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The Conformation and Activity Relationship of Fused Analogs of DuP753

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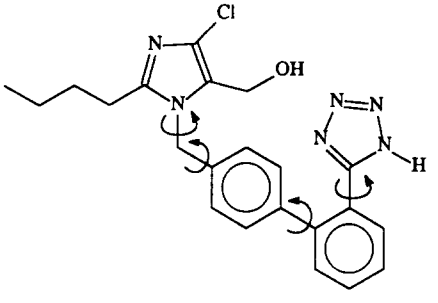
Abstract—We have prepared three conformationally restricted analogs of DuP753 in which one of the phenyl rings in the biphenyl moiety is fused to the imidazole ring, and have investigated the conformation–biological activity relationship of these compounds. Conformational analysis on DuP753 and these compounds confirms that a specific 3-dimensional arrangement of pharmacophoric elements is essential for biological activity.

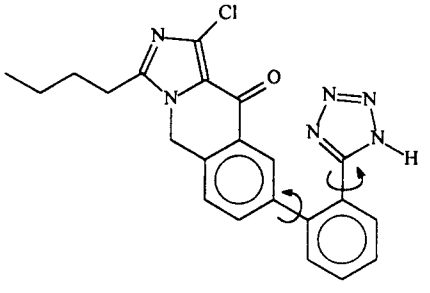
Introduction

The renin–angiotensin system (RAS)[1] plays an important role in the regulation of blood pressure and fluid homeostasis and electrolyte balance. Angiotensin II (AII),[1,2] an octapeptide produced in the blood stream by the action of the angiotensin-converting enzyme (ACE) on the biologically inactive decapeptide angiotensin I (AI) by cleavage of angiotensinogen by renin, is the most potent pressor agent and the most important product of the renin–angiotensin cascade. Biochemical effects of the active hormone AII, such as vasoconstriction, aldosterone release, and renal reabsorption of sodium are thought to be mediated by the actions of membrane-bound receptors present on various tissues and organs such as adrenal cortex, heart, kidney, arterioles, and sympathetic nerve endings.

Inhibition of the RAS by renin inhibitors,[3] ACE inhibitors,[4] and AII receptor antagonists[5] continues to be the most active area of the drug discovery for the treatment of hypertension, congestive heart failure, and possibly chronic renal failure. Ideally, the most direct approach to interfere with the RAS would be to inhibit the binding of the effector hormone AII at the receptor level. This specific approach to inhibit the RAS offers considerable potential for the treatment of hypertension with minimal side effects.



1 (DuP753)



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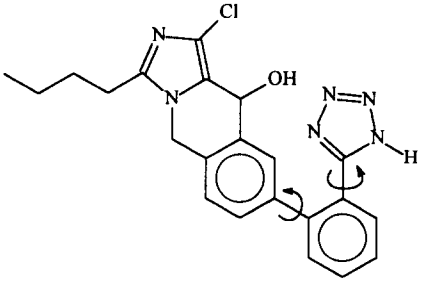

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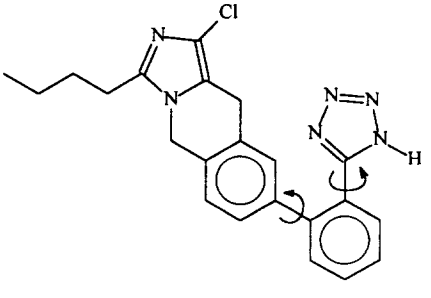

