The present invention relates to trans-derivatives of Formula (I) wherein R₁ is hydrogen, halogen or lower alkyl; R₂ is hydrogen, lower alkyl or -(CH₂)ₙCN; R₃ is hydrogen or CF₃; n is 1 or 2; the dotted line may be a bond or not; and to pharmaceutically acceptable acid addition salts thereof. Encompassed by the present formula I are compounds of Formulas (IA) and (IB). The compounds of (I) are good inhibitors of the serotonin transporter (SERT inhibitors) and simultaneously, they have a good activity on the NK-1 receptor (dual effect). By virtue of their efficacy as SERT inhibitors, the compounds in the present invention are particularly useful for the treatment of CNS disorders and psychotic disorders, in particular in the treatment or prevention of depressive states and/or in the treatment of anxiety.
The present invention relates to trans-derivatives of formula

wherein

- $R^1$ is hydrogen, halogen or lower alkyl;
- $R^2$ is hydrogen, lower alkyl or $-(CH_2)_nCN$;
- $R^3$ is hydrogen or $CF_3$;
- $n$ is 1 or 2;
- the dotted line may be a bond or not;
- and to pharmaceutically acceptable acid addition salts thereof.

Encompassed by the present formula I are compounds of formulas IA and IB

The compounds of formula I are good inhibitors of the serotonin transporter (SERT inhibitors) and simultaneously, they have a good activity on the NK-1 receptor (dual effect). By virtue of their efficacy as SERT inhibitors, the compounds in the present invention are particularly useful for the treatment of CNS disorders and psychotic disorders, in particular in the treatment or prevention of depressive states and/or in the treatment of anxiety.

SERT Inhibitors including the selective serotonin transporter inhibitors, also called selective serotonin reuptake inhibitors (SSRTs), have become the most frequently
prescribed antidepressant drugs. They are believed to exert their effect by increasing extracellular 5-HT levels in the serotoninergic terminal fields such as the hippocampus and prefrontal cortex. However, approximately 30% of patients appear to be resistant to SSRI treatment. In addition, those patients who do benefit from SSRI treatment often exhibit various side-effects which include sexual dysfunction, gastrointestinal distress, insomnia and in some cases anxiogenesis due to their indirect activation (through elevation of 5-HT levels) of all 5-HT receptors. Furthermore, a common problem in current antidepressant therapies is their slow onset of action, since a delay of about 4 weeks is normally observed between the beginning of the treatment and alleviation of the symptoms. The delay appears to parallel the progressive desensitization of somatodendritic 5HT\textsubscript{1A} receptors, increasing serotoninergic function, thus allowing alleviation of depressive symptoms.

Therefore, the object of the present invention was to find compounds which have SERT inhibitory activity with an additional beneficial effect on the onset of action and which allow major improvements for SSRI-resistant patients, e.g. with a reduced anxiogenic or even anxiolytic profile.

It has surprisingly been found that present compounds of formula I have a good activity as SERT inhibitors and that they are concomitantly active as NK-1 receptor antagonists. NK-1 antagonists are believed to indirectly modulate 5-HT function via noradrenergic pathways and have been shown to attenuate presynaptic 5HT\textsubscript{1A} receptor function (Bioorg. Med. Chem., Lett. 12, (2002), 261-264).

Thus, combination of serotonin uptake inhibition with NK-I antagonism may lead to compounds with an improved onset of action and a better efficacy during the treatment of depressive/anxiolytic states.

The compounds of the present invention combine serotonin transporter inhibition and NK-I antagonism.

Recent reports have indicated that the combination of a SSRI and a NK-I antagonist produces beneficial responses in animal models of anxiety and depression such as guinea-pig pup maternal separation vocalization, with relatively reduced doses (W098/475 14; Bioorg. Med. Chem. Lett. 12(2), 261-264 (2002) and Bioorg. Med. Chem. Lett. 12(21), 3195-3198 (2002)).

This suggests that by adopting a dual approach which is mechanistically dissimilar, a synergism between the two modes of action may occur, enabling enhanced responses. This may not only be beneficial in patients resistant to treatment with SSRI alone but also in improving the rapidity of onset of therapeutic action. A drug with a dual
mode of action potentially allows for a reduction in dosing and therefore a decreased risk of side effects as compared to a combination of two drugs.

In the patent literature the combined NK-1/SSRI approach has also been proposed as a potential treatment for obesity (WO98/47514).

WO2005/032464 describes trans-phenyl pyrrolidine ethers which are tachykinin receptor antagonists. Now it has surprisingly been found that a small group of trans-derivatives of piperidine or tetrahydropyridine derivatives of the present formula I are SERT inhibitors and simultaneously, they have a good activity as NK-I receptor antagonists. A drug with a dual mode of action combines the advantages of both receptor sites, and the dosage of the drug may therefore be reduced, thus leading to a decreased risk of side effects as compared to a combination of two drugs.

