Research & Reviews: Journal of Medicinal & Organic Chemistry

Synthesis and Anticonvulsant Activity of Indolo-Imidazolone Hybrid Molecules

Asif Husain[1*], Aftab Ahmad[2], Fahad Al-Abbasi[3], Shah Alam Khan[4]
[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard (Hamdard University), New Delhi-110062, India
[2]Jeddah Community College, King Abdulaziz University, Jeddah 21589, Kingdom of Saudi Arabia
[3]Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah 21589, Kingdom of Saudi Arabia
[4]Department of Pharmacy, Oman Medical College, Muscat, Sultanate of Oman

Research Article

Received date: 02/04/2015
Accepted date: 18/05/2015
Published date: 24/05/2015

***For Correspondence**

Asif Husain, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard University, New Delhi-110 062, India, Tel: +91-11-26059681, 26059688, ext. 5647; Fax: +91-11-26059663;

E-mail: drasifhusain@yahoo.com, ahusain@jamiahamdard.ac.in

Keywords: Indole, imidizalolone, Mice, Anticonvulsants.

SUMMARY

A series of hybrid molecules comprising of indole and imidazolone moieties (4a-g and 5a,b) was synthesized with a view to obtain promising anticonvulsant molecules. Anticonvulsant activity of the title compounds was determined in MES and scPTZ animal models. Neurotoxicity studies were also performed to estimate the undesired effects of the compounds. Majority of the compounds showed appreciable activity against both the animal models whereas compounds 5a and 5b showed good activity and could be considered as leads for further investigations.

INTRODUCTION

A variety of compounds belonging to different chemical classes are used as anticonvulsant drugs [1-3]. The older generation of clinically active antiepileptic drugs are derived from hydantoins, oxazolidinediones, succinimides and glutarimides, and can be defined as a nitrogen containing heterocyclic system having one or two phenyl rings and one or more carbonyl groups [4,5]. Compounds derived from iodole moiety are reported to have important biological activities including potential anticonvulsant activities [6-10]. Literature survey reveals that imidazolones have been a subject of intensive investigations because of their wide spectrum of pharmacological actions including anticonvulsant [11-14]. They have also been utilized as building blocks in the synthesis of heterocyclic compounds of potential pharmaceutical interest [15]. Combining two different bioactive heterocyclic moieties (hybrid compounds) in a single molecule have resulted in compounds with synergistic or increased pharmacological actions [13,14].

There are different types of epilepsy and they are not based on a single underlying mechanism but of multifactorial in origin. Epilepsy is a chronic neurological disorder that is characterized by recurrent unprovoked seizures [16]. It has been postulated that these seizures are transient signs and/or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain [17].

In a significant number of epilepsies genetic or familial disposition also plays an important role in seizure precipitation. Epilepsy is usually controlled but not cured with medication however; over 30-40% of people with epilepsy do not have seizure control even with the best available medications [3,18]. Therefore, new anticonvulsant drugs are still needed and search continues to obtain potential and safer anticonvulsant compounds.

In view of these points and in continuation of our work on indole derivatives [19], it was thought worthwhile to study some new indoles having imidazolinone moiety with an aim to get promising anticonvulsant molecules. Thus a new series of hybrid compounds, indolyl-imidazolone derivatives, was synthesized and tested for their anticonvulsant and neurotoxicity activities.

EXPERIMENTAL

Chemistry

Melting points were determined in open capillary tubes in a liquid paraffin bath and are uncorrected. The IR spectra were recorded in potassium bromide pellets using a Perkin-Elmer 1725X spectrophotometer. ^{1}H-NMR spectra were recorded on Varian E-360 MHz or Bruker spectropsin DPX-300MHz with tetramethylsilane (TMS) as an internal standard. The splitting pattern abbreviations are as follows: s, singlet; br, broad signal; d, doublet; dd, double doublet; t, triplet; m, multiplet. Mass spectra were recorded on a Jeol JMS-D 300 instrument fitted with a JMS 2000 data system at 70 eV. Spectral data are consistent with the assigned structures. Microanalysis of the compounds was done on Perkin-Elmer model 240 analyzer and the values were found in a range of ± 0.4% theoretical value for the element analyzed (C, H, N). The progress of the reactions was monitored on silica gel G plates using iodine vapours as visualizing agent. The starting material, 2-Phenyl-1*H*-indole (1), was prepared by the condensation of acetophenone with phenyl hydrazine HCl in presence of fused zinc by ` Fischer indole reaction "conditions as per the reported method [19]. The product was crystallized from benzene to obtain colorless shining flakes of 2-phenyl-1*H*-indole (1). The the physical constant and spectral data are in good agreement with the reported literature values.

