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Synthesis and Pharmacological Evaluation of Some Novel Imidazole Derivatives for Their Potential Anti-Hypertensive Activity

Anju Goyal

Chitkara College of Pharmacy, Chitkara University,
Punjab, INDIA
Email: anju.goyal@chitkara.edu.in

Jitender Singh

Lord Shiva College of Pharmacy, Sirsa,
Haryana, INDIA

Dharam Pal Pathak

Delhi Institute of Pharamceutical Sciences And Research,
New Delhi, INDIA

Abstract

Benzimidazole, which is a heterocyclic nucleus, plays an important role in various medicines. A number of therapeutic agents such as H1 antihistaminic agent clemizole, a potent opioid analgesic etonitazene, nonnucleoside antiviral compound enviroxime, for promotion of excretion of uric acid irtemazole, non sedating antihistaminic agent astemizole, anti ulcer drugs omeprazole and pentoprazole, antihelmintic thiabendazole, antinematodal nocodazole etc. are based on benzimidazole heterocyclic nucleus. The synthesis of various benzimidazole derivatives by the reaction of ortho phenylene diamine I with various organic acids to yield 2-substituted benzimidazole derivatives II which on further treatment with nitric acid and sulphuric acid yielded 5-nitro-2-substituted benzimdazoles III. Coupling of this compound with halogenated beta picoline V yielded the title compounds. The structures of synthesized compounds were elucidated mainly by spectral evidence. All the compounds were screened for their anti-hypertensive activity. The compounds exhibited moderate to significant activities.

Key Words: *Synthesis, benzimidazoles, anti-inflammatory activity, anti-convulasant activity*

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1 INTRODUCTION

Cardiovascular diseases are a cause of significant number of mortalities among deaths reported due to various diseases. One of the most common ailments of cardiovascular system is hypertension. A patient as per guidelines is said to be hypertensive when blood pressure measures of 140/90mmHg (systolic/diastolic pressure). Hypertension also involves slow

degenerative changes of vascular system of body leading to haemorrhage of arteries of vital organs leading to serious fatal consequences. Some of clinical strategies involved in the treatment of hypertension are diuretics, beta adrenergic blockers, aldosterone antagonist and ACE inhibitors.

Imidazole is a planer five-member heterocyclic ring with 3C and 2N atom and in ring N is present in 1st and 3rd positions. The imidazole ring is a constituent of several important natural products, including purine, histamine, histidine and nucleic acid. Being a polar and ionisable aromatic compound, it improves pharmacokinetic characteristics of lead molecules and thus used as a remedy to optimize solubility and bioavailability parameters of proposed poorly soluble lead molecules. Imidazole derivatives have occupied a unique place in the field of medicinal chemistry. The incorporation of the imidazole nucleus is an important synthetic strategy in drug discovery (Kumari, S., *et al.,* 2010). Substituted imidazoles are reported to posess a number of significant and diverse biological activities including antihistaminic (Aranjo, C. V. *et al.,* 2008), analgesic (Castro, I.O and Galvao, P.A.A. 1977), anti ulcer (Briseno-B, G. *et al*., 1977), antiviral (Pandey, V.K. *et al.,* 2005; Jerchee, D. and Leibigs, F. H, 1952, and Kholer, P. 2001) antihelmintic (Freyne, E.J.E. *et al.,* 1988), anti-hypertensive (Levin, J. *et.al*, 1944; Bradhury, R.H. *et al.*, 1992), anti inflammatory (Hamor, G.H, 1986), and gout curing properties (Hamor, G.H, 1986). A large number of therapeutic agents have been synthesized from imidazole nucleus which has demonstrated considerable potency. Moreover there is an increasing demand for novel therapeutic agents with significant anti-hypertensive activity and fewer side effects. So, as a part of our programme of synthesis and biological evaluation of imidazole derivatives (Dureja, H., *et al.,* 2002 and Balakumar, P. *et al*, 2005), it was decided to synthesize some novel derivatives of imidazole by coupling them with alpha picoline and evaluate them for anti-hypertensive activity.

