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Short communication

Synthesis and pharmacological evaluation of new 4-[2-(7-heterocyclemethoxynaftalen-2-ylmethoxy)ethyl]benzoic acids as LTD_4-antagonists

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Abstract – A group of new 4-[2-(7-heterocyclemethoxynaftalen-2-ylmethoxy)ethyl]benzoic acids have been synthesized and pharmacologically evaluated as LTD_4-antagonists. Thiazole derivatives, especially 4-[2-[7-(4-cyclobutylthiazole-2-ylmethoxyl)naphthalen-2-ylmethoxy]ethyl]benzoic acid, present considerable activity and improved pharmacokinetic profiles in comparison with our quinoline containing lead molecule confirming the interest of our compounds as potentially oral antiasthmatics and that the 4-alkylthiazole system can be considered as bioisosteric of the quinoline ring at least in our series of compounds. © 2000 Éditions scientifiques et médicales Elsevier SAS

LTD_4-antagonists / oral antiasthmatics / bioisosters / 4-alkylthiazoles

1. Introduction

Over the last few years numerous specific LTD_4 antagonists have been prepared and advanced into clinical studies demonstrating beneficial roles in human bronchial asthma [1–4]. Some of them, such as the indole-based antagonist ICI-204,219 [5] (Zafirlukast), the benzamide ONO-1078 [6] (Pranlukast), and the quinoline MK-0476 [7] (Montelukast) are currently in advanced clinical development as therapeutic agents for the treatment of asthma.

On the basis of the large body of knowledge of structure–activity studies of LTD_4 antagonists, a pharmacophore hypothesis has been described [8, 9] and applied [10] by us. This pharmacophore accounts for several compounds in advanced development level and has been successfully applied in our laboratories to design new lead compounds [11, 12]. From these studies, the quinoline containing LM-1468 (**1**, *figure 1*) emerged as a highly potent in vitro LTD_4 antagonist and was orally active in animal asthma models [11].

One of the striking features of the quinoline class of compounds was the apparent necessity for the 2-substituted quinoline functionality for potent LTD_4 antagonist activity [13]. However, thiazoles, benzothiazoles and other nitrogen-containing heterocycles have been reported as quinoline bioisosters in LTD_4 antagonism research [14–17]. These replacements maintain and, in some cases, increase the in vitro and in vivo potency. Based on these observations we wished to search this kind of substitution on our quinoline-containing LTD_4 antagonist of LM-1468, with the aim of increasing its activity and improving its pharmacokinetic profile. We report here the synthesis and preliminary pharmacological activity of compounds **2a–2d** (*figure 1*) that represent the replacement of the quinoline heterocycle in compound LM-1468 by 6,7-dichlorothieno[3,2-b]pyridine, 4-isopropylthiazole, 4-cyclobutylthiazole and 5-fluorobenzothiazole, respectively.

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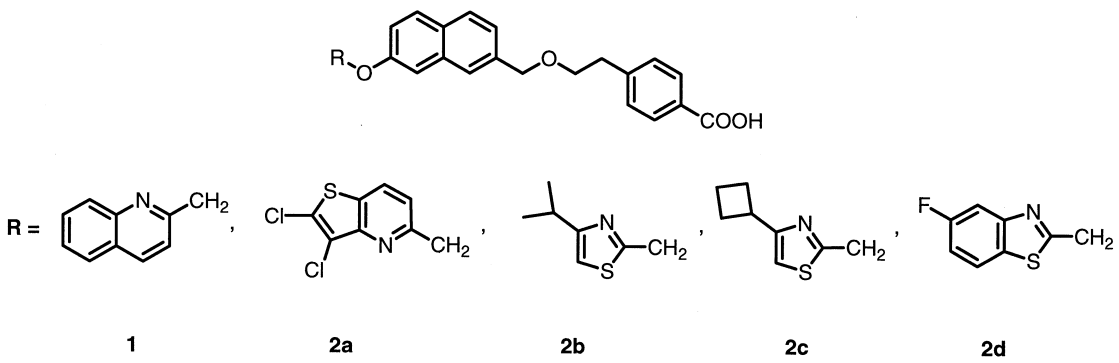

Figure 1. Compounds **1** and **2a–2d**.

2. Chemistry

The synthesis (*figure 2*) starts with the commercial 2,7-dihydroxynaphtalene, protected as a methoxymethyl (MOM) derivative (**3**) in the usual way [18]. Compound **3** was converted into **6** by means of the three-step method described by Kingsbury et al. [19]: formation of the triflate (**4**) over the unprotected OH, carbonilation catalysed by Pd(II) in methanol/DMSO as solvent, and reduction of the methyl ester (**5**) giving the desired hydroxymethyl derivative (**6**).

The conversion of the hydroxyl group of **6** into a good leaving group was more difficult than expected. After trying several alternatives the procedure finally used consists of the formation of the chloromethyl derivative **7** via the reaction between one equivalent of tosyl chloride and the lithium salt of **6** in tetrahydrofuran. The yield of **7** was excellent. The process appears to pass through the tosylate and nucleophilic substitution by the chloride being present in the medium. The conversion of allylic alcohols to chlorides by reaction with mesyl chloride is described [20], but in the presence of an excess of lithium chloride. The use of tetrahydrofuran as solvent is critical, due to the solubility of the lithium chloride (formed in situ) in it, favouring in this way the substitution process. When different ethers were used as solvent the yields in **7** were clearly lower. This product (**7**) is unstable in neutral aqueous medium, probably because the chloride is substituted in some extension by water forming small amounts of hydrochloric acid that removes the protecting group, provoking the decomposition of the product in a few minutes. However, it has proved that **7** is stable in aqueous basic medium at least for a reasonable period of time and, for this reason, was used directly in the next reaction (carried out in aqueous basic medium) without further manipulation.

The next step was the preparation of the key intermediate **8** from **7** and (4-cyanophenyl)ethanol. Such transformation proved to not be trivial and we have developed [21] a general procedure for the synthesis of this kind of aryl phenetyl ether using the phase transfer catalysis (PTC) method: equimolar amounts of starting reagents, a two phase system formed by 1:1 methylene chloride and aqueous 50% (w/v, 12.5 M) sodium hydroxide, and tetrabutylammonium hydrogen sulphate in a 5% molar relation.

