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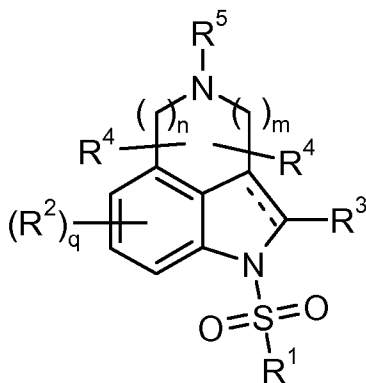
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(54) Title: TRICYCLIC ISOQUINOLINE DERIVATIVES FOR TREATMENT OF OBESITY



(I)

(57) Abstract: The present invention relates to novel compounds of formula (I): wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as described herein, to pharmaceutical compositions comprising the compounds, to processes for their preparation, as well as to the use of the compounds for the preparation of a medicament against 5-HT₆ receptor-related disorders.

TRICYCLIC ISOQUINOLINE DERIVATIVES FOR TREATMENT OF OBESITY

TECHNICAL FIELD

5 The present invention relates to novel compounds, to pharmaceutical compositions comprising the compounds, to processes for their preparation, as well as to the use of the compounds for the preparation of a medicament against 5-HT₂ receptor-related disorders.

10 BACKGROUND OF THE INVENTION

Obesity is a condition characterized by an increase in body fat content resulting in excess body weight above accepted norms. Obesity is the most important nutritional disorder in the western world and represents a major health problem in all industrialized
15 countries. This disorder leads to increased mortality due to increased incidences of diseases such as cardiovascular disease, digestive disease, respiratory disease, cancer and type 2 diabetes. Searching for compounds that reduce body weight has been going on for many decades. One line of research has been activation of serotonergic systems, either by direct activation of serotonin receptor subtypes or by inhibiting
20 serotonin reuptake. The exact receptor subtype profile required is however not known.

Serotonin (5-hydroxytryptamine or 5-HT), a key transmitter of the peripheral and central nervous system, modulates a wide range of physiological and pathological functions, including anxiety, sleep regulation, aggression, feeding and depression. Multiple serotonin receptor subtypes have been identified and cloned. One of these, the
25 5-HT₂ receptor, was cloned by several groups in 1993 (Ruat, M. et al. (1993) *Biochem. Biophys. Res. Commun.* 193: 268-276; Sebben, M. et al. (1994) *NeuroReport* 5: 2553-2557). This receptor is positively coupled to adenylyl cyclase and displays affinity for antidepressants such as clozapine. The effect of 5-HT₂ antagonist and 5-HT₂ antisense oligonucleotides to reduce food intake in rats has been reported (Bentley, J.C. et al.
30 (1999) *Br J Pharmacol. Suppl.* 126, P66; Bentley, J.C. et al. (1997) *J. Psychopharmacol. Suppl.* A64, 255; Woolley MX. et al. (2001) *Neuropharmacology* 41: 210-219).

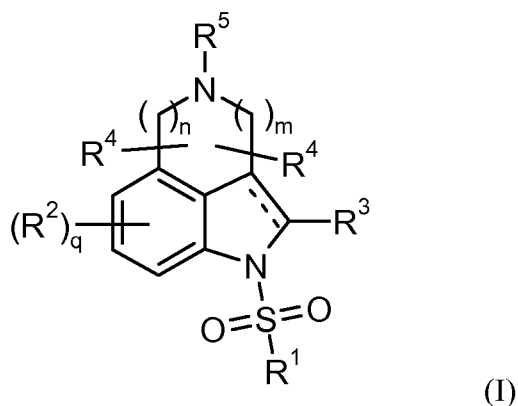
Compounds with enhanced affinity and selectivity for the 5-HT₂ receptor have been identified, e.g. in WO 00/34242 and by Isaac, M. et al. (2000) 6-

Bicyclopiperazinyl-l-arylsulphonylindoles and 6-Bicyclopiperidinyl-l-arylsulphonylindoles derivatives as novel, potent and selective 5-HT β receptor antagonists. Bioorganic & Medicinal Chemistry Letters 10: 1719-1721 (2000), Bioorganic & Medicinal Chemistry Letters 13: 3355-3359 (2003), Expert Opinion
5 Therapeutic Patents 12(4) 513-527 (2002).

DISCLOSURE OF THE INVENTION

It has surprisingly been found that the compounds according to the present
10 invention show affinity for the 5-HT β receptor at nanomolar range. Compounds according to the present invention and their pharmaceutically acceptable salts have 5-HT β receptor antagonist, agonist and partial agonist activity, preferably antagonist activity, and are believed to be of potential use in the treatment or prophylaxis of obesity and type 2 diabetes, to achieve reduction of body weight and of body weight
15 gain, as well as in the treatment or prophylaxis of disorders of the central nervous system such as anxiety, depression, panic attacks, memory disorders, cognitive disorders, epilepsy, sleep disorders, migraine, anorexia, bulimia, binge eating disorders, obsessive compulsive disorders, psychoses, Alzheimer's disease, Parkinson's disease, Huntington's chorea and/or schizophrenia, panic attacks, Attention Deficit Hyperactive
20 Disorder (ADHD), withdrawal from drug abuse (e.g. abuse of amphetamine, cocaine abuse and/or nicotine), neurodegenerative diseases characterized by impaired neuronal growth, and pain. The reduction of body weight and of body weight gain (e.g. treating body-weight disorders) is achieved *inter alia* by reduction of food intake. As used herein, the term "body weight disorders" refers to the disorders caused by an imbalance
25 between energy intake and energy expenditure, resulting in abnormal (e.g., excessive) body weight. Such body weight disorders include obesity.

One object of the present invention is a compound of the formula (I)



wherein:

----- represents a single bond or a double bond;

m and n are each independently selected from 1, 2, and 3,
provided that $m + n \leq 4$;

R^1 is a group selected from:

- (a) d_{-6} -alkyl,
- (b) C_{3-7} -cycloalkyl,
- (c) C_{3-6} -alkenyl,
- (d) aryl,
- (e) aryl- C_{2-6} -alkenyl,
- (f) aryl- Ci_{-6} -alkyl,
- (g) heteroaryl,
- (h) heteroaryl- C_{2-6} -alkenyl, and
- (i) heteroaryl- Ci_{-6} -alkyl,

wherein any heteroaryl or aryl residue, alone or as part of another group, is optionally independently substituted in one or more positions with a substituent selected from:

- (a) halogen,
- (b) d_{-6} -alkyl,
- (c) hydroxy- Ci_{-6} -alkyl,
- (d) fluoro- Ci_{-6} -alkyl,
- (e) C_{3-7} -cycloalkyl,
- (f) hydroxy- Cs^{\wedge} -cycloalkyl,
- (g) fluoro- C_{3-7} -cycloalkyl,
- (h) methyl- C_{3-7} -cycloalkyl,

- (i) C₃₋₄-cycloalkyl-Ci₋₃-alkyl,
 (j) C₃₋₄-cycloalkyl(hydroxy)-Ci₋₃-alkyl,
 (k) Ci₋₆-alkoxy,
 (l) fluoro-Ci₋₆-alkoxy,
 5 (m) Ci₋₂-alkoxy-Ci₋₄-alkyl,
 (n) C₃₋₇-cycloalkoxy,
 (o) fluoro-C₃₋₇-cycloalkoxy,
 (p) methyl-C₃₋₇-cycloalkoxy,
 (q) C₂₋₆-alkenyl,
 10 (r) fluoro-C₂₋₆-alkenyl,
 (s) C₂₋₆-alkynyl,
 (t) hydroxy,
 (u) -SCF₃,
 (v) -SCF₂H,
 15 (w) -SO₂NR⁶R⁶,
 (x) -S(O)_eR⁷, wherein e is 0, 1, 2 or 3,
 (y) -OSO₂R⁷,
 (z) -CN,
 (aa) -NR⁶R⁶,
 20 (ab) -NHSO₂R⁷,
 (ac) -NR⁸COR⁷,
 (ad) -NO₂,
 (ae) -CONR⁶R⁶,
 (af) -CO-R⁷,
 25 (ag) -COOH,
 (ah) Ci₋₆-alkoxycarbonyl,
 (ai) aryl,
 (aj) heteroaryl,
 (ak) aryloxy, and
 30 (al) heteroaryloxy,

wherein any (ai) aryl or (aj) heteroaryl, alone or as part of another group, is optionally substituted in one or more positions with a substituent selected from:

- (a) halogen,
 (b) Ci-4-alkyl,

(c) Ci_{-4} -alkoxy,

(d) $-\text{CF}_3$, and

(e) $-\text{CN}$;

q is selected from 0-3;

5 each R^2 is independently selected from:

(a) halogen,

(b) d_{-6} -alkyl,

(c) hydroxy- Ci_{-6} -alkyl,

(d) fluoro- Ci_{-6} -alkyl,

10 (e) C_{3-7} -cycloalkyl,

(f) hydroxy- C_{3-7} -cycloalkyl,

(g) fluoro- C^{\wedge} -cycloalkyl,

(h) methyl- C_{3-7} -cycloalkyl,

(i) C_{3-4} -cycloalkyl- Ci_{-3} -alkyl,

15 (j) C_{3-4} -cycloalkyl(hydroxy)- Ci_{-3} -alkyl,

(k) Ci_{-6} -alkoxy,

(l) fluoro- Ci_{-6} -alkoxy,

(m) Ci_{-2} -alkoxy- Ci_{-4} -alkyl,

(n) C_{3-7} -cycloalkoxy,

20 (o) fluoro- C_{3-7} -cycloalkoxy,

(p) methyl- C_{3-7} -cycloalkoxy,

(q) C_{2-6} -alkenyl,

(r) fluoro- C_{2-6} -alkenyl,

(s) C_{2-6} -alkynyl,

25 (t) hydroxy,

(u) $-\text{SCF}_3$,

(v) $-\text{SCF}_2\text{H}$,

(w) $-\text{SO}_2\text{NR}^6\text{R}^6$,

(x) $-\text{S}(\text{O})_e\text{R}^7$, wherein e is 0, 1, 2 or 3,

30 (y) $-\text{OSO}_2\text{R}^7$,

(z) $-\text{CN}$,

(aa) $-\text{NR}^6\text{R}^6$,

(ab) $-\text{NHSO}_2\text{R}^7$,

(ac) $-\text{NR}^8\text{COR}^7$,

- (ad) $-\text{NO}_2$,
 (ae) $-\text{CONR}^6\text{R}^6$,
 (af) $-\text{CO}-\text{R}^7$,
 (ag) $-\text{OCONR}^6\text{R}^6$,
 5 (ah) $-\text{CO}-\text{R}^7$, and
 (ai) $-\text{O}-\text{CH}_2\text{-aryl}$;

wherein any aryl residue is optionally substituted in one or more positions with a substituent selected from:

- (a) halogen,
 10 (b) Ci_{-4} -alkyl,
 (c) Ci_{-4} -alkoxy,
 (d) $-\text{CF}_3$, and
 (e) $-\text{CN}$;

R^3 is a group selected from:

- 15 (a) hydrogen,
 (b) d_{-6} -alkyl,
 (c) C_{3-7} -cycloalkyl,
 (d) C_{3-4} -cycloalkyl- Ci_{-3} -alkyl,
 (e) hydroxy- Ci_{-4} -alkyl
 20 (f) hydroxy- C_{3-7} -cycloalkyl,
 (g) C_{3-4} -cycloalkyl(hydroxy)- Ci_{-3} -alkyl,
 (h) Ci_{-2} -alkoxy- Ci_{-4} -alkyl,
 (i) $-\text{COOR}^8$,
 (j) $-\text{CONR}^6\text{R}^6$,
 25 (k) $-\text{CO}-\text{R}^7$,
 (l) $-\text{CN}$,
 (m) halogen,
 (n) aryl, and
 (o) heteroaryl;

30 wherein any heteroaryl or aryl residue is optionally independently substituted in one or more positions with a substituent selected from:

- (a) halogen,
 (b) Ci_{-4} -alkyl,
 (c) Ci_{-4} -alkoxy,

(d) $-\text{CF}_3$, and

(e) $-\text{CN}$;

each R^4 is independently selected from:

(a) hydrogen,

5 (b) C_{1-4} -alkyl,

(c) fluoro- C_{1-4} -alkyl,

(d) C_{3-5} -cycloalkyl,

(e) fluoro- C_6 -cycloalkyl,

(f) C_6 -cycloalkyl-methyl,

10 (g) hydroxy- C_{1-4} -alkyl,

(h) cyano;

(i) methoxy,

(j) hydroxy, and

(k) oxo,

15 provided that when R^4 is hydroxy or oxo, then either m or n is 2 or 3, and

R^4 is not attached on a carbon in alpha position to the ring nitrogen atom;

R^5 is a group selected from:

(a) hydrogen,

(b) C_{1-4} -alkyl,

20 (c) fluoro- C_{1-4} -alkyl,

(d) 2-cyanoethyl,

(e) hydroxy- C_{2-4} -alkyl,

(f) C_{3-4} -alkenyl,

(g) C_{3-4} -alkynyl,

25 (h) C_{3-6} -cycloalkyl,

(i) methyl- C_{3-7} -cycloalkyl

(j) fluoro- C_{3-7} -cycloalkyl,

(k) C_{3-4} -cycloalkyl- C_{1-4} -alkyl,

(l) C_{1-4} -alkoxy- C_{2-4} -alkyl,

30 (m) $-\text{N}(\text{R}^6)_2\text{-C}_{2-4}$ -alkyl,

(n) imidazolyl-methyl, and

(o) pyrrolidinyl-methyl;

each R^6 is a group independently selected from:

(a) hydrogen,

- (b) d-e-alkyl,
- (c) fluoro-C₂₋₆-alkyl, and
- (d) C₃₋₇-cycloalkyl, or

two R⁶ groups together with the nitrogen to which they are attached form
 5 a heterocyclic ring optionally substituted with methyl;
 each R⁷ is a group independently selected from:

- (a) hydrogen,
- (b) d-e-alkyl,
- (c) fluoro-Ci₁₋₆-alkyl,
- 10 (d) C₃₋₇-cycloalkyl,
- (e) methyl-C₃₋₇-cycloalkyl,
- (f) C₃₋₄-cycloalkyl-Ci₁₋₃-alkyl,
- (g) aryl, and
- (h) heteroaryl,

15 wherein any heteroaryl or aryl residue is optionally independently substituted in
 one or more positions with a substituent selected from:

- (a) halogen,
- (b) Ci₁₋₄-alkyl,
- (c) Ci₁₋₄-alkoxy,
- 20 (d) -CF₃, and
- (e) -CN;

each R⁸ is independently a group selected from:

- (a) hydrogen,
- (b) d-e-alkyl,
- 25 (c) fluoro-Ci₁₋₆-alkyl, and
- (d) C₃₋₇-cycloalkyl,

or R⁷ and R⁸ together with the atoms to which they are attached form a lactam
 ring when present in the group NR⁸COR⁷, or R⁷ and R⁸ together with the atoms to
 which they are attached form a sultam ring when present in the group NR⁸SO₂R⁷, and
 30 pharmaceutically acceptable salts, hydrates, solvates, geometrical isomers,
 tautomers, optical isomers, and prodrug forms thereof.

Preferred compounds of the Formula (I) include those wherein

----- represents a double bond.

Preferred compounds of the Formula (I) include those wherein m and n are each
 5 independently selected from 1 and 2, provided that $m + n \leq 3$.

Preferred compounds of the Formula (I) include those wherein R^1 is a group selected from:

- (a) aryl, in particular phenyl
- 10 (b) heteroaryl, in particular furanyl, thienyl, isoxazolyl, imidazolyl, thiazolyl, pyridyl, imidazothiazolyl, benzo furanyl, dihydrobenzo furanyl, benzothienyl, benzothiazolyl,
- wherein any heteroaryl or aryl residue is unsubstituted or independently substituted in one or more positions with a substituent selected from:
- 15 (a) halogen,
- (b) C_{1-6} -alkyl, in particular C_{1-4} -alkyl,
- (c) fluoro- C_{1-6} -alkyl, in particular fluoro- C_{1-2} -alkyl,
- (d) C_{1-6} -alkoxy, in particular C_{1-2} -alkoxy,
- (e) fluoro- C_{1-6} -alkoxy, in particular fluoro- C_{1-2} -alkoxy, and
- 20 (f) -CN.

Preferred compounds of the Formula (I) include those wherein q is 0, 1, or 2, and (when q is 1 or 2) each R^2 is independently a group selected from:

- (a) halogen,
- 25 (b) C_{1-2} -alkyl,
- (c) fluoro- C_{1-2} -alkyl,
- (d) C_{1-2} -alkoxy,
- (e) fluoro- C_{1-2} -alkoxy,
- (f) hydroxy, and
- 30 (g) -O-SO₂-CF₃.

Preferred compounds of the Formula (I) include those wherein R^3 is a group selected from:

- (a) hydrogen,
- (b) C₁₋₂-alkyl,
- (c) -F, and
- (d) -Cl.

5

Preferred compounds of the Formula (I) include those wherein each R⁴ is independently a group selected from:

- (a) hydrogen,
- (b) methyl, and
- (c) oxo.

10

Preferred compounds of the Formula (I) include those wherein R⁵ is a group selected from:

- (a) hydrogen,
- (b) C₁₋₃-alkyl,
- (c) N(R⁶)₂-C₂₋₄-alkyl-,
- (d) imidazolyl-methyl, and
- (e) pyrrolidinyl-methyl.

15

20 Preferred compounds of the Formula (I) include those wherein each R⁶ is independently a group selected from:

- (a) hydrogen, and
- (b) methyl.

25 Preferred compounds of the Formula (I) include those wherein $m + n = 2$.

Examples of preferred compounds wherein $m + n = 2$ include compounds wherein:

$\overset{\text{-----}}{\text{-----}}$ represents a double bond;

R¹ is a group selected from

30

- (a) phenyl, or
- (b) benzothienyl,

wherein phenyl is unsubstituted or independently substituted in one or two positions with a substituent selected from:

- (a) trifluoromethyl,
- (b) chloro,
- (c) methyl, and
- (d) methoxy;

5 q is 0;

R³ and R⁴ are hydrogen; and

R⁵ is a group selected from:

- (a) hydrogen,
- (b) methyl,
- 10 (c) ethyl,
- (d) dimethylamino ethyl,
- (e) imidazol-2-yl-methyl, and
- (f) pyrrolidinyl-methyl.

15 Specifically preferred compounds of the Formula (I), wherein m + n = 2, are:


- 1-(phenylsulfonyl)-1, 3,4,5-tetrahydropyrrolo[4,3,2-de]isoquino line,
- 4-methyl-1-(phenylsulfonyl)-1, 3,4,5-tetrahydropyrrolo[4,3,2-de]isoquino line,
- 4-(1H-imidazol-2-ylmethyl)-1-(phenylsulfonyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline,
- 20 • N,N-dimethyl-2-[1-(phenylsulfonyl)- 1,5-dihydropyrrolo[4,3,2-de]isoquinolin-4(3H)-yl]ethanamine,
- 4-ethyl-1 -(phenylsulfonyl)- 1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquino line,
- 1-(phenylsulfonyl)-4-(pyrrolidin-2-ylmethyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline,
- 25 • 1-(phenylsulfonyl)-4-(pyrrolidin-3-ylmethyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline,
- 1-[(2-chlorophenyl)sulfonyl]-4-ethyl-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline,
- 4-ethyl- 1- {[2-(trifluoromethyl)phenyl]sulfonyl} - 1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline,
- 30 • 1-(1-benzothien-2-ylsulfonyl)-4-ethyl-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline, and

- 4-ethyl- 1-[(2-methoxy-5-methylphenyl)sulfonyl]- 1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline.

Other preferred compounds of the Formula (I) include those wherein $m + n = 3$.

5

Examples of preferred compounds wherein $m + n = 3$ include compounds wherein:

 represents a double bond;

R^1 is a group selected from

- (a) phenyl,
- 10 (b) furanyl,
- (c) thienyl,
- (d) isoxazolyl,
- (e) imidazolyl,
- (f) thiazolyl,
- 15 (g) pyridyl,
- (h) imidazothiazolyl,
- (i) benzo furanyl,
- (j) dihydrobenzo furanyl,
- (k) benzothienyl, and
- 20 (l) benzothiazolyl,

wherein R^1 is unsubstituted or independently substituted in one or more positions with a substituent selected from:

- (a) fluoro,
- (b) chloro,
- 25 (c) bromo,
- (d) methyl,
- (e) ethyl,
- (f) n-propyl,
- (g) isopropyl,
- 30 (h) tert-butyl,
- (i) trifluoromethyl,
- (j) methoxy,
- (k) ethoxy, and

(1) cyano;

q is 0 or 1;

R² is a group selected from:

(a) methoxy,

5 (b) ethoxy,

(c) hydroxy, and

(d) -O-SO₂-CF₃;

R³ is hydrogen;

each R⁴ is independently a group selected from

10 (a) hydrogen,

(b) methyl, and

(c) oxo,

wherein at least one R⁴ is hydrogen; and

R⁵ is a group selected from

15 (a) hydrogen,

(b) methyl, and

(c) ethyl.

