

NEW COMPOUNDS

TECHNICAL FIELD

5 The present invention relates to novel spirooxindole derivatives, and pharmaceutically acceptable salts thereof, with an analgesic effect. The compounds of the invention can thus be used in the prevention and treatment of pain. In further aspects, the invention relates to compounds for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a
10 pharmaceutically acceptable salt thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above. The invention also relates to new intermediates for use in the preparation of the novel compounds.

15 BACKGROUND ART

Certain spirooxindole derivatives are known as intermediates in the syntheses of vasopressin receptor ligands from U.S. Patent No. 5,728,723 (Elf Sanofi).

20 Patent applications WO 9741125 (SKB), WO 9711697 (MSD), WO 9527712 (CEMAF), and WO 9315051 (Elf) also discloses spirooxindoles as synthetic intermediates.

Certain spirooxindole derivatives are known as local anesthetics from Kornet and Thio, *Journal of Medicinal Chemistry* 1976, 19, 892-8. This publication discloses racemic
25 mixtures and biological studies were limited to toxicity (LD₅₀) in mice and local anesthetic activity (rat sciatic nerve blocking) in which test the compounds were found inferior to lidocaine. No analgesic effects of the spirooxindole derivatives are mentioned.

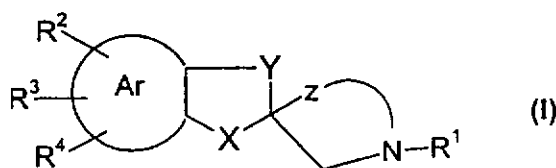
However, there remains a need for new therapeutic agents to treat chronic pain. Chronic pain can be caused by injury to nerves or by a variety of lesions. As of today there is no clear understanding why some, more or less visible injuries may elicit pain. Medical doctors often find even strong analgesics, such as opioids, distressfully inefficacious when the pain state is involving the nervous system itself, peripheral as well as central. These pain states are often referred to as neuropathic pain. As a final resort clinicians often prescribe drugs which are not considered true analgesics but which by trial and error have been found partly useful. Such agents include tricyclic antidepressants, for example amitriptylin, anticonvulsants like carbamazepine and gabapentin, and some local anesthetics and antiarrhythmics, especially mexiletine.

It has surprisingly been found that certain spirooxindole derivatives exhibit good analgesic properties and are particularly effective in the treatment of chronic pain.

DISCLOSURE OF THE INVENTION

It has surprisingly been found that compounds of the Formula I, which are spirooxindole derivatives, are particularly effective analgesic compounds and thereby suitable in the treatment of pain.

In one aspect, the present invention thus relates to compounds of the general Formula I



or a pharmaceutically acceptable salt thereof, wherein

R¹ is

- a) H,
- b) substituted or unsubstituted C₁-C₆ alkyl,
- c) C₁-C₆ alkoxy C₂-C₆ alkyl,
- d) C₁-C₆ alkylthio C₂-C₆ alkyl,
- 5 e) halogenated C₁-C₆ alkyl,
- f) aryl C₁-C₆ alkyl,
- g) C₁-C₆ alkenyl, or
- h) C₁-C₆ cycloalkyl C₁-C₂ alkyl;

10 R² is

- a) H,
- b) C₁-C₆ alkyl,
- c) C₂-C₄ alkynyl,
- d) halogen,
- 15 e) substituted or unsubstituted carbamoyl,
- f) substituted or unsubstituted carbamoyloxy,
- g) C₁-C₆ alkylcarbonyl,
- h) C₁-C₆ alkoxy carbonyl,
- i) C₁-C₆ alkylcarbonyloxy,
- 20 j) hydroxy-substituted C₁-C₆ alkyl,
- k) cyano,
- l) nitro,
- m) amino,
- n) halogenated C₁-C₆ alkyl,
- 25 o) halogenated C₁-C₆ alkoxy,
- p) halogenated C₁-C₆ alkylthio,
- q) C₁-C₆ alkylsulfinyl,
- r) C₁-C₆ alkylsulfonyl,
- s) C₁-C₄ alkylsulfinylalkyl,
- 30 t) C₁-C₄ alkylsulfonylalkyl,

- u) C₁-C₆ alkylsulfonylamino,
- v) halogenated C₁-C₆ alkylsulfonylamino,
- w) halogenated C₁-C₂ alkylsulfonyloxy,
- x) aminosulfonyl,
- 5 y) aminosulfonyloxy,
- z) aryl,
- aa) heteroaryl,
- bb) arylcarbonyl,
- cc) heteroarylcarbonyl,
- 10 dd) arylsulfinyl,
- ee) heteroarylsulfinyl,
- ff) arylsulfonyl,
- gg) heteroarylsulfonyl, in which any aromatic moiety is optionally substituted,
- hh) C₁-C₆ alkylcarbonylamino,
- 15 ii) C₁-C₆ alkoxycarbonylamino,
- jj) C₁-C₆ alkyl-thiocarbonyl,
- kk) C₁-C₆ alkoxy-thiocarbonyl,
- ll) formyl, or
- mm)alkoxysulfonylamino;

20

R³ is

- a) H,
- b) C₁-C₆ alkyl,
- c) halogen,
- 25 d) C₁-C₆ alkoxy,
- e) halogenated C₁-C₄ alkyl,
- f) halogenated C₁-C₆ alkoxy,
- g) halogenated C₁-C₆ alkylthio,
- h) C₁-C₄ alkylsulfinyl,
- 30 i) C₁-C₄ alkylsulfonyl,

- j) C₁-C₄ alkylsulfinyl C₁-C₆ alkyl,
k) C₁-C₄ alkylsulfonyl C₁-C₆ alkyl,
l) C₁-C₄ alkylsulfonylamino,
m) halogenated C₁-C₄ alkylsulfonylamino,
5 n) aminosulfonyl, or
o) aminosulfonyloxy;

R⁴ is

- a) H,
10 b) C₁-C₄ alkyl, or
c) halogen;

- R² and R³ may together with the carbon atoms to which they are attached, form a saturated or unsaturated ring, optionally containing one or more further heteroatoms, and/or
15 optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, cyano, amino, C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂-N-, CN, NH₂SO₂, NH₂CO-, or C₁-C₆ alkyl-CO-;

- Any amino moiety in R²-R⁴ can optionally be substituted with one or two C₁-C₆ alkyl
20 groups which may be part of a ring;

Ar is

- a) benzene,
b) pyridine,
25 c) thiophene,
d) pyrazine,
e) pyrimidine,
f) oxazole,
g) thiazole,
30 h) pyrrole,

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- i) pyrazole, or
- j) furan;

X is

- 5 a) -NHCO-,
- b) -CONH-,
- c) -NH-SO₂-,
- d) -SO₂NH-,
- e) -OCH₂-,
- 10 f) -NHCH₂-, or
- g) -NHCOCH₂-;

Y is

- a) -CH₂-,
- 15 b) -CH(C₁-C₆ alkyl)-,
- c) -C(C₁-C₆ alkyl)₂-, or
- d) a single bond;

Z is

- 20 a) -CH₂CH₂CH₂-,
- b) -CH₂CH₂CH₂CH₂-,
- c) -CH=CHCH₂-,
- d) -CH=CHCH₂CH₂-, or
- e) -CH₂CH=CHCH₂-;

25

provided that when X is -NHCOCH₂- then Y cannot be -CH₂-;

and

excluding the racemic compounds wherein Ar is benzene, R^2-R^4 is hydrogen, X is NHCO, Y is a single bond, Z is $-CH_2CH_2CH_2-$, and R^1 is ethyl or n-propyl.

The pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers are
5 within the scope of the invention. It should be understood that also all the diastereomeric forms possible are within the scope of the invention.

It will also be appreciated by those skilled in the art, although derivatives of compounds of formula I may not possess pharmacological activity as such, they may be administered
10 parenterally or orally and thereafter metabolized in the body to form compounds of the invention which are pharmacologically active. Such derivatives, of which the N-oxide is one example, may therefore be described as "prodrugs". All prodrugs of compounds of formula I are included within the scope of the invention.

15 Depending on the process conditions the final products of the Formula I are obtained either in neutral or salt form. Salt forms include hydrates and other solvates and also crystalline form polymorphs. Both the free base and the salts of these end products are within the scope of the invention.

20 Acid addition salts of the new compounds may in a manner known *per se* be transformed into the free base using basic agents such as alkali or by ion exchange. The free base obtained may also form salts with organic or inorganic acids.

In the preparation of acid addition salts, preferably such acids are used which form suitably
25 pharmaceutically acceptable salts. Examples of such acids are hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic carboxylic or sulfonic acids, aromatic or heterocyclic carboxylic or sulfonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, p-hydroxybenzoic acid, embonic acid,

methanesulfonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, halogenbenzenesulfonic acid, toluenesulfonic acid or naphthalenesulfonic acid.

All crystalline form polymorphs are within the scope of the invention.

5 Preferred compounds of the invention are those of Formula I wherein

R^1 is

- a) H,
- b) C_1 - C_4 alkyl,
- 10 c) C_1 - C_4 alkoxy C_1 - C_4 alkyl,
- d) C_1 - C_4 alkylthio C_1 - C_4 alkyl,
- e) fluorinated C_1 - C_4 alkyl,
- f) aryl C_1 - C_4 alkyl,
- g) C_1 - C_4 alkenyl, or
- 15 h) cyclopropylmethyl;

R^2 is

- a) H,
- b) C_1 - C_4 alkyl,
- 20 c) C_2 - C_3 alkynyl,
- d) halogen,
- e) substituted or unsubstituted carbamoyl,
- f) substituted or unsubstituted carbamoyloxy,
- g) C_1 - C_3 alkylcarbonyl,
- 25 h) C_1 - C_3 alkoxycarbonyl,
- i) C_1 - C_3 alkylcarbonyloxy,
- j) hydroxy-substituted C_1 - C_3 alkyl,
- k) cyano,
- l) fluorinated C_1 - C_3 alkoxy,
- 30 m) fluorinated C_1 - C_6 alkylthio,

- n) C₁-C₃ alkylsulfinyl,
- o) C₁-C₃ alkylsulfonyl,
- p) C₁-C₃ alkylsulfinyl C₁-C₆ alkyl,
- q) C₁-C₄ alkylsulfonyl C₁-C₆ alkyl,
- 5 r) C₁-C₃ alkylsulfonylamino,
- s) halogenated C₁-C₃ alkylsulfonylamino,
- t) sulfamoyl,
- u) sulfamoyloxy,
- v) aryl,
- 10 w) heteroaryl,
- x) heteroarylsulfinyl,
- y) arylsulfonyl,
- z) heteroarylsulfonyl, in which any aromatic moiety is optionally substituted,
- aa) C₁-C₄ alkylcarbonylamino,
- 15 bb) C₁-C₃ alkoxy-carbonylamino,
- cc) C₁-C₃ alkyl-thiocarbonyl, or
- dd) C₁-C₃ alkoxy-thiocarbonyl;

R³ is

- 20 a) H,
- b) C₁-C₄ alkyl, or
- c) halogen;

R⁴ is

- 25 a) H,
- b) C₁-C₄ alkyl, or
- c) halogen,

- R² and R³ may together with the carbon atoms to which they are attached, form a saturated
- 30 or unsaturated ring, optionally containing one or more further heteroatoms, and/or

optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, cyano, amino, C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂-N-, CN, NH₂SO₂, NH₂CO-, or C₁-C₆ alkyl-CO-;

- 5 Any amino moiety in R²-R⁴ can optionally be substituted with one or two C₁-C₆ alkyl groups which may be part of a ring;

Ar is

- a) benzene,
10 b) pyridine,
c) thiophene,
d) pyrazine,
e) pyrimidine,
f) oxazole,
15 g) thiazole,
h) pyrrole,
i) pyrazole, or
j) furan;

20 X is

- a) -NHCO-,
b) -CONH-,
c) -NH-SO₂-, or
d) -SO₂NH-;

25

Y is

- a) -CH₂-,

- b) $-\text{CH}(\text{C}_1\text{-C}_6 \text{ alkyl})-$,
- c) $-\text{C}(\text{C}_1\text{-C}_6 \text{ alkyl})_2-$ or
- d) a single bond;

5 Z is

- a) $-\text{CH}_2\text{CH}_2\text{CH}_2-$,
- b) $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$,
- c) $-\text{CH}=\text{CHCH}_2-$,
- d) $-\text{CH}=\text{CHCH}_2\text{CH}_2-$, or
- 10 e) $-\text{CH}_2\text{CH}=\text{CHCH}_2-$;

provided that when X is $-\text{NHCOCH}_2-$ then Y cannot be $-\text{CH}_2-$;

and

excluding the racemic compounds wherein Ar is benzene, $\text{R}^2\text{-R}^4$ is hydrogen, X is NHCO ,

15 Y is a single bond, Z is $-\text{CH}_2\text{CH}_2\text{CH}_2-$, and R^1 is ethyl or n-propyl.

More preferred compounds of the invention are those of Formula I wherein

R^1 is

- 20 a) H,
- b) $\text{C}_1\text{-C}_4$ alkyl, or
- c) $\text{C}_1\text{-C}_4$ alkoxy $\text{C}_1\text{-C}_4$ alkyl;

R^2 is

- 25 a) H,
- b) $\text{C}_1\text{-C}_4$ alkyl,
- c) halogen,
- d) substituted or unsubstituted carbamoyl,
- e) substituted or unsubstituted carbamoyloxy,
- 30 f) $\text{C}_1\text{-C}_2$ alkylcarbonyl,

- g) C₁-C₃ alkoxycarbonyl,
- h) cyano,
- i) fluorinated C₁-C₂ alkoxy,
- j) fluorinated C₁-C₆ alkylthio,
- 5 k) C₁-C₃ alkylsulfinyl,
- l) C₁-C₃ alkylsulfonyl,
- m) C₁-C₂ alkylsulfonylamino,
- n) C₁-C₃ alkylcarbonylamino, or
- o) C₁-C₃ alkoxycarbonylamino;

10

R³ is

- a) H,
- b) C₁-C₄ alkyl, or
- c) halogen;

15

R⁴ is

- a) H,
- b) C₁-C₄ alkyl, or
- c) halogen;

20

R² and R³ may together with the carbon atoms to which they are attached, form a saturated or unsaturated ring, optionally containing one or more further heteroatoms, and/or optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, cyano, amino, C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂-N-, CN, NH₂SO₂, NH₂CO-, or C₁-C₆ alkyl-CO-;

25

Any amino moiety in R²-R⁴ can optionally be substituted with one or two C₁-C₆ alkyl groups which may be part of a ring;

30 Ar is

- a) benzene,
b) pyridine,
c) thiophene,
d) pyrazine,
5 e) pyrimidine,
f) oxazole,
g) thiazole,
h) pyrrole,
i) pyrazole, or
10 j) furan;

X is

- a) -NHCO-,
b) -CONH-,
15 c) -NH-SO₂-, or
d) -SO₂NH-;

Y is

- a) -CH₂-,
20 b) -CH(C₁-C₆ alkyl)-,
c) -C(C₁-C₆ alkyl)₂-, or
d) a single bond;

Z is

- 25 a) -CH₂CH₂CH₂-,
b) -CH₂CH₂CH₂CH₂-,
c) -CH=CHCH₂-,
d) -CH=CHCH₂CH₂-, or
e) -CH₂CH=CHCH₂-;

excluding the racemic compounds wherein Ar is benzene, R^2 - R^4 is hydrogen, X is NHCO, Y is a single bond, Z is $-\text{CH}_2\text{CH}_2\text{CH}_2-$, and R^1 is ethyl or n-propyl.