2 EXPERIMENTAL

2.1 Material and Methods

All the chemicals and reagents used were of Analar grade and were procured from M/s S.D. Fine Ltd, India, M/s Otto Ltd, India and Sigma Chemicals Co., USA. All the solutions used for the synthesis were prepared by using distilled water. Melting points were determined by using open capillary method and are uncorrected. The IR spectra of compounds were recorded on Perkin Elmer Infra Red Spectrophotometer in KBr disc and absorption bands are expressed in cm^{-1}. NMR spectra were recorded on Brucker AC 300F (300 MHz) spectrometer using TMS as internal standard. Reactions were

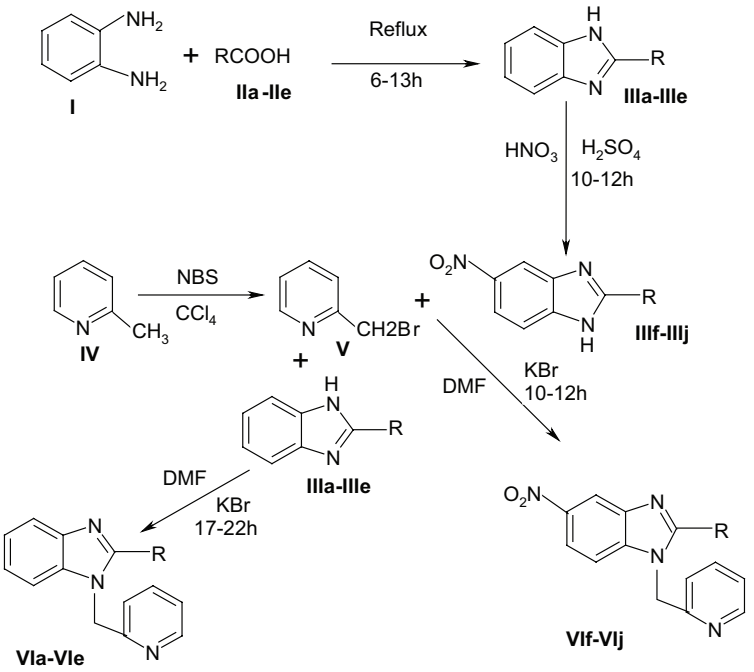

Figure 1: Synthetic Scheme-1

monitored by thin layer chromatography on pre-coated plates using different solvent systems. The purity of synthesized compounds was ascertained by TLC using iodine vapours as visualizing agents. The blood pressure was recorded on Powerlab/4SP Data Acquisition, AD Instruments Pvt. Ltd. Australia.

2.2 Synthesis

2.2.1 2-Substituted Benzimidazoles IIIa-IIIe

Ortho phenylene dia mine (I) (0.25 M) and appropriately substituted organic acids (II) (0.5 M) were reacted by heating under reflux for 6-13 h. The reaction mixture was cooled and basified to a pH of 7-8. The crude product so obtained (III) was dissolved in 95% ethanol and was suitably digested with activated charcoal. The boiling water was then added to the filtrate till the appearance of slight turbidity. The solution was made clear by adding a few drops of ethanol and kept for recrystallization. Needle shaped crystals were obtained. Fig 1.

2.2.2 5-Nitro 2-Substituted Benzimidazoles (IIIf-IIIj)

Concentrated nitric acid (7.5 mL) was placed in 3-necked RBF fitted with a mechanical stirrer. The flask was immersed in ice cold water and concentrated sulphuric acid (7.5 mL) was added slowly down the condensor with slow stirring. Afterwards, 2-substituted benzimidazole derivative (IIIa-IIIe) was added in portion over a period of 1h at such a rate that the temperature did not exceed 35^0C. After continuous stirring for 10-13 h, the reaction mixture was poured very slowly over crushed ice with vigorous stirring. The product (IIIf-IIIj) was filtered and washed with cold water.

2.2.3 Bromo methyl Pyridine (V)

Reaction of 2-methyl pyridine (IV) (0.25 M) with N-bromo succinamide (NBS) (0.25 M) and benzolyl peroxide (0.25 M) in CCl_4 for 8.3 h yielded the product (V), which was filtered and cooled overnight at room temperature.

