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Original article

Angiotensin II – AT_1 receptor antagonists: Design, synthesis and evaluation of substituted carboxamido benzimidazole derivatives

Dhvanit I. Shah, Manu Sharma, Yogita Bansal, Gulshan Bansal*, Manjeet Singh

Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, 147 002 Punjab, India

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Abstract

A series of 5-(alkyl and aryl)carboxamido benzimidazole derivatives had been designed, synthesized and evaluated for in vitro angiotensin II – AT_1 receptor antagonism and in vivo antihypertensive activities. The pharmacological activities were inversely related to the size of alkyl and aryl substituents. It can be suggested that compounds with lower alkyl groups at 5-position of benzimidazole nucleus demonstrated potent antihypertensive activity.

Keywords: Benzimidazole; Carboxamido; AT_1 receptor antagonists; Receptor surface model; Antihypertensive

1. Introduction

Angiotensin II (Ang II) AT_1 receptor antagonists like losartan **1** and candesartan **2** (Fig. 1) are preferred antihypertensives due to their better therapeutic spectrum and fewer side effects [1–3]. Sartans are appropriately substituted heterocyclic head coupled through a methylene linker to pendent biphenyl system bearing an acidic function; viz. candesartan is an effective competitive Ang II antagonist with benzimidazole nucleus as the heterocyclic head [4]. The substituent at 6-position on the nucleus increases the activity whereas small substituent at 5-position decreases the activity [5]. Compounds containing triazole nucleus are also reported as AT_1 receptor antagonists and their protypical derivative **3** exhibits non-competitive antagonism [6]. The 5-substituted benzimidazole derivatives **4** and **5** (Fig. 1) were designed and synthesized earlier by our laboratory in which 5-nitro derivatives **4** were found to be more potent than **2** whereas the corresponding amino derivatives **5** were less potent than **2** but more potent than **1** [7]. Further, extended binding profile (Fig. 2A) demonstrated an increase in activity with appropriate substituent at 5-position [7]. Therefore, we hypothesized that extension of chemical group at 5-position may occupy either L3 pocket or some additional pocket in the receptor to increase antihypertensive activity. We designed *N*-(alkyl and aryl)carbonyl derivatives **6** of **5** with expectations that alkyl or aryl residues of **6** may not reach L3 pocket. A receptor surface model generated for 1,2,4-triazol-3-one based AT_1 antagonist **7** (Fig. 1) reveals that large lipophillic residue at 2-position of the triazolone nucleus is responsible for binding through van der Wal and electrostatic interactions with the pocket on receptor surface [8]. A previous study has identified a similar pocket in AT_1 receptor (L4 in Fig. 2B) interacting with benzimidazolyl moiety of **2** in a GRID plot obtained by 3D-QSAR correlation through GOLPE procedure [9]. The amino acids responsible for interactions of different AT_1 antagonists with the receptor have been established by various homology modeling and docking studies [10,11]. Therefore, we expected that 5-alkyl or aryl residues of **6** can be accommodated in L4 due to lipophilic interactions with tyrosine, histidine, tryptophan and leucine. Hence, the present study has been undertaken to synthesize 5-(substituted carboxamido) benzimidazole derivatives **6a–6g** and evaluate their antihypertensive activities taking **1** and **2** as reference compounds.

* Corresponding author. Tel.: +91 175 3046255; fax: +91 175 2283073.
E-mail address: gulshanbansal@rediffmail.com (G. Bansal).

