to a solution of *tert*-butyl ((1*S*)-3-(3-hydroxy-3,4-dihydrobenzo[*b*][1,4]oxazepin-5(2*H*)-yl)-3-oxo-1-phenylpropyl)carbamate (**Intermediate 10**, 0.565 g, 1.370 mmol) in DCM (5 mL) under nitrogen. The reaction was stirred at room temperature for 18h. The reaction was diluted with DCM and $\text{Na}_2\text{S}_2\text{O}_3$ was added. The suspension was stirred at room temperature for 15 min. The aqueous phase was extracted
25 with DCM, followed by EtOAc. The organics were combined, dried (MgSO_4) and concentrated *in vacuo* to afford the title compound.

MS ES^- : 409

Intermediate 12: 7-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepine

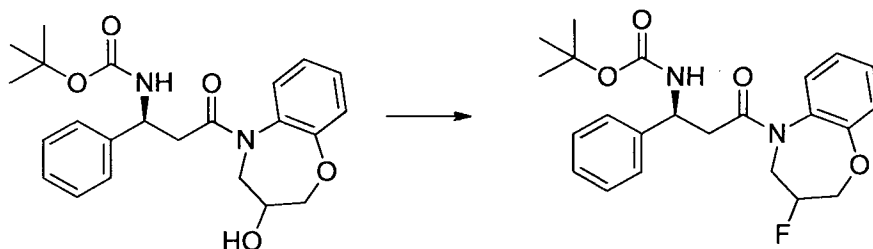


Prepared as described for **Intermediate 1** using 6-fluoro-3,4-dihydro-2H-1-benzopyran-4-one (1g, 5.99 mmol), to afford the title compound.

^1H NMR (400 MHz, CDCl_3) δ ppm 1.94 - 2.20 (m, 2 H), 3.20 - 3.24 (m, 2H), 3.65 - 3.78 (br. s, 1 H), 4.01 - 4.06 (m, 2 H), 6.38 - 6.45 (m, 2 H), 6.83 - 6.87 (m, 1 H)

MS ES^+ : 168

Intermediates 13 and 14: *tert*-butyl N-[(1S)-3-(3-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-oxo-1-phenylpropyl]carbamate



DAST (0.801 mL, 6.07 mmol) was added to a solution of *tert*-butyl ((1S)-3-(3-hydroxy-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-3-oxo-1-phenylpropyl)carbamate

(**Intermediate 10**, 0.695 g, 1.213 mmol) in DCM (5 mL) under nitrogen at 0 °C. The reaction was stirred at room temperature for 18h. The reaction was cooled to 0 °C and

DAST (0.801 mL, 6.07 mmol) was added. The reaction was left to stir at room temperature for 2h. The reaction was quenched with water and diluted with DCM. The organic phase was collected, washed with water, dried (MgSO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-100% EtOAc in petroleum ether on silica). The resulting residue was purified by chiral SFC (ChiralPak Lux-C4, 20% IPA) to afford the two title compounds.

Intermediate 13: *tert*-butyl N-[(1S)-3-(3-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-oxo-1-phenylpropyl]carbamate

Fastest running isomer

MS ES^+ : 415

Retention time = 1.49 min

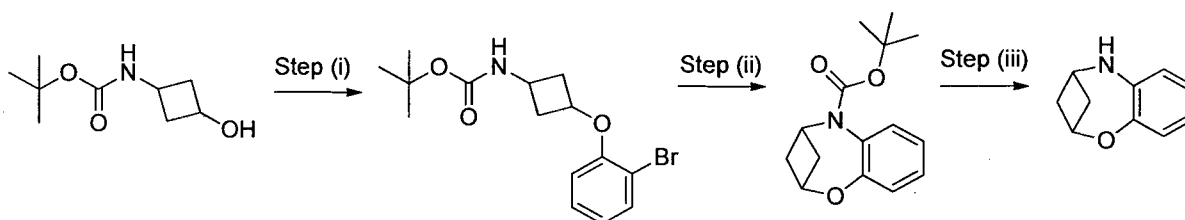
Intermediate 14: *tert*-butyl N-[(1*S*)-3-(3-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-oxo-1-phenylpropyl]carbamate

Slowest running isomer

MS ES⁺: 415

5 Retention time = 1.47 min

Intermediate 15: 2,3,4,5-tetrahydro-2,4-methanobenzo[b][1,4]oxazepine



Step (i): *tert*-butyl N-[3-(2-bromophenoxy)cyclobutyl]carbamate

10 DIAD (1.090 mL, 5.61 mmol) was added to a solution of *tert*-butyl N-(3-hydroxycyclobutyl)carbamate (1 g, 5.34 mmol), 2-bromophenol (0.924 g, 5.34 mmol) and triphenylphosphine (1.401 g, 5.34 mmol) in THF (15 mL) at 0°C. The mixture was stirred, allowed to warm to RT and then to stand for 2h. The mixture was partitioned between DCM and NaOH (1 M). The aqueous phase was extracted with DCM. The combined
15 organic phases were dried and concentrated *in vacuo*. The residue was purified by flash chromatography (20-30% EtOAc in petroleum ether on silica) to afford the title compound.
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.30 - 1.45 (m, 9 H), 1.94 - 2.08 (m, 2 H), 2.74 - 2.85 (m, 2 H), 3.65 - 3.78 (m, 1 H), 4.37 - 4.50 (m, 1 H), 6.82 - 6.92 (m, 1 H), 6.93 - 6.99 (m, 1 H), 7.20 - 7.27 (m, 1 H), 7.28 - 7.35 (m, 1 H), 7.53 - 7.62 (m, 1 H)

20 MS ES⁺:

Step (ii): *tert*-butyl 3,4-dihydro-2,4-methanobenzo[b][1,4]oxazepine-5(2H)-carboxylate

25 A solution/suspension of *tert*-butyl 3-(2-bromophenoxy)cyclobutylcarbamate (0.660 g, 1.929 mmol) and bis(3,5-bis(trifluoromethyl)phenyl)(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (0.310 g, 0.386 mmol) in toluene (15 mL) was degassed and a nitrogen atmosphere introduced three times. Sodium *tert*-butoxide (0.371 g, 3.86 mmol) and Pd₂(dba)₃ (0.177 g, 0.193 mmol) were added. The mixture was degassed and a nitrogen atmosphere introduced three times. The mixture was heated at 60 °C for 24h. The

mixture was partitioned between water and EtOAc. The organic phase was dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash chromatography (15-30% EtOAc in petroleum ether) to afford the title compound.

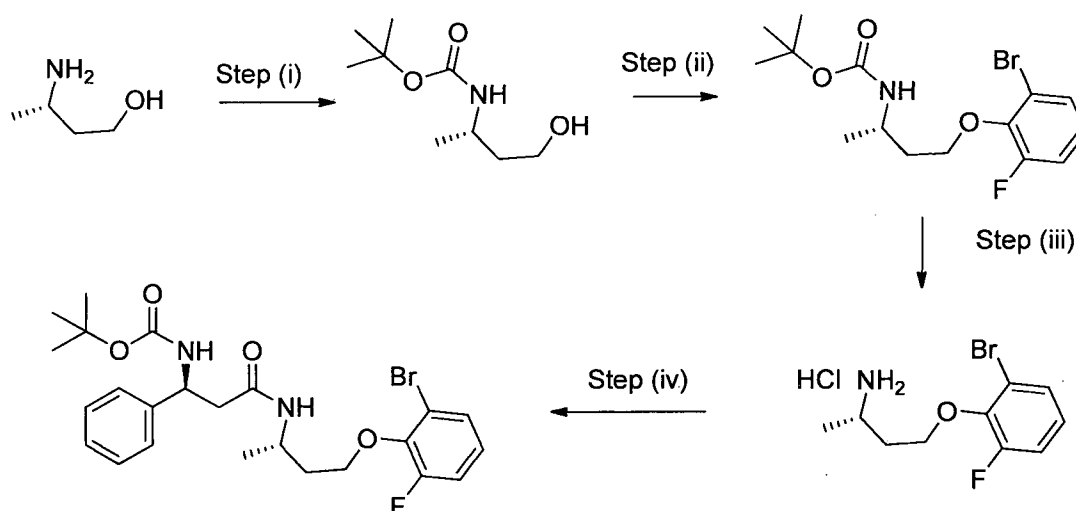
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.41 (s, 9 H), 1.72 - 1.82 (m, 2 H), 2.59 - 2.70 (m, 2 H), 4.59 - 4.67 (m, 1 H), 4.82 - 4.89 (m, 1 H), 6.95 - 7.03 (m, 2 H), 7.08 - 7.16 (m, 1 H), 7.29 - 7.36 (m, 1 H)
MS ES⁺: 206 (M-^tBu)

Step (iii): 2,3,4,5-tetrahydro-2,4-methanobenzo[b][1,4]oxazepine

HCl (4 M in dioxane) (0.892 mL, 3.57 mmol) was added to a solution of tert-butyl 3,4-dihydro-2,4-methanobenzo[b][1,4]oxazepine-5(2H)-carboxylate (0.233 g, 0.892 mmol) in DCM (3 mL). The mixture was stirred and allowed to stand for 2.5h. The mixture was partitioned between DCM and NaOH (1 M). The aqueous phase was extracted with DCM. The combined organic phases were dried (MgSO₄) and concentrated *in vacuo* to afford the title compound.

MS ES⁺: 162

Intermediate 16: tert-butyl N-[(1S)-2-{[(2S)-4-(2-bromo-6-fluorophenoxy)butan-2-yl]carbamoyl}-1-phenylethyl]carbamate



Step (i): tert-butyl N-[(2S)-4-hydroxybutan-2-yl]carbamate

Di-tert-butyl dicarbonate (2.60 mL, 11.22 mmol) was added to a solution of (S)-3-aminobutan-1-ol (1.00 g, 11.2 mmol) in MeOH (10 mL) at room temperature. The mixture was stirred at room temperature and allowed to stand. The mixture was partitioned between

water and DCM. The aqueous phase was extracted with DCM. The combined organic phases were dried (MgSO₄) and concentrated *in vacuo*. The residue was dissolved in DCM (10 mL), dried (MgSO₄) and concentrated *in vacuo* to afford the title compound.

¹H NMR (400 MHz, CD₃CN) δ ppm 1.11 (d, *J* = 6.69 Hz, 3 H), 1.41 (s, 9 H), 1.44 - 1.51 (m, 1 H), 1.55 - 1.69 (m, 1 H), 2.85 - 3.05 (m, 1 H), 3.43 - 3.58 (m, 2 H), 3.61 - 3.80 (m, 1 H), 5.13 - 5.34 (m, 1 H)

Step (ii): *tert*-butyl N-[(2*S*)-4-(2-bromo-6-fluorophenoxy)butan-2-yl]carbamate

DIAD (2.29 mL, 11.76 mmol) was added to a solution of (*S*)-*tert*-butyl (4-hydroxybutan-2-yl)carbamate (2.12 g, 11.2 mmol), 2-bromo-6-fluorophenol (2.14 g, 11.20 mmol) and triphenylphosphine (2.94 g, 11.20 mmol) in THF (20 mL) at room temperature. The mixture was stirred at room temperature and allowed to stand for 18h. The mixture was partitioned between DCM and NaOH (1M). The aqueous phase was extracted with DCM. The combined organic phases were dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash chromatography (20% EtOAc in petroleum ether) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.08 (d, *J* = 6.60 Hz, 3 H), 1.37 (s, 9 H), 1.74 - 1.89 (m, 2 H), 3.64 - 3.82 (m, 1 H), 3.95 - 4.13 (m, 2 H), 6.69 - 6.81 (m, 1 H), 7.03 - 7.15 (m, 1 H), 7.26 - 7.37 (m, 1 H), 7.42 - 7.49 (m, 1 H)

MS ES⁺: 306 (M-*t*Bu)

Step (iii): (2*S*)-4-(2-bromo-6-fluorophenoxy)butan-2-amine hydrochloride

HCl (4 M in dioxane) (3.81 mL, 15.24 mmol) was added to a solution of *tert*-butyl N-[(2*S*)-4-(2-bromo-6-fluorophenoxy)butan-2-yl]carbamate (3.68 g, 10.16 mmol) in DCM (15 mL) at room temperature. The mixture was stirred at room temperature and allowed to stand for 18h. Further HCl (4 M in dioxane) (8.89 mL, 35.6 mmol) was added and the mixture was diluted with MeOH (15 mL), stirred and allowed to stand for 18h. The mixture was concentrated *in vacuo*, adding DCM to assist removal of dioxane, to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.29 (d, *J* = 6.60 Hz, 3 H), 1.77 - 1.96 (m, 1 H), 2.09 - 2.25 (m, 1 H), 3.28 - 3.55 (m, 2 H), 4.06 - 4.24 (m, 2 H), 7.05 - 7.17 (m, 1 H), 7.31 - 7.41 (m, 1 H), 7.44 - 7.53 (m, 1 H), 8.09 (br. s, 3 H)

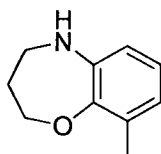
MS ES⁺: 262

Step (iv): *tert*-butyl N-[(1*S*)-2-{[(2*S*)-4-(2-bromo-6-fluorophenoxy)butan-2-yl]carbamoyl}-1-phenylethyl]carbamate

HATU (0.800 g, 2.100 mmol) was added to a stirred solution of (3*S*)-3-[[*tert*-butoxy)carbonyl]amino]-3-phenylpropanoic (0.53 g, 2 mmol) and DIPEA (0.770 mL, 4.40 mmol) in DMF (8 mL) at room temperature. The mixture was stirred at room temperature for 5 minutes. (2*S*)-4-(2-bromo-6-fluorophenoxy)butan-2-amine hydrochloride (0.60 g, 2.000 mmol) was added and the mixture was stirred until homogeneous and allowed to stand for 2h. The mixture was partitioned between water and EtOAc. THF and water were added. The aqueous phase was extracted with EtOAc. The combined organic phases were dried (MgSO₄) and concentrated *in vacuo* to ca. 20 mL. The resulting suspension was filtered, washed with ether and air-dried to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.03 (d, *J* = 6.60 Hz, 3 H), 1.34 (s, 9 H), 1.67 - 1.82 (m, 2 H), 2.39 - 2.47 (m, 2 H), 3.65 - 4.02 (m, 4 H), 4.82 - 4.94 (m, 1 H), 7.03 - 7.13 (m, 2 H), 7.17 - 7.28 (m, 4 H), 7.29 - 7.42 (m, 2 H), 7.43 - 7.51 (m, 1 H), 7.61 - 7.71 (m, 1 H)
MS ES⁺: 509

Intermediate 17: 9-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepine

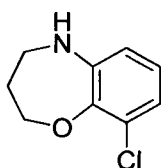


Prepared as described for **Intermediate 1** using 8-methyl-3,4-dihydro-2H-1-benzopyran-4-one (1g, 6.13 mmol), to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.95 - 2.08 (m, 2 H), 2.24 (s, 3 H), 3.17 - 3.27 (m, 2 H), 3.70 (br. s, 1 H), 4.04 - 4.14 (m, 2 H), 6.57 - 6.62 (m, 1 H), 6.67 - 6.73 (m, 1 H), 6.74 - 6.82 (m, 1 H)

MS ES⁺: 164

Intermediate 18: 9-chloro-2,3,4,5-tetrahydro-1,5-benzoxazepine

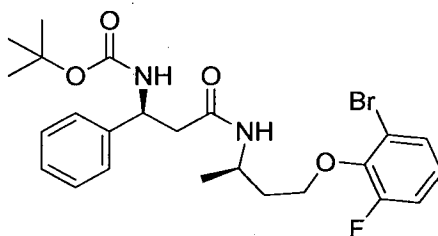


Prepared as described for **Intermediate 1** using 8-chloro-3,4-dihydro-2H-1-benzopyran-4-one (1g, 5.45 mmol), to afford the title compound.