Particularly preferred compounds of the invention are those of Formula I wherein

5

R^1 is H;

R^2 is

- a) H,
- 10 b) C_1 - C_4 alkyl, or
- c) halogen;

R^3 is

- a) H,
- 15 b) C_1 - C_4 alkyl, or
- c) halogen;

R^4 is

- a) H,
- 20 b) C_1 - C_4 alkyl, or
- c) halogen;

Ar is

- a) benzene, or
- 25 b) pyridine;

X is

- a) $-\text{NHCO}-$,
- b) $-\text{CONH}-$, or
- 30 c) $-\text{NH}-\text{SO}_2-$;

Y is a single bond;

Z is

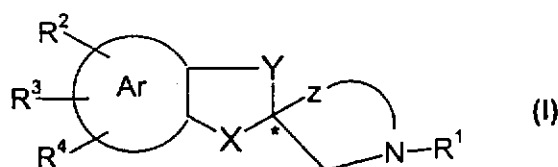
- 5 a) $\text{CH}_2\text{CH}_2\text{CH}_2-$, or
b) $-\text{CH}=\text{CHCH}_2-$,

excluding the racemic compounds wherein Ar is benzene, R^2-R^4 is hydrogen, X is NHCO ,
Y is a single bond, Z is $-\text{CH}_2\text{CH}_2\text{CH}_2-$, and R^1 is ethyl or n-propyl.

10

It has furthermore surprisingly been found that the (S)-enantiomers of the compounds of
formula I possess a higher analgesic activity than the (R)-enantiomers and are thus
preferred for therapeutic use before the latter and the racemic mixtures.

- 15 Another aspect of the present invention is therefore the S-enantiomer, referring to the
marked spirocarbon, of the compounds of the general Formula I



- 20 or a pharmaceutically acceptable salt thereof, as defined above.

The following definitions shall apply throughout the specification and the appended
claims:

- 25 The term "C₁-C₆ alkyl" denotes a cyclic or linear, straight or branched, substituted or
unsubstituted alkyl group having from 1 to 6 carbon atoms. Examples of said alkyl include,

but is not limited to methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, cyclohexyl, and cyclopentyl.

The term "C₁-C₆ alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

5

The terms "C₁-C₄ alkyl", "C₁-C₃ alkyl", "C₁-C₂ alkyl" have the corresponding meaning as "C₁-C₆ alkyl".

The term "halogen" includes fluoro, chloro, bromo and iodo groups.

10

The term "aryl" denotes a substituted or unsubstituted C₆-C₁₄ aromatic hydrocarbon and includes, but is not limited to, benzene, naphthalene, indene, anthracene, fenantrene, and fluorene.

15

The term "substituted" denotes *e.g.* an C₁-C₆ alkyl, C₁-C₆ alkylaryl or aryl group as defined above which is substituted by one or more alkyl, alkoxy, halogen, amino, thiol, nitro, hydroxy, acyl, cyano or oxo groups.

The term "heteroatoms" denotes a nitrogen, oxygen, sulfur, or a phosphorous atom.

20

Most preferred compounds according to the invention are listed in the following table. The compounds can be in neutral form or in salt form as earlier indicated, for example in hydrochloride form.

- 5-Fluorospiro[indolin-3,3'-piperidin]-2-one
- 25 • 5-Fluoro-1'-isopropylspiro[indolin-3,3'-piperidin]-2-one
- (*R*)-5-Fluoro-1'-isopropylspiro[indolin-3,3'-piperidin]-2-one
- (*S*)-5-Fluoro-1'-isopropylspiro[indolin-3,3'-piperidin]-2-one
- 5,7-Difluorospiro[indolin-3,3'-piperidin]-2-one acetate
- 5,7-Difluoro-1'-isopropylspiro[indolin-3,3'-piperidin]-2-one
- 30 • (*S*)-5,7-Difluoro-1'-isopropylspiro[indolin-3,3'-piperidin]-2-one

- 1', 5-Dimethylspiro[indolin-3,3'-piperidin]-2-one
- 5-Methyl-1'-isopropylspiro[indolin-3,3'-piperidin]-2-one
- 6-Methyl-1'-isopropylspiro[indolin-3,3'-piperidin]-2-one
- 4-Methylspiro[indolin-3,3'-piperidin]-2-one
- 5 • 4-Methyl-1'-isopropylspiro[indolin-3,3'-piperidin]-2-one
- 4-Methyl-1'-propylspiro[indolin-3,3'-piperidin]-2-one
- 7-Fluorospiro[indolin-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one
- (S)-(+)-7-Fluorospiro[indolin-3,3'-piperidin]-2-one
- Spiro[indolin-3,3'-piperidin]-2-one
- 10 • 1'-Ethylspiro[indolin-3,3'-piperidin]-2-one
- 1'-Propylspiro[indolin-3,3'-piperidin]-2-one
- 1'-Isopropylspiro[indolin-3,3'-piperidin]-2-one
- 1'-Allylspiro[indolin-3,3'-piperidin]-2-one
- 1'-Cyclopropylmethylspiro[indolin-3,3'-piperidin]-2-one
- 15 • 1'-Butylspiro[indolin-3,3'-piperidin]-2-one
- 1'-s-Butylspiro[indolin-3,3'-piperidin]-2-one
- (S)-(+)-1'-Propylspiro[indolin-3,3'-piperidin]-2-one
- 1'-Propylspiro[4-azaindolin-3,3'-piperidin]-2-one
- 1'-Butylspiro[4-azaindolin-3,3'-piperidin]-2-one
- 20 • 1'-sec-Butylspiro[4-aza-indolin-3,3'-piperidin]-2-one
- 1'-Propyl-5-chlorospiro[7-aza-indolin-3,3'-piperidin]-2-one
- 1'-Propylspiro[7-azaindolin-3,3'-piperidin]-2-one
- 1'-Propyl-6-methylspiro[7-azaindolin-3,3'-piperidin]-2-one
- 1'-Propylspiro[isindolin-3,3'-piperidin]-1-one hydrochloride
- 25 • 1'-Isopropylspiro[indoline-3,3'-piperidine] hydrochloride
- 2,3-Dihydro-1*H*-1'-Propylspiro[thieno[3,2-*b*]pyrrol-3,3'-piperidin]-2-one
- 2,3,1',2',3',6'-Hexahydro-1*H*-spiro[thieno[3,2-*b*]pyrrol-3,3'-pyridin]-2-one
- 2,3,1',2',3',6'-Hexahydro-1*H*-spiro[5,8-diazaindol-3,3'-pyridin]-2-one
- 1',2',3',4'-Tetrahydrospiro[indolin-3,3'-(7*H*)-azepin]-2-one
- 30 • 1',2',3',4'-Tetrahydrospiro[7-azaindolin-3,3'-(7*H*)-azepin]-2-one

- 1'-Ethyl-1',2',3'4'-tetrahydrospiro[4-azaindolin-3,3'-(7H)-azepin]-2-one
- 1'-Propylspiro[indolin-3,3'-piperidin]-2-one 1'-oxide

Further most preferred compounds according to the invention:

5

Also these compounds can be in neutral form or in salt form as earlier indicated.

(S)-5-Chloro-7-fluorospiro[indolin-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one

(S)-5-Methylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one

(S)-5,6-Dimethylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one

10 (S)-6-Methylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one

(S)-5-Chlorospiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one

(S)-5,7-Difluorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one

(S)-7-Chlorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one

(S)-7-Fluoro-5-methylspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one

15 (S)-5-Methoxyspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one

(S)-5-Chlorospiro[indoline-3,3'-piperidin]-2-one

PREPARATION

20 The present invention also provides the following processes for the preparation of compounds of the general Formula I. The compounds of the present invention can be prepared by methods known in the art using commercially available, or readily prepared, starting materials. Many useful methods for synthesis of oxindoles are reviewed by G.M. Karp in *Org. Prep. Proced. Int.* 1993, 25, 481-513, which is incorporated herein by
25 reference.

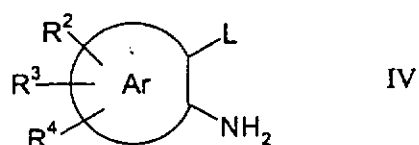
It is to be understood that certain functional groups may interfere with other reactants or reagents under the reaction conditions and therefore may need temporary protection. The

use of protecting groups is described in 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1991).

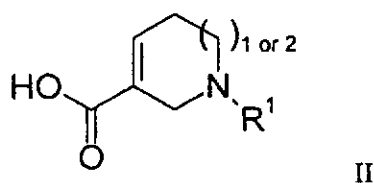
Process A

A process for manufacture of compounds with the general Formula I comprises the following steps:

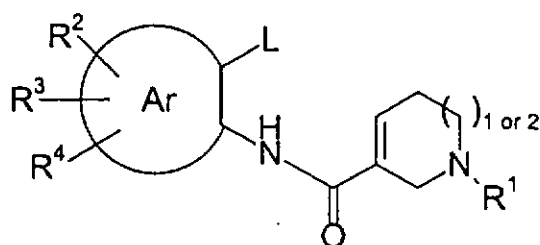
a) Compounds of Formula IV



wherein L is a halogen or a trifluoromethylsulfonyloxy group, Ar, R²-R⁴ are as defined in Formula I, or can be converted into such groups later in the synthesis sequence, is coupled with a compound of the general Formula II, or a corresponding lower alkyl ester, e.g. methyl or ethyl ester,



wherein R¹ is as defined for Formula I or is a nitrogen protecting group, e.g. a Boc group, to give a compound of the general Formula VII



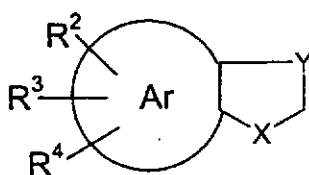
VII

- b) The resulting amide of the general Formula VII is then cyclized using Heck reaction conditions with palladium as a catalyst or sometimes under radical generating conditions to give, after optional removal of protecting groups, a compound of the general formula I

When the above formed spiro compound contains a double bond this may be hydrogenated over a metal catalyst to give the corresponding saturated compound, or by other methods well known to those skilled in the art. The product is thereafter deprotected, if necessary, or the cyclized protected intermediate compound may be further reacted with, for example organometallic reagents, to give new compounds of the invention in which an alkyl or alkynyl group is substituted for a bromine or an aryl- or alkylsulfonyloxy group.

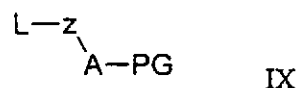
Process B

a) Compounds of Formula IV

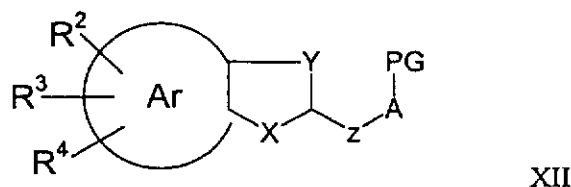


IV

- wherein Ar, R²-R⁴, Y are as defined in Formula I, and X is -NHCO- or -NH-SO₂ are alkylated with a compound of the general Formula IX



wherein Z is as defined in Formula I, L is a bromine, iodine, aryl or alkylsulfonyloxy group, *e.g.* trifluoromethylsulfonyloxy group, A is oxygen or nitrogen, and PG is a suitable protecting group or, when A is nitrogen, equals R¹ of Formula I, to give compounds of the general formula XII



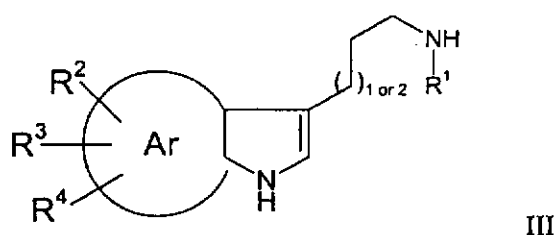
wherein Ar, R², R⁴, Y, and Z are as defined in Formula I, X is -NHCO-, or -NH-SO₂-, A is oxygen or nitrogen and PG is a suitable protecting group or, when A is nitrogen, equals R¹ of Formula I.

b) An optional transformation step is performed when A is oxygen, wherein the oxygen function is converted into the corresponding amino function by methods well known in the art. One suitable way of accomplishing this conversion is to remove the protecting group to generate the corresponding primary alcohol, which is thereafter converted into a suitable leaving groups, *e.g.* a tosylate group. The leaving group is thereafter displaced by a suitable amino nucleophile to give a compound of the general formula XII, wherein A is nitrogen.

c) Compounds of the general formula XII can thereafter and after optional removal of protecting groups be cyclized to the spiro system to give compounds of the formula I under standard Mannich conditions.

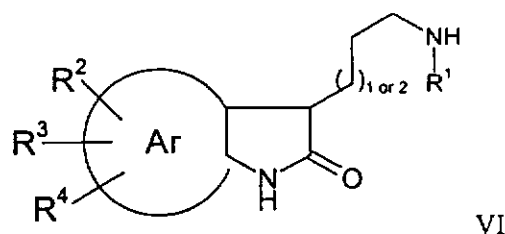
5 *Process C*

a) Compounds of the general Formula III



10

wherein Ar, R¹-R⁴ are as defined in Formula I or R¹ is a benzylic protecting group, are oxidised into compounds of the general Formula VI,

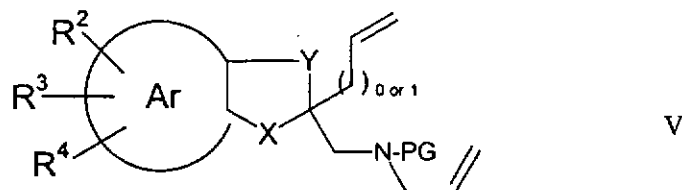


15 wherein Ar, R¹-R⁴ are as defined in Formula I or R¹ is a benzylic protecting group, as is described in Kornet and Thio, *Journal of Medicinal Chemistry* 1976, 19, 892-8 or as referred to in the previously mentioned review by Karp.

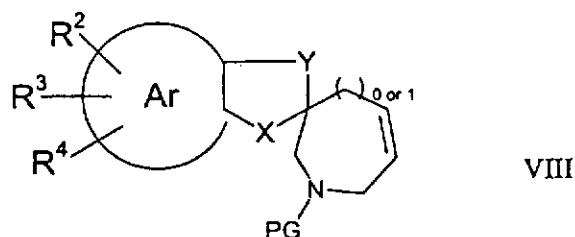
c) Compounds of the general Formula VI are thereafter cyclized under standard Mannich
20 reaction conditions to give a compound of the general Formula I.

