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Research Article

Synthesis, characterization and pharmacological evaluation of some new 6(2-Chloro 3,5-substituted phenyl)-1,2,4-triazine derivatives

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Abstract

6(2-Chloro 3,5-substituted phenyl)-1,2,4-triazine derivatives were synthesized and studied for evaluation of anticonvulsant activity by maximal electroshock test and neurotoxicity by rotarod motor test. Some compounds were displayed protection against induced seizures at a dose level 100 mg/kg after 0.5 and 4.0 h and while some compounds were displayed neurotoxicity at highest administered dose (300 mg/kg) after 4.0 h. Screening data revealed that one compound was found most active in series with little CNS depressant effect without neurotoxicity when compared to standard drugs Phenytoin and Carbamazepine.
Keywords: Triazine derivatives, Anticonvulsant activity, Epilepsy, Phenytoin, Carbamazepine.

1. Introduction

Epilepsy is one of most common chronic neurological disorders and epidemiological studies done by WHO, indicated the alarming increase of 2-4 million new cases every year to the already prevailing 50 million epileptic patients worldwide[1-3]. In recent years, several new drugs such as Lamotrigine, and Vigabatrin have been added as therapeutic agents for treatment of epilepsy but in about 30% of patients showed significant resistant against it and moreover, many drugs have dose related toxicity and idiosyncratic side effects[4-5]. So the continued search for safer and more effective new drugs are necessary.

The essential structural features which could be responsible for an interaction with the active site of voltage-gated sodium channels were (i) aryl ring center or the lipophilic group (A), (ii) an electron donor atom (D), (iii) a hydrogen bond acceptor (HA) and (iv) a hydrogen bond donor (HD) units[6-7]. All titled compounds (**5a-j**) comprised the essential pharmacophoric elements (Figure 1) that are necessary for good anticonvulsant activity[8].

Keeping in view of above mentioned pharmacological importance of 1,2,4-triazine compounds, synthesis of 6(2-Chloro 3,5-substituted phenyl)-1,2,4-triazine derivatives has been performed and screened for their anticonvulsant activity.

2. Materials and methods

2.1 Chemistry

All reagents and solvents for synthesis were supplied by S.D. Fine Chemicals (India) and Spectrochem chemicals (India). Silica gel-GF coated aluminum plates were used for monitoring the reactions by using UV light or iodine vapors as visualizing agents and ethyl acetate-n-hexane solvent system was used as TLC mobile phase. Melting points of compounds were determined by using digital melting point apparatus and were uncorrected. The IR spectra were obtained on Nicolet 5PC FTIR spectrophotometer (KBr pellets, λ-max in cm^{-1}) and ^{1}H-NMR spectra

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of compounds were measured on Brucker Model-300 NMR spectrometer using DMSO-d_6 as solvent while Mass spectra of the synthesized compounds were recorded on Jeol SX- 102/DA-6000 spectrometer.

Synthesis of semicarbazones or thiosemicarbazones (3a-j)

Semicarbazones and thiosemicarbazones (**3a-j**) were prepared according to the procedure reported by Hlavac *et al*. and Aanandhi *et al*.[9-10].

Synthesis of 6-(2-amino-3,5-substituted phenyl)-1,2,4-triazines (4a-j)

6-(2-Amino-3,5-substituted phenyl)-1,2,4-triazines (**4a-j**) were prepared according to the procedure reported by Hlavac *et al*. and Eid *et al*.[9,11].

General procedure for synthesis of of 6(3,5-substituted-2-chloro phenyl)-1,2,4-triazine derivatives (5a-j)

6-(2-Amino-3,5-substituted phenyl)-1,2,4-triazine (**4a-j**, 0.8 mmol) was dissolved in 10% sodium hydroxide solution with heating and after cooling, sodium nitrite (0.9 mmol) was added, then resultant mixture was cooled in an ice bath to 5 °C and ice cold mixture of water and hydrochloric acid was added dropwise. After stirring for 15 minutes, the resulting diazonium salt solution was carefully added to a solution of copper (I) chloride (0.5 mmol) in 8 mL hydrochloric acid (37%) and 8 mL water. The mixture was stirred at room temperature overnight. Then precipitated product was filtered, washed with water, dried and recrystallized by ethanol.

