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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

A rational design, synthesis, characterization, and antihypertensive activities of some new substituted benzimidazoles

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Abstract A series of 5-substituted benzimidazoles were designed, synthesized, and evaluated for in vivo antihypertensive activity by acute renal hypertension on guinea pig. All the compounds of the series elicit remarkable activity in comparison to standard drug (losartan). The activity is found to be relatively better in substituted alkylamino group at 5-position of benzimidazole. The maximum activity that is almost equipotent with losartan is observed with four compounds DR-13, DR-14, DR-15, and DR-16.

Keywords Hypertension · Benzimidazole · Angiotensin II antagonist · Acute renal hypertension

Introduction

Hypertension is the most common cardiovascular disease which in fact, affects about half of all people belonging to age group 65 and above and the cause for this disease is not specific (**Hardman *et al.* 2001). The failure to reduce risk of cardiovascular disease (CVD) in hypertensive patients relates partially to the failure of conventional antihypertensive drugs like adrenergic blockers (e.g., atenolol, propanalol, etc.) and diuretics to cause crucial pathophysiological mechanism of blood pressure (BP) elevation and target organ damage. This led to development of new class of drugs that target both BP and related structural and functional abnormalities of the heart and blood vessels. Renin angiotensin system (RAS) (Ferrario, 1990) is the most direct, precise, complete, specific, and effective approach to antagonize AngII at its receptor site. These drugs have proved that, by lowering the BP effectively, they are better tolerated than other classes of drugs and are devoid of side effects such as dry cough and angioedema caused by non-specific action of ACE inhibitors (Cockcroft *et al.*, 1993). Carini *et al.* (1991) proposed a structure–activity relationship (SAR) of AT_1 receptor antagonist, which suggested that the activity is improved by the presence of a biphenyl group of losartan, able to fit into a third hydrophobic pocket; a tetrazole group or an acidic isostere at the ortho position of the biphenyl group able to interact with basic residue of the AT_1 receptor; a short alkyl chain at the 2 position of the heterocyclic, for the efficient binding to the receptor and which could fit into a second lipophilic pocket in the AT_1 receptor; a heterocyclic ring, to act as an acceptor in a hydrogen-bonding interaction with the receptor; and a moiety hydroxyl methyl group of losartan, which is capable of a hydrogen-bonding interaction with the AT_1 receptor. Bulky substituents on to the losartan, like chlorine atom, could occupy a large hydrophobic cavity in the AT_1 receptor. This pharmacophore feature can be best exemplified by the extremely potent benzimidazole antagonist CV-11194 (Naka and Kubo, 1999), and Telmisartan which is clinically used AngII antagonist. Numerous datasets reported in the literature were subjected to QSAR analysis for the purpose of designing novel angiotensin II receptor antagonists (Balasubramanian *et al.*, 2007; Belvisi *et al.*, 1996; Datar *et al.*, 2004a, b; Kurup *et al.*, 2001; Pandya and Chaturvedi, 2004, 2005; Pandya *et al.*, 2001; Yan *et al.*, 2007; Yoo *et al.*, 1999; Jain and Chaturvedi, 2008, 2009a, b).

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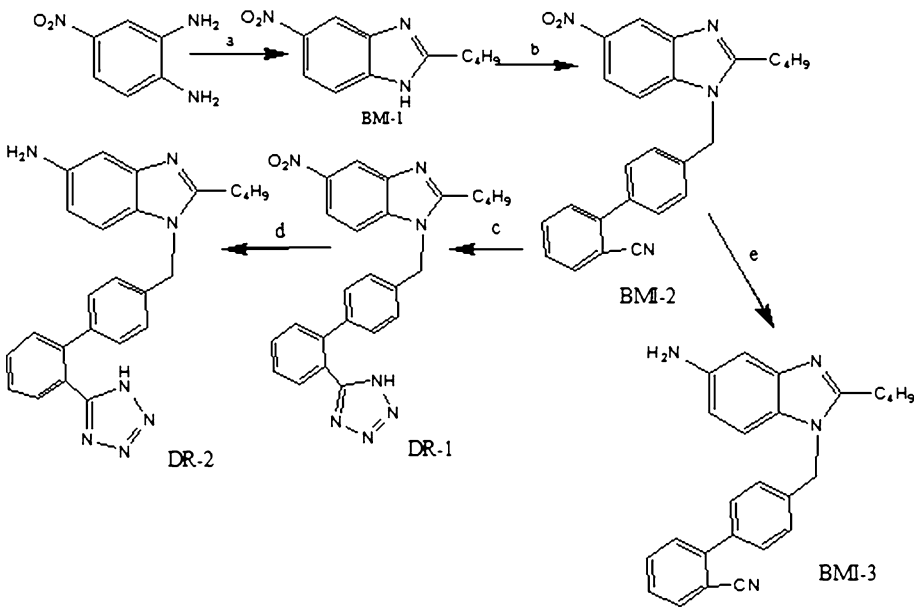
Bali *et al.* (2005) reported on the basis of previous study that extension of chemical group at 5-position may occupy either L3 pocket or some additional pocket in the receptor to increase antihypertensive activity. It was also hypothesized that further extension at nitrogen atom of NO_2 group with substituents (like alkyl amino group) may strengthen the binding interactions through lipophillic and/or H-bonding interactions with pocket L3 or L4. Shah *et al.* (2008) and Kaur *et al.* (2008) exploited the 5-position of benzimidazole with the syntheses of carboxaamido and sulfonyl groups and reported compounds which are more active than or equally active as Candesartan. Kohara *et al.* (1996) reported that the 5-oxo-1,2,4-oxadiazole and its thio analog are lipophillic bioisosteric replacement for the tetrazole unit, and that their derivatives exhibit enhanced activity and oral bioavailability. Kubo *et al.* (1993a) studied 2-substitution on benzene ring of the bezimidazoles with the various substituents. 2-Alkyl benzimidazole-based AT_1 receptor antagonist bearing *N*-phenylpyrrole moiety at position 1 was also studied by Jin *et al.* (2007), Among the different substituents, a lipophilic group with H-bond-accepting capabilities (acylureas) at 6-position (Ries *et al.*, 1993) and carboxylic function at 7-position of benzimidazole nucleus has been found to be favorable for AngII antagonism. Further, a linear butyl chain and an ethoxy group are required at position 2 in 6-substituted benzimidazole and in benzimidazole-7-carboxylic acid derivatives, respectively.

