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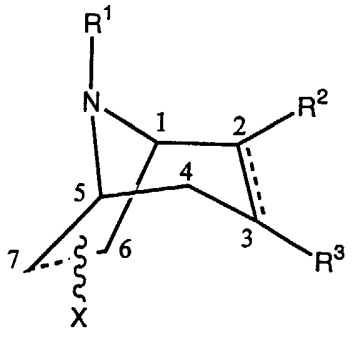
(54) Title: TROPANE DERIVATIVE, CHELATION PRODUCT COMPRISING THIS TROPANE DERIVATIVE AND A METAL OR A METAL COMPLEX, AND RADIOPHARMACEUTICAL



(I)

(57) Abstract: La présente invention se rapporte à un dérivé du tropane, à un produit de chélation constitué de ce dérivé de tropane et d'un métal ou d'un complexe de métal et à un radiopharmaceutique comprenant ledit produit. Le dérivé du tropane de la présente invention est de formule (I) suivante : *(formule)*dans laquelle X représente un composé de chélation d'un métal ou d'un complexe de métal, les carbones 5 et 6 étant liés ou non entre eux,dans laquelle : R_1 est un alkyle ou un alcényl, R_2 est de la forme -COOZ avec Z choisi parmi H, ou un groupe alkyle, R_3 représente un groupe phényle; un groupe phénylalkyle ou phénylalkényle; un groupe benzoate ou un groupe oxo, et dans laquelle la liaison entre les carbones 2 et 3 est une liaison simple ou double.

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TROPANE DERIVATIVE, CHELATION PRODUCT COMPRISING THIS TROPANE DERIVATIVE AND A METAL OR A METAL COMPLEX, AND RADIOPHARMACEUTICAL

DESCRIPTION

TECHNICAL FIELD

The present invention relates to a tropane derivative, to a chelation product comprising this tropane derivative and a metal or a metal complex, and to a radiopharmaceutical comprising the said product.

The tropane derivatives of the present invention can be used as radiopharmaceuticals for diagnosis and therapy, in particular when they are labelled. They can be used as medicaments, in particular for the treatment of diseases involving transporters of neuromediators, such as serotonin and dopamine.

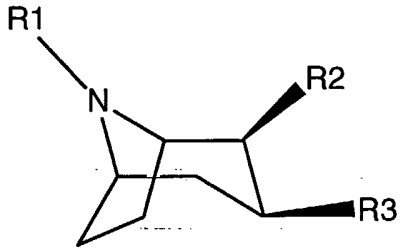
Inhibition of the transporation of dopamine, in particular by cocaine derivatives, leads to an increase in the level of dopamine in the postsynaptic area of the neurone. Anomalies in dopaminergic neurotransmission are involved in neurodegenerative or psychiatric diseases, such as Parkinson's disease, Alzheimer's disease and schizophrenia.

Given the important role of the dopamine transporter in regulating neurotransmission, the development of radioligands emitting gamma radiation capable of attaching to the dopamine transporter with a high affinity and selectivity is necessary for the visualization of this transporter, in order to be able diagnose diseases in the early stage, to be able to assess the change in the density of dopamine

transporters during a disease, and to monitor the effects of a therapy administered to a patient.

PRIOR ART

The tropane derivatives of formula (A) below are recognized as being active in some cerebral reuptake processes, such as dopamine reuptake, serotonin reuptake, acetylcholine reuptake, and the like.



(A)

The specificity of one derivative with respect to another is related to the substituents R1, R2 and R3 and to their configuration in space.

Each substituent is essential to the recognition and to the specificity of the molecule for its receptor. Each position has a distinguishing feature which is essential to recognition and the formation of binding. By virtue of these specificities, the molecule bonded to the receptor leads to a biological process and to an effect on the nervous system.

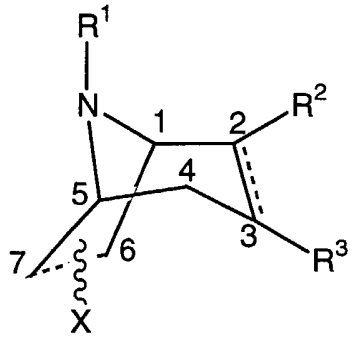
In order to diagnose pathologies related to alterations in the reuptake of various neuromediators, it has long been imagined by us that it might be possible for us to replace one of the substituents by a substituent having a radioactive element while retaining good affinity of the radiolabelled molecule for its receptor. This was confirmed for molecules

derived from cocaine, such as β-CIT, PE2I or Datscan, which have a group substituted by a radioactive halogen.

Technetium derivatives have been produced, including Trodat, which unfortunately have only a weak in vivo specificity. In addition, they exhibit the disadvantage of being rather poor in crossing the haematoencephalic barrier (HEB).

DESCRIPTION OF THE INVENTION

It is a specific aim of the present invention to overcome in particular the abovementioned disadvantages by providing a tropane derivative of following formula (I):



in which X represents a compound for chelation of a metal or of a metal complex attached, directly or indirectly, as desired: to the carbon in the 6 position, to the carbon in the 7 position or simultaneously to the carbons in the 6 and 7 positions, the 6 and 7 carbons being bonded or not bonded to one another in this last option,

and in which:

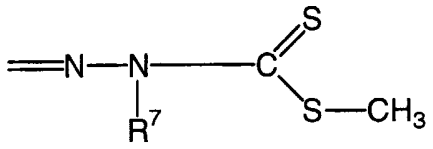
R^1 is a linear or branched alkyl or alkenyl comprising from 1 to 6 carbon atoms which is optionally substituted by a halogen; an ester,

R^2 is of the form -COOZ with Z chosen from H or a linear or branched C_1 to C_6 alkyl group optionally substituted by a halogen atom,

R^3 represents a phenyl group which is unsubstituted or substituted by one or more halogen atom(s), alkyl group(s) or alkoxy group(s); a phenylalkyl or phenylalkylene group, the linear or branched alkyl or alkylene group of which comprises 1 to 6 carbon atoms and the phenyl group of which is optionally substituted by one or more halogen atom(s) or alkyl group(s) comprising from 1 to 6 carbon atoms; a benzoate group or an oxo group,

the bond between the 2 and 3 carbons being a single or double bond.

According to a first embodiment of the present invention, the compound X for chelation of a metal or of a metal complex can be in the form $-R^5$ attached to the carbon in the 6 position and in the form $-R^6$ attached to the carbon in the 7 position, R^5 and R^6 having the formula (Y)



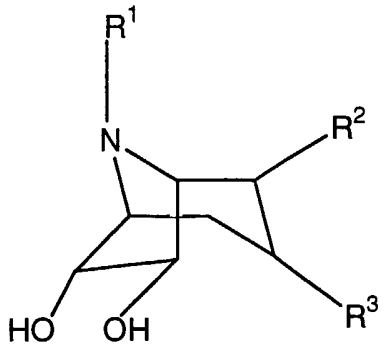
(Y)

with R^7 chosen from H or CH_3.

According to a further alternative form of this first embodiment of the present invention, the carbons in the 6 and 7 positions are bonded to one another.

The tropane derivatives in accordance with this alternative form can be manufactured by a process comprising the following stages:

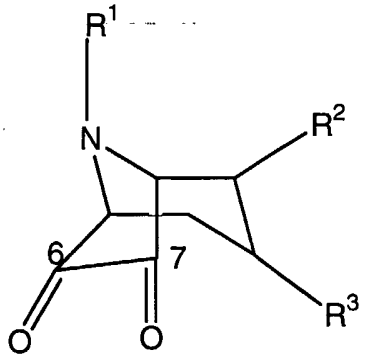
- manufacture of a tropane derivative of following formula (II):



(II)

R^1, R^2 and R^3 being as defined in this document,

- conversion of the tropane derivative of formula (II) to a tropane derivative of following formula (III):



(III)

- optionally conversion of the oxo functional groups to -COOH, $-NH_2$ or $-COOR^9$ functional groups, R^9 being a C_1 to C_3 alkyl,

- attachment of R^5 and R^6, defined above as compound of formula (Y), to the 6 and 7 positions, optionally after conversion of the oxo groups.

The structure of the tropane bicycle is rigid. This structure allows the molecule to cross the haematoencephalic barrier and to attach to the receptor the complexing agent for the metal or for the metal complex, for example Te or Re, on the unrecognized face of the tropane in the 6 and 7 position.

The specificity of the product is a function in particular of the substituents on the 1, 2 and 3 positions, which are specific for different receptors. In addition, the affinity of these tropane derivatives and their specificity for their target is greater than that of the derivatives of the prior art, in particular because of the removal of steric hindrance from the chelation compound. These advantages, relating to the present invention, are found for all the tropane derivatives defined by the formula (I) above.

According to a second alternative form of this first embodiment of the present invention, the carbons in the 6 and 7 positions are not bonded to one another.

These derivatives have the distinguishing feature of only being recognized by their receptor once complexed with a metal, for example a radioactive metal, as the radiolabelling, and generally the complexing with the metal, overcomes the absence of bond between the carbons in the 6 and 7 positions of the open ring of the tropane derivative and makes it possible, without the said bond, to reform a closed and biologically active tropane ring. The "precursor", that is to say the "open" tropane derivative, that is to say without a bond between the carbons in the 6 and 7 positions, itself has a structure which is different from that of tropane and which does not interact with the receptor.

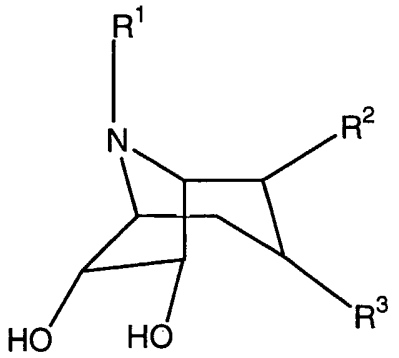
This derivative therefore has a natural selectivity which advantageously makes it possible to avoid the usual stage of purification of the compounds after radiolabelling and before injection. This is because the unlabelled derivative, that is to say having its open ring, is not rigid. For this reason, it does not cross or only to a slight extent crosses the

haematoencaphalic barrier (HEB). It is only once it is labelled that it recovers its rigid bicycle form capable of crossing the HEB, in other words that it becomes biologically active.

This derivative is very useful in a kit formulation as there is no competition between the final labelled product and its unlabelled precursor in vivo.

The tropane derivatives in accordance with this second alternative form of the first embodiment of the present invention can be manufactured by a process comprising the following stages:

- manufacture of a tropane derivative of following formula (II):

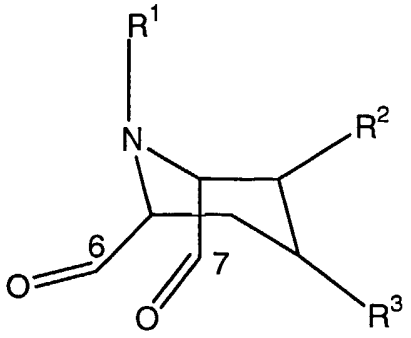


(II)

et

R^1, R^2 and R^3 being as defined above,

- conversion of the tropane derivative of formula (II) to a tropane derivative of following formula (IV):



(IV)

et

- optionally conversion of the oxo functional groups to -COOH, $-NH_2$ or $-COOR^9$ functional groups, R^9 being a C_1 to C_3 alkyl,

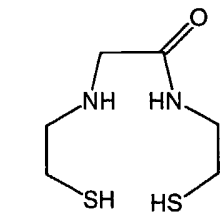
- attachment of R^5 and R^6, defined above as compound of formula (Y), to the 6 and 7 positions, optionally after conversion of the oxo groups.

According to a second embodiment of the present invention, the compound X for chelation of a metal or a metal complex can be a bisdithiocarbonate structure attached to the carbon in the 6 position or to the carbon in the 7 position.

In this second embodiment of the present invention, the chelation compound can be attached directly or indirectly to the 6 or 7 carbon of the tropane ring.

When it is attached indirectly to the tropane ring, attachment can take place via a spacer group chosen from $-(CH_2)_n-$ or $-(CH_2O)_n-$, n representing an integer such that $1 \leq n \leq 10$. The spacer group can also be bonded to one of the following functional groups: -O-, -COO-, -OCO-, -CONH-, -NHCO-, -S-, -NH-, and the like. The spacer group can also be composed very simply of a functional group chosen from: -O-, -COO-, -OCO-, -CONH, -NHCO-, -S-, -NH-, and the like.

