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EXPEDITIOUS SYNTHESIS OF 2-ARYL SUBSTITUTED IMIDAZOLINES AND IMIDAZOLES

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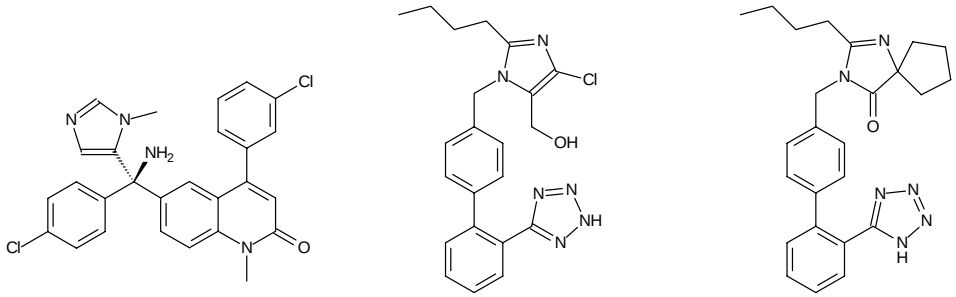
Abstract - A versatile and efficient method for the synthesis of 2-aryl substituted imidazolines and imidazoles bearing a carboxylate group on C-4 is reported. Three different synthetic pathways were explored, compared and optimized. The selected procedure involves condensation of methyl 2,3-diaminopropionate with different imino ethers. The ring closure, monitored by LC-MS analysis, was facilitated by heating at reflux in ethanol leading to increase the rate of cyclization.

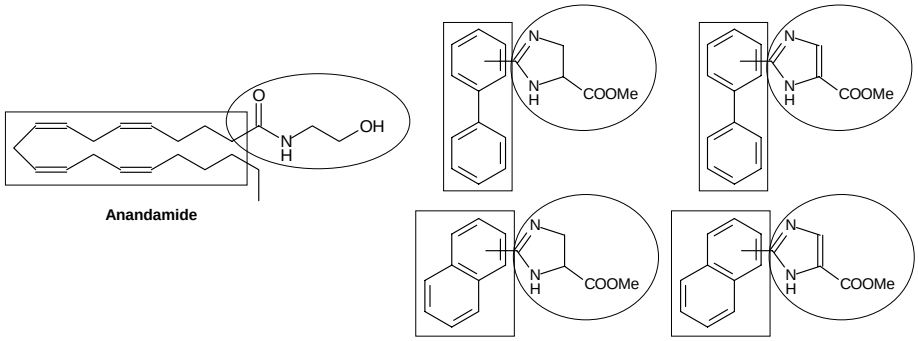
1,3-Oxazole, thiazole and imidazole derivatives are the subjects of intensive research. These heterocycles mimicking amide bond can be viewed as natural conformationally constrained unusual peptides which could counteract problems that limit clinical applications[1-4] of peptides such as : (i) rapid degradation by many specific or nonspecific peptidases under physiological conditions ; (ii) conformational flexibility which allows a peptide to bind to more than one receptor or receptor subtype ; (iii) poor absorption and transportation. In addition these heterocycles constitute excellent chelating agents able to bind to many metalloenzymes. A large number of strategies have also employed imidazoline and imidazole to develop original compounds. For example, these heterocycles were introduced in the design of farnesyl protein transferase inhibitors such as Zarnestra[5] or new efficient non peptidic medicinal compounds.[6] Moreover, the replacement of amino acids by heterocyclic groups has been used in the design of AT_1 angiotensin II antagonists such as Losartan[7] or Irbesartan[8] and analogues[9,10] (Scheme 1).



Scheme 1

Thus, we planned to incorporate imidazole and imidazoline rings for the design of new anticancer agents. Our goal is to develop an efficient and hydrolyse-resistant analogues of anandamide, an endogenous lipid which acts as a cannabinoid receptor ligand and has potent anticarcinogenic activities in several cancer cell types.[11-14] Then, to design such cannabimimetic compounds, we have developed and optimized methods for the preparation of various imidazoline and imidazole derivatives. These compounds include different biaryl-type structures and a 5-membered heterocycle, mimicking the arachidonic chain of anandamide[15] and the amide function of anandamide, respectively[16] (Scheme 2).

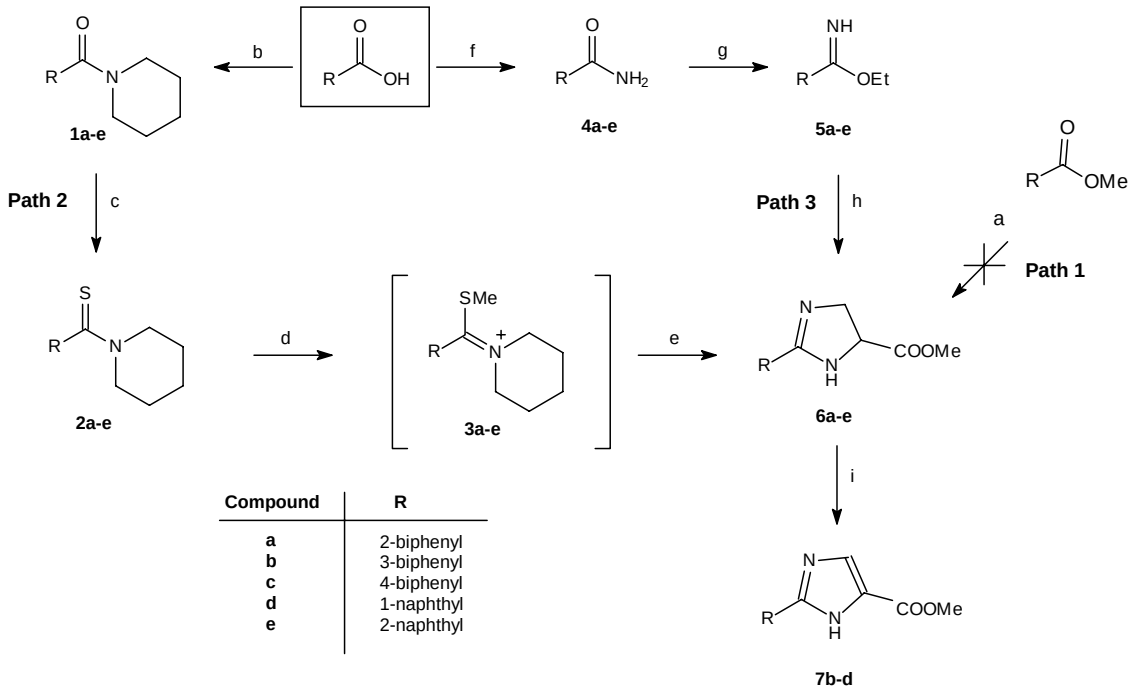
In this paper we report the preparation of biarylimidazolines and imidazoles bearing a carboxylate group on C-4. Three different synthetic pathways were explored, compared and optimized to furnish the imidazolines (Scheme 3). The biarylimidazole compounds were obtained directly from the corresponding imidazolines.