Process D

a) Compounds of the general Formula V

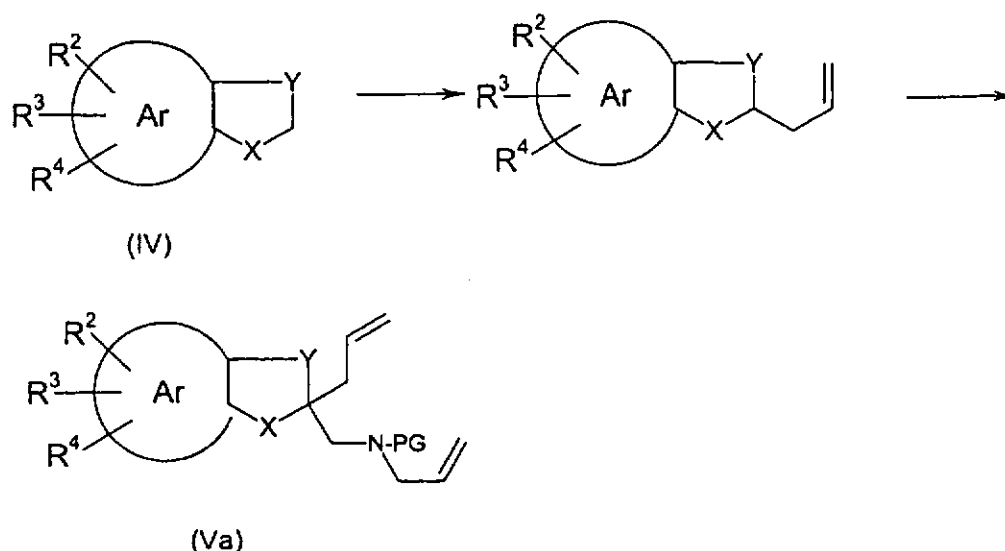


wherein Ar, R²-R⁴, X and Y are as defined in Formula I and PG is an amino protecting group, is ring-closed using a ruthenium or molybdene complex as a catalyst under standard reaction conditions to give compounds of the general formula VIII



This metathesis reaction is described in more detail in the review by Grubbs, R.H. and Chang, S. *Tetrahedron* 1998, 54, 4413-50.

The intermediate V may be prepared by methods known to the one skilled in the art, for example by alkylation of the intermediate IV with e.g. allyl bromide followed by a Mannich reaction with a secondary amine to give a compound of the general formula Va, as is schematically shown below.



In process B and C the amino protecting group used is preferably an easily removable group, for example groups belonging to the arylmethyl class which can be readily removed by hydrogenolysis, thus releasing the secondary amine of formula I ($R^1=H$). Said compound can be converted to a tertiary amine, by alkylating methods well known in the art. Other suitable protective groups that are described in the organic chemical literature is, for example, an allyl carbamate or a 4-methoxybenzyl group.

Many interconversions of the R^2 and R^3 groups are also evident to one skilled in the art.

Compounds of the general formula I prepared in this way are racemic. As is well known in the art resolution of the two enantiomers can be conveniently achieved by classical crystallization methods by using a chiral acid such as L- or D-ditoluoyltartaric acid or (+) or (-)-1-camphorsulfonic acid in a suitable solvent such as acetone, water, alcohol, ethyl acetate or their mixture. Another method to achieve the same goal is to separate the enantiomers by chromatography on a chiral column such as Chiralcel OD or Kromasil TBB which are commercially available. A further well known means to obtain pure enantiomers is by preparing a derivative of a racemic intermediate, for example an amide

of a secondary amine, with an enantiomerically pure acid and then separating the so formed diastereomers by crystallization or by chromatography.

MEDICAL USE

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In a further aspect, the present invention relates to compounds of the formula I for use in therapy, in particular for use in the treatment of pain. The invention also provides the use of a compound of the formula I in the manufacture of a medicament for the treatment of pain.

10

The novel compounds of the present invention are useful in therapy, especially for the treatment and/or prophylaxis of pain of widely different origins and causes and include acute as well as chronic pain states. Examples are pain caused by chemical, mechanical, radiation, thermal, infectious or inflammatory tissue trauma or cancer, postoperative pain, headache and migraine, various arthritic and inflammatory conditions such as osteo and rheumatoid arthritis, myofascial and low back pain.

Also neuropathic conditions of central or peripheral origin can be treated or prevented with the compounds of the invention. Examples of these pain conditions are trigeminal neuralgia, postherpetic neuralgia (PHN), diabetic mono/poly neuropathy, nerve trauma, spinal cord injury, central post stroke, multiple sclerosis and Parkinson's disease.

Other pain states of visceral origin such as caused by ulcer, dysmenorrhea, endometriosis, IBS, dyspepsia etc. can also be treated or prevented with the compounds of the invention.

The compounds of the invention are useful as therapeutic agents in disease states with inappropriate neuronal activity or in neuroprotection for example as anticonvulsants in epilepsy, in the treatment of itch, tinnitus, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), Alzheimer, stroke, cerebral ischaemia, traumatic brain injury, Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm

disorders, insomnia & narcolepsy), tics (e.g. Tourette's syndrome), and muscular rigidity (spasticity).

A primary aim of the invention is to use compounds of the formula I for oral treatment of
5 neuropathic or central pain states.

The compounds of the invention are also useful for treatment of effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines.

10

In a further aspect the invention provides the use of a compound of formula I, or a pharmaceutically acceptable salt or solvate, thereof as a therapeutic agent, in particular for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression.

15

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, the dosages will be in the range of 0.1 to 1000 mg per day of active substance.

20

PHARMACEUTICAL FORMULATIONS

In yet a further aspect, the invention relates to pharmaceutical compositions containing at least one compound of the present invention, or a pharmaceutically acceptable salt thereof,
25 as active ingredient.

For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, intravenous, subcutaneous, tracheal, bronchial, intranasal, pulmonary, transdermal, buccal, rectal, parenteral or other mode of administration. The

pharmaceutical formulation contains a compound of the invention in combination with one or more pharmaceutically acceptable ingredients. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compounds is between 0.1–95% by weight of the preparation.

In the preparation of pharmaceutical formulations containing a compound of the present invention the compound selected may be mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture may then be processed into granules or pressed into tablets.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Hard gelatine capsules may contain granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, cornstarch, amylopectin, cellulose derivatives or gelatine.

Dosage units for rectal administration may be prepared (i) in the form of suppositories which contain the active substance mixed with a neutral fat base; (ii) in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing the active ingredient and the remainder consisting, for example, of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and

polyethylene glycol. If desired, such liquid preparations may contain coloring agents, flavouring agents, preservatives, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

5

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent. These solutions may also contain stabilizing ingredients, preservatives and/or buffering ingredients. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent before use.

10

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 0.1 to 1000 mg per day of active substance.

15

The compounds according to the present invention can also be used in formulations, together or in combination for simultaneous, separate or sequential use, with other active ingredients, such as

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- a) opioid analgesics, for example morphine, ketobemidone or fentanyl
- b) analgesics of the NSAID class, for example ibuprofene, selecoxib or acetylsalicylic acid
- c) amino acids such as gabapentin or pregabalin
- d) analgesic adjuvants such as amitriptyline or mexiletine
- 25 e) NMDA antagonists for example ketamine or dextrometorfan
- f) sodium channel blocking agents for example lidocaine
- g) anticonvulsants, for example carbamazepine or lamotrigine
- h) cannabinoids

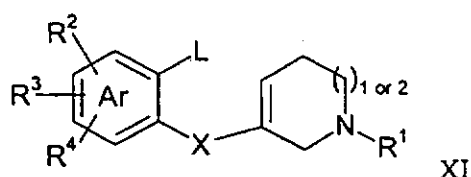
INTERMEDIATES

A further aspect of the invention is new intermediate compounds which are useful in the
5 synthesis of compounds according to the invention.

Thus, the invention includes

(a) a compound of the formula XI

10



wherein Ar, R¹-R⁴ and X are as defined for Formula I, L is bromide, iodide, or triflate and
R¹ may also be a nitrogen protecting group, such as a alkoxycarbonyl or a benzyl group, of
15 which *t*-butoxycarbonyl is especially preferred and X, when containing a nitrogen atom,
may optionally be substituted with a *t*-butoxycarbonyl group.

EXAMPLES

20 1. PREPARATION OF COMPOUNDS OF THE INVENTION

All chemicals and reagents were used as received from suppliers. ¹³C and ¹H nuclear
magnetic resonance (NMR) spectra were recorded on a Varian Unity 400 (400 MHz)
spectrometer. Silica gel chromatography (SGC) was carried out on silica gel 60 (230-400
25 mesh). Mass spectrometry (MS) was carried out in the positive thermospray (TSP+),
chemical ionization (CI), or in the electron impact (EI) modes.

Other abbreviations: Boc, *t*-butoxycarbonyl; DCM, dichloromethane; EtOAc, ethyl acetate.

EXAMPLE 1.

5 5-Fluorospiro[indoline-3,3'-piperidin]-2-one hydrochloride

STEP A. *t*-Butyl 3-(2-bromo-4-fluorophenylcarbamoyl)-1,2,5,6-tetrahydropyridine-1-carboxylate. 2-Bromo-4-fluoroaniline (2.53 g, 13.3 mmol) was dissolved in dichloromethane (30 mL) under N₂-atmosphere and trimethylaluminium (2.0 M in
10 hexanes, 8 mL) was added. The solution was stirred during 15 minutes, whereupon a solution of 5,6-dihydro-2*H*-pyridine-1,3-dicarboxylic acid 1-*t*-butyl ester 3-methyl ester (3.67 g, 13.3 mmol) in DCM (20 mL) was added. The mixture was refluxed overnight and saturated NaHCO₃ was carefully added followed by DCM. The aqueous phase was extracted with DCM. The crude product was purified by chromatography on silica gel
15 using a gradient of toluene to acetonitrile to give the title compound (4.55 g) in 86 % yield as an yellow oil. R_f 0.54 (toluene/acetonitrile 3:1). MS(TSP+) *m/z* calcd for [M+NH₄]⁺: 416, 418, observed: 416, 418.

STEP B. *t*-Butyl 3-[(2-bromo-4-fluorophenyl)-(*t*-butoxycarbonyl)-carbamoyl]-1,2,5,6-tetrahydropyridine-1-carboxylate. The product from STEP A (3.51 g) was dissolved in
20 dry acetonitrile under N₂-atmosphere. 4-Dimethylaminopyridine (120 mg, 0.98 mmol) and di-*t*-butyl dicarbonate (2.08 g, 9.53 mmol) were added. After reaction overnight the acetonitrile was stripped off and the residue was dissolved in diethyl ether (200 mL). The ethereal phase was extracted with 0.2 M aqueous solution of citric acid (3×50 mL) and
25 then with saturated NaHCO₃ (3×50 mL). The product was purified by chromatography on silica gel using a gradient of toluene to acetonitrile to give the title compound in 91 % yield as a yellow oil. MS(TSP+) *m/z* observed: 516, 518 (20%).

STEP C. Di-*t*-butyl 5-fluoro-2-oxospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-1,1'-dicarboxylate. The amide from STEP B (994 mg, 1.99 mmol) was dissolved in
30

acetonitrile (20 mL) under N₂-atmosphere. Triphenylphosphine (133 mg, 0.51 mmol), triethylamine (0.42 mL, 3 mmol) and palladium acetate (50 mg, 0.22 mmol) were added. The mixture was refluxed for 5 days under N₂-atmosphere. The crude product was purified by chromatography on silica gel and eluted with a gradient of toluene to acetonitrile to give the title compound (604 mg) in 73 % yield as a yellow oil. R_f 0.58 (toluene/acetonitrile 3:1). MS(CI, NH₃) *m/z* 436.

STEP D. *t*-Butyl 5-fluoro-2-oxospiro[indoline-3,3'-(1,2,3,6-tetrahydro-pyridin)]-1'-carboxylate. The compound from STEP A (1.00 g, 2.50 mmol) was cyclised to the title compound (382 mg) in 48 % yield following the same procedure as described in STEP C. MS (TSP+) *m/z* [M+H]⁺: 319.

STEP E. Di-*t*-butyl 5-fluoro-2-oxospiro[indoline-3,3'-piperidin]-1,1'-dicarboxylate. The product from STEP C (590 mg, 1.41 mmol) was hydrogenated in absolute ethanol (20 mL) using PtO₂ and H₂ (3.5 atm) for 2 days. The reaction mixture was filtered using 00H-filter paper and the solvent was evaporated to give the title compound (563 mg) in 95 % yield. MS (TSP+) *m/z* calcd for [M-BOC+H]⁺: 321, observed: 321.

STEP F. *t*-Butyl 5-fluoro-2-oxospiro[indoline-3,3'-piperidin]-1'-carboxylate. The product from STEP D (344 mg, 1.08 mmol) was transformed to the title compound (295 mg) following the same procedure as described in STEP E. MS (TSP+) *m/z* [M+H]⁺: 321.

STEP G. 5-Fluorospiro[indoline-3,3'-piperidin]-2-one hydrochloride. The product from STEP E (563 mg, 1.34 mmol) was dissolved in methanol (10 mL) and was treated with HCl (2.5 M ethereal solution, 5 mL). The solvents were stripped off to give the product (341 mg) in 99 % yield as a white solid. The same procedure was also applied to the product from STEP F. MS(TSP+) *m/z* calcd for [M-Cl]⁺: 221, observed: 221.

EXAMPLE 2

5-Fluoro-1'-isopropylspiro[indoline-3,3'-piperidin]-2-one hydrochloride.

The amine from EXAMPLE 1 was alkylated using PROCEDURE 1, Method A. The crude product was purified by chromatography on silica gel using a gradient of toluene to acetonitrile/triethyl amine 100:5 to give the amine in 64 % yield. ^{13}C -NMR (CDCl_3) δ 182.3, 158.5 (d, J 236 Hz), 136.4, 135.9, 114.4 (d, J 26 Hz), 113.4 (d, J 25 Hz), 109.8, 54.8, 53.9, 49.2, 48.9, 32.0, 21.7, 18.0, 17.6. It was converted to the title compound with HCl in ether. MS(TSP+) m/z calcd for $[\text{M}-\text{Cl}]^+$: 263, observed: 263.

EXAMPLE 3

10 (R)-5-Fluoro-1'-isopropylspiro[indoline-3,3'-piperidin]-2-one hydrochloride.
5-Fluoro-1'-isopropyl-spiro[indoline-3,3'-piperidin]-2-one (215 mg) from EXAMPLE 2 was chromatographed on a Kromasil TBB column eluting with hexane/1-propanol/1-butanol 99:0.5:0.5. The pure stereoisomer (72 mg) was collected as the first eluting peak in 67 % yield and an enantiomeric excess of 97 %. $[\alpha]_{589}^{22}$ -1.18°, $[\alpha]_{365}^{22}$ -10.0° (c 1.01, CHCl_3). It was converted to the title compound. $[\alpha]_{589}^{22}$ -6.93° (c 1.01, MeOH).

EXAMPLE 4

(S)-5-Fluoro-1'-isopropylspiro[indoline-3,3'-piperidin]-2-one.

