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Synthesis and Biological Evaluation of Benzimidazolyl Biphenyl Derivatives as Antihypertensive Agents

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Abstract : Recent studies have shown that the interaction between benzimidazole scaffold and angiotensin II receptor may have potential therapeutic benefits. A series of analogues synthesis has been carried out for selected benzimidazole derivatives having electron donor and acceptor substituents 5-nitro, 6-methyl, 6-chloro, 6, 7-dichlorogroup and at 2-position trifluoromethyl, hydroxy ethyl groups and were evaluated for the antihypertensive activity in rats. The authenticity and purity of synthesized have been established through appropriate spectral and chromatographic techniques like TLC, IR, NMR and Mass spectrophotometric methods. Out of all the evaluated compounds, compound 4'-((6-methyl-2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl) methyl)-[1, 1'-biphenyl]-2-carboxylic acid (3b) showed improved antihypertensive activity. Biological activity of synthesized compounds was carried out using rat blood pressure measurement experiment i.e. noninvasive blood pressure(NIBP); induction of hypertension developed by administration of corticosteroid dexamethasone intramuscularly. The maximum fall in blood pressure produced by standard drug losartan was compare with synthesized compounds. Finally it is concluded that different substituted benzimidazole derivatives has appreciable and selective action against angiotensin II induced hypertension.
Keywords : Benzimidazole, Biphenyl,Tetrazole, Antihypertensive activity, angiotensin II.

1. Introduction

The biphenyl benzimidazoles have potent antihypertensive action as compared to the previous related drugs due to better availability upon the oral administration, 2- position of biphenyl is essential for the activity[1.] 5 substituted aryl or alkyl carboxamido derivatives have reported to possess Angiotensin-II AT1 receptor antagonistic activity so are good antihypertensive agents[2]. The benzoderivative of imidazole is referred to as benzimidazole[3]. Although benzimidazole is the commonest name of the parent compound of the series, other names such as benzimidazoleand1,3-benzodiazoleis often used.Monoacyl derivative of orthophenylenediamine isreadily converted into the corresponding benzimidazole by the action of heat alone. Theseconversions are generally carried out at a temperature somewhat above the melting point of the starting compounds.

This is a convenient method for preparing benzimidazoles when monoacyl derivatives are easily obtainable. The procedure may be improved by heating the monoacyl derivative ofdiamine in an atmosphere of nitrogen to prevent oxidation[4]. The diacyl derivatives of o-phenylenediamineare also converted into benzimidazolesbut higher temperatures are required[5].Benzimidazoleis also synthesized from o-phenylenediamine and mono or di-basic acid. In this method, the diamine is simply heated with excess acid[6]. This procedure has been recommended as a means of identifying fatty acid alpha-hydroxy acid as well asphenylacetic acid and diphenylacetic acid are converted into the corresponding benzimidazoles when heated with o-phenylenediamine. Phillips modification of the above procedureconsists in refluxing withthe o-phenylenediamine and mono basic acidin 4N hydrochloric acid. The benzimidazole is then precipitated by

neutralizing the solution with ammonium hydroxide[7].Benzoic acidgives only traces of 2-phenylbenzimidazole. Apparently this method is not applicable to the aromatic monobasic acid. Benzimidazole derivative is associated with various types of pharmacokinetic and pharmacodynamic properties. Benzimidazole nucleusis one of the bioactive heterocyclic compounds that exhibit a range of biological activities. Specifically, this nucleus is a constituent of vitamin B12[8]. The pharmacological activities of the benzimidazole containing moiety have been well documented[9]. Albendazole, Mebendazole and Thiabendazole are widely used as anthelmintic drugs[10].

1. Experimental

1.1. General procedure for synthesis of 2-trifluoromethyl substituted benzimidazole (1a, 1b , 1d)

In a typical experiment, 0.01 mol substituted O-Phenylenediamine, 0.01 mol of trifluoroacetic acid and 25 mL of conc. Hydrochloric acid was taken in an RBF and refluxed for 6hrs. The reaction was monitored by TLC. A test portion was dumped in water and basified with ammonia solution. The solid was extracted with Ethyl acetate and TLC of this ethyl acetate extract was checked for the completion of reaction. After completion of the reaction, the reaction mixture was poured in ice-cold water. It was then basified with concentrated ammonia solution. The solid precipitated was filtered immediately and dried. Crude product was recrystallized from ethanol. The % yield, melting point and R_f value were reported and tabulated [11].