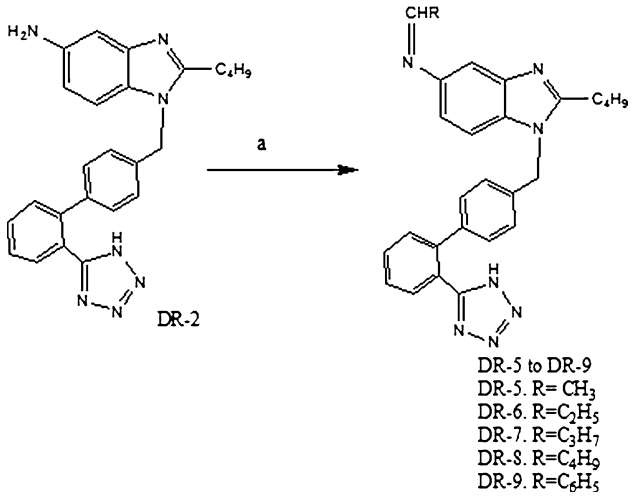
Keeping in mind the above facts, it was thought worthwhile to design the novel surrogates of the 5-substituted benzimidazoles followed by their syntheses and evaluation of antihypertensive activity based on structure of AngII AT-1 antagonist with improved pharmacological profile. The designed compounds on the basis of literature survey have all the expected structural features: a benzimidazole ring is attached to a biphenyl nucleus, which is attached to an acidic fragment. The acidic fragment is a –tetrazole group present in all the designed 16 compounds—from DR-1 to DR-16.

Experimental

All the chemicals and reagents used in the syntheses were of synthetic grade (Merck, National, SD fine, Ranchem, Lobachem, and Sigma Aldrich). The schemes used for the syntheses of compounds (DR-1 to DR-16) are shown in Schemes 1, 2, 3, 4. Melting points were determined by open capillary method using melting point apparatus model VMP-DS (manufacturer, Veego Company) and are shown as uncorrected in Table 1. The time required for completion of the reaction was monitored by thin layer chromatography that was performed on precoated TLC silica gel 60 F254, 0.2-mm thickness on aluminum sheet, and spots were exposed in iodine chamber and UV chamber. IR spectra were recorded on a Shimadzu (8400 S) FTIR Spectrophotometer. ^{1}H NMR spectra were recorded for the pure products in DMSO-d_6 using a Bruker advance 400 MHz NMR spectrometer from SAIF, Punjab University. The Dart-MS was recorded on a JEOL-AccuTOFJMS-T100LC mass spectrometer having a Dart (direct analysis in real time) source by ESI + method. The elemental analysis of the synthesized compounds was performed on elemental analyzer, Heraeus Vario EL III/Carlo Ebra 1108. Physico-analytic data, and the spectral data of the newly synthesized compounds are shown in Tables 1 and 2, respectively.



Scheme 1 Syntheses of starting materials BMI-1–3 and DR-1 and DR-2. Reagent and condition: *a* velaric acid, phosporus oxychloride, 170 °C; *b* DMF, K_2CO_3, 4-bromo methyl 2′cynobiphenyl, 27 °C; *c* ammonium chloride, sodium azide, 120 °C; *d* and *e* $Sncl_2$, HCl, 70 °C



Scheme 2 Syntheses of DR-5–DR-9. Reagent and condition: aldehydes and ethanol

Syntheses

The starting material 2-butyl-5-*n*itrobenzimidazole (BMI-1), 2-butyl-1-[(2′-cynobiphenyl-4-yl) methyl]-1H-benzimidazole-5-nitro(BMI-2) and 2-butyl-1-[(2′-cyanobiphenyl-4-yl) methyl]-1H-benzimidazole-5-amino (BMI-3) were prepared by the described methods given below and characterized by FTIR and TLC (Scheme 1).

Synthesis of 2-butyl-5-nitrobenzimidazole (BMI-1)

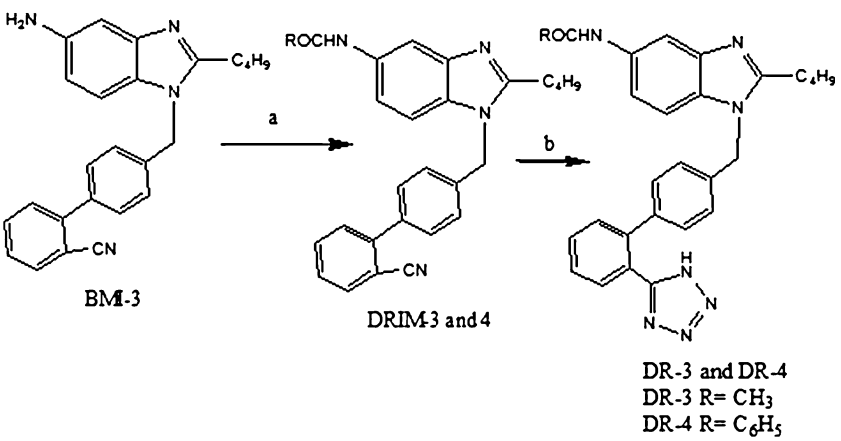
A solution of 75 mmol of 1,2-diamino-4-nitrobenzene and 85 mmol of valeric acid, and 120 mL of $POCl_3$ was heated under reflux for 3.5 h. The mixture was then poured in 1.5 L of ice water, the pH was then adjusted to 8–10 by the addition of concentrated ammonia, and the solution was then extracted with ethyl acetate. The extract was dried, the solvent was evaporated, and residue was purified by washing with *n*-hexane, and by silica gel column chromatography and eluting with DCM/ethanol (98:5 v/v) to give BMI-1 as brown solid. Compound was confirmed by TLC.

Synthesis of 2-butyl-1-[(2′-cynobiphenyl-4-yl)methyl]-1H-benzimidazole-5-nitro (BMI-2)

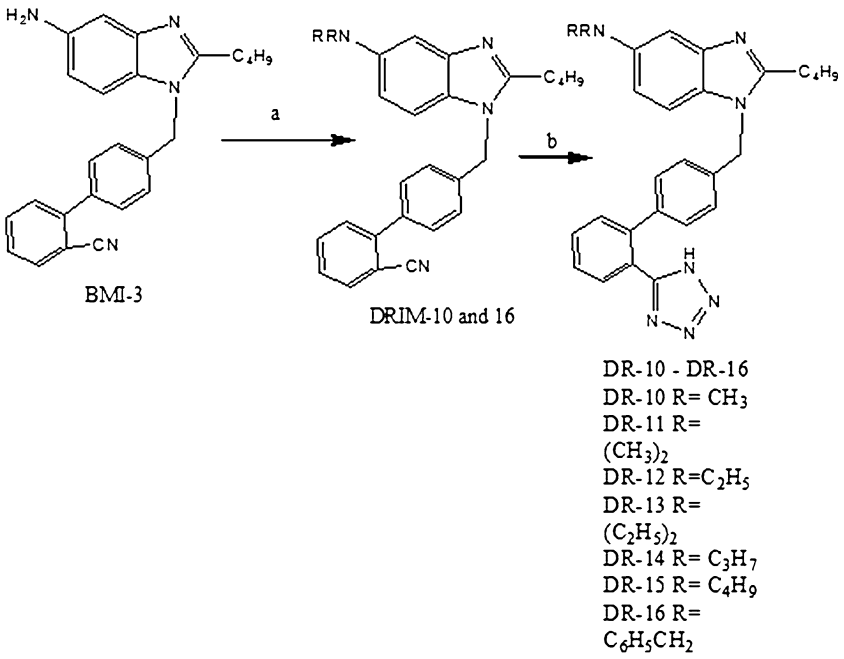
43 mmol of BMI-1 was dissolved in 60 mL of DMF (dimethyl formamide) and stirred vigorously under nitrogen atmosphere with 40 mmol of potassium carbonate at 27 °C for 1 h. To the resulting mixture, 43 mmol of 4-bromomethyl 2′cynobiphenyl in 60 mL of DMF was added drop wise with dropping funnel in 1 h. The reaction was allowed to proceed for further 11 h and solvent removed under vacuum. Residue was treated with 20 mL of dilute HCl and extracted with ethyl acetate. The organic layer was washed with brine solution, distilled water and dried over anhydrous sodium sulfate. The solvent was evaporated and a brownish semisolid (BMI-2) was obtained. BMI-2 was purified by column chromatography using the mobile phase DCM/ethanol in the ratios of 50:1 and then 25:1. Yellow liquid was obtained.

