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(54) Title: 1-PHENYLALKANECARBOXYLIC ACID DERIVATIVES FOR THE TREATMENT OF NEURODEGENERATIVE
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(57) **Abrégé/Abstract:**

1-Phenylalkanecarboxylic acid derivatives, the processes for the preparation thereof and the use thereof in the treatment and/or prevention of neurodegenerative diseases such as Alzheimer's disease.



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(54) Title: 1-PHENYLALKANECARBOXYLIC ACID DERIVATIVES FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

(57) Abstract: 1-Phenylalkanecarboxylic acid derivatives, the processes for the preparation thereof and the use thereof in the treat-
ment and/or prevention of neurodegenerative diseases such as Alzheimer's disease.

WO 2004/074232 A1

1-PHENYLALKANECARBOXYLIC ACID DERIVATIVES FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

The present invention concerns 1-phenylalkanecarboxylic acids, pro-
drugs and bioisosters on the carboxylic moiety thereof. The invention is also
directed to a process for their preparation and the use thereof in the prevention
or in the therapeutical treatment of neurodegenerative diseases, in particular
5 Alzheimer's disease.

INTRODUCTION

Alzheimer's disease is a neurodegenerative disorder characterized by
atrophy of the cerebral cortex and by a massive loss of cortical neurons and
cholinergic projections of the nucleus basalis towards the cortex. From a
10 histopathologic point of view there is a diffuse presence of extracellular and
perivascular neuritic plaques and intracellular neurofibrillary tangles in the
cerebral parenchyma of Alzheimer patients.

Neuritic plaques are mainly composed of aggregates of a protein with
39-43 amino acid residues known as β -amyloid (β A), and, depending on the
15 numbers of aminoacids, $A\beta_{39}$, $A\beta_{40}$, $A\beta_{42}$ and $A\beta_{43}$.

In addition to these histopathologic lesions, there is lack in some
neurotransmitters, particularly acetylcholine, serotonin, noradrenalin,
dopamine, glutamate and substance P. The pharmacological approaches aimed
at increasing acetylcholine cerebral levels, mainly through acetylcholine-
20 esterase inhibitors, attained poor results from the clinical standpoint, or
anyhow results which cannot significantly prevent the progress of the disease.
For this reason, in recent years interest has been focused on the mechanisms
of formation of the main pathologic lesions in the brain of the patients, namely
both neuritic plaques and neurofibrillary tangles, and more effective
25 therapeutical approaches have been looked for.

PRIOR ART

Epidemiological studies evidenced that chronic administration of non steroid anti-inflammatory drugs (NSAIDs) significantly decreases the onset of Alzheimer's disease in the population regularly taking these drugs. The
5 mechanism underlying such NSAID preventive action has not been fully elucidated yet, but is apparently connected with their ability of inhibiting cyclooxygenase (COX) enzymes.

More recently, a novel pharmacological action of some non steroid anti-inflammatory drugs (NSAIDs) has been described: indomethacin, sulindac,
10 ibuprofen and flurbiprofen can selectively reduce the production of the most neurotoxic isoform of β -amyloid peptide in cell cultures, namely the form containing 42 amino acids ($A\beta_{42}$), thus favouring the release of a less harmful isoform, $A\beta_{38}$ (Weggen et al., Nature 2001; 414 (6860): 212-6). However, the inhibition of the production of $A\beta_{42}$, which can be ascribed to the interaction
15 of these drugs with γ -secretase (a macromolecular/multiprotein enzymatic complex with aspartyl-protease activity) has been observed *in vitro* at very high concentrations. Plasma and cerebral levels corresponding to the dosages used in the *in vitro* experimentation could significantly increase in treated patients the risk of side effects typical of COX inhibitors, such as
20 gastrointestinal bleeding and perforating ulcers.

WO 01/78721 claims a method of preventing, delaying or reversing the progression of Alzheimer's disease by administering an $A\beta_{42}$ lowering agent, under conditions in which levels of $A\beta_{38}$ are increased and levels of $A\beta_{42}$ are left unchanged. Furthermore, methods and materials for identifying and
25 developing $A\beta_{42}$ lowering agents and methods for identifying agents that increase the risk of developing, or hasten progression of, Alzheimer's disease, are disclosed. The examples concern indomethacin and flufenamic acid derivatives, but no examples concerning flurbiprofen derivatives are reported.

Jantzen et al, *J Neurosci* 2002; 22: 2246-2254, described a flurbiprofen derivative capable of releasing nitric oxide. The paper generically states that flurbiprofen derivatives are apparently more efficacious than other NSAIDs in clearing β -amyloid deposits, but no mention concerning any $A\beta_{42}$ lowering selective activity is made.

In this therapeutical scenario, and in the light of the potential problems of conventional NSAIDs, novel derivatives having more selective and more potent inhibitory activity on the peptide $A\beta_{42}$ while inhibiting to a lesser extent, or not inhibiting at all, cyclooxygenase would be a significant improvement in therapies aimed at preventing the onset of Alzheimer's disease and/or at delaying the cognitive decline that represent an early stage disease.

Substituted 1-phenyl-2,2-dialkyl carboxylic derivatives were described as anti-inflammatory, analgesic and antipyretic agents in GB 1,198,212, US 3,978,071, US 757,136, GB 1,352,723, JP49100089 and JP 50046669.

3-Halo-4-alkyl- or cycloalkyl- substituted 1-phenylcycloalkanecarboxylic derivatives were described in JP-4,7047,375 and FR-2,012,285, as substances with the same activity.

In the paper from Kuzuna S et al (Takeda Kenkyushoho 1975, 34, 467-473) dealing with a structure-activity study of a series of phenylacetic derivatives, it is generically stated that the introduction of a cyclopropane group at the position of α carbon atom decreases the anti-inflammatory and analgesic activities.

In WO 99/41224 novel biaryl-acetic acid derivatives with anti-inflammatory activity as cyclooxygenase-2 inhibitors, useful for the treatment of a number of diseases, including Alzheimer's disease, are claimed.

