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Synthesis and Anticonvulsant Activity of Novel Substituted Phenyl Indoloimidazole Derivatives

N. Kumar, P.K. Sharma, V.K. Garg and P. Singh
Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, NH-58, Baghpat By-pass Crossing, Delhi-Haridwar Highway, Meerut-250005, India

Corresponding Author: Nitin Kumar, Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, NH-58, Baghpat By-pass Crossing, Delhi-Haridwar Highway, Meerut-250005, India

ABSTRACT

A number of new N-1-phenyl-3-substituted phenyl indolo (2, 3) imidazole derivatives were synthesized and evaluated for their anticonvulsant activity. The titled compounds were obtained by condensing different aromatic aldehyde with N-1-phenyl isatin in presence of ammonium acetate and glacial acetic acid. All the newly synthesized compounds were screened for their anticonvulsant activity using maximal electroshock seizure method taking diazepam as standard drug. Among the synthesized compounds, compound 1b and 1c showed highly significant anticonvulsant activity and could be considered as leads for further investigations.

Key words: Imidazole, isatin, anticonvulsant activity, indole, diazepam

INTRODUCTION

Imidazole is a planar five-member ring system with 3C and 2N atom in 1st and 3rd positions. It exists in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms (Bhatnagar *et al*., 2011). Imidazole is one of the most fascinating classes of compound recognized for various pharmacological activities such as anti-HIV, anti-convulsant (Renukadevi *et al*., 1997), anti-inflammatory, antimicrobial (Kumar *et al*., 2010), Inhibitors of thromboxane A_2 synthase (Cozzi *et al*., 1993), antihistaminic (Mohan and Kumar, 2002), tranquillizer etc. Several approaches are available for the synthesis of imidazole. Reaction between α-halo ketone and amidine, dehydrogenation of imidazolones in the presence of sulphur and Radiszeski synthesis are some of the commonly used method for the preparation of imidazoles (Drabu *et al*., 2007, 2006). On the basis of various literature it shows that isatin derivatives also have known to be associated with broad spectrum of biological activity like antibacterial (Alagarsamy *et al*., 2004), anti-inflammatory (Alagarsamy *et al*., 2003), analgesic (Sridhar and Sreenivasulu, 2001), anti-viral, antifungal, anti-tubercular (Tran *et al*., 2002), etc. Encouraged by these observations we have synthesized various substituted indoloimidazoles derivatives and screen them for anticonvulsant activity. Convulsion or epilepsy is the most common neurological problems with the incidence of 3% in the population (Ibrahim *et al*., 2008). Epilepsy is more likely to occur in younger children or person over the age of 65 years however it can occur at any time (Tripathi, 2008). Epilepsy is a cerebral disorder which is characterized by paroxysmal, excessive and hypersynchronous discharges of large numbers of neurons from the central nervous system (Nikalje *et al*., 2011). The diagnosis and localization of pathological processes which involved in

epilepsy, the recording of brain activity by EEG have becomes most important (El-Gohary *et al.*, 2008). Epileptic patients have impaired physical, psychological and social functioning which leads to economic loss and diminished quality of life (Ramezani *et al.*, 2008). It is second most common disorder after stroke (Siddiqui and Alam, 2010). Modern conventional antiepileptic drugs are effective in approx 50% of patients and these drugs have wide range of side effect such as chronic toxicity, teratogenecity etc. (Usman *et al.*, 2008).

The objective of this study was to synthesize and evaluate the new derivatives of phenyl indoloimidazole and evaluate their anticonvulsant activity. Various substituted indoloimidazole (1a-e) were synthesized by Phenyl isatin and substituted aryl aldehyde. The compounds were confirmed by spectral analysis such as IR, NMR and mass spectral data.

MATERIALS AND METHODS

This study was carried out from 10th December 2009 to 13th November 2010 in the Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, Meerut, India.

