# Synthesis, Anticonvulsant Acitivity and Screening of Some Novel 1, 5-Disubstituted-4-Chloro-IH-Imidazole Derivatives

**Rutuja Sonawane[1], Dr. Chandrakant Magdum[2]**
[1-]Indira College of Pharmacy,Tathawde,Pune,
[2-] Kasegaon education society's Rajarambapu College of Pharmacy, Sangli, Maharashtra

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**ABSTRACT :**
The synthesis of some novel 1, 5-disubstituted-4-chloro-IH-imidazole was carried out and was evaluated for anticonvulsant activity. , 5-disubstituted-4-chloro-IH-imidazole were obtained from imines and p-tolunesulfonyl methyl cyanide (TOSMIC). Imines were prepared from commercially available amines and aldehydes.
**Keywords:** 1, 5-disubstituted-4-chloro-imidazoles, anticonvulsant activity.

## INTRODUCTION:

Epilepsy is a common neurological disorder characterized by unprovoked seizures that affects at least 0.5 to 1 % of the population worldwide (45-100 million people) (1). Although conventional antiepileptic drugs (AEDs): phenobarbital, primidone, phenytoin, carbamazepine, ethosuximide and benzodiazepine, are already in clinical use, some types of seizures are still not adequately treated with current therapy and have limitations or intolerable side effects (1-3). In response to these limitations several new drugs like oxcarbazepine, lamotrigine, topiramate, gabapentin, zonisamide, tiagabine, phenytoin, vigabatrin and felbamate have been strongly advocated to optimally manage seizures (3). However, there is a significant group of patients (up to 40%) who are resistant to the available antiepileptic drugs (4-7). Hence, there is an urgent need to develop new antiepileptic compounds with a more selectivity and lower toxicity (8) which continues to be an area of investigation in medicinal chemistry.

In recent years, the field of antiepileptic drug development (ADD) has become quite dynamic, affording many promising research opportunities.

Mechanistic approaches are increasingly being facilitated by the new wave of research in epileptics(9). Recent studies revealed that the substituted imidazole derivatives have attracted much attention due to their broad spectrum of pharmacological activities such as anti-inflammatory, analgesic, antimicrobial, antiviral, antifungal, antitubercular, anticancer and anticonvulsant (10-16).

Literature survey shows that imidazole-hetero cyclic compounds could be new classes of anticonvulsant agents by virtue of their potential anticonvulsant properties (17-19). Here, we present the synthesis, anticonvulsant of a series of unpublished 1,5-disubstituted-4-chloro- imidazole derivatives[20]**(3a-f).**

## MATERIAL AND METHODS:

Melting points was taken on electrothermal digital melting point apparatus and are uncorrected. Completion of the reaction was determined by single spotted TLC, structures of the compound were confirm by Infrared (IR), Proton Nuclear magnetic resonance (lH NMR) and **IR** spectra were recorded using KBr disc on a JASCO FTIR-410.1H~NMR spectra were recorded in CDCl3 solution on FTNMR, varian mercury 300Hz and proton chemical shifts are relative to tetramethyl silane as internal standard. Visualization of the compound on chromatographic plates was done by exposure to iodine vapours.

### Chemicals:

All the chemicals and solvents used were mostly of AR grade obtained from Loba Chemie Pvt. Ltd, Mumbai, Sigma Aldrich, Rajesh Chemicals and S.D. Fine Chem Ltd. The melting points were determined in open glass capillary tubes containing liquid paraffin and are uncorrected. Purity of the compounds was checked on thin layer chromatography (TLC) plates using silica gel G (Research Lab) and the solvent system benzene-acetone (9:1 and 8:2, v/v) and toluene-ethyl acetate-formic acid (TEF) (5:4:1, v/v/v);

***Corresponding author:**
**Rutuja Sonawane**,
Indira College of Pharmacy,Tathawde,Pune.
E-mail: sonawanerutuja@gmail.com

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The spots were visualized under iodine vapors or UVlight. The IR spectra were obtained in KBr pellets on BIO-RAD FTS FT-IR spectrophotometer. The lH NMR spectra were recorded on DPX-300 NMR spectrometer and BRUKER-400 Ultra Shied™ spectrometer using tetramethylsilane (TMS) as an internal standard in DMSO/$CDCl_3$. Chemical shifts (δ) are expressed in ppm.The physical constants, spectral data and anti-convulsant screening of the synthesized compounds are presented in Tables 1, 2 and 3, respectively.