SUMMARY OF THE INVENTION

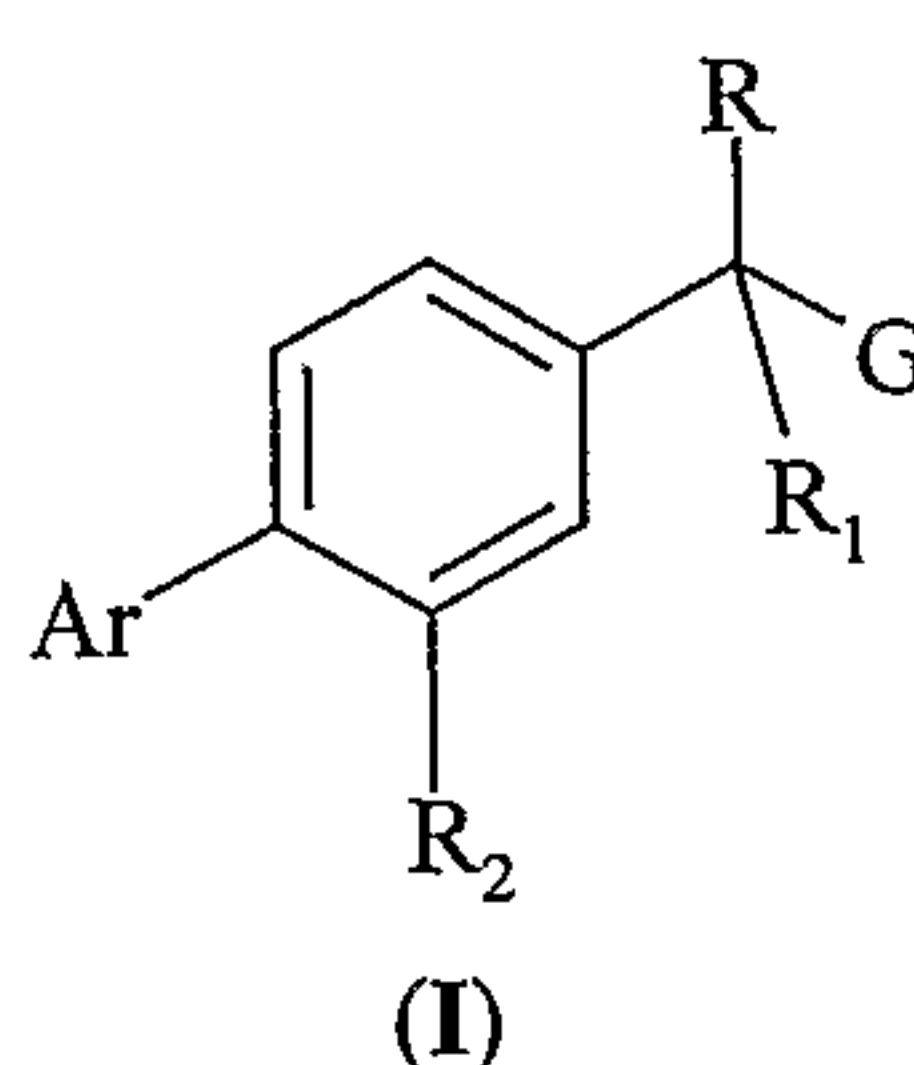
The present invention concerns 1-phenylalkanecarboxylic acids, their pro-drugs, and bioisosters on the carboxylic moiety, the process for the

preparation thereof, pharmaceutical compositions containing them and the use thereof in the prevention or therapeutical treatment of neurodegenerative diseases, in particular Alzheimer's disease.

The compounds of the invention inhibit the release of $A\beta_{42}$ peptide thereby being able to modulate gamma-secretase activity without affecting other important metabolic processes.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of general formula (I):



10 wherein:

R and R_1 are the same and are selected from the group of linear or branched C_1 - C_4 alkyl;

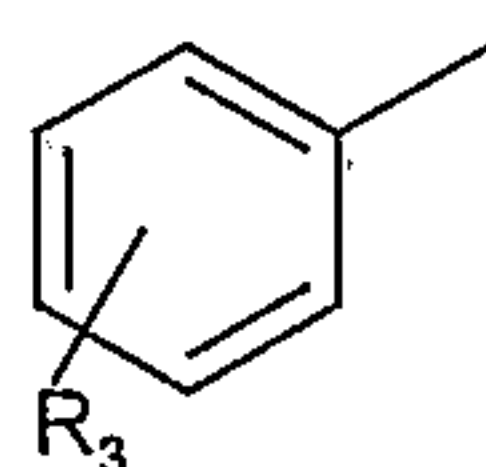
otherwise they form a 3 to 6 carbon atoms ring with the carbon atom to which they are linked;

15 G is:

- a $COOR''$ group wherein R'' is H, linear or branched C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl or ascorbyl;
- a $CONH_2$ or a $CONHSO_2R'''$ group wherein R''' is linear or branched C_1 - C_4 alkyl or C_3 - C_6 cycloalkyl;
- 20 - a tetrazolyl residue;

R_2 is H, CF_3 , OCF_3 or a halogen selected from the group of F, Cl, Br, I, preferably fluorine.

Ar is a group of formula



wherein R_3 represents one or more groups independently selected from:

- halogen as previously defined;
 - CF_3 ;
 - C_3 - C_8 cycloalkyl optionally substituted with one or more C_1 - C_4 alkyl
5 and/or oxo groups;
 - $CH=CH_2$;
 - CN ;
 - CH_2OH ;
 - methylenedioxy or ethylenedioxy;
 - 10 - NO_2
 - phenyl optionally substituted with one or more of the following groups:
halogen; CF_3 ; OCF_3 ; OH ; linear or branched C_1 - C_4 alkyl; a saturated
heterocycle with at least 4 carbon atoms and at least 1 heteroatom; C_3 - C_8
cycloalkyl in turn optionally substituted with one or more of the
15 following groups linear or branched C_1 - C_4 alkyl, CF_3 or OH ;
 - OR_4 or $NHCOR_4$ wherein R_4 is CF_3 , linear or branched C_2 - C_6 alkenyl or
alkynyl; benzyl; phenyl optionally substituted with one or more of the
following groups: halogen, CF_3 , OCF_3 , OH , linear or branched C_1 - C_4
alkyl; a saturated eterocycle with at least 4 carbon atoms and at least 1
20 heteroatom; C_3 - C_8 cycloalkyl in turn optionally substituted with one or
more of the following groups: linear or branched C_1 - C_4 alkyl, CF_3 or OH ;
 - SR_5 , SO_2R_5 or COR_5 wherein R_5 is linear or branched C_1 - C_6 alkyl;
- otherwise Ar is a heterocycle ring selected from the group of thiophene,
benzothiophene, dibenzothiophene, thianthrene, pyrrole, pyrazole, furan,
25 benzofuran, dibenzofuran, indole, isoindole, benzofurane, imidazole,
benzoimidazole, oxazole, isoxazole, benzoxazole, thiazole, pyridine,
pyrimidine, pyrazine, pyridazine, quinoline, isoquinoline, quinazoline,
quinoxaline, cinnoline, pyrazole, pyran, benzopyran, pyrrolizine, phtalazine,

1,5-naphthyridine, 1,3-dioxole, 1,3-benzodioxole, optionally substituted with one or more groups R_3 as defined above;

pharmaceutically acceptable salts and esters thereof.

A first group of preferred compounds is that in which:

- 5 R and R_1 form a 3 carbon atoms ring with the carbon atom to which they are linked;
- R_2 is fluorine;
- G is COOR'' , wherein R'' is H, linear or branched $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl or ascorbyl;
- 10 Ar is phenyl as defined above.

A second group of preferred compounds is that in which:

- R and R_1 form a 3 carbon atoms ring with the carbon atom to which they are linked;
- R_2 is fluorine;
- 15 G is CONH_2 or $\text{CONHSO}_2\text{R}'''$ wherein R''' is linear or branched $\text{C}_1\text{-C}_4$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl;
- Ar is phenyl as defined above.

