Synthesis and AT1 affinity evaluation of benzamidophenyl analogs of known AT1 receptor ligands with similar aromatic skeleton

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Abstract
Taking as model compound the amido-derivative 1 described in the literature from Duncia's group as a good AngII antagonist, we have synthesized a new series of compounds (2-7) in which the principal structural variations reside in the inversion of the amidic sequence between the two phenyl ring and/or in the type of heteroaromatic substituent linked to this portion. The new compounds synthesized were evaluated for their AT1 affinity through binding assays carried out on rat liver membranes using [^{125}I]Sar1,Ile8-angiotensin II as radioligand.

Keywords: Sartan, AT1 antagonist, binding affinity, benzamidophenyl-derivative

Introduction

The renin-angiotensin system (RAS) plays a fundamental role in the regulation of blood pressure, electrolyte balance, and endocrine functions related to cardiovascular disease. The RAS is a proteolytic cascade in which angiotensinogen released by the kidney is converted into the inactive decapeptide angiotensin I by renin. In turn, angiotensin I is cleft of the two terminal aminoacids by angiotensin-converting enzyme (ACE) to form the octapeptide angiotensin II (AngII). This peptide exerts many physiological effects [1] on blood pressure and electrolyte balance and it is directly involved in the contraction of the vascular smooth muscle and in aldosterone secretion. In addition to its well-known biological actions, it also influences renal, hepatic, endocrine and reproductive functions and has specific actions in the CNS.[2] Recent findings[3,4] indicate the involvement of this peptide also in situations concerning tissue remodeling, such as cardiac hypertrophy and cancer. All these responses are mediated by two distinct subtypes of AngII receptors [type 1 (AT1) and type 2 (AT2)]. In particular, AT1 receptors mediate all of the known effects associated to AngII that constitutes the principal target

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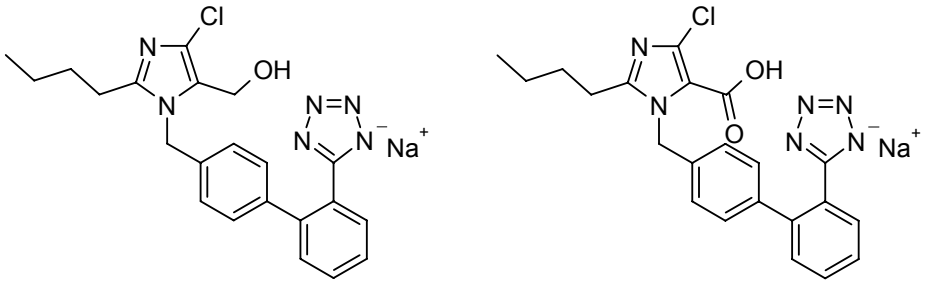
of an effectiveness therapy against the cardiovascular pathology. The AngII effects may be reduced by inhibiting almost partially the enzyme responsible of biosynthesis of AngII or through the interaction with AT1 receptor.

For these reasons, it became important to study the development of antagonists of AngII subtype 1 receptor (AT1 antagonists or sartans) viewed as a new class of antihypertensive used in the treatment of hypertension, [5] heart failure [6] and renal diseases.[7]

The first non-peptide AT1 antagonist which represents the prototype of the sartans was losartan. The major active metabolite of losartan, EXP3174, generated by the oxidation of the 5-hydroxymethyl group on the imidazole ring, is 10-40 times more potent than losartan itself and is therefore responsible for the majority of its pharmacological activity.



Losartan **EXP3174**

Figure 1. Molecular structures of losartan and its active metabolite (EXP3174).

To date, many orally available sartans have been developed and are used in the treatment of both hypertension and damage associated with diseases like atherosclerosis and diabetes. In particular, the good properties of new non peptide AngII antagonists, such as losartan, have stimulated the design of many different congeners. All these drugs contain some common structural features represented by a biphenyl fragment bearing an acidic moiety (i.e.: tetrazole, carboxylic- or sulphonamidocarboxyl- group), linked to a heteroaromatic or acyclic system by means of a methylene group. Almost all of the chemical manipulations within the fundamental skeleton of sartans, concerned the substitution of the imidazole ring of losartan with several variously substituted heteroaromatic groups or acyclic structures. [8]

The Duncia group reported a series of compounds,[9] in which, as in the derivative **1,** the tetrazolyl-substituted biphenyl portion is replaced by a carboxy-substituted benzamido phenyl moiety. Some of the synthesized compounds showed a potent AngII antagonist activity. On this basis, taking as a molecular model the compound **1**, we have brought some chemical manipulations to evaluate their effects on the AT1 antagonism in the class of the benzamidophenyl sartans. (figure 2)

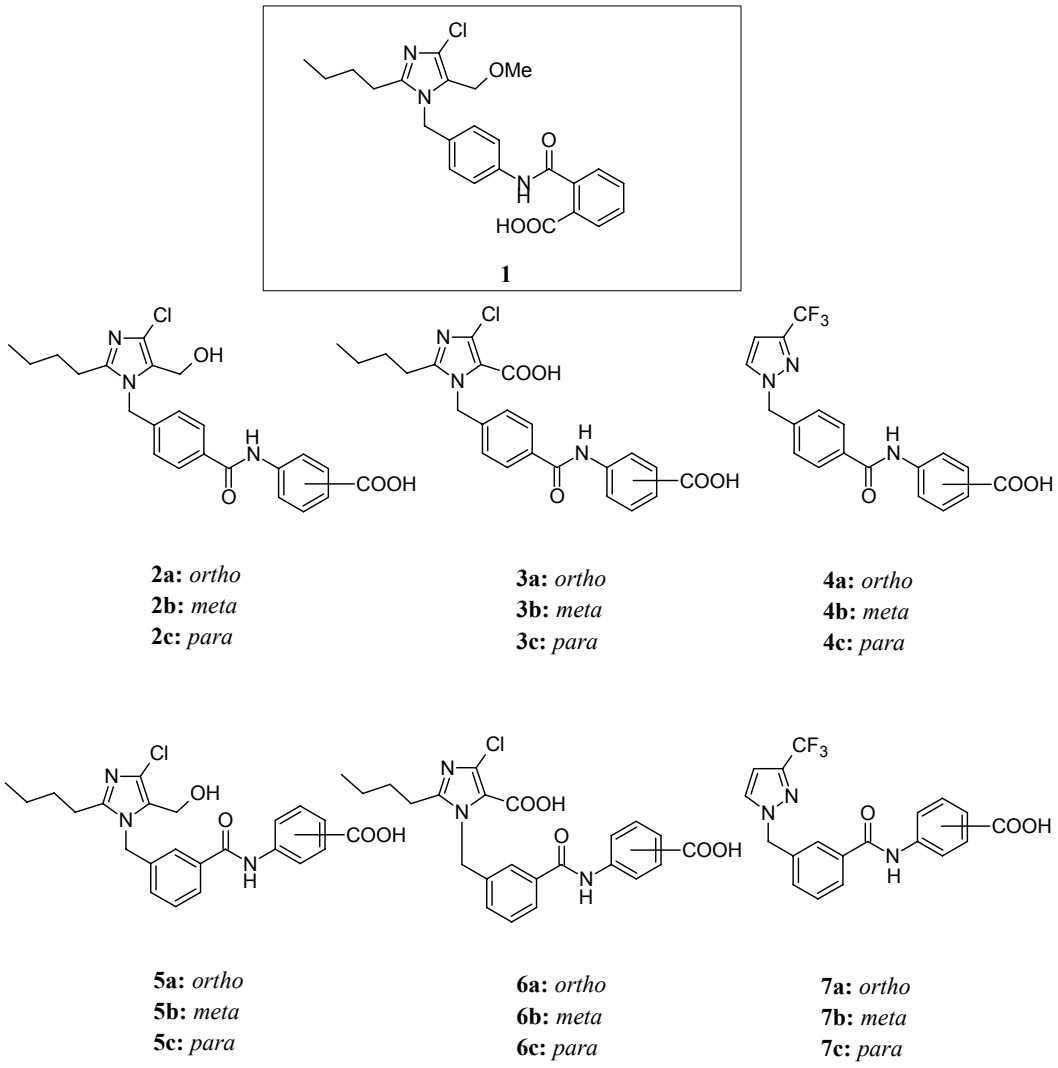


Figure 2. Structures of lead-compound **1** and derivatives **2-7.**

The first modification that we carried out, concerned the reversion of the amide bond of the model compound (**1**) to obtain derivatives **2a, 3a** in which the methoxymethyl group linked to the 5 position of imidazole (**1**) is replaced by the hydroxymethyl moiety of losartan (**2a**), or by the carboxylic function of the active metabolite of losartan (EXP-3174) (**3a**), respectively. In addition, in order to obtain further information about the steric requisites necessary for a good interaction with AT1 receptor, we have also synthesized the isomers **2b,c** and **3b,c** in which the carboxylic function of the benzoic portion is in the *meta* (**2b, 3b**) and *para* position (**2c, 3c**).

Compounds **4a-c** were successively synthesized in order to evaluate the effect of the replacement of the structurally complex imidazole portion of **2a-c** and **3a-c**, also present in losartan and in its metabolite EXP3174, with another heterocyclic system such as the pyrazole substituted in 3 position with an electron-withdrawing group (trifluoromethyl) hypothesizing that this substituent may favour the interaction with the AT1 receptor.

Compounds **5a-c**, **6a-c**, and **7a-c** were also prepared as structural isomers of derivatives **2a-c**, **3a-c**, and **4a-c** respectively, in which the carboxamidobenzoic- group is linked in position 3 of the aromatic ring.

Table 1. Melting points and yields of final products **2-7**

Compound	Substrate	Mp, °C	Yield, %
2a	$C_{23}H_{24}ClN_3O_4$	150-152	41
2b	$C_{23}H_{24}ClN_3O_4$	170-172	57
2c	$C_{23}H_{24}ClN_3O_4$	180-182	80
3a	$C_{23}H_{22}ClN_3O_5$	191-193	80
3b	$C_{23}H_{22}ClN_3O_5$	122-124	85
3c	$C_{23}H_{22}ClN_3O_5$	135-137	47
4a	$C_{19}H_{14}F_3N_3O_3$	145-147	33
4b	$C_{19}H_{14}F_3N_3O_3$	190-192	52
4c	$C_{19}H_{14}F_3N_3O_3$	>230	75
5a	$C_{23}H_{24}ClN_3O_4$	104-106	90
5b	$C_{23}H_{24}ClN_3O_4$	168-170	40
5c	$C_{23}H_{24}ClN_3O_4$	88-90	55
6a	$C_{23}H_{22}ClN_3O_5$	179-181	79
6b	$C_{23}H_{22}ClN_3O_5$	105-107	52
6c	$C_{23}H_{22}ClN_3O_5$	120-122	55
7a	$C_{19}H_{14}F_3N_3O_3$	153-155	61
7b	$C_{19}H_{14}F_3N_3O_3$	178-180	44
7c	$C_{19}H_{14}F_3N_3O_3$	170-172	42

The 5'-hydroxymethylimidazole derivatives **2a-c** and **5a-c** and their analogues carboxylic acids (**3a-c** and **6a-c**) were synthesized according to the procedure reported in Scheme 1.