6-(2-chlorophenyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**5a**)

Yield: 21 %, R_f: 0.43; m.p.: 264-267 ^{0}C; IR (KBr) (ν_{max} cm^{-1}): 3186 (NH, triazine$_{Amide}$), 3037 (=C-H, Ar), 1706 (C=O, Cyclic$_{Amide}$), 1664 (C=N str); ^{1}H NMR (300 MH$_Z$, DMSO-d_6) δ (ppm): 6.70-7.85 (m, 4H, ArH), 12.23 (s, 1H, =NNH), 12.52 (s, 1H, NH); MS (ES+) *m/z*: 224.6 (M^++1); Anal. calcd for $C_9H_6ClN_3O_2$ (223.0149): C 48.32; H 2.72; N 18.75; found: C 48.34; H 2.71; N 18.77%.

6-(2-chlorophenyl)-3,4-dihydro-3-thioxo-1,2,4-triazin-5(2*H*)-one (**5b**)

Yield: 63 %; R_f: 0.61; m.p.: 163-166 ^{0}C; IR (KBr) (ν_{max} cm^{-1}): 3198 (NH, CONH), 3071 (=C-H, Ar), 1689 (C=O, Cyclic$_{Amide}$), 1654 (C=N str); ^{1}H NMR (300 MH$_Z$, DMSO-d_6) δ (ppm): 7.14-7.63 (m, 4H, ArH), 12.29 (s, 1H, =NNHCS), 13.97 (s, 1H, NH); MS (ES+) *m/z*: 340.5 (M^++1); Anal. calcd for $C_9H_6ClN_3OS$ (238.9920): C 45.12; H 2.50; N 14.55; found: C 45.14; H 2.51; N 14.57%.

6-(2-chloro-5-fluorophenyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**5c**)

Yield: 44 %; R_f: 0.54; m.p.: 273-275^{0}C; IR (KBr) (ν_{max} cm^{-1}): 3248 (NH, triazine$_{Amide}$), 3069 (=C-H, Ar), 1697 (C=O, Cyclic$_{Amide}$), 1673 (C=N str); ^{1}H NMR (300 MH$_Z$, DMSO-d_6) δ (ppm): 7.08-7.58 (m, 3H, ArH), 12.26 (s, 1H, =NNH), 12.73 (s, 1H, NH); MS (ES+) *m/z*: 242.4 (M^++1); Anal. calcd for $C_9H_5ClFN_3O_2$ (241.0054): C 44.72; H 2.05; N 17.42; found: C 44.73; H 2.04; N 17.40%.

6-(2-chloro-5-fluorophenyl)-3,4-dihydro-3-thioxo-1,2,4-triazin-5(2*H*)-one (**5d**)

Yield: 67 %; R_f: 0.68; m.p.: 284-287 ^{0}C; IR (KBr) (ν_{max} cm^{-1}): 3191 (NH, CONH), 3077 (=C-H, Ar), 1705 (C=O, Cyclic$_{Amide}$), 1655 (C=N str); ^{1}H NMR (300 MH$_Z$, DMSO-d_6) δ (ppm): 6.65-7.70 (m, 3H, ArH), 12.48 (s, 1H, =NNHCS), 13.22 (s, 1H, NH); MS (ES+) *m/z* : 258.5 (M^++1); Anal. calcd for $C_9H_5ClFN_3OS$ (256.9826): C 41.93; H 1.98; N 16.28; found: C 41.92; H 1.99; N 16.26%.

6-(2,5-dichlorophenyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**5e**)

Yield: 73 %; R_f: 0.63; m.p.: 171-174^{0}C; IR (KBr) (ν_{max} cm^{-1}): 3207 (NH, triazine$_{Amide}$), 3021 (=C-H, Ar), 1696 (C=O, Cyclic$_{Amide}$), 1648 (C=N str); ^{1}H NMR (300 MH$_Z$, DMSO-d_6) δ (ppm): 7.13-7.91 (m, 3H, ArH), 11.96 (s, 1H, =NNH), 13.27 (s, 1H, NH); MS (ES+) *m/z:* 259.2 (M^++1); Anal. calcd for $C_9H_5Cl_2N_3O_2$ (256.9759): C 41.92; H 1.98; N 16.30; found: C 41.91; H 1.99; N 16.31%.

