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Design, synthesis, and evaluation of novelly substituted benzimidazole compounds as angiotensin II receptor antagonists

Alka Bali,[a] Yogita Bansal,[b] M. Sugumaran,[b] Jatinder Singh Saggu,[b] P. Balakumar,[b] Gurpreet Kaur,[b] Gulshan Bansal,[b,*] Ajay Sharma[c] and Manjeet Singh[b]

[a]*University Institute of Pharmaceutical Sciences, Punjab University, Chandigarh, India*
[b]*Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala 147 002, India*
[c]*Division of Pharmacology, Zydus Cadila Limited, Ahmadabad, India*

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Abstract—5-Nitrobenzimidazole derivatives with varying substituents at 2-position have been designed, synthesized, and evaluated for angiotensin II antagonistic activity. A drug–receptor interaction model has been proposed.

1. Introduction

Angiotensin II (Ang II) receptor antagonists are widely accepted as novel antihypertensives clinically because of lesser side effects and better therapeutic profiles than ACE inhibitors. Losartan,[1,2] the protypical agent of this category, served as lead for the development of newer Ang II receptor antagonists.[3] Varied substitutions in benzimidazole nucleus have been extensively studied for this purpose. Among the different substituents, a lipophilic group with H-bond accepting capability (acylureas) at 6-position,[4] and a carboxylic function at 7-position[5] of benzimidazole nucleus have been found to be favorable for Ang II antagonism. Further, a linear butyl chain and an ethoxy group is required at position 2 in 6-substituted benzimidazole and in benzimidazole-7-carboxylic acid derivatives, respectively. However, position 5 in this nucleus has not been exploited much. A series of triazole derivatives with different substituents at C-5 of the triazole nucleus has been reported where a benzylthio group increases the activity substantially. A further presence of carboxy group at ortho position of benzylthio moiety makes the compound **1** even more active than losartan. The binding profile of **1** with AT_1 receptors proposed in literature (Fig. 1a) depicts that site L3 accommodates the benzyl group whereas site B/H interacts with carboxylate group.[6] A critical analysis of structure of 5-substituted benzimidazole compounds suggests that a similar group at this position may take an orientation analogous to that taken up by carboxylate of **1** (Fig. 1b). Hence, compounds **8** are designed with nitro group at position 5, and a correlation of relative orientations of nitro and carboxylate of **8** and **1**, respectively, is established by determining the distances between O^1 and N^4 of **1** and O^1 and C^1 of **8** in their energy minimized conformations using computer software ChemOffice 6.0. These distances have been found to be very similar (4.638 Å in **1** and 4.236 Å in **8**) (Fig. 1). Hence these compounds are expected to have greater activity than losartan. Further, different alkyl groups are substituted at position 2 of benzimidazole nucleus to optimize an appropriate alkyl group in 5-substituted benzimidazole derivatives.

Hence, the present study has been conducted to design, synthesize, and evaluate 5-nitrobenzimidazole derivatives **8a–d** bearing *n*-butyl, ethoxymethyl, *n*-propyl, and ethyl chain at 2-position. For the synthesis of pendant carboxylbiphenyl methyl moiety of the target compounds, a novel three-step method has been devised with improved yields. This novel synthetic route did not lead to formation of some carcinogenic by-products as reported with the other methods.[7–12] The biological activity of these compounds has been determined taking losartan and candesartan as reference compounds.

Keywords: 5-Substituted benzimidazole; Angiotensin II; Antagonists; Candesartan; Losartan.
* Corresponding author. Tel.: +91 9855166102; fax: +91 1752283073; e-mail: gulshanbansal@rediffmail.com