More preferred compounds of the Formula (I) wherein m + n = 3 are compounds

20 wherein:

R¹ is a group selected from

(a) phenyl, which may be unsubstituted or independently substituted in one or two positions with a substituent selected from: chloro, fluoro, methyl, ethyl, isopropyl, n-propyl, tert-butyl, methoxy, ethoxy, trifluoromethyl, and cyano;

25

(b) thienyl, independently substituted in one or two positions with a substituent selected from chloro and methyl,

(c) benzofuranyl,

(d) bromo-dihydrobenzofuranyl,

30

(e) benzothiazolyl,

(f) imidazolyl, independently substituted in one or two positions with methyl,

(g) chloro imidazothiazolyl,

- (h) benzothieryl, which may be unsubstituted or substituted in one or two position with a substituent selected from chloro and methyl,
- (i) dimethylfuryl,
- (j) dimethylthiazolyl, ,
- 5 (k) dimethylisoxazolyl, and
- (l) pyridinyl.

Specifically preferred compounds of the Formula (I) wherein $m + n = 3$ are:

- 4-methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[3,4,5-cd]indole,
- 10 • 4-ethyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[3,4,5-cd]indole,
- 1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 5-methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[3,4,5-cd]indole,
- 7-methoxy-6-methyl- 1-(phenylsulfonyl)-3 ,4,5 ,6-tetrahydro- 1H-azepino[5 ,4,3-
- 15 cd]indole,
- 6-methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indol-7-ol,
- 6-methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indol-7-yl trifluoromethanesulfonate,
- 7-methoxy-5,6-dimethyl- 1-(phenylsulfonyl)-3 ,4,5 ,6-tetrahydro- 1H-
- 20 azepino[5,4,3-cd]indole,
- 7-ethoxy-6-methyl- 1-(phenylsulfonyl)-3 ,4,5 ,6-tetrahydro- 1H-azepino[5 ,4,3-cd]indole,
- 1-[(2-chloro-6-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 25 • 1-[(3-chloro-2-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(3-chloro-4-fluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2-chlorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 30 • 1-[(3-chlorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(4-chlorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(3-fluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(4-fluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,

- 1-[(2,6-difluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2,5-difluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(3,5-difluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2,4-difluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 5 • 1-[(3,4-difluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(4-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2,5-dimethyl-3-thienyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 10 • 1-[(2,5-dimethylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(3,5-dimethylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[[4-fluoro-3-(trifluoromethyl)phenyl]sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 15 • 1-(1-benzofuran-2-ylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-(1,3-benzothiazol-6-ylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(1-methyl-1H-imidazol-4-yl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 20 • 1-[(6-chloroimidazo[2,1-b][1,3]thiazol-5-yl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[[2-(trifluoromethyl)phenyl]sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 25 • 1-(1-benzothien-2-ylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(5-fluoro-2-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[[3-(trifluoromethyl)phenyl]sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 30 • 1-[[4-(trifluoromethyl)phenyl]sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 4-methyl-2-(3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indol-1-ylsulfonyl)benzonitrile,

- 1-[(4,5-dichloro-2-thienyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(4-tert-butylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2,5-dimethyl-3-furyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2,4-dimethyl-5-thiazol-5-yl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(3,5-dimethylisoxazol-4-yl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(5-chloro-2-thienyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 4-(3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indol-1-ylsulfonyl)benzonitrile,
- 3-(3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indol-1-ylsulfonyl)benzonitrile,
- 1-[(4-methoxyphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2-methoxy-6-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2-methoxy-5-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2-methoxy-4-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-(1-benzothien-3-ylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(4-isopropylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(4-propylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(5-ethyl-2-methoxyphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(5-bromo-2,3-dihydro-1-benzofuran-7-yl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2-ethoxy-5-isopropylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 6-methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-(phenylsulfonyl)-1,4,5,6-tetrahydro-3H-azepino[5,4,3-cd]indol-3-one,

- 1-[(1,2-dimethyl-1H-imidazol-4-yl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 2-fluoro-5-(3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indol-1-ylsulfonyl)benzonitrile,
- 5 • 1-(pyridin-3-ylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole, and
- 1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indol-3-ol.

The compounds of Formula (I) may be agonists, partial agonists or antagonists for the 5-HT₂ receptor. Preferably, the compounds act as partial agonists or antagonists for the 5-HT₂ receptor. More preferably the compounds act as antagonists for the 5-HT₂ receptor. The term "partial agonist of the 5-HT₂ receptor" means a compound which binds to the human 5-HT₂ receptor and do not fully antagonize 5-HT-induced cAMP formation in the intrinsic activity assay described herein (see "Biological Tests").

Another object of the present invention is a compound of Formula (I) for use in therapy, especially for use in the treatment or prophylaxis of a 5-HT₂ receptor-related disorder.

Examples of 5-HT₂ receptor-related disorders include: obesity, type II diabetes, disorders of the central nervous system such as anxiety, depression, panic attacks, memory disorders, cognitive disorders, epilepsy, sleep disorders, migraine, anorexia, bulimia, binge eating disorders, obsessive compulsive disorders, psychoses, Alzheimer's disease, Parkinson's disease, Huntington's chorea, schizophrenia, attention deficit hyperactive disorder (ADHD), withdrawal from drug abuse (e.g. abuse of cocaine, amphetamine and/or nicotine), neurodegenerative diseases characterized by impaired neuronal growth, and pain.

Another object of the present invention is a pharmaceutical formulation comprising a compound of Formula (I) as active ingredient, in combination with a pharmaceutically acceptable diluent or carrier, especially for use in the treatment or prophylaxis of a 5-HT₂ receptor-related disorder.

Another object of the present invention is a method for treating a human or animal subject suffering from a 5-HT₂ receptor-related disorder. The method can include administering to a subject (e.g., a human or an animal, dog, cat, horse, cow) in need

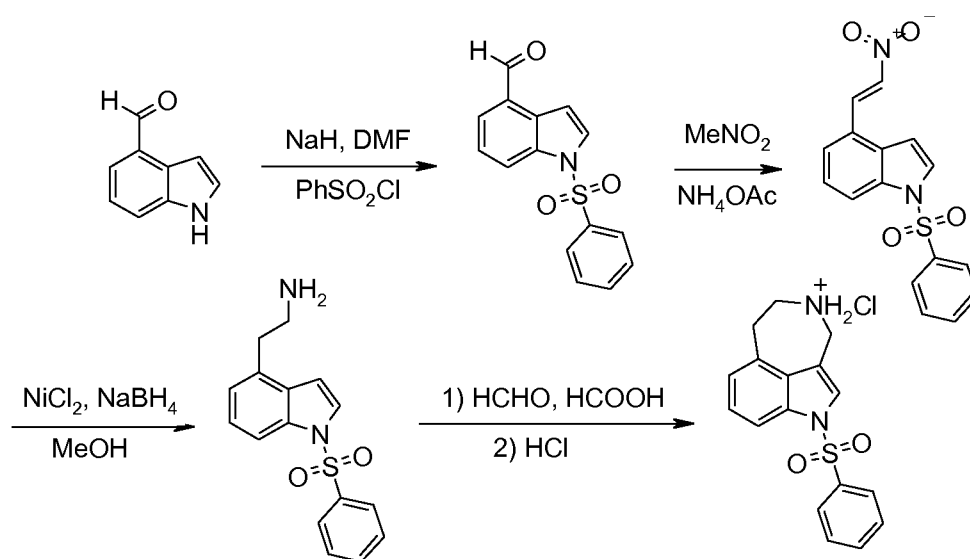
thereof an effective amount of one or more compounds of Formula (I), their salts, or compositions containing the compounds or salts.

Another object of the present invention is a method for reducing body weight or reducing body weight gain. The method comprises administering to a subject in need thereof an effective amount of a compound of the Formula (I).

The methods delineated herein can also include the step of identifying that the subject is in need of treatment of the 5-HT₂ receptor-related disorder. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g., opinion) or objective (e.g., measurable by a test or diagnostic method).

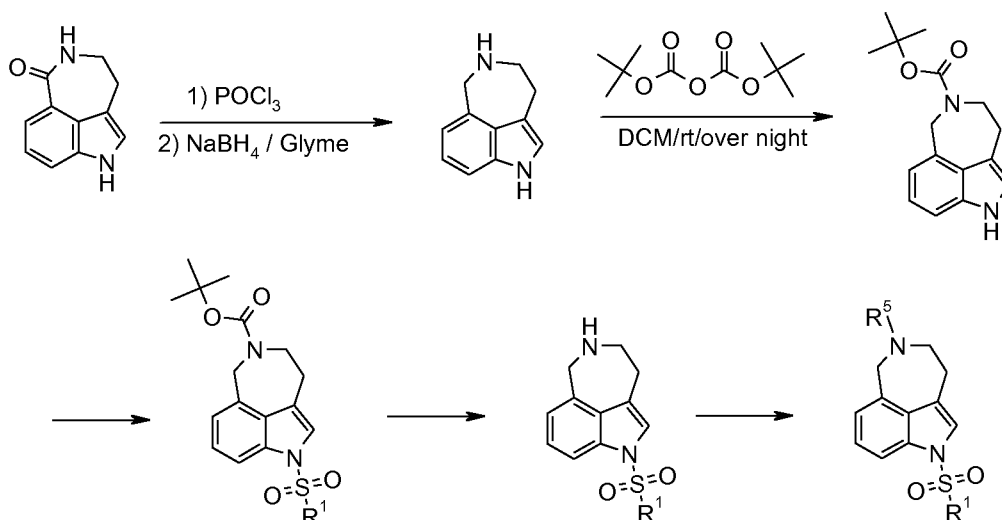
Another object of the present invention is a cosmetic composition comprising a compound as mentioned above as active ingredient, in combination with a cosmetically acceptable diluent or carrier, to achieve reduction of body weight and/or of body weight gain.

Another object of the present invention is a process for the preparation of a compound according to formula (I) of the invention comprising the following steps:



and optionally thereafter forming a pharmaceutically acceptable salt of the compound of formula (I).

Another object of the present invention is a process for the preparation of a compound according to formula (I) of the invention comprising the following steps:



and optionally thereafter forming a pharmaceutically acceptable salt of the compound of formula (I).

Methods for carrying out the the reactions described above are well known to those skilled in the art and/or are illustrated herein.

The chemicals used in the synthetic routes delineated herein may include, for example, solvents, reagents, catalysts, and protecting group and deprotecting group reagents. The methods described above may also additionally include steps, either before or after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the compounds.

In addition, various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations useful in synthesizing applicable compounds are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

The chemical structures in the schemes herein depict variables that are hereby defined commensurately with chemical groups (moieties, atoms, etc.) of the corresponding position in the compound formulae herein, whether identified by the same variable name (e.g., any R group (R₁, R₂, etc.)) or not. The suitability of a chemical group in a compound structure for use in synthesis of another compound structure is within the knowledge of one of ordinary skill in the art.

The compounds of formula (I) may possess one or more chiral carbon atoms, and they may therefore be obtained in the form of optical isomers, e.g. as a pure

enantiomer, or as a mixture of enantiomers (racemate) or as a mixture containing diastereomers. The separation of mixtures of optical isomers to obtain pure enantiomers is well known in the art and may, for example, be achieved by fractional crystallization of salts with optically active (chiral) acids or by chromatographic separation on chiral
5 columns. All isomeric forms possible (pure enantiomers, diastereomers, tautomers, racemic mixtures and unequal mixtures of two enantiomers) for the compounds delineated are within the scope of the invention. When the compounds described herein contain olefinic double bonds of geometric asymmetry, it is intended to include both trans and cis (E and Z) geometric isomers.

10 The compounds of the formula (I) may be used as such or, where appropriate, as pharmacologically acceptable salts (acid or base addition salts) thereof. The pharmacologically acceptable addition salts mentioned above are meant to comprise the therapeutically active non-toxic acid and base addition salt forms that the compounds are able to form. Compounds that have basic properties can be converted to their
15 pharmaceutically acceptable acid addition salts by treating the base form with an appropriate acid. Exemplary acids include inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulphuric acid, phosphoric acid; and organic acids such as formic acid, acetic acid, propanoic acid, hydroxyacetic acid, lactic acid, pyruvic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, benzenesulphonic acid,
20 toluenesulphonic acid, methanesulphonic acid, trifluoroacetic acid, fumaric acid, succinic acid, malic acid, tartaric acid, citric acid, salicylic acid, α -aminosalicylic acid, pantoic acid, benzoic acid, ascorbic acid and the like. Exemplary base addition salt forms are the sodium, potassium, calcium salts, and salts with pharmaceutically acceptable amines such as, for example, ammonia, alkylamines, benzathine, and amino
25 acids, such as, e.g. arginine and lysine. The term addition salt as used herein also comprises solvates which the compounds and salts thereof are able to form, such as, for example, hydrates, alcoholates and the like.

For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration.
30 Pharmaceutical formulations are usually prepared by mixing the active substance, or a pharmaceutically acceptable salt thereof, with conventional pharmaceutical excipients. Examples of excipients are water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such formulations may also

contain other pharmacologically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like. Usually, the amount of active compounds is between 0.1-95% by weight of the preparation, preferably between 0.2-20% by weight in preparations for parenteral use and more
5 preferably between 1-50% by weight in preparations for oral administration.

The formulations can be further prepared by known methods such as granulation, compression, microencapsulation, spray coating, etc. The formulations may be prepared by conventional methods in the dosage form of tablets, capsules, granules, powders, syrups, suspensions, suppositories or
10 injections. Liquid formulations may be prepared by dissolving or suspending the active substance in water or other suitable vehicles. Tablets and granules may be coated in a conventional manner.

The dose level and frequency of dosage of the specific compound will vary depending on a variety of factors including the potency of the specific compound
15 employed, the metabolic stability and length of action of that compound, the patient's age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the condition to be treated, and the patient undergoing therapy. The daily dosage may, for example, range from about 0.001 mg to about 100 mg per kilo of body weight, administered singly or multiply in doses, e.g.
20 from about 0.01 mg to about 25 mg each. Normally, such a dosage is given orally but parenteral administration may also be chosen.

DEFINITIONS

25 The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "Ci₆-alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said Ci₆-alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and
30 straight- and branched-chain pentyl and hexyl. For parts of the range "Ci₆-alkyl" all subgroups thereof are contemplated such as Ci₅-alkyl, Ci₄-alkyl, Ci₃-alkyl, Ci₂-alkyl, C₂₋₆-alkyl, C₂₋₅-alkyl, C₂₋₄-alkyl, C₂₋₃-alkyl, C₃₋₆-alkyl, C₄₋₅-alkyl, etc. Likewise, "aryl-Ci₆-alkyl" means a Ci₆-alkyl group substituted by an aryl group. Examples include benzyl, 2-phenylethyl, 1-phenylethyl and 1-naphthylmethyl.

Unless otherwise stated, "fluoro-Ci₆-alkyl" means a Ci₆-alkyl group substituted by one or more fluorine atoms. Examples of said fluoro-Ci₆-alkyl include 2-fluoroethyl, fluoromethyl, trifluoromethyl and 2,2,2-trifluoroethyl.

Unless otherwise stated or indicated, the term "hydroxy-Ci₄-alkyl" denotes a
5 straight or branched alkyl group that has a hydrogen atom thereof replaced with OH. Examples of said hydroxy-Ci₄-alkyl include hydroxymethyl, 2-hydroxy ethyl, 2-hydroxypropyl and 2-hydroxy-2-methylpropyl.

Unless otherwise stated or indicated, the term "Ci₆-alkoxy" denotes a straight or branched alkoxy group having from 1 to 6 carbon atoms. Examples of said C₁₋₆-alkoxy
10 include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, t-butoxy and straight- and branched-chain pentoxy and hexoxy. For parts of the range "Ci₆-alkoxy" all subgroups thereof are contemplated such as Ci₅-alkoxy, Ci₄-alkoxy, Ci₃-alkoxy, Ci₂-alkoxy, C₂₋₆-alkoxy, C₂₋₅-alkoxy, C₂₋₄-alkoxy, C₂₋₃-alkoxy, C₃₋₆-alkoxy, C₄₋₅-alkoxy, etc.

Unless otherwise stated or indicated, "fluoro-Ci₆-alkoxy" means a C₁₋₆-alkoxy
15 group substituted by one or more fluorine atoms. Examples of said fluoro-Ci₆-alkoxy include trifluoromethoxy, difluoromethoxy, monofluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, and 1,1,2,2-tetrafluoroethoxy.

Unless otherwise stated or indicated, the term "Ci₄-alkoxy-C₂₋₄-alkyl" denotes a
20 straight or branched alkoxy group having from 1 to 4 carbon atoms connected to an alkyl group having from 1 to 4 carbon atoms. Examples of said Ci₄-alkoxy-C₂₋₄-alkyl include methoxymethyl, ethoxymethyl, iso-propoxymethyl, n-butoxymethyl, and t-butoxymethyl. For parts of the range "Ci₄-alkoxy-C₂₋₄-alkyl" all subgroups thereof are contemplated such as Ci₃-alkoxy-C₂₋₄-alkyl, Ci₄-alkoxy-C₂₋₃-alkyl, Ci₂-alkoxy-C₂₋₃-
25 alkyl, C₂₋₄-alkoxy-C₂₋₄-alkyl, C₂₋₃-alkoxy-C₂₋₄-alkyl, C₂₋₄-alkoxy-C₂₋₃-alkyl, etc.

Unless otherwise stated or indicated, the term "C₂₋₆-alkenyl" denotes a straight or branched alkenyl group having from 2 to 6 carbon atoms. Examples of said C₂₋₆-alkenyl include vinyl, allyl, 2,3-dimethylallyl, 1-butenyl, 1-pentenyl, and 1-hexenyl. For parts of the range "C₂₋₆-alkenyl" all subgroups thereof are contemplated such as C₂₋₅-alkenyl, C₂₋₄-alkenyl, C₂₋₃-alkenyl, C₃₋₆-alkenyl, C₄₋₅-alkenyl, etc. Likewise, "aryl-C₂₋₆-alkenyl" means a C₂₋₆-alkenyl group substituted by an aryl group. Examples of said aryl-C₂₋₆-alkenyl include styryl and cinnamyl.
30

Unless otherwise stated or indicated, the term "fluoro-C₂₋₆-alkenyl" denotes a straight or branched alkenyl group having from 2 to 6 carbon atoms substituted by one

or more fluorine atoms. Examples of said fluoro-C2-6-alkenyl include 1-fluoro vinyl, 1,2-difluorovinyl, trifluorovinyl, and 2-fluoro-2-propen-1-yl.

Unless otherwise stated or indicated, the term "C3₄-alkynyl" denotes a straight or branched alkynyl group having from 3 to 4 carbon atoms. Examples of said C₃₋₄-alkynyl include 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, and 1-methylprop-2-yn-1-yl.

Unless otherwise stated or indicated, the term "C3₇-cycloalkyl" denotes a cyclic alkyl group having a ring size from 3 to 7 carbon atoms. Said cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. For parts of the range "C₃₋₇-cycloalkyl" all subgroups thereof are contemplated such as C₃₋₆-cycloalkyl, C₃₋₅-cycloalkyl, C₃₋₄-cycloalkyl, C₄₋₇-cycloalkyl, C₄₋₆-cycloalkyl, C₄₋₅-cycloalkyl, C₅₋₇-cycloalkyl, C₆₋₇-cycloalkyl, etc.

Unless otherwise stated or indicated, the term "C3₄-cycloalkyl-Ci₃-alkyl" denotes a straight or branched Ci₃-alkyl group substituted by a C3₄-cycloalkyl group. An exemplary "C₃₋₄-cycloalkyl-Ci₃-alkyl" group includes cyclopropylmethyl.

Unless otherwise stated or indicated, the term "hydroxy-C3₇-cycloalkyl" denotes a cyclic alkyl group having a ring size from 3 to 7 carbon atoms, that has a hydrogen atom thereof replaced with OH. Examples of said hydroxy-C3₇-cycloalkyl include 1-hydroxy-cyclopropyl, 2-hydroxy-cyclopropyl, 1-hydroxy-cyclobutyl, 2-hydroxy-cyclobutyl, etc.

