Nonpeptide Angiotensin II Receptor Antagonists. Synthesis, in Vitro Activity, and Molecular Modeling Studies of *N*-[(Heterobiaryl)methyl]imidazoles†

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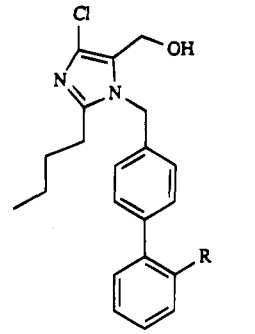
With the aim of explaining the influence of the structural changes on the biphenylic moiety on the activity, a series of *N*-[(heterobiaryl)methyl]imidazoles (**I**), constructed on the model of DuPont compounds by replacing either the central or terminal phenyl ring with a heteroaromatic one, such as furan, thiophene, thiazole, and pyridine, was synthesized. Compared to the reference DuPont compound (EXP-7711), all the heterobiaryl derivatives showed a reduced potency both in receptor binding (rat adrenal capsular membranes) and in the functional assay (angiotensin II-induced contraction of rabbit aorta strips). The lower activity was justified by the extensive molecular modeling studies, which took into consideration the conformational and electrostatic features of several heterobiaryl derivatives. On the basis of the results obtained, it was hypothesized that the central aromatic ring of the biarylic portion works as a spacer, orienting in the right way the terminal phenyl ring, whose electronic distribution is, instead, crucial to its fitting well with a lipophilic pocket at the receptor site.

Introduction

The role of the renin–angiotensin system (RAS) and its importance in the regulation of blood pressure in humans are now well established.[1] In the kidney, RAS produces angiotensinogen which is converted by renin to angiotensin I, which in turn is transformed by the angiotensin converting enzyme (ACE) to angiotensin II (AII), the effector vasoconstrictor hormone. The regulation of the RAS, through the inhibition of ACE, is used clinically for the treatment of hypertension. Renin inhibitors are also effective in lowering blood pressure, although their clinical use has been hampered until now due to poor oral bioavailability. An alternative, and perhaps a more advantageous, mode of RAS modulation is the direct antagonism of AII binding at the receptor. The problems of early peptidic AII antagonists (e.g., Saralasin), such as partial agonism and lack of oral activity, have only recently been overcome by the discovery of nonpeptidic imidazole derivatives such as DUP-753 which is still undergoing extensive clinical evaluation.[2]

Starting from DUP-753, or the corresponding carboxy derivative EXP-7711[3] (Figure 1), a great number of structurally related compounds have been prepared by several laboratories. The structural modifications have covered both the imidazole ring and the biphenylic moiety. With regard to the latter, some examples recently reported are the benzofuranyl derivatives (Glaxo[4]), the rigid analog naphthalene derivatives (Ciba[5]), the cycloalkenylphenyl derivatives (Eli Lilly[6]), and the pyrrole derivatives (Searle[7]). While the benzofuranyl derivatives were found to be potent and specific AII antagonists, the last three compounds displayed a weaker activity than the DuPont compounds.



DUP-753 R = 5-tetrazolyl

EXP-7711 R = CO_2H

Figure 1. Angiotensin II receptor antagonists.

With the aim of obtaining a better insight into how these types of structural changes affect the biological activity and to potentially find an alternative to the biphenylic moiety, we focused our attention on a series of derivatives of general formula **I** (Table 1); these derivatives were constructed on the model of DuPont compounds by replacing either the central or terminal phenyl ring with a heteroaromatic one. Five-membered rings like furan and thiophene were substituted at the central phenyl, while five- and six-membered rings like furan, thiophene, thiazole, and pyridine were substituted at the terminal phenyl.

During the development of the imidazopyridine class of AII antagonists, also the Merck group became interested in examining the effect of replacing either the central or distal phenyl ring of the biphenyl element by a thiophene or a furan.[8] Replacement of the tetrazole-bearing phenyl by a pyridine has been also addressed in the imidazopyridine series of AII inhibitors,[9] while the replacement of the central ring of the biphenyl fragment by a pyridine has been tested in triazole-

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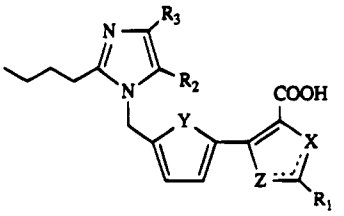
Table 1. AII Receptor Binding and Antagonistic Activity of 1-Heteroaryl-Substituted Imidazoles

(Formula I)



compd	R_1	R_2	R_3	X	Y	Z	binding (RACM),[a] K_i (μM)	rabbit aorta,[b] pA_2
6a	H	CH_2OH	Cl	O	CH=CH	CH	>10	≤5.0
7a	H	Cl	CH_2OH	O	CH=CH	CH	>10	6.0 ± 0.3
6b	H	CH_2OH	Cl	S	CH=CH	CH	14.5 ± 3.9	≤5.0
6c	H	CH_2OH	Cl	CH=CH	O	CH	>10	5.2 ± 0.2
7c	H	Cl	CH_2OH	CH=CH	O	CH	9.7 ± 3.7	5.8 ± 0.1
6d	H	CH_2OH	Cl	CH=CH	S	CH	>10	≤5.0
7d	H	Cl	CH_2OH	CH=CH	S	CH	11.6 ± 3.8	5.7 ± 0.2
6e	CH_3	CH_2OH	Cl	S	CH=CH	N	>10	≤5.0
7e	CH_3	Cl	CH_2OH	S	CH=CH	N	>10	≤5.0
6f	H	CH_2OH	Cl	N=CH	CH=CH	CH	3.3 ± 0.4	6.1 ± 0.2
7f	H	Cl	CH_2OH	N=CH	CH=CH	CH	>10	≤5.0
6g	H	CH_2OH	Cl	CH=CH	CH=CH	N	9.8 ± 2.7	≤5.0
7g	H	Cl	CH_2OH	CH=CH	CH=CH	N	>10	≤5.0
6h	H	CH_2OH	Cl	CH	CH=CH	CH=N	6.7 ± 1.3	<5.0
EXP-7711	H	CH_2OH	Cl	CH=CH	CH=CH	CH	0.35 ± 0.08	6.9 ± 0.2

[a] RACM: rat adrenal capsular membranes (adrenal cortex), using [^{125}I]Sar^{1}Ile^8-AII as ligand. Values are expressed as K_i (mean ± SEM) of at least three determinations. [b] Antagonism of AII-induced contraction of rabbit endothelium-denuded aorta strips.

containing antagonists.[10] Results in agreement with the arguments presented in this paper have been reported for all these new AII receptor inhibitors containing phenylthiophenes, phenylfurans, and phenylpyridines on a heterocyclic nucleus other than imidazole.[11]

This paper describes the synthesis and the AII antagonist properties of compounds **I** and the extensive molecular modeling studies performed on some of these compounds with the aim of explaining the influence on the activity of the structural changes on the biphenylic moiety.

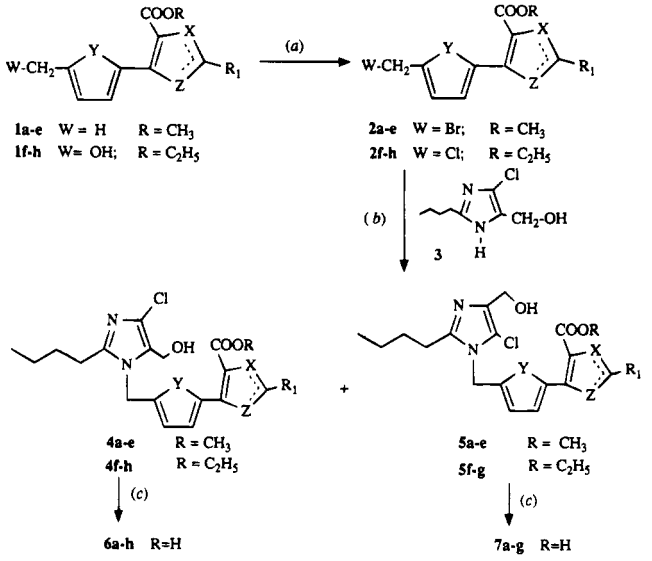
Molecular Modeling

The reliability of our hypothesis was first verified on the basis of results obtained in a previously performed 3D-QSAR study. This study was carried out to recognize the 3D geometrical requirements for the binding of nonpeptide AII antagonists.[12] A heterogenous training set including 13 compounds showing different levels of binding affinity (none featuring general formula **I**) was considered. The comparative analysis of the 3D geometrical features of these compounds was realized by the combined use of conformational analysis and chemometrics and led to the definition of general spatial functionality relationships necessary for receptor binding. Conformational analysis, using the molecular mechanics MM2 method, was carried out for each molecule to obtain the conformational minima within 8 kcal/mol of the global minimum. These minima (about 9000 conformers) were described by 10 interatomic distances that define the relative spatial disposition of five relevant functional groups belonging to all the molecules. A structure–activity relationship between the 3D molecular descriptors and the biological data was then assessed by chemometric techniques; cluster analysis was applied to reduce the large number of conformational minima found for each molecule. The centroid (i.e., the vector of the variables' means) of each cluster was calculated; it represents the average spatial disposition of the conformers forming the cluster. By substituting similar conformations forming a cluster with the centroid of that cluster, the number of objects was reduced to 734. Principal component analysis verified whether all the 3D descriptors used were required for an exhaustive description of the system. The 10-dimensional problem was then reduced to an 8-dimensional one. At this point, the 734 centroids, described by eight interatomic distances, were distributed in two biological classes: 449 centroids, belonging to molecules with IC_{50} values in the angiotensin II AT_1 receptor-binding assay of <1 μM, were assigned to the active class, while 274 centroids, belonging to molecules with IC_{50} values of >1 μM, were assigned to the inactive one. Finally a new classification method, linear discriminant classification tree (LDCT),[13] which integrates the tree methodology classification and the classical linear discriminant analysis (LDA) procedure, was applied on this data set and led to a multivariate decision tree, characterized by low complexity and easy interpretability. The thus constructed geometrical model was employed to predict, on the basis of the eight interatomic distances selected, the biological behavior (active or inactive) of several compounds of general formula **I** (see Table 1).

Chemistry

Scheme 1 describes the general synthetic pathway to the heterobiaryl derivatives **6a–h** and **7a–g** listed in Table 1. The bromination of compounds **1a–e**, performed with *N*-bromosuccinimide in carbon tetrachloride in the presence of dibenzoyl peroxide, always left traces of an α,α-dibromo derivative and unreacted material.[7] The same methodology was applied to the synthesis of pyridine derivatives **2f–h**, but the yield was very low, probably due to the formation of N-alkylated pyridinium salt derivatives. This drawback was overcome by synthesizing the corresponding but less reactive and more stable chloro derivatives **2f–h**; the [(hydroxymethyl)phenyl]pyridines **1f–h** were reacted with thionyl chloride at room temperature, and no attempt was made to isolate the final products (Scheme 1).