Synthesis of 2-butyl-1-[(2′-cyanobiphenyl-4-yl) methyl]-1H-benzimidazole-5-amino (BMI-3)

15 mmol of BMI-2 was placed in three-necked RBF and dissolved in 50 mL of anhydrous ethanol, then acidified with concentrated HCl (10 mL), and heated to 70 °C under reflux. To this mixture, 30 mmol of stannous chloride dihydrates was added with slow stirring for 45 min, and the reaction conditions were maintained for further 7 h. The insoluble material was filtered off, and the filtrate was



Scheme 3 Syntheses of DR-3 to DR-4. Reagent and conditions: *a* acyl chloride; *b* sodium azide; ammonium chloride, 120 °C



Scheme 4 Syntheses of DR-10 to DR-16. Reagent and conditions: **a** alkyl amines, triethyl amine; **b** sodium azide, ammonium chloride, 120 °C

Table 1 Structure and physicochemical data of newly synthesized compounds

Compound code	R_1	Molecular formula	Mp (°C)	Yield (%)	*Rf* value	Analysis calc./found (%)			
						C	H	N	O
DR-1	NO_2	$C_{25}H_{23}N_7O_2$	160–162	40	0.35	66.20,	5.08	21.60	7.03
DR-2	NH_2	$C_{25}H_{25}N_7$	150–152	38	0.42	70.86,	5.92	23.12	–
DR-3	$NHCOCH_3$	$C_{27}H_{27}N_7O$	250–252	45	0.35	69.56	5.80	21.02	3.40
DR-4	$NHCOC_6H_5$	$C_{32}H_{29}N_7O$	270–272	42	0.32	72.82	5.53	18.55	3.01
DR-5	$CH_3CH{=}N$	$C_{27}H_{27}N_7$	117–119	51	0.22	72.12	5.99	21.75	–
DR-6	$C_2H_5CH{=}N$	$C_{28}H_{29}N_7$	122–124	50	0.21	72.45	6.28	21.12	–
DR-7	$C_3H_7CH{=}N$	$C_{29}H_{31}N_7$	130–132	41	0.20	72.89	6.52	20.51	–
DR-8	$C_4H_9CH{=}N$	$C_{30}H_{33}N_7$	178–180	52	0.24	73.21	6.55	19.90	–
DR-9	$C_6H_5CH{=}N$	$C_{32}H_{29}N_7$	120–121	54	0.20	75.10	5.68	19.12	–
DR-10	$NHCH_3$	$C_{26}H_{27}N_7$	120–122	50	0.35	71.35	6.20	22.38	–
DR-11	$N(CH_3)_2$	$C_{27}H_{29}N_7$	132–134	49	0.34	71.80	6.42	21.69	–
DR-12	NHC_2H_5	$C_{27}H_{29}N_7$	136–138	40	0.34	71.79	6.42	21.68	–
DR-13	$N(C_2H_5)_2$	$C_{29}H_{33}N_7$	142–144	43	0.32	72.60	6.92	20.40	–
DR-14	NHC_3H_7	$C_{28}H_{31}N_7$	140–142	45	0.33	72.20	6.68	21.03	–
DR-15	NHC_4H_9	$C_{29}H_{33}N_7$	148–150 °C	45	0.32	72.52	6.92	20.40	–
DR-16	$NHCH_2C_6H_5$	$C_{32}H_{31}N_7$	148–150	45	0.30	74.73	6.02	19.02	–

concentrated in vacuo. The residue was diluted with water, basified with 5 % sodium hydroxide solution, and was extracted with dichloromethane. The extract was washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed under vacuum. Product was purified by column chromatography using DCM/ethanol in ratios of 99:1 and 98:2. A colorless sticky product of benzimidazole intermediate-3 (BMI-3) was obtained.

General procedure of syntheses of compounds from DR-1 to DR-16

2-Butyl-1-[[2′-(1H tetrazol-5-yl) biphenyl-4-yl] methyl]-1H benzimidazole-5-nitro (DR-1).

A mixture of 16 mmol of BMI-2, 120 mmol of sodium azide, and 120 mmol ammonium chloride in 30 mL DMF

