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SYNTHESIS AND BIOLOGICAL SCREENING OF BENZIMIDAZOLE DERIVATIVES

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Benzimidazoles, heterocyclic compounds, Piperidine, N methylcyclo- hexyl amine, Di propyle amine, N methyl cyclohexyl amine, 1 phenyl piperazine, N ethyl piperazine

Abbreviation:
Dimethyl Farmamide: DMF, *o*-Phenylene Diamine: *ortho*-Phenylene Diamine, DMSO: Dimethyl Sulphoxide, P1: Piperidine, P2: N methylcyclo- hexyl amine, P3: Di propyle amine, P4: N methyl cyclohexyl amine, P5: 1 phenyl piperazine, P6: N ethyl piperazine

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ABSTRACT

The synthesis of benzimidazoles derivative involves subsequent synthesis of 4-(2-chloro-ethoxy)-benzaldehyde, 4 methyl benzaldehyde followed by benzimidazoles derivative by reaction between amines derivatives and o-phenylenediamine in dimethyl farmamide (DMF) as solvent in the presence of iodine as a catalyst. Iodine is a commercial and environmentally benign catalyst. The yield of all benzimidazole derivatives was found to be in the range of 75 – 94%. The purity of the compounds was ascertained by melting point and TLC. The synthesized compounds were characterized by using IR, ^{1}H NMR, and MASS spectral data together with elemental analysis. The synthesized benzimidazole compounds were screened for analgesic and anticonvulsant activity in albino rat (100-200gm) by using Writhing test and maximal electroshock (MES). Out of all compound studied only PS-3, PS-4, PS-5 and PS-6 showed significant analgesic activities and response against MES test.

INTRODUCTION: Benzimidazoles and its derivatives represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities and these are well-documented in literature. They show selective neuropeptides YY1 receptor antagonists [1], potent inhibitors of TIE-2 and VEGFER-2 tyrosine kinase receptors [2], agents [3], gamma-amino butyric acid (GABA) agonists, and 5-HT3 antagonists [4].

Substituted benzimidazole derivatives have found commercial application in veterinarian medicine as anthelmintic agents and in diverse human therapeutic areas such as treatment of ulcers and antihistaminic [5]. Similarly, the general synthesis of benzimidazoles is by the condensation reaction of 1, 2-phenylenediamine with carboxaldehydes, carboxylic acids [6, 7], or their derivatives [8, 9] such as, chlorides, nitriles, and orthoesters, under strong acidic conditions, with high temperatures. Benzimidazoles have also been prepared on a solid phase to prove a combinatorial approach [8, 9]. The most popular strategies for their synthesis utilize N-alkylation of an unsubstituted benzimidazole [11]. Ammonium salts are inexpensive, commercially available reagents for few organic transformation reactions such as halogenation of aromatic compounds and synthesis of 3, 4-dihydropyrimidine-2(1H)-ones [12].

However, there are no reports of the use of ammonium salts as catalysts for the synthesis of benzimidazoles. In continuation, on the synthesis of heterocycles [13, 14] and on the development of synthetic methodologies [15, 17], we herein report a facile method for the synthesis of benzimidazoles by the reaction between amines derivatives and o-phenylenediamine in dimethyl formamide (DMF) as solvent in the presence of iodine as a catalyst, in very good yields.

Anxiety is a psychological and physiological state characterized by cognitive, somatic, emotional, and behavioral components. These components combine to create an unpleasant feeling that is typically associated with uneasiness, fear or worry. Anxiety is a generalized mood or condition that occurs without an identifiable triggering stimulus.

As such, it is distinguished from fear, which occurs in the presence of an observed threat. Additionally, fear is related to the specific behaviors of escape and avoidance, whereas, anxiety is the result of threats that are perceived to be uncontrollable or unavoidable. Some reports state that benzimidazoles possess anti-anxiety activity [18].

MATERIALS AND METHODS:

Chemicals used: *p*-Hydroxyl Benzaldehyde, Absolute Ethanol, Butanol, Sodium Carbonate, Potassium Carbonate Linker (ethane, propane), Different Sec Amine, Acetone, Sodium Chloride, Ice, Iodine, Dimethyl Formamide (DMF), *o*-Phenylene Diamine.

Apparatus used: Round bottom flask, Beaker, Iodine chamber, Petri disc, Measuring cylinder, Gloss rod, TLC plate, Water bath, Oven, Heating Mental, Graduated pipette, Melting Point apparatus.