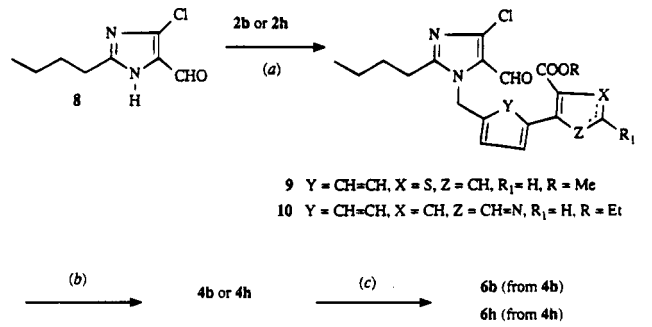
Scheme 1[a]



a:	Y = CH=CH	R = CH_3	X = O	Z = CH	R_1 = H
b:	Y = CH=CH	R = CH_3	X = S	Z = CH	R_1 = H
c:	Y = O	R = CH_3	X = CH=CH	Z = CH	R_1 = H
d:	Y = S	R = CH_3	X = CH=CH	Z = CH	R_1 = H
e:	Y = CH=CH	R = CH_3	X = S	Z = N	R_1 = CH_3
f:	Y = CH=CH	R = C_2H_5	X = N=CH	Z = CH	R_1 = H
g:	Y = CH=CH	R = C_2H_5	X = CH=CH	Z = N	R_1 = H
h:	Y = CH=CH	R = C_2H_5	X = CH	Z = CH=N	R_1 = H

[a] (*a*) Method A—NBS, benzoyl peroxide; CCl_4, Δ; compounds **1a–e**; method B—$SOCl_2$, $CHCl_3$, room temperature; compounds **1f–h**; (*b*) NaH (80%), DMF, room temperature; (*c*) NaOH, MeOH—H_2O, Δ.

Scheme 2[a]

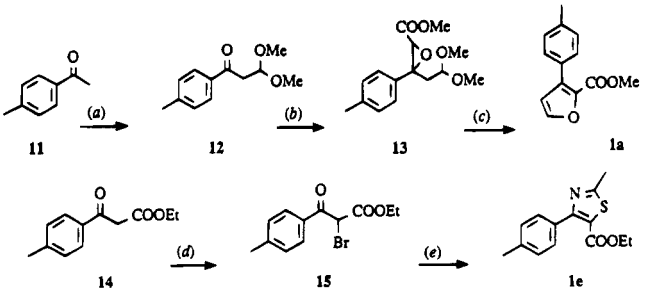


[a] (*a*) K_2CO_3, DMF, room temperature; (*b*) $NaBH_4$, EtOH, room temperature; (*c*) NaOH, MeOH—H_2O, Δ.

The alkylation of the sodium salt of the known 2-butyl-4-chloro-5-(hydroxymethyl)-1*H*-imidazole[14] (**3**), generated by sodium hydride in DMF, with the halo derivatives **2a–h** produced a mixture of approximately equal amounts of the two regioisomers **4a–h** and **5a–g**. These isomers were separated by flash chromatography, and as reported earlier,[15] the one eluting faster was the 4-chloro-5-hydroxymethyl isomer (structure confirmed by NMR experiments). Compounds **4b,h** were obtained according to Scheme 2 by the regioselective alkylation of 2-butyl-4-chloro-5-formyl-1*H*-imidazole (**8**)[14] using the appropriate bromo or chloro derivatives **2b,h** in dimethylformamide in the presence of potassium carbonate and subsequent reduction of the resulting intermediates **9** and **10** with sodium borohydride.

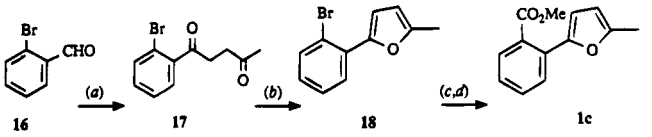
Finally, hydrolysis to the target acids **6a–h** and **7a–g**

Scheme 3[a]



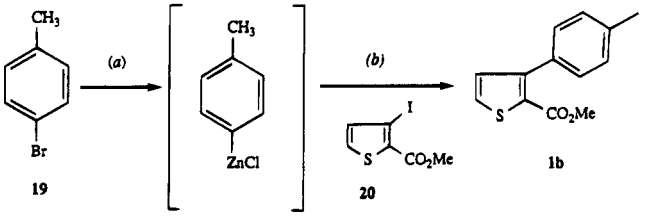
[a] (*a*) MeONa, HCO_2Me, Et_2O, Δ; then HCl(g), MeOH, 20 °C; (*b*) MeONa, $ClCH_2CO_2Me$, Et_2O, 0 °C; (*c*) *p*-TsOH, 4 Å molecular sieves, benzene, Δ; (*d*) Br_2, CCl_4, Δ; (*e*) $MeCSNH_2$, EtOH, Δ.

Scheme 4[a]



[a] (*a*) CH_2=CHCOMe, thiazolium salt, Et_3N, 70 °C; (*b*) *p*-TsOH, 4 Å molecular sieves, benzene, Δ; (*c*) *n*-BuLi, THF, −78 °C, CO_2(g); (*d*) CH_2N_2.

Scheme 5[a]



[a] (*a*) *t*-BuLi, Et_2O, −78 °C, $ZnCl_2$; (*b*) $NiCl_2(PPh_3)_2$, THF—Et_2O, room temperature.

was accomplished in alkaline medium. The biarylic intermediates **1a–h** were synthesized by several different routes employing cyclization and condensation reactions (compounds **1a,c,e**; Schemes 3 and 4) or palladium- and nickel-catalyzed biarylic cross-coupling reactions[16] (compounds **1b,d,f–h**; Schemes 5–7).

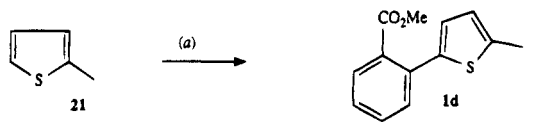
According to Scheme 3, the furan derivative **1a** was prepared by acid-catalyzed isomerization of the epoxide **13**.[17] We found that the best yield was obtained when the intermediate **13** was treated with a catalytic amount of *p*-toluenesulfonic acid in refluxing dry benzene in the presence of 4 Å molecular sieves. Thiazole **1e** was obtained by condensing the bromo keto ester **15** and thioacetamide in refluxing ethanol.

The furan **1c** was conveniently prepared starting from the 1,4-dicarbonyl compound **17**, prepared according to Stetter's procedure.[18] After cyclization of **17**, the resulting bromo derivative **18** was first transformed into the acid by lithiation followed by carbonation and finally into the methyl ester **1c** (Scheme 4).

As an alternative, we chose a more straightforward procedure, based on biarylic cross-coupling reactions,[16a] to synthesize thiophene and pyridine derivatives (**1b,d,f–h**). The coupling reaction of the zinc derivative, prepared from *p*-bromotoluene, with iodide **20** in the presence of $NiCl_2(PPh_3)_2$ as catalyst provided thiophene **1b** in satisfactory yield (Scheme 5).

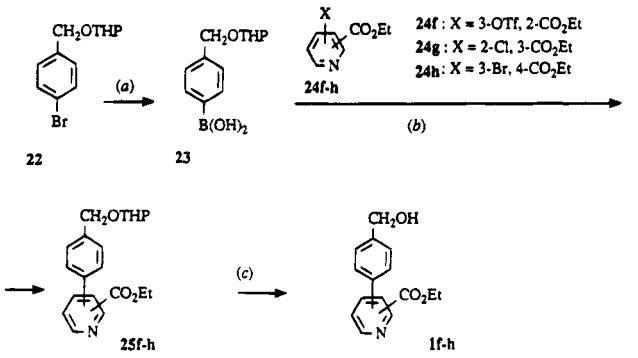
Analogously, the reaction of methyl 2-iodobenzoate with the thienylzinc derivative, generated "in situ" from 2-methylthiophene (**21**) treated with *n*-BuLi and subsequent addition of zinc chloride, furnished the thiophene

Scheme 6[a]



[a] (a) *n*-BuLi, Et_2O, −78 °C, $ZnCl_2$; methyl 2-iodobenzoate, $NiCl_2(PPh_3)_2$, room temperature.

Scheme 7[a]



[a] (a) *n*-BuLi, THF, −78 °C, $B(OCH_3)_3$, HCl, pH 6.5; (b) $Pd(PPh_3)_4$ (5% mol), Na_2CO_3 (2 M), DME, Δ (LiCl for **25f**); (c) *p*-TSOH, MeOH, Δ.

analog **1d** in good yield (Scheme 6). Similarly, good results were obtained from the coupling of boronic acid **23** with the appropriate halopyridine **24g–h** or triflate derivative **24f**, in the presence of $Pd(PPh_3)_4$ as catalyst, according to Suzuki's methodology.[16b] The yields for compounds **25f–h** ranged from 45% to 82% (Scheme 7).

Finally, the usual acid-catalyzed deprotection of the tetrahydropyranyl ethers **25f–h** afforded the alcohols **1f–h**.

Biology

The newly synthesized compounds, **6a–h** and **7a–g**, were examined for binding affinity in rat adrenal capsular membrane, using [^{125}I]Sar^{1}Ile^8-angiotensin II as the radioligand (K_i), and for AII antagonism of induced contraction in endothelium-denuded aorta strips (pA_2). The K_i and pA_2 values resulting from these assays are listed in Table 1. Compared to the reference compound (EXP-7711), all the heterobiaryl derivatives showed a reduced potency both in receptor binding and in the functional test.

Discussion

Like the AII antagonists previously studied, several derivatives of Table 1 were investigated by a conformational search followed by a cluster analysis to obtain a limited number of informative centroids; the developed geometrical model was then employed to classify the centroids of each examined heterocompound.

The multivariate decision tree, obtained by means of LDCT on the 734 training set centroids described by eight variables and distributed in two biological classes, is characterized by four active, one inactive, and two fuzzy leaves. A leaf, which represents a final situation of the classification tree (the intermediate situations are usually called nodes), is assigned to the class for which there is the majority of the samples; when two classes are equally represented, the leaf is not assigned but considered fuzzy. When the LDCT model is used for prediction, the centroids of the studied compounds are assigned to the various leaves, on the basis of the values assumed by the eight interatomic distances. Each compound's class is then predicted according to the class of the leaves where the major part of the compound's centroids falls. In this step, the fuzzy leaves are considered inactive and the tested compounds are classified by the tree model only as active or inactive. The LDCT method not only permits the classification of unknown compounds on the basis of the selected variables but can also establish the reliability of the classification by verifying the degree of similarity between the variables' values of the tested molecules and those of the training set AII antagonists. This is possible by requiring the program to search for the discriminant function (a linear combination of all the variables) that gives rise to the maximum separation between the active training set centroids in a leaf (if the leaf was assigned to the active class) and the tested centroids falling within that leaf. If a poor separation is obtained, the similarity degree between the two groups is high; if the separation is complete, the similarity degree is low. In this latter case, the prediction cannot be considered reliable.

