Brief Articles

Comparison of 3D Structures and AT_1 Binding Properties of Pyrazolidine-3,5-diones and Tetrahydropyridazine-3,6-diones with Parent Antihypertensive Drug Irbesartan

Bertrand Le Bourdonnec,*,† Christine Cauvin,‡ Emmanuelle Meulon,† Saïd Yous,† Jean-François Goossens,§ François Durant,‡ Raymond Houssin,† and Jean-Pierre Hénichart†

Institut de Chimie Pharmaceutique Albert Lespagnol and Laboratoire de Chimie Analytique, Faculté des Sciences Pharmaceutiques et Biologiques, Université de Lille 2, Rue du Professeur Laguesse, BP 83, F-59006 Lille, France, and Facultés Universitaires Notre-Dame de la Paix, Laboratoire de Chimie Moléculaire Structurale, Rue de Bruxelles, 61, B-5000 Namur, Belgium

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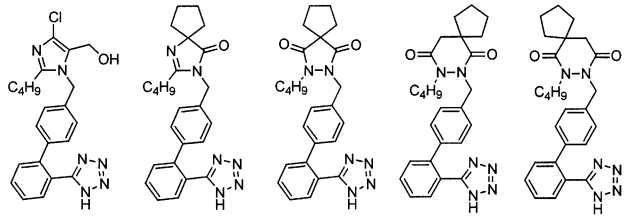
A new series of nonpeptide AT_1 receptor antagonists were recently developed, based on the structure of irbesartan (Le Bourdonnec et al. *J. Med. Chem.* **2000**, *43*, 2685−2697). The lead compound **1** displayed high selectivity for the AT_1 receptor subtype but lower binding affinity than irbesartan. As expected from molecular modeling studies, extension of the pyrazolidine-3,5-dione scaffold to the six-membered heterocycle tetrahydropyridazine-3,6-dione led to an enhancement of the binding affinity toward the AT_1 receptor.

Introduction

The renin angiotensin system (RAS) plays an important role in the regulation of blood pressure through the actions of angiotensin II (AII) (vasoconstriction, aldosterone secretion, renal sodium reabsorption, and norepinephrine release) and thus is an appropriate target for therapeutic intervention in hypertension.[1] The discovery by the DuPont group of a series of (biphenylmethyl)imidazoles as nonpeptidic potent and orally active AII receptor (AT_1 subtype) antagonists has opened up a completely new field in AII antagonist research, and structure−activity relationships (SAR) for this class of compounds have been intensively explored.[2−4] A number of studies have appeared in which the imidazole moiety of losartan (Chart 1) is successively replaced by other heterocycles indicating that the AT_1 receptor is quite permissive in accepting this region of the nonpeptide antagonists. A SAR analysis of the losartan type AT_1 antagonists has brought to light key elements implied in the drug−receptor interaction:[5] a bulky substituent (the chlorine atom of losartan and the tetramethylene group of irbesartan,[6,7] (Chart 1)), which could occupy a large hydrophobic cavity in the AT_1 receptor; an alkyl chain (the butyl chain of losartan and irbesartan), which could fit into a second lipophilic pocket in the AT_1 receptor; a biaromatic structure (the biphenyl group of losartan and irbesartan) able to fit into a third hydrophobic pocket; an acidic group (the tetrazole group of losartan and irbesartan) able to interact with a basic residue of the AT_1 receptor; a moiety (hydroxymethyl group of losartan and carbonyl group of irbesartan), which is capable of a hydrogen-bonding interaction with the AT_1 receptor; a heterocyclic nitrogen (at the 3-position of the imidazole ring of losartan and at the 3-position of the imidazolinone ring of irbesartan) acting as a hydrogen bond acceptor. On the basis of the structure of irbesartan, we replaced the nitrogen at the 3-position of the imidazolinone ring by a carbonyl group, which could maintain hydrogen bond characteristics. Thus, we prepared a series of pyrazolidine-3,5-diones in which the two heterocyclic carbonyl groups are believed to interact by specific hydrogen bonding with the receptor.[8] One of the most active compounds, **1** (Chart 1), displayed high affinity for the AT_1 receptor, good selectivity for AT_1 vs AT_2, and potent in vitro antagonist activity. However, the difference of affinity between **1** [K_i (AT_1) = 25 nM] and irbesartan [K_i (AT_1) = 2 nM] suggested that the carbonyl group at the 5-position of the pyrazolidinedione ring of **1** is not positioned in the optimal orientation in order to mimic the nitrogen at the 3-position of the imidazolinone ring of irbesartan. Here, we report a comparative structural analysis of irbesartan and compound **1** by X-ray crystallography and molecular modeling. On the basis of the

