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SYNTHESIS OF NOVEL IMIDAZO [1, 2-a] PYRIDINE FOR THEIR POTENT ANTICONVULSANT ACTIVITY

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Keywords:

Imidazo[1,2-a]pyridine, Anticonvulsant, Imidazole, Pyridine, MES method, Amino Pyridine

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ABSTRACT: Synthesis of a Derivatives of imidazo[1,2-a]pyridines with potent activity. Synthetic approaches allowing for variation of the 2-Amino Pyridines as well as other imidazopyridine substituents are outlined and resulting effects on anticonvulsant activity are highlighted. An experimental evaluation of anticonvulsant activity of synthesized Imidazo[1,2-a]pyridine derivatives by Maximal Electro Shock (MES) induce methods.

INTRODUCTION: One aspect of medicinal chemistry deals with the incorporation of newly emerged pharmacophores on already existing biologically active moieties to produce newer molecules with higher efficacy. In the development of organic therapeutic agents, medicinal chemists have explored numerous approaches to find and develop organic compounds that are now available in dosage forms suitable for the treatment of illness and often for the maintenance of health of human beings. Imidazo[1,2-a]pyridine are having the number of biological activities. The biological activities like anti-tuberculosis, anti-inflammatory, anticonvulsant, antimicrobial, antiviral, herpesviruses, anticoccidal, antiprotozoal *etc*. Imidazo[1,2-a] pyridine showed diversified pharmacological activities. In view of potential biological activity of Imidazo[1,2-a]pyridine, it was considered worthwhile to synthesized some Imidazo[1,2-a]pyridine as possible anticonvulsant.

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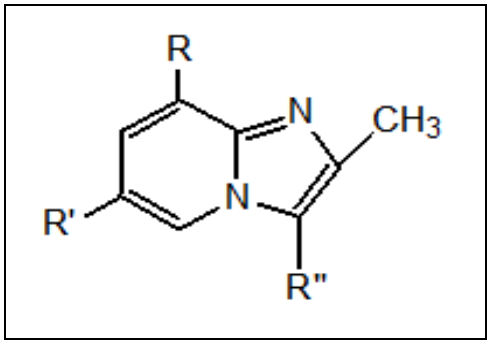
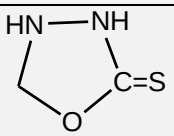
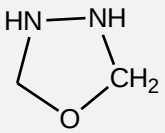
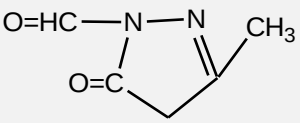
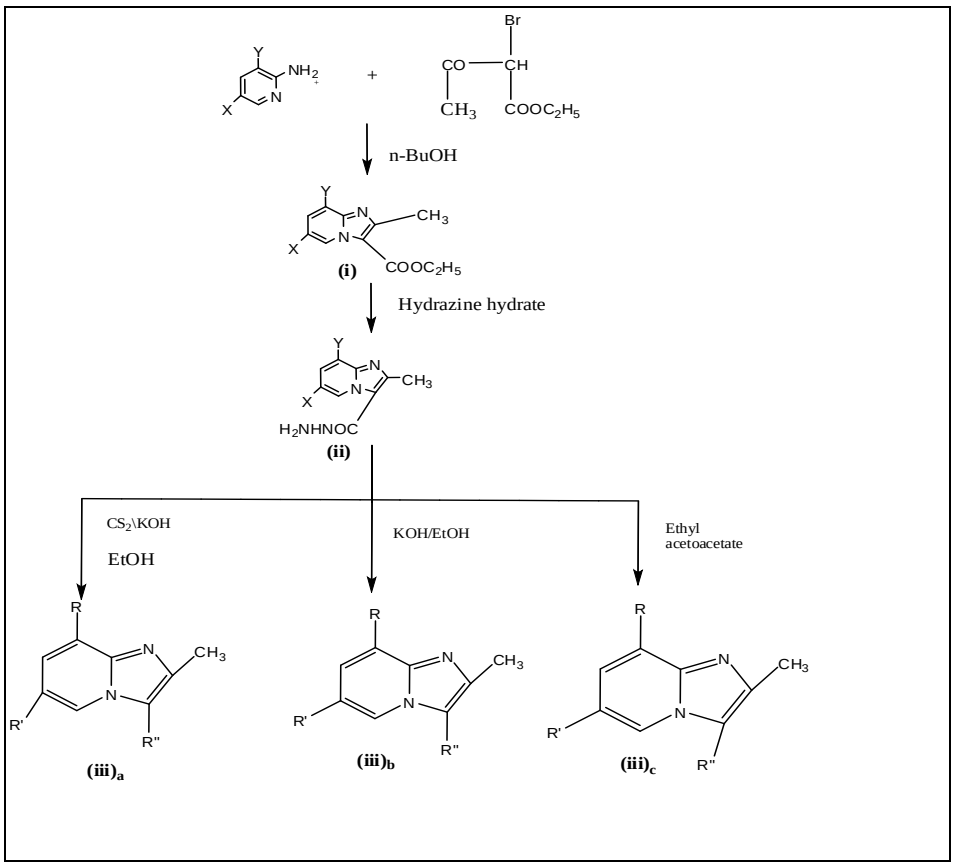