2.2.4 Title Compounds (VIa-VIj)

Appropriately substituted benzimidazole (III) (0.1 M) was dissolved in Dimethyl formamide (DMF) a nd 2.5 g potassium carbonate. The mixture was stirred vigorously at room temperature on a mechanical stirrer for 1 h. To the reaction mixture, a suspension of Bromomethyl pyridine (V) (0.1M) in DMF was added dropwise with stirring for 1h. The reaction mixture was

Table 1: Physical and analytical data of synthesized compounds

Comp. No.	R	M.P. (°C)	Yield (%)	Molecular Formula	Molecular Weight	R_f value
VIa	H	82	53%	$C_{13}H_{11}N_3$	210	0.80
VIb	$-CH_3$	168	61%	$C_{14}H_{13}N_3$	224	0.81
VIc	$-C_2H_5$	104	48%	$C_{15}H_{15}N_3$	238	0.89
VId	$-C_3H_7$	134	51%	$C_{16}H_{17}N_3$	252	0.92
VIe	$-C_4H_9$	110	38%	$C_{17}H_{19}N_3$	266	0.69
VIf	H	104	60%	$C_{13}H_{10}N_4O_2$	255	0.70
VIg	$-CH_3$	152	59%	$C_{14}H_{12}N_4O_2$	269	0.90
VIh	$-C_2H_5$	148	53%	$C_{15}H_{14}N_4O_2$	283	0.84
VIi	$-C_3H_7$	58	52%	$C_{16}H_{16}N_4O_2$	297	0.90
VIj	$-C_4H_9$	66	51%	$C_{17}H_{18}N_4O_2$	311	0.80

*TLC solvent: $CHCl_3$:MeOH=97:3

Table 2: Spectral data of Synthesized Compounds

Compd	IR (KBr) cm^{-1}	H^1 N.M.R. ($CDCl_3$)
VIa	3097 (Aromatic C-H Stretch); 2944 (Aliphatic C-H Stretch); 1933, 1896 (Di-substituted benzene); 1703 (C=N Stretch); 1587 (C=C Stretch); 1458 (CH_2bending); 1245 (C-N Stretch); 746 (Ortho disubstituted benzene (oop))	δ = 8.90 (1H, s, -CH Imidazole); 8.31 (1H, d, -CH at α to nitrogen in pyridine ring); 4.76 (2H, s, -CH2 linker); 6.9-7.74 (7H, m, Aromatic protons)
VIb	3114 (Aromatic C-H Stretch); 2980 (Aliphatic C-H Stretch); 1918, 1876 (Di-substituted benzene); 1655 (C=N Stretch); 1555 (C=C Stretch); 1450 (CH_2 bending); 1350.9(CH3 bending); 1270 (C-N Stretch); 734 (oop)	δ = 8.31 (1H, d, -CH at α to nitrogen in pyridine ring); 4.76 (2H, s, -CH2 linker); 7.0-7.64 (7H, m, Aromatic protons); 2.66 (s, 3H, -CH3)
VIc	3053 (Aromatic C-H Stretch); 2973 (Aliphatic C-H Stretch); 1919, 1771 (Di-Substituted benzene); 1621 (C=N Stretch); 1588 (C=C Stretch); 1456 (CH_2 bending); 1378 (CH_3 bending); 1270 (C-N Stretch); 741 (oop)	δ = 8.03 (1H, d, -CH at α to nitrogen in pyridine ring); 4.74 (2H, s, -CH_2 linker); 6.8-7.55 (7H, m, Aromatic protons); 2.97 (q, 2H, -CH_2), 1.43 (t, 3H, -CH_3)
VId	3050 (Aromatic C-H Stretch); 2928 (Aliphatic C-H Stretch); 1923, 1771 (Di-Substituted benzene); 1622(C=N Stretch); 1537 (C=C Stretch); 1452 (CH_2 Bending); 1315(CH_3 bending); 1260 (C-N Stretch); 747 (oop)	δ = 8.60 (1H, d, -CH at α to nitrogen in pyridine ring); 4.76 (2H, s, -CH_2 linker); 6.70-7.54 (7H, m, Aromatic protons); 2.92 (t, 2H, -CH2), 1.88 (m, 2H, -CH_2), 1.04 (t, 3H, -CH_3)
VIe	3140 (Aromatic C-H Stretch); 2928 (Aliphatic C-H Stretch); 1929, 1889 (Di-substituted benzene); 1622 (C=N Stretch); 1579 (C=C Stretch); 1417 (CH_2 Bending); 1311(CH_3 bending); 1271 (C-N Stretch); 745 (oop)	δ = 8.60 (1H, d, -CH at α to nitrogen in pyridine ring); 4.77 (2H, s, -CH_2 linker); 6.82-7.57 (7H, m, Aromatic protons); 2.97 (t, 2H, -CH_2), 1.85 (m, 2H, -CH_2), 1.43 (m, 2H, -CH_2), 0.91 (t, 3H, -CH_3)
VIf	3103 (Aromatic C-H Stretch); 2815 (Aliphatic C-H Stretch); 1901, 1773 (Di-substituted benzene); 1623 (C=N Stretch); 1591 (C=C Stretch); 1513, 1480 (-N=O aromatic stretch);1345 (C-N Stretch); 741 (oop)	δ = 8.60 (1H, s, -CH imidazole), 8.16 (1H, s, -CH at β to nitrogen of imidazole & α to carbon containing nitro group), 7.90 (1H, d, -CH at α to nitrogen in pyridine ring); 4.72 (2H, s, -CH_2 linker); 6.32-7.60 (5H, m, Aromatic protons)
VIg	3107 (Aromatic C-H Stretch) ; 2919 (Aliphatic C-H Stretch); 1901, 1706 (Di-Substituted benzene); 1630 (C=N Stretch); 1592 (C=C Stretch); 1512, 1490 (-N=O aromatic stretch); 1418 (CH2 bending); 1383 (CH_3 bending); 1270 (C-N Stretch); 738 (oop)	δ = 8.50 (1H, s, -CH at β to nitrogen of imidazole & α to carbon containing nitro group), 8.10 (1H, d, -CH at α to nitrogen in pyridine ring); 4.2 (2H, s, -CH_2 linker); 6.30-7.44 (5H, m, Aromatic protons); 2.95 (3H, s, -CH_3)