^1H NMR (400 MHz, CDCl_3) δ ppm 1.97 - 2.11 (m, 2 H), 3.22 - 3.35 (m, 2 H), 3.79 (br. s., 1 H), 4.14 - 4.23 (m, 2 H), 6.55 - 6.64 (m, 1 H), 6.72 - 6.82 (m, 1 H), 6.83 - 6.91 (m, 1 H)

5 MS ES^+ : 184

Intermediate 19: *tert*-butyl N-[(1S)-2-{[(2R)-4-(2-bromo-6-fluorophenoxy)butan-2-yl]carbamoyl}-1-phenylethyl]carbamate

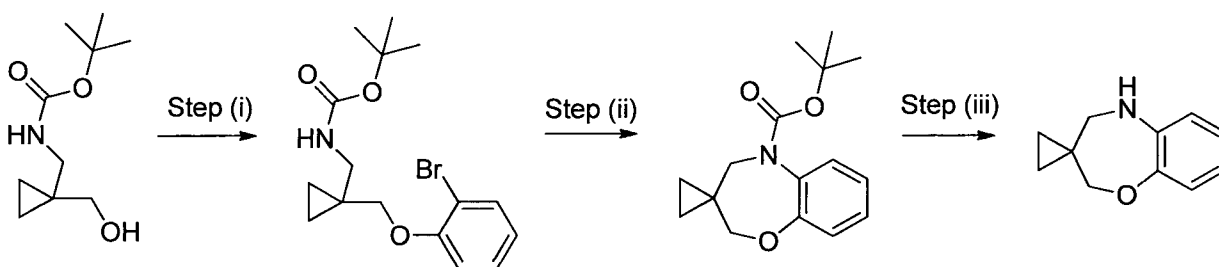


10 Prepared as described for **Intermediate 15** using (R)-3-aminobutan-1-ol (1 g, 11.22 mmol) and 2-bromo-6-fluorophenol (2.12g, 11.1 mmol) to afford the title compound.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.90 - 1.00 (m, 3 H), 1.23 - 1.40 (m, 9 H), 1.67 - 1.89 (m, 2 H), 2.39 - 2.47 (m, 2 H), 3.86 - 4.06 (m, 3 H), 4.81 - 4.96 (m, 1 H), 7.04 - 7.19 (m, 2 H), 7.21 - 7.42 (m, 6 H), 7.42 - 7.49 (m, 1 H), 7.61 - 7.71 (m, 1 H)

15 MS ES^+ : 509

Intermediate 20: 4,5-dihydro-2H-spiro[1,5-benzoxazepine-3,1'-cyclopropane]



Step (i) *tert*-butyl N-([1-(2-bromophenoxy)methyl]cyclopropyl)methylcarbamate

20 A solution of *tert*-butyl N-([1-(hydroxymethyl)cyclopropyl]methyl)carbamate (1.00 g, 4.97 mmol), 2-bromophenol (0.537 mL, 4.97 mmol) and triphenylphosphine (1.30 g, 4.97 mmol) in THF (30 mL) was treated drop wise with DIAD (1.02 mL, 4.97 mmol). The reaction was stirred at room temperature for 18h under nitrogen. The reaction was partitioned between EtOAc and water and the organic phase was collected, dried (MgSO_4)

and concentrated *in vacuo*. The crude material was purified by flash chromatography (0-50% EtOAc in petroleum ether on silica) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.47 - 0.60 (m, 4 H), 1.36 (s, 9 H), 3.09 - 3.17 (m, 2 H), 3.90 (s, 2 H), 6.81 - 6.93 (m, 2 H), 7.00 - 7.08 (m, 1 H), 7.27 - 7.38 (m, 1 H), 7.52 - 7.61 (m, 1 H)

MS ES⁺: 318 (M-^tBu)

Step (ii) *tert*-butyl 4,5-dihydro-2H-spiro[1,5-benzoxazepine-3,1'-cyclopropane]-5-carboxylate

A suspension of *tert*-butyl N-({1-[(2-bromophenoxy)methyl]cyclopropyl}methyl)-carbamate (0.30 g, 0.84 mmol), sodium *tert*-butoxide (0.162 g, 1.684 mmol), bis(3,5-bis(trifluoromethyl)phenyl)(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine and Pd₂(dba)₃ (0.077 g, 0.084 mmol) in toluene (10 mL) was degassed and refilled with nitrogen gas three times. The reaction was heated to 80°C for 2.5h. The reaction was cooled to room temperature and diluted with EtOAc, washed with water, followed by brine, dried (MgSO₄) and concentrated *in vacuo* to afford the title compound. MS ES⁺: 176 (M-Boc)

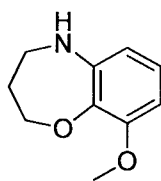
Step (iii) 4,5-dihydro-2H-spiro[1,5-benzoxazepine-3,1'-cyclopropane]

HCl (4M in dioxane, 1.68 mL, 6.71 mmol) was added to a solution of *tert*-butyl 4,5-dihydro-2H-spiro[1,5-benzoxazepine-3,1'-cyclopropane]-5-carboxylate (0.40 g, 1.119 mmol) in dioxane (5 mL) under nitrogen. The reaction was stirred at room temperature for 18h. HCl (4M in dioxane, 1.68 mL, 6.71 mmol) was added and the reaction was heated to 80 °C for 2h. The reaction was concentrated *in vacuo*, dissolved in EtOAc, washed with bicarbonate solution, followed by water and brine, dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-100% EtOAc in petroleum ether on silica) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.52 (s, 4 H), 2.84 - 2.95 (m, 2 H), 3.74 (s, 2 H), 5.34 (br. s, 1 H), 6.57 - 6.68 (m, 1 H), 6.74 - 6.84 (m, 3 H)

MS ES⁺: 176

Intermediate 21: 9-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepine

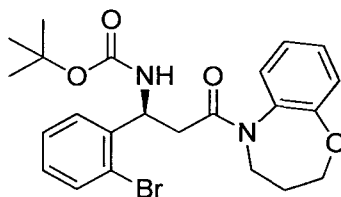


Prepared as described for **Intermediate 1** using 8-methoxy-3,4-dihydro-2H-1-benzopyran-4-one (1g, 5.61 mmol), to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.97 - 2.07 (m, 2 H), 3.21 - 3.30 (m, 2 H), 3.65 - 3.81 (m, 1 H), 3.84 (s, 3 H), 4.11 - 4.22 (m, 2 H), 6.32 - 6.39 (m, 1 H), 6.42 - 6.48 (m, 1 H), 6.76 - 6.83 (m, 1 H)

MS ES⁺: 180

Intermediate 22: *tert*-butyl N-[(1S)-1-(2-bromophenyl)-3-oxo-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]carbamate



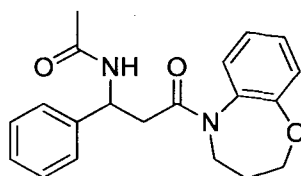
HATU (798 mg, 2.100 mmol) was added to a solution of (3S)-3-(2-bromophenyl)-3-[[*tert*-butoxy]carbonyl]amino}propanoic acid (0.688 g, 2.00 mmol) and DIPEA (0.384 mL, 2.200 mmol) in DMF (5 mL) at room temperature. The mixture was stirred at room temperature for 5 minutes and 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.298 g, 2.00 mmol) was added. The mixture was stirred until homogeneous and allowed to stand for 18h. The mixture was partitioned between water and EtOAc. The organic phase was dried (MgSO₄) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (20-50% EtOAc in petroleum ether on Silica) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.93 - 1.51 (m, 9 H), 1.67 - 1.98 (m, 2 H), 2.02 - 2.15 (m, 1 H), 2.31 - 2.45 (m, 1 H), 2.54 - 2.85 (m, 2 H), 3.60 - 3.81 (m, 1 H), 4.25 - 4.35 (m, 1 H), 4.53 - 4.67 (m, 1 H), 5.13 - 5.36 (m, 1 H), 6.98 - 7.40 (m, 7 H), 7.46 - 7.56 (m, 1 H)

MS ES⁺: 475

2. Examples

Example 1: N-[3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]acetamide

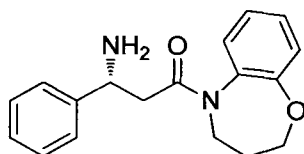


HATU (0.096 g, 0.25 mmol) was added to a solution of 3-acetamido-3-phenylpropanoic acid (0.050 g, 0.24 mmol), DIPEA (0.046 mL, 0.27 mmol) and 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.036 g, 0.24 mmol) in DMF (0.5 mL). The mixture was stirred and allowed to stand for 18h. The mixture was purified by reverse phase preparative HPLC to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.65 - 1.92 (m, 4 H), 2.60 - 2.84 (m, 3 H), 3.52 - 3.78 (m, 2 H), 3.93 - 4.42 (m, 1 H), 4.48 - 4.64 (m, 1 H), 5.15 - 5.28 (m, 1 H), 6.92 - 7.40 (m, 9 H), 8.11 - 8.25 (m, 1 H)

MS ES⁺: 339

Example 2: (3R)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one

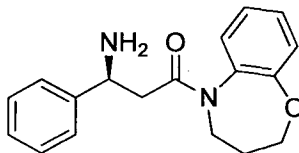


HATU (0.120 g, 0.315 mmol) was added to a solution of (3R)-3-[[*tert*-butoxy]carbonyl]amino}-3-phenylpropanoic (0.080 g, 0.30 mmol) and DIPEA (0.058 mL, 0.33 mmol) in DMF (0.5 mL) at room temperature. The mixture was stirred and allowed to stand. After 5 min, 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.045 g, 0.30 mmol) was added. The mixture was stirred at room temperature for 2h. HCl (4M in dioxane) (0.750 mL, 3.00 mmol) was added and the reaction was stirred at room temperature for 1h. The mixture was stirred at 60 °C for 1h. The mixture was basified with NaOH (2M) and extracted with DCM. The organic phase was concentrated *in vacuo* and the residue was purified by reverse phase preparative HPLC to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.68 - 2.23 (m, 5 H), 2.64 - 2.83 (m, 1 H), 3.54 - 3.73 (m, 1 H), 4.05 - 4.69 (m, 4 H), 6.94 - 7.48 (m, 9 H)

MS ES⁺: 297

Example 3: (3S)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one



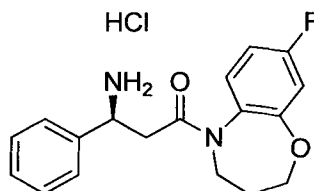
5 Prepared as described for **Example 2** using (3S)-3-[[*(tert*-butoxy)carbonyl]amino]-3-phenylpropanoic (0.080 g, 0.30 mmol) and 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.045 g, 0.30 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.68 - 2.25 (m, 6 H), 2.69 - 2.83 (m, 1 H), 3.57 - 3.75 (m, 1 H), 4.07 - 4.19 (m, 1 H), 4.24 - 4.45 (m, 1 H), 4.54 - 4.67 (m, 1 H), 6.85 - 7.53

10 (m, 9 H)

MS ES⁺: 297

Example 4: (3S)-3-amino-1-(8-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one hydrochloride



15

HATU (0.798 g, 2.10 mmol) was added to a solution of (3S)-3-[[*(tert*-butoxy)carbonyl]amino]-3-phenylpropanoic (531 mg, 2.00 mmol) and DIPEA (0.768 mL, 4.40 mmol) in DMF (5 mL). The mixture was stirred at room temperature. After 5 min, 8-fluoro-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (**Intermediate 1**, 0.334 g, 2.00 mmol)

20 was added. The mixture was stirred until homogeneous and allowed to stand for 18h. The mixture was partitioned between water and EtOAc. The organic phase was washed with water, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash chromatography (20-50% EtOAc in petroleum ether on silica) to afford *tert*-butyl N-[(1S)-3-(8-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-oxo-1-phenylpropyl]carbamate.

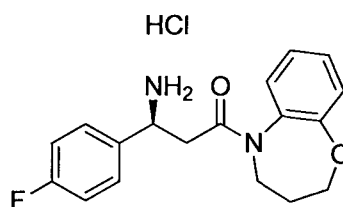
25 HCl (4M in dioxane) (3.38 mL, 13.51 mmol) was added to a solution of *tert*-butyl N-[(1S)-3-(8-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-oxo-1-phenylpropyl]carbamate (0.560 g, 1.35 mmol) in DCM (5 mL). The reaction was stirred at room temperature for

3.5h. The mixture was concentrated *in vacuo* and the residue was triturated with ether, filtered and dried. The solid was partitioned between NaOH (1M) and DCM. The aqueous phase was extracted with DCM. The combined organic phases were dried (MgSO₄) and concentrated *in vacuo*. The residue was dissolved in minimal ether and HCl (4M in dioxane, *ca.* 2 eq) was added. The resulting crystals were filtered, washing with ether and drying under vacuum to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.59 - 1.85 (m, 2 H), 1.99 - 2.18 (m, 1 H), 2.70 - 2.83 (m, 1 H), 2.89 - 3.14 (m, 1 H), 3.60 - 3.83 (m, 1 H), 3.89 - 4.20 (m, 1 H), 4.31 - 4.65 (m, 2 H), 6.83 - 7.11 (m, 2 H), 7.17 - 7.65 (m, 6 H), 8.19 - 8.51 (m, 3 H)

MS ES⁺: 315

Example 5: (3S)-3-amino-3-(4-fluorophenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one hydrochloride

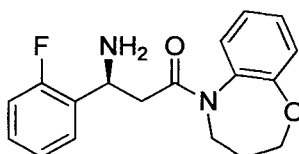


Prepared as described for **Example 4** using (3S)-3-(4-fluorophenyl)-3-([(tert-butoxy)carbonyl]amino}propanoic acid (0.567 g, 2.00 mmol) and 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.298 g, 2.00 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.62 - 1.79 (m, 1 H), 1.93 - 2.13 (m, 1 H), 2.65 - 2.83 (m, 1 H), 2.93 - 3.13 (m, 1 H), 3.58 - 3.75 (m, 1 H), 3.94 - 4.14 (m, 1 H), 4.31 - 4.75 (m, 3 H), 7.00 - 7.70 (m, 8 H), 8.24 - 8.50 (m, 3 H)

MS ES⁺: 315

Example 6: (3S)-3-amino-3-(2-fluorophenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one



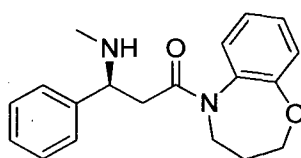
Prepared as described for **Example 2** using (3S)-3-(2-fluorophenyl)-3-([(tert-butoxy)carbonyl]amino}propanoic acid (0.567 g, 2.00 mmol) and 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.298 g, 2.00 mmol) to afford the title compound.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 1.64 - 1.91 (m, 2 H), 1.97 - 2.27 (m, 3 H), 2.65 - 2.86 (m, 1 H), 3.58 - 3.78 (m, 1 H), 4.00 - 4.27 (m, 1 H), 4.31 - 4.70 (m, 3 H), 6.93 - 7.46 (m, 8 H)

MS ES^+ : 315

5

Example 7: (3S)-3-(methylamino)-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one



A solution of methyl iodide (0.023 mL, 0.36 mmol) in DMF (0.5 mL) was added to a suspension of (3S)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one (**Example 3**, 0.089 g, 0.30 mmol) and Cs_2CO_3 (0.108 g, 0.33 mmol) in DMF (1 mL). The mixture was stirred at room temperature for 3h. The mixture was diluted with 2M NaOH and partitioned between water and EtOAc. The organic phase was concentrated *in vacuo* and the residue was purified by reverse phase preparative HPLC to afford the title compound.