Unless otherwise stated or indicated, the term "C3₄-cycloalkyl(hydroxy)-Ci₃-alkyl" denotes a straight or branched Ci₃-alkyl group substituted by a C₃₋₄-cycloalkyl group and a hydroxy group. Said C3₄-cycloalkyl and hydroxy groups may be attached to the same or to different carbon atoms of the Ci₃-alkyl group. Preferably, the C3₄-cycloalkyl and hydroxy groups are attached to the same carbon atom. An exemplary "C₃₋₄-cycloalkyl(hydroxy)-Ci₃-alkyl" group includes cyclopropyl(hydroxy)-methyl.

Unless otherwise stated or indicated, the term "methyl-C3₇-cycloalkyl" denotes a C3₇-cycloalkyl group substituted by one or two methyl groups. Examples of said "methyl-C₃₋₇-cycloalkyl" include 4-methylcyclohexyl, 3,3-dimethylcyclopentyl and 1-methylcyclopropyl.

Unless otherwise stated or indicated, the term "methyl-C3₇-cycloalkoxy" denotes a C3₇-cycloalkoxy group substituted by one or two methyl groups. Examples of said "methyl-C3₇-cycloalkoxy" include 4-methylcyclohexyloxy, 3,3-dimethylcyclopentyloxy and 1-methylcyclopropyloxy.

Unless otherwise stated or indicated, the term "fluoro-C₃₋₇-cycloalkyl" denotes a C₃₋₇-cycloalkyl group substituted by one or two fluorine atoms. Examples of said "fluoro-C₃₋₇-cycloalkyl" include 2,2-difluorocyclopropyl and 4-fluorocyclohexyl.

Unless otherwise stated or indicated, the term "fluoro-C₃₋₇-cycloalkoxy" denotes
5 a C₃₋₇-cycloalkoxy group substituted by one or two fluorine atoms. Examples of said "fluoro-C₃₋₇-cycloalkoxy" include 2,2-difluorocyclopropyloxy and 4-fluorocyclohexyloxy.

Unless otherwise stated or indicated, the term "aryl" refers to a hydrocarbon ring system of one, two, or three, preferably one or two, rings, having at least one aromatic
10 ring and having from 6-14, preferably 6-10, carbon atoms. Examples of aryls are phenyl, pentalenyl, indenyl, indanyl, 1,2,3,4-tetrahydronaphthyl, 1-naphthyl, 2-naphthyl, fluorenyl and anthryl. The aryl rings may be optionally substituted. Likewise, aryloxy refers to an aryl group bonded to an oxygen atom.

An aryl group can be linked to the remainder of the molecule through any
15 available ring carbon whether the ring carbon is in an aromatic ring or in a partially saturated ring.

The term "heteroaryl" refers to a mono- or bicyclic aromatic ring system, only one ring need be aromatic, and the said heteroaryl moiety can be linked to the remainder of the molecule via a carbon or nitrogen atom in any ring, and having from 5 to 10 ring
20 atoms (mono- or bicyclic), in which one or more of the ring atoms are other than carbon, such as nitrogen, sulphur, oxygen and selenium. Examples of such heteroaryl rings include furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, imidazothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, chromanyl, quinazolinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, indazolyl, pyrazolyl,
25 pyridazinyl, quinolinyl, isoquinolinyl, benzofuranyl, dihydrobenzofuranyl, benzodioxolyl, benzodioxinyl, benzothienyl, benzimidazolyl, benzothiazolyl, benzothiadiazolyl, and benzotriazolyl groups. If a bicyclic heteroaryl ring is substituted, it may be substituted in any ring.

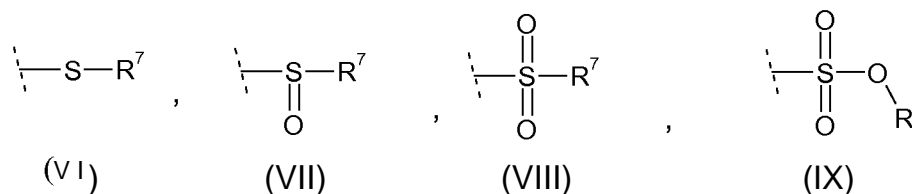
Unless otherwise stated or indicated, the term "heterocyclic" refers to a non-
30 aromatic (i.e., partially or fully saturated) mono- or bicyclic ring system having 4 to 10 ring atoms with at least one heteroatom such as O, N, or S, and the remaining ring atoms are carbon. Preferably, "heterocyclic" refers to a fully saturated non-aromatic monocyclic ring system with 4 to 7 ring atoms and in which one or two atoms are heteroatoms selected from O, N and S, and the remaining ring atoms are carbon.

Examples of heterocyclic groups include piperidyl, tetrahydropyranyl, tetrahydrofuranyl, azepinyl, azetidiny, pyrrolidinyl, morpholinyl, imidazoliny, thiomorpholinyl, pyranyl, dioxanyl, and piperazinyl groups. When present in heterocyclic groups, the sulfur atom may optionally be in an oxidized form (i.e., S=O or O=S=O).

Unless otherwise stated or indicated, the term "carbocyclic" refers to a non-aromatic (i.e., partially or fully saturated) monocyclic ring system having 3 to 6 carbon ring atoms. Examples of carbocyclic rings include cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclopentene, cyclohexene.

Unless otherwise stated or indicated, the term "halogen" shall mean fluorine, chlorine, bromine or iodine.

The term $-S(O)_eR^7$, wherein e is 0, 1, 2 or 3, has the meaning as illustrated by formula (VI) - (IX):



The term "lactam" refers to a lactam group selected from 2-azetidinon-1-yl, 2-pyrrolidon-1-yl and 2-piperidinon-1-yl.

The term "sultam" refers to a sultam group selected from tetrahydro- 1,1 - dioxido-2H-1,2-thiazin-2-yl and 1,1-dioxido-2-isothiazolidinyl.

Unless otherwise stated or indicated, the term "oxo" denotes =O (i.e., an oxygen atom joined to a carbon atom through a double bond).

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

"Pharmaceutically acceptable" means being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

"Treatment" as used herein includes prophylaxis of the named disorder or condition, or amelioration or elimination of the disorder once it has been established.

"An effective amount" refers to an amount of a compound that confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e.,

measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect).

The term "prodrug forms" means a pharmacologically acceptable derivative, such as an ester or an amide, which derivative is biotransformed in the body to form the active drug. Reference is made to Goodman and Gilman's, The Pharmacological basis
5 of Therapeutics, 8th ed., Mc-Graw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p. 13-15; and "The Organic Chemistry of Drug Design and Drug Action" by Richard B. Silverman. Chapter 8, p 352. (Academic Press, Inc. 1992. ISBN 0-12-643730-0).

The following abbreviations have been used:

10 eq. means equivalents
CV means Coefficient of Variation,
DCM means dichloromethane,
DMSO means dimethyl sulphoxide,
EDTA means ethylenediamine tetraacetic acid,
15 EGTA means ethylenebis(oxyethylenenitrilo)tetraacetic acid,
HEPES means 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid,
HPLC means high performance liquid chromatography,
LSD means lysergic acid, diethylamide,
MeCN means acetonitrile,
20 SPA means Scintillation Proximity Assay,
TFA means trifluoroacetic acid,
THF means tetrahydrofuran,
UV means ultraviolet,
MeOH means methanol,
25 MW means microwave oven,
Boc means t-butoxycarbonyl,
LAH means lithium aluminum hydride,
TEA means triethylamine.

30 All isomeric forms possible (pure enantiomers, diastereomers, tautomers, racemic mixtures and unequal mixtures of two enantiomers) for the compounds delineated are within the scope of the invention. Such compounds can also occur as cis- or trans-, *E*- or *Z*- double bond isomer forms. All isomeric forms are contemplated.

The compounds of the formula (I) may be used as such or, where appropriate, as pharmacologically acceptable salts (acid or base addition salts) thereof. The pharmacologically acceptable addition salts mentioned above are meant to comprise the therapeutically active non-toxic acid and base addition salt forms that the compounds are able to form. Compounds that have basic properties can be converted to their pharmaceutically acceptable acid addition salts by treating the base form with an appropriate acid. Exemplary acids include inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulphuric acid, phosphoric acid; and organic acids such as formic acid, acetic acid, propanoic acid, hydroxyacetic acid, lactic acid, pyruvic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, benzenesulphonic acid, toluenesulphonic acid, methanesulphonic acid, trifluoroacetic acid, fumaric acid, succinic acid, malic acid, tartaric acid, citric acid, salicylic acid, p-aminosalicylic acid, pamoic acid, benzoic acid, ascorbic acid and the like. Exemplary base addition salt forms are the sodium, potassium, calcium salts, and salts with pharmaceutically acceptable amines such as, for example, ammonia, alkylamines, benzathine, and amino acids, such as, e.g. arginine and lysine. The term addition salt as used herein also comprises solvates which the compounds and salts thereof are able to form, such as, for example, hydrates, alcoholates and the like.

For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. Pharmaceutical formulations are usually prepared by mixing the active substance, or a pharmaceutically acceptable salt thereof, with conventional pharmaceutical excipients. Examples of excipients are water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such formulations may also contain other pharmacologically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like. Usually, the amount of active compounds is between 0.1-95% by weight of the preparation, preferably between 0.2-20% by weight in preparations for parenteral use and more preferably between 1-50% by weight in preparations for oral administration.

The formulations can be further prepared by known methods such as granulation, compression, microencapsulation, spray coating, etc. The formulations may be prepared by conventional methods in the dosage form of tablets, capsules, granules, powders, syrups, suspensions, suppositories or

injections. Liquid formulations may be prepared by dissolving or suspending the active substance in water or other suitable vehicles. Tablets and granules may be coated in a conventional manner.

In a further aspect the invention relates to methods of making compounds of any
5 of the formulae herein comprising reacting any one or more of the compounds of the formulae delineated herein, including any processes delineated herein. The compounds of the formula (I) above may be prepared by, or in analogy with, conventional methods.

The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. A pharmaceutically
10 acceptable acid addition salt may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Examples of addition salt forming acids are mentioned above.

The compounds of formula (I) may possess one or more chiral carbon atoms,
15 and they may therefore be obtained in the form of optical isomers, e.g. as a pure enantiomer, or as a mixture of enantiomers (racemate) or as a mixture containing diastereomers. The separation of mixtures of optical isomers to obtain pure enantiomers is well known in the art and may, for example, be achieved by fractional crystallization of salts with optically active (chiral) acids or by chromatographic separation on chiral
20 columns.

The chemicals used in the synthetic routes delineated herein may include, for example, solvents, reagents, catalysts, and protecting group and deprotecting group reagents. The methods described above may also additionally include steps, either
25 before or after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the compounds.

In addition, various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations useful in synthesizing applicable compounds are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers
30 (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

The necessary starting materials for preparing the compounds of formula (I) are either known or may be prepared in analogy with the preparation of known compounds.

The dose level and frequency of dosage of the specific compound will vary depending on a variety of factors including the potency of the specific compound employed, the metabolic stability and length of action of that compound, the patient's age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the condition to be treated, and the patient undergoing therapy. The daily dosage may, for example, range from about 0.001 mg to about 100 mg per kilo of body weight, administered singly or multiply in doses, e.g. from about 0.01 mg to about 25 mg each. Normally, such a dosage is given orally but parenteral administration may also be chosen.

The invention will now be further illustrated by the following non-limiting Examples. The specific examples below are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. All publications cited herein are hereby incorporated by reference in their entirety.

Methods

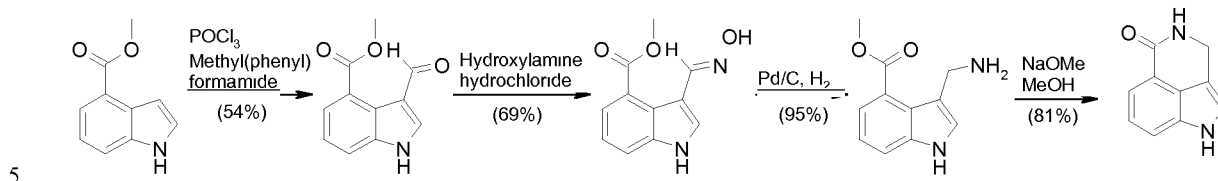
¹H nuclear magnetic resonance (NMR) and ¹³C NMR were recorded on a Bruker Advance DPX 400 spectrometer at 400.1 and 100.6 MHz, respectively, or alternatively, on a Varian Inova 400 spectrometer at 400 and 100.5 MHz respectively, or alternatively, on a Bruker NMR 500 spectrometer at 500.1 MHz and 125.1 MHz, respectively or alternatively, on a JEOL eclipse 270 spectrometer at 270.0 MHz and 67.5 MHz, respectively. All spectra were recorded using residual solvent as internal standard.

Preparative HPLC/MS was performed on a Waters/Micromass Platform ZQ system and preparative HPLC/UV was performed on a Gilson system in accordance to the experimental details specified in the examples. Analytical HPLC-MS was performed using an Agilent 1100 Series Liquid Chromatograph/Mass Selective Detector (MSD) to obtain the pseudo molecular [M + H]⁺ ion of the target molecules. Preparative flash chromatography was performed on Merck silica gel 60 (230-400 mesh). The compounds were named using ACD Name 6.0 (or later versions thereof). Microwave reactions were performed with a Personal Chemistry Smith Creator using 0.5-2 mL or 2-5 mL Smith Process Vials fitted with aluminum caps and septa.

Intermediate 1

3,4-Dihydropyrrolo [4,3,2-de]isoquinolin-5(IH)-one

This intermediate was prepared according to a literature procedure (M. E. Flaugh, T. A. Crowell, J. A. Clemens, B. D. Sawyer *J. Med. Chem.* **1979**, 22, 63-68).



Intermediate 2

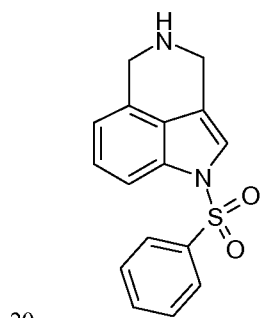
1-(Phenylsulfonyl)-3,4-dihydropyrrolo[4,3,2-de]isoquinolin-5(IH)-one

10 Benzenesulfonyl chloride (140 mg, 0.79 mmol), NBu_4HSO_4 (24 mg, 0.07 mmol) and 4M aq. NaOH (2 mL) were, in that order, added to 3,4-Dihydropyrrolo[4,3,2-de]isoquinolin-5(IH)-one, Intermediate 1 (124 mg, 0.72 mmol) in DCM (10 mL). The reaction was stirred at room temperature for 2 h and then extracted with water and DCM (x2). The product seems to be only partially soluble in DCM and some solid material in the water layer was filtered off and added to the DCM layer, which was concentrated and dried to give 227 mg of the title compound, as a light brown solid. MS m/z 313 $[\text{M} + \text{H}]^+$.

15

Example 1

1-(Phenylsulfonyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline



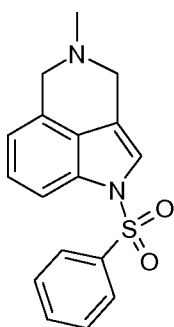
BH3:SMe₂ (205 μL , 2.2 mmol) was added dropwise over 5 min. to a refluxing mixture of 1-(phenylsulfonyl)-3,4-dihydropyrrolo[4,3,2-de]isoquinolin-5(IH)-one, Intermediate 2, (225 mg, 0.72 mmol) in dry THF (10 mL) with continuous reflux for 2.5 h. Additional two portions BH₃:SMe₂ (100 μL x 2) were added (2.5 h reflux between the additions).
25 Reflux was continued for 5 h after the last addition, then room temperature over night. The reaction was quenched by addition of HCl in MeOH (1.25 M, 4 mL) and reflux 1 h.

The solvent was evaporated and the crude mixture was extracted with DCM (x2) and sat. Na₂CO₃(aq). The organic layers were combined, dried and concentrated. Purification was performed by flash column chromatography (3-5% MeOH in DCM) which gave 66 mg of the title compound as a beige solid. MS *m/z* 299 [M + H]⁺.

5

Example 2

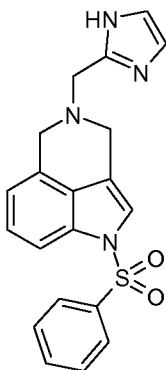
4-Methyl-1-(phenylsulfonyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline trifluoroacetate



- 10 Formaldehyde (37% in water, 55 μ L, 0.76 mmol) and NaBH₃CN (104 mg, 1.65 mmol) were added to 1-(phenylsulfonyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline, Example 1 (23 mg, 0.07 mmol) in dry MeCN (3 mL). The reaction was irradiated with microwaves for 10 min. at 130 °C, filtered and concentrated. The crude product was purified by preparative HPLC (YMCcolumn 150x30 mm, 20-50% MeCN, 0.1% TFA).
- 15 This gave 17 mg of the title compound as a brown gum. MS *m/z* 313 [M + H]⁺.

Example 3

4-(1*H*-Imidazol-2-ylmethyl)-1-(phenylsulfonyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline bis(trifluoroacetate)



20

The experimental for Example 2 was followed using 1*H*-imidazole-2-carbaldehyde (16 mg, 0.18 mmol), AcOH (46 μ L, 0.81 mmol), Na(OAc)₃BH₃ (51 mg, 0.24 mmol) and 1-

(phenylsulfonyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline, Example 1 (27 mg, 0.08 mmol) in dry THF (4 mL). Preparative HPLC (YMCcolumn 150x30 mm, 32-62% MeCN, 0.1% TFA). This gave 1.7 mg of the title compound, as a brown gum. MS m/z 379 $[M + H]^+$.

5

Intermediate 3

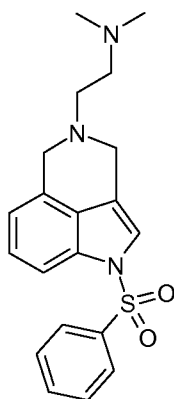
1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline

LAH (IM in THF, 8.7 mL, 8.7 mmol) was added to 3,4-Dihydropyrrolo[4,3,2-de]isoquinolin-5(1H)-one, Intermediate 1 (300 mg, 1.72 mmol) in dry THF (only partly dissolved) under N_2 . The mixture was stirred at reflux for 2 h and a color change from light brown to green was noticed after 1 h. Water (330 μ L), NaOH (aq., 15%, 330 μ L) and water (1.0 mL) were, in that order, added and the resulting precipitation was filtered off. The eluate was dried (Na_2SO_4), filtered and concentrated to give the crude product. The material was used without further purification.

15

Example 4

7V[^]V-Dimethyl-2-[1-(phenylsulfonyl)-1,5-dihydropyrrolo[4,3,2-de]isoquinolin-4(3H)-yl] **ethanamine bis(trifluoroacetate)**



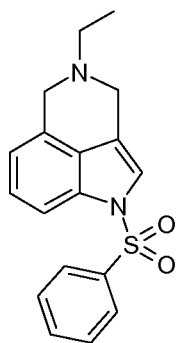
1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline, Intermediate 3 (45 mg, 0.28 mmol), NEt_3 (236 μ L, 1.71 mmol) and JV,JV-dimethylglycylchloride hydrochloride (90 mg, 0.57 mmol) were dissolved in dry DCM (10 mL) by sonication and stirred at room temperature for 1.5 h. The mixture was extracted with DCM (x2) and aq. sat. Na_2CO_3 /brine. The organic layers were combined dried (Na_2SO_4), filtered and concentrated to give 69 mg crude material. 2/5 of this material (28 mg, 0.12 mmol) was added to dry THF (3 mL, not dissolved) and LAH (IM in THF, 0.575 mL, 0.575 mmol) was added. The mixture was stirred at reflux for 60 min. (clear solution). Water (22 μ L),

25

15% aq. NaOH (22 μ L) and water (66 μ L) were added and the resulting precipitation was filtered off. The eluate was dried (Na_2SO_4), filtered and concentrated to give 26 mg crude material. Half of this material (13 mg, 0.057 mmol) was dissolved in dry THF (2 mL) and NaH (60% dispersion in mineral oil, 11 mg, 0.28 mmol) was added. The mixture was stirred at ambient temperature for 50 min., then phenylsulfonyl chloride (8 mL, 0.06 mmol) in dry THF (0.5 mL) was added with continuous stirring for 1 h. The reaction was cooled on ice bath and quenched with 2 drops of water, acidified with 1 drop of cone. HCl and concentrated. The crude product was purified by preparative HPLC (ACEcolumn 50x21.1 mm, 16-46% MeCN, 0.1% TFA). This gave 15 mg of the title compound as a colorless solid. MS m/z 370 $[\text{M} + \text{H}]^+$.

