



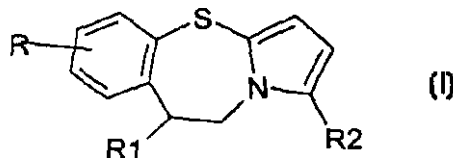
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(54) Title: PYRROLO[2,1-b][1,3]BENZOTHIAZEPINES WITH ATYPICAL ANTIPSYCHOTIC ACTIVITY

(57) Abstract

New polycondensated heterocycles with a pyrrolo[2,1-b][1,3]benzothiazepine structure of the formula (I), where the groups defined as in the description are disclosed. As compared to known antipsychotic agents, the compounds according to the invention present substantial activity associated with a simultaneous reduction in unwanted extrapyramidal symptoms. The compounds which are the subject of the invention described herein can be formulated in pharmaceutical compositions for the treatment of psychoses such as, for example, schizophrenia.



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Pyrrolo[2,1-b][1,3]benzothiazepines with atypical antipsychotic activity

The present invention relates to the field of antipsychotic drugs, in particular to polycondensated heterocycles with a
5 pyrrolo[2,1-b][1,3]benzothiazepine structure.

STATE OF THE ART

The intervention of dopamine and dopaminergic neurons in the pathology of a variety of psychiatric and neurological disorders has been amply documented (Caine, D.B., Therapeutics and
10 Neurology; Blackwell Scientific Publications, Oxford 1980, p. 281). In addition, it is also known that drugs which are active on dopamine receptors may play an important role in the therapy of such disorders; there is therefore considerable interest in the effects of dopamine agonist and antagonist compounds on dopaminergic
15 receptors, particularly with a view to their therapeutic implications.

Chlorpromazine and aloperidol have long been the treatment of choice for acute and chronic schizophrenia. It has been postulated that these drugs relieve the positive symptoms of the disease by blocking dopaminergic transmission in certain areas of the brain.
20 Chlorpromazine and aloperidol are defined as "typical neuroleptic agents": their action is characterised by remission of the symptoms of schizophrenia, accompanied, however, by unwanted extrapyramidal collateral symptoms (motor disorders, catalepsy, hyperprolactinaemia, etc.). The elimination of these adverse effects

therefore constitutes an important objective in the development of new neuroleptic therapies.

Clinical trials have demonstrated that not only dopamine antagonists but also 5-HT₂ antagonist compounds are capable of improving the symptoms of schizophrenia; in particular, it has been observed that the co-administration of 5-HT₂ antagonists and "typical" antipsychotic agents reduces the incidence of extrapyramidal symptoms as compared to treatment with neuroleptic agents alone (Psychopharmacol., 99, 1989, S18-S27; Niemeggers et al. in 5-HT₂ Receptor Antagonists in Schizophrenia, Racagni Ed., Elsevier Publishers, 1991, Vol. 1, pp. 535-537).

Further developments in this sense have led to the generation of drugs with a mixed antagonist component, i.e. which are active on different receptors.

15 Clozapine (8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine) is an antipsychotic agent capable of simultaneously antagonising dopamine on D₂ receptors and serotonin on 5-HT₂ receptors. This new action profile, called "atypical", allows schizophrenia to be treated with a lower incidence of extrapyramidal symptoms (J. Med. Chem., 39, 1996, pp. 1172-20 1188).

Unfortunately, the occurrence of cases of agranulocytosis has limited the therapeutic use of this drug (Lancet. 1975, 2, 657).

Octoclotheperin (8-chloro-10-(4-methylpiperazino)-10,11-25 dihydrodibenzo[b,f]thiepin) is a compound partly endowed with

"atypical" activity. Its pharmacological activity has been studied in relation to the optical isomers of this compound (J. Med. Chem., 1991, 34, 2023-2030): a slightly greater effect on schizophrenia by the (S) form is unfortunately associated with a greater incidence of extrapyramidal effects, so that its use has been withdrawn from clinical trials. The (R) isomer presents a more "atypical" profile, with fewer side effects, but also an inferior general potency. Moreover, the two isomers prove to be endowed with the same activity as 5-HT₂ and D₁ antagonists.

In view of the studies cited above, the need for antipsychotic agents with substantial therapeutic activity and without side effects remains unsatisfied. In particular, the search continues for antipsychotic agents which present greater neuroleptic activity and a lower incidence of extrapyramidal effects.

It has now surprisingly been found that polycondensated heterocycles with a pyrrolo[2,1-b][1,3]benzothiazepine are endowed with an interesting pharmacological profile as antipsychotic activity.

ABSTRACT OF THE INVENTION

The present invention describes polycondensated heterocycles with a pyrrolo[2,1-b][1,3]benzothiazepine structure. As compared to known antipsychotic agents, the compounds according to the invention present substantial activity associated with a simultaneous reduction in unwanted extrapyramidal symptoms. The compounds object of the invention described herein can be

formulated in pharmaceutical compositions for the treatment of psychoses such as, for example, schizophrenia.

Accordingly, it is an object of the present invention polycondensated heterocycles with a pyrrolo[2,1-
5 b][1,3]benzothiazepine structure as disclosed in the formula (I) below.

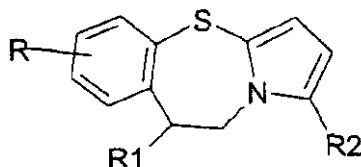
Another object of the present invention is a process for the preparation of said compounds.

Still another object of the present invention is the use of said
10 compounds as medicaments, in particular as antipsychotic agents, for the treatment of psychosis, such as schizophrenia, paranoid states, manic-depressive states, affective disorders, social withdrawal, personality regression, or hallucinations.

In its industrial aspects, the present invention provides
15 pharmaceutical compositions comprising at least a compound of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The invention described herein relates to new derivatives with a neuroleptic action, corresponding to the following structural
20 formula (I):



where:

R = H, Cl, Br, F, I, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ alkyl, C₅-C₆ cycloalkyl;

R₁ = dialkylamine, 4-alkyl-1-piperazinyl, 4-hydroxyalkyl-1-piperazinyl, 1-imidazolyl, 4-alkyl-1-piperidinyl

R₂ = hydrogen, C₁-C₄ alkoxy, C₁-C₄ alkylthio;

and the pharmaceutically acceptable salts thereof.

The formula (I) derivatives possess a chiral carbon atom in position 9 on the benzothiazepine ring. The invention described herein comprises both the formula (I) derivative in racemic form and the single (R) and (S) isomers, separately.

In formula (I), R preferably represents bromine, chlorine, fluorine or hydrogen, more preferably chlorine or fluorine; R₁ preferably a 4-methylpiperazinyl group; and R₂ preferably hydrogen.

Preferred derivatives according to the invention are the products:

(±)-9-(4-methylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-

b][1,3]benzothiazepine, hereinafter referred to as (±)-**3a**;

(±)-7-chloro-9-(4-methylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-

b][1,3]benzothiazepine, hereinafter referred to as (±)-**3b (ST1455)**;

(+)-7-chloro-9-(4-methylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-

b][1,3]benzothiazepine, particularly preferred, hereinafter referred to as (+)-**3b (ST1460)**

(±)-7-fluoro-9-(4-methylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine, hereinafter referred to as **(3c) (ST1456)**;

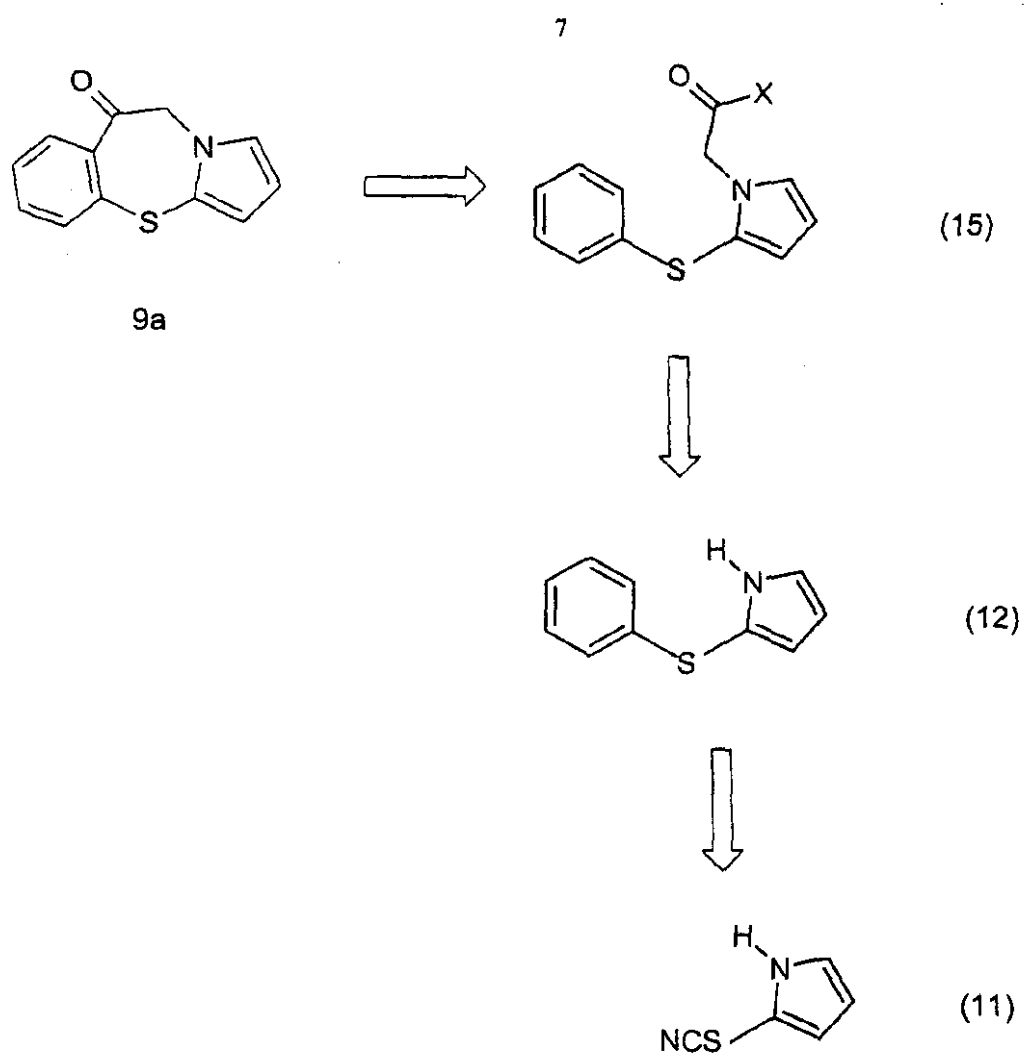
(±)-7-fluoro-9-(4-ethylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine **(4c) (ST1457)**;

5 (±)-7-fluoro-9-[4-(2'-hydroxyethylpiperazin-1-yl)]-9,10-dihydropyrrolo[2,1b][1,3] benzothiazepine **(5c) (ST1458)**;

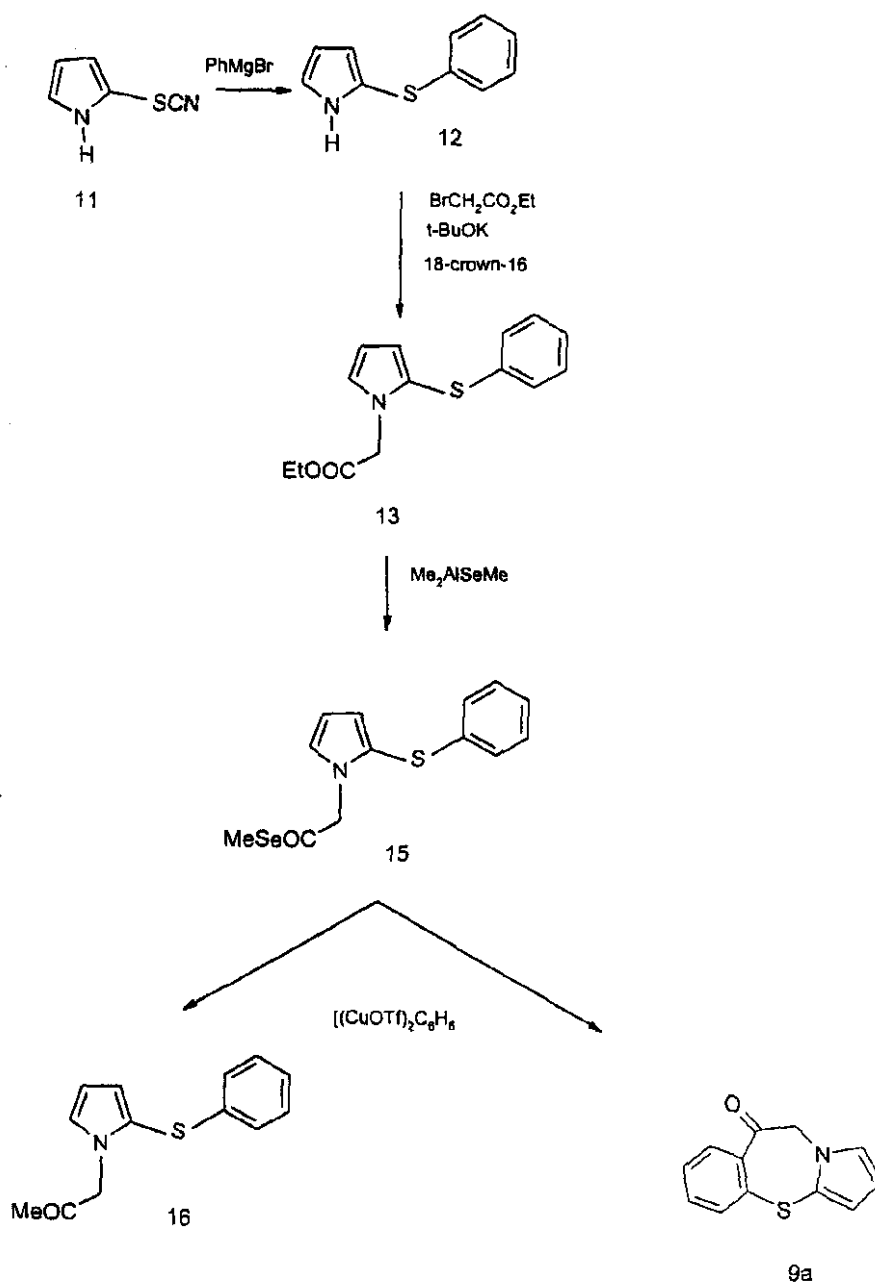
The invention described herein also relates to new, effective methods of synthesis to obtain the new pyrrolo[2,1-b][1,3]benzothiazepine structures. One of the problems encountered
10 was that of realising a cyclisation method that made it possible to obtain the particular formula (I) tricyclic system with high yields.

