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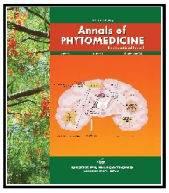

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Synthesis and biological evaluation of some substituted benzimidazole derivatives as antihypertensive activities

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Abstract

A new compound benzimidazole derivative was designed, synthesized and evaluated as a novel antihypertensive activity. A number of substituted benzimidazole were synthesized in good yields and the structures were corroborated on the basis of IR, ^{1}H NMR, Mass, and elemental analysis data. Structure activity relationship studies revealed that the substitutions at the benzimidazole ring attached to the acidic group bearing biphenyl system moiety play a significant role in governing the antihypertensive activity substitution with chloro, hydroxyl, methyl, and methoxy groups at 2 and 4-positions of phenyl ring on aniline moiety increases the antihypertensive activity significantly.

1. Introduction

Hypertension is considered as one of the leading risk factor for human morbidity and mortality for its effects on target organs such as heart, brain, kidneys and so on. It has the potency of future debilitating cardiovascular disease (Murugesan *et al.,* 2002). However, even if one does not exhibit symptoms, long-term high blood pressure is the major risk factor for numerous pathologies, such as stroke or heart failure (Higuchi *et al.,* 2007). It is estimated that an overall 1.13 billion people worldwide have hypertension, most of them (two-thirds) living in low-and middle-income countries and affects around 30% of the adult population (Gupta *et.al.,* 2022; Shaikh *et al.,* 2022). Every year, more and more studies are being performed on herbal remedies for high blood pressure. There are many herbal drugs like punarnava, barberry, rouwolfia, garlic, ginger, ginseng and arjuna which can safely use for the treatment of hypertension (Agrawal *et al.,* 2010). Several evidences exist to demonstrate that herbs derived from medicinal plants have been utilized for the treatment of various ailments, as well as for healing and enhancing physical and mental health in practically all ancient civilizations (Malik *et al.,* 2020; Bushra *et al.,* 2020; Desai *et al.,* 2021). Angiotensin II (AII) receptor blockers are a class of molecules that act in the renin angiotensin system, RAS through binding to the AT_1 receptor (angiotensin II receptor type 1, AT_1R) and preventing its activity. AT_1R is a g-protein-coupled receptor that is responsible for AII pathophysiological actions (Higuchi *et al.,* 2007). Angiotensin II type 1 (AT_1) receptor antagonists; namely, the angiotensin II type 1 receptor blockers (ARBs), are selective for AT_1 receptors, and act on the angiotensin II synthetic pathway independently (Ni *et al.,* 2012). The first of this class of molecules was losartan, which was approved by the FDA in 1995, and it was released to the market in April 1995. Specifically, Duncia and his team published the discovery of DuP753 (losartan), a potent, orally active nonpeptide angiotensin II (AII) receptor and other derivatives (Duncia *et al.,* 1992). Losartan is the first oral non-peptide angiotensin II receptor antagonist with low molecular weight. It binds to the AT_1 receptor with high affinity, specificity, and slow dissociation rate (Weber, 1992; Colin, 1995). 5-substituted benzimidazole nucleus coupled through a methylene linker to pendent biphenyl system bearing a carboxyl group, and nitro group at 5-position, which had been found to be favourable for angiotensin II antagonism (Bali *et al.,* 2005). A series of 5-(alkyl and aryl carboxamido) derivatives with evaluation for *in vitro* angiotensin II 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 (Shah *et al.,* 2008). 5-position of benzimidazole with the carboxaamido and sulfonyl groups which are more active than or equally active as candesartan (Kaur *et al.,* 2008). 5-nitro benzimidazole with 1,4-disubsituted or 1,5-disubsituted indole derivatives as novel angiotensin II receptor antagonist and hypertensive rats and renal hypertensive rats (Zhu *et al.,* 2014). 5-oxo-1,2,4-oxadiazole derivatives with 1, 4-disubsituted or 1, 5-disubsituted indole group was designed, synthesized, and pharmacologically evaluated. These derivatives displayed high affinities to the AT_1 receptor at the same order of magnitude to losartan (Zhu *et al.,* 2016). Hence, the present study has been conducted to design, synthesize and evaluate chloro and nitro at the 5th position of benzimidazole derivatives bearing substituted anilines chain at different position. Basically R, R1, R2 and R3 are the four substitution sites have been identified for substitution purpose. R = Cl and NO_2; R1 substituted anilines, R3 and R2 an acidic group

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(carboxylic or tetrazole) bearing biphenyl system through a methylene linker given in Figure 1.

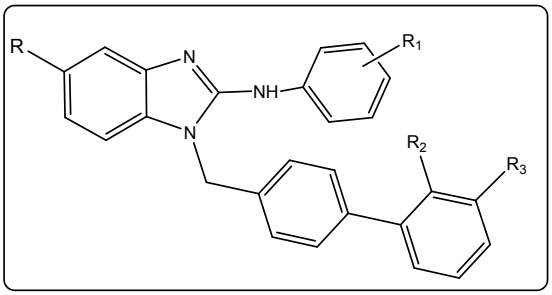

Figure 1: Lead compound.

2. Materials and Methods

All the chemicals used were of synthetic grade chemicals of Sigma Aldrich and Spectrochem. Melting points were determined on an electro thermal melting point apparatus in open capillary method and are uncorrected. The infrared spectroscopy was done on shimadzu DZU 8400S at School of Pharmacy, Devi Ahilya Vishwavidyalaya, Indore. ^{1}H-NMR spectra were recorded on a model AVANCE III 400 ascend bruker bio spin instrument and mass spectra (high resolution mass) at Indian Institute of Technology, Indore. The synthesis of the compounds was done in the following sequential steps (Table1; Figure 2).

2.1 Synthesis of arylisothiocyanate

A 500 ml three necked flask equipped with a powerful mechanical stirrer, a separating funnel and the third neck loosely stoppered. The flask was cooled in a freezing mixture of ice and salt and introduced 4.1 ml concentrated ammonia solution and carbon disulfide 2.4 ml. The mixture was stirred and aniline/substituted aniline (0.01 M) was run from the separating funnel during about 20 min. A heavy precipitated ammonium phenyl dithicarbamate got separate which was transferred into a 5 litres round bottom flask after form extraction with distilled water. To this, solution of lead nitrate (0.02 M) in distilled water was added. Lead sulphide got precipitated. The mixture was steam distillation into a receiver H_2SO_4 (5.0 ml) as long as the organic material passes over 2-3 litres of distillate. The oil was separated dried over anhydrous $CaCl_2$ and distilled under reduced pressure to get aryl isothicyanate as shown in Figure 2.

2.2 Synthesis of N-aryl-n'-(2-amino) arylthiourea

To a solution of substitituted chloro/nitro-ortho phenylenediamine (0.1 M) in 20 ml of dry glyme, aryl isothicyanate (0.01 M) was added and the mixture was stirred overnight at room temperature. The precipitated N-aryl-n-(2-amino) arylthiourea product was collected and recrystallized from methanol. Thus, crystals of N-aryl-n'-(2-amino) arylthiourea were obtained in good yield (78%) as shown in Figure 2.