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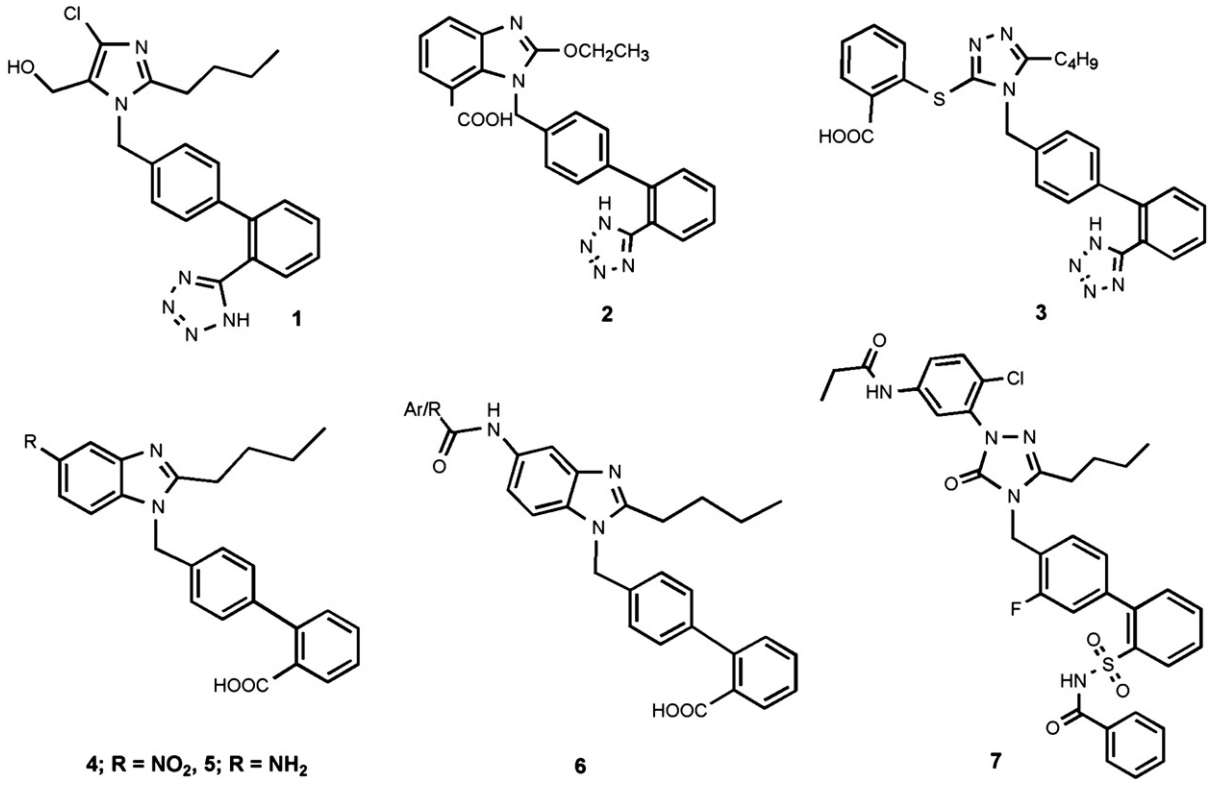

Fig. 1. Angiotensin II – AT_1 receptor antagonists.

2. Results and discussion

2.1. Chemistry

The synthetic route described in Fig. 3 was employed to synthesize the target compounds **6a**–**6g**. The key intermediate **5** was prepared by coupling of 2-*n*-butyl benzimidazole nucleus (II) with pendent biphenyl moiety (V) followed by nitration, and subsequent reduction of the nitro group as reported earlier [7]. Further, acylation of amino group with different acylating reagents was performed to synthesize target compounds. Compounds **6a** and **6b** were prepared by reaction of **5** with acetic anhydride and propionic anhydride, respectively, whereas compounds **6c**–**6g** were prepared by reacting **5** with butanoyl chloride, pentanoyl chloride, benzoyl chloride, 2-chloro benzoyl chloride and 4-chloro benzoyl chloride, respectively. Each compound was purified by crystallization and purity was ascertained by chromatographic techniques. The compounds were characterized on the basis of spectral evidences.