6-(2,5-dichlorophenyl)-3,4-dihydro-3-thioxo-1,2,4-triazin-5(2*H*)-one (**5f**)

Yield: 28 %; R_f: 0.56; m.p.: 283-285^{0}C; IR (KBr) (ν_{max} cm^{-1}): 3119 (NH, CONH), 3065 (=C-H, Ar), 1714 (C=O, Cyclic$_{Amide}$), 1663 (C=N str); ^{1}H NMR (300 MH$_Z$, DMSO-d_6) δ (ppm): 6.80-7.85 (m, 3H, ArH), 12.87 (s, 1H, =NNHCS), 14.28 (s, 1H, NH); MS (ES+) *m/z* : 275.3 (M^++1); Anal. calcd for $C_9H_5Cl_2N_3OS$ (272.9530): C 39.40; H 1.86; N 15.30; found C 39.41; H 1.84; N 15.32%.

6-(5-bromo-2-chlorophenyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**5g**)
Yield: 49 %; R_f: 0.45; m.p.: 222-225^{0}C; IR (KBr) (ν_{max} cm^{-1}): 3221 (NH, triazine$_{Amide}$), 3050 (=C-H, Ar), 1709 (C=O, Cyclic$_{Amide}$), 1650 (C=N str); ^{1}H NMR (300 MH$_{Z,}$ DMSO-d_6) δ **(**ppm): 6.79-7.45 (m, 3H, ArH), 12.07 (s, 1H, =NNH), 12.39 (s, 1H, NH); MS (ES+) *m/z* : 303.7 (M^++1); Anal. calcd for $C_9H_5BrClN_3O_2$ (300.9254): C 35.70; H 1.65; N 13.92; found: C 35.72; H 1.69; N 13.90%.

6-(5-bromo-2-chlorophenyl)-3,4-dihydro-3-thioxo-1,2,4-triazin-5(2*H*)-one (**5h**)
Yield: 54 %; R_f: 0.59; m.p.: 179-182^{0}C; IR (KBr) (ν_{max} cm^{-1}): 3275 (NH, CONH), 3017 (=C-H, Ar), 1708 (C=O, Cyclic$_{Amide}$), 1627 (C=N str) cm^{-1}; ^{1}H NMR (300 MH$_{Z,}$ DMSO-d_6) δ **(**ppm): 6.91-7.53 (m, 3H, ArH), 12.71 (s, 1H, =NNHCS), 13.51 (s, 1H, NH); MS (ES+) *m/z*: 319.8 (M^++1); Anal. calcd for $C_9H_5BrClN_3OS$ (316.9025): C 33.90; H 1.56; N 25.10; found: C 33.90; H 1.56; N 25.10%.

6-(3,5-dibromo-2-chlorophenyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**5i**)
Yield: 43 %; R_f: 0.75; m.p.: 196-199^{0}C; IR (KBr) (ν_{max} cm^{-1}): 3179 (NH, triazine$_{Amide}$), 3023 (=C-H, Ar), 1716 (C=O, Cyclic$_{Amide}$), 1667 (C=N str); ^{1}H NMR (300 MH$_{Z,}$ DMSO-d_6) δ **(**ppm): 6.96-7.75 (m, 2H, ArH), 11.88 (s, 1H, =NNH), 12.83 (s, 1H, NH); MS (ES+) *m/z*: 382.8 (M^++1); Anal. calcd for $C_9H_4Br_2ClN_3O_2$ (378.8359): C 28.36; H 1.04; N 11.01; found: C 28.38; H 1.03; N 11.04%.

6-(3,5-dibromo-2-chlorophenyl)-3,4-dihydro-3-thioxo-1,2,4-triazin-5(2*H*)-one (**5j**)
Yield: 69 %; R_f: 0.55; m.p.: 185-187^{0}C; IR (KBr) (ν_{max} cm^{-1}): 3214 (NH, CONH), 3025 (=C-H, Ar), 1714 (C=O, Cyclic$_{Amide}$), 1656 (C=N str); ^{1}H NMR (300 MH$_{Z,}$ DMSO-d_6) δ **(**ppm): 7.26-7.91 (m, 2H, ArH), 12.88 (s, 1H, =NNHCS), 13.42 (s, 1H, NH); MS (ES+) *m/z:* 398.6 (M^++1); Anal. calcd for $C_9H_4Br_2ClN_3OS$ (394.813): C 27.18; H 1.04; N 10.60; found: C 27.21; H 1.06; N 10.54%.