S. no	R	R'	R"
1.	H	H	
2.	H	CH_3	
3.	OH	H	

MATERIALS AND METHODS: Synthesized Imidazo[1,2-a]pyridine were prepared as per method described in the literature [1 - 3]. The procedure involves in the three steps (**Scheme I**) as stated below:



SCHEME: 1

Step 1: Synthesis of Ethyl 2-Methylimidazo[1,2-a]pyridine-carboxylate (i): To a suitably substituted 2-aminopyridine (0.02 mol) in n-Butanol (50ml) was added the 2-bromoacetoacetate (0.2 mol). The mixture was refluxed under stirring for 8-15 hr and then cooled. The progress of reaction was monitored by TLC. Solvent was evaporated under reduce pressure, and the residue in $CHCl_3$, washed with 5% $NaHCO_3$, and dried (Na_2SO_4). Evaporation of the solvent gave a residue of compound (i) was allowed to crystallize. The yield was obtained 72 % and m.p. was 72 °C.

Step 2: Synthesis of 2-Methylimidazo[1,2-a]pyridine-3-carboxylic Acid Hydrazide: Ethyl 2-methylimidazo[1,2-a]pyridine-3-carboxylate (i) (0.02 mol) was heated under reflux with 99% of $H_2NNH_2.2H_2O$ in 96% C_2H_5OH (30ml) for 10 hr. and then cooled. The crystals formed of compound (ii) were washed with H_2O, dried and recrystallized from C_2H_5OH (96%). The yield was obtained 35% and m.p. was 180 °C.

Step 3: Synthesis of 4-(2-Methyl-Imidazo[1,2-a]pyridine-3yl)- [1,3,4] oxadiazolidine- 2'-thione (iii)a: To a solution of 2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid hydrazide (ii) (0.01 mol) and potassium hydroxide (0.01 mol) in 96% C_2H_5OH (50ml) was added carbon di-sulphide (10ml) with stirring. When the addition was completed, the reaction mixture was refluxed for 14-15 hr. the contents were cooled and the solvent was distilled off. The residue was dissolved in water, filtered and the filtrate was finally acidified with acetic acid, the solidified product was finally filtered, dried and recrystallized from methanol.

S. No	Substitution R	R'	Melting point	% Yield
1.	H	H	168°C	55%
2.	H	CH_3	135°C	72%
3.	OH	H	210°C	38%

Synthesis of 2-Methyl-3-[1,3,4]oxadiazolidin-3-yl-Imidazo[1,2-a]pyridine (iii)b: To a solution of 2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid hydrazide (ii) (0.01 mol) and potassium hydroxide (0.01 mol) in 96% C_2H_5OH (50ml) with stirring. When the addition was complete, the reaction mixture was refluxed for 14-15 hr the contents were cooled and the solvent was distilled off. The residue was dissolved in water, filtered and the filtrate was finally acidified with acetic acid, the

solidified product was finally filtered, dried and recrystallized from methanol.