The various synthesis methods described herein include a cyclisation reaction of a derivative comprising a phenyl group and a pyrrole group, where the cyclisation leads to the formation of a [1,3]
15 thiazepine ring. The result of said cyclisation reaction is preferably a pyrrolobenzothiazepinone, which can be transformed into a formula (I) derivative by substituting the keto group on the thiazepine ring with a group selected from the definitions given above for the radical R_1 .

20 A process for the synthesis of formula (I) products is illustrated in Scheme 1A in its essential steps, and in Scheme 1B in detail.



Scheme 1 A



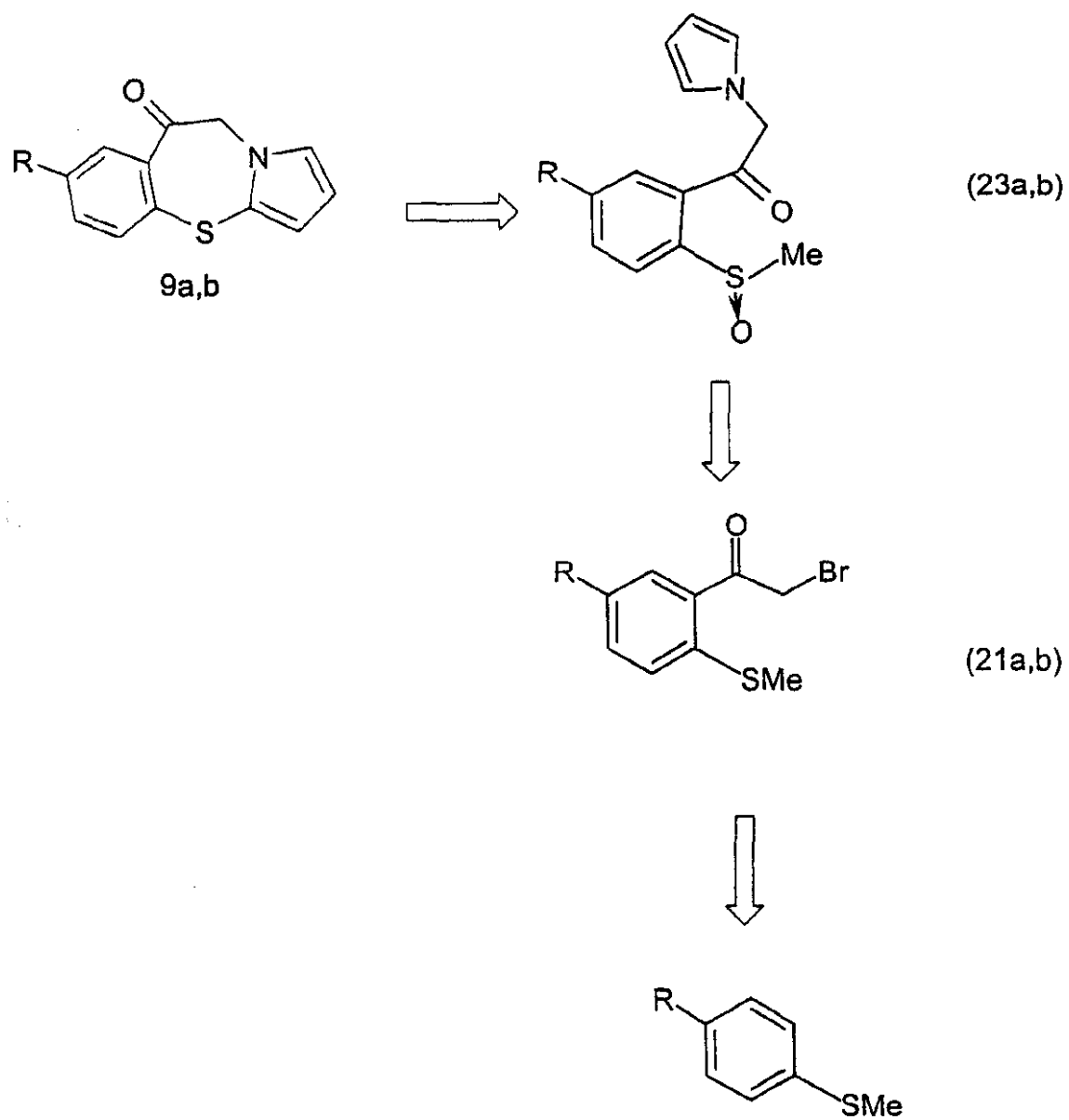
Scheme 1 B

With reference to Scheme 1B, the process involves the reaction of 2-thiocyanate-pyrrole (11) with phenyl magnesium bromide to form thioether (12). Thioether (12), subjected to esterification and transacylation reactions, gives rise to the derivative methylselenolate (15) comprising a phenyl group and a pyrrole group. Derivative (15) is then subjected to a cyclisation reaction, with formation of product (9a) (pyrrolobenzothiazepinone). The cyclisation reaction is conducted in the presence of a crystalline complex of triflate copper (I) and benzene.

Lastly, product (9a) is transformed into a formula (I) derivative by means of subsequent modifications of the keto group on the thiazepine ring to obtain derivatives with R₁ as described above.

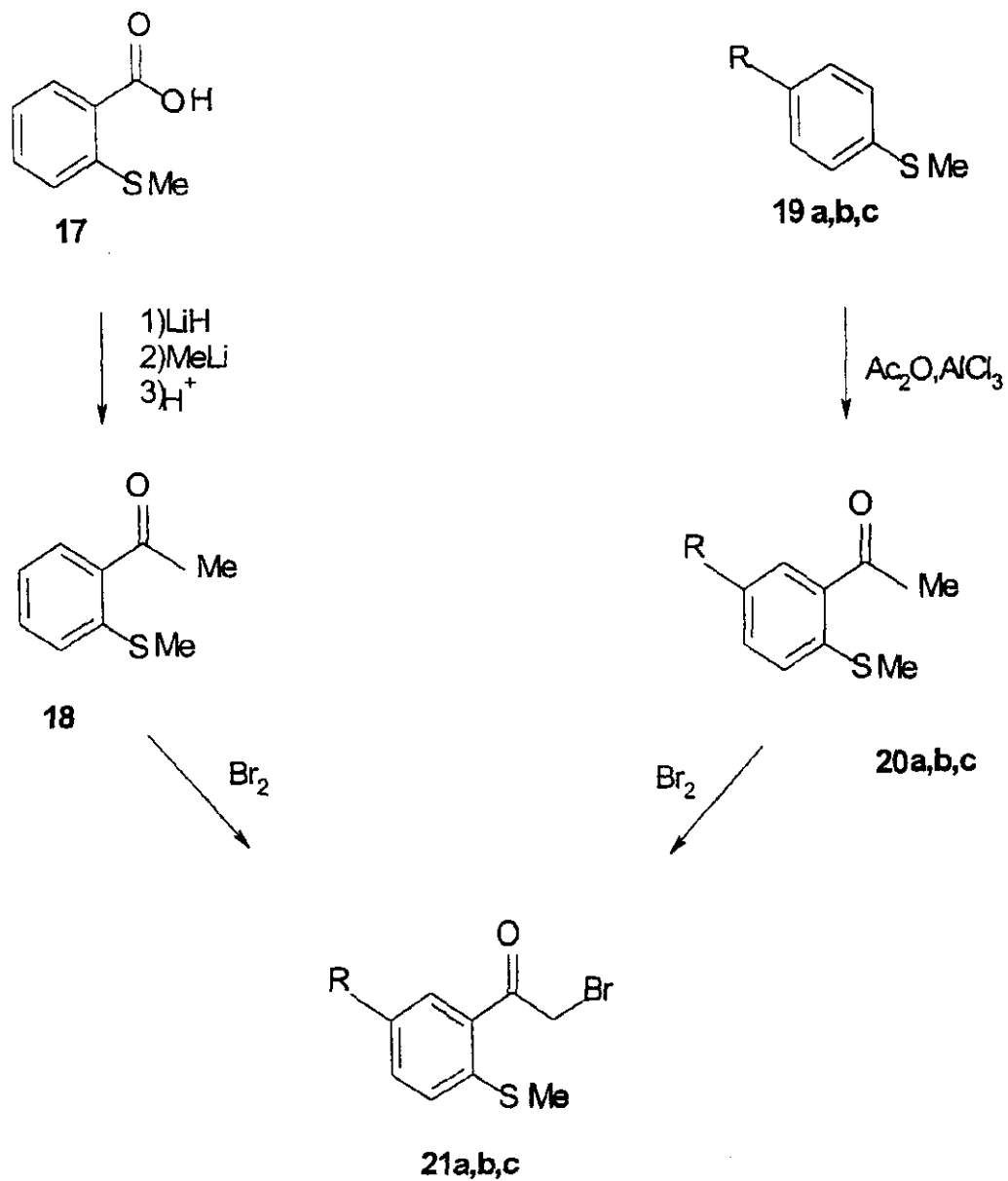
One preferred process for the synthesis of formula (I) products is illustrated in Scheme 2A in its essential steps and in Schemes 2B in detail.