Synthesis of 5-nitro-2-(trifluoromethyl)-1H-benzo[d]imidazole (1c)

10mL of concentrated nitric acid was placed in three necked flask and equal quantity of sulphuric acid (1:1) was added slowly. The mixture was kept in the ice cold water then compound 2-trifluoromethyl benzimidazole (1.5 g) was mixed in portions during 30 min under room temperature. After stirred continuously for 3-4 hours and reaction monitored by TLC, after completion of reaction the reaction mixture was poured slowly over crushed ice with stirring. The precipitated product was filtered out and washed with cold water. The product was recrystallized from acetone; melting point & % yield were reported.

Synthesis of 2-hydroxyethyl substituted benzimidazole (1e, 1f, 1h, 1i)

In a typical experiment, 0.092 mol of substituted O-phenylenediamine and 0.1 mol of lactic acid and 15 ml of conc. hydrochloric acid was taken in an RBF and refluxed for 6 h. The reaction was monitored by TLC. A test portion was dumped in the water and basified with ammonia solution. The solid was extracted with ethyl acetate and TLC of this ethyl acetate extract was checked for the completion of the reaction. After completion of the reaction, the reaction mixture was poured in ice-cold water. It was then basified with conc. Ammonia solution. The solid precipitated was filtered immediately and dried. Crude product was recrystallized from ethanol. The % yield, melting point and R_f value were reported and tabulated.

Synthesis of 1-(5-nitro-1H-benzo[d]imidazol-2-yl) ethanol (1g)

10 mL of concentrated nitric acid was placed in three necked flask and equal quantity of concentrated sulphuric acid (1:1) was added slowly. The mixture was kept in the ice cold water then compound 2-hydroxyethyl benzimidazole 0.01mol was mixed in portions during 30min under room temperature. After stirred continuously for 3-4 hours and reaction monitored by TLC, after completion of reaction, the reaction mixture was poured slowly over crushed ice with stirring. The precipitated product was filtered out and washed with cold water. Product was recrystallized from acetone; melting point & % yield were reported and tabulated [12,13,14].

Synthesis of [1, 1'–biphenyl]-2 -carboxylic acid (2a)

Potassium hydroxide 0.53 mol was fused at 180-200^o C in a two-necked RBF fitted with a mechanical stirrer. Finely powdered 9H-fluorenone 0.055 mol was added in six portions over 30 min with vigorous stirring and the temperature was maintained at 180-200^o C for further 30 min. The hot slurry was then poured in ice-cold water with vigorous stirring. The resulting suspension was filtered at pump. The filtrate was acidified with concentrated HCl to pH 5.0 resulting in precipitation of byproduct, which was filtered under suction, washed with distilled water, and the filtrate was again acidified with concentrated HCl.

The precipitated product was filtered under suction and dried in air. The product as recrystallized from absolute alcohol and confirmed by melting point and TLC[15].

Synthesis of 4'-(acetamidomethyl)-[1, 1'-biphenyl]-2-carboxylic acid (2b)

Biphenyl-2-carboxylic acid 0.05 mol was dissolved in concentrated H_2SO_4 ,12.2 ml Acetamide 0.15 mol was added in one portion followed by the addition of paraformaldehyde 0.05 mol in portions. The solution was heated at 55^oC along with stirring for 3 h and the hot mixture was poured over ice cold water. The resulting solid was filtered out. The crude product was recrystallized by absolute alcohol and confirmed by melting point & TLC.

Synthesis of 4'-(chloromethyl)-[1, 1'-biphenyl]-2-carboxylic acid (2)

4'-Acetamidomethyl-biphenyl-2-carboxylic acid 0.03mol and phosphorous oxychloride 0.063 mol were taken in a RBF, DMF 2ml and xylene 2ml were added and the reaction mixture was refluxed for 7 h, cooled and washed with water. It was evaporated to give a light yellow crystalline product. The product was confirmed by melting point & TLC.

1.1. Condensation of substituted benzimidazole& 4'-Chloromethyl biphenyl-2-carboxylic acid (3)

The 2-Trifluoromethyl benzimidazole derivative was dissolved in DMF(10mL) and stirred vigorously with potassium carbonate at room temperature for 1 h. To the resulting suspension, 4-chloromethylbiphenyl-2'-carboxylic acid (2c) 0.00116 mol, previously dissolved in DMF 10 ml, was added drop wise with stirring over a period of 1 h. The reaction was allowed to proceed for further 12 h till the reaction completion and after completion of reaction it was dumped in the water. The obtained precipitate was treated with dilute HCl 20 ml and extracted with ethyl acetate. The organic layer was washed with brine, distilled water and dried over anhydrous sodium sulphate. The obtained was product further analyzed by TLC, melting point and spectral analysis.Similar procedure and quantities were taken for synthesis 2-Hydroxyethyl benzimidazole derivative. The compounds were characterized by IR, NMR and MS [16].