Table 2 Spectral data of newly synthesized compounds

Compd.	FTIR(KBr/cm^{-1}) (observed)	^{1}H NMR (DMSO-d_6) (d, ppm)	^{13}C NMR (DMSO-d_6) (δ, ppm)	MS (M^+)
DR-1	3398 (N–H), 3031 (C–H Ar), 2920 (C–H aliphatic), 2840 (C–H aliphatic), 1623 (C=N), 1604–1569&1455–1438 (C=C Ar.), 1510 (N=O sym), 1378 (N=O asy), 1122 (C–N)	8.47–7.32 (m, 11H, Ar–H), 5.44 (s, 2H, CH_2), 2.87 (t, 2H, CH_2), 1.59 (qu, 2H, CH_2), 1.30 (sx, 2H, CH_2), 0.90 (t, 3H, CH_3)	160–158, 44–111, 47.51, 35.17, 29.30, 22.41, 14.00	453
DR-2	3438, 3398, 3320 (NH_2 Asy and sym & N–H (Tetrazole), 3025 (C–H Ar), 2924 (C–H aliphatic), 2843 (C–H aliphatic), 1621 (C=N), 1605–1565 &1478–1438 (C=C Ar.), 1113 (C–N)	7.98–6.67 (m, 11H, Ar–H), 5.44 (s, 2H, CH_2), 3.27 (s, 2H, NH_2), 2.87 (t, 2H, CH_2), 1.59 (qu, 2H, CH_2), 1.30 (sx, 2H, CH_2) 0.90 (t, 3H, CH_3)	160–158, 137, 106, 47.51, 35.1729.30, 22.41, 14.00	423
DR-3	3388 (N–H), 3025 (C–H Ar), 2992 (C–H aliphatic), 2840 (C–H aliphatic), 1646 (C=O), 1621 (C=N), 1606–1552&1478–1434 (C=C Ar.), 1117 (C–N)	8.26 (s, 1H, NH), 8.06–7.37 (m, 11H, Ar–H), 5.44 (s, 2H, CH_2), 2.87 (t, 2H, CH_2), 2.05 (s, 3H, CH_3), 1.5 (qu, 2H, CH_2), 1.30 (sx, 2H, CH_2), 0.90 (t, 3H, CH_3)	170, 160–158, 137–112, 47.51, 35.17, 29.30 (CH_2), 23.82 ($COCH_3$), 22.41, 14.00	465
DR-4	3388 (N–H), 3025 (C–H Ar), 2992, 2943 (C–H aliphatic), 2840 (C–H aliphatic), 1646 (C=O), 1621 (C=N), 1606–1552 &1478–1438 (C=C Ar.), 1117 (C–N)	9.19 (s, 1H, NH), 8.13–7.03 (m, 16H, Ar–H), 5.44 (s, 2H, CH_2), 2.87 (t, 2HCH_2), 1.59 (qu, 2H, CH_2), 1.30 (sx, 2H, CH_2), 0.90 (t, 3H, CH_3)	166, 160–158, 137–110, 47.51, 35.17, 29.30, 22.40, 14.00	527
DR-5	3383 (N–H), 3015 (C–H Ar), 2986, (C–H aliphatic), 2808 (C–H aliphatic), 1627 (C=N), 1609–1565 &1452–1396 (C=C Ar.), 1123 (C–N)	8.0–7.15 (m, 12H, 11ArH&1H, CH=N), 5.44 (s, 2H, CH_2), 2.87 (t, 2HCH_2), 1.89 (d, 3H, CH_3), 1.59 (qu, 2H, CH_2), 1.30 (sx, 2H, CH_2), 0.90 (t, 3H, CH_3)	164, 160–158, 138–107, 47.51 (CH_2), 35.17, 29.30, 22.86, 22.40, 14.00	449
DR-6	3385 (N–H), 3021 (C–H Ar), 2988, 2954 (C–H aliphatic), 2818 (C–H aliphatic), 1624 (C=N), 1609–1559 &1452–1421 (C=C Ar.), 1123 (C–N)	7.98–7.15 (m, 12H, 11HAr–H&1H, CH=N), 5.44 (s, 2H, CH_2), 2.87 (t, 2HCH_2), 2.19 (qu, 2H, CH_2), 1.59 (qu, 2H, CH_2), 1.30 (sx, 2H, CH_2), 1.01 (t, 3H, CH_3) 0.90 (t, 3H, CH_3)	162, 160–158, 139–107, 47.51, 35.17, 29.30, 26.67, 22.41 (CH_2), 14.00 (CH_3), 9.0	463
DR-7	3386 (N–H), 3010 (C–H Ar), 2978, 2954 (C–H aliphatic), 2848 (C–H aliphatic), 1644 (C=N), 1605–1569 &1462–1431 (C=C Ar.), 1125 (C–N)	7.98–7.15 (m, 12H, 11HAr–H& 1H, CH=N), 5.44 (s, 2H, CH_2), 2.87 (t, 2HCH_2), 2.19 (q, 2H, CH_2), 1.66 (Sx, 2H, CH_2) 1.59 (qu, 2H, CH_2), 1.30 (sx, 2H, CH_2), 0.94 (t, 3H, CH_3) 0.90 (t, 3H, CH_3)	165, 160–158, 139–107, 47.51, 35.17, 34.74, 29.30, 22.41, 20.75, 14.00, 12.95	477
DR-8	3378 (N–H), 3022 (C–H Ar), 2975, 2949 (C–H aliphatic), 2843 (C–H aliphatic), 1638 (C=N), 1611–1561 &1477–1431 (C=C Ar.), 1133 (C–N)	7.98–7.16 (m, 12H, 11HAr–H& 1H, CH=N), 5.42 (s, 2H, CH_2), 2.86 (t, 2HCH_2), 2.33 (q, 2H, CH_2), 1.56 (m, 4H, CH_2, CH_2) 1.34 (sx, 2H, CH_2), 1.30 (sx, 2H, CH_2), 0.93 (t, 3H, CH_3) 0.90 (t, 3H, CH_3)	165, 160–158, 137–108, 47.51, 35.17, 34.57, 30.00, 29.30, 22.40, 14.00	491
DR–9	3387 (N–H), 3012 (C–H Ar), 2977, 2949 (C–H aliphatic), 2813 (C–H aliphatic), 1628 (C=N), 1600–1561 &1457–1441 (C=C Ar.), 1122 (C–N)	8.66 (s, 1H, CH=N), 7.98–7.16 (m, 16H, Ar–H), 5.44 (s, 2H, CH_2), 2.87 (t, 2HCH_2), 1.59 (qu, 2H, CH_2), 1.30 (sx, 2H, CH_2), 0.90 (t, 3H, CH_3)	165, 160–158, 139–103, 47.51, 35.17, 29.30, 22.41, 14.00	511
DR-10	3381 (N–H), 3016 (C–H Ar), 2965, 2916 (C–H aliphatic), 2823 (C–H aliphatic), 1625 (C=N), 1599–1565 &1458–1396 (C=C Ar.), 1123 (C–N)	7.98–6.57 (m, 11H, ArH), 5.44 (s, 2H, CH_2), 3.75 (s, 1H, NH) 2.87 (t, 2HCH_2), 2.75 (s, 3H, CH_3) 1.59 (qu, 2H, CH_2), 1.30 (sx, 2H, CH_2), 0.90 (t, 3H, CH_3)	160–158, 138–104, 47.51, 37.51, 35.17, 29.30, 22.40, 14.00	437
DR-11	3385 (N–H), 3021 (C–H Ar), 2988, 2954 (C–H aliphatic), 2818 (C–H aliphatic), 1624 (C=N), 1609–1559 &1452–1421 (C=C Ar.), 1123 (C–N	7.98–6.69 (m, 11H, Ar–H), 5.44 (s, 2H, CH_2), 3.06 (s, 6H, (CH_3) 2 NH), 2.87 (t, 2HCH_2), 1.59 (qu, 2H, CH_2), 1.30 (sx, 2H, CH_2), 0.90 (t, 3H, CH_3)	160–158, 142–107, 47.51, 41.00, 35.17, 29.30, 22.41, 14.00	451
DR-12	3383 (N–H), 3015 (C–H Ar), 2986, 2934 (C–H aliphatic), 2808 (C–H aliphatic), 1627 (C=N), 1599–1528 &1458–1396 (C=C Ar.), 1127 (C–N)	7.98–6.64 (m, 11H, ArH), 5.43 (s, 2H, CH_2), 3.15 (s, 1H, NH) 3.45 (q, 2H, CH_2), 2.87 (t, 2H, CH_2), 1.59 (qu, 2H, CH_2), 1.31 (sx, 2H, CH_2), 1.15 (t, 3H, , CH_3) 0.90 (t, 3H, CH_3)	160–158, 138–107, 47.51, 37.50, 35.17 29.30, 22.40, 14.00, 13.00	451
DR-13	3386 (N–H), 3015 (C–H Ar), 2986, 2934 (C–H aliphatic), 2808 (C–H aliphatic), 1627 (C=N), 1599–1565&1458–1396 (C=C Ar.), 1123 (C–N)	7.98–6.64 (m, 11H, Ar–H), 5.44 (s, 2H, CH_2), 3.40 (q, 4H, (CH_2) 2 N) 2.87 (t, 2H, CH_2), 1.59 (qu, 2H, CH_2), 1.30 (sx, 2H, CH_2), 1.12 (t, 6H, (CH_3CH_2) 2 N), 0.90 (t, 3H, CH_3)	160–158, 129–104, 47.50, 46.00, 35.17, 29.30, 22.40, 14.00, 12.00	479