Scheme 2

Many approaches for the preparation of imidazoline have been described. Nevertheless, to propose an efficient method for the synthesis of our target molecules, we considered that the use of methyl 2,3-diaminopropionate as starting material, leading to incorporate directly the carboxylate in C-4 position of the heterocycle, constituted the most efficient way. The second point to develop our methodology results in the difficulty to incorporate directly bicyclic moieties in C-2 position. The majority of the procedures described proved to be inefficient for our target molecules. The precursors cannot be easily employed in aromatic series (e.g. biphenylnitrile derivatives for example) or in a large set of compounds.

However three methods focused our attention and employed precursors which can be easily obtained from commercial bicyclic acids.



Reagents and conditions : a) methyl 2,3-diaminopropionate hydrochloride, $AlMe_3$, toluene, 15 h, 50°C b) DIEA, HBTU, HOBt, piperidine, CH_2Cl_2 , 24 h, 68 to 99% c) P_4S_{10}, toluene, reflux, 6 h, 45 to 99% d) CH_3I, reflux, 4 h e) DIEA, methyl 2,3-diaminopropionate hydrochloride, MeOH, reflux, 28 h, 27 to 57% f) $(Boc)_2O$, pyridine, NH_4HCO_3, dioxane, 24 h, 72 to 99% g) Et_3OBF_4, CH_2Cl_2, 24 h, 47 to 82% h) methyl 2,3-diaminopropionate hydrochloride, EtOH, reflux, 6 h, 24 to 60% i) DBU, CCl_4, CH_3CN, pyridine, 24 h, 61 to 95%.

Scheme 3

Firstly, we tried to generate the imidazoline ring by reaction of a biaryl ester with methyl 2,3-diaminopropionate in the presence of trimethylaluminum (Scheme 3, Path 1).[17,18] Aluminum organic reagents play an increasingly important role in effecting simple chemical transformations. Several examples reported preparation of 2-substituted imidazolines from ester. Nevertheless, the methodologies ultimately proved to be inefficient for our target molecules and obliged us to consider another approach (Scheme 3, Path 2). The procedure described by Gilbert and Rees was adapted.[19,20] The methodology involves condensation of diamines with different *S*-methylthioimidates. Thus, the different biarylcarboxylic acids used as starting materials were converted in quantitative yields into corresponding piperidine amides (**1a-e**) with HBTU as a coupling agent. The non-commercially 3-biphenylcarboxylic acid was prepared using palladium-catalysed cross-coupling reaction between Grignard reagent and 3-bromobenzoic acid, according to a described procedure.[21] The conversion of amides (**1a-e**) into thioamides (**2a-e**) was achieved using phosphorus pentasulfide in refluxing toluene and the treatment

with methyl iodide afforded the (*S*)-methylthioimidate salts (**3a-e**). No reaction was observed when amides (**1a-e**) were refluxed in toluene or xylene with Lawesson's reagent. The (*S*)-methylthioimidate salts (**3a-e**) were not isolated but condensed *in situ* with the methyl 2,3-diaminopropionate in refluxing methanol to provide the biarylimidazoline compounds (**6b-e**) in 27% to 57% yields (Table 1). However, this synthetic pathway did not lead to ortho and meta substituted imidazolines (**6a** and **6b**). The formation of the (*S*)-methylthioimidate salts (**3a**) was highlighted by thin layer chromatography, but the condensation with the diamino ester did not carry out. We have attributed this lack of reaction to the steric constraint brought by the ortho-biphenyl moiety. Concerning compound (**6b**), the product could not be purified by classical methodologies as flash-chromatography.

Compounds	Yield (Path 2)	Yield (Path 3)
6a	Not obtained	24 %
6b	Not purified	56 %
6c	57 %	60 %
6d	27 %	34 %
6e	48 %	59 %

Table 1. Yields for the cyclization into imidazolines (**6a-e**)

To continue with our investigation, we applied the procedure described by Jones and Ward[22] (Scheme 3, Path 3). The imidazoline ring was obtained by a condensation of an imino ether initially prepared with a diamine. Thus, different biarylcarboxylic acids were first converted in high yields in primary amides (**4a-e**) following Pozdnev's method using $(Boc)_2O$.[23] The biarylcarboxylic acids were activated with $(Boc)_2O$ into a corresponding mixed anhydrides as intermediates which readily react with ammonium hydrogen carbonate. Treatment of these amides (**4a-e**) with triethyloxonium tetrafluoroborate gave the corresponding imino ethers (**5a-e**).[24] The different imidazolines (**6a-e**) were then obtained by condensation of methyl 2,3-diaminopropionate with the imino ethers (**5a-e**). In order to optimize this cyclization step, we investigated the effect of the solvent on the ring closure by LC-MS. The reaction between the methyl 2,3-diaminopropionate and the imino ether (**5c**) was monitored by LC-MS and carried out with five different solvents (chloroform, acetonitrile, ethanol, tetrahydrofurane and dimethylformamide) in order to get the most wide range. Conversion rates according to solvent and time were determined through molecular weights of the imino ether (**5c**) and the imidazoline product (**6c**) (Chart 1). The highest conversion rate was obtained after 6 h in refluxing ethanol. Acetonitrile appeared also to be a good solvent for cyclization, with a nearby conversion rate in the same time of reaction. All

the conversion rates were limited by the formation of a by-product. The molecular weight of this by-product supports the hypothesis of a partial recovery of the imino ether (**5c**) in primary amide (**4c**). This recovery appeared to be more important in tetrahydrofurane and dimethylformamide, and was accompanied in dimethylformamide by a light degradation of the imidazoline (**6c**). In chloroform, cyclization seemed to be slower than in other solvents and stopped to evolve after 7 days.