Analytical work: Melting point were determined using melting point apparatus. Reaction was monitored using thin Layer chromatography on silica gel-G plate using methanol: chloroform (9:1) and UV chamber as visualizing agent.

SYNTHESIS:

Step 1:

Synthesis of 4-(2-chloro-ethoxy)-benzaldehyde: Equimolar amount of p-hydroxy benzaldehyde and potassium carbonate dissolved in 6ml of ethanol and also add linker like (1bromo 2 chloro ethane) respectively, were mixed and The mixture was refluxed for 12-18 hr at 60°C in heating mantle and 4-(2-chloro-ethoxy)-benzaldehyde was obtained from the crude extract (**See fig. 1**).

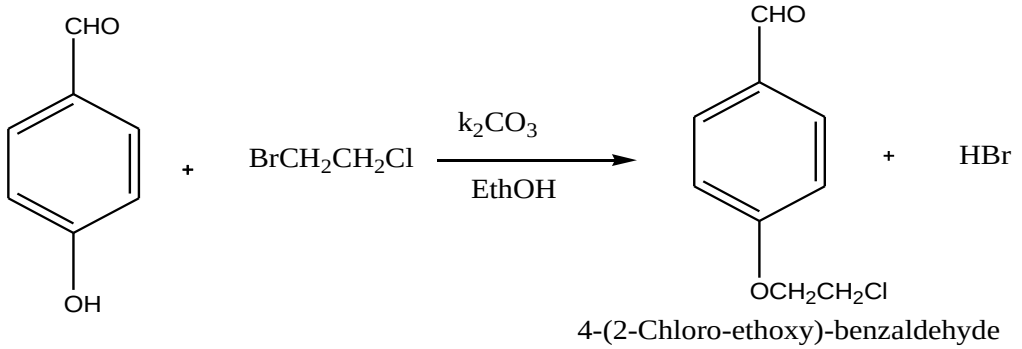


FIG. 1: SYNTHESIS OF 4-(2-CHLORO-ETHOXY)-BENZALDEHYDE

Step 2:

Synthesis of 4 methyl benzaldehyde: Equimolar amount of 4-(2-chloro-ethoxy)-benzaldehyde, sec amine like (piperidine) and two mole of sodium carbonate as catalyst dissolve in 6ml of butanol as solvent were refluxed for 18hr at 90°C in water bath and the mixture was obtained know as amine derivative(**See fig. 2**).

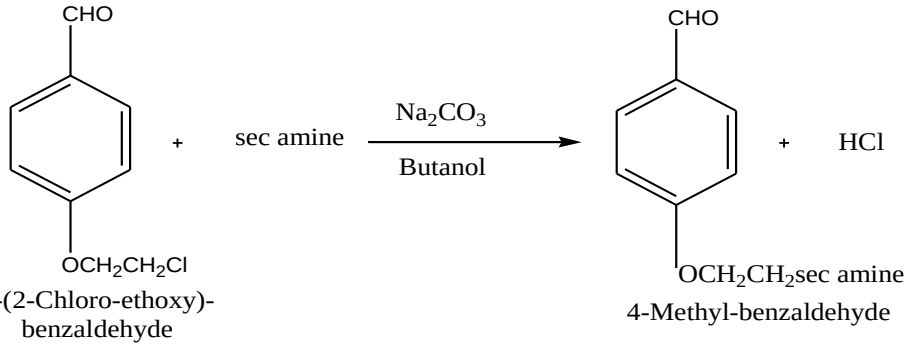


FIG. 2: SYNTHESIS OF 4- METHYL BENZALDEHYDE

Step 3:

Synthesis of benzimidazole derivative: The equimolar amount of amines derivatives and o-phenylenediamine were diluted in equimolar amount of dimethyl formamide (DMF) as solvent to a different round bottom flask and both are mixed and stirred for 30 min. and this solution was keeping for overnight and then in this solution we added iodine as catalyst in little amount live this solution for 4 to 5hr at 35-40^{o}C. Finally after 5hr this solution was pour in brine ice solution to avoid emulsified. The mixture was filtered and product was obtained. Because of impurity, washing will be done via sodium bi sulfite & sodium bi carbonate and then recrystalline by absolute ethanol. We obtained pure compound (**See fig. 3**).