The step from **8** to **9**, removal of the MOM group, was carried out in a conventional way described in the literature [22] with practically quantitative yield. The last steps for the preparation of target compounds **2a–d** were the formation of the second ether linkage by reaction between **9** and the previously prepared heterocycles 2,3-dichloro-5-chloromethyl-thieno[3,2-b]pyridine (**10a**) [23], 2-chloromethyl-4-isopropylthiazole (**10b**) [24], 2-chloromethyl-4-cyclobutylthiazole (**10c**) [24] and 5-fluoro-2-bromomethylbenzothiazole (**10d**) [25], finishing with the hydrolysis of the cyano group.

Contrary to the former ether linkage the reaction took place by direct reaction between **9** and **10a–d** in acetonitrile/K_2CO_3 in the presence of potassium iodide, yielding compounds **11a–d** without special problems. The hydrolysis of the nitrile group into the carboxylic acid was carried out by heating **11a–c** in 35% sodium hydroxide in ethanol, obtaining **2a–c** with good yields. However, in the case of **11d** the benzothiazole system suffered opening of the heterocyclic ring as a consequence of the nucleophilic attack of the hydroxyl over the 2-position. Working in less concentrated basic conditions it is possible to avoid the opening of the heterocycle but in this case the nitrile is only partially converted into the acid group. For this reason, to obtain **2d** it was necessary to change the order of the reactions: firstly, the nitrile **9**

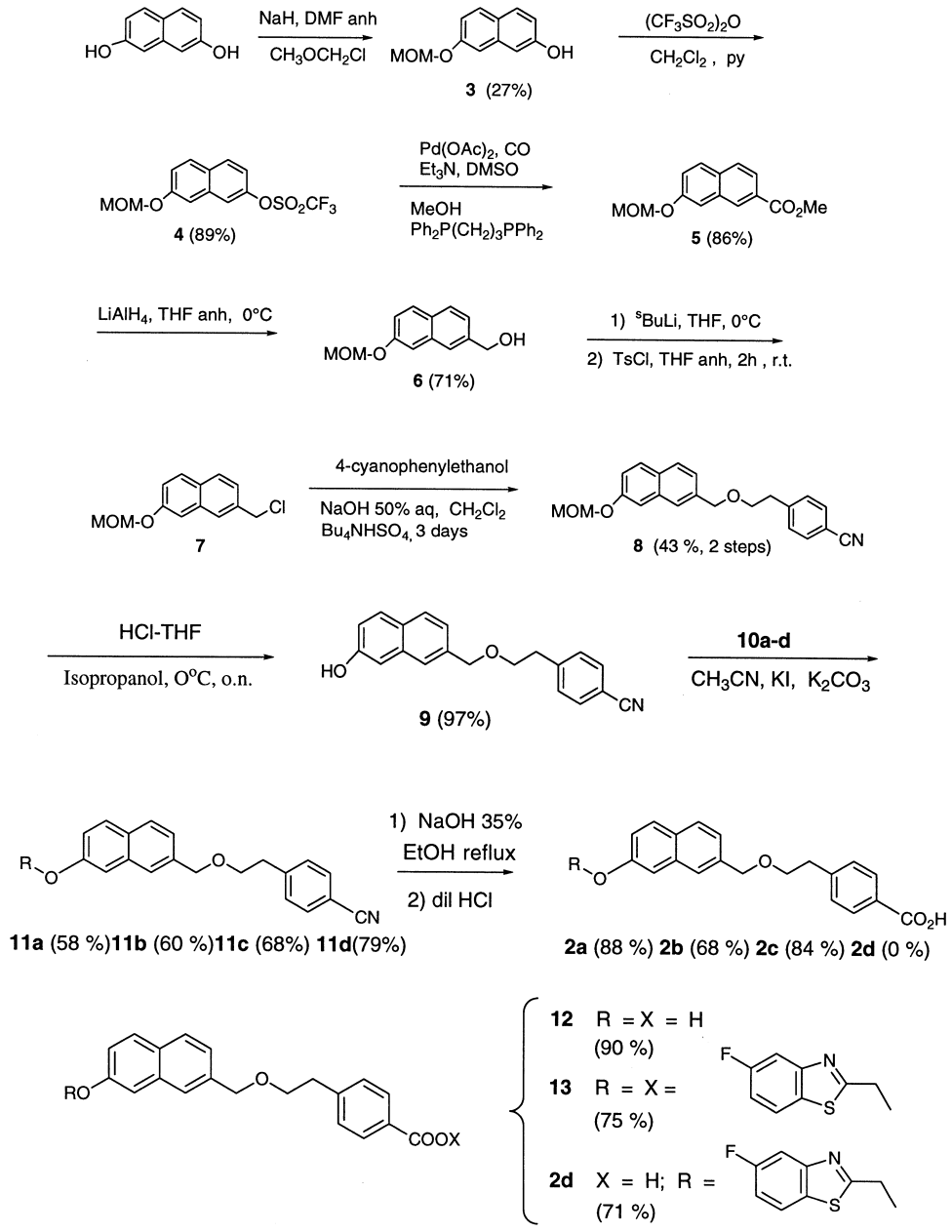

Figure 2. Synthesis of compounds **3**–**13**.

was hydrolysed in basic medium as usual giving **12**; after that the reaction between **12** and **10d** was carried out as before yielding the product of double benzylic substitution **13** that was hydrolysed in diluted basic conditions affording **2d** without opening the benzothiazole ring.

3. Biological results and discussion

The affinities of the synthesized compounds for the LTD_4 receptor were determined by specific binding of $[^3H]LTD_4$ to guinea-pig lung membrane preparations (see

Table I. Pharmacological effects of synthesised compounds against LTD_4 actions and preliminary pharmacokinetic parameters in mice after oral treatment.