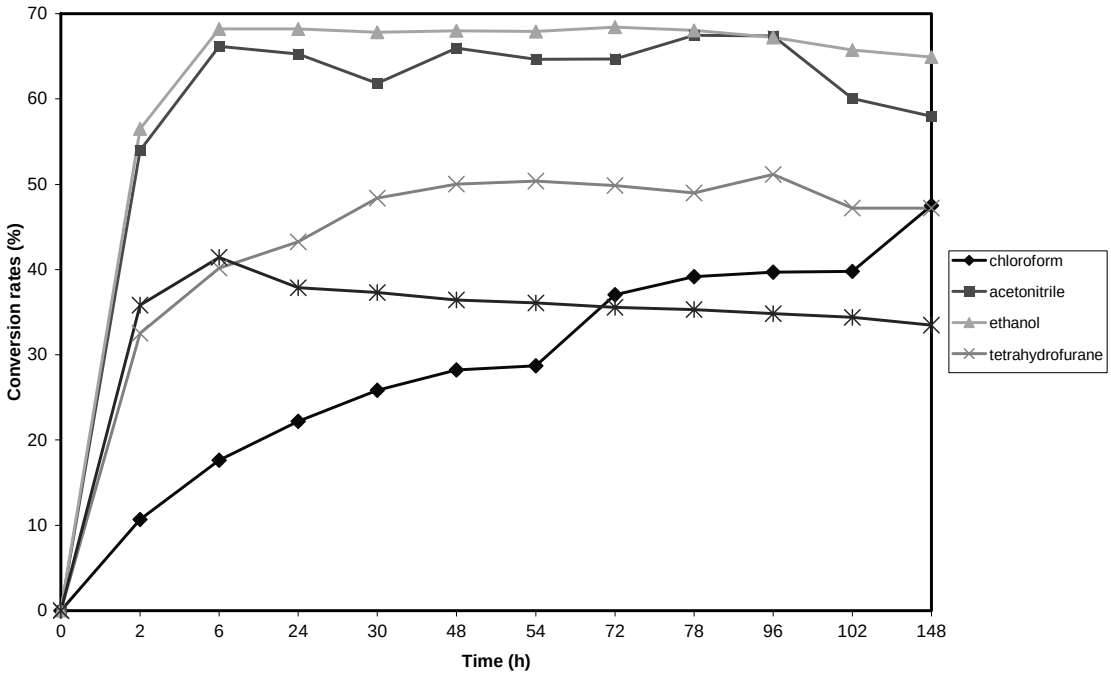


Chart 1

All imidazolines (**6a-e**) were then obtained and prepared according to this procedure with EtOH at reflux. As regard to path 1, yields were improved and this methodology allowed to obtain all imidazolines (**6a-e**). The preparation of imidazoles from imidazolines is well described.[25-29] Different methods were investigated and yields obtained were in the same range. The imidazolines (**6b-d**) were then dehydrogenated into the corresponding imidazoles (**7b-d**) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in a mixture of carbone tetrachloride, pyridine and acetonitrile.

In conclusion, we described a versatile and efficient method to prepare different 2-aryl substituted imidazolines and imidazoles. Optimization of the procedure was explored. The purification of the products was found to be flexible enough to obtain appreciable quantities of compounds. This protocol opens a way for the synthesis of other various 2-substituted imidazolines and imidazoles that can be incorporated as a building unit with various biological and pharmacological properties.

EXPERIMENTAL SECTION

General. THF was distilled from sodium/benzophenone prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Analytical TLC was performed on precoated Kieselgel $60F_{254}$ plates (Merck) ; compounds were visualized by UV and/or with iodine. Silica gel Kieselgel Si 60 (230-400 mesh, Merck) was used for chromatography. Mp were determined with a Büchi 530 capillary melting point apparatus and remain uncorrected. The structures of all compounds were supported by IR spectrum (FT-Bruker Vector 22 instrument) and, if possible, by ^{1}H NMR spectrum at 300 MHz on a Bruker DPX-300 spectrometer in DMSO-d_6 or in $CDCl_3$ at ambient temperature. Chemical shifts (δ) are reported in ppm downfield from TMS, *J* values are in hertz. Elemental analyses were performed by the "Service Central d'Analyses" at the CNRS, Vernaison, France. LC-MS ($APCI^+$) was performed on a Thermo Electron Surveyor MSQ system equipped with a TSK gel Super-ODS (4.6 x 50 mm, 2 μm) and a DAD detector. Compounds were dissolved in MeOH and injected through a 10 μL loop. Elution was performed with the following two systems: solution A (0.1 % formic acid in H_2O) and solution B (0.08 % formic acid, 20 % H_2O, 79.92 % CH_3CN). LC-MS retention times were obtained, at flow rates of 2.75 mL/min, using a gradient run 100% eluent A during 1 min, from 100% eluent A to 50% eluent B over the next 5 min, then 50% eluent B during 1 min.