A third group of preferred compounds is that in which:

- both R and R_1 are methyl;
- 20 R_2 is fluorine;
- G is COOR'' wherein R'' is as defined above;
- Ar is phenyl as defined above.

A fourth group of preferred compounds is that in which:

- both R and R_1 are methyl;
- 25 R_2 is fluorine;
- G is CONH_2 or $\text{CONHSO}_2\text{R}'''$, wherein R''' is as defined above;
- Ar is phenyl as defined above.

A fifth group of preferred compounds is that in which:

R and R₁ form a 3 carbon atoms ring with the carbon atom to which they are linked;

R₂ is fluorine;

G is COOR" wherein R" is as defined above;

5 Ar is a heterocycle as defined above.

A sixth group of preferred compounds is that in which:

both R and R₁ are methyl;

R₂ is fluorine;

G is COOR" wherein R" is as defined above;

10 Ar is a heterocycle as defined above.

Particularly preferred are the following compounds:

2-methyl-2(2-fluoro-4'-trifluoromethylbiphen-4-yl)propionic acid (CHF 4810);

2-methyl-2(2-fluoro-4'-cyclohexyl biphen-4-yl)propionic acid (CHF 4961);

15 1-(2-fluoro-4'-trifluoromethylbiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5022);

1-(4'-cyclohexyl-2-fluorobiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5023);

20 1-(4'-benzyloxy-2-fluorobiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5042);

1-(2-fluoro-4'-isopropoxybiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5044);

1-(2-fluoro-3'-trifluoromethoxybiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5045);

25 1-(2-fluoro-4'-trifluoromethoxybiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5046);

1-(2-fluoro-3'-trifluoromethylbiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5058);

1-(4'-cyclopentyl-2-fluorobiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5059);

1-(4'-cycloheptyl-2-fluorobiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5060);

5 1-(2'-cyclohexyl-2-fluorobiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5061);

1-(2-fluoro-4'-hydroxybiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5070);

10 1-[2-fluoro-4'-(tetrahydropyran-4-yloxy)biphenyl-4-yl]-cyclopropane-carboxylic acid (CHF 5071);

1-(2,3',4'-trifluorobiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5073);

1-(3',4'-dichloro-2-fluorobiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5074);

15 1-(3',5'-dichloro-2-fluorobiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5075);

1-(3'-chloro-2,4'-difluorobiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5076);

1-(4-benzo[b]thiophen-3-yl-3-fluorophenyl)cyclopropanecarboxylic acid (CHF 5077);

20 1-(2-fluoro-4'-prop-2-ynyloxy-biphenyl-4-yl)-cyclopropanecarboxylic acid (CHF 5078);

1-(4'-cyclohexyloxy-2-fluoro-biphenyl-4-yl)-cyclopropanecarboxylic acid (CHF 5079);

25 1-[2-fluoro-4'-(tetrahydropyran-4-yl)-biphenyl-4-yl]-cyclopropanecarboxylic acid (CHF 5080);

1-[2-fluoro-4'-(4-oxo-cyclohexyl)-biphenyl-4-yl]-cyclopropanecarboxylic acid (CHF 5081);

2-(2''-fluoro-4-hydroxy-[1,1':4',1'']tert-phenyl-4''-yl)-cyclopropanecarboxylic

acid (CHF 5083);

1-[4'-(4,4-dimethylcyclohexyl)-2-fluoro[1,1'-biphenyl]-4-yl]-cyclopropane-carboxylic acid (CHF 5084);

1-[2-fluoro-4'-[[4-(trifluoromethyl)benzoyl]ammino][1,1'-biphenyl]-4-yl]-
5 cyclopropanecarboxylic acid (CHF 5094);

1-[2-fluoro-4'-[[4-(trifluoromethyl)cyclohexyl]oxy][1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid (CHF 5096);

1-[2-fluoro-4'-[(3,3,5,5-tetramethylcyclohexyl)oxy][1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid (CHF 5102);

10 1-[4'-[(4,4-dimethylcyclohexyl)oxy]-2-fluoro[1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid (CHF 5103);

1-(2,3',4''-trifluoro[1,1':4',1''-tert-phenyl]-4-yl)-cyclopropanecarboxylic acid (CHF 5104);

1-(2,2',4''-trifluoro[1,1':4',1''-tert-phenyl]-4-yl)-cyclopropanecarboxylic acid
15 (CHF 5105);

1-(2,3'-difluoro-4''-hydroxy[1,1':4',1''-tert-phenyl]-4-yl)-cyclopropane-carboxylic acid (CHF 5106);

1-(2,2'-difluoro-4''-hydroxy[1,1':4',1''-tert-phenyl]-4-yl)-cyclopropane-carboxylic acid (CHF 5107);

20 2-(2-fluoro-3',5'-bis(chloro)biphen-4-yl)propionic acid amide (CHF 5125).

A more preferred group of compounds is that in which R and R₁ form a 3 carbon atoms ring with the carbon atom to which they are linked;

R₂ is fluorine;

G is COOH;

25 Ar is phenyl substituted with one or more groups in such a way as that the log P (the partition coefficient between n-octanol and water) of the whole molecule is equal or higher than 4.5 as calculated *in silico* by using the software QikProp[®] release version 2.1 (Schrodinger Inc).

It has indeed been found that the higher the log P of the molecule, the greater is the inhibition potency of the release of A β ₄₂ peptide and that particularly potent compounds are those whose log P is equal or higher than 4.5, preferably higher than 5.0.