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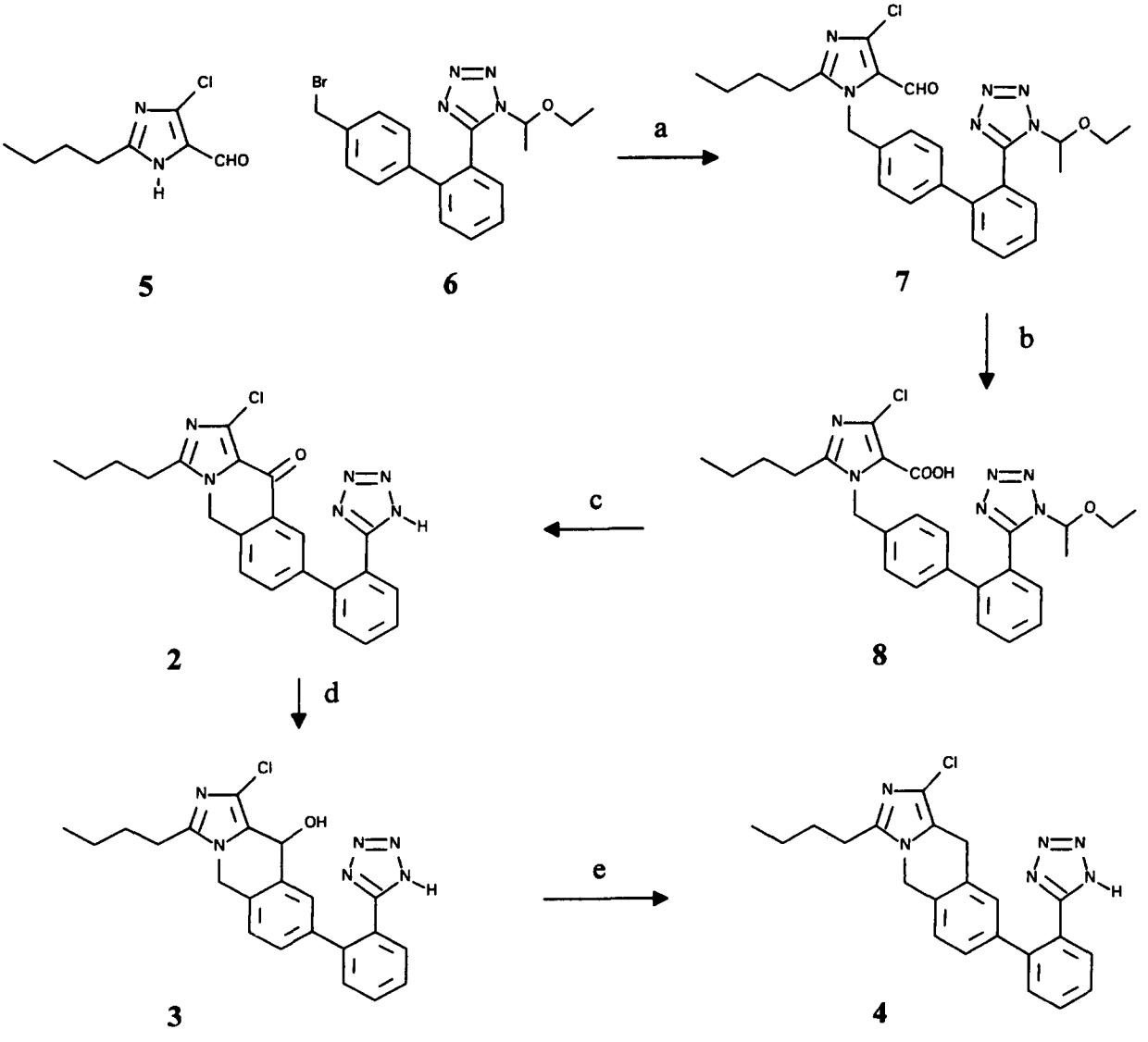
Figure 1. The four model compounds. The arrowed bonds were varied in the molecular modeling study.

Until recently most of the known AII receptor antagonists have been peptide analogs of AII[5b,6] and known to have common problems normally associated with peptides such as poor oral absorption, short plasma half lives and rapid clearance. Furthermore, many of them are known to exhibit a partial agonistic activity. However, the discovery of nonpeptide AII antagonists[7] has provided a new opening in this area. The first report on the prototype imidazole-based nonpeptide AII antagonists was disclosed by the Takeda group.[8] Structural modifications of Takeda's lead compound by DuPont have led to the discovery of DuP753 (losartan, **1**)[6b,9] which is currently undergoing clinical trials.

In the previous studies with the DuP753 series,[9c,10] it was proposed that there are three pharmacophoric elements in the molecule: nitrogen atoms on the imidazole ring, carbon atoms of butyl side chain and a tetrazole moiety. In the present work, we have synthesized the structurally rigid compounds **2–4**, in which one of the phenyl rings in the biphenyl moiety is fused to the imidazole ring, and have investigated the conformation–activity relationship of these compounds concerning the necessary arrangement of pharmacophoric elements in the 3-dimensional space.

Results and Discussion

The synthesis of the fused compounds **2–4**, is shown in Figure 2. The tetrazole protected imidazole aldehyde **5** was *N*-alkylated with bromo compound **6** to give **7**. The



a) K_2CO_3, DMF, room temp., 5 hrs
b) $KMnO_4$, KH_2PO_4, t-BuOH, room temp., 5 hrs
c) 1) oxalyl chloride, reflux, 30 min.
2) $AlCl_3$, CS_2, reflux, 30 min.
d) $NaBH_4$, MeOH-THF, reflux, 30 min.
e) Et_3SiH, $BF_3.Et_2O$, CH_2Cl_2, reflux, 2 hrs

Figure 2. The synthesis of the three conformationally restricted analogs of DuP753.

aldehyde group was then oxidized to the acid derivative **8**. The carboxylic acid group was converted to the acid chloride and then acid chloride was subjected to Friedel–Craft conditions to give the compound **2**. The carbonyl group on **2** was reduced to the corresponding alcohol **3**. The alcohol group in **3** can be reduced to give **4** by reacting with triethylsilane in the presence of boron trifluoride.

Table 1. The percent inhibition of the four model compounds

Compounds	10^{-5}M[a]	10^{-6}M[a]
DuP753	93.2	85.2
2	4.1	0.9
3	0.1	0.0
4	0.0	0.0

[a]The percent inhibition at the indicated concentration.

Binding assays for these compounds were carried out by using AII receptors prepared from Wistar rat liver microsomes and 3 nM of [^{3}H] angiotensin II was used as hot ligand. The percent inhibition of these compounds at the concentrations of 10^{-5} M and 10^{-6} M is shown in Table 1.