62 mg was collected from EXAMPLE 3 as the second enantiomer in 58 % yield and an enantiomeric excess of 99 %. $[\alpha]_{589}^{22}$ +1.05°, $[\alpha]_{365}^{22}$ +9.32° (c 1.03, CHCl_3). It was converted to the hydrochloride. $[\alpha]_{589}^{22}$ +6.22° (c 1.03, MeOH).

EXAMPLE 5

5,7-Difluorospiro[indoline-3,3'-piperidin]-2-one acetate.

25

STEP A. 1-Benzyl-N-(2-bromo-4,6-difluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxamide. The title compound was prepared from 2-bromo-4,6-difluoroaniline and 1-benzyl-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester as described in EXAMPLE 1. R_f 0.53 (toluene/acetonitrile/tri-ethyl amine 10:10:1).

STEP B. 5,7-Difluoro-1'-benzylspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one.

The product from STEP A was cyclized as described in EXAMPLE 1.

- 5 **STEP C. 5,7-Difluorospiro[indoline-3,3'-piperidin]-2-one acetate.** The product from STEP B was hydrogenated in glacial acetic acid (20 mL) using 10 % Pd/C and H₂ (3.5 atm) for 24 hours. The title compound was obtained in 86 % yield as a crystalline solid. MS(TSP+) *m/z* calcd for [M-AcO]⁺: 239, observed: 239.

10 **EXAMPLE 6**

5,7-Difluoro-1'-isopropylspiro[indoline-3,3'-piperidin]-2-one hydrochloride.

- The amine from the previous EXAMPLE was alkylated as described in EXAMPLE 2 to give the free amine of the title compound in 58 % yield as a white solid. ¹³C-NMR (CDCl₃) δ 180.3, 157.9 (d, *J* 240 Hz), 146.0 (d, *J* 244 Hz), 137.8, 123.2 (d, *J* 11 Hz), 110.3 (d, *J* 25 Hz), 102.6 (dd, *J* 21, 21 Hz), 54.9, 53.9, 49.4, 48.7, 32.1, 21.6, 18.1, 17.6. It was converted to the hydrochloride. MS(TSP+) *m/z* calcd for [M-Cl]⁺: 281, observed: 281.
- 15

EXAMPLE 7**(S)-5,7-Difluoro-1'-isopropylspiro[indoline-3,3'-piperidin]-2-one hydrochloride.**

- 20 **STEP A. Chromatography.** 5,7-Difluoro-1'-isopropyl-spiro[indoline-3,3'-piperidin]-2-one (231 mg) from the preceding example was chromatographed on a Kromasil TBB column eluting with hexane/1-propanol/1-butanol 98:1:1. (*R*)-5,7-Difluoro-1'-isopropyl-spiro[indoline-3,3'-piperidin]-2-one (94 mg) was collected as the first enantiomer in 81 % yield and an enantiomeric excess of 97.6 %. -0.30° (c 1.00, CHCl₃). (*S*)-5,7-Difluoro-1'-isopropyl-spiro[indoline-3,3'-piperidin]-2-one was collected as the second peak (92 mg) in 80 % yield and an enantiomeric excess of 98.4 %, +0.12° (c 1.00, CHCl₃).
- 25

STEP B. (S)-5,7-Difluoro-1'-isopropylspiro[indoline-3,3'-piperidin]-2-one hydrochloride. The (S)-enantiomer from STEP A was converted to the hydrochloride to give the title compound as a white solid, 6.20° (c 1.00, MeOH).

5 **EXAMPLE 8**

1',5-Dimethylspiro[indoline-3,3'-piperidin]-2-one hydrochloride.

The title compound was prepared from 2-Bromo-4-methyl-aniline and arecholine hydrobromide as described in EXAMPLE 1. MS(TSP+) *m/z* calcd for [M-Cl]⁺: 231,
10 observed: 231

EXAMPLE 9

5-Methyl-1'-isopropyl-spiro[indoline-3,3'-piperidin]-2-one hydrochloride

15 The title compound was obtained from 2-bromo-4 methyl-aniline and methyl N-benzyl-1,2,3,6-tetrahydropyridin-3-carboxylate as described in EXAMPLE 1. MS(TSP+) *m/z* calcd for [M-Cl]⁺: 259, observed: 259.

EXAMPLE 10

20 6-Methyl-1'-isopropyl-spiro[indoline-3,3'-piperidin]-2-one hydrochloride.

The title compound was obtained as described in EXAMPLE 9 starting with 2-iodo-5-methyl-aniline. MS(TSP+) *m/z* calcd for [M-Cl]⁺: 259, observed: 259

25 **EXAMPLE 11**

6-Trifluoromethyl-1'-isopropyl-spiro[indoline-3,3'-piperidin]-2-one hydrochloride

The title compound was obtained as described in EXAMPLE 9 starting with 3-amino-4-bromo-benzotrifluoride. MS(TSP+) *m/z* calcd for [M+H]⁺: 439, 441, observed: 439, 441.

EXAMPLE 12.**4-Methylspiro[indoline-3,3'-piperidin]-2-one hydrochloride**

The title compound was obtained as described in EXAMPLE 9 starting with 2-Bromo-3-methylaniline. [M]⁺: 217, observed: 217. It was converted to the hydrochloride.

EXAMPLE 13**4-Methyl-1'-isopropylspiro[indoline-3,3'-piperidin]-2-one hydrochloride.**

The compound from the previous EXAMPLE was alkylated to the title compound using PROCEDURE 1, Method A. ¹³C-NMR (CDCl₃): δ 181.4, 141.0, 134.6, 130.4, 127.9, 125.2, 107.5, 61.0, 56.2, 54.1, 53.7, 48.6, 28.3, 21.2, 19.9, 19.5, 11.9.

EXAMPLE 14**4-Methyl-1'-propylspiro[indoline-3,3'-piperidin]-2-one hydrochloride.**

The compound from EXAMPLE 12 was alkylated to the title compound. ¹³C-NMR of the base (CDCl₃): δ 181.5, 141.1, 134.7, 130.8, 127.8, 125.2, 107.5, 54.6, 50.9, 49.7, 28.6, 21.6, 19.8, 19.3, 15.9. MS(TSP+) *m/z* calcd for [M-Cl]⁺: 259, observed: 259.

EXAMPLE 15**(S)-(+)-4-Methylspiro[indoline-3,3'-piperidin]-2-one hydrochloride.**

The title compound was prepared by separating the N-bocylated compound from EXAMPLE 12 on a Kirasil TBB column and removing the Boc group from the collected product in 1M HCl in methanol. [M-Cl]⁺: 217, observed: 217.

EXAMPLE 16**(S)-(+)-4-Methyl-1'-propylspiro[indoline-3,3'-piperidin]-2-one hydrochloride.**

The compound from the previous EXAMPLE was alkylated to the title compound using PROCEDURE 1, Method B.

EXAMPLE 17**7-Fluorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.**

The title compound was prepared from 2-bromo-6-fluoroaniline following the steps described in EXAMPLE 16 but deprotecting the dibocylated unsaturated intermediate. [M-Cl]⁺: 219, observed: 219.

EXAMPLE 18**(S)-(+)-7-Fluorospiro[indoline-3,3'-piperidin]-2-one hydrochloride**

The title compound was prepared by separating the N-bocylated precursor on a Kirasil TBB column and removing the Boc group from the collected product in 1M HCl in methanol. [M-Cl]⁺: 219, observed: 219.

EXAMPLE 19**Spiro[indoline-3,3'-piperidin]-2-one hydrochloride**

STEP A. t-Butyl 5-(2-bromophenylcarbamoyl)-1,2,5,6-tetrahydropyridin-1-carboxylate. 2-Bromaniline was amidated to the title compound as described in EXAMPLE 1. MS(TSP+) *m/z* calcd for [M+NH₄]⁺: 398, 400, observed: 398, 400.

STEP B. t-Butyl 3-[(2-bromophenyl)-(t-butoxycarbonyl)-carbamoyl]-1,2,5,6-tetrahydropyridine-1-carboxylate. The compound from STEP A was bocylated to the title compound by dissolving in DCM and add di-tert-butylidicarbonate (1.2 equiv.), triethylamine (1.2 equiv.) and dimethylaminopyridine (0.07 equiv). MS(TSP+) *m/z* calcd for [M+NH₄]⁺: 498, 500, observed: 498, 500.

STEP C. Di-*t*-butyl 2-oxospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridio)]-1,1'-dicarboxylate. Obtained according to EXAMPLE 1, STEP C.

STEP D. Di-*t*-butyl 2-oxospiro[indoline-3,3'-piperidin]-1,1'-dicarboxylate. Obtained
5 according to EXAMPLE 1, STEP D.

STEP E. Spiro[indoline-3,3'-piperidin]-2-one hydrochloride. The compound from the previous step was deprotected by dissolving in 1M HCl in methanol and stirring for 1 hour. Evaporation of solvents gave the title compound. ¹³C-NMR (d₄-MeOH): 180.6, 140.5,
10 129.5, 129.2, 122.8, 122.7, 110.5, 47.4, 43.7, 30.0, 23.5, 17.4 ppm

EXAMPLE 20

1'-Ethylspiro[indoline-3,3'-piperidin]-2-one.

The compound was prepared according to PROCEDURE 1, Method A by reaction with
15 spiro[indoline-3,3'-piperidin]-2-one and acetaldehyde (5 equivalents). Yield: 45 mg (26 %). ¹³C NMR of the HCl-salt (CD₃OD): 89.6, 19.8, 31.3, 46.3, 54.2, 54.3, 55.1, 111.5, 123.9, 124.4, 130.4, 131.3, 142.6, 182.3

EXAMPLE 21

1'-Propyl-spiro[indoline-3,3'-piperidin]-2-one hydrochloride

The compound was prepared according to PROCEDURE 1, Method A by reaction with
20 spiro[indoline-3,3'-piperidin]-2-one and propionaldehyde (5 equivalents). Yield 65 %.

EXAMPLE 22

1'-Isopropylspiro[indoline-3,3'-piperidin]-2-one.

The compound was prepared according to PROCEDURE 1, Method A by reaction with
25 spiro[indoline-3,3'-piperidin]-2-one and acetone (5 equivalents). Yield: 75 %.

¹³C NMR (CDCl₃): 817.6, 17.7, 21.7, 32.1, 48.6, 48.8, 54.0, 54.8, 109.6, 121.6, 126.2, 127.2, 134.8, 140.1, 182.4; MS (CI, CH₄): m/z (rel. int.) 245 (M+1, 100)

EXAMPLE 23**1'-Allylspiro[indoline-3,3'-piperidin]-2-one.**

The compound was prepared according to PROCEDURE 1, Method B by reaction of spiro[indoline-3,3'-piperidin]-2-one with allyl bromide (1.1 equivalents).

5 ^{13}C NMR (CDCl_3): δ 21.2, 31.3, 48.4, 53.3, 58.1, 61.6, 109.5, 117.2, 121.6, 125.7, 127.4, 134.3, 135.1, 140.0, 181.6; MS (CI, CH_4): m/z (rel. int.) 243 (M+1, 100)

EXAMPLE 24**1'-Cyclopropylmethylspiro[indoline-3,3'-piperidin]-2-one.**

10 The compound was prepared according to PROCEDURE 1, Method A by reaction of spiro[indoline-3,3'-piperidin]-2-one with 3 equiv. of cyclopropanecarboxaldehyde. Yield: 90 %. ^{13}C NMR (CDCl_3): δ 3.8, 4.0, 8.3, 21.4, 31.8, 48.6, 53.3, 58.4, 63.6, 109.7, 121.7, 126.1, 127.4, 134.7, 140.0, 182.2; MS (CI, CH_4): m/z (rel. int.) 257 (M+1, 100)

EXAMPLE 25**1'-Butylspiro[indoline-3,3'-piperidin]-2-one.**

The compound was prepared according to PROCEDURE 1, Method A by reaction with spiro[indoline-3,3'-piperidin]-2-one and butyraldehyde (10 equiv.). ^{13}C NMR (CDCl_3): δ 14.1, 20.6, 21.7, 29.1, 32.0, 49.0, 53.8, 58.5, 58.9, 109.9, 121.9, 126.4, 127.6, 134.9,
20 140.2, 182.4; MS (TSP): m/z (rel. int.) 260/259 (M^+ , 25/100)

EXAMPLE 26**1'-s-Butylspiro[indoline-3,3'-piperidin]-2-one.**

The compound was prepared according to PROCEDURE 1, Method A by reaction with
25 spiro[indoline-3,3'-piperidin]-2-one and 2-butanone (3 equivalents). Yield: 46 %.
 ^{13}C NMR (CDCl_3): δ 11.5, 11.6, 13.3, 13.3, 21.7, 21.9, 26.4, 26.5, 32.1, 32.1, 46.1, 48.6, 49.0, 50.9, 52.4, 56.6, 61.2, 62.5, 109.6, 121.5, 121.6, 126.4, 126.5, 127.2, 134.7, 134.9, 140.1, 140.1, 182.4, 182.5; MS (CI, CH_4): m/z (rel. int.) 259 (M+1, 100)

EXAMPLE 27

1'-Isobutylspiro[indoline-3,3'-piperidin]-2-one hydrochloride.

The compound was prepared according to PROCEDURE 1, Method A by reaction with spiro[indoline-3,3'-piperidin]-2-one and isobutyraldehyde (3 equivalents). Purification on SiO₂ twice (eluent: DCM/MeOH). Yield: 88 mg. ¹³C NMR (CD₃OD): 821.2, 21.3, 22.7, 26.7, 32.9, 50.2, 55.4, 60.4, 68.3, 110.6, 122.6, 127.4, 128.6, 136.0, 141.8, 183.0; MS (CI, CH₄): m/z (rel. int.) 259 (M+1, 100)

EXAMPLE 28**1'-Cyclobutylspiro[indoline-3,3'-piperidin]-2-one hydrochloride.**

The compound was prepared according to PROCEDURE 1, Method A by reaction with spiro[indoline-3,3'-piperidin]-2-one and cyclobutanone (5 equivalents). ¹³C NMR of the HCl-salt (CD₃OD): δ 14.4, 19.4, 26.1, 26.9, 31.2, 46.1, 50.4, 53.9, 61.6, 111.5, 123.9, 124.6, 130.4, 131.3, 142.6, 182.2; MS (CI, CH₄): m/z (rel. int.) 257 (M+1, 100).

EXAMPLE 29**1'-Methoxyethylspiro[indoline-3,3'-piperidin]-2-one hydrochloride.**

The compound was prepared according to PROCEDURE 1, Method B by reaction with spiro[indoline-3,3'-piperidin]-2-one and 2-chloroethyl methylether (1.2 equivalents) and potassium iodide (catalytic amount). EtOAc was used for extraction. Yield: 74 % ¹³C NMR (CDCl₃): 821.8, 31.8, 48.8, 54.2, 58.0, 58.8, 59.2, 70.8, 109.8, 122.0, 126.4, 127.6, 134.8, 140.2, 182.0. The HCl salt was prepared. MS (TSP): m/z (rel. int.) 262/261 (M⁺, 16/100).