2.3 Synthesis of 2-arylaminobenzimidazole [Intermediate-1]

To a suspension of N-aryl-n-(2-amino) aryl thiourea (0.1 M), cyclization (Wang *et al.,* 2004), followed by CuCl (0.01 M). The resulting mixture was heated to 80°C and kept at this temperature for 30 min. The reaction mixture was then cooled and filtered. The slurry was filtered to get 2-arylaminobenzimidazole intermediate-[1] as shown in Figure 2 and Table 1.

2.4 Synthesis of biphenyl 3-carboxylic acid [Ms 1-14]

To a solution of 2-arylaminobenzimidazole (0.01 M) intermediate [1] derivative in 50 ml of DMSO, potassium *tert*-butyrate (0.01 M) was added, and stirred for 30 minutes at room temperature. To this, 4'-bromomethyl- biphenyl-3-carboxylic acid intermediate [2] (0.25 M) was added and stirred for 14 h. The mixture was poured into distilled water and extracted with ethyl acetate, then the combined extracts were dried using magnesium sulphate and evaporated and residue was purified by silica gel column chromatography by eluting with ethanolic acetate or methanol to get the designed compounds shown in Table 1 and Figure 2.

2.5 Synthesis of biphenyl tetrazole [Ms 15-28]

To a solution of 2-arylaminobenzimidazole intermediate [1], 0.01 M derivative in 50 ml of DMSO, potassium tert-butyrate (0.01 M) was added, stirred for 30 min at room temperature. To this of 42 -bromomethyl- biphenyl-2-carbonitrile intermediate [3], (0.25 M) was added and stirred for 14 h. The mixture was poured into distilled water and extracted with ethyl acetate, then the combined extracts were dried using magnesium sulphate and evaporated and residue was purified by silica gel column chromatography by eluting with ethanolic acetate or methanol to get the intermediate compound-3. A mixture of intermediate [3] (0.1M), sodium azide (0.01 mol), dimethylformide about 30 ml and iminyl chloride (10.0 ml) was heated in an oil bath for 8 h. The solvent was removed under reduced pressure and residue was dissolved 100 ml of distilled water and carefully acidified to pH 2. Then solution was cooled to 10°C, and the compound was recrystallized from absolute ethanol and purified by column chromatography by eluting with ethanolic acetate or methanol as shown in Table 1 and Figure 2. Spectral data of newly synthesized compounds given below:

2.5.1 4'-[(5-Chloro-2-(2-chloro-phenylamino)-1H-benzo[d]imidazol-1-yl) methyl] biphenyl-3-carboxylic acid

Melting point 168-169°C; R_f : 0.68 ; IR (n, cm^{-1}); 3515 (O-H stretching), 3364 (N-H stretching), 3050 (C-H, sp^2), 3010-2720 (Bp, COOH, cher.), 2870 (C-H, sp^3), 1715 (C=O), 1415 cm-1 (C-O-H in-plane bending),1611 (C=C; C=N), 1605,1515,1395 (C--C, ring str.),722 (CH_2), 710, 645(sub. phenyl), 550 (C-Cl). ^{1}HNMR (d ppm); 4.95 (s, 2H, CH_2), 5.51 (s, 1H, NH), 7.12-7.65 (m, 15H, Ar-H), 10.25 (bs, 1H, COOH), molecular formula- $C_{27}H_{19}Cl_2N_3O_2$, mass [m/z] = 487.08.

2.5.2 4'-[(5-Chloro-2-(4-hydroxyphenylamino)-1H-benzo[d]imidazol-1-yl) methyl] biphenyl-3-carboxylic acid

Melting point 204-205°C; R_f : 0.72;IR (n, cm^{-1}); 3514(O-H stretching), 3356 (N-H stretching), 3047(C-H, sp^2), 3013-2728 (bp, COOH, cherac.), 2864 (C-H, sp^3), 1705 (C=O), 1427 cm^{-1} (C-O-H in-plane bending),1614 (C=C;C=N), 1608, 1519, 1390 (C--C, ring str.), 718 (CH_2), 713, 641 (sub. phenyl), 546 (C-Cl). ^{1}HNMR (d ppm); 4.98 (s, 2H, CH_2), 5.12 (s, 1H, NH), 7.21-7.75 (m, 15H, Ar-H), 10.31 (bs, 1H, COOH),12.12(bs,OH), molecular formula- $C_{27}H_{20}ClN_3O_3$, mass [m/z] =470.03.

2.5.3 4'-[2-(4-Bromo-phenylamino)-5-chloro-1H-benzo[d] imidazol-1-yl)methyl] biphenyl-3-carboxylicacid

Melting point 188-191°C; R_f : 0.64; IR (n, cm^{-1}); 3507 (O-H stretching), 3368 (N-H stretching), 3026 (C-H, sp^2), 3026-2741 (bp, COOH, cheract.), 2860 (C-H, sp^3), 1715 (C=O), 1440 cm^{-1} (C-

O-H in-plane bending), 1624 (C=C; C=N), 1610, 1533, 1372 (C═C, ring str.),718 (CH_2), 719 ,654 (sub. phenyl), 612 (C-Br), 558 (C-Cl). ^{1}HNMR (d ppm); 4.96 (s, 2H, CH_2), 5.16 (s, 1H, NH), 7.22-7.69 (m, 15H, Ar-H), 10.18 (bs, 1H, COOH), molecular formula- $C_{27}H_{19}BrClN_3O_2$, mass [m/z] =531.82.

2.5.4 4'-[(5-Chloro-2-(4-fluorophenylamino)-1H-benzo[d]imidazol-1-yl) methyl] biphenyl-3-carboxylic acid

mp 182-183°C; R_f : 0.56; IR (n, cm^{-1}); 3528(O-H stretching), 3361 (N-H stretching), 3036 (C-H, sp^2), 3055-2769 (bp, COOH, cherac.) 3022-2744, 2865 (C-H, sp^3), 1711 (C=O), 1431cm^{-1}(C-O-H in-plane bending), 1614 (C=C; C=N), 1603, 1519, 1363 (C═C, ring str.), 712 (CH_2), 716, 658 (sub. phenyl), 615 (C-F bend), 549 (C-Cl bend). ^{1}HNMR (d ppm); 4.88 (s, 2H, CH_2), 5.06 (s, 1H, NH), 7.20-7.72 (m, 15H, Ar-H), 10.24 (bs, 1H, COOH). Molecular formula- $C_{27}H_{19}ClFN_3O_2$; Mass [m/z] = 472.41.

2.5.5 4'-[(5-Chloro-2-(4-methyl-phenylamino)-1H-benzo[d]imidazol-1-yl) methyl] biphenyl-3-carboxylic acid

Melting point 173-174°C; R_f : 0.66; IR (n, cm^{-1}); 3513(O-H stretching), 3348 (N-H stretching), 3025(C-H, sp^2), 3024-2740(bp, COOH, cherac.), 2857 (C-H, sp^3), 1721 (C=O), 1424 cm^{-1} (C-O-H in-plane bending), 1614 (C=C; C=N), 1614, 1514, 1369 (C═C, ring str.), 716 (CH_2), 713, 660 (sub. phenyl), 553(C-Cl). ^{1}HNMR (d ppm); 2.41 (s, 3H, CH_3), 4.94 (s, 2H, CH_2), 5.13(s, 1H, NH), 7.26-7.74 (m, 15H, Ar-H), 10.14 (bs, 1H, COOH). Molecular formula- $C_{28}H_{22}clN_3O_2$, mass [m/z] = 468.13.