Table 2 continued

Compd.	FTIR(KBr/cm^{-1}) (observed)	^{1}H NMR (DMSO-d_6) (d, ppm)	^{13}C NMR (DMSO-d_6) (δ, ppm)	MS (M^+)
DR-14	3386 (N–H), 3010 (C–H Ar), 2978, 2954 (C–H aliphatic), 2848 (C–H aliphatic), 1644 (C=N), 1605–1569&1462–1431 (C=C Ar.), 1125 (C–N)	7.98–6.61 (m, 11H, ArH), 5.42 (s, 2H, CH_2), 3.76 (s, 1H, NH) 3.30 (t, 2H, CH_2NH), 2.87 (t, 2H, CH_2), 1.57 (sx, 4H, CH_2), 1.30 (sx, 2H, CH_2), 0.90 (t, 6H, CH_3)	160–158, 138–104, 47.51, 46.00, 35.17, 29.30, 22.62, 22.40, 14.00, 11.00	465
DR-15	3386 (N–H), 3010 (C–H Ar), 2978, 2954 (C–H aliphatic), 2848 (C–H aliphatic), 1634 (C=N), 1603–1545&1466–1433 (C=C Ar.), 1122 (C–N)	7.96–6.73 (m, 11H, Ar–H), 5.44 (s, 2H, CH_2), 3.76 (s, 1H, NH) 3.30 (t, 2H, CH_2NH), 2.87 (t, 2H, CH_2), 1.59 (qu, 2H, CH_2), 0.89 (t, 6H, CH_3)	160–158, 138–104, 47.51, 43.85, 35.17, 30.00, 29.30, 22.41, 20.00, 14.00	479
DR-16	3385 (N–H), 3021 (C–H Ar), 2988, 2954 (C–H aliphatic), 2818 (C–H aliphatic), 1624 (C=N), 1609–1559 &1452–1421 (C=C Ar.), 1123 (C–N)	7.95–7.16 (m, 16H, Ar–H), 5.44 (s, 2H, CH_2), 4.31 (s, 2H, CH_2NH) 3.89 (s, 1H, NH), 2.87 (t, 2H, CH_2), 1.59 (q, 2H, CH_2), 1.30 (sx, 2H, CH_2), 0.90 (t, 3H, CH_3)	160–158, 139–107, 47.51, 47.11, 35.17, 29.30, 22.40, 22.08, 14.00	513

was stirred at 120 °C for 3.5 days. The reaction mixture was diluted with water and acidified to pH 3–4 with 1 N HCl. The precipitate was collected by filtration, and washed with water. Product was purified by column chromatography using the mobile phase DCM/ethanol in the ratio of 98:2.

2-Butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-1-H-Benzimidazole-5-amino (DR-2)

10 mmol of DR-1 was placed in three-necked RBF and dissolved in anhydrous ethanol and acidified with conc. HCl and heated to 70 °C under reflux. To this mixture, 30 mmol of stannous chloride dihydrates was added with slow stirring for 45 min, and reaction conditions were maintained for further 7 h. The mixture was cooled to room temperature, and the insoluble material was filtered, and then the solvent was removed under vaccuum. Water was added, and the pH was adjusted to 7 with 5 % sodium hydroxide solution. The residue was extracted with dichloromethane. The extract was washed with brine and distilled water, and then dried over anhydrous $MgSO_4$. Solvent was removed under vacuum. Product was purified by column chromatography using DCM/ethanol.

2-Butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-N-(1H-benzimidazol-5-yl) acetamide (DR-3)

2-Butyl-1-[(2′-cyanobiphenyl-4-yl) methyl]-1H-benzimidazole-5-acetamide (DRIM-3) To a stirred solution of 0.65 mmol of BMI-3 in 4 mL of pyridine, 0.65 mmol of acetoyl chloride was added slowly at 0 °C. Reaction was carried out under nitrogen; after stirring for 1 h at 25 °C, the mixture was poured into ice water (13 mL). The precipitated solid was filtered off, dried, and kept for use in the next step (ii).

Conversion of 2-butyl-1-[(2′-cyanobiphenyl-4-yl) methyl]-1H-benzimidazole-5-acetamide(DRIM-3) to 2-butyl-1-[[(1H-tetrazole-5-yl)biphenyl-4-yl] methyl)]-N-(1H-benzimidazol-5-yl)acetamide (DR-3) A mixture of 0.56 mmol DRIM-3, 8.4 mmol of sodium azide and 8.4 mmol of ammonium chloride in 15 mL DMF was stirred at 120 °C for 3.5 days. The reaction mixture was diluted with water and acidified to pH 3–4 with 1 N HCl. The precipitate was collected by filtration, and purified by column chromatography using the mobile phase DCM/ethanol in the ratio of 98:2 (Scheme 2).

Synthesis of 2-butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-N-(1H-benzimidazol-5-yl) benzamide (DR-4)

Synthesis of 2-butyl-1-[(2-cyanobiphenyl-4-yl) methyl]-1H-benzimidazole-5-benzamide (DRIM-4) Benzoyl chloride, 1 mmol, was added drop wise from a dropping funnel for 15 min under stirring in an ice-cooled mixture of 1 mmol of BMI-3 in 10 mL of DCM and 1.5 mmol of Triethylamine in 50 mL RBF. The mixture was then stirred at 0 °C under nitrogen. After completion of the reaction (monitored by TLC), the reaction mixture was washed with aqueous $NaHCO_3$ and dried over anhydrous $MgSO_4$. Evaporation of the solvent was done under vacuum to yield colorless oil, and the compound was kept for further use in the next step.

