Nelivaptan has a relatively short degradation half-life; at 10 mg/kg p.o. its duration of action is reported as being "*longer than 4 h*" (C. Serradeil-Le Gal et al, CNS Drug Reviews 2005, Vol. 11, No. 1, pp. 53–68).

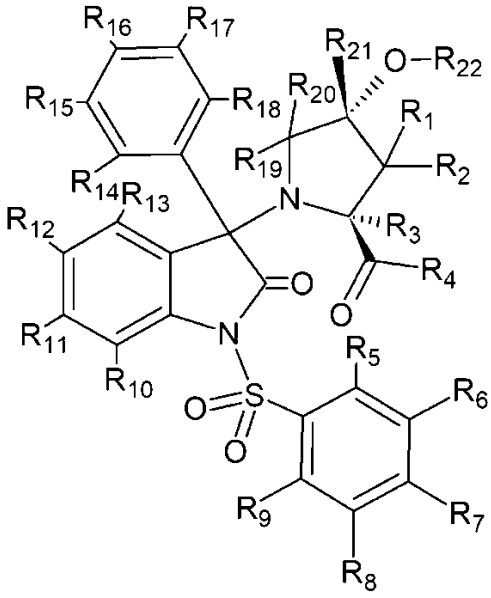
It would be desirable to provide vasopressin receptor antagonists selective for the V_{1b} subtype having a longer degradation half-life, e.g. in order to allow less frequent dosing.

While generally methods to increase the degradation half-life of pharmaceutical agents, like adding halogen atoms (e.g. Gunaydin et al, ACS Med. Chem. Lett. 2018, 9, 528−533), are known in the art, none of the methods is reliable and rather all methods are based on trial and error.

Applicants have discovered that deuterated 1,3 dihydro-2H-indole-2-one derivatives have surprisingly a significantly increased degradation half-life, which thus allows less frequent dosing.

Summary

The present disclosure relates to a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R_1, R_2, R_3, R_{19}, R_{20}, and R_{21} are individually selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxy,

R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, and R_{18} are individually selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy,

R_4 is selected from the group consisting of C_{1-4} alkylamino, C_{1-4} haloalkylamino, di-C_{1-4} alkylamino, di-C_{1-4} haloalkylamino, and azetidin-1-yl,

R_{22} is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -$(CH_2)_n$-CO-R_{38}, and -CO-$(CH_2)_n$-$NR_{39}R_{40}$,

R_{38} is selected from the group consisting of hydrogen, hydroxy and C_{1-4} alkyl,

R_{39} and R_{40} are individually selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} haloalkyl, or R_{39} and R_{40}, together with the nitrogen atom to which they are attached, constitute a heterocyclic group selected from the group consisting of: azetidin-1-yl, pyrrolidin-1-yl, piperid-1-yl, piperazin-1-yl, morpholin-4-yl and thiomorpholin-4-yl; and

integer n is 1 or 2, provided that at least one hydrogen of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, or R_{21} is enriched in deuterium.

In an example, the compound comprises at least an amount of deuterium as follows:

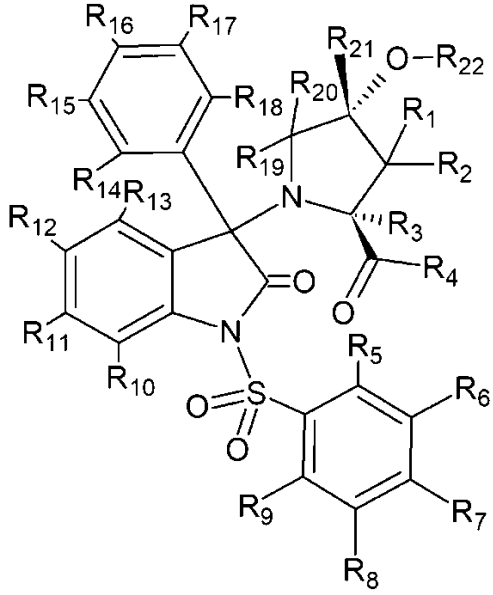
a) at least one hydrogen of R_4, which is selected from C_{1-4} alkylamino or di-C_{1-4} alkylamino, is enriched in deuterium, and/or

b) at least one hydrogen of R_5, R_7, or R_{14}, which are individually selected from C_{1-4} alkyl or C_{1-4} alkoxy, is enriched in deuterium, and

c) optionally at least one hydrogen of R_1, R_2, R_3, R_6, R_8, R_9, R_{10}, R_{11}, R_{13}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, or R_{21} is enriched in deuterium.