1.2. Spectral dataof synthesized compounds

4'-((2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl) methyl)-[1, 1'-biphenyl]-2-carboxylic acid (3a)

Yellow solid, yield: 55%, MP 224-226^0C. FTIR (KBr, cm^{-1}): OH & C-H stretch (2800-3600), C=O stretch (1715.76), C-Cl stretching (745.52), Aliphatic C-H stretching 2924.21, (C-N stretch) 1285.61, (C-F stretch) 1127.44, 1155.41, 1191.0. ^{1}H NMR (400 MHz, DMSO-D_6):δ7.26-7.12 (m, Ar-H), δ 4.99 (t 2H CH_2), δ 11.0 (s 1H OH).^{13}C NMR (100MHz, DMSO-D_6): 117.6 (C-F), 52.3 (-CH_2), 166 (C=O), 127-136 (Ar CH). MS-MS: $[M]^+$ 397.11. Composition: C (66.67%), H (3.81%), F (14.38%), N (7.07%), O (8.07%).

4'-((6-methyl-2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl) methyl)-[1, 1'-biphenyl]-2-carboxylic acid (3b)

Brown solid, yield: 52%, MP 242-246^0C. FTIR (KBr, cm^{-1}): OH & C-H stretch (2900-3500), C=O stretch (1715.76), C-Cl stretch (741.66), C-F stretch (1139.98, 1171.81, 1192.06), C-N stretch (1268.25), Aliphatic C-H Stretching (1268.25). ^{1}H NMR (400 MHz, DMSO-D_6): δ7.14-7.9 (m, Ar-H), δ 5.50(t 2H CH_2), δ2.44(q 3H CH_3). ^{13}C NMR (100MHz, DMSO-D_6):117.2 (C-F), 51.6 (-CH_2), 165.8 (C=O), 21 (-CH_3). MS-MS: $[M]^+$ 411.12. Composition: C (67.31%), H (4.18%), F (13.89%), N (6.83%), O (7.80%).

4'-((5-nitro-2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl) methyl)-[1, 1'-biphenyl]-2-carboxylic acid (3c)

Yellow solid, yield:49%, MP 228-232^0C. FTIR (KBr, cm^{-1}):OH & C-H stretch (2800-3600), C=O stretch (1714.79), C-Cl stretch (741.66), Aliphatic C-H stretch (2859.59), C-N stretch (1346.37), C-F stretch (1163.13, 1193.99, 1233.53), NO_2 (1527.69, 1487.18). ^{1}H NMR (400 MHz, DMSO-D_6): δ7.33-7.85 (m 11H Ar-H), δ 5.46-5.5 (t 2H CH_2),δ 11.0 (s H OH). ^{13}C NMR (100MHz, DMSO-D_6): 117.2 (C-F), 51.6 (-CH_2), 165.8 (C=O), 139-140 (C-N), 144 (C-NO_2). MS-MS: $[M]^+$ 442.09. Compositions: C, 59.87; H, 3.20; F, 12.91; N, 9.52; O, 14.50.

4'-((6-chloro-2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl) methyl)-[1, 1'-biphenyl]-2-carboxylic acid (3d)

Yellow Orange solid, yield: 51 %, MP 248-252^{0}C. FTIR (KBr, cm^{-1}): OH & C-H stretch (2800-3600), C=O stretch (1717.68), C-Cl stretch (741.66), Aliphatic C-H stretch (2900), C-N stretch (1346.37), C-F stretch (1076.33, 1114.9, 1287.54), NO_2 (1527.69, 1487.18). ^{1}H NMR (400 MHz, DMSO-D_6): δ7.29-7.62 (m, Ar-H), δ5.46 (t 2H CH_2),δ 11.0 (s H OH), δ 8.10-8.39 (s H Benzimidazole H). ^{13}C NMR (100MHz, DMSO-D_6): 117.2 (C-F), 51.6 (-CH_2), 165.8 (C=O), 139-140 (C-N), 129 (C-Cl). MS-MS: [M]$^+$ 431.07. Compositions: C (61.33%), H (3.28%), Cl (8.23%), F (13.23%), N (6.50%), O (7.43%).