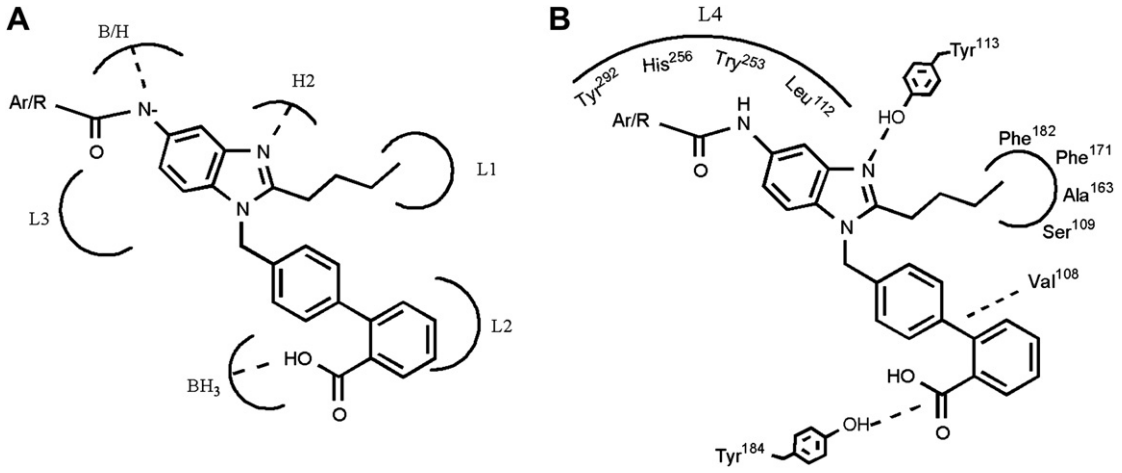

Fig. 2. Extended binding profile (A) where L3 can accommodate a bulky substituent at 6-position, B/H acts either as a basic or H-bond donor site for 5-substituent while Ar/R may find another pocket and a drug-receptor interaction model (B) showing accommodation of 5-substituent of **6** in L4.

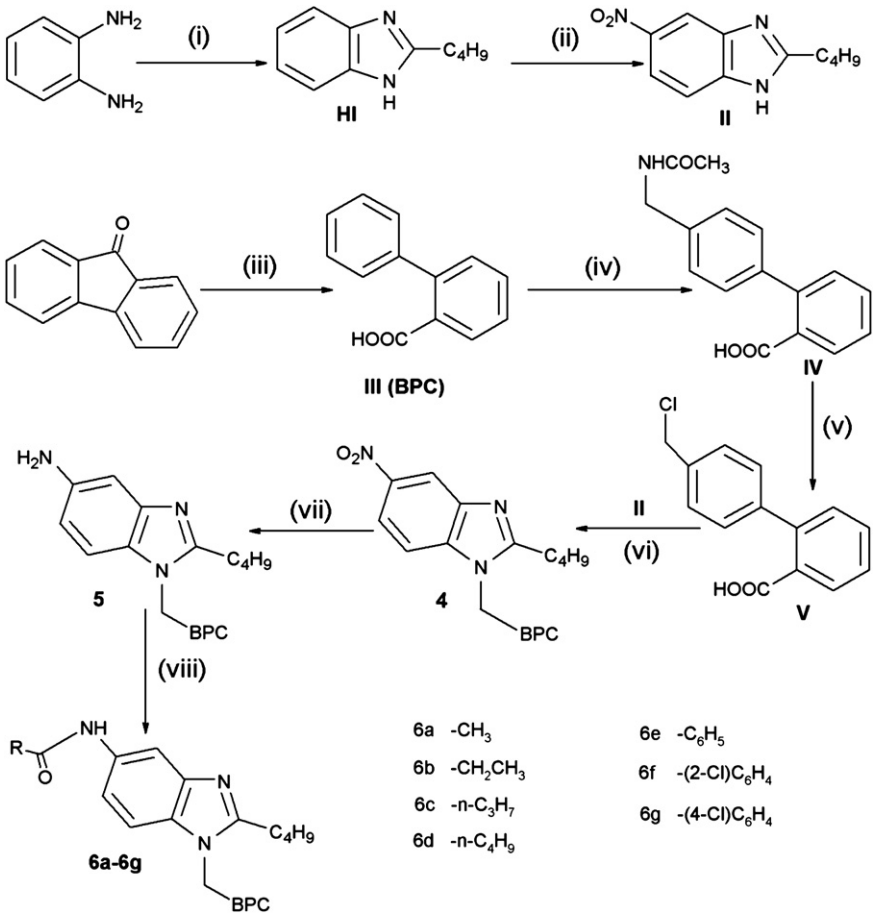

Fig. 3. Synthetic scheme (i) pentanoic acid, reflux, 6 h; (ii) H_2SO_4, HNO_3, 0–5 °C, 10 h; (iii) KOH, 180–200 °C, dil. HCl; (iv) acetamide, paraformaldehyde, H_2SO_4, heat, stirring; (v) $POCl_3$, xylene, DMF, reflux; (vi) pyridine; (vii) Zn/NaOH, reflux, 3 h (viii) Method A or Method B as in Section 4.