In this embodiment of the present invention, the compound X can advantageously be chosen from:



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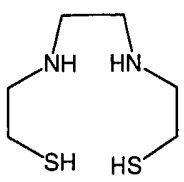

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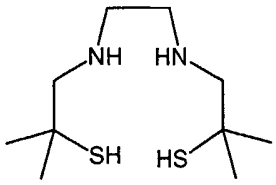
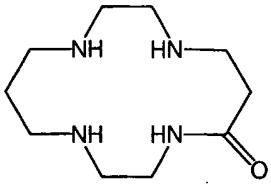
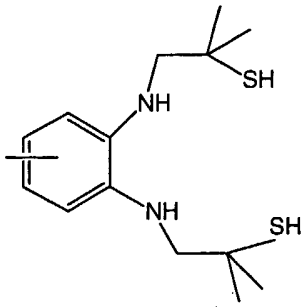


(a8)



(a9)



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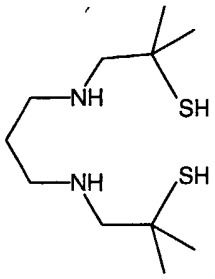

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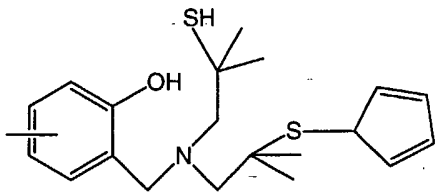

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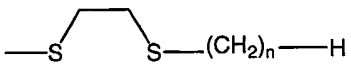

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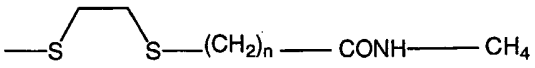

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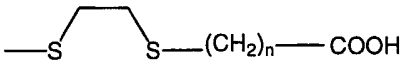

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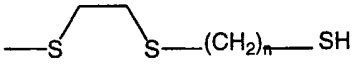

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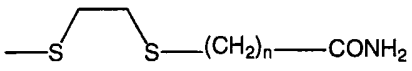

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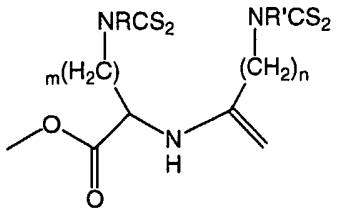
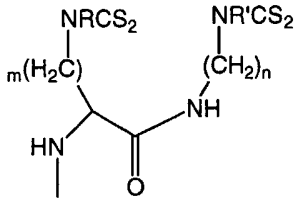
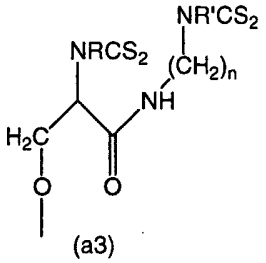


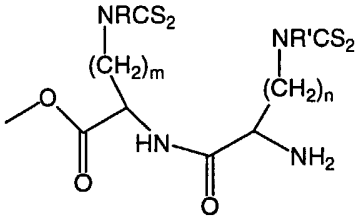
(a1)



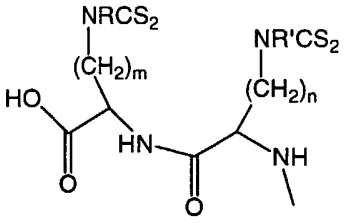
(a2)



(a3)



(a4)



(a5)

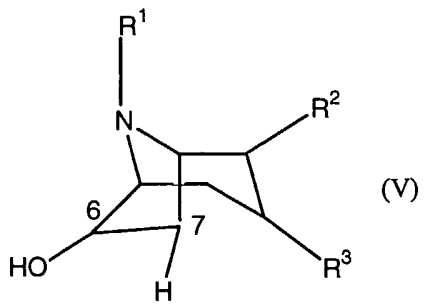
with independently n = 1 to 10 and m = 1 to 10; R and R' being identical or different and representing H or an alkyl or alkoxy group comprising from 1 to 6 carbon atoms.

Advantageously, n = m = 4.

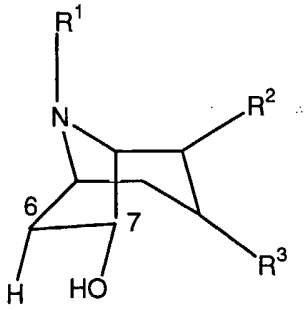
According to the present invention, the structures a6 to a11 are advantageously bonded to the tropane derivative via a carbon or nitrogen atom of their main chain.

The tropane derivatives in accordance with this second embodiment of the present invention can be manufactured by a process comprising the following stages:

- manufacture of a tropane derivative of following formula (V) or (VI):



(V)



(VI)

where R^1, R^2 and R^3 are as defined above,

- attachment to the OH in the 6 position of the tropane derivative (V) or to the OH in the 7 position of the tropane derivative (VI) of a compound X for chelation of a metal or of a metal complex, such as one of those defined above.

Whatever the tropane derivatives of the present invention, they can comprise the substituents R^1, R^2 and R^3 as defined above for the formula (I).

For example, R^1 can be, inter alia, an alkyl group, such as methyl, ethyl, propyl, isopropyl, and the like, or an alkenyl group, such as ethenyl, 1-propenyl, 2-propenyl, and the like. The alkyls and alkenyls can be substituted by an iodine, a bromine or a fluorine. The alkyls can be mono- or polysubstituted.

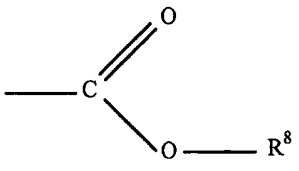
For example, R^2 can be an ester of the form -COOZ where Z is an alkane or alkene derivative comprising from 1 to 6 carbon atoms which is optionally substituted by a halogen.

For example, R^3 can be a substituted or unsubstituted aromatic group; this can be a substituted

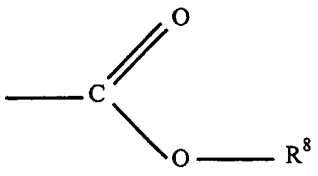
or unsubstituted naphthyl derivative but this can also be a hydrogen or a substituted or unsubstituted benzyl.

Advantageously, and independently of one another, the substituents can be as follows:

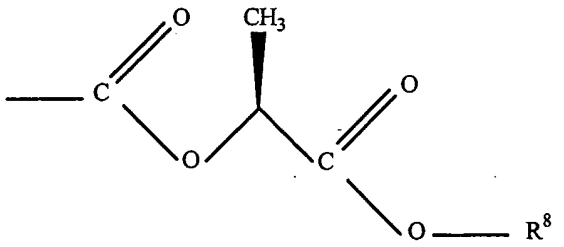
- R^1 can be chosen from: H, $-CH_3$,



- R^2 can be chosen from:

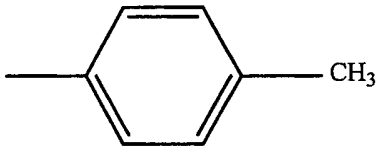


and



where R^8 is a methyl, ethyl or propyl radical, and

R^3 is, for example



According to the present invention, the substituents R^2 and R^3 of the compound (I) can, independently of one another, be in an α or β conformation with respect to the tropane ring.

The specificity of one derivative of the present invention with respect to another is related to the substituents R^1, R^2 and R^3 and to their configuration in space. The face on which the

substituents are found is the face which is recognized by the receptor. The steric hindrance of the complexing combination alters the recognition face and the approach to the receptor, and also the attachment of the molecule to the receptor.

Each substituent is essential to the recognition and to the specificity of the molecule for its receptor. Each position has a distinguishing feature which is essential to the recognition and the formation of binding(s). By virtue of these specificities, the molecule bonded to the receptor leads to a biological process and to an effect on the nervous system.

The references [1] to [19] in the list of references below describe various chemical procedures of the state of the art which can be used for the preparation of the derivatives of the present invention, in particular for the synthesis of the tropane ring and for the attachment of the substituents to the 2 and 3 positions and to the nitrogen of the tropane ring.

The tropane derivatives of the present invention have an improved activity in the study of some cerebral reuptake processes, such as dopamine reuptake, serotonin reuptake and acetylcholine reuptake.

The tropane derivatives of the present invention additionally exhibit the advantage of attaching a complexing combination for metals, such as Tc, without hindering the face recognized by the receptor during its biological activity. There is no hindrance of the substituents in the 1, 2 and 3 positions of the ring by this complexing combination.

They therefore have greater affinities for the receptor than those of the compounds of the prior art.

They can be used, for example, bonded by chelation to a metal or a metal complex.

The present invention consequently also relates to a chelation product comprising a tropane derivative according to the present invention and a metal or a metal complex.

The metal can, for example, be a transition metal, for example chosen from Tc, Ru, Co, Cu, Pt, Fe, Cs, Ir, Re, Cr, Mo, Mn, Ni, Rh, Pd, Nb, Sn and Ta, or one of their isotopes or oxides.

The metal complex can, for example, be a nitrido complex of radioactive transition metals which can be used as radiopharmaceutical products for diagnosis or therapy.

The radiopharmaceutical products using the ^{99m}Tc radionucleide are very useful in nuclear medicine for diagnosis because of their physical and chemical characteristics. Technetium complexes which can be used for the present invention are described, for example, by E. Deutsch et al. in: Progr. Inorg. Chem. (Australia), vol. 30, pp. 75-106, 1983, and preparation processes are described by J. Baldas et al. in J. Chem. Soc. Dalton Trans., 1961, pp. 1796-1801, in Int. Appl. Radiot. Isot., 36 (1985), pp. 133-139, in International Patent Application WO 85/03063 and in Patent Applications EP-A-537 242 and EP-A-0 403 524.

The complexes which can be used for therapy can, for example, be rhenium complexes.

According to the invention, the metal can advantageously be chosen from Tc, Re, TcN, TcO, TcO_2, ReO, ReN and ReO_2.

The tropane derivative of the present invention is therefore of use in the manufacture of a medicament or a product for diagnosis, for example in the manufacture of a radiopharmaceutical for therapy or for diagnosis.

It is of use in the manufacture of a radiopharmaceutical having an improved effectiveness for visualizing the reuptake of dopamine or serotonin.

Likewise, the chelation product of the present invention is of use in the manufacture of a radiopharmaceutical for therapy or diagnosis.

In particular, the chelation product of the present invention is of use in the manufacture of a radiopharmaceutical for visualizing the reuptake of dopamine or serotonin.

Use may be made, in preparing a chelation product according to the present invention, of any process known to a person skilled in the art comprising the manufacture of a tropane derivative of the present invention according to one of the processes defined above and a reaction for the complexing of a metal or of a metal complex by the said chelation compound X in order to obtain the said chelation product.

This metal or metal complex can be one of those mentioned above.

The present invention also makes it possible to form a diagnostic kit comprising a tropane derivative

corresponding to the above formula (I). This kit is a powerful diagnostic tool.

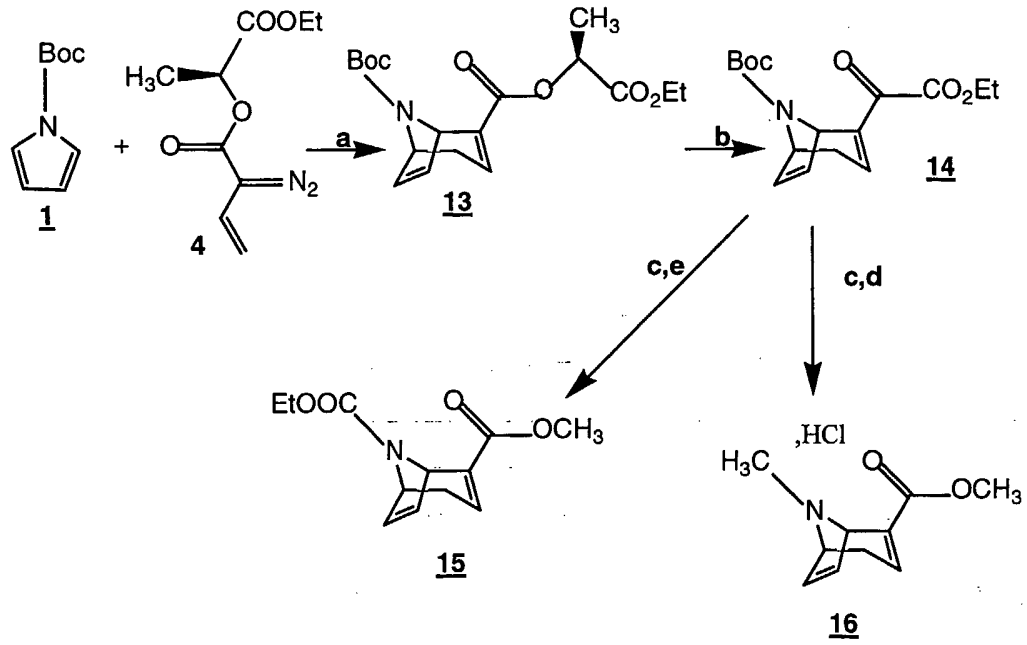
The complexing system situated on the 6 and 7 positions of the ring according to the present invention avoids presenting an obstacle to the pharmacophoric groups (R^1, R^2 and R^3) responsible for the attachment to the transporters of the monoamines. The novelty is based in particular on the fact that the derivatives of the present invention act both as carrier molecule and as system for complexing the technetium. One of the advantageous properties is the change from a piperidine structure not recognized by the transporters of the monoamines, in the molecule not comprising technetium, to a recognized tropane structure, when the metal is included therein.

Other characteristics and advantages will become more fully apparent to a person skilled in the art on reading the examples which follow, given by way of illustration and without implied limitation.

EXAMPLES

EXAMPLE I: SYNTHESIS OF TROPANE DERIVATIVES ACCORDING TO THE PRESENT INVENTION HYDROXYLATED IN THE 6 AND 7 POSITIONS OF THE TROPANE RING

EXAMPLE OF SYNTHESES No. 1



Synthetic Scheme No. 1

Conditions and reactants: (a) Rh(II) octanoate, hexane, 1h 30 reflux; (b) MeONa/MeOH, 2 hours at ambient temperature; (c) TFA, CH_2Cl_2, 2 hours; (d) 1) H_2CO, K_2CO_3, CH_3CN, 2 hours at ambient temperature. 2) $KaBH_3CN$, 12 hours at ambient temperature. 3) HCl; (e) EtOCOCl, benzene, Na_2CO_3, 12 hours.

1) Preparation of compound 1: N-(tert-Butyloxy-carbonyl)pyrrole.

Di(tert-butyl) dicarbonate (61.9 g; 283 mmol) and 4-(N,N-dimethylamino)pyridine (DMAP; 2.8 g; 22.9 mmol) are added to a solution of pyrrole (20.25 g; 302 mmol) in predistilled acetonitrile (30 ml). The

reaction mixture is stirred under argon for 3 days at ambient temperature.

After evaporating the solvent under vacuum, the brown oil obtained is taken up in ether and then washed with saturated aqueous ammonium chloride solution (150 ml) and saturated sodium chloride solution (150 ml). The organic phase is finally dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum.

The oily residue is then purified by chromatography on silica gel (pentane/ether: 9/1).

The product 1 is then obtained in the form of a light oil.

The yield is 78% (38.55 g; 230 mmol).

2) Preparation of compound 4: (1S)-2-Ethoxy-1-methyl-2-oxoethyl 2-diazo-3-butanoate.