It has been shown that trans-derivatives of formula I (piperidine or tetrahydropyridine) have a dual activity and therefore they can share the advantages as mentioned above. In the table below are shown NK-1 and SERT activities of compounds of present trans-derivatives of formula I, compared with structure-related trans-derivatives of formulas II and III, not encompassed by the present invention.
<table>
<thead>
<tr>
<th>Structure</th>
<th>pKi hSERT</th>
<th>pKi hNK1</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure 1" /></td>
<td>8.21</td>
<td>7.9</td>
<td>1 of I present invention</td>
</tr>
<tr>
<td><img src="image2" alt="Structure 2" /></td>
<td>6.97</td>
<td>8.09</td>
<td>2 of I present invention</td>
</tr>
<tr>
<td><img src="image3" alt="Structure 3" /></td>
<td>6.85</td>
<td>7.67</td>
<td>3 of I present invention</td>
</tr>
<tr>
<td><img src="image4" alt="Structure 4" /></td>
<td>7.77</td>
<td>6.83</td>
<td>4 of I present invention</td>
</tr>
<tr>
<td><img src="image5" alt="Structure 5" /></td>
<td>7.96</td>
<td>8.05</td>
<td>5 of I present invention</td>
</tr>
<tr>
<td><img src="image6" alt="Structure 6" /></td>
<td>7.49</td>
<td>7.62</td>
<td>6 of I present invention</td>
</tr>
<tr>
<td><img src="image7" alt="Structure 7" /></td>
<td>7.49</td>
<td>8.5</td>
<td>7 of I present invention</td>
</tr>
</tbody>
</table>
Related compounds of formulas II and III have a high selectivity to the NK-1 receptor (not desired in the present case).
The data has been generated in accordance with the following assays:

hSERT SPA binding assay

HEK-293 cells stably expressing recombinant human SERT are maintained with DMEM high glucose with 10% FBS, 300 µg/ml G418 and 2 mM L-Glutamine and incubated at 37 °C with 5% CO₂. Cells are released from culture flasks using PBS for 1-2 min. The cells are subsequently centrifuged at 1000 g’s for 5 min and resuspended in PBS prior to being used in the membrane preparation.

Cells are homogenized using a Polytron in 50 mM Tris (pH 7.4). Centrifuged at 48,000 xg for 15 min, and the pellet resuspended in fresh buffer. After a second centrifugation, the pellet is re-homogenized and resuspended in fresh buffer. Typically, membrane portions are aliquoted in 3mg/ml (w:v) and stored at -80 °C.

A serial dilution of test compounds in 50 mM Tris-HCl, 120 mM NaCl, KCl 5 mM (pH 7.4) is made in a white Optiplate (Packard) (100 µl/well) and the radioligand [3]H Citalopram (Specific activity: 60-86 Ci/mmol, Final concentration: 1 nM) is added at 50 µl/well. Membrane and beads are prepared to a ratio of 5 µg:0.6 mg, with 0.6 mg PVT-WGA Amersham beads (Cat# RPQ0282V) added per well. 50 µl of the membrane/beads mixture is added to the assay plate for a final volume of 200 µl. The mixtures are allowed to stand at room temperature for one hour, and are then counted on a Packard TopCount.

The % inhibition is calculated for each compound tested (with 100% binding being the value obtained with the incubation of membrane/beads and radioligand in buffer without compound minus the non-specific binding measured in presence of 1µM Fluoxetine). The concentration producing 50% inhibition (IC50) is determined using an iterative non-linear curve fitting technique. The inhibition dissociation constant (Ki) of each compound is determined according to the method of Cheng-Prusoff.

hNK-1 binding assay

The affinity of test compounds for the NK-1 receptor was evaluated at human NK-1 receptors in CHO cells transfected with the human NK-1 receptor using the Semliki virus expression system and radio labelled with [3]H substance P (final concentration 0.6 nM).

Binding assays were performed in HEPES buffer (50 mM, pH 7.4) containing BSA (0.04%) leupeptin (8 µg/ml), MnCl₂ (3 mM) and phosphoramidon (2 µM). Binding assays consisted of 250 µl of membrane suspension (1.25 x 10⁵ cells/assay tube), 125 µl of buffer of displacing agent and 125 µl of [3]H substance P. Displacement curves were determined with at least ten concentrations of the compound. The assay tubes were incubated for 60 min at room temperature after which time the tube contents were rapidly filtered under vacuum through GF/C filters presoaked for 60 min with PEI (0.3
% ) with 2 x 2 ml washes of HEPES buffer (50 mM, pH 7.4). The radioactivity retained on the filters was measured by scintillation counting. All assays were performed in duplicate in at least 2 separate experiments.

The inhibition dissociation constant (Ki) of each compound for NK1 is determined as described above for hSERT.

References
- Rupniak, N.M.J. Elucidating the antidepressant actions of substance P (NK1 receptor) antagonists. Current Opinion in Investigational Drugs, 3(2), 257-261 (2002).
- WO98/47514 Al. Use of an NK1 receptor antagonist and an SSRI for treating obesity.
- WO03/015784 Al. 2-Substituted 1-arylpiperazines as tachykinin antagonists and/or serotonin reuptake inhibitors.

Objects of the present invention are the compounds of formula I per se, the use of compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases related to activation of Serotonin Transporter (SERT), such as for the treatment of depression and anxiety, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I in the control or prevention of illnesses such as depression and anxiety.
The invention includes all trans-derivatives and their pharmaceutically active salts.

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain group containing from 1 to 7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred alkyl groups are groups with 1-4 carbon atoms.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

Preferred compounds of formula I are those of formula IA, for example the following compounds:

(-)-(3'S,4'R)-3-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-(4-fluoro-phenyl)-piperidine,

(-)-(3'S,4'R)-3-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-(4-fluoro-phenyl)-piperidine,

(-)-(3'S,4'R)-3-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-(4-fluoro-phenyl)-piperidin-1-yl-acetonitrile,

(-)-(3'S,4'R)-4-(4-fluoro-phenyl)-3-(3-trifluoromethyl-benzyloxymethyl)-piperidine,

(3'S,4'R,5'S)-3-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-phenyl-piperidine or

(-)-(3'S,4'R,5'S)-3-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-c>-tolyl-piperidine.