2.2. Pharmacological evaluation

2.2.1. Antagonism of angiotensin II receptor

The antagonistic activity of compounds **6a–6g** was determined on isolated rat aortic ring using force transducers and BIOPAC four channel recorder systems (BIOPAC systems INC., Santa Barbara, CA, USA). Linear regression was employed to plot the dose response curve between the developed tension and negative molar concentration of angiotensin II. Paired student's '*t*' test was employed for statistical analysis. The antagonistic activity was expressed as pA_2 values (Table 1). The pA_{10} values were also determined to establish the mode of antagonism [12]. Comparison of the pA_2 and pA_{10} values indicates that **6a–6d** are non-competitive antagonists ($pA_2 - pA_{10} > 1$) whereas the other compounds are competitive antagonists ($pA_2 - pA_{10} < 1$). The antagonistic potential of targeted compounds **6a–6g** was wide ranging (**6a** > **6b** ≫ **6c** > **6e** > **6f** > **6d** > **6g**). Compounds **6a** and **6b** are more potent whereas **6c–6g** are less potent in comparison to **1** and **2**. The activity of **6a** was superior to **1** and **5** but equivalent to **2** whereas the activity of **6b** is better than **1** but equivalent to **5**. However, the activity decreases with increase in bulk of the alkyl/aryl residues. It suggests that a small lipophillic group (methyl) can be accommodated without affecting interaction of –NH– of 5-substituent with L4 pocket which is limited mainly by Tyr^{292}, His^{256}, Try^{253} and Leu^{112} (Fig. 2B). The gradual decrease in activity from compound **6c** to **6g** can be attributed to overfilling and/or unfavorable steric interactions of lipophilic and bulky tyrosine, histidine and tryptophan residues of L4 with longer alkyl groups.

Table 1
Pharmacological activity of the target and the reference compounds

Compound (mg kg^{-1})	pA_2	pA_{10}	Decrease in MABP (mm of Hg)	$pA_2 - pA_{10}$	Mode of antagonism
6a (3)	8.0 ± 0.31	5.9 ± 0.27	33.5 ± 1.4***,***	2.1	NC
6b (3)	7.7 ± 0.26	4.7 ± 0.19	36.2 ± 1.9	3.0	NC
6c (3)	7.1 ± 0.24	4.4 ± 0.21	26.4 ± 0.8	2.7	NC
6d (3)	6.4 ± 0.25	3.7 ± 0.12	21.7 ± 0.7	2.7	NC
6e (3)	6.6 ± 0.29	6.0 ± 0.31	19.8 ± 0.6	0.6	C
6f (3)	6.5 ± 0.25	5.8 ± 0.28	20.3 ± 0.9	0.7	C
6g (3)	6.2 ± 0.28	5.4 ± 0.23	12.0 ± 0.4	0.8	C
5 (3)	7.8 ± 0.22	7.0 ± 0.25	33.3 ± 1.2	0.8	C
1 (5)	7.4 ± 0.34	6.5 ± 0.30	29.7 ± 1.1	0.9	C
2 (5)	8.0 ± 0.29	7.1 ± 0.26	31.8 ± 1.3	0.9	C

All values ($n = 6$) represent mean ± SEM; NC, non-competitive; C, competitive; *$p < 0.05$ vs 5; **$p < 0.05$ vs 1; ***$p < 0.05$ vs 2.

2.2.2. Antihypertensive activity

Hypertension in rats was induced by desoxycortisone acetate (40 mg kg^{-1}, s.c.) and mean arterial blood pressure (MABP) was measured by cannulating carotid artery [13] to pressure transducer attached to BIOPAC systems. The standardization of in vivo dose was done by administering compound **5** in dose range of 0.1, 0.3, 1.0, 3.0, 10.0 and 30.0 mg kg^{-1} intraperitonealy. The plateau effect was produced at doses of 3.0, 10.0 and 30.0 mg kg^{-1}, and hence the other compounds (**6**) were evaluated at doses of 1.0, 3.0 and 10.0 mg kg^{-1}. The antihypertensive activity was measured as a decrease in MABP (mm of Hg) taking **1** and **2** as reference compounds (Table 1). The data were statistically analyzed by performing one way analysis of variance followed by tukey's multiple range test and $p < 0.05$ was considered to be statistical significant. The antihypertensive activity is found to correspond to the in vitro activity for each compound except for **6a** and **6b**. The antihypertensive activity of **6a** is equivalent to that of **5**. Though antagonistic activity of **6b** is less than that of **6a**, but decrease in MABP is found to be the maximum with **6b**. This deviation may be attributed to minor increase in bulk due to ethyl group. The latter may decrease the drug–receptor interaction due to steric hindrance leading to decreased in vitro activity but on the other hand it can be favorable to optimum partitioning in body fluids leading to better in vivo activity.