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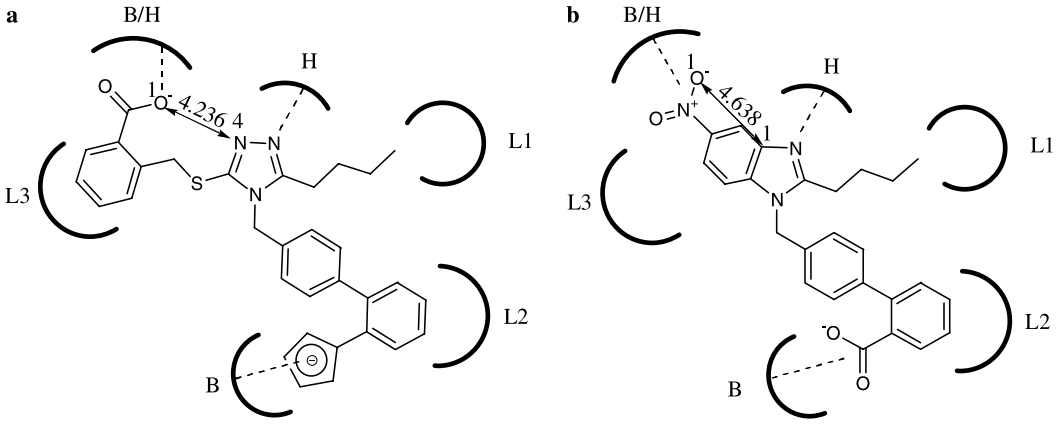

Figure 1. (a) Binding profile of **1** where L1–L3 are lipophilic pockets, B is basic site, H is H-bond donor site, and B/H is either a basic or H-bond donor site.(b) Proposed binding profile of benzimidazole derived compounds where L3 can accommodate a bulky substituent at 6-position and B/H acts either as a basic or H-bond donor site for substituents at 5-position.

2. Chemistry

Synthetic scheme (Fig. 2) for target compounds was divided into two steps. Step I involved synthesis of 2-alkylbenzimidazoles **2** by condensation reaction of *o*-phenylenediamine with the respective carboxylic acids **1**. The corresponding 5-nitro derivatives **3** were prepared by nitration under controlled temperature conditions.[13] Step II includes the novel sequential combination of three routine reactions to synthesize 2′-carboxybiphenyl methylene chloride. Biphenyl-2-carboxylic acid **4** was prepared by potash fusion of 9*H*-flourenone,[14] which was then subjected to aromatic substitution reaction using paraformaldehyde and acetamide in concd sulfuric acid[15] to affect intermediate, 4-acetamidomethyl biphenyl-2′-carboxylic acid **5**. The reaction mixture showed three components in TLC, which were separated by column chromatography using silica gel (100–120 mesh) as stationary phase and chloroform as mobile phase. The required component was identified as third fraction which was subjected to substitution reaction with phosphorus oxychloride in xylene and dimethyl formamide[15] to produce the pendant moiety 4-(chloromethyl)biphenyl-2′-carboxylic acid **6**. Coupling of intermediates **2a** and **3** with **6** using anhydrous potassium carbonate in dimethyl formamide resulted in target compounds **7a** and **8**, respectively, and finally reduction of **8a** with zinc in sodium hydroxide produced the final target compound **9a**. The compounds synthesized were characterized on the basis of analytical data and spectral evidences.[16]