As can be seen from Table 1, the compounds **2–4**, are almost completely devoid of activity in the AII receptor binding assay. The complete loss of the activity suggests that these compounds are lacking some elements necessary for biological activity. The fact that the compound **3** which contains the same functional groups as in DuP753 (**1**) is not active, suggests that the 3-dimensional arrangement of pharmacophoric elements might be more important and crucial for good binding activity.

Therefore, the conformation of the molecules and the relative arrangement of these elements in the 3-dimensional space is carefully scrutinized. First with DuP753, conformers which have energy level within 1 kcal mol^{-1} of the lowest energy conformation were selected and they were superimposed by a least-squares fit on three atoms: 1-nitrogen, 2-carbon and 5-carbon of the imidazole moiety as shown in Figure 3. It is apparent in Figure 3 that all conformers fall into four sets depending on the positions of their tetrazole group. Furthermore, conformers with relatively lower energies fall into two sets in which the biphenyltetrazole moiety locates either side of the imidazole plane. In the set of lowest energy conformers, the angle between the imidazole plane and the biphenyl tetrazole group is about 75°.

A similar approach was used for the compounds **2–4**. Figure 4 shows the superimposition of the low energy conformers ($\Delta E \leq 1$ kcal mol^{-1}) of the compounds, **2**(a), **3**(b) and **4**(c), respectively. Conformers are overlapped in the same manner as used in Figure 3.

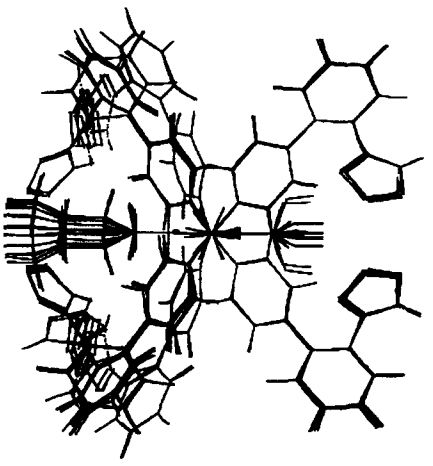


Figure 3. Superimposition on the conformations of DuP753 with energy within 1.0 kcal mol^{-1} of the minimum energy conformation.

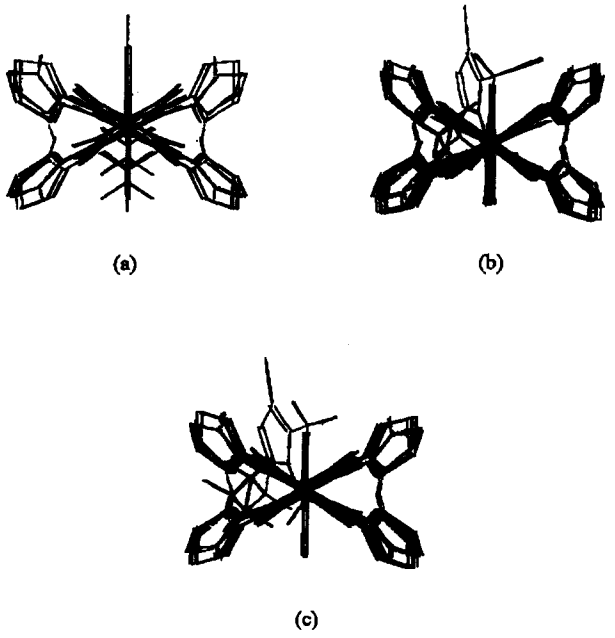


Figure 4. Superimposition on the conformations of the (a) **2**, (b) **3** and (c) **4** compound with energy within 1.0 kcal mol^{-1} of the minimum energy conformation, respectively.

Most biologically active molecules can exist in numerous conformations and the conformations can be altered during the interaction with the receptor. Therefore, it is more reasonable to deal with a group of relatively low energy conformers rather than with few low energy conformers. Figure 5 shows the superimposition of the lowest energy conformation of each of the four compounds. The blue, red, violet and green colors represent DuP753, **2**, **3** and **4**, respectively.

It is clear from Figure 5 that the space occupied by the tetrazole moiety from the compounds **2–4** is clearly different from that of DuP753. In the case of DuP753, an acute angled triangle is formed by the butyl, imidazole, and tetrazole groups. On the contrary, in the case of