Preferred compounds of formula I are further those of formula I-B, for example the following compound

5-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-o-tolyl-1,2,3,6-tetrahydro-pyridine.

The novel trans-derivatives of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example by processes described below, which processes comprise

a) reacting a compound of formula
with sodium hydride and a compound of formula

followed by treatment with acid such as HCl or trifluoroacetic acid to give a compound of formula

wherein X is Cl, Br or I and R^1 and R^3 are as described above, or

b) reacting a compound of formula

with a compound of formula

R^2CHO

to a compound of formula

1-2
wherein \( R^2 \) is \((\text{CH}_i)_n\text{CN}\) for \( n = 1 \) or 2, or lower alkyl, with the exception of methyl and the other substituents are as described above, or

c) reacting a compound of formula

\[
\begin{align*}
R^1 & \text{H} \\
& \text{N}
\end{align*}
\]

with a compound of formula \( R^3 X \), wherein \( X \) is halide

to a compound of formula

\[
\begin{align*}
R^1 & \text{H} \\
& \text{N}
\end{align*}
\]

or

d) deprotecting a compound of formula

\[
\begin{align*}
R^1 & \text{H} \\
& \text{N}
\end{align*}
\]

10

to a compound of formula

\[
\begin{align*}
R^1 & \text{H} \\
& \text{N}
\end{align*}
\]

wherein \( R^1 \) is as described above,
and,
15

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

Schemes I to 4 show the preparation of compounds of formula I in more
The starting material used in schemes 1 to 4 are known compounds or maybe prepared by methods known in the art.

**Scheme 1**

\[
\begin{align*}
1) & \quad \text{ZnX} \\
\text{VIII} & \quad \text{Pd(PPh}_3\text{)}_4, \text{ THF, RT} \\
\text{IX} & \quad \text{NaOH, Dioxan} \\
& \quad X = \text{halide}
\end{align*}
\]

**Scheme 2**

\[
\begin{align*}
\text{Ru(OAc)}_2(\text{diphosphine ligand}) \\
\text{Et}_3\text{N, H}_2 (40 \text{ bar}) \\
\text{MeOH, 80 °C} \\
\text{X} & \quad \text{MeOH, PPh}_3, \text{ DEAD} \\
\text{XI} & \quad \text{THF, RT}
\end{align*}
\]

\[
\begin{align*}
\text{XI} & \quad \text{NaOMe, reflux} \\
\text{XII} & \quad \text{aq. NaOH, dioxane} \\
& \quad \text{RT} \\
& \quad \text{HCl}
\end{align*}
\]

\[
\begin{align*}
\text{XIII} & \quad \text{BH}_3, \text{SMe}_2, \text{ THF, RT} \\
\text{II} & \quad \text{HCl, MeOH}
\end{align*}
\]

**Scheme 3**

\[
\begin{align*}
1) & \quad \text{Br} \\
\text{III} & \quad \text{NaH, DMF, RT} \\
& \quad \text{HCl, MeOH}
\end{align*}
\]

**Scheme 4**

\[
\begin{align*}
\text{I-1} & \quad \text{HCl}
\end{align*}
\]
Scheme 3

\[ \text{R}^2 \text{X}, \text{K}_2 \text{CO}_3, \text{CH}_3 \text{CN} \]
\[ X = \text{hahde} \]

\[ \text{I-1} \]

1) \( \text{R}^2 \text{CHO}, \text{MeOH}, \text{reflux} \)
2) \( \text{NaBH}_4\text{CN}, 0 \degree \text{C} \)

\[ \text{I-2} \]

Scheme 4

\[ \text{VI} \]

1) \( \text{BnBr}, \text{CH}_3\text{CN}, \text{reflux} \)
2) \( \text{NaBH}_4, \text{EtOH}, 35-50 \degree \text{C} \)

\[ \text{VII} \]

1) 1-chloroethyl chloroformate, 1,2-dichloroethane, 50 \degree \text{C} 
2) \( \text{MeOH}, \text{reflux} \)
3) \( \text{HCl}, \text{Et}_2\text{O} \text{or MeOH} \)

Intermediate 1

4-(4-Fluoro-phenyl)-5,6-dihydro-2 \( H \)-pyridine-1,3-dicarboxylic acid \( l\text{-}\text{tert-buty}l \) ester

a) 4-Trifluoromethanesulfonyloxy-5,6-dihydro-2 \( H \)-pyridine-1,3-dicarboxylic acid \( l\text{-}\text{tert-buty}l \) ester 3-methyl ester
To a solution of 4-oxo-piperidine-1,3-dicarboxylic acid l-tert-butyl ester 3-methyl ester (8.64 g, 33.5 mmol) in 230 ml THF was added sodium hydride (suspension in oil, 55 %, 3.26 g, 74.6 mmol) at 0°C. After stirring for 30 min. at 0°C N-phenyltrifluoromethanesulfonimide (20.4 g, 56.0 mmol) was added. The ice-water bath was removed and the reaction mixture was stirred for 2 days. Quenching with ice was followed by concentration in vacuo to remove THF. The residue was diluted with tert-butyl methyl ether and washed with three portions of 1 M aqueous sodium hydroxide solution. The organic layer was washed with brine and dried over sodium sulfate. Concentration in vacuo gave the crude title compound with a purity of 90 % (11.4 g, 26.4 mmol, 71 %).