Synthesis of 2-phenyl-1H-indole-3-carbaldehyde (2): It was synthesized from 2-Phenyl-1*H*-indole (1) by using Vilsmeier Haack reaction conditions [19]. Briefly, 25 mL of anhydrous Dimethylformamide (DMF) was stirred at 0^{0}C for 15 min and then 0.01 mol of phosphorous oxychloride was added drop wise and stirred at 0^{0}C for 1 h. 0.05 mol of 1 was dissolved in anhydrous DMF and added drop wise to above formylation complex solution at temperature below 10^{0}C. The solution was warmed to 35-40^{0}C and kept for stirring for 1.5 h. The mixture was diluted with water and refluxed for 10 min. The solution was cooled and kept overnight to obtain the solid product which was recrystalized from ethanol to gave colorless crystals. yield 88%, Rf (Benzene: Petroleum ether, 8:2) 0.31, m.p. 247°C; IR (cm^{-1}, KBr): 3300 (NH), 3037, 1702 (C=O), 1590, 1560; ^{1}H-NMR (DMSO-d_6, ppm): δ 7.33-7.76 (m, 8H, H-4,5,6 of indole + 5H of phenyl), 8.15 (br, 1H, H-7), 9.95 (s, 1H, CHO). MS: m/z 221 (M$^+$), 220 (M-1), 191 (M-CHO), 165 [M-(HCN+H)].

Synthesis of 2-phenyl-4-[(2-phenyl-indolin-3-yl)methylene)oxazol-5(4H)-one (3)[19]: A mixture of compound (2) (0.01 mol, 2.22 g), benzoylglycine (0.01 mol, 1.79 g), fused sodium acetate (0.015 mol, 1.22 g) and acetic anhydride (7.15 mL) was placed in a round bottom flask fitted with a $CaCl_2$ guard tube and heated on a burner with constant shaking. When the reaction mixture liquified completely, it was transferred to a water bath and heated for another 2h. Ethanol (10 mL) was added slowly to the cooled reaction mixture and the contents allowed to stand overnight. A solid which separated out was filtered, washed with hot water and crystallized from acetone; Orange needles, yield 55%, Rf (Toluene: Ethyl acetate: Formic acid, 5:4:1) 0.82, m.p. 210°C; IR (cm^{-1}, KBr): 3294 (NH), 3020, 1625 (C=O), 1631,1568; ^{1}H-NMR (δ) ($CDCl_3$); 7.45-7.66 (m, 13H, H-4,5,6 of indole+10H of two phenyl rings), 7.90 (br, 1H, H-7), 8.13 (s, 1H, olefinic proton). MS: m/z 364 (M$^+$), 231, 220, 165.

General procedure for synthesis of 1,2,4-trisubstituted-1H-imidazol-5(4H)-one (4a-g and 5a-b): Equimolar quantities of (3) (0.01 mol, 3.6 g) and aromatic amine/monoethanolamine/ ethylenediamine (0.01 mol) were fused together in an oil bath for 1h. After cooling to room temperature, crushed ice was added to the reaction mixture to give a solid mass which was crystallized from a solvent/solvent mixture to give TLC pure crystals.

1,2-Diphenyl-4-[(2-phenylindolin-3-yl)methylene]-1H-imidazol-5(4H)b-one (4a): Orange crystals, yield 52%, Rf (Benzene: Petroleum ether, 8:2) 0.35, m.p. 247°C; IR (cm^{-1}, KBr): 3287 (NH), 3041, 1720 (C=O), 1635, 1497; ^{1}H-NMR ($CDCl_3$); δ 7.11-7.64 (m, 14H, H-4,5,6 of indole+10H of two phenyl rings of imidazolone moiety), 7.68-7.73 (m, 5H, phenyl of indole moiety), 7.91 (br, 1H, H-7), 8.20 (s, 1H, olefinic proton). MS: m/z 439 (M$^+$), 231, 180. Anal calcd. for $C_{30}H_{21}N_3O$: C,81.98; H, 4.82; N, 9.56. Found: C, 82.17; H, 4.80; N, 9.60.