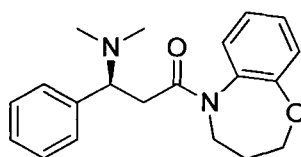
15

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 1.93 - 2.08 (m, 4 H), 2.12 - 2.30 (m, 2 H), 2.32 - 2.47 (m, 1 H), 2.58 - 2.82 (m, 1 H), 3.53 - 4.08 (m, 3 H), 4.30 - 4.69 (m, 2 H), 6.88 - 7.43 (m, 9 H)

MS ES^+ : 311

20

Example 8: (3S)-3-(dimethylamino)-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one



A solution of methyl iodide (0.023 mL, 0.36 mmol) in DMF (0.5 mL) was added to a suspension of (3S)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one (**Example 3**, 0.089 g, 0.30 mmol) and Cs_2CO_3 (0.108 g, 0.33 mmol) in DMF (1 mL). The mixture was stirred at room temperature for 3h. The mixture was diluted with 2M

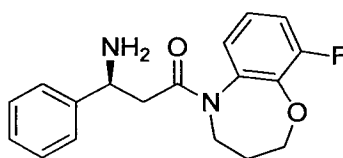
25

NaOH and partitioned between water and EtOAc. The organic phase was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.72 - 1.86 (m, 1 H), 2.04 (s, 3 H), 2.14 (s, 3 H), 2.61 - 2.90 (m, 3 H), 3.50 - 4.00 (m, 3 H), 4.46 - 4.86 (m, 2 H), 6.97 - 7.18 (m, 4 H), 7.20 - 7.28 (m, 4 H), 7.30 - 7.37 (m, 1 H)

MS ES⁺: 325

Example 9: (3S)-3-amino-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one

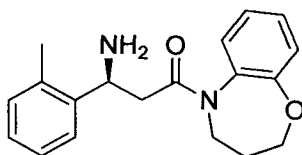


Prepared as described for **Example 2** using (3S)-3-{[(*tert*-butoxy)carbonyl]amino}-3-phenylpropanoic (0.265 g, 1.00 mmol) and 9-fluoro-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (**Intermediate 2**, 0.167 g, 1.00 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.56 - 1.88 (m, 2 H), 2.01 - 2.15 (m, 1 H), 2.71 - 2.90 (m, 1 H), 2.93 - 3.18 (m, 1 H), 3.60 - 3.86 (m, 1 H), 4.05 - 4.17 (m, 1 H), 4.39 - 4.64 (m, 2 H), 6.93 - 7.50 (m, 8 H), 8.37 (br. s., 3 H)

MS ES⁺: 315

Example 10: (3S)-3-amino-3-(2-methylphenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one

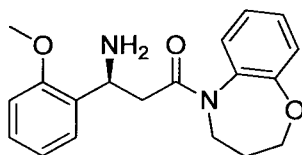


Prepared as described for **Example 2** using (3S)-3-(2-methylphenyl)-3-{[(*tert*-butoxy)carbonyl]amino}propanoic acid (0.140 g, 0.50 mmol) and 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.075 g, 0.50 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.63 - 1.94 (m, 4 H), 2.31 - 2.47 (m, 1 H), 2.66 - 2.82 (m, 1 H), 3.52 - 3.78 (m, 2 H), 4.17 - 4.43 (m, 2 H), 4.47 - 4.71 (m, 2 H), 6.93 - 7.22 (m, 7 H), 7.23 - 7.39 (m, 3 H)

MS ES⁺: 311

Example 11: (3S)-3-amino-3-(2-methoxyphenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one

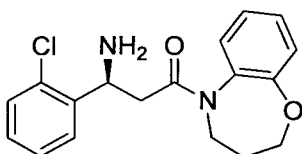


Prepared as described for **Example 2** using (3S)-3-(2-methoxyphenyl)-3-{[(*tert*-butoxy)carbonyl]amino}propanoic acid (0.148 g, 0.50 mmol) and 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.075 g, 0.50 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.66 - 1.83 (m, 1 H), 1.98 - 2.10 (m, 1 H), 2.22 - 2.42 (m, 1 H), 2.65 - 2.85 (m, 1 H), 3.58 - 3.73 (m, 4 H), 4.19 - 4.39 (m, 2 H), 4.45 - 4.70 (m, 2 H), 6.77 - 7.35 (m, 10 H)

MS ES⁺: 327

Example 12: (3S)-3-amino-3-(2-chlorophenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one

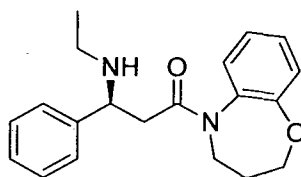


Prepared as described for **Example 2** using (3S)-3-(2-chlorophenyl)-3-{[(*tert*-butoxy)carbonyl]amino}propanoic acid (0.150 g, 0.50 mmol) and 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.075 g, 0.50 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.71 - 1.83 (m, 1 H), 2.20 - 2.45 (m, 2 H), 2.67 - 2.83 (m, 1 H), 3.62 - 3.76 (m, 1 H), 4.27 - 4.42 (m, 1 H), 4.44 - 4.55 (m, 1 H), 4.56 - 4.73 (m, 2 H), 6.97 - 7.43 (m, 9 H), 7.43 - 7.55 (m, 1 H)

MS ES⁺: 331

Example 13: (3S)-3-(ethylamino)-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one

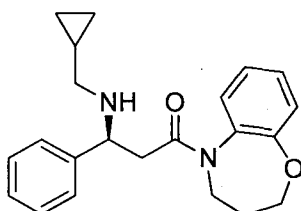


Prepared as described for **Example 7** using iodoethane (0.094 g, 0.60 mmol) and (3S)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one (**Example 3**, 0.148 g, 0.50 mmol) to afford the title compound.

- ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.81 - 0.98 (m, 3 H), 1.66 - 1.81 (m, 1 H), 1.88 - 2.45 (m, 5 H), 2.62 - 2.83 (m, 1 H), 3.51 - 3.73 (m, 1 H), 3.78 - 4.09 (m, 2 H), 4.32 - 4.68 (m, 2 H), 6.86 - 7.49 (m, 9 H)

MS ES⁺: 325

- Example 14:** (3S)-3-[(cyclopropylmethyl)amino]-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one

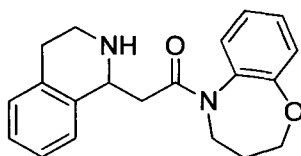


Prepared as described for **Example 7** using (bromomethyl)cyclopropane (0.081 g, 0.60 mmol) and (3S)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one (**Example 3**, 0.148 g, 0.50 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.01 - 0.06 (m, 2 H), 0.31 - 0.45 (m, 2 H), 0.75 - 0.90 (m, 1 H), 1.70 - 1.91 (m, 2 H), 2.00 - 2.40 (m, 4 H), 2.70 - 2.83 (m, 1 H), 3.56 - 3.90 (m, 2 H), 3.97 - 4.16 (m, 1 H), 4.37 - 4.69 (m, 2 H), 6.94 - 7.52 (m, 9 H)

MS ES⁺: 351

Example 15: 1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-2-(1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-one

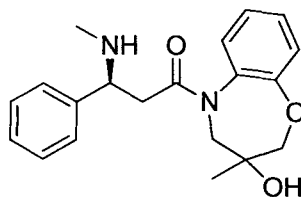


Prepared as described for **Example 2** using 2-{2-[(*tert*-butoxy)carbonyl]-1,2,3,4-tetrahydroisoquinolin-1-yl}acetic acid (0.087 g, 0.30 mmol) and 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.045 g, 0.30 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.73 - 1.85 (m, 1 H), 1.97 - 2.16 (m, 1 H), 2.23 - 2.38 (m, 1 H), 2.54 - 3.06 (m, 6 H), 3.60 - 3.82 (m, 1 H), 4.03 - 4.22 (m, 1 H), 4.25 - 4.50 (m, 2 H), 4.61 - 4.78 (m, 1 H), 6.66 - 7.48 (m, 8 H)

MS ES⁺: 323

Example 16: (3S)-1-(3-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(methylamino)-3-phenylpropan-1-one



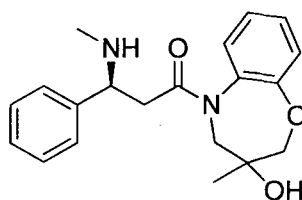
HCl (4M in dioxane, 0.062 mL, 0.246 mmol) was added to a solution of *tert*-butyl N-[(1S)-3-(3-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-oxo-1-phenylpropyl]-N-methylcarbamate (**Intermediate 8**, 0.018g, 0.041 mmol) in DCM (3 mL). The mixture was stirred at room temperature and allowed to stand for 18h. The mixture was partitioned between DCM and NaOH (1M). The organic phase was dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by reverse phase preparative HPLC to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.16 (s, 3 H), 2.20 (s, 3 H), 2.51 - 2.63 (m, 1 H), 2.68 - 2.78 (m, 1 H), 2.85 - 2.95 (m, 1 H), 3.40 - 3.58 (m, 2 H), 3.95 - 4.06 (m, 1 H), 4.88 - 4.99 (m, 1 H), 6.88 - 6.97 (m, 2 H), 7.10 - 7.16 (m, 1 H), 7.17 - 7.28 (m, 7 H), 7.30 - 7.37 (m, 1 H)

MS ES⁺: 341

Retention time: 1.24 min

Example 17: (3S)-1-(3-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(methylamino)-3-phenylpropan-1-one



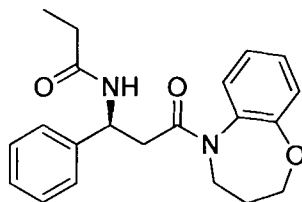
Prepared as described for **Example 16** using *tert*-butyl N-[(1S)-3-(3-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-oxo-1-phenylpropyl]-N-methylcarbamate (**Intermediate 9**, 0.029 g, 0.066 mmol) and HCl (4M in dioxane, 0.099 mL, 0.396 mmol) to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.20 (s, 3 H), 2.19 (s, 3 H), 2.36 - 2.54 (m, 2 H), 2.72 - 2.84 (m, 1 H), 3.52 - 3.59 (m, 1 H), 3.95 - 4.04 (m, 1 H), 4.07 - 4.14 (m, 1 H), 4.94 - 5.05 (m, 1 H), 5.31 (s, 1 H), 6.94 - 7.02 (m, 2 H), 7.04 - 7.15 (m, 2 H), 7.17 - 7.29 (m, 5 H), 7.30 - 7.36 (m, 1 H)

MS ES⁺: 341

Retention time: 1.22 min

Example 18: N-[(1S)-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]propanamide

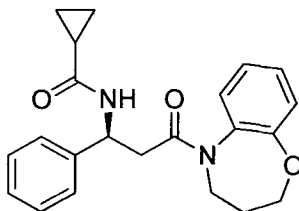


Propanoyl chloride (0.020 g, 0.22 mmol) was added to a solution of (3S)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one (**Example 3**, 0.059 g, 0.20 mmol) and DIPEA (0.038 mL, 0.22 mmol) in MeCN (1 mL). The mixture was stirred at room temperature for 30 min. The mixture was diluted with EtOH and purified by reverse phase preparative HPLC to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.79 - 1.05 (m, 3 H), 1.55 - 1.85 (m, 2 H), 1.85 - 2.17 (m, 3 H), 2.30 - 2.46 (m, 1 H), 2.59 - 2.84 (m, 2 H), 3.51 - 3.77 (m, 1 H), 3.92 - 4.42 (m, 1 H), 4.51 - 4.64 (m, 1 H), 5.17 - 5.37 (m, 1 H), 6.92 - 7.44 (m, 8 H), 8.05 - 8.19 (m, 1 H)

MS ES⁺: 353

Example 19: N-[(1S)-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]cyclopropanecarboxamide

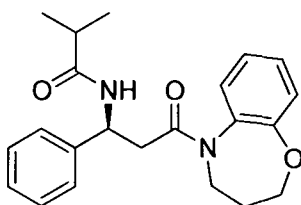


Prepared as described for **Example 18** using cyclopropanecarbonyl chloride (0.023 g, 0.22 mmol) and (3S)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one (**Example 3**, 0.059 g, 0.20 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.44 - 0.79 (m, 4 H), 1.44 - 1.56 (m, 1 H), 1.61 - 2.06 (m, 2 H), 2.31 - 2.48 (m, 1 H), 2.64 - 2.82 (m, 2 H), 3.52 - 3.80 (m, 1 H), 3.97 (d, J = 11.83 Hz, 1 H), 4.55 (d, J = 13.30 Hz, 1 H), 5.22 - 5.35 (m, 1 H), 6.94 - 7.39 (m, 9 H), 8.34 - 8.53 (m, 1 H)

MS ES⁺: 365

Example 20: 2-methyl-N-[(1S)-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]propanamide

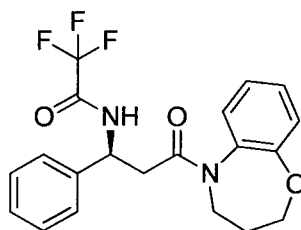


Prepared as described for **Example 18** using 2-methylpropanoyl chloride (0.023 g, 0.22 mmol) and (3S)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one (**Example 3**, 0.059 g, 0.20 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.83 - 1.04 (m, 6 H), 1.65 - 1.83 (m, 2 H), 2.22 - 2.46 (m, 2 H), 2.62 - 2.83 (m, 2 H), 3.53 - 3.77 (m, 1 H), 3.93 - 4.41 (m, 1 H), 4.52 - 4.63 (m, 1 H), 5.16 - 5.36 (m, 1 H), 6.91 - 7.38 (m, 9 H), 7.98 - 8.17 (m, 1 H)