All the heterobiaryl derivatives examined were classified by the multivariate decision tree as active compounds, e.g., the major part of their centroids fell in the active leaves of the model. A further search for similarity showed that all compounds of general formula **I** with a terminal heterocyclic ring possess interatomic distances very close to those of the DuPont biphenylic analog, while the compounds with a central five-membered heteroaromatic ring possess different values of some interatomic distances. Nevertheless we decided to synthesize both classes of the heterobiaryl derivatives. Unfortunately in the binding assay, all the compounds reported in Table 1 revealed a low affinity for the AII receptor.

In an attempt to rationalize the biological behavior of these heterobiaryl derivatives, we further investigated their conformational properties and, in particular, analyzed their most relevant rotatable bonds. It was found that replacing the central phenyl ring with a five-membered heterocycle had no effect on the imidazole and central ring dispositions but placed the heterocycle and the terminal phenyl ring in an almost planar disposition. This torsional behavior probably arises from a conjugative interaction whose effect prevails over the steric and electrostatic repulsions that can generally be alleviated by deviation from planarity,[19] like in the biphenylic moiety where the two aromatic rings are staggered by about 60°. It is worth noting that in the Glaxo benzofuranyl derivatives the replacement of the C3 hydrogen atom on the benzofuran with bromine resulted in a marked enhancement of the activity.[4] Therefore the planarity between the central heterocyclic ring and the terminal phenylic ring could well explain the low binding affinity of this class of heteroaryl compounds; probably the terminal aromatic ring is no longer oriented to advantageously interact with the receptor site.

These conclusions nicely agree with the geometric arguments suggested by Rivero and colleagues[8] to explain the lack of binding affinity for imidazopyridine analogs with a central five-membered ring. Replacement of the central phenyl of the biphenyl fragment by a thiophene or a furan is shown by Rivero to have a profound effect on the overall conformation of the molecule and to produce AII antagonists which poorly

align their pharmacophoric elements to the corresponding atoms in the parent biphenyl structure. On the contrary, quantum mechanical calculations[20] and pharmacologic profiles[10] suggest that replacement of the central phenyl by a six-membered heterocycle (e.g., pyridine) only slightly affects the biaryl disposition.

The terminal heterobiaryl derivatives under study were also shown to favor a nonplanar disposition of the biaryl moiety; therefore this class of compounds, on the basis of the analyzed interatomic distances and rotatable bonds, shows a conformational behavior quite similar to that of the DuPont biphenylic analogs.[21] The activity of these compounds was not comparable to that of the DuPont compounds. This can be explained by hypothesizing that the introduction of a terminal heterocycle ring could modify the charge distribution of the antagonist. Therefore the overall molecular electrostatic potential (MEP) distributions of compounds EXP-7711 (Figure 1, Table 1), the reference biphenylic antagonist, and **6a**,**f**–**h** (Table 1) were computed. In fact, since MEP is a physically meaningful representation of how a molecule is perceived in its vicinity,[22] comparisons of the potential distributions provide a useful tool to compare molecular analogs that act at a common receptor site. MEP was computed from a semiempirical MNDO wave function in points belonging to 3D uniform solid grids using the program MOPAC 5.0 ESP.[23] The results provided by a previous comparative analysis of MEP computational methods[24] and the dimensions of the compounds under study suggested this decision. With regard to the choice of the molecular conformations to be used for MEP calculations, we considered the global minimum, derived from the conformational analysis, of EXP-7711 and the conformers of the heterocompounds **6a**,**f**–**h** that give the best superimposition value with the former (the five atoms used in the geometrical approach were superimposed using MACROMODEL V3.1X[25]). Conformational features common to the five minimum energy structures are a nonplanar disposition of the biaryl moiety and hydrogen bonding between the hydroxylic and acidic functions.

The isopotential surfaces at −20 kcal/mol for molecules **6a** (green contours) and **6f** (red contours) are represented in Figure 2; the isopotential surface at −20 kcal//mol of EXP-7711 (blue contours) is also overlapped by superimposing the atoms belonging to the imidazolic rings. Since comparisons of less negative MEP values give the same results, we chose to represent the isopotential surfaces at −20 kcal/mol to make the interpretation of the figure easier. Thus the blue negative potential contours of the biphenylic compound are exclusively localized around the imidazolic ring, the hydroxylic group, and the carboxyl group; no contours are visible in the region of the terminal phenyl ring at this constant MEP value. It can be observed that the negative surfaces of the heterocompounds present a topology quite similar to that of the biphenylic one, but both are characterized by a considerable protrusion that extends from the region of the carboxylic group to the heteroatom placed on the terminal aromatic ring.

The isopotential surfaces at −20 kcal/mol of the molecules **6g** (pink contours) and **6h** (orange contours) are shown in Figure 3. Both overlap to the corresponding isopotential surface of EXP-7711 (blue contours). Although the superimposition of pink (or orange) contours and blue contours is considerable, a clear difference exists between the MEP distribution of these heterocompounds and that of the reference compound. The protrusion in the region of the terminal aromatic ring shown by the isopotential surfaces at −20 kcal/mol of **6a**,**f** with respect to that of EXP-7711 (Figure 2) becomes, in compounds **6g**,**h**, a completely isolated negative MEP region. In the pyridine series under study, it is worth noting that the receptor-binding affinity tends to lower as the heteroatom (and its negative MEP well) goes away from the carboxyl groups (and its negative isopotential contours).

By hypothesizing that within the receptor site there exists a lipophilic pocket into which the terminal aromatic ring fits, a negative MEP region on the plane around the aromatic ring could be reflected in an unfavorable interaction with the receptor. Therefore the replacement of the terminal phenyl ring with a heteroaromatic one gives rise to a change in the electrostatic behavior of the antagonist, which could well explain the reduced activity of this class of heterobiaryl derivatives.[26]

Conclusions

A series of heterobiaryl-substituted imidazoles, constructed on the model of DuPont nonpeptide AII receptor antagonist EXP-7711 by a replacement of the central or terminal phenyl ring with a five- or six-membered heteroaromatic one, were discussed. All the new compounds were found to be less active than the biphenylic analogs in the pharmacological assays for both AII receptor binding and AII antagonist activity.

The conformational and electrostatic features of several heterobiaryl derivatives were investigated in an attempt to explain their low binding affinity. Replacement of the central phenyl of the biphenyl by a thiophene or furan was observed to appreciably affect the overall 3D structure of the molecule. The reduced activity shown by these central heterobiaryl compounds could be justified by the almost planar disposition of the biaryl moiety, which could allow the structure to exist in conformations not optimal for receptor binding. On the contrary, the terminal heterocompounds under study show a conformational behavior very close to that of the biphenylic analogs, but they are characterized by a long-range MEP distribution that could explain their low affinity. In fact negative potential contours in the plane of the terminal aromatic ring surrounding the heteroatom could give rise to unfavorable interactions with a hypothetic lipophilic pocket at the receptor site.

In conclusion, on the basis of the results previously discussed, we hypothesize that the central aromatic ring of the biaryl moiety works as a spacer, orienting in the right way the terminal aromatic ring whose electronic distribution is, instead, crucial to its fitting well with a lipophilic pocket at the receptor site.

Experimental Section

General. Thin-layer chromatography was performed on silica gel plates (60 F_{254}; Merck). Flash chromatography was performed using silica gel (Kieselgel 60, 230–400 mesh). Melting points were measured with a Büchi 535 apparatus and are uncorrected. ^{1}H-NMR spectra were obtained with a Brucker AC-200 spectrometer and are reported as ppm downfield from Me_4Si, with multiplicity, number of protons, and coupling constants in hertz. Electron impact (EI) mass spectra were obtained with a VB 7070 EQ-HF mass spectrometer. Where elemental analyses are indicated for C,H,N, analytical

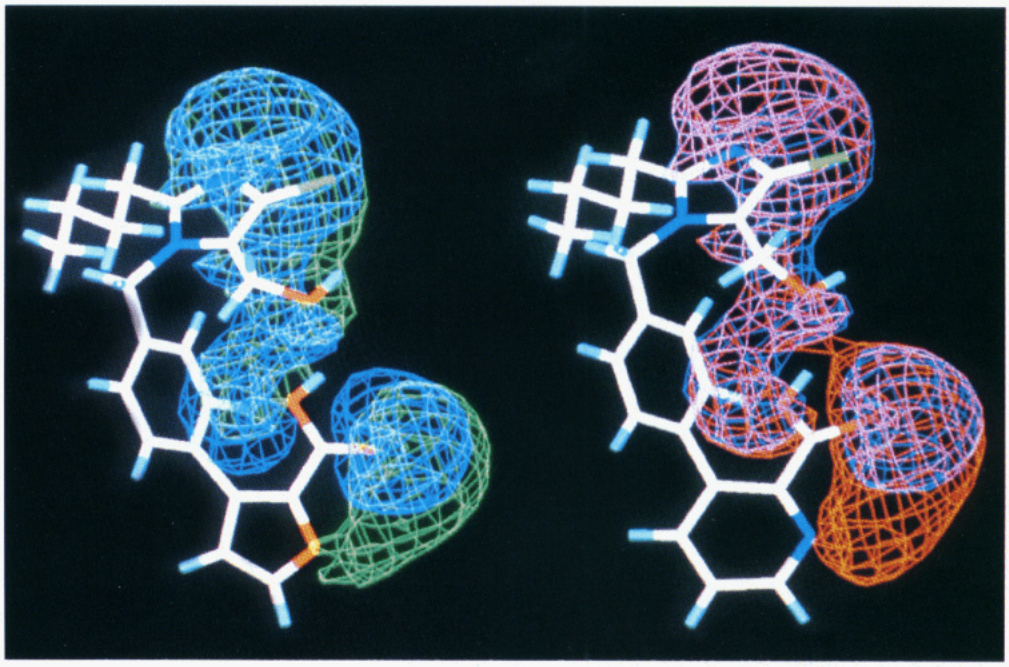


Figure 2. Isopotential surfaces at −20 kcal/mol of **6a** (left, green contours) and **6f** (right, red contours), both superimposed to the isopotential surface at −20 kcal/mol of EXP-7711 (blue contours).