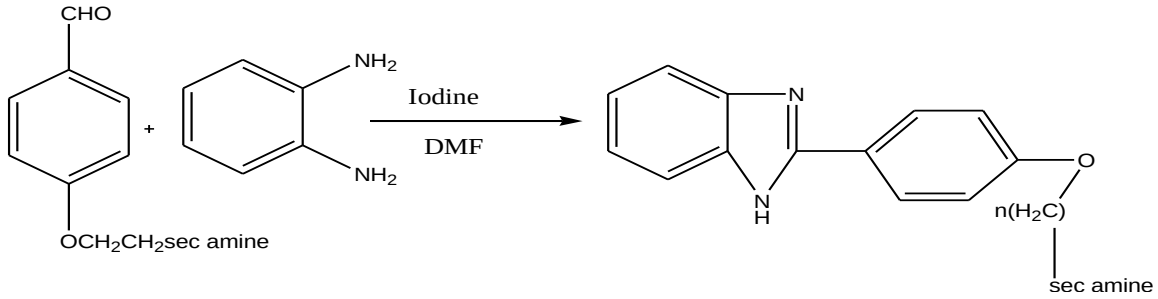


FIG. 3: SYNTHESIS OF BENZIMIDAZOLE DERIVATIVE

General structure:

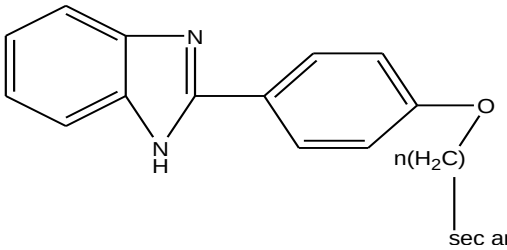
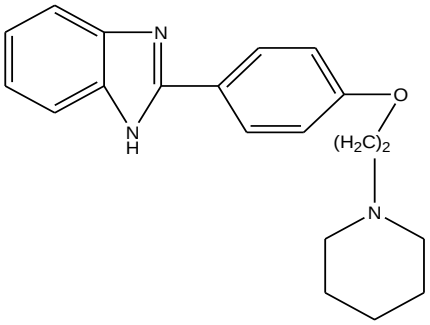


FIG. 4: GENERAL STRUCTURE OF BENZIMIDAZOLE DERIVATIVE

Compound: P1



2-(4-Ethoxy-phenyl)-1*H*-benzoimidazole; compound with 1-methyl-piperidine

FIG. 5: 2- (4- ETHOXY- PHENYL)- 1H- BENZOIMIDAZOLE; COMPOUND WITH 1-METHYL-PIPERIDINE

Interpretation of Spectrum: Table 1

TABLE: 1. PHYSICAL AND ANALYTICAL DATA OF SYNTHESIZED COMPOUNDS

CODE NO.	P1	P2	P3	P4	P5	P6
R (Sec amine)	Piperidine	N methylcyclo-hexyl amine	Di propyle amine	N methyl cyclohexyl amine	1 phenyl piperazine	N ethyl piperazine
M. F.	$C_{18}H_{23}N_3O$	$C_{23}H_{29}N_3O$	$C_{22}H_{27}N_3O$	$C_{22}H_{25}N_30$	$C_{25}H_{26}N_40$	$C_{22}H_{28}N_4O$
M.Wt.	297	363	349	347	398	364
N (linker)	1bromo 2 chloro ethane	1 bromo 3 chloro propane	1 bromo 3 chloro propane	1 bromo 2 chloro ethane	1 bromo 2 chloro ethane	1 bromo 3 chloro propane
%YIELD	$70^{0}/_{0}$	$53^{0}/_{0}$	$48^{0}/_{0}$	$30^{0}/_{0}$	$60^{0}/_{0}$	$46^{0}/_{0}$
M. PT	140^{o}C	160^{o}C	130^{o}C	170^{o}C	160^{o}C	120^{0} C
COLOUR	Yellow Powder	White Powder	White powder	White powder	White crystals	White powder

Biological Screening: In the efforts of establish the effect of the synthesized compound; the biological screening was carried out on the following lines.

1. **Analgesic activity**
2. **Anticonvulsant activity**

For the pharmacological study the drug solution (1mg/ml) of the synthesized compound were made in DMSO. For all the studies on the albino rat (100-200gm) of either sex were used. They were administered, the drug intraperitoneally (i.p.). Each experiment group constitute of four animals, housed in separate cages. All experiments were carried out with the consent of Institutional Animal Ethical committee of the institute.