Preferably, both a) and b) are fulfilled.

In an aspect, the present disclosure relates to a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R_1, R_2, R_3, R_{19}, R_{20}, and R_{21} are individually selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxy,

R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, and R_{18} are individually selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy,

R_4 is selected from the group consisting of C_{1-4} alkylamino, C_{1-4} haloalkylamino, di-C_{1-4} alkylamino, di-C_{1-4} haloalkylamino, and azetidin-1-yl,

R_{22} is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -$(CH_2)_n$-CO-$R_{38,}$ and -CO-$(CH_2)_n$-$NR_{39}R_{40}$,

R_{38} is selected from the group consisting of hydrogen, hydroxy and C_{1-4} alkyl,

R_{39} and R_{40} are individually selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} haloalkyl, or R_{39} and R_{40}, together with the nitrogen atom to which they are attached, constitute a heterocyclic group selected from the group consisting of: azetidin-1-yl, pyrrolidin-1-yl, piperid-1-yl, piperazin-1-yl, morpholin-4-yl and thiomorpholin-4-yl; and

integer n is 1 or 2,

wherein

a) at least one hydrogen of R_4, which is selected from C_{1-4} alkylamino or di-C_{1-4} alkylamino, is enriched in deuterium, and/or

b) at least one hydrogen of R_5, R_7, or R_{14}, which are individually selected from C_{1-4} alkyl or C_{1-4} alkoxy, is enriched in deuterium, and

c) optionally at least one hydrogen of R_1, R_2, $R_{3,}$ R_6, R_8, R_9, R_{10}, R_{11}, $R_{13,}$ R_{15}, R_{16}, R_{17}, $R_{18,}$ R_{19}, R_{20}, or R_{21} is enriched in deuterium.

In an example,

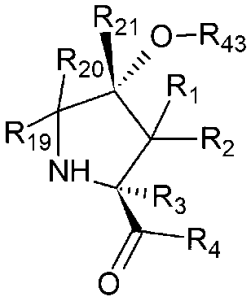
a) at least one hydrogen, preferably all hydrogens, of R_4, which is selected from C_{1-4} alkylamino or di-C_{1-4} alkylamino, is enriched in deuterium, and/or

b) at least one hydrogen, preferably all hydrogens, of R_5, R_7, or R_{14}, which are individually selected from C_{1-4} alkyl or C_{1-4} alkoxy, is enriched in deuterium, and

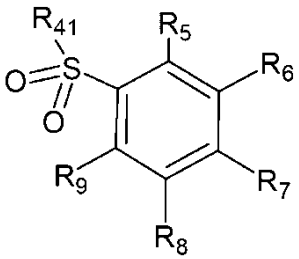
c) optionally at least one hydrogen of R_1, R_2, $R_{3,}$ R_6, R_8, R_9, R_{10}, R_{11}, $R_{13,}$ R_{15}, R_{16}, R_{17}, $R_{18,}$ R_{19}, R_{20}, or R_{21} is enriched in deuterium. Preferably, both a) and b) are fulfilled.

In an example , the present disclosure provides a process for the preparation of a compound of formula (I):

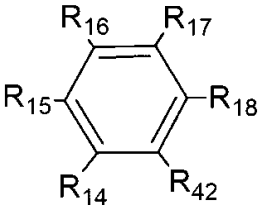
the process comprising a step of reacting at least one of the following compounds of formulae (VI), (VII), (VIII), or (IX)



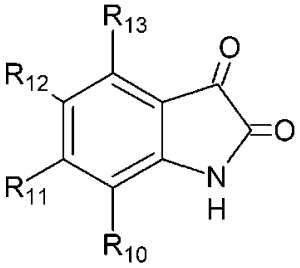
(VI)



(VII)



(VIII)



(IX)