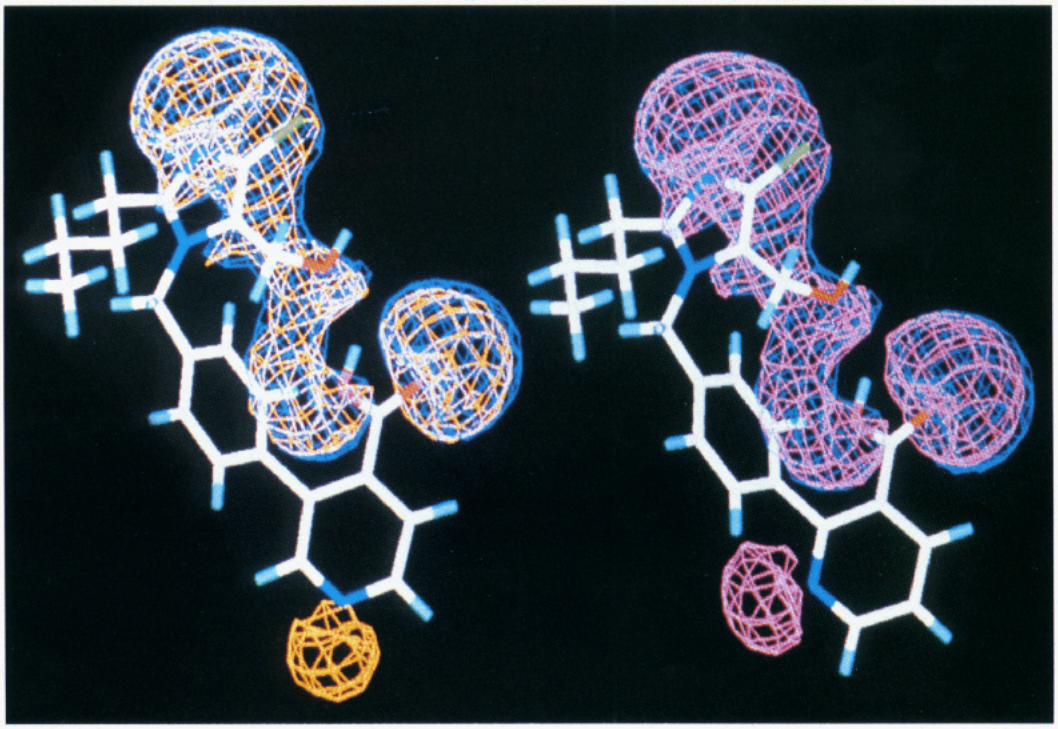


Figure 3. Isopotential surfaces at −20 kcal/mol of **6g** (right, pink contours) and **6h** (left, orange contours), both superimposed to the isopotential surface at −20 kcal/mol of EXP-7711 (blue contours).

values are within 0.4% of calculated values. Where solvation is indicated, the presence of solvent was verified by NMR.

Methyl 3-(4-Methylphenyl)furan-2-carboxylate (1a). In a glass apparatus equipped with a bypassed dropping funnel filled with 4 Å molecular sieves between the flask and the reflux condenser, compound **13** (10.8 g, 38.6 mmol) was dissolved in 100 mL of dry C_6H_6 and *p*-TsOH·H_2O (1.1 g, 5.8 mmol) was added. The mixture was refluxed for 3 h and cooled to room temperature, and the resulting dark solution was washed with aqueous $NaHCO_3$ first and then with brine and finally dried (Na_2SO_4). Evaporation in vacuo of the solvent gave a dark oil. The crude product was purified by flash chromatography (AcOEt/hexane, 1:9) to afford compound **1a** as a yellow oil (5.8 g, 70%): ^{1}H-NMR ($CDCl_3$) δ 7.56 (d, 1H, J = 1.7 Hz), 7.47 (d, 2H, J = 8.1 Hz), 7.23 (d, 2H, J = 8.1 Hz), 6.61 (d, 1H, J = 1.7 Hz), 3.85 (s, 3H), 2.39 (s, 3H).

Methyl 3-(4-Methylphenyl)thiophene-2-carboxylate (1b). To a stirred solution of 4-bromotoluene (**19**) (3.1 g, 18.2 mmol) in 40 mL of dry Et_2O under N_2 atmosphere at −78 °C was added dropwise 15 mL of *t*-BuLi (1.5 M in pentane). The resulting suspension was allowed to warm to room temperature, stirred for 1 h, and then transferred via cannula in a flask containing a solution of $ZnCl_2$ (2.6 g, 19.5 mmol) in 20 mL of Et_2O and 40 mL of THF. After stirring for 2 h at 25 °C, the yellow solution obtained was gradually added via cannula to a solution of methyl 3-iodo-2-thiophenecarboxylate (**20**) (3.5 g, 13 mmol) (prepared from 3-iodo-2-thiophenecarboxylic acid[27] by esterification with MeOH in the presence of H_2SO_4) and $NiCl_2(PPh_3)_2$ (0.25 g, 0.4 mmol) in 50 mL of THF. The resulting dark solution was stirred overnight and poured into

100 mL of cold 0.5 N HCl. The organic phase was separated, washed with brine, and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was purified by flash chromatography (hexane/benzene, 6:4) to afford compound **1b** as a white solid (1.5 g, 50%): mp 72–74 °C; ^{1}H-NMR ($CDCl_3$) δ 7.50 (d, 1H, J = 5.0 Hz), 7.35 (d, 2H, J = 8.2 Hz), 7.24 (d, 2H, J = 8.2 Hz), 7.08 (d, 1H, J = 5.0 Hz), 3.79 (s, 3H), 2.40 (s, 3H).

Methyl 2-(5-Methylfuran-2-yl)benzoate (1c). A solution of *n*-BuLi (1.6 M in hexane, 28.4 mL) was added dropwise to a solution of **18** (10.0 g, 42.2 mmol) in 120 mL of dry THF at −78 °C, and then it was stirred at this temperature for 1 h. CO_2 was then bubbled for 30 min into the solution of the lithium derivative. The cold bath was removed; the reaction mixture was allowed to warm to room temperature and stirred for an additional 3 h. The solvent was evaporated in vacuo, and the resulting solid was suspended in 200 mL of hexane/Et_2O (5:1) and stirred for 1 h. After filtration, the white powder obtained was dissolved in H_2O, acidified with 2 N HCl (pH 2), and extracted twice with Et_2O. The organic layer was washed with brine and dried, and the solvent was evaporated in vacuo. Crude 2-(5-methylfuran-2-yl)benzoic acid was obtained as a brown oil. The acid was dissolved in 100 mL of dry Et_2O and treated with an excess of a solution of CH_2N_2 in Et_2O. The solvent was evaporated and the residue distilled at reduced pressure (0.8 mmHg, 170 °C) to give **1c** as a colorless oil (5.5 g, 60%): ^{1}H-NMR ($CDCl_3$) δ 7.60 (m, 2H), 7.45 (m, 1H), 7.29 (m, 1H), 6.48 (d, 1H, J = 3.2 Hz), 6.05 (d, 1H, J = 3.2 Hz), 3.84 (s, 3H), 2.33 (s, 3H).

Methyl 2-(5-Methylthien-2-yl)benzoate (1d). To a stirred solution of 2-methylthiophene (9.8 g, 100 mmol) in 100 mL of dry Et_2O at −78 °C under a N_2 atmosphere was added dropwise 66 mL of *n*-BuLi (1.6 M in hexane). The resulting slurry was allowed to warm to room temperature, stirred for 1 h, and then transferred via cannula into a solution of $ZnCl_2$ (14.6 g, 107 mmol) in 160 mL of THF and 80 mL of Et_2O. After stirring for 2 h at 25 °C, the yellow solution obtained was gradually added via cannula to a flask containing methyl 2-iodobenzoate (28.0 g, 107 mmol) and $NiCl_2(PPh_3)_2$ (1.26 g, 1.9 mmol) dissolved in 150 mL of THF. The resulting brown solution was stirred overnight and poured into cold 1 N HCl. The organic phase was separated, washed with brine, and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was purified by flash chromatography (*i*-Pr_2O/hexane, 15:85) to afford **1d** as a yellow oil (14.0 g, 85%): ^{1}H-NMR ($CDCl_3$) δ 7.68 (m, 1H), 7.25–7.48 (m, 3H), 6.83 (dd, 1H, J = 5.1, 1.0 Hz), 6.72 (m, 1H), 3.77 (d, 3H, J = 1.0 Hz), 2.51 (d, 3H, J = 1.0 Hz).

Ethyl 2-Methyl-4-(4-methylphenyl)thiazole-5-carboxylate (1e). A mixture of **15** (4.4 g, 15.4 mmol) and thioacetamide (1.4 g, 18.5 mmol) in 30 mL of dry EtOH was refluxed for 4 h. After cooling, the solvent was removed in vacuo. The resulting residue was dissolved in H_2O and made alkaline with cold 10% NaOH (pH 10). The alkaline solution was extracted twice with Et_2O, and the organic layer was washed with brine and dried (Na_2SO_4). After removal of the solvent under vacuum, the crude product was purified by flash chromatography (AcOEt/hexane, 1:9) to give **1e** (1.7 g, 41%) as a yellow powder: mp 60.62 °C; ^{1}H-NMR ($CDCl_3$) δ 7.62 (d, 2H, J = 8.3 Hz), 7.24 (d, 2H, J = 8.3 Hz), 4.25 (q, 2H, J = 6.3 Hz), 2.73 (s, 3H), 2.39 (s, 3H), 1.28 (t, 3H, J = 6.3 Hz).

Ethyl 3-[4-(Hydroxymethyl)phenyl]pyridine-2-carboxylate (1f). A solution of **25f** (2.5 g, 7.3 mmol) in 30 mL of MeOH was refluxed in the presence of a catalytic amount of *p*-TsOH·H_2O until TLC indicated completion. After evaporation, the residue was dissolved in CH_2Cl_2 and washed first with saturated $NaHCO_3$ solution and then with brine. Removal of the solvent in vacuo afforded compound **1f** as an amorphous white solid (1.72 g, 92%): mp 97–99 °C; ^{1}H-NMR ($CDCl_3$) δ 8.65 (dd, 1H, J = 4.6, 1.6 Hz), 7.75 (dd, 1H, J = 7.9, 1.7 Hz), 7.50–7.32 (m, 5H), 4.76 (s, 2H), 4.24 (q, 2H, J = 7.2 Hz), 2.20 (br s, 1H), 1.17 (t, 3H, J = 7.2 Hz). The following compounds were analogously prepared.

Ethyl 2-[4-(Hydroxymethyl)phenyl]pyridine-3-carboxylate (1g). Starting from **25g** (1.81 g, 5.2 mmol), compound **1g** was obtained as a yellow oil (1.3 g, 97%): ^{1}H-NMR ($CDCl_3$) δ 8.74 (dd, 1H, J = 4.8, 1.8 Hz), 8.08 (dd, 1H, J = 7.8, 1.8 Hz), 7.50–7.30 (m, 5H), 4.75 (s, 2H), 4.16 (q, 2H, J = 7.1 Hz), 3.00 (br s, 1H), 1.07 (t, 3H, J = 7.1 Hz).

Ethyl 3-[4-(Hydroxymethyl)phenyl]pyridine-4-carboxylate (1h). Starting from **25h** (2.0 g, 5.8 mmol), compound **1h** was obtained as a colorless oil (1.45 g, 97%): ^{1}H-NMR ($CDCl_3$) δ 8.64 (d, 1H, J = 5.1 Hz), 8.31 (d, 1H, J = 0.7 Hz), 7.63 (dd, 1H, J = 51, 0.7 Hz), 7.44 (d, 2H, J = 8.2 Hz), 7.26 (d, 2H, J = 8.2 Hz), 4.76 (s, 2H), 4.16 (q, 2H, J = 7.2 Hz), 3.20 (br s, 1H), 1.07 (t, 3H, J = 7.2 Hz).