3. Conclusion

Substitution at 5-amino group on benzimidazole nucleus with diverse alkylcarbonyl chains produced AT_1 antagonists with wide-ranging activities. An alkyl group, not longer than methyl, can be accommodated in the L4 pocket. The antihypertensive activity can be increased by selecting an appropriate alkyl group so that optimum in vivo partitioning of the molecule is achieved without significant effect on the H-bonding interaction of –NH– with L4 pocket. In the present study, compound **6b** bearing ethyl group exhibits better antihypertensive activity than the in vitro AT_1 receptor antagonism.

4. Experimental

The melting points were recorded in open sulfuric acid bath and uncorrected. ^{1}H NMR spectra were recorded on Bruker AC 30 NMR Spectrometer (300 MHz), mass spectra were recorded on Vg Micro Mass 7070F spectrometer and GC–MS (Gcq) Spectrometer and FT-IR spectra were recorded on FT-IR Perkin-Elmer 1710 series. In ^{1}H NMR, chemical shifts were reported in δ values using tetramethylsilane as internal standard with multiplicities (br-broad, s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet, dd-double doublet) and number of protons in the solvent indicated. The coupling constants (J) were expressed in Hz. IR spectra were recorded as KBr pellets. The elemental analyses were performed on Heraus CHN–O rapid elemental analyzer. When necessary, solvents and reagents were dried prior to use over KOH or anhydrous Na_2SO_4 or fused $CaCl_2$. The intermediates I–V, **4** and **5** were prepared as described in our earlier report [7]. The target compounds (**6a–6g**) were prepared by acylation using one of the two following methods.

Method A: Acetylating agent (0.1 M) was added to a mixture of **5** (0.015 M) and 1 ml of conc. H_2SO_4 in a round bottom flask (RBF). The reaction mixture was refluxed for 45 min and subsequently boiled to remove excess of the acetylating agent. The contents were cooled to room temperature and poured in ice chilled water. The product was separated as white lumps which were recrystallized from ethanol to produce the product as white crystals.

Method B: Acyl chloride (0.1 M) was added drop wise from a dropping funnel over 15 min with stirring to a solution of **5** (0.015 M) and 50 ml of 20% NaOH in 250 ml RBF. The stirring was continued at 60 °C for another 30 minutes and the resulting solid product was recrystallized from hot ethanol to produce white needle shaped crystals.

*4.1. 4′-(5-Acetylamino-2-butyl-benzoimidazol-1-ylmethyl)-biphenyl-2-carboxylic acid (**6a**)*

The compound was prepared by *Method A* using acetic anhydride as acetylating agent. Yield 48%, m.p. 168–170 °C, IR (KBr): 3600–2900 (O–H and N–H); 1702 (C=O); 1578 (Amide II). Anal. Calcd for $C_{27}H_{27}N_3O_3$: C, 73.45; H, 6.16; N, 9.52. Found: C, 72.61; H, 6.11; N, 8.65. δ_H (300 MHz, $CDCl_3$) 0.95 (t, 3H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 1.46 (sx, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 2.01 (qv, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 2.16 (s, 2H, CH_2); 2.41 (s, 3H, $NHCOCH_3$); 3.38 (t, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 7.39–7.42 (m, 3H, ArH); 7.46 (d, 2H, $J = 6$ Hz, ArH); 7.92 (d, 1H, $J = 6$ Hz, ArH); 8.04–8.17 (m, 3H, ArH); 8.38 (dd, 1H, $J = 8$ Hz; 2 Hz, ArH); 8.72 (d, 1H, $J = 2$ Hz, ArH); 9.41 (b, 1H, *COOH*); 9.12 (b, 1H, *CONH*). MS (ESI): 442 (M + 1).