MS m/e (%): 334 (M+H+ - C4H8, 100).

b) 4-(4-Fluoro-phenyl)-5,6-dihydro-2 H-pyridine-1,3-dicarboxylic acid l-tert-butyl ester

To a mixture of 4-trifluoromethanesulfonyloxy-5,6-dihydro-2 H-pyridine-1,3-dicarboxylic acid l-tert-butyl ester 3-methyl ester (10.1 g, 25.9 mmol), 4-fluorophenylzinc bromide solution (0.5 M in THF, 86.3 ml, 43.1 mmol) and 290 ml THF was added tetrakis(triphenylphosphine)palladium(0) (0.83 g, 0.72 mmol) at RT. After stirring for 6 h the reaction was quenched with ice. The mixture was diluted with tert-butyl methyl ether and washed with 2 M aqueous sodium carbonate solution. The aqueous layer was extracted with two portions of tert-butyl methyl ether. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo. Purification of the residue by flash chromatography (heptane / ethyl) gave the title compound as a lightly yellow amorphous residue (6.8 g, 71 %).
A mixture of 4-(4-fluoro-phenyl)-5,6-dihydro-2 H-pyridine-1,3-dicarboxylic acid tert-butyl ester 3-methyl ester (6.8 g, 20 mmol), 100 ml 1,4-dioxane and 100 ml 2 M NaOH was stirred at RT for 20 h. After extraction of the reaction mixture with two portions of tert-butyl methyl ether, the combined organic layers were extracted with 1 M aqueous sodium hydroxide solution (100 ml). The combined aqueous layers were cooled to 0 °C by addition of ice (150 g) and acidified to pH 1 with ice-cold 4 M aqueous hydrochloric acid solution (70 ml). The aqueous layer was extracted with three 150 ml-portions of ethyl acetate. The combined organic layers were washed with brine (50 ml), dried over sodium sulfate and concentrated in vacuo. Crystallization of the crude acid (6.4 g) from a mixture of n-heptane and ethyl acetate (19:1, 120 ml) gave the title compound as white crystals (5.1 g, 78%).

MS m/e (%): 320 (M-H+, 100).

Intermediate 2

4-phenyl-5,6-dihydro-2 H-pyridine-1,3-dicarboxylic acid tert-butyl ester

The title compound was obtained as white crystals in comparable yields according to the procedures described above for the preparation of 4-(4-fluoro-phenyl)-5,6-dihydro-2 H-pyridine-1,3-dicarboxylic acid tert-butyl ester using phenylzinc iodide instead of 4-fluorophenylzinc bromide in step b).
MS m/e (%): 302 (M-H+, 100)

Intermediate 3

4-o-Toryl-5,6-dihydro-2 H-pyridine-1,3-dicarboxylic acid l-tert-butyl ester

To a 1 M solution of o-tolylmagnesium chloride in THF (6.26 ml, 41.5 mmol) was added dropwise a freshly prepared solution of dried zinc chloride (8.48 g, 62.2 mmol) in dry THF (200 ml) at 0°C. After completed addition the reaction mixture was allowed to slowly warm to room temperature over a period of 1 h. To this mixture were added a solution of 4-trifluoromethanesulfonyl-oxy-5,6-dihydro-2 H-pyridine-1,3-dicarboxylic acid l-tert-butyl ester 3-methyl ester (10.7 g, 27.5 mmol) in THF (270 ml) and tetrakis(triphenylphosphine)palladium(0) (0.96 g, 0.83 mmol). After stirring for 6 h at room temperature the reaction was quenched with ice. The mixture was diluted with tert-butyl methyl ether and washed with 2 M aqueous sodium carbonate solution. The aqueous layer was extracted with two portions of tert-butyl methyl ether. The combined organic layers were washed with water and brine, dried over sodium sulfate and concentrated in vacuo. Purification of the residue by flash chromatography (heptane / ethyl acetate) gave the title compound as a light yellow viscous oil (6.31 g, 69%).

MS m/e (%): 332 (M+H+, 16).

b) 4-o-Tolyl-5,6-dihydro-2 H-pyridine-1,3-dicarboxylic acid l-tert-butyl ester
The title compound was obtained as white crystals after crystallization from n-heptane/ethyl acetate 19:1 in comparable yield according to the procedure described above for the preparation of 4-(4-fluoro-phenyl)-5,6-dihydro-2 H-pyridine-1,3-dicarboxylic acid l-tert-butyl ester using 4-o-tolyl-5,6-dihydro-2 H-pyridine-1,3-dicarboxylic acid l-tert-butyl ester 3-methyl ester instead of 4-(4-fluoro-phenyl)-5,6-dihydro-2 H-pyridine-1,3-dicarboxylic acid l-tert-butyl ester 3-methyl ester in step c).

MS m/e (%): 316 (M-H+, 100)

Example 1

(-)-(3S',4R)-3-(3,5-Bis-trifluoromethyl-benzyloxymethyl)-4-(4-fluoro-phenyl)piperidine hydrochloride

a) (+)-(3R,4R)-4-(4-Fluoro-phenyl)-piperidine-1,3-dicarboxylic acid l-tert-butyl ester

In a glove box (O₂ content ≤ 2 ppm) a 35 ml autoclave equipped with a 15 ml glass insert and a magnetic stirring bar was charged with 4-(4-fluoro-phenyl)-5,6-dihydro-2 H-pyridine-1,3-dicarboxylic acid l-tert-butyl ester (0.300 g, 0.934 mmol), [Ru(OAc)₂((S)-3,5-Xyl-4-MeO)-MeOBIP HEP] (9.67 mg, 0.00936 mmol), triethylamine (15 mg, 0.16 mmol, 0.16 eq.) and 5 ml of methanol. The asymmetric hydrogenation was run for 42 h at 80°C under 40 bar of hydrogen. After cooling to room temperature the pressure was released from the autoclave, the methanol solution was diluted with 50 ml of tert-butyl methyl ether and extracted with two 50-ml portions of a 1 M aqueous sodium hydroxide solution. The aqueous layer was poured on ice, acidified with ice-cold 2 M aqueous hydrochloric acid solution to pH 1 and extracted with two 100-ml portions of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo to give (+)-(3R,4R)-4-(4-fluoro-phenyl)-piperidine-1,3-dicarboxylic acid l-tert-butyl ester in 89% yield (0.27 g) and with 96.6% ee.