The compound (1S)-2-ethoxy-1-methyl-2-oxoethyl 2-diazo-3-butanoate (6.95 g; 30.45 mmol) is dissolved in absolute ethanol (30 ml) and then the solution is cooled to 0°C in an ice bath. Sodium borohydride (2 g; 52.88 mmol) is then added in small portions over 10 minutes. After 2 hours at 0°C, the solution obtained is poured into an ice-cold saturated aqueous NH_4Cl solution (150 ml) and is then extracted with dichloromethane (4 × 60 ml).

The organic phases are combined and backextracted with a cold saturated aqueous NaCl solution (150 ml). After drying the organic phase with Na_2SO_4 and filtering, the solvent is evaporated at 25°C under vacuum, resulting in the intermediate alcohol in the form of a bright yellow oil (6.21 g; 26.97 mmol).

This oil is dissolved in dry dichloromethane (50 ml) and triethylamine (23.2 ml; 16.64 g; 164.51 mmol) and then the solution is cooled at 0°C in an ice bath. A solution of $POCl_3$ (5.8 ml; 9.51 g; 62.03 mmol) in dry CH_2Cl_2 (20 ml) is then added dropwise over 15 min and the reaction mixture is left to slowly reheat to ambient temperature overnight with stirring. The solution obtained is subsequently poured into ice-cold water (300 ml) and then extracted with ether (5 × 60 ml).

The organic phases are combined and washed with a saturated aqueous $NaHCO_3$ solution (100 ml) and then with saturated sodium chloride solution (100 ml). The solvent is then evaporated under reduced pressure and the brown oil obtained is carefully triturated in a pentane/ether (1/1) solution.

After filtering and evaporating the solvent under vacuum, the compound 4 is purified by chromatography on silica gel (pentane/ether : 4/1) and recovered in the form of an orange oil.

The yield is 45% (2.90 g; 13.70 mmol).

3) Preparation of compound 13: (1S)-2-Ethoxy-1-methyl-2-oxoethyl (1R,5R)-8-[(1,1-dimethylethoxy)carbonyl]-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate.

This chemical reaction is referenced "**a**" in Synthetic Scheme No. 1.

A solution of protected pyrrole (compound 1) (0.177 mol) and of rhodium(II) octanoate (0.442 mmol) in hexane (150 ml) is brought to reflux for 1h 30 under argon. After the rhodium complex has dissolved, the diazo compound (compound 4) (28.27 mmol), in solution in hexane (20 ml), is added dropwise over 1 hour. At

the end of the addition, the reaction mixture is left at reflux for 1h 30.

After cooling and evaporating the solvent under vacuum, the product is purified by chromatography on silica gel (pentane/ether: 4/1 then 3/2). The excess protected pyrrole is recovered and then the expected compound is isolated in the form of an orange-coloured oil.

The yield is 82%.

4) Preparation of compound 14: Methyl (1R,5R)-8-[(1,1-dimethylethoxy)carbonyl]-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate.

This chemical reaction is referenced "**b**" in Synthetic Scheme No. 1.

General procedure: A solution of the appropriate tropane (0.18 mol) in CH_3OH (200 ml) is added over 15 min to a solution of CH_3ONa (1.44 mmol) in dry methanol (850 ml) at 0°C and under argon. The reaction medium is stirred for 1 hour and then it is concentrated under reduced pressure. A saturated aqueous NH_4Cl solution (1 l) is added and the aqueous solution is extracted with ether (3 × 300 ml).

The organic phases are combined, backextracted with saturated sodium chloride solution (500 ml), dried and then filtered. The solvent is then evaporated and the residue is purified by column chromatography on silica gel (ether/pentane).

The yield is 95%.

5) Preparation of compound 15: Methyl (1R,5R)-8-(ethoxycarbonyl)-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate.

This chemical reaction is referenced "**c,e**" in Synthetic Scheme No. 1.

Trifluoroacetic acid (500 µl; 0.65 mmol; 16 equivalents) is added to a solution of compound **14** (105 mg; 0.396 mmol) in benzene (15 ml). The reaction takes place at ambient temperature and under argon for 18 h. The solution is subsequently basified to pH 8-9 by addition of solid K_2CO_3 and ethyl chloroformate (200 µl; 1.58 mmol; 4 equivalents) is added. The reaction mixture is left at ambient temperature and under argon for 12 hours.

After evaporating the benzene under vacuum, the white powder obtained is suspended in water (40 ml). The aqueous phase is then extracted with ether (3 × 20 ml). The ethereal phase formed is washed with a saturated aqueous $NaHCO_3$ solution (20 ml) and then a saturated aqueous NaCl solution (20 ml). It is finally dried over anhydrous Na_2SO_4.

After filtering and evaporating under vacuum, the crude product is purified by chromatography on silica gel (pentane/ether 3:2) to produce compound 15 in the form of an orange-coloured oil.

The yield is 90% (85 mg).

6) Preparation of compound 16: Methyl (1R,5R)-8-methyl-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate.

This chemical reaction is referenced "**c,d**" in Synthetic Scheme No. 1.

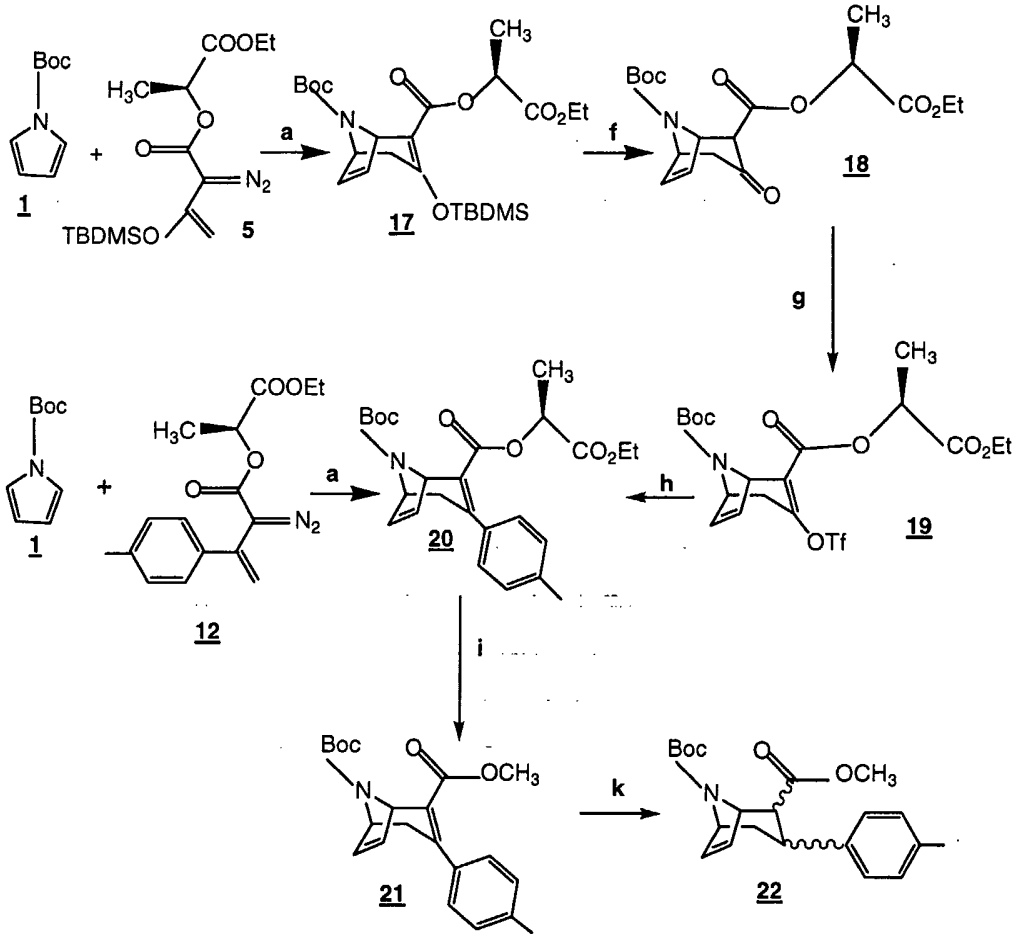
The tropane derivative **14** (159 mg; 0.6 mmol) is dissolved in acetonitrile dried over a molecular sieve. After addition of trifluoroacetic acid (1 ml; 13 mmol), the reaction mixture is stirred for 24 hours and then basified with K_2CO_3. A large excess of 37% formaldehyde in water is then added (10 equivalents). The excess K_2CO_3 is filtered off and a large excess of $NaBH_3CN$ (10 equivalents) is added to the filtrate recovered.

After stirring overnight at ambient temperature, a saturated aqueous $NaHCO_3$ solution is added. The phases are separated and the aqueous phase is extracted with chloroform. The organic phases collected are washed with a saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum.

The residue obtained is taken up in water and acidified by addition of a dilute HCl solution. The aqueous phase is washed with ether and is then evaporated. Compound **16** is then obtained in the hydrochloride form.

The yield is 64%.

EXAMPLE OF SYNTHESES No. 2



Synthetic Scheme No. 2

Conditions and reactants: (a) Rh(II) octanoate, hexane, 1h 30 under reflux; (f) TBAF, THF, 0°C, 1 hour; (g) 1) NaHMDS, THF, -78°C, 2) $PhNTf_2$, THF, 12 hours; (h) p-tolylboronic acid, Pd_2dba_3, LiCl, 2.0M Na_2CO_3/H_2O, DME, 1 hour under reflux; (i) CH_3ONa, CH_3OH, 24 hours at ambient temperature; (k) SmI_2, CH_3OH, THF, -78°C, 1 hour.

1) Preparation of compound 1: see synthesis No. 1 above.

2) Preparation of compound 3: (1S)-2-Ethoxy-1-methyl-2-oxoethyl 2-diazo-3-oxobutanoate.

This chemical reaction is not represented in Synthetic Scheme No. 2.

A solution of appropriate compound (0.215 mol) and of p-acetamidobenzenesulphonyl azide (p-ABSA; 50 g; 0.208 mol) in dry acetonitrile (250 ml) is prepared with stirring and then triethylamine is added (32 ml). One minute after the addition, a cream-coloured precipitate is formed. The reaction is then left under vigorous stirring at ambient temperature and under argon for 24 hours.

The reaction mixture is subsequently filtered and the precipitate is washed with ether. The filtrate obtained is evaporated under vacuum, resulting in a viscous brown oil, which is carefully triturated with a pentane/ether (1/1) mixture and then filtered through celite.

The filtrate is concentrated under reduced pressure and the brown oil obtained is purified by chromatography on silica gel (eluent = pentane/ether: 4/1). The product 3 is provided in the form of a pale yellow oil.

The yield is 92% (45.42 g; 0.199 mol).

3) Preparation of compound 5: (1S)-2-Ethoxy-1-methyl-2-oxoethyl 3-[(1,1-dimethylethoxy)dimethylsiloxy]-2-diazo-3-butenoate.

This chemical reaction is not represented in Synthetic Scheme No. 2.

Triethylamine (2 ml; 14.3 mmol) is added to a solution of compound 3 (3.1 g; 13.5 mmol) in dry CH_2CH_2 (25 ml) at 0°C and under argon. tert-Butyldimethylsilyl

trifluoromethanesulphonate (TBDMSOTf; 2.8 ml; 12.2 mmol) is added slowly and then the reaction medium is stirred at 0°C for 45 min. The reaction mixture is subsequently diluted in hexane (100 ml) and then washed with an aqueous sodium bicarbonate solution (100 ml) and saturated sodium chloride solution (100 ml).

After drying the organic phase over anhydrous Na_2SO_4 and then evaporating the solvent under vacuum, the expected product **5** is recovered in the form of a bright orange oil which does not require additional purification.

The yield is 95% (4.44 g; 12.98 mmol).

4) Preparation of compound 12: (1S)-2-Ethoxy-1-methyl-2-oxoethyl 3-p-tolyl-2-diazo-3-butenoate.

This chemical reaction is not represented in Synthetic Scheme No. 2.

Compound **12** was prepared from compound **11** with a yield of 45% using the procedure described for compound **3**.

5) Preparation of compound 17: (1S)-2-Ethoxy-1-methyl-2-oxoethyl (1R,5R)-8-[(1,1-dimethylethoxy)carbonyl]-3-[(1,1-dimethylethoxy)dimethylsiloxy]-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate.

This chemical reaction is referenced "**a**" in Synthetic Scheme No. 2.

This compound was prepared from compound **5** with a yield of 75% using the general procedure described for compound **13**.

6) Preparation of compound 18: (1S)-2-Ethoxy-1-methyl-2-oxoethyl (1R,5R)-8-[(1,1-dimethylethoxy)carbonyl]-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-2-carboxylate.

This chemical reaction is referenced "**f**" in Synthetic Scheme No. 2.

A 1M solution in THF of tetrabutylammonium fluoride (TBAF; 7.0 ml; 7.0 mmol) is added dropwise to a solution of compound **17** (3.38 g; 7.0 mmol) in freshly distilled THF (25 ml). The reaction medium is stirred at ambient temperature for 45 minutes and 100 ml of water are added.

The solution is extracted with ether (4 × 100 ml) and the organic phases are combined, dried (Na_2SO_4) and evaporated under vacuum. The crude product obtained is subsequently purified by chromatography on silica gel (1/1 pentane/ether) to give a mixture of tautomers of the expected product **18** in the form of an oil.

7) Preparation of compound 19: (1S)-2-Ethoxy-1-methyl-2-oxoethyl (1R,5R)-8-[(1,1-dimethylethoxy)carbonyl]-3-(trifluoromethanesulphonyloxy)-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate.

This chemical reaction is referenced "**g**" in Synthetic Scheme No. 2.

Sodium bis(trimethylsilyl)amide, as a 1.0M solution in THF (NaHMDS; 2.85 ml; 2.245 mmol), is slowly added to a solution of **18** (0.750 g; 2.041 mmol) in dry THF (40 ml) at -78°C and under argon. After stirring at -78°C for 30 min, N-phenyltrifluoromethanesulphonimide (0.735 g; 2.057 mmol) is added all at once and the reaction medium is subsequently left to slowly reheat to ambient temperature and is stirred overnight. The THF is

evaporated and the residue is taken up in dichloromethane (50 ml) and then washed with water (100 ml) and a saturated aqueous NaCl solution (100 ml).