**Experimental :**

**Step I: Preparation of Schiff's Bases.**

Procedure:

The synthesis of Schiff's bases was carried out by the reaction of various derivatives of aniline (0.lM) and aromatic aldehydes (0.lM) in the presence of glacial acetic acid in methanol. The reaction mixture was refluxed for 3-4 hrs, cooled and poured in cold water. The separated solid was filtered off and the residue was recrystallised with methanol.

The melting point and other details are given in table No.1

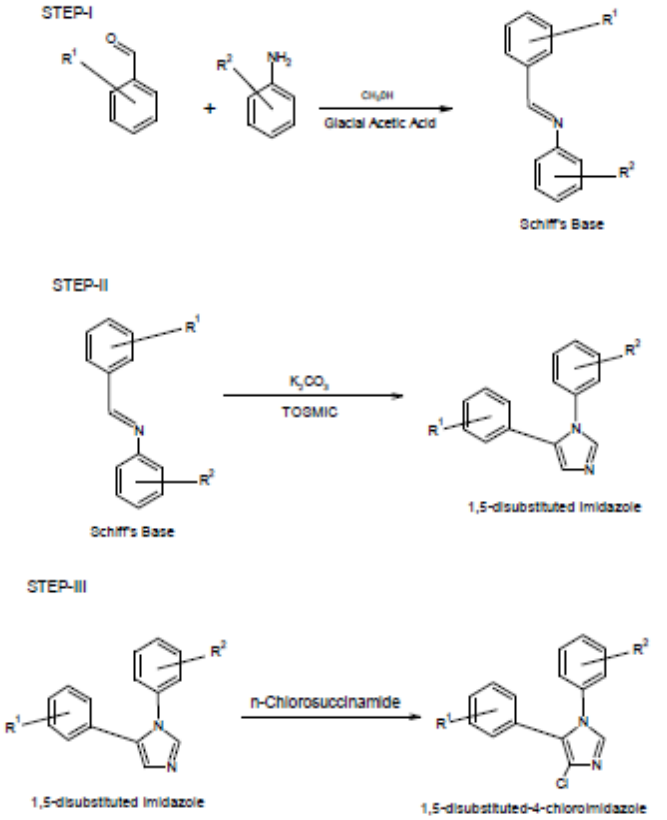


**Table 1. Physical data of the title compounds (1a-f).**

| Compd | R1 | R2 | Mol. Formula (Mol. Wt.) | M.P. (o C) | Yield (%) | Rf- Value |
|---|---|---|---|---|---|---|
| 1a | 4-OH | 2-$CH_3$ | $C_{14}H_{13}N_1O_1$ | 75°C | 60 % | 0.96 |
| 1b | 4-OH | 2,4-$CH_3$ | $C_{15}H_{15}N_1O_1$ | 135°C | 63 % | 0.83 |
| 1c | 4-OH | 2,6-$CH_3$ | $C_{15}H_{15}N_1O_1$ | 173°C | 67 % | 0.85 |
| 1d | 2-$NO_2$ | 2,4-$CH_3$ | $C_{15}H_{14}N_2O_2$ | 75°C | 70 % | 0.67 |
| 1e | 2-$NO_2$ | 2-$CH_3$ | $C_{14}H_{12}N_2O_2$ | 66°C | 65 % | 0.70 |
| 1f | 4-$OCH_3$ | 2,4-$CH_3$ | $C_{16}H_{18}N_1O_1$ | 60°C | 66 % | 0.77 |