2-Biphenyl(piperidino)methanone (1a) To a mixture of 2-biphenylcarboxylic acid (1.00 g, 5.04 mmol), HBTU (3.83 g, 10.1 mmol) and HOBt (0.34 g, 2.52 mmol) in dry CH_2Cl_2 was added DIEA (1.76 mL, 10.1 mmol) slowly dropwise. After stirring at rt for 45 min, piperidine (0.55 mL, 5.55 mmol) was added slowly dropwise and the stirring was continued for 24 h. The reaction mixture was then filtrated and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to provide **1a** (1.33 g, 99%) as a white solid, mp 84-85°C. IR : 1621 (CO), 841 (CH aromatic), 746 (CH aromatic) cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 0.54 (m, 1H), 1.12 (m, 1H), 1.22 (m, 1H), 1.35 (m, 2H), 1.45 (m, 1H), 2.70 (m, 1H), 2.88 (m, 1H), 3.41 (m, 1H), 3.69 (m, 1H), 7.32-7.47 (m, 8H), 7.50 (d, 1H, *J* = 7.0 Hz). MS : m/z 266 (MH^+).

3-Biphenyl(piperidino)methanone (1b) Starting from 3-biphenylcarboxylic acid (1.12 g, 5.65 mmol), compound (**1b**) was synthesized using the procedure described for **1a**. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) gave 1.02 g (68%) as a white solid, mp 89-90°C. IR : 1619 (CO), 741 (CH aromatic), 697 (CH aromatic) cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 1.53 (m, 2H), 1.68 (m, 4H), 3.39 (m, 2H), 3.74 (m, 2H), 7.36 (m, 2H), 7.51 (m, 3H), 7.60 (d, 2H, *J* = 7.8 Hz), 7.62 (m, 2H). MS : m/z 266 (MH^+).

4-Biphenyl(piperidino)methanone (1c) Starting from 4-biphenylcarboxylic acid (2.00 g, 10.1 mmol), compound (**1c**) was obtained using the procedure described for **1a**. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) gave 2.52 g (94%) as a white solid, mp 98-99°C. IR : 1631 (CO), 849 (CH aromatic), 744 (CH aromatic) cm^{-1}. ^1H NMR (DMSO-d_6) : δ 1.51 (m, 3H), 1.61 (m, 3H), 3.33 (m, 2H), 3.52 (m, 2H), 7.40 (t, 1H, *J* = 7.2 Hz), 7.44-7.51 (m, 4H), 7.70 (d, 2H, *J* = 8.1 Hz), 7.72 (d, 2H, *J* = 8.1 Hz). MS : m/z 266 (MH^+).

1-Naphthyl(piperidino)methanone (1d) Similarly to the procedure described for **1a**, compound (**1d**) was prepared starting from 1-naphthoic acid (1.50 g, 8.71 mmol) and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to afford 2.06 g (99%) as a white solid, mp 95-96°C. IR : 1626 (CO), 815 (CH aromatic), 804 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 1.41 (m, 2H), 1.66 (m, 2H), 1.73 (m, 2H), 3.14 (m, 2H), 3.88 (m, 2H), 7.40-7.55 (m, 4H), 7.87-7.84 (m, 3H). MS : m/z 240 (MH^+).

2-Naphthyl(piperidino)methanone (1e) As described for **1a**, compound (**1e**) was obtained from 2-naphthoic acid (2.00 g, 11.6 mmol) and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to give 2.75 g (99%) as a white solid, mp 110-111°C. IR : 1615 (CO), 834 (CH aromatic), 808 (CH aromatic), 760 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 1.26 (m, 2H), 1.69 (m, 4H), 3.39 (m, 2H), 3.78 (m, 2H), 7.50 (m, 3H), 7.85 (m, 3H), 7.89 (s, 1H). MS : m/z 240 (MH^+).

2-Biphenyl(piperidino)methanethione (2a) To a suspension of **1a** (1.20 g, 4.52 mmol) in dry toluene (100 mL) was added phosphorus pentasulfide (0.70 g, 3.17 mmol). The reaction mixture was refluxed under nitrogen atmosphere for 6 h, filtered and evaporated *in vacuo*. The crude residue was purified by column chromatography on silica gel (CH_2Cl_2) to provide **2a** (1.06 g, 83%) as a yellow solid, mp 128-129°C. IR : 1492 (CS), 760 (CH aromatic), 743 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 0.74 (m, 1H), 1.26 (m, 1H), 1.44 (m, 3H), 1.64 (m, 1H), 2.92 (m, 1H), 3.20 (m, 1H), 4.00 (m, 1H), 4.21 (m, 1H), 7.33-7.48 (m, 8H), 7.64 (d, 1H, *J* = 6.9 Hz). MS : m/z 282 (MH^+).

3-Biphenyl(piperidino)methanethione (2b) Starting from **1b** (1.50 g, 5.65 mmol), compound (**2b**) was synthesized using the procedure described for **2a**. Purification by column chromatography on silica gel (CH_2Cl_2) gave 0.72 g (45%) as a yellow solid, mp 75-76°C. IR : 1488 (CS), 757 (CH aromatic), 701 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 1.60 (m, 2H), 1.78 (m, 2H), 2.30 (m, 2H), 3.58 (m, 2H), 4.40 (m, 2H), 7.25 (m, 1H), 7.39 (m, 2H), 7.44 (d, 2H, *J* = 7,3 Hz), 7.48 (t, 1H, *J* = 8.3 Hz), 7.56 (d, 1H, *J* = 8.3 Hz), 7.58 (s, 1H), 7.61 (d, 1H, *J* = 8.3 Hz). MS : m/z 282 (MH^+).

4-Biphenyl(piperidino)methanethione (2c) Starting from **1c** (2.45 g, 9.23 mmol), compound (**2c**) was obtained using the procedure described for **2a**. Purification by column chromatography on silica gel (CH_2Cl_2) gave 1.30 g (50%) as a yellow solid, mp 182-183°C. IR : 1496 (CS), 768 (CH aromatic), 694 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 1.61 (m, 2H), 1.80 (m, 4H), 3.60 (m, 2H), 4.38 (m, 2H), 7.37 (m, 3H), 7.45 (t, 2H, *J* = 7.1 Hz), 7.56 (d, 2H, *J* = 7.9 Hz), 7.59 (d, 2H, *J* = 7.9 Hz). MS : m/z 282 (MH^+).

