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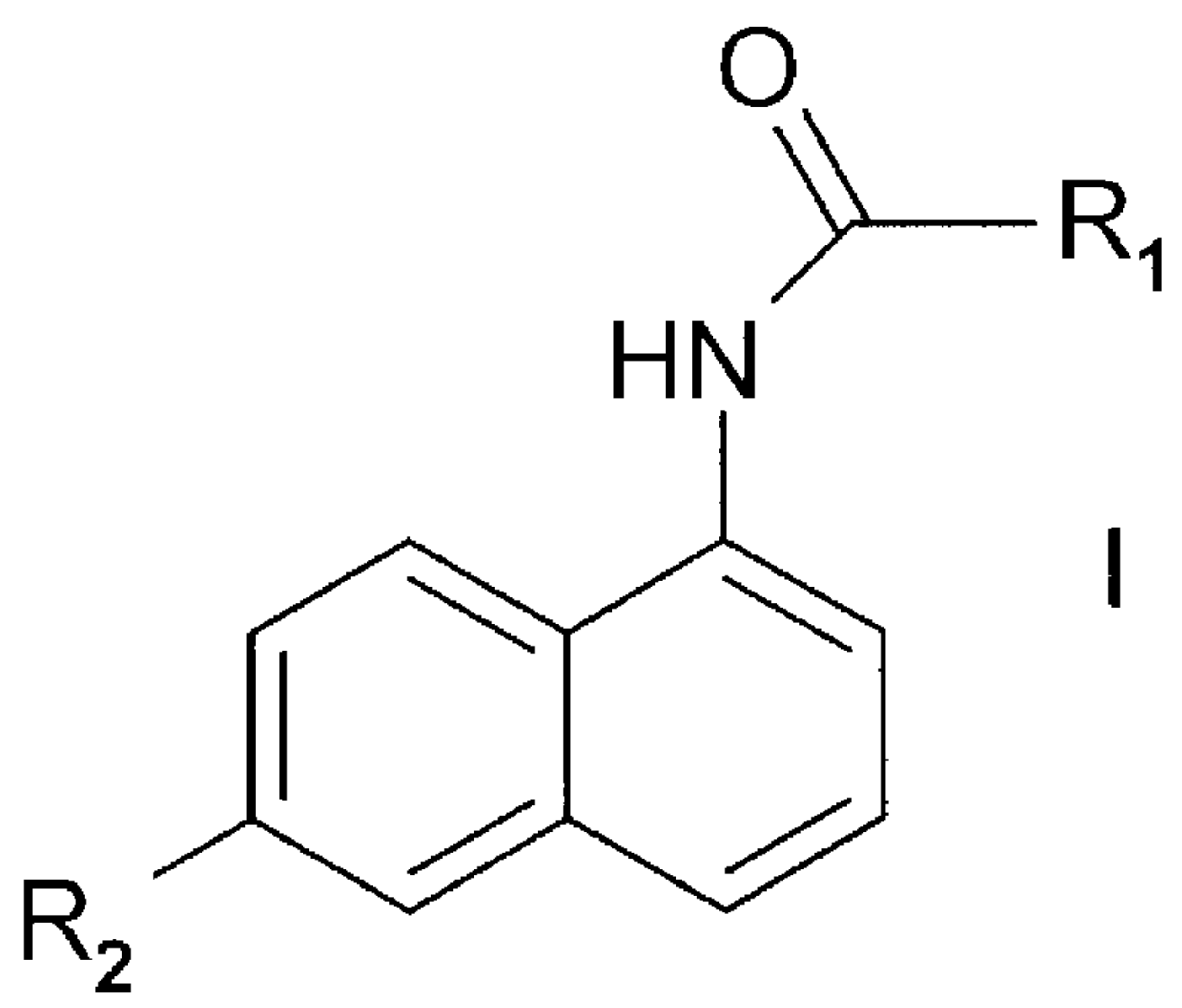
(54) Titre : PROCEDE D'OBTENTION DE NOUVEAUX DERIVES DE NAPHTALENE POUR LE DIAGNOSTIC IN VIVO DE LA MALADIE D'ALZHEIMER

(54) Title: METHOD FOR OBTAINING NOVEL DERIVATIVES OF NAPHTHALENE FOR THE IN VIVO DIAGNOSIS OF ALZHEIMER'S DISEASE



I

(57) Abrégé/Abstract:

The invention relates to chemistry and in particular to the field involved in the organic synthesis of compounds belonging to the category of naphthalene or bicyclic aromatics, used in the detection of amyloid plaques. These novel naphthalene derivatives have general formula: (I), (II), wherein: R represents groups that are independent of one another. In formula (I), R_1 represents -alkylenyl-C(O)NH- alkylenyl-R_3, -alkylenyl-C(O)O-R_4; R_3 represents -COOH, -OH, -SH, -NH_2, -alkyl-NH, -alkyl-/V- dithiocarbamate of salts of alkaline earth metals; R_4 represents H, succinimide group; and R_2 represents -H, - alkyl. In formula (II), R_1 represents -alkyl, -alkylenyl-halide, -alkylenyl-hidroxyl, -alkylenyl-O- arylsulfonate, alkylenyl-O-alkylsulfonate; R_2 represents-halide, -alkylenyl-O-arylsulfonate, - alkylenyl-O-alkylsulfonate, -alkylenyl-halide, -CH(O), -HC=C$(CN)_2$, -HC=CHNO_2, - alkylenyl-NH_2, -alkylenyl-NH-alkyl, -alkylenyl-alkyl-Λ/-dithiocarbamate of alkaline salts. The terms "alkyl" and "alkylenyl" refer to linear or branched aliphatic chains, preferably with between 1 and 4 carbon atoms, and the term halide refers to fluorine, bromine or iodine. These compounds are neutral, lipophilic and of low molecular weight, allowing same to pass through the blood-brain barrier and adhere to amyloid plaques. The invention relates to methods for obtaining naphthalene derivatives in good yields, which are practical, economical and can be adapted to larger-scale manufacture. We are not aware of any reference in the prior art to the compounds presented in this application.

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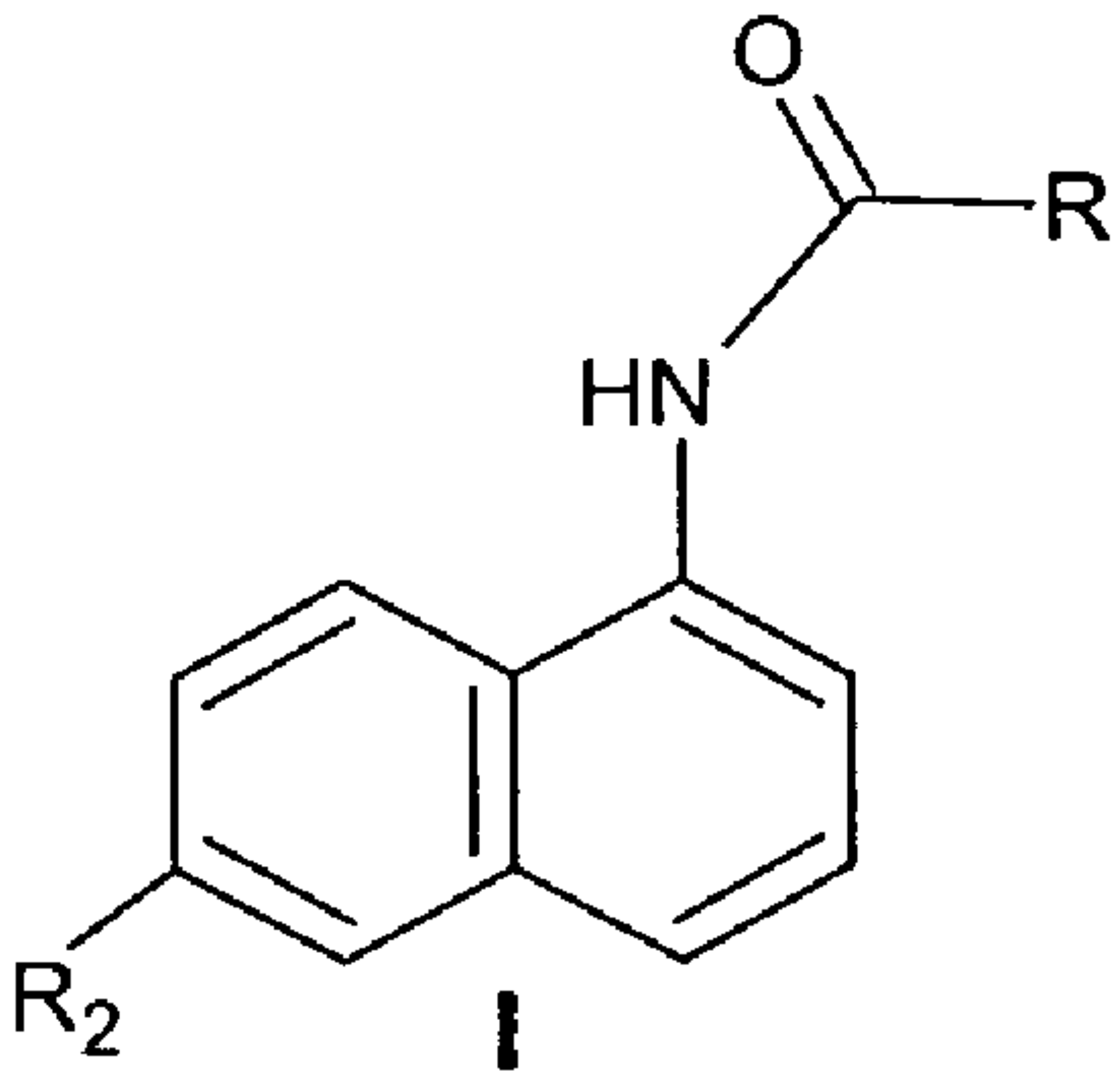
[Continúa en la página siguiente]

(54) Title: METHOD FOR OBTAINING NOVEL DERIVATIVES OF NAPHTHALENE FOR THE *IN VIVO* DIAGNOSIS OF ALZHEIMER'S DISEASE

(54) Título : PROCEDIMIENTO DE OBTENCIÓN DE NUEVOS DERIVADOS DE NAFTALENO PARA EL DIAGNÓSTICO *IN VIVO* DE LA ENFERMEDAD DE ALZHEIMER