S. No	Substitution R	R'	Melting point	% Yield
1.	H	H	156°C	45%
2.	H	CH_3	188-191°C	71%
3.	OH	H	208-210°C	67%

Synthesis of 5-Methyl-2- (2-Methyl-Imidazo[1,2-a]pyridine-3-Carbonyl)-2,4-dihydro-Pyrazol-3-one (iii)c: To a mixture of 2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid hydrazide (ii) and ethyl acetoacetate both in equimolar amount (0.02 mol) were refluxed in methanol (50ml) for 6-8 hr. after cooling the reaction mixture, a solid separated out which was filtered and dried after washing with pet ether (60-80 °C). Recrystallization was done from methanol.

S. No	Substitution R	R'	Melting point	% Yield
1.	H	H	125°C	78%
2.	H	CH_3	228°C	84%
3.	OH	H	205°C	75%

RESULT AND DISCUSSION: Spectral data of synthesized imidazo[1,2-a]pyridine.

TABLE 1: IR SPECTRA, PMR SPECTRA, MASS SPECTRA

S. No	Compound Code	Vibration	Frequency in cm^{-1}	Signal Position	Realtive no. of proton	Molecular Weight
1.	A-1	C=S Str	1237.73	5.30-8.48	6H	234
		C=N Str	1542.04	2.0-2.25	4H	
2.	B-1	N-H Str	3124.37	4.73-8.37	8H	204
		C-O-C Str	1146.76	2.04-2.34	4H	
3.	C-1	C=O Str	1622.97	6.86-8.43	4H	256
		C=N Str	1564.32	1.94-2.52	8H	
4.	A-2	C=S Str	1245.85	5.30-8.86	5H	248
		C=N Str	1540.50	2.10-2.31	7H	
5.	B-2	N-H Str	3299.99	4.72-8.83	7H	218
		C-O-C Str	1166.15	2.12-2.30	7H	
		C-H Str	2858.87			
6.	C-2	C=N Str	1540.99	7.22-8.79	3H	270
		C=O Str	1662.96	1.93-2.50	11H	
7.	A-3	C=S Str	1236.77	5.31-8.29	6H	250
		O-H Str	3438.37	2.01-25	4H	
8.	B-3	N-H Str	3341.30	4.71-8.30	8H	220
		C-O-C Str	1029.62	2.08-2.27	4H	
		O-H Str	3438.37			
9.	C-3	C=N Str	1471.22	6.50-8.29	4H	272
		C=O Str	1644.05	1.92-2.59	8H	
		O-H Str	3454.37			

Determination of Anti-Convulsant Activity: An experimental evaluation of anticonvulsant activity of synthesized Imidazo[1,2-a]pyridine derivatives by Maximal Electro Shock (MES) induce methods. The Maximal Electro Shock (MES) induced convulsion in animal's represents grand mal type of epilepsy. In Maximal Electro Shock convulsion electric shock is applied through the corneal. The maximal Electro Shock convulsions are divided in five phases.

- Tonic Flexion
- Tonic Extensor
- Clonic Convulsion
- Stupor
- Recovery/Death

Male albino mice weight (25-35gm) were used to test drug (synthesized Imidazo[1,2-a]pyridine Maximal Electro Shock (MES) method induced seizures. Female animals were excluded because of fact that estrus cycle influences the sezures threshold.

Animal were housed in polypropylene cage with dust free rice husk as bedding material under laboratory condition with controlled environment of temperature 25 °C ± 2 °C humidity (60% ± 10%) and before subjecting them to experimentation, the animals were given a week of time to get acclimatized with laboratory condition. The animals were fasted overnight before the experiment.

Drugs:

a) **Standard Sample:** The concentration of Phenytoin Sodium was prepared in 1% Tween 80 solution and the concentration of final solution was 2.5mg/ml and to equate the activity with that of compound synthesized.
b) **Test Sample:** Suspension of synthesized derivatives was prepared in 1% Tween 80 having concentration of 2.5mg/ml.

Requirements: Test tube, Mice, Syringes, Needles, Electroconvulsometer, Volumetric Flask, Oral Feeding Needle etc.