EXAMPLE 30**1'-Methylthioethylspiro[indoline-3,3'-piperidin]-2-one hydrochloride.**

The compound was prepared according to PROCEDURE 1, Method B by reaction with spiro[indoline-3,3'-piperidin]-2-one, 2-chloroethyl methylsulfide (1.2 equivalents) and potassium iodide (catalytic amount). ¹³C NMR (CDCl₃): 815.9, 21.7, 31.8, 31.9, 48.9, 53.3, 58.0, 58.8, 109.8, 122.1, 126.6, 127.7, 134.6, 140.2, 181.9.

The HCl salt was prepared. MS (EI, 70 eV): m/z (rel. int.) 278/277 (M⁺, 16/100).

EXAMPLE 31**1'-Methoxypropylspiro[indoline-3,3'-piperidin]-2-one hydrochloride.**

The compound was prepared according to PROCEDURE 1, Method B by reaction with
5 spiro[indoline-3,3'-piperidin]-2-one, 3-chloropropyl methyl ether (1.2 equivalents) and
potassium iodide (catalytic amount). ¹³C NMR (CDCl₃): δ 21.8, 27.3, 32.0, 48.8, 53.8, 55.4,
58.8, 58.9, 71.1, 109.6, 122.0, 126.6, 127.7, 134.8, 140.0, 181.4.
The HCl salt was prepared. MS (TSP): m/z (rel. int.) 276/275 (M⁺, 15/100).

10 EXAMPLE 32**(S)-1'-(3-Fluoropropyl)spiro[indoline-3,3'-piperidin]-2-one hydrochloride.**

The racemic compound was prepared according to PROCEDURE 1, Method B by reaction
of spiro[indoline-3,3'-piperidin]-2-one with 1-bromo-3-fluoropropane (1.0 equivalent).
EtOAc was used for extraction. Yield: 69 %. ¹³C NMR (CDCl₃): δ 21.8, 28.0 (d, J_F = 20
15 Hz), 31.8, 48.9, 53.9, 54.3 (d, J_F = 5 Hz), 58.7, 81.7, 83.3, 110.0, 122.0, 126.2, 127.7,
134.7, 140.3, 182.1. The racemate was separated on the Kirasil TBB column and the HCl
salt was prepared.

EXAMPLE 33**20 (S)-(+)-1'-Propylspiro[indoline-3,3'-piperidin]-2-one.**

1'-Propyl-1H-spiro[indole-3,3'-piperidin]-2-one (2.9 g, 11.9 mmol) and di-p-toluoyl-L-
tartronic acid (4.6 g, 11.9 mmol) were dissolved in ethanol (50 ml) at 40-50°C. Water was
added in small portions (totally 50 ml) at the same temperature leaving a clear solution
which was slowly cooled to 5 °C. The crystals (3.53 g) were collected the next day. A
25 second crystallisation was carried out in a similar manner using the same volume of
solvents yielding pure (S)-1'-propylspiro[indole-3,3'-piperidinium]-2-one di-p-toluoyl-L-
tartrate (3.2 g) which was converted to the corresponding amine by a treatment with an
excess of aqueous sodium bicarbonate. The amine was extracted into ethyl acetate, the
extracts were dried over sodium sulfate and concentrated in vacuum. The residue was
30 dissolved in acetonitrile and treated with a 1.5 fold molar excess of hydrochloric acid.

Removal of the volatiles in vacuum and coevaporation with acetonitrile yielded (S)-1'-propylspiro[indole-3,3'-piperidinium]-2-one hydrochloride (1.13 g, 78%), $[\alpha]_D^{20} +91.9^\circ$ (c 1.00, H₂O). The absolute configuration was established by X-ray crystallography of the di-*p*-toluoyl-L-tartrate.

EXAMPLE 34

(R)-(-)-1'-Propylspiro[indoline-3,3'-piperidin]-2-one

The mother liquid from the first crystallisation in the previous EXAMPLE, consisting mostly of the other diastereomeric salt was treated with NaHCO₃/ethyl acetate to leave the levorotatory amine. This was treated with 1 mol. eq. of di-*p*-toluoyl-D-tartronic acid and the salt was crystallised from 50% aqueous ethanol. A similar further treatment as in EXAMPLE 27 yielded (R)-1'-propylspiro[indole-3,3'-piperidinium]-2-one hydrochloride (1.09 g, 75%), $[\alpha]_D^{20} -91^\circ$ (c 1.00, H₂O).

EXAMPLE 35

Spiro[indoline-3,3'-perhydroazepin]-2-one

STEP A. N-Benzyl-4-(3-indolyl)-butanamine. Lithium aluminum hydride (4.8 g) was added to a solution of *N*-benzyl-3-indolebutanamide (18.73 g) in dry THF (200 mL) at nitrogen atmosphere and at 0 °C. After stirring at reflux for 15 h and work-up with sodium hydroxide the title compound was obtained as pale yellow crystals (16.4 g).

STEP B. 3-(4-(Benzylamino)-butyl)-indolin-2-one. Conc hydrochloric acid (90 mL) was added to a solution of the compound from the previous step in DMSO (38 mL) and MeOH (8 mL). After stirring for 30 min at 0 °C and 30 min at room temperature the mixture was poured onto ice followed by extractive work-up. The title compound was obtained as a crude orange oil (16.2 g).

STEP C. 1'-Benzylspiro[indoline-3,3'-perhydroazepin]-2-one. A solution of the compound from the previous step (15.5 g) was cyclised via a Mannich reaction following

the procedure described in *J Med Chem* 1976, 19, 892. Evaporation, extractive work-up and purification on silica gave the title compound as a yellow oil (2.4 g).

STEP D. Spiro[indoline-3,3'-perhydroazepin]-2-one hydrochloride. The compound
5 from the previous step was hydrogenated in acetic acid over 10% Pd/C at 40 psi H₂ for 48 h. Evaporation and extractive work-up gave the title compound as a yellow solid (1.51 g). MS (TSP+) m/z: 217 (M+H⁺, 100) which was converted to the title compound.

EXAMPLE 36

10 1'-Propylspiro[4-azaindoline-3,3'-piperidin]-2-one.

STEP A. tert-Butyl 3-[(2-bromo-3-pyridyl)carbamoyl]-1,2,5,6-tetrahydropyridine-1-carboxylate. 2-Bromo-3-pyridineamine (3.0 g, 17.3 mmol) and 1,2,5,6-tetrahydro-1,3-pyridinedicarboxylic acid 1-tert-butyl ester 3-methyl ester (5.05 g, 20.8 mmol) were
15 dissolved in DCM (80 ml). To the solution trimethylaluminium (26 mmol, 2M solution) was slowly added at 0°C. The mixture was refluxed overnight. Work-up and purification on silica gel using 60% ethyl acetate in heptane as an eluent gave 5.65 g (85%) of the title compound.

20 STEP B. tert-Butyl 3-[N-(2-bromo-3-pyridyl)-N-(tert-butoxycarbonyl)carbamoyl]-1,2,5,6-tetrahydropyridine-1-carboxylate. The compound from STEP A was dissolved in DCM and di-tert-butyl-dicarbonate (3.85 g, 17.6 mmol) was added followed by triethylamine (2.51 ml, 18.0 mmol) and dimethylaminopyridine (0.17 g, 1.4 mmol). After stirring the mixture for 1 h at room temperature methanol was added and the volatiles were
25 removed in vacuum. Purification of the product on a column packed with silica gel using 40% ethyl acetate in heptane as an eluent afforded 6.74 g, (95%) of the title compound.

STEP C. Di-*t*-butyl 2-oxo-1,1'-spiro[4-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-1,1'-dicarboxylate. The compound from STEP B was dissolved in acetonitrile (80 ml),
30 palladium acetate (0.37 g, 1.67 mmol) and triphenylphosphine (1.0 g, 3.8 mmol) were

added and finally triethylamine (2.9 ml, 20.8 mmol). The mixture was refluxed under nitrogen for 2.5 hours. Work-up gave the title compound (4.13 g, 74 %).

STEP D. Di-*t*-butyl 2-oxo-1,1'-spiro[4-azaindoline-3,3'-piperidin]-1,1'-dicarboxylate.

- 5 The compound from STEP C was hydrogenated in methanol over 10% Pd/C at 50 psi H₂ for 3 h. Purification on a column packed with silica gel using 60% ethyl acetate in heptane as an eluent gave the title compound (82%).

STEP E. 1'-Propylspiro[4-azaindoline-3,3'-piperidin]-2-one. The compound from STEP

- 10 D was deprotected using a mixture of 36% hydrochloric acid, methanol and dioxane (1:1:5 volume per cent) at room temperature for 10 h. The volatiles were removed and the crude spiro[4-aza-indole-3,3'-piperidin]-2-one was alkylated according to PROCEDURE 1, Method A. The product was purified on a column with silica gel using 10-20% methanol in ethyl acetate as an eluent to give the title compound (57 %). ¹³C NMR, δ ppm: 12.9, 20.6,
15 22.0, 31.0, 49.0, 55.2, 58.1, 62.0, 117.3, 123.4, 136.6, 143.6, 155.4, 181.7.

EXAMPLE 37

1'-Butylspiro[4-azaindoline-3,3'-piperidin]-2-one.

- The title compound was synthesised according to the procedure described in EXAMPLE
20 29 using butanal. ¹³C NMR, δ ppm: 15.1, 21.8, 22.0, 29.6, 31.0, 49.0, 55.3, 58.2, 60.0, 117.2, 123.4, 136.6, 143.7, 155.4, 181.7.

EXAMPLE 38

1'-*s*-Butylspiro[4-aza-indoline-3,3'-piperidin]-2-one.

- 25 was synthesised according to EXAMPLE 30 using sec-butanal. ¹³C NMR, δ ppm: 21.6, 21.9, 22.0, 26.3, 30.9, 49.1, 55.8, 58.4, 67.8, 117.2, 123.4, 136.5, 143.6, 155.4, 181.7.

EXAMPLE 39

1'-Propyl-5-chlorospiro[7-aza-indoline-3,3'-piperidin]-2-one.

STEP A. 3-Bromo-5-chloro-2-pyridineamine. To 5-chloro-2-pyridineamine (3 g, 23.3 mmol) dissolved in acetic acid (40 ml) a solution of bromine (1.29 ml, 25 mmol) in acetic acid was added dropwise at 10°C. The mixture was stirred for 2 h at room temperature and then concentrated. Work-up and purification on a column packed with silica gel using 40% ethyl acetate in heptane as an eluent yielded the title compound as a colourless powder (3.58 g, 74%).

STEP B. *t*-Butyl 3-[N-(3-bromo-5-chloro-2-pyridyl)-N-(tert-butoxycarbonyl)carbamoyl]-1,2,5,6-tetrahydropyridine-1-carboxylate. The compound from STEP A was treated in a similar manner as was described in EXAMPLE 29, STEPS A and B affording the title compound in good yield.

STEP C. Di-*t*-butyl 5-chloro-2-oxo-1,1'-spiro[7-azaindoline-3,3'-piperidin]-1,1'-dicarboxylate. The previous amide was cyclized as described in EXAMPLE 29, STEP C and the resulting product was hydrogenated in methanol under 50 psi H₂ over 10% Pd/C for 20 hours to give the title compound after chromatographic separation on silica gel. The dechlorinated compound was also obtained in 40% yield.

STEP D. 5-Chloro-spiro[7-azaindoline-3,3'-piperidin]-2-one. The cyclized product from the previous step was deprotected as described in EXAMPLE 29.

STEP E. 1'-Propyl-5-chloro-spiro[7-azaindoline-3,3'-piperidin]-2-one. The compound from the previous step was converted to the title compound as described in EXAMPLE 29. ¹³C NMR, δ ppm: 12.8, 21.0, 22.8, 32.3, 49.9, 54.5, 59.3, 61.4, 118.6, 119.3, 135.2, 146.7, 156.7, 181.1.

EXAMPLE 40

1'-Propylspiro[7-azaindoline-3,3'-piperidin]-2-one

The dechlorinated product from EXAMPLE 33, Step C, was deprotected and alkylated as described in the previous example. ^{13}C NMR, δ ppm: 12.7, 20.8, 22.7, 32.2, 50.3, 54.1, 59.3, 61.4, 123.3, 127.0, 135.8, 145.4, 154.3, 180.4.

5 **EXAMPLE 41**

1'-Propyl-6-methylspiro[7-azaindoline-3,3'-piperidin]-2-one

STEP A. **2-Amino-6-methylpyrid-3-yl trifluoromethanesulfonate**. To a stirred suspension of 2-amino-6-methylpyridin-3-ol (2g) in DCM (50 ml) containing triethylamine
10 (2.2g), trifluoromethanesulfonic anhydride (5.3g) was added under N_2 at -78°C . After the mixture became homogeneous, it was allowed to warm to -20°C and then quenched with aqueous NaHCO_3 . Work-up by extraction into chloroform purification on silica gel using 40% ethyl acetate in heptane as an eluent afforded the title compound (86%).

15 STEP B. **4-(6-Methyl-3-trifluoromethanesulfonyloxypyrid-2-ylcarbamoyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid *t*-butyl ester**. The compound from STEP A was treated in a similar manner as was described in EXAMPLE 29, STEP A affording the title compound in 42% yield.

20 STEP C. ***t*-Butyl 6-methyl-2-oxo-spiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-1'-carboxylate**. The compound from STEP B was treated in a similar manner as was described in EXAMPLE 29, STEP C affording the title compound in 76% yield.

STEP D. ***t*-Butyl 6-methyl-2-oxo-spiro[7-azaindoline-3,3'-piperidin]-1'-carboxylate**.
25 The compound from STEP C was treated in a similar manner as was described in EXAMPLE 29, STEP D affording the title compound in 85% yield.

STEP E. **6-Methyl-1'-propylspiro[7-azaindoline-3,3'-piperidin]-2-one dihydrochloride**.
The compound from STEP D was treated in a similar manner as was described in
30 EXAMPLE 29, STEP E affording the title compound in 66% yield. ^{13}C NMR, δ ppm:

12.8, 21.0, 22.9, 24.2, 32.4, 49.7, 54.7, 59.6, 61.4, 117.5, 127.0, 135.4, 156.4, 156.9, 181.5.

It was converted to the dihydrochloride by treatment with HCl in ethanol and evaporation of solvents.

5 **EXAMPLE 42**

1'-Propylspiro[isoindoline-3,3'-piperidin]-1-one hydrochloride

STEP A. **2-Bromo-N-(3-pyridyl)benzamide**. To a solution of 2-bromobenzoylchloride (11.6 g) in dry pyridine (50 ml) at rt., 3-aminopyridine (5.0 g) dissolved in dry pyridine
10 was added. After stirring for 12 hours and extractive work-up 7.77 g of the title product was obtained as white crystals. MS(ESP+) m/z: 279 (M+H+, 98), 277 (M+H+, 100).

STEP B. **2-Bromo-N-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)benzamide**. To a stirred solution of the compound from Step A (6.0 g) in dry toluene (100 ml) propylbromide (13.0
15 g) was added. The reaction mixture was stirred at 80 °C for 16 hours. The precipitated oil was dissolved in MeOH (100 ml) and sodium borohydride (6.0 g) was added slowly at rt. After 3 hours of reaction time, work-up and chromatography on silica gel with ethyl acetate/n-heptane as the eluent 6.65 g of the title product was obtained as an oil. MS(TSP+) m/z: 325 (M+H+, 92), 323 (M+H+, 100).