Compound	Binding	AML % inhib.[2]		BC % inhib.[3]	Preliminary oral pharmacokinetics [4]		
	K_i(nM)[1]	1 h	8 h		C_{MAX} (μg/mL)	T_{MAX} h	AUC (μg/mL/h)
1	2.7 ± 0.4	74.1 ± 4.0 (*n* = 10)	30.4 ± 10.7 (*n* = 4)	77.1 ± 3.9 (*n* = 4)	2.13	1	15.43
2a	56.6 ± 28.0	23.2 ± 10.9 (*n* = 4)	N.T.	50.9 ± 7.8 (*n* = 6)	4.06	2	16.8
2b	2.69 ± 1.70	57.2 ± 7.6 (*n* = 4)	44.7 ± 5.5 (*n* = 4)	47.2 ± 2.6 (*n* = 6)	4.21	1	20.44
2c	4.2 ± 1.8	78.8 ± 6.2 (*n* = 4)	41.4 ± 7.0 (*n* = 5)	82.5 ± 6.7 (*n* = 6)	5.20	0.5	21.36
2d	6.4 ± 4.9	37.3 ± 5.5 (*n* = 6)	N.T.	N.T.	1.56	2	9.35

[1] K_i values for competition of compounds in [^{3}H]LTD_4 specific binding to guinea-pig lung membranes. Values are the mean ± SD of at least three experiments performed on different days. [2] Oral effect of compounds on airway microvascular leakage (AML) into trachea, induced by LTD_4 in guinea-pigs. Effect is expressed as % inhibition (mean ± SEM) in *n* treated animals with respect to control group treated with vehicle. Compounds were administered orally at 1 μmol/kg dose, 1 and 8 h before LTD_4 challenge. [3] Oral effect of compounds on LTD_4-induced bronchoconstriction in anaesthetized guinea-pigs (BC), expressed as percent inhibition (mean ± SEM of *n* animals) with respect to the bonchospastic effect achieved in absence of treatment. Compounds were oral dosed at 6 μmol/kg 1 h before second LTD_4 challenge. [4] Preliminary plasma pharmacokinetic parameters in mice of tested compounds. Compounds were orally given at 15 mg/kg. Plasma samples were analysed 0.5, 1, 2, 4, 6, 8 and 16 h after administration. Three animals per time were bled. Parameters were estimated from the curve plasma levels vs. time, where each point represented the mean of three bled animals.

Pharmacology section). The in vivo oral efficacy was assessed in LTD_4-induced broncoconstriction (BC) in anaesthetized guinea-pigs and in LTD_4-induced airway microvascular leakage (AML) into guinea-pig trachea. In addition, a preliminary pharmacokinetic profile of these compounds has been carried out in the mouse after single oral administration (OP) (*table I*).

The in vitro tests show that the substitution of the quinoline ring for the thiazole one (**2b** and **2c**) maintains the activity of our lead compound (**1**), contrary to that observed in the other two cases (**2a** and **2d**). Particularly important is that the receptor affinity decreases when the quinoline is substituted by the thieno[3,2-b]pyridine system (**2a**) in contradiction with the observed behaviour in previously described systems [22].

The binding assay shows that the substitution of the quinoline ring for the thiazole one (**2b** and **2c**) or for the benzothiazole system (**2d**) maintains the receptor affinity of our lead compound (**1**). On the contrary, when the quinoline ring is replaced by a 5,7-dichlorothieno[2,3]-pyridine system, the binding affinity dramatically decreases, showing a behaviour contrary to that described for other series of LTD_4 antagonists [22].

The compounds with a 4-alkylthiazole moiety (**2b** and **2c**) also display the best oral in vivo activity, especially **2c** that has an activity profile analogous to the lead compound **1**, showing a slightly longer duration of action in the in vivo trachea permeability assay (41% inhibition at 8 h for **2c** vs. 30% inhibition for **1**). The pharmacokinetic assay carried out in the mouse has allowed us to observe that compounds **2b** and **2c** show an improved pharmacokinetic profile in comparison to the lead compound **1**. Obviously, a correlation between the observed pharmacokinetic data and the in vivo activity is not possible to perform due to the species in these two assays being different. According to the decreased binding affinity, compounds **2a** and **2d** also display a low oral activity in the in vivo assay.

4. Conclusions

The alkylthiazole compounds **2b** and **2c** have been developed from quinoline compound LM-1468 as new and orally active LTD_4 antagonists. These compounds, specially **2c**, display remarkable in vitro and in vivo activities as LTD_4 antagonists, comparable to the lead compound **1**, with a slightly improved pharmacokinetic profile. In this kind of compound, the alkylthiazole system can be considered as a bioisoster of the quinoline ring present in the structure of LM-1468. The cyclobutylthiazole **2c** has been selected for further development.

5. Experimental protocols

5.1. Pharmacology

5.1.1. Radioligand binding assay of [^{3}H]LTD$_4$ in guinea-pig lung membranes

Membrane fractions containing Cys-LT receptors were prepared according to the method described by Mong et al. [26] and protein concentration was determined using the method of Bradford [27]. Drug competition assays were conducted as previously described [28], briefly: binding mixtures containing [^{3}H]LTD$_4$ (0.5 nM), membrane preparations (150 µg protein/mL) and different concentrations of competing agents, were incubated at 25 °C for 30 min. Binding reactions were stopped by filtration and the radioactivity retained on rinsed filters was determined by a liquid scintillation counter. The specific binding was defined as the difference between the amount of radioligand bound in the absence and presence of LTD$_4$ (1 µM). Data from drug competition experiments were analysed by a non-linear least-square regression analysis using programs of Equilibrium Binding Data Analysis (EBDA by McPherson, Elservier-BIOSOFT) and Ki calculated by the Cheng-Prusoff equation.

5.1.2. Measurement of bronchoconstriction in anesthetized guinea-pigs

Male Dunkin Hartley guinea-pigs were anaesthetized with urethane and treated with d-tubocurarine to prevent spontaneous respiratory movements. Body temperature was controlled electronically (Crison 639 K) and maintained at 34.5 °C. The animals were ventilated mechanically through a tracheal cannula. Changes in insufflation pressure were monitored on a Letica 2006 polygraph. The basal value of insufflation pressure remained stable for at least 2 h and no significant changes were produced by i.v. saline administration. At the end of the stabilization period (30 min) the guinea-pigs were challenged with i.v. LTD$_4$ (2 µg/kg). Preliminary experiments showed that at least two reproducible responses to the spasmogen could be evoked at an interval of 60 min in the same animal. To assess the pharmacological modulation of these bronchospastic responses by the Cys-LT antagonists under study, compounds were orally administered 1 h before the second challenge with the spasmogen. Antagonistic effect is expressed as percent inhibition of LTD$_4$-induced bronchospasm compared with first LTD$_4$ challenge before treatment, or as the dose of antagonist required to inhibit 50% bronchoconstriction.