*4.2. 4′-(2-Butyl-5-propionylamino-benzoimidazol-1-ylmethyl)-biphenyl-2-carboxylic acid (**6b**)*

The compound was prepared by Method A using propionic anhydride as acetylating agent. Yield 47%, m.p. 171–173 °C, IR (KBr): 3600–2900 (O–H and N–H); 1706 (C=O); 1576 (Amide II). Anal. Calcd for $C_{28}H_{29}N_3O_3$: C, 73.82; H, 6.42; N, 9.22. Found: C, 72.88; H, 6.29; N, 8.89. δ_H (300 MHz, $CDCl_3$) 0.95 (t, 3H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 1.46 (sx, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 2.01 (qv, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 2.06 (s, 2H, CH_2); 2.41 (q, 2H, $J = 7$ Hz, $NHCOCH_2CH_3$); 2.45 (t, 3H, $J = 7$ Hz, $NHCOCH_2CH_3$); 3.38 (t, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 7.39–7.42 (m, 3H, ArH); 7.45 (d, 2H, $J = 6$ Hz, ArH); 7.95 (d, 1H, $J = 6$ Hz, ArH); 8.04–8.15 (m, 3H, ArH); 8.35 (dd, 1H, $J = 8$ Hz; 2 Hz, ArH); 8.77 (d, 1H, $J = 2$ Hz, ArH); 9.41 (b, 1H, *COOH*); 9.19 (b, 1H, *CONH*). MS (ESI): 456 (M + 1).

*4.3. 4′-(2-Butyl-5-butyrylamino-benzoimidazol-1-ylmethyl)-biphenyl-2-carboxylic acid (**6c**)*

The compound was prepared by Method B using butanoyl chloride. Yield 44%, m.p. 174–176 °C, IR (KBr): 3600–2900

(O–H and N–H); 1705 (C=O); 1577 (Amide II). Anal. Calcd for $C_{29}H_{31}N_3O_3$: C, 74.18; H, 6.65; N, 8.95. Found: C, 73.08; H, 6.54; N, 8.72. δ_H (300 MHz, $CDCl_3$) 0.94–0.98 (m, 6H, $CH_2CH_2CH_2CH_3$ and $NHCOCH_2CH_2CH_3$); 1.46 (sx, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 1.88 (sx, 2H, $J = 7$ Hz, $NHCOCH_2CH_2CH_3$); 2.01 (qv, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 2.06 (s, 2H, CH_2); 2.47 (t, 2H, $J = 7$ Hz, $NHCOCH_2CH_2CH_3$); 3.38 (t, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 7.37–7.41 (m, 3H, ArH); 7.43 (d, 2H, $J = 6$ Hz, ArH); 7.94 (d, 1H, $J = 6$ Hz, ArH); 8.05–8.14 (m, 3H, ArH); 8.33 (dd, 1H, $J = 8$ Hz; 2 Hz, ArH); 8.74 (d, 1H, $J = 2$ Hz, ArH); 9.56 (b, 1H, *COOH*); 9.21 (b, 1H, *CONH*). MS (ESI): 470 (M + 1).

4.4. 4′-(2-Butyl-5-pentanoylamino-benzoimidazol-1-ylmethyl)-biphenyl-2-carboxylic acid (**6d**)

The compound was prepared by Method B using pentanoyl chloride. Yield 46%, m.p. 176–178 °C, IR (KBr): 3600–2850 (O–H and N–H); 1707 (C=O); 1576 (Amide II). Anal. Calcd for $C_{30}H_{33}N_3O_3$: C, 74.51; H, 6.88; N, 8.69. Found: C, 73.18; H, 6.76; N, 8.52. δ_H (300 MHz, $CDCl_3$) 0.97–1.02 (m, 6H, $CH_2CH_2CH_2CH_3$ and $NHCOCH_2CH_2CH_2CH_3$); 1.44–1.51 (m, 4H, $CH_2CH_2CH_2CH_3$ and $NHCOCH_2CH_2CH_2CH_3$); 1.97 (qv, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 2.08 (qv, 2H, $J = 7$ Hz, $NHCOCH_2CH_2CH_2CH_3$); 2.13 (s, 2H, CH_2); 2.51 (t, 2H, $J = 7$ Hz, $NHCOCH_2CH_2CH_2CH_3$); 3.38 (t, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 7.35–7.42 (m, 3H, ArH); 7.44 (d, 2H, $J = 6$ Hz, ArH); 7.96 (d, 1H, $J = 6$ Hz, ArH); 8.04–8.12 (m, 3H, ArH); 8.31 (dd, 1H, $J = 8$ Hz; 2 Hz, ArH); 8.72 (d, 1H, $J = 2$ Hz, ArH); 9.49 (b, 1H, *COOH*); 9.22 (b, 1H, *CONH*). MS (ESI): 484 (M + 1).