20 STEP C. **2-Iodo-N-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)benzamide**. To a stirred solution of 2-iodo-N-pyridin-3-ylbenzamide (8.32 g) in dry toluene (200 ml) was added benzyl bromide (5.1 g). The reaction mixture was stirred at 100 °C for 16 hours. The solvent was decanted from the precipitated crystals which were dissolved in MeOH (150
25 ml) and the treated with sodium borohydride to give 7.9 g of the title compound as white-yellow crystals. MS(TSP+) m/z: 419 (M+H+, 100).

STEP D. **1'-Propylspiro[isoindoline-3,3'-piperidin]-1-one hydrochloride**. The compound from STEB B (6.60 g) was cyclised according to the general Heck procedure
30 described in EXAMPLE 1 to give an oil which was chromatographed on silica gel with

ethyl acetate/n-heptane as the eluent to give 830 mg 1'-propylspiro-[isoindoline-3,3'-1,2,3,6-tetrahydropyridin]-1-one as an oil. This compound was hydrogenated as described in EXAMPLE 1 yielding the free base of the title compound as white crystals. The title compound was also prepared from cyclization of the STEP C compound followed by
5 hydrogenation-debenzylation plus propylation. ¹³C NMR (CDCl₃): δ 169.44, 150.10, 131.77, 131.58, 128.51, 124.14, 121.56, 62.74, 60.87, 60.26, 53.24, 34.88, 23.34, 19.00, 11.82.; MS(TSP+) m/z: 245 (M+H⁺, 100); MS(CI, NH₃): 245 (M+H⁺, 100), 180 (3). Mp: 110 - 112°.

The title compound was prepared by treating it with HCl in Et₂O. Anal. Calcd for
10 C₁₅H₂₁ClN₂O: C, 64.13; H, 7.53; N 10.01 Found: C, 64.25; H, 7.6; N, 10.0.

EXAMPLE 43

Spiro[3,4-dihydro-1H-quinoline-3,3'-piperidin]-2-one hydrochloride

15 STEP A. 1-*t*-Butyl 3-ethyl 3-(2-nitrobenzyl)-1,3-piperidinedicarboxylate. To a solution of ethyl 1-*t*-butyloxycarbonyl-3-piperidinecarboxylate (1.5 g) in THF (10 ml) at -78 °C was added lithium hexamethyldisilazide (8.74 ml of a 1M solution in THF). A solution of 2-nitrobenzyl bromide (1.5 g) in THF (5 ml) was added dropwise at -78 °C and the reaction mixture was allowed to reach room temperature. Work-up and chromatography on
20 silica gel with ethyl acetate/petroleum benzene 5:1 as eluent gave 1.3 g of the title compound.

STEP B. 1-*t*-Butyl spiro[3,4-dihydro-1H-quinoline-3,3'-piperidin]-2-one-1-carboxylate. To a solution of 1-*t*-butyl 3-ethyl 3-(2-nitrobenzyl)-1,3-
25 piperidinedicarboxylate (1.2 g) in methanol (25 ml) 10% Pd/C (0.3 g) was added and the mixture was hydrogenated at 30 psi for 2 h. The mixture was filtered and concentrated to yield 0.95 g of the title compound.

STEP C. Spiro[3,4-dihydro-1H-quinoline-3,3'-piperidin]-2-one hydrochloride. The
30 compound (0.90 g) from STEP B was debocylated in ethyl acetate HCl-diethyl ether and

the deprotected amine was precipitated as the hydrochloride salt. ^{13}C NMR (CD_3OD , 400MHz): δ 20.24, 29.95, 37.14, 38.83, 45.01, 50.28, 116.26, 122.08, 124.74, 129.00, 129.83, 137.42, 175.17.

5 **EXAMPLE 44**

1'-Propylspiro[3,4-dihydro-1H-quinoline-3,3'-piperidin]-2-one hydrochloride.

Spiro[3,4-dihydro-(1H)-quinoline-3,3'-piperidin]-2-one (0.55 g) was propylated according to the general PROCEDURE 1, Method A. The crude product was purified by flash chromatography on silica gel with DCM/methanol 9:1 as eluent to give 0.44 g of the title
10 compound as the free base. ^{13}C NMR (CDCl_3 , 400MHz): δ 11.74, 19.85, 21.18, 29.12, 33.28, 40.82, 54.47, 57.34, 60.51, 114.67, 122.90, 123.03, 127.17, 128.59, 136.48, 175.64. The product was converted to the hydrochloride by dissolving the base in diethyl ether and precipitate with HCl in Et_2O .

15 **EXAMPLE 45**

1'-Isopropylspiro[indoline-3,3'-piperidine] hydrochloride. To a solution of 1'-

isopropylspiro[indoline-3,3'-piperidin]-2-one (0.2 g) in THF (10 ml) borane-dimethyl sulfide complex in THF (2 M solution, 0.90 ml) was added. The reaction mixture was refluxed for 1 h. The solvent was evaporated in vacuo and the residue was refluxed with
20 one equivalent of HCl (g) in ethanol for 30 minutes. After work-up the residue was purified by flash chromatography on silica gel with ethyl acetate as eluent to yield 0.12 g of the base. ^{13}C NMR (CDCl_3 , 400MHz): δ 16.3, 19.6, 23.7, 35.1, 46.2, 50.2, 54.9, 57.2, 57.3, 109.7, 118.2, 123.2, 128.0, 135.9, 151.8. It was converted to the hydrochloride with HCl in ether.

25

EXAMPLE 46

1'-Methylspiro[2,3-dihydrobenzofuran-3,3'-piperidine] hydrochloride

STEP A. 2-Iodophenyl (1-methyl-1,2,5,6-tetrahydro-3-pyridinyl)methyl ether. To an ice-cooled stirred solution of triphenylphosphine (1.54 g) and diethyl azodicarboxylate
30 (0.92 ml) in THF (20 ml) 2-iodophenol (1.27 g) and (1-methyl-1,2,5,6-tetrahydro-3-

pyridyl)methanol (0.5 g) were added. The mixture was stirred for 72 h at room temperature. The solvent was evaporated and the residue was purified by chromatography on silica gel with first ethyl acetate and then 10 % methanol in DCM as eluent to yield 0.98 g of the title compound.

5 STEP B. 1'-Methylspiro[2,3-dihydrobenzofuran-3,3'-(1,2,3,6-tetrahydropyridin)]. The previous compound (0.42 g) was cyclized following the procedure in EXAMPLE 1 using tri-o-tolylphosphine to yield 0.2 g of the title compound.

10 STEP C. 1'-Methylspiro[2,3-dihydrobenzofuran-3,3'-piperidine] hydrochloride. To a solution of the previous compound (0.2 g) in acetic acid (10 ml) 10% Pd/C (0.1 g) was added and the mixture was hydrogenated in a Parr apparatus at 50 psi for 6 h. The residue after filtering and evaporation of solvents gave 0.2 g of the title compound. ¹³C NMR (CDCl₃, 400MHz): δ 22.9, 34.1, 46.1, 46.6, 55.5, 65.0, 81.0, 109.6, 120.1, 123.1, 128.5,
15 133.9, 158.5. It was converted to the hydrochloride.

EXAMPLE 47

1'-Propylspiro[2,3-dihydrobenzofuran-3,3'-piperidine] hydrochloride

20 STEP A. Spiro[2,3-dihydrobenzofuran-3,3'-(1,2,3,6-tetrahydropyridine)]. To a stirred solution of the product from EXAMPLE (0.32 g) in 1,2-dichloroethane (20 ml) 1-chloroethyl chloroformate (0.46 g) was added and the mixture was refluxed for 36 h. After concentration methanol (10 ml) was added and the mixture was refluxed for 4 h. Concentration gave 0.3 g of the product.

25 STEP B. 1'-Propylspiro[2,3-dihydrobenzofuran-3,3'-(1,2,3,6-tetrahydropiperidine)]. The previous compound was propylated according to PROCEDURE 1, METHOD B giving the title compound in 60 % yield.

STEP C. 1'-Propylspiro[2,3-dihydrobenzofuran-3,3'-piperidine] hydrochloride. The previous compound was hydrogenated at 50 psi for 6 h over Pd/C. Work-up yielded the title compound. ¹³C NMR (CDCl₃): δ 12.1, 20.2, 22.8, 34.8, 46.2, 54.1, 60.5, 63.0, 81.8, 109.9, 120.3, 123.2, 128.6, 133.9, 159.5. It was converted to the hydrochloride.

5

EXAMPLE 48**Spiro[3,4-dihydro-1H-quinoline-4,3'-piperidin]-2-one hydrochloride.**

STEP A. N-(2-Iodophenyl)-2-(4-pyridinyl)acetamide. A solution of 3-pyridylacetic acid
10 (2.0 g) and triethylamine (2.0 mL) in dry THF (20 mL) was treated at -10° C with isobutyl chloroformate (2.0 mL). After 10 minutes at -10° C, a solution of 2-iodo-aniline (3.6 g) in THF (10 mL) was added. The reaction mixture was allowed to stir while slowly warming to room temperature. The solvent was evaporated, and the residue was partitioned between ethyl acetate and saturated NaHCO₃ solution. The organic layer was dried over MgSO₄,
15 filtered, the solvent was evaporated and the residual oil was purified by flash chromatography to yield 1.0 g of the title product. MS (TSP+) *m/z* [M+H]⁺: 339.

STEP B. 2-(1-Benzyl-1,2,3,6-tetrahydro-4-pyridinyl)-N-(2-iodophenyl)acetamide.

Benzyl bromide (1.0 g) was added to a solution of N-(2-iodophenyl)-2-(4-
20 pyridinyl)acetamide (1.0 g) in acetone. The mixture was stirred at reflux over night. The resulting viscous oil was decanted and used without further purification. To a stirred solution of the pyridinium salt in methanol (20 mL) was added portionwise NaBH₄ (0.14 g) at 0° C during 1 hour. On completion of the addition, the resulting mixture was allowed to warm to room temperature and stirred overnight. Water was added carefully and the
25 resulting mixture was concentrated *in vacuo*. The residue was extracted twice with ethyl acetate. The organic layer was dried over MgSO₄, filtered, the solvent was evaporated and the residual oil was purified by flash chromatography to yield 1.0 g of the title product. MS (TSP+) *m/z* [M+H]⁺: 433.

STEP C. 1'-Benzylspiro[3,4-dihydro-1H-quinoline-4,3'-1,2,3,6-tetrahydropyridin]-2-one. The product from STEP B (0.7 g) was dissolved in acetonitrile (20 mL) and triethylamine (0.50 mL) under N₂-atmosphere. After 0.5 h tri-*o*-tolylphosphine (90 mg) and palladium acetate (36 mg) were added in one portion. The mixture was refluxed for 18 hours under N₂-atmosphere. The crude product was purified by chromatography on silica gel and eluted with ethyl acetate to give the title compound (0.3 g) as a yellow oil. MS (TSP+) *m/z* [M+H]⁺: 305.

STEP D. Spiro[3,4-dihydro-1H-quinoline-4,3'-piperidin]-2-one hydrochloride. The product from STEP C was hydrogenated in glacial acetic acid (20 mL) using 10 % Pd/C and H₂ (3.5 atm) for 18 hours. The catalyst was filtered off and the solution was concentrated *in vacuo*. The residue was dissolved in DCM and saturated NaHCO₃ solution and the water layer was extracted three times with DCM. The organic layer was dried over MgSO₄, filtered, the solvent was evaporated to yield 0.13 g of the title compound as the free base. ¹³C NMR (CDCl₃, 400MHz): δ 22.0, 33.3, 36.2, 38.3, 46.5, 54.3, 116.1, 123.3, 124.9, 127.6, 130.5, 136.6, 171.3. The product was converted to the hydrochloride by dissolving the base in ethyl acetate and precipitate with HCl in Et₂O.

EXAMPLE 49

(S)-(-)-5-Methylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one dihydrochloride

STEP A. *t*-Butyl 3-(3-bromo-5-methyl-2-pyridylcarbamoyl)-1,2,5,6-tetrahydropyridine-1-carboxylate. It was prepared analogously to EXAMPLE 36, STEP A. in a yield of 53 %.

STEP B. *t*-Butyl 3-[N-(3-bromo-5-methyl-2-pyridyl)-N-(tert-butoxycarbonyl)carbamoyl]-1,2,5,6-tetrahydropyridine-1-carboxylate. The compound

from STEP A was converted to the semisolid title compound in a yield of 50 % as described in EXAMPLE 36, STEP B.

STEP C. Di-*t*-butyl 5-methyl-2-oxo-1,1'-spiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-1,1'-dicarboxylate. The compound from STEP B was treated as described in EXAMPLE 36, STEP C to give the title compound in 80 % yield.

STEP D. *t*-Butyl 5-methyl-2-oxo-1,1'-spiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-1'-carboxylate. The compound from STEP C was treated in methanol at reflux with 10 equivalents of ammonium acetate for 2 h. The residue after evaporation of solvent was purified by SGC (EtOAc:isohexanes 1:1 to pure EtOAc) to give the title compound as a white solid. Due to the presence of rotamers it was difficult to obtain good NMR spectra.

STEP E. (S)-(+)-*t*-Butyl 5-methyl-2-oxo-1,1'-spiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-1'-carboxylate. The compound from STEP D was chromatographically resolved on a Kirasil TBB column using heptane/2-PrOH 9:1 as an eluent and recycling the eluate twice.

STEP F. (S)-(-)-5-Methylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one dihydrochloride. The compound from STEP E, second peak, was deprotected using 0.5 M HCl in methanol-ether at room temperature for 15 h. Evaporation of solvents gave the title compound in quantitative yield. It is tentatively assigned the *S* configuration based on its elution pattern on the chiral column. MS (TSP+) m/z [M+H]⁺: 216.
[α]_{D²²}²² -36° (c 1.0, MeOH).

EXAMPLE 50

(R)-(+)-5-Methylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one dihydrochloride.

The material from STEP E, first peak, was deprotected similarly. ^{13}C -NMR (d_4 -MeOH): 177.6, 152.5, 143.0, 135.6, 131.7, 129.8, 127.4, 123.7, 47.7, 45.6, 42.2, 17.9 ppm. $[\alpha]_{\text{D}}^{25} +39^\circ$ (c 1.04, MeOH).

5 **EXAMPLE 51**

(S)-5,6-Dimethylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride

STEP A. *t*-Butyl 3-(3-bromo-5,6-dimethyl-2-pyridylcarbamoyl)-1,2,5,6-tetrahydropyridine-1-carboxylate. It was prepared analogously to EXAMPLE 36, STEP A starting from 3-bromo-5,6-dimethyl-2-pyridineamine (J. Heterocycl. Chem. 1994, 31, 1641-5) in a yield of 57 % after SGC (EtOAc: heptane 1:1 $\rightarrow$ 4:1). MS (TSP+) m/z $[\text{M}+1]^+$: 410 and 412.