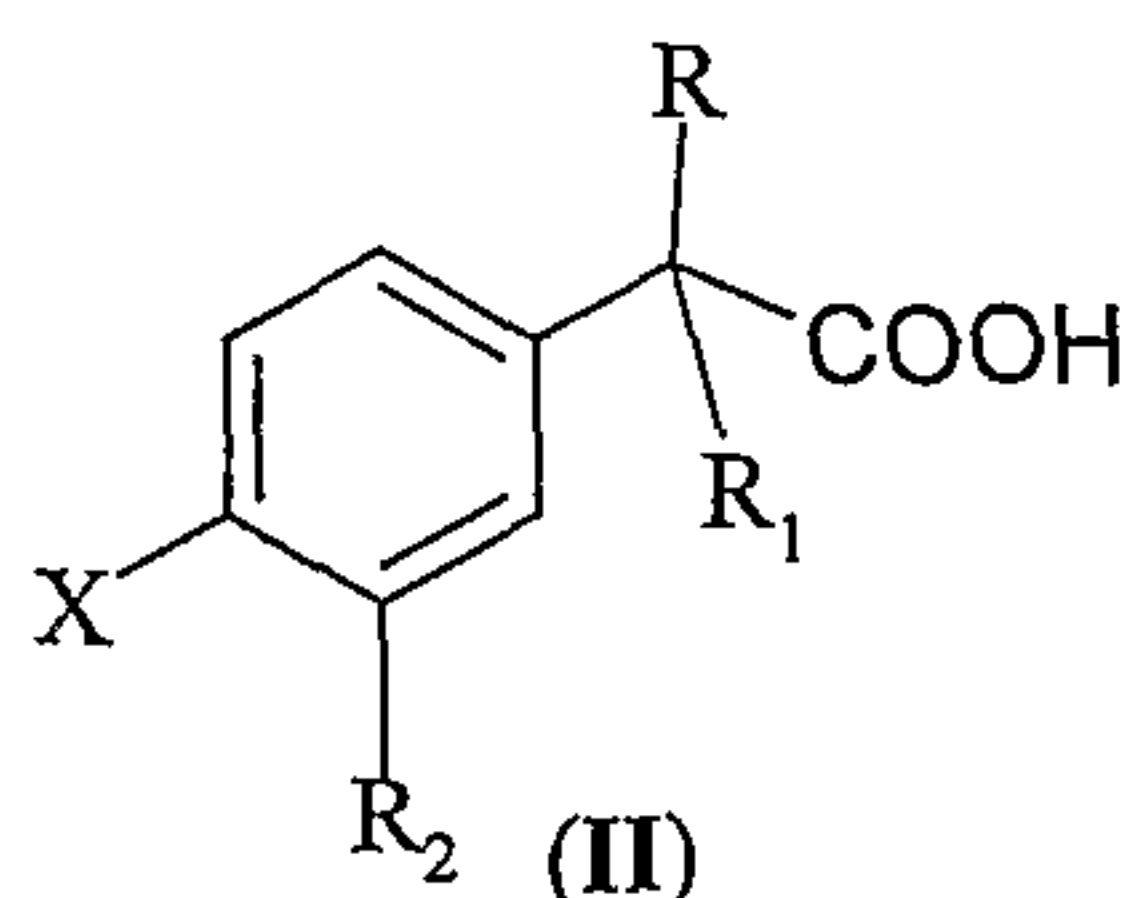
5 Examples of these compounds are CHF 5022, CHF 5074, CHF 5096, CHF 5105, CHF 5106 and CHF 5107.

The invention also relates to the pharmaceutically acceptable salts and esters prepared in order to increase the crossing of the hemato-encephalic barrier.

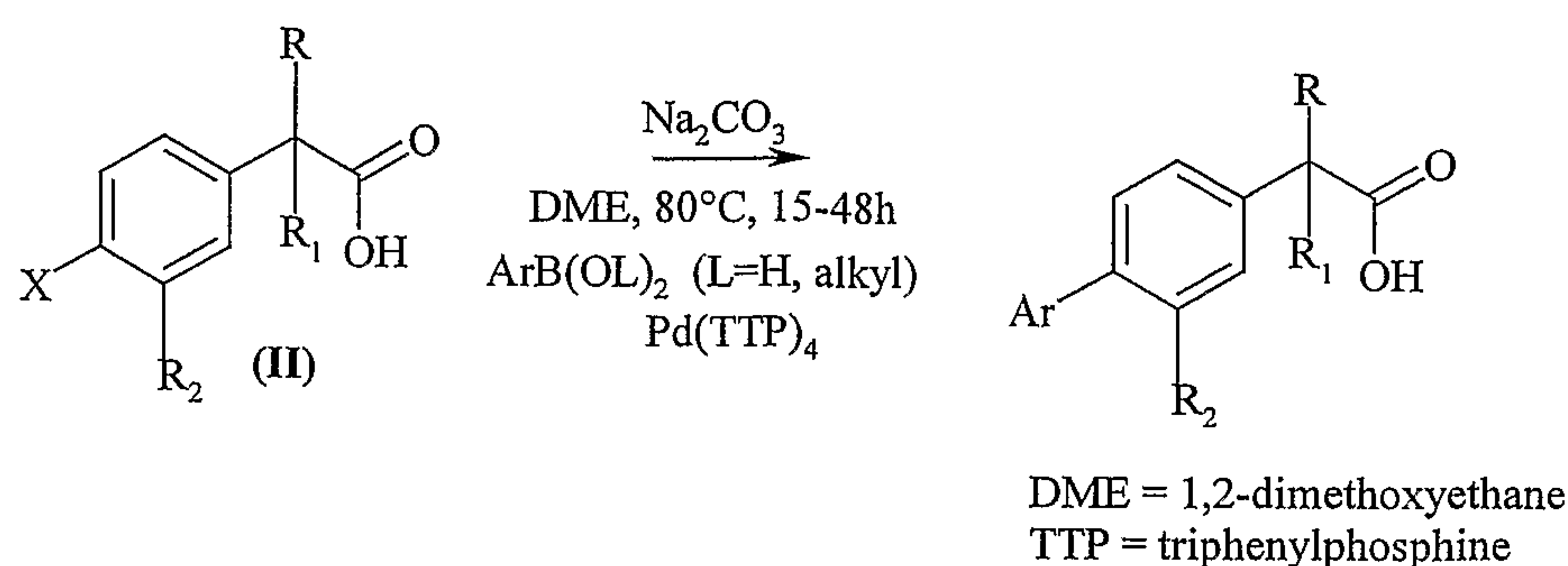
10 A further object of the present invention are the compounds of formula (I) as medicaments, in particular the use thereof in the preparation of pharmaceutical compositions for the treatment and/or the prevention of neurodegenerative diseases such as Alzheimer's disease.

Still a further object of the invention are solid or liquid pharmaceutical
15 compositions, preferably for the oral use, comprising at least one compound of formula (I) in admixture with pharmaceutically acceptable excipients and/or carriers, for example those described in Remington's Pharmaceutical Sciences Handbook, XVII Ed., Mack Pub., N.Y., U.S.A..

The compounds of general formula (I) wherein R" is H can be prepared
20 according to methods of literature by palladium-catalyzed reaction between an aryl halide of formula (II)



in which R, R₁ and R₂ are as defined above and X is bromine or iodine,
25 preferably iodine, with a boronic acid or ester ArB(OL)₂ in which L is an alkyl chain, under the conditions reported in Scheme 1.