The melting point was taken in open capillary tube and is uncorrected. I.R. spectra (KBr) were recorded on FTIR Spectrophotometer (Shimadzu FTIR 84005, 4000-400 cm^{-1}). ^{1}H NMR spectra were recorded on a JEOL AL 300 FTNMR 300 MHz spectrometer in $CDCl_3$ using TMS as an internal standard. ^{13}C NMR Spectra obtained from IIT Delhi. Mass Spectra were obtained from Central Drug Research Institute CDRI, Lucknow. The homogeneity of the compounds was described by TLC. All chemical used were of AR grade (Sigma-Aldrich; Acros organics).

General procedure for the synthesis of N-1-Phenyl-3-(substituted phenyl)-indole-2, 3-Imidazole (Compound 1a-e): Isatin was reacted with different arylaldehydes (Fig. 1) in presence of ammonium acetate and glacial acetic acid at 40-60°C for 4-5 h, cool the reaction mixture and add excess of methanol, kept overnight for complete precipitation. The precipitate obtained was filtered and recrystallized with methanol.

Anticonvulsant activity: Maximal Electroshock Seizure (MES method): The albino mice were stimulated through corneal electrodes to 50 mA current at a pulse of 60 Hz alternating current for 0.2 sec. The mice were previously administered orally with the test drug solution in 1% CMC (Carboxymethyl cellulose) suspension at three dose levels (50, 100 and 300 mg kg^{-1}), the anticonvulsant activity was assessed after 30 min interval of administration. The abolition of hind limb tonic extensor spasm was recorded as a measure of anticonvulsant activity. The diazepam was used as a standard drug (Vogel and Vogel, 2002).

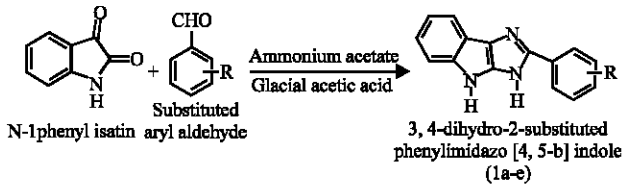

Fig. 1: Synthesis of N-1-Phenyl-3 (subsituted phenyl)-indol-2, 3-Inidazole (compoond 1a-e)

Statistical analysis: Anti-convulsant activity of synthesized NCE's at the dose (50, 100 and 300 mg kg^{-1}, p.o) in female albino mice for single administration. All the values were expressed as Mean±SEM and ***$p \leq 0.001$ indicates the level of statistical significance as compared with control. Data was analysed by one-way Anova and post hoc analysis done by Turkey's test.

RESULTS AND DISCUSSION

All the newly synthesized compounds 3,4-dihydro-2-substituted phenylimidazo[4,5-b]indole (1a-e) was confirmed on the basis of spectroscopic data given below.

4-(3,4-dihydroimidazo[4,5-b]-indol-2-yl)-N,N dimethylbenzenamine (1a): IR (Kbr) Vmax: 1311.50 cm^{-1}(C-N str.), 1662.52 cm^{-1} (C = N str.), 1596.95 cm^{-1} (C = C str.), 729.04 cm^{-1} (C-H, bending), 1535.23 cm^{-1}(N-H str., Sec. amine), 813.90 cm^{-1} (N-H str., Sec. amine). ^{1}H NMR ($CDCl_3$-d_6 300 MHz, δ ppm): 3.09 (s, 6H, CH_3), 6.70-7.76 (m, 8H, Aryl-H), 9.74 (s, 1H, N-H, 1 and 6). ^{13}C NMR ($CDCl_3$-d_6 300 MHz, δ ppm): 154.21, 131.82, 124.98, 119.14, 110.85, 39.91 ppm. EIMS m z^{-1} (relative intensity): 276.3 (100%), 277.3 (18.6%).

3,4-dihydro-2-(4-nitrophenyl)imidazo[4,5-b]indole (1b): IR (Kbr) Vmax: 1296.08 cm^{-1} (C-N str.), 1681.81 cm^{-1} (C = N str.), 1569.95 cm^{-1} (C = C str.), 3078.18 cm^{-1}(C-H, str.) 744.47 cm^{-1} (C-H, bending), 1519.80 cm^{-1}(N-H str., Sec. amine), 852.48 cm^{-1}(N-H bending, Sec. amine), 1519.80 cm^{-1} (NO_2 asymmetric bending) 1346.22 cm^{-1} (NO_2 symmetric bending). ^{1}H NMR ($CDCl_3$-d_6 300 MHz, δ ppm): 7.28-7.40 (m, 8H, Aryl-H), 10.8 (s, 1H, N-H, 1 and 6).