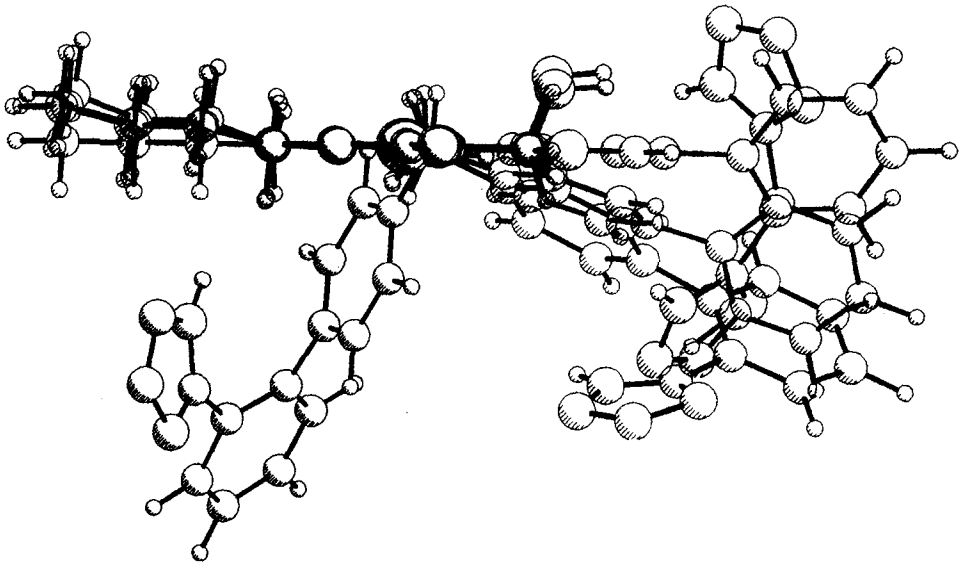


Figure 5. Superimposition on the lowest energy conformations of the four model compounds. The blue, red, violet and green colors represent the DuP753, **2**, **3** and **4** respectively.

compounds **2**–**4**, almost a straight line is formed by these groups.

Conventionally, a pharmacophoric arrangement can be expressed in terms of distances between pharmacophoric groups. As shown in Figure 6, the distance between the centroid of the imidazole ring and the centroid of the tetrazole ring is about 6.271, 8.229, 7.276 and 6.477 Å in the lowest energy conformation of **1**, **2**, **3** and **4**, respectively. Furthermore, the distance between the centroid of the tetrazole ring and the farthest carbon atom of the butyl chain is about 5.661, 12.900, 12.950

