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Synthesis and pharmacological evaluation of some substituted imidazoles

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Abstract

Titled compounds N-1-phenyl 3- substituted phenyl indolo (2, 3) imidazole was prepared by condensing different aryl aldehydes with N-1-phenyl isatin in presence of ammonium acetate and glacial acetic acid. N-1-phenyl isatin was prepared by reaction of isatin with chloro benzene in presence of tetrahydrofuran and triethyl amine. Synthesized compounds were checked for there anticonvulsant activity.

Key words: Anticonvulsant activity, Isatin, indolo-imidazole, Maximal Electroshock Method.

Introduction

Epilepsy is a group of disorders of the CNS characterized by paroxysmal cerebral dysrthymia, manifasting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic body movements (convulsions), sensory or psychiatric phenomena. Epilepsy is a common chronic neurological disorder characterized by recurrent unprovoked seizures. These seizures are transient sign and /or symptoms of abnormal, excessive or synchronous neuronal activity in the brain. Epilepsy has a focal origin in the, manifestations depends on the site of the focus, regions into which the discharges spread and postical depression of these regions. About 50 million people world wide have epilepsy, with almost 90% of these people being in developing countries. Epilepsy is more likely to occur in young children, or people over the age of 65 years, however it can occur at any time [1].

Imidazole ring plays a critical role in many aspects of biological structure and function. As in addition to its role in defining protein structure, the imidazole ring of histidine often serves as a catalyst site for enzyme action. Histidine is an important mediator of the immune response and also functions as a neurotransmitter and imidazole ribosides are important intermediates in purine biosynthesis [2]. Imidazoles as pharmacologically active compounds has instituted a diverse array of synthetic approaches to the heterocycles [3]. Benzimidazole ring plays an important heterocyclic pharmacophore in drug discovery. These compounds carrying different substituents in the benzimidazoles structure are associated with a wide range of biological activities [4].

Imidazole and indole moieties show different biological activities. It was considered worthwhile to synthesize the compounds having both moieties in a single molecule to enhance their biological activity with reduced side effects, as produced by multi drug therapy. In view of the above-mentioned facts, we intend to synthesize some substituted Indoloimidazoles and screen them for anticonvulsant activity.

Materials and Methods

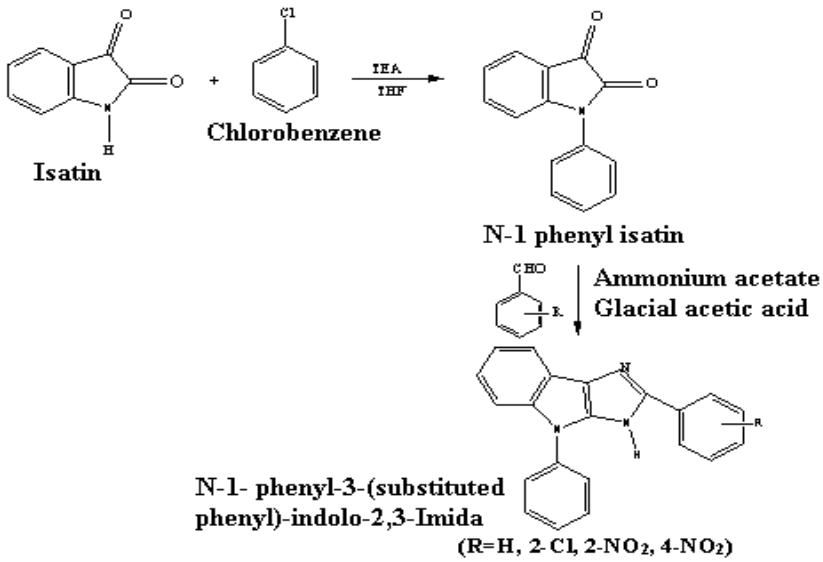
Experimental Work

Synthesis:

Step-1: Synthesis of N-1-Phenyl Isatin (I)

Isatin was reacted with chlorobenzene in presence of tetrahydrofuran and triethyl amine at 55 ^{0}C for eight hours. After completion of reaction, reaction mixture was cooled to room temperature and methanol is added in excess and kept overnight at room temperature. The precipitate was filtered and recrystallized with ethanol.

Scheme



Step – 2: Synthesis of N-1-Phenyl-3-(substituted phenyl)-indole-2,3-Imidazole(Ia-Id)
N-1-Phenyl isatin was reacted with different arylaldehydes in presence of ammonium acetate and glacial acetic acid at 80 ^{0}C for 8-10 hrs, cool the reaction mixture and add excess of methanol and kept overnight. The precipitate was filtered and recrystallized with methanol.