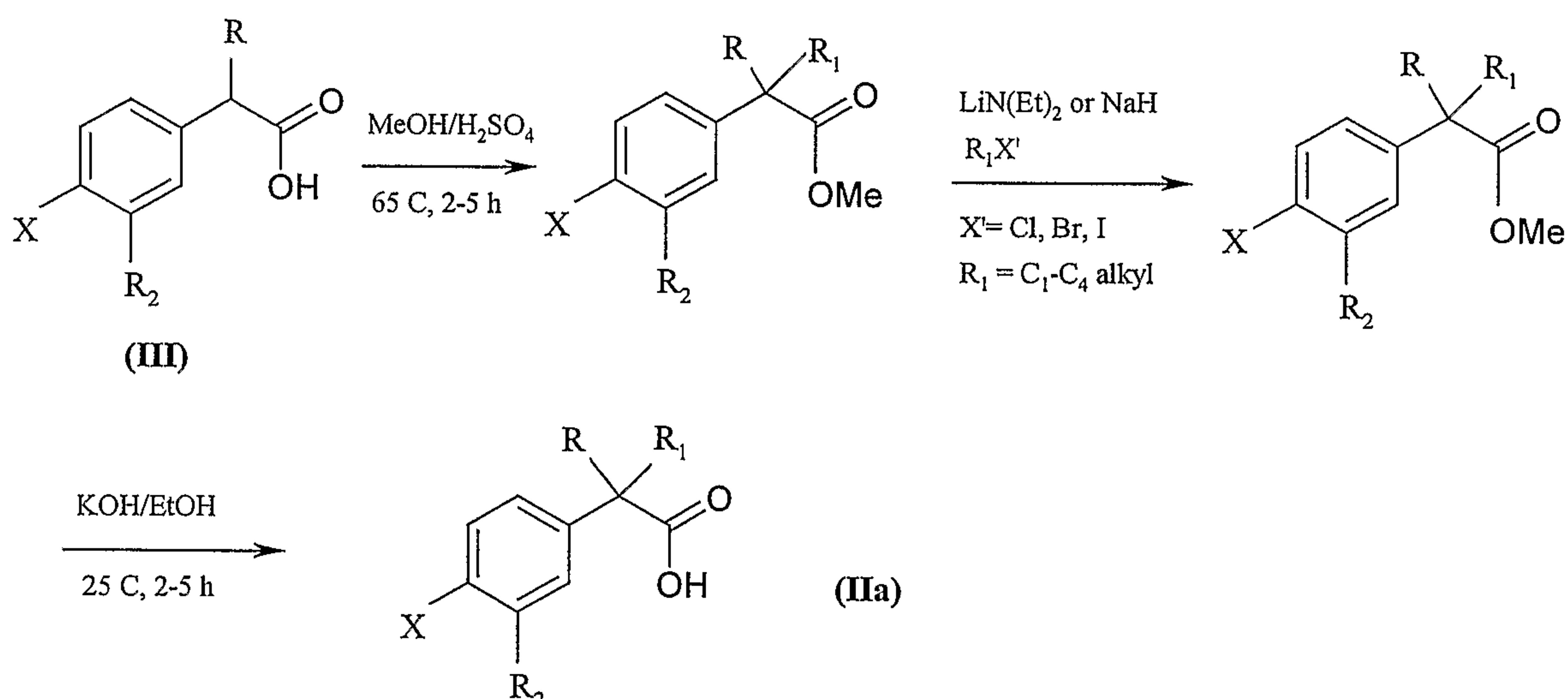
Scheme 1

The compounds of formula (II) are commercially available, or can be prepared according to the following synthetic routes.

Derivatives in which R and R₁ are straight or branched C₁-C₄ alkyl (IIa).

Said compounds can be prepared according to the synthetic route shown in Scheme 2, starting from the arylacetic acids of formula (III) in which R and R₂ are as defined above and X is bromine or iodine.

The acid of formula (III) is esterified, alkylated, and optionally hydrolysed if the group G in the final product is COOH.

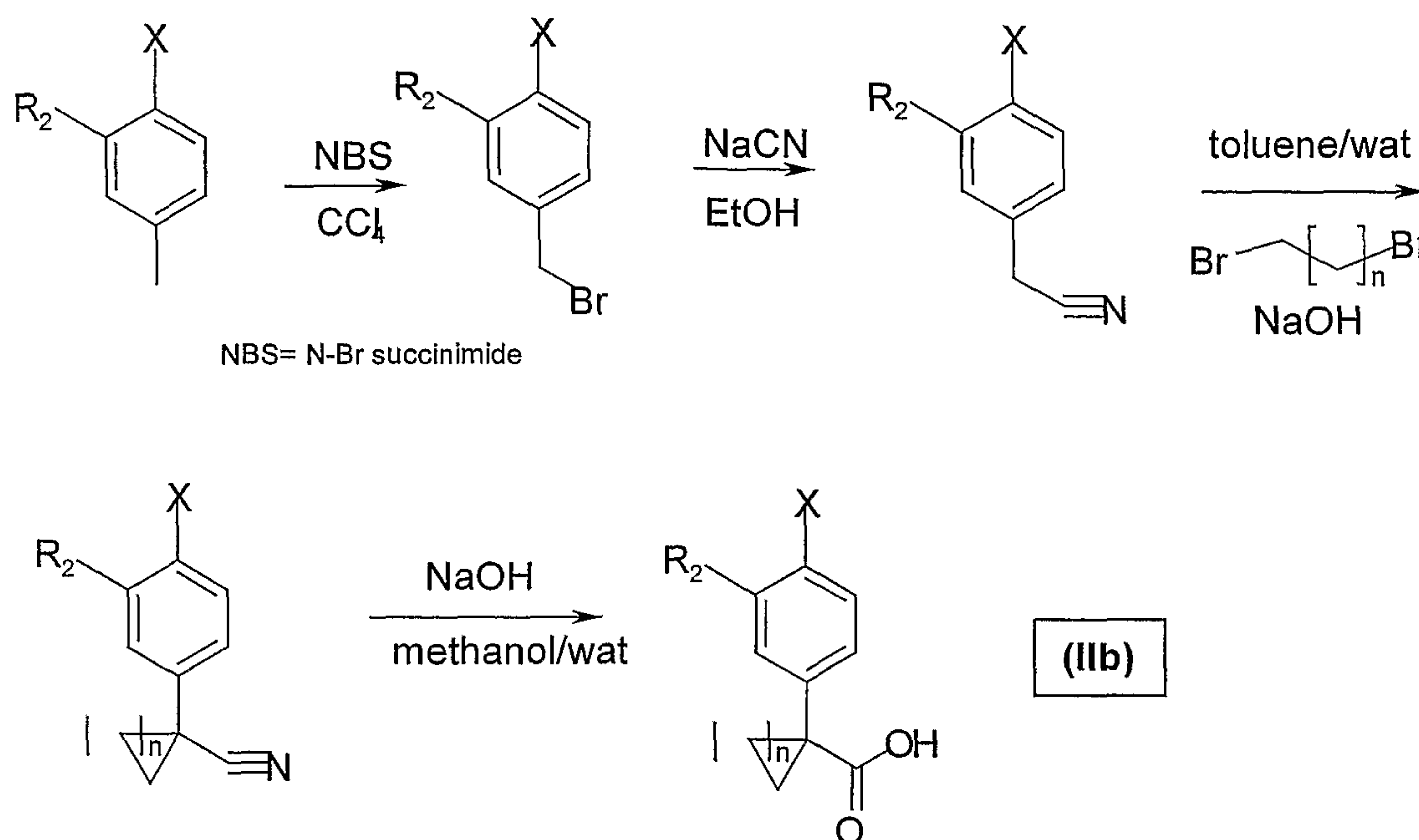


Scheme 2

Derivatives in which R and R₁ form a 3-6 carbon ring with the carbon atom to which they are linked (IIb)

Said compounds are either commercially available, or can be prepared

according to the synthetic route reported in Scheme 3 in which n is an integer of 1 to 4.



Scheme 3

5 Boronic acids or the corresponding boronates are either commercially available or can be prepared from the corresponding halide according to methods known in literature.