Chart 1. Structures of Losartan, Irbesartan, and Compounds **1**−**3**



* To whom correspondence should be addressed. Tel: 484-595-1061. Fax: 484-595-1551. E-mail: blebourdonnec@adolor.com.
† Institut de Chimie Pharmaceutique Albert Lespagnol, Université de Lille 2.
‡ Laboratoire de Chimie Moléculaire Structurale.
§ Laboratoire de Chimie Analytique, Université de Lille 2.

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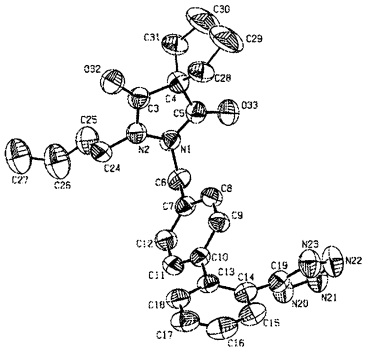


Figure 1. Ortep view of compound **1** with displacement ellipsoids drawn at the 50% probability level**.** Only the conformation with the highest occupancy factors of the disordered butyl and spiropentyl groups is shown. Hydrogen atoms are omitted for clarity.

modeling studies, we show that the replacement of the pyrazolidine-3,5-dione scaffold of **1** by a tetrahydropyridazine-3,6-dione heterocycle (Chart 1) is accompanied by an increase of affinity toward the AT_1 receptor.

X-ray Structural Analysis and Molecular Modeling

The X-ray analysis of **1** (Figure 1) indicates that the biphenyl group is positioned nearly orthogonal to the pyrazolidine-3,5-dione heterocycle. The two phenyl rings are distorted by 48.7° because of the presence of the tetrazole group. The tetrazole moiety is not coplanar to the terminal phenyl ring: the angle between the planes of the two rings is 55.6°. Similar structural features have been previously observed in the crystal structure of irbesartan[9] and other losartan type AT_1 antagonists.[10−12] The molecular modeling studies were conducted on the structures of **1** and irbesartan. We used the DISCO[13] (DIStance COmparison) program, an algorithm available in the Sybyl[14] software, to superimpose the two derivatives. The first step of the DISCO search routines consists of identifying all potential pharmacophoric site points in each molecule. The site point assignments include aromatic and aliphatic ring centroids, functional groups with a hydrogen bond donor (−OH, $-NH_2$, etc.) or acceptor (C═O, −OH, etc.) potential, and external site points that represent receptor-associated hydrogen bond acceptors or donors. Because the two ligands are flexible, we generated individual conformer databases using CONFEX[15] (CONFormation EXploration). At the end of the CONFEX procedure, we obtained two databases of 18 and 20 conformers for **1** and irbesartan with energy ranges (energy difference between the highest and the lowest energy conformer) of 6.5 and 4.5 kcal/mol, respectively. Some conformations among the conformer databases were found to be similar to the crystal structures. The conformational databases were then exported into the DISCO program to perform the superimposition of the two compounds. Among the different superimposition models proposed by DISCO, we selected those that fit into the hypothetical pharmacophore of the nonpeptide AT_1 antagonists (see Introduction) and those that showed a good overlay of the two compounds. These latter models display the following features (Figure 2a): (i) a H-bond acceptor group (carbonyl moieties at positions 5 and 3 of the