2-(4-chlorophenyl)-3,4-dihydroImidazo[4,5-b]indole (1c): IR (Kbr) Vmax: 1292.22 cm^{-1} (C-N str.), 1685.67 cm^{-1} (C = N str.), 1488.94 cm^{-1}(C = C str.), 833.19 cm^{-1}(C-H, str.), 1488.94 cm^{-1} (N-H str., Sec. amine), 833.19 cm^{-1} (N-H bending, Sec. amine), 682.75 cm^{-1} (C-Cl). ^{1}H NMR ($CDCl_3$-d_6 300 MHz, δ ppm): 7.28-7.86 (m, 8H, Aryl-H), 10.00 (s, 1H, N-H, 1 and 6). ^{13}C NMR ($CDCl_3$-d_6 300 MHz, δ ppm): 144.51, 136.09, 134.65, 133.89, 129.84, 128.82, 128.28, 122.10, 121.0 and 114.5 ppm.

3,4-dihydro-2-(2-nitrophenyl)imidazo[4,5-b]indole (1d): IR (Kbr) Vmax: 1330.79 cm^{-1} (C-N str.), 1670.24 cm^{-1} (C = N str.), 1577.66 cm^{-1} (C = C str.), 856.34 cm^{-1} (C-H, str. bending), 1461.94 cm^{-1} (N-H str., Sec. amine), 786.90 cm^{-1}(N-H bending, Sec. amine), 1195.78 cm^{-1}. ^{1}H NMR ($CDCl_3$-d_6 300 MHz, δ ppm): 6.93-7.54 (m, 8H, Aryl-H), 9.40 (s, 1H, N-H, Indole), 9.8 (s, 1H, N-H, Imidazole).

3,4-dihydro-2-(2,4-dinitrophenyl)imidazo[4,5-b]indole (1e): IR (Kbr)Vmax: 1346.22 cm^{-1} (C-N str.), 1704.96 cm^{-1} (C = N str.), 1608.52 cm^{-1} (C = C str.), 833.19 cm^{-1}(C-H, bending), 1488.94 cm^{-1} (N-H str., Sec. amine), 813.90 cm^{-1}(N-H bending, Sec. amine), 1535.23 cm^{-1} (NO_2 asymmetric bending) 1346.22 cm^{-1} (NO_2 symmetric bending). ^{1}H NMR ($CDCl_3$-d_6 300MHz, δ ppm): 6.99-8.30 (m, 7H, Aryl-H), 8.3 (s, 1H, N-H, Imidazole), 9.44 (s, 1H, N-H, Indole). EIMS m z^{-1} (relative intensity): 323.1 (100 %).

All the newly synthesized 3,4-dihydro-2-substituted phenylimidaz o[4,5-b]indole derivatives were tested *in-vivo* in order to evaluate their anticonvulsant activity. Previous studies proved that the presence of oxygen-containing substituents, particularly carbonyl, hydroxy, methoxy or

ethylenedioxy, associates to the anticonvulsant properties of the imidazole-containing anticonvulsant agents (Walker *et al.*, 1981) and branching or lengthening of the aliphatic chain between imidazole and aryl moieties in some derivatives exerts no more effect on the anticonvulsant activity (Nardi *et al.*, 1981).