10 The compounds of formula (I) wherein G is COOR", where R" is linear or branched C₁-C₄ alkyl, C₃-C₆ cycloalkyl or ascorbyl, can be prepared by esterifying the compounds of formula (I) in which G is COOH.

15 The compounds of formula (I) in which G is CONH₂ or CONHSO₂R''' where R''' is linear or branched C₁-C₄ alkyl or C₃-C₆ cycloalkyl can be prepared by reaction of the corresponding esters with NH₃ or the amine NH₂SO₂R'''.

15 The compounds of formula (I) in which G is tetrazolyl can be prepared from compounds of formula (I) according to known methods, for example transforming the carboxylic acid into amide, dehydrating the amide to nitrile and reacting the latter with tributyltin azide.

EXAMPLES**EXAMPLES OF CHEMICAL PREPARATION****Example 1 - Preparation 2-methyl-2-(2-fluoro-4'-trifluoromethylbiphen-4-yl)propionic acid (CHF 4810)****5 Preparation of methyl [2-(2-fluoro-4'-trifluoromethylbiphen-4-yl)]propionate**

A solution of 2-(2-fluoro-4'-trifluoromethylbiphenyl-4-yl)propionic acid (0.2 g, 0.64 mmol) in methanol (3 ml) is added with 98% sulfuric acid (0.5 g) and refluxed for 2.5 hours. The solvent is removed under vacuum, the residue is taken up with ethyl acetate (5 ml) and washed with a 5% NaHCO₃ solution (5 ml), then with water. The solution is dried over Na₂SO₄ and concentrated under vacuum to afford an oil (0.2 g, 95%).

HPLC - UV purity (215 nm): 99%

Preparation of methyl [2-methyl-2-(2-fluoro-4'-trifluoromethylbiphen-4-yl)]propionate

15 A solution of methyl [2-(2-fluoro-4'-trifluoromethylbiphen-4-yl)]propionate (0.2 g, 0.61 mmol) in anhydrous THF (3 ml) at 0°C and under nitrogen atmosphere, is added with 60% NaH (30 mg, 0.75 mmol). The mixture is stirred for 30 minutes and added with CH₃I (70 µl, 0.91 mmol). After 3h the mixture is concentrated under vacuum and taken up with ethyl acetate (5 ml). The resulting solution is washed with a 5% NaHCO₃ solution (5 ml), then with water, dried over Na₂SO₄, concentrated under vacuum to give an oil (0.18 g, 87%) which is used for the subsequent reaction without further purification.

25 Preparation of 2-methyl-2-(2-fluoro-4'-trifluoromethylbiphen-4-yl)propionic acid

A solution of methyl [2-methyl-2-(2-fluoro-4'-trifluoromethylbiphen-4-yl)]propionate (0.18 g, 0.53 mmol) in ethanol (5 ml) is added with KOH (60 mg, 1 mmol) and kept under stirring for 3h at room temperature. The mixture

is diluted with H₂O (5 ml) and the solution is washed with ethyl ether (5 ml). The organic phase is discarded. The aqueous phase is acidified to pH=2 with HCl, then extracted with ethyl acetate (10 ml). The organic phase is dried over Na₂SO₄ and concentrated under vacuum to give a white solid, which is
5 purified by flash chromatography on SiO₂ (eluent hexane/ethyl acetate 8/2 v/v) to obtain the product as a white solid (16 mg, 10%).

HPLC - UV purity (215 nm): 97%.

¹H NMR (DMSO-d₆): 12.56 (s br, 1H); 7.84 (d, 2H); 7.78 (d, 2H); 7.57 (dd, 1H); 7.32 (s, 1H); 7.29 (m, 1H); 1.52 (s, 6H);

10 MS (EI): 326 m/z (M⁺), 281, 253.

Following the same procedure and using the suitable reactive, compound, CHF 4961 was prepared.

Example 2 - Preparation of 1-(2-fluorobiphenyl-4-yl)cyclopropanecarboxylic acid (CHF 5041)

15 **Preparation of 4-bromo-3-fluorobenzyl bromide**

A solution of 4-bromo-3-fluorotoluene (10 g, 0.053 moles) in carbon tetrachloride (100 ml) is added with N-bromosuccinimide, (NBS; 14 g, 0.08 moles). The mixture is refluxed, added with dibenzoyl peroxide (100 mg, 0.4 mmols), refluxed for 1 hour, then cooled at room temperature and extracted
20 with water. The aqueous phase is discarded, the organic phase is washed with brine, dried over sodium sulfate and concentrated under vacuum to give an oil (16 g) which is subjected to chromatography on a silica gel column (150 g), eluting with hexane, to afford the product.

Preparation of 4-bromo-3-fluorophenylacetonitrile

25 A solution of 4-bromo-3-fluorobenzyl bromide (12.2 g, 0.03 moles) in ethanol (100 ml) is added with NaCN (2 g, 0.04 moles) and refluxed for 2 hours. The mixture is concentrated under vacuum; the resulting residue is taken up with water, then extracted with ethyl acetate. The organic phase is

washed with brine, dried over sodium sulfate and concentrated under vacuum to give a dark oil (10 g), which is subjected to chromatography on a silica gel column (150 g), eluting with hexane:ethyl ether 7:3, to afford the product in the solid form.

5 Preparation of 4-bromo-3-fluorophenylcyclopropanenitrile

A solution of 4-bromo-3-fluorophenylacetonitrile (5 g, 23 mmol) in toluene (20 ml) is added with 35 mmol of 1,2-dibromoethane, a 50% NaOH aqueous solution (20 ml) and tetrabutylammonium bromide (1.6 g, 5 mmol). The mixture is kept under stirring at room temperature for 5-12 hours, then
10 diluted with water and extracted with ethyl acetate. The organic phase is washed with 1N HCl, then with brine, finally dried and concentrated under vacuum to give a brown solid, which is subjected to chromatography on a silica gel column (200 g), eluting with hexane-ethyl ether 1-1, to afford the product in the solid form.

15 Preparation of 4-bromo-3-fluorophenylcyclopropanecarboxylic acid

A suspension of 4-bromo-3-fluorophenylcyclopropanenitrile (21 mmol) in methanol (10 ml) is added with a 35% NaOH aqueous solution (40 ml) and a 35% H₂O₂ aqueous solution (3 ml), then is refluxed for 4 hours, cooled at room temperature and added with 2N HCl (250 ml). The precipitated
20 solid is collected by filtration and redissolved in a 5% NaHCO₃ aqueous solution (300 ml). The insoluble fraction is filtered off and the clear filtrate is acidified to pH=2 with 2N HCl. The product precipitates as a white solid, which is recovered by filtration and dried under vacuum.

Preparation of 1-(2-fluorobiphenyl-4-yl)cyclopropanecarboxylic acid

25 800 mg (3.1 mmol) of 4-bromo-3-fluorophenylcyclopropanecarboxylic acid and 650 mg (3.4 mmol) of phenylboronic acid are suspended in 8 ml of a 2M K₂CO₃ aqueous solution. The mixture is added with tetrabutylammonium bromide (960 mg, 3 mmol) and palladium(II) acetate

(40 mg, 0.18 mmoles) and heated at 130°C in a closed reactor for 30 minutes. After cooling at room temperature, the mixture is added with 2M HCl (25 ml) and extracted with ethyl acetate. The organic phase is washed with 1N HCl, then with brine, finally dried and concentrated under vacuum to give an oil
5 (1.7 g), which is crystallized from isopropyl ether-hexane to afford the product as a white solid (0.2 g).