1-(4-Chlorophenyl)-2-phenyl-4-[(2-phenylindolin-3-yl)methylene]-1H-imidazol-5(4H)-one (4b): Dark orange crystals, yield 64%, Rf (Benzene: Acetone, 8:2) 0.52, m.p. 190-192°C; IR (cm^{-1}, KBr): 3303 (NH), 3074, 1726 (C=O), 1648, 1590, 745 (C-Cl); ^{1}H-NMR ($CDCl_3$): δ 7.08-7.72 (m, 17H, H-4,5,6 of indole+14H of three phenyl rings), 8.02 (br, 1H, H-7), 8.21 (s, 1H, olefinic proton); MS: m/z 473/475 (isotopic M$^+$), 275, 214; Anal calcd. For $C_{30}H_{20}ClN_3O$: C, 76.02; H, 4.25; N, 8.87. Found: C, 76.40; H, 4.22; 8.81.

1-(2-Chlorophenyl)-2-phenyl-4-[(2-phenylindolin-3-yl)methylene]-1H-imidazol-5(4H)-obne (4c): Orange crystals, yield 46%, Rf (Benzene: Acetone, 8:2) 0.50, m.p. 210 °C; IR (cm^{-1}, KBr): 3275 (NH), 2997, 1731 (C=O), 1665, 1572, 738 (C-Cl); ^{1}H-NMR ($CDCl_3$): δ 7.03-7.68 (m, 17H, H-4,5,6 of indole+14H of three phenyl rings), 7.96 (br, 1H, H-7), 8.18 (s, 1H, olefinic proton); MS: m/z 473/475 (isotopic M$^+$), 275, 91; Anal calcd. For $C_{30}H_{20}ClN_3O$; C, 76.02; H, 4.25; N, 8.87. Found: C, 76.18; H, 4.20; 8.96.

1-(4-Methylphenyl)-2-phenyl-4-[(2-phenylindolin-3-yl)methylene]-1H-imidazol-5(4H)-one (4d): Orange-red shining crystals, yield 78%, Rf (Benzene: Petroleum ether, 8:2) 0.46, m.p. 255°C; IR (cm^{-1}, KBr): 3282 (NH), 3005, 1726 (C=O), 1648, 1592; ^{1}H-NMR ($CDCl_3$): δ 2.43 (s, 3H, CH_3), 6.96-7.53 (m, 17H, H-4,5,6 of indole+14H of three phenyl rings), 7.92 (br, 1H, H-7), 8.06 (s, 1H, olefinic proton); MS: m/z 453 (M^+), 220, 194, 165, 91; Anal calcd. For $C_{31}H_{23}N_3O$: C, 82.10: H, 5.11: N, 9.27. Found C, 82.42; H, 5.00; N, 9.24.

1-(2-Methylphenyl)-2-phenyl-4-[(2-phenylindolin-3-yl)methylene]-1H-imidazol-5(4H)-one (4e): Orange shining crystals, yield 57%, Rf (Benzene: Petroleum ether, 8:2) 0.41, m.p. 272-274 °C; IR (cm^{-1}, KBr): 3290 (NH), 2998, 1734 (C=O), 1637, 1583; ^{1}H-NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3), 6.91-7.60 (m, 17H, H-4,5,6 of indole+14H of three phenyl rings), 7.77 (br, 1H, H-7), 7.93 (s, 1H, olefinic proton); MS: m/z 453(M^+), 194, 165, 91; Anal calcd. for $C_{31}H_{23}N_3O$; C, 82.10: H, 5.11: N, 9.27. Found: C, 82.21; H, 4.90; N, 9.22.

1-(4-Methoxyphenyl)-2-phenyl-4-[(2-phenylindolin-3-yl)methylene]-1H-imidazol-5(4H)-one (4f): Brown crystals, yield 64%, Rf (Benzene: methanol, 8:2) 0.50, m.p. 170°C; IR (cm^{-1}, KBr): 3312 (NH), 2977, 1726 (C=O), 1616; 1493; ^{1}H-NMR (DMSO-d_6): δ 3.83 (s, 3H, OCH_3), 7.05-7.62 (m, 17H, H-4,5,6 of indole+14H of three phenyl rings), 7.91 (br, 1H, H-7), 8.08 (s, 1H, olefinic proton), 8.31. MS: m/z 469(M^+), 231, 210, 77; Anal calcd. For $C_{31}H_{23}N_3O_2$: C, 79.30; H, 4.94; N, 8.95. Found: C, 79.00; H, 4.92; N, 8.92.