Methyl 3-[4-(Bromomethyl)phenyl]furan-2-carboxylate (2a). A solution of **1a** (2.10 g, 9.2 mmol), NBS (1.80 g, 9.2 mmol), and dibenzoyl peroxide (0.04 g, 0.16 mmol) in 100 mL of CCl_4 was refluxed for 3 h. After cooling to room temperature, succinimide was removed by filtration and the resulting solution was washed with H_2O and brine and finally dried (Na_2SO_4). Evaporation gave the crude product (2.50 g, 87%) as a yellow oil which was utilized in the next step without further purification: ^{1}H-NMR ($CDCl_3$) δ 7.58 (m, 5H), 6.61 (d, 1H, J = 2.2 Hz), 4.52 (s, 2H), 3.85 (s, 3H). The following compounds were analogously prepared.

Methyl 3-[4-(Bromomethyl)phenyl]thiophene-2-carboxylate (2b). Starting from **1b** (2.00 g, 8.6 mmol), compound **2b** (2.40 g, 88%) was obtained as a low-melting solid and used without purification: ^{1}H-NMR ($CDCl_3$) δ 7.50 (m, 5H), 7.05 (d, 1H, J = 6.2 Hz), 4.54 (s, 2H), 3.78 (s, 3H).

Methyl 2-[2-(Bromomethyl)furan-5-yl]benzoate (2c). Starting from **1c** (3.00 g, 13 mmol), compound **2c** (3.3 g, 80%) was obtained as a brown oil and used without purification: ^{1}H-NMR ($CDCl_3$) δ 7.50 (m, 4H), 6.50 (d, 1H, J = 8.2 Hz), 6.46 (d, 1H, J = 8.1 Hz), 4.54 (s, 2H), 3.84 (s, 3H).

Methyl 2-[2-(Bromomethyl)thien-5-yl]benzoate (2d). Starting from **1d** (1.0 g, 4.3 mmol), compound **2d** (1.2 g, 90%) was obtained as a brown oil and used without purification: ^{1}H-NMR ($CDCl_3$) δ 7.75 (d, 1H, J = 8.3 Hz), 7.48 (m, 3H), 7.05 (d, 1H, J = 6 Hz), 6.84 (d, 1H, J = 3.6 Hz), 4.75 (s, 2H), 3.76 (s, 3H).

Ethyl 4-[4-(Bromomethyl)phenyl]-2-methylthiazole-5-carboxylate (2e). Starting from **1e** (1.50 g, 5.7 mmol), compound **2e** (1.65 g, 85%) was obtained as a low-melting solid and used without purification: ^{1}H-NMR ($CDCl_3$) δ 7.70 (d, 2H, J = 8.3 Hz), 7.43 (d, 2H, J = 8.3 Hz), 4.52 (s, 2H), 4.23 (d, 2H, J = 8.1 Hz), 2.73 (s, 3H), 1.27 (t, 3H, J = 8.1 Hz).

Preparation of Chloro Derivatives 2f–h: General Procedure. To a solution of compounds **1f–h** (10 mmol) in 50 mL of absolute EtOH was added 10 mL of 1 N HCl and the solvent evaporated under vacuum. The remaining solid was dissolved in 20 mL of $CHCl_3$ and treated with 3.6 mL (50 mmol) of thionyl chloride. The reaction mixture was stirred at room temperature until TLC indicated completion (3–5 h). The solvent was evaporated, and the residue was treated with toluene to remove traces of thionyl chloride. The residue was converted into the corresponding free base by treating the ethereal suspension of the crude hydrochloride with aqueous $NaHCO_3$ solution. The aqueous phase was again extracted twice with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered, and added to 20 mL of dry DMF. The evaporation of Et_2O without heating afforded a ≈0.5 N solution of compounds **2f–h** in DMF which was immediately utilized in the next step for the preparation respectively of compounds **4f**, **5f** (from **2f** and **3**), **4g**, **5g** (from **2g** and **3**), and **10** (from **2h** and **8**).

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[1-[2-(methoxycarbonyl)furan-3-yl]-4-phenyl]methyl]-1*H*-imidazole (4a) and the Corresponding Regioisomer 5a. In a flask under a nitrogen atmosphere containing a suspension of NaH (80%, 0.13 g, 4.2 mmol) in 5 mL of dry DMF at 25 °C, a solution of 2-butyl-4-chloro-5-(hydroxymethyl)-1*H*-imidazole[14] (**3**) (0.81 g, 4.2 mmol) in 15 mL of DMF was gradually added. After 1 h, a solution of **2a** (1.25 g, 4.2 mmol) in 5 mL of DMF was added dropwise. The reaction mixture was stirred for 16 h at 25 °C and concentrated in vacuo, and the residue was partitioned between AcOEt and H_2O. The organic phase was washed several times with brine and finally dried (Na_2SO_4). The crude product was purified by flash chromatography (AcOEt/hexane, 7:3) to afford by elution **4a** (0.41 g, 25%) and **5a** (0.37 g, 21%) as white foams, used in the next step without further purification. **4a**: ^{1}H-NMR ($CDCl_3$) δ 7.60 (m, 3H), 7.05 (d, 2H, J =

8.3 Hz), 6.60 (d, 1H, J = 2.2 Hz), 5.25 (s, 2H), 4.50 (s, 2H), 3.85 (s, 3H), 2.60 (t, 2H, J = 8.1 Hz), 1.65 (m, 2H), 1.30 (m, 2H), 0.86 (t, 3H, J = 8.1 Hz). **5a**: ^{1}H-NMR ($CDCl_3$) δ 7.50 (m, 3H), 7.05 (d, 2H, J = 8.3 Hz), 6.55 (s, 1H), 5.08 (s, 2H), 4.56 (s, 2H), 3.79 (s, 3H), 2.50 (t, 2H, J = 8.1 Hz), 1.55 (m, 2H), 1.25 (m, 2H), 0.85 (t, 3H, J = 8.1 Hz). The following compounds were analogously prepared.

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2-[2-(methoxycarbonyl)phenyl]furan-5-yl]methyl]-1*H*-imidazole (4c) and the Corresponding Isomer 5c. Starting from **2c** (2.50 g, 8.3 mmol), compounds **4c** (0.75 g, 23%) and **5c** (0.62 g, 18%) were obtained in order after purification by flash chromatography (AcOEt/hexane, 6:4) as viscous oils. **4c**: ^{1}H-NMR ($CDCl_3$) δ 7.80–7.30 (m, 4H), 6.50 (d, 1H, J = 3.2 Hz), 6.35 (d, 1H, J = 3.2 Hz), 5.17 (s, 2H), 4.66 (s, 2H), 3.69 (s, 3H), 2.70 (t, 2H, J = 8.1 Hz), 1.70 (m, 2H), 1.40 (m, 2H), 0.90 (t, 3H, J = 8.1 Hz). **5c**: ^{1}H-NMR ($CDCl_3$) δ 7.80–7.30 (m, 4H), 6.49 (d, 1H, J = 3.4 Hz), 6.32 (d, 1H, J = 3.4 Hz), 5.04 (s, 2H), 4.55 (s, 2H), 3.72 (s, 3H), 2.75 (t, 2H, J = 8.1 Hz), 1.70 (m, 2H), 1.40 (m, 2H), 0.90 (t, 3H, J = 8.1 Hz).

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2-[2-(methoxycarbonyl)phenyl]thien-5-yl]methyl]-1*H*-imidazole (4d) and the Corresponding Regioisomer 5d. Starting from **2d** (2.4 g, 7.6 mmol), compounds **4d** (1.1 g, 35%) and **5d** (0.8 g, 25%) were obtained in order by flash chromatography (AcOEt/hexane, 6:4) as white foams. **4d**: ^{1}H-NMR ($CDCl_3$) δ 7.75 (d, 1H, J = 7.8 Hz), 7.55–7.30 (m, 3H), 6.85 (m, 2H), 5.34 (s, 2H), 4.61 (s, 2H), 3.73 (s, 3H), 2.72 (t, 2H, J = 7.2 Hz), 1.79–1.45 (m, 4H), 0.91 (t, 3H, J = 7.2 Hz). **5d**: ^{1}H-NMR ($CDCl_3$) δ 7.78 (m, 1H), 7.48–7.31 (m, 3H), 6.86 (m, 2H), 5.22 (s, 2H), 4.58 (s, 2H), 3.73 (s, 3H), 2.74 (t, 2H, J = 7.1 Hz), 1.72 (m, 2H), 1.34 (m, 2H), 0.92 (t, 3H, J = 7.1 Hz).

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[1-[5-(methoxycarbonyl)-2-methylthiazol-4-yl]-4-phenyl]methyl]-1*H*-imidazole (4e) and the Corresponding Regioisomer 5e. Starting from **2e** (1.4 g, 3.9 mmol), compounds **4e** (0.63 g, 34%) and **5e** (0.35 g, 20%) were obtained in order by flash chromatography (AcOEt/hexane, 9:1), as white foams. **4e**: ^{1}H-NMR ($CDCl_3$) δ 7.70 (d, 2H, J = 8.3 Hz), 7.02 (d, 2H, J = 8.3 Hz), 5.25 (s, 2H), 4.46 (s, 2H), 4.20 (q, 2H, J = 8.1 Hz), 2.73 (s, 3H), 2.52 (t, 2H, J = 8.1 Hz), 1.70 (m, 2H), 1.25 (m, 2H + 3H), 0.88 (t, 3H, J = 8.1 Hz). **5e**: ^{1}H-NMR ($CDCl_3$) δ 7.70 (d, 2H, J = 8.5 Hz), 7.05 (d, 2H, J = 8.5 Hz), 5.13 (s, 2H), 4.59 (s, 2H), 4.23 (q, 2H, J = 8.1 Hz), 2.73 (s, 3H), 2.60 (t, 2H, J = 8.1 Hz), 1.65 (m, 2H), 1.30 (m, 2H + 3H), 0.88 (t, 3H, J = 8.1 Hz).

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[1-[2-(ethoxycarbonyl)pyridin-3-yl]-4-phenyl]methyl]-1*H*-imidazole (4f) and the Corresponding Regioisomer 5f. Starting from **2f** (0.69 g, 2.5 mmol), compounds **4f** (0.55 g, 58%) as a solid and **5f** (0.12 g, 13%) as a viscous oil were obtained by flash chromatography (AcOEt/hexane, 7:3). **4f**: mp 109–114 °C; ^{1}H-NMR ($CDCl_3$) δ 8.63 (dd, 1H, J = 4.8; 1.6 Hz), 7.71 (dd, 1H, J = 7.8, 1.6 Hz), 7.46 (dd, 1H, J = 7.8, 4.8 Hz), 7.31 (dd, 2H, J = 8.2 Hz), 7.06 (d, 2H, J = 8.2 Hz), 5.29 (s, 2H), 4.49 (s, 2H), 4.22 (q, 2H, J = 7.2 Hz), 3.10 (br s, 1H), 2.56 (t, 2H, J = 7.3 Hz), 1.65–1.33 (m, 4H), 1.14 (t, 3H, J = 7.2 Hz), 0.87 (t, 3H, J = 7.3 Hz). **5f**: ^{1}H-NMR ($CDCl_3$) δ 8.68 (dd, 1H, J = 4.8, 1.6 Hz), 7.72 (dd, 1H, J = 7.8, 1.6 Hz), 7.47 (dd, 1H, J = 7.8, 4.8 Hz), 7.33 (d, 2H, J = 8.3 Hz), 7.10 (d, 1H, J = 8.3 Hz), 5.15 (s, 2H), 4.61 (s, 2H), 4.23 (q, 2H, J = 7.2 Hz), 2.59 (t, 2H, J = 7.3 Hz), 1.65 (quint, 2H, J = 7.3 Hz), 1.34 (sext, 2H, J = 7.3 Hz), 1.14 (t, 3H, J = 7.2 Hz), 0.89 (t, 3H, J = 7.3 Hz).

