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Synthesis of Benzimidazole Derivatives: As Anti-hypertensive Agents

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Abstract: A new series of non peptide angiotensin(A-II) receptor antagonist has been prepared. This N-(biphenyl methyl) imidazoles e.g. 5-substituted (amino) -2-phenyl-1-(2'-carboxy biphenyl-4-yl) benzimidazoles differ from the previously reported and related compounds in that they produce a potent hypertensive effect upon oral administration. The earlier series were generally active only when administered intravenously. It has been found that 2'-position of biphenyl is essential. Only ortho substituted acid possess both high affinity for the AII receptor and oral anti-hypertensive potency.

Keywords: Benzimidazole Derivative, Anti-hypertensive agent, Synthesis

Introduction

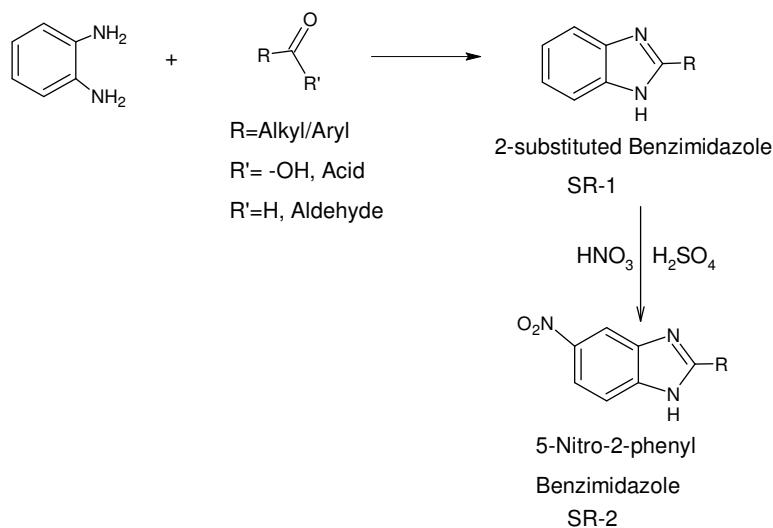
The renin-angiotensin system (RAS¹) is known to play an important role in cardiovascular regulation² and the maintenance of blood pressure and electrolyte balance. AngiotensinII³ (AngII) is active hormone of RAS and it mediates a variety of physiological functions through stimulation of specific receptors. There are at least two distinct receptor sub-types⁴⁻⁵ designed as AT₁ and AT₂. The AT₁ receptor mediates most of the known AngII physiologic functions such as vasoconstriction and aldosterone release. The potential role for non peptide

AngII receptor antagonists in the treatment of hypertension has well been demonstrated by AT₁-selective AngII such as losartan. The physiological functions of AT₂ receptor are not clearly defined but AT₂ receptor mediated effects of AngII have been implicated in renal free water clearance⁶⁻⁷. AngII receptor antagonists are expected to have similar therapeutic effects and indications as the ACE inhibitors without unwanted side effects associated inhibition of other ACE mediated pathways, such as bradykinin metabolism. Initial research in this area led to the discovery of peptide analog such as saralasin ([sar¹-Ala⁸]-AngII) which displayed potent and selective AngII receptor antagonist activity both *in vivo* and *in vitro*. However, these peptides had limited therapeutic utility due to partial agonist activity short duration of action and lack of appreciable oral bioavailability⁸. Only in recent years a number of non peptide AngII antagonists that show promise as inhibitors of the RAS been reported⁹. All these antagonists possess a central aromatic nucleus bearing the pharmacophores indispensable for activity and notably a polar function adjacent to biphenyl substituents while a polar function in this area of molecule seems to be necessary to maintain activity¹⁰.