4'-((2-(1-hydroxyethyl)-1H-benzo[d]imidazol-1-yl) methyl)-[1, 1'-biphenyl]-2-carboxylic acid (3A)

Orange solid, yield: 59(%), MP 216-220^{0}C. FTIR (KBr, cm^{-1}): OH & C-H stretch (2800-3600), C=O stretch (1714.79), Aliphatic C-H stretch (2863.45), C-N stretch (1295.26), CH_2 bend (1456.32), C=C aromatic stretch 1612.56. ^{1} H NMR (400 MHz, DMSO-D_6): δ 3.65 (s, OH alc.), δ 7.29-8.55 (m 11H Ar-H), δ7.59 (s 1H Benzimidazole H), 4.99 (t 2H CH_2), δ 1.49 (q 3H CH_3). ^{13}C NMR (100MHz, DMSO-D_6):129-136 (C-H Ar), 167 (C=O), 63.8 (-CH-OH) 52(-CH_2), 22.4(CH-CH_3). MS-MS: [M]$^+$ 373.15. Composition: C (74.18%), H (5.41%), N (7.52%), O (12.89%).

4'-((2-(1-hydroxyethyl)-6-methyl-1H-benzo[d]imidazol-1-yl) methyl)-[1, 1'-biphenyl]-2-carboxylic acid (3B)

Brown solid, yield: 54 (%), MP 262-264^{0}C. FTIR (KBr, cm^{-1}): OH & C-H stretch (2800-3600), C=O stretch (1710.93), 739.73, Aliphatic C-H stretch (2848.98), C-N stretch (1249.93), CH_2 bend (1445.71), C=C stretch (1600-1610). ^{1}H NMR (400 MHz, DMSO-D_6): δ 3.65 (s 1H OH alc.), δ 7.39-7.85 (m 11H Ar-H), δ 4.99 (t 2H CH_2). ^{13}C NMR (100MHz, DMSO-D_6):128-136 (C-H Ar), 166.6 (C=O), 63.8 (-CH-OH), 52 (-CH_2), 22.4 (CH-CH_3), 21 (C-CH_3). MS-MS: [M]$^+$ 386.17. Composition: C, 74.59; H, 5.74; N, 7.25; O, 12.42.

4'-((2-(1-hydroxyethyl)-5-nitro-1H-benzo[d]imidazol-1-yl) methyl)-[1, 1'-biphenyl]-2-carboxylic acid (3C)

Yellow solid, yield: 51 (%), MP 254-258^{0}C. FTIR (KBr, cm^{-1}): OH & C-H stretch (2800-3600), C=O stretch (1712.86), Aromatic vibration (739.73), Aliphatic C-H stretch (2848.98), C-N stretch (1249.93), CH_2 bend (1445.71), NO_2 (1494.8). ^{1}H NMR (400 MHz, DMSO-D_6): δ 3.65 (d 1H OH alc.), δ 7.39-7.85 (m 11H Ar-H), δ 4.99 (t 2H CH_2), δ 1.49-1.50 (q 3H CH_3). ^{13}C NMR (100MHz, DMSO-D_6):129-136 (C-H Ar), 167 (C=O), 63.8 (-CH-OH) 52 (-CH_2), 22.8 (CH-CH_3), 144 (C-NO_2). MS-MS: [M]$^+$ 417.17. Composition: C (74.59%), H (5.74), N (7.25%), O (12.42%).

4'-((6-chloro-2-(1-hydroxyethyl)-1H-benzo[d]imidazol-1-yl) methyl)-[1, 1'-biphenyl]-2-carboxylic acid (3D)

Yellow solid, yield: 45 (%), MP 234-238^{0}C. FTIR (KBr, cm^{-1}): OH & C-H stretch (2800-3600), C=O stretch 1716.72, C-Cl stretch (733.95), Aliphatic C-H stretch (2922.28), C-N stretch (1287.54), CH_2 bend (1441.84), C=C aromatic stretch (1599.06). ^{1}H NMR (400 MHz, DMSO-D_6) : δ 1.62 (d 3H CH_3), δ 4.94 (q 1H CH), δ4.9(s 1H OH) ,δ 4.99 (t 2H CH_2) , δ7-8 (m 11H Ar-H) ,δ 12.41 (s 1H OH). ^{13}C NMR (100MHz, DMSO-D_6):129-136 (C-H Ar), 167 (C=O), 64 (-CH-OH) 52 (-CH_2), 22.8 (CH-CH_3), 129 (C-Cl). MS-MS: [M]$^+$ 406.11. Composition: C (67.90%), H (4.71%), Cl (8.71%), N (6.89%), O (11.80%).

4'-((5, 6-dichloro-2-(1-hydroxyethyl)-1H-benzo[d]imidazol-1-yl) methyl)-[1, 1'-biphenyl]-2-carboxylic acid (3E)

Yellowish White solid, yield: 48(%), MP 246-248^{0}C. FTIR (KBr, cm^{-1}): OH & C-H stretch (2800-3600), C=O stretch 1714.7, Aromatic vibration/C-Cl stretch (745.52/ 776.68), Aliphatic C-H stretch (2918.42), C-N stretch (1296.22), CH_2 bend (1450.53), C=C aromatic stretch (1608.7) .^{1}H NMR (400 MHz, DMSO-D_6): δ7.297.85 (m 10H Ar-H), δ 8.30 (d 1H Benzimidazole H). ^{13}C NMR (100MHz, DMSO-D_6):129-136 (C-H Ar), 167 (C=O), 63 (-CH-OH), 52 (-CH_2), 22 (CH-CH_3), 128 (C-Cl). MS-MS: [M]$^+$ 440.07. Composition: C (62.60%), H (4.11%), Cl (16.07%), N (6.35), O (10.88%).