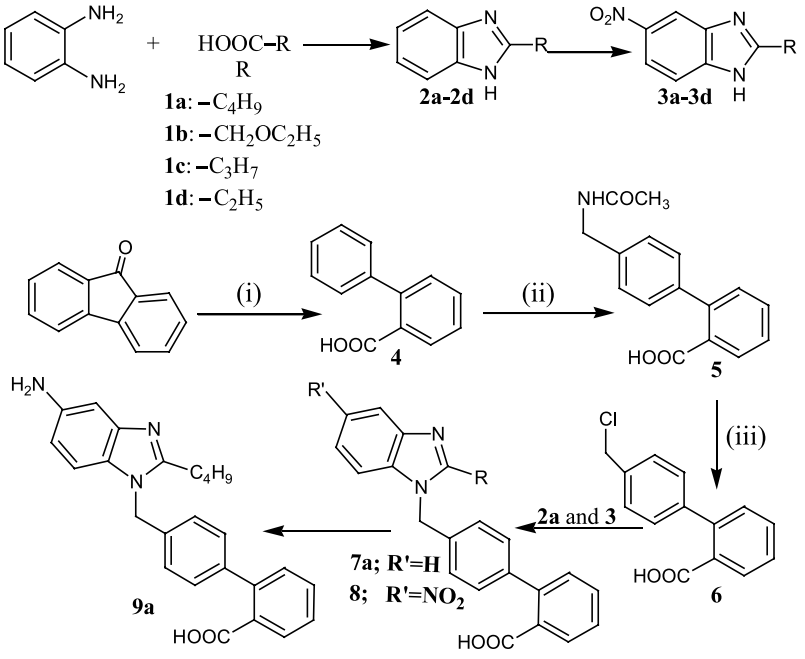

Figure 2. Synthetic scheme. (i) KOH, 180–200 °C, dil HCl; (ii) acetamide, paraformaldehyde, H_2SO_4, heat, stirring; (iii) $POCl_3$, xylene, DMF, reflux, H_2O.

3. Biological activity

Ang II receptor antagonism was determined on endothelium removed isolated rat aortic ring using force transducers and BIOPAC four-channel recorder (BIOPAC Systems Inc., Santa Barbara, CA, USA). The activity was expressed as pA_2 values (Table 1). pA_{10} values were also determined to establish the mode of antagonism.[17]

3.1. Statistical analysis

Linear regression was employed to plot the CRC between developed tension and negative log molar concentration of angiotensin II. Paired Student '*t*' test was employed for statistical analysis, $p < 0.05$ was considered to be statistically significant.

4. Results and discussions

Ang II antagonism by compounds with same functional group at 2-position has been found to be a function of substituent at 5-position. Presence of amino group has increased the activity substantially over the unsubstituted one (**9a** vs **7a**). The maximum activity has been observed with nitro group (compound **8a**). This suggests that there are some sites in the receptor pocket, which can interact with the functional groups at position 5. The higher activity of **8a** over **9a** suggests that this group at 5-position should be either ionic or H-bond acceptor. Decrease in length of alkyl chain from *n*-butyl to *n*-propyl **8c** and to ethyl **8d** has decreased the activity indicating that *n*-butyl group is required to be present at 2-position when 5-position of benzimidazole nucleus is substituted. The less activity of 2-ethoxymethyl analog **8b** than the corresponding 2-*n*-butyl analog **8a** suggests that presence of any electronic element in the linear alkyl chain is not conducive to activity. Compound **8a** has been found to be even more active than the reference compounds losartan and candesartan. The higher activity of 5-nitro derivatives may be ascribed to the ability of nitro group to act as H-bond acceptor with respect to the receptor site. Moreover, the bulk of nitro group may optimally ''fill up'' the receptor pocket and hence results in closer proximity to the interacting surface of the receptor. It may consequently increase their affinity to the receptor site. The noncompetitive mode of antagonism of **8** further suggests that such receptor pocket may not be accessible to the natural ligand, Ang II. Moreover, comparison of molecular surface areas (MSAs) of losartan, candesartan and **1** indicate that increase in activity can be directly correlated with MSA (Table 2). Hence, the higher activity of **8a** over candesartan can be attributed to this MM parameter. Lesser activity of **9a** with respect to candesartan and **8a** further supports this proposition. Hence, in the light of these inferences, a drug–receptor interaction model has been proposed (Fig. 1b) which includes an additional receptor pocket (B/H site) capable of accommodating a bulky group and act as a H-bond donor leading to greater drug–receptor interaction area and hence activity.

Table 1. The comparative Ang II antagonism of the target and reference compounds

Compound	R	pA_2[*]	pA_{10}	(pA_2 − pA_{10})	Mode[#]
7a	–*n*-C_4H_9	6.45	5.81	0.65	C
9a	–*n*-C_4H_9	7.8[a]	6.9[a,b]	0.9	C
8a	–*n*-C_4H_9	8.50[a,b]	1.8	6.7	NC
8b	–CH_2OEt	7.3	1.7	5.6	NC
8c	–*n*-C_3H_7	7.1	2.9	4.2	NC
8d	–Et	7.0	3.4	3.6	NC
Losartan		7.4	6.5	0.9	C
Candesartan		8.02	7.1	0.82	C

[a] $p < 0.05$ vs losartan.
[b] $p < 0.05$ vs candesartan.
[*] $n = 5$.
[#] Mode of antagonism (NC, noncompetitive; C, competitive).