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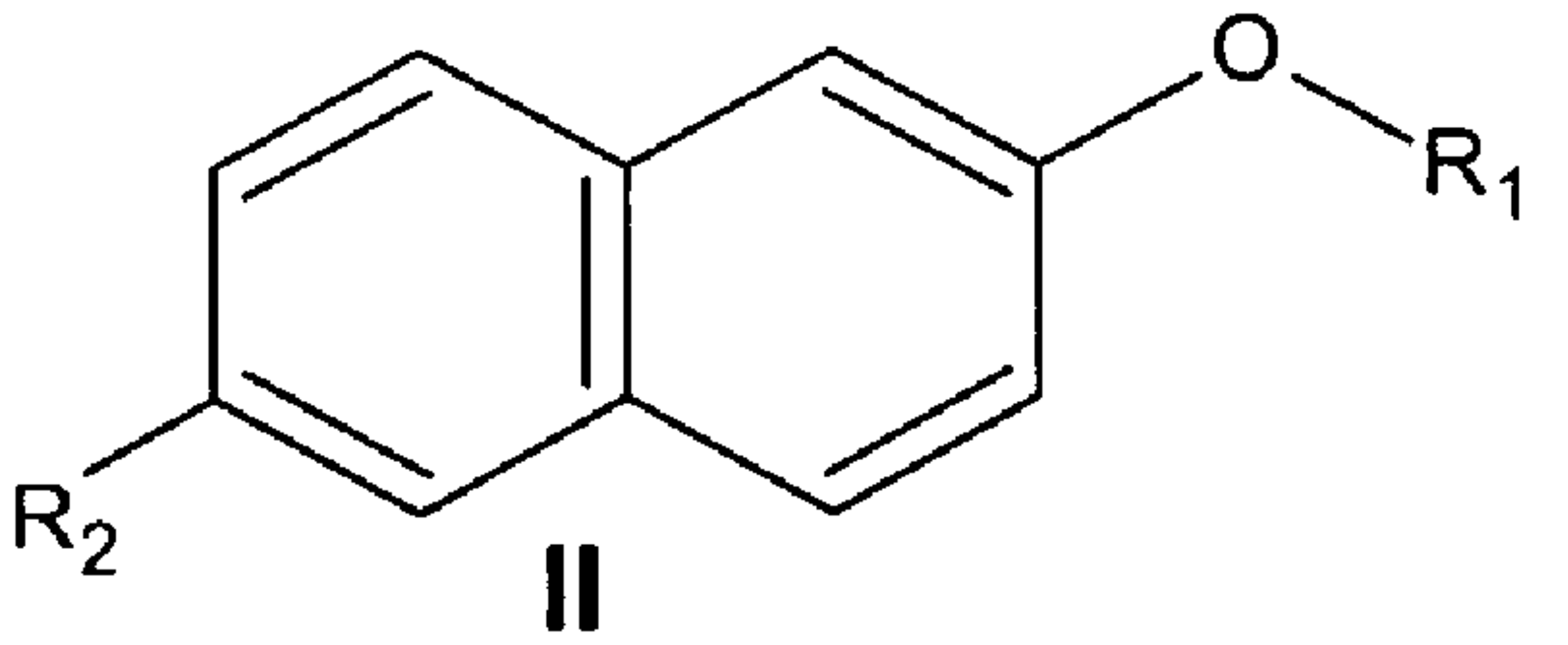

II

(57) Abstract: The invention relates to chemistry and in particular to the field involved in the organic synthesis of compounds belonging to the category of naphthalene or bicyclic aromatics, used in the detection of amyloid plaques. These novel naphthalene derivatives have general formula: (I), (II), wherein: R represents groups that are independent of one another. In formula (I), R_1 represents -alkylenyl-C(O)NH- alkylenyl-R_3, -alkylenyl-C(O)O-R_4; R_3 represents -COOH, -OH, -SH, $-NH_2$, -alkyl-NH, -alkyl-/V-dithiocarbamate of salts of alkaline earth metals; R_4 represents H, succinimide group; and R_2 represents -H, -alkyl. In formula (II), R_1 represents -alkyl, -alkylenyl-halide, -alkylenyl-hidroxyl, -alkylenyl-O- arylsulfonate, alkylenyl-O-alkylsulfonate; R_2 represents -halide, -alkylenyl-O-arylsulfonate, - alkylenyl-O-alkylsulfonate, -alkylenyl-halide, -CH(O), $-HC=C(CN)_2$, $-HC=CHNO_2$, -alkylenyl-NH_2, -alkylenyl-NH-alkyl, -alkylenyl-alkyl-Λ/-dithiocarbamate of alkaline salts. The terms "alkyl" and "alkylenyl" refer to linear or branched aliphatic chains, preferably with between 1 and 4 carbon atoms, and the term halide refers to fluorine, bromine or iodine. These compounds are neutral, lipophilic and of low molecular weight, allowing same to pass through the blood-brain barrier and adhere to amyloid plaques. The invention relates to methods for obtaining naphthalene derivatives in good yields, which are practical, economical and can be adapted to larger-scale manufacture. We are not aware of any reference in the prior art to the compounds presented in this application.

(57) Resumen:

[Continúa en la página siguiente]

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Esta invención se relaciona con la rama de la Química, en particular con el campo de la síntesis orgánica de compuestos que pertenecen a la categoría de aromáticos bicíclicos o naftalénicos, utilizados en la detección de placas amiloideas. Estos nuevos derivados de naftaleno tienen fórmula general: (I), (II). Donde R representa a grupos independientes entre sí. En I: R_1: -alquilenil-C(O)NH- alquilenil-R_3, -alquilenil-C(O)O-R_4; R_3: -COOH, -OH, -SH, -NH_2, -alquil-NH, -alquil-/V- ditiocarbamato de sales de metales alcalino térreo; R_4: H, grupo succinimido; R_2: -H, - alquil. En II: R_1: -alquilo, -alquilenil-haluro, -alquilenil-hidroxilo, -alquilenil-O- arilsulfonato, alquilenil-O-alquilsulfonato; R_2:-haluro, -alquilenil-O-arilsulfonato, - alquilenil-O-alquilsulfonato, -alquilenil-haluro, -CH(O), -HC=C$(CN)_2$, -HC=$CHNO_2$, - alquilenil-NH_2, -alquilenil-NH-alquil, -alqu¡lenil-alquil-Λ/-ditiocarbamato de sales alcalinas. Los términos "alquil" y "alquilenil" se refieren a cadenas alifáticas lineales o ramificadas, preferentemente de 1 a 4 átomos de carbono y el término haluro a Flúor, Bromo o Yodo. Estos compuestos son neutros, lipofílicos y de bajo peso molecular por lo que atraviesan la barrera hematoencefálica y se adhieren a las placas amiloideas. La presente invención proporciona los procedimientos para la obtención de derivados de naftaleno con buenos rendimientos, que pueden ser prácticos, económicos y ser adaptados a una manufactura a mayor escala. No tenemos conocimiento de que los compuestos presentados en esta invención hayan sido reportados anteriormente.

METHOD FOR OBTAINING NOVEL DERIVATIVES OF NAPHTHALENE FOR THE *IN VIVO* DIAGNOSIS OF ALZHEIMER'S DISEASE

DESCRIPTION.

The present invention is related to the branch of chemistry, particularly with obtaining new naphthalene derivatives and its labeling with radionuclides used in nuclear medicine for imaging diagnostic, which includes gamma ray emitters such as technetium 99 metastable (^{99m}Tc), iodine 123 or 131 (^{123}I or ^{131}I) and others, as well as positron emitters: fluorine 18 (^{18}F), carbon 11 (^{11}C), oxygen 15 (^{15}O) and others, with the aim of displaying neuropathological deposits in the brain through images from nuclear medicine and providing early diagnosis of Alzheimer's disease or other diseases that might be associated with the presence of these neuro-deposits (such as rheumatoid arthritis and others).

Alzheimer's disease (AD) affects about 20 to 40% of the elderly population. It is estimated that, at a global scale, 18 to 22 million people suffer from AD or a related dementia, and it will reach 34 million by 2020. This condition is characterized by the presence of neuropathology deposits in the brain (senile sheets and neurofibrillary tangles), which are involved in the process leading to progressive neuronal degeneration and neuronal death. The neurofibrillary tangles (NFT) are fibrillar aggregates of hyperphosphorylated *tau* protein and are located within neuronal cells. In contrast, senile sheets are found outside them and consist primarily of deposits of β-amyloid peptides (39-42 amino acids). *Gong et al., Proc. Natl. Acad. Sci USA 2003, 10 (18), 10417-22.*

The clinical diagnosis of AD has a moderate reliability and often lacks sensitivity and specificity. Ball et al., in *Neurobiol. Aging. 1997, 18 (4), S1-2*, suggests that its definitive diagnosis is made *post-mortem* through neuropathological examination with the discovery of senile sheets and/or neurofibrillar tangles in neocortical brain sections, which are displayed through staining (colorimetric or fluorescent) with Congo Red (CR), thioflavin or Chrysamine-G.

Since the histopathologic appearance of these structures occurs long before the disease symptoms appear, it is valuable to count with a means of early and *in vivo* diagnosis that allows visualizing the same and that also facilitates monitoring the effectiveness of the therapeutic treatments.

For this purpose, non-invasive methods made through genetic tests, immunoassays and imageneology techniques are under study. In particular, the latter are very favourable, for both, the AD diagnosis and other neurological diseases linked to the presence of neurofibrillary tangles and amyloid sheets, such as: Parkinson's, Down syndrome, hereditary cerebral hemorrhage associated with amyloidosis Dutch type and other diseases associated with amyloidosis.

Neuroimaging techniques include: Positron Emission Tomography (PET), Single Photon Emission Computer Tomography (SPECT) and Magnetic Resonance Imaging (MRI). *Volder et al., Developmental Science, 2002, 5 (3), 344-60.*

To implement the PET technique, it has used different markers utilized in the *in vitro* detection of amyloid structures, such as Congo Red, thioflavin and Chrysamine-G analogs, but with unsatisfactory results. *Zhen et al., J. Med Chem, 1999, 42, 309-24; Dezutter et al., Eur. J. Nucl. Med, 1999, 26, 1392-99.*

Other compounds tested, such as 1- (6 [2-[^{18}F] fluorethyl)(methyl)amino] naphthalene-2-yl) ethanone (^{18}F-FENE) and 2-(1-(6- [(2- [^{18}F] fluorethyl)(methyl)amino]-2-naphthyl) ethyl) malononitrile (^{18}F-FDDNP, *Barrio et al.* in *WO0010614, WO2005040337* and *US2004072371; Kepe et al.* in *WO2006083378* and *Agdeppa et al., 2001, J. Neurosci., 21, 24, 189*) labelled with the isotope fluorine 18 (t ½ = 109.8 min), which have been used in the *in vivo* detection of pathological deposits of AD and detected with the PET technique. It has also been described by Small et al.(*N. Engl. J Med 2006, 355, 25, 2652-63*), that it is possible to differentiate patients with cognitive impairment from those with AD.

Other compounds have also labeled with fluorine 18 or carbon 11 (t ½ = 20.4 min), which are derived from benzothiazole, imidazole, stilbene, acridine or styrylbenzoxazol with few promising results. The use of PET visualization technique is limited by: the high cost of equipment, the type of isotope used are generated in a cyclotron located within the nuclear medicine service or close to it and the short disintegration period, which requires that the obtained radiopharmaceuticals must be used immediately.

Moreover, the imaging SPECT technique is more advantageous since its equipment is less expensive and the generation and prices of the usual isotopes are more affordable, allowing this technique to be more widespread.

In particular, technetium ($t_{½}$= 6.02 h., $E\gamma$ = 140 keV) is used in more than 80% of routine nuclear medicine diagnosis because it can be used in low doses and therefore the patient receives less radiation. Furthermore, it is obtained from a generator of ^{99}Mo/ ^{99m}Tc, which is available on the market at relatively cheap prices. This radioisotope has as special feature that is able to form stable complexes with organic compounds related to biological structures, presenting donor atoms. All these advantages point to the need of including a diagnosis, which may be used in SPECT technique, which is reliable for quantification and visualization of amyloid deposits in the brain.

There are numerous patents relating to the use of ^{99m}Tc as a marker to diagnose various brain pathologies.

Among them is the invention of Li-Han et al. (*TW438596*) which describes the production of Tropane radiopharmaceutical ^{99m}Tc-TRODAT as selective marker of the dopamine transporter, for the detection of pre-synaptic neuronal degeneration in Parkinson's disease, without ruling out other diseases such as AD. Furthermore, Zhu et al. in *CN1072020* describes a complex of ^{99m}Tc-ethylcysteinate diethyl ester (^{99m}Tc-ECD), which crosses the blood brain barrier and it is used for cerebral perfusion studies. With this aim, they have studied other neutral and lipophilic complexes of ^{99m}Tc-containing functional groups of amide, amine, thioether, thiol and oximes especially of the propylamineoximine type (*EP0194843, GB8426845D0, EP0123504, EP0229718 and US5690904*). In general, these patents describe procedures for obtaining suitable ligands for the ^{99m}Tc, in order to improve retention of the complex in the brain, and their *in vivo* stabilities and guarantee a good SPECT image quality. However, using these complexes of ^{99m}Tc for the diagnosis of AD has had unsatisfactory results.