Compd	IR (KBr) cm^{-1}	H^1 N.M.R. ($CDCl_3$)
VIh	3095 (Aromatic C-H Stretch); 2982 (Aliphatic C-H Stretch); 1895, 1755 (Di-Substituted benzene); 1671 (C=N Stretch); 1591 (C=C Stretch); 1517, 1490 (-N=O aromatic stretch); 1474 (CH_3 bending); 1490 (CH_2 bending); 1274 (C-N Stretch); 737 (oop)	δ = 8.45 (1H, s, -CH at β to nitrogen of imidazole & α to carbon containing nitro group), 8.12 (1H, d, -CH at α to nitrogen in pyridine ring); 4.55 (2H, s, -CH_2 linker); 6.09-7.57 (5H, m, Aromatic protons); 2.90 (2H, q, -CH_2); 1.45 (3H, t, -CH_3)
VIi	3102 (Aromatic C-H Stretch); 2965 (Aliphatic C-H Stretch); 1912, 1772 (Di-substituted benzene); 1628 (C=N Stretch); 1595 (C=C Stretch); 1517, 1441 (-N=O stretch); 1440 (CH_2 bending); 1384 (CH_3 Bending); 1265(C-N-stretch); 738 (oop)	δ = 8.45 (1H, s, -CH at β to nitrogen of imidazole & α to carbon containing nitro group), 8.10 (1H, d, -CH at α to nitrogen in pyridine ring); 4.85 (2H, s, -CH_2 linker); 6.1-7.58 (5H, m, Aromatic protons); 2.69 (2H, q, -CH_2); 1.94 (2H, m, -CH_2); 1.03 (3H, t, -CH_3)
VIj	3140 (Aromatic C-H Stretch); 2960 (Aliphatic C-H Stretch); 1889, 1363 (Di-substituted benzene); 1672 (C=N Stretch); 1594 (C=C Stretch); 1513, 1441 (-N=O Stretch); 1470 (CH_2 bending); 1310 (CH_3 Bending); 1223(C-N stretch); 737 (oop)	δ = 8.47 (1H, s, -CH at β to nitrogen of imidazole & α to carbon containing nitro group), 8.15 (1H, d, -CH at α to nit rogen in pyridine ring); 4.1 (2H, s, -CH_2 linker); 5.9-7.57 (5H, m, Aromatic protons); 2.94 (2H, q, -CH_2); 2.45 (2H, m, -CH2); 1.98 (2H, m,-CH_2); 1.05 (3H, t, -CH_3)

allowed to proceed further for 10-23 h and the excess solvent was removed under vacuum. The residue thus obtained was treated with 20 mL dilute HCl and extracted with ethyl acetate given in Synthetic scheme-1. The organic layer was washed with brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to afford the product (VI) as a brownish amorphous solid. Physical and analytical data of synthesized compounds is summarized in Table-1 and characterization data in Table-2.