2. Biological Evaluation

2.1. Experimental design,

Drugs and chemicals:

Dexamethasone: For induction of hypertension.
Losartatan: Standard.
DMSO: Vehicle.
Test: 3a-3E

Dexamethasone induced Hypertension[17].

The adult male rats were divided into 5 groups of 4 rats each.

Group I: Control: Animals received no treatment but were given vehicle DMSO (0.1mL/kg i.p) only.
Group II: Dexamethasone: Animals received dexamethasone 0.5 mg i.m.
Group III: Standard: Animals received losartan 0.1 mg/day i.p for a week.
Group IV: Test I: Animals received 0.5 mg i.m dexamethasone & 100 µg i.p for a week.
Group V: Test II: Animals received 0.5 mg i.m dexamethasone & 100 µg i.p for a week.

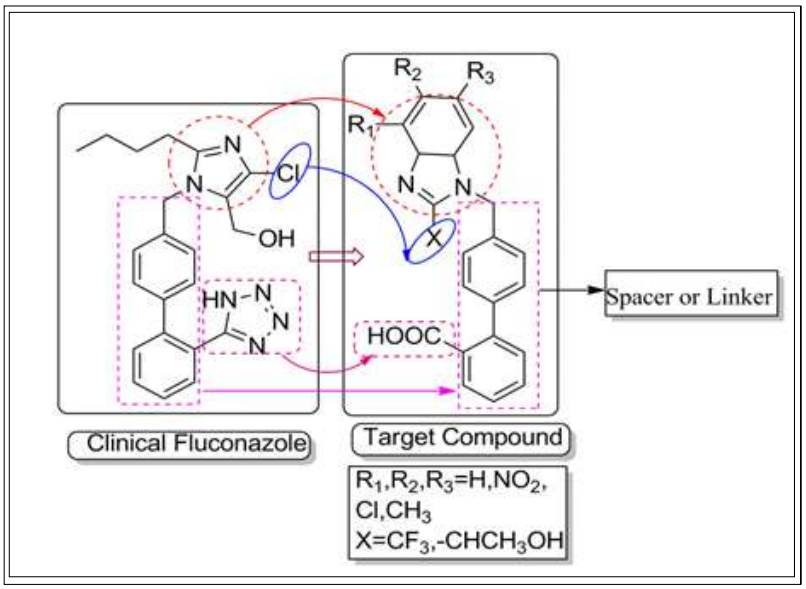
3.2.Procedure for measurement of systolic blood pressure (SBP) by noninvasive (indirect) method.

The rats were trained for at least one week until the blood pressure (BP) was steadily recorded with minimal stress and restrain. Administration of Dexamethasone i.m. for 5 days in rats produced a significant elevation ($p<0.05$) in systolic blood pressure (SBP) as measured by tail cuff method on III, IV and V^{th} day when compared to control rats. Administration of test samples and standard for 5 days in dexamethasone treated hypertensive rats produced a significant elevation ($p<0.05$) in systolic blood pressure (SBP) as measured by tail cuff method on III, IV and V dayas compared with SBP of dexamethasone hypertensive rats, thus implying an antihypertensive effect[18].