After drying the organic phase over anhydrous Na_2SO_4 and evaporating the solvent under vacuum, compound **19** is purified by chromatography on silica gel (pentane/ether: 4/1) and isolated in the form of an oil.

The yield is 22% (0.225 g; 0.449 mmol).

8) Preparation of compound 20: (1S)-2-Ethoxy-1-methyl-2-oxoethyl (1R,5R)-8-[(1,1-dimethylethoxy)carbonyl]-3-(p-tolyl)-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate.

This chemical reaction is carried out by the routes referenced "**h**" or "**a**" in Synthetic Scheme No. 2, depending on the precursor used.

- Chemical reaction referenced "**h**":

The compound triflate **19** (0.650 g; 1.01 mmol), p-tolylboronic acid (0.230 g; 1.692 mmol) LiCl (0.115 g; 2.733 mmol), tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3; 52 mg; 0.057 mmol) and a 2.0M aqueous Na_2CO_3 solution (1.26 ml) are mixed in 1,2-dimethoxyethane (DME; 6 ml) under argon and then heated at reflux for 1 hour.

After returning to ambient temperature, the solution obtained is filtered through celite and washed with ether. The filtrate is subsequently basified with concentrated aqueous ammonia solution and washed with a saturated aqueous NaCl solution. The organic phase is dried over anhydrous Na_2SO_4, the solvents are evaporated

under vacuum and the oily residue is purified by chromatography on silica gel (pentane/ether: 4/1) to produce the expected product **20** in the form of a light oil.

The yield is 33% (0.190 g; 0.430 mmol).

- Chemical reaction reference "**a**": It follows the same procedure as that described above for the synthesis of compound **13**, using the compounds **1** and **12**.

9) Preparation of compound 21: Methyl (1R,5R)-8-[(1,1-dimethylethoxy)carbonyl]-3-(p-tolyl)-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate.

This compound was prepared from **20** with a yield of 95% using the general procedure described above for the synthesis of compound **14**.

10) Preparation of compound 22: Methyl (1R,2R,3R,5R)-8-[(1,1-dimethylethoxy)carbonyl]-3-(p-tolyl)-8-azabicyclo[3.2.1]oct-6-ene-2-carboxylate.

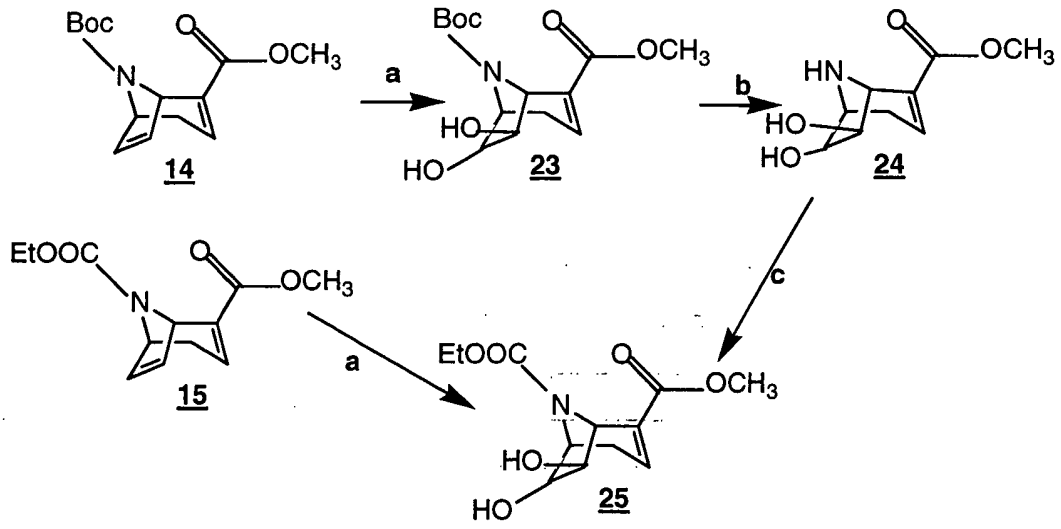
This chemical reaction is referenced "**k**" in Synthetic Scheme No. 2.

A solution of tropane derivative (0.1 mmol) in dry THF, at -78°C and under argon, is prepared. A 0.1M solution of samarium iodide (0.45 mmol) in THF is added, the dry mixture is stirred for 30 min and then anhydrous methanol (0.5 ml) is added. After stirring for 2 hours at -78°C, acetic acid (0.5 ml) is added and then the reaction mixture is basified with aqueous ammonia solution and extracted with ether. The organic phases are combined, dried (Na_2SO_4) and filtered, and the solvent is evaporated under vacuum.

The residue obtained is subsequently purified by column chromatography on silica gel (pentane/ether) to produce the four expected isomeric products.

The yield is 85%.

EXAMPLE OF SYNTHESES No. 3



Synthetic Scheme No. 3

1) Preparation of compound 23: Methyl (1R,5R,6R,7R)-8-[(1,1-dimethylethoxy)carbonyl]-6,7-dihydroxy-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylate.

This chemical reaction is referenced "**a**" in Synthetic Scheme No. 2.

Compound **14** (0.8 mmol) is dissolved in acetone (20 ml) and a 2.5% solution of osmium tetroxide in tert-butanol (0.9 mmol) is added. The combined mixture is heated at reflux with stirring under argon for 12 hours. After returning to ambient temperature, the reaction is neutralized by addition of a large excess of sodium bisulphite and stirred for 1 h. The solvents are evaporated and the residue obtained is taken up in water and extracted with diethyl ether (3 × [lacuna]).

The organic phases are combined and then backextracted with a saturated aqueous NaCl solution (2 × [lacuna]).

After drying the ethereal phase over Na_2SO_4, the solvent is evaporated to result, without additional purification, in the expected compound **23**.

The yield is 99%.

2) Preparation of compound 24: Methyl (1R,5R,6R,7R)-6,7-dihydroxy)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylate.

This chemical reaction is referenced "**b**" in Synthetic Scheme No. 3.

Trifluoroacetic acid (500 µl; 6.33 mmol; 16 equivalents) is added to a solution of derivative **23** (105 mg; 0.396 mmol) in dichloroethane (15 ml). The reaction medium is stirred at ambient temperature and under argon for 1 hour. The solvent is evaporated under vacuum and the residue is taken up in water and then washed with ether. The aqueous phase is evaporated to result in the ammonium trifluoroacetate **24**, which does not require additional purification.

The yield is 95%.

3) Preparation of compound 25: Methyl (1R,5R)-8-(ethoxycarbonyl)-6,7-dihydroxy-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylate.

This chemical reaction is referenced "**c**" or "**a**" in Synthetic Scheme No. 3.

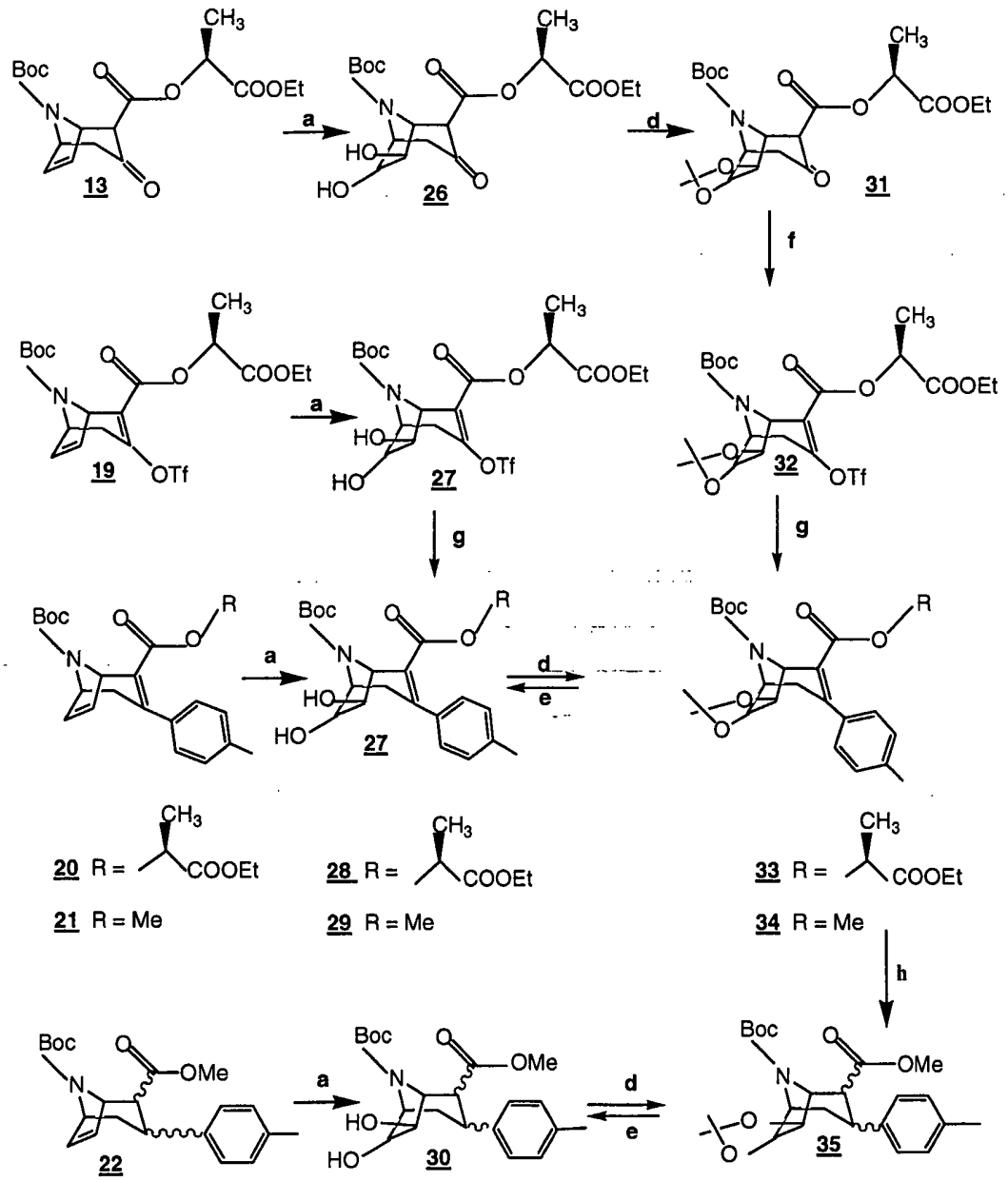
- Procedure "**c**": Prepared from **15** with a yield of 99% using the procedure described for **23**.

- Procedure "**b**": The ammonium trifluoroacetate compound **24** (0.396 mmol) is dissolved in benzene (10 ml) and, after addition of solid K_2CO_3 to pH 8-9, ethyl chloroformate (200 µl; 1.57 mmol; 4 equivalents) is added. The reaction mixture is stirred at ambient temperature and under argon for 12 hours. After evaporating the benzene under vacuum, the white powder obtained is suspended in water (40 ml). The aqueous phase is then extracted with ether (3 × 20 ml). The ethereal phase formed is washed with a saturated aqueous $NaHCO_3$ solution (20 ml) and then a saturated aqueous NaCl solution (20 ml). It is finally dried over anhydrous Na_2SO_4.

After filtering and evaporating under vacuum, the crude product is purified by chromatography on silica gel (pentane/ether 3:2) to produce compound **25** in the form of a white solid.

The yield is 90% (85 mg).

EXAMPLE OF SYNTHESES No. 4



Synthetic Scheme No. 4

Conditions and reactants: (a) $KMnO_4$, CH_3CN, under reflux, 12 hours; (b) TFA, CH_2Cl_2, 2 hours; (c) EtOCOCl, benzene, K_2CO_3, 12 hours at ambient temperature; (d) $(CH_3)_2C(OCH_3)_2$, DMF, cat. PTSA, ambient temperature, 8 hours; (e) PTSA, CH_3OH, ambient temperature, 1 hour; (f) 1) NaHMDS, THF, -78°C, 2)

$PhNTf_2$, THF, 12 hours; (g) p-tolylboronic acid, Pd_2dba_3, LiCl, 2.0M Na_2CO_3/H_2O, DME, 1 hour under reflux; (h) SmI_2, CH_3OH, THF, -78°C, 1 hour.

1) Preparation of compound 26: (1S)-2-Ethoxy-1-methyl-2-oxoethyl (1R,5R,6R,7R)-8-[(1,1-dimethylethoxy)carbonyl]-6,7-dihydroxy-3-oxo-8-azabicyclo[3.2.1]octane-2-carboxylate.

This chemical reaction is referenced "**a**" in Synthetic Scheme No. 4.

This compound is prepared from compound **13** with a yield of 99% using the procedure described above for compound **23**.

2) Preparation of compound 27: (1S)-2-Ethoxy-1-methyl-2-oxoethyl (1R,5R,6R,7R)-8-[(1,1-dimethylethoxy)carbonyl]-6,7-dihydroxy-3-(trifluoromethanesulphonyloxy)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylate.

This chemical reaction is referenced "**a**" in Synthetic Scheme No. 4.

This compound is prepared from **19** with a yield of 99% using the procedure described for compound **23**.

3) Preparation of compound 28: (1S)-2-Ethoxy-1-methyl-2-oxoethyl (1R,5R,6R,7R)-8-[(1,1-dimethylethoxy)carbonyl]-6,7-dihydroxy-3-(p-tolyl)-8-azabicyclo[3.2.1]-oct-2-ene-2-carboxylate.

This chemical reaction is referenced "**a**" in Synthetic Scheme No. 4.

This compound is prepared from compound **20** with a yield of 99% using the general procedure described for compound **23**.