**Table 2. Physical data of the title compounds (2a-f).**

| Compd | R1 | R2 | Mol. Formula (Mol. Wt.) | M.P. (o C) | Yield (%) | Rf- Value |
|---|---|---|---|---|---|---|
| 2a | 4-OH | 2-$CH_3$ | $C_{15}H_{14}N_2O_1$ | 70°C | 60 % | 0.6 |
| 2b | 4-OH | 2,4-$CH_3$ | $C_{16}H_{16}N_1O_1$ | 75°C | 66 % | 0.8 |
| 2c | 4-OH | 2,6-$CH_3$ | $C_{16}H_{16}N_2O_1$ | 81°C | 63 % | 0.5 |
| 2d | 2-$NO_2$ | 2,4-$CH_3$ | $C_{16}H_{15}N_3O_2$ | 73°C | 59 % | 0.63 |
| 2e | 2-$NO_2$ | 2-$CH_3$ | $C_{15}H_{13}N_3O_2$ | 85°C | 55 % | 0.1 |
| 2f | 4-$OCH_3$ | 2,4-$CH_3$ | $C_{17}H_{18}N_2O_1$ | 73°C | 60 % | 0.93 |

**Table 3. Physical data of the title compounds (3a-f).**

| Compd | R1 | R2 | Mol. Formula (Mol. Wt.) | M.P. (o C) | Yield (%) | Rf Value |
|---|---|---|---|---|---|---|
| 3a | 4-OH | 2-CH3 | $C_{15}H_{13}N_2O_1Cl$ | 75° C | 59 % | 0.6 |
| 3b | 4-OH | 2,4-CH3 | $C_{16}H_{15}N_2O_1Cl$ | 86° C | 65 % | 0.53 |
| 3c | 4-OH | 2,6-CH3 | $C_{16}H_{15}N_2O_1Cl$ | 73° C | 60 % | 0.5 |
| 3d | 2-NO2 | 2,4-CH3 | $C_{15}H_{14}N_3O_1Cl$ | 80° C | 55 % | 0.7 |
| 3e | 2-NO2 | 2-CH3 | $C_{15}H_{12}N_2O_1Cl$ | 60 ° C | 43 % | 0.4 |
| 3f | 4-OCH3 | 2,4-CH3 | $C_{15}H_{13}N_2O_1Cl$ | 79° C | 56 % | 0.61 |

Solvent of crystallization - ethanol, 'Melting point of the compounds at their decomposition, Solvent system -toluene:ethyl acetate:formic acid (5:4:1, v/v/v) and benzene:acetone (8:2,7:3 v/v) .

**Table 4. Elemental analysis for C, H, N were within ± 0.4% of the theoretical value.**

| Compd | IR (KBr),cm-1 | 1H-NMR (DMSO-d6),δ (ppm) /MS data |
|---|---|---|
| 3a | 3443(CH),1631(C=N),1390(C=C),1313(C-N) | 2.49(3H,s,CH3),7.633(1H,s,OH),7.705-7.805(14H,m,ArH),8.96(1H,s,imidazole) |
| 3b | 2950(CH),1645(C=N),1397(C=C),1316(C-N) | 3.682(3H,s,CH3),7.64(1H,s,Ar),7.69-7.98(14H,m,ArH),8.119(1H,s,imidazole) |
| 3c | 2922(CH),1680(C=N),1388(C=C),1221(C-N) | 2.49(3H,s,CH3),7.533(1H,s,OH),7.705-7.805(14H,m,ArH)8.110(1H,s,imidazole) |
| 3d | 3443(CH),1674(C=N),1390(C=C),1313(C-N) | 2.74-2-90(3H,s,CH3),7.255(14H,m,ArH),8.90(1H,s,imidazole) |
| 3e | 3454(CH),1709(C=N),1371(C=C),1296(C-N) | 2.45-2.75(3H,s,CH3),7.32-7.80(14H,m,ArH),7.831(1H,s,imidazole) |
| 3f | 3416(CH),1637(C=N),1354(C=C),1296(C-N) | 2.71(3H,s,CH3),7.254-7.86(14H,m,ArH),8.96(1H,s,imidazole) |

**Table 5. Anticonvulsant and neurotoxicity screening of the title compounds (3a-f).**

| | *i.p.* injection in mice' | | | |
|---|---|---|---|---|
| Compd. | (MES screen) | | (scPTZ) | |
| | 0.5 h | 4h | 0.5 h | 4h |
| 3a | - | - | 300 | - |
| 3b | 100 | 300 | 300 | 300 |
| 3c | 100 | - | - | - |
| 3d | 100 | 300 | 300 | - |
| 3e | 300 | - | x | x |
| 3f | 100 | 300 | - | 300 |
| Phenytoin | 30 | 30 | | |
| CBZ | 30 | 100 | | |