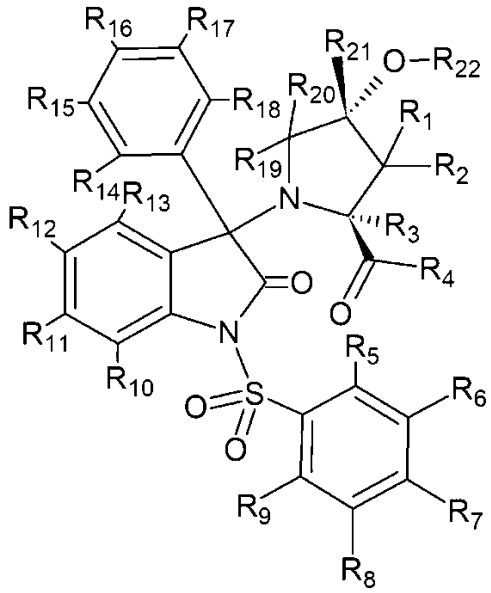
wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are as defined for formula (I), R_{41} is a halogen or an activating ester residue, R_{42} is a halogen, and R_{43} is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, $-(CH_2)_n$-CO-R_{38}, -CO-$(CH_2)_n$-$NR_{39}R_{40}$, and a hydroxyl protecting group, provided that at least one hydrogen of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, or R_{21} of the compound of formulae (VI), (VII), (VIII), or (IX) used is enriched in deuterium, wherein preferably

a) at least one hydrogen of R_4, which is selected from C_{1-4} alkylamino or di-C_{1-4} alkylamino, is enriched in deuterium, and/or

b) at least one hydrogen of R_5, R_7, or R_{14}, which are individually selected from C_{1-4} alkyl or C_{1-4} alkoxy, is enriched in deuterium, and

c) optionally at least one hydrogen of R_1, R_2, R_3, R_6, R_8, R_9, R_{10}, R_{11}, R_{13}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, or R_{21} is enriched in deuterium.

In another aspect, the present disclosure relates to a process for the preparation of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R_1, R_2, R_3, R_{19}, R_{20}, and R_{21} are individually selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxy,

R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, and R_{18} are individually selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy,

R_4 is selected from the group consisting of C_{1-4} alkylamino, C_{1-4} haloalkylamino, di-C_{1-4} alkylamino, di-C_{1-4} haloalkylamino, and azetidin-1-yl,

R_{22} is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -$(CH_2)_n$-CO-R_{38}, and -CO-$(CH_2)_n$-$NR_{39}R_{40}$,

R_{38} is selected from the group consisting of hydrogen, hydroxy and C_{1-4} alkyl,

R_{39} and R_{40} are individually selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} haloalkyl, or R_{39} and R_{40}, together with the nitrogen atom to which they are attached, constitute a heterocyclic group selected from the group consisting of: azetidin-1-yl, pyrrolidin-1-yl, piperid-1-yl, piperazin-1-yl, morpholin-4-yl and thiomorpholin-4-yl; and

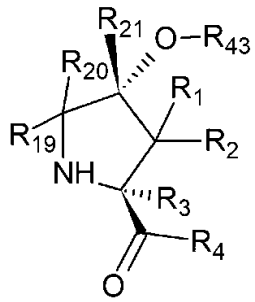
integer n is 1 or 2, wherein

a) at least one hydrogen of R_4, which is selected from C_{1-4} alkylamino or di-C_{1-4} alkylamino, is enriched in deuterium, and/or

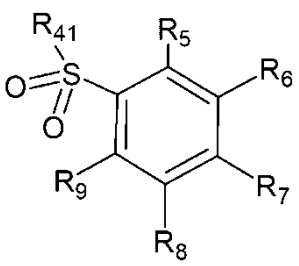
b) at least one hydrogen of R_5, R_7, or R_{14}, which are individually selected from C_{1-4} alkyl or C_{1-4} alkoxy, is enriched in deuterium, and

c) optionally at least one hydrogen of R_1, R_2, R_3, R_6, R_8, R_9, R_{10}, R_{11}, R_{13}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, or R_{21} is enriched in deuterium,

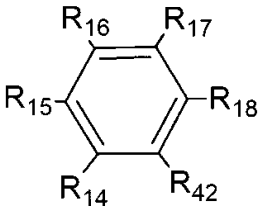
the process comprising a step of reacting at least one of the following compounds of formulae (VI), (VII), (VIII), or (IX)



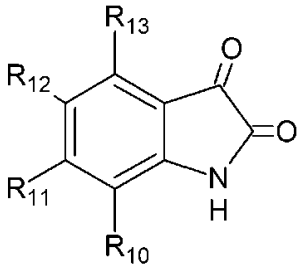
(VI)



(VII)



(VIII)



(IX)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are as defined for formula (I),

R_{41} is a halogen or an activating ester residue,

R_{42} is a halogen, and

R_{43} is R_{22} or a hydroxyl protecting group.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a compound according to formula (I) as disclosed herein and a pharmaceutical acceptable carrier.