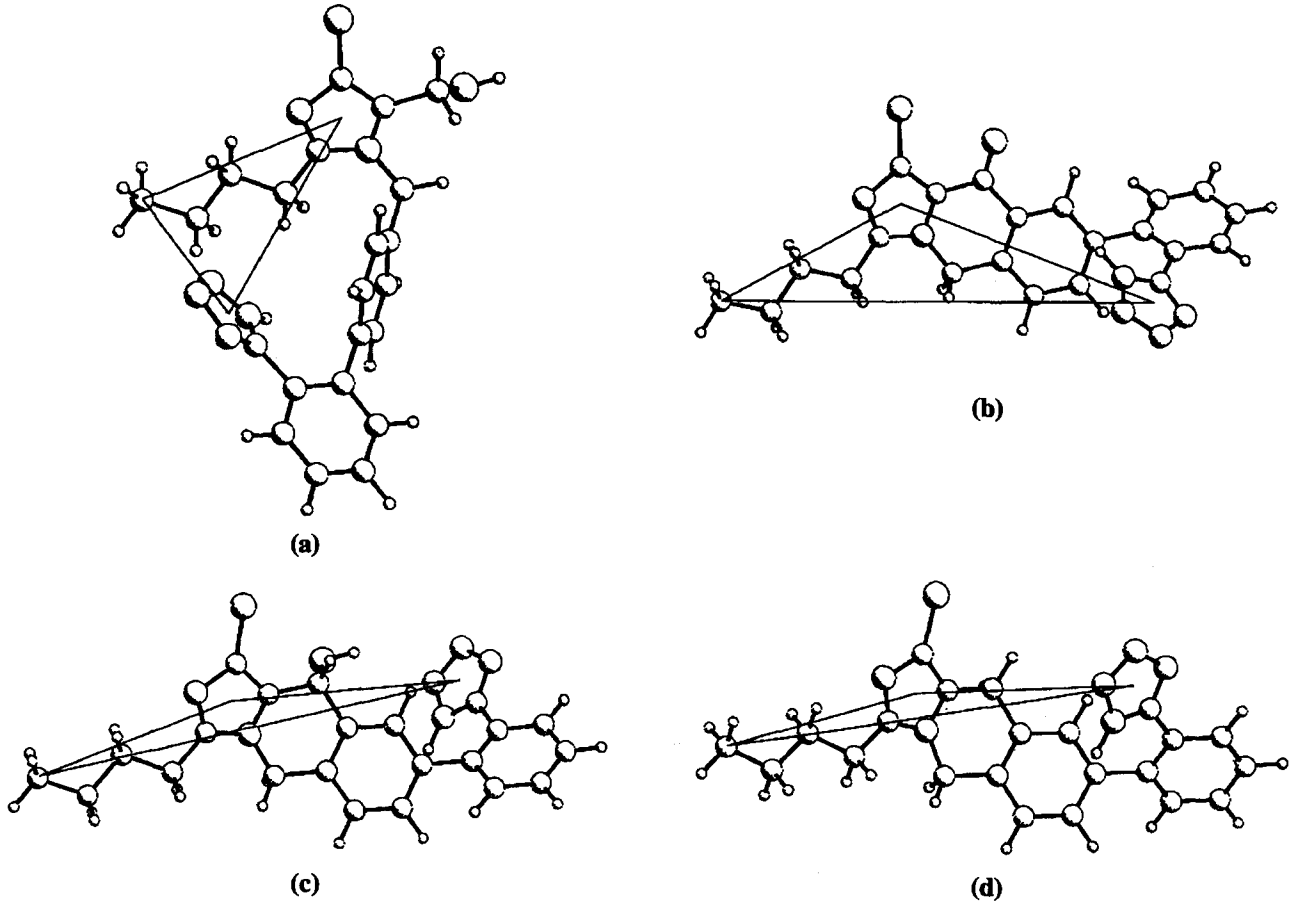


Figure 6. The lowest energy conformation of (a) DuP753, (b) **2**, (c) **3** and (d) **4**. The distance between the centroid of the imidazole ring and the centroid of the tetrazole ring: (a) 6.271, (b) 8.229, (c) 7.276 and (d) 6.477 Å. The distance between the centroid of tetrazole ring and the farthest carbon atom of butyl chain: (a) 5.661, (b) 12.900, (c) 12.950, and (d) 11.799 Å.

and 11.799 Å in compounds **1**, **2**, **3** and **4**, respectively. These data also clearly indicate that the 3-dimensional arrangement of three pharmacophoric elements is quite different between DuP753(**1**) and the conformationally rigid compounds **2–4**. This might explain why the conformationally rigid compounds **2–4** are not active in the AII binding assay.

Conclusion

In this study, our goal was to define the 3-dimensional arrangement of the pharmacophoric elements for a good binding to the AII receptor. This study confirms that a particular arrangement of three pharmacophoric groups (imidazole ring, butyl chain and acidic tetrazole group) is essential for a good AII receptor binding as in the case of DuP753.

Experimental

AII binding assay

Angiotensin II receptors from Wistar rat liver microsomes were prepared as previously described. The pellet from final spin was resuspended in assay buffer, containing 50 mM Trizma base, 5 mM $MgCl_2$, 0.25% bovine serum albumin, pH 7.2. Test compounds were dissolved at 1 mM in DMSO and serially diluted to two concentrations for activity screening.

Binding assays were performed in triplicate tubes by incubating aliquots of freshly prepared particulate fraction (0.15–0.20 mg of protein: measured by Biorad DC protein assay kit) with 3 nM [^{3}H] angiotensin II (New England Nuclear) and test compounds in 12 × 100 borosilicated glass tubes in a final volume of 0.5 mL assay buffer. Total binding and nonspecific binding were tested with vehicle and unlabelled 1 mM angiotensin II respectively to calculate the per cent inhibition.

After incubation in a shaking incubator for 60 min at 25 °C, the reaction was terminated by addition of 3 mL of cold wash buffer containing 50 mM Trizma base, 5 mM $MgCl_2$, pH 7.2 and the bound/free radioactivity were separated rapidly through glass fiber filters (GF/C Whatman, presoaked with assay buffer) with a Brandel cell harvester. The filters were washed with an additional 3 mL of cold wash buffer and trapped radioactivity was measured by a Packard scintillation counter.

In typical experiments, the nonspecific binding was about 10% of total binding. After correction for nonspecific binding, the bound radioactivity in the presence of a given concentration of test compound was compared to specific binding in the control to determine the per cent inhibition.

Molecular modeling

Molecular modeling studies were carried out to probe the conformational preferences of the biphenyltetrazole moiety in the imidazole AII antagonists. All computations were carried out by using the graphics modeling package SYBYL version 6.0,[11] running on a Silicon Graphics IRIS (4D/310 GTX) workstation. The energetically favorable conformations of four compounds were determined by molecular mechanics calculations and atomic charges were calculated by the Gasteiger–Marsili method. Low energy conformers were identified by minimizing (MAXMIN2) the starting geometries generated by stepwise rotation (in steps of 30° in the range of 0° to 330°) of single bonds indicated by the arrows in Figure 1. Although a butyl group in the 2-position of the imidazole ring is possible for a free rotation, a fully extended form was used in order to simplify the calculations.

Synthesis

3-Butyl-1-chloro-8-[2-(1H-tetrazol-5-yl)-phenyl]-5,10-dihydro-imidazo[1,5-b]isoquinolin-1-one (2). To a solution of 2-butyl-5-chloro-3*H*-imidazole-4-carbaldehyde (**5**) (2.5 g, 13.40 mmol) in 30 mL of dimethylformamide was added 5-(4'-bromomethylbiphenyl-2-yl)-1-(1-ethoxyethyl)-1*H*-tetrazole (**6**) (5.7 g, 14.74 mmol) and potassium carbonate (5.55 g, 40.20 mmol). The reaction mixture was then stirred at room temperature for 5 h. The reaction mixture was diluted with 150 mL of ethyl acetate. The solution was washed with 100 mL of water twice and the ethyl acetate layer was concentrated under vacuum. The residue was purified by silica gel column chromatography (elution: hexane:ethyl acetate = 3:1) to give 5.61 g (85%) of 2-butyl-5-chloro-3-{2'-[1-(1-ethoxyethyl)-1*H*-tetrazol-5-yl]biphenyl-4-ylmethyl}-3*H*-imidazole-4-carbaldehyde (**7**).