5.1.3. LTD$_4$-induced airway microvascular leakage into guinea-pig trachea

Guinea-pigs were anaesthetized with urethane and treated with indomethacin (i.v.) and propanolol. Animals were artificially ventilated with a constant volume by a tracheal cannula attached to a constant volume respirator. A catheter was inserted into the jugular vein for the administration of LTD$_4$ and Evans Blue. One minute after the administration of Evans blue (30 mg/kg), the animal was challenged with LTD$_4$ (2 µg/kg i.v.) and 5 min later the chest cavity was opened, and Evans blue dye was washed out by perfusion via thoracic aorta with saline. The trachea was then removed and Evans blue extracted. Microvascular leakage was evaluated from the amount of Evans blue determined spectrophotometrically and expressed as ng/mg tissue. The baseline was determined by the administration of saline containing Evans blue. Compounds were given orally 1, 3 and 8 h before LTD$_4$ challenge. Effect of tested compounds was expressed as percent inhibition of increase of airway microvascular leakage with respect to vehicle treated animals.

5.1.4. Oral absorption evaluation

Compounds were orally administered to male Swiss mice at a selected dose of 15 mg/kg as suspensions in DMSO:Tween 20:H$_2$0 (8:3:89) or intravenously as solutions in Tween 20:PBS (2:98). The measurement times were set as follows: 0.5, 1, 2, 4, 6, 8 and 16 h. After each time the corresponding animals were humanely killed, blood samples gathered by cardiac puncture and plasma were obtained by centrifugation (1 500 *g*, 10 min). Samples were then extracted using ethyl acetate, dried by nitrogen stream and stored at –25 ± 5 °C until reverse phase HPLC analysis. The area under the concentration–time curve (AUC) was determined by the trapezoidal rule from the start to the 6 or 16 h period, whereas the t_{max} corresponds to the time to reach the maximum concentration (C_{max}).

5.2. Chemistry

Melting points were determined in a Köfler apparatus provided with a Reichert Thermovar microscope and are uncorrected. TLC was carried out on SiO_2 (silica Gel 60 F_{254}, Merck 0.063–0.200 mm) and spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica Gel 60 A CC, Merck). Organic extracts were dried over anhydrous Na_2SO_4 and solutions were evaporated under reduced pressure with a rotary evaporator. IR spectra were recorded on a Nicolet 510 FT-IR spectrometer. NMR spectra were measured with Varian Gemini-200 (200 MHz) and Varian Gemini-300 (300 MHz) spectrometers; data are given in δ referenced to TMS.

Mass spectra were measured in the electron impact (EI) or chemical impact (CI, CH_4) modes with a Hewlett-Packard 5988A spectrometer. Elemental analyses were performed on a Perkin Elmer 240 apparatus in the Centro de Investigación y Desarrollo del Consejo Superior de Investigaciones Científicas of Barcelona and in all cases were within ± 0.4% of theoretical values. IR, ^{13}C-NMR and MS data are presented as supplementary material.

5.2.1. 7-Methoxymethoxy-2-naphthol **3**

Commercial 60% suspension of sodium hydride (2.48 g, 62 mmol) in mineral oil was washed in inert atmosphere three times with anhydrous hexane; the solvent was removed by decantation and the solid was dried under vacuum. DMF (25 mL) was added and over this suspension at room temperature and under nitrogen, 2,7-dihydroxynaphthalene (10 g, 62 mmol) dissolved in DMF (25 mL) and chloromethyl methyl ether (4.5 mL) were added; the mixture was stirred for 30 min. The crude was poured onto a mixture of water and ice (50 mL) and was extracted with ethyl acetate. The organic layer was dried and evaporated to give material which was purified by column chromatography, eluting with hexane/ethyl acetate (2:1); **3** (3.4 g, 27%) was obtained as a colourless oil; δ_H (200 MHz, $CDCl_3$) 7.69 (d, *J* = 8.8 Hz, 2H, Ar), 7.24 (d, *J* = 2.6 Hz, 1H, Ar), 7.04 (m, 3H, Ar), 5.29 (s, 2H, OCH_2), 4.95 (s, 1H, OH) and 3.52 (s, 3H, OCH_3).

5.2.2. Methyl 7-methoxymethoxy-2-naphthalencarboxylate **5**

Anhydrous pyridine (2.4 mL) and trifluoromethanesulfonic anhydride (6.1 g, 21.6 mmol) were added under nitrogen atmosphere to a solution of **3** (3.4 g, 16.6 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0 °C maintaining this temperature for 1 h, after that the mixture was diluted with ethyl ether (100 mL), washed with saturated $NaHCO_3$ solution, water, and saturated NaCl solution. The organic layer was dried and evaporated to give 7-methoxymethoxy-2-trifluomethylsulfonyloxynaphthalene **4** (4.9 g, 89%) as a colourless oil, which was used without further purification; δ_H (200 MHz, $CDCl_3$) 7.78 (m, 3H, Ar), 7.32 (m, 3H, Ar), 5.30 (s, 2H, OCH_2) and 3.53 (s, 3H, OCH_3). To a solution of **4** (4.9 g, 14.6 mmol) in anhydrous methanol (80 mL), Et_3N (7.9 mL), DMSO (100 mL), $Pd(OAc)_2$ (98 mg) and 1,3-bis(diphenylphosphino)propane (169 mg) were added. A flow of CO was passed for 10 min and the reaction mixture was heated at 75 °C for 3 h under CO atmosphere. After this time, the reaction mixture was cooled and filtered through celite and the solvent was removed. The residue was dissolved in ethyl ether, successively washed with water, 5% HCl, and a saturated solution of NaCl, dried and the solvent was removed. The crude product was purified by column chromatography with CH_2Cl_2 and **5** (3.1 g, 86%) was isolated as a yellowish oil; δ_H (200 MHz, $CDCl_3$) 8.50 (s, 1H, Ar), 7.93 (dd, *J* = 8.8 Hz, *J* = 1.8 Hz, 1H, Ar), 7.51 (m, 2H, Ar), 7.49 (d, *J* = 2.6 Hz, 1H, Ar), 7.31 (dd, *J* = 8.8 Hz, *J* = 2.6 Hz, 1H, Ar), 5.29 (s, 2H, OCH_2), 3.96 (s, 3H, CO_2CH_3), 3.52 (s, 3H, OCH_3).