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[1-[3-(ethoxycarbonyl)pyridin-2-yl]-4-phenyl]methyl]-1H-imidazole (4g) and the Corresponding Regioisomer 5g. Starting from **2g** (1.9 g, 6.9 mmol), compounds **4g** (0.57 g, 20%) and **5g** (0.72 g, 27%) were obtained by flash chromatography (AcOEt/hexane, 8:2) as viscous oils. **4g**: ^{1}H-NMR ($CDCl_3$) δ 8.75 (dd, 1H, J = 4.8, 1.8 Hz), 8.13 (dd, 1H, J = 7.8, 1.8 Hz), 7.50 (d, 2H, J = 8.3 Hz), 7.35 (dd, 2H, J = 7.8, 4.8 Hz), 7.05 (d, 2H, J = 8.3 Hz), 5.29 (s, 2H), 4.47 (s, 2H), 4.17 (q, 2H, J = 7.1 Hz), 2.57 (t, 2H, J = 7.5 Hz), 2.40 (br s, 1H), 1.68–1.34 (m, 4H), 1.09 (t, 3H, J = 7.2 Hz), 0.88 (t, 3H, J = 7.5 Hz). **5g**: ^{1}H-NMR ($CDCl_3$) δ 8.76 (dd, 1H, J = 4.8, 1.7 Hz), 8.13 (dd, 1H, J = 7.8, 1.7 Hz), 7.51 (d, 2H, J = 8.1 Hz), 7.35 (dd, 1H, J = 7.8, 4.8 Hz), 7.09 (d, 2H, J = 8.1 Hz), 5.16 (s, 2H), 4.60 (s, 2H), 4.16 (q, 2H, J = 7.1 Hz), 2.60 (t, 2H, J = 7.5 Hz), 1.65 (quint, 2H, J = 7.5 Hz), 1.34 (sext, 2H, J = 7.5 Hz), 1.06 (t, 3H, J = 7.1 Hz), 0.88 (t, 3H, J = 7.5 Hz).

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[1-[2-(methoxycarbonyl)thien-3-yl]-4-phenyl]methyl]-1*H*-imidazole (4b). To a stirred mixture of **9** (0.5 g, 1.0 mmol) in 10 mL of EtOH at 25 °C was gradually added $NaBH_4$ (40 mg, 1.1 mmol). After 30 min, the reaction mixture was cooled to 0 °C and treated with 10% AcOH until gas evolution ceased. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography (AcOEt/hexane, 60:40) to yield compound **4b** as a white solid (0.40 g, 90%): mp 114–118 °C; ^{1}H-NMR ($CDCl_3$) δ 7.60 (d, 1H, J = 5.3 Hz), 7.48 (d, 2H, J = 8.3 Hz), 7.09 (d, 1H, J = 5.3 Hz), 7.05 (d, 2H, J = 8.3 Hz), 5.25 (s, 2H), 4.51 (s, 2H), 3.77 (s, 3H), 2.62 (t, 2H, J = 8.0 Hz), 1.68 (m, 2H), 1.25 (m, 2H), 0.88 (t, 3H, J = 8.0 Hz).

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[1-(4-ethoxycarbonyl)pyridin-3-yl]-4-phenyl]methyl]-1*H*-imidazole (4h). Starting from **10** (0.20 g, 0.45 mmol) and after purification by flash chromatography (AcOEt/hexane, 80:20), compound **4h** was obtained (0.19 g, 95%) as a viscous oil: ^{1}H-NMR ($CDCl_3$) δ 8.70 (d, 1H, J = 5.1 Hz), 8.62 (s, 2H), 7.65 (d, 1H, J = 5.1 Hz), 7.31 (d, 2H, J = 8.2 Hz), 7.07 (d, 2H, J = 8.2 Hz), 5.29 (s, 2H), 4.52 (s, 2H), 4.17 (q, 2H, J = 7.1 Hz), 2.59 (t, 2H, J = 7.3 Hz), 1.68–1.35 (m, 4H), 1.09 (t, 3H, J = 7.1 Hz), 0.89 (t, 3H, J = 7.3 Hz).

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[1-(2-carboxyfuran-3-yl)-4-phenyl]methyl]-1*H*-imidazole (6a). Compound **4a** (0.35 g, 0.8 mmol) was dissolved in a mixture of 15 mL of MeOH and 8 mL of 4 N NaOH and refluxed for 3 h. After cooling, the solvent was evaporated under vacuum and the resulting residue was dissolved in 10 mL of H_2O. Treatment with 2 N HCl (pH 4) gave a white solid which was collected by filtration and dried (0.16 g, 50%): mp 172–174 °C; ^{1}H-NMR (DMSO-d_6) δ 7.55 (m, 3H), 7.03 (d, 2H, J = 8.2 Hz), 6.60 (s, 1H), 5.25 (s, 2H), 4.53 (s, 1H), 2.57 (t, 2H, J = 8.1 Hz), 1.70–1.30 (m, 4H), 0.78 (t, 3H, J = 8.1 Hz); MS (EI) m/e 388 (M). Anal. ($C_{20}H_{21}ClN_2O_4 \cdot 0.75H_2O$) C,H,N. The following compounds were analogously prepared.

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[1-(2-carboxythien-3-yl)-4-phenyl]methyl]-1*H*-imidazole (6b). Starting from **4b** (0.18 g, 0.4 mmol), compound **6b** (0.14 g, 80%) was obtained as a white solid: mp 144–147 °C; ^{1}H-NMR (DMSO-d_6) δ 7.81–7.07 (m, 6H), 5.27 (s, 2H), 4.35 (s, 2H), 2.52 (t, 2H, J = 8.1 Hz), 1.55–1.13 (m, 4H), 0.75 (t, 3H, J = 8.1 Hz). Anal. ($C_{20}H_{21}ClN_2O_3S \cdot 0.8H_2O$) C,H,N.

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[5-(2-carboxyphenyl)furan-2-yl]methyl]-1*H*-imidazole (6c). Starting from **4c** (0.30 g, 0.7 mmol), compound **6c** (0.14 g, 48%) was obtained as an ivory solid: mp 121–124 °C); ^{1}H-NMR (DMSO-d_6) δ 7.40–7.59 (m, 4H), 6.69 (d, 1H, J = 4.2 Hz), 6.52 (d, 1H, J = 4.2 Hz), 5.26 (s, 2H), 4.47 (s, 2H), 2.70 (t, 2H, J = 8.1 Hz), 1.62–1.27 (m, 4H), 0.85 (t, 3H, J = 8.1 Hz); MS (EI) m/e 388 (M). Anal. ($C_{20}H_{21}ClN_2O_4$) C,H,N.

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[5-(2-carboxyphenyl)thien-2-yl]methyl]-1*H*-imidazole (6d). Starting from **4d** (0.8 g, 1.9 mmol), compound **6d** (0.6 g, 78%) was prepared as a yellow solid: mp 89–92 °C; ^{1}H-NMR ($CDCl_3$) δ 7.82–7.41 (m, 4H), 6.92–6.85 (m, 1H + 1H), 5.32 (s, 2H), 4.59 (s, 2H), 2.64 (t, 2H, J = 8.1 Hz), 1.65 (m, 2H), 1.35 (m, 2H), 0.86 (t, 3H, J = 8.1 Hz); MS (EI) m/e 404 (M). Anal. ($C_{20}H_{21}ClN_2O_3S \cdot 0.25H_2O$) C,H,N.

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[1-(5-carboxy-2-methylthiazol-4-yl)-4-phenyl]methyl]-1*H*-imidazole (6e). Starting from **4e** (0.42 g, 0.9 mmol), compound **6e** (0.27 g, 68%) was prepared as a white solid: mp 153–156 °C; ^{1}H-NMR (DMSO-d_6) δ 7.70 (d, 2H, J = 8.3 Hz), 7.10 (d, 2H, J = 8.3 Hz), 5.30 (s, 2H), 4.34 (s, 2H), 2.68 (s, 3H), 2.50 (t, 2H, J = 8.1 Hz), 1.49 (m, 2H), 1.29 (m, 2H), 0.80 (t, 3H, J = 8.1 Hz). Anal. ($C_{20}H_{22}ClN_3O_3S \cdot 0.5H_2O$) C,H,N.

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[1-(2-carboxypyridin-3-yl)-4-phenyl]methyl]-1*H*-imidazole (6f). Starting from **4f** (0.90 g, 2.0 mmol), compound **6f** (0.52 g, 65%) was prepared as a white solid: mp 170–175 °C; ^{1}H-NMR (CD_3OD) δ 8.58 (d, 1H, J = 4.8 Hz), 7.90 (d, 1H, J = 7.8 Hz), 7.62 (m, 1H), 7.45 (d, 2H, J = 8.2 Hz), 7.15 (d, 2H, J = 8.2 Hz), 5.36 (s, 2H), 4.48 (s, 2H), 2.60 (t, 2H, J = 7.0 Hz), 1.61–1.22 (m, 4H), 0.85 (t, 3H, J = 7.2 Hz). Anal. ($C_{21}H_{22}ClN_3O_3$) C,H,N.

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[1-(3-carboxypyridin-2-yl)-4-phenyl]methyl]-1*H*-imidazole (6g). Starting from **4g** (0.75 g, 1.7 mmol), compound **6g** (0.38 g, 55%) was prepared as a white solid: mp 178–181 °C); ^{1}H-NMR (CD_3OD) δ 8.67 (d, 1H, J = 4.9 Hz), 8.22 (d, 1H, J = 7.8 Hz), 7.52 (m, 3H), 7.16 (d, 2H, J = 8.4 Hz), 5.38 (s, 2H), 4.48 (s, 2H), 2.61 (t, 2H, J = 7.2 Hz), 1.21–1.65 (m, 4H), 0.87 (t, 3H, J = 7.2 Hz). Anal. ($C_{21}H_{22}ClN_3O_3$) C,H,N.

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[1-(4-carboxypyridin-3-yl)-4-phenyl]methyl]-1*H*-imidazole (6h). Starting from **4h** (0.53 g, 1.2 mmol), compound **6h** (0.34 g, 71%) was obtained as a white solid: mp 115–119 °C; ^{1}H-NMR (CD_3OD) δ 8.64 (d, 1H, J = 5.1 Hz), 8.59 (s, 1H), 7.72 (d, 1H, J = 5.1 Hz), 7.45 (d, 2H, J = 8.3 Hz), 7.17 (d, 2H, J = 8.3 Hz), 5.37 (s, 2H), 4.49 (s, 2H), 2.60 (t, 2H, J = 7.2 Hz), 1.20–1.65 (m, 4H), 0.85 (t, 3H, J = 7.2 Hz). Anal. ($C_{21}H_{22}ClN_3O_3 \cdot 0.75H_2O$) C,H,N.