2.5.6 4'-(5-Chloro-2-phenylamino)-1H-benzo[d]imidazol-1-ylmethyl] biphenyl-3 carboxylic acid

Melting point 142-144°C; R_f : 0.71; IR (n, cm^{-1}); 3516 (O-H stretching), 3353 (N-H stretching), 3022 (C-H, sp^2), 3017-2734 (bp, COOH, cherac.), 2850 (C-H, sp^3), 1720 (C=O), 1426 cm^{-1} (C-O-H in-plane bending), 1617 (C=C; C=N), 1604, 1529, 1351 (C═C, ring str.), 724 (CH_2), 716, 657 (sub. phenyl),551(C-Cl). ^{1}HNMR (d ppm); 4.92 (s, 2H, CH_2), 5.10(s, 1H, NH), 7.21-7.85 (m, 16H, Ar-H), 10.17 (bs, 1H, COOH), molecular formula- $C_{27}H_{20}ClN_3O_2$; mass [m/z] = 453.16.

2.5.7 4'-[(5-Chloro-2-(2-methoxy phenyl amino)-1H-benzo[d]imidazol-1-yl) methyl] biphenyl-3-carboxylic acid

Melting point 180 - 181°C; R_f : 0.53; IR (n, cm^{-1}); 3491 (O-H stretching), 3367 (N-H stretching), 3048 (C-H, sp^2), 3028-2741 (bp, COOH, cherac.), 2816 (C-H, sp^3), 1716 (C=O), 1451 cm^{-1} (C-O-H in-plane bending),1633 (C=C; C=N), 1619, 1536, 1344 (C═C, ring str.), 713 (CH_2), 701, 631 (sub. phenyl), 546 (C-Cl). ^{1}HNMR (d ppm); 3.73 (s, 3H, °CH_3), 4.95 (s, 2H, CH_2), 5.12(s, 1H, NH), 7.16-7.89 (m, 15H, Ar-H), 10.11 (bs, 1H, COOH). Molecular formula- $C_{28}H_{22}ClN_3O_3$; Mass [m/z] = 483.51.

2.5.8 4'-[2-(2-Chloro-phenylamino)-5-nitro-1H-benzo[d]imidazol-1-yl methyl] biphenyl-3-carboxy licacid

Melting point 146 - 147°C; R_f : 0.74; IR (n, cm^{-1}); 3489 (O-H stretching), 3383(N-H stretching), 3014(C-H, sp^2), 3046-2719 (Bp, COOH, cherac.), 2838 (C-H, sp^3), 1710 (C=O), 1413cm^{-1} (C-OH in-plane bending),1622 and 1342 (C=C and C=N ring stretching), 1613, 1536 (C═C, ring stretching), 1541 and 1353 (NO_2 asymmetrical and symmetrical stretching), 704 (CH_2), 712, 663 (sub. phenyl), 556 (C-Cl). ^{1}HNMR (d ppm); 4.96 (s, 2H, CH_2), 5.04 (s, 1H, N-H), 7.26-7.98 (m,15H, Ar-H), 10.11 (bs, 1H, COOH). Molecular formula- $C_{27}H_{19}ClN_4O_4$; Mass [m/z] = 499.06.

2.5.9 4'-[2-(4-hydroxy-phenylamino)-5-nitro-1H-benzo[d]imidazol-1-ylmethyl] biphenyl-3-carboxylic acid

Melting point 194 - 195°C; R_f : 0.79; IR (n, cm^{-1}); 3610 (OH), 3547(O-H, carboxylic), 3411(N-H stretching), 3041 (C-H, sp^2), 3053-2731 (bp, COOH, cherac.), 2867 (C-H, sp^3), 1709 (C=O), 1426 cm^{-1} (C-OH in-plane bending), 1616 and 1358 (C=C and C=N ring stretching), 1609, 1536 (C═C, ring stretching), 1561 and 1348 (NO_2 asymmetrical and symmetrical stretching), 718 (CH_2), 706, 662 (sub. phenyl). ^{1}HNMR (d ppm); 4.90 (s, 2H, CH_2), 5.13(s, 1H, N-H), 7.23-8.08 (m, 15H, Ar-H), 10.02 (bs, 1H, COOH). 13.62(bs,1H,OH). Molecular formula- $C_{27}H_{20}N_4O_5$; Mass [m/z] =481.94.

2.5.10 4'-[2-(4-bromo-phenylamino)-5-nitro-1H-benzo[d]imidazol-1-ylmethyl] biphenyl-3-carboxylic acid

Melting point 208 - 209 °C; R_f : 0.65; IR (n, cm^{-1}); 3491(broad O-H, carboxylic), 3432(N-H stretching), 3014(C-H, sp^2), 3042 - 2714 (bp, COOH, cherac.), 2838 (C-H, sp^3), 1715 (C=O), 1403 cm^{-1} (C-OH in-plane bending),1639 and 1327 (C=C and C=N ring stretching), 1616, 1528 (C═C, ring stretching), 1546 and 1331 (NO_2 asymmetrical and symmetrical stretching),725 (CH_2),746, 631 (sub. phenyl), 541 (C-Br). ^{1}HNMR (d ppm); 4.98 (s, 2H, CH_2), 5.16(s, 1H, N-H), 7.19-7.80(m, 15H, Ar-H), 9.96 (bs, 1H, COOH), molecular formula- $C_{27}H_{19}BrN_4O_4$; mass [m/z] = 544.

2.5.11 4'-[2-(4-Fluoro-phenylamino)-5-nitro—1H-benzo[d]imidazol-1- yl methyl] biphenyl-3-carboxylic acid

Melting point 188 - 189°C; R_f :0.69; IR (n, cm^{-1}); 3513(O-H, carboxylic), 3463(N-H stretching), 3017(C-H, sp^2), 3064-2758 (bp, COOH, cherac.), 2879 (C-H, sp^3), 1713 (C=O), 1431 cm^{-1} (C-OH in-plane bending), 1663 and 1342 (C=C and C=N ring stretching),1638,1521 (C═C, ring stretching),1530 and 1317 (NO_2-asymmetrical and symmetrical stretching), 720 (CH_2),716, 627 (sub. phenyl), 593 (C-F). ^{1}HNMR (d ppm); 4.94 (s, 2H, CH_2), 5.12(s, 1H, N-H), 7.22-7.89(m, 15H, Ar-H), 10.01 (bs, 1H, COOH), molecular formula- $C_{27}H_{19}FN_4O_4$; mass [m/z] = 482.96.

2.5.12 4'-(5-Nitro-2-*p*-tolylamino-1H-benzo[d]imidazol-1-ylmethyl] biphenyl- 3 - carboxylic acid

Melting point 155-156 °C; R_f : 0.51; IR (n, cm^{-1}); 3562(O-H, carboxylic), 3494(broad N-H stretching), 2987(C-H, sp^2), 3017-2770 (bp, COOH, cherac.), 2864 (C-H, sp^3), 1704 (C=O), 1450 cm^{-1} (C-OH in-plane bending), 1641 and 1324 (C=C and C=N ring stretching), 1610,1548 (C═C, ring stretching),1538 and 1338 (NO_2 asymmetrical and symmetrical stretching),703 (CH_2), 711, 634 (sub. phenyl). ^{1}HNMR (d ppm);2.46 (s, 3H, CH_3), 4.88 (s, 2H, CH_2), 5.15 (s, 1H, N-H), 7.15-8.13 (m, 15H, Ar-H), 9.86 (bs, 1H, COOH), molecular formula- $C_{28}H_{22}N_4O_4$; mass [m/z] = 477.94.