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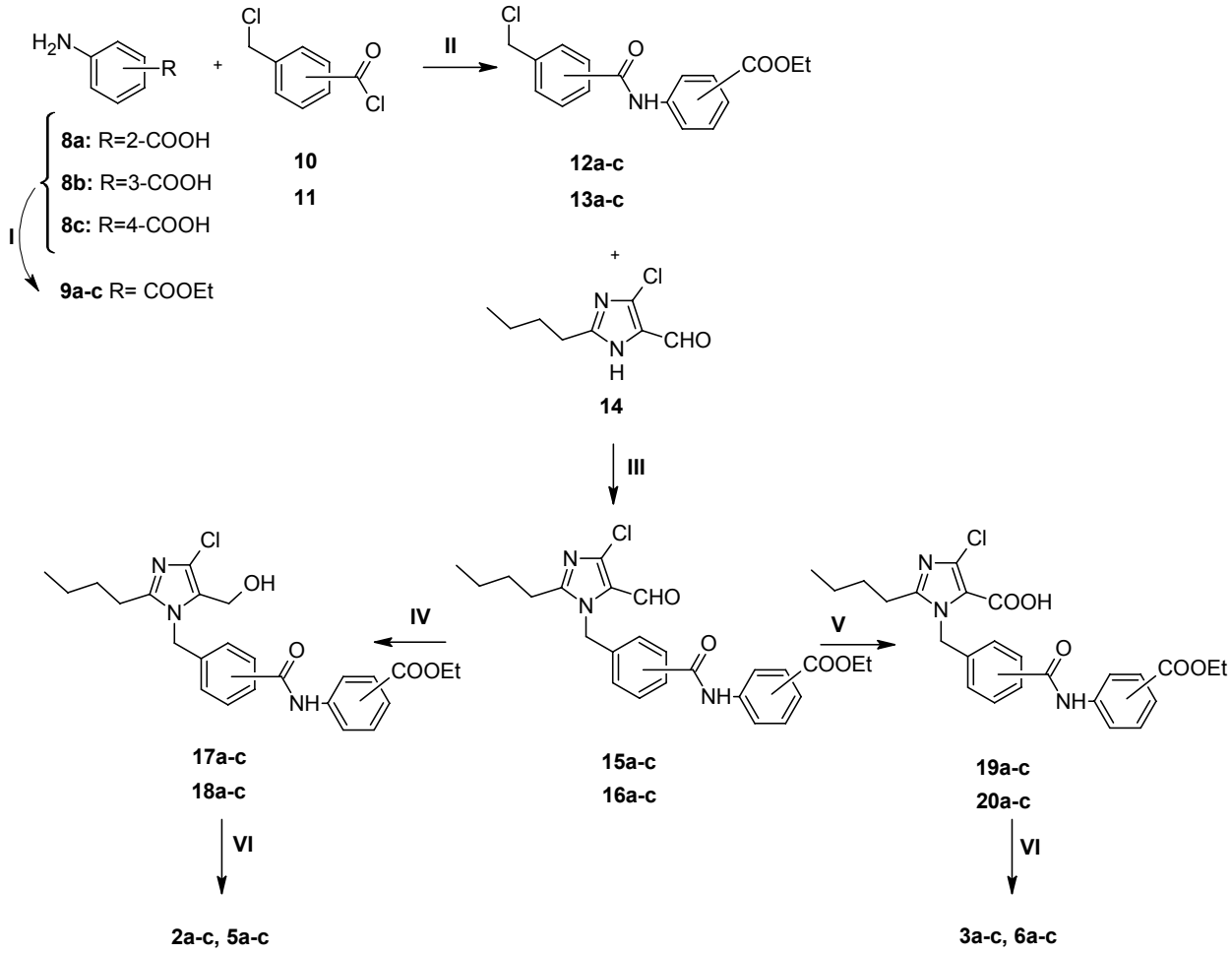


Scheme 1. Reagents and reaction conditions: **I:** $SOCl_2$, EtOH, reflux, 48h; **II:** Et_3N, CH_2Cl_2, r.t., 20h; **III:** K_2CO_3, DMAC, r.t., 12h; **IV:** $NaBH_4$, MeOH, r.t., 1h; **V:** t-BuOH, $NaClO_2$, NaH_2PO_4, H_2O; VI: KOH 50%, MeOH, reflux, 2h.

The reaction of the appropriate (amino)benzoic acid **8a-c** with $SOCl_2$ and EtOH afforded the ethylic esters **9a-c** which were subsequently N-alkylated with 4-(chloromethyl)-benzoylchloride (**10**) or 3-(chloromethyl)benzoylchloride (**11**) in the presence of a catalytic amount of NEt_3 to give the carboxamido-derivatives **12a-c** and **13a-c**, respectively.

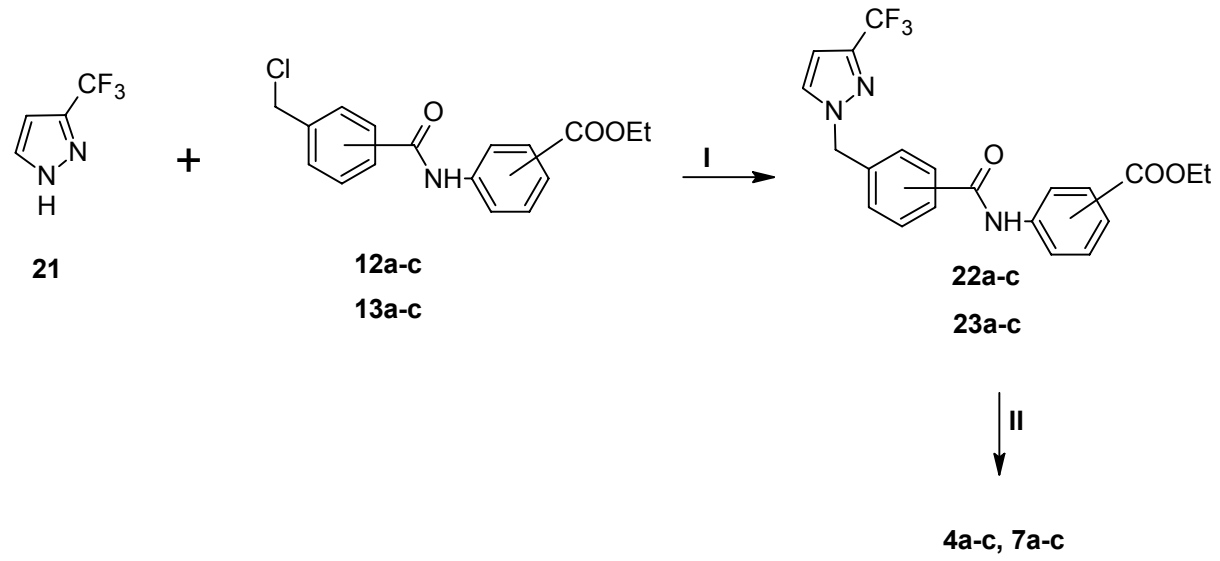
Compounds **15a-c**, **16a-c** were obtained by a condensation reaction of chloromethyl-derivatives (**12a-c, 13a-c**) and the 2-butyl-4-chloro-5-imidazolecarboxaldehyde (**14**), in the presence of DMAC and K_2CO_3.

The intermediates **15a-c** and **16a-c** were then submitted to reduction with $NaBH_4$ in MeOH to afford the 5-hydroxymethyl-derivatives **17a-c** and **18a-c** or to an oxidation with $NaClO_2$ and a buffer solution of NaH_2PO_4 (pH = 4.3) to obtain derivatives **19a-c**, **20a-c.**

The esters **17-20** were refluxed with an aqueous solution of KOH 50% to give the corresponding acids **2,3,5,6**.

The key intermediate **14** was selected to promote the N-alkylation at the nitrogen atom in position 1 rather than in position 3.[10]

Reaction of 3-trifluoromethylpyrazole (**21**) and chloromethyl-derivatives **12a-c** and **13a-c** in the presence of K_2CO_3 and a catalytic amount of KI afforded the esters **22a-c** and **23a-c** that were then hydrolysed to the corresponding acids **4a-c** and **7a-c** following the same procedure described above for the imidazole-derivatives **2,3,5,6**.(Scheme 2).



Scheme 2. Reagents and reaction conditions: **I:** K_2CO_3, KI, CH_3CN, reflux, 5h; **II:** KOH 50%, MeOH, reflux, 3h.

Results and Discussion

Compounds **2-7** have been tested for their AT1 affinity through a binding assay carried out on rat liver membrane using [^{125}I]Sar^1,Ile^8-angiotensina II as radioligand.

In the same tests were also evaluated the AT1 affinities of the ester intermediates (**17a,b,c-20a,b,c**, **22a-c** and **23a-c**). All synthesized compounds were not active towards AT1 receptor; in particular, only the acid derivatives **5a** and **4b,c** showed a modest affinity with percentage inhibition values close to 40% at 10 μM. As concerns the esters intermediates only compound **19c** showed a percentage inhibition value of 50%.

These results seem to indicate that the simple reversion of the amido-function of model-compound **1** induced a dramatic loss of affinity towards the AT1 receptor, independently from other molecular variables such as the nature of the substituents on the imidazole nucleus, the position of the amidic junction between the two phenyl rings or the acidic moiety on the benzoic system, or the different type of heterocyclic system (imidazole or pyrazole).

This negative result may be attributed to different molecular geometries of the new compounds with respect to that of model compound **1**, because of the reversion of the amido-function. This simple chemical manipulation may be hindering an optimal fit of the new compounds with the receptor site.

A docking study was carried out in order to explain the experimentally observed low AT1 affinity. For this purpose a previously developed model of the AT1 receptor was used.[11] Figure 3A shows the docking of compound **1** into the AT1 receptor model, the carboxy-substituted benzamido phenyl moiety of **1** was positioned between TM3, TM6 and TM7, in a lipophilic cavity principally delimited by V3.32(108), V179, W6.48(253), H6.51(256), I7.39(288) and Y7.43(292). The carboxylic function forming an intramolecular H-bond with the nitrogen of the amido group (forming a pseudo-seven member heterocycle), it was directed towards the extracellular side of the receptor, and interacted with T175 and Y184, which are two residues of the second extracellular loop (EL2) and with H6.51(256). As regards the 2'-butyl substituent, it was directed towards TM4, and interacted in a secondary lipophilic pocket created by S3.33(109), L3.36(112), Y3.37(113), A4.60(163), F171 and F182 of EL2, while the hydroxymethyl group formed an H bond with K5.42(199). Mutagenesis data suggested an important role for V3.32(108), A4.60(163) and K5.42(199),[12] supporting our binding hypothesis. The reversion of the amido-function of compound **1** induced the loss of affinity towards AT1 receptor. Figure 3B shows the docking of compound **5a**: the inversion of the amido-function determined the formation of a six member pseudocycle and an overturning of the disposition of the carboxylic group, directed towards the intracellular side of the receptor. This binding disposition determined the loss of the electrostatic interactions of the carboxylic group with T175, Y184 and H6.51(256), thus explaining its lower affinity.