Experimental:

1. **Analgesic activity:** Writhing test were performed for analgesic activity. Mice of either sex with a weight between 20 and 25g were used. Group of 6 animals are used for controls and treated mice. Preferably, two groups of 6 mice are used as control. Test animals are administered the drug and the standard at various pre-treatment times prior to acetic acid (0.6%, 0.1ml/1.0kg) administration. The mice are placed individually into glass beakers and five min allow elapsing. The mice are then observed for a period of ten min and the numbers of writhes are records for each animal.

For scoring purposes, a writhes is indicated by stretching of abdomen simultaneous stretching of at least one hind limb. The formula for computing percent inhibition is average writhes in the controls groups minus writhes in the drug group divided by writhes in the control group times 100%.

The time period with the greatest percent of inhibition is considered the peak time. A dose range is reserved for interesting compound or those which inhibit writhing more then 70% compound with less then 70% inhibition are considered to have minimal activity (**see table 2**).

2. **TABLE 2: ANALGESIC ACTIVITY OF SYNTHESIZED COMPOUNDS**

Code No.	Dose (mg/kg)	No. of mice	No. of writhing in mice (after 20 min.)	Mean Writhing	% inhibition	t- value	p- value
Control	-	1	16	15	-		
		2	15				
		3	15				
		4	14				
Aspirin	30	1	06	5.50	62.33	18.00	0.0001
		2	05				
		3	06				
		4	05				
PS-3	30	1	12	11.5	23.4	7.56	0.0002
		2	11				
		3	13				
		4	10				
PS-4	50	1	07	6.5	55.7	20.59	0.0001
		2	08				
		3	05				
		4	06				
PS-5	50	1	05	4.5	71	7.92	0.0001
		2	04				
		3	05				
		4	04				
PS-6	50	1	09	8.5	43.4	5.1962	0.002
		2	07				
		3	08				
		4	10				

3. **Anticonvulsant activity:** Anticonvulsant activity was studied against maximal electroshock (MES) Induced convulsion in mice (**see table 3**). Albino mice weighing 18-25g of either sex were used for the study. Animal were maintained on adequate diet and allowed fee access to food and water expect for short period during which they were removed from the cage for testing. The animals will be screened 24hr before the experiment. A current of 120mA will be given in the foot of the animals for 0.2 sec. normal saline is used as the conductivity medium. Only those animals which produced tonic convulsion will be selected. Next day, the selected animals will be divided into groups and administered the synthesized compounds. After an hour the electric shock was given to the animals and observations made for tonic convulsion, if any seizer was induced in mice by delivering electroshock of 50mA for 0.2sec by an electroconvulsiometer through a pair of pinna electrode.

TABLE 3: ANTI-CONVULSANT ACTIVITY OF SYNTHESIZED COMPOUNDS

Code No.	Dose (mg/kg)	No. of Animals	Mean recovery time	% inhibition	t- value	P-value
Control	NS	5	191 ± 2.12	__	__	__
Epsolin	25	5	46 ± 1.58	75.91	122.55	0.2815
PS-3	30	5	54 ± 1.22	70.72*	125.06	0.1463
PS-4	30	5	77 ± 2.91	58.16*	70.080	0.2365
PS-5	30	5	82.4 ± 5.72	55.86*	39.761	0.0502
PS-6	30	5	64.8 ± 1.92	65.07*	98.546	0.4171

RESULT: In the efforts of establish the effect of the synthesized compound; the biological screening was carried out on these activities [1]. Analgesic activity- Out of all compound studied only PS-3, PS-4, PS-5 and PS-6 showed significant analgesic activities. Other compound did not produce significant analgesic activity [2]. Anticonvulsant activity- Out of all compound studied only PS-3, PS-4, PS-5 and PS-6 produced activities at 30 mg/kg b.wt .dose using MES test.

CONCLUSION: The present study describes a simple, inexpensive, and easy method for synthesis of benzimidazole derivatives in a stipulated time, without using any drastic conditions. The yield of all benzimidazole derivatives were found to be in the range of 75-94%. The purity of the compounds was ascertained by a melting point and TLC. The assigned structure was further established by IR, ^{1}HNMR, and MS spectral studies.New benzimidazole derivatives are synthesized by electron-rich olefines [7, 8 and 9] with appropriate reagents. All compounds studied in this work were screened for their *in vitro* antimicrobial activities against the standard strains:

From the present study, it can be concluded that the benzimidazole derivatives can potentially be developed into useful anti-anxiety agents, which can prompt future researchers to synthesize a series of benzimidazole derivatives containing a wide variety of substituent's, with the aim of producing a novel heterocyclic system, with enhanced activity.

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