Example 5

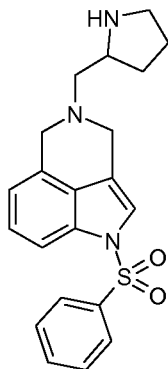
4-Ethyl-1-(phenylsulfonyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline
trifluoroacetate



15 Acetaldehyde (11 μ L, 0.18 mmol), AcOH (34 μ L, 0.60 mmol) and $\text{Na}(\text{OAc})_3\text{BH}_3$ (52 mg, 0.24 mmol) were added to 1-(phenylsulfonyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline, Example 1 (18 mg, 0.06 mmol) in dry THF (3 mL). The reaction mixture was irradiated with microwaves for 12 min. at 130°C, filtered and concentrated. The crude product was purified by preparative HPLC (ACEcolumn 50x21.1 mm, 15-45% MeCN, 0.1% TFA). This gave 8 mg of the title compound as a colorless gum. MS m/z 127 $[\text{M} + \text{H}]^+$.

Example 6

1-(phenylsulfonyl)-4-(pyrrolidin-2-ylmethyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline bis(trifluoroacetate)



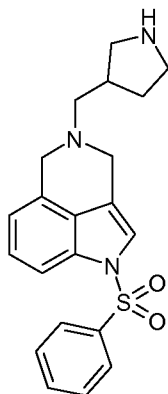
5

Tert-butyl 2-formylpyrrolidine-1-carboxylate (18 mg, 0.09 mmol), AcOH (17 μ L, 0.30 mmol) and Na(OAc)sBH₃ (26 mg, 0.12 mmol) were added to 1-(phenylsulfonyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline, Example 1 (9 mg, 0.03 mmol) in dry THF (3 mL). The reaction mixture was irradiated with microwaves for 12 min. at 130°C, filtered and concentrated. The residue was dissolved in MeOH/conc. HCl (4:1, 1.5 mL) and irradiated with microwaves for 3 min. at 100 °C, filtered and concentrated. The crude product was purified by preparative HPLC (ACE column 50x21.1mm, 11-41% MeCN, 0.1% TFA). This gave 11 mg of the title compound as a light yellow gum. MS *m/z* 382 [M + H]⁺.

15

Example 7

1-(Phenylsulfonyl)-4-(pyrrolidin-3-ylmethyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline trifluoroacetate



20 The experimental for

Example 6 was followed using tert-butyl 3-formylpyrrolidine-1-carboxylate (18 mg, 0.09 mmol). Preparative HPLC (ACE column 50x21.1 mm, 9-39% MeCN, 0.1% TFA). This gave 11 mg of the title compound as a colorless gum. MS m/z 382 $[M + H]^+$.

5 Intermediate 4

4-Ethyl-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline

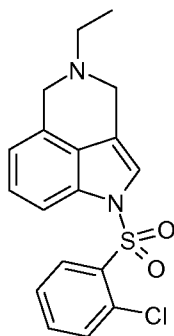
LiAlH₄ (0.440 g, 11.6 mmol) was added in portions to a solution of 3,4-dihydropyrrolo[4,3,2-de]isoquinolin-5(1H)-one, Intermediate 1 (0.4 g, 2.32 mmol) in dry THF (20 ml). The mixture was brought to reflux for 3 hours, cooled, diluted with aqueous THF and filtered. The solid cake was washed with THF (2x) and the residue was evaporated to give a light brown solid. This brown solid was dissolved in MeOH (20 ml) and acetaldehyde (0.334 g, 7.6 mmol) and sodiumtriacetoxy borohydride (0.482 g, 2.3 mmol) were added. The mixture was stirred for 1 hour and evaporated to half its volume and partitioned between IN Na₂CO₃ and dichloromethane. The organic phase was washed with brine, dried (MgSO₄) and evaporated. The crude product was purified by flash chromatography using 10% MeOH to 50% MeOH in dichloromethane with 1% NEt₃. Yield: 142 mg. Grey solid. MS m/z 187 $[M + H]^+$.

General procedure for sulfonylation used in Example 8-1 1:

20 4-Ethyl-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline, Intermediate 4 (0.015 g, 0.081 mmol), requisite sulfonyl chloride (0.16 mmol) and tetrabutylammonium hydrogensulfate (5 mg, 0.016 mmol) were dissolved in dichloromethane (1 ml) and NaOH (0.01 g, 0.24 mmol) in water (0.3 ml) was added. The mixture was stirred at room temperature overnight and water (1 ml) was added to each vial and the organic phase was collected, evaporated and purified as described below.

Example 8

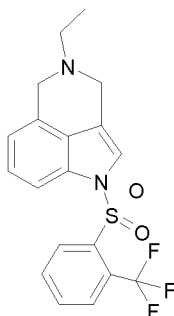
1-[(2-Chlorophenyl)sulfonyl]-4-ethyl-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline



Sulfonyl **chloride**: 2-chlorophenylsulfonyl **chloride** (34 mg, 0.16 mmol). Purified by reversed phase preparative HPLC using XTerra Prep MS C18 5 μ m 19x50 mm, flow 25 ml/min, 50mM pHIO NH₄HCO₃ / ACN, fractions collected based on UV-signal (254 nm). Prep Gradient start 37. Prep gradient gradient stop 67. The purest fractions were pooled and the acetonitrile was evaporated. Yield: 8.6 mg. Light yellow solid. MS m/z 361 [M + H]⁺.

Example 9

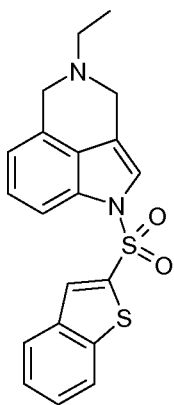
4-Ethyl- 1- {[2-(trifluoromethyl)phenyl] sulfonyl} -1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline



Sulfonyl chloride: 2-(trifluoromethyl)benzenesulfonyl chloride (39 mg, 0.16 mmol). Purified by reversed phase preparative HPLC using XTerra Prep MS C18 5 μ m 19x50 mm, flow 25 ml/min, 50mM pHIO NH₄HCO₃ / ACN, fractions collected based on UV-signal (254 nm). Prep Gradient start 39. Prep gradient gradient stop 69. The purest fractions were pooled and evaporated. Yield: 6.7 mg. Brown solid. MS m/z 395 [M + H]⁺.

Example 10

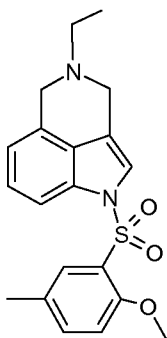
1-(1-Benzothien-2-ylsulfonyl)-4-ethyl-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline



Sulfonylchloride: 1-benzothiophene-2-sulfonyl **chloride** (38 mg, 0.16 mmol).
 Purified by reversed phase preparative HPLC using XTerra Prep MS C18 5 μ m 19x50 mm, flow 25ml/min, 50mM pHIO NH₄HCO₃ / ACN, fractions collected based on UV-
 5 signal (254nm). Prep Gradient start 44. Prep gradient gradient stop 74. The purest fractions were pooled and evaporated. Yield: 1.1 mg. Yellow solid. MS m/z 383 [M + H]⁺.

Example 11

10 4-Ethyl-1-[(2-methoxy-5-methylphenyl)sulfonyl]-1,3,4,5-tetrahydropyrrolo[4,3,2-
de]isoquinoline



Sulfonyl **chloride**: 6-methoxy-m-toluenesulfonylchloride (0.035 g, 0.16 mmol).
 Purified by reversed phase preparative HPLC using XTerra Prep MS C18 5 μ m
 15 19x50mm, flow 25ml/min, 50mM pHIO NH₄HCO₃ / ACN, fractions collected based on UV-signal (254nm). Prep Gradient start 36. Prep gradient gradient stop 66. The purest fractions were pooled and evaporated. Yield: 0.5 mg. Offwhite solid. MS m/z 371 [M + H]⁺.

Intermediate 5

1-(Phenylsulfonyl)-1 *H*-indole-4-carbaldehyde

1*H*-Indole-4-carbaldehyde (24.8 g, 0.17 mol) was dissolved in dry DMF (500 ml), cooled in ice-bath and NaH (7.5 g (60% suspension in oil), 0.19 mol, 1.1 eq.) was added. After stirring for a few minutes, the cold bath was removed and the rxn mixture was stirred at room temperature for 40 min. under Ar. The insoluble NaH clumps were brought in solution by means of sonication for a few minutes. The mixture was cooled in ice-bath and benzenesulfonyl chloride (23.9 ml, 0.188 mol, 1.1 eq.) was added dropwise over 3 min. The reaction mixture was stirred at room temperature for 1 hour, then poured slowly into a mixture of water (1 L) and EtOAc (200 ml). The aqueous phase was extracted with EtOAc (5x100 ml), the organic phase was washed with brine (200 ml), dried over Na₂SO₄ and evaporated. The residue was purified on silica flash column using petroleumether/EtOAc (1:1) giving the product as a colorless crystalline solid. Yield: 45.5 g. MS *m/z* 286 [M + H]⁺.

15

Intermediate 6

4-[(ϵ)-2-Nitrovinyl]-1-(phenylsulfonyl)-1 *H*-indole

1-(Phenylsulfonyl)-1 *H*-indole-4-carbaldehyde, Intermediate 5 (45.4 g, 0.159 mol) was dissolved in nitromethane (300 ml) and ammonium acetate (4.9 g, 0.064 mol, 0.4 eq.) was added. Mixture was heated at reflux for 4 hours and left overnight at room temperature. Water (150 ml) was added, organic phase was separated. The aqueous phase was extracted with DCM (3x50 ml). Combined organic phase was washed with brine and dried on Na₂SO₄. The crude material (HPLC purity 85%) was passed through a silica column using DCM/EtOAc (8:1) as eluent. The product containing fractions were evaporated to a small volume when crystallization started. The yellow crystals were filtered, washed with petrolether/EtOAc (2:1), and dried in vacuo. Yield: 33.1 g. MS *m/z* 329 [M + H]⁺.

25

Intermediate 7

2-[1-(Phenylsulfonyl)-1 *H*-indol-4-yl]ethanamine

4-[(ϵ)-2-nitrovinyl]-1-(phenylsulfonyl)-1*H*-indole, Intermediate 6 (32.1 g, 97.8 mmol) was mixed with dry THF (100 ml), stirred for 5 min, then dry MeOH was added (400 ml). Mixture was cooled in ice-bath and sodium borohydride (14.8 g, 0.39 mol) was added in small portions over a period of 30 minutes.

30

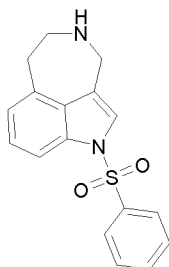
Preparation of NiB2 catalyst: Nickel (II) chloride hexahydrate (46.5 g, 0.196 mol) was dissolved in MeOH (200 ml), the solution cooled in ice-bath and sodium borohydride (22.3 g, 0.587 mol) was added in small portions with vigorous stirring over 30 min. (N.B. Reaction is very exothermic with vigorous gas evolution!) The black suspension
5 is stirred for additional 15 minutes at room temperature

This catalyst suspension is added to the main reaction mixture at 0°C and sodium borohydride (38 g, 1.0 mol) is carefully added in small portions over 1 hour. Reaction mixture was stirred for additional 2 hours at room temperature, filtered through a pad of MeOH/NH₃ aq. impregnated silica. The silica pad was washed with
10 MeOH/NH₃ aq. and MeOH was evaporated in vacuo from the filtrate. Water (500 ml) was added to the residue and the mixture was extracted with diethylether. The organic layer was washed with brine, dried over Na₂SO₄, evaporated and the residue was purified on silica using DCM/MeOH/NH₃ aq. (40:8:0.5), giving the desired amine as a syrup. Yield: 12.2 g. MS *m/z* 301 [M + H]⁺.

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Example 12

1-(Phenylsulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[3,4,5-*cd*]indole hydrochloride

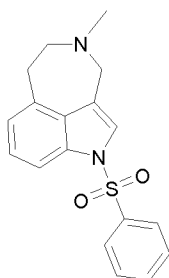


2-[1-(Phenylsulfonyl)-1 *H*-indol-4-yl]ethanamine, Intermediate 7 (7.05 g, 23.5 mmol)
20 was dissolved in formic acid (70 ml) and formaldehyde solution (14 ml, as a 37% sol. in water, 187 mmol) was added. Reaction mixture was stirred at room temperature for 20 hours, poured into water (700 ml) and extracted with DCM. The DCM extract was washed with 2% NaOH solution in water (500 ml), brine, dried on Na₂SO₄ and evaporated. The residue was purified on silica using DCM/MeOH/NH₃ aq. (50:5:0.5),
25 giving the desired amine as a syrup. This material was dissolved in EtOAc and saturated HCl solution in dioxane was added dropwise until precipitation was complete. Solution was diluted with diethylether, the salt was filtered off, washed with diethylether and dried. The dry salt was dissolved in *n*-PrOH/MeOH by heating, MeOH was removed on rotavap and diethylether was added slowly giving crystalline off-white precipitate of the

desired product, which was filtered, washed with ether and dried in vacuo. Yield: 4.2 g.
MS m/z 313 $[M + H]^+$.

Example 13

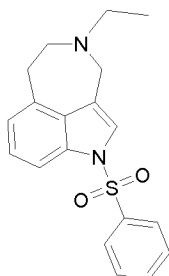
5 4-Methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[3,4,5- *c*']indole
hydrochloride



1-(Phenylsulfonyl)-3,4,5,6-tetrahydro-1*H*-azepino[3,4,5-*c*']indole hydrochloride,
Example 12 (100 mg, 0.3 mmol) was dissolved in THF (4 mL) before sodium
10 triacetoxyborohydride (203 mg, 1.0 mmol) and acetic acid (191 mg, 3.2 mmol) was
added. Aqueous formaline (37 %, 1 mL) was added and the reaction mixture was heated
in MW at 70 °C for 300 s. The reaction mixture was evaporated and the crude product
was purified by preparative HPLC using System B, 100 mM NH_4HCO_3 / MeCN (36-
66% MeCN). The product was isolated and transformed to the hydrochloride. 15.2 mg of
15 the pure product was isolated as a yellow oil, yield 12%. MS m/z 327 $[M + H]^+$.

Example 14

4-Ethyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[3,4,5- *c*']indole
hydrochloride



20 1-(Phenylsulfonyl)-3,4,5,6-tetrahydro-1*H*-azepino[3,4,5-*c*']indole hydrochloride,
Example 12 (70 mg, 0.2 mmol) was dissolved in THF (4 mL) before sodium
triacetoxyborohydride (142 mg, 0.7 mmol) and acetic acid (134 mg, 2.2 mmol) was
added, acetaldehyde (14.7 mg, 0.3 mmol) was added and the reaction mixture was

heated in MW at 70°C for 600 s. The reaction mixture was evaporated and the crude product was purified by preparative HPLC (33-63), using Xterra column. The product was isolated and transformed to the hydrochloride. 12.9 mg of the pure product was isolated as a clear oil. MS m/z 341 $[M + H]^+$.

5

Intermediate 8

2-Nitroethyl acetate

This compound was prepared according to M. E. Flaugh, T. A. Crowell, J. A. Clemens, B. D. Sawyer *J. Med. Chem.*, **1979**, 22, pp. 63-68. Acetic anhydride (8.06 g, 79.0 mmol) and NaOAc (1.45 g, 17.7 mmol) were mixed and heated. Two drops of pyridine were added. 2-nitroethanol (6.45 g, 70.8 mmol) was carefully added to the suspension at 30-35 °C during 30 min. Thereafter the mixture was stirred overnight at room temperature. The next morning the mixture contained undissolved NaOAc and a new orange precipitate. The reaction mixture was taken up between CHCl₃ and water, washed 1x with water, 1x with brine and dried with MgSO₄. Thereafter the solvent was evaporated under reduced pressure at 40°C. The remaining orange oil was co-evaporated first with chloroform and then five times with toluene and finally with chloroform to get the 6.90 g of pure compound.

20 Intermediate 9

Methyl 3-(2-Nitroethyl)-1*H*-indole-4-carboxylate

A solution of methyl 1*H*-indole-4-carboxylate (7.34 g, 41.9 mmol), 2-nitroethyl acetate (6.90 g, 51.9 mmol) and 4-tert-butylcatechol (0.026 g, 0.16 mmol) in xylene (50 mL) was refluxed for 6 hrs. The solvent was evaporated under reduced pressure to give a residual dark oily raw product that was purified by short column chromatography on silica using ethyl acetate-light petroleum as eluent. The product was obtained as yellowish solid material in 79% yield. Mp: 103°C. MS m/z 249 $[M + H]^+$.

Intermediate 10

30 1,3,4,5-Tetrahydro-6*H*-azepino[5,4,3-*c*']indol-6-one

Methyl 3-(2-nitroethyl)-1*H*-indole-4-carboxylate, Intermediate 9 (7.38 g, 29.8 mmol) was dissolved in methanol (200 mL) by heating and aqueous 2M HCl (460 mL) was added. Zinc powder (46.2 g, 706 mmol) was added portion wise by vigorous stirring.

The resulting mixture was heated under reflux for 2h. The hot reaction mixture was filtered and the filtrate was treated with aqueous 2M NaOH (560 mL) and filtered again. The filter cake was washed with methanol. The methanol was removed under reduced pressure and the aqueous mixture was extracted three times with ethyl acetate. The organic solution was washed with water and brine dried with magnesium sulfate, filtered and evaporated to dryness. It was obtained a yellowish crystalline material with the yield of 4.62 g. Recrystallisation from the dichloromethane-methanol mixture gave the product of very high purity. Mp. 234°C. MS m/z 187 $[M + H]^+$.

Intermediate 11

1,3,4,5-Tetrahydro-6 *H*-azepino[5,4,3-*c*]indol **and** 2,2a,3,4,5,6-hexahydro-1 *H*-azepino[5,4,3-*cd*]indole

Intermediate 10 (175 mg, 0.94 mmol) was added to phosphoryl chloride (1 mL) at room temperature. The solution was stirred for 15 min and excess phosphoryl chloride then removed at room temperature under vacuum. The resultant oil was placed under high vacuum for 20 min to remove residual phosphoryl chloride and then dissolved in glyme (4 mL). The solution was cooled in ice and sodium borohydride (114 mg, 3 mmol) was added with vigorous stirring. The reaction mixture was warmed to room temperature, stirred for 1 h, and cooled in ice and 10% hydrochloric acid (2 mL) was added dropwise. The glyme was evaporated and water added. After extraction with ether, sodium hydroxide was added to the aqueous solution (to about pH 10), followed by extraction with ether. The basic extracts were dried over $MgSO_4$ and concentrated. The crude product were purified with column chromatography (SiO_2 ; $CHCl_3$: MeOH: NH_3 95:4.5:0.5) and used directly in the next step. 30% of the starting material was recovered in this separation.

Intermediate 12

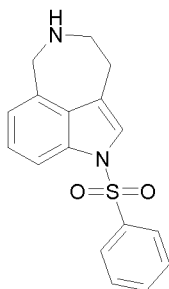
tert-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-*c*]indole-5-carboxylate

The pure 1:1 mixture of 1,3,4,5-Tetrahydro-6 *H*-azepino[5,4,3-*c*]indole and 2,2a,3,4,5,6-hexahydro-1-*f*-azepino[5,4,3-*c*]indole, Intermediate 11 (172 mg, 1 mmol) was dissolved in DCM (10 mL) and added ***di-tert-butyl*** dicarbonate (436 mg, 2 mmol). The reaction mixture was stirred at room temperature over night. Solvent was removed and the residue was purified by chromatography (SiO_2 , ethyl acetate: cyclohexane 1:5). The expected product ***tert-butyl*** 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-*c*]indole-5-

carboxylate was isolated from crude mixture of products and was pure enough for the next step synthesis.

Example 15

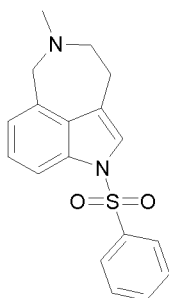
5 1-(Phenylsulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3- *c*']indole



NaH (60% in mineral oil, 66 mg, 0.4 mmol) was added to a solution of *tert-butyl* 1,3,4,6-tetrahydro-5/*f*-azepino[5,4,3-*c*J]indole-5-carboxylate, Intermediate 12 (51 mg, 0.2 mmol) in 800 μ L of dry DMF). The reaction mixture was shaken at room temperature for 10 minutes and phenylsulfonyl chloride (66.2 mg, 0.4 mmol, in 600 μ L of dry DMF) was added. The reaction mixture was shaken at room temperature for 10-20 minutes. The reaction was quenched by adding 4 mL of mixture a mixture of methanol and acetic acid (1:1). Boc-deprotection was carried out by adding 4 mL of solution of TFA/DCM (1:1). 2M NH_3 in MeOH was added to the crude reaction (2 X 10 mL) and the solvent was removed under vacuum. The crude product was purified by preparative HPLC using System B, 100 mM NH_4HCO_3 / MeCN (10-50% MeCN). 50 mg of the pure product was isolated as an off-white solid. MS m/z 313 $[\text{M} + \text{H}]^+$.