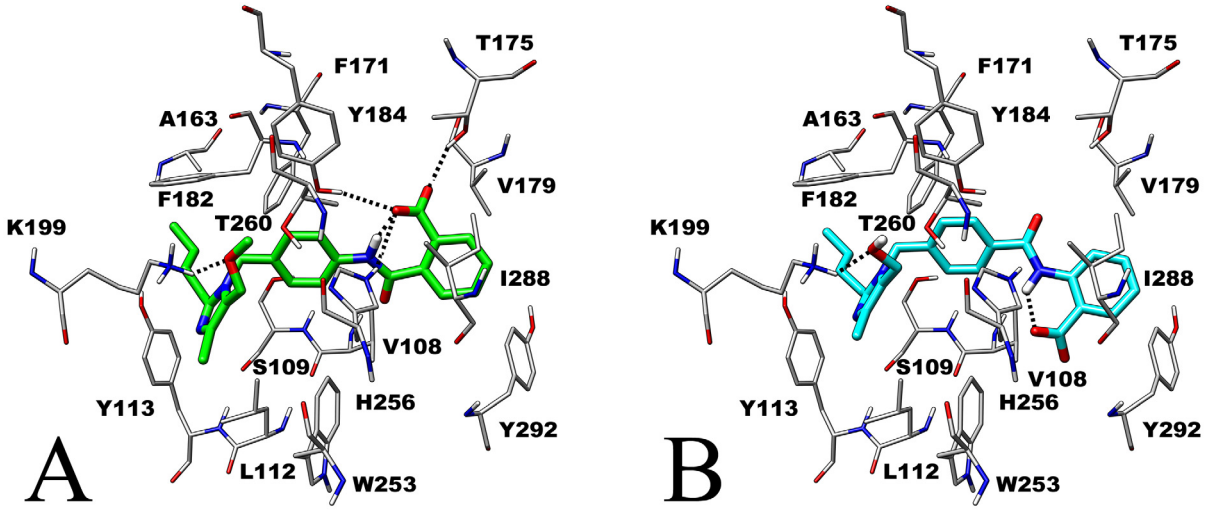


Figure 3. Compound **1** (on the left) and **5a** (on the right) docked in the AT1 binding site.

Experimental Section

General Procedures. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were taken as paraffin oil mulls or as liquid films on a Nicolet/Avatar, 360FT. NMR spectra were obtained with a Varian Gemini 200 MHz spectrometer. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane and referenced from solvent references. Mass spectra were obtained on a Hewlett-Packard 5988 A spectrometer using a direct injection probe and an electron beam energy of 70 eV. The elemental compositions of the compounds agreed to within ± 0.4% of the calculated value. Chromatographic separation was performed on silica gel columns by flash (Kieselgel 40, 0.040–0.063 mm; Merck) or gravity column (Kieselgel 60, 0.063–0.200 mm; Merck) chromatography. Reactions were followed by thin-layer chromatography (TLC) on Merck aluminum silica gel (60 F_{254}) sheets that were visualised under a UV lamp. Evaporation was performed *in vacuo* (rotating evaporator). Sodium sulfate was always used as the drying agent. Commercially available chemicals were purchased from Sigma-Aldrich.

General procedure for preparation of compounds 2a,b,c-7a,b,c

To a solution of the corresponding ester **17a,b,c-20a,b,c, 22a-c, 23a-c** (0.76 mmol) in MeOH (2.8 mL) was added dropwise an aqueous solution of KOH 50% (0.13 mL). The resulting solution was refluxed for 2h, then, after cooling, the solvent was evaporated. The residue was acidified to pH 3 with HCl 1 N and the aqueous phase was extracted with AcOEt. The organic phase was dried and the solvent was evaporated. The crude product was purified by crystallization from AcOEt/hexane to give **2a,b,c-7a,b,c.**

2-[(4-{[4-Chloro-2-butyl-5-(hydroxymethyl)-1*H*-imidazolyl]methyl}benzoyl)amino]benzoic acid (2a). (138 mg, 0.31 mmol, yield 41 %): ^{1}H NMR (DMSO-d_6) δ 0.78 (t, 3H, *J* = 7.1 Hz, CH_3); 1.09-1.28 (m, 2H, CH_2); 1.39-1.50 (m, 2H, CH_2); 2.36-2.48 (m, 2H, CH_2); 4.35 (s, 2H, CH_2OH); 5.37 (s, 2H, CH_2N); 7.18-7.23 (m, 1H, Ar); 7.27 (d, 2H, *J* = 7.9 Hz, AA'XX'); 7.63-7.07 (m, 1H, Ar); 7.93 (d, 2H, *J* = 7.9 Hz, AA'XX'); 8.05 (d, 1H, *J* = 8.1 Hz, Ar); 8.69 (d, 1H, *J* = 8.1 Hz, Ar); 12.13 ppm (br s, 1H). MS *m/z*: 442 (M^+, 3). Anal. Calcd for $C_{23}H_{24}ClN_3O_4$: C 62.52; H 5.44; N 9.51; Found: C 62.59; H 5.07; N 9.16.

3-[(4-{[4-Chloro-2-butyl-5-(hydroxymethyl)-1*H*-imidazolyl]methyl}benzoyl)amino]benzoic acid (2b). (191 mg, 0.43 mmol, yield 57 %): ^{1}H NMR (CD_3COCD_3) δ 0.83 (t, 3H, *J* = 7.2 Hz, CH_3); 1.19-1.36 (m, 2H, CH_2); 1.52-1.67 (m, 2H, CH_2); 2.58 (t, 2H, *J* = 7.8 Hz, CH_2); 4.51 (s, 2H, CH_2OH); 5.45 (s, 2H, CH_2N); 7.27 (d, 2H, *J* = 7.8 Hz, AA'XX'); 7.45-7.53 (m, 2H, Ar); 7.79 (d, 1H, *J* = 7.5 Hz, Ar); 8.02 (d, 2H, *J* = 7.8 Hz, AA'XX'); 8.15 (d, 1H, *J* = 8.2 Hz, Ar); 8.49 (br s, 1H); 9.72 ppm (br s, 1H). MS *m/z*: 442 (M^+, 4). Anal. Calcd for $C_{23}H_{24}ClN_3O_4$: C 62.52; H 5.44; N 9.51; Found: C 62.54; H 5.16; N 9.09.

4-[(4-{[4-Chloro-2-butyl-5-(hydroxymethyl)-1*H*-imidazolyl]methyl}benzoyl)amino]benzoic acid (2c). (269 mg, 0.61 mmol, yield 80 %): IR: 1685 (C=O of acid), 1640 (C=O of amide) cm^{-1}. ^{1}H NMR (CD_3COCD_3) δ 0.83 (t, 3H, *J* = 7.1 Hz, CH_3); 1.28-1.36 (m, 2H, CH_2); 1.55-1.63 (m,

2H, CH_2); 2.55 (t, 2H, *J* = 7.5 Hz, CH_2); 4.51 (s, 2H, CH_2OH); 5.44 (s, 2H, CH_2N); 7.26 (d, 2H, *J* = 8.1 Hz, Ar); 7.94-8.02 (m, 6H, Ar); 9.81 ppm (br s, 1H). ^{13}C NMR (CD_3COCD_3): δ 167.18; 166.20; 148.70; 144.46; 142.15; 137.47; 135.30; 131.39; 128.96; 127.29; 126.56; 122.92; 120.30; 53.24; 47.90; 30.37; 27.22; 22.96; 14.02. MS *m/z*: 442 (M^+,10). Anal. Calcd for $C_{23}H_{24}ClN_3O_4$: C 62.52; H 5.44; N 9.51; Found: C 62.52; H 5.44; N 9.51.

2-{[4-[(4-Chloro-2-butyl-5-carboxy-1*H*-imidazolyl)methyl]benzoyl]amino}benzoic acid (3[a]). (277 mg, 0.61 mmol, yield 80 %): ^1H NMR (DMSO-d_6) δ 0.80 (t, 3H, *J* = 7.1 Hz, CH_3); 1.20-1.31 (m, 2H, CH_2); 1.49-1.57 (m, 2H, CH_2); 2.61 (d, 2H, *J* = 7.4 Hz, CH_2); 5.67 (s, 2H, CH_2N); 7.17-7.24 (m, 3H, Ar); 7.62-7.70 (m, 1H, Ar); 7.91 (d, 2H, *J* = 7.3 Hz, Ar); 8.05 (d, 1H, *J* = 7.6 Hz, Ar); 8.67 (d, 1H, *J* = 8.4 Hz, Ar); 12.13 ppm (br s, 1H). MS *m/z*: 441 (M^+,8). Anal. Calcd for $C_{23}H_{22}ClN_3O_5$: C 60.60; H 4.83; N 9.22; Found: C 60.59; H 4.48; N 9.11.

3-{[4-[(4-Chloro-2-butyl-5-carboxy-1*H*-imidazolyl)methyl]benzoyl]amino}benzoic acid (3b). (294 mg, 0.65 mmol, yield 85 %): IR: 1690 (C=O of acid), 1641 (C=O of amide) cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.82 (t, 3H, *J* = 7.1 Hz, CH_3); 1.22-1.33 (m, 2H, CH_2); 1.48-1.59 (m, 2H, CH_2); 2.61 (d, 2H, *J* = 7.5 Hz, CH_2); 5.68 (s, 2H, CH_2N); 7.14 (d, 2H, *J* = 8.0 Hz, AA'XX'); 7.42-7.51 (m, 2H, Ar); 7.67 (d, 1H, *J* = 7.5 Hz, Ar); 7.93 (d, 2H, *J* = 8.0 Hz, AA'XX'); 7.90-8.10 (m, 1H, Ar); 8.39 (br s, 1H); 12.13 ppm (br s, 1H). ^{13}C NMR (CD_3COCD_3): δ 167.30; 166.05; 160.81; 153.25; 150.81; 140.44; 138.07; 132.90; 132.00; 129.62; 128.87; 127.05; 125.69; 125.29; 124.21; 122.21; 49.03; 30.00; 27.29; 22.92; 13.98. MS *m/z*: 441 (M^+,20). Anal. Calcd for $C_{23}H_{22}ClN_3O_5$: C 60.60; H 4.83; N 9.22; Found: C 60.31; H 4.90; N 9.35.

4-{[4-[(4-Chloro-2-butyl-5-carboxy-1*H*-imidazolyl)methyl]benzoyl]amino}benzoic acid (3c). (90 mg, 0.20 mmol, yield 47 %): ^1H NMR (DMSO-d_6) δ 0.81 (t, 3H, *J* = 7.1 Hz, CH_3); 1.20-1.33 (m, 2H, CH_2); 1.48-1.59 (m, 2H, CH_2); 2.61 (d, 2H, *J* = 7.2 Hz, CH_2); 5.67 (s, 2H, CH_2N); 7.14 (d, 2H, *J* = 8.2 Hz, AA'XX'); 7.80-8.00 (m, 6H, Ar); 10.52 ppm (br s, 1H). MS *m/z*: 441 (M^+,19). Anal. Calcd for $C_{23}H_{22}ClN_3O_5$: C 60.60; H 4.83; N 9.22; Found: C 60.78; H 4.52; N 9.40.