10

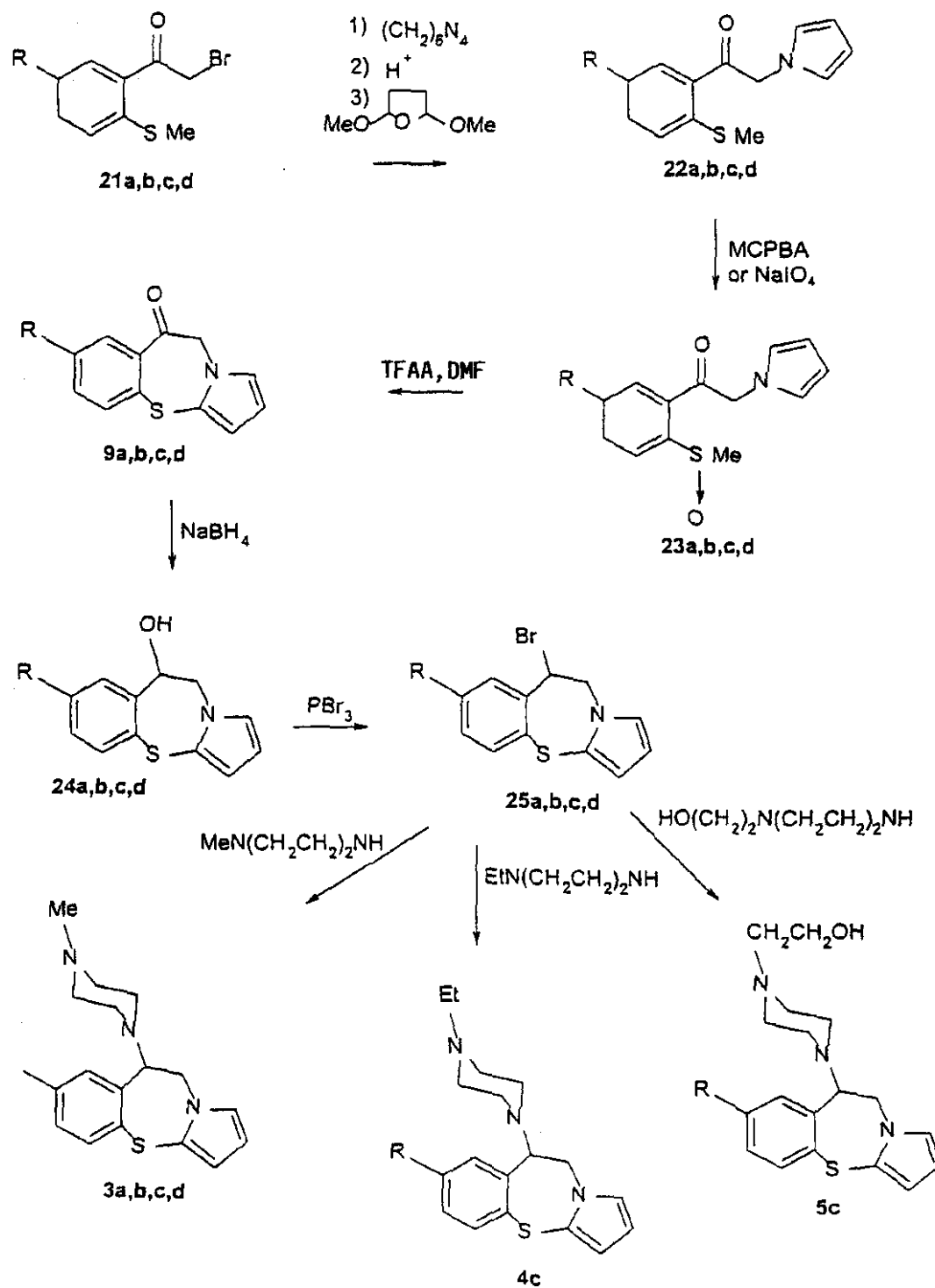


Scheme 2A

SCHEME 2B/1



where R=H,Cl,F
21a=H; 21b=Cl; 21c=F



R = H, Cl, Br, F

SCHEME 2B/2

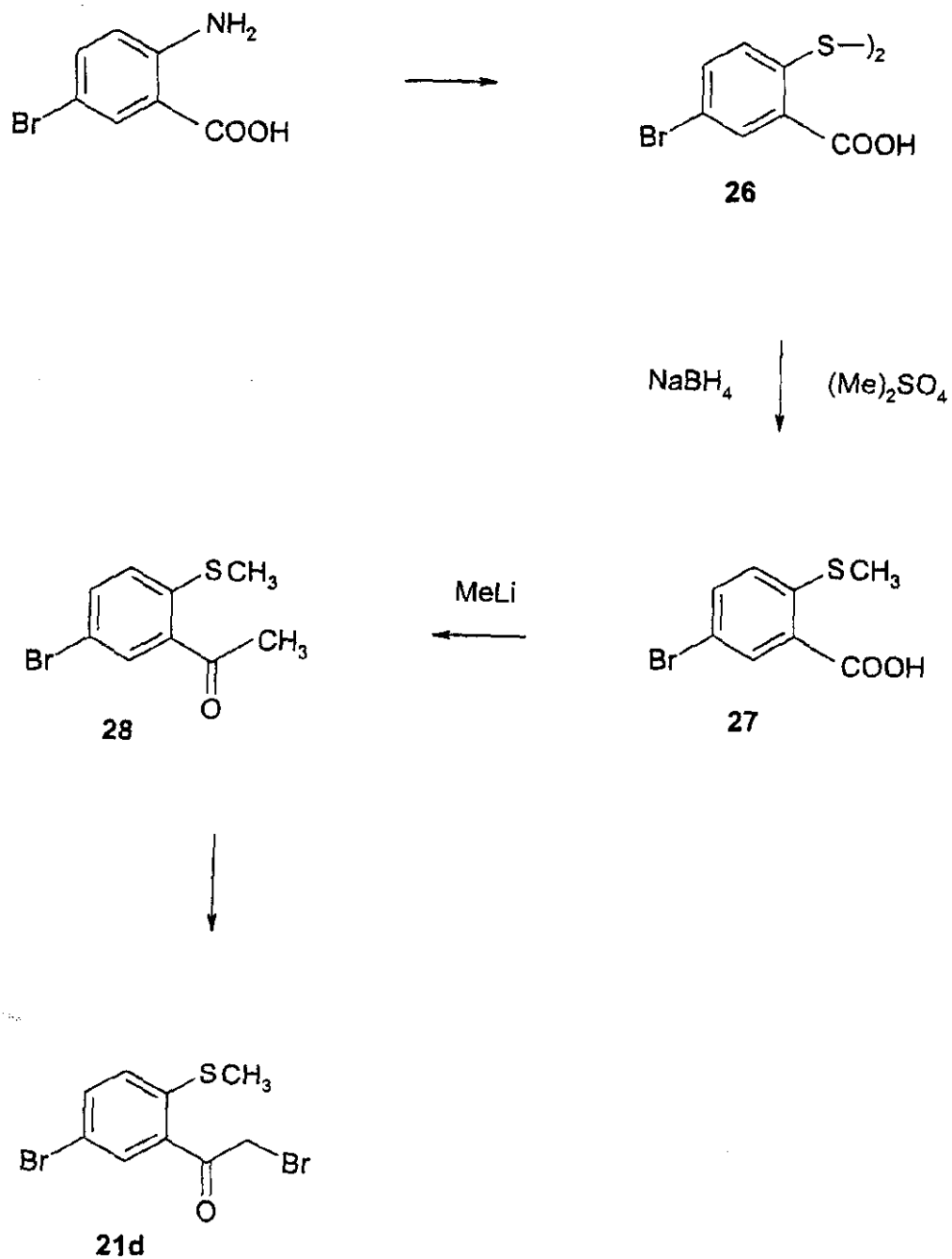
With reference to Schemes 2B/1 and 2B/2, the process involves the formation of the intermediate product (**21a,b,c**. SCHEME 2B/1; bromophenylethanone; **21a**: R = H; **21b**: R = Cl; **21c** = F). As far as the intermediate compound **21d** is concerned, the
5 synthetic path is outlined in the Scheme C below.

The intermediate product (**21a,b,c,d**) is transformed into the corresponding sulphoxide (**23a,b,c,d**). The latter, when subjected to a cyclisation reaction, leads to the formation of the product (**9a,b,c,d**) (pyrrolobenzothiapinone). The cyclisation reaction is
10 conducted in the presence of trifluoroacetic anhydride and dimethylformamide.

This second synthesis method is preferred in that the cyclisation reaction and consequent formation of the thiazepine ring occur with distinctly greater yields.

15 Products (**9a**), (**9b**), (**9c**) and (**9d**), obtained with the different synthesis methods described above are then transformed into a formula (I) derivative by substituting the keto group with a group selected from the definitions given above for the radical R₁.

SCHEME C



It is then always possible to resolve the racemic products, however they are obtained, into the two active isomers by means of fractionated crystallisation of the diastereoisomeric salts obtained by salification with an optically active acid, such as tartaric acid, 5 dibenzoyltartaric acid, camphoric acid, or camphor-sulphonic acid.

A detailed description of the above-mentioned synthesis methods is presented in the experimental part.

A further subject of the invention described herein consists in pharmaceutical compositions comprising formula (I) 10 derivatives in combination with pharmacologically acceptable excipients and vehicles and optionally with additional active ingredients which are useful in the treatment of psychoses.

Examples of such optional active ingredients are the phenothiazines (e.g. chlorpromazine), the thioxanthenes (e.g. 15 chlorprothixene, thiorixene), the butyrophenones (e.g. alogaperidol), the dihydroindolones (e.g. molindone), the dibenzoxazepines (e.g. loxapine), the Rauwolfia alkaloids, etc.

Formula (I) compounds can be formulated in solid, liquid or semisolid pharmaceutical forms. Examples of liquid formulations are 20 injectable solutions or solutions for oral use, syrups, elixirs, suspensions and emulsions. Examples of solid forms are tablets, capsules, microcapsules, powders and granulates.

Formula (I) compounds are endowed with a pronounced neuroleptic and antipsychotic activity. This enables them to be used 25 in the prevention and treatment of psychoses such as schizophrenia,

paranoid states, manic-depressive states, affective disorders, social withdrawal, personality regression, hallucinations, appetite disorders (anorexia) and related disorders. Additional indications may be analgesia/anaesthesia, neuroleptic anaesthesia, anxiety
5 manifestations in the elderly, and extrapyramidal disturbances. The invention described herein therefore includes the use of formula (I) products in the preparation of medicinal products which are useful for the prevention and treatment of said disorders.

Some of the formula (I) products have an interesting $D_3:D_1$
10 ratio, indicating them useful in the treatment of the negative symptoms of schizophrenia involving the emotional and cognitive spheres such as, for instance, dementia.

As documented in the experimental part, the "atypicality" of the neuroleptic action of formula (I) derivatives makes it possible to treat
15 the above-mentioned pathologies effectively, at the same time reducing to a minimum the extrapyramidal side effects normally associated with the classic antipsychotic agents. The substantial receptor activity that characterises these compounds also makes it possible to considerably reduce the dose necessary to achieve a
20 therapeutic response, thus reducing toxicity and accumulation phenomena. The reduction of the daily dose is an aspect of particular interest in the treatment of chronic diseases such as schizophrenia, which require prolonged exposure to the drug.

Formula (I) compounds can be administered over a dosage
25 range generally varying from 0.02 to 200 mg/kg, depending upon

the severity of the disease to be treated and its acute or chronic component. Doses outside the range indicated are, however, possible in particular conditions, under the supervision of a doctor.

The invention is now illustrated by means of the following examples.

EXPERIMENTAL PART

1. Chemistry

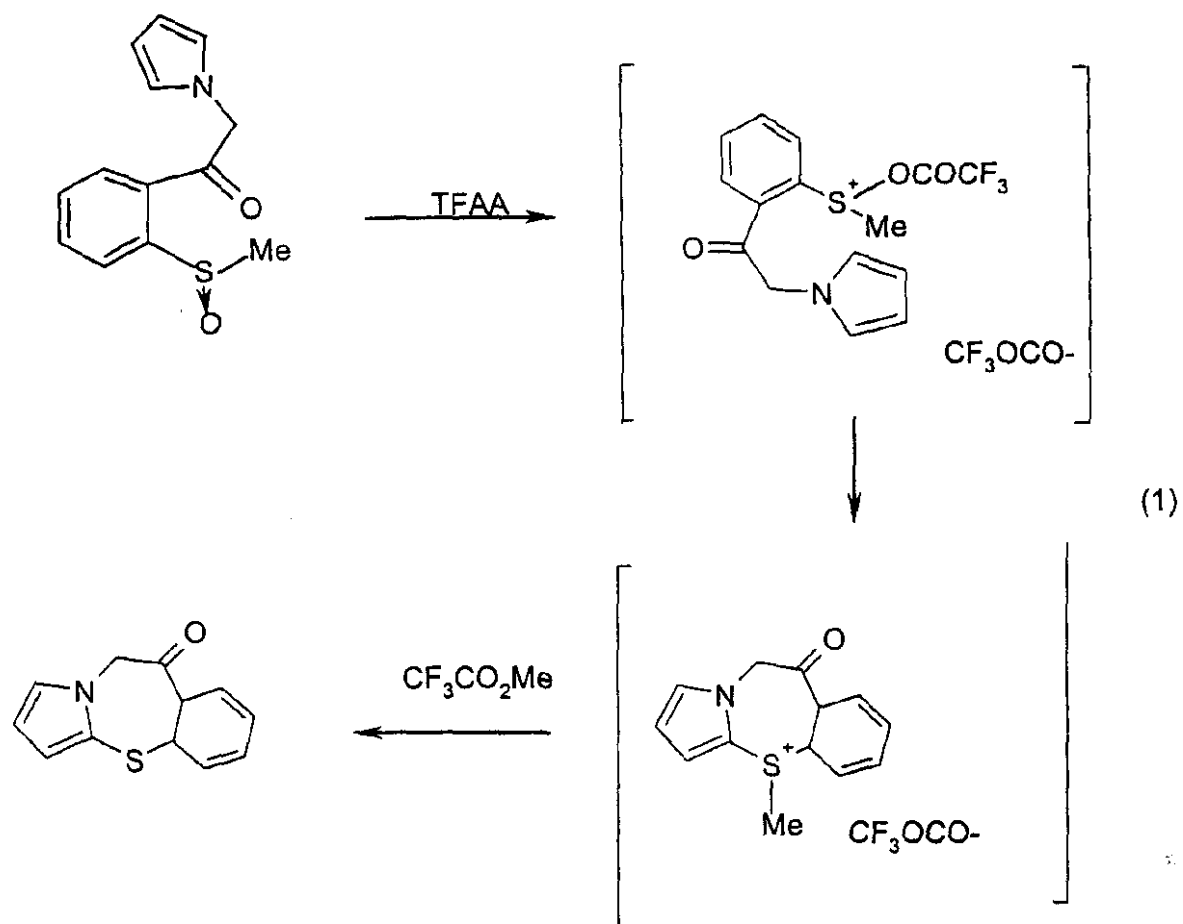
1.1 Synthetic approaches

The synthesis of the new pyrrolo[2,1-b][1,3]benzothiazepine structure was accomplished by adopting the two retrosynthetic approaches described in Schemes 1A and 2A. The synthesis is based on a cyclisation method to obtain the pyrrolobenzothiazepinone intermediate products **9a,b**. Scheme 1A gives our retrosynthetic analysis of compound **9a**. When pyrrolo was treated with copper thiocyanate in methanol, thiocyanation occurred in a few minutes, obtaining 2-thiocyanopyrrolo **11** with good yields. The Grignard reaction with phenylmagnesium bromide (**12**), followed by alkylation with ethyl bromoacetate, produced ester **13** with a high overall yield.

Ester **13** may serve as a starting product in carrying out the cyclisation to **9a**, on the basis of an acylation reaction promoted by copper(I). In fact, dimethyl aluminium methylselenolate was used to obtain selenoester **15**. Like the thioesters, this selenoester could be used in the carbon-carbon bond formation reaction. Consequently, by exposure of **15** to the highly reactive crystalline complex of triflate copper(I) and benzene $[(\text{CuOTf})_2\text{PhH}]$, the tricyclic compound **9a** was

obtained together with ketone **16** and other unidentified reaction products.

Another synthesis method, shown in Scheme 2A, was based on a thionium ion intermediate. This made it possible to prepare the key tricyclic intermediates **9a,b,c,d** in conditions of Pummerer rearrangement, starting from sulphoxides, which in turn were prepared from 1-[2-(methylthio)phenyl]ethanones. As shown in Scheme 2B/1, the key intermediate products **21a,b,c** were prepared by bromination of the corresponding phenylethanones **18** and **20**, which in turn were prepared, respectively, by reaction of methyl lithium and the lithium salt of 2-(methylthio)benzoic acid **17**, or from (methylthio)benzene, 1-chloro- or 1-fluoro-4-(methylthio)benzene **19a,b,c**, with a Friedels-Crafts reaction with acetic anhydride. Subsequently (SCHEME 2B/2), the bromophenylethanones **21a,b,c,d** were transformed into the pyrrole derivatives **22a,b,c,d**. Oxidation, for example with sodium periodate or 3-chloroperbenzoic acid (MCPBA) (**23a,b,c,d**), followed by exposure of these sulphoxides to trifluoroacetic anhydride produced the ketones **9a,b,c,d** with a yield of 40%. The mechanism proposed for the cyclisation stage is given in Scheme 2B/3.



Scheme

The "interrupted" Pummerer rearrangement started with activation of the oxygen of the sulfoxide followed by attachment of the pyrrole ring to the sulphur which shifted the trifluoroacetate ion. The sulphonium salt then underwent the shift of the methyl group, generating the new heterocyclic system and methyltrifluoroacetate. Starting from the ketones **9a,b,c,d** (Fig. 2B/2), the piperazine ring was introduced according to a standard method. Reduction of ketones **9a,b,c,d** then yielded the alcohols **(±)-24a,b,c,d** which were transformed into the corresponding derivatives **(±)-25a,b,c,d** by means of PBr₃. By treating **(±)-25a,b,c,d** with N-methylpiperazine, the end product **(±)-3a,b,c,d** was obtained. The thiazepine **(±)-3a,b** was resolved into the enantiomorphs **(+)-3b** and **(-)-3b** by means of HPLC, using a Chiralpak AD amylose column, or equivalent means.

1.2 Materials and Methods

The melting points were determined using an Electrothermal 8103 device and were not corrected. The IR spectra were recorded with Perkin-Elmer 398 and FT 1600 spectrophotometers. The ¹H-NMR spectra were recorded with a Bruker 200 MHz spectrometer and a Varian 500 MHz spectrometer with TMS as internal standard; the chemical shift values (δ) are given in ppm and the coupling constants (J) in Hertz. All reactions were carried out in an argon atmosphere. Progress of the reactions was monitored by TLC on silica gel plates (Riedel-de-Haen, Art. 37341). Merck silica gel (Kieselgel 60) was used for the chromatography columns (70-230 mesh) and for the flash chromatography columns (230-400 mesh).

Extracts were dried on MgSO_4 and the solvents removed at reduced pressure. The HPLC separation was carried out using a Chiralpak AD Amylose column (097-702-40808) (length x diameter = 250 mm x 10 mm). The elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer, and the results are within 0.4% of the theoretical value, unless otherwise specified. The yields refer to purified, non-optimised products.