5.2.3. 7-Methoxymethoxy-2-hydroxymethylnaphthalene **6**

To 1 M $LiAlH_4$ solution in THF (0.64 mL) at 0 °C, **5** (80 mg, 0.32 mmol) in THF (15 mL) was added. The mixture was maintained at the same temperature for 1 h, then water (1 mL), 3.5 M NaOH (1 mL), water (1.5 mL) and ethyl ether (10 mL) were successively added. After stirring for 15 min the mixture was filtered through celite. The solvent was dried and removed, the residue was purified by column chromatography, eluting with hexane: EtOAc (4:1) yielding **6** (46 mg, 71%) as a white solid; m.p. 40–41 °C; δ_H (200 MHz, $CDCl_3$) 7.72 (m, 3H, Ar), 7.34 (m, 2H, Ar), 7.19 (dd, *J* = 8.8 Hz, *J* = 2.6 Hz, 1H, Ar), 5.27 (s, 2H, OCH_2O), 4.78 (s, 2H, CH_2O), 3.51 (s, 3H, OCH_3).

5.2.4. 4-[2-(7-Methoxymethoxynaphthalen-2-ylmethoxy)ethyl]benzonitrile **8**

Thirteen molar *sec*BuLi in cyclohexane (3.5 mL) was added slowly to a solution of **6** (0.9 g, 4.13 mmol) in anhydrous THF (20 mL) under nitrogen at 0 °C. The mixture was stirred for 10 min, tosyl chloride (0.78 g, 4.13 mmol) in anhydrous THF (7 mL) was added and the agitation was maintained for 4 h. The reaction mixture was then poured onto a cool solution of 2% $NaHCO_3$ (25 mL) and extracted with ethyl ether, the organic layer was dried and the solvent was evaporated to give a white, unstable solid. This solid was immediately dissolved in 50% NaOH (10 mL) and a solution of Bu_4NHSO_4 (120 mg) and 2-(4-cianophenyl)ethanol (0.73 g, 4.95 mmol) in CH_2Cl_2 (10 mL) was then added; the mixture was stirred for 3 days. CH_2Cl_2 (25 mL) was then added, the organic phase was separated, the aqueous solution was extracted twice with CH_2Cl_2; the resulting organic extract was washed with saturated NaCl solution, dried and the solvent removed. The crude product was purified by column chromatography over silica gel containing 2.5% of Et_3N with hexane: CH_2Cl_2 6:1 as eluent, yielding **8** (0.61 g, 43%) as a white solid; m.p. 75–75.5 °C; δ_H (300 MHz, $CDCl_3$) 7.75 (d, *J* = 8.7 Hz, 1H, Ar), 7.73 (d, *J* = 8.4 Hz, 1H, Ar) 7.59 (s, 1H, Ar), 7.57 (d, *J* = 8.4 Hz, 2H, Ph), 7.35 (s, 1H, Ar), 7.33 (d, *J* = 8.4 Hz, 2H, Ph), 7.22 (m, 2H, Ar), 5.30 (s, 2H, OCH_2O), 3.73 (t, *J* =

6.3 Hz, PhCH$_2$CH$_2$O), 3.53 (s, 3H, OCH$_3$), 2.98 (t, *J* = 6.3 Hz, PhCH$_2$CH$_2$O).

5.2.5. 4-[2-(7-Hydroxynaphthalen-2-ylmethoxy)-ethyl]benzonitrile **9**

HCl 2 N (30 mL) was added to a solution of **8** (0.6 g, 1.73 mmol) in THF (30 mL) and isopropanol (0.5 mL) under nitrogen; the mixture was stirred for 28 h at 30 °C. The organic solvents were then removed, the aqueous layer was extracted with EtOAc, the organic layer washed with a saturated solution of NaCl, dried and evaporated, yielding **9** (0.50 g, 97%) as a yellowish solid; m.p. 132–134 °C; δ_H (300 MHz, $CDCl_3$) 7.69 (d, *J* = 8.7 Hz, 2H, Ar), 7.56 (d, *J* = 8.4 Hz, 2H, Ph), 7.46 (s, 1H, Ar), 7.32 (d, *J* = 8.4 Hz, 2H, Ph), 3.72 (t, *J* = 6.6 Hz, 2H, PhCH$_2$CH$_2$O), 2.97 (t, *J* = 6.6 Hz, 2H, PhCH$_2$CH$_2$O).

5.2.6. 4-[2-[7-(2,3-Dichlorothieno[3,2-b]pyridyl-5-methoxy)naphthalen-2-ylmethoxy]ethyl]benzonitrile **11a**

Anhydrous K_2CO_3 (66 mg, 0.48 mmol), 5-chloromethyl-2,3-dichlorothieno[3,2-*b*]pyridine (60 mg, 0.24 mmol) dissolved in anhydrous acetonitrile (1 mL), KI (15 mg) were added to a solution of **9** (60 mg, 0.24 mmol) in anhydous acetonitrile (2 mL) under nitrogen and the mixture was then refluxed for 3 h. The reaction mixture was then cooled to room temperature and ethyl ether (5 mL) and water (5 mL) were added. The organic layer was separated and dried, the solvent was removed and the crude product was purified by column chromatography with hexane: EtOAc 2:1 as eluent, obtaining **11a** (60 mg, 58%) as a brown oil; δ_H (300 MHz, $CDCl_3$) 8.01 (d, *J* = 8.4 Hz, 1H, Het), 7.73 (dd, *J* = 8.7 Hz, 2H, Ar), 7.64 (d, *J* = 8.4 Hz, 1H, Het), 7.55 (d, *J* = 8.4 Hz, 2H, Ph), 7.54 (s, 1H, Ar), 7.32 (d, *J* = 8.4 Hz, 2H, Ph), 7.12 (m, 3H, Ar), 5.48 (s, 2H, ArOCH$_2$), 4.61 (s, 2H, ArCH$_2$O), 3.72 (t, *J* = 6.6 Hz, 2H, PhCH$_2$CH$_2$O), 2.97 (t, *J* 6.6, 2H, PhCH$_2$CH$_2$O).