In another aspect of the present disclosure relates to a compound as disclosed herein or a pharmaceutical composition as disclosed herein for use as medicament.

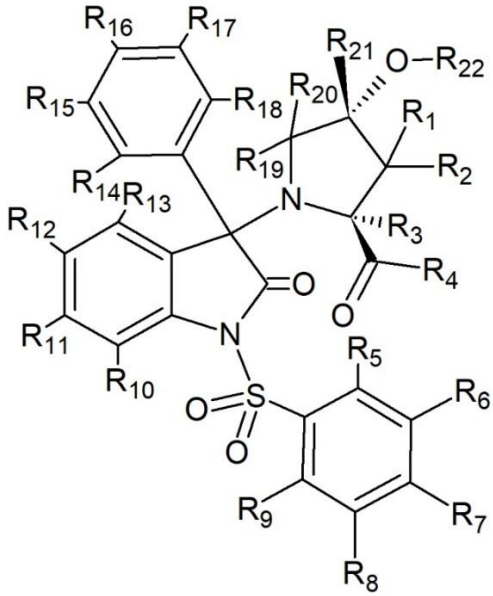
In an example, the present disclosure relates to a compound according to formula (I) according to the first example or a pharmaceutical composition according to the third example of the present disclosure for the treatment or prophylaxis of disorders of the central nervous system, in particular anxiety or depression.

In another aspect, the present disclosure relates to use of a compound as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment or prophylaxis of disorders of the central nervous system, in particular of anxiety or depression

In another aspect, the present disclosure relates to a compound according to formula (X):

Claims

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R_1, R_2, R_3, R_{19}, R_{20}, and R_{21} are individually selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxy,

R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, and R_{18} are individually selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy,

R_4 is selected from the group consisting of C_{1-4} alkylamino, C_{1-4} haloalkylamino, di-C_{1-4} alkylamino, di-C_{1-4} haloalkylamino, and azetidin-1-yl,

R_{22} is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -$(CH_2)_n$-CO-R_{38}, and -CO-$(CH_2)_n$-$NR_{39}R_{40}$,

R_{38} is selected from the group consisting of hydrogen, hydroxy and C_{1-4} alkyl,

R_{39} and R_{40} are individually selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} haloalkyl, or R_{39} and R_{40}, together with the nitrogen atom to which they are attached, constitute a heterocyclic group selected from the group consisting of: azetidin-1-yl, pyrrolidin-1-yl, piperid-1-yl, piperazin-1-yl, morpholin-4-yl and thiomorpholin-4-yl; and

integer n is 1 or 2,

wherein

a) at least one hydrogen of R_4, which is selected from C_{1-4} alkylamino or di-C_{1-4} alkylamino, is enriched in deuterium, and/or

b) at least one hydrogen of R_5, R_7, or R_{14}, which are individually selected from $C_{1\text{-}4}$ alkyl or $C_{1\text{-}4}$ alkoxy, is enriched in deuterium, and

c) optionally at least one hydrogen of R_1, R_2, R_3, R_6, R_8, R_9, R_{10}, R_{11}, R_{13}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, or R_{21} is enriched in deuterium.

2. The compound according to claim 1, wherein

a) at least one hydrogen of R_1, R_2, R_3, R_6, R_8, R_9, R_{10}, R_{11}, R_{13}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, or R_{21} is enriched in deuterium,

b) at least one hydrogen of R_4, which is dimethylamino, is enriched in deuterium, and/or

c) at least one hydrogen of R_5, R_7, or R_{14}, which are methoxy, is enriched in deuterium.