2.5.13 4'-(5-Nitro-2-phenylamino-1H-benzo[d]imidazol-1-ylmethyl] biphenyl-3-carboxylic acid

Melting point 133 - 134°C; R_f : 0.75; IR (n, cm^{-1}); 3521(O-H, carboxylic), 3507 (N-H stretching), 2964(C-H, sp^2), 3029-2748(bp,

COOH, cherac.), 2855 (C-H, sp^3), 1714 (C=O), 1437 cm^{-1} (C-OH in-plane bending),1627 and 1351 (C=C and C=N ring stretching), 1605, 1568 (C---C, ring stretching),1540 and 1326 (NO_2 asymmetrical and symmetrical stretching),714 (CH_2),737, 653 (sub. phenyl). ^{1}HNMR (d ppm); 4.94 (s, 2H, CH_2), 5.12 (s, 1H, N-H), 7.24-7.93 (m, 16H, Ar-H), 10.13 (bs, 1H, COOH), molecular formula- $C_{27}H_{20}N_4O_4$; mass [m/z] = 463.72.

2.5.14 4'-[2-(2-Methoxy-phenylamino)-5-nitro-1H-benzo[d]imidazol-1 ylmethyl] biphenyl-3-carboxylic acid

Melting point 234 - 235°C; R_f : 0.63; IR (n, cm^{-1}); 3529 (O-H, carboxylic), 3549 (N-H stretching), 3017 (C-H, sp^2), 3022-2716 (bp, COOH, cherac.), 2838 (C-H, sp^3), 1717 (C=O), 1431 cm^{-1} (C-OH in-plane bending),1622 and 1359 (C=C and C=N ring stretching), 1608, 1547 (C---C, ring stretching),1546 and 1315 (NO_2 asymmetrical and symmetrical stretching), 711 (CH_2),692, 633 (sub. phenyl). ^{1}HNMR (d ppm); 3.62 (s, 3H, °CH3), 4.97 (s, 2H, CH_2), 5.14 (s, 1H, N-H), 7.16-7.85 (m, 15H, Ar-H), 10.14 (bs, 1H, COOH). Molecular formula- $C_{28}H_{22}N_4O_5$; Mass [m/z] =494.11.

2.5.15 (2-Chloro-phenyl)-{5-chloro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl methyl]-1H benzo[d]imidazol-2-yl}-amine

Melting point 169 - 170°C; R_f : 0.70; IR (n, cm^{-1}); 3245(N-H stretching), 3043(C-H, sp^2), 2872 (C-H, sp^3), 1871(N=N), 1645 (C=C; C=N), 1602, 1505, 1387 (C---C, ring str.), 910,805,740 (sub. phenyl), 719 (CH_2), 542 (C-Cl). ^{1}HNMR (d ppm); 4.52 (s, 2H, CH_2), 5.12(s, 1H, NH), 5.51(s, 1H, N-H tetrazole ring), 7.18-7.89 (m, 15H, Ar-H). Molecular formula- $C_{27}H_{19}Cl_2N_7$; Mass [m/z] = 512.04.

2.5.16 4'-{5-Chloro-1-[2'- (1H-tetrazole-5-yl) - biphenyl-4-ylmethyl] - 1H- benzo [d] imidazol-2-ylamino}-phenol

Melting point 195 - 196°C; R_f : 0.57; IR (n, cm^{-1}); 3612 (O-H stretching), 3241(N-H stretching), 3034(C-H, sp^2), 2867 (C-H, sp^3), 1873(N=N), 1651 (C=C;C=N),1605,1514,1382 (C---C, ring str.),905,801,744 (sub. phenyl),716 (CH_2), 545 (C-Cl). ^{1}HNMR (d ppm); 4.53 (s, 2H, CH_2), 5.10(s, 1H, NH), 5.48(s, 1H, N-H tetrazole ring), 7.18-7.89 (m, 15H, Ar-H),11.51 (bs,1H,O-H), molecular formula- $C_{27}H_{20}ClN_7O$; mass [m/z] = 494.

2.5.17 (4'-Bromo-phenyl)-{5-Chloro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl methyl] -1H-benzo[d]imidazol-2-yl}-amine

Melting point 177 - 178°C; R_f : 0.62; IR (n, cm^{-1}); 3248 (N-H stretching), 3038(C-H, sp^2), 2864 (C-H, sp^3), 1865(N=N), 1656 (C=C; C=N), 1614, 1508, 1376 (C---C, ring str.), 899, 816, 741 (sub. phenyl), 714 (CH_2), 603.7 (C-Br bend), 548 (C-Cl bend). ^{1}HNMR (d ppm); 4.50 (s, 2H, CH_2), 5.14 (s, 1H, NH), 5.44(s, 1H, N-H tetrazole ring), 7.24-7.82 (m, 15H, Ar-H). Molecular formula- $C_{27}H_{19}BrClN_7$; Mass [m/z] = 557.

2.5.18 {5-Chloro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzo[d] imidazol-2-yl}-(4-fluoro-phenyl)-amine

Melting point 165 - 166°C; R_f : 0.49; IR (n, cm^{-1}); 3271 (broad N-H stretching), 3018(C-H, sp^2), 2849 (C-H, sp^3), 1876(N=N), 1638 (C=C; C=N), 1617, 1524, 1368 (C---C, ring str.), 912,807,736 (sub. phenyl), 711 (CH_2), 616 (C-F bend), 543 (C-Cl bend). ^{1}HNMR (d ppm); 4.47 (s, 2H, CH_2), 5.08(s, 1H, NH), 5.46(s, 1H, N-H tetrazole ring), 7.17-7.73 (m, 15H, Ar-H). Molecular formula- $C_{27}H_{19}ClFN_7$; Mass [m/z] = 496.

2.5.19 {5-Chloro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzo[d] imidazol-2-yl}-p-tolyl-amine

Melting point 157 - 158°C; R_f : 0.79; IR (n, cm^{-1}); 3257 (broad N-H stretching), 3025(C-H, sp^2), 3075 (C-H, sp^3), 2868 (C-H, sp^3), 1862(N=N), 1653(C=C; C=N), 1614, 1507, 1383(C---C, ring str.), 923,821,718 (sub. phenyl), 709 (CH_2), 553 (C-Cl bend). ^{1}HNMR (d ppm); 2.41 (s, 3H, CH_3), 4.39 (s, 2H, CH_2), 5.13(s, 1H, NH), 5.54(s, 1H, N-H tetrazole ring), 7.25-7.91 (m, 15H, Ar-H). molecular formula- $C_{28}H_{22}ClN_7$; mass [m/z] = 492.