4) Preparation of compound 29: Methyl (1R,5R,6R,7R)-8-[(1,1-dimethylethoxy)carbonyl]-6,7-dihydroxy-3-(p-tolyl)-azabicyclo[3.2.1]oct-2-ene-2-carboxylate.

This chemical reaction is referenced "**a**" in Synthetic Scheme No. 4.

This compound is prepared from compound **21** with a yield of 99% using the general procedure described for compound **23**.

5) Preparation of compound 30: Methyl (1R,2R,3R,5R,6R,7R)-8-[(1,1-dimethylethoxy)carbonyl]-6,7-dihydroxy-3-(p-tolyl)-8-azabicyclo[3.2.1]octane-2-carboxylate.

This chemical reaction is referenced "**a**" in Synthetic Scheme No. 4.

This compound is prepared from compound **22** with a yield of 99% using the general procedure described for compound **23**.

6) Preparation of compound 31: (1S)-2-Ethoxy-1-methyl-2-oxoethyl (1R,5R,6R,7R)-8-[(1,1-dimethylethoxy)carbonyl]-6,7-(isopropylidenedioxy)-3-oxo-8-azabicyclo-[3.2.1]octane-2-carboxylate.

This chemical reaction is referenced "**d**" in Synthetic Scheme No. 4.

2,2-Dimethoxypropane (2.9 mmol) and a spatula tip of para-toluenesulphonic acid are added to a solution of tropanediol (0.58 mmol) in dry DMF (20 ml). The mixture is stirred at ambient temperature and under argon for 12 hours. The solution is subsequently diluted with saturated sodium chloride solution (30 ml)

and then extracted with diethyl ether (4 × 20 ml). The organic phases are combined and dried (Na_2SO_4), and the solvent is evaporated to give an oily residue which is purified by chromatography on silica gel with pentane/ether as mobile phase.

The expected compound is isolated in the form of an oil.

7) Preparation of compound 32: (1S)-2-Ethoxy-1-methyl-2-oxoethyl (1R,5R,6R,7R)-8-[(1,1-dimethylethoxy)carbonyl]-6,7-(isopropylenedioxy)-3-(trifluoromethanesulphonyloxy)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylate.

This chemical reaction is referenced "**f**" in Synthetic Scheme No. 4.

This compound is prepared from compound **31** with a yield of 20% using the general procedure described for compound **19**.

8) Preparation of compound 33: (1S)-2-Ethoxy-1-methyl-2-oxoethyl (1R,5R,6R,7R)-8-[(1,1-dimethylethoxy)carbonyl]-6,7-(isopropylidenedioxy)-3-(p-tolyl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylate.

These chemical reactions are referenced "**g**" or "**d**" in Synthetic Scheme No. 4.

- Procedure "**g**": Prepared from compound **32** with a yield of 90% using the general procedure described for compound **20**.

- Procedure "**d**": Prepared from compound **28** with a yield of 85% using the general procedure described for compound **31**.

9) Preparation of compound 34: Methyl (1R,5R,6R,7R)-8-[(1,1-dimethylethoxy)carbonyl]-6,7-(isopropylidene-dioxy)-3-(p-tolyl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylate.

These chemical reactions are referenced "**g**" or "**d**" in Synthetic Scheme No. 4.

- Procedure "**g**": Prepared from compound **33** with a yield of 90% using the general procedure described for compound **14**.

- Procedure "**d**": Prepared from compound **29** with a yield of 85% using the general procedure described for compound **31**.

10) Preparation of compound 35: Methyl (1R,2R,3R,5R,6R,7R)-8-[(1,1-dimethylethoxy)carbonyl]-6,7-(isopropylidenedioxy)-3-(p-tolyl)-8-azabicyclo-[3.2.1]octane-2-carboxylate.

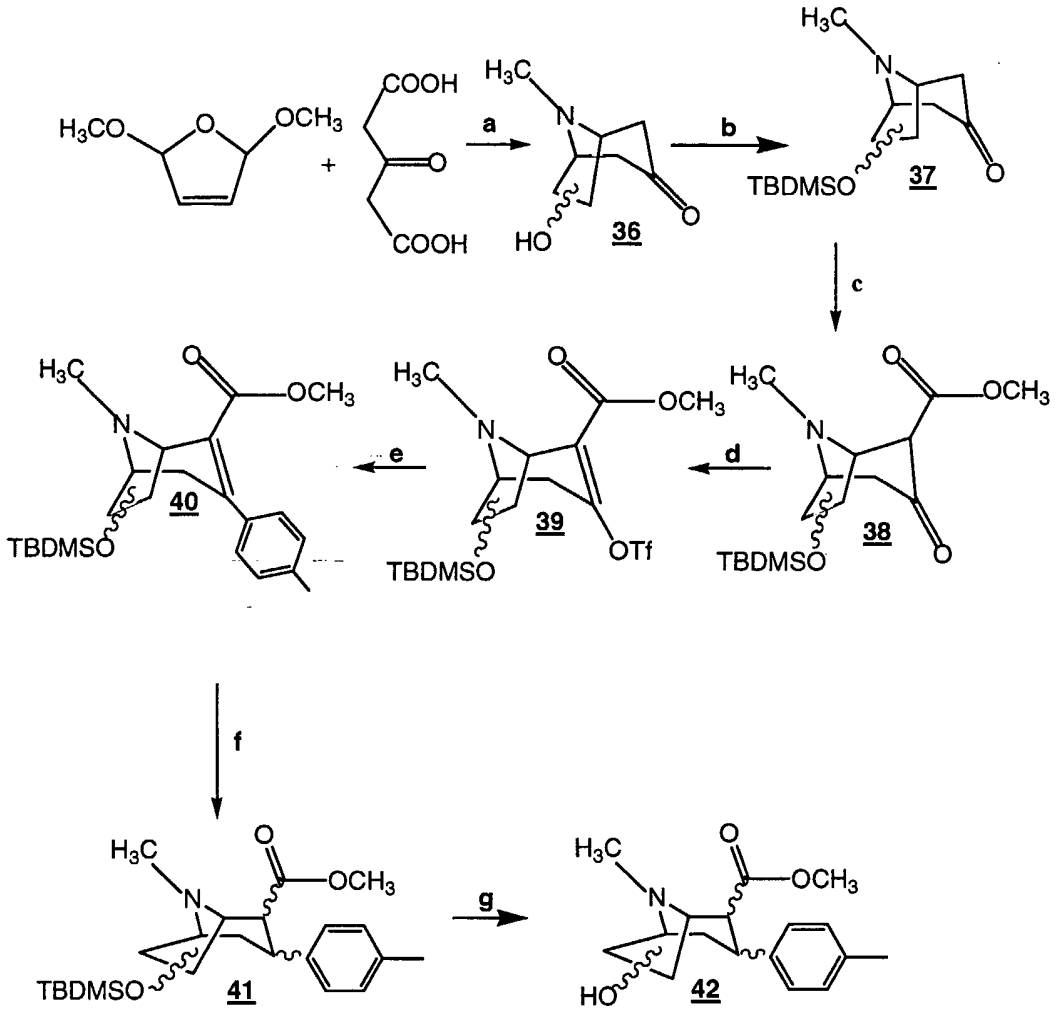
These chemical reactions are referenced "**h**" or "**d**" in Synthetic Scheme No. 4.

- Procedure "**h**": Prepared from compound **34** with a yield of 90% using the general procedure described for compound **22**.

- Procedure "**d**": Prepared from compound **30** with a yield of 85% using the general procedure described for compound **31**.

EXAMPLE II: SYNTHESES OF TROPANE DERIVATIVES ACCORDING TO THE PRESENT INVENTION HYDROXYLATED IN THE 5 OR 6 POSITIONS OF THE TROPANE RING

EXAMPLE OF SYNTHESES No. 5



Synthetic Scheme No. 5

Conditions and reactants: (a) 1) 3N HCl, 16 hours; 2) NaOH, H_2O, NaOAc, two days; (b) TBDMSCl, imidazole, DMF, at ambient temperature, 24 hours; (c) 1) LDA, -78°C, THF, 2 hours; 2) $MeCO_2CN$, THF, -78°C to ambient temperature, 3 hours; (d) NaHMDS, $PhNTf_2$, THF, -78°C to ambient temperature, 12 hours; (e) p-tolylboronic acid, Pd_2dba_3, LiCl, 2.0M Na_2CO_3/H_2O, DME, 1 hour under reflux; (f) SmI_2, CH_3OH.

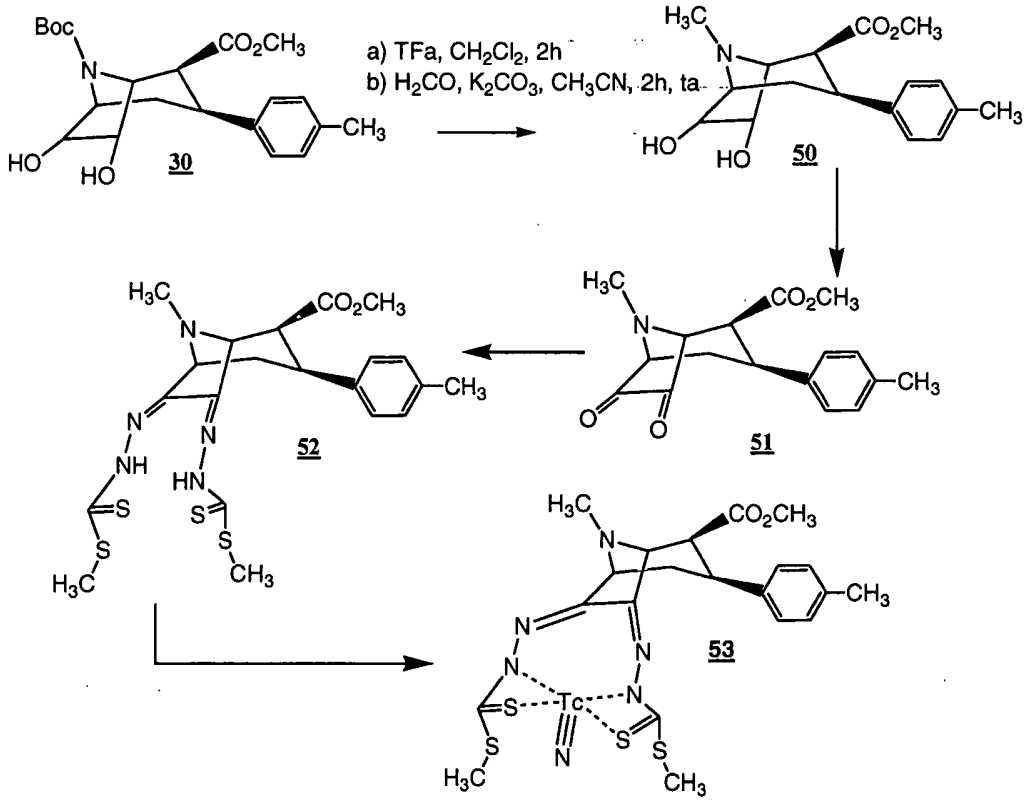
The procedure used is that described in J. Med. Chem., 2000, **43**, 3282-3294.

This is because this procedure makes it possible to obtain compounds **36** to **42** represented above in Synthetic Scheme No. 4.

EXAMPLE III: COUPLING OF COMPOUNDS OF THE PRESENT INVENTION WITH A CHELATING AGENT

A) Coupling of a compound according to the first alternative form of the first embodiment of the present invention

EXAMPLE OF SYNTHESES No. 6



Synthetic Scheme No. 6

1) Preparation of compound 51: Methyl (1S,2S,3S,5R)-8-methyl-6,7-dioxo-3-(p-tolyl)-8-azabicyclo[3.2.1]octane-2-carboxylate.

A solution of 20 mmol of DMSO in 10 ml of dried and distilled CH_2Cl_2 is cooled below -65°C and then trifluoroacetic acid (15 mmol) in 5 ml of CH_2Cl_2 is slowly added. After 10 minutes, a solution of methyl (1S,2S,3S,5R,7S)-8-methyl-6,7-dihydroxy-3-(p-tolyl)-8-azabicyclo[3.2.1]octane-2-carboxylate (compound **50**; 5 mmol) in 10 ml of CH_2Cl_2 is slowly added so as to maintain the temperature below -65°C.

The mixture is stirred for 30 minutes and then 4 ml of triethylamine are added dropwise, still at -65°C. After returning to ambient temperature (40 minutes), the reaction mixture is washed with water (20 ml) and the aqueous phase is reextracted with methylene chloride. The organic phases are combined, dried over Na_2SO_4 in CH_2Cl_2 and evaporated.

The product **51** is purified by chromatography on a column of silica (eluent: ether/5% Et_3N).

The yield is 85%.

2) Preparation of compound 52: Methyl (1S,2S,3S,5R)-8-methyl-6,7-bis(5-methyldithiocarbaza)-3-(p-tolyl)-8-azabicyclo[3.2.1]octane-2-carboxylate.

100 µmol of derivative **51** in 3 ml of anhydrous methanol and 210 µmol of S-methyl dithiocarbazate (DTCZ, 2 equivalents), freshly recrystallized from toluene (melting point: 81°C), are introduced into a round-bottomed flask. The reaction medium is heated at 60°C for one hour and then left to cool overnight with stirring. The solvent is evaporated and the residue obtained is purified by crystallization.

The yield is 70%.

3) Preparation of compound 53: Radiolabelling with technetium nitrido

- SYNTHESIS OF THE INTERMEDIATE TcN

100 µg of tin chloride, 5 mg of succinyl dihydrazide (SDH) and 5 mg of 1,2-propanediamine-N,N,N',N'-tetraacetic acid (PDTA) were lyophilized in a labelling flask. 3 ml of TcO_4 (60 mCi) are added to this lyophilizate. Reaction is allowed to take place for 15 minutes.