3. Results and Discussion

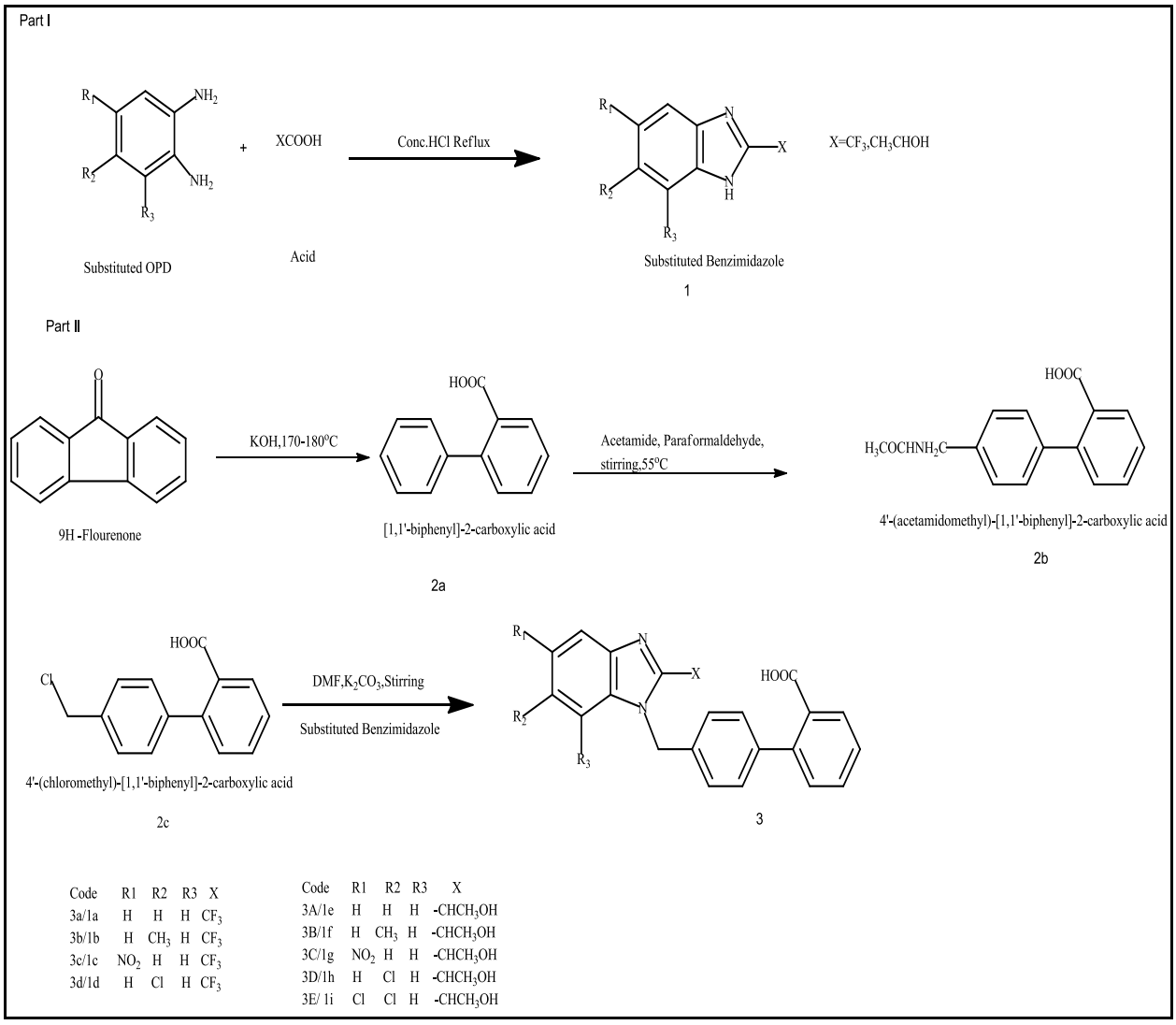
4.1. Rational design of benzimidazolyl biphenyl derivatives.

- A biphenyl group (The presence of a linker chain between the two phenyl moieties reduces the activity). It acts as a spacer connecting the acidic group with other features, could be replaced by other similar spacers.
- The tetrazole group is similar to the carboxylic function in terms of size and acidity but is apparently more stable metabolically; its use as a carboxylic acid mimic in analogues of biologically active compounds has therefore attracted increasing interest. [19]
- Such derivatives often exhibit different potencies and selectivities in their pharmacological profiles as compared with their carboxylic counterparts. The discovery by researchers at DuPont [20,21]of a promising nonpeptide angiotensin receptor antagonist containing a 5-aryltetrazole moiety is only one of many examples arising from the impressive amount of work on these derivatives as can be judged by the number of publications, especially in the patent literature, that have appeared in the past few years.
- A short alkyl chain at the 2-position of the heterocycle, for efficient binding to the receptor. The n-butyl group of the model compound provides hydrophobic binding and, most likely mimics the side chain of Ile 5 of angiotensin II.
- Substitution can vary at R position, the different R group , including a carboxylic acid, hydroxyl methyl group, a ketone, a benzimidazole group are present in currently available ARB's and are thought to interact with AT_1 receptor though ionic, ion-dipole, or dipole-dipole bonds [22].



4.2. Chemistry

SCHME 1: General Synthetic Route for synthesis of benzimidazolyl biphenyl derivatives.