Specifically, for the early diagnosis of AD, the aforementioned pigments have been marked with ^{99m}Tc, ^{123}I or ^{11}C, used for amyloid structures *postmortem* staining, such as the Congo Red and its benzothiazoles and benzidine derivatives (*US5008099, US6114175, US6133259, US6417178*). These radiopharmaceuticals have shown favourable results in studies *in vitro*, but failed *in vivo* diagnosis. In addition, Klunk et al. in *US6168776* argue that many of these compounds have carcinogenic properties.

Other Congo Red complexes labeled with ^{99m}Tc are described in *US6379650* by Wesley et al., where they obtained neutral and lipophilic ligands using diamine dithiolates. However, these complexes do not cross the blood-brain barrier due to the presence of sulphonic groups and also the inventors reported that theses complexes have high toxicity.

Sharma et al. in *US2006039859* describes a variation in the use of Congo Red, which is used to label peptides. These new derivatives are capable of crossing the blood brain barrier and bind to the amyloid structures. As an extension of the patent, it is reported that the peptide portion of these derivative functions as a ligand of ^{99m}Tc. However, the results described are unsatisfactory which may be due to the high molecular weight of the complexes in question.

Other types of molecules that bind specifically to the deposition of insoluble amyloid protein, are styrylbenzenes and pyridine derivatives (*Zhuang et al., J. Med. Chem, 2001, 44, 12, 1905-14; Kung et al., Mol. Imaging Biol, 2003, 5, 6, 418-26*). In particular, derivatives of stilbene showed by Kung et al. in *WO03018070* and *WO2006066104* have been effective as inhibitors of amyloid aggregation. However, as described by these authors in *Nucl. Med Biol, 2005, 32, 2,171-84*, conjugates of these compounds with ^{99m}Tc have not shown favourable results for the *in vivo* detection of AD.

It is known; following epidemiological studies, that the use of anti-inflammatory drugs reduces the relative risk of developing AD, among them is naproxen, which count with a naphthalene ring (*Agdeppa et al., 2003 Neurosciences, 117, 723-30*).

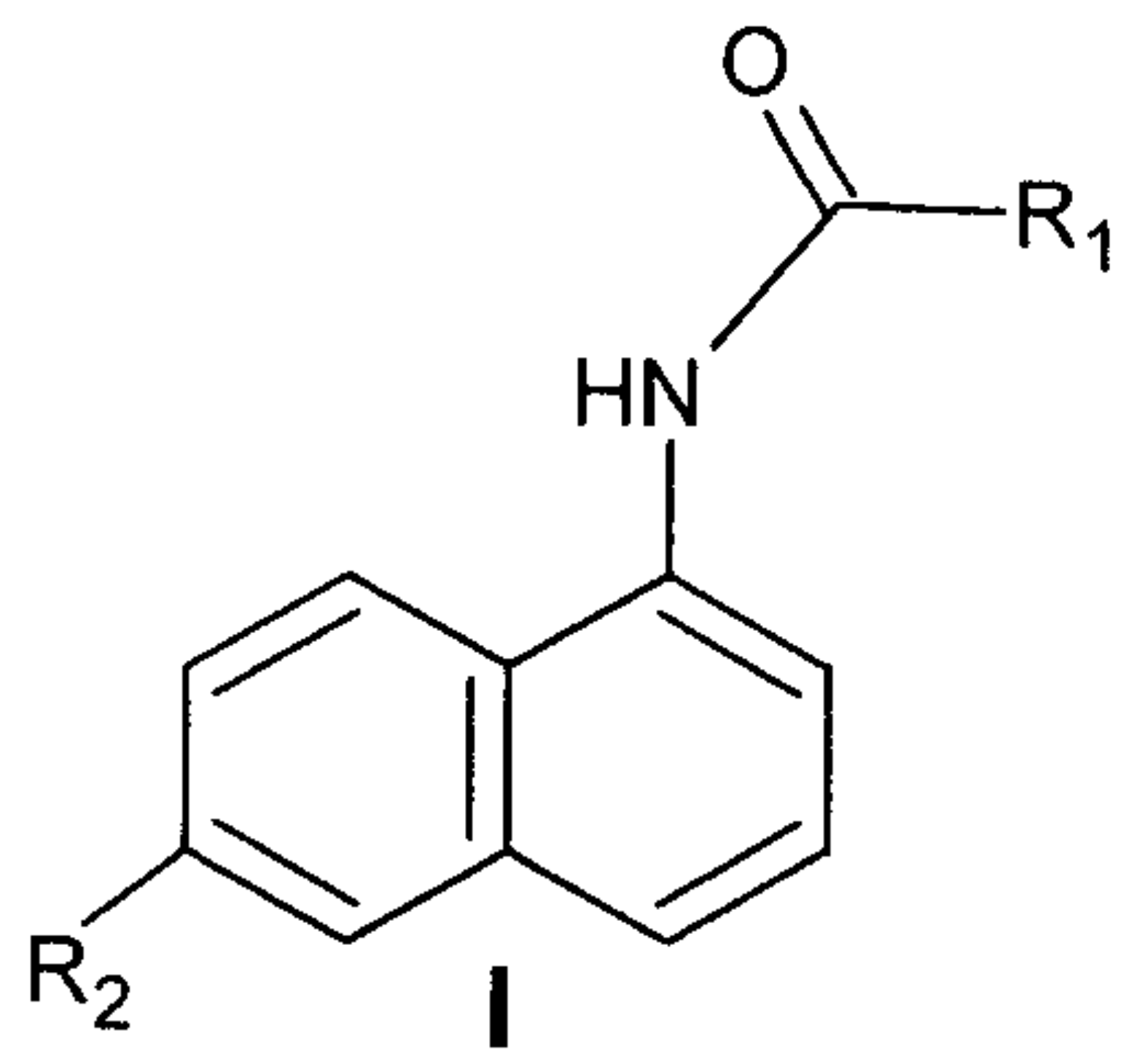
On this basis, naphthalene rings present in the Congo Red have been susceptible to chemical modifications, for the purpose of evaluating these compounds for *in vivo* diagnosis of AD. So, Steven et al. in *US4933156* show, among others, the first derivative of Congo Red identified for this purpose, marked with radioactive isotopes of iodine. Moreover, Kung et al. described in *US2006051293* the thioflavin derivatives which may have substituent groups such as naphthyle, among others, and which are able to form lipophilic neutral complexes with ^{99m}Tc. Also Gallo et al. refer in *WO0200603* the use of pamoic acid, its derivatives and analogues, for the treatment of diseases characterized by deposition of amyloid aggregates. In particular, pamoic acid is a derivative of naphthoic acid, which has in its structure two rings of naphthalene and forms complexes with radioactive isotopes such as indium, gadolinium and technetium. In short, in these patents compounds described are obtained through complex and laborious synthesis procedures, from expensive raw materials.

Minetti et al. in *WO2007045593* describes other naphthyl derivatives, which also inhibit amyloid aggregation and, according to its inventors, surprisingly, cross the blood brain barrier. These compounds, besides being present in pharmaceutical compositions for treating this condition, can also be used for diagnosis through different imaging techniques. In this case, one element of the compounds structure is replaced by a carbon, hydrogen or oxygen radioactive isotope, or they also form stable compounds with radioisotopes of iodine, indium, gadolinium or technetium.

In the application *WO02075318* of Wischik et al. is presented a method for determining neurofibrillary degeneration associated to *tauopathy*, as manifested in AD, which describes new ligands of sulphonated benzothiazol type. This invention claimed ligands with groups that form complexes with technetium and also one of the proposed formulas has naphthyl as a substituent group, among others. Similarly, Hays et al. in *WO9716194* describes some naphthyl-azo compounds, which inhibit amyloid aggregation and can be labeled with radioisotopes to diagnose. However, there is no data or examples of *in vivo* experiments that support this application and there is no reference in the claims to a particular radioisotope.

The present invention relates to derivatives of naphthalene, which show hydrophobic properties and are therefore able to cross the blood brain barrier and are related to characteristic pathological biostructures of AD. In addition, these compounds have the function of forming stable compounds with gamma ray emitters such as technetium 99 metastable (^{99m}Tc), iodine 123 or 131 (^{123}I or ^{131}I) and others, as well as positron emitters: fluorine-18 (^{18}F), carbon 11 (^{11}C) and oxygen 15 (^{15}O) and others. Also, these compounds may bear appropriate functional groups, such as fluorine-19 atom, which allow the obtaining of nuclear magnetic resonance imaging. The visualization of these marked biostructures is done with the proper instrumentation for each case, which allows observing and quantifying the distribution of the labeled compound within the brain. An extension of this invention's object is that it provides synthesis procedures of a series of hydrophobic compounds labeled with gamma emitters or fluorine 19 (^{19}F). Another object of this invention is that these compounds can be used as diagnosis of diseases characterized by the appearance of amyloid tissue. They can be used as therapeutic agents of the aforementioned diseases.

This invention provides novel derivatives of naphthalene and its obtaining procedures through chemical synthesis. In particular, these new compounds are characterized by crossing the blood brain barrier and bind selectively to the senile sheets that appear in Alzheimer's disease. The present invention involves obtaining derivatives that correspond to the structures **I** and **II**.



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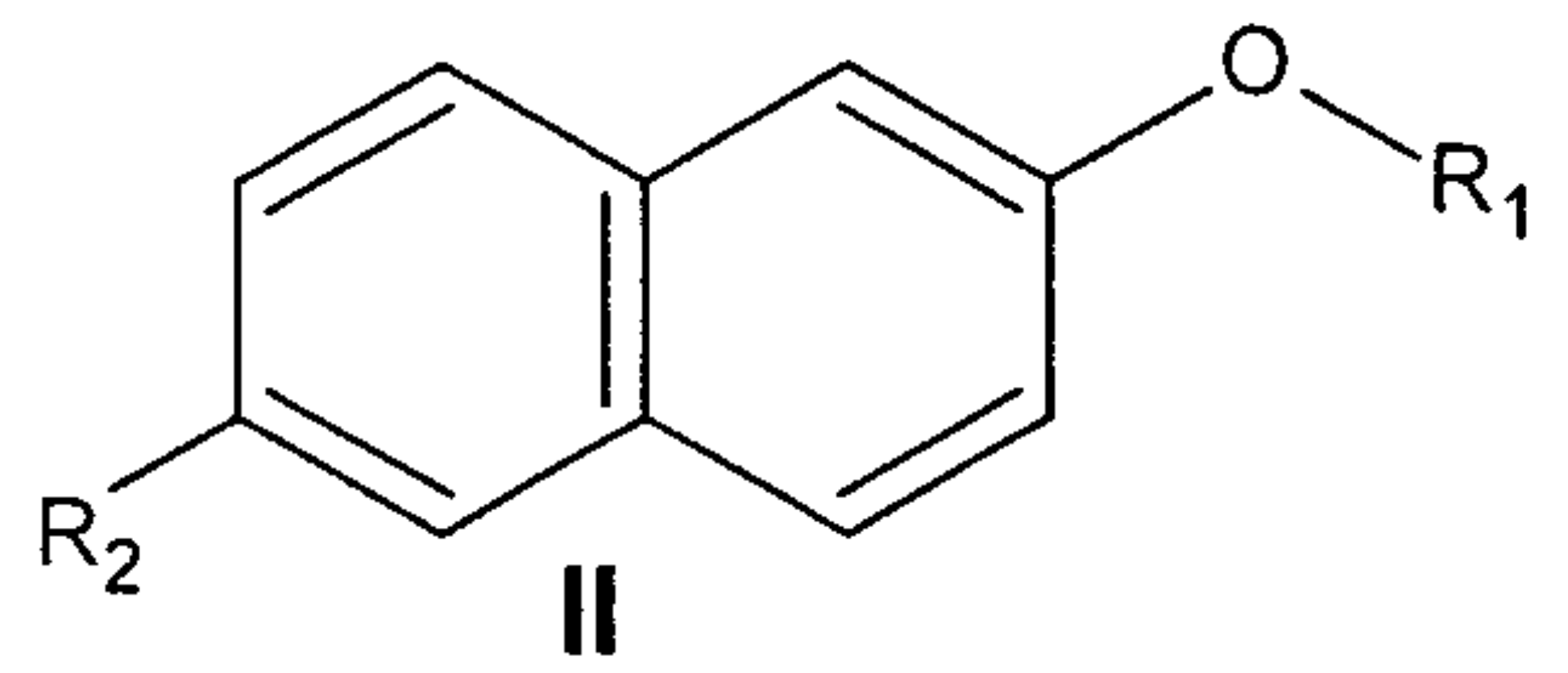


II

In structures **I** and **II** the R terms are independent.