Conversion of 2-butyl-1-[(2′-cyanobiphenyl-4-yl) methyl]-1H-benzimidazole-5-benzamide (DRIM-4) to 2-butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-N-(1H-benzimidazol-5-yl)benzamide (DR-4) A mixture of, 0.65 mmol of DRIM-4,, 9.7 mmol of sodium azide and 9.7 mmol of ammonium chloride in 15 mL DMF was stirred at 120 °C for 3.5 days. Reaction is also monitored through TLC, and after completion of reaction, the reaction

mixture was diluted with water and acidified to attain pH 3-4 with 1 N HCl. The precipitate was collected by filtration, and purified by column chromatography using the mobile phase DCM/ethanol in the ratio of 95:5.

General scheme of syntheses of compounds DR-5 to DR-9

To 50 mL of RB Flask fitted with reflux condenser, a solution of 0.5 mmol of aldehyde in 5 mL of ethanol was added drop wise to a well-stirred solution of 0.5 mmol of DR-2 in 15 mL of boiling ethanol. The reaction mixture was refluxed, and after completion of reaction (monitored by TLC), the solvent was evaporated under reduced pressure. The solid precipitate produced was filtered off, washed with dilute ethanol, and purified by recrystallization using boiling ethanol, as shown in Scheme 3.

2-Butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-N-methyl-1H-benzimidazol-5-amine(DR-10)

Synthesis of 2-butyl-1-[(2′-cyanobiphenyl-4-yl) methyl]-1H-benzimidazole-5-methyl amine (DRIM-10) To the mixture of 2 mmol of BMI-3 and 1 mmol of methyl Iodide in 20 mL DCM, 2 mmol of triethyl amine was added, and the final mixture was stirred overnight. Reaction was carried out under nitrogen. After completion of reaction (monitored by TLC), water was added. The separated organic layer was washed with brine and water and then dried over anhydrous $MgSO_4$. Solvent was evaporated under reduced pressure. Product was purified by column chromatography using mobile phase DCM:methanol in the ratio of 99:1, and the remaining colorless sticky residue was used for further reaction.

Conversion of 2-butyl-1-[(2′-cyanobiphenyl-4-yl) methyl]-1H-benzimidazole-5-amine(DRIM-4) to 2-butyl-1-[[(1H-tetrazole-5-yl)biphenyl-4-yl] methyl)]-N-methyl-1H-benzimidazol-5-amine (DR-10) A mixture of 0.5 mmol of DRIM-10, 7.5 mmol of sodium azide, and 7.5 mmol of ammonium chloride in 25 mL DMF was stirred at 120 °C for 3.5 days. The reaction mixture was diluted with water and acidified to pH 3–4 with 1 N HCl. The precipitate was collected by filtration, and purified by column chromatography using the mobile phase DCM/methanol in the ratio of 98:2. (Scheme 4).

2-Butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-N,N-dimethyl-1H-benzimidazol-5-amine(DR-11)

Synthesis of 2-butyl-1-[(2′-cyanobiphenyl-4-yl) methyl]-1H-benzimidazole-5-dimethyl amine (DRIM-11) The mixture of 0.75 mmol of DRIM-10 and 1.0 mmol of methyl iodide in 20 mL of DCM was stirred for overnight at room temperature with 2 mmol of Triethyl amine. After completion of the reaction (monitored by TLC), the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in 5 mL of DCM and washed with 5 mL of distilled water. The aqueous layer was washed with 3 × 5 mL fractions of DCM. The collected organic fractions were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to yield the crude sticky product and kept for further use in the next step.

Conversion of 2-butyl-1-[(2′-cyanobiphenyl-4-yl) methyl]-1H-benzimidazole-5-diethyl amine (DRIM-12) to 2-butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-N,N-Methyl-1H-benzimidazol-5-amine (DR-11) A mixture of 0.65 mmol of DRIM-11, 9.7 mmol of sodium azide and 9.7 mmol of ammonium chloride in 30 mL DMF was stirred at 120 °C for 3.5 days. The reaction mixture was diluted with water and acidified to pH 3–4 with 1 N HCl. The precipitate was collected by filtration, and purified by column chromatography using the mobile phase DCM/methanol in the ratio of 99:1.

2-Butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-N-ethyl-1H-benzimidazol-5-amine (DR-12)

Synthesis of 2-butyl-1-[(2′-cyanobiphenyl-4-yl)methyl]-1H-benzimidazole-5-ethyl amine (DRIM-12) The mixture of 2 mmol of BMI-3 and 1 mmol of ethyl bromide in 20 mL DCM was stirred overnight to which 2 mmol of triethyl amine was also added. Reaction was carried out under nitrogen. After completion of reaction (monitored by TLC), water was added. The separated organic layer was washed with brine and water and then dried over anhydrous $MgSO_4$. Solvent was evaporated under reduced pressure. Product was purified by column chromatography using mobile phase DCM: methanol in the ratio of 98:2, and a colorless semisolid product was obtained and kept for further use in the reaction.

Conversion of 2-butyl-1-[(2′-cyanobiphenyl-4-yl) methyl]-1H-benzimidazole-5-ethyl amine (DRIM-12) to 2-Butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-N-ethyl-1H-benzimidazol-5-amine (DR-12) A mixture of 0.65 mmol of DRIM-12, 9.5 mmol of sodium azide and 9.5 mmol of ammonium chloride in 25 mL DMF was stirred at 120 °C for 3.5 days. The reaction mixture was diluted with water and acidified to pH 3–4 with 1 N HCl. The precipitate was collected by filtration, and purified by column chromatography using the mobile phase DCM/methanol in the ratio of 95:5.

Synthesis of 2-butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-N, N-diethyl-1H-benzimidazol-5-amine (DR-13)

Synthesis of 2-butyl-1-[(2′-cyanobiphenyl-4-yl) methyl]-1H-benzimidazole-5-diethyl amine (DRIM-13) The mixture of 0.75 mmol of DRIM-12 and 1.0 mmol of ethyl bromide in 20 mL of DCM was stirred for overnight at room temperature with 2.0 mmol of triethyl amine. After completion of the reaction (monitored by TLC), the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in 5 mL of DCM and washed with 5 mL of distilled water. The aqueous layer was washed with 3 × 5 mL fractions of DCM. The collected organic fractions were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to yield the crude semisolid product, which was kept for further use in the next step.

Conversion of synthesis of 2-butyl-1-[(2′-cyanobiphenyl-4-yl)methyl]-1H-benzimidazole-5-diethyl amine (DRIM-13) to Synthesis of 2-Butyl-1-[[(1H-tetrazole-5-yl)biphenyl-4-yl]methyl)]-N,N-diethyl-1H-benzimidazol-5-amine (DR-13) A mixture of 0.65 mmol of DRIM-13, 9.5 mmol of sodium azide and 9.5 mmol of ammonium chloride in 30 mL DMF was stirred at 120 °C for 3.5 days. The reaction mixture was diluted with water and acidified to pH 3–4 with 1 N HCl. The precipitate was collected by filtration, and purified by column chromatography using the mobile phase DCM/methanol in the ratio of 99:1.