MS m/e (%): 322 (M-H+, 100).

GC method for ee determination:

A 2-mg sample of the title compound was converted to the methyl ester by treatment with 0.5 ml of an approximately 0.5 M solution of diazomethane in diethyl ether at room
temperature. After evaporation of excess diazomethane and diethyl ether under a gentle stream of argon the residue was dissolved in 1 mL of ethyl acetate. BGB-175 column, 10 m*0.1 mm*df 0.1 μm, hydrogen 230 kPa, split ratio 1 : 300; temperature gradient 100 - 200 °C, program with 2 °C/min; injector temperature 200 °C, detector temperature 210 °C. Retention times: 46.59 min (methyl ester of (+)-acid), 46.76 min (methyl ester of (-)-acid).

b) (+)-(3 R,4R)-4-(4-Fluoro-phenyl)-piperidine-1,3-dicarboxylic acid l-tert-butyl ester 3-methyl ester

To a solution of triphenylphosphine (3.82 g, 14.6 mmol) in 70 mL tetrahydrofuran was added diethyl azodicarboxylate (2.53 g, 14.6 mmol) at 0 °C. After 30' methanol (4.55 mL, 112.0 mmol) and a solution of (+)-(3/?,4/?)-4-(4-fluoro-phenyl)-piperidine-1,3-dicarboxylic acid l-tert-butyl ester (3.62 g, 11.2 mmol, 93.6% ee) in 30 mL tetrahydrofuran were added subsequently at 0-5 °C. The reaction mixture was stirred for 20 h at room temperature. Quenching with water was followed by extraction with tert-butyl methyl ether (3 x 100ml). The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure and purified by flash chromatography (n-heptane / ethyl acetate) to give the title compound (3.55 g, 94%) as a colorless oil.

MS m/e (%): 338 (M+H +, 28).

[CC]D = +68.69 (c = 0.310, CHCl 3)

[CC]578 = +71.27 (c = 0.310, CHCl 3)

[CC]365 = +221.60 (c = 0.310, CHCl 3)

c) (-)-(35',4/?)-4-(4-Fluoro-phenyl)-piperidine-1,3-dicarboxylic acid l-tert-butyl ester
A mixture of (+)-(3R,4R)-4-(4-fluoro-phenyl)-piperidine-1,3-dicarboxylic acid l-tert-
butyl ester 3-methyl ester (3.55 g, 10.5 mmol) and sodium methoxide (1.14 g, 21.1 mmol) 
in 100 ml anhydrous toluene was heated at reflux over night. After cooling to room 
temperature the reaction mixture was quenched with water and concentrated in vacuo. 
The residue was dissolved in a mixture of 100 ml 1,4-dioxane and 50 ml 2 M aqueous 
sodium hydroxide solution. After stirring at RT for 5 h the mixture was diluted with 
water and washed with two portions of tert-butyl methyl ether. The aqueous layer 
was cooled to 0°C, acidified to pH 1-2 with ice-cold 1 M aqueous hydrochloric acid solution 
and extracted with three portions of tert-butyl methyl ether. The combined organic layers 
were dried over sodium sulfate and concentrated in vacuo. Flash column 
chromatography and crystallization from heptane/ethyl acetate 9:1 (30 ml) gave the title 
compound as white crystals (1.76 g, 52 %, 97.5% ee).

MS m/e (%): 322 (M-H+, 100).

[cc]d = -0.650 (c = 0.154, CHCl3)

HPLC method for ee determination:

Chiralpak-OD-H column, 25 cm*4.6 mm, 95 % n-heptane + 5 % 2-propanol with 0.1 % 
trifluro acetic acid, flow 0.7 ml/min, 30 °C, 0.001 ml injection volume, 210 nm. Retention 
times: (-)-acid 9.5 min, (+)-acid 11.5 min.

Assignment of the absolute configuration

The absolute configuration of the title compound was assigned as (3S,4R) by comparison 
of the optical rotation and the retention time by HPLC analysis on a Chiralpak-OD-H 
column with the values of a sample of (-)-(3S,4R)-4-(4-fluoro-phenyl)-piperidine-1,3-
dicarboxylic acid 1-tert-butyl ester which was derived from (-)-(35,4R)-4-(4-fluoro-phenyl)- 
l-methyl-piperidine-3-carboxylic acid methyl ester (prepared as described in 
WO0129031) as follows:

A solution of (-)-(35,4R)-4-(4-fluoro-phenyl)- 
l-methyl-piperidine-3-carboxylic acid methyl ester (575 mg, 2.29 mmol) and 1-chloroethyl chloroformate (393 mg, 2.75 mmol)
in 5 ml 1,2-dichloroethane was heated at reflux for 4 h. After cooling to room
temperature and evaporation of the solvent in vacuo the residue was dissolved in 5 ml
methanol. The solution was heated at reflux for 1 h, followed by cooling to room
temperature and concentration in vacuo. The residue was dissolved in 11.5 ml of a 2 M
aqueous solution of hydrochloric acid and heated at reflux over night. After cooling the
reaction mixture to 0 °C on an ice-water bath were added consecutively 2.8 ml of a 32%
aqueous solution of sodium hydroxide and a solution of di-t-o-t-butyl dicarbonate (1.00 g,
4.58 mmol) in 15 ml 1,4-dioxane. The ice-water bath was removed after completed
addition and stirring was continued at room temperature for 4 h. The pH of the reaction
mixture was adjusted to 8 by the addition of 1 M aqueous sodium hydroxide solution.
Washing with two portions of tert-butyl methyl ether was followed by back-extraction of
the combined organic layers with 1 M aqueous sodium hydroxide solution. The combined aqueous layers were cooled to 0 °C, acidified to pH 1 with ice-cold 4 M
aqueous hydrochloric acid solution and extracted with three portions of ethyl acetate.
The combined organic layers were washed with brine, dried over sodium sulfate and
concentrated in vacuo to give (-)-(3S,4 R)-4-(4-fluoro-phenyl)-piperidine-1,3-
dicarboxylic acid 1-tert-butyl ester (590 mg, 80%) with 93.8% ee.
MS m/e (%): 322 (M-H+, 100).
[a] D = -0.867 (c = 0.462, CHCl₃)

To a solution of (-)-(3 S,4 R)-4-(4-fluoro-phenyl)-piperidine-1,3-dicarboxylic acid 1-tert-
butyl ester (1.71 g, 5.29 mmol) in 35 ml THF was added a 2 M borane dimethylsulfide
complex solution in THF (5.44 ml, 10.9 mmol) at 0 °C. The mixture was stirred for 15
min at 0 °C and then at room temperature over night. After cooling to 0 °C the reaction
was quenched by the addition of methanol. Stirring was continued until no evolution of
gas was observed any more. The reaction mixture was diluted with water and extracted
with 3 portions of tert-butyl methyl ethyl. The combined organic layers were dried over
sodium sulfate and concentrated in vacuo. Flash chromatography gave 1.58 g (94%) of the title compound as a colorless viscous oil.

MS m/e (%): 310 (M+H+, 32)

e) (-)-(3'S,4'R)-3-(3,5-Bis trifluoromethyl-benzyloxymethyl)-4-(4-fluoro-phenyl)-piperidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4R)-4-(4-fluoro-phenyl)-3-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester (1.58 g, 5.11 mmol) in 30 ml DMF were added 0.29 g (6.0 mmol) sodium hydride (50% in mineral oil) at 0 °C. The reaction mixture was allowed to warm to room temperature. After 20 min, 3,5-bis(trifluoromethyl)benzyl bromide (3.14 g, 10.2 mmol) was added. Stirring at room temperature for 2 h was followed by quenching with water and extraction with three portions of tert-butyl methyl ether. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, heptane / ethyl acetate) to give 3.4 g (> 100%) of the title compound as a white solid.

MS m/e (%): 536 (M+H+, 13)

[a] D= -5.26 (c = 0.362, CHCl₃)

f) (-)-(3S,4R)-3-(3,5-Bis trifluoromethyl-benzyloxymethyl)-4-(4-fluoro-phenyl)-piperidine hydrochloride

A solution of (-)-(3S,4R)-3-(3,5-bis trifluoromethyl-benzyloxymethyl)-4-(4-fluoro-phenyl)-piperidine-1-carboxylic acid tert-butyl ester (1.10 g, 2.05 mmol) in a 1.25 M solution of hydrochloric acid in methanol (16.4 ml, 3.3 mmol) was stirred for 30 min. at 40 °C. The reaction mixture was concentrated to dryness and the residue was partitioned
between tert-butyl methyl ether and a 1 M aqueous sodium hydroxide solution. After extraction with three portions of tert-butyl methyl ether the combined organic layers were dried over sodium sulfate and concentrated in vacuo to 0.890 g (99.5%) of the title compound as a colorless white solid.

**Example 2**

\(-\)-(3-S',4R)-3-(3,5-Bis-trifluoromethyl-benzyloxymethyl)-4-(4-fluoro-phenyl)-piperidine

A solution of \(-\)-(3-S',4R)-3-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-(4-fluoro-phenyl)-piperidine (121 mg, 0.278 mmol) and paraformaldehyde (67 mg, 2.2 mmol) in 5 ml of methanol was heated at reflux for 2.5 h. The mixture was cooled to 0 °C, treated with sodium cyanoborohydride (37 mg, 0.56 mmol) and stirred for 30 min. Quenching with 2 M aqueous hydrochloric acid solution was followed by basification to pH 14 with 2 M aqueous sodium hydroxide solution and extraction with three portions of tert-butyl methyl ether. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Flash column chromatography gave 85 mg (68%) of the title compound as a colorless amorphous solid.

**Example 3**

\(-\)-[(3-S,4R)-3-(3,5-Bis-trifluoromethyl-benzyloxymethyl)-4-(4-fluoro-phenyl)-piperidin-1-yl]-acetonitrile
A mixture of (-)-(3S,4R)-3-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-(4-fluorophenyl)-piperidine (150 mg, 0.345 mmol), bromoacetonitrile (45 mg, 0.37 mmol) and potassium carbonate (95 mg, 0.69 mmol) in 4 ml of acetonitrile was stirred at room temperature over night. Quenching with water was followed by extraction with three portions of tert-butyl methyl ether. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Flash column chromatography gave 163 mg (99.7\%) of the title compound as a white solid.