To a solution of **7** (2.04 g, 4.14 mmol) in 30 mL of *tert*-butanol was added potassium phosphate (10 mL of 1.25 M aq. solution) and potassium permanganate (6.62 mL of 1 M aq. solution). The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with 150 mL of ethyl acetate. The solution was washed with 100 mL of water twice and the ethyl acetate layer was concentrated under vacuum. The residue was purified by silica gel column chromatography (elution: 10% methanol in ethyl acetate) to give 1.58 g (75%) of 2-butyl-5-chloro-3-{2'-[1-(1-ethoxyethyl)-1*H*-tetrazol-5-yl]biphenyl-4-ylmethyl}-3*H*-imidazole-4-carboxylic acid (**8**).

To a solution of **8** (2.7 g, 5.31 mmol) in 10 mL of methylene chloride was added oxalyl chloride (1.4 mL, 15.93 mmol). The reaction mixture was refluxed for 30 min and then concentrated to give a crude acid chloride. To this residue in 25 mL of carbon disulfide was added anhydrous aluminum chloride (2.12 g, 15.93 mmol) and the reaction mixture was refluxed for 3 h. The reaction was quenched by adding water dropwise. The reaction mixture was diluted with 150 mL of methylene chloride. The solution was washed with 100 mL of water twice and the organic layer was concentrated under vacuum. The residue was purified

by silica gel column chromatography (elution: hexane:ethyl acetate = 1:1) to give 1.29 g (58%) of 3-butyl-1-chloro-8-[2-(1*H*-tetrazol-5-yl)-phenyl]-5,10-dihydro-imidazo[1,5-*b*]isoquinolin-1-one (2): mp 197–198 °C; ^{1}H NMR ($CDCl_3$) δ 1.0 (*t*, 3H), 1.40–1.59 (*m*, 2H), 1.76–1.94 (*m*, 2H), 2.75–2.87 (*t*, 2H), 5.35 (*s*, 2H), 7.38–7.73 (*m*, 5H), 8.05 (*d*, 1H), 8.30 (*d*, 2H); MS 418.1309; ^{13}C NMR ($CDCl_3$) 13.748, 22.473, 26.771, 28.757, 44.698, 121.651, 122.198, 126.072, 127.317, 128.493, 130.336, 131.243, 131.822, 133.147, 133.826, 134.923, 140.440, 140.842, 149.615, 152.726, 164.560, 173.157.

3-Butyl-1-chloro-8-[2-(1H-tetrazol-5-yl)-phenyl]-5,10-dihydro-imidazo[1,5-b]isoquinolin-1-ol (3). To a solution of **2** (1.5 g, 3.58 mmol) in 20 mL of the solvent mixture (methanol:THF = 3:1) was added $NaBH_4$ (0.41 g, 10.74 mmol) and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with 50 mL of water and the pH of the solution was adjusted to 3–4 with 1 N HCl aq. solution. The reaction mixture was then extracted with ethyl acetate (50 mL × 2). The ethyl acetate layer was dried with Na_2SO_4 and then concentrated under vacuum to give a crude product which was recrystallized in ethyl acetate:methylene chloride (1:1) to give **3** (1.43 g, 95%) in tan solid: mp 130–131 °C; ^{1}H NMR ($CDCl_3$) δ 0.98 (*t*, 3H), 1.40–1.52 (*m*, 2H), 1.68–1.85 (*m*, 2H), 2.74 (*t*, 2H), 3.72 (*s*, 3H), 5.04–5.21 (*m*, 2H), 5.88 (*s*, 1H), 7.34–7.60 (*m*, 6H), 7.90 (*d*, 1H).

3-Butyl-1-chloro-8-[2-(1H-tetrazol-5-yl)-phenyl]-5,10-dihydro-imidazo[1,5-b]isoquinoline (4). To a solution of **3** (1.0 g, 2.40 mmol) in 30 mL of methylene chloride was added triethylsilane (1.1 mL, 7.1 mmol) and boron trifluoride etherate (0.6 mL, 4.7 mmol). The reaction mixture was then refluxed for 2 h. The reaction mixture was diluted with 50 mL of methylene chloride. The solution was washed with 100 mL of water twice and the methylene chloride layer was concentrated under vacuum. The residue was purified by silica gel column chromatography (elution: hexane:ethyl acetate = 2:1) to give **4** (0.6 g, 62%) in colorless solid: mp 135–137 °C; ^{1}H NMR ($CDCl_3$) δ 0.98 (*t*, 3H), 1.36–1.55 (*m*, 2H), 1.70–1.87 (*m*, 2H), 2.75 (*t*, 2H), 3.98 (*s*, 2H), 5.05 (*s*, 2H), 7.10–7.33 (*m*, 3H), 7.47–7.70 (*m*, 3H), 8.01 (*d*, 1H), 8.30 (*s*, 1H); MS 404.1516.