Where in **I**: $\mathbf{R_1}$: is selected from the group alkylenyl-C(O)NH-alkylenyl-R_3,-alkylenyl-C(O)O-R_4. $\mathbf{R_3}$: is selected from the group -COOH, -OH, -SH, -NH_2, -alkyl-NH, -alkyl-N-dithiocarbamate alkaline earth metal salts. $\mathbf{R_4}$: is selected from the succinimidyl group, $\mathbf{R_2}$: is selected from the group -H, -alkyl.

In this structure, the term “alkyl” is characterized by a linear or branched aliphatic chain, hydrogen and saturated carbon atoms, comprising a methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl or *iso*-butyl groups. The term “alkylenyl” refers to a divalent analog of a linear or branched alkyl group, preferably ethylenyl (CH_2CH_2) or butylenyl ($CH_2CH_2CH_2CH_2$) radicals.

where in **II**: $\mathbf{R_1}$: is selected from the group -alkyl, and $\mathbf{R_2}$ is selected from the groups -alkylenyl-*O*-arylsulfonate, -alkylenyl-halide, -CH(O), alkylenyl-NH_2, -alkylenyl-NH-alkyl, -alkylenyl-alkyl-*N*-dithiocarbamate salts such as cesium, potassium or sodium. The term “alkyl” is characterized by a linear or branched aliphatic chain, hydrogen and saturated carbon atoms, preferably methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl or *iso*-butyl. The term “alkylenyl” refers to a divalent analog of a linear or branched alkyl group, preferably propylenyl (-CH_2CH_2 CH_2) radical. The term halide refers to fluorine, bromine or iodine.

or,

$\mathbf{R_1}$: is selected from the groups: -alkylenyl-halide, -alkylenyl-*O*-arylsulfonate and $\mathbf{R_2}$: is selected from the groups: -halide, -alkylenyl-*O*-arylsulfonate, -alkylenyl-*O*-alkylsulfonate, -alkylenyl-halide, -CH(O), -HC=C$(CN)_2$, -HC=$CHNO_2$, -alkylenyl-NH_2, -alkylenyl-NH-alkyl, -alkylenyl-alkyl-*N*-dithiocarbamate salts such as cesium, potassium or sodium. The term “alkylenyl” refers to a divalent analog of a linear or branched alkyl group, preferably propylenyl (-CH_2CH_2 CH_2) radical. The term halide refers to fluorine, bromine or iodine.

The present invention also includes tautomeric forms, geometric and optically active isomers and enantiomers, diastereomers and racemic mixtures of compounds defined by the structures **I** and **II**.

This invention has, as one of its objectives, to provide synthesis general procedures for obtaining new derivatives of naphthalene with good yields, as it is illustrated in Figures 1 and 2, which should not be regarded in any way as a constrain of the present invention. The procedures are practical, inexpensive and can be adapted to manufacturing at a larger scale.

In general, Figure 1 shows the compounds with structure **I**, which can be obtained from the naphthylamine raw material very accessible in the market. In principle, the naphthylamine reacts with succinic anhydride in the presence or absence of a tertiary amine (whose pKa is between 4 and 8, preferably *N*-methylmorpholine), to form compounds 1-(1-naphthyl)-2, 5-pyrrolidinone (**1**, step a) or 4-(1-naphthylamine)-4-oxobutanoic acid (**2**, step b), respectively. Obtaining these compounds allows introducing, through various reactions, spacer arms in position α-(or 1-) of naphthalene molecule. With the same purpose, it is also obtained the *N*-hydroxysuccinimide ester of the 4-(1-naphthylamino)-4-oxobutanoic acid (**3**, step d). The condensation reaction of 2 with *N*-hydroxysuccinimide (NHS) occurs in presence of a condensing agent like dicyclohexylcarbodiimide (DCC) and preferably with 1, 4-anhydrous 1,4-dioxane as solvent. In this synthesis is obtained a high yield without the need of purifying product **3** for later use.

Then, the naphthyl derivative **3** is used as acylating agent. The compound **3** is selective for primary amino groups, such as linear or branched aliphatic diamines (ethylenediamine, propylenediamine, 1-methyl-1, 2-ethylenediamine, butylenediamine) and polyfunctional amines such as α-aminoacids; thioamines, aminoalcohols and aminocarboxylic acids (α-aminoisobutyric acid, 2-aminoethanethiol, ethanolamine, β-alanine, 6-aminohexanoic acid, etc.). The reaction conditions are (temperature, solvent, time, etc.) and generate no corrosive waste. Finally, with this reaction a further lengthening of the chain of spacer arm is achieved so as to obtain the following new compounds: **4**, **5** (step e), **6** and **7** (step c).

These compounds can also be obtained by a new procedure through a *one-pot* technique, which is an innovation. With this purpose the compound **3** is obtain *in situ*, then it reacted with an excess of diamine (e.g. ethylenediamine and 1,4-butylenediamine) or an aminocarboxylic acid (e.g. β-alanine and 6-aminohexanoic acid) to obtain derivatives **4**, **5**, **6** and **7**, which carry an acid or amino terminal group. Specifically, the excess of the diamine is to ensure that no side products are formed such as diamines *N*, *N*'-disubstituted, leading to a dramatic decrease in the synthesis yield. The reaction is carried out at room temperature and in the presence of an organic solvent, preferably 1, 4-anhydrous 1,4-dioxane, to obtain good yields.

In the same way and with similar yields, derivatives **6** and **7** are obtained from the reaction of the naphthyl derivative (**1**) with the diamine excess (step c *, Figure 1) at reflux and in the presence of an anhydrous organic solvent, preferably 1, 4-dioxane or DMF. So far, we have not found reports of these compounds in literature.

This patent also shows the procedure for obtaining derivatives **8** (step f, Figure 1), from the reaction of *N*-alkylation (step f-*a*) of the previously described amino-terminal derivatives (**6** and **7**), in the presence of different alkylating agents (CH_3I, C_2H_5Br, $(CH_3)_2SO_4$, $(C_2H_5)_2SO_4$), inorganic bases (K_2CO_3, Cs_2CO_3, CsOH) and solvents (acetone, DMF). These new alkyl derivatives (described example: compound **8a**) react with CS_2 in the presence of CsOH, producing dithiocarbamate compounds (step f-*b*). They can be used as potential ligands of the ^{99m}Tc, like its synthetic precursors the derivatives

The iodine labeling methods are classified into direct or indirect, according to the type of bond established between the iodine and the compound to be marked. In direct methods, radioactive iodine is easy incorporated with high efficiency to the aromatic ring of organic compounds. In this invention this procedure is used to label the compound **6** (step g, Figure 1), specifically through the iodogen or chloramide method (*Saha on Fundamentals of Nuclear Pharmacy. Radiopharmaceutical and Methods of Radiolabeling. Fourth Ed Springer-Verlag, USA. 1998, p.: 93-97*). This procedure has a labeling efficiency ranging between 70 and 80% and high specific activity since there is non-isotopic or sample dilution. This labeling procedure can be extended to other molecules described here that have another spacer arm. We are not aware of literature reports regarding these labeled compounds.

On the other hand, the compounds with structure **II** can be obtained from the affordable 2-naphthol raw material. The general procedure shown in Figure 2, which consists of 5 reaction steps of synthesis, specifically aims to introduce a mono-fluorinated alkyl chain in position 6- of the 2-methoxynaphthalene.

The first reaction step is the bromination of 2-naphthol (pKa 9.23) carried out through a procedure already described by Koelsch in *Organic Synthesis, Coll., 1955, 3, 132* and Reddy et al., in *Organic process research and Development, 1999, 3, 121-25*. Thus, the 2-naphthol reacts with molecular bromine in presence of glacial acetic acid as solvent and the 1, 6-dibromo-2-naphthol intermediate is formed and reducing with Sn. This reduction is selective due to the dibrominated derivative is thermodynamic instability and the 6-bromo-2-naphthol (**10**) is obtained.

The step b of Figure 2 is the reaction of *O*-alkylation of **10** to obtain the 6-bromo-2-methoxynaphthalene (**11**). Reddy et al. described this procedure in *Organic Process Research and Development, 1999, 3, 121-25*, from the reaction between **10** and dimethylsulfate as alkylating agent in the presence of K_2CO_3 as base and a mixture of acetone-water as solvent, at 60 °C. However, under these conditions the reaction conversion is very low, even though DMF acetone used as solvents and the reaction is refluxed for 3 to 72 hours. The use of cesium bases (CsOH and Cs_2CO_3) compared to their counterparts in Li^+, Na^+, K^+ and Rb^+, is currently reported in the alkylation reactions due to the so-called "cesium effect". (*Welton in Chem Rev., 1999, 99, 2071-83; Kim et al. in J. Am. Chem. Soc. 2002, 124, 10278-9; Gerstenberger et al. in Angew. Chem. Int. Ed. Engl., 1981, 20, 647-67*). Then, Cs_2CO_3 base are successfully used in the reaction of *O*-alkylation of **10** with different alkylating agents (alkyl sulfates, alkyl halides, alkyl dihalides). The reaction occurs rapidly with dimethylsulfate in acetone (as solvent) at room temperature. The yield of compound **11** is practically quantitative.

In the third step of synthesis (step c, Figure 2) **11** reacts with Mg in the presence of iodine traces to obtain the Grignard reagent (**12**), according to general procedure described by Kidwell et al. (*Organic Synthesis, Coll., 1973, 5, 918*). This intermediate is not isolated and it is subsequently used in cross-coupling reaction (step d). In the present invention, this synthesis is performed, in general, from a reaction of an aryl magnesium halide with an alkyl halide or sulfonate ester and a copper complex as catalyst. In this procedure, carried out in an inert atmosphere, the order of the reagent addition and temperature play an important role. Specifically, if it is added the Grignard reagent **12** to the mixture of 1,3-propanediol di-*p*-tosylate with the copper catalytic (Li_2CuCl_4 or Li_2CuCl_3) which is between -70 °C to -15 °C, 3-(6-methoxy-2-naphthyl)propyl-4-methylbenzenesulfonate (**13**) is obtained with good yields. This new compound, **13**, is a valuable intermediate in the next synthetic step which is an innovation of this patent.