2-[(4-{[3-(Trifluoromethyl)-1*H*-pyrazolyl]methyl}benzoyl)amino]benzoic acid (4a). (97 mg, 0.25 mmol, yield 33 %): ^1H NMR (CD_3COCD_3) δ 5.60 (s, 2H, CH_2N); 6.70-6.72 (m, 1H, pyrazole); 7.16-7.26 (m, 1H, Ar); 7.49-7.74 (m, 4H, Ar, pyrazole); 7.98-8.06 (m, 2H, Ar); 8.18 (d, 1H, *J* = 8.1 Hz, Ar); 8.90-9.00 (m, 1H, Ar); 12.13 ppm (br s, 1H). MS *m/z*: 389 (M^+, 3). Anal. Calcd for $C_{19}H_{14}F_3N_3O_3$: C 58.61; H 3.50; N 10.79; Found: C 58.25; H 3.15; N 10.48.

3-[(4-{[3-(Trifluoromethyl)-1*H*-pyrazolyl]methyl}benzoyl)amino]benzoic acid (4b). (152 mg, 0.39 mmol, yield 52 %): IR: 1700 (C=O of acid), 1641 (C=O of amide) cm^{-1}. ^1H NMR (CD_3COCD_3) δ 5.58 (s, 2H, CH_2N); 6.70-6.72 (m, 1H, pyrazole); 7.44-7.54 (m, 3H, Ar); 7.77-7.81 (m, 1H, Ar); 8.00-8.04 (m, 3H, Ar, pyrazole); 8.13-8.18 (m, 2H, Ar); 8.51 (br s, 1H); 9.71 ppm (br s, 1H). ^{13}C NMR (CD_3COCD_3): δ 167.42; 166.10; 143.71; 141.00; 132.97; 132.11; 129.64; 128.87; 128.76; 128.05; 125.72; 125.34; 123.90; 123.67; 122.26; 105.31; 56.55. MS *m/z*: 389 (M^+, 5). Anal. Calcd for $C_{19}H_{14}F_3N_3O_3$: C 58.61; H 3.50; N 10.79; Found: C 59.00; H 3.87; N 10.65.

4-[(4-{[3-(Trifluoromethyl)-1*H*-pyrazolyl]methyl}benzoyl)amino]benzoic acid (4c). (222 mg, 0.57 mmol, yield 75%): ^{1}H NMR (CD_3COCD_3) δ 5.58 (s, 2H, CH_2N); 6.69-6.71 (m, 1H, pyrazole); 7.76 (d, 2H, *J* = 8.2 Hz, Ar); 7.95-8.06 (m, 7H, Ar, pyrazole); 9.80 ppm (br s, 1H). MS *m/z*: 389 (M^+, 10). Anal. Calcd for $C_{19}H_{14}F_3N_3O_3$: C 58.61; H 3.50; N 10.79; Found: C 58.73; H 3.72; N 10.58.

2-[(3-{[4-Chloro-2-butyl-5-(hydroxymethyl)-1*H*-imidazolyl]methyl}benzoyl)amino]benzoic acid (5a). (302 mg, 0.68 mmol, yield 90 %): ^{1}H NMR (CD_3COCD_3) δ 0.81 (t, 3H, *J* = 7.1 Hz, CH_3); 1.19-1.39 (m, 2H, CH_2); 1.51-1.66 (m, 2H, CH_2); 2.61 (d, 2H, *J* = 7.1 Hz, CH_2); 4.54 (s, 2H, CH_2OH); 5.47 (s, 2H, CH_2N); 7.21 (t, 1H, *J* = 8.0 Hz, Ar); 7.38 (d, 1H, *J* = 8.0 Hz, Ar); 7.54-7.71 (m, 2H, Ar); 7.79 (s, 1H, Ar); 7.93 (d, 1H, *J* = 7.2 Hz, Ar); 8.18 (d, 1H, *J* = 8.0 Hz, Ar); 8.88-8.93 (m, 1H, Ar); 12.29 ppm (br s, 1H). MS *m/z*: 441 (M^+, 3). Anal. Calcd for $C_{23}H_{24}ClN_3O_4$: C 62.52; H 5.44; N 9.51; Found: C 62.59; H 5.07; N 9.16.

3-[(3-{[4-Chloro-2-butyl-5-(hydroxymethyl)-1*H*-imidazolyl]methyl}benzoyl)amino]benzoic acid (5b). (134 mg, 0.30 mmol, yield 40 %): ^{1}H NMR (DMSO-d_6) δ 0.78 (t, 3H, *J* = 7.3 Hz, CH_3); 1.14-1.29 (m, 2H, CH_2); 1.39-1.49 (m, 2H, CH_2); 2.45-2.51 (m, 2H, CH_2); 4.34 (s, 2H, CH_2OH); 5.35 (s, 2H, CH_2N); 7.21 (d, 1H, *J* = 8.2 Hz, Ar); 7.44-7.55 (m, 2H, Ar); 7.66-7.74 (m, 2H, Ar); 7.91 (d, 1H, *J* = 7.5 Hz, Ar); 8.02 (d, 1H, *J* = 7.7 Hz, Ar); 8.39 (s, 1H, Ar); 10.45 ppm (br s, 1H, NH). MS *m/z*: 441 (M^+, 6). Anal. Calcd for $C_{23}H_{24}ClN_3O_4$: C 62.52; H 5.44; N 9.51; Found: C 62.54; H 5.16; N 9.09.

4-[(3-{[4-Chloro-2-butyl-5-(hydroxymethyl)-1*H*-imidazolyl]methyl}benzoyl)amino]benzoic acid (5c). (185 mg, 0.42 mmol, yield 55 %): IR: 1702 (C=O of acid), 1648 (C=O of amide) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 0.78 (t, 3H, *J* = 7.1 Hz, CH_3); 1.14-1.29 (m, 2H, CH_2); 1.39-1.50 (m, 2H, CH_2); 2.38-2.46 (m, 2H, CH_2); 4.34 (s, 2H, CH_2OH); 5.35 (s, 2H, CH_2N); 7.22 (d, 1H, *J* = 7.5 Hz, Ar); 7.52 (t, 1H, *J* = 7.5 Hz, Ar); 7.72 (s, 1H, Ar); 7.87-7.96 (m, 5H, Ar); 10.55 ppm (br s, 1H, NH). ^{13}C NMR (CD_3COCD_3): δ 167.29; 166.31; 148.78; 144.31; 141.49; 138.65; 136.43; 132.59; 131.37; 130.42; 129.78; 127.44; 126.93; 126.54; 120.30; 53.15; 47.94; 30.35; 27.14; 22.90; 14.02. MS *m/z*: 441 (M^+, 25). Anal. Calcd for $C_{23}H_{24}ClN_3O_4$: C 62.52; H 5.44; N 9.51; Found: C 62.52; H 5.44; N 9.51.

2-{[3-[(4-Chloro-2-butyl-5-carboxy-1*H*-imidazolyl)methyl]benzoyl]amino}benzoic acid (6a). (273 mg, 0.60 mmol, yield 79 %): ^{1}H NMR (DMSO-d_6) δ 0.79 (t, 3H, *J* = 7.1 Hz, CH_3); 1.21-1.31 (m, 2H, CH_2); 1.48-1.57 (m, 2H, CH_2); 2.64 (d, 2H, *J* = 7.0 Hz, CH_2); 5.69 (s, 2H, CH_2N); 7.18-7.28 (m, 2H, Ar); 7.53-7.68 (m, 3H, Ar); 7.84 (d, 1H, *J* = 7.5 Hz, Ar); 8.06 (d, 1H, *J* = 8.0 Hz, Ar); 8.67 (d, 1H, *J* = 8.4 Hz, Ar); 12.13 ppm (br s, 1H). MS *m/z*: 441 (M^+,11). Anal. Calcd for $C_{23}H_{22}ClN_3O_5$: C 60.60; H 4.83; N 9.22; Found: C 60.28; H 5.15; N 9.53.

3-{[3-[(4-Chloro-2-butyl-5-carboxy-1*H*-imidazolyl)methyl]benzoyl]amino}benzoic acid (6b). (180 mg, 0.39 mmol, yield 52 %): IR: 1682 (C=O of acid), 1643 (C=O of amide) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 0.79 (t, 3H, *J* = 7.1 Hz, CH_3); 1.20-1.31 (m, 2H, CH_2); 1.46-1.57 (m, 2H, CH_2); 2.62 (d, 2H, *J* = 7.1 Hz, CH_2); 5.68 (s, 2H, CH_2N); 7.15 (d, 1H, *J* = 7.7 Hz, Ar); 7.44-7.58 (m, 3H, Ar); 7.67-7.70 (m, 2H, Ar); 7.91 (d, 1H, *J* = 7.9 Hz, Ar); 8.02 (d, 1H, *J* = 7.1 Hz, Ar); 8.38 (br s, 1H); 10.45 ppm (br s, 1H). ^{13}C NMR (CD_3COCD_3): δ 167.38; 166.07; 160.74; 153.36;

140.34; 138.80; 137.27; 136.50; 132.06; 130.09; 129.73; 129.64; 127.23; 126.76; 125.74; 125.34; 122.21; 118.15; 49.01; 30.00; 27.31; 22.90; 13.98. MS *m/z*: 441 (M^+,20). Anal. Calcd for $C_{23}H_{22}ClN_3O_5$: C 60.60; H 4.83; N 9.22; Found: C 60.72; H 4.76; N 8.90.

4-{[3-[(4-Chloro-2-butyl-5-carboxy-1*H*-imidazolyl)methyl]benzoyl]amino}benzoic acid (6c). (190 mg, 0.42 mmol, yield 55 %): ^{1}H NMR (DMSO-d_6) δ 0.80 (t, 3H, *J* = 7.1 Hz, CH_3); 1.18-1.32 (m, 2H, CH_2); 1.46-1.57 (m, 2H, CH_2); 2.63 (d, 2H, *J* = 7.1 Hz, CH_2); 5.68 (s, 2H, CH_2N); 7.17 (d, 1H, *J* = 7.3 Hz, Ar); 7.49-7.58 (m, 1H, Ar); 7.66 (s, 1H, Ar); 7.87-7.96 (m, 4H, Ar); 8.02 (d, 1H, *J* = 7.1 Hz, Ar); 10.57 ppm (br s, 1H). MS *m/z*: 441 (M^+,9). Anal. Calcd for $C_{23}H_{22}ClN_3O_5$: C 60.60; H 4.83; N 9.22; Found: C 60.35; H 5.20; N 9.16.

2-[(3-{[3-(Trifluoromethyl)-1*H*-pyrazolyl]methyl}benzoyl)amino]benzoic acid (7a). (180 mg, 0.46 mmol, yield 61 %): ^{1}H NMR (DMSO-d_6) δ 5.56 (s, 2H, CH_2N); 6.78 (d, 1H, *J* = 2.0 Hz, pyrazole); 7.18-7.25 (m, 1H, Ar); 7.50-7.70 (m, 3H, Ar, pyrazole); 7.88-7.91 (m, 2H, Ar); 8.06 (dd, 1H, *J* = 1.4, 8.1 Hz, Ar); 8.16 (d, 1H, *J* = 1.4 Hz, Ar); 8.68 ppm (d, 1H, *J* = 7.5 Hz, Ar). MS *m/z*: 389 (M^+, 15); 137 (M^+-HNPhCOOH, 100). Anal. Calcd for $C_{19}H_{14}F_3N_3O_3$: C 58.61; H 3.50; N 10.79; Found: C 58.42; H 3.65; N 10.73.