2-Butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-N-propyl-1H-benzimidazol-5-amine(DR-14)

2-Butyl-1-[(2′-cyanobiphenyl-4-yl)methyl]-1H-benzimidazole-5-propyl amine (DRIM-14) To the stirred mixture of 0.8 mmol of BMI-3 and 2 mmol of triethyl amine in 5 mL of DCM, 1 mmol of Propyl bromide was added and stirred overnight. After completion of the reaction (monitored by TLC), the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in 5 mL of DCM and washed with 5 mL of distilled water. The aqueous layer was washed with 3 × 5 mL fractions of DCM. The collected organic fractions were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to yield the crude product. The product was purified by Column chromatography using mobile phase DCM: methanol in ratio of 95:5. A colorless semisolid product was obtained for use in a further step.

Conversion of 2-butyl-1-[(2′-cyanobiphenyl-4-yl) methyl]-1H-benzimidazole-5-propyl amine (DRIM-14) to 2-butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-N-propyl-1H-benzimidazol-5-amine (DR-14) A mixture of 0.5 mmol of DRIM-14, 7.5 mmol of sodium azide and 7.5 mmol of ammonium chloride in 10 mL DMF was stirred at 120 °C for 3.5 days. After completion of reaction, the reaction mixture was diluted with water and acidified to pH 3-4 with 1 N HCl. The precipitate was collected by filtration, and purified by column chromatography using the mobile phase DCM/methanol in the ratio of 95:5.

2-Butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-N-butyl-1H-benzimidazol-5-amine(DR-15)

2-Butyl-1-[(2′-cyanobiphenyl-4-yl)ethyl]-1H-benzimidazole-5-butylamine (DRIM-15) The mixture of 0.75 mmol of BMI-3 and 0.75 mmol of butyl bromide in DCM was stirred overnight with 2 mmol of triethyl amine. After completion of the reaction (monitored by TLC) the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in 5 mL of DCM and washed with 5 mL of distilled water. The aqueous layer was washed with 3 × 5 mL fractions of DCM. The collected organic fractions were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to yield the crude product. The product purified by column chromatography using mobile phase DCM: methanol in ratio of 98:2. A sticky transparent mass was obtained for use in a further step.

2-Butyl-1-[(2′-cyanobiphenyl-4-yl)methyl]-1H-benzimidazole-5-butylamine (DRIM-15) to 2-Butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-N-butyl-1H-benzimidazol-5-amine (Derivative-15) A mixture of 0.5 mmol of DRIM-15, 7.5 mmol of sodium azide and 7.5 mmol of ammonium chloride in 10 mL DMF was stirred at 120 °C for 3.5 days. After completion of reaction which was also monitored through TLC, the reaction mixture was diluted with water and acidified to pH 3–4 with 1 N HCl. The precipitate was collected by filtration, and purified by column chromatography using the mobile phase DCM/methanol in the ratio of 95:5. White solid product was obtained.

2-Butyl-1-[[(1H-tetrazole-5-yl)biphenyl-4-yl]methyl)]-N-benzyl-1H-benzimidazol-5-amine(DR-16)

2-Butyl-1-[(2′-cyanobiphenyl-4-yl) methyl]-1H-benzimidazole-5-benzylamine (DRIM-16) The mixture of 0.75 mmol of BMI-3 and 1 mmol of benzyl chloride was stirred over night in 10 mL of DCM with 2 mmol of triethyl amine. After completion of the reaction (monitored by TLC), the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in 5 mL of DCM and washed with 5 mL of distilled water. The aqueous layer was washed with 3 × 5 mL fractions of DCM. The

collected organic fractions were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to yield the crude product. The product was purified with column chromatography using mobile phase DCM: methanol in ratio of 97:3. A transparent semisolid product was obtained for use in a further step.

2-Butyl-1[(2′-cyanobiphenyl-4-yl) methyl]-1H-benzimidazole-5-benzyl amine (DRIM-16) to 2-butyl-1-[[(1H-tetrazole-5-yl)biphenyl-4-yl]methyl)]-N-benzyl-1H-benzimidazol-5-amine (DR-16) A mixture of 0.5 mmol of DRIM-16, 7.5 mmol of sodium azide and 7.5 mmol of ammonium chloride in 10 mL DMF was stirred at 120 °C for 3.5 days. Reaction was also monitored through TLC and after completion of reaction, the reaction mixture was diluted with water and acidified to pH 3-4 with 1 N HCl. The precipitate was collected by filtration, and purified by column chromatography using the mobile phase DCM/methanol in the ratio of 98:2.

Antihypertensive activity in vivo

In methodology, recordings of BP in anesthetized guinea pig (700-725 gm) provided by the Institutional Animal House of B.R. Nahata College of Pharmacy, Mandsaur (139/F/09/IAEC/BRNCP/08-09/Mandasur) using acute renal hypertension BP measurement model were carried out (Hauser *et al.*, 2005; Gilani *et al.*, 2005; Cherinet *et al.*, 2002).

The animal was anesthetized by intraperitoneal injection of mixture of ketamine hydrochloride and xylazine. After induction of anesthesia, left renal artery was blocked by means of artery clamp for 45 min. Clamping of the left renal artery raised the systolic pressure. Then, trachea was cannulated to avoid any disturbance in respiration of animals during surgery. The jugular vein was cannulated. The 0.5 mL dose of normal saline was given to animal via jugular vein, and subsequently all test and standard compounds were given to animal by this route. The carotid artery was cannulated and attached with pressure transducer. A Mercury manometer, Physiograph (Student physiographic, 3 Channel, Biodevice by Incolab, Ambala), BP transducer, and strain gage coupler were used for the study.

This pressure transducer was previously calibrated by means of mercury manometer, and a calibration pressure curve was obtained. After attaching the carotid cannula, the renal artery clamp was removed, which caused a sharp increase in the BP because of activation of renin angiotensin system and rise in the plasma renin level.

Standard losartan solution at a dose of 3 mg/kg was administrated via jugular vein, and after giving drug dose the mice were allowed to wait till BP was not reached up to base line level. Then take responses of test compounds same as standard. The standard and test compounds were administered one by one in juggler vein, and response was observed, i.e., decrease in BP on physiograph paper. Changes in BP produced by the 16 synthesized compounds were compared to that of losartan, and three responses of each sample were taken to obtain mean BP as shown in Table 3. Data were expressed as mean and standard error of the mean of three experiments. Data were statistically compared as repeated measures using one way ANOVA followed by Dunnet test (Prism Graph pad Trial Version-5). $P < 0.05$ in two-tailed tests was considered significant.