5.2.7. 4-[2-[7-(4-Isopropylthiazole-2-ylmethoxy)-naphthalen-2-ylmethoxy]ethyl] benzonitrile **11b**

Anhydrous K_2CO_3 (136 mg, 0.98 mmol), 2-chloromethyl-4-isopropylthiazole (88 mg, 0.50 mmol) solved in anhydrous acetonitrile (2 mL) and KI (15 mg) were added to a solution of **9** (125 mg, 0.41 mmol) in anhydrous acetonitrile (3 mL), under nitrogen and then refluxed for 3 h. The reaction mixture was then cooled to room temperature and ethyl ether (5 mL) and water (5 mL) were added. The organic layer was separated and dried, the solvent was removed and the crude product was purified by column chromatography with hexane: EtOAc 2:1 as eluent, obtaining **11b** (108 mg, 60%) as a yellowish solid; m.p. 75–76 °C; δ_H (300 MHz, $CDCl_3$) 7.74 (d, *J* = 8.7 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H, Ar), 7.59 (b s, 1H, Ar), 7.56 (d, *J* = 8.1 Hz, 2H, Ph),7.33 (d, *J* = 8.1 Hz, 2H, Ph), 7.23 (m, 3H, Ar), 6.90 (d, *J* = 0.6 Hz, 1H, HetCH), 5.45 (s, 2H, ArOCH$_2$), 4.63 (s, 2H, ArCH$_2$O) 3.73 (t, *J* = 6.6 Hz, 2H, PhCH$_2$CH$_2$O), 3.13 (sept, *J* = 6.9 Hz, 1H, CH(CH$_3$)$_2$), 2.98 (t, *J* = 6.6 Hz, 2H, PhCH$_2$CH$_2$O), 1.34 (d, *J* = 6.9 Hz, 6H, CH(CH$_3$)$_2$).

5.2.8. 4-[2-[7-(4-Cyclobutylthiazole-2-ylmethoxyl)-naphthalen-2-ylmethoxy] ethyl]benzonitrile **11c**

Anhydrous K_2CO_3 (110 mg, 0.79 mmol), 2-chloromethyl-4-cyclobutylhiazole (74 mg, 0.40 mmol) solved in anhydrous acetonitrile (2 mL), KI (15 mg) were added to a solution of **9** (100 mg, 0.33 mmol) in anhydrous acetonitrile (3 mL), under nitrogen and then refluxed for 3 h. After this time, the reaction mixture was cooled at room temperature and ethyl ether (5 mL) and water (5 mL) were added. The organic layer was separated, and dried, the solvent was removed and the crude product was purified by column chromatography with hexane: EtOAc 2:1 as eluent, obtaining **11c** (113 mg, 62%) as a brown oil; δ_H (300 MHz, $CDCl_3$) 7.75 (d, *J* = 8.7 Hz, 1H, Ar), 7.73 (d, *J* = 8.1 Hz, 1H, Ar), 7.59 (b s, 1H, Ar), 7.56 (d, *J* = 8.4 Hz, 2H, Ph), 7.33 (d, *J* = 8.4 Hz, 2H, Ph), 7.23 (m, 3H, Ar), 6.93 (d, *J* = 0.6 Hz, 1H, HetCH), 5.46 (s, 2H, ArOCH$_2$), 4.66 (s, 2H, ArCH$_2$O), 3.73 (m, 3H), 3.13 (sept, *J* = 6.9 Hz, 1H, CH(CH$_3$)$_2$), 2.98 (t, *J* = 6.9 Hz, 2H, PhCH$_2$CH$_2$O), 2.40–1.80 (m, 6H, cbutyl).

5.2.9. 4-[2-(7-Hydroxy-2-naphtylmethoxy)ethyl]benzoic acid **12**

Thirty-five percent aqueous NaOH (10 mL) was added to a solution of **9** (250 mg, 0.82 mmol) in ethanol (20 mL) The solution was refluxed for 3 h. The homogeneous reaction mixture was cooled to 0 °C and 3 M HCl was added until a precipitate formed. The solvent was removed and the residue was dissolved in ethyl ether; the organic solution was dried and evaporated, yielding **12** (238 mg, 90%) as a slightly brown solid; m.p. 205–207 °C; δ_H (300 MHz, CD_3OD) 7.99 (d, *J* = 8.4 Hz, 2H, Ar), 7.80–7.60 (m, 4H, Ar), 4.64 (s, 2H, ArCH$_2$O), 3.76 (t, *J* = 6.6 Hz, 2H, PhCH$_2$CH$_2$O), 2.99 (t, *J* = 6.6 Hz, 2H, PhCH$_2$CH$_2$O).

5.2.10. 5-Fluorobenzotiazol-2-il 4-[2-[7-(5-fluorobenzothiazole-2-ylmethoxy) naphthalen-2-ylmethoxy]ethyl]benzoate **13**

Anhydrous K_2CO_3 (265 mg, 1.90 mmol), 2-bromomethyl-5-fluorobenzothiazole (207 mg, 0.84 mmol) solved in anhydrous acetonitrile (5 mL), KI (15 mg) were added to a solution of **12** (130 mg, 0.42 mmol) in anhydrous acetonitrile (10 mL), under nitrogen and then refluxed for 3 h. The reaction mixture was cooled at room temperature and ethyl ether (10 mL) and water (10 mL)

were added. The organic layer was separated and dried, the solvent removed and the crude product was purified by column chromatography with hexane: EtOAc 7:3 as eluent, obtaining **13** (205 mg, 75%) as an orange solid; m.p. 122–123 °C; δ_H (300 MHz, $CDCl_3$) 8.06 (d, *J* = 7.8 Hz, 2H, Ph), 7.83–7.68 (m, 6H, Ar), 7.59 (bs, 1H, Ar), 7.35 (d, *J* = 7.8 Hz, 2H, Ph), 7.30–7.15 (m, 5H, Ar), 5.73 (s, 2H, CO_2CH_2Het), 5.58 (s, 2H, OCH_2Het), 4.64 (s, 2H, $ArCH_2O$), 3.75 (t, *J* = 6.6 Hz, 2H, $PhCH_2\underline{CH_2}O$), 3.01 (t, *J* = 6.6 Hz, 2H, $Ph\underline{CH_2}CH_2O$).