Example 16

20 5-Methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3- *c*']indole

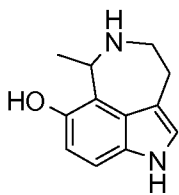


1-(Phenylsulfonyl)-3,4,5,6-tetrahydro-1/*f*-azepino[5,4,3-*c*']indol, Example 15 (34.4 mg, 0.11 mmol) was dissolved in DME (2 mL) and added formaldehyde (37% Wt. solution in water, 0.1 mL, 1.1 mmol), acetic acid (0.05 mL, 0.7 mmol) and sodium

triacetoxyborohydride (156 mg, 0.7 mmol). The reaction mixture was stirred at room temperature for 24 H. The reaction was quenched by adding 1 M NaOH (5 mL). Aqueous phase (pH about 14) was separated and was then extracted with DCM (3 X 5 mL). The combined organic phases was washed with water and brine, and dried with
 5 MgSO₄. The solvent was removed under vacuum. 20 mg pure product was obtained as an off-white solid. MS *m/z* 327 [M + H]⁺.

Intermediate 13

6-Methyl-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3- *cd*]indol-7-ol



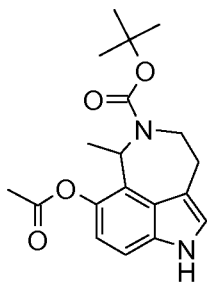
10

To a solution of serotonin*HCl (5.02 g, 23.6 mmol) in MeOH (200 mL) was added TEA (200 mL) and the mixture was stirred at room temperature for 30 min. The reaction mixture was then put under an oxygen atmosphere (balloon) and was stirred at reflux temperature (68°C) for 24 hours. The solvent from the brown mixture was
 15 evaporated at reduced pressure and the resulting oil (10g) was plug-applied on a column of silica (L=90 mm q=60 mm) and chromatographed initially with CHCl₃/MeOH/(aq 25% NH₃) 90/10/1 about two column volumes, followed by 80/20/2. The pure fractions were pooled and the solvent was evaporated at reduced pressure to give 0.41g of a brown solid. MS *m/z* 203 [M + H]⁺.

20

Intermediate 14

tert-Butyl 7-(acetyloxy)-6-methyl-1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3- *cd*]indole-5-carboxylate

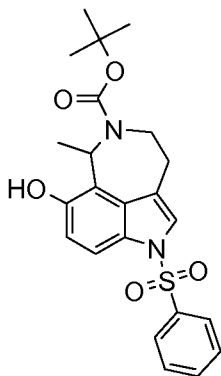


25 To a solution of 6-methyl-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-*cd*]indol-7-ol, Intermediate 13 (340 mg, 1.7 mmol) in MeOH (10 mL) was added (BOC)₂O (513 mg,

2.4 mmol) and the reaction mixture was stirred at room temperature for 30 minutes (95% conversion). Pyridine (0.5 mL) was added and the mixture was left at room temperature over night. The solvent was evaporated at reduced pressure and the resulting residue was dissolved in pyridine (4 mL), cooled on an ice bath, Ac₂O (1 mL) was added and the stirred mixture was allowed to slowly reach room temperature over night. The mixture was concentrated under reduced pressure and the residue was co-evaporated twice with toluene. The dark brown oil (0.9 g) was chromatographed on a column of silica, initially with 100% CHCl₃ followed by CHCl₃/MeOH 99.5/0.5. Evaporation of pure pooled fractions yielded 241 mg of the title compound as a light yellow oil. MS m/z 289 [M + H -isobutene]⁺.

Intermediate 15

tert-Butyl 7-hydroxy-6-methyl-1-(phenylsulfonyl)-1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-*cd*]indole-5-carboxylate



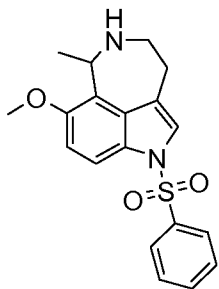
15

A solution of tert-butyl 7-(acetyloxy)-6-methyl-1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-*cJ*]indole-5-carboxylate, Intermediate 14 (241 mg, 0.7 mmol) in dry DMF (4mL) was cooled on an ice bath, benzene sulphonyl chloride (210 mg, 1.2 mmol) was added and followed by NaH (34 mg, 1.4 mmol) added in small portions during one minute. The mixture was stirred for two minutes whereafter 2M NaOH (0.5 mL) was added and the mixture was left at room temperature over night. The mixture was diluted with water (10 mL) and HOAc (0.5 mL) was carefully added to the brown turbid solution resulting in the precipitation of an off white solid. More water (20 ml) was added and the solids were filtered off and dried to give 245 mg of off-white crystals. MS m/z 343 [M + *H*-BOC]⁺.

25

Example 17

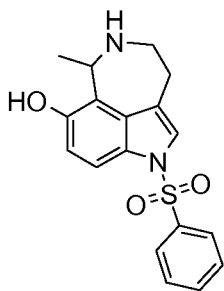
7-Methoxy-6-methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole trifluoroacetate



To a solution of tert-butyl 7-hydroxy-6-methyl-1-(phenylsulfonyl)- 1,3,4,6-tetrahydro-
 5 5*H*-azepino[5,4,3-*cd*]indole-5-carboxylate, Intermediate 15 (39 mg, 0.079 mmol) in
 acetone (10 mL) was added K₂CO₃ (110 mg, 0.79 mmol) followed by MeI (79 mg, 0.55
 mmol) and the mixture was heated at reflux over night. The solvent from the filtered
 solution was evaporated at reduced pressure and the resulting oil was dissolved in
 DCM/TFA 50/50 (1 mL) and was left at room temperature over night. The solvent was
 10 evaporated at reduced pressure, the resulting oil was dissolved in MeOH with a drop of
 25% aq NH₃ and the crude was purified by preparative HPLC (Xterra C18, 10 mM
 NH₄CO₃ (pH 10) - CH₃CN) to give 11.9 mg of the title compound as a brown oil. MS
 m/z 357 [M + H]⁺.

15 Example 18

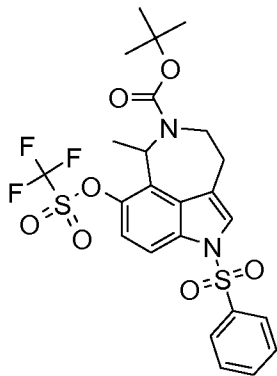
6-Methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-*cd*]indol-7-ol



A 50/50 mixture of DCM/TFA (1 mL) was added to tert-butyl 7-hydroxy-6-methyl-1-
 (phenylsulfonyl)-1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-*cd*]indole-5-carboxylate,
 20 Intermediate 15 (16 mg, 0.036 mmol) and the mixture was stirred at room temperature
 for one hour. The solvent was evaporated at reduced pressure and the crude product was
 purified by preparative HPLC (Xterra C18, 10 mM NH₄CO₃ (pH 10) - CH₃CN) to give
 6.9 mg of the title compound. MS m/z 343 [M + H]⁺.

Intermediate 16

tert-Butyl 6-methyl-1-(phenylsulfonyl)-7-[[[(trifluoromethyl)sulfonyl]oxy]-1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3- *c*']indole-5-carboxylate



5

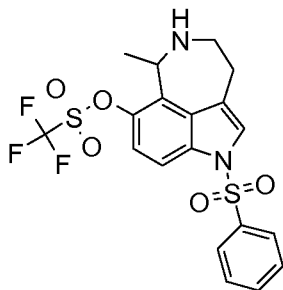
tert-butyl 7-hydroxy-6-methyl- 1-(phenylsulfonyl)- 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-*c*']indole-5-carboxylate, Intermediate 15 (80 mg, 0.18 mmol), *N*-phenyltrifluoromethanesulfonimide (129 mg, 0.36 mmol) DCM (3 mL) and *N,N*-diisopropylethylamine (DIPEA) (70 mg, 0.54 mmol) were mixed into a 16 mm test tube with screw cap. The reaction mixture was stirred at room temperature over night, an additional equivalent of *N*-phenyltrifluoromethanesulfonimide and DIPEA was added together with more DCM (6 mL) and the turbid mixture was stirred for another two days. The clear solution was washed with acidic (pH<1, HCl) ice water and brine. The solvent was evaporated at reduced pressure and the resulting solid was triturated with a minute amount of cold MeOH (1 mL). White crystals were filtered off and dried to give 60 mg of product. MS *m/z* 519 [*M* + *H* - isobutene]⁺.

15

Example 19

6-Methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3- *c*']indol-7-yl trifluoromethanesulfonate trifluoroacetate

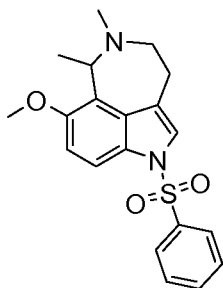
20



tert-Butyl 6-methyl- 1-(phenylsulfonyl)-7- {[trifluoromethyl)sulfonyl]oxy }-1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-*c*]indole-5-carboxylate, Intermediate 16 (12.6 mg, 0.022 mmol) was dissolved in a 50/50 mixture of DCM/TFA (1 mL) and left at room temperature for one hour. The evaporated crude product was purified by preparative HPLC (ACE C8 5 mm, water containing 0.1% TFA - CH₃CN) to give 7.2 mg of the title compound as a light brown oil. MS *m/z* 474 [M + H]⁺.

Example 20

7-Methoxy-5,6-dimethyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-*cd*]indole

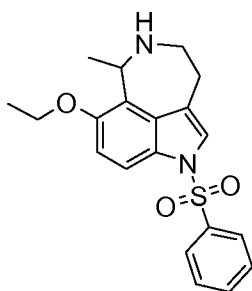


To 7-Methoxy-6-methyl- 1-(phenylsulfonyl)-3,4,5,6-tetrahydro- 1*H*-azepino[5,4,3-*c*]indole, Example 17, (11.4 mg, 0.032 mmol) in DCE (2 mL) was added sodium triacetoxy borohydride (20 mg, 0.096 mmol) followed by a drop of aq. cone. formaldehyde (11 mg, 0.10 mmol) and the mixture was stirred at 40°C for one hour. The organic phase was washed twice with 0.1 M NaOH and the oil from the evaporated organic phase was purified by preparative HPLC (Xterra C18, 10 mM NH₄CO₃ (pH 10) - CH₃CN) to give 7.5 mg of the title compound as an off white oil. MS *m/z* 371 [M + H]⁺.

20

Example 21

7-Ethoxy-6-methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-*cd*]indole



tert-Butyl 7-hydroxy-6-methyl- 1-(phenylsulfonyl)- 1,3,4,6-tetrahydro-5 *H*-azepino[5 ,4,3-
cJ]indole-5-carboxylate, Intermediate 15 (16 mg, 0.036 mmol), acetone (5 mL), K₂CO₃
(50 mg, 0.36 mmol) and EtI (34 mg, 0.22 mmol) were added into a 16 mm test tube
5 with screw cap and the suspension was stirred at 62°C over night. The solvent from the
filtered mixture was evaporated at reduced pressure and the residue was dissolved in
DCM/TFA 50/50 (1 mL) and left in room temperature for two hours. The solvent was
evaporated at reduced pressure and the crude was purified by preparative HPLC (Xterra
C18, 10 mM NH₄CO₃ (pH 10) - CH₃CN) to give 9.0 mg (67%) of the title compound
10 as a brown oil. MS m/z 371 [M + H]⁺.

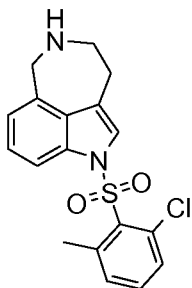
General procedure for sulfonylation used in Example 22-Example 70:

NaH (95%; ca. 3 mg, 0.125 mmol, 2.5 eq) was added to a slurry of *tert-butyl* 1,3,4,6-
tetrahydro-5/*f*-azepino[5,4,3-*c* *d*T]indole-5-carboxylate, Intermediate 12 (14 mg, 0.050
15 mmol) in dry CH₃CN (350 µL). The vial was immediately flushed with N₂, sealed and
agitated at room temperature for 1.5 h. To the reaction mixture was added (through the
septum) a solution of the sulfonyl chloride (0.75 mmol, 1.5 eq) dissolved in dry CH₃CN
(150 µL) and the agitation was continued for 3 h. TFA (100 µL) was added to the
reaction mixture giving the deprotected product after 2-16 h reaction time. The reaction
20 mix was diluted with H₂O (100 µL) and MeOH (ca.1000 µL), and was purified by
preparative reverse phase HPLC (ACE Cs, 5µm 21x50mm, flow 25ml/min, 0.1% TFA
in MilliQ H₂O- CH₃CN) to give the product as the corresponding trifluoroacetate salt.
Sulfonyl chlorides which were not soluble in CH₃CN were added directly to the reaction
mixtures as solids.

25

Example 22

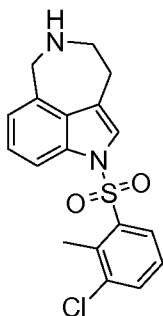
1-[(2-Chloro-6-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-
cd]indole trifluoroacetate



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2-chloro-6-
 methylbenzenesulfonyl chloride (17 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 13.3 mg of product. MS (ESI) m/z 361 $[M + H]^+$.

Example 23

1-[(3-Chloro-2-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-
cd]indole trifluoroacetate



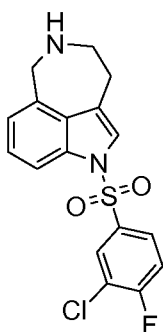
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 3-chloro-2-
 methylbenzenesulfonyl chloride (17 mg, 0.75 mmol) as described in the general
 procedure above, to give 5.2 mg of product. MS (ESI) m/z 361 $[M + H]^+$.

15

Example 24

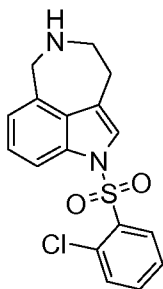
1-[(3-Chloro-4-fluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-
cd]indole trifluoroacetate



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5/f-azepino[5,4,3-
 c<]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 3-chloro-4-
 fluorobenzenesulfonyl chloride (17 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 10.1 mg of product. MS (ESI) m/z 365 $[M + H]^+$.

Example 25

**1-[(2-Chlorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino [5,4,3-*cd*]indole
 trifluoroacetate**



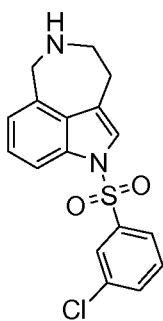
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2-
 chlorobenzenesulfonyl chloride (16 mg, 0.75 mmol) as described in the general
 procedure above, to give 11.7 mg of product. MS (ESI) m/z 347 $[M + H]^+$.

15

Example 26

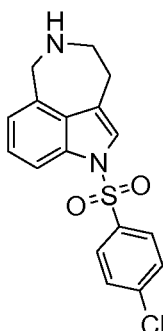
**1-[(3-Chlorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino [5,4,3-*cd*]indole
 trifluoroacetate**



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 3-
 chlorobenzenesulfonyl chloride (16 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 1.2 mg of product. MS (ESI) m/z 347 $[M + H]^+$.

Example 27

1-[(4-Chlorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-*c**d*] indole
 trifluoroacetate



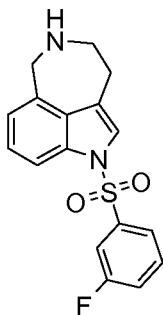
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 4-
 chlorobenzenesulfonyl chloride (16 mg, 0.75 mmol) as described in the general
 procedure above, to give 13.1 mg of product. MS (ESI) m/z 331 $[M + H]^+$.

15

Example 28

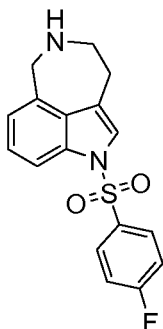
1-[(3-Fluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino [5,4,3-*cd*]indole
 trifluoroacetate



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 3-
 fluorobenzenesulfonyl chloride (15 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 9.7 mg of product. MS (ESI) m/z 347 $[M + H]^+$.

Example 29

**1-[(4-Fluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino [5,4,3-*cd*]indole
 trifluoroacetate**



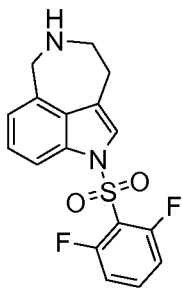
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 4-
 fluorobenzenesulfonyl chloride (15 mg, 0.75 mmol) as described in the general
 procedure above, to give 12.0 mg of product. MS (ESI) m/z 331 $[M + H]^+$.

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Example 30

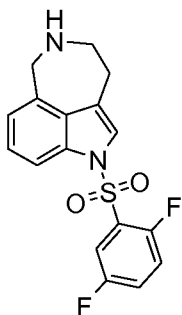
**1-[(2,6-Difluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino [5,4,3-*cd*]indole
 trifluoroacetate**



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5/f-azepino[5,4,3-
 c<i>i>indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2,6-
 difluorobenzenesulfonyl chloride (16 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 10.8 mg of product. MS (ESI) m/z 349 $[M + H]^+$.

Example 31

**1-[(2,5-Difluorophenyl)sulfonyl] -3,4,5,6-tetrahydro-1 *H*-azepino [5,4,3-*cd*]indole
 trifluoroacetate**



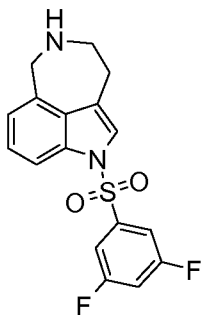
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 cd\indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2,5-
 difluorobenzenesulfonyl chloride (16 mg, 0.75 mmol) as described in the general
 procedure above, to give 9.4 mg of product. MS (ESI) m/z 349 $[M + H]^+$.

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Example 32

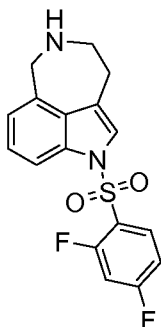
**1-[(3,5-Difluorophenyl)sulfonyl] -3,4,5,6-tetrahydro-1 *H*-azepino [5,4,3-*cd*]indole
 trifluoroacetate**



The title compound was prepared from *tert*-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 cJ]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 3,5-
 difluorobenzenesulfonyl chloride (16 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 9.9 mg of product. MS (ESI) m/z 349 [M + H]⁺.

Example 33

**1-[(2,4-Difluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino [5,4,3-*cd*]indole
 trifluoroacetate**



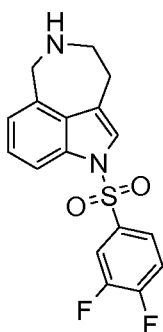
10

The title compound was prepared from *tert*-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 cJ]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2,4-
 difluorobenzenesulfonyl chloride (16 mg, 0.75 mmol) as described in the general
 procedure above, to give 9.6 mg of product. MS (ESI) m/z 349 [M + H]⁺.

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Example 34

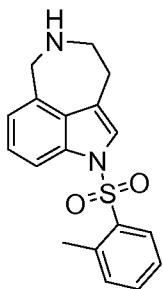
**1-[(3,4-Difluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino [5,4,3-*cd*]indole
 trifluoroacetate**



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5/f-azepino[5,4,3-
 c<ij>indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 3,4-
 difluorobenzenesulfonyl chloride (16 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 7.4 mg (32%) of product. MS (ESI) m/z 349 $[M + H]^+$.

Example 35

1-[(2-Methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3- *cd*]indole
 trifluoroacetate



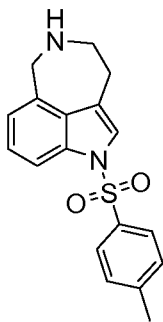
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 cd\indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2-
 methylbenzenesulfonyl chloride (14 mg, 0.75 mmol) as described in the general
 procedure above, to give 8.2 mg of product. MS (ESI) m/z 327 $[M + H]^+$.

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Example 36

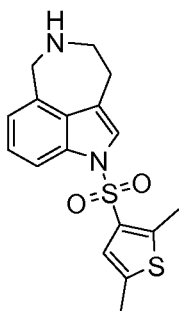
1-[(4-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3- *cd*]indole
 trifluoroacetate



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 4-
 methylbenzenesulfonyl chloride (14 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 12.5 mg of product. MS (ESI) m/z 327 $[M + H]^+$.