Table 2. Comparative molecular surface areas of target and reference compounds

Compound	Molecular surface area (Å^2)
8a	388.322
8b	370.754
Losartan	367.638
Candesartan	375.166
1	470.272

5. Summary

Substituted benzimidazole nucleus coupled to carboxylbiphenyl methyl group has been designed, synthesized, and evaluated for Ang II antagonism. Compound with nitro group at 5-position and *n*-butyl chain at 2-position have been found to be more potent than candesartan. Hence, a new binding profile has been proposed where an additional receptor pocket in the binding site can accommodate bulky but H-bond acceptor group and this pocket may not be accessible to natural ligands and even losartan and candesartan. Additionally, a novel and simple method for synthesis of pendant biphenyl moiety has been devised to improve safety and yield. Further designing and synthesis of compounds with other such functional groups at 5-position are underway.

References and notes

1. Dunica, J. V.; Chiu, A. T.; Carini, D. J.; Gregory, G. B.; Johnson, A. L.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1990**, *33*, 1312.
2. Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierc, M. E.; Price, W. A.; Santella, J. B., III; Wells, J.; Wexler, R.; Wong, C.; Yoo, S. E.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525.
3. Wexler, R. R.; Greenleen, W. J.; Irvin, J. D.; Goldberg, M. R.; Prendergast, K.; Smith, R. D.; Timmermans, P. B. M. E. M. *J. Med. Chem.* **1996**, *39*, 625.
4. Ries, U. J.; Mihm, G.; Narr, B.; Hasselbach, K. M.; Wittneben, H.; Entzeroth, M.; Van Meel, J. C. A.; Wienen, W.; Kavel, N. H. *J. Med. Chem.* **1993**, *36*, 4040.
5. Kubo, K.; Kohara, Y.; Imamiya, E.; Sugiura, Y.; Inada, Y.; Furukawa, Y.; Nishikawa, K.; Naka, T. *J. Med. Chem.* **1993**, *36*, 2182.