The fourth step of synthesis (step e, Figure 2) refers to the obtaining of a fluorinated derivative, based on studies by Kim et al. in *J. Org. Chem, 2003, 68, 4281-5*. This nucleophilic substitution reaction occurs with the use of an alkali metal fluoride (KF, CsF and RbF) in the presence of an ionic liquid, such as 1-*n*-butyl-3-methylimidazolium (bmim) (BF_4^-, PF_6^-, SbF_6^-, triflate [OTf^-], bis(trifluoromethanesulfonyl)imide [NTf_2^-], OAc^-) and acetonitrile as solvent. In this invention, the reaction takes place with **13** preferably, in the presence of CsF and (bmim) (BF_4^-) to obtain the new derivative 2-(3-fluoropropyl)-6-methoxynaphthalene (**14**).

Chemical compounds that cross the blood brain barrier (BBB) should be neutral and lipophilic and also, have a low molecular weight. The partition coefficient (P) provides a measure of the compound lipophilicity and is closely related to drug distribution in the body, its absorption in tissues and its route of excretion (*Meade et al. in Curr. Opin. Neurobiol., 2003, 13, 5, 597-602*). One method used to determine this parameter is that of radiotracers which relates the radiotracer`s activity or number of counts in the octanol organic phase with that of the aqueous phase. In this invention the compounds labeling is carried out using the Imethod (^{131}I).

According to studies Dischino et al. (*The Journal of Nuclear Medicine, 1983, 24, 11, 1030-38*), the optimal values of partition coefficient, which ensure that the compound crosses the BBB, are in the range of 0.9 to 2.5. On the other hand, there has been established by J. Levin in *Med. Chem., 1980, 23, 682-84*, that to cross the BBB by passive diffusion, the molecular weight values must range between 400 and 657 Da. In this invention, the synthesized compounds have values of molecular weights between 200 and 450 Da, and their partition coefficients; expressed as log P measured in octanol/water, range between 2.1 and 2.5.

The current invention shows that the synthesized compounds have values of molecular weights and partition coefficients that correspond to the values set for other compounds that cross the BBB. In summary, the compounds described herein, have the advantage of being used as staining agents of amyloid plaques present in AD as they show correspondence with these parameters.

In this invention the compositions of naphthalene derivatives labeled with ^{131}I, injected into rats, rapidly cross the blood brain barrier and have an appropriate retention time. As non-limiting example, Figure 3 shows the distribution in rats of compound **6** labeled with ^{131}I, (**9**) after its intravenous injection. Thus, an arrow indicates the detection of the compound in the region of interest (maximum uptake at about 3 min.) and then starts the slow excretion of the radioiodinated compound.

In preferred embodiments, the invention comprises derivatives of compounds of structure I wherein:

- i) R_1 is $-(CH_2)_nCONH(CH_2)_m-R_3$ wherein n = 2, 3 or 4; m = 2, 3, 4, 5 or 6; R_3 is -COOH; R_2 is -H, or -alkyl; and combinations thereof;
- ii) R_1 is $-(CH_2)_nCONH(CH_2)_m-R_3$ wherein n = 2, 3 or 4; m = 2, 3, 4, 5 or 6; R_3 is $-NH_2$, $-NHCH_3$ or $-NHC_2H_5$ and R_2 is -H, or -alkyl; and combinations thereof;
- iii) R_1 is $-(CH_2)_nCONH(CH_2)_m-R_3$ wherein n = 2, 3 or 4; m = 2, 3, 4, 5 or 6; R_3 is $-NR_4R_5$ wherein R_4 is -H, $-CH_3$ or $-C_2H_5$ and R_5 is C(S)SW, W is Na^+, K^+ or Cs^+; R_2 is -H, or -alkyl; and combinations thereof;
- iv) R_1 is $-(CH_2)_nCONH(CH_2)_m-R_3$ wherein n = 2, 3 or 4; m = 2, 3, 4, 5 or 6; R_3 is -OH; R_2 is -H, or -alkyl; and combinations thereof;
- v) R_1 is $-(CH_2)_nCONH(CH_2)_m-R_3$ wherein n = 2, 3 or 4; m = 2, 3, 4, 5 or 6; R_3 is -SH; R_2 is -H, or -alkyl; and combinations thereof; and
- vi) R_1 is $-(CH_2)_nC(O)O-R_4$ wherein n= 2, 3 or 4; R_4 is a succinimidyl radical; R_2 is -H, or -alkyl; and combinations thereof.

In further preferred embodiments, the invention includes the following processes for preparing derivatives of compounds of structure I:

- a) reacting:
  - i) an N-hydroxysuccinimide ester of 4-(1-naphthylamino)-4-oxobutanoic acid;

  with
  - ii) a compound having primary amino groups wherein said compound comprises:
    - a) an aliphatic diamine; or
    - b) a polyfunctional amine selected from the group consisting of α-amino acids, thioamines, aminoalcohols, and aminocarboxylic acids;

  in a solvent;

- b) reacting:
  - i) an N-hydroxysuccinimide ester of 4-(1-naphthylamino)-4-oxobutanoic

acid;

with

ii) a compound having primary amino groups wherein said compound comprises:

  a) an aliphatic diamine wherein the aliphatic diamine is one selected from the group consisting of ethylenediamine, propylenediamine, 1-methyl-1,2-ethylenediamine and butylenediamine; or

  b) a polyfunctional amine selected from the group consisting of α-aminoisobutyric acid, 2-aminoethanethiol, ethanolamine, β-alanine and 6-aminohexanoic acid;

in a solvent;

c) a one-pot process comprising reacting:

i) 4-(1-naphthylamino)-4-oxobutanoic acid;

with

ii) N-hydroxysuccinimide in the presence of dicyclohexylcarbodiimide, to obtain *in situ* an N-hydroxysuccinimide ester of 4-(1-naphthylamino)-4-oxobutanoic acid and further reacting the N-hydroxysuccinimide ester of 4-(1-naphthylamino)-4-oxobutanoic acid with an excess of diamine or an aminocarboxylic acid;

d) reacting:

i) 1-(1-naphthyl)-2, 5-pyrrolidinedione;

with

ii) an excess of a diamine;

in a refluxing solvent;

e) reacting:

i) 1-(1-naphthyl)-2, 5-pyrrolidinedione;

with

ii) an excess of an aminocarboxylic acid in presence of triethylamine;

in a refluxing solvent;

f) reacting:

i) a compound of structure I where R_1 is -alkylenyl-C(O)NH-alkylenyl-R_3 and R_3 is -NH_2;

with

ii) a compound selected from CH_3I, C_2H_5Br, $(CH_3)_2S0_4$ and $(C_2H_5)_2S0_4$; in a solvent comprising an inorganic base selected from K_2C0_3, Cs_2C0_3 and CsOH;

g) reacting:

i) a compound of structure I where R_1 is -alkylenyl-C(O)NH-alkylenyl-R_3 and R_3 is -NH_2;

with

ii) a compound selected from CH_3I, C_2H_5Br, $(CH_3)_2S0_4$ and $(C_2H_5)_2S0_4$; in a solvent comprising an inorganic base selected from K_2C0_3, Cs_2C0_3 and CsOH and reacting the product with CS_2 in a solvent comprising an alkaline earth base at a reaction temperature between -10 and 30°C.

In an additional preferred embodiment, the invention comprises a process for labelling comprising using a ^{99m}Tc compound of structure I and a chelating ligand, having sulfur, nitrogen or oxygen atoms.

In a further preferred embodiment, the invention comprises a compound of structure I, wherein the compound further comprises a positron-emitting isotope selected from the group consisting of ^{11}C, ^{15}0, and ^{18}F.

Figures content description.

Figure 1 shows the general procedure for synthesis of derivatives with structure **I**, which includes the most relevant reaction conditions (a: succinic anhydride, NMM; b: succinic anhydride, c, c *: ethylenediamine or 1, 4-butylenediamine d: NHS, DCC, e: 6-aminocaproic acid or β-alanine, f: a) CH_3I, base, b) CS_2, CsOH; g: in $CHCl_3$ (^{131}I).

Figure 2 shows the general procedure of synthesis of 2,6-naphthyl derivatives with structure **II**, which includes the most significant reaction conditions (a: Br_2, Sn, glacial acetic acid; b: dimethylsulfate, base, acetone; c: Mg, THF, Ar, d: 1,3-propanediol di-*p*-tosylate (PrDiTs), Li_2CuCl_4, THF, Ar; e: 1-butyl-3-methylimidazolium tetrafluoroborate, CsF, CH_3CN).

Figure 3 shows the distribution of the *N*1-(2-aminoethyl)-*N*4-(1-naphthyl) succinimide (**6**) compound labeled with ^{131}I, after its intravenous injection in rats. The arrow indicates the detection of the compound in the region of interest (maximum uptake at about 3 min.).

The obtaining procedures of naphthalene derivatives showed in the present invention are further illustrated by the following examples, which should not be regarded in any way, as constrain of the present invention. The compounds obtained were also appropriately characterized by spectroscopic techniques such as IR, ^1H and ^{13}C NMR and Mass.

Example 1: 1-(1-naphthyl)-2,5-pyrrolidinedione (**1**).

1-naphthylamine (5 g, 34.96 mmol) is dissolved in 50 mL of anhydrous 1,4-dioxane. Then, succinic anhydride (6.99 g, 69.92 mmol) and *N*-methylmorpholine (NMM, 7.6 mL, d=0.92 g/mL, 69.92 mmol) are added. The reaction mixture is heated at reflux for 5 hours. Once the reaction is completed (TLC), the solvent is removed by rotoevaporation. The solid residue is re-dissolved and re-crystallized from ethanol to obtain 5.2 g of compound **1** (Yield: 66%). Mp.: 153.5-154.5 °C (Lit: 153 °C). ESI-MS (m/z) = 226 $(M+1)^+$.

Example 2: 4-(1-naphthylamino)-4-oxobutanoic acid (**2**).

1-naphthylamine (10 g, 69.84 mmol) and succinic anhydride (13.96 g, 140 mmol) are dissolved in 100 mL of anhydrous 1, 4-dioxane. The reaction mixture is refluxed for 2 h. and later, cooled to precipitate a violet solid which is filtered and washed with 1, 4-dioxane. Recrystallization from ethanol gave 15.82 g of white solid. Yield: 93%. Mp.: 167-169 °C. ESI-MS (m/z) = 244 $(M + 1)^+$.

Example 3: 4-(1-naphthylamino)-4-oxobutanoic acid *N*-hydroxysuccinimide ester (**3**).

Compound **2** (2 g, 8.23 mmol), *N*-hydroxysuccinimide (NHS) (1.42 g, 12.34 mmol) and dicyclohexylcarbodiimide (DCC) (2.54 g, 12.33 mmol) are dissolved in 32 mL of anhydrous 1,4-dioxane. The reaction mixture is refluxed for 3 h. and then cooled at room temperature in order to remove by filtration the dicyclohexylurea (DCU) formed. The filtrate is rotoevaporated and cooled and the obtained white solid is separated by filtration and it is washed with plenty of water and diethyl ether, and air-dried to obtain 2.29 g of product. Yield: 87%, Mp.: 168-171 °C. ESI-MS (m/z) = 341 $(M + 1)^+$.

Example 4: N-[4-(1-naphthylamino)-4-oxobutanoyl]-ß-alanine(**4**).