MS m/e (%): 475 (M+H\(^{+}\), 100)

[a] \(\Delta D = -46.16\) (c = 0.496, CHCl \(_3\))

Example 4

(-)-(3S',4R)-4-(4-Fluoro-phenyl)-3-(3-trifluoromethyl-benzyloxymethyl)-piperidine hydrochloride

The title compound was obtained as a light yellow amorphous solid in comparable yields according to steps e) and f) of the procedure described above for the preparation of (-)-(3S,4R)-3-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-(4-fluoro-phenyl)-piperidine hydrochloride using 3-trifluoromethylbenzyl bromide instead of 3,5-bis(trifluoromethyl)benzyl bromide in step e).

MS m/e (%): 368 (M+H\(^{+}\), 100)

[\(\Delta\)]D = -39.93 (c = 0.431, CHCl \(_3\))

Example 5

(3SR,4RS)-3-(3,5-Bis-trifluoromethyl-benzyloxymethyl)-4-phenyl-piperidine hydrochloride

The title compound was obtained as a light yellow amorphous solid in comparable yields according to the procedure described above for the preparation of (-)-(3S',4R)-3-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-(4-fluoro-phenyl)-piperidine hydrochloride using
(3S,4R,5S)-4-(phenyl)-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester instead of (-)-(3S,4R)-4-(4-fluoro-phenyl)-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester in step d).

MS m/e (%): 418 (M+H +, 100)

Example 6

(-)-(α5')-3-(3,5-Bis-trifluoromethyl-benzyloxymethyl)-4-<6>-tolyl-piperidine hydrochloride

a) (++)-(αS)-4-o-Tolyl-piperidine-1,3-dicarboxylic acid l-tert-butyl ester

The title compound was obtained as white crystals in 98.1% ee after crystallization from n-heptane/ethyl acetate according to the procedure described above for the preparation of (+)-(3R,4R)-4-(4-fluoro-phenyl)-piperidine-1,3-dicarboxylic acid l-tert-butyl ester described above using Ru(OAc)2((S)-BITIANP) instead of [Ru(OAc)3((S)-3,5-Xyl-4-MeO)-MeOBIPHEP].

MS m/e (%): 318 (M-H +, 100)

[a] D= +78.71 (c = 0.700, CHCl3)

HPLC method for ee determination:

Chiralpak-ADH column, 25 cm*4.6 mm, 85 % n-heptane + 15 % ethanol with 1 % trifluoro acetic acid, flow 0.7 ml/min, 20 °C, 0.005 ml injection volume, 215 nm. Retention times: (-)-acid 8.1 min, (+)-acid 8.8 min.

b) (-)(α5m')-3-(3,5-Bis-trifluoromethyl-benzyloxymethyl)-4-<6>-tolyl-piperidine hydrochloride
The title compound was obtained as a colorless amorphous solid in comparable yields according to steps b) to f) of the procedure described above for the preparation of (-)-(3S;4R)-3-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-(4-fluoro-phenyl)-piperidine hydrochloride using (+)-(ds)-4-ø-tolyl-piperidine-1,3-dicarboxylic acid l-tert-butyl ester instead of (+)-(3 R,4R)-4-(4-fluoro-phenyl)-piperidine-1,3-dicarboxylic acid l-tert-butyl ester in step b).

MS m/e (%): 432 (M+H +, 100)

\[\text{[CC]} \delta = -33.36 \text{ (c = 0.408, CHCl}_3\text{)}\]

Example 7

5-(3,5-Bis-trifluoromethyl-benzyloxymethyl)-4-ø-tolyl-1,2,3,6-tetrahydro-pyridine hydrochloride

a) 1-Benzyl-3-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-ø-tolyl-pyridinium bromide

To a solution of 3-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-ø-tolyl-pyridine (prepared as described in DE 10008042 Al; 150 mg, 0.353 mmol) and benzyl bromide (60 mg, 0.35 mmol) in 3 ml acetonitrile was heated at reflux for 5 h. The mixture was concentrated in vacuo and the residue was purified by flash column chromatography to give 163 mg (78%) of the title compound as a white solid.

MS m/e (%): 516 (M +, 100).

b) 1-Benzyl-5-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-ø-tolyl-1,2,3,6-tetrahydro-pyridine

A solution of 1-benzyl-3-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-ø-tolyl-pyridinium bromide (163 mg, 0.273 mmol) in 6 ml of ethanol was added sodium borohydride (10 mg, 0.26 mmol) at 0°C. The mixture was heated to 35°C and stirred at this temperature over night. Another portion of sodium borohydride (10 mg, 0.26 mmol)
was added and the mixture was heated to 50 °C for 2 h. After cooling to room
temperature and quenching with water the mixture was diluted with a saturated aqueous
solution of sodium carbonate and extracted with three portions of tert-butyl methyl
ether. The combined organic layers were dried over sodium sulfate and concentrated in
vacuo. Flash column chromatography gave 78 mg (55%) of the title compound as a light
yellow oil.
MS m/e (%): 520 (M+H⁺, 100).

**A mixture of 1-benzyl-5-(3,5-bis-trifluoromethyl-benzyloxy)methyl)-4-o-tolyl- 1,2,3,6-tetrahydro-pyridine**

A mixture of 1-benzyl-5-(3,5-bis-trifluoromethyl-benzyloxy)methyl)-4-o-tolyl- 1,2,3,6-
tetrahydro-pyridine (76 mg, 0.15 mmol), potassium carbonate (20 mg, 0.15 mmol) and
1-chloroethyl chloroformate (23 mg, 0.16 mmol) in 3 ml of 1,2-dichloroethane was
heated at 50 °C for 3 h. The mixture was filtered and concentrated in vacuo. The residue
was dissolved in 2 ml of methanol and heated at reflux over night. Evaporation of the
solvent in vacuo was followed by flash column chromatography to give the free base of
the title compound. Dissolution in a 2 M solution of hydrochloric acid in diethyl ether
and concentration in vacuo gave 57 mg (84%) of the title compound as a white solid.