2.5.20 {5-Chloro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzo[d] imidazol-2-yl} phenyl-amine

Melting point 148 - 149 °C; R_f : 0.73; IR (n, cm^{-1}); 3265 (N-H stretching), 3041(C-H, sp^2), 2849 (C-H, sp^3), 1873(N=N), 1662 (C=C; C=N), 1601, 1511, 1370 (C---C, ring str.), 914,804,724 (sub. phenyl), 713 (CH_2), 550 (C-Cl bend). ^{1}HNMR (d ppm); 4.48 (s, 2H, CH_2), 5.11(s, 1H, NH), 5.50(s, 1H, N-H tetrazole ring), 7.20-7.83 (m, 16H, Ar-H), molecular formula- $C_{27}H_{20}ClN_7$; mass [m/z] = 478.

2.5.21 {5-Chloro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzo[d] imidazol-2-yl}-(2-methoxy-phenyl)-amine

Melting point 172 - 173°C, R_f : 0.64; IR (n, cm^{-1}); 3281 (N-H stretching), 3048 (C-H, sp^2), 2854 (C-H, sp^3), 1863 (N=N), 1671 (C=C; C=N), 1618, 1514, 1378 (C---C, ring str.), 911,825,719 (sub. phenyl), 706 (CH_2), 551 (C-Cl bend). ^{1}HNMR (d ppm); 3.68 (s, 3H, °CH_3),4.51 (s, 2H, CH_2), 5.13(s, 1H, NH), 5.52(s, 1H, N-H tetrazole ring), 7.24-8.08 (m, 15H, Ar-H), molecular formula- $C_{28}H_{22}ClN_7O$; mass [m/z] = 507.61.

2.5.22 {2-Chloro-phenyl)-{5-nitro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl] -1H-benzo[d]imidazol-2-yl}-amine

Melting point 211 - 212°C, R_f : 0.50; IR (n, cm^{-1}); 3281 (broad N-H stretching), 3073(C-H, sp^2), 2891 (C-H, sp^3), 1882(N=N stretching) 1627 and 1351 (C=C and C=N ring stretching), 1598, 1555, 1396 (C---C, ring stretching), 1562 and 1317 (NO_2 asymmetrical and symmetrical stretching), 719 (CH_2), 716, 685 (sub. phenyl), 547 (C-Cl). ^{1}HNMR (d ppm); 4.89 (s, 2H, CH_2), 5.13 (s, 1H, N-H),5.51(s, NH tetrazole ring), 7.13-7.87 (m, 15H, Ar-H), molecular formula- $C_{27}H_{19}ClN_8O_2$; mass [m/z] = 523.

2.5.23 4-{5-Nitro-1-[2-(1H-tetraole-5-yl)-biphenyl-4-ylmethyl]-1H-benzimidazole -2-ylamino}-phenol

Melting point 153 - 154°C; R_f : 0.74; IR (n, cm^{-1}); 3597 (O-H stretching), 3317 (N-H stretching), 3065 (C-H, sp^2), 2921 (C-H, sp^3), 1869 (N=N stretching) 1631 and 1330 (C=C and C=N ring stretching), 1585, 1519, 1375 (C---C, ring stretching), 1540 and 1312 (NO_2 asymmetrical and symmetrical stretching), 721 (CH_2), 711, 652 (sub. phenyl). ^{1}HNMR (d ppm); 4.89 (s, 2H, CH_2), 5.13 (s, 1H, N-H), 5.51(s, NH tetrazole ring), 7.13-7.87 (m, 15H, Ar-H), 11.73 (bs,1H,O-H) , molecular formula- $C_{27}H_{20}N_8O_3$; mass [m/z] = 505.

2.5.24 [Ms-24] (4-Bromo-phenyl)-{5-nitro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl methyl] -1H-benzo[d]imidazol-2-yl}-amine

Melting point 178 - 179°C, R_f : 0.69; IR (n, cm^{-1}); 3274 (N-H stretching), 3038 (C-H, sp^2); 2968 (C-H, sp^3), 1844 (N=N stretching) 1646 and 1331 (C=C and C=N ring stretching), 1568, 1547, 1326 (C---C, ring stretching), 1557 and 1368 (NO_2 asymmetrical and symmetrical stretching), 740 (CH_2), 718, 633 (sub. phenyl), 597 (C-Br). ^{1}HNMR (d ppm); 4.95 (s, 2H, CH_2), 5.06 (s, 1H, N-H), 5.56(s, NH tetrazole ring), 7.19-7.78 (m, 15H, Ar-H), molecular formula- $C_{27}H_{19}BrN_8O_2$; mass [m/z] = 567.

2.5.25 (4-fluoro-phenyl)-{5-nitro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl] -1H-benzo[d]imidazol-2-yl}-amine

Melting point 211 - 212°C; R_f : 0.66; IR (n, cm^{-1}); 3286 (broad N-H stretching), 3014(C-H, sp^2), 2980 (C-H, sp^3), 1861 (N=N stretching) 1636 and 1318 (C=C and C=N ring stretching), 1601, 1565, 1348 (C---C, ring stretching), 1546 and 1359 (NO_2 asymmetrical and symmetrical stretching), 728 (CH_2), 735, 617 (sub. phenyl), 628 (C-F). ^{1}HNMR (d ppm); 4.93 (s, 2H, CH_2), 5.12 (s, 1H, N-H), 5.48 (s, NH tetrazole ring), 7.28-7.90 (m, 15H, ar-H), molecular formula- $C_{27}H_{19}FN_8O_2$; mass [m/z] = 506.

2.5.26 {5-nitro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzo[d] imidazol-2-yl}-p-tolyl-amine

Melting point 160 - 161°C; R_f : 0.71; IR (n, cm^{-1}); 3326 (N-H stretching), 3025 (C-H, sp^2), 2961 (C-H, sp^3), 1849 (N=N stretching) 1617 and 1347 (C=C and C=N ring stretching), 1592, 1572, 1330 (C---C, ring stretching), 1516 and 1349 (NO_2 asymmetrical and symmetrical stretching), 713 (CH_2), 719, 608 (sub. phenyl). ^{1}HNMR (d ppm); 2.47 (s, 3H, CH_3), 4.96 (s, 2H, CH_2), 5.15 (s, 1H, N-H), 5.53 (s, NH tetrazole ring), 7.15-7.96 (m, 15H, Ar-H), molecular formula- $C_{28}H_{22}N_8O_2$; mass [m/z] = 503.

2.5.27 {5-nitro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-1H-benzo[d] imidazol-2-yl}-phenyl-amine

Melting point 135 - 136 °C; R_f : 0.62; IR (n, cm^{-1}); 3315 (broad N-H stretching), 3046 (C-H, sp^2), 2938 (C-H, sp^3), 1834 (N=N stretching) 1628 and 1359 (C=C and C=N ring stretching), 1618, 1541, 1378 (C---C, ring stretching), 1541 and 1351 (NO_2 asymmetrical and symmetrical stretching), 736 (CH_2), 721, 628 (sub. phenyl). ^{1}HNMR (d ppm); 4.93 (s, 2H, CH_2), 5.11 (s, 1H, N-H),5.47 (s, NH tetrazole ring), 7.21-7.84 (m, 16H,Ar-H), molecular formula- $C_{27}H_{20}N_8O_2$; mass [m/z] = 487.91.