2-Butyl-5-chloro-4-(hydroxymethyl)-1-[[1-(2-carboxyfuran-3-yl)-4-phenyl]methyl]-1*H*-imidazole (7a). Starting from **5a** (0.32 g, 0.8 mmol), compound **7a** (0.17 g, 55%) was obtained as a yellow solid: mp 195 °C; ^{1}H-NMR (DMSO-d_6) δ 7.92 (d, 1H, J = 2.3 Hz), 7.62 (d, 2H, J = 8.3 Hz), 7.05 (d, 2H, J = 8.3 Hz), 6.83 (d, 1H, J = 8.3 Hz), 6.83 (d, 1H, J = 2.3 Hz), 5.21 (s, 2H), 4.26 (s, 2H), 2.62 (t, 2H, J = 8.1 Hz), 1.22–1.58 (m, 2H + 2H), 0.82 (t, 3H, J = 8.1 Hz); MS (EI) *m/e* 388 (M). Anal. ($C_{20}H_{21}ClN_2O_4$) C, H, N.

2-Butyl-5-chloro-4-(hydroxymethyl)-1-[[5-(2-carboxyphenyl)furan-2-yl]methyl]-1*H*-imidazole (7c). Starting from **5c** (0.45 g, 1.1 mmol), compound **7c** (0.24 g, 55%) was obtained as a yellow solid: mp 196–200 °C; ^{1}H-NMR (DMSO-d_6) δ 7.41–7.60 (m, 4H), 6.68 (d, 1H, J = 4.2 Hz), 6.50 (d, 1H, J = 4.2 Hz), 5.16 (s, 2H), 4.23 (s, 2H), 2.78 (t, 2H, J = 8.1 Hz), 1.31–1.67 (m, 4H), 0.84 (t, 3H, J = 8.1 Hz); MS (EI) *m/e* 388 (M). Anal. ($C_{20}H_{21}ClN_2O_4$) C, H, N.

2-Butyl-5-chloro-4-(hydroxymethyl)-1-[[5-(2-carboxyphenyl)thien-2-yl]methyl]-1*H*-imidazole (7d). Starting from **5d** (0.42 g, 1.0 mmol), compound **7d** (0.2 g, 52%) was obtained as a white solid: mp 62–64 °C; ^{1}H-NMR ($CDCl_3$) δ 7.89–7.37 (m, 4H), 6.95–6.88 (m, 2H), 5.20 (s, 2H), 4.51 (s, 2H), 2.50 (t, 2H, J = 8.1 Hz), 1.30 (m, 2H), 1.15 (m, 2H), 0.76 (t, 3H, J = 8.1 Hz). Anal. ($C_{20}H_{21}ClN_2O_3S$) C,H,N.

2-Butyl-5-chloro-4-(hydroxymethyl)-1-[[1-(5-carboxy-2-methylthiazol-4-yl)-4-phenyl]methyl]-1*H*-imidazole (7e). Starting from **5e** (0.35 g, 0.8 mmol), compound **7e** (0.12 g, 40%) was prepared as an ivory solid: mp 162–165 °C; ^{1}H-NMR (DMSO-d_6) δ 7.72 (d, 2H, J = 8.2 Hz), 7.05 (d, 2H, J = 8.2 Hz), 5.23 (s, 2H), 4.29 (s, 2H), 2.60 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 0.82 (t, 3H, J = 8.1 Hz). Anal. ($C_{20}H_{22}ClN_3O_3S \cdot 0.5H_2O$) C,H,N.

2-Butyl-5-chloro-4-(hydroxymethyl)-1-[[1-(2-carboxypyridin-3-yl)-4-phenyl]methyl]-1*H*-imidazole (7f). Starting from **5f** (0.5 g, 1.1 mmol), compound **7f** (0.26 g, 59%) was prepared as a yellow solid: mp 184–186 °C; ^{1}H-NMR (CD_3OD) δ 8.61 (dd, 1H, J = 4.8, 1.5 Hz), 7.93 (dd, 1H, J = 7.8, 1.5 Hz), 7.64 (dd, J = 7.8, 1.5 Hz), 7.47 (d, 2H, J = 8.3 Hz), 7.29 (d, 2H, J = 8.3 Hz), 5.54 (s, 2H), 4.64 (s, 2H), 3.00 (t, 2H, J = 7.3 Hz), 1.65 (quint, 2H, J = 7.3 Hz), 1.36 (sext, 2H, J = 7.3 Hz), 0.90 (t, 3H, J = 7.3 Hz). Anal. ($C_{21}H_{22}ClN_3O_3 \cdot 0.5H_2O$) C,H,N.

2-Butyl-5-chloro-4-(hydroxymethyl)-1-[[1-(3-carboxypyridin-2-yl)-4-phenyl]methyl]-1*H*-imidazole (7g). Starting from **5g** (0.62 g, 1.4 mmol), compound **7g** (0.3 g, 78%) was prepared as an ivory solid: mp 184–186 °C); ^{1}H-NMR (CD_3OD) δ 8.66 (dd, 1H, J = 4.9, 1.8 Hz), 8.18 (dd, 1H, J = 7.8, 1.8 Hz), 7.58 (d, 2H, J = 8.4 Hz), 7.48 (dd, 1H, J = 7.8, 4.9 Hz), 7.17 (d, 2H, J = 8.4 Hz), 5.34 (s, 2H), 4.53 (s, 2H), 2.72 (t, 2H, J = 7.3), 1.57 (quint, 2H, J = 7.3 Hz), 1.34 (sext, 2H, J = 7.3 Hz), 0.88 (t, 3H, J = 7.3 Hz). Anal. ($C_{21}H_{22}ClN_3O_3 \cdot H_2O$) C,H,N.

2-Butyl-4-chloro-5-formyl-1-[[1-[2-(methoxycarbonyl)-thien-3-yl]-4-phenyl]methyl]-1*H*-imidazole (9). A mixture of 2-butyl-4-chloro-5-formyl-1*H*-imidazole (**8**)[14] (0.2 g, 1.1 mmol), bromo derivative **2b** (0.33 g, 1.1 mmol), and K_2CO_3 (0.45 g, 3.2 mmol) in 15 mL of dry DMF was stirred for 24 h at 25 °C. The solvent was evaporated under vacuum and the residue partitioned between AcOEt and H_2O. The organic phase was separated, washed with brine, and dried (Na_2SO_4). The crude product was purified by flash chromatography (AcOEt/hexane, 6:4) to afford compound **9** as a white foam (0.33 g, 75%): ^{1}H-NMR ($CDCl_3$) δ 9.76 (s, 1H), 7.62–7.30 (m, 3H), 7.18–7.03 (m, 3H), 5.58 (s, 2H), 3.77 (s, 3H), 2.72 (t, 2H, J = 8.0 Hz), 1.72 (m, 2H), 1.48 (m, 2H), 0.89 (t, 3H, J = 8.0 Hz). The following compound was analogously prepared.

2-Butyl-4-chloro-5-formyl-1-[[1-[4-ethoxycarbonyl)pyridin-3-yl]-4-phenyl]methyl]-1*H*-imidazole (10). Starting from **8** (0.24 g, 1.3 mmol) and **2h** (0.42 g, 1.5 mmol) and after purification by flash chromatography (AcOEt/hexane, 4:6), compound **10** was obtained as a viscous oil (0.45 g, 84%): ^{1}H-NMR ($CDCl_3$) δ 8.77 (s, 1H), 8.71 (d, 1H, J = 5.0 Hz), 8.63 (s, 1H), 7.64 (dd, 1H, 5.0, 0.5 Hz), 7.30 (d, 2H, J = 8.4 Hz), 7.12 (d, 2H, J = 8.4 Hz), 5.61 (s, 2H), 4.15 (q, 2H, J = 7.1 Hz), 2.67 (t, 2H, J = 7.3 Hz), 1.74 (quint, 2H, J = 7.3 Hz), 1.37 (sext, 2H, J = 7.3 Hz), 1.04 (t, 3H, J = 7.1 Hz), 0.91 (t, 3H, J = 7.3 Hz).

3,3-Dimethoxy-1-(4-methylphenyl)propan-1-one (12). A mixture of 4-methylacetophenone (**11**) (33 g, 250 mmol) and HCO_2Me (18 g, 300 mmol) was added to a slurry of $NaOCH_3$ (16 g, 250 mmol) in 200 mL of dry Et_2O as slowly as to maintain gentle reflux. After 2 h of stirring, Et_2O was distilled under vacuum and 68 mL of a 7.4 N dry HCl methanolic solution was added. The temperature of the mixture was lowered to 20 °C, and stirring was continued for 2 h. Then a 1 N KOH methanolic solution was added until the mixture was alkaline. The resulting insoluble inorganic salts were removed by filtration, and the organic phase was evaporated under vacuum. The residue was purified by flash chromatography (AcOEt/hexane, 1:4) to afford pure compound **12** as a yellow oil (20.5 g, 40%); ^{1}H-NMR ($CDCl_3$) δ 7.82 (d, 2H, J = 8.2 Hz), 7.22 (d, 2H, J = 8.2 Hz), 4.98 (t, 1H, J = 5.4 Hz), 3.39 (s, 6H), 3.22 (d, 2H, J = 5.4 Hz), 2.39 (s, 3H).

Methyl 5,5-Dimethoxy-3-(4-methylphenyl)-2,3-epoxypentanoate (13). To a mixture of **12** (7.9 g, 38.9 mmol) and methyl chloroacetate (5.4 g, 60.0 mmol) in 100 mL of dry Et_2O cooled to −10 °C was gradually added $NaOCH_3$ (4.1 g, 7.50 mmol) at a rate which allowed the temperature to be maintained below 0 °C. The solution was then allowed to warm to room temperature and stirred overnight. The solution was cooled to 0 °C, and 5% AcOH was added (pH 4). The organic phase was separated and the aqueous phase extracted twice with 50 mL of Et_2O. The combined organic phases were washed with aqueous $NaHCO_3$ and brine and finally dried (Na_2SO_4). After evaporation under vacuum, a brown oil was obtained (10.2 g, 97%). The crude product was utilized as a mixture of diastereoisomers, without further purification: ^{1}H-NMR ($CDCl_3$) δ 7.40–7.10 (m, 4H), 4.35 (m, 1H), 3.81 (s, 3H), 3.46 (s, 1H), 3.73 (s, 1H, minor isomer), 3.44 (s, 3H, minor isomer).

Ethyl 2-Bromo-3-(4-methylphenyl)-3-oxopropanoate (15). To a stirred solution of ethyl 3-(4-methylphenyl)-3-oxopropanoate (**14**)[28] (3.4 g, 16.5 mmol) in refluxing CCl_4 was added dropwise a solution of Br_2 (2.7 g, 16.5 mmol) in 8 mL of CCl_4. After 30 min, the solvent was evaporated in vacuo to give compound **15** as a brown oil (4.5 g, 96%). The crude product was utilized without further purification: ^{1}H-NMR ($CDCl_3$) δ 7.88 (d, 2H, J = 8.2 Hz), 7.28 (d, 2H, J = 8.2 Hz), 5.64 (s, 1H), 4.26 (q, 2H, J = 6.4 Hz), 2.41 (s, 3H), 1.23 (t, 3H, J = 6.4 Hz).