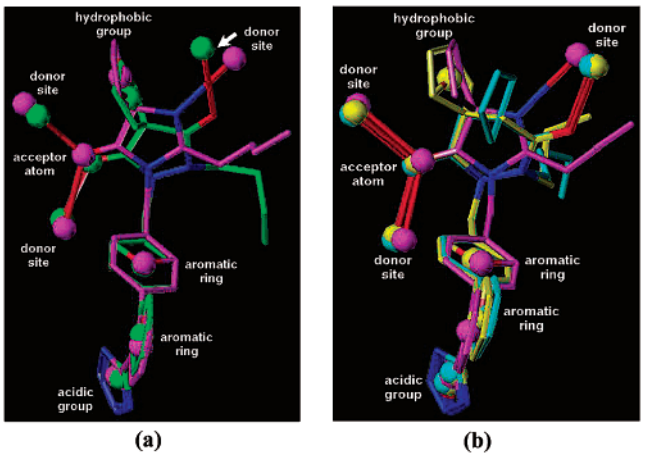
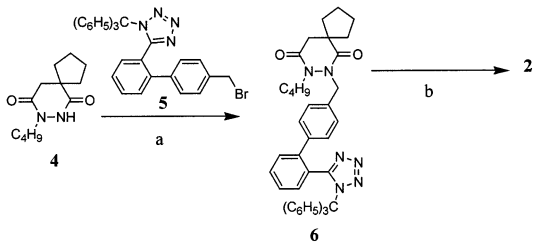


Figure 2. (a) Superimposition of compound **1** (green) onto irbesartan (magenta). (b) Superimposition of compounds **2** (yellow) and **3** (cyan) onto irbesartan (magenta). The pharmacophoric features are represented by colored balls.

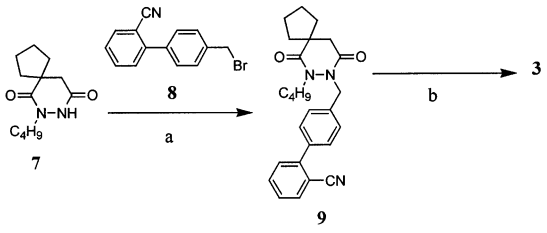
imidazolinone and pyrazolidinedione heterocycles, respectively) and the corresponding external donor site points; (ii) a H-bond donor group of the receptor, interacting with the carbonyl moiety at position 5 of the pyrazolidinedione scaffold of **1** and with the nitrogen atom at position 3 of the imidazolinone moiety of irbesartan; (iii) the center of mass of the phenyl rings of the two compounds; (iv) the center of mass of the spirocyclopentyl rings of the two compounds; and (v) the centers of the tetrazole moieties. The superimposition model represented in Figure 2a showed that the donor sites corresponding to the carbonyl moiety at position 5 of the pyrazolidinedione ring of **1** and to the nitrogen atom at position 3 of the imidazolinone ring of irbesartan (see white arrow in Figure 2a) are not as well-superimposed as the other features. The distance between the two donor sites is 1.3 Å. The correlation of these observations with the binding affinity results led us to hypothesize that the carbonyl moiety at the 5-position of the pyrazolidinedione heterocycle of **1** is not properly oriented in order to interact with a H-bond donor residue of the AT_1 receptor. On the basis of this hypothesis, structural modifications were investigated in order to enhance the AT_1 binding affinity of compound **1**. The extension of the pyrazolidine-3,5-dione scaffold to a tetrahydropyridazine-3,6-dione heterocycle was proposed in order to optimize the orientation of the carbonyl moiety at the 5-position of the pyrazolidinedione heterocycle of **1**. The position of the spirocyclopentyl group on the central heterocycle led to distinguish the two regioisomers **2** and **3** (Chart 1). According to the previous procedure, the two isomers **2** and **3** were separately superimposed with irbesartan. The conformational databases generated by CONFEX for compounds **2** and **3** contained 23 and 20 conformers with energy ranges of 6.5 and 5.5 kcal/mol, respectively. The superimposition models generated by DISCO highlighted a better fit of **2** with irbesartan (Figure 2b). Indeed, the distance between the carbonyl moiety at the 6-position of the tetrahydropyridazinedione heterocycle of **2** and **3** and the nitrogen atom at the 3-position of the imidazolinone ring of irbesartan is lower than 0.7 Å. Furthermore, the superimposition model shows a better overlap between the cyclopentyl groups of **2** and