2.5.28 (2-methoxy-phenyl)-{5-nitro-1-[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl methyl]-1H-benzo[d]imidazol-2-yl}-amine

Melting point 142 - 143°C; R_f : 0.57; IR (n, cm^{-1}); 3327(broad N-H stretching), 3057 (C-H, sp^2), 2940 (C-H, sp^3), 1803 (N=N stretching) 1612 and 1367 (C=C and C=N ring stretching), 1624, 1535, 1360 (C---C, ring stretching), 1546 and 1331 (NO_2 asymmetrical and symmetrical stretching), 710 (CH_2), 722, 651 (sub. phenyl).^{1}HNMR (d ppm); 3.70 (s, 3H, °CH_3), 4.90(s, 2H, CH_2), 5.14 (s, 1H, N-H),5.52 (s,1H, NH tetrazole ring), 7.21-8.17 (m, 15H, Ar-H), molecular formula- $C_{28}H_{22}N_8O_3$; mass [m/z] = 518.

2.6 Antihypertensive activity

The present work was mainly intended to establish the moieties which are responsible for antihypertensive activity. The antihypertensive drugs were evaluated by studying their response on elevated blood pressure. The newly synthesized twenty eight compounds were tested for their antihypertensive activity. Male albino rats (wistar strain) weighing between 150-200 g were provided by the Animal House of Pinnacle Biomedical Research Institute, Bhopal. Acute renal hypertension blood pressure measurement model were carried out (Hauser *et al.,* 2005; Gilani *et al.,* 2005; Vogel, 1996; Jain *et al.,* 2013). The statistical analysis was performed using prism graph pad trial version-3 software. The data were presented as means ± SEM.; a repeated measures analysis of variance was used to obtain the statistical significance between and within the groups. The comparison between various groups was performed by one-way analysis of variance, ANOVA, and the effect in treatment groups were compared with toxic control group by dunnet multiple comparison test. $p<0.01$ was considered to be significant.

Table 1: Structure of designed substituted benzimidazole compounds

S. No.	Code No.	R	R_1	R_2	R_3
1	Ms-1	Cl	2-Cl	H	-COOH
2	Ms-2	Cl	4-OH	H	-COOH
3	Ms-3	Cl	4-Br	H	-COOH
4	Ms-4	Cl	4-F	H	-COOH
5	Ms-5	Cl	4-CH_3	H	-COOH
6	Ms-6	Cl	H	H	-COOH
7	Ms-7	Cl	2-°CH_3	H	-COOH
8	Ms-8	NO_2	2-Cl	H	-COOH
9	Ms-9	NO_2	4-OH	H	-COOH
10	Ms-10	NO_2	4-Br	H	-COOH
11	Ms-11	NO_2	4-F	H	-COOH
12	Ms-12	NO_2	4-CH_3	H	-COOH
13	Ms-13	NO_2	H	H	-COOH
14	Ms-14	NO_2	2-°CH_3	H	-COOH
15	Ms-15	Cl	2-Cl	Tetrazole	H
16	Ms-16	Cl	4-OH	Tetrazole	H
17	Ms-17	Cl	4-Br	Tetrazole	H
18	Ms-18	Cl	4-F	Tetrazole	H
19	Ms-19	Cl	4-CH_3	Tetrazole	H
20	Ms-20	Cl	H	Tetrazole	H
21	Ms-21	Cl	2-°CH_3	Tetrazole	H
22	Ms-22	NO_2	2-Cl	Tetrazole	H
23	Ms-23	NO_2	4-OH	Tetrazole	H
24	Ms-24	NO_2	4-Br	Tetrazole	H
25	Ms-25	NO_2	4-F	Tetrazole	H
26	Ms-26	NO_2	4-CH_3	Tetrazole	H
27	Ms-27	NO_2	H	Tetrazole	H
28	Ms-28	NO_2	2-°CH_3	Tetrazole	H

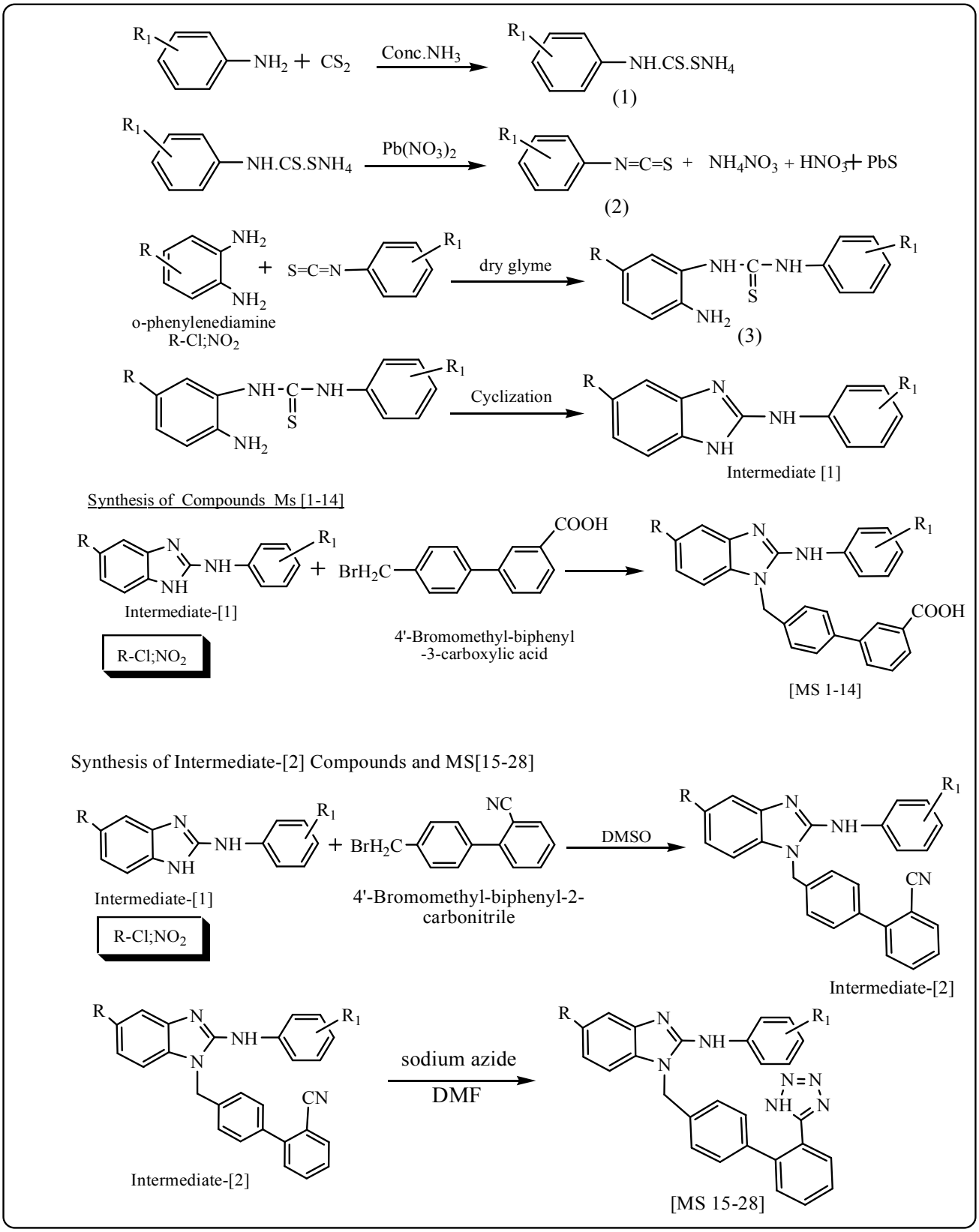

Figure 2: Synthetic pathway for substituted benzimidazole compounds.