To a dissolution of **2** (500 mg, 2.06 mmol) in 13 mL of anhydrous 1,4-dioxane are added NHS (283 mg, 2.46 mmol) and DCC (507 mg, 2.46 mmol). The reaction mixture is refluxed for 3 h. and then cooled at room temperature in order to remove the dicyclohexylurea (DCU) formed. Then, ß-alanine (248 mg, 2.78 mmol) is added and the mixture is heated for 20 h. at 60 °C. The solution is rotoevaporated to dryness and the crude product is purified by column chromatography with chloroform as mobile phase. 230 mg of a white solid is obtained. Yield: 40%. Mp.: 180.5-181.8 °C. ESI-MS (m/z) = 316 $(M.+ 1)^+$.

Example 5: 6-{[4-(1-naphthylamino)-4-oxobutanoyl]amino}hexanoic acid (**5**).

Compound **2** (1 g, 4.4 mmol), DCC (0.9 g, 4.4 mmol), 6-aminocaproic acid (0.6 g, 7.6 mmol) and triethylamine (0.6 mL, 4.3 mmol) are added in 40 mL of DMF and the reaction mixture is refluxed for 6 hours. Then, the reaction mixture is rotoevaporated to dryness and the crude product is recrystallized from ethanol. The solid, thus obtained, is dried over P_2O_5 to yield 0.28 g of **5**. Yield: 18%. Mp.: 229-231 °C. ESI-MS (m/z) = 344 $(M.+1)^+$.

Example 6: *N*1-(2-aminoethyl)-N4-(1-naphthyl) succinimide (**6**).

Method A (*one pot*): Compound **2** (500 mg, 2.06 mmol) and NHS (283 mg, 2.46 mmol) are dissolved in 5 mL of anhydrous 1,4-dioxane under dry atmosphere of N_2. Next, a solution of DCC (507 mg, 2.46 mmol) in 8 mL of anhydrous 1,4-dioxane is added dropwise through a pressure equalizing dropping funnel. The reaction mixture is refluxed for 2 h. and then cooled at room temperature in order to remove the dicyclohexylurea (DCU) formed. A solution of ethylenediamine (0.18 mL, 2.7 mmol) in 1 mL of 1, 4-dioxane is added. The reaction mixture is stirred at room temperature for 30 min. and then cooled to precipitate a white solid that is filtered, washed with 1,4-dioxane and acetone, and air-dried to yield 584 mg of the product (98%). Recrystallization from ether yielded 85% of pure **6**. Mp.: 128.9-130.5 °C.

Method B: Compound **1** (2.58 g, 11.47 mmol) and ethylenediamine (7.66 mL, 11.4 mmol) are dissolved in 30 ml of anhydrous 1, 4-dioxane and refluxed for 2 h. and then cooled at room temperature. 15 mL of diethyl ether is added in order to precipitate a white solid that is filtered and washed with diethyl ether to obtain 3.27 g of product. Recrystallization from acetone yielded 63 % of pure **6**. Mp.: 128.9-130.5 °C. ESI-MS (m/z) = 287 $(M + 1)^+$.

Example 7: *N*1-(4-aminobutyl)-*N*4-(1-naphthyl) succinamic (**7**).

Method A: Compound **2** (2.12 g, 8.72 mmol), NHS (1.42 g, 12.34 mmol) and DCC (2.54 g, 12.33 mmol) are dissolved in 30 mL of anhydrous 1, 4-dioxane and then refluxed for 3 h. Then, the reaction mixture is cooled at room temperature to remove the DCU formed. 1,4-Butylenediamine (2.6 mL (26.14 mmol) is slowly dropped and the reaction mixture is stirred for 30 min. at room temperature. The mixture is rotoevaporated to dryness and the crude product re-dissolved in 10 ml of $CHCl_3$ is washed with water (3 x 5 mL). Next, the organic phase is dried with anhydrous Na_2SO_4 and rotoevaporated to dryness. Diethyl ether (10 mL) is added to precipitate in cold a white solid. Yield: 72%. Mp.: 142.2-150.8 °C.

Method B: Compound **1** (1.832 g, 8.1 mmol), triethylamine (1.94 mL, 14 mmol) and 1,4-butylenediamine (1.66 mL, 16.6 mmol) are dissolved in 30 mL of DMF and the mixture is refluxed for 1 hour. After solvent elimination, the product is purified by column chromatography with ethyl acetate and ethyl acetate: methanol (10:2), as mobile phases. Yield: 11%. Mp.: 142.2-150.8 ° C. ESI-MS (m/z) = 315 $(M + 1)^+$.

Example 8: *N*1-[2 - (methylamino) ethyl]-*N*4-(1-naphthyl) succinimide (**8a**).

A slurry of activated molecular sieves 4Å (500 mg) in 8 mL of anhydrous DMF is added $CsOH \cdot H_2O$ (280 mg, 1.7 mmol), and the mixture is stirred for 10 minutes. Next, compound **6** (485 mg, 1.7 mmol) in 1 mL of anhydrous DMF is added and stirred the mixture for 30 min. at room temperature. Then, to this reaction mixture, CH_3I (124 µL, 2 mmol) in 0.5 mL of anhydrous DMF is added and stirred for 24 h., at room temperature. The mixture is thus filtered and rotoevaporated to dryness. The crude product is washed with NaOH (1 N) and extracted with ethyl acetate. The organic phase is dried with Na_2SO_4 and purified by column chromatography with ethyl acetate as mobile phase. Yield: 70%. Mp.: 120 °C (dec.). ESI-MS (m/z) = 300 $(M + 1)^+$.

Example 9: Sodium salt of the acid methyl (2 - ([4 - (1-naphthylamine)-4-oxobutanoil] amino) ethyl) carbamoditionic (**8b**).

Compound **8a** (299 mg, 1 mmol) is added to a suspension of NaOH (80 mg, 2 mmol) in 3 mL of dry diethyl ether. The reaction mixture is cooled in an ice bath and stirred vigorously for 30 min., to slowly drop CS_2 (121 µL, 2 mmol) in 0.5 mL of ether. Then, the mixture is stirred for 30 min. in cold and then, at room temperature for 2 hours. Solids are filtered and washed with dry diethyl ether. Yield: 75%. Mp.: (dec.). ESI-MS (m/z) = 398 $(M + 1)^+$.

Example 10: *N*1-(2-aminoethyl)-*N*4-(1-naphthyl) succinimide-^{131}I (**9**).

Labeling with ^{131}I: To a tube with Iodogen covered walls (the tubes are impregnated with 250 to 500 µL of a Iodogen solution (0.2 mg/mL in $CHCl_3$), under an atmosphere of dry nitrogen) is added 503.2 MBq (13.6 mCi) of ^{131}I and stirred for 10 min. at room temperature. Then 100 µL of a solution of **6** (7.7 10^{-3} mol/L) in PBS (pH 8.5) is added and the reaction mixture is thus stirred for another 15 minutes. The mixture is decanted in order to remove the ^{131}I free by filtration through filters of 3 MM Whatman paper impregnated with silver nitrate.

Example 11: 6-bromo-2-methoxynaphthalene (**11**).

6-Bromo-2-naphthol (**10**) is obtained from the reaction between 2-naphthol and molecular bromine in glacial acetic acid according to procedure described by Reddy et al. in *Organic Process Research and Development, 1999, 3, 121-25.*

To a solution of Cs_2CO_3 (7.55 g, 23.3 mmol) and 6-bromo-2-naphthol (4.6 g, 17.9 mmol) in 45 mL of acetone, $(CH_3)_2SO_4$ (2.2 mL, 23.3 mmol) is added dropwise and stirred for 30 min. at room temperature. The reaction mixture is rotoevaporated and the crude is washed with water and extracted with $CHCl_3$. The organic phase is dried with $MgSO_4$ and cooled to precipitate 4.45 g of a white solid. Yield: 91%. Mp.: 101.4-103.7 °C (lit.: 103 - 105 °C).

Example 12: 3-(6-methoxy-2-naphthyl)propyl 4-methylbenzenesulfonate (**13**).

Preparation of Grignard reagent: according to general procedure described by Kidwell et al. in *Organic Synthesis, Coll., 1973, 5, 918*. In particular, in this invention, the reagent obtaining process is carried out in a flask with Mg (0.363 g, 14.95 mmol) and a small crystal of I_2, previously flame-dried and the atmosphere replaced with dry Ar. Then, 1 mL (0.709 g, 2.99 mmol) of a solution of **11**, in 3 mL of THF, is added dropwise to the flask. The reaction mixture is slowly heated to reflux until the boiling becomes spontaneous and a white sludge is formed. After that, the rest of the solution is added dropwise and refluxed for 4 h. until the formation of **12**.

Preparation of the catalyst Li_2CuCl_4: according to general procedure described by Burns et al., in *J. Chem. Soc. 1997, 119, 2125-2133.*

To a flask, previously flame-dried and evacuated with Ar, a solution of 1,3-propanediol di-p-tosylate(PrDiTs) (1.26 g, 3,289 mmol) in 1 mL of THF is added. Then, 1.79 mL of catalyst Li_2CuCl_4 is added. The reaction mixture is cooled at -30 °C and the Grignard reagent is added dropwise. Once the addition process is finished, the mixture is maintained at 8 °C for 24 h. and later at room temperature for 48 hours. The product is thus purified by column chromatography with a mixture of n-hexane: dichloromethane (100:0 to 80:20) as mobile phase. Yield: 15%. Mp.: dec. ESI-MS (m/z) = 371 $(M+1)^+$.

Example 13: 2-(3-fluoropropyl)-6-methoxynaphthalene (**14**).

3 mL of $(bmim)(BF_4)$ is added to 3 mL of a solution of H_2O (90 μL, 5 mmol) in CH_3CN with **13** (370 mg, 1 mmol). Then, anhydrous CsF (760 mg, 5 mmol) is added. The reaction mixture is stirred at 100 ° C for 2 hours. Upon completion of the reaction, the product of interest is extracted with diethyl ether (3 x 5 mL). The organic phase is dried ($MgSO_4$) and concentrated to dryness to purify by column chromatography (ethyl acetate: hexane as mobile phase). Yield: 40%. Mp.: dec. ESI-MS (m / z) = 219 $(M + 1)^+$.