5.2.11. 4-[2-[7-(2,3-Dichlorothieno[3,2-b]pyridyl-5-methoxy)naphthalen-2-ylmethoxy]ethyl]benzoic acid **2a**

Thirty-five percent aqueous NaOH (5 mL) was added to a solution of **11a** (55 mg, 0.11 mmol) in ethanol (7 mL). The solution was refluxed for 3 h, the homogeneous reaction mixture was cooled to 0 °C, 3 M HCl was added until a precipitate formed. The solvent was removed and the residue was dissolved in ethyl ether; the organic solution was dried and evaporated, yielding **2a** (52 mg, 88%) as a yellow solid; m.p. 141–142 °C; anal. $C_{28}H_{21}Cl_2NO_4S.1/2H_2O$; δ_H (300 MHz, $CDCl_3$) 8.06 (d, *J* = 8.1 Hz, 2H, Ph), 8.04 (d, *J* = 8.4 Hz, 1H, Het), 7.71 (d, *J* = 8.4 Hz, 1H, Het), 7.69 (d, *J* = 7.5 Hz, 1H, Ar), 7.68 (d, *J* = 8.7 Hz, 1H, Ar), 7.34 (d, *J* = 8.1 Hz, 2H, Ph), 7.31 (s b, 1H, Ar), 7.22 (dd, *J* = 8.7 Hz, *J* = 2.4 Hz, 1H, Ar), 7.18 (dd, *J* = 8.7 Hz, *J* = 2.4 Hz, 1H, Ar), 7.01 (d, *J* = 2.4 Hz, 1H, Ar), 5.45 (s, 2H, $ArOCH_2$), 4.65 (s, 2H, $ArCH_2O$), 3.76 (t, *J* = 6.6 Hz, 2H, $PhCH_2\underline{CH_2}O$), 3.00 (t, *J* = 6.6 Hz, 2H, $Ph\underline{CH_2}CH_2O$).

5.2.12. 4-[2-[7-(4-Isopropylthiazole-2-ylmethoxy)-naphthalen-2-ylmethoxy]ethyl]benzoic acid **2b**

Thirty-five percent aqueous NaOH was added to a solution of **11b** (100 mg, 0.23 mmol) in ethanol (10 mL). The solution was refluxed for 3 h. The homogeneous reaction mixture was then cooled to 0 °C, 3 M HCl was added until a precipitate formed. The solvent was removed and the residue was dissolved in ethyl ether; the organic solution was dried and evaporated, yielding **2b** (72 mg, 68%) as a yellow solid; m.p. 117–118 °C; % anal. $C_{27}H_{27}NO_4S.1/2H_2O$; δ_H (300 MHz, $CDCl_3$) 8.06 (d, *J* = 8.1 Hz, 2H, Ph), 7.72 (d, *J* = 8.4 Hz, 1H, Ar), 7.71 (d, *J* = 8.4 Hz, 1H, Ar), 7.41 (s ample, 1H, Ar), 7.34 (d, *J* = 8.1 Hz, 2H, Ph), 7.22 (m, 2H, Ar), 7.08 (d, *J* = 2.4 Hz, Ar), 6.91 (d, *J* = 0.6 Hz, 1H, HetCH), 5.46 (s, 2H, $ArOCH_2$), 4.65 (s, 2H, $ArCH_2O$), 3.73 (t, *J* = 6.6 Hz, 2H, $PhCH_2\underline{CH_2}O$), 3.13 (sept, *J* = 6.9 Hz, 1H, $\underline{CH}(CH_3)_2$), 2.98 (t, *J* = 6.6 Hz, 2H, $Ph\underline{CH_2}CH_2O$), 1.35 (d, *J* = 6.9 Hz, 6H, $\underline{CH}(CH_3)_2$).

5.2.13. 4-[2-[7-(4-Cyclobutylthiazole-2-ylmethoxyl)-naphthalen-2-ylmethoxy]ethyl]benzoic acid **2c**

Thirty-five percent aqueous NaOH (5 mL) was added to a solution of **11c** (80 mg, 0.17 mmol) in ethanol (7 mL) The solution was refluxed for 3 h. The homogeneous reaction mixture was cooled to 0 °C, 3 M HCl was added until a precipitate formed. The solvent was removed and the residue was dissolved in ethyl ether; the organic solution was dried and evaporated, yielding **2c** (67 mg, 84%) as an oil. Anal. $C_{28}H_{27}NO_4S.1/2H_2O$; δ_H (300 MHz, $CDCl_3$) 8.60–8.20 (b s, OH), 8.05 (d, *J* = 8.4 Hz, 2H, Ph), 7.72 (d, *J* = 9.0 Hz, 1H, Ar), 7.71 (d, *J* = 8.4 Hz, 1H, Ar), 7.45 (s, 1H, Ar), 7.33 (d, *J* = 8.4 Hz, 2H, Ph), 7.22 (m, 2H, Ar), 7.10 (d, *J* = 2.7 Hz, 1H, Ar), 6.92 (d, *J* = 0.9 Hz, 1H, Het CH), 5.46 (s, 2H, $ArOCH_2$), 4.65 (s, 2H, $ArCH_2O$), 3.73 (m, 3H), 3.00 (t, *J* = 6.6 Hz, 2H, $Ph\underline{CH_2}CH_2O$), 2.20–1.85 (m, 6H, cbutyl).