Table 2: Antihypertensive activity of synthesised compounds

S. No.	Code No.	Change mean arterial bloodpressure (MABP mm-Hg)	Total change in systolic blood pressure (mm-Hg)
-	**Control**	156.4 ± 2.41	-
-	**Standard**	108.6 ± 1.37	48
1	Ms-1	114 ± 3.77**	42
2	Ms-2	112 ± 3.18**	44
3	Ms-3	121 ± 2.11*	35
4	Ms-4	115 ± 1.81**	41
5	Ms-5	120 ± 2.66*	36
6	Ms-6	133 ± 1.35	23
7	Ms-7	110 ± 3.29**	46
8	Ms-8	128 ± 1.32	28
9	Ms-9	123 ± 1.68*	33
10	Ms-10	127 ± 2.53	29
11	Ms-11	126 ± 1.32**	30
12	Ms-12	113 ± 3.13**	43
13	Ms-13	120 ± 3.63*	36
14	Ms-14	124 ± 1.42	32
15	Ms-15	109 ± 1.19**	47
16	Ms-16	119 ± 2.48*	37
17	Ms-17	127 ± 2.17*	29
18	Ms-18	122 ± 3.12*	34
19	Ms-19	116 ± 1.65**	40
20	Ms-20	125 ± 3.31*	31
21	Ms-21	115 ± 1.88**	41
22	Ms-22	120 ± 1.65*	36
23	Ms-23	130 ± 2.20	26
24	Ms-24	124 ± 3.13*	32
25	Ms-25	122 ± 4.15*	34
26	Ms-26	142 ± 3.82*	14
27	Ms-27	140 ± 3.41*	16
28	Ms-28	117 ± 2.52*	39

Each value represents the mean ± SEM; one-way analysis of variance, ANOVA.

*Significant; ** Very Significant

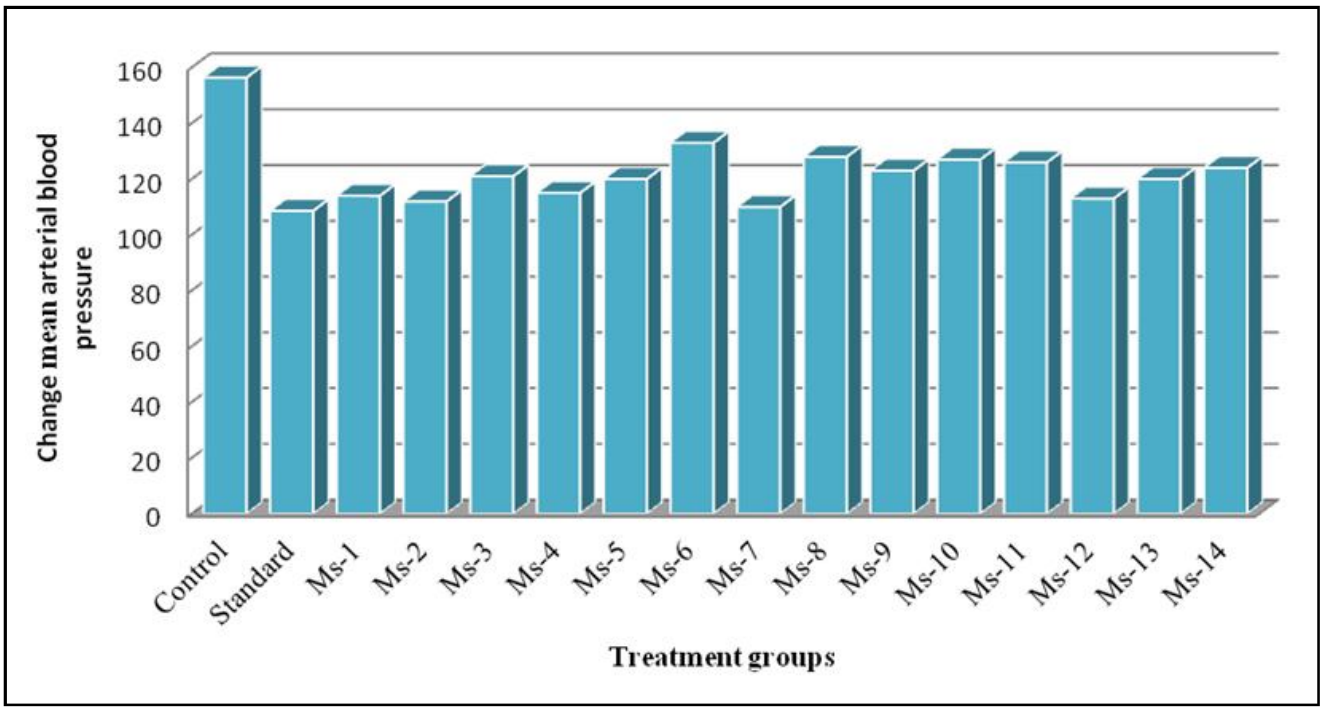

Figure 3: Comparsion of antihypertensive activity of synthesized compounds.