1-Naphthyl(piperidino)methanethione (2d) Similarly to the procedure described for **2a**, compound (**2d**) was prepared starting from **1d** (1.50 g, 6.27 mmol) and purified by column chromatography on silica gel (CH_2Cl_2) to afford 1.58 g (99%) as a yellow solid, mp 116-117°C. IR : 1491 (CS), 796 (CH aromatic), 773 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 1.46 (m, 2H), 1.74 (m, 2H), 1.91 (m, 2H), 3.20 (m, 2H), 4.48 (m, 1H), 4.57 (m, 1H), 7.52-7.34 (m, 4H), 7.78-7.87 (m, 3H). MS : m/z 256 (MH^+).

2-Naphthyl(piperidino)methanethione (2e) As described for **2a**, compound (**2e**) was obtained from **1e** (2.72 g, 11.4 mmol) and purified by column chromatography on silica gel (CH_2Cl_2) to give 1.74 g (60%) as a yellow solid, mp 135-136°C. IR : 1493 (CS), 858 (CH aromatic), 821 (CH aromatic), 746 (CH aromatic) cm^{-1}. ^1H NMR (DMSO-d_6) : δ 1.53 (m, 2H), 1.72 (m, 4H), 3.52 (m, 2H), 4.34 (m, 2H), 7.40 (d, 1H, *J* = 8.8 Hz), 7.55 (t, 2H, *J* = 8.8 Hz), 7.80 (m, 1H), 7.92 (d, 2H, *J* = 7.9 Hz), 7.94 (s, 1H). MS : m/z 256 (MH^+).

2-Phenylbenzamide (4a) To a mixture of 2-biphenylcarboxylic acid (1.50 g, 7.57 mmol) and di-*tert*-butyl dicarbonate (2.15 g, 9.84 mmol) in dioxane (50 mL) was added pyridine (0.60 mL, 7.57 mmol). After stirring at rt for 15 min, ammonium hydrogen carbonate (0.78 g, 9.84 mmol) was added and the stirring was purchased for 24 h. The reaction mixture was then diluted with water and the resulting precipitate was collected, washed with water, dried and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to provide **4a** (1.08 g, 72%) as a white solid, mp 179-180°C. IR : 1642 (CO), 1618 (NH), 1397 (CN), 776 (CH aromatic), 741 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 5.27 (bs, 1H), 5.64 (bs, 1H), 7.39 (t, 1H, *J* = 7.5 Hz), 7.46 (m, 6H), 7.50 (dd, 1H, *J* = 7.5 Hz, *J* = 1.4 Hz), 7.79 (dd, 1H, *J* = 7.5 Hz, *J* = 1.4 Hz). MS : m/z 198 (MH^+).

3-Phenylbenzamide (4b) Starting from 3-biphenylcarboxylic acid (1.50 g, 7.57 mmol), compound (**4b**) was synthesized using the procedure described for **4a**. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) gave 1.40 g (94%) as a white solid, mp 172-173°C. IR : 1668 (CO), 1628 (NH), 1394 (CN), 741 (CH aromatic), 699 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 5.87 (bs, 1H),

6.19 (bs, 1H), 7.40 (t, 1H, *J* = 7.3 Hz), 7.48 (t, 2 H, *J* = 7.3 Hz), 7.54 (t, 1H, *J* = 7.6 Hz), 7.63 (d, 2H, *J* = 7.3 Hz), 7.77 (d, 1H, *J* = 7.6 Hz), 7.80 (d, 1H, *J* = 7.6 Hz), 8.08 (s, 1H). MS : m/z 198 (MH^+).

4-Phenylbenzamide (4c) Starting from 4-biphenylcarboxylic acid (2.50 g, 12.6 mmol), compound (**4c**) was obtained using the procedure described for **4a**. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) gave 2.41 g (97%) as a white solid, mp 234-235°C. IR : 1647 (CO), 1616 (NH), 1410 (CN), 852 (CH aromatic), 738 (CH aromatic) cm^{-1}. ^1H NMR (DMSO-d_6) : δ 7.41 (m, 2H), 7.50 (t, 1H, *J* = 7.1 Hz), 7.73 (d, 2H, *J* = 7.5 Hz), 7.76 (d, 2H, *J* = 8.3 Hz), 7.98 (d, 2H, *J* = 8.3 Hz), 8.05 (bs, 2H). MS : m/z 198 (MH^+).

1-Naphthamide (4d) Similarly to the procedure described for **4a**, compound (**4d**) was prepared starting from 1-naphthoic acid (2.00 g, 11.6 mmol) and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to afford 1.95 g (98%) as a white solid, mp 206-207°C. IR : 1662 (CO), 1616 (NH), 1366 (CN), 779 (CH aromatic), 734 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 6.02 (bs, 2H), 7.49 (t, 1H, *J* = 8.2 Hz), 7.58 (m, 2H), 7.73 (d, 1H, *J* = 7.0 Hz), 7.90 (d, 1H, *J* = 8.2 Hz), 7.96 (d, 1H, *J* = 8.2 Hz), 8.44 (d, 1H, *J* = 8.2 Hz). MS : m/z 172 (MH^+).

2-Naphthamide (4e) As described for **4a**, compound (**4e**) was obtained from 2-naphthoic acid (2.00 g, 11.6 mmol) and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to give 1.97 g (99%) as a white solid, mp 197-198°C. IR : 1655 (CO), 1611 (NH), 1414 (CN), 840 (CH aromatic), 788 (CH aromatic), 721 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 5.82 (bs, 1H), 6.24 (bs, 1H), 7.59 (m, 2H), 7.87 (d, 1H, *J* = 8.6 Hz), 7.90 (d, 1H, *J* = 9.7 Hz), 7.94 (d, 1H, *J* = 7.6 Hz), 7.96 (d, 1H, *J* = 8.6 Hz), 8.37 (s, 1H). MS : m/z 172 (MH^+).