3-[(3-{[3-(Trifluoromethyl)-1*H*-pyrazolyl]methyl}benzoyl)amino]benzoic acid (7b). (130 mg, 0.33 mmol, yield 44 %): IR: 1689 (C=O of acid), 1645 (C=O of amide) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 5.54 (s, 2H, CH_2N); 6.76-6.80 (m, 1H, pyrazole); 7.44-7.58 (m, 3H, Ar, pyrazole); 7.51 (d, 1H, *J* = 7.7 Hz, Ar); 7.91-8.05 (m, 3H, Ar); 8.15 (s, 1H, Ar); 8.39 ppm (s, 1H, Ar). MS *m/z*: 389 (M^+, 12); 137 (M^+-HNPhCOOH, 100). ^{13}C NMR (CD_3COCD_3): δ 167.40; 166.11; 144.44; 140.45; 137.87; 137.27; 136.65; 132.82; 131.99; 131.10; 129.78; 129.67; 128.31; 128.00; 125.78; 125.38; 122.28; 105.35; 56.71. MS *m/z*: 389 (M^+,17). Anal. Calcd for $C_{19}H_{14}F_3N_3O_3$: C 58.61; H 3.50; N 10.79; Found: C 58.75; H 3.28; N 10.89.

4-[(3-{[3-(Trifluoromethyl)-1*H*-pyrazolyl]methyl}benzoyl)amino]benzoic acid (7c). (124 mg, 0.32 mmol, yield 42 %): ^{1}H NMR (DMSO-d_6) δ 5.54 (s, 2H, CH_2N); 6.77-6.80 (m, 1H, pyrazole); 7.46-7.60 (m, 2H, Ar); 7.86-7.93 (m, 6H, Ar); 8.14-8.16 ppm (m, 1H, pyrazole). MS *m/z*: 389 (M^+, 58). Anal. Calcd for $C_{19}H_{14}F_3N_3O_3$: C 58.61; H 3.50; N 10.79; Found: C 58.34; H 3.15; N 10.94.

General procedure for the preparation of compounds 9a-c

Thionyl chloride (1.60 mL, 22.00 mmol) was added dropwise to a solution of the opportune aminobenzoic acid **8a-c** (2.00 g; 15.00 mmol) in EtOH absolute (23 mL), cooled at 0 °C. The resulting mixture was refluxed for 48h, then the solvent was evaporated and the aqueous phase was extracted with AcOEt. The organic phase was washed with aqueous KOH, dried over $NaSO_4$ and the solvent evaporated to give **9a-c**.

Ethyl 2-aminobenzoate (9a). (1.61 g, 9.75 mmol, yield 65 %) from **8a**: ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3H, *J* = 7.1 Hz, CH_3); 4.33 (q, 2H, *J* = 7.1 Hz, CH_2); 6.07-6.69 (m, 2H, Ar); 7.22-7.31 (m, 1H, Ar); 7.87 ppm (d, 1H, *J* = 8.4 Hz, Ar). Anal. Calcd for $C_9H_{11}NO_2$: C 65.45; H 6.71; N 8.48; Found: C 65.06; H 6.53; N 7.92.

Ethyl 3-aminobenzoate (9b). (2.23 g, 13.50 mmol, yield 90 %) from **8b**: ^{1}H NMR ($CDCl_3$) δ 1.36 (t, 3H, *J* = 7.1 Hz, CH_3); 4.33 (q, 2H, *J* = 7.1 Hz, CH_2); 6.81-6.87 (m, 1H, Ar); 7.19 (t, 1H, *J* = 7.8 Hz, Ar); 7.35 (s, 1H, Ar); 7.39 ppm (d, 1H, *J* = 7.7 Hz, Ar). Anal. Calcd for $C_9H_{11}NO_2$: C 65.45; H 6.71; N 8.48; Found: C 65.23; H 6.60; N 8.02.
Ethyl 4-aminobenzoate (9c). (1.04 g, 6.30 mmol, yield 42 %) from **8c**: ^{1}H NMR (DMSO-d_6) δ 1.28 (t, 3H, *J* = 7.1 Hz, CH_3); 4.23 (q, 2H, *J* = 7.1 Hz, CH_2); 6.87 (d, 2H, *J* = 8.6 Hz, AA'XX'); 7.77 ppm (d, 2H, *J* = 8.6 Hz, AA'XX'). Anal. Calcd for $C_9H_{11}NO_2$: C 65.45; H 6.71; N 8.48; Found: C 65.31; H 6.48; N 8.25.

General procedure for the preparation of compounds 12a-c and 13a-c
A solution of the opportune amine **9a-c** (0.45 g; 2.51 mmol) and triethylamine (1 mL) in CH_2Cl_2 (5 mL) was added dropwise to a solution of 4-(chloromethyl)benzoyl chloride **10** (or of 3-(chloromethyl)benzoylchloride **11**) (0.47 g; 2.51 mmol) in CH_2Cl_2 (3 ml). The reaction mixture was stirred at room temperature for 20h, and then washed with 1N HCl and 1N NaOH. The solvent was dried and evaporated to give the amide **12a-c, 13a-c**.
Ethyl-2-[(4-chloromethyl-benzoyl)amino]-benzoate (12a). (438 mg, 1.38 mmol, 55 %) from **9a** and **10**: ^{1}H NMR ($CDCl_3$) δ 1.44 (t, 3H, *J* = 7.1 Hz, CH_3); 4.43 (q, 2H, *J* = 7.1 Hz, CH_2); 4.65 (s, 2H, CH_2Cl); 7.14 (t, 1H, *J* = 7.7 Hz, Ar); 7.53-7.65 (m, 3H, Ar); 8.03-8.17 (m, 3H, Ar); 8.92 (d, 1H, *J* = 8.4, Ar); 12.13 ppm (br s, 1H, NH). Anal. Calcd for $C_{17}H_{16}ClNO_3$: C 64.26; H 5.04; N 4.40; Found: C 64.19; H 4.80; N 4.32.
Ethyl-3-[(4-chloromethyl-benzoyl)amino]-benzoate (12b). (295 mg, 0.93 mmol, 37 %) from **9b** and **10**: ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3H, *J* = 7.1 Hz, CH_3); 4.36 (q, 2H, *J* = 7.1 Hz, CH_2); 4.64 (s, 2H, CH_2Cl); 7.42-7.50 (m, 1H, Ar); 7.52 (d, 2H, *J* = 8.1 Hz, AA'XX'); 7.82-7.87 (m, 1H, Ar); 7.88 (d, 2H, *J* = 8.1 Hz, AA'XX'); 8.00-8.11 ppm (m, 2H, Ar). Anal. Calcd for $C_{17}H_{16}ClNO_3$: C 64.26; H 5.04; N 4.40; Found: C 63.89; H 5.40; N 4.09.
Ethyl-4-[(4-chloromethyl-benzoyl)amino]-benzoate (12c). (318 mg, 1.00 mmol, 40 %) from **9c** and **10**: ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3H, *J* = 7.1 Hz, CH_3); 4.37 (q, 2H, *J* = 7.1 Hz, CH_2); 4.64 (s, 2H, CH_2Cl); 7.52 (d, 2H, *J* = 8.2 Hz, AA'XX'); 7.74 (d, 2H, *J* = 8.7 Hz, AA'XX'); 7.87 (d, 2H, *J* = 8.2 Hz, AA'XX'); 8.07 ppm (d, 2H, *J* = 8.7 Hz, AA'XX'). Anal. Calcd for $C_{17}H_{16}ClNO_3$: C 64.26; H 5.04; N 4.40; Found: C 64.07; H 5.21; N 4.46.
Ethyl-2-[(3-chloromethyl-benzoyl)amino]benzoate (13a). (183 mg, 0.58 mmol, 23 %) from **9a** and **11**: ^{1}H NMR ($CDCl_3$) δ 1.44 (t, 3H, *J* = 7.1 Hz, CH_3); 4.43 (q, 2H, *J* = 7.1 Hz, CH_2); 4.68 (s, 2H, CH_2Cl); 7.14 (dt, 2H, *J* = 1.2, 8.5 Hz, Ar); 7.49-7.65 (m, 3H, Ar); 7.98 (m, 1H, Ar); 8.08-8.13 (m, 2H, Ar); 8.91 (dd, 1H, *J* = 1.0, 8.5 Hz, Ar); 12.12 ppm (br s, 1H). Anal. Calcd for $C_{17}H_{16}ClNO_3$: C 64.26; H 5.04; N 4.40; Found: C 64.10; H 5.32; N 4.57.
Ethyl-3-[(3-chloromethyl-benzoyl)amino]benzoate (13b). (318 mg, 1.00 mmol, 40 %) from **9b** and **11**: ^{1}H NMR ($CDCl_3$) δ 1.36 (t, 3H, *J* = 7.1 Hz, CH_3); 4.33 (q, 2H, *J* = 7.1 Hz, CH_2); 4.60 (s, 2H, CH_2Cl); 7.38-7.47 (m, 2H, Ar); 7.53-7.57 (m, 1H, Ar); 7.79-7.84 (m, 2H, Ar); 7.90 (s, 1H, Ar); 8.04-8.09 (m, 1H, Ar); 8.16 (s, 1H, Ar); 8.38 ppm (br s, 1H, NH). Anal. Calcd for $C_{17}H_{16}ClNO_3$: C 64.26; H 5.04; N 4.40; Found: C 64.33; H 5.25; N 4.73.

Ethyl-4-[(3-chloromethyl-benzoyl)amino]benzoate (13c). (358 mg, 1.13 mmol, 45 %) from **9c** and **11**: ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3H, *J* = 7.1 Hz, CH_3); 4.37 (q, 2H, *J* = 7.1 Hz, CH_2); 4.65 (s, 2H, CH_2Cl); 7.46-7.62 (m, 2H, Ar); 7.75 (d, 2H, *J* = 8.6 Hz, AA'XX'); 7.81-7.85 (m, 1H, Ar); 7.91 (s, 1H, Ar); 8.07 ppm (d, 2H, *J* = 8.6 Hz, AA'XX'). Anal. Calcd for $C_{17}H_{16}ClNO_3$: C 64.26; H 5.04; N 4.40; Found: C 64.01; H 5.39; N 4.45.

General procedure for the preparation of compounds 15a-c, **16a-c**

To a solution of the opportune arilmethylchloride **12a-c, 13a-c** (0.25 g, 0.75 mmol) in DMAC (2.1 mL) was added 2-butyl-4-chloro-5-formil-imidazole **14** (0.14 g; 0.76 mmol) dissolved in DMAC (0.85 ml). The resulting solution was cooled to –10°C and K_2CO_3 (99 mg; 0.72 mmol) was added. The mixture was stirred at room temperature for 12h, then the suspension was filtered and the solvent evaporated to give compounds **15a-c**, **16a-c**.