MS m/e (%): 430 (M+H⁺, 100)
Claims

1. Trans-derivatives of formula

wherein

R\textsuperscript{1} is hydrogen, halogen or lower alkyl;
R\textsuperscript{2} is hydrogen, lower alkyl or \(-\text{CH}_2\text{CN}\);
R\textsuperscript{3} is hydrogen or CF\textsubscript{3};
n is 1 or 2;
the dotted line may be a bond or not;
and pharmaceutically acceptable acid addition salts thereof.

2. Compounds of formula

according to claim 1,

wherein

R\textsuperscript{1} is hydrogen, halogen or lower alkyl;
R\textsuperscript{2} is hydrogen, lower alkyl or \(-\text{CH}_2\text{CN}\);
R\textsuperscript{3} is hydrogen or CF\textsubscript{3};
n is 1 or 2;
and pharmaceutically acceptable acid addition salts thereof.

3. Compounds of formula
according to claim 1,

wherein

$R^1$ is hydrogen, halogen or lower alkyl;

$R^2$ is hydrogen, lower alkyl or -(CH$_i$)$_n$ CN;

$R^3$ is hydrogen or CF$_3$;

n is 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

4. Compounds of formula I-A according to claim 2, which compounds are

(-)-(3$S'$.4$R$)-3-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-(4-fluoro-phenyl)-piperidine,

(-)-(3$S'$.4$R$)-3-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-(4-fluoro-phenyl)-piperidine,

5. Compounds of formula I-B according to claim 3, which compound is

5-(3,5-bis-trifluoromethyl-benzyloxymethyl)-4-o-tolyl-1,2,3,6-tetrahydro-pyridine.

6. Process for preparation of compounds of formula I and their pharmaceutically acceptable salts, which process comprises

a) reacting a compound of formula
with sodium hydride and a compound of formula

\[
\text{III}
\]

followed by treatment with acid such as HCl or trifluoroacetic acid to give a compound of formula

\[
\text{I-1}
\]

wherein \(X\) is Cl, Br or I and \(R^1\) and \(R^3\) are as described above, or

b) reacting a compound of formula

\[
\text{I-1}
\]

with a compound of formula

\[
R^2\text{CHO}
\]

to a compound of formula

\[
\text{1-2}
\]
wherein $R^2$ is $(\text{CH}_i)_n \text{CN}$ for $n = 1$ or 2, or lower alkyl, with the exception of methyl and the other substituents are as described above, or

c) reacting a compound of formula

\[
\begin{align*}
R^1 & \text{H} \\
\text{O} & \text{CF}_3
\end{align*}
\]

I-1

5 with a compound of formula $R^3X$, wherein $X$ is halide to a compound of formula

\[
\begin{align*}
R^1 & \text{H} \\
\text{O} & \text{CF}_3
\end{align*}
\]

I

or

d) deprotecting a compound of formula

\[
\begin{align*}
R^1 & \text{H} \\
\text{O} & \text{CF}_3
\end{align*}
\]

VII

to a compound of formula

\[
\begin{align*}
R^1 & \text{H} \\
\text{O} & \text{CF}_3
\end{align*}
\]

I-B'

wherein $R^1$ is as described above, and,

15 if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.
7. A compound according to claim 1, whenever prepared by a process as claimed in claim 6 or by an equivalent method.

8. A medicament containing one or more compounds as claimed in claim 1 and pharmaceutically acceptable excipients.

9. A medicament according to claim 8 for the treatment of illnesses based on the Serotonin Transporter (SERT) Inhibitors.

10. A medicament according to claims 8 and 9, wherein the illnesses are anxiety and depression.

11. The use of a compound as claimed in claim 1 for the manufacture of medicaments for the treatment of anxiety and depression.

12. The invention as herein before described.

***
### A. CLASSIFICATION OF SUBJECT MATTER

INV.: C07D211/22  A61K31/451  A61P25/24

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

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D  A61K  A61P

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

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

EPO-Internal, WPI Data, CHEMABS Data, BEILSTEIN Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>US 5 328 917 A (OAKOBSEN PALLE [DK] ET AL) 12 July 1994 (1994-07-12) column 1, line 35 - column 2, line 19 column 14, line 4 - line 5</td>
<td>1, 2, 7-10</td>
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</table>

Further documents are listed in the continuation of Box C. See patent family annex.

- **X**: Special categories of cited documents
- **X** document defining the general state of the art which is not considered to be of particular relevance
- **A** earlier document but published on or after the international filing date
- **B** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- **D** later document published prior to the international filing date but later than the priority date claimed
- **I** document defining the general state of the art which is not considered to be of particular relevance
- **I** document member of the same patent family
- **P**: later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- **X**: document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- **Y**: document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Date of the actual completion of the international search: 29 May 2007

Date of mailing of the international search report: 11/06/2007

Name and mailing address of the ISA/Authorized officer:

European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV RIVIERA, Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016

Johnson, C laire
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</table>
Continuation of Box II.2

Claims Nos.: 12

Claim 12 does not comply with Article 6 PCT - either it refers to subject-matter already claimed in claims 1-11, in which case it is redundant and lacks conciseness, or it refers to unspecified subject-matter mentioned in the description, in which case it is not clear.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.:
   12
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

   see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

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Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.
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<tr>
<td>US 5328917 A</td>
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<td>24-10-2000</td>
<td>GB 2347423 A</td>
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