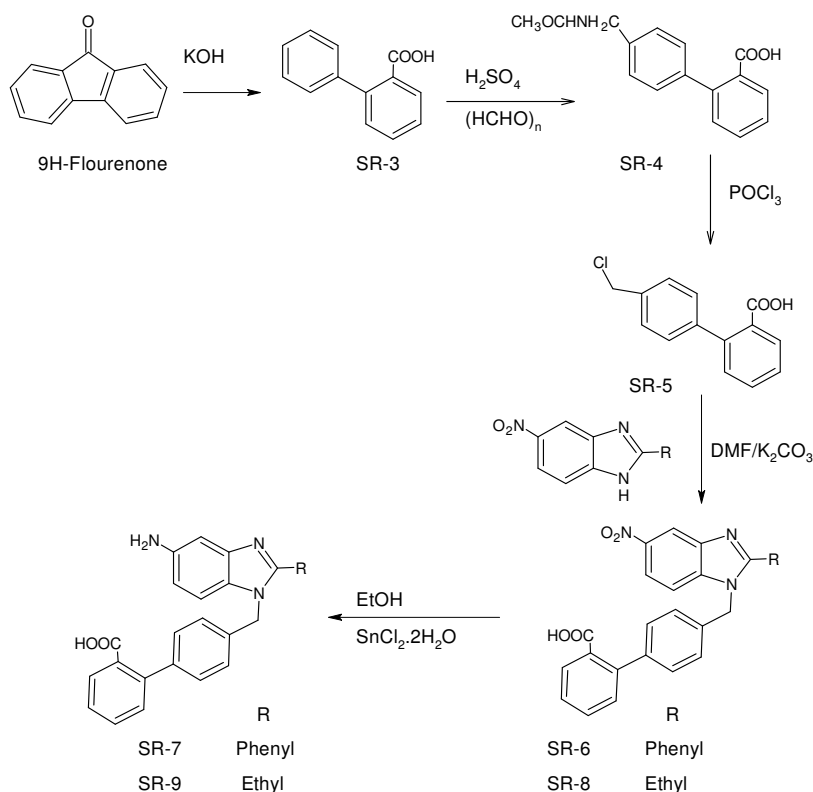
Experimental

Melting points were determined in open capillary tubes and are uncorrected. The time required for completion of the reaction was monitored by TLC using Silica gel-G plates and spots were exposed in iodine chamber. IR spectra were recorded on a Perkin Elmer 1800 (FTIR) spectrometer ¹H NMR spectra (DMSO) were taken on a DRX-300 spectrometer (300 MHz) using TMS as internal standard and chemical shifts are expressed in δ ppm.

First we synthesized 2-phenyl Benzimidazole. In this method the reactants are condensed in the presence of an oxidant such as cupric acetate¹¹. An improvement on the conventional method is the use of sodium bisulfite addition adduct of the aldehyde¹². The reactions are carried out in boiling ethanol, yields are good [e.g. 2-phenyl (90%), 2-(3-pyridyl) (97%)] and there is little risk of decomposition of liable substituents.



Scheme – 1



Scheme – 2

SR-1: (2-phenyl Benzimidazole)

o-Phenyl diamine (2.7 gm) was dissolved in a mixture of methanol/water (200 ml, v/v 1:1). To this, benzaldehyde (5.3gm) in methanol (50ml) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (7gm in water (100ml)) were added sequentially while stirring the solution. The reaction mixture was then heated to reflux under vigorous stirring for three hours after this a reddish pale precipitate was formed. The mixture was filtered hot and then washed with water to afford a yellow solid. The precipitate was redissolved in ethanol (150ml) and to this, HCl (24 ml) and solution of $\text{Na}_2\text{SxH}_2\text{O}$ was added in water (100 ml). At this stage, the reaction mixture was heated at reflux for 1 hour, resulting in the formation of black slurry. Reaction mixture was allowed to cool to room temperature and filtered through a pad of celite to remove the precipitated CuS. The filtrate was treated with ammonia solution to pH 8-9 and then concentrated to yield a reddish pale precipitate. After filtration and vacuum evaporation, compound we were obtained as reddish solid.

Yield: 72%, MP 256-258°C, IR (KBr) (cm^{-1}): 3390-3462 N-H str.), 3150 (ArH str.), 1650-1550 (C=C & C=N str.), 750 (monosub. Benz. Ring). ^1H NMR(DMSO): 9.5, (s, br., NH); 8.12-7.7 (m, 4H, ArH), 7.03-7.55 (m, 5H, ArH).

SR -2: (5-Nitro 2-phenyl Benzimidazole)

10.75ml 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 SR No. 1 (6.72gm) was mixed in portions during ½ hour under room temperature. After stirred continuously for 12 hours 45 minutes and then the reaction mixture was poured slowly over crushed ice with stirring. The precipitated product was filtered out and washes with cold water. The final product SR-2 was formed as yellowish pale.

Yield: 7.8gm (88%).