HPLC (215 nm) 98%.

MS (EI; TSQ 700; parameters 180 C; 70 V; 200 uA): 256 (M+.); 210; 196.

¹H-NMR (DMSO): 12.41 (s br, 1H); 7.56-7.35(m, 6H); 7.27(m, 1H); 7.24 (s,
10 1H); 1.48(m, 2H); 1.22(m, 2H).

Following the same procedure as described in Example 1, starting from the suitable 4-bromophenylcycloalkanecarboxylic acids and using the appropriate reagents, compounds CHF 5022, CHF 5023 CHF 5042, CHF 5045, CHF 5046, CHF 5058, CHF 5059, CHF 5060, CHF 5061, CHF 5070,
15 CHF 5071, CHF 5073, CHF 5074, CHF 5075, CHF 5076, CHF 5077, CHF 5078, CHF 5079, CHF 5080, CHF 5081, CHF 5083, CHF 5084, CHF 5094, CHF 5096, CHF 5102, CHF 5103, CHF 5104, CHF 5105, CHF 5106, CHF 5107 and CHF 5002 were prepared.

Example 3 - Pharmacological activity

20 Inhibition of A β ₄₂ release in the supernatant of H4-15x cells

H4-15x cells (human neuroglioma cells transfected with the human gene encoding for the precursor of β -amyloid protein APP695) were cultured in flasks (in incubator at 37°C, under aqueous vapour saturated atmosphere with 5% carbon dioxide), in the presence of hygromycin and blasticidin,
25 which maintain the selective pressure for the cells continuously expressing the gene of interest.

When the cells reached about 90% confluency, they were collected and re-seeded in 24 wells plates (2 x 10⁵ cells each), in 0.5 ml of complete culture

medium. After approx. 24 hours, when the cells had adhered to the well surface and reached confluency, the medium of each well was replaced with 0.5 ml of fresh culture medium, supplemented with a compound (I) to 100 micromolar final concentration. Each tested concentration was repeated in triplicate. The molecules used for the treatment were previously dissolved in dimethylsulfoxide (DMSO) or in a dimethylsulfoxide/water mixture, the final concentration of DMSO in the wells not exceeding 1%. Thus the prepared plates were incubated again overnight (14-16 hours); afterwards the cell supernatant was taken from each well and $A\beta_{42}$ and $A\beta_{40}$ proteins were quantitated. The assay was carried out with an instrumentation for microplates chemoluminescence analysis, which allows to separately quantify the two proteins and is based on the immobilization of an analyte-antibody complex on paramagnetic microbeads. One of the antibodies of this complex is marked with a ruthenium compound which, upon electrochemical excitement, gives a light signal, having intensity proportional to the amount of analyte present.

Inhibition of cyclooxygenase-1 (COX-1) in rat whole blood

Whole blood was taken from the rat abdominal aorta and immediately placed in heparinized tubes. Aliquots of heparinized blood (500 μ l) were preincubated with 100 μ M concentration of the tested compounds or with the only carrier (DMSO) for 1 h at 37°C. Eicosanoid production was induced by addition of calcium ionophore A23187 (final concentration 5×10^{-5} M) and was interrupted after 30 minute incubation by quickly placing the samples in dry ice. Thereafter, samples were centrifuged (12000 g x 3 minutes at 4°C) and the production of TxB_2 thromboxane B2 was calculated by radioimmunoassay.

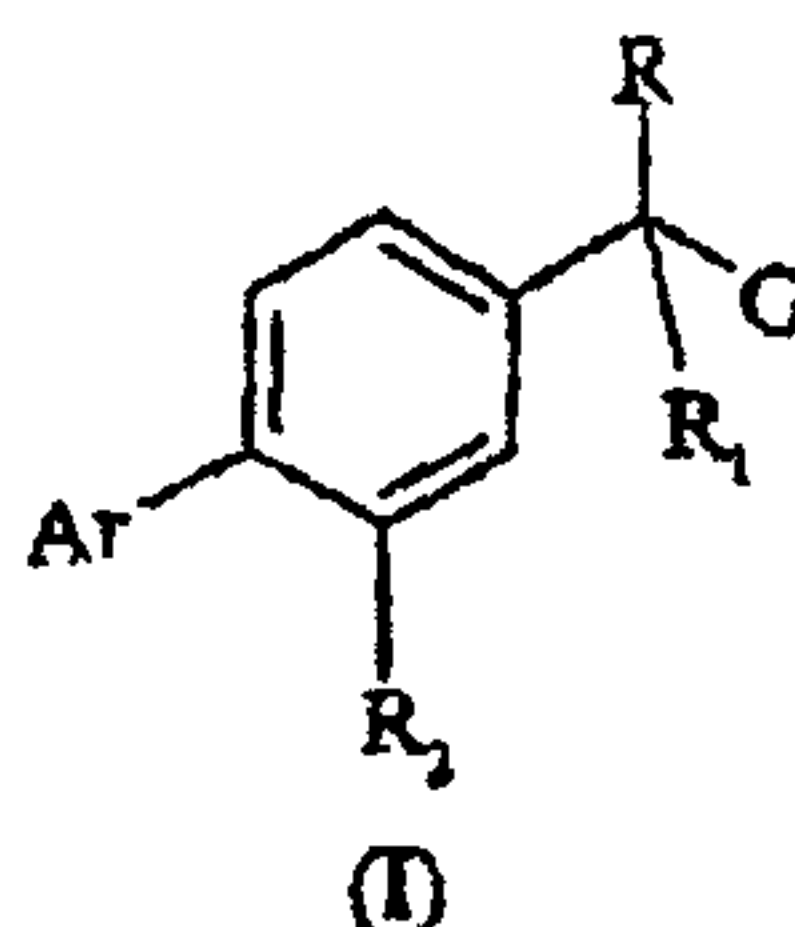
The results expressed as percent inhibition of $A\beta_{42}$ release at 100 μ M and percent COX-1 inhibitory activity at the same concentration are reported in Table 1. Flurbiprofen used as comparison at the same concentration showed approx. 25% inhibition of $A\beta_{42}$ release and 100% COX-1 inhibitory activity.

Table 1: Percent inhibition of A β ₄₂ release and percent COX-1 inhibitory activity of representative compounds of the invention at 100 μ M concentration.