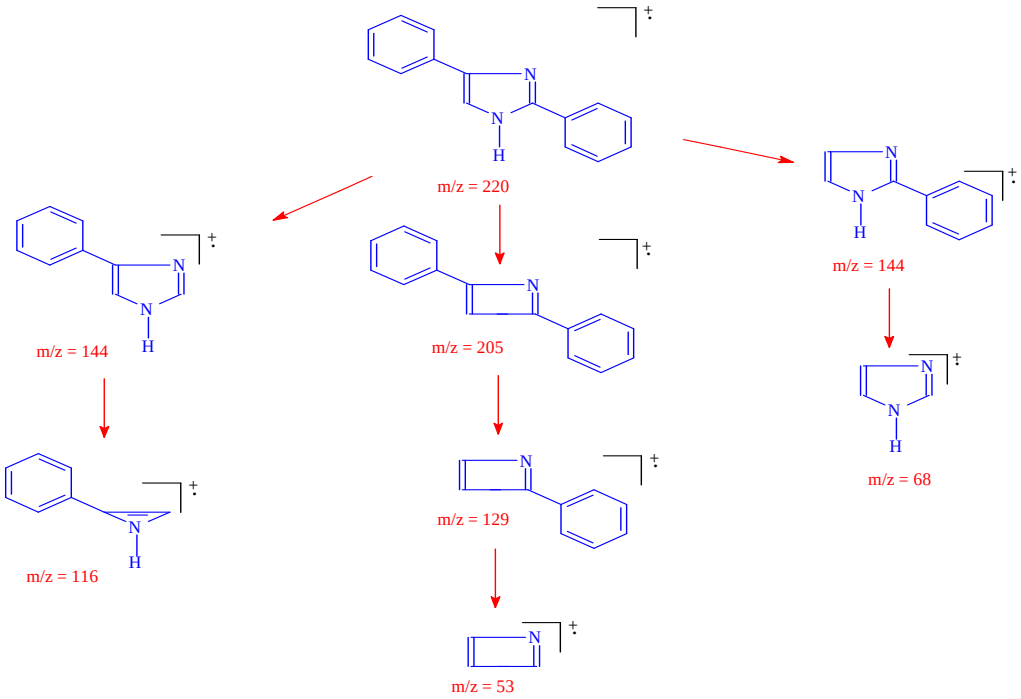
Table 1. Physical characteristics of the compound

S. no	Comp.	R	R_f value	M.pt (°C)	Yield (%)
1	I	--	0.79	48-50	75.76
2	Ia	H	0.82	70-72	49.45
3	Ib	Cl	0.64	84-86	72.60
4	Ic	2-NO_2	0.71	92-94	64.46
5	Id	4-NO_2	0.63	104-106	56.46

Table 2. Spectral characterization of the synthesized compounds

S. no	Comp.	MASS	IR	^{1}HNMR
1	I	m/z 223(M^+), 207, 146, 130, 114, 65, 44	1710(C=O), 1630(C=C), 1280(C-N)	δ 6.98 - 7.39 (m, 9H, aromatic protons)
2	Ia	m/z 220(M^+), 205, 144, 129, 116, 68, 53.	1630(C=C), 1270(C-N), 1680(C=N)	δ 6.31 – 8.26 (m, 14H, aromatic protons), 13.24 (s, 1H, NH imidazole)
3	Ib	m/z 256(M^+), 223, 204, 140, 126, 114, 62, 48.	1630(C=C), 1280(C-N), 1660(C=N), 630(C-Cl)	δ 6.43 – 8.17 (m, 13H, aromatic protons), 11.31 (s, 1H, NH imidazole)
4	Ic	m/z 266(M^+), 258, 220, 202, 136, 78.	1640(C=C), 1260(C-N), 1678(C=N), 1330(N-O)	δ 6.26 – 7.96 (m, 13H, aromatic protons), 12.14 (s, 1H, NH imidazole)
5	Id	m/z 266(M^+), 258, 220, 202, 136, 78.	1650(C=C), 1290(C-N), 1680(C=N) 1340(NO)	δ 6.31 – 8.16 (m, 13H, aromatic protons), 13.19 (s, 1H, NH imidazole)

Mass fragmentation pattern of imidazoles



Biological Screening:

Anticonvulsant activity

Anticonvulsant activity is evaluated by Maximal Electroshock Method (MES). Each compound was administered as an i.p. injection at dose level of 30 mg/kg and the anticonvulsant activity was assessed after 0.5 hr and 3 hrs intervals of administration. Maximal electroshock seizures were elicited in mice by delivering a 60 Hz, 50 mA electrical stimuli for 0.2 sec via ear clip electrodes. The maximal seizure typically consists of a short period of tonic extension of the hind limbs and a final clonic episode. Blockade of the hind limbs tonic extensor component due to the drug treatment is taken as the end point [5].

Table no.-3. Anticonvulsant and Neurotoxicity activity of synthesized compounds

S. No.	Comp. code	Dose	% Protection	Neurotoxicity
1	Standard (Phenytoin)	30	100	X
2	Ia	30	33.33	--
3	Ib	30	83.33	X
4	Ic	30	83.33	X
5	Id	30	33.33	--

n- Number of animals = 6, X – does not show neurotoxicity,
Dose- mg/kg body weight, ROA- I.P.; -- neurotoxicity - not checked.

Neurotoxicity Study

The mice were trained to stay on an accelerating rotarod that rotates at 10 revolutions /min and is 3.2 cm in diameter. Trained mice were given i.p. injection of the test compounds in dose of 30 mg/kg. Unimpaired mice can easily remain on a rod rotating at this speed. Neurological deficit e.g. ataxia, sedation, hyperexcitability is indicated by the inability of the mice to maintain equilibrium on the rod for at least 1 min in each of three concurrent trails [5].

Results and Discussion

All the synthesized compounds were confirmed by the ^{1}HNMR, IR and MASS spectral characterization. Some of the synthesized compounds showed significant anticonvulsant activity. Substitution of chloro and nitro group at 2nd position in the substituted ring showed significant anticonvulsant activity without neurotoxicity while hydrogen and 4-nitro substitution does not showed the anticonvulsant activity.

Conclusion

On the basis of above mentioned fact it is concluded that the chloro and nitrosubstitution at 2nd position in the substituted phenyl ring showed significant anticonvulsant activity.

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