Example 37

1-(2,5-Dimethylthiophenyl)sulfonyl-1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-*cd*]indole
 trifluoroacetate



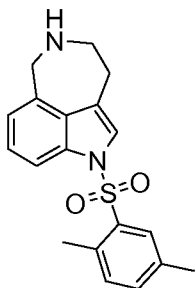
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2,5-
 dimethylthiophene-3-sulfonyl chloride (16 mg, 0.75 mmol) as described in the general
 procedure above, to give 9.8 mg of product. MS (ESI) m/z 347 $[M + H]^+$.

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Example 38

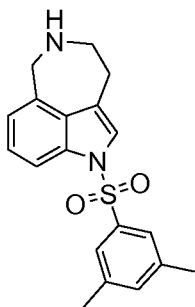
1-[(2,5-Dimethylphenyl)sulfonyl]-1,3,4,5,6-tetrahydro-5 *H*-azepino [5,4,3-*cd*]indole
 trifluoroacetate



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2,5-
 dimethylbenzenesulfonyl chloride (15 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 12.1 mg of product. MS (ESI) m/z 341 $[M + H]^+$.

Example 39

1-[(3,5-Dimethylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3- *cd*]indole
 hydrochloride



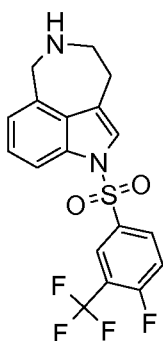
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 3,5-
 dimethylbenzenesulfonyl chloride (15 mg, 0.75 mmol) as described in the general
 procedure above, to give 8.9 mg of product. MS (ESI) m/z 341 $[M + H]^+$.

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Example 40

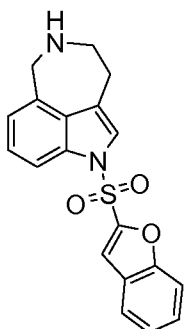
1-{[4-fluoro-3-(trifluoromethyl)phenyl]sulfonyl}-3,4,5,6-tetrahydro-1 *H*-
 azepino[5,4,3-*cd*]indole trifluoroacetate



The title compound was prepared from *tert*-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 4-fluoro-3-
 (trifluoromethyl)benzenesulfonyl chloride (20 mg, 0.75 mmol) as described in the
 5 general procedure above, to give 10.3 mg of product. MS (ESI) m/z 399 $[M + H]^+$.

Example 41

1-(1-Benzofuran-2-ylsulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3- *cd*]indole
 trifluoroacetate



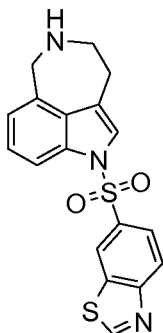
10

The title compound was prepared from *tert*-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 1-benzofuran-2-
 sulfonyl chloride (16 mg, 0.75 mmol) as described in the general procedure above, to
 give 3.6 mg of product. MS (ESI) m/z 353 $[M + H]^+$.

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Example 42

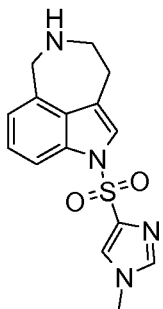
1-(1,3-Benzothiazol-6-ylsulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3- *cd*]indole
 trifluoroacetate



The title compound was prepared from *tert*-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 1,3-benzothiazole-6-
 sulfonyl chloride (18 mg, 0.75 mmol) as described in the general procedure above, to
 5 give 3.6 mg of product. MS (ESI) m/z 370 $[M + H]^+$.

Example 43

1-[(1-Methyl-1 *H*-imidazol-4-yl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-
cd]indole trifluoroacetate



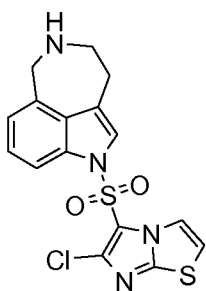
10

The title compound was prepared from *tert*-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 1-methyl-1 *H*-
 imidazole-4-sulfonyl chloride (14 mg, 0.75 mmol) as described in the general procedure
 above, to give 11.0 mg of product. MS (ESI) m/z 317 $[M + H]^+$.

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Example 44

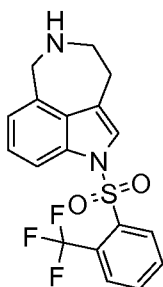
1-[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-
 azepino[5,4,3-*cd*]indole trifluoroacetate



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5H-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 6-chloroimidazo[2,1-
 b][1,3]thiazole-5-sulfonyl chloride (19 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 3.9 mg of product. MS (ESI) m/z 393 $[M + H]^+$.

Example 45

1-([2-(Trifluoromethyl)phenyl]sulfonyl)-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-
 c*d*]indole trifluoroacetate



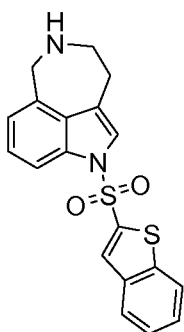
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5*H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2-
 (trifluoromethyl)benzenesulfonyl chloride (18 mg, 0.75 mmol) as described in the
 general procedure above, to give 1.9 mg of product. MS (ESI) m/z 381 $[M + H]^+$.

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Example 46

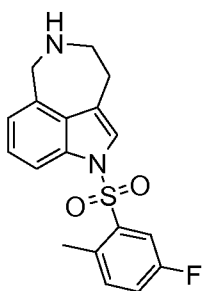
1-(1-Benzothien-2-ylsulfonyl)-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*c**d*]indole
 trifluoroacetate



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 1-benzothiophene-2-
 sulfonyl chloride (18 mg, 0.75 mmol) as described in the general procedure above, to
 5 give 9.9 mg of product. MS (ESI) m/z 369 $[M + H]^+$.

Example 47

1-[(5-Fluoro-2-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-
cd]indole trifluoroacetate



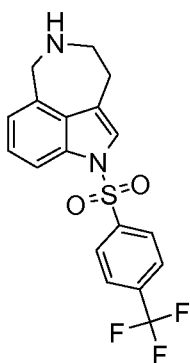
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 5-fluoro-2-
 methylbenzenesulfonyl chloride (16 mg, 0.75 mmol) as described in the general
 procedure above, to give 14.5 mg of product. MS (ESI) m/z 345 $[M + H]^+$.

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Example 48

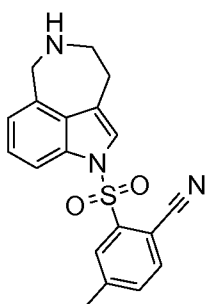
1-[[4-(Trifluoromethyl)phenyl]sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-
cd]indole trifluoroacetate



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 4-trifluoromethyl
 benzenesulfonyl chloride (18 mg, 0.75 mmol) as described in the general procedure
 5 above, to give 13.9 mg of product. MS (ESI) m/z 381 $[M + H]^+$.

Example 49

4-Methyl-2-(3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-*c*[^]indol-1-ylsulfonyl)benzonitrile
 trifluoroacetate



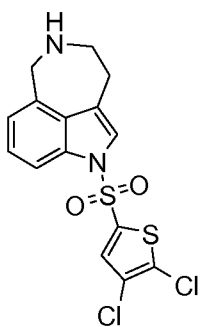
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2-cyano-5-
 methylbenzenesulfonyl chloride (16 mg, 0.75 mmol) as described in the general
 procedure above, to give 1.3 mg of product. MS (ESI) m/z 352 $[M + H]^+$.

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Example 50

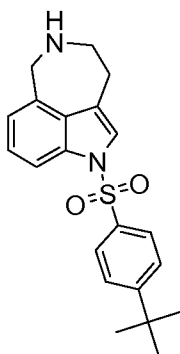
1-[(4,5-Dichloro-2-thienyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-*c*[<]]indole
 trifluoroacetate



The title compound was prepared from *tert*-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 4,5-
 dichlorothiophene-2-sulfonyl chloride (19 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 4.0 mg of product. MS (ESI) m/z 387 $[M + H]^+$.

Example 51

1-[(4-*tert*-Butylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino [5,4,3-*cd*]indole
 trifluoroacetate



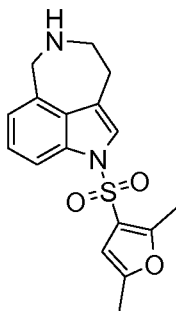
10

The title compound was prepared from *tert*-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 4-*tert*-
 butylbenzenesulfonyl chloride (18 mg, 0.75 mmol) as described in the general
 procedure above, to give 13.1 mg of product. MS (ESI) m/z 369 $[M + H]^+$.

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Example 52

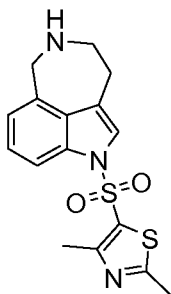
1-[(2,5-Dimethyl-3-furyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3- *cd*]indole
 trifluoroacetate



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2,5-dimethylfuran-3-
 sulfonyl chloride (15 mg, 0.75 mmol) as described in the general procedure above, to
 5 give 11.6 mg of product. MS (ESI) m/z 331 $[M + H]^+$.

Example 53

1-[(2,4-Dimethyl-1,3-thiazol-5-yl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-
 c*d*]indole trifluoroacetate



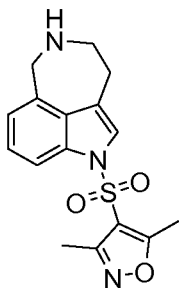
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2,4-dimethyl-1,3-
 thiazole-5-sulfonyl chloride (16 mg, 0.75 mmol) as described in the general procedure
 above, to give 6.1 mg of product. MS (ESI) m/z 348 $[M + H]^+$.

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Example 54

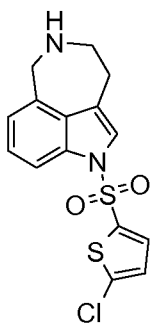
1-[(3,5-Dimethylisoxazol-4-yl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-
 c*d*]indole trifluoroacetate



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5H-azepino[5,4,3-cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 3,5-dimethylisoxazole-4-sulfonyl chloride (15 mg, 0.75 mmol) as described in the general procedure above, to give 7.9 mg of product. MS (ESI) m/z 332 $[M + H]^+$.

Example 55

1-[(5-Chloro-2-thienyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole trifluoroacetate



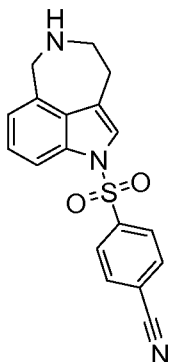
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5H-azepino[5,4,3-cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 5-chlorothiophene-2-sulfonyl chloride (16 mg, 0.75 mmol) as described in the general procedure above, to give 5.7 mg of product. MS (ESI) m/z 353 $[M + H]^+$.

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Example 56

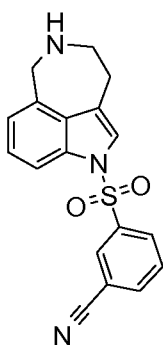
4-(3,4,5,6-Tetrahydro-1H-azepino[5,4,3-cd]indol-1-ylsulfonyl)benzonitrile trifluoroacetate



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5H-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 4-
 cyanobenzenesulfonyl chloride (15 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 6.4 mg of product. MS (ESI) m/z 338 $[M + H]^+$.

Example 57

3-(3,4,5,6-Tetrahydro-1 *H*-azepino[5,4,3-*c**d*]indol-1-ylsulfonyl)benzonitrile
trifluoroacetate



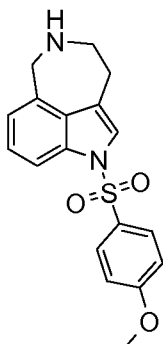
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5H-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 3-
 cyanobenzenesulfonyl chloride (15 mg, 0.75 mmol) as described in the general
 procedure above, to give 10.1 mg of product. MS (ESI) m/z 338 $[M + H]^+$.

15

Example 58

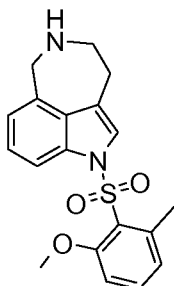
1-[(4-Methoxyphenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino [5,4,3-*c**d*]indole
trifluoroacetate



The title compound was prepared from *tert*-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 4-
 methoxybenzenesulfonyl chloride (16 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 12.3 mg of product. MS (ESI) m/z 343 $[M + H]^+$.

Example 59

1-[(2-Methoxy-6-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-
 c*d*]indole trifluoroacetate



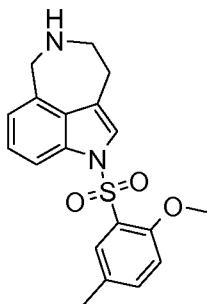
10

The title compound was prepared from *tert*-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2-methoxy-6-
 methylbenzenesulfonyl chloride (17 mg, 0.75 mmol) as described in the general
 procedure above, to give 6.4 mg of product. MS (ESI) m/z 357 $[M + H]^+$.

15

Example 60

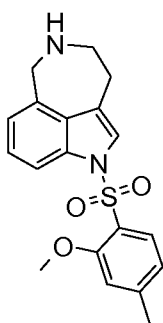
1-[(2-Methoxy-5-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-
 c*d*]indole trifluoroacetate



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5*f*-azepino[5,4,3-
c]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2-methoxy-5-
 methylbenzenesulfonyl chloride (17 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 3.6 mg of product. MS (ESI) m/z 357 $[M + H]^+$.

Example 61

1-[(2-methoxy-4-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-
cd]indole trifluoroacetate



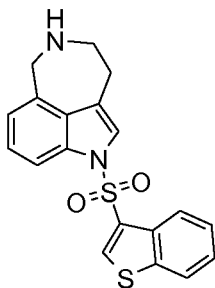
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2-methoxy-4-
 methylbenzenesulfonyl chloride (17 mg, 0.75 mmol) as described in the general
 procedure above, to give 17.4 mg of product. MS (ESI) m/z 357 $[M + H]^+$.

15

Example 62

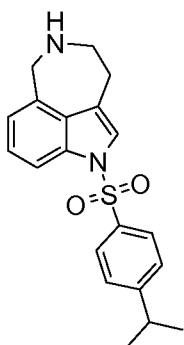
1-(1-Benzothien-3-ylsulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3- *cd*]indole
 trifluoroacetate



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5H-azepino[5,4,3-*cd*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 1-benzothiophene-3-sulfonyl chloride (18 mg, 0.75 mmol) as described in the general procedure above, to
 5 give 5.2 mg of product. MS (ESI) m/z 369 $[M + H]^+$.

Example 63

1-[(4-Isopropylphenyl)sulfonyl] -3,4,5,6-tetrahydro-1 *H*-azepino [5,4,3-*cd*]indole trifluoroacetate

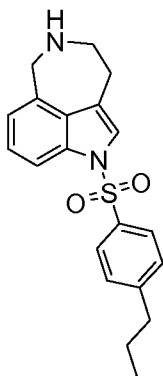


10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5H-azepino[5,4,3-*cd*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 4-isopropylbenzenesulfonyl chloride (16 mg, 0.75 mmol) as described in the general procedure above, to give 9.5 mg of product. The NMR spectrum contains signals from
 15 what seems to be two regioisomers in a ratio of 3:1. MS (ESI) m/z 355 $[M + H]^+$.

Example 64

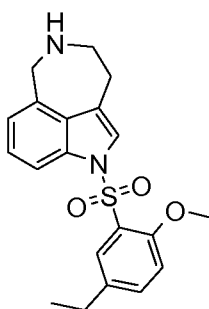
1-[(4-Propylphenyl)sulfonyl] -3,4,5,6-tetrahydro-1 *H*-azepino [5,4,3-*cd*]indole trifluoroacetate



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 4-*n*-
 propylbenzenesulfonyl chloride (16 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 8.9 mg of product. MS (ESI) m/z 355 $[M + H]^+$.

Example 65

1-[(5-Ethyl-2-methoxyphenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-
 c*d*]indole trifluoroacetate



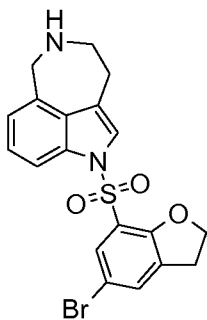
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 5-ethyl-2-
 methoxybenzenesulfonyl chloride (18 mg, 0.75 mmol) as described in the general
 procedure above, to give 9.1 mg of product. MS (ESI) m/z 371 $[M + H]^+$.

15

Example 66

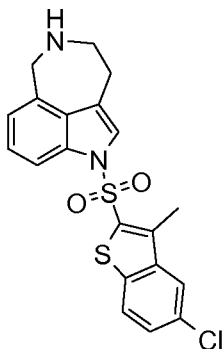
1-[(5-Bromo-2,3-dihydro-1-benzofuran-7-yl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-
 azepino[5,4,3-*cd*]indole trifluoroacetate



The title compound was prepared from *tert*-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 5-bromo-2,3-
 dihydro-1-benzofuran-7-sulfonyl chloride (22 mg, 0.75 mmol) as described in the
 5 general procedure above, to give 3.9 mg of product. MS (ESI) m/z 433 $[M + H]^+$.

Example 67

1-[(5-Chloro-3-methyl-1-benzothiophen-2-yl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-
azepino[5,4,3-*cd*]indole trifluoroacetate



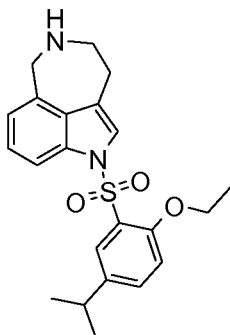
10

The title compound was prepared from *tert*-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 c*d*]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 5-chloro-3-methyl-1-
 benzothiophene-2-sulfonyl chloride (21 mg, 0.75 mmol) as described in the general
 procedure above, to give 4.2 mg of product. MS (ESI) m/z All $[M + H]^+$.

15

Example 68

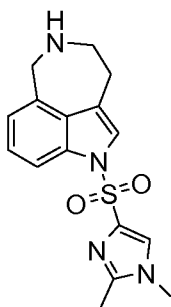
1-[(2-Ethoxy-5-isopropylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-
 c*d*]indole trifluoroacetate



The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5H-azepino[5,4,3-cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 2-ethoxy-5-isopropylbenzenesulfonyl chloride (20 mg, 0.75 mmol) as described in the general procedure above, to give 14.5 mg of product. MS (ESI) m/z 399 $[M + H]^+$.

Example 69

1-[(1,2-Dimethyl-1H-imidazol-4-yl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole trifluoroacetate



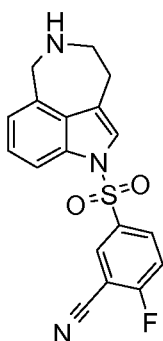
10

The title compound was prepared from *tert-butyl* 1,3,4,6-tetrahydro-5H-azepino[5,4,3-cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 1,2-dimethyl-1H-imidazole-4-sulfonyl chloride (15 mg, 0.75 mmol) as described in the general procedure above, to give 15.6 mg of product. MS (ESI) m/z 331 $[M + H]^+$.

15

Example 70

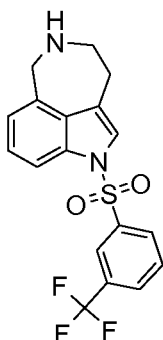
2-Fluoro-5-(3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indol-1-ylsulfonyl)benzonitrile trifluoroacetate



The title compound was prepared from *tert*-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 3-cyano-4-
 fluorobenzenesulfonyl chloride (17 mg, 0.75 mmol) as described in the general
 5 procedure above, to give 14.6 mg of product. MS (ESI) m/z 356 $[M + H]^+$.

Example 71

1-([3-(Trifluoromethyl)phenyl]sulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-
 cd]indole trifluoroacetate



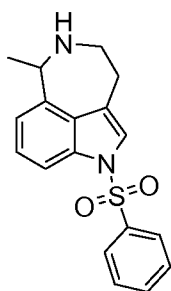
10

The title compound was prepared from *tert*-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-
 cd]indole-5-carboxylate, Intermediate 12 (14 mg, 0.05 mmol) and 3-
 trifluoromethylbenzenesulfonyl chloride (18 mg, 0.75 mmol) as described in the general
 procedure above, to give 1.7 mg of product. MS (ESI) m/z 381 $[M+H]^+$.

15

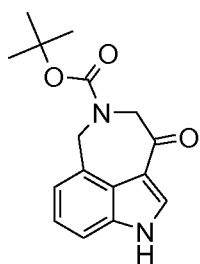
Example 72

6-Methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3-*cd*]indole



A solution of tert-butyl 6-methyl-1-(phenylsulfonyl)-7-
 {[(trifluoromethyl)sulfonyl]oxy}-1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-*Q*]indole-5-
 carboxylate, Intermediate 16 (16 mg, 0.028 mmol) in MeOH (4 mL) and was carefully
 5 added to a 16 mm test tube containing Pd/C (35 mg). The suspension was purged with
 N₂, ammonium formate (88 mg, 1.4 mmol) was added in one portion, the mixture was
 N₂-purged once more and the mixture was stirred at room temperature over two days.
 The detriflated intermediate was purified with preparative HPLC (ACE C8 5 mm, water
 containing 0.1% TFA - CH₃CN). The pure fraction was evaporated at reduced pressure,
 10 DCM/TFA 50/50, (1 mL) was added and the mixture was left at room temperature for
 one hour. The crude was purified by preparative HPLC (Xterra C18, 10 mM NH₄CO₃
 (pH 10) - CH₃CN) to give 0.8 mg of the title compound as a white oil. MS (ESI) *m/z*
 326 [M + H]⁺.