MS ES⁺: 367

Example 21: 2,2,2-trifluoro-N-[(1S)-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]acetamide

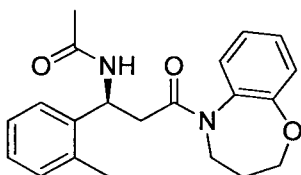


TFAA (0.050 g, 0.24 mmol) was added to a solution of (3S)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one (**Example 3**, 0.059 g, 0.20 mmol) in MeCN (1 mL). The mixture was stirred at room temperature for 5 min. Further DIPEA (0.084 mL, 0.48 mmol) was added, followed by more TFAA (0.101 g, 0.48 mmol) and the reaction was allowed to stand for 5 min. The mixture was basified (DIPEA) and purified by reverse phase preparative HPLC to afford the title compound.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.62 - 1.88 (m, 2 H), 2.63 - 2.96 (m, 2 H), 3.55 - 3.81 (m, 1 H), 3.94 - 4.16 (m, 1 H), 4.32 - 4.68 (m, 2 H), 5.20 - 5.46 (m, 1 H), 6.92 - 7.50 (m, 9 H), 9.68 - 9.90 (m, 1 H)

MS ES $^+$: 393

Example 22: N-[(1S)-1-(2-methylphenyl)-3-oxo-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]acetamide

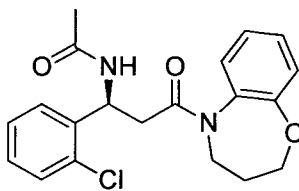


Prepared as described for **Example 18** using acetyl chloride (0.013 g, 0.165 mmol) and of (3S)-3-amino-3-(2-methylphenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one (**Example 10**, 0.047 g, 0.15 mmol) to afford the title compound.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.57 - 1.85 (m, 4 H), 1.88 - 2.10 (m, 1 H), 2.14 - 2.38 (m, 3 H), 2.61 - 2.82 (m, 2 H), 3.51 - 3.78 (m, 1 H), 3.93 - 4.09 (m, 1 H), 4.30 - 4.63 (m, 2 H), 5.33 - 5.53 (m, 1 H), 6.94 - 7.45 (m, 8 H), 8.00 - 8.21 (m, 1 H)

MS ES $^+$: 353

Example 23: N-[(1S)-1-(2-chlorophenyl)-3-oxo-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]acetamide

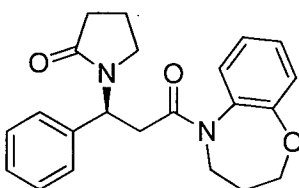


Prepared as described for **Example 18** using acetyl chloride (0.013 g, 0.17 mmol) and (3S)-3-amino-3-(2-chlorophenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one (**Example 12**, 0.050 g, 0.15 mmol) to afford the title compound.

- 5 ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.63 - 1.89 (m, 4 H), 2.23 - 2.41 (m, 1 H), 2.60 - 2.92 (m, 2 H), 3.49 - 3.85 (m, 2 H), 4.18 - 4.39 (m, 1 H), 4.49 - 4.68 (m, 1 H), 5.42 - 5.63 (m, 1 H), 6.97 - 7.56 (m, 8 H), 8.09 - 8.23 (m, 1 H)

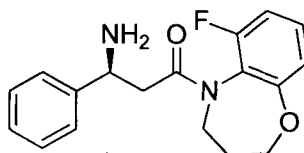
MS ES⁺: 373

- 10 **Example 24: 1-[(1S)-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]pyrrolidin-2-one**



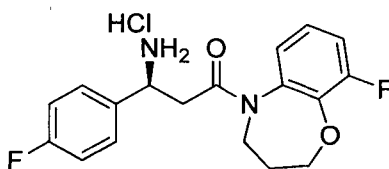
- 4-Chlorobutanoyl chloride (0.044 g, 0.32 mmol) was added to a stirred solution of (3S)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one (**Example 3**, 0.089 g, 0.30 mmol) and DIPEA (0.058 mL, 0.33 mmol) in DCM (2 mL). The mixture was stirred at room temperature for 5 min. The mixture was washed with water and the aqueous phase was extracted with DCM. The combined organic phases were dried (MgSO₄) and concentrated *in vacuo*. The residue was dissolved in DMF (2 mL). NaH (60% dispersion in mineral oil, 0.013 g, 0.33 mmol) was added and the mixture was stirred under nitrogen and then allowed to stand for 30 min. Further NaH (60% dispersion in mineral oil, 0.013 g, 0.33 mmol) was added. The mixture was stirred under nitrogen and then allowed to stand for 30 min. The mixture was diluted with EtOAc and washed with water. The organic phase was concentrated *in vacuo* and the residue was purified by reverse phase preparative HPLC to afford the title compound.

- 25 ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.17 - 1.39 (m, 1 H), 1.52 - 2.03 (m, 4 H), 2.06 - 2.27 (m, 2 H), 2.56 - 3.10 (m, 4 H), 3.52 - 3.75 (m, 1 H), 4.25 - 4.45 (m, 1 H), 4.54 - 4.74 (m, 1 H), 5.42 - 5.59 (m, 1 H), 6.81 - 7.48 (m, 9 H)

MS ES⁺: 365**Example 25: (3S)-3-amino-1-(6-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one**

HATU (0.120 g, 0.32 mmol) was added to a solution of (3S)-3-[[*tert*-butoxy)carbonyl]amino}-3-phenylpropanoic (0.080 g, 0.30 mmol) and DIPEA (0.058 mL, 0.33 mmol) in MeCN (1 mL) at room temperature. The mixture was stirred for 5 min. 6-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepine (**Intermediate 5**, 0.050 g, 0.30 mmol) was added and the reaction was stirred under nitrogen until homogeneous and allowed to stand for 48h. The reaction was heated to 40-50 °C for 1h. The mixture was partitioned between water and EtOAc. The organic phase was dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash chromatography (20-50% EtOAc in petroleum ether on silica). The resulting residue was taken up in DCM (1 mL) and treated with HCl (4M in dioxane) (0.375 mL, 1.50 mmol). The mixture was stirred at room temperature and allowed to stand for 2h. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase preparative HPLC, the combined fractions were extracted with DCM and the combined organic phases were concentrated *in vacuo* to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.07 - 1.22 (m, 1 H), 1.36 - 1.48 (m, 1 H), 1.80 - 1.90 (m, 1 H), 2.10 - 2.47 (m, 2 H), 2.49 - 2.65 (m, 1 H), 2.72 - 2.86 (m, 1 H), 3.62 - 3.81 (m, 1 H), 4.23 - 4.58 (m, 2 H), 4.81 - 4.98 (m, 1 H), 6.80 - 6.98 (m, 2 H), 7.16 - 7.28 (m, 4 H), 7.29 - 7.33 (m, 2 H)

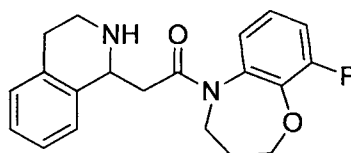
MS ES⁺: 315**Example 26: (3S)-3-amino-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(4-fluorophenyl)propan-1-one hydrochloride**

A solution of (3S)-3-(4-fluorophenyl)-3-[[*(tert*-butoxy)carbonyl]amino}propanoic acid (0.25 g, 0.882 mmol), 9-fluoro-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (**Intermediate 2**, 0.148 g, 0.882 mmol) and TEA (0.246 mL, 1.77 mmol) in DCM (5 mL) was treated with T3P (50% in EtOAc, 0.780 mL, 1.32 mmol) and stirred at room temperature for 18h. More TEA (0.246 mL, 1.77 mmol) and T3P (0.780 mL, 1.32 mmol) was added and the reaction was stirred at room temperature for a further 1h. The reaction was diluted with DCM, washed with water, dried (phase separator) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (0-50% EtOAc in petroleum ether on silica). A solution of the resulting residue in DCM (5 mL) was treated with HCl (4M in dioxane, 0.927 mL, 3.71 mmol) and stirred at room temperature for 1h. Ether was added and the precipitate was filtered and air-dried to afford the title compound.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.55 - 1.88 (m, 2 H), 1.92 - 2.21 (m, 1 H), 2.70 - 2.86 (m, 1 H), 2.92 - 3.13 (m, 1 H), 3.61 - 3.82 (m, 1 H), 4.01 - 4.22 (m, 1 H), 4.39 - 4.67 (m, 2 H), 6.91 - 7.69 (m, 7 H), 8.28 (br. s., 3 H)

MS ES⁺: 333

Examples 27 and 28: 1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-2-(1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-one



HATU (0.399 g, 1.05 mmol) was added to a solution of 2-{2-[[*(tert*-butoxy)carbonyl]-1,2,3,4-tetrahydroisoquinolin-1-yl}acetic acid (0.291 g, 1.00 mmol) and DIPEA (0.192 mL, 1.10 mmol) in DMF (1 mL) at room temperature. The mixture was stirred for 5 min and 9-fluoro-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (**Intermediate 2**, 0.167 g, 1.00 mmol) was added. The mixture was stirred until homogeneous and allowed to stand for 72h. The mixture was partitioned between water and EtOAc. The organic phase was concentrated *in vacuo* and the residue was purified by flash chromatography (20-50% EtOAc in petroleum ether on silica). The resulting residue was taken up in DCM (3 mL) and treated with HCl (4M in dioxane) (0.806 mL, 3.22 mmol). The mixture was stirred at room temperature and allowed to stand for 18h. The mixture was concentrated *in vacuo* and the resulting residue was partitioned between DCM and NaOH (0.5M). The organic phase was dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash chromatography (20-50%

EtOAc in petroleum ether on KP-NH). The resulting residue was purified by chiral SFC (ID Daicel CHIRALPAK, 34% MeOH + 0.2% diethylamine) to afford the title compounds.

Example 27: fastest running stereoisomer

¹H NMR (400 MHz, CDCl₃) δ ppm 1.79 - 1.95 (m, 1 H), 2.00 - 2.54 (m, 3 H), 2.59 - 2.97 (m, 5 H), 2.99 - 3.20 (m, 1 H), 3.70 - 3.88 (m, 1 H), 4.40 - 4.62 (m, 2 H), 4.83 - 4.96 (m, 1 H), 6.74 - 7.21 (m, 7 H)

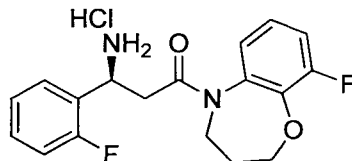
MS ES⁺: 341

Example 28: slowest running stereoisomer

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.66 - 1.95 (m, 3 H), 2.07 - 2.37 (m, 2 H), 2.54 - 2.76 (m, 4 H), 2.79 - 3.12 (m, 2 H), 3.53 - 3.79 (m, 2 H), 4.21 - 4.32 (m, 1 H), 4.97 - 5.12 (m, 1 H), 6.93 - 7.13 (m, 4 H), 7.15 - 7.27 (m, 3 H), 7.29 - 7.37 (m, 2 H)

MS ES⁺: 341

Example 29: (3S)-3-amino-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(2-fluorophenyl)propan-1-one hydrochloride

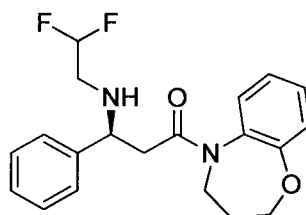


Prepared as described for **Example 26** using (3S)-3-(2-fluorophenyl)-3-[(*tert*-butoxy)carbonyl]amino}propanoic acid (0.250 g, 0.88 mmol), and 9-fluoro-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (**Intermediate 2**, 0.148 g, 0.88 mmol) to afford the title compound.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.52 - 1.94 (m, 2 H), 1.96 - 2.19 (m, 1 H), 2.56 - 2.89 (m, 2 H), 2.95 - 3.24 (m, 1 H), 3.58 - 3.85 (m, 1 H), 4.35 - 4.64 (m, 1 H), 4.71 - 4.97 (m, 1 H), 6.87 - 7.70 (m, 7 H), 8.43 (br. s., 3 H)

MS ES⁺: 333

Example 30: (3S)-3-[(2,2-difluoroethyl)amino]-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one

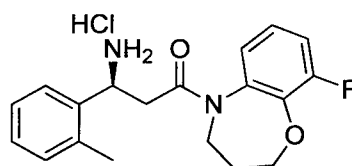


1,1-Difluoro-2-iodoethane (0.080 mL, 0.90 mmol) was added to a solution of (3S)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one (**Example 3**, 0.050 g, 0.15 mmol) and DIPEA (0.157 mL, 0.90 mmol) in MeCN (1 mL). The reaction
 5 was stirred in the microwave for 30 min at 160 °C. 1,1-Difluoro-2-iodoethane (0.080 mL, 0.90 mmol) was added and the mixture heated in the microwave at 170 °C for 45 min. The mixture was diluted with EtOAc, washed with water, dried (MgSO₄) and concentrated *in vacuo*. The resulting residue was purified by reverse phase preparative HPLC to afford the title compound.