15 STEP B. *t*-Butyl 3-[N-(3-bromo-5,6-dimethyl-2-pyridyl)-N-(tert-butoxycarbonyl)carbamoyl]-1,2,5,6-tetrahydropyridine-1-carboxylate. The compound from STEP A was converted to the crude title compound in a yield of 100 % as described in EXAMPLE 36, STEP B. MS (TSP+) m/z $[\text{M-Boc} + 1]^+$ 410 and 412.

20 STEP C. Di-*t*-butyl 5,6-dimethyl-2-oxo-1,1'-spiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-1,1'-dicarboxylate. The compound from STEP B was treated as described in EXAMPLE 36, STEP C to give the title compound in 70 % yield.

STEP D. *t*-Butyl 5,6-dimethyl-2-oxo-1,1'-spiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-1'-carboxylate. The compound from STEP C was treated in 25 methanol at reflux with 10 equivalents of ammonium acetate for 2 h. The residue after evaporation of solvent was purified by SGC (EtOAc:heptane 1:1) to give the title compound as a white solid. Due to the presence of rotamers it was difficult to obtain good NMR spectra. MS (TSP+) m/z $[\text{M}+1]^+$ 330.

STEP E. (S)-*t*-Butyl 5,6-dimethyl-2-oxo-1,1'-spiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-1'-carboxylate. The compound from STEP D was chromatographically resolved on a Kirasil TBB column using heptane/2-PrOH 95:5 as an eluent and recycling the eluate twice.

5

STEP F. (S)-5,6-Dimethylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one dihydrochloride. The compound from STEP E, second peak (190 mg), was deprotected using 0.5 M HCl in methanol-ether at room temperature for 15 h. Evaporation of solvents gave the title compound in quantitative yield. It is tentatively assigned the *S* configuration based on its elution pattern on the chiral column. MS (TSP+) m/z $[M+H]^+$: 230. $^1\text{H-NMR}$ (d_4 -MeOH): 7.80 (s, 1H), 6.11 (d, 1H), 5.54 (d, 1H), 3.75 (m, 2H), 3.52 (dd, 2H), 2.42 (s, 3H), 2.18 (s, 2H).

10

The following EXAMPLES 52-81 were prepared analogously to EXAMPLE 49 and 51 starting with an aniline or other aromatic amine. The mono-Boc protected intermediates were separated using a Kirasil TBB (PROCEDURE 2) or Chiralpak AD column. All resolved compounds obtained from the last eluting peak on the Kirasil TBB column are assumed to have the *S* configuration, and vice versa.

15

EXAMPLE 52

(S)-5-Chlorospiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one dihydrochloride.

$^{13}\text{C-NMR}$ (D_2O), δ : 42.1, 45.5, 48.0, 123.7, 126.2, 126.7, 127.7, 135.2, 146.4, 154.9, 180.0

20 ppm.

EXAMPLE 53

(R)-5-Chlorospiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one dihydrochloride.

30 MS (TSP+) m/z $[M+H]^+$: 235

EXAMPLE 54

(R)-6-Methylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one
dihydrochloride.

5 $^{13}\text{C-NMR}$ (D_2O): δ 20.3, 42.0, 45.2, 47.3, 120.5, 123.1, 124.7, 127.3, 140.2, 151.7, 153.4,
179.3 ppm.

EXAMPLE 55

(S)-6-Methylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one
10 dihydrochloride. MS (TSP+) m/z $[\text{M}+\text{H}]^+$: 216

EXAMPLE 56

(S)-7-Fluorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.
 $^{13}\text{C-NMR}$ ($\text{d}_4\text{-MeOH}$): 179.7, 149.9, 147.5, 133.3, 131.0, 130.4, 126.3, 125.9, 125.1,
15 125.0, 121.16, 121.13, 117.9, 117.7, 109.5, 47.0, 42.6, 30.7 ppm.

EXAMPLE 57

(R)-7-Fluorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.
MS (TSP+) m/z $[\text{M}+\text{H}]^+$: 219

20 EXAMPLE 58

(S)-4-Methylspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.
 $^{13}\text{C-NMR}$ ($\text{d}_4\text{-MeOH}$): 180.1, 143.4, 137.0, 131.0, 127.1, 126.4, 126.3, 125.2, 109.5, 45.6,
42.8, 17.8 ppm.

25 EXAMPLE 59

(R)-4-Methylspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.
MS (TSP+) m/z $[\text{M}+\text{H}]^+$: 215

EXAMPLE 60

30 (S)-Spiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

MS (TSP+) m/z $[M+H]^+$: 201. ^{13}C -NMR (d_4 -MeOH): δ 180.0, 141.6, 131.1, 127.1, 125.5, 125.4, 124.3, 117.2, 47.2, 43.0 ppm.

EXAMPLE 61

5 (R)-Spiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

MS (TSP+) m/z $[M+H]^+$: 201

EXAMPLE 62

(R)-5,7-Difluorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

10 MS (TSP+) m/z $[M+H]^+$: 237.

EXAMPLE 63

(S)-5,7-Difluorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

MS (TSP+) m/z $[M+H]^+$: 237

15

EXAMPLE 64

(R)-5-Trifluoromethoxyspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

^{13}C -NMR (d_4 -MeOH): 179.9, 146.1, 142.4, 132.1, 126.0, 125.9, 124.3, 123.2, 120.7,

20 119.6, 112.6, 111.8, 46.6, 42.6, 30.7 ppm.

EXAMPLE 65

(S)-5-Trifluoromethoxyspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

25 MS (TSP+) m/z $[M+H]^+$: 285

EXAMPLE 66

(R)-5-Chlorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

MS (TSP+) m/z $[M+H]^+$: 235. ^1H -NMR (d_4 -MeOH): 7.4 (m, 1H), 7.37 (d, 1H), 6.97 (d,

30 1H), 6.22 (d, 1H), 5.65 (d, 1H), 3.90 (m, 1H), 3.60 (m, 1H).

EXAMPLE 67

(S)-5-Chlorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

MS (TSP+) m/z $[M+H]^+$: 235

EXAMPLE 68

(R)-5-Chloro-7-fluorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

MS (TSP+) m/z $[M+H]^+$: 253. 1H -NMR (d_4 -MeOH): 7.3 (m, 2H), 6.2 (m, 1H), 5.7 (m,

1H), 3.9 (m, 1H), 3.6 (m, 1H). Enantiomeric purity 98.0 %.

EXAMPLE 69

(S)-5-Chloro-7-fluorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

MS (TSP+) m/z $[M+H]^+$: 253.

EXAMPLE 70

(R)-7-Chlorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

MS (TSP+) m/z $[M+H]^+$: 235. ^{13}C -NMR (d_4 -MeOH): 180.0, 141.6, 132.5, 131.4, 126.7,

126.1, 125.6, 124.3, 117.2, 47.2, 43.0 ppm.

EXAMPLE 71

(S)-7-Chlorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

MS (TSP+) m/z $[M+H]^+$: 235.

EXAMPLE 72

(S)-6-Chlorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

MS (TSP+) m/z $[M+H]^+$: 235. ^{13}C -NMR (d_4 -MeOH): 180.4, 145.1, 137.0, 129.4, 127.0,

126.8, 126.0, 124.4, 112.6, 47.1, 43.0 ppm.

EXAMPLE 73

(S)-5-Methylspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

^{13}C -NMR (CDCl_3) δ 180.2, 140.6, 134.1, 131.2, 130.4, 127.0, 125.9, 125.2, 111.5, 48.0, 47.1, 42.7, 21.1. MS(ESP+) m/z calcd for $[\text{M}-\text{Cl}]^+$: 215, observed: 215.

5

EXAMPLE 74

(S)-5-Fluorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

MS (TSP+) m/z $[\text{M}+\text{H}]^+$: 219. ^1H -NMR (d_4 -MeOH): 7.1, 7.0, and 6.9 (3 m, 3H), 6.18 (d, 1H), 5.57 (d, 1H), 3.85 (dd, 2H), 3.52 (s, 2H).

10

EXAMPLE 75

(S)-4-Chlorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

MS (TSP+) m/z $[\text{M}+\text{H}]^+$: 235.

15 **EXAMPLE 76**

(R)-4-Methoxyspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

MS (TSP+) m/z $[\text{M}+\text{H}]^+$: 231. ^{13}C -NMR (CDCl_3) δ 179.7, 157.7, 144.2, 132.6, 126.5, 124.5, 115.8, 107.2, 105.1, 56.3, 48.1, 45.8, 42.7.

20 **EXAMPLE 77**

(R)-6-Methoxyspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride

MS (TSP+) m/z $[\text{M}+\text{H}]^+$: 231.

EXAMPLE 7825

(S)-7-Fluoro-5-methylspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride

MS (TSP+) m/z $[\text{M}+\text{H}]^+$: 233.

EXAMPLE 7930

5-Fluorospiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride

MS (TSP+) m/z $[M+H]^+$: 220.

EXAMPLE 80

(S)-6-Fluorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride.

5 MS (TSP+) m/z $[M+H]^+$: 219. 1H NMR (CD_3OD): δ 7.1 (m, 1H), 6.6 (m, 2H), 6.0 (d, 1H), 5.5 (d, 1H), 3.7 (s, 2H), 3.1 (s, 1H), 1.1 (s, 1H).

EXAMPLE 81

(S)-5-Methoxyspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one hydrochloride

10 MS (TSP+) m/z $[M+H]^+$: 231. 1H NMR ($CDCl_3$, 400 MHz) δ 6.9 (d, 1H), 6.8 (dd, 1H), 6.7 (d, 1H), 6.1 (d, 1H), 5.6 (d, 1H), 3.9 (s, 2NH), 3.8 (s, 2H), 3.5 (d, 1H), 3.4 (d, 1H), 3.1 (s, 3H).

EXAMPLE 82

15 6H-4,5-Dihydro-2-methylspiro[pyrrolo[2,3-c]pyrazole-4,3'-(1,2,3,6-tetrahydropyridin)]-5-one hydrochloride.

The compound is made from commercially available 3-amino-4-bromo-1-methylpyrazole following the general procedure via Heck cyclisation described in Example 49.

20 EXAMPLE 83

6H-4,5-Dihydro-2-methylspiro[thieno[2,3-b]pyrrole-4,3'-(1,2,3,6-tetrahydropyridin)]-5-one hydrochloride.

The compound is made from known N-Boc-2-amino-4-iodothiophene following the general procedure via Heck cyclisation described in Example 49.

25

EXAMPLE 84

5-Chlorospiro[indoline-3,3'-piperidin]-2-one hydrochloride.

The compound from EXAMPLE 65 was hydrogenated over Pd/C at 3 bar in ethanol. MS (TSP+) m/z $[M+H]^+$: 237.

30

EXAMPLE 85**Spiro[indoline-3,3'-(1,3,4,7-tetrahydro-2H-azepin)]-2-one hydrochloride.**

STEP A. 3-Allyl-3-[allyl(methyl)aminomethyl]-indolin-2-one. Oxindole was acylated
5 with ethyl acetate in the presence of sodium ethoxide as described (Chem. Abstr. 1953, 47,
p7488). The crude product (9.16 g; 52.3 mmol) was treated with sodium hydride (56
mmol) in DMF at ice bath temperature for 30 min. Allyl bromide (51 mmol) was added
and the reaction mixture left at room temperature overnight. The crude product after
workup was purified by SGC (EtOAc/isohexanes 1:2). The acetyl group was removed by
10 treatment with triethylamine/water 1:1 at 65 °C for 12 h and the the 3-allyloxindole thus
obtained was treated with an excess of allylmethylamine and one equivalent of
paraformaldehyde in acetic acid at 70 for 4 h. The crude material after evaporation of
solvents was partitioned between DCM and basic water. SGC using EtOAc/isohexanes 1:1
gave a reddish oil of the title product(83 %).

15 STEP B. N'-Methylspiro[indoline-3,3'-(1,3,4,7-tetrahydro-2H-azepin)]-2-one.

The product from the previous step (258 mg; 1.0 mmol) was treated with
bis(tricyclopentylphosphine)benzylidene-Ru(IV) dichloride (104 mg; 0.14 mmol) in dry
toluene under nitrogen at 60 °C for three days. An additional 60 mg of the Ru-catalyst was
added and the heating continued overnight. SGC after evaporation of solvents yielded 55
20 mg (21 %) of the title compound.

STEP C. t-Butyl 2-oxospiro[indoline-3,3'-(1,3,4,7-tetrahydro-2H-azepine)]-1'-
carboxylate. The spiro compound from STEP B (180 mg) was demethylated by treatment
with 1-chloroethyl chloroformate in 1,2-dichloroethane at reflux for 2 h followed after
evaporation of excess formate by heating in methanol-THF-water for 1 h. The secondary
25 amine was bocylated by treatment with (Boc)₂O and the product was chromatographed on
the Kirasil TBB column using heptane/iPrOH 9:1 as the eluent; two peaks were collected.

STEP D. (S)-Spiro[indoline-3,3'-(1,3,4,7-tetrahydro-2H-azepin)]-2-one hydrochloride.
The material from the second peak from STEP C (47 mg) was dissolved in methanol (5 ml)
30 and treated with HCl in ether (1.5 ml) at room temperature overnight. The title compound

was obtained upon removal of solvents. MS (TSP+) m/z $[M+H]^+$: 215. ^{13}C NMR: (CD₃OD): 181.0, 142.1, 132.7, 132.2, 130.4, 125.7, 124.8, 123.8, 111.6, 53.8, 47.6, 47.5, 35.4 ppm.

5 **PROCEDURE 1**

Exemplified general methods for synthesis of tertiary amines by alkylation of a secondary amine

METHOD A

10 To a stirred solution of spiro[indoline-3,3'-piperidin]-2-one and a corresponding aldehyde or ketone (in excess) in methanol, sodiumcyanoborohydride (about 2 eq) was added. The pH was adjusted to about pH 4-6 with acetic acid and the solution was stirred at room temp for about 18 - 60h. Concentration and extraction (EtOAc / 1-2 M NH₃), drying of the combined organic phases and evaporation gave a crude product. Purification by flash
15 column chromatography (SiO₂, eluent: toluene/acetonitrile/triethylamine or acetone/isohexane) gave the title compound.

METHOD B

To a stirred solution of a spiro[indoline-3,3'-piperidin]-2-one in acetonitrile or DMF
20 potassium carbonate (1.0 - 1.4 equivalents) and a corresponding alkyl halide (1.1 - 1.5 equivalents) was added at 0 °C or room temp. The reaction mixture was stirred at room temp - 60 °C for 2 - 15 h. Concentration and extraction (DCM/water), drying of the combined organic phases and evaporation gave a crude product. Purification by flash
column chromatography (SiO₂, eluent: acetone/isohehexane or
25 toluene/acetonitrile/triethylamine) gave the title compound.

PROCEDURE 2

Examples of resolving racemates by chiral HPLC

The resolution of 1'-isopropylmethylspiro[indoline-3,3'-piperidin]-2-one (861 mg) was
30 performed by chiral HPLC on a Kirasil TBB (50 x 250 mm) column. Eluent: heptane/1-

PrOH/1-BuOH 97 : 2: 1. About 170 mg was loaded on the column each time and the substance was recycled twice on the column; 370 mg of (R)-enantiomer (> 99% ee) and 380 mg of the (S)-enantiomer (93 % ee) were isolated.