References and Notes

1. (a) Martin, P.; Bachmann, B.; Ganten, D. *Trends Cardiovasc. Med.* **1992**, *2*, 94; (b) Ferrario, C. M. *J. Cardiovasc. Pharmacol.* **1990**, *15* (Suppl. 3), 51; (c) Vallotton, M. B. *Trends Pharmacol. Sci.* **1987**, *8*, 69; (d) Garrison, J. C.; Peach, M. J. In: *The Pharmacological Basis of Therapeutics*, p. 749, Gilman, A. G.; Rall, T. W.; Nies, A. S.; Taylor, P., Eds; Pergamon Press; New York, 1990.

2. (a) Moore, G. J. *Comprehensive Medicinal Chemistry*, Vol. 3, pp. 961–980, Pergamon Press; New York, 1990; (b) For a review, see: Dzau, V. J. *J. Hypertension* **1989**, *7*, 933; (c) Urata, H.; Kinoshita, A.; Misono, K. S.; Bumpus, F. M.; Husain, A. *J. Biol. Chem.* **1990**, *265*, 22348; (d) Timmermans, P. B. M. W. M.; Benifield, P.; Chiu, A. T.; Herblin, W. F.; Wong, P. C.; Smith, R. D. *Am. J. Hypertension* **1992**, *5*, 221S.

3. (a) Greenlee, W. J.; Siegl, P. K. S. *Ann. Rep. Med. Chem.* **1992**, *27*, 59; (b) Greenlee, W. J. *Med. Res. Rev.* **1990**, *10*, 173.

4. (a) Ondetti, M. A.; Cushman, D. W. *J. Med. Chem.* **1981**, *24*, 355; (b) Ondetti, M. A.; Rubin, A.; Cushman, D. W. *Science* **1977**, *196*, 441; (c) Patchett, A. A.; Harris, E.; Tristram, E. W.; Wyvratt, M. J.; Wu, M. T.; Taub, D.; Peterson, E. R.; Ikeler, T. J.; ten Broeke, J.; Payne, L. G.; Ondeyka, D. L.; Thorsett, E. D.; Greenlee, W. J.; Lohr, N. S.; Hoffsommer, R. D.; Joshua, H.; Ruyle, W. V.; Rothrock, J. W.; Aster, S. D.; Maycock, A. L.; Robinson, F. M.; Hirschmann, R.; Sweet, C. S.; Ulm, E. H.; Gross, D. M.; Vassil, T. C.; Stone, C. A. *Nature* **1980**, *288*, 280; (d) Waeber, B.; Nussberger, J.; Brunner, H. R. In: *Hypertension: Pathophysiology, Diagnosis and Management*, p. 2209, Laragh, J. H.; Brenner, B. M., Eds; Raven Press; New York, 1990.

5. (a) Timmermans, P. B. M. W. M.; Wong, P. C.; Chiu, A. T.; Herblin, W. F. *Trends Pharmacol. Sci.* **1991**, *12*, 55; (b) Streeten, D. H. P.; Anderson, Jr G. H. In: *Clinical Pharmacology of Antihypertensive Drugs* (*Handbook of Hypertension*); Vol. 5, p. 264, Doyle, A. I., Ed.; Elsevier; Amsterdam, 1984; (c) Johnson, A. L.; Carini, D. J.; Chiu, A. T.; Duncia, J. V.; Price, Jr W. A.; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Timmermans, P. B. M. W. M. *Drug News Perspect.* **1990**, *3*, 337; (d) Hodges, J. C.; Hamby, J. M.; Blankley, C. J. *Drugs Future* **1992**, *17*, 575.

6. (a) Dutta, A. S. In: *Advances in Drug Research*, Vol. 21, p. 147, Testa, B., Ed.; Academic Press; London, 1991; (b) Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M. *Med. Res. Rev.* **1992**, *12*, 149.