4.5. 4′-(5-Benzoylamino-2-butyl-benzoimidazol-1-ylmethyl)-biphenyl-2-carboxylic acid (**6e**)

The compound was prepared by Method B using benzoyl chloride. Yield 56%, m.p. 171–173 °C, IR (KBr): 3600–2900 (O–H and N–H); 1690 (C=O); 1578 (Amide II). Anal. Calcd for $C_{32}H_{29}N_3O_3$: C, 76.32; H, 5.80; N, 8.34. Found: C, 75.28; H, 5.70; N, 8.19. δ_H (300 MHz, $CDCl_3$) 0.96 (t, 3H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 1.49 (sx, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 2.02 (qv, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 2.13 (s, 2H, CH_2); 3.39 (t, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 7.33–7.36 (m, 6H, ArH); 7.43 (dd, 2H, $J = 8$ Hz; 1 Hz, ArH); 7.96–8.02 (m, 3H, ArH); 8.02–8.09 (m, 4H, ArH); 8.35 (dd, 1H, $J = 8$ Hz; 1 Hz, ArH); 8.76 (d, 1H, $J = 1$ Hz, ArH); 9.56 (b, 1H, *COOH*); 9.24 (b, 1H, *CONH*). MS (ESI): 504 (M + 1).

4.6. 4′-[2-Butyl-5-(2-chloro-benzoylamino)-benzoimidazol-1-ylmethyl]-biphenyl-2-carboxylic acid (**6f**)

The compound was prepared by Method B using 2-chloro-benzoyl chloride. Yield 49%, m.p. 175–177 °C, IR (KBr): 3600–2900 (O–H and N–H); 1695 (C=O); 1577 (Amide II). Anal. Calcd for $C_{32}H_{28}ClN_3O_3$: C, 71.43; H, 5.25; N, 7.81. Found: C, 70.29; H, 5.14; N, 7.69. δ_H (300 MHz, $CDCl_3$) 0.95 (t, 3H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 1.46 (sx, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 2.01 (qv, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 2.09 (s, 2H, CH_2); 3.38 (t, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 7.35–7.39 (m, 5H, ArH); 7.53–7.56 (m, 2H, ArH); 8.00 (d, 2H, $J = 7$ Hz, ArH); 8.09 (d, 4H, $J = 7$ Hz, ArH); 8.35 (dd, 1H, $J = 8$ Hz; 3 Hz, ArH); 8.76 (d, 1H, $J = 3$ Hz, ArH); 9.43 (b, 1H, *COOH*); 9.19 (b, 1H, *CONH*). MS (ESI): 538 (M + 1).

4.7. 4′-[2-Butyl-5-(4-chloro-benzoylamino)-benzoimidazol-1-ylmethyl]-biphenyl-2-carboxylic acid (**6g**)

The compound was prepared by Method B using 4-chloro-benzoyl chloride. Yield 49%, m.p. 175–177 °C, IR (KBr): 3600–2900 (O–H and N–H); 1687 (C=O); 1538 (Amide II). Anal. Calcd for $C_{32}H_{28}ClN_3O_3$: C, 71.43; H, 5.25; N, 7.81. Found: C, 70.26; H, 5.09; N, 7.67. δ_H (300 MHz, $CDCl_3$) 0.94 (t, 3H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 1.45 (sx, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 2.04 (qv, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 2.12 (s, 2H, CH_2); 3.39 (t, 2H, $J = 8$ Hz, $CH_2CH_2CH_2CH_3$); 7.36–7.39 (m, 4H, ArH); 7.46–7.53 (m, 2H, ArH); 7.97–8.06 (m, 4H, ArH); 8.14–8.17 (m, 3H, ArH); 8.48 (dd, 1H, $J = 8$ Hz; 3 Hz, ArH); 8.72 (d, 1H, $J = 3$ Hz, ArH); 9.43 (b, 1H, *COOH*); 9.21 (b, 1H, *CONH*). MS (ESI): 538 (M + 1).

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