Ethyl-2-phenyl-1-benzenecarboximidate (5a) To a solution of **4a** (0.93 g, 4.72 mmol) in CH_2Cl_2 (100 mL) cooled at 0°C was added triethyloxonium hexafluorophosphate (1.43 g, 5.19 mmol). After stirring at rt for 24 h, the reaction mixture was poured into ice-cold solution of sodium carbonate 1M (150 mL). The layers were separated by decantation : the organic layer was recuperated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to provide **5a** (0.87 g, 82%) as a yellow oil. IR : 1638 (CN), 1074 (CO), 774 (CH aromatic), 745 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : 1.06 (t, 3H, *J* = 7.1 Hz), 4.08 (q, 2H, *J* = 7.1 Hz), 7.33-7.43 (m, 7H), 7.48 (t, 1H, *J* = 7.6 Hz), 7.57 (d, 1H, *J* = 7.6 Hz). MS : m/z 226 (MH^+).

Ethyl-3-phenyl-1-benzenecarboximidate (5b) Starting from **4b** (1.22 g, 6.19 mmol), compound (**5b**) was synthesized using the procedure described for **5a**. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) gave 0.66 g (47%) as a yellow oil. IR : 1636 (CN), 1074 (CO), 762 (CH aromatic), 717 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 1.45 (t, 3H, *J* = 7.1 Hz), 4.39 (q, 2H, *J* = 7.1 Hz), 7.40 (t, 1H, *J* = 7.1 Hz), 7.48 (t, 1H, *J* = 7.9 Hz), 7.50 (t, 2H, *J* = 7.1 Hz), 7.62 (d, 2H, *J* = 7.1 Hz), 7.70 (d, 1H, *J* = 7.9 Hz), 7.75 (d, 1H, *J* = 7.9 Hz), 7.98 (s, 1H). MS : m/z 226 (MH^+).

Ethyl-4-phenyl-1-benzenecarboximidate (5c) Starting from **4c** (2.39 g, 12.1 mmol), compound (**5c**) was obtained using the procedure described for **5a**. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) gave 1.64 g (60%) as a yellow oil. IR : 1627 (CN), 1085 (CO), 774 (CH aromatic), 737 (CH aromatic) cm^{-1}. ^1H NMR (DMSO-d_6) : δ 1.34 (t, 3H, *J* = 7.1 Hz), 4.27 (q, 2H, *J* = 7.1 Hz), 7.41 (t, 1H, *J* = 7.1 Hz), 7.48 (dd, 2H, *J* = 7.6 Hz, *J* = 7.1 Hz), 7.73 (d, 2H, *J* = 8.6 Hz), 7.76 (d, 2H, *J* = 8.6 Hz), 7.62 (d, 2H, *J* = 7.6 Hz). MS : m/z 226 (MH^+).

Ethyl-1-naphthalenecarboximidate (5d) Similarly to the procedure described for **5a**, compound (**5d**) was prepared starting from **4d** (1.69 g, 9.87 mmol) and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to afford 1.08 g (55%) as a yellow oil. IR : 1639 (CN), 1086 (CO), 801 (CH aromatic), 777 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 1.48 (t, 3H, *J* = 7.0 Hz), 4.51 (q, 2H, *J* = 7.0 Hz), 7.48 (t, 1H, *J* = 7.0 Hz), 7.54 (m, 2H), 7.60 (t, 1H, *J* = 7.0 Hz), 7.88 (m, 2H), 8.12 (d, 1H, *J* = 7.6 Hz). MS : m/z 200 (MH^+).

Ethyl-2-naphthalenecarboximidate (5e) As described for **5a**, compound (**5e**) was obtained from **4e** (2.36 g, 13.8 mmol) and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to give 1.70 g (62%) as a yellow oil. IR : 1638 (CN), 1077 (CO), 861 (CH aromatic), 819 (CH aromatic), 754 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 1.51 (t, 3H, *J* = 7.1 Hz), 4.46 (q, 2H, *J* = 7.1 Hz), 7.52-7.60 (m, 2H), 7.80-7.98 (m, 4H), 8.32 (d, 1H, *J* = 8.2 Hz). MS : m/z 200 (MH^+).

Methyl 2-(2-biphenyl)-4,5-dihydro-1*H*-5-imidazolecarboxylate (6a)

Method A: compound (**6a**) could not be obtained from method A.

Method B : To a suspension of **5a** (0.50 g, 2.2 mmol) in dry EtOH (50 mL) was added methyl 2,3-diaminopropionate hydrochloride (0.41 g, 2.66 mmol). The reaction mixture was softly refluxed under nitrogen atmosphere for 7 days. The solvent was then removed *in vacuo* and the crude residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to afford **6b** (0.15 g, 24%) as a

yellow oil. IR : 1737 (CO), 1614 (CN), 779 (CH aromatic), 743 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 3.74 (s, 3H), 3.78-3.82 (m, 2H), 4.43 (t, 1H, *J* = 9.4 Hz), 7.34-7.42 (m, 7H), 7.49 (t, 1H, *J* = 7.6 Hz), 7.78 (d, 1H, *J* = 7.6 Hz). MS : m/z 281 (MH^+). Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found : C, 73.02; H, 5.48; N, 9.96.

Methyl 2-(3-biphenyl)-4,5-dihydro-1*H*-5-imidazolecarboxylate (6b)

Method A: compound (**6b**) could not be isolated from method A.

Method B : As described for **6a**, compound (**6b**) was obtained from **5b** (0.50 g, 2.2 mmol) and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to give 0.35 g (56%) as a yellow oil. IR : 1771 (CO), 1623 (CN), 763 (CH aromatic), 717 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 3.70 (s, 3H), 3.84 (m, 1H), 3.94 (m, 1H), 4.63 (dd, 1H, *J* = 7.5 Hz, *J* = 11.0 Hz), 7.40 (t, 1H, *J* = 7.5 Hz), 7.50 (t, 2H, *J* = 7.5 Hz), 7.54 (t, 1H, *J* = 8.0 Hz), 7.13 (d, 2H, *J* = 7.5 Hz), 7.80 (d, 1H, *J* = 8.0 Hz), 7.87 (d, 1H, *J* = 8.0 Hz), 8.14 (s, 1H). MS : m/z 281 (MH^+). Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found : C, 72.65; H, 5.41; N, 10.08.