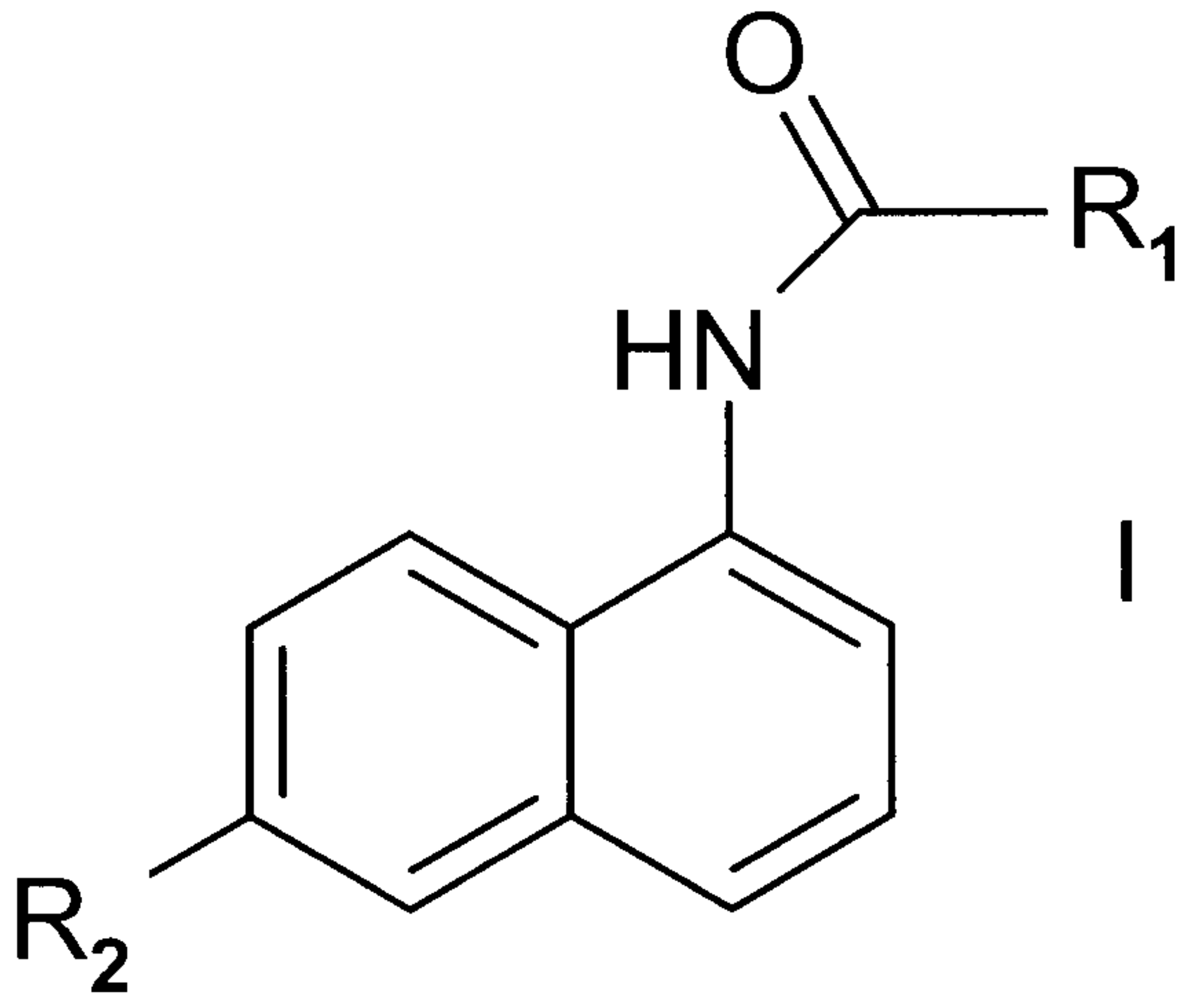
Example 14: Labeling studies and biodistribution in rats. Compound: *N*1-(2-aminoethyl)-*N*4-(1-naphthyl) succinimide-^{131}I (**9**).

Determination of partition coefficients: A solution of **9** (20 μL), prepared as described in example 10, is added to a mixture of 3 ml of *n*-octanol and 3 ml of distilled water. After stirring and leaving to stand the mixture, aliquots of 20 μL from each phase are taken to determine the radiometric distribution ratio by an activity meter (CRC 35R, Capintec Inc.). This procedure is repeated to the radiopharmaceutical of ^{99m}Tc-ECD as reference, which is used for cerebral perfusion studies. Partition coefficient of **9**: 0.54 (logP = -0.27) and ^{99m}Tc-ECD: 40.6 (logP = 1.6).

Animal studies: A solution of **9** 15 MBq (407 Ci), prepared as described above, is administered to male Wistar rats (160 g, n = 3) through the lateral tail vein. Then, images are taken every 15 seconds, for 30 min. (120 images) with a gamma camera (Medis Nucline TH22, Hungary), with a peak centered at 360 keV and a window of ± 25%. The image processing is performed on a processing station Segami (USA).

CLAIMS :

1. A naphthalene derived compound comprising the structure I:



I

wherein:

R_1 is -alkylenyl-C(O)NH-alkylenyl-R_3, or -alkylenyl-C(O)O-R_4;

R_2 is H, or alkyl;

R_3 is -COOH, -OH, -SH, -NH_2, -NH-alkyl, or an -N(-alkyl)-dithiocarbamate alkaline earth metal salt; and

R_4 is a succinimidyl group;

wherein:

the term "alkyl" is a group selected from the group consisting of methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl and *iso*-butyl; and

the term "alkylenyl" is a C_1-C_6 hydrocarbon radical.

2. The compound of claim 1, wherein:

R_1 is $-(CH_2)_nCONH(CH_2)_m-R_3$ where n = 2, 3 or 4 and m = 2, 3, 4, 5 or 6;

R_3 is -COOH; and

combinations thereof.

3. The compound of claim 1, wherein:

R_1 is $-(CH_2)_nCONH(CH_2)_m-R_3$ where n = 2, 3 or 4 and m = 2, 3, 4, 5 or 6;

R_3 is $-NH_2$, $-NHCH_3$ or $-NHC_2H_5$; and

combinations thereof.

4. The compound of claim 1, wherein:

R_1 is $-(CH_2)_nCONH(CH_2)_m-R_3$ where n = 2, 3 or 4 and m = 2, 3, 4, 5 or 6;

R_3 is $-NR_5R_6$;

R_5 is $-CH_3$ or $-C_2H_5$;

R_6 is -C(S)SW where W is Na^+, K^+ or Cs^+; and

combinations thereof.

5. The compound of claim 1, wherein:

R_1 is $-(CH_2)_nCONH(CH_2)_m-R_3$ where $n = 2$, 3 or 4 and $m = 2$, 3, 4, 5 or 6;

R_3 is $-OH$; and

combinations thereof.

6. The compound of claim 1, wherein:

R_1 is $-(CH_2)_nCONH(CH_2)_m-R_3$ where $n = 2$, 3 or 4 and $m = 2$, 3, 4, 5 or 6;

R_3 is $-SH$; and

combinations thereof.

7. The compound of claim 1, wherein:

R_1 is $-(CH_2)_nC(O)O-R_4$ where $n= 2$, 3 or 4; and

combinations thereof.

8. A process for preparing the compound of claim 1, comprising reacting:

i) an *N*-hydroxysuccinimide ester of 4-(1-naphthylamino)-4-oxobutanoic acid;

with

ii) a compound having primary amino groups wherein said compound is:

a) an aliphatic diamine; or

b) a polyfunctional amine selected from the group consisting of α-amino acids, thioamines, aminoalcohols, and aminocarboxylic acids;

in a solvent.

9. The process of claim 8, wherein the aliphatic diamine is one selected from the group consisting of ethylenediamine, propylenediamine, 1-methyl-1,2-ethylenediamine and butylenediamine, and the polyfunctional amine is selected from the group consisting α-aminoisobutyric acid, 2-aminoethanethiol, ethanolamine, β-alanine and 6-aminohexanoic acid.

10. The process of claim 8, wherein the process is a one-pot process comprising reacting:

i) 4-(1-naphthylamino)-4-oxobutanoic acid;

with

ii) *N*-hydroxysuccinimide in the presence of dicyclohexylcarbodiimide,

to obtain *in situ* an *N*-hydroxysuccinimide ester of 4-(1-naphthylamino)-4-oxobutanoic acid and further reacting the *N*-hydroxysuccinimide ester of 4-(1-naphthylamino)-4-oxobutanoic acid with an excess of diamine or an aminocarboxylic acid.

11. A process for preparing a naphthalenic derivative of structure I as defined in claim 1, comprising reacting:

i) 1-(1-naphthyl)-2, 5-pyrrolidinedione;

with

ii) an excess of a diamine,

in a refluxing solvent.

12. A process for preparing a naphthalenic derivative of structure I as defined in claim 1, comprising reacting:

i) 1-(1-naphthyl)-2, 5-pyrrolidinedione;

with

ii) an excess of an aminocarboxylic acid in presence of triethylamine;

in a refluxing solvent.

13. The process for preparing an alkylaminonaphthalenic derivative of structure I as defined in claim 1, comprising reacting:

i) a compound of structure I where R_1 is -alkylenyl-C(O)NH-alkylenyl-R_3 and R_3 is NH_2;

with

ii) a compound selected from CH_3I, C_2H_5Br, $(CH_3)_2SO_4$ and $(C_2H_5)_2SO_4$;

in a solvent comprising an inorganic base selected from K_2CO_3, Cs_2CO_3 and CsOH.

14. A process for preparing the compound of claim 1, comprising reacting:

i) one of the alkylaminonaphthalenic derivatives as defined in claim 13;

with

ii) CS_2;

in a solvent comprising an alkaline earth base at a reaction temperature between -10 and 30°C.

15. The compound of claim 1, said compound being linked to a gamma emitter iodine radioisotope selected from ^{123}I and ^{131}I.

16. The compound of claim 1, said compound being a stable complex with ^{99m}Tc.

17. A process for preparing the stable complex of ^{99m}Tc as defined in claim 16, comprising reacting:

i) a naphthalenic derivative of structure I where R_1 is -alkylenyl-C(O)NH-alkylenyl-R_3, and R_3 is selected from the group consisting of -COOH, -OH, -SH, $-NH_2$, -NH-alkyl and -N(-alkyl)-dithiocarbamate alkaline earth metal salts;

with

ii) ^{99m}Tc in the presence of a chelating ligand, having sulfur, nitrogen or oxygen atoms selected from the group consisting of 2,2'-oxidietanthiol and *N*1-(2-aminoethyl) -1,2-ethanediamine.

18. The compound of claim 1, wherein the structure I further comprises a positron-emitting isotope selected from the group consisting of ^{11}C, ^{15}O, and ^{18}F.

19. The compound as defined in claim 15, 16 or 18 for use in an *in vivo* diagnostic method to display the density of amyloid sheets in a mammal brain using a technique selected from the group consisting of computed tomography single photon emission (SPECT), positron emission tomography (PET), and nuclear magnetic resonance imaging (MRI).

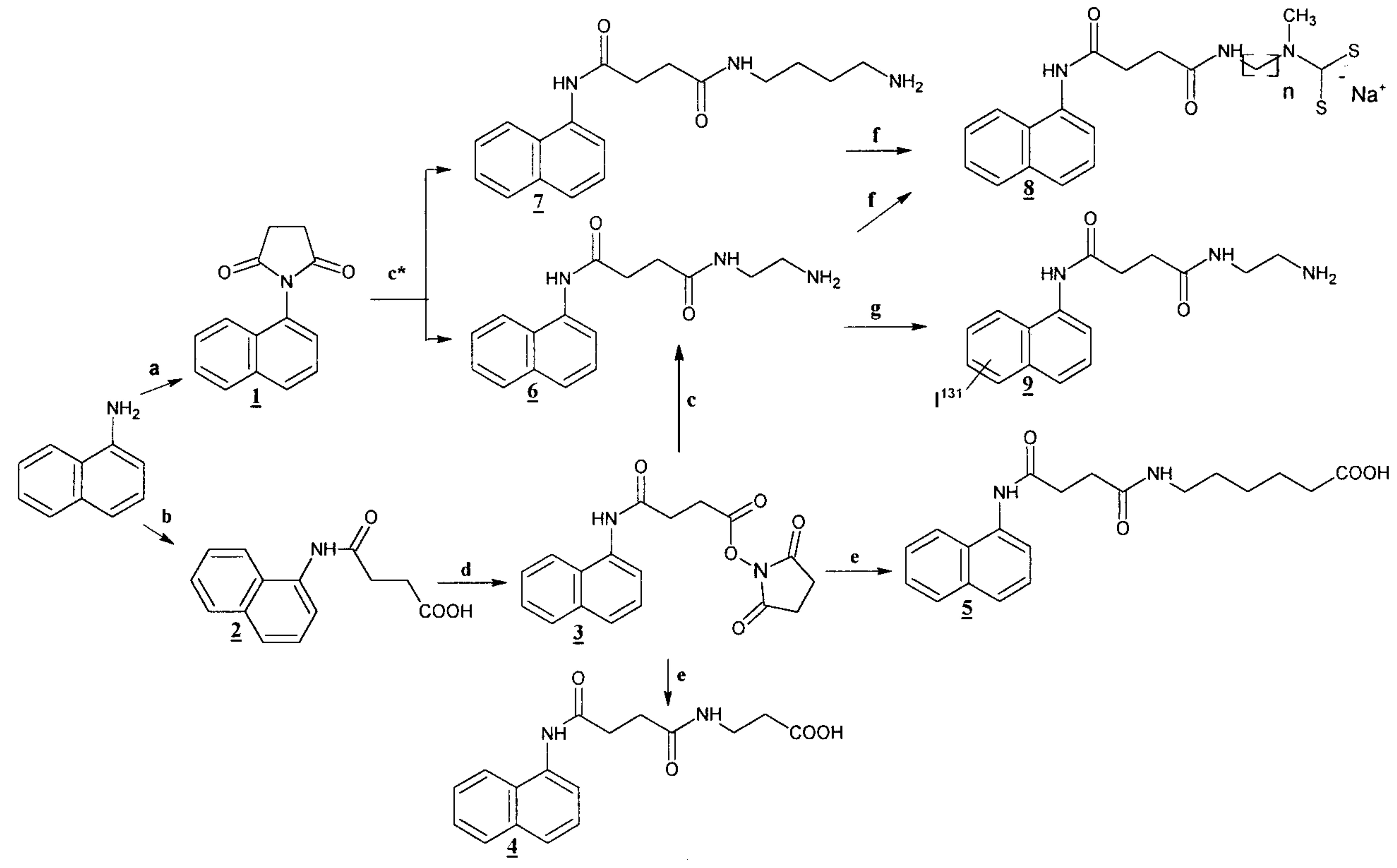


Figure 1.