5.2.14. 4-[2-[7-(5-fluorobenzothiazole-2-ylmethoxy)-naphthalen-2-ylmethoxy]ethyl]benzoic acid **2d**

Two percent aqueous NaOH (4 mL) was added to a solution of **13** (150 mg, 0.23 mmol) in ethanol (12 mL). The solution was refluxed for 24 h the homogeneous reaction mixture was cooled 0 °C, 3 M HCl was added until a precipitate formed. The solvent was removed and the residue was purified by column chromatography with hexane:EtOAc 3:2 as eluent, yielding **2d** (79 mg, 71%) as a yellow solid; m.p. 165–167 °C; anal. $C_{28}H_{22}FNO_4S.1/2H_2O$; δ_H (300 MHz, CD_3COCD_3) 8.15 (dd, *J* = 8.7 Hz, *J* = 5.4 Hz, 1H, Ar), 8.01 (d, *J* = 8.4 Hz, 2H, Ph), 7.92–7.80 (m, 3H, Ar), 7.73 (s ample, 1H, Ar), 7.48 (m, 1H, Ar), 7.46 (d, *J* = 8.4 Hz, 2H, Ph), 7.34 (m, 3H, Ar), 5.74 (s, 2H, OCH_2Het), 4.71 (s, 2H, Ar CH_2O), 3.83 (t, *J* = 6.3 Hz, 2H, $PhCH_2\underline{CH_2}O$), 3.06 (t, *J* = 6.3 Hz, 2H, $Ph\underline{CH_2}CH_2O$).

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References

[1] Musser J.H., Kreft A.F., Drugs Future 15 (1990) 73–80.

[2] Jacobs R.T., Veale C.A., Wolanin D.J., Annu. Rep. Med. Chem. 27 (1992) 109–117.

[3] Larsen J.S., Acosta E.P., Ann. Pharmacother. 27 (1993) 898–903.

[4] Brooks C.D.W., Summers J.B., J. Med. Chem. 39 (1996) 2629–2654.

[5] Matassa V.G., Maduskuie T.P., Shapiro H.S., Hesp B., Snyder D.W., Aharony D.C., Krell R.D., Keith R.A., J. Med. Chem. 33 (1990) 1781–1790.

[6] Nakai H., Konno M., Kosuge S., Sakuyama S., Toda M., Arai Y. et al., J. Med. Chem. 31 (1988) 84–91.

[7] Labelle M., Belley M., Gareau Y., Gauthier J.Y., Guay D., Gordon R. et al., Bioorg. Med. Chem. Lett. 5 (1995) 283–288.

[8] Palomer A., Giolitti A., García M.L., Cabré F., Mauleón D., Carganico G., in: Sanz F., Manault F. (Eds.), Trends in QSAR and Molecular Modelling ’94, Editoral Prous, Barcelona, 1995.

[9] Zwaagstra M.E., Schoenmakers S.H.H.F., Nederkoorn P.H.J., Gelens E., Timmerman H., Ming-Qiang Z., J. Med. Chem. 41 (1998) 1439–1445.

[10] Griera R., Armengol M., Reyes A., Alvarez M., Palomer A., Cabré F. et al., Eur. J. Med. Chem. 32 (1997) 547–570.

[11] Pascual J., Fos E., García M.L., Borràs L., Montserrat X., Palomer A. et al., XIIIth Int. Symposium on Med. Chemistry, P184, Paris (1994).

[12] Pascual J., García M.L., Borràs L., Montserrat X., González G., Santiso S. et al., XIVth Int. Symposium on Med. Chemistry, P2.30, Maastricht (1996).

[13] von Sprecher A., Beck A., Gerspacher M., Bray M.A., Chimia 46 (1992) 304–311.

[14] Andrews E.G., Antognoli G.W., Breslow R., Carta M.P., Carty T.J., Chambers R.J. et al., Bioorg. Med. Chem. Lett. 5 (1995) 1365–1370.

[15] Masamune H., Eggler J.F., Marfat A., Melvin L.S., Rusek F.W., Tickner J.E., Cheng J.B., Shirley J.T., Bioorg. Med. Chem. Lett. 5 (1995) 1371–1376.

[16] Lau C.K., Dufresne C., Gareau Y., Zamboni R., Labelle M., Young R.N. et al., Bioorg. Med. Chem. Lett. 5 (1995) 1615–1620.

[17] Labelle M., Gareau Y., Dufresne C., Lau C.K., Belley M., Jones T.R. et al., Bioorg. Med. Chem. Lett. 5 (1995) 2551–2556.

[18] Townsend C.A., Davis S.G., Chistensen S.B., Link J.C., Lewis C.P., J. Am. Chem. Soc. 103 (1981) 6885–6888.

[19] Kingsbury W.D., Pendrak I., Leber J.O., Boehm J.C., Mallet B., Sarau H.M. et al., J. Med. Chem. 36 (1993) 3308–3320.

[20] Collington E.W., Meyers A.L., J. Org. Chem. 36 (1971) 3044–3045.

[21] López-Calahorra F., Ballart B., Hombrados F., Martí J., Synthetic Comm. 28 (1998) 795–799.

[22] Yardley J.P., Fletcher H., Synthesis 244 (1976).

[23] Young R.N., Xiang Y.B., Labelle M., Lau C.K., Leblanc Y., Dufresne C., Gareau Y., Merk Frost Canada Ind., Eur. Pat. Appl. EP 604114; C. A., 122 (1994) 10021j.

[24] Zamboni R., Dufresne C., Lau C.K., Merk Frost Canada Ind., PCT Int. Appl. WO 9321168; C. A., 120 (1993) 270373f.

[25] Prepared by conventional radical benzylic bromination from the commercial 5-fluoro-2-methylbenzothiazole.

[26] Mong S., Wu H.L., Hogaboom G.K., Clark M.A., Crooke S.T., Eur. J. Pharmacol. 102 (1984) 1–11.

[27] Bradford M., Anal. Biochem. 72 (1989) 248–254.

[28] Cabré F., Carabaza F., García A.M., Calvo L., Ferrer X., Ruiz A. et al., Inflamm. Res. 44 (1995) 5260.