Compound	% inhibition of A β ₄₂ release	% COX-1 inhibitory activity
CHF 4961	76.6	5.2
CHF 4810	58.0	-
CHF 5022	55.4	0.0
CHF 5045	56.4	8.3
CHF 5046	70.4	2.6
CHF 5058	54.8	0.0
CHF 5070	22.4	0.0
CHF 5071	28.1	0.4
CHF 5073	67.4	4.8
CHF 5074	79.2	0.5
CHF 5076	71.4	5.5
CHF 5078	57.5	3.6
CHF 5080	51.8	0.3
CHF 5081	52.3	6.1
CHF 5083	81.1	-
CHF 5096	70.0	0.8
CHF 5105	90.7	1.9
CHF 5106	79.9	0.0
CHF 5107	83.3	1.1

CLAIMS

1. A compound of general formula (I):



wherein:

R and R₁ are the same and are linear or branched C₁-C₄ alkyl;

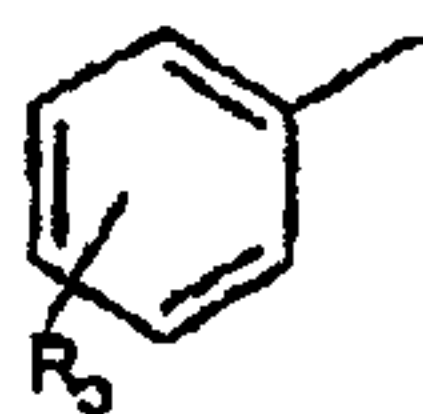
or they form a 3 to 6 carbon atoms ring with the carbon atom to which they are linked;

G is:

- a COOR" group wherein R" is H, linear or branched C₁-C₄ alkyl, C₃-C₆ cycloalkyl, or ascorbyl;
- a CONH₂ or a CONHSO₂R''' group wherein R''' is linear or branched C₁-C₄ alkyl or C₃-C₆ cycloalkyl;
- a tetrazolyl residue;

R₂ is H, CF₃, OCF₃ or a halogen selected from the group consisting of F, Cl, Br, and I.

Ar is a group of formula



wherein R₃ represents one or more groups independently selected from:

- halogen as previously defined;
- CF₃;
- C₃-C₈ cycloalkyl optionally substituted with one or more C₁-C₄ alkyl and/or oxo groups;
- CH=CH₂;
- CN;

- CH₂OH;
 - methylenedioxy or ethylenedioxy;
 - NO₂
 - phenyl optionally substituted with one or more of the following groups:
halogen; CF₃; OCF₃; OH; linear or branched C₁-C₄ alkyl; a saturated heterocycle with at least 4 carbon atoms and at least 1 heteroatom; C₃-C₈ cycloalkyl optionally substituted with one or more of the following groups:
linear or branched C₁-C₄ alkyl, CF₃ or OH;
 - OR₄ or NHCOR₄ wherein R₄ is CF₃, linear or branched C₂-C₆ alkenyl or alkynyl; benzyl; phenyl optionally substituted with one or more of the following groups: halogen, CF₃, OCF₃, OH, linear or branched C₁-C₄ alkyl; a saturated heterocycle with at least 4 carbon atoms and at least 1 heteroatom; C₃-C₈ cycloalkyl optionally substituted with one or more of the following groups: linear or branched C₁-C₄ alkyl, CF₃ or OH;
 - SR₅, SO₂R₅ or COR₅ wherein R₅ is linear or branched C₁-C₆ alkyl;
or Ar is a heterocycle ring selected from the group consisting of thiophene, benzothiophene, dibenzothiophene, thianthrene, pyrrole, pyrazole, furan, benzofuran, dibenzofuran, indole, isoindole, benzofurane, imidazole, benzoimidazole, oxazole, isoxazole, benzoxazole, thiazole, pyridine, pyrimidine, pyrazine, pyridazine, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline, pyrazole, pyran, benzopyran, pyrrolizine, phtalazine, 1,5-naphtiridine, 1,3-dioxole, and 1,3-benzodioxole, optionally substituted with one or more groups R₃ as defined above;
pharmaceutically acceptable salts and esters thereof;
with the condition that when R and R₁ are CH₃, R₂ is fluorine.
2. A compound as claimed in claim 1 wherein R₂ is fluorine.
 3. A compound as claimed in claim 1, wherein R and R₁ form a 3 carbon

atom ring with the carbon atom to which they are linked; R_2 is fluorine; G is a COOR" group in which R'' is H, linear or branched C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl or ascorbyl; Ar is phenyl as defined in claim 1.

4. A compound as claimed in claim 1, wherein R and R_1 form a 3 carbon atom cycle with the carbon atom to which they are linked; R_2 is fluorine; G is a CONH₂ or CONHSO₂R''' in which R''' is linear or branched C_1 - C_4 alkyl or C_3 - C_6 cycloalkyl; Ar is phenyl as defined in claim 1.

5. A compound as claimed in claim 1, wherein both R and R_1 are CH₃; R_2 is fluorine; G is COOR" in which R'' is as defined in claim 1; Ar is phenyl as defined in claim 1.

6. A compound as claimed in claim 1, wherein both R and R_1 are CH₃; R_2 is fluorine; G is a CONH₂ or CONHSO₂R''' in which R''' is as defined in claim 4; Ar is phenyl substituted with an optionally substituted phenyl.

7. A compound as claimed in claim 1, wherein R and R_1 form a 3 carbon atoms ring with the carbon atom to which they are linked; R_2 is fluorine; G is a COOR" group in which R'' is as defined in claim 1; Ar is a heterocycle as defined in claim 1.

8. A compound as claimed in claim 1, wherein both R and R_1 are CH₃; G is a COOR" group in which R'' is as defined in claim 1; R_2 is fluorine; Ar is a heterocycle as defined in claim 1.

9. A compound as claimed in claim 1 selected from the group consisting of:

- 1-(2-fluoro-4'-trifluoromethylbiphenyl-4-yl)cyclopropane-carboxylic acid (CHF 5022);
- 1-(3',4'-dichloro-2-fluorobiphenyl-4-yl)cyclopropane-carboxylic acid (CHF 5074);
- 1-[2-fluoro-4'-[[4-(trifluoromethyl)cyclohexyl]oxy][1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid (CHF 5096);

- 1-(2,2',4''-trifluoro[1,1':4',1'',-tert-phenyl]-4-yl)-cyclopropane-carboxylic acid (CHF 5105);
- 1-(2,3'-difluoro-4''-hydroxy[1,1':4',1'',-tert-phenyl]-4-yl)-cyclopropanecarboxylic acid (CHF 5106); and
- 1-(2,2'-difluoro-4''-hydroxy[1,1':4',1'',-tert-phenyl]-4-yl)-cyclopropanecarboxylic acid (CHF 5107).

10. A pharmaceutical composition containing a compound as claimed in any one of claims 1 to 9 in admixture with pharmaceutically acceptable carriers and/or excipients.

11. A pharmaceutical composition as claimed in claim 10, in a form for oral administration.

12. Use of a compound as claimed in any one of claims 1 to 9, for decreasing the production of the neurotoxic peptide $A\beta_{42}$ in subjects suffering from Alzheimer's disease.

13. Use of a compound as claimed in any one of claims 1 to 9, for the preparation of a medicament for the preventive or therapeutical treatment of neurodegenerative diseases.

14. Use of a compound as claimed in any one of claims 1 to 9, for the treatment of Alzheimer's disease.