2.3 Structure Activity Relationship

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 (Walia, R. *et al*., 2011). 5 substituted aryl or alkyl caboxamido derivatives have reported to possess Angiotensin-II AT1 receptor antagonistic activity so are good antihypertensives agents (Shah, D. *et al*, 2007).

3 BIOLOGICAL SCREENING

3.1 Spontaneous hypertensive rats (SHRs) of 200±20g body weight were used in study

Animals were procured from Laboratory Haryana agricultural university, Hissar. All animals were kept in polyacrylic cages and maintained under standard housing conditions (room temperature 24-27^{0}C and humidity 60-65% with 12:12 light: dark cycles). Food was provided in the form of dry pellets and water ad libitum. All experiments involving animals complies with the ethical standards of animal handling and approved by Institutional Animal Ethics Committee (Approval number LSCP/IAEC/06/01).

Spontaneous hypertensive rats (SHRs) of 200±20g body weight were used. Rats were divided into 6 groups, each group had 6 animals. Animals in normal control and negative control groups received distilled water. Rats were anaesthetized by intraperitoneal injection of urethane (dose 1.6g/kg). The tracheotomy was cannulated to facilitate spontaneous respiration and artificial ventilation at tidal volume of 10ml/kg with stroke rate of 45/ml. The femoral vein was cannulated with polyethylene tubing for administration of test compounds. For measurement of haemodynamic parameters a cannula is inserted into artery femoral for continuous monitoring of blood pressure – mean arteriolar blood pressure (MAP) and heart rate. When stable haemodynamic conditions were achieved, adrenaline (1mg/kg i.v.) and isoprenaline (0.25 mg/kg i.v.) were administered. When base line values again established, increasing doses of test substance was given intravenously. In case of no effect, the interval between successive doses was 15 min, otherwise 60 min. When base line values were again established, the dose of test samples (**VIa-VIj**) were given at dose of 20mg/kg, i.p in different groups and change in MAP was compared with prazocin (3mg/kg) treated group and vehicle treated control group. To check for α- or β-blocking activity adrenaline and isoprenaline administration is repeated after injection of the highest dose of test compound. If the test compound shows significant effect or no effect, a standard antihypertensive compound was administered for comparison purpose (Crestani, S. *et.al*, 2011).

4 STATISTICAL ANALYSIS

The results are expressed as the mean± SEM for each group. Statistical differences were evaluated using a oneway analysis of variance (ANOVA) followed by Dunnett´s test. Results were considered to be statistically significant at $p<0.05$.

5 RESULTS AND DISCUSSION

The required starting material 2-substituted benzimidazole **IIIa-IIIe** was synthesized by reacting equimolar quantities of o-phenylene diamine **I** and appropriate organic acids i.e. acetic acid, formic acid, propionic acid, butyric acid and valeric acid. Compound **II** was nitrated at position 5 by adopting standard procedures. On the other hand, 3-methyl pyridine was heated under reflux with N-bromo succinimide (NBS) and benzoyl peroxide in CCl_4 to yield bromomethyl pyridine **V**. Bromomethyl pyridine was coupled with 2- and 2,5-disubstituted benzimidazoles which yielded the title compounds. The result of the physico-chemical properties of all nineteen synthesized compounds is as shown in Table 1.

The compounds were obtained in good to excellent yield. The melting points of

Compounds varied from 50-168°C. The completion of each reaction was monitored by TLC spotting with the Rf values duly calculated. The structures of newly synthesized compounds were also elucidated by spectroscopic means which include IR, UV and NMR spectral studies as in Table 2.

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 (Walia, R. *et al*., 2011). 5 substituted aryl or alkyl caboxamido derivatives have reported to possess Angiotensin-II AT1 receptor antagonistic activity so are good antihypertensives agents (Shah, D. *et al*, 2007).

All the synthesized compounds were screened for anti-hypertensive activity. There were no significant differences in baseline blood pressure, heart rate or cardiac output between all experimental groups, as shown by ANOVA ($P > 0.05$). In the control group, the i.p. injection of the vehicle did not induce significant effects on the cardio-vascular parameters throughout the recording period.The i.p. injection of increasing doses of randomly selected ten derivatves of N, J, 3n4, 4n3 series(20 mg/kg) elicited short-lasting (1–3 min) but dose-dependent hypotensive responses that were paralleled by reductions of MAP, SVR were of 26 ± 5% ($n = 5$, $P < 0.05$) accompanied by a slight reductions of the heart rate. The compounds VIh and VI J were found to be more active than standard while compounds VIg and VI i were found to be equipotent and others show significant activity but less than standard. Biological activity data of synthesized compounds is summarized in Table-3.