1.3 Preparation of the compounds

2-(phenylthio)pyrrole (12)

To a solution of phenyl magnesium bromide (prepared from bromobenzene (0.75 ml) and magnesium chips (0.19 g, 7.8 mmol) in anhydrous THF (20 ml), cooled to 0°C , was slowly added a solution of 2-thiocyanopyrrole 11 (0.5 g, 4.0 mmol) in anhydrous THF (20 ml). After stirring at 0°C for 30 min, the mixture was poured into crushed ice and extracted with ethyl acetate. The organic phase was washed with 20% NH_4Cl , anhydriified and evaporated. The residue was purified by chromatography (35% hexane in chloroform) to give 0.6 g (93% yield) of **12** as colourless prisms: melting point $86-87^\circ\text{C}$ (hexane); IR (CHCl_3) 3420 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.20 (br s, 1H), 7.25-6.85 (m, 5H), 6.92 (m, 1H), 6.55 (m, 1H), 6.31 (m, 1H). Anal. ($\text{C}_9\text{H}_9\text{NS}$): C, H, N.

Ethyl ester of 2-(phenylthio)pyrrole-1-acetic acid (13)

To a mixture of 18-Crown-6 (20 mg, 0.074 mmol) and potassium tertbutoxide (0.166 mg, 1.48 mmol) in anhydrous THF (5 ml) was added a solution of **12** (0.2 g, 1.14 mmol) in anhydrous THF

(5 ml) under nitrogen. After 2 hours at ambient temperature, a solution of ethyl bromoacetate (0.254 ml, 2.28 mmol) in anhydrous THY (1 ml) was added dropwise. After stirring for 30 min at ambient temperature and the addition of 5 ml of water, the solvent was removed at reduced pressure and the residue extracted with EtOAc. The organic layers were washed with a saturated solution of NaCl, anhydriified and evaporated. The residue was chromatographed (30% hexane in chloroform) to give 0.28 g (96% yield) of **13** as colourless prisms: melting point 101-102°C (cyclohexane); IR (CHCl₃) 1760 cm⁻¹; ¹H NMR (CDCl₃) δ 7.25-6.90 (m, 5H); 6.61 (m, 1H), 6.31 (m, 1H), 4.68 (s, 2H), 4.05 (q, 2H, J = 7.0 Hz), 1.14 (t, 3H, J = 7.1 Hz). Anal. (C₁₄H₁₅NO₂S): C, H, N.

Methyl ester of 2-(phenylthio)pyrrole-1-selenoacetic acid (15)

A solution of dimethylaluminium methylselenolate (2.2 mmol) (prepared by heating a solution of trimethylaluminium in toluene with selenium in powder form for 2 hours at reflux temperature under argon) in anhydrous toluene (1.1 ml) was added dropwise to a solution of **13** (0.57 g, 2.2 mmol) in anhydrous dichloromethane (5 ml) cooled to 0°C, under nitrogen. The mixture was agitated at 0°C for 45 min, heated to ambient temperature and stirred for another 45 min. Water (2 ml) was added and the mixture was extracted with EtOAc. The organic layers were washed with a saturated NaCl solution, anhydriified and evaporated. The crude product was purified by distillation (85°C/0.1 mm Hg) to give 0.6 g (97% yield) of **15** as a colourless oil: IR (t.q.) 1720 cm⁻¹; ¹H NMR (CDCl₃) δ 7.24-

6.95 (m, 6H); 6.69 (m, 1H), 6.37 (m, 1H), 4.69 (s, 2H), 2.11 (s, 3H)
m/z 311 (40, M⁺), 188, 155, 109, 91 (100). Anal. (C₁₃H₁₃SeNOS): C,
H, N.

1-[2-(methylthio)phenyl]ethanone (18)

5 To a suspension of lithium hydride (0.57 g, 6.7 mmol) in
anhydrous 1,2-dimethoxyethane (5 ml), stirred vigorously, was
added dropwise a solution of acid **17** (1.0 g, 5.9 mmol) in anhydrous
1,2-dimethoxyethane. The suspension was refluxed for 2,5 hours,
cooled to -10°C and added with methyl-lithium (4.2 ml, 6.7 mmol,
10 1,6 M) in the space of 30 min. The reaction mixture was stirred for 2
hours at ambient temperature. HCl 1N was added to the mixture,
which was extracted with ethyl ether. The organic layers were
washed with a saturated NaCl solution, anhydrified and
concentrated. Chromatography of the crude product (5% benzene in
15 dichloromethane) gave 0.78 g (79% yield) of **18** as colourless prisms,
the spectroscopic data for which were identical to those reported in
the literature.

1-[5-chloro-2-(methylthio)phenyl]ethanone (20b)

A mixture of **19b** (1.0 g, 6.3 mmol), anhydrous aluminium
20 chloride (1.88 g, 13.5 mmol) and carbon sulphide (20 ml) was heated
to reflux under argon and acetic anhydride (0.46 ml, 6.3 mmol) was
added dropwise. After reflux for 4 h, the solution was poured onto
crushed ice and 20 ml of HCl 6N were added. The mixture was
extracted with EtOAc and the organic layers were washed with a
25 saturated NaCl solution, anhydrified and concentrated. The oily

residue was chromatographed (30% hexane in chloroform) to give 0.5 g (40% yield) of **20b** as a waxy solid: IR (t.q.) 1670 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.83 (d, 1H, $J = 2.1\text{ Hz}$); 7.44 (dd, 1H), 7.29 (d, 1H, $J = 8.1\text{ Hz}$), 2.63 (s, 3H), 2.41 (s, 3H). Anal. ($\text{C}_9\text{H}_9\text{ClOS}$): C, H.

5 **2-Bromo-1-[2-(methylthio)phenyl]ethanone (21a).**

The title compound was obtained starting from **18** and following the procedure as described below to obtain **21c**. **21a** was obtained as colorless prism (69% yield): mp $81-82^\circ\text{C}$ (hexanes); IR (nujol) 1690 cm^{-1} , ^1H NMR (CDCl_3) δ 8.00-7.80 (m, 2H), 7.35 (m, 2H),
10 5.53 (s, 2H), 2.27 (s, 3H) Anal. ($\text{C}_9\text{H}_9\text{BrOS}$) C, H

2-Bromo-1-[5-chloro-2(methylthio)phenyl]ethanone (21b).

The title compound was obtained starting from **20b** and following the procedure as described below to obtain **21c**. **21b** was obtained as colorless prism (62% yield); mp $97-98^\circ\text{C}$ (hexanes); IR
15 (CHCl_3) 1685 cm^{-1} , ^1H NMR (CDCl_3) δ 7.98-7.73(m, 3H), 5.57(s, 2H), 2.31(s, 3H).

Anal. ($\text{C}_9\text{H}_8\text{BrClOS}$) C, H.

1-[2-(methylthio)phenyl]-2-pyrrol-1-yl)ethanone (22a)

To a solution of **21a** (2.1 g, 8.6 mmol) in 20 ml of anhydrous
20 DMF, was added hexamethylene tetramine in portions. The solid formed was filtered, washed with chloroform and dried.

The hexamethylenetetrammonium salt thus obtained was added to a concentrated HCl solution (3 ml) in 8 ml of ethanol.

The mixture was stirred for 96 hours in the dark at ambient temperature. The white solid (NH_4Cl) was filtered and the solution vacuum-concentrated.

The residue was crystallised by ethanol, and 2-amino-1-[2-(methyl-thio)phenyl]ethanone hydrochloride was obtained with a yield of 78%; ^1H NMR (DMSO-d_6) δ 8.43 (br s, 2H); 8.11-7.31 (m, 5H), 4.59 (d, 2H, $J = 3.2$ Hz), 2.46 (s, 3H). Anal. ($\text{C}_9\text{H}_{12}\text{ClNOS}$): C, H, N.

The 2-amino-1-[2-(methylthio)phenyl]ethanone hydrochloride was dissolved in an aqueous solution of sodium acetate, glacial acetic acid and 2.5 dimethoxy tetrahydrofuran. After stirring for 15 min at 100°C , the mixture was cooled and extracted with ethyl acetate. The organic layer was washed with NaHCO_3 , dried and evaporated. The crude product was chromatographed (CHCl_3) to give **22a** with a yield of 50%; melting point $113\text{-}114^\circ\text{C}$ (hexane); IR (nujol) 1690 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.74-7.23 (m, 4H), 6.66 (m, 2H), 6.21 (m, 2H), 5.25 (d, 2H, $J = 3.4$ Hz), 2.44 (s, 3H). Anal. ($\text{C}_{13}\text{H}_{13}\text{NOS}$): C, H, N.

1-[5-chloro-2-(methylthio)phenyl]-2-pyrrol-1-yl]ethanone (**22b**)

Starting from **21b** (5.58 g, 20.0 mmol), 2-amino-1-[5-chloro-2-(methyl-thio)phenyl]ethanone hydrochloride was obtained using the procedure described in the previous example: yield 75%; ^1H NMR (DMSO-d_6) δ 8.41 (br s, 2H); 8.10-7.28 (m, 3H), 4.48 (d, 2H, $J = 3.2$ Hz), 2.42 (s, 3H). Anal. ($\text{C}_9\text{H}_{11}\text{Cl}_2\text{NOS}$): C, H, N.

Starting from 2-amino-1-[5-chloro-2-(methylthio)phenyl]ethanone hydro-chloride, the titre compound was obtained as colourless prisms using the procedure described to obtain **22a**: 51% yield; melting point 124-125°C (hexane); IR (nujol) 1720 cm⁻¹; ¹H NMR (CDCl₃) δ 7.62 (d, 1H, J = 2.3 Hz); 7.45 (dd, 1H, J = 8.2, 2.3 Hz), 7.29 (d, 1H, J = 8.2 Hz), 6.65 (m, 2H), 6.22 (m, 2H), 5.21 (s, 2H), 2.43 (s, 3H); ¹³C NMR (CDCl₃) δ 194.2, 140.6, 134.5, 132.4, 130.1, 128.9, 127.7, 121.8, 109.2, 56.6, 16.6. Anal. (C₁₃H₁₂ClNOS): C, H, N.

1-[2-(methylsulphinyl)phenyl]-2-pyrrol-1-yl)ethanone (23a)

To a suspension of sodium periodate (0.55 g, 2.6 mmol) in methanol (7 ml) and water (1.4 ml) was added a solution of **22a** (0.6 g, 2.6 mmol) in methanol (2 ml). After stirring for 24 hours at ambient temperature the sodium iodate was removed by filtration and the filtrate was evaporated. The residue was chromatographed (5% EtOAc in dichloromethane) to give 0.59 g of **23a** (92% yield) as colourless prisms: melting point 174-175°C (ethanol); IR (nujol) 1710, 1090 cm⁻¹; ¹H NMR (CDCl₃) δ 8.42-7.64 (m, 4H), 6.66 (m, 2H), 6.27 (m, 2H), 5.44 (0.5 ABq, 1H, J = 18.0 Hz), 5.27 (0.5 ABq, 1H, J = 18.0 Hz), 2.80 (s, 3H). Anal. (C₁₃H₁₃NO₂S): C, H, N.

1-[5-chloro-2-(methylsulphinyl)phenyl]-2-pyrrol-1-yl)ethanone (23b)

The titre compound was prepared starting from **22b** (1.1 g, 4.45 mmol) using the procedure described above for **23a**: colourless prisms (89% yield): melting point 218-219°C (ethanol); IR (nujol)

1710, 1080 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.37 (d, 1H, $J = 8.0$ Hz); 7.85 (m, 2H), 6.66 (m, 2H), 6.28 (m, 2H), 5.40 (0.5 Abq, 1H, $J = 17.7$ Hz), 5.25 (0.5 ABq, 1H, $J = 17.8$ Hz), 2.79 (s, 3H); ^{13}C NMR (CDCl_3) δ 193.4, 149.6, 136.9, 134.7, 132.5, 128.8, 127.0, 121.8, 109.8, 55.7, 44.3. Anal. ($\text{C}_{13}\text{H}_{12}\text{ClNO}_2\text{S}$): C, H, N.

9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepin-9-one (9a)

Method A: to a highly reactive solution of the crystalline complex of triflate copper(I) and benzene (0.81 g, 1.6 mmol) in anhydrous benzene (20 ml), cooled to 0°C , was added a solution of selenoester **15** (0.5 g, 1.6 mmol) in anhydrous benzene (11 ml) and the mixture was left to stir at ambient temperature for 16 hours. Ethyl ether (10 ml) was added, the organic phase was washed with ammonia 6N, anhydriified and concentrated. The crude product was chromatographed (5% hexane in dichloromethane) to give 51 mg of **9a** (12% yield) as colourless prisms. Ketone **16** (55% yield) was also recovered as a dense oil. Compound **9a**: melting point $94-95^\circ\text{C}$ (hexane); IR (CDCl_3) 1690 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.14-7.30 (m, 4H); 6.88 (m, 1H), 6.42 (m, 1H), 6.12 (m, 1H), 5.15 (s, 2H); ^{13}C NMR (CDCl_3) δ 190.9, 136.1, 133.3, 132.3, 130.8, 127.6, 123.9, 120.2, 114.4, 109.2, 57.6. MS m/z 265 (10, M^+), 215 (100), 187, 154, 115, 97. Anal. ($\text{C}_{12}\text{H}_9\text{NOS}$): C, H, N.

Compound **16**: IR (t.q.) 1670 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.22-6.81 (m, 6H); 6.70 (m, 1H), 6.42 (m, 1H), 4.61 (s, 2H), 2.20 (s, 3H). MS m/z 231 (100, M^+). Anal. ($\text{C}_{13}\text{H}_{13}\text{NOS}$): C, H, N.

Method B: trifluoroacetic anhydride (1.0 ml, 7.4 mmol) was added dropwise to just distilled N,N-dimethylformamide (8 ml) cooled to 0°C. After stirring for 20 min at 0°C, a solution of **23a** (1.0 g, 4.0 mmol) was added in just distilled N,N-dimethyl formamide (24 ml) and after 15 min at 0°C and 1 hour at ambient temperature, the pH of the dark red solution was brought to 7 with NaOH 1N and the mixture was stirred for another 30 min. Extraction with dichloromethane, anhydrification of the extracts and evaporation of the solvent gave an oily residue which was chromatographed (30% hexane in chloroform). Compound **9a** was obtained with a 45% yield.