Ethyl-2-{[4-((2-butyl-4-chloro-5-formyl-1*H*-imidazolyl)methyl)benzoyl]amino}benzoate (15a). Purified by column chromatography eluting with AcOEt/*n*-hexane (8:2) afforded **15a** (89 mg, 0.19 mmol, yield 25 %) from **12a**: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 7.2 Hz, CH_3); 1.25-1.37 (m, 2H, CH_2); 1.42 (t, 3H, *J* = 7.1 Hz, CH_3); 1.61-1.75 (m, 2H, CH_2); 2.58-2.66 (m, 2H, CH_2); 4.40 (q, 2H, *J* = 7.1 Hz, CH_2); 5.63 (s, 2H, CH_2N); 7.09-7.20 (m, 3H, Ar); 7.56- 7.64 (m, 1H, Ar); 8.02 (d, 2H, *J* = 8.1 Hz, Ar); 8.08-8.12 (m, 1H, Ar); 8.90 (d, 1H, *J* = 8.6 Hz, Ar); 9.76 (s, 1H, CHO); 12.12 ppm (br s, 1H, NH). MS *m/z*: 389 (M^+,17). Anal. Calcd for $C_{25}H_{26}ClN_3O_4$: C 64.17; H 5.56; N 8.98; Found: C 64.05; H 5.71; N 8.83.

Ethyl-3-{[4-((2-butyl-4-chloro-5-formyl-1*H*-imidazolyl)methyl)benzoyl]amino}benzoate (15b). (316 mg, 0.67 mmol, yield 90 %) from **12b**: ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, *J* = 7.3 Hz, CH_3); 1.24-1.37 (t, 3H, *J* = 7.1 Hz, CH_3); 1.41 (m, 2H, CH_2); 1.60-1.75 (m, 2H, CH_2); 2.60 (t, 2H, *J* = 7.6 Hz, CH_2); 4.35 (q, 2H, *J* = 7.1 Hz, CH_2); 5.58 (s, 2H, CH_2N); 7.10 (d, 2H, *J* = 7.8 Hz, Ar); 7.42 (t, 1H, *J* = 7.9 Hz, Ar); 7.78-7.87 (m, 3H, Ar); 8.05 (d, 1H, *J* = 8.1 Hz, Ar); 8.13 (d, 1H, *J* = 1.3 Hz, Ar); 8.42 (s, 1H, CHO); 9.73 ppm (br s, 1H, NH). Anal. Calcd for $C_{25}H_{26}ClN_3O_4$: C 64.17; H 5.56; N 8.98; Found: C 63.77; H 5.96; N 8.50.

Ethyl-4-{[4-((2-butyl-4-chloro-5-formyl-1*H*-imidazolyl)methyl)benzoyl]amino}benzoate (15c). (316 mg, 0.67 mmol, yield 90 %) from **12c**: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 7.2 Hz, CH_3); 1.24-1.39 (t, 3H, *J* = 7.1 Hz, CH_3); 1.42 (m, 2H, CH_2); 1.61-1.79 (m, 2H, CH_2); 2.56-2.65 (m, 2H, CH_2); 4.35 (q, 2H, *J* = 7.1 Hz, CH_2N); 5.59 (s, 2H, CH_2); 7.12 (d, 2H, *J* = 8.1 Hz, AA'XX'); 7.50 (d, 2H, *J* = 7.8 Hz, AA'XX'); 7.84 (d, 2H, *J* = 7.8 Hz, AA'XX'); 8.04 (d, 2H, *J* = 8.1 Hz, AA'XX'); 9.73 ppm (s, 1H, CHO). Anal. Calcd for $C_{25}H_{26}ClN_3O_4$: C 64.17; H 5.56; N 8.98; Found: C 63.97; H 5.45; N 8.95.

Ethyl-2-{[3-((2-butyl-4-chloro-5-formyl-1*H*-imidazolyl)methyl)benzoyl]amino}benzoate (16a). Purified by crystallization from EtOH afforded **16a** (196 mg, 0.42 mmol, yield 56 %) from **13a**: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, *J* = 7.3 Hz, CH_3); 1.25-1.48 (m, 2H, CH_2); 1.44 (t, 3H, *J* = 7.1 Hz, CH_3); 1.58-1.76 (m, 2H, CH_2); 2.66 (t, 2H, *J* = 7.3 Hz, CH_2); 4.44 (q, 2H, *J* = 7.1 Hz, CH_2); 5.65 (s, 2H, CH_2N); 7.33 (t, 1H, *J* = 7.9 Hz, Ar); 7.26-7.30 (m, 1H, Ar); 7.47- 7.64 (m, 2H, Ar); 7.72 (s, 1H, Ar); 7.98 (d, 1H, *J* = 7.9 Hz); 8.10 (dd, 1H, *J* = 1.6, 8.1 Hz, Ar); 8.89 (d,

1H, *J* = 8.4 Hz, Ar); 9.79 (s, 1H, CHO); 12.11 ppm (br s, 1H, NH). Anal. Calcd for $C_{25}H_{26}ClN_3O_4$: C 64.17; H 5.56; N 8.98; Found: C 64.31; H 5.68; N 8.75.

Ethyl-3-{[3-((2-butyl-4-chloro-5-formyl-1*H*-imidazolyl)methyl)benzoyl]amino}benzoate (16b). (284 mg, 0.61 mmol, yield 80 %) from **13b**: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, *J* = 7.1 Hz, CH_3); 1.23-1.41 (m, 2H, CH_2); 1.37 (t, 3H, *J* = 7.1 Hz, CH_3); 1.55-1.71 (m, 2H, CH_2); 2.62 (t, 2H, *J* = 7.3 Hz, CH_2); 4.35 (q, 2H, *J* = 7.1 Hz, CH_2); 5.57 (s, 2H, CH_2N); 7.12 (d, 1H, *J* = 7.7 Hz, Ar); 7.37-7.46 (m, 3H, Ar); 7.73- 7.82 (m, 2H, Ar); 8.05 (d, 1H, *J* = 8.1 Hz, Ar); 8.15 (s, 1H, Ar); 8.77 (br s, 1H, NH); 9.20 ppm (s, 1H, CHO). Anal. Calcd for $C_{25}H_{26}ClN_3O_4$: C 64.17; H 5.56; N 8.98; Found: C 64.09; H 5.34; N 8.85.

Ethyl-4-{[3-((2-butyl-4-chloro-5-formyl-1*H*-imidazolyl)methyl)benzoyl]amino}benzoate (16c). (316 mg, 0.67 mmol, yield 90 %) from **13c**: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 7.1 Hz, CH_3); 1.33-1.43 (m, 2H, CH_2); 1.39 (t, 3H, *J* = 7.1 Hz, CH_3); 1.65-1.74 (m, 2H, CH_2); 2.58-3.68 (m, 2H, CH_2); 4.37 (q, 2H, *J* = 7.1 Hz, CH_2); 5.60 (s, 2H, CH_2N); 7.12 (d, 1H, *J* = 8.1 Hz, Ar); 7.40-7.52 (m, 2H, Ar); 7.74 (d, 2H, *J* = 8.7 Hz, AA'XX'); 8.05 (d, 2H, *J* = 8.7 Hz, AA'XX'); 8.37 (s, 1H, Ar); 9.74 ppm (s, 1H, CHO). Anal. Calcd for $C_{25}H_{26}ClN_3O_4$: C 64.17; H 5.56; N 8.98; Found: C 64.23; H 5.31; N 8.79.

General procedure for the preparation of compounds 19a-c, **20a-c**

A solution of $NaClO_2$ (531 mg, 5.87 mmol) and NaH_2PO_4 (534 mg, 4.45 mmol) in H_2O (5.0 mL) was added dropwise to a solution of compound **15a-c, 16a-c** (300 mg, 0.64 mmol) in t-BuOH (5.0 mL). The mixture was stirred for 7 h at room temperature, then AcOEt was added and the organic phase was separated and washed with H_2O and NaCl. The organic phase was evaporated obtained a residue that was dissolved in AcOEt and extracted with $NaHCO_3$. The aqueous layer was acidified to pH=3 with 1N HCl and extracted with AcOEt. The organic phase was dried over $NaSO_4$ and the solvent was evaporated to yield **19a-c, 20a-c**.

Ethyl-2-{[4-((2-butyl-4-chloro-5-carboxy-1*H*-imidazolyl)methyl)benzoyl]amino}benzoate (19a). Purified by trituration with n-hexane afforded **19a** (161 mg, 0.33 mmol, 52% yield) from **15a**: mp 128-130 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, *J* = 7.1 Hz, CH_3); 1.28-1.45 (m, 2H, CH_2); 1.42 (t, 3H, *J* = 7.1 Hz, CH_3); 1.60-1.72 (m, 2H, CH_2); 2.62 (t, 2H, *J* = 7.5 Hz, CH_2); 4.42 (q, 2H, *J* = 7.1 Hz, CH_2); 5.62 (s, 2H, CH_2N); 7.09-7.16 (m, 3H, Ar); 7.59 (t, 1H, *J* = 7.1 Hz, Ar); 7.99-8.11 (m, 3H, Ar); 8.89 (d, 1H, *J* = 8.4 Hz, Ar); 12.11 ppm (br s, 1H, NH). Anal. Calcd for $C_{25}H_{26}ClN_3O_5$: C 62.05; H 5.38; N 8.69; Found: C 61.96; H 5.56; N 8.39.

Ethyl-3-{[4-((2-butyl-4-chloro-5-carboxy-1*H*-imidazolyl)methyl)benzoyl]amino}benzoate (19b). (263 mg, 0.54 mmol, 85% yield) from **15b**: mp 72-74 °C; ^{1}H NMR (DMSO-d_6) δ 0.81 (t, 3H, *J* = 7.3 Hz, CH_3); 1.23-1.36 (m, 2H, CH_2); 1.33 (t, 3H, *J* = 7.1 Hz, CH_3); 1.47-1.59 (m, 2H, CH_2); 2.62 (t, 2H, *J* = 7.1 Hz, CH_2); 4.33 (q, 2H, *J* = 7.1 Hz, CH_2); 5.67 (s, 2H, CH_2N); 7.14 (d, 2H, *J* = 8.3 Hz, AA'XX'); 7.50 (t, 1H, *J* = 8.0 Hz, Ar); 7.69 (d, 1H, *J* = 8.0 Hz, Ar); 7.93 (d, 2H, *J* = 8.3 Hz, AA'XX'); 8.04-8.08 (m, 1H, Ar); 8.40-8.42 (m, 1H, Ar); 10.45 ppm (br s, 1H, NH). Anal. Calcd for $C_{25}H_{26}ClN_3O_5$: C 62.05; H 5.38; N 8.69; Found: C 62.10; H 5.02; N 8.41.

Ethyl-4-{[4-((2-butyl-4-chloro-5-carboxy-1*H*-imidazolyl)methyl)benzoyl]amino}benzoate (19c). (139 mg, 0.29 mmol, 45% yield) from **15c**: mp 155-158 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, *J* = 7.3 Hz, CH_3); 1.25-1.43 (m, 2H, CH_2); 1.39 (t, 3H, *J* = 7.1 Hz, CH_3); 1.60-1.70 (m, 2H, CH_2); 2.62 (t, 2H, *J* = 7.6 Hz, CH_2); 4.36 (q, 2H, *J* = 7.1 Hz, CH_2); 5.58 (s, 2H, CH_2N); 7.07 (d, 2H, *J* = 7.8 Hz, AA'XX'); 7.72 (d, 2H, *J* = 8.5 Hz, AA'XX'); 7.82 (d, 2H, *J* = 7.8 Hz, AA'XX'); 8.02 (d, 2H, *J* = 8.5 Hz, AA'XX'); 8.25 ppm (br s, 1H, NH). Anal. Calcd for $C_{25}H_{26}ClN_3O_5$: C 62.05; H 5.38; N 8.69; Found: C 61.81; H 5.23; N 8.65.