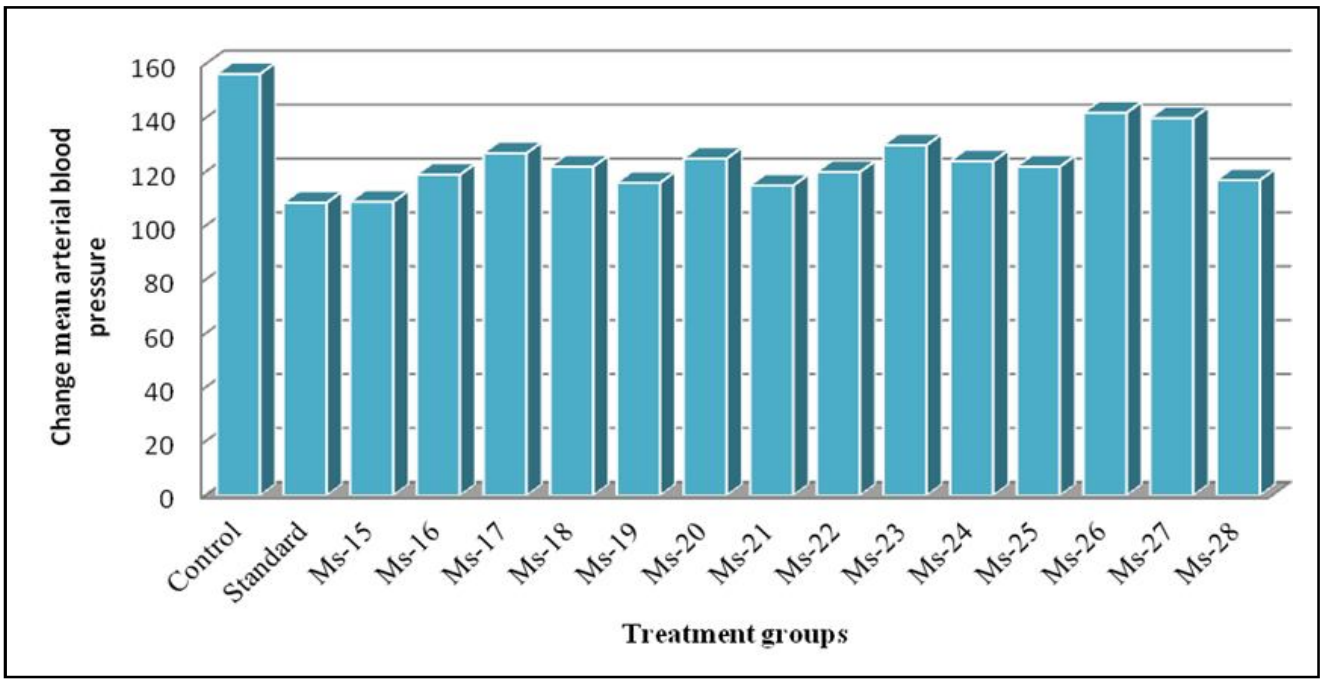

Figure 4: Comparsion of antihypertensive activity of synthesized compounds.

3. Results

The structures of all the synthesized compounds have been ascertained on the basis of IR, ^{1}H NMR and mass spectral studies. Infrared spectroscopy was done on shimadzu DZU 8400S at School of Pharmacy, Devi Ahilya Vishwavidyalaya, Indore using KBR pellet. It is revealed from the obtained infrared spectrum of a compound 4'-[(5-Chloro-2-(2-chlorophenylamine)-1H-benzo[d]imidazol-1-yl) methyl] biphenyl-3-carboxylic acid that a well defined peak at 3515 cm^{-1} is assignable to the O-H vibrational mode which is involved in the hydrogen bonding functionality in the compounds. A classic signal at 3364 cm^{-1} can be attributed to the existence of -NH moiety. A broad signal ranging from 3010-2720 is the peculiar feature to characterize the presence of -COOH group. A few well defined peaks at 3050 cm^{-1} and 2870 cm^{-1} are due to C-H stretching frequencies of sp^{2} and sp^{3} modes, respectively. A clear peak at 1715 cm^{-1} can be

safely assigned to the C=O functionality of carboxylic group. Furthermore a series of different peaks noticed at 1605, 1515 and 1395 are the key features to assign the skeletal (C=C, ring) stretching vibrational modes. ^{1}H NMR spectrum of a compound 4'-[(5-Chloro-2-(2-chlorophenylamine)-1H-benzo[d]imidazol-1-yl) methyl] biphenyl-3-carboxylic acid delineate a singlet peak at d 4.95 ppm owing to presence of -CH_2 functionality which is flanked between benzimidazole nucleus and biphenyl rings. Another singlet at d 5.51 ppm is assignable to the labile proton of NH group. A pattern of multiplet peaks in the range of d 7.12-7.65 is the characteristic feature of various aromatic protons. Also a broad hamp at d 10.25 indicates the existence of -OH group and thereby characterizes the existence of carboxylic entity. In the present study a blood pressure measuring technique was used to determine the effect of the synthesized compounds on the cardiovascular parameters.

4. Discussion

The compounds exhibit stretching {1 [(2-(1H-tetrazol-5-yl) biphenyl-4-yl) methyl)-5-chloro-N-(2-chlorophenyl-1H-benzo[d]imidazol-2-amine} that a band at ~3300 cm^{-1} pertaining to the NH moiety, whereas characteristics C-H vibrational modes °Ccur in their due region between 3100-3000 cm^{-1} and 3000-2850 cm^{-1} corresponding to sp^2 and sp^3 hybridized state of the carbon, respectively. A significant peak in the range of 1871 cm^{-1} can be attributed to N=N group and their justifies feature to show the presence of tetrazole nucleus bearing this functionality. More over skeletal vibrations of aromatic ring are found to show their stretching modes hereby to 1602 cm^{-1}, 1505 cm^{-1} and 1387 cm^{-1}. Also substitution in the phenyl ring is justified by the presence of a number of peaks in the region between 1000-600 cm^{-1}. A significant peak at 722 cm^{-1} is attributed to the existence of methylene bridge (-CH_2) between benzimidazole and phenyl ring nuclei. Similarly, from ^{1}H NMR spectrum of {1 [(2-(1H-tetrazol-5-yl) biphenyl-4-yl) methyl)-5-chloro-N-(2-chlorophenyl-1H- benzo[d]imidazol-2-amine}, it is revealed that a well defined singlet peak 4.52 ppm is due to the presence –CH_2 functionality. More over emergence of two peaks at d 5.12 and d 5.51 are attributable to the labile protons of –NH moiety. All compounds exhibit a pattern of multiplet singlet in the region d7.21-7.85 ppm which is the clear remarkable feature to elicit the presence of aromatic ring protons in these compounds. The fragmentation pattern obtained in the mass spectra was according to anticipated structure. The fall in blood pressure produced by standard losartan was from 156 mm Hg to 108 mm Hg, 48 mm Hg (Figure 3 and 4). Almost all the compounds showed potent antihypertensive activity when compared with standard losartan drug. Whereas compounds Ms-01 with chloro group at 5th position benzimidazole moiety and 2-chlorophenylamine ring as an electron withdrawing moiety have shown good antihypertensive activity from initial value. Compound Ms-12 having nitro group substituent as electron withdrawing group at 5th position of benzimidazole moiety show good activity. Compounds Ms-02 with chloro group at 5th position benzimidazole moiety and 4-hydroxyphenylamine ring as an electron donating group have shown good antihypertensive activity from initial value. The compounds Ms -03, Ms-05, Ms-09, Ms-13, Ms-16, Ms-22, Ms-25 and Ms-28 showed antihypertensive activity to a lesser extent as compared to losartan. The compounds Ms-17, Ms-18, Ms-20, and Ms-24 have shown the least antihypertensive activity. Other compounds Ms-08, Ms-10. Remaining three compounds showed considerable antihypertensive activity Ms-06, MS-26 and MS-27. The antihypertensive effect of all compounds differs in maximum fall in mean arterial blood pressure, MABP produced from initial valve (Table 2; Figure 3 and 4). The compounds showed moderate decrease in hypertension.

5. Conclusion

Structure activity relationship studies revealed that the substitutions at the benzimidazole ring attached to the acidic group (carboxylic or tetrazole) bearing biphenyl system moiety play a significant role in governing the antihypertensive activity and of these compounds showed that, the chloro, hydroxy, methoxy, groups at R1 position in substituted benzimidazole ring enhance the antihypertensive activity, which might serve as new templates in the synthesis and development of potent therapeutic agents. It can be concluded on the basis of structure–activity relationships that groups like 2-Chloro, 4-hydroxy 4-fluoro, 4-methyl and 2-methoxy in aniline ring moiety at 2, and 4-positions increase the activity as shown by the compound MS-01, MS-02, MS-04, MS-07, MS-15, MS-19 and MS-21. The high antihypertensive activity compound MS-07 may be attributed to the presence of methoxy group. The presence of electron donating group showed very good activity.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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