7-chloro-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepin-9-one (9b)

The titre compound was obtained with a yield of 42%, as colourless prisms, starting from **23b** and adopting the procedure as described for **9a** (Method B): melting point 106-107°C (hexane); IR (CDCl₃) 1690 cm⁻¹; ¹H NMR (CDCl₃) δ 8.14 (d, 1H, J = 2.2 Hz); 7.49 (d, 1H, J = 8.1 Hz), 7.38 (dd, 1H, J = 8.0, 2.3 Hz), 6.88 (m, 1H), 6.43 (m, 1H), 6.12 (m, 1H), 5.14 (s, 2H); ¹³C NMR (CDCl₃) δ 189.7, 138.3, 133.3, 137.3, 134.1, 133.1, 132.2, 131.9, 124.1, 119.5, 114.7, 109.5, 57.3. MS m/z 250 (20, M⁺), 249 (100), 221, 216, 188, 158, 110. Anal. (C₁₂H₈ClNOS): C, H, N.

(±)-9,10-dihydro-9-hydroxypyrrolo[2,1-b][1,3]benzothiazepine (24a)

To a solution of **9a** (61 mg, 0.23 mol) in anhydrous methane (1 ml), cooled to 0°C and under nitrogen, were added aliquots of sodium borohydride (80 mg, 0.23 mmol). After stirring for 1 hour at 0°C, the reaction was stopped with water (1 ml) and the mixture
5 extracted with EtOAc. The organic layers were washed with brine, anhydriified and concentrated. The residue was chromatographed (15% EtOAc in dichloromethane) to give **24a** (64 mg, 92% yield) as colourless prisms: melting point 101-102°C (ethanol); IR (nujol) 3300 cm⁻¹; ¹H NMR (CDCl₃) δ 7.47-7.12 (m, 4H), 6.86 (m, 1H), 6.33 (m,
10 1H), 6.02 (m, 1H), 5.08 (m, 1H), 4.89 (dd, 1H, J = 13.9, 1.7 Hz), 4.28 (dd, 1H, J = 13.9, 6.0 Hz), 2.05 (d, 1H, J = 9.6 Hz). Anal. (C₁₂H₁₁NOS): C, H, N.

(±)-7-chloro-9,10-dihydro-9-hydroxypyrrolo[2,1-b][1,3]benzothiazepine (24b)

15 The titre compound was obtained starting from **9b** (112 mg, 0.45 mmol) using the procedure described above: 88% yield; melting point 118-119°C (ethanol); IR (CHCl₃) 3300 cm⁻¹; ¹H NMR (CDCl₃) δ 7.48 (d, 1H, J = 2.1 Hz); 7.32 (d, 1H, J = 8.0 Hz), 7.15 (dd, 1H, J = 8.1, 2.1 Hz), 6.88 (m, 1H), 6.34 (m, 1H), 6.11 (m, 1H), 5.02 (m, 1H),
20 4.85 (dd, 1H, J = 13.9, 1.9 Hz), 4.29 (dd, 1H, J = 13.9, 6.6 Hz), 2.10 (dd, 1H, J = 9.6 Hz). Anal. (C₁₂H₁₀ClNOS): C, H, N.

(±)-9-bromo-9,10-dihdropyrrolo[2,1-b][1,3]benzothiazepine (25a)

To a solution of **24a** (0.26 g, 1.0 mmol) in anhydrous ethyl ether (4 ml) was added dropwise a solution of PBr₃ (0.13 g, 0.5
25 mmol) in anhydrous ethyl ether (1 ml) and the reaction mixture was

kept at reflux temperature for 2 hours under nitrogen. Anhydrous ethanol was added (0.2 ml) and the resulting solution was heated to reflux temperature for another hour. Five ml of an aqueous solution of 5% Na_2CO_3 were then added, the organic phase was separated, anhydrified and evaporated. The crude product was chromatographed (hexane and chloroform 1:1) to give **25a** (0.2 g, 64% yield) as colourless prisms: melting point 115-116°C (cyclohexane); ^1H NMR (CDCl_3) δ 7.46-7.09 (m, 4H); 6.93 (m, 1H), 6.39 (m, 1H), 6.12 (m, 1H), 5.75 (dd, 1H, $J = 6.9, 2.6$ Hz), 5.07 (dd, 1H, $J = 14.7, 2.6$ Hz), 4.61 (dd, 1H, $J = 14.7, 6.9$ Hz). Anal. ($\text{C}_{12}\text{H}_{10}\text{BrNOS}$): C, H, N.

($\pm$)-9-bromo-7-chloro-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine (25b)

The titre compound was obtained starting from **24b** (0.31 g, 1.6 mmol) using the procedure described above: 51% yield; melting point 106-107°C (cyclohexane); ^1H NMR (CDCl_3) δ 7.45 (d, 1H, $J = 2.1$ Hz); 7.27 (d, 1H, $J = 8.6$ Hz), 7.11 (dd, 1H, $J = 8.6, 2.1$ Hz), 6.92 (m, 1H), 6.39 (m, 1H), 6.12 (m, 1H), 5.63 (dd, 1H, $J = 7.0, 2.3$ Hz), 5.06 (dd, 1H, $J = 14.4, 2.3$ Hz), 4.61 (dd, 1H, $J = 14.0, 7.0$ Hz). ^{13}C NMR (CDCl_3) δ 139.9, 134.1, 133.2, 131.7, 131.5, 128.9, 125.6, 119.6, 114.6, 108.1, 51.2, 51.0. Anal. ($\text{C}_{12}\text{H}_9\text{BrClNOS}$): C, H, N.

Example 1**(±)-9-(4-methylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-b][1,3]benzo-thiazepine (3a)**

A mixture of **25a** (0.65 g, 2.0 mmol) and N-methylpiperazine (1.1 ml, 10.0 mmol) was heated to 130°C for 2 hours under argon, cooled, poured onto crushed ice and extracted with ethyl ether. The organic extracts collected were washed with brine, anhydri-fied and concentrated. The residue was chromatographed (EtOAc) to give 0.45 g (75% yield) of **3a** as colourless prisms: melting point 206-207°C (hexane); ¹H NMR (CDCl₃) δ 7.49-7.09 (m, 4H); 6.87 (m, 1H), 6.29 (m, 1H), 4.68 (dd, 1H, J = 14.4, 8.6 Hz), 4.51 (dd 1H, J = 14.4, 3.7 Hz), 2.56-2.34 (m, 8H), 2.23 (s, 3H); ¹³C NMR (CDCl₃) δ 138.1, 134.6, 132.9, 130.4, 127.3, 126.9, 123.9, 121.7, 113.3, 107.7, 66.1, 55.9, 48.8, 46.6. 46.1. MS m/z 299 (100, M⁺), 219, 200, 167, 149, 113. Anal. (C₁₇H₂₁N₃S): C, H, N.

Example 2**(±)-7-chloro-9-(4-methylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine (3b) (ST1455)**

The titre compound was obtained starting from **25b** (0.3 g, 0.95 mmol) using the procedure described above. **3b** was obtained as colourless prisms (68% yield): melting point 210-211°C (hexane); ¹H NMR (CDCl₃) δ 7.51 (d, 1H, J = 2.4 Hz); 7.30 (d, 1H, J = 8.5 Hz), 7.06 (dd, 1H, J = 8.5, 2.4 Hz), 6.86 (m, 1H), 6.29 (m, 1H), 6.05 (m, 1H), 4.71 (dd, 1H, J = 14.0, 8.6 Hz), 4.45 (dd, 1H, J = 14.0, 3.4 Hz), 3.95 (dd, 1H, J = 8.6, 3.4 Hz), 2.65-2.25 (m, 8H), 1.42 (s, 3H); ¹³C

NMR (CDCl₃) δ 140.1, 133.2, 133.0, 132.4, 131.6, 127.3, 123.9, 121.1, 113.6, 107.9, 65.9, 55.8, 55.7, 47.7, 45.9, 44.9, 26.8. MS m/z 333 (10, M⁺), 250, 233 (100), 201, 166, 139. Anal. (C₁₇H₂₀ClN₃S): C, H, N. The dihydrochloride salt (named hereinafter

5 **ST1468**) was obtained by dissolving an analytical sample in HCl 1N in methanol. The solvent was evaporated and the residue recrystallised (methanol and ethyl ether 1:1). Anal. (C₁₇H₂₂Cl₃N₃S), C, H, N.

Example 3

10 **Semipreparatory chiral separation of ($\pm$)-3b**

First of all, the hydrochloride salt of ($\pm$)-**3b** was purified on a short column filled with silica gel, using dichloromethane and methanol (9:1) as the eluent. The purified solvent was converted to the free base. Evaporation of the solvent gave an oily residue which

15 was dissolved in isopropanol and the solution was diluted with hexane until the 95:5 ratio was obtained. For the separation of the enantiomers, a 10-15 mg/ml concentration of the racemic mixture was made. A mixture of hexane (plus 0.1% triethylamide) and isopropanol was used as the mobile phase.

20 A gradient-type mixer maintained the ratio between the solvents hexane and isopropanol at 95:5. Injection amounts were 100 μ l per injection. The enantiomers were collected using a fraction collector. Only fractions with a signal above 10% (10 mV) of the total scale were collected. The amounts with signals below 10% were

25 collected separately and used for a second purification. The purity of

both enantiomers was determined by weighing the trace peaks separately.

(+)-**3b**: ^1H NMR (500 Mhz, CDCl_3) δ 7.52 (d, 1H, $J = 2.4$ Hz); 7.32 (d, 1H, $J = 8.3$ Hz), 7.09 (dd, 1H, $J = 2.4, 8.3$ Hz), 6.88 (m, 1H), 6.30 (m, 1H), 6.07 (m, 1H), 4.71 (dd, 1H, $J = 8.8, 14.2$ Hz), 4.50 (dd, 1H, $J = 3.9, 14.7$ Hz), 3.97 (dd, 1H, $J = 3.4, 8.8$ Hz), 2.55 (m, 4H), 2.40 (m, 4H), 2.27 (s, 3H); ^{13}C NMR (500 MHz, CDCl_3) δ 139.9, 133.0, 132.9, 132.3, 131.6, 127.3, 123.8, 121.0, 113.5, 107.9, 88.2, 65.8, 55.6, 48.6, 45.9, 45.8; purity (ee) 94.6%; $[\alpha]_{\text{D}} = +46.0^\circ$ (c 0.48, MeOH). The respective dihydrochloride, obtained as in the case of compound ($\pm$)**3b**, was named **ST1469**.

(-)-**3b**: ^1H NMR (500 Mhz, CDCl_3) δ 7.53 (d, 1H, $J = 2.3$ Hz); 7.32 (d, 1H, $J = 8.3$ Hz), 7.09 (dd, 1H, $J = 6.8$ Hz), 6.88 (m, 1H), 6.30 (m, 1H), 6.07 (m, 1H), 4.71 (dd, 1H, $J = 9.3, 14.5$ Hz), 4.48 (dd, 1H, $J = 3.4, 14.2$ Hz), 3.98 (dd, 1H, $J = 2.9, 8.8$ Hz), 2.49 (m, 8H), 2.27 (s, 3H); ^{13}C NMR (500 MHz, CDCl_3) δ 140.0, 133.0, 132.9, 132.3, 131.6, 127.3, 123.8, 121.0, 113.5, 107.9, 88.2, 65.8, 55.6, 48.6, 45.9, 45.8; purity (ee) 98%; $[\alpha]_{\text{D}} = -47.9^\circ$ (c 0.54, MeOH). The respective dihydrochloride, obtained as in the case of compound ($\pm$)**3b**, was named **ST1470**.

Example 4

($\pm$)-7-Fluoro-9-(4-methylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine (**3c**) (**ST1456**)

The synthesis of the (**3c**) was been performed as described in Scheme 2B/1 and 2B/2 where c = F.

1-[5-Fluoro-2-(methylthio)phenyl]ethanone (20c).

A mixture of 4-fluorothioanisole (**19c**) (4 g, 28.13 mmol), anhydrous aluminium chloride (8.40 g, 63.02 mmol) and carbon disulphide (89 ml) was heated at reflux under argon atmosphere, and acetic anhydride (2.65 ml, 28.07 mmol) was added dropwise in 2 h. After refluxing for 24h, the solution was poured into crushed ice, water (62.48 ml) and concentrated hydrochloric acid (2.68 ml). The organic phase was separated and water extracted with dichloromethane (3×30 ml), the organic layers were washed with brine, dried and concentrated. The oily residue was chromatographed (50% petroleum ether 40-60° in dichloromethane) to afford **20c** (2.98g) as a colourless crystalline solid, mp 82.0-84.3°C (58% yield). ¹H NMR (CDCl₃) δ 7.49-7.43 (dd, 1H, J=9.23, 2.44 Hz); 7.29-7.11 (m, 2H); 2.57 (s, 3H); 2.39 (s, 3H).

2-Bromo-1-[5-fluoro-2-(methylthio)phenyl]ethanone (21c).

To a stirring solution of **20c** (2.07 g, 11.34 mmol), carbon tetrachloride (62 ml) and glacial acetic acid (2.07 ml) was added at room temperature a solution of bromine (μL 546.6, 10.66 mmol) in carbon tetrachloride (34 ml). The first drop was added and after 20 minutes the solution was added dropwise in 4 hours. After stirring for 16 hours the solvent was distilled and to the residue was added water and solid sodium bicarbonate (to pH 7), the organic phase was separated and water extracted with dichloromethane (3×30 ml), the organic layers were dried and evaporated. The crude product was chromatographed (70% petroleum ether 40-60° in

dichloromethane) to give 1.90g of **21c** as a yellowish solid (64% yield). ¹H NMR (CDCl₃) δ 7.47-7.42 (dd, 1H, J=8.85, 2.84 Hz); 7.38-7.18(m, 2H); 4.42 (s, 2H); 2.43 (s, 3H).

1-[5-Fluoro-2-(methylthio)phenyl]-2-(pyrrol-1-yl)ethanone (22c).

5 To a stirring solution of hexamethylenetetramine (3.18 g, 22.70 mmol) in chloroform (29.6 ml) at room temperature was added dropwise in 5 minutes a solution of **21c** (1.90 g, 7.20 mmol) in chloroform (16 ml). As soon as the solid formed the solution was rapidly filtered and the desired product was collected as a yellow
10 amorphous solid that was washed with chloroform, dried and used for the following reaction; (99% yield).