10 ¹H NMR (400 MHz, CDCl₃) δ ppm 1.69 - 1.86 (m, 1 H), 2.08 - 2.43 (m, 3 H), 2.45 - 2.91 (m, 4 H), 3.57 - 3.78 (m, 1 H), 3.96 - 4.48 (m, 2 H), 4.77 - 4.90 (m, 1 H), 5.53 - 5.95 (m, 1 H), 6.87 - 7.27 (m, 8 H), 7.28 - 7.36 (m, 1 H)

MS ES⁺: 361

15 **Example 31: (3S)-3-amino-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(2-methylphenyl)propan-1-one hydrochloride**

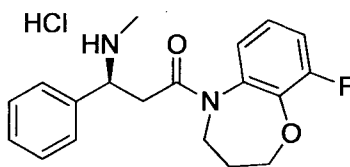


Prepared as described for **Example 26** using (3S)-3-(2-methylphenyl)-3-([(tert-butoxy)carbonyl]amino}propanoic acid (0.25 g, 0.90 mmol) and 9-fluoro-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (**Intermediate 2**, 0.15 g, 0.90 mmol) to afford the title
 20 compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.44 - 1.79 (m, 2 H), 1.79 - 2.09 (m, 1 H), 2.22 - 2.38 (m, 3 H), 2.57 - 2.78 (m, 1 H), 2.86 - 3.10 (m, 1 H), 3.51 - 3.78 (m, 1 H), 3.90 - 4.10 (m, 1 H), 4.32 - 4.53 (m, 1 H), 4.62 - 4.87 (m, 1 H), 6.80 - 7.42 (m, 7 H), 8.20 (br. s., 3 H)

25 MS ES⁺: 329

Example 32: (3S)-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(methylamino)-3-phenylpropan-1-one hydrochloride



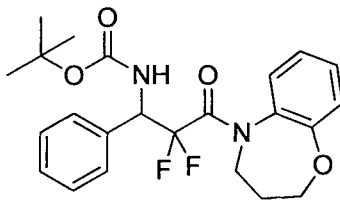
Prepared as described for **Example 4** using (3S)-3-{{(*tert*-

butoxy)carbonyl](methyl)amino}-3-phenylpropanoic acid (**Intermediate 3**, 0.263 g, 0.94 mmol) and 9-fluoro-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (**Intermediate 2**, 0.157 g, 0.94 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.42 - 1.88 (m, 2 H), 2.25 - 2.43 (m, 3 H), 2.56 - 2.88 (m, 2 H), 3.00 - 3.28 (m, 1 H), 3.53 - 4.09 (m, 2 H), 4.36 - 4.61 (m, 2 H), 6.86 - 7.68 (m, 8 H), 8.79 - 9.25 (m, 2 H)

MS ES⁺: 329

Example 33: *tert*-butyl N-[2,2-difluoro-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]carbamate

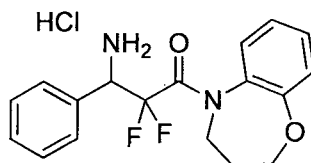


HATU (0.28 g, 0.730 mmol) was added to a solution of 3-((*tert*-butoxycarbonyl)amino)-2,2-difluoro-3-phenylpropanoic acid (**Intermediate 6**, 0.20 g, 0.66 mmol) and pyridine (0.054 mL, 0.66 mmol) in DMF (1 mL) under nitrogen. After 10 min 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.099 g, 0.66 mmol) was added. The reaction was stirred at room temperature for 24h. The crude reaction mixture was diluted with DCM (10 mL) and washed with saturated sodium bicarbonate solution. The organic phase was washed with water, dried (phase separator) and concentrated *in vacuo*. The crude product was purified by reverse phase preparative HPLC to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.25 - 1.43 (m, 9 H), 1.62 - 1.84 (m, 1 H), 2.78 - 2.93 (m, 1 H), 3.49 - 3.73 (m, 1 H), 3.81 - 4.15 (m, 2 H), 4.36 - 4.58 (m, 1 H), 5.35 - 5.56 (m, 1 H), 5.76 (s, 1 H), 7.01 - 7.16 (m, 3 H), 7.17 - 7.47 (m, 6 H)

MS ES⁺: 433

Example 34: 3-amino-2,2-difluoro-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one hydrochloride

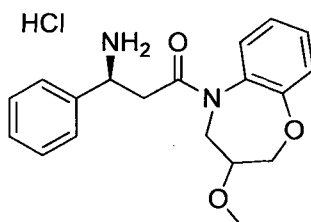


HCl (4M in dioxane, 0.31 mL, 1.249 mmol) was added to a solution of *tert*-butyl N-[2,2-difluoro-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]carbamate (**Example 33**, 0.090 g, 0.21 mmol) in dioxane (0.5 mL) under nitrogen. The reaction was heated to 100 °C for 10 min. The reaction was concentrated *in vacuo* and dried at 80 °C under vacuum to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.42 - 1.59 (m, 1 H), 1.62 - 1.84 (m, 1 H), 2.78 - 2.99 (m, 1 H), 3.52 - 3.73 (m, 1 H), 3.88 - 4.12 (m, 1 H), 4.32 - 4.56 (m, 1 H), 5.11 - 5.38 (m, 1 H), 6.77 - 7.68 (m, 9 H), 8.58 - 9.09 (m, 3 H)

MS ES⁺: 333

Example 35: (3S)-3-amino-1-(3-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one hydrochloride

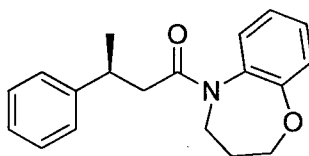


Prepared as described for **Example 34** using 3-methoxy-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.20 g, 1.12 mmol) and (3S)-3-[(*tert*-butoxy)carbonyl]amino}-3-phenylpropanoic (0.31 g, 1.12 mmol) to afford the title compound.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 2.60 - 2.86 (m, 1 H), 3.11 - 3.42 (m, 6 H), 3.59 - 3.81 (m, 1 H), 4.05 - 4.43 (m, 1 H), 4.53 - 5.09 (m, 2 H), 6.92 - 7.65 (m, 9 H), 8.29 - 8.59 (m, 3 H)

MS ES⁺: 327

Example 36: (3S)-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)butan-1-one

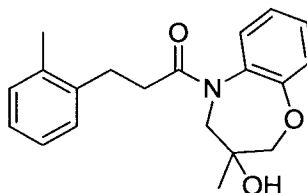


HATU (0.12 g, 0.32 mmol) was added to a solution of (3S)-3-phenylbutanoic acid (49.3 mg, 0.30 mmol) and DIPEA (0.058 mL, 0.33 mmol) in DMF (1 mL) at room temperature. The mixture was stirred for 5 minutes. 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.045 mg, 0.30 mmol) was added. The mixture was stirred until homogeneous and allowed to stand for 2h. The reaction mixture was purified by reverse phase preparative HPLC to afford the title compound.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.94 - 1.32 (m, 3 H), 1.68 - 1.82 (m, 1 H), 1.93 - 2.18 (m, 1 H), 2.26 - 2.49 (m, 2 H), 2.65 - 2.85 (m, 1 H), 2.93 - 3.25 (m, 1 H), 3.54 - 3.78 (m, 1 H), 4.05 - 4.43 (m, 1 H), 4.53 - 4.68 (m, 1 H), 6.88 - 7.39 (m, 9 H)

MS ES^+ : 296

Example 37: 1-(3-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(2-methylphenyl)propan-1-one



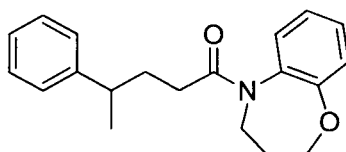
Oxalyl chloride (0.180 mL, 2.05 mmol) was added to a solution of 3-(2-methylphenyl)propanoic acid (0.224 g, 1.37 mmol) in DCM (2 mL). A drop of DMF was added to the reaction. The mixture was stirred at room temperature and allowed to stand. After *ca.* 1.5 h the mixture was concentrated *in vacuo* whilst maintaining the temperature below 30 °C, adding DCM to assist removal of oxalyl chloride. The residue was dissolved in DCM (*ca.* 2 mL) and added dropwise to a solution of 3-methyl-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ol (0.350 g, 1.37 mmol) and DIPEA (0.358 mL, 2.05 mmol) in DCM (2 mL) at 0 °C. The reaction was allowed to warm to room temperature for 24h. The crude reaction mixture was diluted with DCM and washed with saturated sodium bicarbonate solution. The organic phase was collected, washed with water, dried (phase separator) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-50% EtOAc in petroleum ether on silica). The crude mixture was

further purified by flash chromatography (0-50% EtOAc in petroleum ether on silica) to afford the title compound.

¹H NMR (300 MHz, CDCl₃) δ ppm 1.20 (s, 3 H), 2.15 (s, 3 H), 2.47 - 2.64 (m, 2 H), 2.77 - 3.01 (m, 3 H), 3.43 - 3.55 (m, 2 H), 3.93 - 4.08 (m, 1 H), 4.80 - 4.95 (m, 1 H), 6.97 - 7.18 (m, 7 H), 7.23 - 7.27 (m, 1 H)

MS ES⁺: 326

Example 38: 4-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)pentan-1-one

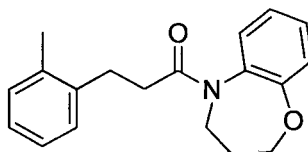


Prepared as described for **Example 36** using 4-phenylpentanoic acid (0.054 g, 0.30 mmol) and 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.045 g, 0.300 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.97 - 1.14 (m, 3 H), 1.55 - 1.87 (m, 4 H), 1.91 - 2.08 (m, 2 H), 2.52 - 2.60 (m, 1 H), 2.63 - 2.76 (m, 1 H), 3.56 - 3.71 (m, 1 H), 4.27 - 4.42 (m, 1 H), 4.55 - 4.67 (m, 1 H), 6.94 - 7.37 (m, 9 H)

MS ES⁺: 310

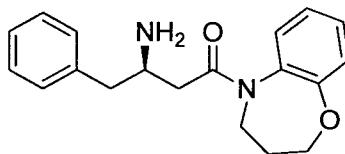
Example 39: 3-(2-methylphenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one



Prepared as described for **Example 36** using 3-(2-methylphenyl)propanoic acid (0.050 g, 0.30 mmol) and 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.045 g, 0.30 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.69 - 1.82 (m, 1 H), 1.90 - 2.20 (m, 5 H), 2.32 - 2.47 (m, 1 H), 2.60 - 2.91 (m, 3 H), 3.59 - 3.78 (m, 1 H), 4.28 - 4.38 (m, 1 H), 4.55 - 4.71 (m, 1 H), 6.85 - 6.99 (m, 1 H), 6.99 - 7.21 (m, 5 H), 7.22 - 7.34 (m, 2 H)

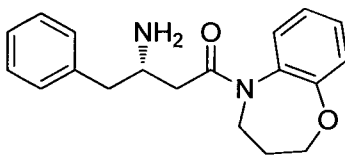
MS ES⁺: 296

Example 40: (3R)-3-amino-4-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)butan-1-one

Prepared as described for **Example 2** using (3R)-3-{[(*tert*-butoxy)carbonyl]amino}-4-phenylbutanoic acid (0.084 g, 0.30 mmol) and 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.045 g, 0.30 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.37 - 1.49 (m, 1 H), 1.69 - 2.08 (m, 4 H), 2.11 - 2.45 (m, 3 H), 2.67 - 2.80 (m, 1 H), 3.11 - 3.26 (m, 1 H), 3.59 - 3.76 (m, 1 H), 4.30 - 4.47 (m, 1 H), 4.57 - 4.71 (m, 1 H), 6.96 - 7.38 (m, 9 H)

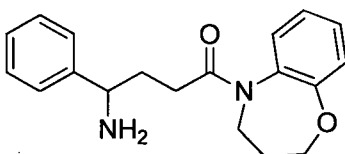
MS ES⁺: 311

Example 41: (3S)-3-amino-4-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)butan-1-one

Prepared as described for **Example 2** using (3S)-3-{[(*tert*-butoxy)carbonyl]amino}-4-phenylbutanoic acid (0.084 g, 0.30 mmol) and 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.045 g, 0.30 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.29 - 1.50 (m, 2 H), 1.70 - 2.09 (m, 3 H), 2.13 - 2.45 (m, 2 H), 2.56 - 2.82 (m, 2 H), 3.15 - 3.26 (m, 1 H), 3.60 - 3.77 (m, 1 H), 4.33 - 4.43 (m, 1 H), 4.58 - 4.69 (m, 1 H), 6.96 - 7.34 (m, 9 H)

MS ES⁺: 311

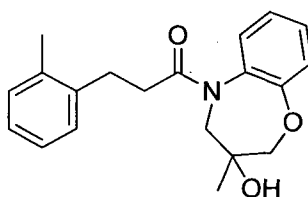
Example 42: 4-amino-4-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)butan-1-one

Prepared as described for **Example 2** using 4-[[*tert*-butoxy]carbonyl]amino}-4-phenylbutanoic acid (0.084 g, 0.30 mmol) and 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.045 g, 0.30 mmol) to afford the title compound.

¹H NMR (300 MHz, CDCl₃) δ ppm 1.70 - 2.11 (m, 4 H), 2.12 - 2.34 (m, 2 H), 2.75 (br. s., 1 H), 3.61 - 3.91 (m, 2 H), 4.44 (br. s., 1 H), 4.82 (br. s., 1 H), 6.96 - 7.27 (m, 9 H)

MS ES⁺: 311

Examples 43 and 44: 1-(3-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(2-methylphenyl)propan-1-one



Oxalyl chloride (0.180 mL, 2.05 mmol) was added to a solution of 3-(2-methylphenyl)propanoic acid (0.224 g, 1.37 mmol) in DCM (2 mL). A drop of DMF was added to accelerate the reaction. The mixture was stirred at room temperature and allowed to stand. After *ca.* 1.5h the mixture was concentrated *in vacuo* while maintaining the temperature below 30 °C. The residue was dissolved in DCM (2 mL) and added drop wise to a solution of 3-methyl-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ol (0.350 g, 1.37 mmol) and DIPEA (0.358 mL, 2.05 mmol) in DCM (2 mL) at 0 °C and the reaction was allowed to warm to room temperature for 24h. The crude reaction mixture was diluted with DCM, washed with saturated sodium bicarbonate solution, followed by water, dried (phase separator) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-50% EtOAc in petroleum ether on silica). The crude product was further purified by flash chromatography (0-50% EtOAc in petroleum ether on silica). The resulting residue was purified by chiral SFC (AD Daicel CHIRALPAK, 18% MeOH) to afford the title compounds.

Example 43: fastest running enantiomer

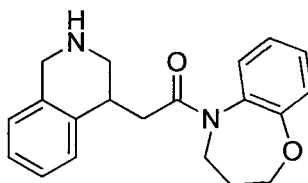
¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 0.93 - 1.28 (m, 3 H), 2.06 (s, 3 H), 2.16 - 2.35 (m, 1 H), 2.37 - 2.48 (m, 1 H), 2.58 - 2.95 (m, 2 H), 3.20 - 3.31 (m, 1 H), 3.77 - 4.02 (m, 1 H), 4.55 - 4.79 (m, 1 H), 4.85 - 5.35 (m, 1 H), 6.82 - 7.38 (m, 8 H)

MS ES⁺: 326

Example 44: slowest running enantiomer

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 0.98 - 1.24 (m, 3 H), 2.01 - 2.34 (m, 3 H), 2.39 - 2.48 (m, 1 H), 2.59 - 3.03 (m, 3 H), 3.18 - 3.31 (m, 1 H), 3.75 - 4.02 (m, 1 H), 4.47 - 4.81 (m, 1 H), 4.97 - 5.26 (m, 1 H), 6.83 - 7.34 (m, 8 H)

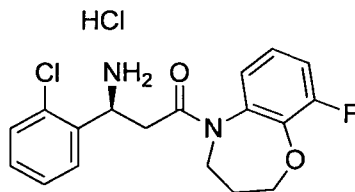
5 MS ES⁺: 326

Example 45: 1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-2-(1,2,3,4-tetrahydroisoquinolin-4-yl)ethan-1-one

10 Prepared as described for **Example 2** using 2-{2-[(*tert*-butoxy)carbonyl]-1,2,3,4-tetrahydroisoquinolin-4-yl}acetic acid (0.291 g, 1.00 mmol) and 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.149 g, 1.00 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.69 - 1.86 (m, 1 H), 1.89 - 2.15 (m, 1 H), 2.17 - 2.43 (m, 1 H), 2.62 - 2.97 (m, 2 H), 3.07 - 3.52 (m, 3 H), 3.62 - 3.79 (m, 1 H), 3.90 - 4.10 (m, 2 H), 4.27 - 4.46 (m, 1 H), 4.58 - 4.74 (m, 1 H), 6.69 - 7.65 (m, 9 H)

15 MS ES⁺: 323

Example 46: (3S)-3-amino-3-(2-chlorophenyl)-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one hydrochloride