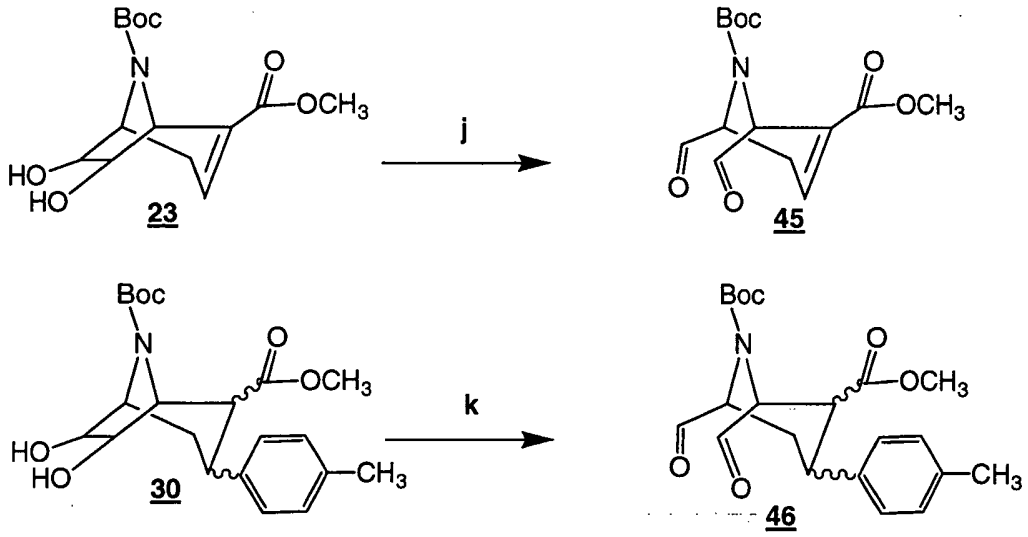
- COMPLEXING

2 mg of tropane-Schiff base derivative (compound **52**) in 200 µl of ethanol are added to 1 ml of TcN. The reaction is allowed to take place for thirty minutes. The reaction is analysed by HPLC.

The labelling yield is greater than 95%.

B) Coupling of a compound according to the second alternative form of the first embodiment of the present invention

EXAMPLE OF SYNTHESES No. 7



Synthetic Scheme No. 7

Conditions and reactants: (j) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 30 minutes at ambient temperature; (k) $NaIO_4$, EtOH, H_2O, $(NH_4)_2SO_4$, 0°C, 30 minutes.

1) Preparation of compound 45: Methyl (1R,5R)-6-[(1,1-dimethylethoxy)carbonyl]-1,5-dihydrocarbonyl-6-azacyclohex-2-ene-2-carboxylate.

A solution of sodium periodate (0.5 mmol) in water (2 ml) is added to a solution of tropanediol derivative (compound 23 described above) (0.3 mmol) in absolute ethanol (10 ml) and the combined mixture is stirred at ambient temperature for 30 minutes. The reaction mixture is subsequently neutralized with a saturated aqueous Na_2CO_3 solution and then extracted with ether (3 × 20 ml). The organic phases are combined and dried (Na_2SO_4), and the solvent is evaporated under vacuum.

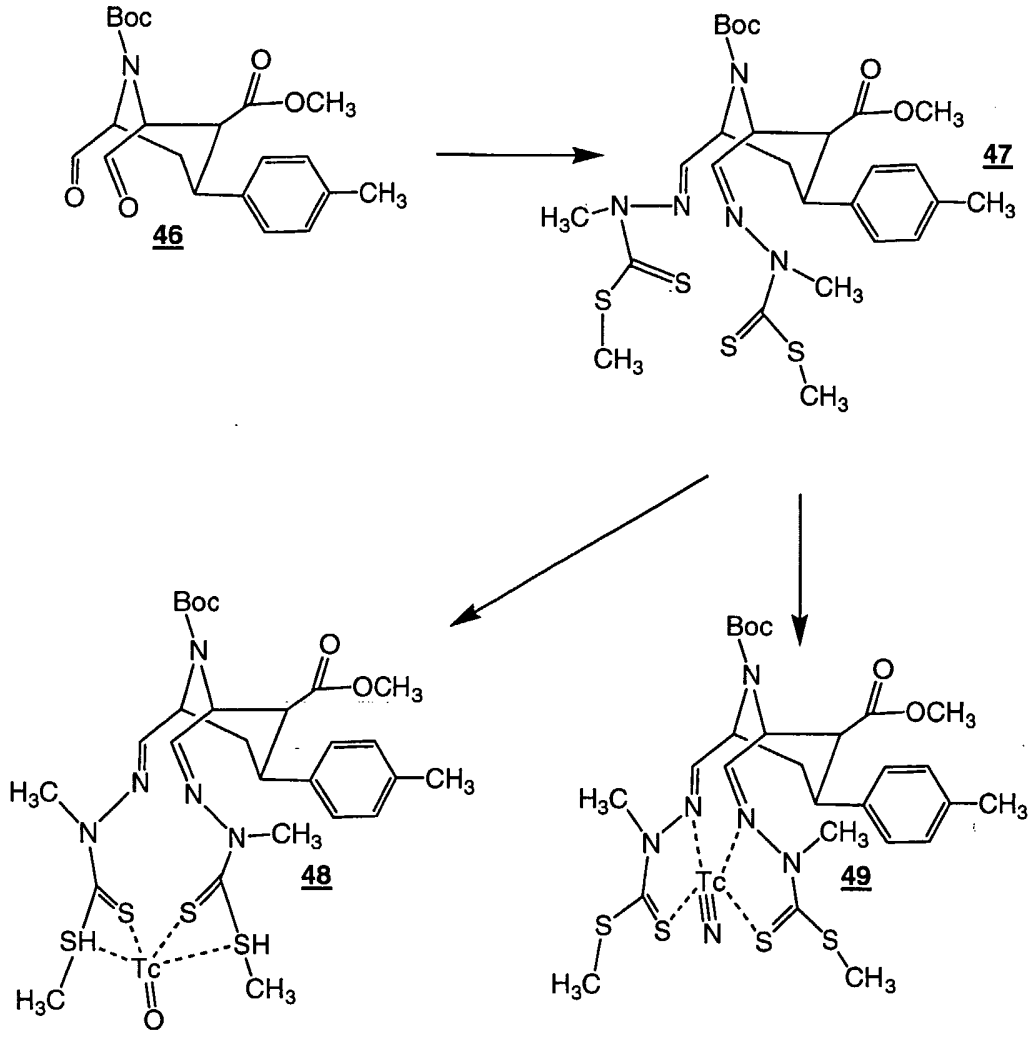
The residue is subsequently purified by chromatography on silica gel with ether as mobile phase.

The yield is 85%.

2) Preparation of compound 46: Methyl (1R,2R,3R,5R)-6-[(1,1-dimethylethoxy)carbonyl]-1,5-dihydrocarbonyl-3-(p-tolyl)-6-azacyclohexane-2-carboxylate.

This compound is prepared from compound **30** with a yield of 70% using the general procedure described above for compound **45**.

EXAMPLE OF SYNTHESES No. 8



Synthetic Scheme No. 8

1) Preparation of compound 47: Methyl (1R,2R,3R,5R)-6-[(1,1-dimethylethoxy)carbonyl]-1,5-bis(S-methyl dithiocarbazate)-3-(p-tolyl)-6-azacyclohexane-2-carboxylate.

353 µmol of tropane derivative in 3 ml of anhydrous methanol and 71 µmol of S-methyl dithiocarbazate (DTCZ, 2 equivalents), freshly recrystallized from toluene (melting point 81°C), are introduced into a round-bottomed flask. The reaction

medium is heated at 60°C for one hour and then allowed to cool overnight with stirring. The solvent is evaporated and the residue obtained is purified by crystallization.

The yield is 50%.

2) Preparation of compound 48: Radiolabelling with TcO

1 ml of TcO_4 is added to a flask comprising 2 mg of compound 47 and 5 mg of $SnCl_2$. Reaction is allowed to take place for 1 hour. The solution is analysed by HPLC.

The labelling yield is greater than 90%.

3) Preparation of compound 49: Radiolabelling with technetium nitrido

- **SYNTHESIS OF THE INTERMEDIATE TcN**

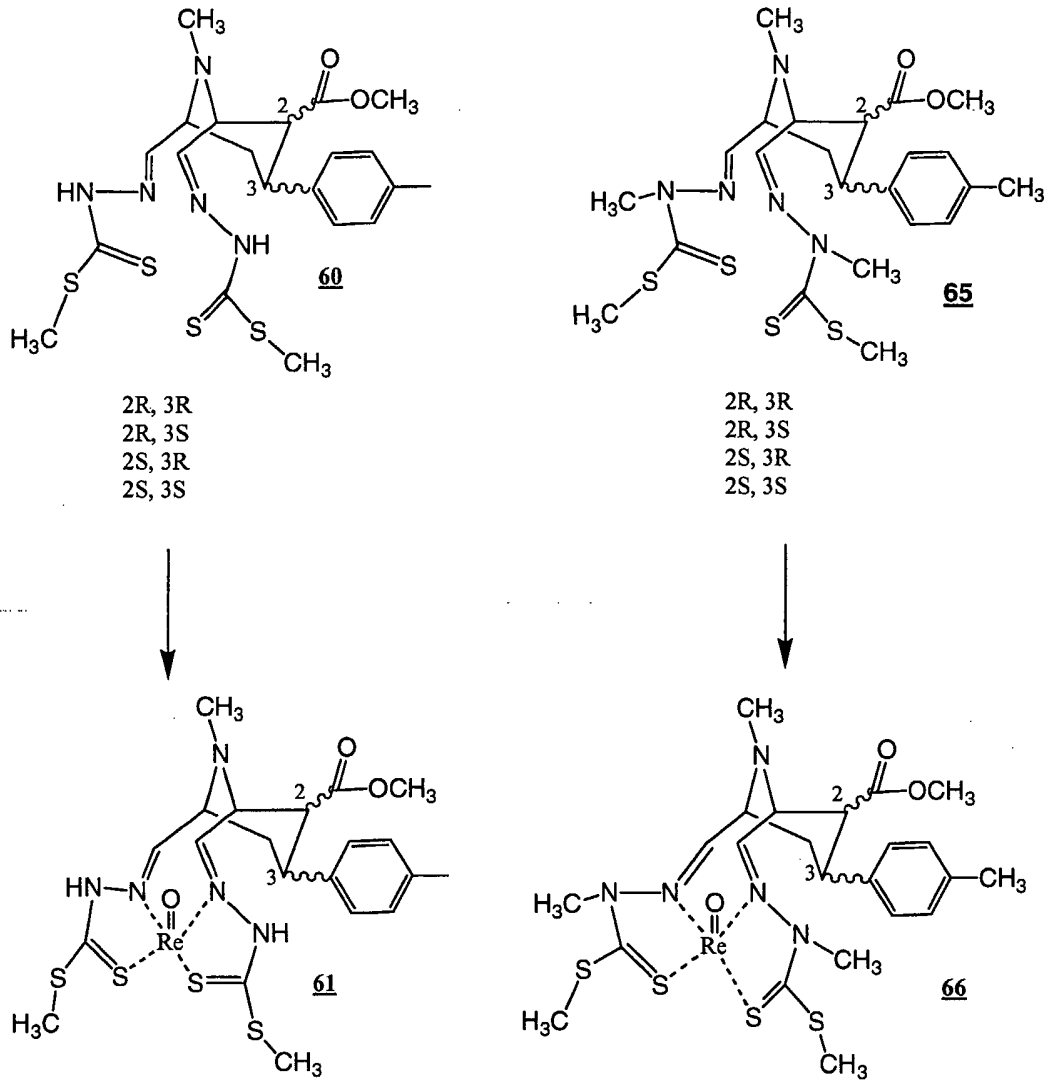
100 µg of tin chloride, 5 mg of succinyl dihydrazide (SDH) and 5 mg of 1,2-propanediamine-N,N,N',N'-tetraacetic acid (PDTA) were lyophilized in a labelling flask. 3 ml of TcO_4 (60 mCi) are added to this lyophilizate. Reaction is allowed to take place for 15 minutes.

- **COMPLEXING**

2 mg of tropane-Schiff base derivative (compound 47) in 200 µl of ethanol are added to 1 ml of TcN. Reaction is allowed to take place for thirty minutes. The reaction is analysed by HPLC.

The labelling yield is greater than 95%.

EXAMPLE OF SYNTHESES No. 9



Synthetic Scheme No. 9

1) Preparation of compounds 60 and 65

These compounds are obtained by the same processes as those used to produce compound 47 above.

2) Preparation of compounds 61 and 66: labelling with RcO

The reactants necessary for labelling with REO are added to a flask comprising 2 mg of compound **60** or **65** and reaction is allowed to take place for 1 hour. The solution is analysed by HPLC.

The labelling yield is greater than 90%.