A suspension of 1-[5-fluoro-2-(methylthio)phenyl]ethanon-2-hexaminium bromide (1.62 g, 4.02 mmol) in methanol (13.3 ml) was warmed to 0°C and was added of concentrated hydrochloric acid
15 (1.86 ml). The mixture was stirred for 96 hours in the dark at room temperature. The white solid (ammonium chloride) was removed by filtration and the obtained solution was evaporated. The residue was recrystallised from ethanol to give 2-amino-1-[5-fluoro-2-(methylthio)phenyl]ethanone hydrochloride as a yellow solid, that
20 was used in the next step without further purification. (98% yield).

To a solution of 2-amino-1-[5-fluoro-2-(methylthio)phenyl]ethanone hydrochloride (4.54 g, 19.27 mmol) in water (29 ml), heated at 90°C, were added trihydrated sodium acetate (2.62 g, 19.27 mmol), glacial acetic acid (17 ml) and 2,5-
25 dimethoxytetrahydrofuran (2.40 ml, 18.50 mmol). After 20 seconds

at 90-100°C the mixture was cooled and extracted with ethyl acetate. The organic layers were washed with a 20% solution of sodium bicarbonate and brine, dried and evaporated. The residue was chromatographed (50% petroleum ether 40-60° in
5 dichloromethane) to afford 2.07g of **22c** as white crystals mp 133.2-134.0°C (50% yield). ¹H NMR (CDCl₃) δ 7.39-7.15 (m, 3H); 6.66-6.65 (m, 2H); 6.22-6.20 (m, 2H); 5.20 (s, 2H); 2.42 (s, 3H). MS m/z 252 (M⁺⁺H), 234, 202 (100), 183, 169, 154, 141, 126, 109, 80.

1-[5-Fluoro-2-(methylsulfinyl)phenyl]-2-(pyrrol-1-yl)ethanone

10 **(23c).**

To a stirred cooled solution of 1-[5-Fluoro-2-(methylthio)phenyl]-2-(pyrrol-1-yl)ethanone (**22c**) (1.76 g, 7.06 mmol) in dichloromethane (12 ml) was added dropwise in 30 minutes a solution of m-chloroperbenzoic acid (71.5% grade, 1.70 g, 7.06 mmol) in dichloromethane (10 ml). After stirring for 45 minutes
15 at 0°C, the mixture was treated with a 5% solution of sodium carbonate in water (41 ml) and was stirred for 15 minutes at room temperature. The organic phase was separated and water was extracted with dichloromethane (3×10 ml). The organic layers were
20 dried and evaporated, the residue was chromatographed (10% dichloromethane in ethyl acetate) to afford 1.02 g of **23c** as white crystals that darkened rapidly (64% yield). ¹H NMR (CDCl₃) δ 8.42-8.35 (m, 1H); 7.61-7.51 (m, 2H); 6.68-6.62 (m, 2H); 6.26-6.24 (m, 2H); 5.41-5.17 (q, 2H, J=31.32, 17.87 Hz); 2.77 (s, 3H).

**7-Fluoro-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepin-9-one
(9c).**

Trifluoroacetic anhydride (1.02 ml) was added dropwise under argon atmosphere to a freshly distilled N,N-dimethylformamide (8 ml) cooled to 0°C. After stirring for 20 minutes at 0°C a solution of **23c** (109 g, 4.12 mmol) in N,N-dimethylformamide (29 ml) was added. After 15 minutes at room temperature water (41 ml) was added to the dark yellow solution and pH was adjusted to 7 with sodium acetate, the mixture obtained was stirred at room temperature for 1 night. Extraction with dichloromethane, drying of the extracts, and evaporation of the solvent gave an oily residue which was chromatographed (30% petroleum ether 40-60° in dichloromethane). The compound **9c** was crystallised from n-hexane as yellowish crystals mp 133.8-134.2° C (20% yield). ¹H NMR (CDCl₃) δ 7.82-7.76 (m, 1H); 7.55-7.49 (m, 1H); 7.18-7.09 (m, 1H); 6.88-6.87 (m, 1H); 6.42-6.40 (m, 1H); 6.12-6.09 (m, 1H); 5.14 (s, 2H). MS m/z 233 (100) (M⁺), 205, 200, 172, 126.

(±)-7-Fluoro-9,10-dihydro-9-hydroxypyrrolo[2,1-b][1,3]benzothiazepine (24c).

To a solution of **9c** (0.037 g 0.16 mmol) in dry tetrahydrofuran (0.5 ml) and dry methanol (0.7 ml), cooled to 0°C under argon atmosphere, was added in portions sodium borohydride (0.09 g, 0.16 mmol). After stirring for 1 hour at 0°C the reaction was quenched with a saturated solution of ammonium chloride (1 ml), the solvent was removed and the mixture was extracted with ethyl

acetate (3×2 ml). The organic layers were dried and evaporated, the crude product was chromatographed (30% petroleum ether 40-60° in dichloromethane) to give **24c** 0.036 g (96% yield). ¹H NMR (CDCl₃) δ 7.40-7.33 (m, 1H); 7.24-7.18 (m, 1H); 6.93-6.84 (m, 2H); 6.33-6.31 (m, 1H); 6.11-6.08 (m, 1H); 5.12-5.04 (m, 1H); 4.91-4.83 (dd, 1H, J=14.22, 2.25 Hz); 4.34-4.24 (dd, 1H, J=14.02, 6.51 Hz); 2.09-2.04 (d, 1H, J=9.83 Hz).

(±)-9-Bromo-7-fluoro-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine (25c).

To a solution of **24c** (0.17 g 0.71 mmol) in dry ethyl ether (3 ml) was added dropwise a solution of phosphorus tribromide (μL 33.5, 0.36 mmol) in dry ethyl ether (0.7 ml); the reaction mixture was refluxed for 2 hours under argon atmosphere. After cooling to room temperature dry ethanol (μL 143) was added and the resulting solution was heated at reflux for 1 hour. Then 4 ml of aqueous sodium carbonate was added; the organic phase was separated, dried and evaporated. The crude product was chromatographed (50% petroleum ether 40-60° in dichloromethane) to give 0.103 g of pure **25c** (48% yield). ¹H NMR (CDCl₃) δ 7.35-7.16 (m, 2H); 6.92-6.82 (m, 2H); 6.39-6.37 (m, 1H); 6.13-6.09 (m, 1H); 5.69-5.64 (m, 1H); 5.10-5.01 (dd, 1H, J=14.57, 2.65 Hz); 4.70-4.59 (dd, 1H, J=14.88, 7.05 Hz).

Example 5**(±)-7-Fluoro-9-(4-methylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1b][1,3]benzothiazepine(3c) ST1456.**

A mixture of **25c** (0.05 g, 0.18 mmol) and N-methylpiperazine
5 (1 ml) was heated at 140°C for 17 hours under argon atmosphere.
The reaction mixture was then cooled, diluted with ethyl acetate (30
ml) and washed with brine. The organic layers were dried,
evaporated and the oily residue was chromatographed (10%
triethylamine in ethyl acetate) to afford 0.037 g of **3c** as a colourless
10 solid mp 213-214°C. (63% yield). ¹H NMR (CDCl₃) δ 7.37-7.26 (m,
2H); 6.85-6.76 (m, 2H); 6.29-6.27 (m, 1H); 6.06-6.03 (m, 1H); 4.78-
4.67 (m, 1H); 4.49-4.40 (dd, 1H, J=14.19, 3.48 Hz); 3.99-3.93 (dd,
1H, J=8.97, 3.39 Hz); 2.64-2.37 (m, 8H); 2.25 (s, 3H). MS m/z 318
(100) (M⁺+H), 277, 218, 185.

15

Example 6**(±)-7-Fluoro-9-(4-ethylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine(4c) ST1457.**

The desired product **4c** was obtained starting from **25c**
(0.053 g, 0.178 mmol), using 4-ethylpiperazine (1 ml). The
20 colourless liquid **4c** was obtained with 73% yield. ¹H NMR (CDCl₃) δ
7.37-7.26 (m, 2H); 6.86-6.75 (m, 2H); 6.29-6.26 (m, 1H); 6.05-6.02
(m, 1H); 4.80-4.68 (m, 1H); 4.48-4.39 (dd, 1H, J=13.95, 3.78 Hz);
3.97-3.91 (dd, 1H, J=9.23, 3.65 Hz); 2.60-2.32 (m, 10H); 1.08-1.00
(t, 3H, J=7.33 Hz). MS m/z 332 (100) (M⁺+H), 277, 218, 185, 115.

25

Example 6

(±)-7-Fluoro-9-[4-(2-hydroxyethyl)piperazin-1-yl]-9,10-dihydropyrrolo[2,1b][1,3] benzothiazepine (5c) ST1458.

A solution of **25c** (0.065 g, 0.218 mmol) β-hydroxyethylpiperazine (μL 59, 0.218 mmol) and 2-butanone (2 ml) was refluxed for 21 hours. The reaction mixture was then evaporated and to the residue was added water and was extracted with ethyl acetate, combined extracts were dried and evaporated. The crude product was chromatographed to give **5c** as a colourless amorphous solid (69% yield). ¹H NMR (CDCl₃) δ 7.37-7.24 (m, 2H); 6.86-6.77 (m, 2H); 6.29-6.27 (m, 1H); 6.06-6.03 (m, 1H); 4.77-4.65 (m, 1H); 4.48-4.40 (dd, 1H, J=14.15, 3.46 Hz); 3.98-3.92 (dd, 1H, J=8.93, 3.50 Hz); 3.59-3.54 (t, 2H, J=5.37 Hz); 2.85 (bs, 1H); 2.57-2.47 (m, 10H). MS m/z 348 (100) (M⁺⁺H), 288, 218, 185.

Example 7

(±)-7-Bromo-9-(4-methylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine (3d).

The synthesis of the (**3d**) was been performed as described in Scheme C and 2B/2 where **d** = **Br**.

Bis-(2-hydroxycarbonyl-4-bromo)phenyldisulphide (26).

To a cooled (0-5°C) stirring solution of 2-amino-5-bromobenzoic acid (1g, 4.63 mmol), sodium hydroxide (0.185 g, 4.63 mmol), water (7.71 ml) and sodium nitrite (0.32 g, 4.63 mmol) was slowly added a solution of concentrated hydrochloric acid (1.44 ml) in water (2.5 ml), the mixture was stirred at 0-5°C for 1 h, than was

neutralised with potassium carbonate and potassium acetate. The cold diazonium salt solution was run into a vigorously stirred solution of potassium ethyl xanthate (2.23g, 13.89 mmol) and water (7.7 ml) previously heated at 75-80°C and was maintaining this temperature during addition and for further 1 h. The reaction mixture was cooled to room temperature and stirred for 1h. Then hydrogen peroxide (3.22 ml) was added and the solution was stirred for 1 night at room temperature. The mixture was filtered and the solution was acidified (on an ice bath) and filtered again. The product that was collected as a yellow amorphous solid was dissolved with aqueous sodium hydroxide and reprecipitated with hydrochloric acid to afford pure **26** (1.02 g) (95% yield). The compound was used in the next step without further purification.

1-[5-Bromo-(2-methylthio)phenyl]hydroxycarbonyl (27).

To a solution of (**26**) (1 g, 2.15 mmol) in 85% ethanol (17.2 ml) and sodium hydroxide, sodium borohydride (0.163 g) was added in portions. The resulting solution was stirred 30 minutes at room temperature and for additional 3 hours at reflux. Then ice was added and the mixture was stirred for 15 minutes at room temperature, a solution of sodium hydroxide (0.302g, 7.55 mmol) in water (1.9 ml) and dimethyl sulphide (376 µL, 3.97 mmol) were added and the reaction mixture was stirred 2.5 hours at reflux. After cooling 1 drop of ammonium hydroxide 30% was added (to destroy the excess of sodium hydroxide), hydrochloric acid was added (pH 3). The solid obtained was collected by filtration. The crude product

was chromatographed (4% formic acid, 20% ethyl acetate in toluene) to afford 1.017 g of **27** as a yellow solid (96% yield). ^1H NMR (DMSO- d_6) δ 7.95-7.94 (d, 1H, $J=2.69$ Hz); 7.72-7.66 (dd, 1H, $J=8.80, 1.95$ Hz); 7.29-7.25 (d, 1H, $J=8.77$ Hz); 2.37 (s, 3H).

5 **1-[5-Bromo-(2-methylthio)phenyl]ethanone (28).**

A stirred solution of (**27**) (0.1 g, 0.40 mmol) in dry tetrahydrofuran (3.03 ml) was cooled to 0°C (ice bath) and treated with methyllithium (1.4 M solution in ether, 1.156 ml, 1.62 mmol). After 2 hours at 0°C under stirring, trimethylchlorosilane (1.03 ml, 10 8.09 mmol) was rapidly added while stirring continued, the ice bath was removed and the reaction mixture was allowed to come to room temperature, then 1 N hydrochloric acid (3.05 ml) was added and the resulting two phase system was stirred at room temperature for 30 minutes. The organic phase was separated and water was 15 extracted with ether (3x5 ml), the combined extracts were dried and evaporated. The crude product was chromatographed (30% petroleum ether 40-60° in dichloromethane) to afford 0.064g of **28** as a yellowish solid mp 71.5-73.0°C (64% yield). ^1H NMR (CDCl_3) δ 7.89-7.88 (d, 1H, $J=1.91$ Hz); 7.57-7.51 (dd, 1H, $J=8.45, 2.48$ Hz); 20 7.18-7.14 (d, 1H, $J=8.48$ Hz); 2.58 (s, 3H); 2.39 (s, 3H).

2-Bromo-1-[5-bromo-2-(methylthio)phenyl]ethanone (21d).

Starting from **28** (0.60 g, 2.43 mmol), the desired product **21d** was obtained following the procedure described for **21c**. The crude product was chromatographed (50% petroleum ether 40-60° in 25 dichloromethane) to give the pure product 0.57 g (72% yield). ^1H

NMR (CDCl₃) δ 7.87-7.58 (d, 1H, J=1.60 Hz); 7.48-7.42 (dd, 1H, J=8.05, 2.08); 7.12-7.16 (d, 1H, J=8.06 Hz); 4.43 (s, 2H); 2.43 (s, 3H).

1-[5-Bromo-2-(methylthio)phenyl]-2-(pyrrol-1-yl)ethanone (22d).

The desired product **22d** was obtained as white crystals, following the procedure described for **22c**; mp 138.0-139.2°C (32% yield). ¹H NMR (CDCl₃) δ 7.76-7.55 (d, 1H, J=1.92 Hz); 7.60-7.54 (dd, 1H, J=8.43, 2.16 Hz); 7.23-7.19 (d, 1H, J=8.82 Hz); 6.65-6.63 (m, 2H); 6.22-6.20 (m, 2H); 5.20 (s, 2H); 2.41 (s, 3H).