Haemodynamic effects shown on Systolic blood pressure (SAP), Diastolic Blood pressure (DAP), Mean Arteriolar Pressure (MAP) and Heart Rate (HR) on SHRs treated with vehicle control and test compounds.

Table 3: Antihypertensive activity of the synthesized compounds

Haemodynamic Parameters					
Groups		**SAP (mmHg)**	**DAP (mmHg)**	**MAP (mmHg)**	**HR (bpm)**
Control	B A	169±6 168±9	145±3 140±4	154±6 149±7	415±23 407±29
VIa	B A	189±7 161±9*	129±5 105±6*	159±6 121±5*	311±19 298±11
VIb	B A	189±7 188±6	124±8 122±4	154±5 151±7	310±18 320±19
VIc	B A	206±15198±18	124±8 119±6	151±6 146±5	359±15 337±21
VId	B A	217±8 213±7	128±6 132±8	160±8 157±9	339±17 330±14
VIe	B A	221±6 213±3	130±5 129±4	157±9 155±8	363±16 347±17
VIf	B A	178±2 176±3	146±7 144±11	151±6 148±9	413±28 402±32
VIg	B A	194±5 187±7	165±8 155±6	180±7 168±6	416±18 409±11
VIh	B A	158±6 144±5*	151±9 141±8*	155±6 142±9*	453±29 459±21
VIi	B A	198±7 197±6	154±7 148±6	176±7 183±8	410±19 406±14
VIj	B A	140±6 138±5	118±7 115±4	127±5 125±4	511±45 465±28
Prazocin (3mg/kg)	B A	199±7 176±8*	156±6 138±4*	168±6 141±3*	418±17 411±15

Haemodynamic effects shown on Systolic blood pressure (SAP), Diastolic Blood pressure (DAP), Mean Arteriolar Pressure (MAP) and Heart Rate (HR) on SHRs treated with vehicle control and test compounds. Values were represented as mean ± SEM; n=5; *p<0.05 vs baseline values.

6 SUMMARY

In the present investigation we reported the synthesis of ten novel substituted benzimidazoles. All the synthesized compounds were characterized by suitable spectroscopic methods such as IR and NMR. Purity of synthesized compounds

was ascertained by chromatographic methods (TLC and column). The synthesized compounds were evaluated for their anti-inflammatory and anti-convulsant potential. All the compounds demonstrated moderate to significant activity. In conclusion 5-nitro-2-substituted alkyl-1-(2-yl-pyridine) benzimidazoles may be explored further for their potential to act as therapeutically active compounds. All the synthesized compounds were screened for anti-hypertensive activity. There were no significant differences in baseline blood pressure, heart rate or cardiac output between all experimental groups, as shown by ANOVA ($P > 0.05$) (Table 3). The compounds VIh and VI J were found to be more active than standard while compounds VIg and VI i were found to be equipotent and others show significant activity but less than standard.

REFERENCES

Aranjo, C. V., Figneiredo, M. R., Kaplan, M. A., Lessa, M. A, Pimenta, D., Tibirica, E. (2008), 'Antihypertensive effects of crude extracts from leaves of Echinodorus grandiflorus', *Fundam Clin Pharmacol*. Vol. 22(2), pp 161-168. http://dx.doi.org/10.1111/j.1472-8206.2008.00565.x

Balakumar, P., Bali, A., Bansal, Y., Bansal, G., Kaur, G., Sugumaram, M., Singh, J. S., Sharma, A. and. Singh, M (2005), 'Design, synthesis, and evaluation of novelly substituted benzimidazole compounds as angiotensin II receptor antagonists'. *Bioorg Med Chem Lett*. Vol. 15(17), pp 3962-3965. http://dx.doi.org/10.1016/j.bmcl.2005.05.054

Bradhury, R.H., Pearce, R.J. and Rober, D.A. (1992), *Chemical Abstract,* 117, 111587.