3. The compound according to claim 1 or 2, wherein

d) R_5, R_7, and R_{14} are a methoxy group,

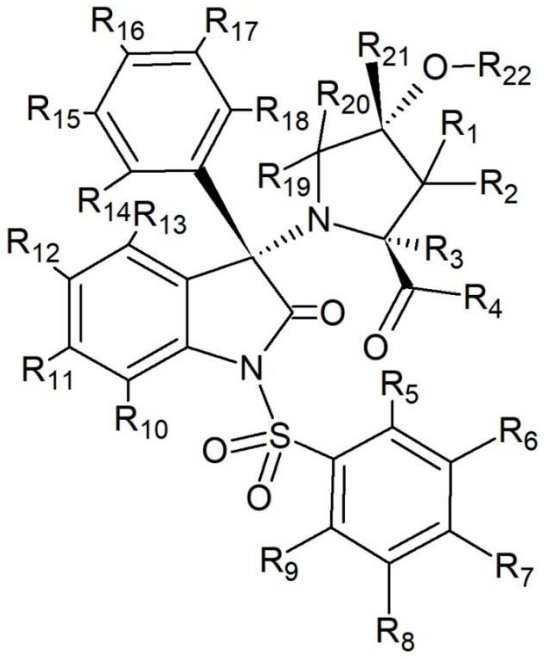
e) R_{12} is a methyl, trifluoromethyl or halogen atom, preferably a chlorine atom,

f) R_{22} is hydrogen, and /or

g) R_1, R_2, R_3, R_6, R_8, R_9, R_{10}, R_{11}, R_{13}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are hydrogen.

4. The compound of formula (I) according to any one of the preceding claims, wherein all six hydrogens, of R_4, which is dimethylamino, and/or all three hydrogens, of R_5, R_7, or R_{14}, which are a methoxy group, is enriched in deuterium.

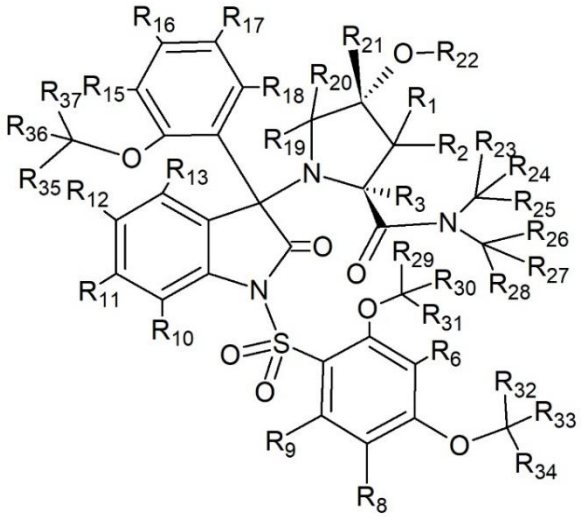
5. The compound according to any one of the preceding claims, which is a compound of formula (II):



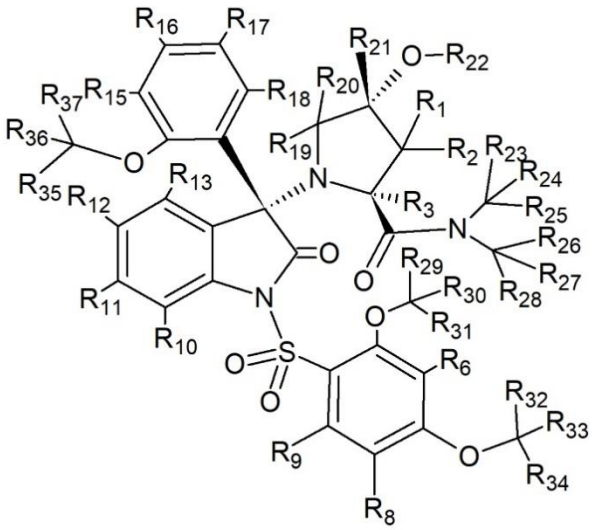
(II),

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, and R_{22} are as defined in claim 1.