1-[5-Bromo-2-(methylsulfinyl)phenyl]-2-(pyrrol-1-yl)ethanone

(23d).

Starting from **22d** (0.27 g, 0.86 mmol), the desired product was obtained following the above-described procedure, as white crystals mp 138.0-139.2°C (75% yield). ¹H NMR (CDCl₃) δ 8.30-8.25 (m, 1H); 8.0-7.96 (m, 2H); 6.64-6.62 (m, 2H); 6.27-6.25 (m, 2H); 5.43-5.18 (q, 2H, J=32.28, 17.92 Hz); 2.77 (s, 3H).

7-Bromo-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepin-9-one (9d).

The reaction to obtain **9d** was carried out, accordingly the procedure described for **9c**, using trifluoroacetic acid as solvent (0.63 ml) and adding solid **23d** (0.20 g, .62 mmol) to the cold (0°C) solution of trifluoroacetic acid and trifluoroacetic anhydride. The desired product **9d** was obtained as yellowish crystals (64% yield). ¹H NMR (CDCl₃) δ 8.22-8.21 (d, 1H, J=1.99 Hz); 7.56-7.51 (dd, 1H, J=8.28, 2.24 Hz); 7.42-7.38 (d, 1H, J=8.42 Hz); 6.87-6.86 (m, 1H);

6.43-6.41 (m, 1H); 6.12-6.09 (m, 1H); 5.13 (s, 2H). MS m/z 293 (100) (M⁺), 265, 261, 232, 214, 186, 154, 115.

(±)-7-Bromo-9,10-dihydro-9-hydroxypyrrolo[2,1-b][1,3]benzothiazepine (24d).

5 Starting from **9d** (0.12 g, 0.39 mmol), the desired product was obtained accordingly the procedure described for **24c** (65% yield). ¹H NMR (CDCl₃) δ 7.63-7.62 (d, 1H, J=1.70 Hz); 7.32-7.21 (m, 2H); 6.88-6.87 (m, 2H); 6.34-6.32 (m, 1H); 6.12-6.09 (m, 1H); 5.02 (s, 1H); 4.90-4.82 (dd, 1H, J=13.86, 1.83 Hz); 4.36-4.25 (dd, 1H, J=14.18, 6.33 Hz); 1.99(s, 1H)

(±)-7,9-dibromo-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine (25d).

Starting from **24d** (0.07 g, 0.25 mmol) the title compound was obtained following the above-described procedure (36% yield). 15 ¹H NMR (CDCl₃) δ 7.59 (m, 1H); 7.28-7.16 (m, 2H); 6.92-6.91 (m, 1H); 6.39-6.37 (m, 1H); 6.13-6.10 (m, 1H); 5.65-5.60 (dd, 1H, J=6.98, 2.57 Hz); 5.09-5.00 (dd, 1H, J=14.65, 2.35 Hz); 4.66-4.55 (dd, 1H, J=14.68, 7.03 Hz).

(±)-7-Bromo-9-(4-methylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-b][1,3] benzothiazepine (3d).

20 Starting from **25d** (0.033 g, 0.092 mmol) the title compound was obtained following the procedure described for **3c** (58% yield). ¹H NMR (CDCl₃) δ 7.64 (s, 1H); 7.35-7.21 (m, 2H); 6.86-6.84 (m, 1H); 6.29-6.26 (m, 1H); 6.06-6.02 (m, 1H); 4.73-4.61 (m, 1H); 4.49-4.40

(dd, 1H, J=14.30, 8.57 Hz); 3.98-3.92 (dd, 1H, J=8.64, 3.53 Hz); 2.57-2.37 (m, 11H).

2. Pharmacology

EXPERIMENTAL PROCEDURES

IN VITRO BINDING ASSAY

D₁, D₂, D₃ and 5-HT_{2a} affinity.

Male CRL:CD(SD)BR-COBS rats (Charles River, Italy) were killed by decapitation (procedures involving animals and their care were conducted in conformity with the institutional guidelines that are in compliance with national (D.L. n. 116, G.U., suppl. 40, Feb. 18, 1992) and international laws and policies (EEC Council Directive 86/609, OJ L 358, 1, Dec. 12, 1987; Guide for the Care and Use of Laboratory Animals, U.S. National Research Council, 1996); their brains were rapidly dissected into the various areas (striatum for DA-1 and DA-2 receptors, olfactory tubercle for DA-3 receptors and cortex for 5-HT_{2A} receptors) and stored at -80°C until the day of assay. Tissues were homogenised in about 50 volumes of Tris HCl, 50 mM, pH 7.4 (for DA-1, DA-2 and 5-HT_{2A} receptors) or Hepes Na, 50 mM, pH 7.5 (for DA-3 receptors), using an Ultra Turrax TP-1810 (2x20 sec.), and centrifuged at 50000g for 10 min. The pellets were resuspended in fresh buffer, incubated at 37°C for 10 min and centrifuged as before. The pellets were then washed once by resuspension in fresh buffer and centrifuged again. The pellets obtained were resuspended in the appropriate incubation buffer (Tris HCl, 50 mM, pH 7.1, containing 10 µM pargyline, 0.1%

ascorbic acid, 120 mM NaCl, 5 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂ for DA-1 and DA-2 receptors; Hepes Na, 50 mM, pH 7.5, containing 1 mM EDTA, 0.005% ascorbic acid, 0.1% albumin, 200 nM eliprodil for DA-3 receptors) just before the binding assay.

5 [3H]SCH 23390 (specific activity 70.3 Ci/mmol, NEN) binding to DA-1 receptors was assayed in a final incubation volume of 0.5 ml, consisting of 0.25 ml of membrane suspension (2 mg tissue/sample), 0.25 ml of [3H]ligand (0.4 nM) and 10 µl of displacing agent or solvent. Non-specific binding was obtained in the
10 presence of 10 µM (-)-cis-flupentixol.

 [3H]Spiperone (specific activity 16.5 Ci/mmol, NEN) binding to DA-2 receptors was assayed in a final incubation volume of 1 ml, consisting of 0.5 ml of membrane suspension (1 mg tissue/sample), 0.5 ml of [3H]ligand (0.2 nM) and 20 µl of displacing agent or
15 solvent. Non-specific binding was obtained in the presence of 100 µM (-)sulpiride.

 [3H]-7-OH-DPAT (specific activity 159 Ci/mmol, Amersham) binding to DA-3 receptors was assayed in a final incubation volume of 1 ml, consisting of 0.5 ml of membranes suspension (10 mg
20 tissue/sample), 0.5 ml of [3H]ligand and 20 µl of displacing agent or solvent. Non-specific binding was obtained in the presence of 1 µM dopamine.

 [3H]Ketanserin (specific activity 63.3 Ci/mol, NEN) binding to 5-HT_{2A} receptors was assayed in a final incubation volume of 1 ml
25 consisting of 0.5 ml of membrane suspension (5 mg tissue/sample),

0.5 ml of [^3H]ligand (0.7 nM) and 20 μl of displacing agent or solvent. Non-specific binding was obtained in the presence of 1 μM methysergide. Incubations (15 min at 37°C for DA-2 and 5-HT_{2A} receptors; 15 min at 25°C for DA-1 receptors; 60 min at 25°C for
5 DA-3 receptors) were stopped by rapid filtration under vacuum through GF/B (for DA-1, DA-2 and 5-HT_{2A} receptors) or GF/C (for DA-3 receptors) filters which were then washed with 12 ml of ice-cold buffer, using a Brandel M-48R. The radioactivity trapped on the filters was counted in 4 ml of Ultima Gold MV (Packard) in a LKB
10 1214 rack beta liquid scintillation spectrometer with a counting efficiency of 60 %.

H₁ affinity

Whole cortexes from male Fischer rats (300-350 g) were homogenised with a Polytron in nine volumes (w/v) of 50 mM Na⁺-K⁺
15 phosphate buffer (pH 7.5). The homogenate was centrifuged at 16500 $\times g$ for 10 min and the particulate fraction was resuspended in the original volume of buffer. In a typical experiment, aliquots of the homogenate (0.3 – 0.4 mg prot.) were incubated at 25°C in 0.50 ml of the same buffer containing [^3H] pyrilamine (2nM) and the
20 displacing drugs.

After 30 min of incubation, 4 ml of ice-cold buffer was added and the bound and free [^3H] pyrilamine were separated by filtration under vacuum through glass fiber filters (Whatman GF/B). The filters were washed three times with 4 ml of buffer, dried, placed in

15 ml of Optifluor, and counted by liquid scintillation spectrometry after a 12 h extraction period.

All assays were done in triplicate and specific binding was defined as the total amount of [^3H] pyrilamine bound minus that bound in the presence of 10^{-4}M of pyrilamine. Protein concentration
5 was determined by the Bradford method.

[^3H] pyrilamine, (20ci/nmol) was obtained from New England Nuclear Corp.

Muscarinic affinity

10 Male Fischer rats (300-350 g) were killed by decapitation and cortices were rapidly removed and homogenised using a Polytron in 20 vol (w/v) of ice-cold 50 mM PBS buffer (pH 7.4). Homogenates were centrifuged at 20000 x g for 15 min. The precipitated material was resuspended in assay buffer and was used for binding assay.

15 Triplicate incubation tubes contained [^3H] QNB (0.16 nM), various concentrations of drug and an aliquot of freshly resuspended tissue (~ 0.4 mg prot) in a final volume of 2 ml. Tubes were incubated at 37°C for 60 min and the incubation was terminated by rapid filtration under vacuum through GF/B glass
20 fiber filters. The filters were rinsed three times with ice-cold buffer using a Brandel filtration apparatus (Gaithersburg, MD, USA) and were placed in vials containing 15 ml of Optifluor®, cooled overnight, and counted in a liquid scintillation. Specific binding was defined as the excess over blanks containing 1 μM Atropine.

[³H] QNB 42 ci/nmole was obtained from New England Nuclear Corp.

Calculations.

Drugs were tested in triplicate at different concentrations, from 10⁻⁵ to 10⁻¹⁰ M. IC₅₀'s, the concentration of drug that caused 50% inhibition of [³H]Ligand binding, was obtained using "Allfit" program running on an IBM personal computer.

IN VIVO TEST

Antagonism of Apomorphine-induced climbing in mouse

Groups of ten mice (CD1 male) were dosed with test compounds by the subcutaneous route 30 minutes before apomorphine and placed individually into cylindrical wire mesh cages (height 14 cm, diameter 12 cm, mesh size 2 mm).

Climbing behaviour was assessed at 5 min intervals for 30 min, starting 5 min after apomorphine (1.3 mg/Kg, s.c.) (Greg C. Rigdon et al. Neuropsychopharmacology Vol.15,.pp231-242 (1996)).

Antagonism of 5-MeO-DMT-induced Head Twitches in mouse

Groups of ten mice of the CD1 strain (male) were utilised to evaluate head twitches induced by 5 methoxy-N,N-dimethyl-tryptamine (5-MeO-DMT) at a subcutaneous dosage of 10 mg/Kg.

The evaluations were begun 6 minutes from the 5-MeO-DMT and lasted 15 minutes (counting the number of head-twitches produced by the animal). The substances were administered subcutaneously 30 minutes before the 5-MeO-DMT (Greg C. Rigdon
5 et al. Neuropsychopharmacology Vol.15,.pp231-242 (1996)).

Extrapyramidal Symptom

The test was performed on male Wistar rats (7-8 animals per group); the catalepsy evaluation was carried out by means of a metallic bar 0.6 cm in diameter positioned 10 cm from the
10 workplace. The substances under study were administered subcutaneously 30 minutes before the first evaluation. The subsequent observations were recorded at 60, 90, 120, 180, 240, 300 minutes from administration.

The test consisted in positioning the animal with its forepaws
15 on the bar and timing how long the animal remained hanging onto the bar employing an end-point of 60 seconds (N. A. Moore et al. Journal of Pharmacology and Experimental Therapeutics Vol. 262 pp 545-551 (1992)).

RESULTS AND DISCUSSION

20 D₁, D₂,D₃ and 5HT_{2a} affinity

Table 1 reports the averages and standard errors in the affinity values expressed as K_i (nM) reported by each product under study with regard to the 5HT₂, D₂, D₁ and D₃ receptors.

These values were compared with the ones relative to reference compounds which are structurally similar to the compounds of the present invention (RS-OctoclothePIN, R-(-)OctoclothePIN; S-(+)-OctoclothePIN) or belonging to the pharmacological class of the atypical antipsychotics (Olanzapine and Clozapine).

Table 1

Compounds	5HT _{2A}	D ₁	D ₂	D ₃
Clozapine	11.00±1.00	353.00±35	250.00±57	312.80±65.07
Olanzapine	12.00±1.00	85.00±3.5	69.00±17	25.80±7.75
RS-OctoclothePIN	0.22±0.02	2.28±0.15	0.36±0.07	2.38±0.37
R-(-)-OctoclothePIN	0.16±0.01	2.02±0.17	3.64±0.46	20.90±4.35
S-(+)-OctoclothePIN	0.14±0.01	1.97±0.53	0.40±0.04	0.75±0.12
(±)-3a	7.85±2.2	160±77	70±17	57±6.2
ST1455	1.14±0.12	27.00±10	3.80±0.5	
ST1460	1.48±0.20	16.40±1.0	49.60±6.0	
ST1461	1.72±0.25	22.00±1.3	2.06±0.2	
ST1456	5.1±0.40	78.00±8.76	37.50±3.01	12.20±3.65
Haloperidol	164.10±23.6	318.30±59.2	4.81±1.0	15.4±3.23
Methysergide	5.3±0.8			
(-)-cis-Flupentixol		37.8±1.7		
Sulpiride			240±58	
Dopamine				11±3.4

The binding evaluations relative to the compound (±)-3a, to the chloro derivative ST1455 and to the fluoro derivative ST1456, show that the substitution in position 7 with a halogen is an important condition for improving the affinities of the formula (I) compounds towards the 5HT_{2A} D₂ and D₃ receptors.

Relative to receptor 5-HT_{2A} the 7-chloro derivatives, raceme (ST 1455) and single isomers (form (+) ST1460, form (-) ST 1461)

demonstrate an affinity that improves, by virtue of substitution with halogen, and proves moderately lower than the one shown by the structurally analogous reference compounds (RS-Octoclothepein, R-(-)-Octoclothepein, S-(+)-Octoclothepein) and greater to that shown by the atypical neuroleptics Clozapine and Olanzapine.