**Step II- Preparations of Imidazoles.**

• Procedure:

The synthesized Schiff's bases were refluxed with Tosylmethyl isocyanide (172 mmol) in presence of $K_2C0_3$ (229 mmol), methanol (795 ml) and dioxane (340 ml) for 2 hrs. Then the solvent was removed and the residue was dissolved in dichloromethane. The layer was separated and aqueous layer was extracted with dichloromethane. The combined organic phases were dried over magnesium sulphate and concentrated. The crude product was recrystallized which gave respective imidazole.

The melting point and other details are given in table No.2

Step III - Preparation of substituted Chloro-derivative of imidazoles".

Procedure:

The synthesized imidazoles then reacted with N-chlorosuccinamide in presence of chloroform. Refluxed for about 18 hrs. Then the solvent was evaporated and dried using solid magnesium sulphate in dessicator. The crude product was recrystallized using alcohol. The melting point and other details are given in table No.3

**Anticonvulsant activity:**

The anticonvulsant screening of the final compounds was done according to the protocols of National Institute of Neurological Disorders and Stroke, NIH (USA). Swiss albino mice (25-30 g) of either sex were used as experimental animals. The mice were kept under standard conditions at an ambient temperature of 25 ± 20C and allowed free access to food and water except at the time they were brought out of the cage. The tested compounds and standard drugs were suspended in 0.5% (CMC) carbomethoxycellulose water mixture or in PEG (polyethylene glycol).

**Maximal electroshock seizure test (MES)**

Maximal electroshock seizure was elicited with a current intensity of 50 mA, 60Hz for 0.2 s *via* ear clip electrodes, with the doses of test compounds (30, 100, 300 mg/kg). The maximal seizure typically consists of a short period of tonic extension of the bind limbs and a final clonic episode. The abolition of the bind limb tonic extensor component of the seizure due to the drug treatment is defined as anti-convulsant activity (21, 22).

**Subcutaneous pentylenetetrazole induced seizure test (scPTZ)**

The subcutaneous pentylene tetrazole test was performed according to the known protocol (23, 24).This method utilizes pentylenetetrazole (75 mg/1cg) administered as a 0.5% solution subcutaneously in the posterior midline that produces seizures in > 95% of animals. The animals were observed for 30 min. Failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5s du-

ration) was defined as protection.

'Doses of 30, 100 and 300 mg/kg were administered; the figures in the table indicate the minimum dose whereby activity was demonstrated in half or more of the mice (n = 6). 'The animals were examined 0.5 and 4 h after injections. The dash (-) indicates an absence of activity at maximum dose administered (300 mglk.g). The cross (x) indicates not tested. 'Data from references (25, 26). CBZ = carbamazepine.

**RESULTS AND DISCUSSION:**

The new derivatives (3a·f) were injected *i.p.* into mice at doses of 30, 100 and 300 mg/kg for anticonvulsant activity (Table 4). All the compounds except 3a showed anti-MES activity indicative of their ability to prevent seizure spread. Compounds that showed protection against MES model at 100 mg/kg include 3b, 3c, 3d, and 3f. Compounds 3b, 3d, 3f, showed activity both at 0.5 and 4.0 h. Thus, only one compound 3d showing activity at a lower dose of 30 mg/kg seems to be very potent in anticonvulsant MES screening. Some of the compounds showed activity only at 0.5 h, indicating that they have rapid onset and shorter duration of action.

In sc PTZ screening, compounds 3a and 3d showed 100% protection at a dose of 300 mg/kg at 0.5 h. So these compounds have quick onset but for shorter duration of action. Some compounds (3b and3f) were also active after 4.0 h extended period of activity.

**CONCLUSION**

The present work indicates that halo and alkoxy substituted phenyl ring of imidazole moiety have given impetus to the present investigation and showed favored MES activity as compared to hydroxyl or unsubstituted rings. Thus, a number of 1, 5-disubstituted-4-chloro-IH-imidazole derivatives exhibited anticonvulsant activity in MES screen. Some of the above mentioned compounds have shown high degree of protection and obviously may have future commitment

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