1-(2-Methoxyphenyl)-2-phenyl-4-[(2-phenylindolin-3-yl)methylene]-1H-imidazol-5(4H)-one (4g): Buff coloured crystals, yield 75%, Rf (Benzene: methanol, 8:2) 0.38, m.p. 186-188°C; IR (cm^{-1}, KBr): 3278 (NH), 2964, 1730 (C=O), 1632, 1508; ^{1}H-NMR (DMSO-d_6): δ 3.91 (s, 3H, OCH_3), 7.08-7.91 (m, 17H, H-4,5,6 of indole+14H of three phenyl rings), 7.88 (br, 1H, H-7), 8.16 (s, 1H, olefinic proton); MS: m/z 469 (M^+), 231, 220, 210, 193, 165, 77; Anal calcd. For $C_{31}H_{23}N_3O_2$: C, 79.30; H, 4.94; N, 8.95. Found: C, 79.26; H, 4.88; N, 8.97.

1-(2-Hydroxyethyl)-2-phenyl-4-[(2-phenylindolin-3-yl)methylene]-1H-imidazol-5(4H)-one (5a): Yellow crystals, yield 92%, Rf (Toluene: Ethyl acetate: Formic acid, 5:4:1) 0.49, m.p. 204°C; IR (cm^{-1}, KBr): 3290 (NH), 3007, 1725 (C=O), 1627, 1492; ^{1}H-NMR (DMSO-d_6): δ 3.37 (t, 2H, -N-CH_2-), 3.92 (m, 2H, -CH_2-OH), 6.96-7.68 (m, 13H, H-4,5,6 of indole+10H of two phenyl rings), 7.82 (br, 1H, H-7), 8.11 (s, 1H, olefinic proton); MS: m/z 407 (M^+), 231, 206, 165, 148, 77; Anal calcd. For $C_{26}H_{21}N_3O_2$: C, 76.64; H, 5.19; N, 10.31. Found: C, 76.42; H, 5.00; N, 10.22.

1-(2-Aminoethyl)-2-phenyl-4-[(2-phenylindolin-3-yl)methylene]-1H-imidazol-5(4H)-one (5b): Red crystals, yield 50%, *Rf* (Benzene: Petroleum ether, 8:2) 0.42, m.p. 274-276°C; IR (cm^{-1}, KBr): 3476, 3290 (NH), 3007, 1725 (C=O), 1627, 1492; ^{1}H-NMR (DMSO-d_6): δ 3.48 (t, 2H, -N-CH_2-), 3.94 (m, 2H, -CH_2-NH_2), 4.38 (br, 2H, NH_2), 7.13-7.59 (m, 13H, H-4,5,6 of indole+10H of two phenyl rings), 7.85 (br, 1H, H-7), 8.18 (s, 1H, olefinic proton); MS: (m/z) 406 (M^+), 205, 165, 77; Anal calcd. for $C_{26}H_{22}N_4O$: C, 76.83; H, 5.46; N, 13.78. Found: C, 76.62; H, 5.23; N, 13.56.

Pharmacology

Anticonvulsant activity results of the title compounds (4a-g & 5a,b) in mice using MES and scPTZ models are summarized in Table 1 together with the neurotoxicity data. To obtain information about undesired side effects, the highly and moderately active compounds were subjected to neurotoxicity (rotorod) test. Swiss albino mice of either sex weighing 25-30 g were used. The animals were housed at room temperature of 25 ± 2°C under 12 h light/12 h dark cycle with free access to food and water *ad libitum*. The studies were undertaken with prior approval from the Institutional Animal Ethics Committee (IAEC) and utmost care was taken to ensure that the animals were treated in the most humane and acceptable manner. Food and water were withdrawn prior to the experiments. All the compounds were dissolved in polyethylene glycol. The compounds were administered *ip* at doses of 30, 100 and 300 mg/kg to mice. Activity was established using the MES and scPTZ tests according to the protocol by Antiepileptic Drug Development Program (ADD), Epilepsy Branch, National Institute of Health, Bethesda, MD, USA [20,21].