6. Ashton, W. T.; Cantone, C. L.; Chang, L. L.; Hutchins, S. M.; Strelitz, R. A.; Mcross, M.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T.; Bunting, P.; Schorn, T. N.; Kivlighn, S. D.; Siegl, P. K. S. *J. Med. Chem.* **1993**, *36*, 591.
7. Kageyama, H.; Miyazaki, T.; Kimura, Y. *Synlett* **1994**, 371.
8. Fanta, P. E. *Chem. Rev.* **1964**, *64*, 613.
9. Gomberg, M.; Bachmann, W. E. *J. Am. Chem. Soc.* **1924**, *46*, 2339.
10. Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383.
11. Lo, Y. S.; Rossano, L. T. U.S. Patents, 130,439, **1992**.
12. Brown, H. C.; Nelson, K. L. *J. Am. Chem. Soc.* **1953**, *75*, 6292.
13. Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry. The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds*; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol. 5, p 429, Part 4a.
14. Kenner, G. W.; Robinson, M. J. T.; Tylor, C. M. B.; Webster, B. R. *J. Chem. Soc., Part II* **1962**, 1756.
15. Manlding, D. R.; Lotts, K. D.; Robinson, S. A. *J. Org. Chem.* **1983**, *48*, 2938.
16. *2-n-Butyl-1-[(2′-carboxybipheny-4yl)methyl] benzimidazole (**7a**)*: yield 42.0%, mp 122–124 °C, IR (KBr): 3600–2700 (O–H); 1660 (C═O); 1420 (C–O–H). Anal. Calcd for $C_{25}H_{24}N_2O_2$: C, 78.13; H, 6.25; N, 7.29. Found: C, 77.29; H, 6.84; N, 7.79. δ_H (300 MHz, $CDCl_3$): 0.90 (t, $J = 7.5$, 3H, $CH_2CH_2CH_2CH_3$); 1.35 (sx, $J = 7.5$, 2H, $CH_2CH_2CH_2CH_3$); 1.67 (qv, $J = 7.5$, 2H, $CH_2CH_2CH_2CH_3$); 2.95 (t, $J = 7.5$, 2H, $CH_2CH_2CH_2CH_3$); 3.04 (s, 2H, CH_2); 6.95 (d, $J = 8$, 2H, ArH); 7.01 (d, $J = 8$, 2H, ArH); 7.53 (dd, $J = 8;2$, 2H, ArH); 7.58 (dd, $J = 8;2$, 2H, ArH); 7.87 (dd, $J = 8;2$, 2H, ArH); 7.92 (dd, $J = 8;2$, 1H, ArH); 8.01 (dd, $J = 8;2$, 1H, ArH); 8.90 (b, 1H, *COOH*). MS (EI): 384 ($M^{\cdot+}$). *2-n-Butyl-5-nitro-1-[(2′-carboxybipheny-4-yl) methyl] benzimidazole (**8a**)*: yield 66.6%, mp 160–162 °C, IR (KBr): 3600–3200 (O–H); 1670 (C═O); 1440 and 1370 (N═O). Anal. Calcd for $C_{25}H_{23}N_3O_4$: C, 69.63; H, 5.36; N, 9.79. Found: C, 69.24; H, 5.81; N, 9.58. δ_H (300 MHz, $CDCl_3$): 0.91 (t, $J = 7.5$, 3H, $CH_2CH_2CH_2CH_3$); 1.43 (sx, $J = 7.5$, 2H, $CH_2CH_2CH_2CH_3$); 1.97 (qv, $J = 7.5$, 2H, $CH_2CH_2CH_2CH_3$); 2.95 (t, $J = 7.5$, 2H, $CH_2CH_2CH_2CH_3$); 3.25 (s, 2H, CH_2); 6.82 (d, $J = 8$, 1H, ArH); 7.46 (d, $J = 2$, 2H, ArH); 7.48 (d, $J = 2$, 2H, ArH); 7.84 (dd, $J = 8;2$, 2H, ArH); 7.94 (d, $J = 2$, 1H, ArH); 8.08 (s, 1H, ArH); 8.24 (d, $J = 8$, 1H, ArH); 8.65 (s, 1H, ArH); 9.58 (b, 1H, *COOH*). MS (EI): 429 ($M^{\cdot+}$). *5-Amino-2-n-butyl-1-[(2′-carboxybipheny-4-yl) methyl] benzimidazole (**9a**)*: yield 64%, mp 168–170 °C, IR (KBr): 3600–2700 (O–H and N–H); 1690 (C═O). Anal. Calcd for $C_{25}H_{25}N_3O_2$: C, 75.19; H, 6.26; N, 10.53. Found: C, 74.65; H, 6.89; N, 9.96. δ_H (300 MHz, $CDCl_3$): 0.90 (t, $J = 7.5$, 3H, $CH_2CH_2CH_2CH_3$); 1.40 (sx, $J = 7.5$, 2H, $CH_2CH_2CH_2CH_3$); 1.75 (qv, $J = 7.5$, 2H, $CH_2CH_2CH_2CH_3$); 2.82 (t, $J = 7.5$, 2H, $CH_2CH_2CH_2CH_3$); 3.10 (s, 4H, CH_2 and NH_2); 6.61 (m, 1H, ArH); 6.77 (d, $J = 2$, 1H, ArH); 7.32 (m, 1H, ArH); 7.43 (d, $J = 6$, 2H, ArH); 7.51 (d, $J = 6$, 2H, ArH); 7.64 (m, 3H, ArH); 7.99 (d, $J = 8$, 1H, ArH); 9.72 (b, 1H, *COOH*). MS (EI): 399 ($M^{\cdot+}$).
17. Schild, H. O. *Br. J. Pharmacol. Chemother.* **1947**, *2*, 189.