Methyl 2-(4-biphenyl)-4,5-dihydro-1*H*-5-imidazolecarboxylate (6c)

Method A : The thioamide (**2c**) (0.50 g, 1.78 mmol) was heated under reflux in methyl iodide (10 mL) under nitrogen atmosphere for 4 h. The solvent was removed *in vacuo* and the residue azeotroped with methanol (2 × 5 mL). The residue was dissolved in dry methanol (10 mL) and a solution of methyl 2,3-diaminopropionate hydrochloride (0.40 g, 1.78 mmol) and DIEA (0.93 mL, 5.33 mmol) in minimum of dry methanol was added. The reaction mixture was refluxed under nitrogen atmosphere for 2 h, left at rt for 24 h and then refluxed for 2 h. The solvent was evaporated *in vacuo* and the resulting residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to provide **6c** (0.29 g, 57%) as a pale orange solid, mp 149-150°C. IR : 1750 (CO), 1618 (CN), 774 (CH aromatic), 737 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 3.79 (s, 3H), 4.14 (d, 2H, *J* = 7.4 Hz), 4.59 (t, 1H, *J* = 7.4 Hz), 7.39 (t, 1H, *J* = 7.4 Hz), 7.45 (d, 2H, *J* = 7.4 Hz), 7.60 (d, 2H, *J* = 7.4 Hz), 7.63 (d, 2H, *J* = 8.1 Hz), 7.87 (d, 2H, *J* = 8.1 Hz). MS : m/z 281 (MH^+). Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found : C, 72.73; H, 5.94; N, 9.87.

Method B : Starting from **5c** (1.40 g, 6.22 mmol), compound (**6c**) was obtained using the method B described for **6a**. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) gave 1.05 g (60%) as a pale orange solid.

Methyl 2-(1-naphthyl)-4,5-dihydro-1*H*-5-imidazolecarboxylate (6d)

Method A : As described for **6b**, compound (**6d**) was obtained from **2d** (1.50 g, 5.87 mmol) and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to give 0.40 g (27%) as an orange oil. IR : 1755 (CO), 1618 (CN), 801 (CH aromatic), 777 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 3.82 (s, 3H), 4.20 (d, 2H, *J* = 8.7 Hz), 4.63 (t, 1H, *J* = 8.7 Hz), 7.47 (t, 1H, *J* = 7.2 Hz), 7.54 (m, 2H), 7.74 (d, 1H, *J* = 7.2 Hz), 7.87 (dd, 1H, *J* = 7.2 Hz, *J* = 2.0 Hz), 7.92 (d, 1H, *J* = 8.6 Hz), 8.62 (d, 1H, *J* = 8.1 Hz). MS : m/z 255 (MH^+). Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found : C, 70.74; H, 5.78; N, 10.93.

Method B : Starting from **5d** (1.62 g, 8.13 mmol), compound (**6d**) was synthesized using the method B described for **6a**. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) gave 0.70 g (34%) as an orange oil.

Methyl 2-(2-naphthyl)-4,5-dihydro-1*H*-5-imidazolecarboxylate (6e)

Method A : Similarly to the method A described for **6b**, compound (**6e**) was prepared starting from **2e** (0.50 g, 1.96 mmol) and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to afford 0.24 g (48%) as a white solid, mp 195-196°C. IR : 1747 (CO), 1611 (CN), 869 (CH aromatic), 825 (CH aromatic), 751 (CH aromatic) cm^{-1}. ^1H NMR (DMSO-d_6) : δ 3.28 (s, 3H), 3.75 (m, 2H), 4.74 (t, 1H, *J* = 7.4 Hz), 7.23 (m, 2H), 7.44 (d, 1H, *J* = 8.7 Hz), 7.58 (d, 2H, *J* = 8.7 Hz), 7.69 (d, 1H, *J* = 8.1 Hz), 8.17 (s, 1H), 10.62 (bs, 1H). MS : m/z 255 (MH^+). Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found : C, 70.68; H, 5.84, N, 10.87.

Method B : Compound (**6e**) was prepared from compound (**5e**) (1.23 g, 6.18 mmol) using the method B described for **6a** and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to provide 0.93 g (59%) as a white solid.

Methyl 2-(3-biphenyl)-1*H*-5-imidazolecarboxylate (7b) To a solution of **6b** (0.17 g, 0.61 mmol) in carbon tetrachloride (10 mL), pyridine (10 mL) and acetonitrile (15 mL) was added DBU (0.37 mL, 2.43 mmol) slowly dropwise. The reaction mixture was stirred at room temperature for 24 h and then evaporated *in vacuo*. The crude residue was dissolved in CH_2Cl_2 and the organic layer was washed with a solution of HCl (0.5 N), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 4:1) to give **7b** (0.10 g, 61%) as a white solid, mp 186-187°C. IR : 1688 (CO), 758 (CH aromatic), 725 (CH aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) : δ 3.88 (s, 3H), 7.38 (t, 1H, *J* = 7.0 Hz), 7.43 (t, 2H, *J* = 7.0 Hz), 7.48 (t, 1H, *J* = 7.9 Hz), 7.56 (d, 2H,

J = 7.0 Hz), 7.60 (t, 1H, *J* = 7.9 Hz), 7.83 (s, 1H), 7.87 (d, 1H, *J* = 7.9 Hz), 8.13 (s, 1H). MS : m/z 279 (MH^+). Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found : C, 73.58; H, 5.39; N, 10.15.

Methyl 2-(4-biphenyl)-1*H*-5-imidazolecarboxylate (7c) Starting from **6c** (0.18 g, 0.64 mmol), compound (**7c**) was obtained using the procedure described for **7b**. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) gave 0.17 g (95%) as a white solid, mp 243-244°C. IR : 1724 (CO), 775 (CH aromatic), 736 (CH aromatic) cm^{-1}. ^1H NMR (DMSO-d_6) : δ 3.80 (s, 3H), 7.39 (t, 1H, *J* = 7.2 Hz), 7.51 (t, 2H, *J* = 7.2 Hz), 7.75 (d, 2H, *J* = 7.2 Hz), 7.81 (d, 2H, *J* = 8.1 Hz), 8.07 (d, 2H, *J* = 8.1 Hz), 8.23 (s, 1H). MS : m/z 279 (MH^+). Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found : C, 73.32; H, 4.97; N, 9.86.