20

HATU (0.523 g, 1.376 mmol) was added to a solution of (3S)-3-(2-chlorophenyl)-3-[[*tert*-butoxy]carbonyl]amino}propanoic acid (0.375 g, 1.251 mmol), 9-fluoro-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (0.209 g, 1.251 mmol) and DIPEA (0.240 mL, 1.376 mmol) in DMF (1.50 mL). The reaction was stirred at room temperature for 72h. The mixture was partitioned between DCM and saturated NaHCO₃ solution. The phases were separated and the aqueous extracted with DCM. The combined organics were concentrated *in vacuo*. The crude product was purified by flash chromatography (0-50% EtOAc in

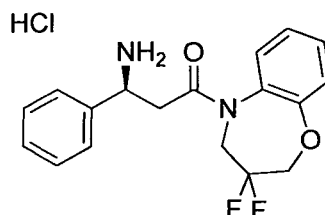
25

petroleum ether on silica). The resulting residue was taken up in DCM (5 mL) under nitrogen gas and HCl (4 M in dioxane) (1.20 mL, 4.80 mmol) was added. The reaction was stirred at room temperature for 3 hours. The reaction mixture was concentrated under a stream of dry nitrogen. The material was loaded onto a SCX cartridge, washed with methanol and eluted with 2M ammonia/methanol solution then concentrated *in vacuo*. The residue was dissolved in DCM (5 mL) and HCl (4 M in dioxane) (0.5 mL, 2.000 mmol) was added. The mixture was stirred at room temperature for 15 min, then concentrated *in vacuo* and triturated with diethyl ether to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.67 - 1.85 (m, 1 H), 1.94 - 2.17 (m, 1 H), 2.56 - 2.86 (m, 2 H), 3.00 - 3.20 (m, 1 H), 3.63 - 3.84 (m, 1 H), 4.18 - 4.62 (m, 2 H), 4.88 - 5.13 (m, 1 H), 6.85 - 7.71 (m, 7 H), 8.51 (br. s., 3 H)

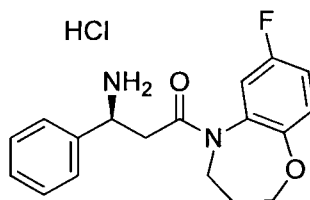
MS ES⁺: 349

Example 47: (3S)-3-amino-1-(3,3-difluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one hydrochloride



DAST (1.803 mL, 13.64 mmol) was added to a solution of *tert*-butyl N-[(1S)-3-oxo-3-(3-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-1-phenylpropyl]carbamate (**Intermediate 11**, 0.560 g, 1.364 mmol) in DCM (10 mL) under nitrogen. The reaction was stirred at room temperature for 24h. The reaction was cooled to 0 °C and quenched with water. The mixture was diluted with DCM, washed with water, dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-50% EtOAc in petroleum ether on silica). The residue was taken up in dioxane (1 mL) under nitrogen gas and HCl (4M in dioxane) (0.656 mL, 2.62 mmol) was added. The reaction was stirred at 80 °C for 1h. The reaction was concentrated *in vacuo* and dried under vacuum at 80 °C for 30 min to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.52 - 2.66 (m, 1 H), 3.01 - 3.26 (m, 1 H), 3.74 - 4.29 (m, 2 H), 4.35 - 4.70 (m, 2 H), 4.82 - 5.08 (m, 1 H), 7.03 - 7.58 (m, 9 H), 8.32 (br. s., 3 H)

MS ES⁺: 333**Example 48: (3S)-3-amino-1-(7-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one hydrochloride**

5

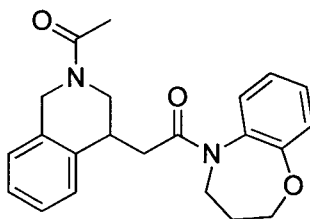
HATU (0.399 g, 1.05 mmol) was added to a solution of (3S)-3-[(*tert*-butoxy)carbonyl]amino}-3-phenylpropanoic (0.265 g, 1.00 mmol) and DIPEA (0.192 mL, 1.10 mmol) in DMF (3 mL) at room temperature. The mixture was stirred for 5 min. 7-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepine (**Intermediate 12**, 0.167 g, 1.00 mmol) was added. The mixture was stirred until homogeneous and allowed to stand for 18h. The mixture was partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with water, dried (MgSO₄) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (20-50% EtOAc in petroleum ether on silica). The resulting residue was dissolved in DCM (5 mL). HCl (4M in dioxane) (1.00 mL, 4.00 mmol) was added and the mixture stirred and allowed to stand for 18h. The mixture was concentrated *in vacuo* to afford the title compound.

10

15

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.66 - 2.39 (m, 5 H), 2.54 - 2.64 (m, 1 H), 2.66 - 2.85 (m, 1 H), 3.51 - 3.75 (m, 1 H), 3.92 - 4.44 (m, 3 H), 4.51 - 4.71 (m, 1 H), 6.93 - 7.49 (m, 8 H)

20

MS ES⁺: 315**Example 49: 2-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)ethan-1-one**

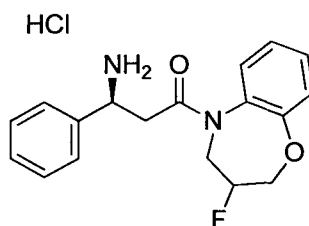
25

Acetyl chloride (0.026 g, 0.330 mmol) was added to a solution of 1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-2-(1,2,3,4-tetrahydroisoquinolin-4-yl)ethan-1-one (Example 45, 0.097 g, 0.300 mmol) and DIPEA (0.063 mL, 0.360 mmol) in DCM (1 mL) and stirred at room temperature for 1h. The mixture was partitioned between water and DCM. The organic phase was concentrated *in vacuo* and the residue was purified by reverse phase preparative HPLC to afford the title compound.

¹H NMR (400 MHz, DMSO) δ ppm 1.70 - 1.86 (m, 1 H), 1.87 - 2.17 (m, 4 H), 2.29 - 2.48 (m, 1 H), 2.66 - 2.88 (m, 1 H), 2.93 - 3.24 (m, 1 H), 3.34 - 3.52 (m, 1 H), 3.56 - 3.88 (m, 2 H), 4.03 - 4.58 (m, 3 H), 4.59 - 4.80 (m, 2 H), 6.86 - 7.42 (m, 8 H)

MS ES⁺: 365

Example 50: (3S)-3-amino-1-(3-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one hydrochloride

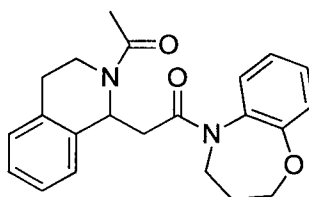


HCl (4M in dioxane) (0.145 mL, 0.579 mmol) was added to a solution of *tert*-butyl N-[(1S)-3-(3-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-oxo-1-phenylpropyl]carbamate (**Intermediate 14**, 0.040 g, 0.097 mmol) in dioxane (0.3 mL) under nitrogen. The reaction was stirred at room temperature for 18h. The reaction was concentrated *in vacuo* to afford the title compound upon drying at 100 °C in a vacuum oven.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.82 - 3.11 (m, 2 H), 3.63 - 3.92 (m, 2 H), 4.39 - 4.67 (m, 2 H), 4.77 - 5.13 (m, 2 H), 6.91 - 7.65 (m, 9 H), 8.14 - 8.50 (m, 3 H)

MS ES⁺: 315

Example 51: 2-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)ethan-1-one

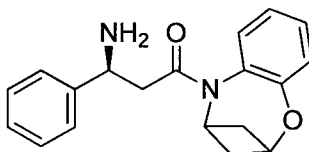


Acetyl chloride (0.007 g, 0.092 mmol) was added to a solution of 1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-2-(1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-one (**Example 15**, 0.027 g, 0.084 mmol) and DIPEA (0.018 mL, 0.100 mmol) in MeCN (1 mL). The mixture was stirred at room temperature for 30 min. The reaction mixture was purified by reverse phase preparative HPLC to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.70 - 1.93 (m, 1 H), 2.11 - 3.03 (m, 10 H), 3.51 - 3.80 (m, 2 H), 4.35 - 4.49 (m, 1 H), 4.80 - 4.97 (m, 1 H), 5.40 - 5.68 (m, 1 H), 6.74 - 7.28 (m, 8 H)

MS ES⁺: 365

Example 52: (3S)-amino-1-{3,4-dihydro-2,4-methanobenzo[b][1,4]oxazepin-5-yl}-3-phenylpropan-1-one

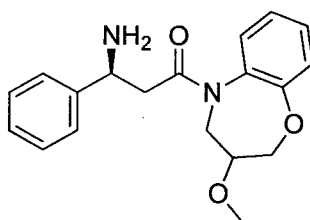


Prepared as described for **Example 2**, using (3S)-3-{{(*tert*-butoxy)carbonyl}amino}-3-phenylpropanoic (0.117 g, 0.44 mmol) and 2,3,4,5-tetrahydro-2,4-methanobenzo[b][1,4]oxazepine (**Intermediate 15**, 0.071 g, 0.440 mmol) to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.36 - 1.50 (m, 2 H), 1.76 - 2.01 (m, 2 H), 2.46 - 2.64 (m, 2 H), 2.65 - 2.79 (m, 2 H), 4.35 - 4.50 (m, 1 H), 4.78 - 5.00 (m, 2 H), 6.94 - 7.26 (m, 7 H), 7.27 - 7.40 (m, 2 H)

MS ES⁺: 309

Examples 53 and 54: (3S)-3-amino-1-(3-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one



Example 35 was purified by chiral SFC (AD Daicel CHIRALPAK, 20% EtOH and 0.2% DEA) to afford the title compounds.

5 **Example 53: fastest running isomer**

¹H NMR (400 MHz, CDCl₃) δ ppm 2.38 - 2.52 (m, 1 H), 2.54 - 2.76 (m, 2 H), 3.36 - 3.83 (m, 6 H), 4.02 - 4.16 (m, 1 H), 4.36 - 4.63 (m, 2 H), 4.89 - 5.09 (m, 1 H), 6.89 - 7.11 (m, 2 H), 7.12 - 7.27 (m, 5 H), 7.29 - 7.39 (m, 2 H)

MS ES⁺: 327

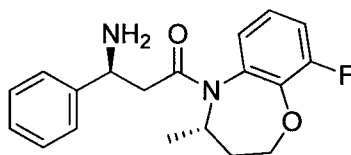
10

Example 54: slowest running isomer

¹H NMR (400 MHz, CDCl₃) δ ppm 2.35 - 2.89 (m, 4 H), 3.39 - 3.84 (m, 6 H), 4.24 - 4.56 (m, 2 H), 4.94 - 5.11 (m, 1 H), 6.85 - 7.04 (m, 2 H), 7.07 - 7.26 (m, 5 H), 7.28 - 7.33 (m, 2 H)

15 MS ES⁺: 327

Example 55: (3S)-3-amino-1-[(4S)-9-fluoro-4-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl]-3-phenylpropan-1-one



20 A solution/suspension of *tert*-butyl ((S)-3-(((S)-4-(2-bromo-6-fluorophenoxy)butan-2-yl)amino)-3-oxo-1-phenylpropyl)carbamate (**Intermediate 16**, 0.050 g, 0.098 mmol) and bis(3,5-bis(trifluoromethyl)phenyl)(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (0.016 g, 0.020 mmol) in toluene (3 mL) was degassed and purged with nitrogen (3 times). Sodium *tert*-butoxide (0.019 g, 0.196 mmol) and Pd₂(dba)₃ (0.009 g, 9.82 μmol) were added. The mixture, now a deep crimson colour, was degassed and purged (3 times) again. The mixture was heated at 100 °C for 4h. The mixture was partitioned between water and EtOAc. The organic phase was collected, dried (MgSO₄)

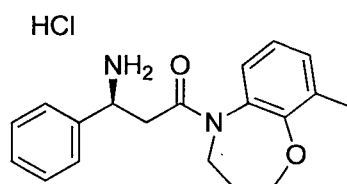
25

and concentrated *in vacuo*. The residue was purified by flash chromatography (20-50% EtOAc in petroleum ether). The resulting residue was dissolved in DCM (0.5 mL) and HCl (4 M in dioxane) (0.1 mL, 0.40 mmol) was added. The reaction was stirred at room temperature for 1h. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase preparative HPLC to afford the title compound.

¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 1.03 (d, *J* = 6.69 Hz, 3 H), 1.52 - 1.62 (m, 2 H), 2.03 - 2.10 (m, 1 H), 2.37 - 2.44 (m, 1 H), 2.59 - 2.65 (m, 1 H), 4.00 - 4.05 (m, 3 H), 4.28 - 4.33 (m, 1 H), 6.87 - 6.93 (m, 1 H), 6.99 - 7.10 (m, 2 H), 7.12 - 7.35 (m, 6 H)

MS ES⁺: 329

Example 56: (3S)-3-amino-1-(9-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one hydrochloride

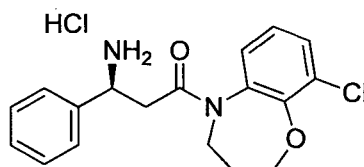


Prepared as described for **Example 4** using (3S)-3-{[(*tert*-butoxy)carbonyl]amino}-3-phenylpropanoic (0.265 g, 1.0 mmol) and 9-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepine (**Intermediate 17**, 0.163 g, 1.0 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.60 - 1.81 (m, 2 H), 2.13 - 2.28 (m, 3 H), 2.43 - 2.49 (m, 1 H), 2.64 - 2.80 (m, 1 H), 2.91 - 3.19 (m, 1 H), 3.46 - 3.68 (m, 1 H), 4.05 - 4.44 (m, 1 H), 4.48 - 4.67 (m, 2 H), 6.87 - 7.26 (m, 3 H), 7.29 - 7.52 (m, 5 H), 8.25 - 8.53 (m, 3 H)

MS ES⁺: 311

Example 57: (3S)-3-amino-1-(9-chloro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one hydrochloride



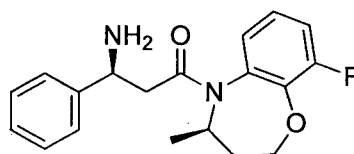
Prepared as described for **Example 4** using (3S)-3-{[(*tert*-butoxy)carbonyl]amino}-3-phenylpropanoic (0.265 g, 1.0 mmol) and 9-chloro-2,3,4,5-tetrahydro-1,5-benzoxazepine (**Intermediate 18**, 0.184 g, 1.0 mmol) to afford the title compound.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.63 - 1.83 (m, 1 H), 2.53 - 2.61 (m, 1 H), 2.70 - 3.22 (m, 2 H), 3.31 - 3.37 (m, 2 H), 3.60 - 3.80 (m, 1 H), 4.41 - 4.72 (m, 2 H), 7.04 - 7.24 (m, 2 H), 7.27 - 7.65 (m, 6 H), 8.25 - 8.69 (m, 3 H)

MS ES $^+$: 331

5

Example 58: (3S)-3-amino-1-[(4R)-9-fluoro-4-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl]-3-phenylpropan-1-one



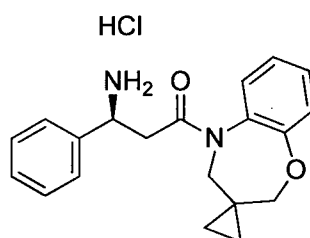
Prepared as described for **Example 55** using *tert*-butyl N-[(1S)-2-{[(2R)-4-(2-bromo-6-fluorophenoxy)butan-2-yl]carbamoyl}-1-phenylethyl]carbamate (**Intermediate 19**, 0.06 g, 0.118 mmol) to afford the title compound.