Briseno, B. G., Nasser, H.and Salido, R. F., (1977), 'Clinical evaluation of 1-beta-D-ribofuranosyl-1, 2, 4-triazole-3-carboxamide'. *Ann N Y Acad Sci*. Vol. 284, pp 272-7. http://dx.doi.org/10.1111/j.1749-6632.1977.tb21960.x

Castro, I.O and Galvao, P.A.A.(1977), 'The effect of l-β-D-ribofuranosyl-l,2,4-triazole-3-carboxamide on acute viral hepatitis', *Ann N Y Acad Sci*. Vol. 284, pp 278-83. http://dx.doi.org/10.1111/j.1749-6632.1977.tb21961.x

Crestani, S., Gasparotto, F. M., Junior, A. G., Kassuya, C. A. L., Lourenco, E. L. B., Marques, M. C. A., Salvador, M. J., Santos, J. E. S., Stefanello, M. E. A. (2011), 'Antihypertensive effects of isoquercitrin and extracts from Tropaeolum majus L.: Evidence for the inhibition of angiotensin converting enzyme', *J Ethnopharmacol*. Vol. 134(2), pp 363-72. http://dx.doi.org/10.1016/j.jep.2010.12.026

Dureja, H., Kumar, V., Saggu, J. S. and Sharma, R. (2002), 'Synthesis and Antihypertensive Activity of Some N-{4-(6-Chloro-5-nitro-1-[2'--(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1H-benzoimidazol-2yl-}-phenyl)-3-(substituted-phenyl)-acryl amides', *Journal Indian Institute Science,* Vol. 82, pp 172.

Fawzia, Z. E-Ablack (2011), 'Synthesis of Some New Benzimidazole Derivatives of Pharmaceutical Interest', *E-Journal of Chemistry,* Vol. 8, pp 748-752. http://dx.doi.org/10.1155/2011/723421

Freyne, E.J.E., Rayemakers, A.H.M., and Sanz, G.C., (1988), *Chemical Abstract*, 109: 73437.

Hamor, G.H. (1986), In*:* Principles of Medicinal Chemistry, Foye W.O. (Editor), Varghese Publishing House, Bombay, 3rd Edition, 503.

Hunger, A. and Kebrle, J. (1957), 'Analgesics and their agonists', Experientia Vol. 13(10), pp 400-1.

Ingle R.G. and Magar D.D. (2011)," Heterocyclic Chemistry of Benzimidazoles And Potential Activities Of Derivatives', *Int J Drug Res Tech,* Vol. 1, pp 26-32.

Jat, R.K., Jat, J.L. and Pathak, D.P. (2006),' Synthesis of benzimidazole derivatives: As Anti-hypertensive agents*, E- Journal of Chem,* Vol. 3, pp 278.

Jerchee, D. and Leibigs, F. H. (1952), *Annal. Chemie*. Vol. 573, pp 173.

Kholer, P. (2001), 'The biochemical basis of anthelmintic action and resistance', *International Journal of Parasitology*, Vol. 31, pp 336.

Kumari, S., Kumar, P.S., Kumar,N. (2010), 'Imidazole and its biological activities: A review', *Der Chemica Sinica,* Vol. 1(3), pp 36-47.

Levin, J. I. and Venkatesan, A. M. (1944), *Chemical Abstract,* Vol. 120, pp 323589.

Lindberg, P. and Nordberg, P. (1986), 'The mechanism of action of the gastric acid secretion inhibitor omeprazole', *J Med Chem,* Vol. 29, pp 1327 . http://dx.doi.org/10.1021/jm00158a001

Olayinka, O. A., Emmanuel, K. E., Abiola Edobor-Osoh and Alice O. A. (2013), 'Facile Synthesis and Characterization of New 2,3-Disubstituted Benzimidazole Derivatives', *Int Res Pure & App Chem,* Vol. 3(1), pp 10-21. http://dx.doi.org/10.9734/IRJPAC/2013/2480

Pandey, V.K., Gupta, V.D. and Tiwari, D.N. (2005), 'Synthesis of Novel Pyrazolidine Dione Substituted Benzimidazole Derivatives And Their Biological Activity', *Ind Hetero Chem,* Vol. 14, pp 219.

Shah, D., Sharma, M., Bansal, Y., Bansal, G. and Singh, M. (2007), 'Angiotensin II--AT1 receptor antagonists: design, synthesis and evaluation of substituted carboxamido benzimidazole derivatives', *Eur J Med Chem*, Vol. 20, pp 1-5.

Walia, R., Md. Hedaitullah1, Naaz, S. F., Iqbal, K., and. Lamba, HS. (2011),' Benzimidazole Derivatives – An Overview'. *Int Res Phar Chem,* Vol. 3, pp 565-564.