Maximal Electroshock Seizure (MES) test

Mice were prescreened 24 h before by delivering maximal electroshock 50 mA; 60 Hz and 0.2 s duration by means of corneal electrodes. A drop of 0.9% sodium chloride was instilled in each eye prior to the application of electrodes in order to prevent death of the animal. Abolition of hind limb tonic extensor component of the seizure in half or more of the animals is defined as protection.

Subcutaneous Pentylenetetrazole Test (scPTZ)

The scPTZ test utilized a dose of pentylenetetrazole 70 mg/kg. This induced clonic seizures lasting for a period of at least five seconds. The test compounds administered at the three graded doses i.e. 30, 100 and 300 mg/kg ip. At the anticipated time the convulsant was administered subcutaneously. Animals were observed over a period of 30 min. Absence of clonic spasm in half or more of the animals in the observed time period indicated a compound's ability to abolish the effect of pentylenetetrazole on seizure threshold.

Neurotoxicity (NT) evaluation

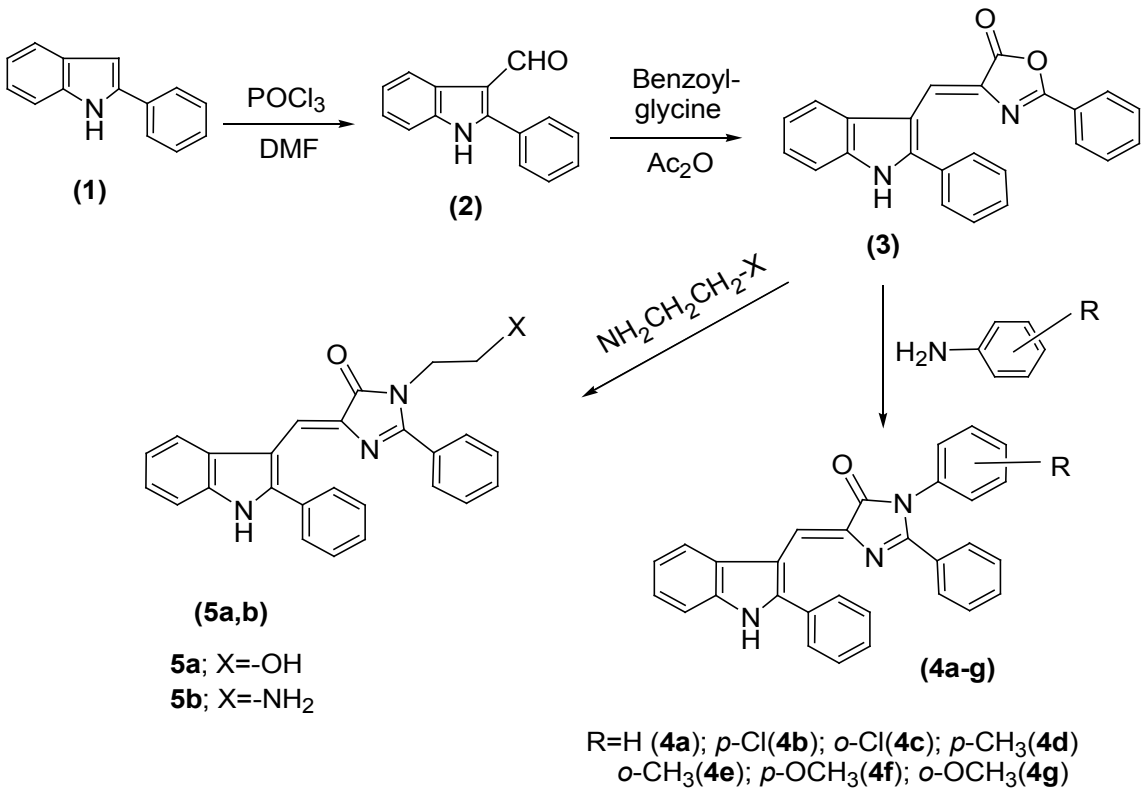
The minimal motor impairment was measured in mice by the rotorod test [22]. The mice were trained to stay on an accelerating rotorod of diameter 3.2 cm that rotates at 10 rpm. Neurotoxicity was indicated by the inability of the animal to maintain equilibration

on the rod for at least one minute in each of the three trials. The dose at which 50% of the animals enabled to balance themselves and fell off the rotating rod was determined.