Compound 1b and 1c have chloro and nitro substitution at para position of the phenyl ring which showed excellent anticonvulsant activity compared to substitutions at any other positions. Whereas those with N, N-dimethyl, 2-nitrophenyl and 2,4-dinitrophenyl substitution showed less significant activity. Though compound 1e have electron withdrawing groups attached to it but due to stearic hinderance of di-nitro substitution results in drastic decrease in activity even when compared to an electron donating group N, N-dimethyl in compound 1a. This concluded that with the increase in dose there is increase in anticonvulsant activity, for this we used three different doses 50, 100 and 300 mg kg^{-1}. Among them 300 mg kg^{-1} dose was found to be more potent. The anticonvulsant activity of the synthesized compounds having substitutions N,N-dimethyl, 4-nitro, 4-chloro, 2-nitro, 2,4-dinitro was found to be 5.16, 2.83, 3.33, 4.66, 5.5, respectively which showed moderate potency when compared to standard drug diazepam. Compound 1b with 300 mg kg^{-1} dose showed highest response of mean value 2.83 and dose with 50 mg kg^{-1} showed lowest response of mean value 4.83. All synthesized compounds have shown significant activity ($p \leq 0.001$).

Physical properties of all the synthesized compounds such as percentage yield, melting point and R_f values are listed in Table 1. Among all the synthesized compounds, 4-Cl and 4-NO_2 substituted derivatives shows maximum percentage yield of values 64 and 58, respectively and R_f values of these two compounds are 0.725 and 0.827 in the solvent system petroleum ether and ethyl acetate (1:1).

Data of anticonvulsant activity of all the synthesized compounds (1a-e) are given in Table 2. In Table 2, extensior value of control, standard and all the synthesized compounds are given. Diazepam was used as standard drug and calculated the extensior value at three different doses of 2, 4 and 12 mg kg^{-1}. The extensior values of synthesized compounds were calculated at the dose of 50, 100 and 300 mg kg^{-1} and all these values were compared with control which shows that synthesized derivative Ib and Ic showing the most significant results ($p \leq 0.001$) at the dose of 300 mg kg^{-1} body weight. Comparison of all three doses of all the synthesized compounds is represented in the form of graph (Table 2).

A novel series of benzimidazole derivatives were synthesized by Hugar *et al.* (2010) which shows that an increase in alkyl groups in the compound shows increase in anticonvulsant activity. Other different imidazole derivatives with chloro and nitro substitution showed more anticonvulsant activity (Jain *et al.*, 2010; Akturka *et al.*, 2002). According to other studies chloro substituted imidazole derivatives showed potent anticonvulsant activity in all halogen substituted compounds (Nagalakshmi, 2008). These research works supports present research work. A novel series of disubstituted benzimidazole derivatives were synthesized. In this synthetic work chain

Table 1: Physical properties of synthesized compounds

Compd. code	R	Yield (%)	M.P (°C)	R_f value
1a	N,N- dimethyl	47	60-62	0.428
1b	4-nitrophenyl	58	108-110	0.827
1c	4-chlorophenyl	64	112-114	0.725
1d	2-nitrophenyl	52	286-288	0.822
1e	2,4-dinitrophenyl	48	172-174	0.741

Table 2: Anticonvulsant activity of synthesized compounds (1a-e)

Compound	Dose (mg kg^{-1})	Hind limb extensior (Mean±SEM)
Control	Normal saline	10.666±0.614
Std (Diazepam)	2	0.833±0.401***
	4	0.666±0.210***
	12	0.5±0.223***
1a	50	6.16±0.980***
	100	5.50±0.428***
	300	5.16±0.654***
1b	50	4.33±0.666***
	100	3.66±0.421***
	300	2.83±0.703***
1c	50	4.83±0.600***
	100	4.0±0.730***
	300	3.33±1.085***
1d	50	6.5±0.428***
	100	6.33±0.557***
	300	4.66±0.760***
1e	50	7.16±0.792***
	100	6.16±0.792***
	300	5.5±0.562***

All the values are expressed as Mean±SEM of six animals in each group. ***(p=0.001) indicates the level of statistical significance as compared with control

lengthening of the carbon at 2nd position is responsible for the anticonvulsants activity (Singh *et al.*, 2010). In the present study we used different substitution such as methyl, nitro, chloro at different positions.

CONCLUSION

Among the synthesized compounds, such as (1b) 3,4-dihydro-2-(4-nitrophenyl) imidazo [4,5-b]indole and (1c) 2-(4-chlorophenyl)-3,4–dihydro-imidazo[4,5-b]indole showed excellent anticonvulsant activity. It may be assumed that further modifications may produce compounds of better activity with less toxic effects.

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