Code	R1	R2	R3	X
3a/1a	H	H	H	CF_3
3b/1b	H	CH_3	H	CF_3
3c/1c	NO_2	H	H	CF_3
3d/1d	H	Cl	H	CF_3

Code	R1	R2	R3	X
3A/1e	H	H	H	$-CHCH_3OH$
3B/1f	H	CH_3	H	$-CHCH_3OH$
3C/1g	NO_2	H	H	$-CHCH_3OH$
3D/1h	H	Cl	H	$-CHCH_3OH$
3E/ 1i	Cl	Cl	H	$-CHCH_3OH$

Synthesis of different biphenyl benzimidazole derivative was carried out by performing various trial and errors and by optimization of available methods of synthesis. Compound 1 reacted with 4'-(chloromethyl)-[1, 1'-biphenyl]-2-carboxylic acid (2***)*** gave final product 3 in yield ranging from 50-60% which is mentioned in experimental part. The synthesized compounds were purified, characterized by TLC, melting point and further they were characterized by spectrophotometric instruments such as IR, NMR and Mass.

Table 1: Physical Properties of 2-Trifluoromethyl Substituted Benzimidazole (1a-1i)

Code	R_1	R_2	R_3	Colour and nature of product	Mol. Wt.	Yield (%)	Mp(^oC)	Mobile Phase	R_f Value
1a	H	H	H	White crystals	186.13	82	206-210	n-hexane: Ethyl acetate	0.35
1b	H	CH_3	H	Brown crystals	200.06	72	174-178	n-hexane: Ethyl acetate	0.43
1c	NO_2	H	H	White	231.03	65	120-124	n-hexane: Ethyl acetate	0.64
1d	H	Cl	H	Pink	220	79	194-196	n-hexane: Ethyl acetate	0.39
1e	H	H	H	White	162.19	76	198-202	Ethyl acetate:n-hexane	0.23
1f	H	CH_3	H	Brown	176.22	73	192-196	Ethyl acetate:n-hexane	0.324
1g	H	NO_2	H	Greenish White	207.19	67	168-172	Ethyl acetate:n-hexane	0.45
1h	H	Cl	H	Cream Colour	196.63	69	200-202	Ethyl acetate:n-hexane	0.29
1i	H	Cl	Cl	Yellow	231.08	63	216-220	Ethyl acetate:n-hexane	0.48

Table No.2: Effect of Synthesized Compounds on Hypertensive Rats

Treatment groups (mg/kg)	Mean change in SBP (mm Hg)				
	Ist Day	IInd Day	III Day	IVth day	Vth Day
Control	102.7± 3.25	109.7±2.19	101.0±0.58	111±3.38	112±0.58
Dexamethasone+ Standard	1031±1.92	105±3.78	105±2.55	108.2±0.62	111.0±0.91
Dexamethasone	101.3±3.71	111.7±2.10	124.7±2.90	133.3±1.85	140.0±0.57
Dexamethasone + 3a	102.0±3.0	104.2±3.5	109.3±3.2	111.2±3.5	115.0±0.61
Dexamethasone + 3b	105±1.51	104.8±3.70	117.8±3.10*	123.2±3.74*	140.0±0.66*
Dexamethasone + 3c	107.0±3.51	109.0±0.57	112.3±0.57#	121.2±3.79#	122.0±1.56#
Dexamethasone + 3d	103.0±2.51	104.1±0.51	103.0±0.58	106.0±0.6	107.2±0.92
Dexamethasone + 3A	102.1±3.1	104.2±0.72	106.2±0.23	108.0±0.66	109.1±0.74
Dexamethasone + 3B	104.1±2.1	106.0±0.23	108.2±0.66	109.5±0.77	110.3±0.56
Dexamethasone + 3C	107.2±1.22	108±0.57	110.0±0.66	109.3±0.72	111.0±1.22
Dexamethasone + 3D	106.2±1.21	105.2±1.61	110.3±3.1	111.6±2.9	113.0±0.57
Dexamethasone + 3E	104.0±1.50	108.1±3.2	109.2±3.0	110.1±2.8	114.0±0.66

SBP systolic blood pressure,* $p<0.05$ when compared to control and # $p<0.05$ when compared to Dexamethasone treated group, mm Hg millimeters of mercury

All values are expressed as mean ± SEM. n=4, *$p<0.05$ when compared to control and # $p<0.05$ when compared to Dexamethasone treated group.

4. Conclusion

Finally it has been concluded that different substituted benzimidazole derivatives has appreciable and selective action against angiotensin II induced hypertension. The present work was mainly intended to establish the moieties which are responsible for Angiotensin-II inhibition. All compounds were evaluated for antihypertensive activity. Out of all the evaluated compounds, compound 4'-((6-methyl-2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl) methyl)-[1,1'-biphenyl]-2-carboxylic acid(3b)was found to be effective anti hypertensive agent and hence was considered representative compound and was completely characterized and analyzed by IR, NMR, and Mass spectroscopy.