6. The compound according to any one of the preceding claims, which is a compound of formula (III) or (IV):



(III)

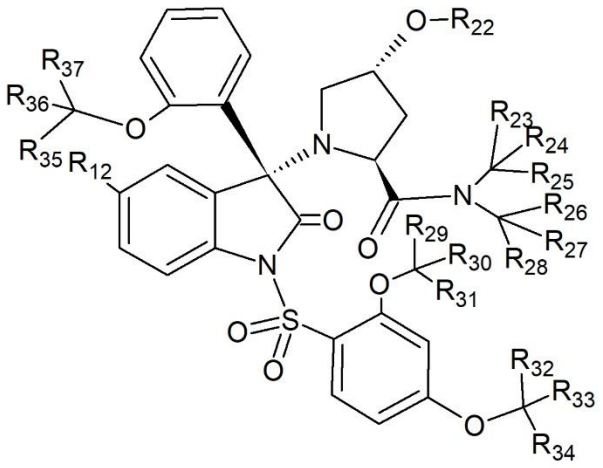


(IV)

wherein R_1, R_2, R_3, R_6, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21} and R_{22} are as defined in claim 1, and

R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36} and R_{37} are hydrogen.

7. The compound according to claim 6, which is a compound of formula (V):



(V)

wherein

R_{22} is as defined in claim 6, preferably hydrogen, and

R_{12} is as defined in claim 6, preferably chlorine.

8. The compound according to claim 7, wherein

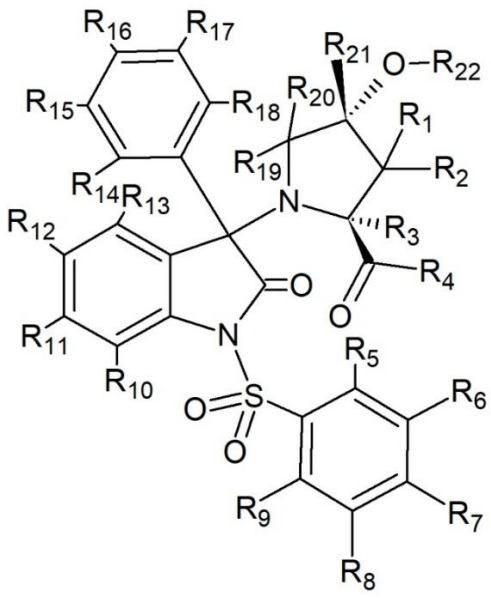
a) R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, and R_{28} are enriched in deuterium,

b) R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, and R_{34} are enriched in deuterium, and/or

c) R_{35}, R_{36} and R_{37} are enriched in deuterium.

9. The compound according to any one of the preceding claims, wherein the enrichment in deuterium is at least 10%, at least 30%, at least 50%, at least 70%, at least 97%, at least 98%, or at least 99%.

10. A process for the preparation of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R_1, R_2, R_3, R_{19}, R_{20}, and R_{21} are individually selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxy,

R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, and R_{18} are individually selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy,

R_4 is selected from the group consisting of C_{1-4} alkylamino, C_{1-4} haloalkylamino, di-C_{1-4} alkylamino, di-C_{1-4} haloalkylamino, and azetidin-1-yl,

R_{22} is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -$(CH_2)_n$-CO-R_{38}, and -CO-$(CH_2)_n$-$NR_{39}R_{40}$,

R_{38} is selected from the group consisting of hydrogen, hydroxy and C_{1-4} alkyl,

R_{39} and R_{40} are individually selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} haloalkyl, or R_{39} and R_{40}, together with the nitrogen atom to which they are attached, constitute a heterocyclic group selected from the group consisting of: azetidin-1-yl, pyrrolidin-1-yl, piperid-1-yl, piperazin-1-yl, morpholin-4-yl and thiomorpholin-4-yl; and

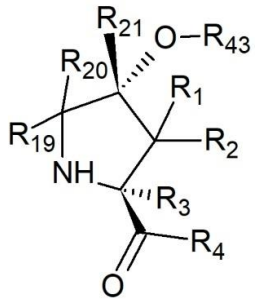
integer n is 1 or 2, wherein

a) at least one hydrogen of R_4, which is selected from C_{1-4} alkylamino or di-C_{1-4} alkylamino, is enriched in deuterium, and/or

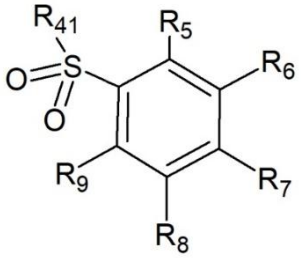
b) at least one hydrogen of R_5, R_7, or R_{14}, which are individually selected from C_{1-4} alkyl or C_{1-4} alkoxy, is enriched in deuterium, and

c) optionally at least one hydrogen of R_1, R_2, R_3, R_6, R_8, R_9, R_{10}, R_{11}, R_{13}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, or R_{21} is enriched in deuterium,