RESULTS AND DISCUSSION

Chemistry

The protocol for synthesis of indolyl-imidazolones is presented in Scheme 1. The starting compound, 2-Phenyl-1*H*-indole (1), and 2-phenyl-1*H*-indole-3-carbaldehyde (2) were prepared by following reported method [19]. Reaction of compound (2) with benzoyl glycine in acetic anhydride in presence of fused sodium acetate gave 2-phenyl-4-[(2-phenyl-indolin-3-yl)methylene)oxazol-5(4*H*)-one (3). Compound (3) on fusion with aromatic amines/monoethanolamine/ethylenediamine furnished nine 1,2,4-trisubstituted-1*H*-imidazol-5(4*H*)-ones (4a-g and 5a,b). The structures of the synthesized compounds were confirmed on the basis of their elemental analysis and spectral data (IR, ^{1}H NMR and mass) results.



Scheme 1: Protocol for synthesis of indole derivatives.

In the IR spectral data, all the compounds showed peaks each around 1650 (C=O), 3200 (NH stretching) cm^{-1}. In the nuclear magnetic resonance spectra (^{1}H-NMR, ppm), the signals of the respective protons of the compounds were verified on the basis of their chemical shifts and showed characteristic peaks at appropriate δ values. The structure of the compounds was further supported by mass spectral data. Elemental data for C, H and N were found within ± 0.4% of the theoretical values.

Pharmacology

Anticonvulsant activity evaluation of the title compounds were performed against two seizure models viz. MES and scPTZ. All the compounds showed encouraging anticonvulsant activity. Compounds 5a and 5b were found to be highly active against MES test at a dose level 30 mg/kg at 0.5 h time interval indicative of their ability to prevent seizure spread at relatively low dose. Compounds that exhibited moderate protection against MES model at 100 mg/kg include 4d, 4e, 4f and 4g at 0.5 h. Thus majority of the compounds showed encouraging anticonvulsant activity at 0.5 h interval indicating that they have rapid onset and shorter duration of action.

In chemo-shock study, those compounds that exhibited considerable activity in MES test, chosen for scPTZ study. Compounds 4f and 5a were found to be active after 0.5 h of the drug administration at a dose of 100 mg/kg. In neurotoxicity studies, rotorod tests were employed to estimate the undesired effects by the compounds, compound 4d and 5b were slightly neurotoxic and the rest of the compounds did not show neurotoxicity (Table 1).

These data show that the presence of 2-hydroxyethyl or 2-aminoethyl in 1-position of imidazolone ring (5a and 5b) with

potential anticonvulsant activities. Replacement of these groups by substituted-phenyl ring at position-1 of the imidazolinone ring resulted in decreased activity.

Table 1: Anticonvulsant and neurotoxicity data of the title compounds (4a-g and 5a,b).

Compound	MES		scPTZ		Neurotoxicity	
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
4a	300	300	nt	nt	nt	nt
4b	300	(-)	nt	nt	nt	nt
4c	(-)	(-)	nt	nt	nt	nt
4d	100	300	300	300	300	(-)
4e	100	300	(-)	(-)	(-)	(-)
4f	100	100	100	300	(-)	(-)
4g	100	300	300	(-)	(-)	(-)
5a	30	100	100	300	(-)	(-)
5b	30	100	300	(-)	300	(-)
Phenytoin[a]	30	30	(-)	(-)	100	100

MES: Maximal Electoshock Seizure, scPTZ :Subcutaneous Pentylenetetrazole Test, Dose of 30, 100 and 300 mg/kg were administered i.p. in mice. The figures indicate the minimum dose whereby bioactivity was demonstrated in half or more mice. The (-) indicates an absence of activity at maximum dose administered (300 mg/kg). The (nt) indicates not tested. [a]Data from reference[23].

CONCLUSION

In conclusion, the present study shows the anticonvulsant potential of the indolo-imidazolone derivatives (4a-g and 5a,b). Among the newer derivatives two compounds, 1-(2-hydroxyethyl)-2-phenyl-4-[(2-phenylindolin-3-yl)methylene]-1*H*-imidazol-5(4*H*)-one (5a) and 1-(2-aminoethyl)-2-phenyl-4-[(2-phenylindolin-3-yl)methylene]-1*H*-imidazol-5(4*H*)-one (5b) emerged as lead compounds. Presence of 2-hydroxyethyl or 2-aminoethyl in 1-position of imidazolone ring increased the anticonvulsant activity of the indolo-imidazoles. It is conceivable that the derivatives showing significant activity can be further modified to exhibit better potency than the standard drug.