1-(2-Bromophenyl)-1,4-pentanedione (17). A mixture of 2-bromobenzaldehyde (20.0 g, 486 mmol), MVK (41.0 g, 585 mmol), 5-(2-hydroxyethyl)-4-methyl-3-benzylthiazolium chloride (24.2 g, 89.7 mmol), and 50 mL of Et_3N was stirred under a N_2 atmosphere at 70 °C for 4 h. The reaction mixture was cooled to room temperature and partitioned between Et_2O (500 mL) and H_2O (200 mL). The aqueous layer was separated and extracted twice with Et_2O. The combined organic extracts was successively washed several times with 2 N HCl and then with brine. After removal of the solvent in vacuo a yellow oil was obtained which was utilized without further purification (110 g, 93%): ^{1}H-NMR ($CDCl_3$) δ 7.65–7.18 (m, 4H), 3.15 (t, 2H, J = 6.3 Hz), 2.89 (t, 2H, J = 6.3 Hz), 2.22 (s, 3H).

2-(2-Bromophenyl)-5-methylfuran (18). In a glass apparatus equipped with a bypassed dropping funnel filled with 4 Å molecular sieves between the flask and the reflux condenser, compound **17** (18.0 g, 74.0 mmol) was dissolved in

200 mL of dry C_6H_6 and refluxed for 12 h in the presence of a catalytic amount of *p*-TsOH·H_2O (0.38 g, 2.2 mmol). After cooling, the resulting dark solution was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (AcOEt/hexane, 5:95) to give **18** as an orange oil (12.2 g, 70%): ^{1}H-NMR ($CDCl_3$) δ 7.79 (dd, 1H, J = 8.2, 2.3 Hz), 7.63 (dd, 1H, J = 8.2, 2.3 Hz), 7.30 (m, 3H), 6.12 (m, 1H), 2.38 (d, 1H, J = 2.3 Hz).

[4-[[(Tetrahydro-2*H*-pyran-2-yl)oxy]methyl]phenyl]boronic Acid (23). To a solution of tetrahydro-2-[(4-bromophenyl)methoxy]-2*H*-pyran (**22**) (14.5 g, 53.5 mmol) (prepared from 4-bromobenzyl alcohol and dihydropyran[29]) in 60 mL of anhydrous THF at −78 °C under a N_2 atmosphere was added dropwise *n*-BuLi (37 mL, 59 mmol of a 1.6 M hexane solution). The mixture was stirred for 45 min and treated with trimethyl borate (16.7 g, 160.4 mmol). The solution was allowed to warm to room temperature overnight. Then it was cooled to 0 °C, diluted with brine, and acidified to pH 6.5 with 5% aqueous HCl. The organic phase was separated and extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried ($MgSO_4$). Removal of the solvent under vacuum afforded compound **23** as an orange oil (13.6 g, 99%) which was utilized without further purification to prepare compounds **25f−h**.

Tetrahydro-2-[[4-[4-(ethoxycarbonyl)pyridin-3-yl]phenyl]methoxy]-2*H*-pyran (25h). To a dried, N_2-purged 3-necked flask with a reflux condenser was added the solution of ethyl 3-bromopyridine-4-carboxylate[30] (**24h**) (3.62 g, 15.7 mmol) in 10 mL of 1,2-DME. $Pd^0(PPh_3)_4$ (0.54 g, 0.47 mmol) was added, and the resulting suspension was allowed to stir for 30 min at room temperature. The solution of boronic acid derivative **23** (7.7 g, 32.6 mmol) in 20 mL of 1,2-DME was then added followed immediately by 22 mL of a 2 M Na_2CO_3 aqueous solution. The reaction mixture was heated to gentle reflux until TLC indicated completion (5−7 h). After cooling, the reaction mixture was diluted with H_2O and Et_2O and filtered over a Celite pad. The aqueous phase was extracted with Et_2O. The organic phase was washed with 1 N NaOH and then with H_2O and finally dried (Na_2SO_4). After evaporation, the crude product was purified by flash chromatography (AcOEt/hexane, 1:1) to yield compound **25h** as a colorless oil (4.40 g, 82%): ^{1}H-NMR ($CDCl_3$) δ 8.71−8.60 (m, 2H), 7.62 (dd, 1H, J = 5.1, 0.7 Hz), 7.44 (d, 2H, J = 8.2 Hz), 7.32 (d, 2H, J = 8.2 Hz), 4.57 (d, 1H, J = 12.3 Hz), 4.17 (q, 2H, J = 7.2 Hz), 4.03−3.88 (m, 1H), 3.62−3.50 (m, 1H), 2.00−1.52 (m, 6H), 1.07 (t, 3H, J = 7.2 Hz). The following compounds were analogously prepared.

Tetrahydro-2-[[4-[2-(ethoxycarbonyl)pyridin-3-yl]phenyl]methoxy]-2*H*-pyran (25f). Using the same procedure described for **25h**, starting from ethyl 3-[[(trifluoromethyl)-sulfonyl]oxy]pyridine-2-carboxylate (**24f**) (8.81 g, 29.4.4 mmol) in the presence of LiCl (3.8 g, 88.2 mmol) and **23** (10.7 g, 45.3 mmol), compound **25f** was obtained as a colorless oil (5.51 g, 55%): ^{1}H-NMR ($CDCl_3$) δ 8.67 (dd, 1H, J = 4.8, 1.6 Hz), 7.75 (dd, 1H, J = 7.8, 1.6 Hz), 7.50−7.32 (m, 5H), 4.85 (d, 1H, J = 12.3 Hz), 4.73 (t, 1H, J = 3.1 Hz), 4.56 (d, 1H, J = 12.3 Hz), 4.24 (q, 2H, J = 7.1 Hz), 4.05−3.88 (m, 1H), 3.65−3.50 (m, 1H), 2.00−1.45 (m, 6H), 1.15 (t, 3H, J = 7.1 Hz).

Tetrahydro-2-[[4-[3-(ethoxycarbonyl)pyridin-2-yl]phenyl]methoxy]-2*H*-pyran (25g). Using the same procedure described for **25h**, starting from ethyl 2-chloropyridine-3-carboxylate (**24g**) (3.47 g, 22.6 mmol) and **23** (8.00 g, 34.0 mmol) and after purification by flash chromatography, compound **25g** was obtained as a colorless oil (3.5 g, 45%): ^{1}H-NMR ($CDCl_3$) δ 8.76 (dd, 1H, J = 4.8, 1.6 Hz), 8.09 (dd, 1H, J = 7.8, 1.8 Hz), 7.55−7.30 (m, 5H), 4.84 (d, 1H, J = 12.5 Hz), 4.71 (t, 1H, J = 3.1 Hz), 4.59 (d, 1H, J = 12.5 Hz), 4.17 (q, 2H, J = 7.1 Hz), 4.02−3.87 (m, 1H), 3.63−3.50 (m, 1H), 2.05−1.50 (m, 6H), 1.07 (t, 3H, J = 7.1 Hz).

Biology. Angiotensin II (AT_1) Receptor-Binding Assay. Rat adrenal capsular membranes were prepared according to Chang and Lotti.[31] Both adrenals were removed from rats (Sprague−Dawley, 250 g; Charles River, Italy), and each one was cut open carefully; the medulla was ejected from the capsules by gentle pressure. Membranes were prepared from the adrenal capsules: tissue was homogenized in 10 mL of Tris-HCl (50 mM) using a polytron (10000 rpm for 30 s) and then centrifuged at 50000*g* for 20 min at 4 °C. The supernatant was discarded and the pellet resuspended in 10 mL of buffer (composition: 10 mM sodium phosphate buffer, pH 7.4, containing 10 mM NaCl, 5 mM EDTA, and 0.1 mM PMSF) using the polytron as described above. The protein content of the homogenate was determined using a Bio-Rad protein assay kit, and the centrifugation was repeated. The supernatant was again discarded, the pellet was resuspended in 30 mL of the above mentioned buffer, and the centrifugation was repeated. The final supernatant was discarded and the pellet resuspended in the assay buffer (10 mM sodium phosphate buffer, pH 7.4, containing 100 mM NaCl, 5 mM EDTA, 0.1 mM PMSF, 0.2 mg/mL soybean trypsin inhibitor, 0.019 mg/mL, 1,10-*O*-phenanthroline, 2 mg/mL BSA heat denaturated and protease free, and 0.14 mg/mL bacitracin) at a protein concentration of 0.04 mg/mL. [^{125}I]Sar^{1}Ile^8-angiotensin II (25 μL) (New England Nuclear) at a concentration of 50 μM was incubated with 25 μL of assay buffer (to define total binding), 1 μM of Sar^1-Ile^8-angiotensin II (to define nonspecific binding), or various concentrations of test substances.

The incubation was initiated by the addition of 200 μL of membrane preparation (0.008 mg of protein/tube) in a final volume of 250 μL. After 3 h at 37 °C, the incubation was terminated by filtration under vacuum (Multiscreen PVDF; 0.66 micron plates) and the residue washed off the filters with 3 × 250 μL of ice cold Tris-HCl (50 mM), pH 7.4. The equilibrium dissociation constants for an inhibitor (K_i) were calculated using the iterative fitting program LIGAND (Cambridge Biosoft, U.K). Replicate curves were analyzed simultaneously by LIGAND and the constants calculated ± approximate standard error.

Antagonism of Angiotensin II-Induced Contraction in Rabbit Aorta. Male New Zealand white rabbits (2−4 kg) were sacrificed by cervical dislocation and exsanguinated. The thoracic aorta was rapidly removed, cleaned of surrounding tissue, and cut into helical strips (3−4 mm wide and 20−25 mm long) according to Furchgott and Bhadrakom.[32]

The endothelium layer was removed mechanically by gently rubbing the luminal surface of the strip with a cotton tip. Strips were mounted in a 10 mL organ bath containing Krebs bicarbonate solution of the following composition (mM): NaCl, 118.4; KCl, 4.7; KH_2PO_4, 1.2; $MgSO_4·7H_2O$, 1.2; $CaCl_2·2H_2O$, 2.5; $NaHCO_3$, 25; dextrose, 11.1. The Krebs buffer was kept at 37 °C and pH 7.4 while bubbling continuously with 5% CO_2 in O_2.

The initial resting tension was set to 1.0*g*, and the aortic strips were allowed to equilibrate for 90 min. At the end of the period, a control cumulative concentration−response curve for AII (10^{-10}−10^{-7} M) was obtained. The tissues were washed several times until the base line was reached; 45 min later, the antagonist was added 15 min before a second challenge with AII (10^{-10}−3.10^{-5} M). Each antagonist was tested at four different increasing concentrations for the determination of the pA_2 values using the Schild equation.[33]

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