Other tertiary amines could be similarly separated. In most cases it proved possible to
5 check the enantiomeric purity of tertiary as well as secondary amines using chiral liquid chromatography on for example a Chiracel OD column.

It also proved possible to separate several mono-Boc derivatives of secondary amine intermediates on the Kirasil TBB column. One example is described in EXAMPLE 49, STEP E.

10

BIOLOGICAL TESTS

1. In vivo experiments

15 The compounds of the invention when given by systemic injection to mice or rats, specifically reduce pain behavior in the formalin test. This test is an accepted model of clinical pain in man, involving elements of nociceptor activation, inflammation, peripheral sensitization and central sensitization (A Tjølsen et al. *Pain* 1992, 51, 5). It can therefore be inferred that the compounds can be used as therapeutic agents to relieve pain of various
20 origins. The compounds of the table "Further most preferred compounds of the invention" exhibit ED 50 doses by subcutaneous administration to mice in the range 0.2-6 µmol/kg. The compounds of formula I also show analgesic activity in the intraarticular FCA (Freund's complete adjuvant) test in the rat, a model of inflammatory pain (Iadarola et al. *Brain Research* 1988, 455, 205-12) and in the Chung nerve lesion test in the rat, a model
25 for neuropathic pain (Kim and Chung. *Pain* 1992, 50, 355). The analgesic effects in the animal models are obtained after doses that do not produce tissue concentrations leading to conduction block in nerve fibers. Thus, the analgesic effects can not be explained by the local anesthetic properties of the compounds mentioned in the publication by Kornet and

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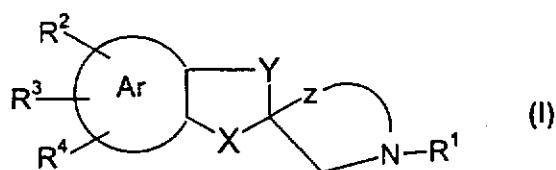
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Thio. Analgesic efficacy after systemic administration is not a general property of drugs with local anesthetic effects (Scott et al. *British Journal of Anaesthesia* 1988, 61, 165-8).

CLAIMS

1. A compound of the formula I

5



in racemic form or in the form of an enantiomer, or a pharmaceutically acceptable salt thereof, wherein

10 R^1 is

- a) H,
- b) substituted or unsubstituted C_1 - C_6 alkyl,
- c) C_1 - C_6 alkoxy C_2 - C_6 alkyl,
- d) C_1 - C_6 alkylthio C_2 - C_6 alkyl,
- 15 e) halogenated C_1 - C_6 alkyl,
- f) aryl C_1 - C_6 alkyl,
- g) C_1 - C_6 alkenyl, or
- h) C_1 - C_6 cycloalkyl C_1 - C_2 alkyl;

20 R^2 is

- a) H,
- b) C_1 - C_6 alkyl,
- c) C_2 - C_4 alkynyl,
- d) halogen,
- 25 e) substituted or unsubstituted carbamoyl,
- f) substituted or unsubstituted carbamoyloxy,
- g) C_1 - C_6 alkylcarbonyl,

- h) C₁-C₆ alkoxy carbonyl,
- i) C₁-C₆ alkyl carbonyloxy,
- j) hydroxy-substituted C₁-C₆ alkyl,
- k) cyano,
- 5 l) nitro,
- m) amino,
- n) halogenated C₁-C₆ alkyl,
- o) halogenated C₁-C₆ alkoxy,
- p) halogenated C₁-C₆ alkylthio,
- 10 q) C₁-C₆ alkylsulfinyl,
- r) C₁-C₆ alkylsulfonyl,
- s) C₁-C₄ alkylsulfinylalkyl,
- t) C₁-C₄ alkylsulfonylalkyl,
- u) C₁-C₆ alkylsulfonylamino,
- 15 v) halogenated C₁-C₆ alkylsulfonylamino,
- w) halogenated C₁-C₂ alkylsulfonyloxy,
- x) aminosulfonyl,
- y) aminosulfonyloxy,
- z) aryl,
- 20 aa) arylcarbonyl,
- bb) arylsulfinyl,
- cc) arylsulfonyl,
- dd) C₁-C₆ alkylcarbonylamino,
- ee) C₁-C₆ alkoxy carbonylamino,
- 25 ff) C₁-C₆ alkyl-thiocarbonyl,
- gg) C₁-C₆ alkoxy-thiocarbonyl,
- hh) formyl, or
- ii) alkoxysulfonylamino;

R^3 is

- 5 a) H,
- b) C_1 - C_6 alkyl,
- c) halogen,
- d) C_1 - C_6 alkoxy,
- e) halogenated C_1 - C_4 alkyl,
- 10 f) halogenated C_1 - C_6 alkoxy,
- g) halogenated C_1 - C_6 alkylthio,
- h) C_1 - C_4 alkylsulfinyl,
- i) C_1 - C_4 alkylsulfonyl,
- j) C_1 - C_4 alkylsulfinyl C_1 - C_6 alkyl,
- 15 k) C_1 - C_4 alkylsulfonyl C_1 - C_6 alkyl,
- l) C_1 - C_4 alkylsulfonylamino,
- m) halogenated C_1 - C_4 alkylsulfonylamino,
- n) aminosulfonyl, or
- o) aminosulfonyloxy;

20

R^4 is

- a) H,
- b) C_1 - C_4 alkyl, or
- c) halogen;

25

R^2 and R^3 may together with the carbon atoms to which they are attached form a saturated or unsaturated ring,

optionally substituted with one or more substituents selected from halogen, C_1 - C_6 alkyl,

C_1 - C_6 alkoxy, CF_3 , OH, cyano, amino, C_1 - C_6 alkyl-NH-, $(C_1$ - C_6 alkyl) $_2$ -N-, CN

30 , NH_2SO_2 , NH_2CO -, or C_1 - C_6 alkyl-CO-;

and wherein any amino moiety in R^2 - R^4 can optionally be substituted with one or two C_1 - C_6 alkyl groups which may be part of a ring;

Ar is

- a) benzene, or
- b) pyridine;

X is

- a) $-NHCO-$,
- b) $-COHN-$, or
- c) $-NH-SO_2-$;

Y is a single bond; and

Z is $-CH=CHCH_2$

and with the proviso that when R^1 is a substituted or unsubstituted C_1 - C_6 alkyl, then R^2 , R^3 and R^4 cannot all be hydrogen.

2. The compound of claim 1, wherein

R^1 is

- a) H,
- b) C_1 - C_4 alkyl,
- c) C_1 - C_4 alkoxy C_1 - C_4 alkyl,
- d) C_1 - C_4 alkylthio C_1 - C_4 alkyl,
- e) fluorinated C_1 - C_4 alkyl,
- f) aryl C_1 - C_4 alkyl,
- g) C_1 - C_4 alkenyl, or
- h) cyclopropylmethyl;

R^2 is

- a) H,
- b) C_1 - C_4 alkyl,

- c) C₂-C₃ alkynyl,
- d) halogen,
- e) substituted or unsubstituted carbamoyl,
- f) substituted or unsubstituted carbamoyloxy,
- 5 g) C₁-C₃ alkylcarbonyl,
- h) C₁-C₃ alkoxycarbonyl,
- i) C₁-C₃ alkylcarbonyloxy,
- j) hydroxy-substituted C₁-C₃ alkyl,
- k) cyano,
- 10 l) fluorinated C₁-C₃ alkoxy,
- m) fluorinated C₁-C₆ alkylthio,
- n) C₁-C₃ alkylsulfinyl,
- o) C₁-C₃ alkylsulfonyl,
- p) C₁-C₃ alkylsulfinyl C₁-C₆ alkyl,
- 15 q) C₁-C₄ alkylsulfonyl C₁-C₆ alkyl,
- r) C₁-C₃ alkylsulfonylamino,
- s) halogenated C₁-C₃ alkylsulfonylamino,
- t) sulfamoyl,
- u) sulfamoyloxy,
- 20 v) aryl,
- w) heteroaryl,
- x) C₁-C₄ alkylcarbonylamino,
- y) C₁-C₃ alkoxycarbonylamino,
- z) C₁-C₃ alkyl-thiocarbonyl, or
- 25 aa) C₁-C₃ alkoxy-thiocarbonyl;

R³ is

- a) H,
- b) C₁-C₄ alkyl, or
- c) halogen;

R⁴ is

- a) H,
- b) C₁-C₄ alkyl, or
- c) halogen

R² and R³ may together with the carbon atoms to which they are attached, form a saturated or unsaturated ring, optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, cyano, amino, C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂-N-, CN, NH₂SO₂, NH₂CO-, or C₁-C₆ alkyl-CO-;

and wherein any amino moiety in R²-R⁴ can optionally be substituted with one or two C₁-C₆ alkyl groups which may be part of a ring.

3. The compound of either claim 1 or 2, wherein

R¹ is

- a) H,
- b) C₁-C₄ alkyl, or
- c) C₁-C₄ alkoxy C₁-C₄ alkyl;

R² is

- a) H,
- b) C₁-C₄ alkyl,
- c) halogen,
- d) substituted or unsubstituted carbamoyl,
- e) substituted or unsubstituted carbamoyloxy,
- f) C₁-C₂ alkylcarbonyl.
- g) C₁-C₃ alkoxycarbonyl,

- h) cyano,
- i) fluorinated C₁-C₂ alkoxy,
- j) fluorinated C₁-C₆ alkylthio,
- k) C₁-C₃ alkylsulfinyl,
- l) C₁-C₃ alkylsulfonyl,
- m) C₁-C₂ alkylsulfonylamino,
- n) C₁-C₃ alkylcarbonylamino, or
- o) C₁-C₃ alkoxycarbonylamino;

R³ is

- a) H,
- b) C₁-C₄ alkyl, or
- c) halogen;

R⁴ is

- a) H,
- b) C₁-C₄ alkyl, or
- c) halogen;

R² and R³ may together with the carbon atoms to which they are attached, form a saturated or unsaturated ring, optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, cyano, amino, C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂-N-, CN, NH₂SO₂, NH₂CO-, or C₁-C₆ alkyl-CO-;

and wherein any amino moiety in R²-R⁴ can optionally substituted with one or two C₁-C₆ alkyl groups which be part of a ring.

4. A compound according to claim 1, wherein

R¹ is H;

R² is

- a) H,

- b) C₁-C₄ alkyl, or
- c) halogen

R³ is

- a) H,
- b) C₁-C₄ alkyl, or
- c) halogen;

R⁴ is

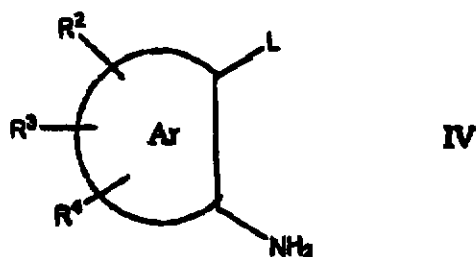
- a) H,
- b) C₁-C₄ alkyl, or
- c) halogen.

5. The compound according to claim 4 wherein X is -NHCO-,
6. The compound according to claim 4, wherein Ar is benzene.
7. The compound according to claim 4, wherein Ar is pyridine.
8. A compound or a pharmaceutically acceptable salt thereof, selected from the group consisting of:
 - (S)-5-chloro-7-fluorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one
 - (S)-5-methylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one
 - (S)-5,6-dimethylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one
 - (S)-6-methylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one
 - (S)-5-chlorospiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one
 - (S)-5,7-difluorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one
 - (S)-7-chlorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one
 - (S)-7-fluoro-5-methylspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one
 - (S)-5-methoxyspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one.

9. The compound (S)-5-chloro-7-fluorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one or a therapeutically acceptable salt thereof.
10. The compound (S)-5-methylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridine)]-2-one or a therapeutically acceptable salt thereof.
11. The compound (S)-5,6-dimethylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one or a therapeutically acceptable salt thereof.
12. The compound (S)-6-methylspiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one or therapeutically acceptable salt thereof.
13. The compound (S)-5-chlorospiro[7-azaindoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one or a therapeutically acceptable salt thereof.
14. The compound (S)-5,7-difluorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one or a therapeutically acceptable salt thereof.
15. The compound (S)-7-chlorospiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one or a therapeutically acceptable salt thereof.
16. The compound (S)-7-fluoro-5-methylspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one or a therapeutically acceptable sale thereof.
17. The compound (S)-5-methoxyspiro[indoline-3,3'-(1,2,3,6-tetrahydropyridin)]-2-one or a therapeutically acceptable salt thereof.
18. A pharmaceutical formulation containing a compound according to any one of claims 1 to 17 as active ingredient in combination with a pharmaceutically acceptable diluent or carrier.
19. Use of a compound to any one of claims 1 to 17 in therapy.

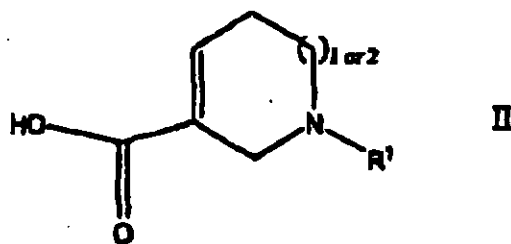
20. Use of a compound according to any one of claims 1 to 17 for the manufacture of a medicament for the treatment of pain.
21. Use of a compound according to any of claims 1 to 17 for the manufacture of a medicament for the treatment of neuropathic or central pain.
22. Use of a compound according to any of claims 20 and 21 for the manufacture of a medicament for oral use.
23. A process for the preparation of a compound according to any one of claims 1, 2 or 4 to 17, comprising:

- a) reacting a compound of formula IV



wherein L is a halogen or a trifluoromethylsulonyloxy group, and Ar, R², R³ and R⁴ are as defined for Formula I in claims 1, 2, or 4 to 17,

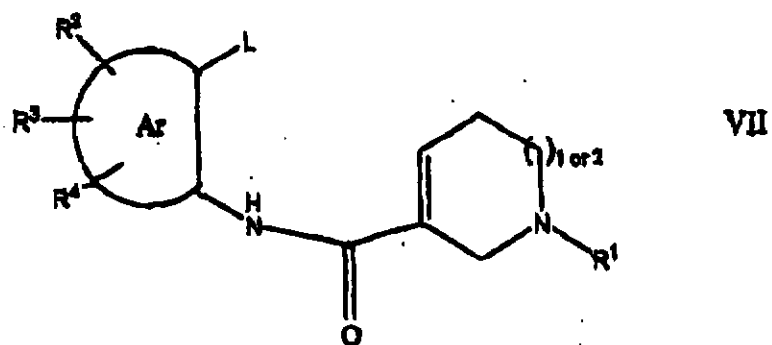
with a compound of Formula II or a corresponding lower alkyl ester



wherein R₁ is as defined for Formula I in claims 1, 2 or 4 to 17 or is a nitrogen protecting group,

to give a compound of Formula VII

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b) cyclizing the compound of Formula VII using a palladium catalyst and optionally removing protecting groups to give said compound.