^1H NMR (400 MHz, Methanol- d_4) δ ppm 0.94 - 1.07 (m, 3 H), 1.56 - 1.66 (m, 1 H), 2.12 - 2.21 (m, 1 H), 2.30 - 2.38 (m, 1 H), 2.56 - 2.63 (m, 1 H), 4.11 - 4.18 (m, 1 H), 4.30 - 4.44 (m, 3 H), 4.91 - 5.01 (m, 1 H), 6.52 - 6.62 (m, 1 H), 6.93 - 7.03 (m, 1 H), 7.10 - 7.45 (m, 7 H)

15

MS ES $^+$: 329

Example 59: (3S)-3-amino-1-{4,5-dihydro-2H-spiro[1,5-benzoxazepine-3,1'-cyclopropane]-5-yl}-3-phenylpropan-1-one hydrochloride



20

Prepared as described for **Example 4** using 4,5-dihydro-2H-spiro[1,5-benzoxazepine-3,1'-cyclopropane] (**Intermediate 20**, 0.22g, 1.19 mmol) and (3S)-3-[(*tert*-butoxy)carbonyl]amino}-3-phenylpropanoic (0.316 g, 1.193 mmol) to afford the title compound.

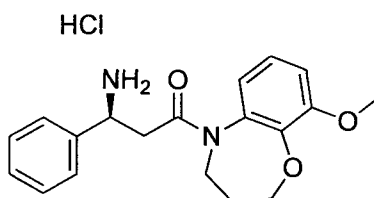
25

^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.21 - 0.50 (m, 3 H), 0.53 - 0.84 (m, 1 H), 2.51 - 2.61 (m, 1 H), 2.87 - 3.10 (m, 2 H), 3.45 - 3.68 (m, 1 H), 3.73 - 3.80 (m, 1 H), 4.04 - 4.21

(m, 1 H), 4.51 - 4.66 (m, 1 H), 6.99 - 7.21 (m, 3 H), 7.28 - 7.47 (m, 6 H), 8.19 - 8.44 (m, 3 H)

MS ES⁺: 323

5 **Example 60: (3S)-3-amino-1-(9-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one hydrochloride**

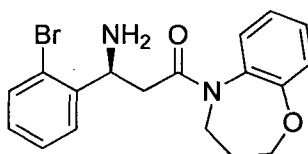


Prepared as described for **Example 4** using 9-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepine (**Intermediate 21**, 0.180 g, 1.00 mmol) and (3S)-3-[[(*tert*-butoxy)carbonyl]amino}-3-phenylpropanoic (0.265 g, 1.00 mmol) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.63 - 1.77 (m, 1 H), 2.09 (s, 1 H), 2.44 - 2.49 (m, 1 H), 2.65 - 2.78 (m, 1 H), 2.92 - 3.13 (m, 1 H), 3.46 - 3.63 (m, 1 H), 3.73 - 3.87 (m, 3 H), 4.10 - 4.42 (m, 1 H), 4.46 - 4.67 (m, 2 H), 6.64 - 6.78 (m, 1 H), 6.86 - 6.94 (m, 1 H), 7.00 - 7.15 (m, 2 H), 7.27 - 7.48 (m, 4 H), 8.24 - 8.57 (m, 3 H)

MS ES⁺: 327

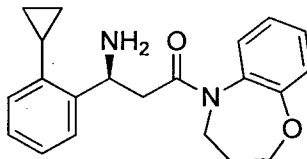
Example 61: (3S)-3-amino-3-(2-bromophenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one



20 A solution of *tert*-butyl N-[(1S)-1-(2-bromophenyl)-3-oxo-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]carbamate (**Intermediate 22**, 0.143 g, 0.10 mmol) in MeOH (3 mL) was treated with HCl (4 M in dioxane) (0.30 ml, 1.200 mmol). The mixture was stirred and allowed to stand for 4h. The mixture was concentrated *in vacuo* and the resulting residue was purified by reverse phase preparative HPLC to afford the title compound.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.66 - 1.87 (m, 1 H), 1.88 - 2.13 (m, 3 H), 2.18 - 2.44 (m, 1 H), 2.52 - 2.61 (m, 1 H), 2.65 - 2.88 (m, 1 H), 3.56 - 3.80 (m, 1 H), 4.22 - 4.73 (m, 3 H), 6.93 - 7.81 (m, 8 H) MS ES^+ : 375

5 **Example 62: (3S)-3-amino-3-(2-cyclopropylphenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one**



A mixture of *tert*-butyl N-[(1S)-1-(2-bromophenyl)-3-oxo-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]carbamate (**Intermediate 22**, 0.143 g, 0.3 mmol),
 10 cyclopropylboronic acid (0.039 g, 0.450 mmol), tripotassium phosphate (0.191 g, 0.900 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.010 g, 0.009 mmol) was dissolved in toluene (5 mL). Water (0.25 mL) was added and mixture was heated at 120 °C for 20 minutes in the microwave. The mixture was partitioned between water and EtOAc. The organic phase was dried (MgSO_4) and concentrated *in vacuo*. The resulting residue was
 15 purified by flash chromatography (20-50% EtOAc in petroleum ether on silica). The residue was further purified by flash chromatography (20-30% EtOAc in petroleum ether on silica). This material was dissolved in MeOH (3 mL) and HCl (4 M in dioxane) (0.30 mL, 1.200 mmol) was added. The mixture was stirred and allowed to stand for 4h. The mixture was concentrated *in vacuo* and the residue was purified reverse phase preparative
 20 HPLC to afford the title compound

^1H NMR (400 MHz, CDCl_3) δ ppm 0.46 - 0.76 (m, 2 H), 0.79 - 1.04 (m, 2 H), 1.66 - 1.76 (m, 1 H), 1.83 (s, 3 H), 2.17 - 2.40 (m, 1 H), 2.41 - 2.71 (m, 2 H), 2.73 - 2.91 (m, 1 H), 3.62 - 3.83 (m, 1 H), 4.31 - 4.50 (m, 1 H), 4.82 - 5.22 (m, 2 H), 6.87 - 7.26 (m, 7 H), 7.30 - 7.46 (m, 1 H)
 25 MS ES^+ : 337

3. Biological efficacy of compounds of the invention

mGluR7 Assay

The ability of the test compounds to activate mGluR7 was determined by their ability to
 30 reduce forskolin stimulated cAMP production. Compounds were assessed in a CRE-

directed luciferase reporter gene assay, using a stable CHO cell line expressing the CRE-luc reporter and human mGluR7 genes. In this cell line, production of cAMP stimulated the transcription of the luciferase gene and luciferase activity was then measured in a luminescent enzyme assay (Steady Glo assay; Promega E2550). Activation of mGluR7
5 decreased the forskolin stimulated luminescence signal.

The day prior to the assay, compounds were serially diluted in DMSO (100x final assay concentration (FAC)), in 384-well plates which were then stored in the dark at room temperature (RT) until use. Cells were seeded at 12.5 k/well in white, clear bottom 384-
10 well plates (Corning 3707) and left for one hour at RT followed by an overnight incubation (37 °C). The following day, the DMSO compound plate was diluted 1:20 (5x FAC) in Opti-MEM I (Life Technologies 11058021). The growth media was removed from the cell plate and replaced with 15 µl Opti-MEM I, followed by a 5 µl addition from the 5x compound plate and a fifteen minute incubation (37 °C). Forskolin (Sigma F3917) was
15 then added to the wells (5 µl of 2.5 µM) and the plate was incubated for five hours (37 °C). During this incubation, the Steady Glo Substrate reagent was warmed to 37 °C. Aliquots (11ml; stored at -20 °C) of this reagent were prepared by dissolving the contents of 1 vial of lyophilised substrate in 100 ml Steady-Glo buffer. A 25 µl addition of the substrate was made to all wells and the plate was incubated for thirty minutes at RT, on a plate shaker
20 (300 rpm; in the dark). Luminescence was then measured using the EnVision Multilabel Reader (Perkin Elmer).

Compound activity was examined using a 10-point, half log concentration-response range and each concentration was tested in duplicate wells. Luminescence values were
25 normalised to 'maximum' (forskolin alone) and 'minimum' (forskolin in the presence of tool mGluR7 agonist) controls. EC₅₀ values were derived from this data using non-linear regression and a four parameter curve fit. The EC₅₀ values for the compounds of the Examples are shown in Table 1.

Results**Table 1**

Ex No.	EC50 (nM)	Ex No.	EC50 (nM)	Ex No.	EC50 (nM)
1	95	2	800	3	68
4	280	5	146	6	63
7	54	8	200	9	167
10	21	11	400	12	13
13	57	14	1	15	211
16	1100	17	-	18	13
19	3	20	11	21	8
22	2	23	4	24	6
25	111	26	109	27	258
28	-	29	38	30	11
31	29	32	100	33	49
34	440	35	200	36	18
37	70	38	15	39	12
40	1500	41	5800	42	730
43	-	44	178	45	1050
46	18	47	12	48	280
49	500	50	84	51	540
52	400	53	70	54	41
55	1650	56	87	57	61
58	27	59	151	60	3090
61	22	62	14		

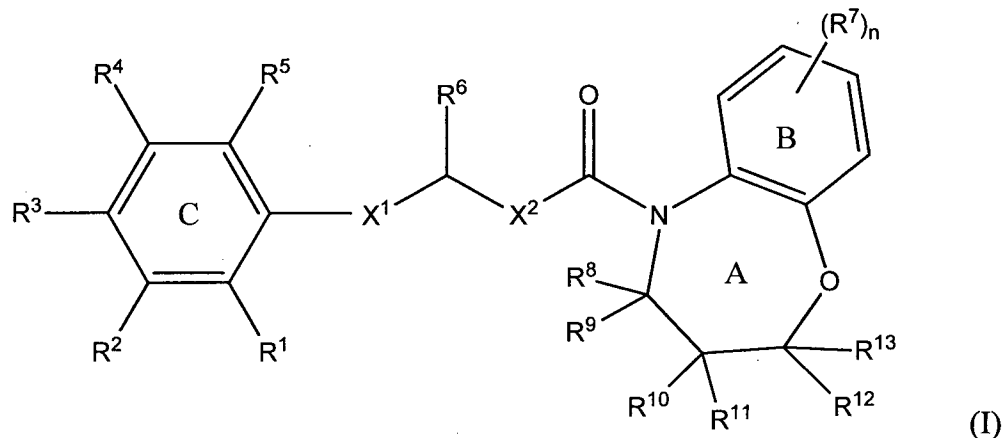
References

1. O'Connor R.M., Finger B.C., Flor P.J. and Cryan J.F., 2010. Metabotropic glutamate receptor 7: at the interface of cognition and emotion. *Eur J Pharmacol.*, 639 (1-3), 123-31.
2. Konieczny J. and Lenda T., 2013 Contribution of the mGluR7 receptor to antiparkinsonian-like effects in rats: a behavioral study with the selective agonist AMN082. *Pharmacol Rep.*, 65 (5), 1194-1203.
3. Greco B., Lopez S., van der Putten H. and Flor P.J., 2010. Amalric M. Metabotropic glutamate 7 receptor subtype modulates motor symptoms in rodent models of Parkinson's disease. *J Pharmacol Exp Ther.*, 332 (3), 1064-71.
4. Bradley S.R., Standaert D.G., Levey A.I. and Conn P.J., 1999. Distribution of group III mGluRs in rat basal ganglia with subtype-specific antibodies. *Ann N Y Acad Sci.*, 868, 531-4.
5. Conn P.J. and Niswender C.M., 2006. mGluR7's lucky number. *Proceedings of the National Academy of Sciences of the United States of America*, 103 (2), 251-2.
6. Hovelsø N., Sotty F., Montezinho L., Pinheiro P., Herrik K. and Mørk A., 2012. Therapeutic Potential of Metabotropic Glutamate Receptor Modulators. *Curr Neuropsychopharmacol.*, 10 (1), 12-48.
7. Kandaswamy R., McQuillin A., Curtis D. and Gurling H., 2014. Allelic Association, DNA Resequencing and Copy Number Variation at the Metabotropic Glutamate Receptor GRM7 Gene Locus in Bipolar Disorder. *Am J Med Genet B Neuropsychiatr Genet.*, 165 (4), 365-72.
8. Palucha-Poniewiera A., Szewczyk B. and Pilc A., 2014.. Activation of the mTOR signaling pathway in the antidepressant-like activity of the mGlu5 antagonist MTEP and the mGlu7 agonist AMN082 in the FST in rats. *Neuropharmacology*, 82, 59-68.
9. Palucha A., Klak K., Branski P., van der Putten H., Flor P.J. and Pilc A., 2007. Activation of the mGlu7 receptor elicits antidepressant-like effects in mice. *Psychopharmacology (Berl)*, 194 (4), 555-62.
10. Kalinichev M., Rouillier M., Girard F., Royer-Urios I., Bournique B., Finn T. et al., 2013. ADX71743, a potent and selective negative allosteric modulator of metabotropic glutamate receptor 7: in vitro and in vivo characterization. *J Pharmacol Exp Ther.*, 344 (3), 624-36.

11. Bolonna A.A., Kerwin R.W., Munro J., Arranz M.J., Makoff A.J., 2001. Polymorphisms in the genes for mGluR types 7 and 8: association studies with schizophrenia. *Schizophr Res.*, 47 (1), 99-103.
12. Friedman, R. A., et al., 2009. GRM7 variants confer susceptibility to age-related
5 hearing impairment. *Hum Mol Genet* 18(4), 785-796.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof



5 wherein

X^1 is absent or is $-\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)-$;

X^2 is $-\text{CH}_2-$, $-\text{CHF}-$, $-\text{CF}_2-$ or $-\text{CH}_2\text{CH}_2-$, provided that when X^1 is $-\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)-$, then X^2 is $-\text{CH}_2-$ only;

R^1 , R^2 , R^3 and R^4 each independently represent hydrogen, halogen, C_1 - C_6 alkyl,

10 C_3 - C_6 cycloalkyl or C_1 - C_6 alkoxy;

either R^5 represents hydrogen, halogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl or C_1 - C_6 alkoxy and R^6 represents hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkylsulphonyl or $-\text{NR}^{14}\text{R}^{15}$, or

when X^1 is absent, R^5 and R^6 together form a linking group, $-\text{[CH}_2\text{]}_m-$, in which m is 2, 3 or 4, wherein up to two $-\text{[CH}_2\text{]}-$ moieties may be replaced by oxygen, NH or $\text{N}(\text{COCH}_3)$ heteroatom moieties provided that if the linking group contains two heteroatom moieties then m is 3 or 4 and the heteroatom moieties are not situated adjacent one another;

n is 0, 1 or 2;

20 each R^7 independently represents halogen, cyano, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl or C_1 - C_6 alkoxy;

each of R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} independently represents hydrogen, hydroxyl, cyano, halogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl or C_1 - C_6 alkoxy; or, alternatively,

(i) R^8 and R^9 together with the carbon atom to which they are attached form a saturated 3-
5 to 6-membered carbocyclic ring; or

(ii) R^{10} and R^{11} together with the carbon atom to which they are attached form a saturated 3- to 6-membered carbocyclic ring; or

(iii) R^{12} and R^{13} together with the carbon atom to which they are attached form a saturated 3- to 6-membered carbocyclic ring; or

10 (iv) R^9 and R^{10} together with the carbon atoms to which they are attached form a saturated 3- to 6-membered carbocyclic ring; or

(v) R^8 and R^{12} together form a methylene bridge,

provided that no more than one carbocyclic ring or methylene bridge according to (i) to (v) above can be present in ring A; and

15 either R^{14} and R^{15} each independently represent hydrogen or a C_1 - C_6 alkyl, C_3 - C_6 cycloalkylmethyl, C_1 - C_6 alkylcarbonyl, C_3 - C_6 cycloalkylcarbonyl or C_1 - C_6 alkoxy carbonyl group, wherein each of the preceding groups is optionally substituted by at least one halogen atom, or

R^{14} and R^{15} together with the nitrogen atom to which they are attached form a
20 saturated 4- to 6-membered heterocyclic ring optionally comprising a further ring heteroatom selected from nitrogen and oxygen, the heterocyclic ring being unsubstituted or substituted by at least one substituent selected from halogen, oxo and C_1 - C_3 alkyl.