Methyl 2-(1-naphthyl)-1*H*-5-imidazolecarboxylate (7d) Similarly to the procedure described for **7b**, the compound was prepared starting from **6d** (0.40 g, 1.57 mmol) and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to afford 0.37 g (93%) as a white solid, mp 226-227°C. IR : 1720 (CO), 808 (CH aromatic), 774 (CH aromatic) cm^{-1}. ^1H NMR (DMSO-d_6) : δ 3.82 (s, 3H), 7.52 (t, 1H, *J* = 7.3 Hz), 7.60-7.64 (m, 3H), 7.84 (d, 1H, *J* = 6.7 Hz), 7.96-8.09 (m, 3H). MS : m/z 253 (MH^+). Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found : C, 71.40; H, 4.91; N, 11.03.

REFERENCES

1 C. Adessi and C. Soto, *Curr. Med. Chem.*, 2002, **9**, 963.

2 A. S. Ripka and D. H. Rich, *Curr. Opin. Chem. Biol.*, 1998, **2**, 441.

3 S. Hanessian, G. McNaughton-Smith, H. G. Lombart, and W. D. Lubell, *Tetrahedron,* 1997, **53**, 12789.

4 K. S. Kee and S. D. Jois, *Curr. Pharm. Design,* 2003, **9**, 1209.

5 P. Angibaud, A. K. Saha, X. Bourdrez, D. W. End, E. Freyne, P. Lezouret, G. Mannens, L. Mevellec, C. Meyer, I. Pilatte, V. Poncelet, B. Roux, G. Smets, J. Van Dun, M. Venet, and W. Wouters, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 4361.

6 R. Millet, J. Domarkas, R. Houssin, P. Gilleron, J.-F. Goossens, P. Chavatte, C. Loge, N. Pommery, J. Pommery, and J.-P. Hénichart, *J. Med. Chem.*, 2004, **47**, 6812.

7 P. B. Timmermans, D. J. Carini, A. T. Chiu, J. V. Duncia, W. A. Proce, G. J. Wells, P. C. Wong, R. R. Wexler, and A. L. Johnson, *Hypertension*, 1991, **18**, 5, III 136.

8 C. A. Bernhart, P. M. Perreaut, B. P. Ferrari, Y. A. Muneaux, J.-L. A. Assens, J. Clément, F. Haudricourt, C. F. Muneaux, J. E. Taillades, M-A. Vignal, J. Gougat, P. R. Guiraudou,

C. A. Lacour, A. Roccon, C. F. Cazaubon, J.-C. Brelière, G. Le Fur, and D. Nisato, *J. Med. Chem.*, 1993, **36**, 3371.

9 B. Le Bourdonnec, E. Meulon, S. Yous, J.-F. Goossens, R. Houssin, and J.-P. Hénichart, *J. Med. Chem.*, 2000, **43**, 2685.

10 B. Le Bourdonnec, C. Cauvin, E. Meulon, S. Yous, J.-F. Goossens, F. Durant, R. Houssin, and J.-P. Hénichart, *J. Med. Chem.*, 2002, **45**, 4794.

11 M. Mimeault, N. Pommery, N. Wattez, C. Bailly, and J.-P. Hénichart, *Prostate*, 2003, **56**, 1.

12 M. Bifulco and V. Di Marzo, *Nat. Med*., 2002, **8**, 547.

13 V. Di Marzo, D. Melck, L. De Petrocellis, and T. Bisogno, *Prostag. Oth. Lipid M.*, 2000, **61**, 43.

14 L. De Petrocellis, D. Melck, A. Palmisano, T. Risogno, C. Laezza, M. Bifulco, and V. Di Marzo, *Proc. Natl. Acad. Sci. USA*, 1998, **95**, 8375.

15 M. Mor, S. Rivara, A. Lodola, P. V. Plazzi, G. Tarzia, A. Duranti, A. Tontini, G. Piersanti, S. Kathuria, and D. Piomelli, *J. Med. Chem*., 2004, **47**, 4998.

16 G. G. Muccioli, N. Fazio, G. K. E., Scriba, W. Poppitz, F. Cannata, J. H., Poupaert, J. Wouters, and D. M. Lambert, *J. Med. Chem.*, 2006, **49**, 417.

17 C. H. Oh, C. S. Lee, J. S. Lee, and J. H. Cho, *Arch. Pharm. Pharm. Med. Chem.*, 2003, **336**, 504.

18 G. Neef, U. Eder, and G. Sauer, *J. Org. Chem*., 1981, **46**, 2824.

19 I. H. Gilbert and D. C. Rees, *Tetrahedron*, 1995, **51**, 22, 6315.

20 R. C. F. Jones and G. J. Ward, *Tetrahedron Lett*., 1988, **29**, 3853.

21 N. A. Bumagin and E. V. Luzikova, *J. Organomet. Chem*., 1997, **532**, 271.

22 R. C. F. Jones and G. J. Ward, *Tetrahedron Lett*., 1988, **29**, 3853.

23 V. F. Pozdnev, *Tetrahedron Lett*., 1995, **36**, 39, 7115.

24 R. J. Bergeron, J. S. McManis, J. B. Dionis, and J. R. Garlich, *J. Org. Chem*., 1985, **50**, 2780.

25 P. P. Fu and R. G. Harvey, *Chem. Rev*., 1978, **78**, 317.

26 J. Cossy and D. Belotti, *Org. Lett*., 2002, **4**, 2557.

27 D. Walker and J. D. Hiebert, *Chem. Rev*., 1967, **67**, 153.

28 R. D. Singer and P. J. Scammells, *Tetrahedron Lett*., 2001, **42**, 6831.

29 U. Tistam, M. Harre, T. Heckrodt, and H. Weinmann, *Tetrahedron Lett*., 2001, **42**, 5385.