7. (a) Middlemiss, D.; Drew, G. M.; Ross, B. C.; Robertson, M. J.; Scopes, D. I. C.; Dowle, M. D.; Akers, J.; Cardwell, K.; Clark, K. L.; Coote, S.; Eldred, C. D.; Hamblett, J.; Hilditch, A.; Hirst, G. C.; Jack, T.; Montana, J.; Panchal, T. A.; Paton, J. M. S.; Shah, P.; Stuart, G.; Travers, A. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 711; (b) Mantlo, N. B.; Charkravarty, P. K.; Ondeyka, D. L.; Siegl, P. K. S.; Chang, R. S.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Schron, T. W.; Sweet, C. S.; Emmert, S. E.; Patchett, A. A.; Greenlee, W. J. *J. Med. Chem.* **1991**, *34*, 2919; (c) Weinstock, J.; Keenan, R. M.; Samanen, J.; Hempel, J.; Finkelstein, J. A.; Franz, R. G.; Gaitanopoulos, D. E.; Girard, G. R.; Gleason, J. G.; Hill, D. T.; Morgan, T. M.; Peishoff, C. E.; Aiyar, N.; Brooks, D. P.; Fredrickson, T. A.; Ohlstein, E. H.; Ruffolo, Jr R. R.; Stack, E. J.; Sulpizio, A. C.; Weidley, E. F.; Edwards, R. M. *J. Med. Chem.* **1991**, *34*, 1514; (d) Bühlmayer, P.; Criscione, L.; Fuhrer, W.; Furet, P.; de Gasparo, M.; Stutz, S.; Whitebread, S. *J. Med. Chem.* **1991**, *34*, 3105; (e) Bovy, P. R.; Collins, J. T.; Olins, G. M.; McMahon, E. G.; Hutton, W. C. *J. Med. Chem.* **1991**, *34*, 2410; (f) Wong, P. C.; Hart, S. D.; Chui, A. T.; Herblin, W. F.; Carini, D. J.; Smith, R. D.; Wexler, R. R.; Timmermans, P. B. M. W. M. *J. Pharmacol. Exp. Ther.* **1991**, *259*, 861; (g) Buckner, S. A.; Hancock, A. A.; Lee, J. Y.; Morse, P.; Oheim, K.; Marsh, K. C.; Bauch, J.; Winn, M.; De, B.; Zydowsky, T. M.; Kerkman, D. J.; DeBernardis, J. F. *Pharmacologist* **1992**, *34*, 164; (h) Lee, J. -Y.; Brune, M.; Warner, R.; Buckner, S.; Winn, M.; De, B.; Zydowsky, T.; Kerkman, D.; DeBernardis, J. *Pharmacologist* **1992**, *34*, 165; (i) Keenan, R. M.; Weinstock, J.; Finkelstein, J. A.; Franz, R. G.; Gaitanopoulos, D. E.; Girard, G. R.; Hill, D. T.; Morgan, T. M.; Samanen, J. M.; Hempel, J. C.; Eggleston, D.; Aiyar, N.; Griffin, E.;

Ohlstein, E. H.; Stack, E. J.; Weidley, E. F.; Edwards, R. M. *J. Med. Chem.* **1992**, *35*, 3858; (j) Keenan, R. M.; Weinstock, J.; Finkelstein, J. A.; Franz, R. G.; Gaitanopoulos, D. E.; Girard, G. R.; Hill, D. T.; Morgan, T. M.; Samanen, J. M.; Peishoff, C. E.; Tucker, L. M.; Aiyar, N.; Griffin, E.; Ohlstein, E. H.; Stack, E. J.; Weidley, E. F.; Edwards, R. M. *J. Med. Chem.* **1993**, *36*, 1880; (k) Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Strelitz, R. A.; MacCoss, M.; Greenlee, W. J.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Bunting, P.; Zingaro, G. J.; Kivlighn, S. D.; Siegl, P. K. S. *J. Med. Chem.* **1993**, *36*, 2558; (l) Dhanoa, D. S.; Bagley, S. W.; Chang, R. S. L.; Lotti, V. J.; Chen, T.-B.; Kivlighn, S. D.; Zingaro, G. J.; Siegl, P. K. S.; Chakravarty, P. K.; Patchett, A. A.; Greenlee, W. J. *J. Med. Chem.* **1993**, *36*, 3738; (m) Carini, D. J.; Duncia, J. V.; Johnson, A. L.; Chiu, A. T.; Price, W. A.; Wong, P. C.; Timmermans, P. B. M. W. *J. Med. Chem.* **1990**, *33*, 1330.

8. (a) Furakawa, Y.; Kishimoto, S.; Nishikawa, K., U.S. Patent 4,340,598 (1982); (b) Furukawa, Y.; Kishimoto, S.; Nishikawa, K., U.S. Patent 4,355,040 (1982).

9. (a) Duncia, J. V.; Chiu, A. T.; Carini, D. J.; Gregory, G. B.; Johnson, A. L.; Price, W. A.; Wells, G. J.; Wong, P. C.; Catabrese, J. C.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1990**, *33*, 1312; (b) Chiu, A. T.; McCall, D. E.; Price, W. A.; Wong, P. C.; Carini, D. J.; Duncia, J. V.; Wexler, R. R.; Yoo, S. E.; Johnson, A. L.; Timmermans, P. B. M. W. M. *J. Pharmacol. Exp. Ther.* **1990**, *252*, 711; (c) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, III J. B.; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525; (d) DuP 753 Losartan Potassium (MK-954) *Drugs Future* **1992**, *17*, 326.

10. (a) Kubo, K.; Inada, Y.; Kohara, Y.; Sugiura, Y.; Ojima, M.; Itoh, K.; Furukawa, Y.; Nishiyawa, K.; Naka, T. *J. Med. Chem.* **1993**, *36*, 1772; (b) Thomas, A. P.; Allott, C. P.; Gibson, K. H.; Major, J. S.; Masek, B. B.; Oldham, A. A.; Ratcliffe, A. H.; Roberts, D. A.; Russell, S. T.; Thomason, D. A. *J. Med. Chem.* **1992**, *35*, 877; (c) De, B.; Winn, M.; Zydowsky, T. M.; Kerkman, D. J.; DeBernardis, J. F.; Lee, J.; Buckner, S.; Warner, R.; Brune, M.; Hancock, A.; Opgenorth, T.; Marsh, K. *J. Med. Chem.* **1992**, *35*, 3714.

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