Scheme 1[a]



[a] Reagents and conditions: (a) K_2CO_3, DMF. (b) HCl (37%), water/THF.

Scheme 2[a]



[a] Reagents and conditions: (a) K_2CO_3, DMF. (b) $(C_4H_9)_3SnCl$, NaN_3, DMF.

irbesartan, as compared to the overlap between the cyclopentyl groups of **3** and irbesartan. Hence, on the basis of these molecular modeling studies, compound **2** is expected to bind to the AT_1 receptor with a better affinity than compounds **1** or **3**. To check our hypothesis, the tetrahydropyridazine-3,6-dione derivatives **2** and **3** were synthesized and evaluated in vitro.

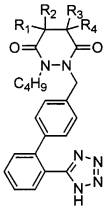
Chemistry

The synthesis of regioisomers **2** and **3** is outlined in Schemes 1 and 2, respectively. Alkylation of *N*-butyltetrahydropyridazine-3,6-dione **4**[16] with *N*-triphenyl-5-[4′-(bromomethyl)biphenyl-2-yl]tetrazole **5** in dimethylformamide (DMF) in the presence of potassium carbonate afforded the desired *N*-alkylated product **6**. The trityl group of **6** was subsequently cleaved by treatment with HCl in water/tetrahydrofuran (THF) to yield the target compound **2** in good yield. Compound **3** was obtained from *N*-butyltetrahydropyridazine-3,6-dione **7**[16] (regioisomer of **4**) by alkylation with 4-(bromomethyl)-2′-cyanobiphenyl **8** followed by formation of the tetrazole ring with tributyltin azide in DMF.

Results and Discussion

The title compounds were tested for their affinity toward the AT_1 and AT_2 receptors as reported previously.[8] The binding data presented in Table 1 showed that compound **2** displayed significantly better affinity toward the AT_1 receptor than the pyrazolidine-3,5-dione analogue **1** and the regioisomer **3**. These results are in agreement with the molecular modeling studies. Hence, the carbonyl function at the tetrahydropyridazinedione 6-position of **2** might be positioned in a favorable orientation to mimic the nitrogen at position 3 of the imidazolinone moiety of irbesartan and interact with specific hydrogen bonding with a donor residue of the AT_1 receptor. Furthermore, the difference of affinity between compound **2** and its regioisomer **3** showed that the position of the cyclopentyl moiety on the tetrahydropyridazine-3,6-dione scaffold is of critical importance for a good fit of these compounds with the AT_1 receptor. The proximity between this lipophilic moiety, which is thought to occupy a hydrophobic cavity in the AT_1 receptor and the carbonyl moiety at the tetrahydropyridazinedione 6-position, seems to play an important role for a good affinity with the receptor. However, compound **2** displays lower binding affinity than irbesartan toward the AT_1 receptor (Table 1). This could be partly attributed to electronic differences between the carbonyle at position 6 of the tetrahydropyridazinedione moiety of **2**, and the nitrogen at position 3 of the imidazolinone moiety of irbesartan. Indeed, calculation of the molecular electrostatic potential of the two heterocycles shows that the attractive potential well-induced by the carbonyle at position 6 of the tetrahydropyridazinedione moiety of **2** is less deep than the attractive potential generated by the nitrogen at position 3 of the imidazolinone moiety of irbesartan (data not shown). As previously observed in the pyrazolidine-3,5-dione series,[8] compounds **2** and **3** displayed only weak affinity toward the AT_2 receptor (% displacement of [^{3}H]AII at 10^{-5} M < 20%). The in vitro antagonist activity and the in vitro binding affinity of compounds **2** and **3** have been evaluated on the same cell preparation (PLC-PRF-5 cell line) in order to directly elaborate the affinity/activity correlation. As shown in Table 1, compound **2** is a more potent inhibitor of the AII-mediated increase in cytosolic Ca^{2+} concentration[8] than its regioisomer. Hence, for these ligands, the functional antagonist properties correlate well with the respective specific binding affinities.