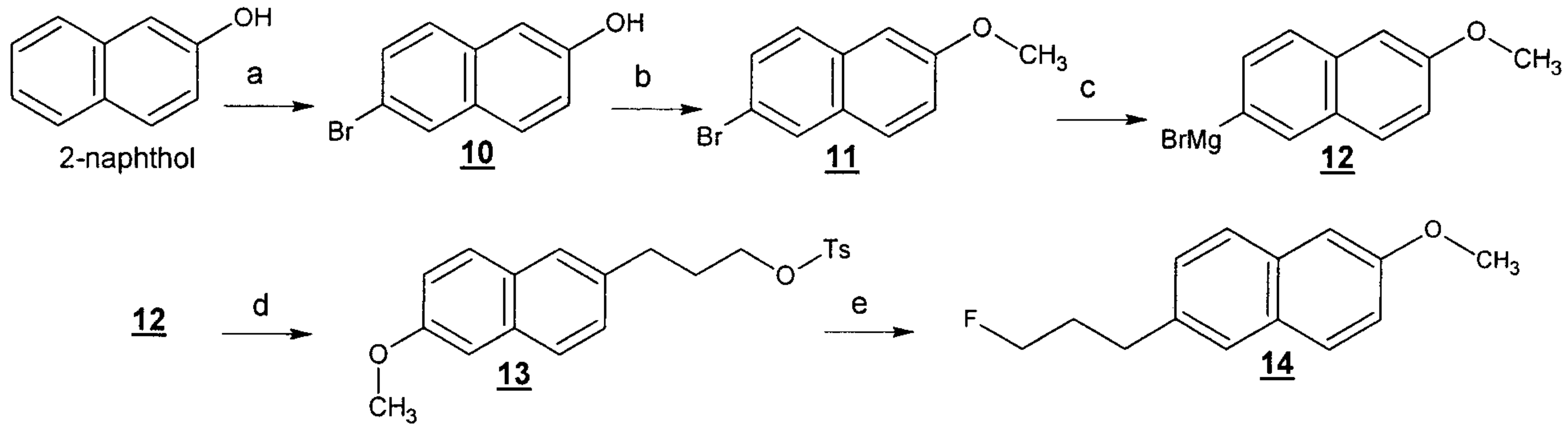

OH
a
2-naphthol
Br
OH
10
b
Br
O
CH3
11
c
BrMg
O
CH3
12
12
d
O
Ts
O
CH3
13
e
O
CH3
F
14

Figure 2.

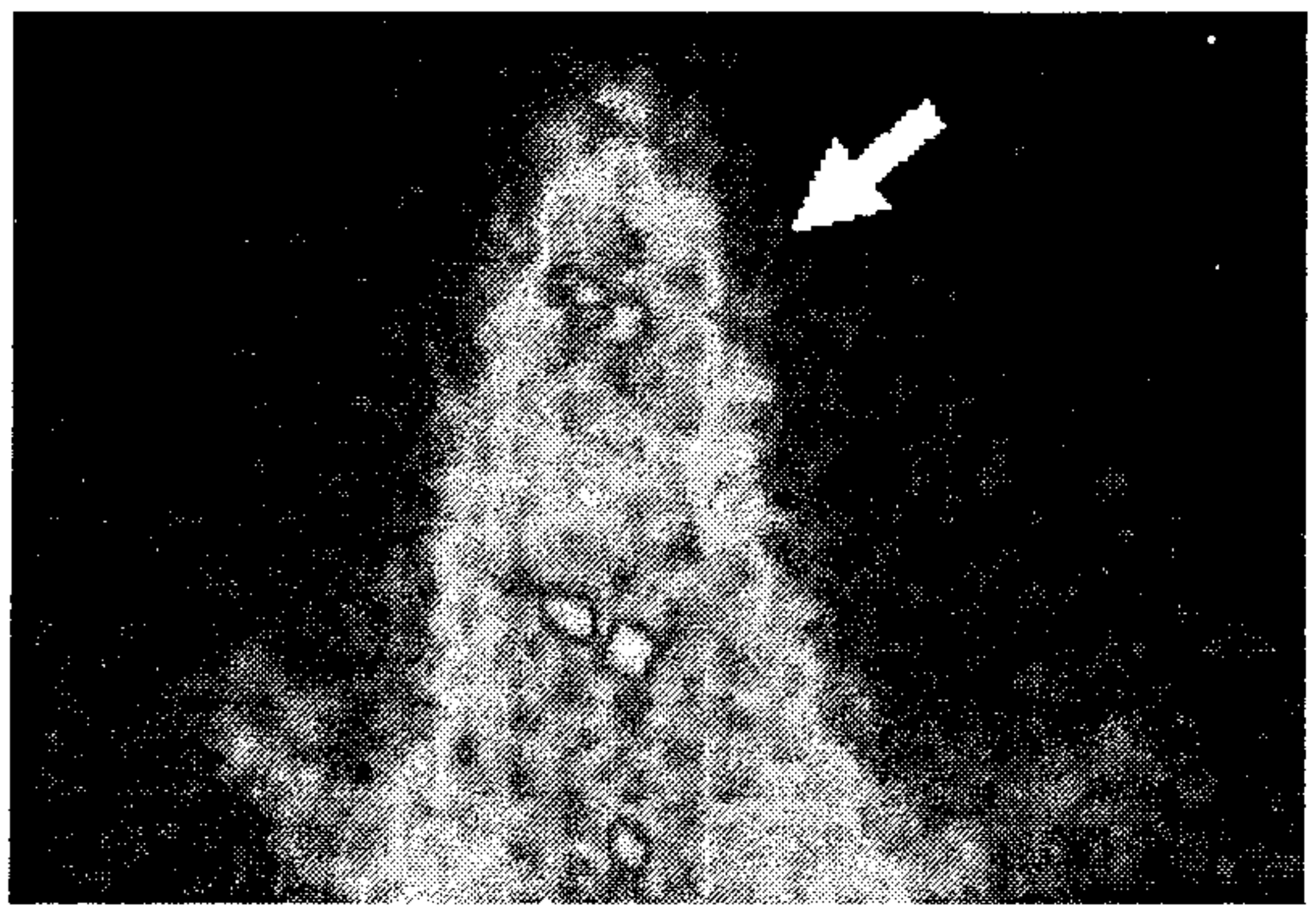
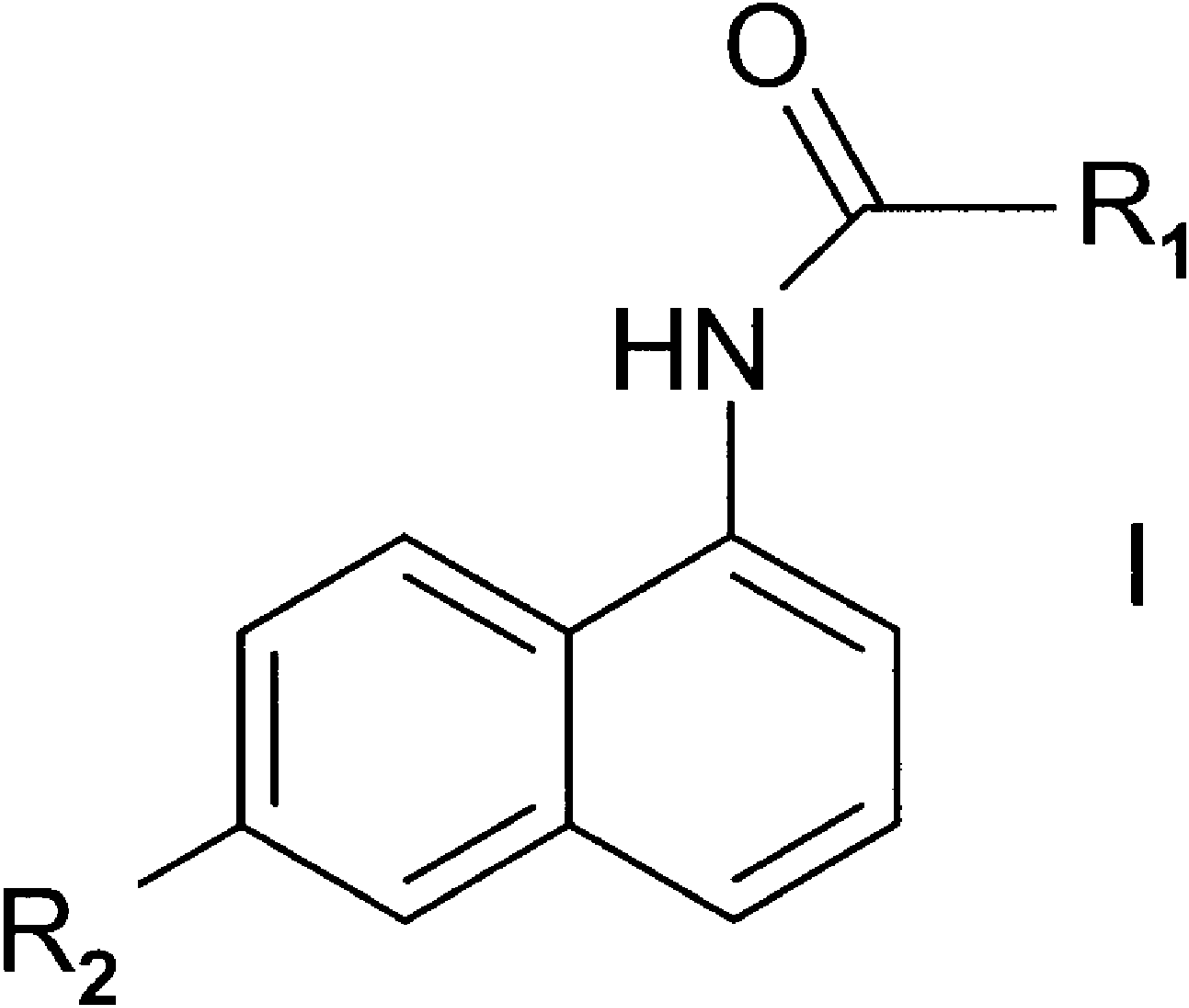


Figure 3.



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