REFERENCES

1. Loscher W, et al. New avenues for anti-epileptic drug discovery and development. Nature Reviews Drug Discovery. 2013; 12: 757-776.
2. Edafiogho IO and Scott KR. Burger's Medicinal Chemistry and Drug Discovery. Jones Wiley & Sons. Inc. (1996).
3. Zhu HL, et al. Medicinal compounds with antiepileptic/anticonvulsant activities. Epilepsia. 2014; 55: 3-16.
4. Malawska B. New anticonvulsant agents. Curr Top Med Chem. 2005; 5: 69-85.
5. Wong MG, et al. Conformational analysis of clinically active anticonvulsant drugs. J Med Chem. 1986; 29: 562-572.
6. Mandour AH, et al. Synthesis, anti-inflammatory, analgesic and anticonvulsant activities of 1,8-dihydro-1-ary1-8-alkyl pyrazolo(3,4-b)indoles. Acta Pharm. 2010; 60: 73-88.
7. Popp FD. Potential anticonvulsants. VIII. Some hydrazones of indole-3-carboxaldehyde J Heterocycl Chem. 1984; 21: 617.
8. Altintas H, et al. Synthesis and evaluation of antimicrobial and anticonvulsant activities of some new 3-[2-(5-aryl-1,3,4-oxadiazol-2-yl/4-carbethoxymethylthiazol-2-yl) imino-4-thiazolidinon-5-ylidene]-5-substituted/nonsubstituted 1H-indole-2-ones and investigation of their structure-activity relationships. Arzneimittelforschung Drug Research. 2006; 56: 239.
9. Husain A., Siddiqui N., Sarafroz M., Khatoon Y., Rasid M., Niyaz Ahmad. Synthesis, Anticonvulsant And Neurotoxicity Screening of Some Novel 1, 2, 4-Trisubstituted-1h-Imidazole Derivatives. Acta Poloniae Pharmaceutica -Drug Research. 2011; 68: 657-663.
10. Sharma V, et al. Biological importance of the indole nucleus in recent years: A comprehensive review J Heterocycl Chem. 2010; 47: 491.
11. Kumar N, et al. Synthesis and Anticonvulsant Activity of Novel Substituted Phenyl Indoloimidazole Derivatives Curr Res Chem. 2011; 3:114.
12. Kononowicz KK, et al. Structure and activity studies on glycine receptor ligands. Part 5. Diphenyl imidazolin-4-one glycinamides Acta Poloniae Pharm.-Drug Research. 1998; 5: 381.
13. Grunwald C et al. Synthesis, pharmacology, and structure-activity relationships of novel imidazolones and pyrrolones as modulators of GABAA receptors. J Med Chem. 2006; 49: 1855.
14. Kalluraya B, et al. Synthesis and biological studies of some imidazolinone derivatives. Boll Chim Farm. 2001; 140: 428.

15. De Luca L. Naturally Occurring and Synthetic Imidazoles: Their Chemistry and Their Biological Activities Curr Med Chem. 2006; 13: 01.

16. Blume W, et al. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. Epilepsia. 2001; 42: 1212.

17. Fisher R, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005; 46: 470.

18. Engel J Jr. Finally, a Randomized, Controlled Trial of Epilepsy Surgery New Eng J Med. 2001; 345-365.

19. Khan MSY. Indole derivatives with anticonvulsant activity against two seizure models Pharmacophore. 2012; 3: 55.

20. Swinyard EA, et al. Franklin, Antiepileptic Drugs. 3rd edn, Raven. Press, New York, 1989; 85.

21. Kupferberg HJ. Antiepileptic drug development program: a cooperative effort of government and industry. Epilepsia. 1989; 30S: 51.

22. Clark CR, et al. Anticonvulsant activity of some 4-aminobenzamides. Med Chem. 1984; 27: 779.

23. White SH, et al. Antiepileptic Drugs 4th edn. Raven Press. New York. 1984; 1995; 99.