Result and discussion

Chemistry

The synthetic scheme employed to synthesize the designed compounds is outlined in Schemes 1, 2, 3, 4. The compounds were prepared through a series of reactions as reported. Synthesis of intermediate 5-nitro 2-butyl benzimidazole from 4-nitro orthophenyl diamine with valeric acid (BMI-1)(Ries *et al.*, 1993) followed by alkylation of BMI-1 in DMF and K_2CO_3 to BMI-2 (Kubo *et al.*, 1993a), and then followed by tritylation of cyano to tetrazole to give DR-1 (Kubo *et al.*, 1993b). Compound DR-1 was subjected

Table 3 Antihypertensive activity of compounds and reference compound

S. no.	Compound no.	Mean arterial blood pressure (mmHg)	Total change in systolic BP (mmHg)
1	Control	149.3 ± 4.055	
2	Standard (Losartan)	115.5 ± 1.333***	34
3	DR-1	134.0 ± 1.555**	15
4	DR-2	130.0 ± 2.309***	19
5	DR-3	126.7 ± 2.906***	22
6	DR-4	121.3 ± 3.712***	28
7	DR-5	122.0 ± 1.155***	27
8	DR-6	131.3 ± 2.404***	18
9	DR-7	132.0 ± 1.155***	17
10	DR-8	127.0 ± 0.577***	27
11	DR-9	124.7 ± 1.764***	25
12	DR-10	137.3 ± 4.372*	12
13	DR-11	120.7 ± 1.764***	29
14	DR-12	120.7 ± 1.764***	29
15	DR-13	116.7 ± 1.764***	33
16	DR-14	117.3 ± 2.404***	32
17	DR-15	118.3 ± 2.848***	31
18	DR-16	118.0 ± 2.000***	31

Statistical analysis: one-way ANOVA followed by Dunnet test

** very significant $P < 0.01$, *** highly significant $P < 0.001$

to reduction to make compound DR-2 by reported method (Jat *et al.*, 2006). DR-2 was converted into to Schiff's base DR-5–DR-9 with aliphatic aldehyde. (Mostafa *et al.*, 2007). Reduction of intermediate BMI-2 with $SnCl_2$/HCl to intermediate BMI-3 was followed by acetylation and alkylation of BMI-3 with the acyl chloride and alkyl halide (Jason *et al.*, 2005). Tritylation of cyano to tetrazole gave DR-3, DR-4, and DR-10–16, respectively. The intermediate was also purified and ascertained by TLC. All compounds were purified by crystallization and column chromatography, and purity was verified by thin-layer chromatography as shown in Table 1. Structures of the compounds were established through FTIR, ^{1H}NMR, ^{13}NMR, and Mass spectral analyses.

In vivo antihypertensive activity

Losartan had maximum fall in Systolic Mean Arterial Blood Pressure (MABP) from a value of 149 mmHg to 115 mmHg, i.e., 34 mm of Hg. Among these compounds, maximum fall was seen in compound DR-13, i.e., 33 mmHg from initial value. While Compounds DR-14, DR-15, and DR-16 showed a reduction in MABP (32, 31, and 31 mmHg, respectively, from initial value as shown in Table 3. Hence, these compounds can be regarded as comparable with losartan in their antihypertensive action in terms of minimum BP values achieved. Compounds DR-10 and DR-1 had shown least activity among the all synthesized compounds. A fall in BP of 19, 18 and 17 mm of Hg was observed in Compounds DR-2, DR-6, and DR-7, respectively, from initial value. A significant fall in BP was observed in compounds in DR-11 and DR-12 (29 mm of Hg) from initial value. Compounds DR-4 and DR-5 were also found to be active in the same range and showed reduction in BP 28 mm and 27 mm of Hg, respectively. Compounds DR-3, DR-8, and DR-9 were also found to be significant in antihypertensive activity and showed fall in BP 22, 27, and 25 mm of Hg. Compounds DR-1, DR-2, DR-10, DR-6, and DR-7 did not show comparable value to losartan. However, they possess antihypertensive effect to some extent. Maximum lowering of BP is seen with compound DR-13 which showed a fall of BP about 33 mmHg and this effect is comparable to the losartan (34 mmHg). Similar activities were shown by compound DR-14, DR-15, and DR-16 as shown in Table 2. Antihypertensive activities exhibited by compounds having the same functional group at 2-position have been found to be a function of substituent at 5-position.The presence of amino group has increased the activity substantially over the other substitution (DR-13DR-16). This suggests that there are some sites in the receptor pocket, which can interact with the functional groups at position 5. In renal acute hypertension model, hypertension is increased by the Renin Angiotensin system because of renal artery blockade. This study suggests that the BP-lowering effect of the compounds might be mediated through Renin angiotensin system. The activity is more in N alkylated at position 5 on benzimidazole compound as compared with the Schiffs base and acylated product at 5-position of benzimidazole. All the active compounds DR-13, DR-14, DR-15, DR-16 having ethylamino, propylamino, butyl amino, and benzylamino substitution at 5-position. However, in compounds DR-13, DR-14, DR-15, and DR-16, the activity is slightly decreasing with the increasing bulkier group of alkyl/aryl residue. Shah *et al.*, (2008) report a series of 5-(alkyl and aryl carboxamido) derivatives with evaluation for in vitro AngII-AT_1 receptor antagonist and in vivo antihypertensive activities and suggest that the pharmacological activities were inversely related to the size of alkyl and aryl substituents. It can be suggested that compounds with lower alkylamino groups at 5-position of benzimidazole nucleus demonstrated potent antihypertensive activity.

Conclusions

Novel substituted benzimidazole DR-1DR-16 possessing nitro, amino, alkyl amino, and acyl groups in position 5 were synthesized in good yield using BMI-1 through BMI-3 as starting materials. The obtained compounds were evaluated for antihypertensive activity in vivo by acute renal hypertension model. All tested compounds showed varied activities. The activity is more in N alkylated at position 5 on benzimidazole compound as compared with the Schiffs base and acylated product at 5 position of benzimidazole. Four compounds 2-Butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-*N,N*-diethyl-1H-benzimidazol-5-amine (DR-13), 2-Butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl]methyl)]-*N*-propyl-1H-benzimidazol-5-amine (DR-14),2-Butyl-1-[(1H-tetrazole-5-yl)biphenyl-4-yl]methyl)]-*N*-butyl-1H-enzimidazol-5-amine (DR-15), and 2-Butyl-1-[[(1H-tetrazole-5-yl) biphenyl-4-yl] methyl)]-*N*-benzyl-1H-benzimidazol-5-amine (DR-16) can be regarded as comparable with losartan in their antihypertensive action in terms of minimum BP values achieved. Further, these compounds may be evaluated in in vitro studies using isolated tissue preparation, and radioligand assay and acute toxicological studies can bring a potential drug candidate from this class of compounds.

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