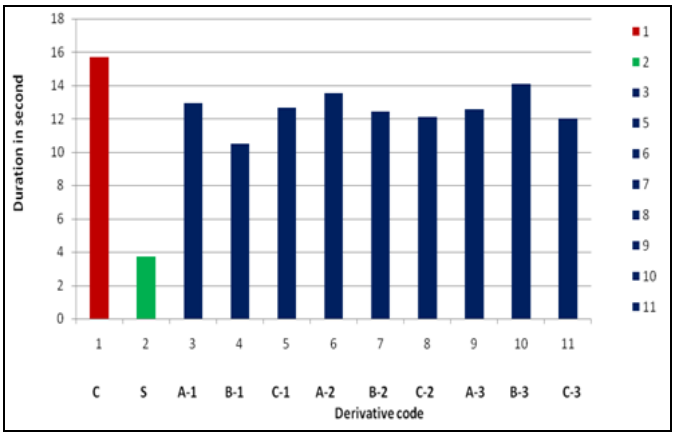
Study of Activity: Weighed and numbered the animals, divided into fourteen groups. Each group contain six animals. One group was used for the study the effect of control (Distilled Water). One group was used for the study the effect of standard drug (Phenytoin Sodium) and another twelve groups were used for the study of the effect of twelve synthesized derivatives. Female mice were excluded for this screening.

Maximal Electro Shock (MES) Induced Seizure in Albino Mice: The albino mice were chosen preliminary screening. Mice which showed extension of hind limb were induced in the study. The seizure was induced by Maximal Electro Shock in albino mice (weight 25-35gm) with help of electro convulsometer by passing current of 60mA for 0.2 second using electrode to the cornea of mice. The drug and distilled water were given one hour prior to induction of convulsion. The animal observed for the extensor phase as well as its duration. The abolition of the extensor phase (tonic phase) in drug treated group was taken as criteria for anticonvulsant activity.

TABLE 2: ANTICONVULSANT ACTIVITY OF SYNTHESIZED DERIVATIVES

S. No.	Dose (100mg/kg)	Flaxer ± SEM (in sec)	HLTE ± SEM (in sec)	Convulsion ± SEM (in sec)	Stupper ± SEM (in sec)	R/D
1.	Control	4.49±0.15	15.72±0.35	19.52±2.79	79.66±0.00	20%
2.	Phenytoin	2.36±0.06	3.72±0.07	11.43±0.23	38.95±0.82	100%
3.	A-1	3.36±0.40	12.96±0.69	20.90±1.31	49.39±6.21	60%
4.	B-1	2.24±0.14	10.52±0.19	22.03±0.76	34.75±6.29	80%
5.	C-1	3.29±0.44	12.68±0.81	23.08±1.19	52.11±5.05	80%
6.	A-2	2.54±0.06	13.52±0.31	21.17±2.28	42.37±2.23	60%
7.	B-2	3.28±0.21	12.42±0.69	22.14±0.84	48.90±5.14	80%
8.	C-2	2.42±0.12	12.12±0.35	23.07±0.68	57.53±1.76	60%
9.	A-3	3.51±0.36	12.56±0.42	26.12±0.94	53.67±3.13	80%
10.	B-3	4.10±0.21	14.10±0.53	24.17±0.70	42.17±2.32	40%
11.	C-3	3.66±0.18	12.02±0.50	22.74±1.23	47.53±5.61	80%

Animals were divided into eleven groups (1-11) for studing anticonvulsant effect of some Imidazo[1,2-a]pyridines derivatives
n = Number of animals, SEM = Standard Error Mean; Standard Drug = Phenytoin Sodium (25mg/kg); Control = Distilled Water, R/D = Recovery / Death.



GRAPH 1: GRAPH PLOTTED BETWEEN EXTENSOR PHASE OF SYNTHESIZED DERIVATIVES, STANDARD (S) AND CONTROL (C)

Standard (S): Phenytoin Sodium
Control (C): Distilled Water

SUMMARY: An experimental evaluation of anticonvulsant activity of synthesized Imidazo[1,2-a]pyridine derivatives by Maximal Electro Shock (MES) induce methods.

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CONFLICTS OF INTEREST: Nil

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