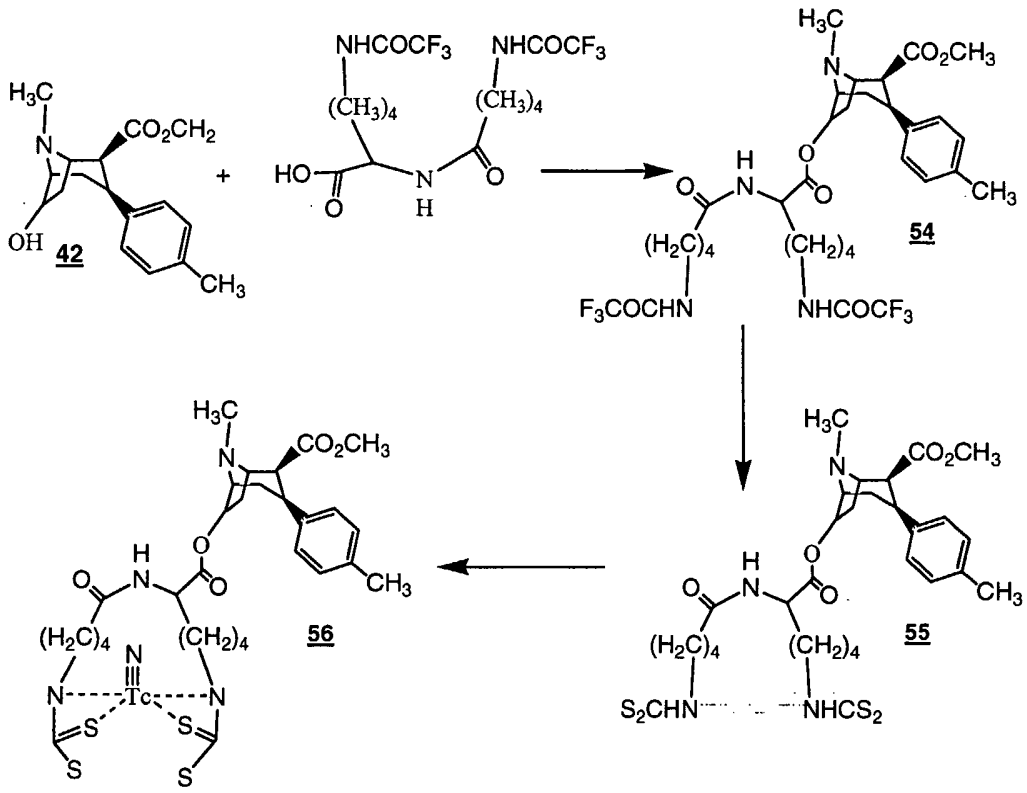
EXAMPLE OF SYNTHESES No. 10

The compounds **60** and **65** of the example of syntheses No. 9 are labelled with RcN (instead of the RcO used to manufacture compounds **61** and **66**).

Compounds **62** and **63** are thus obtained (not represented).

C) Coupling of a compound according to the second embodiment of the present invention

EXAMPLE OF SYNTHESES No. 11



Synthetic Scheme No. 11

1) Preparation of compound 54: Synthesis of methyl (1R,2S,3R,6S)-8-methyl-3-(p-tolyl)-6-[N^{ε},N^{δ}-bis(trifluoroacetyl)-N-(5-aminopentanoyl)lysinyloxy]-8-azabicyclo[3.2.1]octanoate.

0.8 equivalent of N^{ε},N^{δ}-bis(trifluoroacetyl)-N-(5-aminopentanoyl)lysine (0.65 mmol; respectively 293 mg) is added to a solution, stirred at ambient temperature and under an inert atmosphere, of compound **42** (200 mg; 0.8 mmol) in 20 ml of dichloromethane.

0.8 equivalent of DMAP (0.65 mmol; 80 mg) and 0.8 equivalent of EDCI (0.65 mmol, 125 mg) are subsequently added. After stirring for 15 hours, the reaction medium is washed with a 1M hydrochloric acid solution (20 ml) and then with saturated sodium

chloride solution (20 ml). The aqueous phases are systematically re-extracted with dichloromethane (20 ml) and the organic phases are dried over Na_2SO_4 and then filtered.

The solvent is evaporated and compound **54** is recovered in the form of a yellow oil with a yield of 30%.

2) Preparation of compound 55: deprotection and synthesis of the bisdithiocarbamate compound

10 mmol of derivative **54** are dissolved in 5 ml of absolute methanol. 5 ml of a 0.1M solution of piperidine in methanol are added and the mixture is left stirring for 1 hour. The combined mixture is evaporated under vacuum.

The dry residue is taken up in 5 ml of methanol and 3 ml of carbon disulphide are added. The mixture is left stirring for 2 hours. The product obtained is evaporated to dryness and is stored at -18°C.

3) Preparation of compound 56: radiolabelling of compound 55

- **SYNTHESIS OF THE INTERMEDIATE TcN:**

100 µg of tin chloride, 5 mg of succinyl dihydrazide (SDH) and 5 mg of 1,2-propanediamine-N,N,N',N'-tetraacetic acid (PDTA) were lyophilized in a labelling flask.

3 ml of TcO_4 (60 mCi) are added to this lyophilizate. Reaction is allowed to take place for 15 minutes.

- **COMPLEXING**

2 mg of compound **55** in 1 ml of ethanol are added to 1 ml of TcN. The reaction is allowed to take place for one hour. The reaction is analysed by HPLC (reverse phase, methanol-water).

The labelling yield is greater than 95%.

EXAMPLE IV: AFFINITY AND SPECIFICITY OF THE COMPOUNDS ACCORDING TO THE INVENTION IN THE RAT

In this example, the affinity and the specificity of a derivative according to the invention for the dopamine transporter is tested in vivo in the rat.

To this end, 3 batches of male rats of the Wistar strain are used, 6 rats being used per batch:

- Batch number 1 first of all receives an intravenous injection of GBR 12909 (specific inhibitor of the dopamine transporter, manufactured by RBI Bioblock) at a dose of 5 mg/kg and then, 30 minutes later, the radioactive tropane derivative according to the invention is injected into them intravenously at a dose of 8×10^{-6} mg/kg.

- Batch number 2 first of all receives an injection of paroxetine (specific inhibitor of the serotonin transporter, manufactured by Laboratoires Beecham) at a dose of 5 mg/kg and then, 30 minutes later, an injection of a derivative according to the invention, under the same conditions as batch number 1.

- Batch number 3 or the control batch receives only an intravenous injection of a derivative according to the invention.

Two hours later, the animals are sacrificed and the doses of radioactivity present in the tissues of the cerebellum, striatum and frontal cortex are determined.

It is noticed that the attachment of the derivative in accordance with the invention in the striatum is prevented by a preinjection of GBR 12909. The derivative of the invention is therefore specific to the dopamine transporter since saturation of this transporter by a specific inhibitor (GBR 12909) prevents it from attaching.

EXAMPLE V: COMPETITION STUDY

In this example, in vitro studies are carried out on cerebral membrane preparations.

These studies are competition studies between [^{3}H]GBR 12925 (dopamine transporter), [^{3}H]paroxetine (serotonin transporter), [^{3}H]nisoxetine (noradrenaline transporter) and the radioactive derivatives according to the invention.

The inhibition constants Ki obtained with the derivative of the invention in competition with the various ligands are calculated and show that the radioactive derivative according to the invention has a good affinity and a good specificity for the dopamine transporter.

EXAMPLE VI: IN VIVO KINETICS

In this example, an in vivo kinetic study is carried out on the cerebral distribution of the derivative according to the invention in the primate (Cynomologus macaque, female weighing 2 kg,

anaesthetized with ketamine, data acquisition being carried out every 12 minutes with a Ceraspect).

The results of this study show that the derivative according to the invention binds specifically in the central grey nuclei and that an image of these structures is rapidly obtained after injection.

The derivative of the invention is therefore highly advantageous for the in vivo visualization of the dopamine transporter system.

EXAMPLE VII: BIOLOGICAL RESULTS OF THE RADIOLABELLED DERIVATIVES ACCORDING TO THE INVENTION

The model chosen is the rat. The animals are sacrificed at different times after injection. At the times chosen, the brains are removed, and the regions of interest are isolated and counted. The following are derived from these results:

- the crossing of the haematoencephalic barrier (HEB) by the derivative under consideration,

- a striatum to cerebellum ratio.

It is observed that the derivatives according to the invention indeed cross the HEB and preferably accumulate in the striatum, with a high striatum/cerebellum ratio.

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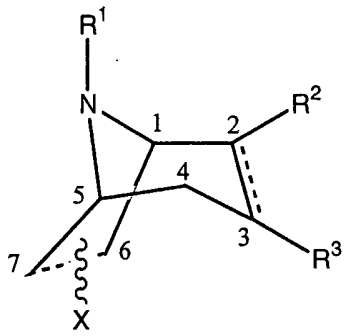
CLAIMS

1. Tropane derivative of following formula (I):



in which X represents a compound for chelation of a metal or of a metal complex attached, directly or indirectly, as desired: to the carbon in the 6 position, to the carbon in the 7 position or simultaneously to the carbons in the 6 and 7 positions, the 6 and 7 carbons being bonded or not bonded to one another in this last option,

and in which:

R^1 is a linear or branched alkyl or alkenyl comprising from 1 to 6 carbon atoms which is optionally substituted by a halogen; an ester,

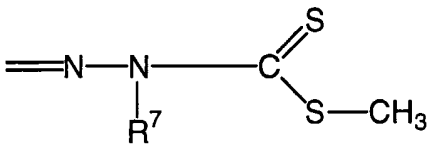
R^2 is of the form -COOZ with Z chosen from H or a linear or branched C_1 to C_6 alkyl group optionally substituted by a halogen atom,

R^3 represents a phenyl group which is unsubstituted or substituted by one or more halogen atom(s), alkyl group(s) or alkoxy group(s); a phenylalkyl or phenylalkylene group, the linear or branched alkyl or alkylene group of which comprises 1 to 6 carbon atoms and the phenyl group of which is optionally substituted by one or more halogen atom(s)

or alkyl group(s) comprising from 1 to 6 carbon atoms; a benzoate group or an oxo group,

the bond between the 2 and 3 carbons being a single or double bond.

2. Tropane derivative according to Claim 1, in which the compound X for chelation of a metal or of a metal complex is in the form $-R^5$ attached to the carbon in the 6 position and in the form $-R^6$ attached to the carbon in the 7 position, R^5 and R^6 having the formula (Y):



(Y)

with R^7 chosen from H or CH_3.

3. Tropane derivative according to Claim 2, in which the carbons in the 6 and 7 positions are bonded to one another.

4. Tropane derivative according to Claim 2, in which the carbons in the 6 and 7 positions are not bonded to one another.

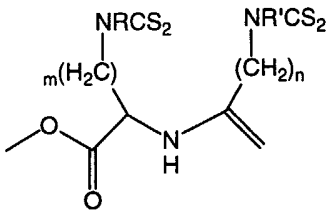
5. Tropane derivative according to Claim 1, in which the compound X for chelation of a metal or of a metal complex is attached indirectly to the tropane ring via a spacer group chosen from $-(CH_2)_n-$ or $-(CH_2O)_n-$, n representing an integer such that $1 \leq n \leq 10$.

6. Tropane derivative according to Claim 1, in which the compound X for chelation of a metal or of a metal complex is a bisdithiocarbamate structure

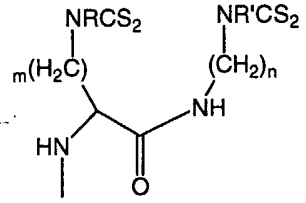
attached to the carbon in the 6 position or to the carbon in the 7 position.

7. Tropane derivative according to Claim 5, in which the compound X for chelation of a metal or of a metal complex is a bisdithiocarbamate structure attached to the carbon in the 6 position or to the carbon in the 7 position.

8. Tropane derivative according to Claim 6, in which the compound X is chosen from:



(a1)



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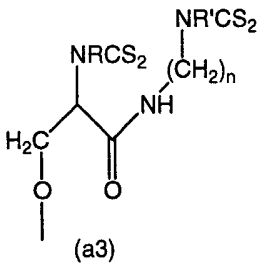

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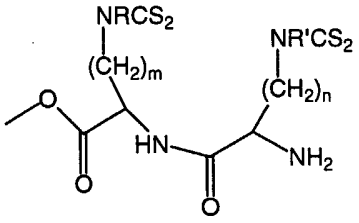

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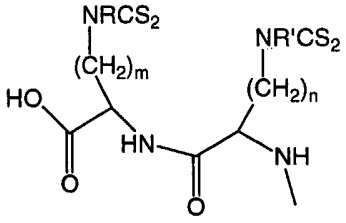
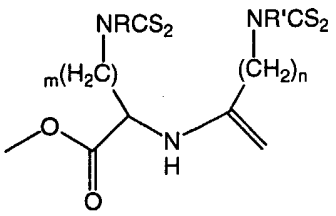


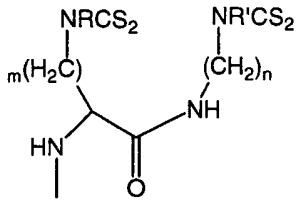
(a5)

with, independently, n = 1 to 10 and m = 1 to 10; R and R' being identical or different and representing H or an alkyl or alkoxy group comprising from 1 to 6 carbon atoms.

9. Tropane derivative according to Claim 7, in which the compound X is chosen from:



(a1)



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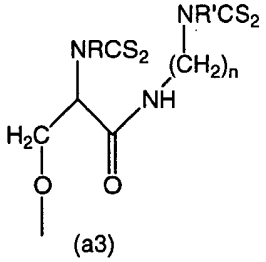

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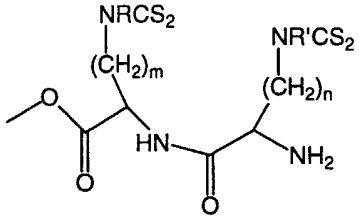

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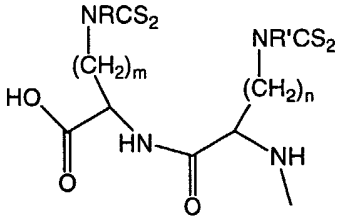


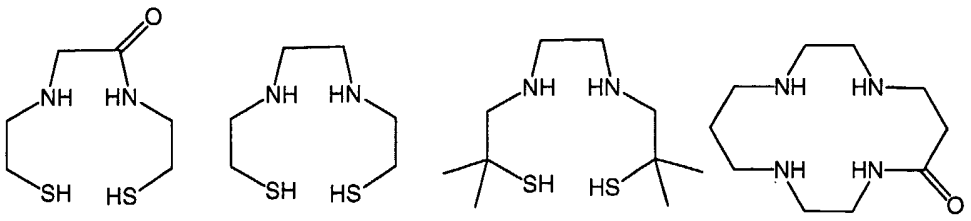
(a5)

with, independently, n = 1 to 10 and m = 1 to 10; R and R' being identical or different and representing H or an alkyl or alkoxy group comprising from 1 to 6 carbon atoms.