Ethyl-2-{[3-((2-butyl-4-chloro-5-carboxy-1*H*-imidazolyl)methyl)benzoyl]amino}benzoate (20a). (133 mg, 0.27 mmol, 43% yield) from **16a**: mp 137-139 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H, *J* = 7.1 Hz, CH_3); 1.27-1.45 (m, 2H, CH_2); 1.41 (t, 3H, *J* = 7.1 Hz, CH_3); 1.59-1.72 (m, 2H, CH_2); 2.65 (t, 2H, *J* = 7.5 Hz, CH_2); 4.43 (q, 2H, *J* = 7.1 Hz, CH_2); 5.63 (s, 2H, CH_2N); 7.08-7.25 (m, 2H, Ar); 7.48 (t, 1H, *J* = 7.9 Hz, Ar); 7.58-7.60 (m, 1H, Ar); 7.73 (d, 1H, *J* = 1.6 Hz, Ar); 7.96 (d, 1H, *J* = 7.9 Hz, Ar); 8.08 (dd, 1H, *J* = 1.6, 8.0 Hz, Ar); 8.88 (d, 1H, *J* = 8.6 Hz, Ar); 12.11 ppm (br s, 1H, NH). Anal. Calcd for $C_{25}H_{26}ClN_3O_5$: C 62.05; H 5.38; N 8.69; Found: C 61.93; H 5.24; N 8.52.

Ethyl-3-{[3-((2-butyl-4-chloro-5-carboxy-1*H*-imidazolyl)methyl)benzoyl]amino}benzoate (20b). (195 mg, 0.40 mmol, 63% yield) from **16b**: ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, *J* = 7.1 Hz, CH_3); 1.25-1.42 (m, 2H, CH_2); 1.38 (t, 3H, *J* = 7.1 Hz, CH_3); 1.59-1.72 (m, 2H, CH_2); 2.63 (t, 2H, *J* = 7.5 Hz, CH_2); 4.36 (q, 2H, *J* = 7.1 Hz, CH_2); 5.56 (s, 2H, CH_2N); 7.05 (d, 1H, *J* = 7.1 Hz, Ar); 7.35-7.47 (m, 2H, Ar); 7.68-7.83 (m, 3H, Ar); 7.94-8.11 (m, 2H, Ar); 8.24 ppm (br s, 1H, NH). Anal. Calcd for $C_{25}H_{26}ClN_3O_5$: C 62.05; H 5.38; N 8.69; Found: C 62.40; H 5.27; N 8.67.

Ethyl-4-{[3-((2-butyl-4-chloro-5-carboxy-1*H*-imidazolyl)methyl)benzoyl]amino}benzoate (20c). (174 mg, 0.36 mmol, 56% yield) from **16c**: mp 85-90 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 7.3 Hz, CH_3); 1.22-1.44 (m, 2H, CH_2); 1.40 (t, 3H, *J* = 7.1 Hz, CH_3); 1.62-1.73 (m, 2H, CH_2); 2.65 (t, 2H, *J* = 7.8 Hz, CH_2); 4.38 (q, 2H, *J* = 7.1 Hz, CH_2); 5.57 (s, 2H, CH_2N); 7.08 (d, 1H, *J* = 7.2 Hz, Ar); 7.42 (t, 1H, *J* = 7.2 Hz, Ar); 7.66-7.78 (m, 4H, Ar); 8.04 (d, 2H, *J* = 7.3 Hz, Ar); 8.20 ppm (br s, 1H, NH). Anal. Calcd for $C_{25}H_{26}ClN_3O_5$: C 62.05; H 5.38; N 8.69; Found: C 61.86; H 5.50; N 8.70.

General procedure for the preparation of compounds 17a-c, **18a-c**

Sodium borohydride (8.4 mg; 0.22 mmol) was added to a solution of the opportune aldehyde **15a-c, 16a-c** (0.36 g; 0.75 mmol) in MeOH (1.60 mL) cooled to -10°C. The resulting solution was stirred at -10°C for 30 min. and then was allowed to warm to room temperature. After 30 min. the mixture was quenched by addition of 50% CH_3COOH (0.03 mL) and the resulting emulsion was extracted with AcOEt. The organic layer was washed with H_2O, dried and evaporated to give crude product **17a-c**, **18a-c**

Ethyl-2-{[4-((2-butyl-4-chloro-5-hydroxymethyl-1*H*-imidazolyl)methyl)benzoyl]amino} benzoate (17a). Purified by column chromatography eluting with AcOEt/*n*-hexane (8:2) afforded **17a** (317 mg, 0.67 mmol, yield 90 %) from **15a**: ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H, *J* = 7.1

Hz, CH_3); 1.21-1.33 (m, 2H, CH_2); 1.42 (t, 3H, *J* = 7.1 Hz, CH_3); 1.55-1.71 (m, 2H, CH_2); 2.54 (t, 2H, *J* = 7.7 Hz, CH_2); 4.40 (q, 2H, *J* = 7.1 Hz, CH_2); 4.49 (s, 2H, CH_2OH); 5.29 (s, 2H, CH_2N); 7.08-7.15 (m, 1H, Ar); 7.13 (d, 2H, *J* = 8.2 Hz, AA'XX'); 7.56-7.60 (m, 1H, Ar); 8.00 (d, 2H, *J* = 8.2 Hz, AA'XX'); 8.07-8.12 (m, 1H, Ar); 8.89 (d, 1H, *J* = 8.4 Hz, Ar); 12.13 ppm (br s, 1H, NH). MS *m/z*: 470 (M^+, 8). Anal. Calcd for $C_{25}H_{28}ClN_3O_4$: C 63.96; H 5.96; N 8.94; Found: C 63.58; H 6.09; N 9.00.

Ethyl-3-{[4-((2-butyl-4-chloro-5-hydroxymethyl-1*H*-imidazolyl)methyl)benzoyl]amino} benzoate (17b). Purified by crystallization from AcOEt/n-hexane (169 mg, 0.36 mmol, yield 48 %) from **15b**: ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3H, *J* = 7.1 Hz, CH_3); 1.20-1.31 (m, 2H, CH_2); 1.38 (t, 3H, *J* = 7.1 Hz, CH_3); 1.53-1.72 (m, 2H, CH_2); 2.50 (t, 2H, *J* = 7.7 Hz, CH_2); 4.40 (q, 2H, *J* = 7.1 Hz, CH_2); 4.49 (s, 2H, CH_2OH); 5.27 (s, 2H, CH_2N); 7.07 (d, 2H, *J* = 7.8 Hz, Ar); 7.43 (t, 1H, *J* = 8.1 Hz, Ar); 7.80-7.90 (m, 3H, Ar); 8.05 (d, 1H, *J* = 8.1 Hz, Ar); 8.12 (s, 1H, Ar); 8.37 ppm (br s, 1H, NH). MS *m/z*: 470 (M^+, 10). Anal. Calcd for $C_{25}H_{28}ClN_3O_4$: C 63.96; H 5.96; N 8.94; Found: C 63.76; H 5.96; N 9.13.

Ethyl-4-{[4-((2-butyl-4-chloro-5-hydroxymethyl-1*H*-imidazolyl)methyl)benzoyl]amino} benzoate (17c). Purified by crystallization from AcOEt/n-hexane to give **17c** (183 mg, 0.39 mmol, 52 %) from **15c**: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, *J* = 7.2 Hz, CH_3); 1.22-1.36 (m, 2H, CH_2); 1.40 (t, 3H, *J* = 7.1 Hz, CH_3); 1.65-1.73 (m, 2H, CH_2); 2.53 (t, 2H, *J* = 7.1 Hz, CH_2); 4.37 (q, 2H, *J* = 7.1 Hz, CH_2); 4.51 (s, 2H, CH_2OH); 5.29 (s, 2H, CH_2N); 7.11 (d, 2H, *J* = 8.2 Hz, AA'XX'); 7.73 (d, 2H, *J* = 8.7 Hz, AA'XX'); 7.86 (d, 2H, *J* = 8.7 Hz, AA'XX'); 8.06 ppm (d, 2H, *J* = 8.2 Hz, AA'XX'). MS *m/z*: 470 (M^+, 15). Anal. Calcd for $C_{25}H_{28}ClN_3O_4$: C 63.96; H 5.96; N 8.94; Found: C 64.24; H 5.75; N 8.99.

Ethyl-2-{[3-((2-butyl-4-chloro-5-hydroxymethyl-1*H*-imidazolyl)methyl)benzoyl]amino} benzoate (18a). Purified by crystallization from AcOEt/n-hexane (144 mg, 0.31 mmol, yield 41 %) from **16a**: mp 89-91 °C; IR: 1670 (C=O of ester); 1600 (C=O of amide) cm^{-1}. ^{1}HNMR ($CDCl_3$) δ 0.83 (t, 3H, *J* = 7.3 Hz, CH_3); 1.20-1.35 (m, 2H, CH_2); 1.46 (t, 3H, *J* = 7.1 Hz, CH_3); 1.55-1.68 (m, 2H, CH_2); 2.49 (t, 2H, *J* = 7.9 Hz, CH_2); 4.46 (q, 2H, *J* = 7.1 Hz, CH_2); 4.62 (s, 2H, CH_2OH); 5.29 (s, 2H, CH_2N); 7.13 (t, 1H, *J* = 7.9 Hz, Ar); 7.30 (d, 1H, *J* = 7.9 Hz, Ar); 7.48-7.65 (m, 3H, Ar); 8.00 (d, 1H, *J* = 7.5 Hz, Ar); 8.10 (d, 1H, *J* = 7.9 Hz, Ar); 8.90 (d, 1H, *J* = 8.2 Hz, Ar); 12.01 ppm (br s, 1H, NH). MS *m/z*: 470 (M^+, 34). Anal. Calcd for $C_{25}H_{28}ClN_3O_4$: C 63.96; H 5.96; N 8.94; Found: C 63.76; H 6.21; N 9.24.

Ethyl-3-{[3-((2-butyl-4-chloro-5-hydroxymethyl-1*H*-imidazolyl)methyl)benzoyl]amino} benzoate (18b). Purified by crystallization from AcOEt/n-hexane offered **18b** (194 mg, 0.41 mmol, yield 55 %) from **16b**: mp 102-104 °C; ^{1}HNMR ($CDCl_3$) δ 0.79 (t, 3H, *J* = 7.3 Hz, CH_3); 1.16-1.31 (m, 2H, CH_2); 1.38 (t, 3H, *J* = 7.1 Hz, CH_3); 1.46-1.64 (m, 2H, CH_2); 2.48 (t, 2H, *J* = 7.3 Hz, CH_2); 4.35 (q, 2H, *J* = 7.1 Hz, CH_2); 4.51 (s, 2H, CH_2OH); 5.23 (s, 2H, CH_2N); 7.16 (d, 1H, *J* = 7.5 Hz, Ar); 7.38- 7.47 (m, 2H, Ar); 7.74-7.86 (m, 3H, Ar); 8.01 (s, 1H, Ar); 8.08 (d, 1H, *J* = 8.4 Hz, Ar); 8.88 ppm (br s, 1H, NH). MS *m/z*: 470 (M^+, 100). Anal. Calcd for $C_{25}H_{28}ClN_3O_4$: C 63.96; H 5.96; N 8.94; Found: C 64.29; H 5.74; N 8.59.