References

1. Shah D I, Sharma M, Bansal Y, Bansal G and Singh M. 2007, Angiotensin II-- AT1 receptor antagonists: Design, synthesis and evaluation of substituted carboxamidobenzimidazole derivatives. Eur J Med Chem.; 20: 1-5. 41.
2. Jat R K, Jat J L and Pathak D P. 2006 ,Synthesis of benzimidazole derivatives: As Anti-hypertensive agents. Eur Journal of Chem. 3: 278.
3. Bansal R. K., 2002. Heterocyclic Chemistry, third Ed. Publisher, New Delhi, New Age International, pp 401.
4. Bistrzycki, Ulffers, 1980. UeberDiacyl-o-Diamine. Ber. 23, 1876.
5. Kelly, Day. 1945. Preparation of 2-phenylnaphth [1, 2] imidazole and 2-methylnaphth [1,2] imidazole. J. Am. Chem. Soc. 67, 1074.
6. Fischer, Veiel. 1905. The chemistry of benzimidazoles. Ber. 38, 320.
7. Philips, 1928. The formation of 2-substituted benziminazoles. J. Chem. Soc. 2393.
8. O'Neil, M.J., Smith, M., Heckelman, 2001. The Merck Index, 13th Ed. Merck & Co Inc., P-1785, 10074.
9. Amari, M., Fodili, M., Nedjar-kolli, B., 2002. Reactivity studies on 4- aminopyrones: Access to benzimidazole and benzimidazolone derivatives. J. Heterocycl. Chem. 39, 811.
10. Kohler, P., 2001. The biochemical basis of anthelmintic action and resistance. Int. J. Parasitol. 31, 336.
11. Wright, J. B. (1951) The chemistry of the benzimidazoles. Chemical Reviews, 48 (3), pp. 397-541.
12. Haugwitz, R, D. and Narayan, V. L. (1975) Pridyl-1H-Benzimidazole N-Oxides. United state patent 3864350.
13. Sharma, M, C., Kohli, D. V. and Sharma, S. (2010), Benzimidazoles derivatives with (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]1H-benzoimidazol-2-yl}-phenyl)-(substituted-benzylidene)-amine with potential angiotensin II receptor antagonists as antihypertensive activity. International J of Drug Delivery, 2 (3), pp. 228-237.
14. Sharma, M, C., Kohli, D. V. and Sharma, S. (2010), Synthesis of 2-Substitued-5-nitro-1[2-(1h-tetrazol-4-ylmethyl]-1h-benzoimidazole with biological evaluation of blood pressure measured by invasive method and tail-cuff method. Journal of Optoelectronics and Biomedical Materials, 2 (2), pp. 45-58
15. Jitender, S, S. et al. (2002) Benzimidazoles with biphenyls: Synthesis of 5- substituted-2-npropyl-1-[(2'-carboxybiphenyl-4-yl-) methyl] benzimidazoles. J of Indian Institute of Sci, 82, pp. 177-182.
16. Pavia, (2001) Introduction to Spectroscopy. 3rd ed. Singapore: Thomson learning IncWallwork, C. J., Parks, D. A. and Schmid-Schonbein, G, W, (2003) Xanthine oxidase activity in the dexamethasone-induced hypertensive rat. Microvascular Research, 66 (1), pp. 30-37.
17. Sharon, L, H, O. et al. (2007) Role of xanthine oxidase in dexamethasone-induced hypertension in rats. Clinical and Experimental Pharmacology & Physiology, 34, pp. 517-519.
18. Middlemiss, D., Watson, and S, P. (1994): A medicinal chemistry case study: An account of an angiotensin II antagonist drug discovery programme. Tetrahedron 50, 13049– 13080.

19. Duncia, J, V., Piece, M, E., Santella III, J. B. (1991): Three synthetic routes to a sterically hindered tetrazole. A new one-step mild conversion of an amide into a tetrazole. J. Org. Chem. 56, 2395–2400.
20. Carini, D, J., Duncia, J, V. January 20 (1988): Angiotensin II receptor blocking imidazoles. Eur Pat Appl EP 0253310 A2.
21. Ismail, M, A, H. et al. (2006) Design and synthesis of new tetrazolyl- and carboxy-biphenylylmethyl-quinazolin-4-one derivatives as angiotensin II AT_1 receptor antagonists. J of med Chem., 49 (5), pp. 1526-1535.
22. Harrod M. (2010) Angiotensin converting enzyme inhibitors, antagonist and Ca blockers : Foyes principle of medicinal chemistry Thomas L. L. et al, 6th Ed. New Delhi: Woltors Kluwer, pp. 754-755.

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