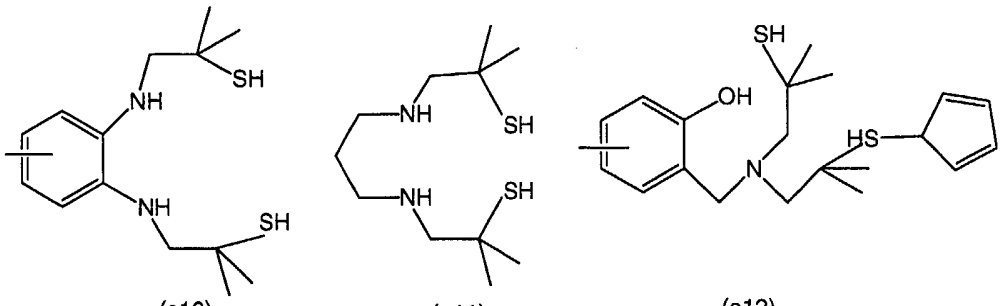
10. Tropane derivative according to Claim 8, in which n = m = 4.

11. Tropane derivative according to Claim 9, in which n = m = 4.

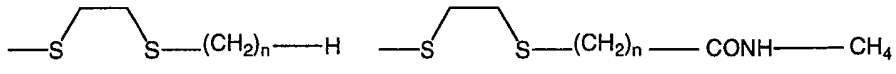
12. Tropane derivative according to Claim 1, in which compound X is chosen from:



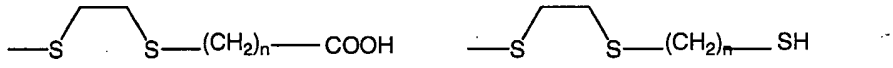
(a6) (a7) (a8) (a9)



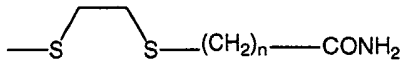
(a10) (a11) (a12)



(a13) (a14)

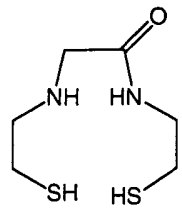


(a15) (a16)

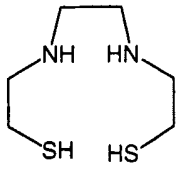


(a17)

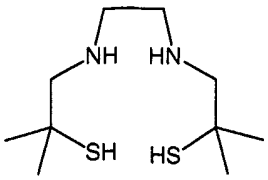
13. Tropane derivative according to Claim 5, in which compound X is chosen from :



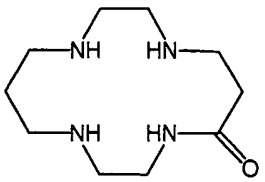
(a6)



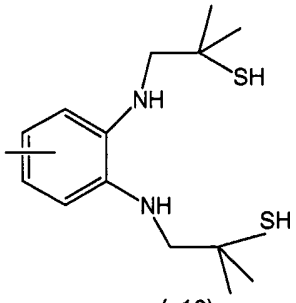
(a7)



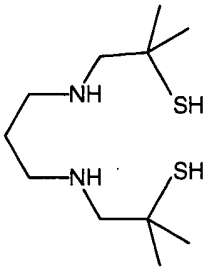
(a8)



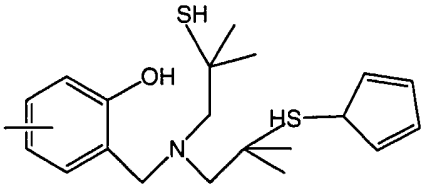
(a9)



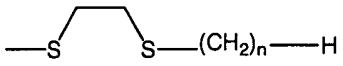
(a10)



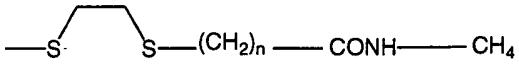
(a11)



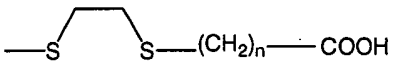
(a12)



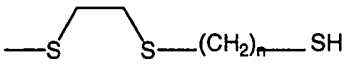
(a13)



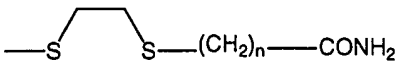
(a14)



(a15)

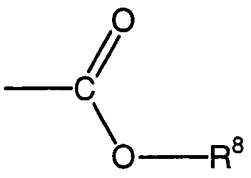


(a16)



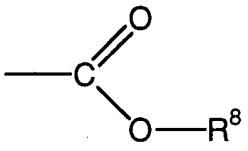
(a17)

14. Tropane derivative according to any one of Claims 1 to 13, in which R^1 is chosen from:

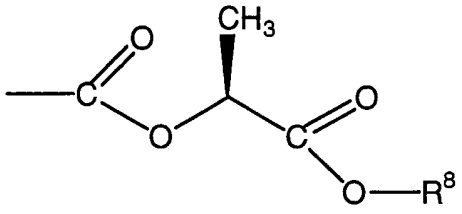
H, $-CH_3$ and 

where R^8 is a methyl, ethyl, propyl or tert-butyl radical.

15. Tropane derivative according to any one of Claims 1 to 13, in which R^2 is chosen from:

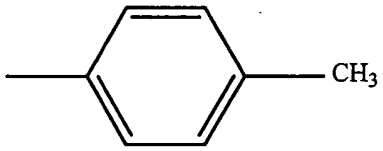


and



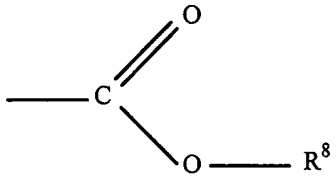
where R^8 is a methyl, ethyl, propyl or tert-butyl radical.

16. Tropane derivative according to Claims 1 to 13, in which R^3 is:

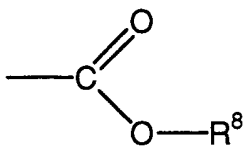


17. Tropane derivative according to Claim 1, in which:

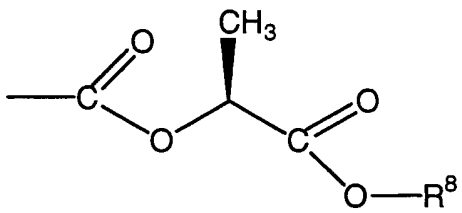
R^1 is chosen from: H, $-CH_3$,



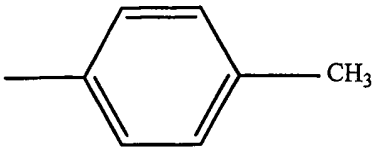
R^2 is chosen from:



et



where R^8 is a methyl, ethyl or propyl radical, and

R^3 is  .

18. Chelation product comprising a tropane derivative according to any one of Claims 1 to 17 and a metal or a metal complex.

19. Chelation product according to Claim 18, in which the metal is chosen from Tc, Re, TcN, TcO, TcO_2, ReO, ReN and ReO_2.

20. Use of a tropane derivative according to any one of Claims 1 to 17 in the manufacture of a medicament or a product for diagnosis.

21. Use of a tropane derivative according to any one of Claims 1 to 17 in the manufacture of a radiopharmaceutical for therapy or for diagnosis.

22. Use of a tropane derivative according to any one of Claims 1 to 17 in the manufacture of a radiopharmaceutical for visualizing the reuptake of dopamine or serotonin.

23. Use of a chelation product according to Claim 18 in the manufacture of a radiopharmaceutical for therapy or diagnosis.

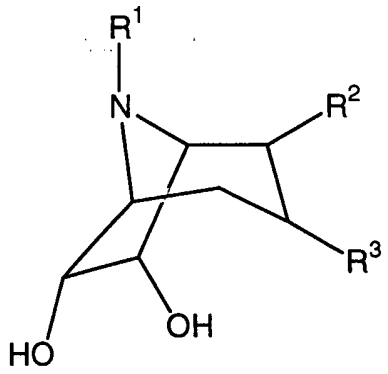
24. Use of a chelation product according to Claim 19 in the manufacture of a radiopharmaceutical for therapy or diagnosis.

25. Use of a chelation product according to Claim 18 in the manufacture of a radiopharmaceutical for visualizing the reuptake of dopamine or serotonin.

26. Use of a chelation product according to Claim 19 in the manufacture of a radiopharmaceutical for visualizing the reuptake of dopamine or serotonin.

27. Process for the manufacture of a tropane derivative according to Claim 3 comprising the following stages:

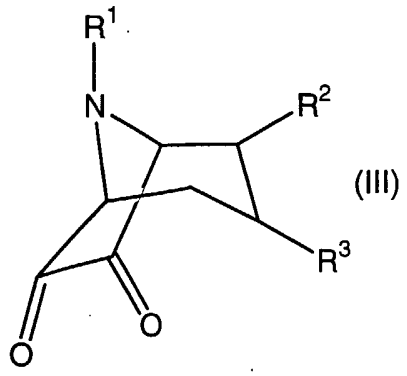
- manufacture of a tropane derivative of following formula (II):



(II)

R^1, R^2 and R^3 being as defined in Claim 1,

- conversion of the tropane derivative of formula (II) to a tropane derivative of following formula (III):



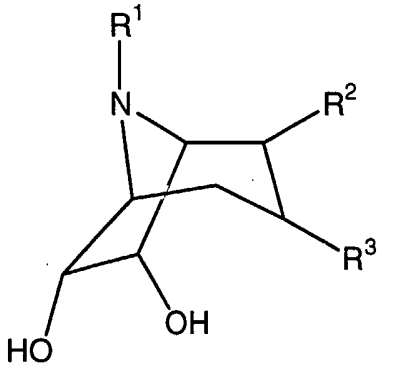
(III)

- optionally conversion of the oxo functional groups to -COOH, $-NH_2$ or $-COOR^9$ functional groups, R^9 being a C_1 to C_3 alkyl,

- attachment of R^5 and R^6 defined in Claim 2 to the 6 and 7 positions, optionally after conversion of the oxo groups.

28. Process for the manufacture of a tropane derivative according to Claim 4 comprising the following stages:

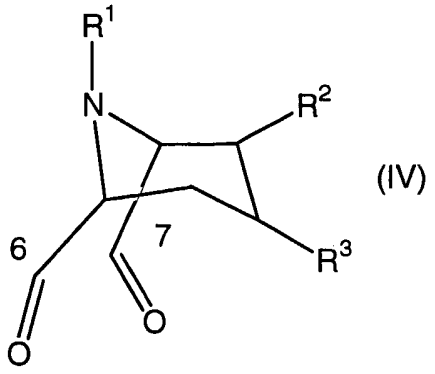
- manufacture of a tropane derivative of following formula II):



(II)

R^1, R^2 and R^3 being as defined in Claim 1,

- conversion of the tropane derivative of formula (II) to a tropane derivative of following formula (IV):

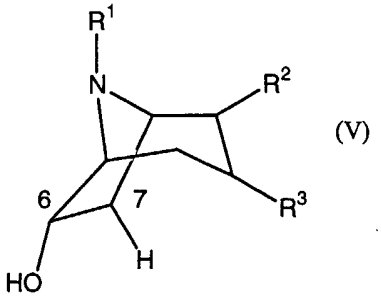


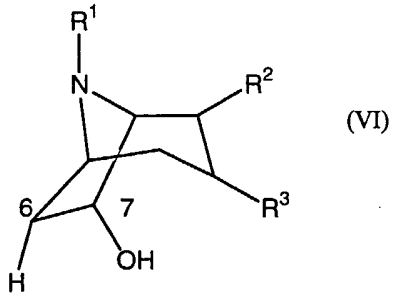
- optionally conversion of the oxo functional groups to -COOH, $-NH_2$ or $-COOR^9$ functional groups, R^9 being a C_1 to C_3 alkyl,

- attachment of R^5 and R^6 defined in Claim 2 to the 6 and 7 positions, optionally after conversion of the oxo groups.

29. Process for the manufacture of a tropane derivative according to Claim 8 comprising the following stages:

- manufacture of a tropane derivative of following formula (V) or (VI):





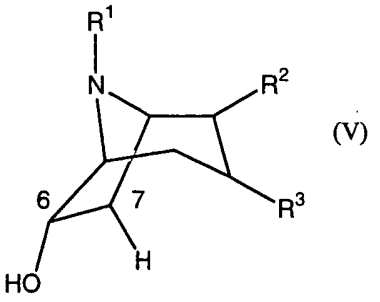
where R^1, R^2 and R^3 are as defined in Claim 1,

- attachment to the OH in the 6 position of the tropane derivative (V) or to the OH in the 7 position of the tropane derivative (VI) of a compound X for

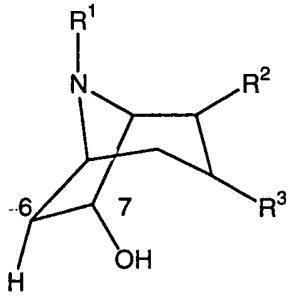
chelation of a metal or of a metal complex as defined in one of preceding Claims 6 to 13.

30. Process for the manufacture of a tropane derivative according to Claim 9 comprising the following stages:

- manufacture of a tropane derivative of following formula (V) or (VI):



(V)



(VI)

where R^1, R^2 and R^3 are as defined in Claim 1,

- attachment to the OH in the 6 position of the tropane derivative (V) or to the OH in the 7 position of the tropane derivative (VI) of a compound X for chelation of a metal or of a metal complex as defined in one of preceding Claims 6 to 13.

31. Process for the preparation of a chelation product as defined in Claim 14, comprising the manufacture of a tropane derivative as defined in Claim 1 according to the process defined in Claim 27, 28, 29 or 30 and a reaction for the complexing of a metal or of a metal complex by the said chelation compound X.

32. Process according to Claim 31, in which the metal or the metal complex is chosen from Tc, Re, TcN, TcO, Tc_2, ReO, ReN and ReO_2.

33. Diagnostic kit comprising a tropane derivative according to any one of Claims 1 to 17.