Ethyl-4-{[3-((2-butyl-4-chloro-5-hydroxymethyl-1*H*-imidazolyl)methyl)benzoyl]amino} benzoate (**18c).** Purified by crystallization from AcOEt/n-hexane offered **18c** (282 mg, 0.60 mmol, yield 80 %) from **16c**: mp 45-47; ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3H, *J* = 7.1 Hz, CH_3); 1.22-1.42 (m, 2H, CH_2); 1.39 (t, 3H, *J* = 7.1 Hz, CH_3); 1.54-1.62 (m, 2H, CH_2); 2.46-2.57 (m, 2H, CH_2); 4.36 (q, 2H, *J* = 7.1 Hz, CH_2); 4.51 (s, 2H, CH_2OH); 5.21 (s, 2H, CH_2N); 7.14 (d, 1H, *J* = 6.8 Hz, Ar); 7.39-7.50 (m, 2H, Ar); 7.69-7.81 (m, 3H, Ar); 7.99-8.02 ppm (m, 2H, Ar). MS *m/z*: 470 (M^+, 48). Anal. Calcd for $C_{25}H_{28}ClN_3O_4$: C 63.96; H 5.96; N 8.94; Found: C 63.66; H 5.71; N 8.90.

General procedure for the preparation of compounds 22a-c and 23a-c

To a solution of 3-(trifluoromethyl)-1*H*-pyrazole **21** (85 mg; 0.63 mmol) in CH_3CN (2.5 ml) were added compound **12a-c, 13a-c** (0.20 g; 0.63 mmol), K_2CO_3 (0.13 g; 0.94 mmol) e KI (13 mg; 0.08 mmol) and the resulting suspension was refluxed for 5h. After this period the mixture was cooled to room temperature and was filtered. The solvent was evaporated to give **22a-c** and **23a-c.**

Ethyl-2-[(4-{[3-(trifluoromethyl)-1*H*-pyrazolyl]methyl}benzoyl)amino]benzoate (22a). (226 mg, 0.54 mmol, yield 86 %) from **12a**: ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, *J* = 7.1 Hz, CH_3); 4.40 (q, 2H, *J* = 7.1 Hz, CH_2); 5.44 (s, 2H, CH_2N); 6.58-6.62 (m, 1H, pyrazole); 7.13 (t, 1H, *J* = 6.9 Hz, Ar); 7.34-7.64 (m, 4H, Ar, pyrazole); 7.94-8.12 (m, 3H, Ar); 8.88-8.93 (m, 1H, Ar); 12.13 ppm (br s, 1H, NH). Anal. Calcd for $C_{21}H_{18}F_3N_3O_3$: C 60.43; H 4.30; N 10.07; Found: C 60.57; H 4.34; N 10.35.

Ethyl-3-[(4-{[3-(trifluoromethyl)-1*H*-pyrazolyl]methyl}benzoyl)amino]benzoate (22b). (236 mg, 0.57 mmol, yield 90 %) from **12b**: ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3H, *J* = 7.1 Hz, CH_3); 4.37 (q, 2H, *J* = 7.1 Hz, CH_2); 5.43 (s, 2H, CH_2N); 6.58 (d, 1H, *J* = 2.4 Hz, pyrazole); 7.33 (d, 2H, *J* = 8.2 Hz, Ar); 7.41-7.54 (m, 1H, Ar); 7.62-7.66 (m, 1H, pyrazole); 7.81-7.90 (m, 3H, Ar); 7.99-8.10 ppm (m, 2H, Ar). Anal. Calcd for $C_{21}H_{18}F_3N_3O_3$: C 60.43; H 4.30; N 10.07; Found: C 60.23; H 4.16; N 10.10.

Ethyl-4-[(4-{[3-(trifluoromethyl)-1*H*-pyrazolyl]methyl}benzoyl)amino]benzoate (22c). Purified by precipitation from Et_2O/n-hexane offered **22c** (123 mg, 0.30 mmol, yield 47 %) from **12c**: IR: 1697 (C=O of ester); 1649 (C=O of amide) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3H, *J* = 7.1 Hz, CH_3); 4.37 (q, 2H, *J* = 7.1 Hz, CH_2); 5.44 (s, 2H, CH_2); 6.58 (d, 1H, *J* = 2.5 Hz, pyrazole); 7.35 (d, 2H, *J* = 8.2 Hz, AA'XX'); 7.44-7.46 (m, 1H, pyrazole); 7.72 (d, 2H, *J* = 8.7 Hz, AA'XX'); 7.87 (d, 2H, *J* = 8.2 Hz, AA'XX'); 8.06 ppm (d, 2H, *J* = 8.7 Hz, AA'XX'). Anal. Calcd for $C_{21}H_{18}F_3N_3O_3$: C 60.43; H 4.30; N 10.07; Found: C 60.01; H 4.17; N 9.90.

Ethyl-2-[(3-{[3-(trifluoromethyl)-1*H*-pyrazolyl]methyl}benzoyl)amino]benzoate (23a). (254 mg, 0.61 mmol, yield 97 %) from **13a**: mp 88-90; ^{1}H NMR ($CDCl_3$) δ 1.43 (t, 3H, *J* = 7.1 Hz, CH_3); 4.42 (q, 2H, *J* = 7.1 Hz, CH_2); 5.46 (s, 2H, CH_2N); 6.55-6.60 (m, 1H, pyrazole); 7.10-7.17 (m, 1H, Ar); 7.39-7.64 (m, 4H, Ar, pyrazole); 7.96-8.02 (m, 2H, Ar); 8.10 (d, 1H, *J* = 7.5 Hz, Ar); 8.90 (d, 1H, *J* = 8.4 Hz, Ar); 12.13 ppm (br s, 1H, NH). MS *m/z*: 417 (M^+, 3). Anal. Calcd for $C_{21}H_{18}F_3N_3O_3$: C 60.43; H 4.30; N 10.07; Found: C 60.13; H 4.54; N 10.32.

Ethyl-3-[(3-{[3-(trifluoromethyl)-1*H*-pyrazolyl]methyl}benzoyl)amino]benzoate (23b). (165 mg, 0.40 mmol, yield 63 %) from **13b**: mp 130-132 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3H, *J* = 7.1 Hz, CH_3); 4.38 (q, 2H, *J* = 7.1 Hz, CH_2); 5.42 (s, 2H, CH_2N); 6.55-6.58 (m, 1H, pyrazole); 7.39-7.54 (m, 3H, Ar, pyrazole); 7.80-7.86 (m, 3H, Ar); 7.96 (s, 1H, Ar); 8.02-8.10 ppm (m, 2H, Ar); MS *m/z*: 417 (M^+, 33). Anal. Calcd for $C_{21}H_{18}F_3N_3O_3$: C 60.43; H 4.30; N 10.07; Found: C 60.69; H 4.43; N 10.28.

Ethyl-4-[(3-{[3-(trifluoromethyl)-1*H*-pyrazolyl]methyl}benzoyl)amino]benzoate (23c). (250 mg, 0.60 mmol, yield 95 %) from **13c**: mp 63-65; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3H, *J* = 7.1 Hz, CH_3); 4.37 (q, 2H, *J* = 7.1 Hz, CH_2); 5.40 (s, 2H, CH_2N); 6.56-6.60 (m, 1H, pyrazole); 7.37-7.50 (m, 2H, Ar, pyrazole); 7.64-7.83 (m, 2H, Ar); 7.73 (d, 2H, *J* = 8.6 Hz, AA'XX'); 8.04 (d, 2H, *J* = 8.6 Hz, AA'XX'); 8.22 ppm (s, 1H, Ar). MS *m/z*: 417 (M^+, 11). Anal. Calcd for $C_{21}H_{18}F_3N_3O_3$: C 60.43; H 4.30; N 10.07; Found: C 60.50; H 4.71; N 10.39.

Angiotensin II receptor binding assay

Male Wistar rats were killed by decapitation, and their livers were rapidly removed. Rat liver membranes were prepared by differential centrifugation, as previously described. [13] Briefly, liver was dissected free of fatty tissue and minced accurately with small scissors, and then about 3g of tissue was homogenized by Polytron Ultra-Turrax (maximal speed for 2 x 30s) in ice cold 20 vol of Tris-HCl 5 mM, sucrose 0.25 M (pH 7.4). The homogenate was centrifuged at 750g for 10 min at 4 °C and the supernatant was filtered through cheesecloth and saved. The pellets were homogenized and centrifuged as before. The combined supernatants were centrifuged at 48,000g for 15 min at 4 °C. The resulting pellet was resuspended in Tris-HCl 5 mM, sucrose 0.25 M (pH 7.4), and centrifuged as above. The final pellets were used immediately or stored frozen at -70 °C before use. The membrane pellet were resuspended in Tris-HCl 50 mM, NaCl 100 mM, $MgCl_2$ 10 mM, EDTA 1 mM, bacitracin 100 μM, PMSF 100 μM, BSA 0.1% (pH 7.4) to obtain a final protein concentration of 2.5 mg/mL. Angiotensin II binding assay was performed incubating aliquots of liver membranes (50 μg) at 25 °C for 180 min in 100 μL assay buffer conteining 25 pM [^{125}I]Sar^1,Ile^8-angiotensin II (Perkin Elmer life Sciences). Non specific binding was measured in the presence of 1 μM angiotensin II and represented 5-10% of total binding.

Binding was terminated by rapid vacuum filtration using GF/G glass fiber filters performing three washes with 4 mL of ice cold NaCl 100 mM, $MgCl_2$ 100 mM buffer. Dried filters disks were counted in a gamma-counter with 92% efficiency. The compound % inhibition values were estimated at 10 μM concentration. For all tested compounds IC_{50} values were not calculable.

Molecular modeling

The ligands were docked in our recently published AT1 model The ligands were submitted to a conformational search of 1000 steps with an energy window for saving structure of 10 KJ/mol. The algorithm used was the Montecarlo method with MMFFs as the forcefield and a distance-dependent dielectric constant of 1.0. The ligands were then minimized using the Conjugated Gradient method until a convergence value of 0.05 kcal/Å•mol, using the same forcefield and dielectric constant used for the conformational search.[14] Then the ligands were docked into the

receptor using the AUTODOCK 3.0 program.[15] The regions of interest used by AUTODOCK were defined by considering atom CZ3 of W6.48(253) as the central residue of a grid of 50, 44, and 48 points in the *x*, *y*, and *z* directions. A grid spacing of 0.375 Å and a distance-dependent function of the dielectric constant were used for the energetic map calculations.
Using the Lamarckian Genetic Algorithm, the compounds were subjected to 100 runs of the AUTODOCK search, in which the default values of the other parameters were used. Cluster analysis was performed on the docked results using an RMS tolerance of 1.0 Å.

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