IR (KBr) (cm⁻¹): 3420 (NH str.), 3080(ArH str.), 1640-1560 (C=C,C=N str.), 1538-1329 (N-O str. NO₂), 756 (1,2-disubstituted benz.).

H¹ NMR(DMSO): 9.3 (s,1H, NH), 7.90-8.23 (m,3H, ArH), 7.66 (m, 5H, ArH).

SR -3: (Biphenyl Carboxylic acid)

15 gm of potassium hydroxide was heated at 180°-200°C in a three necked flask until fusion. 5gm of finely powdered of 9H-Fluorenone was added in five portions over thirty minutes with vigorous stirring and the temperature was maintained at 180°-200°C for further half hour. The fusion mixture was then poured in ice cold water with stirring. The obtained suspension was filtered at pump and then filtrate was acidify with HCl to pH-5 resulting in precipitation of byproduct which was filtered under suction wash with distilled water and the filtrate was again acidify with concerated HCl. The precipitated product was filtered under suction and dried in air. The product was recrystallized from CCl₄ (Carbon tetra chloride). Product SR-3 was formed as whitish.

Yield: 4.5gm (81%). m.p. =106-108°C.

IR (KBr): 3600-2750 (OH Str.), 3060-3020 (Aromatic, C-H str.), 1760 (Carboxylic, C-O str.), 746 (monosub. Benz. Ring).

H¹ NMR (DMSO): δ 9.03 (1H, s, broad, OH), 7.9 (5H, m, J=9.0Hz).

SR-4: (4' Acetamido methyl biphenyl-2-caboxylic acid)

1gm of SR-3 was dissolved in 6.6ml of concentrated H₂SO₄.After that acetamide (0.89gm) and Paraform aldehyde (0.075) gm were added subsequently. The solution was heated at 55°C along with stirring for 3 hours. The hot mixture was poured over ice and cold water. The resulting solid was filtered out.

Yield : 50 mg (21.2%) m.p.-142⁰-144°C.

IR (KBr) 3500-3300 (Broad O-H and N-H stretching), 2958 (C-H str,CH₃), 2840 (C-H str., CH₂), 1756 (Carboxylic, C-O str.), 1636 (C=O str.,Amide), 846 (1,4 disub. Benz. Ring).

H¹ NMR(DMSO): δ 9.1 (s,1H,OH), 7.4-7.65 (m, 8H, ArH), 4.46 (s, 2H,CH₂), 2.10 (s,3H,CH₃).

SR-5: (4' Chloromethylbiphenyl-2-carboxylic acid)

1.4gm of SR-4 was taken in a RBF. 1.598gm of phosphorus oxy chloride was added to 4ml of DMF and further addition of xylene (4ml). The reaction mixture was refluxed for 7 ½ hours. The cold solution was washed with water and evaporated to give a light yellow crystalline product.

Yield: 400mg, m.p. =122⁰-124°C.

IR(KBr) : 3750-3125 (Broad O-H str.) 3125-3000 (Aromatic str.), 2875(C-H str., CH₂), 1742 (Carboxylic, C=O str.), 1602-1454 (C=N, C=C str.), 1296 (C-Ostr), 736 (1,2 disubs.benz. ring), 658 (C-Cl str.)

¹H NMR(DMSO): 8.95 (s, 1H, OH), 7.2-8.23 (m, 8H, ArH), 4.46 (s, 2H, CH₂).

SR-6: (5-Nitro 2- phenyl-[(2' carboxybiphenyl-4-yl) methyl]Benzimidazole

0.4612gm of SR-2 was dissolved in 20ml of DMF (dimethyl formamide) and stirred vigorously with 1.5gm of potassium carbonate at 27⁰C for one hour. To the resulting mixture 0.482gm of SR-5 first dissolved in 20 ml of DMF and then was added dropwise with dropping funnel in 1 hour the reaction was allowed to proceed for further 11 hours and solvent removed under vacuum. Residue was treated with 20ml of dilute HCl and extracted with ethylacetate. The organic layer was washed with brine solution, distilled water and dried over anhydrous sodium sulphate. The solvent was evaporated and a brownish amorphous solid (SR-6) was obtained.

Yield: 0.56 gm, m.p. = 160⁰-162⁰C.

IR (KBr): 3625-3200 (Broad O-H str.), 2868 (C-H str., CH₂), (1750, carboxylic, C=O str.), 1602 (C=N and C=Cstr.), 1543-1332 (N-Ostr., NO₂), 1178 (C-N str.), 830 (1,4 disub. Benz. Ring).