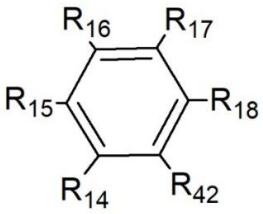
the process comprising a step of reacting at least one of the following compounds of formulae (VI), (VII), (VIII), or (IX)



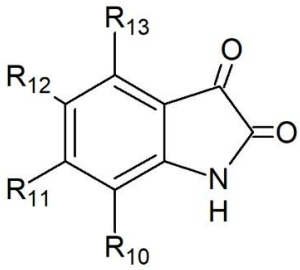
(VI)



(VII)



(VIII)



(IX)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are as defined for formula (I),

R_{41} is a halogen or an activating ester residue,

R_{42} is a halogen, and

R_{43} is R_{22} or a hydroxyl protecting group.

11. The process according to claim 10, wherein

a) in the compound of formula (VI) at least one hydrogen of R_4, which is selected from $C_{1\text{-}4}$ alkylamino or di-$C_{1\text{-}4}$ alkylamino, preferably dimethylamino, is enriched in deuterium, and preferably R_1, R_2, R_3, R_{19}, R_{20} and R_{21} are hydrogen and R_{43} is hydrogen or a hydroxyl protecting group,

b) in the compound of formula (VII) at least one hydrogen of R_5, or R_7, which are individually selected from $C_{1\text{-}4}$ alkyl or $C_{1\text{-}4}$ alkoxy, preferably methoxy, is enriched in deuterium, and preferably R_6, R_8, and R_9 are hydrogen, and/or

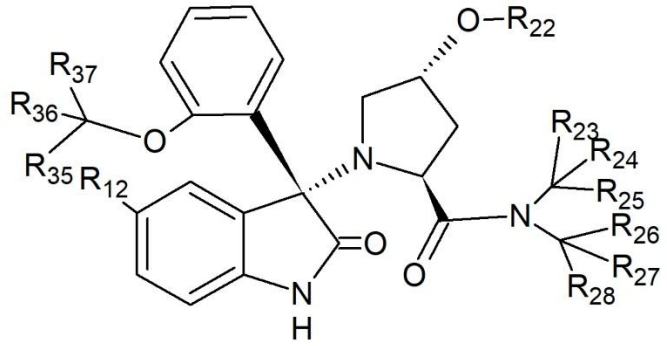
c) in the compound of formula (VIII) at least one, preferably at least two or at least three, hydrogen of R_{14}, which is selected from $C_{1\text{-}4}$ alkyl or $C_{1\text{-}4}$ alkoxy, preferably methoxy, is enriched in deuterium, and preferably R_{15}, R_{16}, R_{17}, and R_{18} are hydrogen.

12. A pharmaceutical composition comprising a compound according to formula (I) according to any one of claims 1 to 9 and a pharmaceutical acceptable carrier.

13. A compound according to any of claims 1 to 9 or the pharmaceutical composition according to claim 12 for use as medicament.

14. Use of a compound according to any of claims 1 to 9, or the pharmaceutical composition according to claim 12, in the manufacture of a medicament for the treatment or prophylaxis of disorders of the central nervous system, in particular of anxiety or depression.

15. A compound according to formula (X):



(X)

wherein

R_{12} is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy, preferably a methyl, trifluoromethyl or halogen, more preferably chlorine,

R_{22} is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, $-(CH_2)_n-CO-R_{38}$, and $-CO-(CH_2)_n-NR_{39}R_{40}$, R_{38} is selected from the group consisting of hydrogen, hydroxy and C_{1-4} alkyl, R_{39} and R_{40} are individually selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} haloalkyl, or R_{39} and R_{40}, together with the nitrogen atom to which they are attached, constitute a heterocyclic group selected from the group consisting of: azetidin-1-yl, pyrrolidin-1-yl, piperid-1-yl, piperazin-1-yl, morpholin-4-yl and thiomorpholin-4-yl; and integer n is 1 or 2; or R_{22} is a hydroxyl protecting group, and

R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{35}, R_{36} and R_{37} are hydrogen, provided that

at least one, preferably at least two or at least three, of R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{35}, R_{36} and R_{37} is enriched in deuterium.