The enantiomers of the ST 1455 chloro-derivative, like those of RS-Octoclothepein, do not present significant differences of affinity towards the 5HT_{2a} receptor, but reveal a marked stereoselectivity of action regarding the capacity of interaction towards the dopaminergic D₂ receptor.

While it is observed that R-(-)-Octoclothepein shows approximately 10 times less affinity with regard to the D₂ receptor with respect to isoform(+), the preferred compound ST 1460, shows approximately 25 times less affinity than the (-) isomer, ST 1461.

It is therefore interesting to note that the preferred product ST 1460 presents a lower activity on the D₂ receptors (involved in the extrapyramidal effects), as compared to what its closest structural analogue R-(-)-Octoclothepein shows, together with an improved affinity for the 5HT₂ and D₁ receptors (involved in the neuroleptic action), as compared to what the reference atypical antipsychotic Olanzapine demonstrates.

In the case of the preferred product ST 1460, it is therefore possible to obtain therapeutic effects associated with a control of extrapyramidal symptoms using lower doses with respect to those necessary for Clozapine or Olanzapine

Concerning the racemic 7-fluoro derivative, ST 1456, for which has been shown an interaction capacity towards the D₂ receptor even below that shown by the best OctoclothePIN enantiomer and towards that shown by Olanzapine, it is believed that it could
5 possess a stereoselectivity of interaction towards the very same receptor, analogously to the racemic chloro-derivative.

Table 2 shows the inhibition constants (pK_i) of the formula (I) compounds and of the reference compounds towards the D₁, D₂ D₃ and 5HT₂ receptors, and the following ratios of relative affinity D₁/D₂
10 and 5HT₂/D₂. This last value, if above 1.12, is considered a valid indication for describing the "atypical" profile of an antipsychotic (Meltzer et al. J. Pharmacol Exp. Ther 251 (1) pp 238-245 1989).

Also reported is the LogY parameter which, considering the relative affinities towards the 5HT₂, D₂, and D₁ receptors of each
15 product identifies and distinguishes a classic antipsychotic (Log Y > 6.48) from an atypical one (Log Y < 6.48) (Meltzer et al. J. Pharmacol Exp. Ther 251 (1) pp 238-245 1989).

Table 2

Compound	D ₁ pKi	D ₂ pKi	5HT _{2A} pKi	D ₁ /D ₂	5HT ₂ /D ₂	Log Y
Clozapine	6.45	6.60	7.96	0.98	1.21	3.95
Olanzapine	7.07	7.16	7.92	0.99	1.11	5.43
RS-Octoclothebin	8.64	9.44	9.66	0.92	1.02	8.02
R-(-)-Octoclothebin	8.69	8.44	9.80	1.03	1.16	5.87
S-(+)-Octoclothebin	8.71	9.40	9.85	0.93	1.05	7.66
(±)-3a	6.8	7.15	8.1	0.95	1.13	4.99
ST1455	7.57	8.42	8.94	0.90	1.06	6.56
ST1460	7.79	7.30	8.83	1.07	1.21	4.67
ST1461	7.66	8.69	8.76	0.88	1.01	7.40
ST1456	7.11	7.43	8.29	0.96	1.12	5.39
Haloperidol	6.50	8.32	6.78	0.78	0.82	9.14

Observation of these results suggests that the preferred compound ST 1460 is superior to its closest structural analogue (-)-
5 Octoclothebin (respectively 1.21 and 1.16) and different from its own racemic form ST1455 and from the isoform(-) ST 1461, for which the above-mentioned parameters describe a profile of classic antipsychotics.

Concerning a comparison with compounds having a known
10 atypical antipsychotic activity, the relative affinity ratio 5-HT₂/D₂ and the LogY value of the preferred compound ST 1460 describe a atypical profile comparable to that of clozapine and superior to olanzapine.

The raceme fluoro derivative ST 1456 is, unlike the racemic
15 chloro-derivative ST1455, an atypical antipsychotic comparable to the reference compound Olanzapine.

Another interesting aspect of some formula (I) compounds that emerges from an examination of the parameters represented in Table 3 is the high value of the D₃/D₁ receptorial affinity ratio they showed.

Table 3

Compound	D ₁ pKi	D ₃ pKi	D ₃ /D ₁
Clozapine	6.45	6.50	1.01
Olanzapine	7.07	7.59	1.07
RS-Octoclothebin	8.64	8.62	1.00
R-(-)-Octoclothebin	8.69	7.68	0.88
S-(+)-Octoclothebin	8.71	9.12	1.05
(±)-3a	6.8	7.24	1.07
ST1456	7.11	7.91	1.11
Haloperidol	6.50	7.81	1.20

Said value is, for everyone, comparable to that determined for the reference compound Olanzapine.

Moreover, the D₃/D₁ value reported by formula (I) compounds clearly distinguishes them from the partially atypical neuroleptic R-(-)- Octoclothebin which shows an 0.88 activity ratio.

The relatively greater D₃/D₁ ratio renders formula (I) products useful in the treatment of the negative symptoms of schizophrenia which involve the emotional and cognitive sphere, such as for example dementia, with respect to Octoclothebin, which with its more active D₁ receptor is oriented towards the control of symptoms linked to muscle tone.

Affinity relative to the H₁ receptors of histamine and muscarinics.

Table 4 reports the average and standard deviations of three determinations which describe the interaction capacity (K_i, nM) of each formula (I) and reference compound towards the H₁ receptor of Histamine and towards the muscarinic receptors.

Table 4

Compound	H ₁ Receptor		Muscarinic Receptors	
	K _i (nM)	E.S.	K _i (nM)	E.S.
Clozapine	14.00	0.00	54.50	0.00
Olanzapine	0.35	0.20	22.10	13.12
RS-Octoclotheperin	1.00	0.08	434.10	31.70
R-(-)-Octoclotheperin	2.32	0.06	154.60	12.70
S-(+)-Octoclotheperin	0.62	0.07	748.60	87.30
ST1455	9.46	1.98	418.20	47.65
ST1460	21.33	12.00	286.40	13.20
ST1461	1.40	0.06	514.50	154.10
ST1456	7.33	1.36	2224.00	105.60
Haloperidol	384.00	0.00		
Pyrilamine	12.20	0.09		
Atropine			2.59	0.01

A study of the mentioned parameters shows that the interaction capacity of the preferred compound ST 1460 towards the H₁ receptor and towards the muscarinic receptors is less marked than that shown by its direct structural analog, the partially atypical neuroleptic R-(-)-Octoclotheperin, and by the reference compounds of

the pharmacological class of the atypical antipsychotics, Clozapine and Olanzapine.

These results render the compound ST 1460 particularly useful in the treatment of schizophrenia and distinguish it from the atypical reference compounds which, by virtue of their greater interaction capacity towards the above-mentioned receptors, associate antipsychotic efficacy with the appearance of the following side effects: dryness of the throat and the respiratory tract, constipation and weight gain.

In vivo TEST

Table 5

Dosage that determines approximately 50% climbing inhibition induced by apomorphine in the mouse

Molecule	DOSE (MG/KG)	DOSE (μMOLES/KG)
Olanzapine	0.12	0.38
Octoclotheperin RS	0.02	0.043
Octoclotheperin R	0.013	0.026
Octoclotheperin S	0.041	0.083
ST 1468	0.052	0.13
ST 1469	0.10	0.24
ST 1470	0.025	0.06

Table 6:

Dosage that determines 50 % of the Head-twitching inhibition
induced by 5-MeO-DMT in the mouse

Molecule	DOSE (MG/KG)	DOSE (µMOLES/KG)
Olanzapine	0.18	0.58
OctoclothePIN RS	0.064	0.14
OctoclothePIN R	0.089	0.18
OctoclothePIN S	0.079	0.16
ST 1468	0.19	0.47
ST 1469	0.196	0.49
ST 1470	0.10	0.24

Table 7

Dosage that determines 100% of catalepsy in rats

MOLECULE	DOSE (MG/KG)	DOSE (μ MOLES/KG)	TIME IN MINUTES OF INSURGENCE OF CATALEPSY IN 100% OF THE ANIMALS
RS-OctoclothePIN	0.6	1.3	120
R-(-)-OctoclothePIN	14.85	30	120
S-(+)-OctoclothePIN	0.3	0.55	300
ST 1468	1.22	3	180
ST 1469	> 12.2	>30	
ST 1470	4.06	10	90

5 Table 5 shows the calculated dosage of each single compound that determines a 50% inhibition to climbing behaviour induced by apomorphine in the mouse, an indication of a dopaminergic activity.

From the results a reduction of the affinity bond which leads to an increase in dosage by the compound under study (ST 1469) can
10 be observed both in vivo as in vitro, in that 0.1 mg/Kg (0.24 μ moles/Kg) are necessary in order to have an antagonism to the effect produced by stimulation of the dopaminergic system, of approximately 50% with respect to R-(-)-OctoclothePIN whose dosage is much lower at 0.013 mg/Kg (0.026 μ moles/Kg), an indication of
15 R-(-)-OctoclothePIN's greater affinity bond.

A lesser affinity to the system classifies it as an Atypical Antipsychotic and makes it comparable to the class of drugs represented by olanzapine.

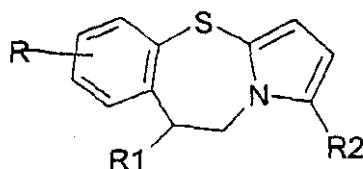
Stimulation of the serotonergic system (table 6) by means of a non-selective agonist of serotonin receptors (5-MeO-DMT) places the compound (ST 1469) in the in vivo studies comparable to Olanzapine (0.19 mg/Kg as opposed to 0.18 mg/Kg) and with less affinity to the serotonergic system with respect to R-(-)-Octoclotheperin (0.089 mg/Kg).

The onset of the extrapyramidal syndrome (catalepsy), a negative effect of the typical neuroleptics, (see table 7) which effect should be lacking in those that are atypical, favours ST 1469 in that at a dosage corresponding to 30 μ moles/Kg R-(-)-Octoclotheperin causes catalepsy in all animals after 120 minutes of treatment while the compound under study does not present catalepsy throughout the entire observation period.

From the in vivo results produced it can be concluded that ST 1469, as characterized by its demonstrated activity on the neurotransmitting systems examined and no insurgence of catalepsy, can be placed in the atypical neuroleptic class of drugs.

CLAIMS

1. Compounds, in racemic form or as isolated optical isomers, having formula (I):



where:

R = H, Cl, Br, F, I, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ alkyl, C₅-C₆ cycloalkyl;

R₁ = dialkylamine, 4-alkyl-1-piperazinyl, 4-hydroxyalkyl-1-piperazinyl, 1-imidazolyl, 4-alkyl-1-piperidinyl

R₂ = hydrogen, C₁-C₄ alkoxy, C₁-C₄ alkylthio;

and the pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1, where R represents chlorine or hydrogen, R₁ a 4-methyl-1-piperazinyl group; and R₂ hydrogen.
3. Compounds according to claim 1, where R represents fluorine, bromine or hydrogen, R₁ a 4-methyl-1-piperazinyl group; and R₂ hydrogen.
4. (±)-9-(4-methylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine.
5. (±)-7-chloro-9-(4-methylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine .
6. (+)-7-chloro-9-(4-methylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine .

7. ($\pm$)-7-fluoro-9-(4-methylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine.
8. ($\pm$)-7-fluoro-9-(4-ethylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine.
- 5 9. ($\pm$)-7-fluoro-9-(4-hydroxyethylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine.
10. ($\pm$)-7-Bromo-9-(4-methylpiperazin-1-yl)-9,10-dihydropyrrolo[2,1-b][1,3]benzothiazepine.
11. Process for the preparation of the compounds of claims 1-10
10 comprising the cyclisation reaction of a derivative containing a phenyl group and a pyrrole group, and where the cyclisation leads to the formation of a 1,3 thiazepine ring.
12. Process according to claim 11, where the result of said cyclisation reaction is a pyrrolobenzothiazepinone, which is
15 transformed into a formula (I) derivative by substituting the keto group on the thiazepine ring with a group selected from the foregoing definitions of the radical R₁.
13. Process according to claim 11, where said derivative containing a phenyl group and a pyrrole group is a 1-[2-(methylsulphinyl)phenyl]-2-(pyrrol-1-yl)ethanone, and the
20 cyclisation reaction is carried out in the presence of trifluoroacetic anhydride and dimethylformamide.
14. Process according to claim 11, where said derivative containing a phenyl group and a pyrrole group is an alkyl ester of 2-(phenylthio)pyrrolo-1-selenoacetic acid and the cyclisation
25

reaction is carried out in the presence of a crystalline complex of triflate copper(I) and benzene.

15. Process for the resolution of racemic compounds of claims 1-10 into the corresponding optically active isomers, by means of
5 fractionated crystallisation of the diastereoisomeric salts obtained by salification with an optically active acid.
16. Compounds of claims 1-10 for use in therapy in racemic form or as single isolated optical isomers.
17. Pharmaceutical composition comprising, in racemic form or as
10 single isolated optical isomers, at least a compound of claims 1-10 in combination with pharmaceutically acceptable excipients and/or vehicles, and optionally with other active ingredients which are useful in the treatment of psychoses.
18. Pharmaceutical composition according to claim 17, in solid or
15 liquid form.
19. Use of the compounds of claims 1-10, in racemic form or as single isolated optical isomers, in the preparation of an antipsychotic medicinal agent for the treatment and prevention of psychoses.
20. 20. Use according to claim 19, where said psychosis takes the form of schizophrenia, paranoid states, manic-depressive states, affective disorders, social withdrawal, personality regression, or hallucinations.
21. Use according to claim 19, in particular of the compounds of
25 claim 1, wherein R is hydrogen, fluorine, bromine, for the

treatment of the negative symptoms of schizophrenia involving the emotional and cognitive spheres.

22. Use according to claim 21, where said negative symptom takes the form of dementia.

Title: 具有典型的精神抑制活性的吡咯并[2, 1-b]苯并三氮杂卓

Abstract:

公开了一种新的具有通式 (I) 结构的吡咯并[2, 1-b]苯并三氮杂卓的缩聚杂环, 在说明书中定义了各基团。与已知的精神抑制剂相比, 本发明的化合物表现出相当大的与不希望的非体外的症状同步减轻相关的活性。这里描述的本发明的主题化合物可以以药用组合物的形式配制, 用于治疗精神疾病如精神分裂症。