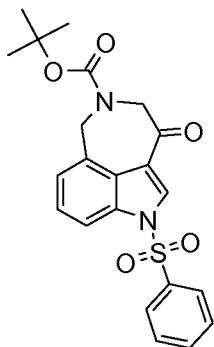
15 Intermediate 17
***tert*-Butyl 3-oxo-1,3,4,6-tetrahydro-5 *H*-azepino [5^S-c[^]indole-5-carboxylate**



tert-butyl 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-*c*]indole-5-carboxylate, Intermediate 12
 (100 mg, 0.37 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (167 mg,
 20 0.73 mmol) in THF/water 9/1 (8ml) was stirred under N₂ over night at room
 temperature. The compound was purified on a Biotage preparative flash column eluting
 with 15-100% EtOAc in petroleum ether 40-65 °C. Obtained 58 mg of the title
 compound. MS (ESI⁺) *m/z* 231 [M + *H*-isobutene]⁺.

Intermediate 18

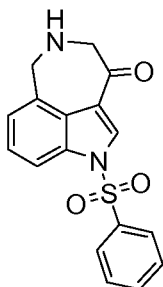
***tert*-Butyl** 3-oxo-1-(phenylsulfonyl)-1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3- *c*']indole-5-carboxylate



- 5 Tert-Butyl 3-oxo-1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-*c*']indole-5-carboxylate, Intermediate 17 (50 mg, 0.17 mmol), tetrabutylammonium hydrogensulfate (8 mg, 0.01 mmol) and benzenesulfonyl chloride (25 μ l, 0.19 mmol) were dissolved in DCM (2 ml). 2.5 M NaOH (77 μ l) was added. The mixture was stirred for 1 h at room temperature. The DCM phase was collected and washed with NaHCO₃(sat.) and water.
- 10 Evaporation gave a residue that was purified on silica 8-66% EtOAc in petroleum ether 45-60°. Obtained 42.4 mg of the title compound as a clear glass. MS (ESI⁺) *m/z* 371 [M + H - isobutene]⁺.

Example 73

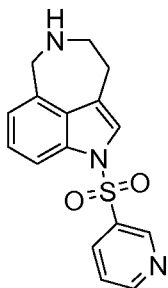
- 15 1-(Phenylsulfonyl)-1,4,5,6-tetrahydro-3 *H*-azepino[5,4,3- *c*']indol-3-one
trifluoroacetate



- tert*-Butyl 3-oxo-1-(phenylsulfonyl)- 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-*c*']indole-5-carboxylate, Intermediate 18 (5.0 mg, 0.012 mmol) was dissolved in DCM (1 ml). TFA (0.5 ml) was added and the solution was heated to boiling. The solvent was evaporated.
- 20 Obtained 5.2 mg of the TFA salt. MS (ESI⁺) *m/z* 327 [M + H]⁺.

Example 74

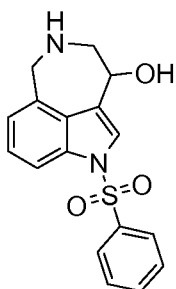
1-(Pyridin-3-ylsulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3- *cd*]indole
bis(trifluoroacetate)



- 5 To a solution of *tert-butyl* 1,3,4,6-tetrahydro-5 *H*-azepino[5,4,3-*cd*]indole-5-carboxylate, Intermediate 12 (25 mg, 0.092 mmol) in DCM (2 mL) were added tetrabutylammonium hydrogensulfate (6.4 mg, 0.02 mmol), 2M NaOH (0.2 mL) and pyridine-3-sulfonyl chloride * HCl (33 mg, 0.18 mmol). The reaction mixture was vigorously stirred at room temperature for one hour. More 2M NaOH (1 mL) was added to the mixture,
10 followed by half an equivalent of the sulphonyl chloride every hour for four hours. Water (10 mL) was added and the aqueous phase was washed twice with CHCl₃ and the combined organic phases were evaporated at reduced pressure. To the resulting oil was added TFA/DCM 50/50 (1 mL) and the mixture was stirred at room temperature over night. The solvent was removed at reduced pressure and the crude was purified
15 with preparative HPLC (ACE C8 5 mm, water containing 0.1% TFA - CH₃CN) to give 4.6 mg of the title compound. MS (ESI) *m/z* 314 [M + H]⁺.

Example 75

- 1-(Phenylsulfonyl)-3,4,5,6-tetrahydro-1 *H*-azepino[5,4,3- *cd*]indol-3-ol
20 **trifluoroacetate**



tert-Butyl 3-oxo-1-(phenylsulfonyl)-1,3,4,6-tetrahydro-5*H*-azepino[5,4,3-*c*]indole-5-carboxylate, Intermediate 18, (11 mg, 0.03 mmol) was dissolved in DCM (1 ml). TFA (0.5 ml) was added and the solution was heated to boiling, and then evaporated. The residue was dissolved in EtOH (3 ml). Sodium borohydride (7.5 mg, 0.2 mmol) was added. The reaction mixture was stirred at room temperature for 45 min. The solution was acidified with acetic acid, and evaporated. The evaporation procedure was repeated twice with the addition of methanol. The crude product was purified by preparative HPLC (ACE C8 5 mm, water containing 0.1% TFA - CH₃CN) to give the title compound, 7 mg.

MS (ESI) m/z 311 $[M + H - H_2O]^+$ and m/z 329 $[M + H]^+$.

BIOLOGICAL TESTS

The ability of a compound according to the invention to bind to a 5-HT₂ receptor, and to be pharmaceutically useful, can be determined using *in vivo* and *in vitro* assays known in the art.

(a) 5-HT₂ receptor binding Assay

Binding affinity experiment for the human 5-HT₂ receptor are performed in HEK293 cells transfected with 5-HT₂ receptor using [³H]-LSD as labeled ligand according to the general method as described by Boess F.G et al. Neuropharmacology 36(4/5) 713-720, 1997.

Materials:

Cell culture

The HEK-293 cell line transfected with the human 5-HT₂ receptor was cultured in Dulbeccos Modified Eagles Medium containing 5 % dialyzed foetal bovine serum, (Gibco BRL 10106-169), 0.5 mM sodium pyruvate and 400 µg/ml Geneticin (G-418) (Gibco BRL1013 1-019). The cells were passaged 1:10, twice a week.

Chemicals

The radioligand [^3H] LSD 60-240 Ci/mmol, obtained from Amersham Pharmacia Biotech, (Buckinghamshire, England) was in ethanol and stored at -20°C . The compounds were dissolved in 100% DMSO and diluted with binding buffer.

5

Disposable

Compounds were diluted in Costar 96 well V-bottom polypropylene plates (Corning Inc. Costar, NY, USA). Samples were incubated in Packard Optiplate (Packard Instruments B.V., Groningen, The Netherlands). The total amount of added radioligand was measured in Packard 24-well Barex plates (Packard Instruments B.V., Groningen, The Netherlands) in the presence of MicroscintTM 20 scintillation fluid (Packard Bioscience, Meriden, CT, USA).

10

Buffer

The binding buffer consisted of 20 mM HEPES, 150 mM NaCl, 10 mM MgCl_2 , and 1 mM, EDTA, pH 7.4.

15

Methods:

Membrane preparation

Cells were grown to approximately 90% confluence on 24.5 x 24.5 mm culture dishes. The medium was aspirated, and after rinsing with ice-cold PBS, the cells were scraped off using 25 ml Tris buffer (50 mM Tris-HCl, 1 mM EDTA, 1 mM EGTA, pH 7.4) and a window scraper. The cells were then broken with a Polytron homogeniser, and remaining particulate matter was removed by low-speed centrifugation, 1000x g for 5 min. Finally, the membranes were collected by high-speed centrifugation (20 000x g), suspended in binding buffer, and frozen in aliquots at -70°C .

20

25

Radioligand binding

Frozen cell membranes were thawed, immediately rehomogenized with a Polytron homogenizer, and coupled to SPA wheat germ agglutinin beads (Amersham Life Sciences, Cardiff, England) for 30 min under continuous shaking of the tubes. After coupling, the beads were centrifuged for 10 minutes at 1000 g, and subsequently suspended in 20 ml of binding buffer per 96-well plate. The binding reaction was then initiated by adding radioligand and test compounds to the bead-membrane suspension.

30

Following incubation at room temperature, the assay plates were subjected to scintillation counting.

The original SPA method was followed except for that membranes were prepared from HEK293 cells expressing the human 5-HT₆ receptor instead of from HeLa cells
5 (Dinh DM, Zaworski PG, Gill GS, Schlachter SK, Lawson CF, Smith MW. Validation of human 5-HT₆ receptors expressed in HeLa cell membranes: saturation binding studies, pharmacological profiles of standard CNS agents and SPA development. (The Upjohn Company Technical Report 7295-95-064 1995;27 December). The specific binding of [³H]-LSD was saturable, while the non-specific binding increased linearly
10 with the concentration of added radioligand. [³H]-LSD bound with high affinity to 5-HT₆ receptors. The K_d value was estimated to 2.6± 0.2 nM based on four separate experiments.

The total binding at 3 nM of [³H]-LSD, the radioligand concentration used in the competition experiments, was typically 6000 dpm, and the specific binding more than
15 70%. 5-HT caused a concentration dependent inhibition of [³H]-LSD binding with an over all average K_i value of 236 nM when tested against two different membrane preparations. The inter assay variability over three experiments showed a CV of 10% with an average K₁ values of 173 nM (SD 30) and a Hill coefficient of 0.94 (SD 0.09). The intra assay variation was 3% (n=4). All unlabelled ligands displaced the specific
20 binding of [³H]-LSD in a concentration-dependent manner, albeit at different potencies. The rank order of affinity for the 5-HT₆ receptor of reference compounds was methiothepin (K_i 2 nM) > mianserin (190 nM) ≈ 5-HT (236 nM) > methysergide (482 nM) > mesulergine (1970 nM).

25 Protein determination

Protein concentrations were determined with BioRad Protein Assay (Bradford M.M. (1976) Anal. Biochem. 72:248-254). Bovine serum albumin was used as standard.

Scintillation counting

30 The radioactivity was determined in a Packard TopCount™ scintillation counter (Packard Instruments, Meriden, CT, USA) at a counting efficiency of approximately 20 % . The counting efficiency was determined in separate sets of experiments.

Saturation experiments

At least 6 concentrations in duplicates of radioligand (0.1-20 nM of [³H]-LSD) were used in saturation experiments. The specific binding was calculated as the difference between total binding and non-specific binding, which was determined as the binding of radioligand in the presence of 5 μM lisuride. B_{max} and the dissociation constant, K_d, were determined from the non-linear regression analysis using equation 1. L_u is the unbound concentration of radioligand, and y is the amount bound.

$$y = \frac{B_{\max} L_u}{L_u + K_d} \quad (\text{equation 1})$$

10 Competition experiments

Total- and non-specific binding of radioligand was defined in eight replicates of each. Samples containing test compound were run in duplicate at 11 concentrations. Incubations were carried out at room temperature for 3 hours. The IC₅₀ value, i.e. the concentration of test compound that inhibited 50% of the specific binding of radioligand, was determined with non linear regression analysis and the K_i value was calculated using equation 2 [Cheng Y.C. Biochem. Pharmacol. 22, 3099-3108, 1973].

$$K_i = \frac{IC_{50}}{1 + \frac{L}{K_d}} \quad (\text{equation 2})$$

L = concentration of radioligand

K_d = Affinity of radioligand

20

(b) 5-HT₆ Intrinsic Activity Assay

Antagonists to the human 5-HT₆ receptor were characterized by measuring inhibition of 5-HT induced increase in cAMP in HEK 293 cells expressing the human 5-HT₆ receptor (see Boess et al. (1997) Neuropharmacology 36: 713-720). Briefly, HEK293/5-HT₆ cells were seeded in polylysine coated 96-well plates at a density of 25,000 / well and grown in DMEM (Dulbecco's Modified Eagle Medium) (without phenol-red) containing 5% dialyzed Foetal Bovine Serum for 48 h at 37°C in a 5% CO₂ incubator. The medium was then aspirated and replaced by 0.1 ml assay medium (Hanks Balance Salt Solution containing 20 mM HEPES, 1.5 mM isobutylmethylxanthine and 1 mg/ml bovine serum albumin). After addition of test substances, 50 μl dissolved in assay medium, the cells were incubated for 10 min at

30

+37°C in a 5% CO₂ incubator. The medium was again aspirated and the cAMP content was determined using a radioactive cAMP kit (Amersham Pharmacia Biotech, BIOTRAK RPA559). The potency of antagonists was quantified by determining the concentration that caused 50% inhibition of 5-HT (at [5-HT]= 8 times EC₅₀) evoked
 5 increase in cAMP, using the formula $IC_{50,corr} = IC_{50} / (1 + [5HT] / EC_{50})$.

The compounds in accordance with the invention have a selective affinity to human 5-HT₆ receptors with K_i and IC_{50,corr} values between 0.1 nM and 5 µM or display a % inhibition of [³H]-LSD ≥ 20 % at 50 nM and are antagonists, agonists or partial agonists at the human 5-HT₆ receptor.

10

TABLE 1

Binding affinity (K_i) at the h5-HT₆ receptor

Example	K _i (nM)
5	21
13	6

15 TABLE 2

Antagonist potency at the h5-HT₆ receptor

Example	IC _{50,corr} (nM)
3	28
15	8

(c) In vivo assay of reduction of food intake

20 For a review on serotonin and food intake, see Blundell, J.E. and Halford, J.C.G. (1998) Serotonin and Appetite Regulation. Implications for the Pharmacological Treatment of Obesity. CNS Drugs 9:473-495.

Obese (ob/ob) mouse is selected as the primary animal model for screening as this mutant mouse consumes high amounts of food resulting in a high signal to noise ratio.
 25 To further substantiate and compare efficacy data, the effect of the compounds on food consumption is also studied in wild type (C57BL/6J) mice. The amount of food consumed during 15 hours of infusion of compounds is recorded.

Male mice (obese C57BL/6JBom-Lep^{ob} and lean wild-type C57BL/6JBom; Bomholtsgaard, Denmark) 8-9 weeks with an average body weight of 50 g (obese) and 25 g (lean) are used in all the studies. The animals are housed singly in cages at 23±1°C, 40-60 % humidity and have free access to water and standard laboratory chow. The
5 12/12-h light/dark cycle is set to lights off at 5 p.m. The animals are conditioned for at least one week before start of study.

The test compounds are dissolved in solvents suitable for each specific compound such as cyclodextrin, cyclodextrin/methane sulphonic acid, polyethylene glycol/methane sulphonic acid, saline. Fresh solutions are made for each study. Doses
10 of 30, 50 and 100 mg kg⁻¹ day⁻¹ are used. The purity of the test compounds is of analytical grade.

The animals are weighed at the start of the study and randomized based on body weight. Alzet osmotic minipumps (Model 200ID; infusion rate 8 µl/h) are used and loaded essentially as recommended by the Alzet technical information manual (Alza
15 Scientific Products, 1997; Theeuwes, F. and Yam, S.I. Ann. Biomed. Eng. 4(4). 343-353, 1976). Continuous subcutaneous infusion with 24 hours duration is used. The minipumps are either filled with different concentrations of test compounds dissolved in vehicle or with only vehicle solution and maintained in vehicle pre-warmed to 37°C (approx. 1h). The minipumps are implanted subcutaneously in the neck/back region
20 under short acting anesthesia (metofane/enflurane). This surgical procedure lasts approximately 5 min.

The weight of the food pellets are measured at 5 p.m. and at 8 p.m. for two days before (baseline) and one day after the implantation of the osmotic minipumps. The weigh-in is performed with a computer assisted Mettler Toledo PR 5002 balance.
25 Occasional spillage is corrected for. At the end of the study the animals are killed by neck dislocation and trunk blood sampled for later analysis of plasma drug concentrations.

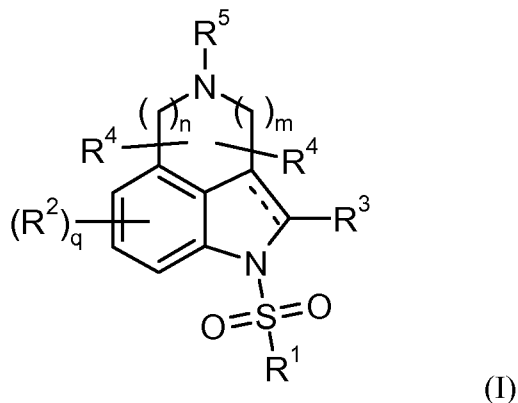
The plasma sample proteins are precipitated with methanol, centrifuged and the supernatant is transferred to HPLC vials and injected into the liquid chromatography
30 /mass spectrometric system. The mass spectrometer is set for electrospray positive ion mode and Multiple Reaction Monitoring. A linear regression analysis of the standards forced through the origin is used to calculate the concentrations of the unknown samples.

Food consumption for 15 hours is measured for the three consecutive days and the percentage of basal level values is derived for each animal from the day before and after treatment. The values are expressed as mean \pm SD and \pm SEM from eight animals per dose group. Statistical evaluation is performed by Kruskal-Wallis one-way ANOVA
5 using the percent basal values. If statistical significance is reached at the level of $p < 0.05$, Mann-Whitney U-test for statistical comparison between control and treatment groups is performed.

The compounds according to the invention show an effect (i.e., reduction of food intake) in the range of 5-200 mg/kg/d.