2. A compound according to claim 1, wherein X^1 is absent.

25

3. A compound according to claim 1 or claim 2, wherein X^2 is $-CH_2-$.

4. A compound according to any one of the preceding claims, wherein R^1 , R^2 , R^3 , R^4 and R^5 each independently represent hydrogen or halogen.

5. A compound according to any one of the preceding claims, wherein R^6 represents
5 $NR^{14}R^{15}$.

6. A compound according to any one of the preceding claims, wherein R^{14} and R^{15} each independently represent hydrogen or a C_1 - C_2 alkyl, cyclopropylmethyl, C_1 - C_3 alkylcarbonyl, cyclopropylcarbonyl or C_1 - C_4 alkoxy carbonyl group, wherein the
10 C_1 - C_2 alkyl and C_1 - C_3 alkylcarbonyl groups are optionally substituted by one to three halogen atoms.

7. A compound according to claim 1, wherein

X^1 is absent or is $-CH_2-$ or $-CH(CH_3)-$;

15 X^2 is $-CH_2-$, $-CF_2-$ or $-CH_2CH_2-$;

R^1 , R^2 , R^3 and R^4 each independently represent hydrogen, fluorine, chlorine, methyl or methoxy;

either R^5 represents hydrogen, fluorine, chlorine, bromine, cyclopropyl, methyl or methoxy and R^6 represents hydrogen, methyl or $-NR^{14}R^{15}$, or

20 when X^1 is absent, R^5 and R^6 together form a linking group, $-[CH_2]_m-$, in which m is 2, 3 or 4, wherein up to two $-[CH_2]-$ moieties may be replaced by oxygen, NH or $N(COCH_3)$ heteroatom moieties provided that if the linking group contains two heteroatom moieties then m is 3 or 4 and the heteroatom moieties are not situated adjacent one another;

25 n is 0 or 1;

R^7 represents halogen, methyl or methoxy;

each of R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} independently represents hydrogen, hydroxyl, fluorine, methyl or methoxy or, alternatively, either R^{10} and R^{11} together with the carbon atom to which they are attached form a saturated 3- to 6-membered carbocyclic ring, or R^8 and R^{12} together form a methylene bridge; and

5 either R^{14} and R^{15} each independently represent hydrogen or a C_1 - C_2 alkyl, cyclopropylmethyl, C_1 - C_3 alkylcarbonyl, cyclopropylcarbonyl or C_1 - C_4 alkoxycarbonyl group, wherein each of the preceding groups is optionally substituted by at least one halogen atom, or

R^{14} and R^{15} together with the nitrogen atom to which they are attached form a
10 saturated 5-membered heterocyclic ring, the heterocyclic ring being unsubstituted or substituted by at least one substituent selected from halogen, oxo and C_1 - C_3 alkyl.

8. A compound according to claim 1, wherein

X^1 is absent;

15 X^2 is $-CH_2-$;

R^1 , R^2 , R^4 and R^5 each represent hydrogen;

R^3 represents hydrogen or fluorine;

R^6 represents $-NR^{14}R^{15}$;

n is 0 or 1;

20 R^7 represents fluorine;

R^8 , R^9 , R^{12} and R^{13} each represent hydrogen;

R^{10} and R^{11} each independently represent hydrogen or fluorine; and

R^{14} and R^{15} each represent hydrogen.

25 9. A compound of formula (I) as defined in claim 1 selected from:

N-[3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]acetamide;

(3R)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-amino-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-amino-1-(8-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;

(3S)-3-amino-3-(4-fluorophenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-amino-3-(2-fluorophenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-(methylamino)-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-(dimethylamino)-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-amino-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;

(3S)-3-amino-3-(2-methylphenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-amino-3-(2-methoxyphenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-amino-3-(2-chlorophenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-(ethylamino)-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-[(cyclopropylmethyl)amino]-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-2-(1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-one;

(3S)-1-(3-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(methylamino)-3-phenylpropan-1-one;

N-[(1S)-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]propanamide;

N-[(1S)-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]cyclopropanecarboxamide;

2-methyl-N-[(1S)-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]propanamide;

2,2,2-trifluoro-N-[(1S)-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]acetamide;

N-[(1S)-1-(2-methylphenyl)-3-oxo-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]acetamide;

5 N-[(1S)-1-(2-chlorophenyl)-3-oxo-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]acetamide;

1-[(1S)-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]pyrrolidin-2-one;

(3S)-3-amino-1-(6-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;

(3S)-3-amino-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(4-fluorophenyl)propan-1-one;

1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-2-(1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-one;

15 (3S)-3-amino-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(2-fluorophenyl)propan-1-one;

(3S)-3-[(2,2-difluoroethyl)amino]-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-amino-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(2-methylphenyl)propan-1-one;

(3S)-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(methylamino)-3-phenylpropan-1-one;

tert-butyl N-[2,2-difluoro-3-oxo-1-phenyl-3-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propyl]carbamate;

25 3-amino-2,2-difluoro-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-amino-1-(3-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;

(3S)-3-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)butan-1-one;

30 1-(3-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(2-methylphenyl)propan-1-one;

4-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)pentan-1-one;

3-(2-methylphenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

- (3R)-3-amino-4-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)butan-1-one;
(3S)-3-amino-4-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)butan-1-one;
4-amino-4-phenyl-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)butan-1-one;
1-(3-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(2-
5 methylphenyl)propan-1-one;
1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-2-(1,2,3,4-tetrahydroisoquinolin-4-
yl)ethan-1-one;
(3S)-3-amino-3-(2-chlorophenyl)-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-
5-yl)propan-1-one;
10 (3S)-3-amino-1-(3,3-difluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-
phenylpropan-1-one;
(3S)-3-amino-1-(7-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-
phenylpropan-1-one;
2-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-1-(2,3,4,5-tetrahydro-1,5-
15 benzoxazepin-5-yl)ethan-1-one;
(3S)-3-amino-1-(3-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-
phenylpropan-1-one;
2-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(2,3,4,5-tetrahydro-1,5-
benzoxazepin-5-yl)ethan-1-one;
20 (3S)-amino-1-{3,4-dihydro-2,4-methanobenzo[b][1,4]oxazepin-5-yl}-3-
phenylpropan-1-one
(3S)-3-amino-1-[(4S)-9-fluoro-4-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-
yl]-3-phenylpropan-1-one;
(3S)-3-amino-1-(9-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-
25 phenylpropan-1-one;
(3S)-3-amino-1-(9-chloro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-
phenylpropan-1-one;
(3S)-3-amino-1-[(4R)-9-fluoro-4-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-
yl]-3-phenylpropan-1-one;
30 (3S)-3-amino-1-{4,5-dihydro-2H-spiro[1,5-benzoxazepine-3,1'-cyclopropane]-5-
yl}-3-phenylpropan-1-one;
(3S)-3-amino-1-(9-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-
phenylpropan-1-one;

(3S)-3-amino-3-(2-bromophenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one;

(3S)-3-amino-3-(2-cyclopropylphenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one; and enantiomers, diastereoisomers and mixtures thereof; and

5 pharmaceutically acceptable salts of any of the foregoing.

10. A compound of formula (I) as defined in claim 1 selected from:

(3S)-3-amino-3-(4-fluorophenyl)-1-(2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)propan-1-one hydrochloride;

10 (3S)-3-amino-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;

(3S)-3-amino-1-(6-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one;

15 (3S)-3-amino-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(4-fluorophenyl)propan-1-one hydrochloride;

(3S)-3-amino-1-(9-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-(2-fluorophenyl)propan-1-one hydrochloride;

(3S)-3-amino-1-(3,3-difluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one hydrochloride;

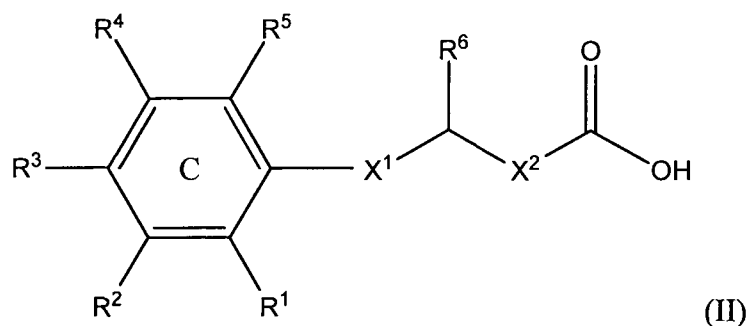
20 (3S)-3-amino-1-(3-fluoro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one hydrochloride;

(3S)-3-amino-1-(9-chloro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-3-phenylpropan-1-one hydrochloride; and

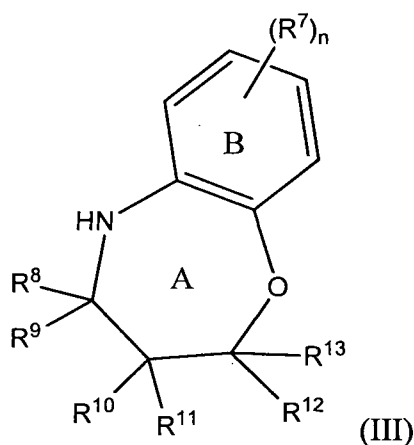
pharmaceutically acceptable salts of any of the foregoing.

25

11. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 which comprises reacting a compound of formula (II), or a salt thereof,



in which X^1 , X^2 , R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined in formula (I) above, with a compound of formula (III), or a salt thereof,



in which n , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} are as defined in formula (I) above;

and optionally thereafter carrying out one or more of the following procedures:

- converting a compound of formula (I) into another compound of formula (I)
- removing any protecting groups
- forming a pharmaceutically acceptable salt.

12. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 10, in association with a pharmaceutically acceptable adjuvant, diluent or carrier, and optionally one or more other therapeutic agents.

13. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 10, for use in therapy.

14. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 10, for use in treating alcohol, drug or nicotine addiction.
15. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as
5 claimed in any one of claims 1 to 10, for use in treating hearing loss or tinnitus.
16. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 10, for use in treating schizophrenia.

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2017/024276

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/06 A61K31/553 C07D267/12 C07D267/14 A61P25/18
A61P25/30 A61P25/32 A61P25/34 A61P25/36 A61P27/16

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHRISTINE E. GEE ET AL: "Blocking Metabotropic Glutamate Receptor Subtype 7 (mGlu7) via the Venus Flytrap Domain (VFTD) Inhibits Amygdala Plasticity, Stress, and Anxiety-related Behavior", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 289, no. 16, 4 March 2014 (2014-03-04), pages 10975-10987, XP055403873, US ISSN: 0021-9258, DOI: 10.1074/jbc.M113.542654 abstract page 10975, right-hand column, paragraph 1 - page 10977, right-hand column, paragraph 2 page 10979; figure 1 page 10984; figure 5 page 10985, right-hand column, paragraph 2 -/--	1-16



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 September 2017

Date of mailing of the international search report

10/10/2017

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Dunet, Guillaume

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2017/024276

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	----- WO 2007/025709 A2 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; FLOR PETER JOSEF [CH]; MA) 8 March 2007 (2007-03-08) abstract pages 22-26 examples 1-148 claims 1-11	1-16
A	----- EP 1 408 042 A1 (BANYU PHARMA CO LTD [JP]) 14 April 2004 (2004-04-14) abstract paragraphs [0064] - [0073] examples 1-33 paragraph [0176] claims 1-9	1-16
A	----- FR 2 182 886 A1 (ROBINS CO INC A H [US]) 14 December 1973 (1973-12-14) page 1, lines 1-21 examples 1-28 claims 1-10	1-16
A	----- K Nagarajan ET AL: "Synthesis of 10,11-dihydrodibenz[b,f][1,4]oxazepine derivatives as potential anticonvulsant & psychotropic agents", Indian Journal of Chemistry - Section B: Organic and Medicinal Chemistry, August 1985 (1985-08), pages 840-844, XP055403980, Retrieved from the Internet: URL:http://repository.ias.ac.in/93498/1/7p.pdf [retrieved on 2017-09-05] abstract * compounds *; page 840 page 841; table 1 page 842; tables 2, 3 pages 842-843	1-16
A	----- WO 2015/106025 A1 (J DAVID GLADSTONE INST A TESTAMENTARY TRUST ESTABLISHED UNDER THE WILL) 16 July 2015 (2015-07-16) abstract pages 50-55; tables 1, 1A paragraphs [0269], [0270], [0283] examples 1-22 claims 1-16 -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/JP2017/024276

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2007025709	A2	08-03-2007	AU 2006286824 A1 BR PI0616594 A2 CA 2620222 A1 CN 101253147 A EP 1924551 A2 EP 2096104 A1 JP 2009506086 A KR 20080049027 A US 2008242698 A1 WO 2007025709 A2	08-03-2007 28-06-2011 08-03-2007 27-08-2008 28-05-2008 02-09-2009 12-02-2009 03-06-2008 02-10-2008 08-03-2007
EP 1408042	A1	14-04-2004	CA 2451057 A1 EP 1408042 A1 JP W02002102807 A1 US 2004176407 A1 WO 02102807 A1	27-12-2002 14-04-2004 30-09-2004 09-09-2004 27-12-2002
FR 2182886	A1	14-12-1973	AU 5280373 A DE 2314392 A1 FR 2182886 A1 JP S4911893 A	05-09-1974 27-09-1973 14-12-1973 01-02-1974
WO 2015106025	A1	16-07-2015	CA 2935944 A1 EP 3091984 A1 JP 2017502073 A US 2016326123 A1 WO 2015106025 A1	16-07-2015 16-11-2016 19-01-2017 10-11-2016 16-07-2015