¹H NMR(DMSO): 9.25 (s, br., OH), 8.75 (m, 3H, ArH), 7.12-7.65 (m, 13H, ArH), 4.01 (s, 2H, CH₂).

SR-7: (5-amino-2-phenyl-[(2' Carboxy biphenyl-4yl methyl]Benzimidazole)

0.9545 gm of SR-6 was placed in three necked RBF and dissolved in anhydrous ethanol and heated to 70⁰C under reflux. To this, 2.6gm stannous chloride dihydrate was added with slow stirring during 45 minutes. and reaction conditions were maintained for further 7 hours. The mixture was cooled to room temperature and pH adjusted to 7 with 5% sodium hydroxide solution. Ethanol was removed under reduced pressure and the residue extracted with dichloromethane. The organic layer was washed with brine, distilled water then dried over anhydrous sodium sulphate. Solvent removed under vacuum. A yellowish amorphous product was obtained.

Yield: 61%, m.p. = 114-116⁰ C.

IR (KBr): 3450-3125 (Broad, O-H, NHstr.), 3080 (Aromatic, C-H str.), 2875 (C-H str., CH₂), 1752 (Carboxylic, C=O str.), 1602-1454 (C=N, C=C str.), 736 (1,2 disub.benz.ring).

¹H NMR(DMSO): 9.8 (s, 1H, NH), 7.4-7.62 (m, 8H, ArH), 4.45 (s, 2H, CH₂), 2.5 (s, 3H, CH₃).

SR-8: (5-nitro-2-ethyl-(2'-carboxybiphenyl-4-yl)methyl benzimidazole)

5-nitro-2-ethyl-benzimidazole (0.4612) was dissolved in 20ml of DMF (dimethyl formamide) and stirred vigorously with 1.5gm of potassium carbonate at 27⁰C for 1 hour. Further reaction was proceeded as in SR-6.

Yield: 68%, m.p. = 156-158⁰.

IR (KBr): 3645-3220 (Broad O-H str.), 2943 (C-H str., CH₃), 2858 (C-H str., CH₂), (1746, carboxylic, C=O str.), 1622 (C=N and C=Cstr.), 1549-1322 (N-O str., NO₂), 1172 (C-N str.), 840 (1,4 disub. Benz. Ring).

¹H NMR(DMSO): 9.3 (s, 1H, NH), 7.4-7.62 (m, 8H, ArH), 4.35 (s, 2H, CH₂), 2.03 (s, 3H, CH₃).

SR-9: (5-amino-2-ethyl-[(2' Caboxy biphenyl-4-yl) methyl] benzimidazole)

SR-8(0.9545gm) was replaced in three necked RBF and dissolved in anhydrous ethanol and heated to 70⁰C under reflux. Next steps are common to SR-7.

Yield: 66%, m.p. =124-126⁰.

IR (KBr): 3643-3120 (Broad O-H str.), 2966 (C-H str.,CH₃), 2867 (C-H str., CH₂), (1741, carboxylic, C=O str.), 1632 (C=N and C=Cstr.), 1539-1328 (N-O str., NO₂), 1178 (C-N str.), 848 (1,4 disub. Benz. Ring).

¹H NMR(DMSO): 9.53 (s,1H,NH), 7.24-7.72 (m,8H,ArH), 4.38 (s,2H,CH₂), 2.13 (s,3H, CH₃).

Results and Discussion

The compounds reported in this paper SR-6, SR-7, SR-8, and SR-9 were the final compound and prepared for antihypertensive activity. Taking Losartan as lead compound we had fused the benzene ring with imidazole and coupling reaction with 4-chloromethyl biphenyl 2'-carboxylic acid (SR-5) to get the resulting compounds which shows hypertensive activity. At the position 2 we took 2-phenyl and 2- ethyl. From the study it was found that compounds that contain ethyl at position -2 gave better result than 2-phenyl. In the biphenyl ring carboxylic group at ortho position is necessary for pharmacological activity. At 2' position tetrazolyl moiety had the best pharmacological activity was found in the literature. At position 5 of benzimidazole NH₂ group gives good activity.