CLAIMS

1. A compound of the Formula (I)



including pharmaceutically acceptable salts, solvates, hydrates, geometrical isomers, tautomers, and optical isomers thereof, wherein:

— represents a single bond or a double bond;

m and n are each independently selected from 1, 2, and 3, provided that $m + n \leq 4$;

R^1 is a group selected from:

- (a) d_{-6} -alkyl,
- (b) C_{3-7} -cycloalkyl,
- (c) C_{3-6} -alkenyl,
- (d) aryl,
- (e) aryl- C_{2-6} -alkenyl,
- (f) aryl- Cl_{-6} -alkyl,
- (g) heteroaryl,
- (h) heteroaryl- C_{2-6} -alkenyl, and
- (i) heteroaryl- Cl_{-6} -alkyl;

wherein any heteroaryl or aryl residue, alone or as part of another group, is optionally independently substituted in one or more positions with a substituent selected from:

- (a) halogen,
- (b) $d-e$ -alkyl,
- (c) hydroxy- Cl_{-6} -alkyl,

- (d) fluoro-Ci₆-alkyl,
 (e) C₃₋₇-cycloalkyl,
 (f) hydroxy-Cs-ycycloalkyl,
 (g) fluoro-Cs-v-cycloalkyl,
 5 (h) methyl-C₃₋₇-cycloalkyl,
 (i) C₃₋₄-cycloalkyl-Ci₃-alkyl,
 (j) C₃₋₄-cycloalkyl(hydroxy)-Ci₃-alkyl,
 (k) Ci₆-alkoxy,
 (l) fluoro-Ci₆-alkoxy,
 10 (m) Ci₂-alkoxy-Ci₄-alkyl,
 (n) C₃₋₇-cycloalkoxy,
 (o) fluoro-C₃₋₇-cycloalkoxy,
 (p) methyl-C₃₋₇-cycloalkoxy,
 (q) C₂₋₆-alkenyl,
 15 (r) fluoro-C₂₋₆-alkenyl,
 (s) C₂₋₆-alkynyl,
 (t) hydroxy,
 (u) -SCF₃,
 (v) -SCF₂H,
 20 (w) -SO₂NR⁶R⁶,
 (x) -S(O)_eR⁷, wherein e is 0, 1, 2 or 3,
 (y) -OSO₂R⁷,
 (z) -CN,
 (aa) -NR⁶R⁶,
 25 (ab) -NHSO₂R⁷,
 (ac) -NR⁸COR⁷,
 (ad) -NO₂,
 (ae) -CONR⁶R⁶,
 (af) -CO-R⁷,
 30 (ag) -COOH,
 (ah) Ci₆-alkoxycarbonyl,
 (ai) aryl,
 (aj) heteroaryl,
 (ak) aryloxy, and

(al) heteroaryloxy;

wherein any (ai) aryl or (aj) heteroaryl, alone or as part of another group, is optionally substituted in one or more positions with a substituent selected from:

- (a) halogen,
- (b) d_{-4} -alkyl,
- (c) Ci_{-4} -alkoxy,
- (d) $-CF_3$, and
- (e) $-CN$;

q is selected from 0-3;

each R^2 is independently selected from:

- (a) halogen,
- (b) d_{-6} -alkyl,
- (c) hydroxy- Ci_{-6} -alkyl,
- (d) fluoro- Ci_{-6} -alkyl,
- (e) C_{3-7} -cycloalkyl,
- (f) hydroxy- C_{3-7} -cycloalkyl,
- (g) fluoro- C_{3-7} -cycloalkyl,
- (h) methyl- C_{3-7} -cycloalkyl,
- (i) C_{3-4} -cycloalkyl- Ci_{-3} -alkyl,
- (j) C_{3-4} -cycloalkyl(hydroxy)- Ci_{-3} -alkyl,
- (k) Ci_{-6} -alkoxy,
- (l) fluoro- Ci_{-6} -alkoxy,
- (m) Ci_{-2} -alkoxy- Ci_{-4} -alkyl,
- (n) C_{3-7} -cycloalkoxy,
- (o) fluoro- C_{3-7} -cycloalkoxy,
- (p) methyl- C_{3-7} -cycloalkoxy,
- (q) C_{2-6} -alkenyl,
- (r) fluoro- C_{2-6} -alkenyl,
- (s) C_{2-6} -alkynyl,
- (t) hydroxy,
- (u) $-SCF_3$,
- (v) $-SCF_2H$,
- (w) $-SO_2NR^6R^6$,
- (x) $-S(O)_eR^7$, wherein e is 0, 1, 2 or 3,

- (y) $-\text{OSO}_2\text{R}^7$,
 (z) $-\text{CN}$,
 (aa) $-\text{NR}^6\text{R}^6$,
 (ab) $-\text{NHSO}_2\text{R}^7$,
 5 (ac) $-\text{NR}^8\text{COR}^7$,
 (ad) $-\text{NO}_2$,
 (ae) $-\text{CONR}^6\text{R}^6$,
 (af) $-\text{CO-R}^7$,
 (ag) $-\text{OCONR}^6\text{R}^6$,
 10 (ah) $-\text{CO-R}^7$, and
 (ai) $-\text{O-CH}_2\text{-aryl}$;

wherein any aryl residue is optionally substituted in one or more positions with a substituent selected from:

- (a) halogen,
 15 (b) Ci_{-4} -alkyl,
 (c) Ci_{-4} -alkoxy,
 (d) $-\text{CF}_3$, and
 (e) $-\text{CN}$;

R^3 is a group selected from:

- (a) hydrogen,
 20 (b) d_{-6} -alkyl,
 (c) C_{3-7} -cycloalkyl,
 (d) C_{3-4} -cycloalkyl- Ci_{-3} -alkyl,
 (e) hydroxy- Ci_{-4} -alkyl
 25 (f) hydroxy- C_{3-y} -cycloalkyl,
 (g) C_{3-4} -cycloalkyl(hydroxy)- Ci_{-3} -alkyl,
 (h) Ci_{-2} -alkoxy- Ci_{-4} -alkyl,
 (i) $-\text{COOR}^8$,
 (j) $-\text{CONR}^6\text{R}^6$,
 30 (k) $-\text{CO-R}^7$,
 (l) $-\text{CN}$,
 (m) halogen,
 (n) aryl, and
 (o) heteroaryl;

wherein any heteroaryl or aryl residue is optionally independently substituted in one or more positions with a substituent selected from:

- (a) halogen,
- (b) C_{1-4} -alkyl,
- (c) C_{1-4} -alkoxy,
- (d) $-\text{CF}_3$, and
- (e) $-\text{CN}$;

each R^4 is independently selected from:

- (a) hydrogen,
- (b) C_{1-4} -alkyl,
- (c) fluoro- C_{1-4} -alkyl,
- (d) C_{3-5} -cycloalkyl,
- (e) fluoro- C_{3-5} -cycloalkyl,
- (f) C_{3-5} -cycloalkyl-methyl,
- (g) hydroxy- C_{1-4} -alkyl,
- (h) cyano,
- (i) methoxy,
- (j) hydroxy, and
- (k) oxo,

provided that when R^4 is hydroxy or oxo, then either m or n is 2 or 3, and R^4 is not attached on a carbon in alpha position to the ring nitrogen atom;

R^5 is a group selected from:

- (a) hydrogen,
- (b) C_{1-4} -alkyl,
- (c) fluoro- C_{1-4} -alkyl,
- (d) 2-cyanoethyl,
- (e) hydroxy- C_{2-4} -alkyl,
- (f) C_{3-4} -alkenyl,
- (g) C_{3-4} -alkynyl,
- (h) C_{3-7} -cycloalkyl,
- (i) methyl- C_{3-7} -cycloalkyl
- (j) fluoro- C_{3-7} -cycloalkyl,
- (k) C_{3-4} -cycloalkyl- C_{1-4} -alkyl,
- (l) C_{1-4} -alkoxy- C_{2-4} -alkyl,

- (m) $-N(R^6)_2-C_{2-4}$ -alkyl,
- (n) imidazolyl-methyl, and
- (o) pyrrolidinyl-methyl;

each R^6 is a group independently selected from:

- 5 (a) hydrogen,
- (b) d-e-alkyl,
- (c) fluoro- C_{2-6} -alkyl, and
- (d) C_{3-7} -cycloalkyl, or
- two R^6 groups together with the nitrogen to which they are attached form
- 10 a heterocyclic ring optionally substituted with methyl;

each R^7 is a group independently selected from:

- (a) hydrogen,
- (b) d₆-alkyl,
- (c) fluoro-Ci₆-alkyl,
- 15 (d) C_{3-7} -cycloalkyl,
- (e) methyl- C_{3-7} -cycloalkyl,
- (f) C_{3-4} -cycloalkyl-Ci₃-alkyl,
- (g) aryl, and
- (h) heteroaryl;

20 wherein any heteroaryl or aryl residue is optionally independently substituted in one or more positions with a substituent selected from:

- (a) halogen,
- (b) Ci-4-alkyl,
- (c) Ci₄-alkoxy,
- 25 (d) $-CF_3$, and
- (e) $-CN$;

each R^8 is independently a group selected from:

- (a) hydrogen,
- (b) d₆-alkyl,
- 30 (c) fluoro-Ci₆-alkyl, and
- (d) C_{3-7} -cycloalkyl,

or R^7 and R^8 together with the atoms to which they are attached form a lactam ring when present in the group NR^8COR^7 , or R^7 and R^8 together with the atoms

to which they are attached form a sultam ring when present in the group $\text{NR}^8\text{SO}_2\text{R}^7$.

2. A compound according to claim 1 wherein
- 5 ----- represents a double bond.
3. A compound according to claim 1 or 2 wherein m and n are each independently selected from 1 and 2, provided that $m + n \leq 3$.
- 10 4. A compound according to any one of claims 1 to 3 wherein R^1 is a group selected from:
- (a) aryl, and
- (b) heteroaryl,
- wherein any heteroaryl or aryl residue is optionally independently substituted in
- 15 one or more positions with a substituent selected from:
- (a) halogen,
- (b) d-e-alkyl,
- (c) fluoro- Ci_{6-} -alkyl,
- (d) Ci_{6-} -alkoxy,
- 20 (e) fluoro- Ci_{6-} -alkoxy, and
- (f) -CN.
5. A compound according to claim 4 wherein any heteroaryl or aryl residue is optionally independently substituted in one or more positions with a substituent
- 25 selected from:
- (a) halogen,
- (b) Ci_{4-} -alkyl,
- (c) fluoro- Ci_{2-} -alkyl,
- (d) Ci_{2-} -alkoxy,
- 30 (e) fluoro- Ci_{2-} -alkoxy, and
- (f) -CN.
6. A compound according to any one of claims 1 to 5 wherein q is 0.

7. A compound according to any one of claims 1 to 5 wherein q is 1 or 2, and each R^2 is independently a group selected from:
- (a) halogen,
 - 5 (b) C_{1-2} -alkyl,
 - (c) fluoro- C_{1-2} -alkyl,
 - (d) C_{1-2} -alkoxy,
 - (e) fluoro- C_{1-2} -alkoxy,
 - (f) hydroxy, and
 - 10 (g) $-O-SO_2-CF_3$.
8. A compound according to any one of claims 1 to 7 wherein R^3 is a group selected from:
- (a) hydrogen,
 - 15 (b) C_{1-2} -alkyl,
 - (c) -F, and
 - (d) -Cl.
9. A compound according to any one of claims 1 to 8 wherein each R^4 independently is a group selected from:
- 20 (a) hydrogen,
 - (b) methyl, and
 - (c) oxo.
10. A compound according to any one of claims 1 to 9 wherein R^5 is a group selected from:
- 25 (a) hydrogen,
 - (b) C_{1-3} -alkyl,
 - (c) $N(R^6)_2-C_{2-4}$ -alkyl-,
 - 30 (d) imidazolyl-methyl, and
 - (e) pyrrolidinyl-methyl.
11. A compound according to any one of claims 1 to 10 wherein each R^6 independently is a group selected from:

- (a) hydrogen, and
- (b) methyl.

12. A compound according to any one of claims 1 to 11 wherein $m + n = 2$.

5

13. A compound according to claim 12 wherein:

$\overset{\text{-----}}{\text{---}}$ represents a double bond;

R^1 is a group selected from

- (a) phenyl, or
- (b) benzothienyl,

10

wherein phenyl is unsubstituted or independently substituted in one or two positions with a substituent selected from:

- (a) trifluoromethyl,
- (b) chloro,
- (c) methyl, and
- (d) methoxy;

15

q is 0;

R^3 and R^4 are hydrogen; and

R^5 is a group selected from:

- (a) hydrogen,
- (b) methyl,
- (c) ethyl,
- (d) dimethylaminoethyl,
- (e) imidazol-2-yl-methyl, and
- (f) pyrrolidinyl-methyl.

20

25

14. A compound according to claim 13, which is selected from:

- 1-(phenylsulfonyl)-1, 3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline,
- 4-methyl-1-(phenylsulfonyl)- 1,3,4,5-tetrahydropyrrolo[4, 3,2-de]isoquinoline,
- 4-(1H-imidazol-2-ylmethyl)- 1-(phenylsulfonyl)- 1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline,

30

- N,N-dimethyl-2-[1-(phenylsulfonyl)- 1,5-dihydropyrrolo[4,3,2-de]isoquinolin-4(3H)-yl]ethanamine,
- 4-ethyl-1-(phenylsulfonyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline,
- 5 • 1-(phenylsulfonyl)-4-(pyrrolidin-2-ylmethyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline,
- 1-(phenylsulfonyl)-4-(pyrrolidin-3-ylmethyl)-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline,
- 10 • 1-[(2-chlorophenyl)sulfonyl]-4-ethyl- 1,3,4,5-tetrahydropyrrolo[4, 3,2-de]isoquinoline,
- 4-ethyl- 1- {[2-(trifluoromethyl)phenyl]sulfonyl} -1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline,
- 1-(1-benzothien-2-ylsulfonyl)-4-ethyl- 1,3,4,5-tetrahydropyrrolo[4, 3,2-de]isoquinoline, and
- 15 • 4-ethyl- 1-[(2-methoxy-5-methylphenyl)sulfonyl]-1, 3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline.

15. A compound according to any one of claims 1 to 11 wherein $m + n = 3$.

20 16. A compound according to claim 15 wherein:

----- represents a double bond;

R^1 is a group selected from:

- (a) phenyl,
- (b) furanyl,
- 25 (c) thienyl,
- (d) isoxazolyl,
- (e) imidazolyl,
- (f) thiazolyl,
- (g) pyridyl,
- 30 (h) imidazothiazolyl,
- (i) benzo furanyl,
- (j) dihydrobenzo furanyl,
- (k) benzothienyl, and

(1) benzothiazolyl,

wherein R¹ is unsubstituted or independently substituted in one or more positions with a substituent selected from:

- (a) fluoro,
- (b) chloro,
- (c) bromo,
- (d) methyl,
- (e) ethyl,
- (f) n-propyl,
- (g) isopropyl,
- (h) tert-butyl,
- (i) trifluoromethyl,
- (j) methoxy,
- (k) ethoxy, and
- (l) cyano;

q is 0 or 1;

R² is a group selected from

- (a) methoxy,
- (b) ethoxy,
- (c) hydroxy, and
- (d) -O-SO₂-CF₃;

R³ is hydrogen;

each R⁴ is independently a group selected from

- (a) hydrogen,
- (b) methyl, and
- (c) oxo,

wherein at least one R⁴ is hydrogen; and

R⁵ is a group selected from:

- (a) hydrogen,
- (b) methyl, and
- (c) ethyl.

17. A compound according to claim 16, which is selected from:

- 4-methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[3,4,5-cd]indole,
- 4-ethyl- 1-(phenylsulfonyl)-3 ,4,5,6-tetrahydro- 1H-azepino[3 ,4,5-cd]indole,
- 5 • 1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 5-methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[3,4,5-cd]indole,
- 7-methoxy-6-methyl- 1-(phenylsulfonyl)-3 ,4,5,6-tetrahydro- 1H-azepino[5,4,3-cd]indole,
- 10 • 6-methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indol-7-ol,
- 6-methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indo 1-7-yl trifluoromethanesulfonate,
- 15 • 7-methoxy-5 ,6-dimethyl- 1-(phenylsulfonyl)-3 ,4,5,6-tetrahydro- 1H-azepino[5,4,3-cd]indole,
- 7-ethoxy-6-methyl- 1-(phenylsulfonyl)-3 ,4,5,6-tetrahydro- 1H-azepino[5,4,3-cd]indole,
- 1-[(2-chloro-6-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 20 • 1-[(3-chloro-2-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(3-chloro-4-fluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 25 • 1-[(2-chlorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(3-chlorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(4-chlorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 30 • 1-[(3-fluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,

- 1-[(4-fluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2,6-difluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 5 • 1-[(2,5-difluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(3,5-difluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2,4-difluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 10 • 1-[(3,4-difluorophenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 15 • 1-[(4-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2,5-dimethyl-3-thienyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2,5-dimethylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 20 • 1-[(3,5-dimethylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-{[4-fluoro-3-(trifluoromethyl)phenyl]sulfonyl}-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 25 • 1-(1-benzofuran-2-ylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-(1,3-benzothiazol-6-ylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(1-methyl-1H-imidazol-4-yl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 30 • 1-[(6-chloroimidazo[2,1-b][1,3]thiazol-5-yl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,

- 1-{[2-(trifluoromethyl)phenyl]sulfonyl}-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-(1-benzothien-2-ylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 5 • 1-[(5-fluoro-2-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-{[3-(trifluoromethyl)phenyl]sulfonyl}-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-{[4-(trifluoromethyl)phenyl]sulfonyl}-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 10 • 4-methyl-2-(3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indol-1-ylsulfonyl)benzonitrile,
- 1-[(4,5-dichloro-2-thienyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 15 • 1-[(4-tert-butylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2,5-dimethyl-3-furyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 20 • 1-[(3,5-dimethylisoxazol-4-yl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(5-chloro-2-thienyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 25 • 4-(3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indol-1-ylsulfonyl)benzonitrile,
- 3-(3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indol-1-ylsulfonyl)benzonitrile,
- 1-[(4-methoxyphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 30 • 1-[(2-methoxy-6-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,

- 1-[(2-methoxy-5-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2-methoxy-4-methylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 5 • 1-(1-benzothien-3-ylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(4-isopropylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 10 • 1-[(4-propylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(5-ethyl-2-methoxyphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(5-bromo-2,3-dihydro-1-benzofuran-7-yl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 15 • 1-[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 1-[(2-ethoxy-5-isopropylphenyl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 6-methyl-1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 20 • 1-(phenylsulfonyl)-1,4,5,6-tetrahydro-3H-azepino[5,4,3-cd]indol-3-one,
- 1-[(1,2-dimethyl-1H-imidazol-4-yl)sulfonyl]-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole,
- 2-fluoro-5-(3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indol-1-ylsulfonyl)benzonitrile,
- 25 • 1-(pyridin-3-ylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole, and
- 1-(phenylsulfonyl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indol-3-ol.

30 18. A compound according to any one of claims 1 to 17 which is a 5-HT₆ receptor antagonist or partial agonist.

19. A compound according to claim 18 which is a 5-HT₆ receptor antagonist.

20. A compound according to any one of claims 1 to 19 for use in therapy.
21. A compound according to any one of claims 1 to 19 for use in the treatment or
5 prophylaxis of a 5-HT₆ receptor-related disorder.
22. A compound according to any one of claims 1 to 19 for use in the reduction of
body weight or reduction of body weight gain.
- 10 23. Use of a compound according to any one of claims 1 to 19 in the manufacture of a
medicament for the treatment or prophylaxis of a 5-HT₆ receptor-related disorder.
24. Use of a compound according to any one of claims 1 to 19 in the manufacture of a
medicament for the reduction of body weight or reduction of body weight gain.
- 15 25. A method for the treatment or prophylaxis of a 5-HT₆ receptor-related disorder,
comprising administering to a mammal, including man, in need of such treatment
an effective amount of a compound according to any one of claims 1 to 19.
- 20 26. A method for the reduction of body weight or reduction of body weight gain,
comprising administering to a mammal, including man, in need of such reduction
an effective amount of a compound according to any one of claims 1 to 19.
- 25 27. A method for modulating 5-HT₆ receptor activity, which comprises administering
to a mammal, including man, an effective amount of a compound according to any
one of claims 1 to 19.
28. A pharmaceutical formulation containing a compound according to any one of
claims 1 to 19 as active ingredient in combination with a pharmaceutically
30 acceptable diluent or carrier.
29. The pharmaceutical formulation according to claim 28 for use in the treatment or
prophylaxis of a 5-HT₆ receptor-related disorder.

- 30 The pharmaceutical formulation according to claim 28 for use in the reduction of body weight or reduction of body weight gain.
- 5 31. A non-therapeutic method for improving the bodily appearance of a mammal, comprising administering to said mammal a compound according to any one of claims 1 to 19 in a dosage effective to reduce appetite, and repeating said dosage until a cosmetically beneficial loss of body weight has occurred.
- 10 32. A cosmetic composition comprising a compound according to any one of claims 1 to 19 as active ingredient, in combination with a cosmetically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/053002

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/06 C07D487/06 A61K31/4745 A61P3/04

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 A61P

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 practical, search terms used)

EPO-Internal , WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 133 287 A (SLASSI ET. AL.) 17 October 2000 (2000-10-17) column 17, line 61 - column 18, line 33; claims; examples	1-32
A	US 2003/229069 A1 (CLARK ET. AL.) 11 December 2003 (2003-12-11) page 11, paragraph 103; claims; examples	1-32
A	US 3 833 591 A (MCMANUS) 3 September 1974 (1974-09-03) column 1, line 25 - line 50; claims; examples	1-32
A	US 3 950 343 A (PHILLIP ET. AL.) 13 April 1976 (1976-04-13) column 2, line 24 - line 65; claims; examples	1-32



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 document 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

6 June 2008

Date of mailing of the international search report

24/06/2008

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/053002

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>R.E. BOWMAN ET. AL.: "1,3,4,5-Tetrahydrobenz[cd] indoles and Related Compounds." JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, no. 15, 1972, pages 1926-1932, XP009101189 page 1928, compound 35 -----</p>	1-32
A	<p>L. STREKOWSKI ET. AL.: "Synthesis of Analogues of the Ergot Alkaloids." JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 37, 2000, pages 1495-1499, XP009101190 page 1496, compounds 17-19 -----</p>	1-32
A	<p>Y. YOKOYAMA ET. AL.: "Optically Active Total Synthesis of Clavicipitic Acid." JOURNAL OF ORGANIC CHEMISTRY, vol. 60, 1995, pages 1486-1487, XP002483151 page 1487, compound 14 -----</p>	1-32

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2008/053002

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 25-27 . 31
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 25-27 and 31 are drawn to therapeutic methods of treatment, the search has been carried out based on the alleged effects of the compounds/compositions.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2008/053002

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6133287	A	17-10-2000	NONE	
US 2003229069	A1	11-12-2003	NONE	
US 3833591	A	03-09-1974	BE 795451 A1	16-08-1973
			DE 2306605 A1	06-09-1973
			FR 2181738 A1	07-12-1973
			GB 1418354 A	17-12-1975
			JP 1027972 C	25-12-1980
			JP 48092400 A	30-11-1973
			JP 55016434 B	01-05-1980
US 3950343	A	13-04-1976	NONE	