Table 1. AT_1 Binding Affinity and In Vitro Antagonist Activity of Tetrahydropyridazine-3,6-diones



compd	R_1	R_2	R_3	R_4	K_i[a] (nM)	IC_{50}[b] (nM)
2	H	H	$(CH_2)_4$		14 ± 1	9 ± 1
3	$(CH_2)_4$		H	H	80 ± 5	102 ± 6
1					25 ± 3	28 ± 3
irbesartan					2 ± 1	4 ± 1

[a] AT_1 binding, human hepatoma cell line, PLC-PRF-5. Each value represents the mean ± SD of three independent experiments. The K_d (dissociation constant), B_{max} (maximal number of binding sites), and Hill coefficient of [^{3}H]AII are given as follows: 1.1 nM, 700 (fmol/mg protein), 1.0 ± 0.2. [b] Inhibition of AII (50 nM)-induced intracellular $[Ca^{2+}]_i$ increase in PLC-PRF-5 cells.

In summary, on the basis of molecular modeling studies, we designed a new series of tetrahydropyridazine-3,6-diones as potent and selective AT_1 receptor antagonists exemplified by compound **2**.

Experimental Section

A. Chemistry. Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^{1}H (80 MHz) NMR spectra were recorded on a Bruker WP80SY spectrometer, and ^{1}H (300 MHz) NMR spectra were recorded on a Bruker AC300P spectrometer. They

are reported in parts per million on the δ scale, from the indicated reference. Electron-impact mass spectra (EI-MS) were obtained on a Finnigan TSQ700 instrument. Combustion analyses were carried out in the Elementar Analysis Department of the CNRS (F-69390 Vernaison). When analyses are indicated by the symbols of the elements, the results are within ±0.4% of theoretical values. Analytical thin-layer chromatography (TLC) was performed on silica gel $60F_{254}$ plates from E. Merck reagents and visualized by UV irradiation and/or iodine. Flash chromatography was conducted with silica gel A (230−430 mesh, E. Merck). Starting materials were purchased from Aldrich and were used as received. Irbesartan and compound **1** were synthesized according to the reported procedure.[6,8]

General Procedure for Alkylation of Compound 4 and 7. K_2CO_3 (5.3 mmol) was added portion wise to a solution of compounds **4** or **7**[16] (1.78 mmol) in DMF (30 mL). The desired alkyl bromide **5** (or **8**) (1.78 mmol) was then added to the reaction mixture, which was allowed to stir for 20 h at room temperature. Water (150 mL) was added, and the resulting suspension was extracted with Et_2O. The combined organic extracts were washed with water and dried ($MgSO_4$), and the solution was concentrated. The crude products were purified by column chromatography (hexanes−EtOAc mixtures of increasing polarity).

8-Butyl-7-[[2′-[1-(triphenylmethyl)-1*H*-tetrazol-5-yl]-(1,1′-biphenyl)-4-yl]methyl]-7,8-diazaspiro[4.5]decane-6,9-dione (6). Yield 77%; R_f 0.41 (hexane/EtOAc = 7:3). IR(KBr): 2957, 1670 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.86 (t, J = 6.6 Hz, 3H), 1.26 (m, 2H), 1.42−1.78 (m, 8H), 2.14 (m, 2H), 2.32 (s, 2H), 3.59 (t, J = 7.7 Hz, 2H), 4.72 (s, 2H), 6.89−8.00 (m, 23H).