Pharmacological Investigation of benzimidazole Derivatives for anti-hypertensive activities

Procedure for development of hypertention for normotensive rats ¹²

1. Albino normotensive rats (Wistar Strain) were taken and they were hypertensitized by cholinomimetic agents for screening of all the synthesized benzimidazole derivatives for there anti-hypertensive activity. Suspension of test compounds was prepared in 1% w/v sodium carboxy methyl cellulose (sodium CMC) and was administered at dose level of 50 and 100 microgram/kg animal body weight to different groups of five rats each. After administration of dose to animal blood pressure was measured by normotensive tail and cuff method using LE-5001 pressure meter. Measurement were done after one hour and three hours interval in step-wise manner as follows:
2. One hour after administration of drug sample, animal was shifted to the restrainer, which restricts the movement of animal.
3. The tail was cleaned with moist cotton to remove the dirty matter and talcum powder was sprayed on tail to make its surface smooth.
4. A tail cuff and pulse transducer was fixed around the tail.
5. Initially animal shows particular pulse level, when the pulse rate is within the normal range. 'STRAT' switch is put on and the recorder records the blood pressure as SBP (systolic blood pressure). DBP (Diastolic blood pressure) and MABP (mean arterial blood pressure), which is displayed on monitor. The pressure can be easily read from the pre-calibrated monitor. Once all the values are displayed the recorder is switched off and for next measurement. Some procedures are allowed once when sufficient pulse level is attained.

Table 1. Hypertension induced in normotensive rat

Compound	Exp. Animal Albino (Wistar) Rat	After 1 hour			After 3 hours		
		SBP	DBP	MABP	SBP	DBP	MABP
SR-6	1	142	108	125	158	102	120
	2	140	106	123	140	104	122
	3	138	104	121	139	103	121
	4	140	104	122	141	105	122
	5	141	109	125	140	108	124
SR-7	1	144	108	120	140	105	118
	2	141	103	119	140	106	117
	3	140	110	124	139	103	118
	4	139	107	120	140	108	122
	5	138	105	121	139	107	121
SR-8	1	142	112	127	140	110	111
	2	140	110	125	140	112	123
	3	141	114	123	141	115	122
	4	140	113	120	142	114	115
	5	138	110	125	140	109	119
SR-9	1	142	110	122	140	102	108
	2	140	107	120	141	106	122
	3	141	110	121	140	104	120
	4	140	105	111	141	104	122
	5	141	108	119	138	105	121

Table 2. Reduction in blood pressure (mm Hg) at a dose of 50 µg/m/kg animal body weight.

Compound	Exp. Animal Albino (Wistar) Rat	After 1 hour			After 3 hours		
		SBP	DBP	MABP	SBP	DBP	MABP
SR-6	1	130	103	112	122	97	105
	2	130	105	113	128	100	109
	3	127	99	108	126	99	108
	4	129	102	111	128	102	111
	5	130	105	113	128	103	111
SR-7	1	131	106	114	130	104	113
	2	128	102	111	130	105	113
	3	134	110	118	128	101	110
	4	131	106	114	133	106	115
	5	130	104	113	131	104	114
SR-8	1	126	110	115	118	108	111
	2	124	109	114	120	110	113
	3	127	112	117	122	114	117
	4	127	111	116	122	112	115
	5	126	110	117	120	108	112
SR-9	1	127	108	114	122	101	108
	2	126	106	113	125	105	112
	3	127	109	115	123	102	109
	4	125	104	111	124	103	110
	5	126	107	113	122	103	109

Table 3. Reduction in blood pressure (mean \pm SEM) at a dose of 50 μ g/kg animal body weight

Compound	After 1 hour			After 3 hours		
	SBP	DBP	MABP	SBP	DBP	MABP
SR – 6	129.2 \pm 0.58	102.8 \pm 1.11	111.4 \pm 0.92	126.4 \pm 1.16	102.2 \pm 1.06	108.8 \pm 1.11
SR – 7	130.0 \pm 0.96	105.6 \pm 1.30	114.0 \pm 1.14	130.4 \pm 0.81	104.0 \pm 0.83	113.0 \pm 0.83
SR – 8	126.0 \pm 0.54	110.4 \pm 0.54	115.8 \pm 0.58	120.4 \pm 0.74	110.4 \pm 1.16	113.6 \pm 1.07
SR – 9	126.2 \pm 0.37	106.8 \pm 0.86	113.2 \pm 0.66	123.2 \pm 0.58	102.8 \pm 0.66	109.6 \pm 0.67

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