7-Butyl-8-[[2′-cyano(1,1′-biphenyl)-4-yl]methyl]-7,8-diazaspiro[4.5]decane-6,9-dione (9). Yield 70%; R_f 0.22 (hexane/EtOAc = 7:3). IR (KBr): 2940, 2920, 2860, 2220, 1660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 7.2 Hz, 3H), 1.24 (m, 2H), 1.45 (m, 2H), 1.60 (m, 8H), 2.51 (s, 2H), 3.79 (t, J = 7.5 Hz, 2H), 4.86 (s, 2H), 7.45 (m, 6H), 7.62 (m, 1H), 7.76 (d, J = 8.2 Hz, 1H).

8-Butyl-7-[[2′-(1*H*-tetrazol-5-yl)(1,1′-biphenyl)-4-yl]-methyl]-7,8-diazaspiro[4.5]decane-6,9-dione (2). HCl (37%) (0.45 mL, 5.48 mmol) was added dropwise to a solution of compound **6** (0.96 g, 1.37 mmol) in 50 mL of a mixture of water/THF (1:4). The mixture was allowed to stir at room temperature for 30 h. THF was removed under reduced pressure, and the solution was made basic with 2 N aqueous NaOH (10 mL), washed with Et_2O, and acidified with 3 N aqueous HCl. The resulting suspension was extracted with Et_2O. The combined organic extracts were washed with water and dried ($MgSO_4$), and the solvent was removed. The resulting precipitate was further purified by crystallization to give **2** as colorless crystals (0.36 g, 58%); mp 143−146 °C (cyclohexane); R_f 0.31 (CH_2Cl_2/MeOH = 9:1). IR (KBr): 3440, 2959, 1667, 1642 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.93 (t, J = 7.0 Hz, 3H), 1.30 (m, 2H), 1.42−1.74 (m, 8H), 2.13 (m, 2H), 2.31 (s, 2H), 3.63 (m, 2H), 4.86 (s, 2H), 7.14−7.62 (m, 8H). EI-MS [$M^{\cdot+}$] 458. Anal. ($C_{26}H_{30}N_6O_2$) C, H, N.

7-Butyl-8-[[2′-(1*H*-tetrazol-5-yl)(1,1′-biphenyl)-4-yl]-methyl]-7,8-diazaspiro[4.5]decane-6,9-dione (3). Tributyltin chloride (2.61 mL, 9.62 mmol) and sodium azide (0.62 g, 9.62 mmol) were added successively to a solution of compound **9** (1 g, 2.40 mmol) in DMF (15 mL). The mixture was heated at 130 °C under nitrogen atmosphere for 12 h. After it was cooled, the solution was poured into ice/water and was then acidified with 6 N aqueous HCl. The resulting precipitate was collected by filtration, washed with water and hexane, and further purified by crystallization to afford **3** as colorless crystals (0.66 g, 61%); mp 198 °C (acetonitrile); R_f 0.50 (EtOAc). IR (KBr): 2960, 2920, 2840, 1670, 1635 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.82 (t, J = 7.1 Hz, 3H), 1.14 (m, 2H), 1.31 (m, 2H), 1.54 (m, 8H), 2.53 (s, 2H), 3.70 (m, 2H), 4.79 (s, 2H), 7.08−7.65 (m, 8H)). EI-MS [$M^{\cdot+}$] 458. Anal. ($C_{26}H_{30}N_6O_2$) C, H, N.

B. Biological Methods. The membrane preparation, AT_1 receptor binding assay (PLC-PRF cells), AT_2 receptor binding assay (calf cerebellum cortex), and measurement of intracellular Ca^{2+} concentration have been described previously.[8]

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Supporting Information Available: Crystallographic details for **1** including tables of atomic coordinates, atomic thermal parameters, bond distances, and angles; molecular modeling experimental details including conformational analysis and superimposition procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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