2.2 Pharmacology

2.2.1 Anticonvulsant screening

Anticonvulsant activity of synthesized compounds (**5a-j**) was carried out by maximal electroshock seizure test[12-13] in male albino mice (CF-1 strain, 18-25 g), were procured from the central animal house of Dr. Kedar Nath Modi Institute of Pharmacaeutical Education and Research, Ghaziabad, Uttar Pradesh and all animal experiments were performed under the protocol approved by institutional animal ethics committee (IAEC) (838/ac/04/CPCSEA). For MES test, 60 Hz of alternating current (50 mA in mice) was delivered for 0.2 s by ear pinna electrodes and compounds were administered in doses of 30, 100 and 300 mg/kg i.p. injection and then activity was assessed after 0.5 and 4 h intervals, with disappearance of hind limb extensor tonic convulsions were observed as a sign of completion of anticonvulsant property.

2.2.2 Neurotoxicity screening

Motor impairment activity of synthesized compounds was performed in mice by rotarod[14] and these mice were trained on an accelerating rotarod (INCO, Ambala, India) so that they can develop habit to stay on rotating rod (6 rpm). The diameter of rod was 3.2 cm and failure to maintain equilibrium on rotating rod for 1 min represents motor impairment property of compounds.

2.2.3 CNS depression study

CNS depressant effect of compounds were evaluated by forced swim model[15] in which a chamber of 20 cm height and 45 cm diameter containing water level for a height of 15 cm at 25±2 °C was used. Two swim sessions were performed one initial 15 min pre-test, and other 5 min post test session after 24 h. Animals were get an i.p. injection of 100 mg/kg of test samples, 30 min before test session. During 5 min test period, time of immobility i.e. passive floating without struggling, making only those movements which were necessary to keep its head above the surface of water was measured.

2.2.4 Computational study

Calculation of physicochemical parameters of titled compounds

A computational study of titled compounds (**5a-j**) was performed for calculation of ADME properties. Polar surface area[16], molecular volume, number of rotatable bonds, milog P, acceptor atoms and number of hydrogen donor and violations of Lipinski's rule of five[17] were predicted by using Molinspiration online property

calculation toolkit[18]. Absorption (% ABS) was predicted by: % ABS = 109-(0.345 × TPSA)[19]. Druglikeness, drugscore and theoretical toxicity risks were also calculated by using Osiris Property Explorer[20-21].

3. Result and discussion

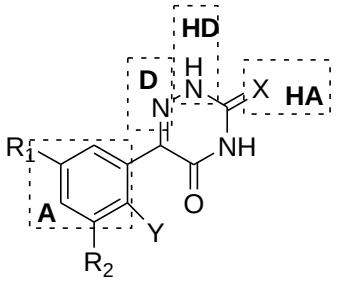
The synthesis of compounds **5a-j** were achieved as depicted in **Scheme 1** and confirmed by FT-IR, ^{1}H-NMR and Mass spectroscopy. Anticonvulsant data of titled compounds (**5a-j**) was summarized in **table 1**, compound **5a** exhibited activity at dose levels of 300 and 100 mg/kg after 0.5 and 4.0 h while compound **5c** showed activity at 300 mg/kg dose level after 0.5 h. Compounds **5e** and **5g** showed protection against induced seizures at dose level 100 mg/kg after 4.0 h.

Compounds **5b**, **5d** and **5f** were found to be inactive. Compounds **5i** and **5j** displayed protection against induced seizures at dose level 100 mg/kg after 0.5 and 4.0 h and compound **5h** was most active compound of series (**5a-j**) showing activity both at 30 and 100 mg/kg after 0.5 and 4.0 h. Compounds **5b**, and **5f** displayed neurotoxicity at highest administered dose level (300 mg/kg) after 4.0 h, while rest compounds were without any neurotoxicity.

Compounds (**5h**, **5i**, and **5j**) having significant anticonvulsant activity also exhibited 46.43, 50.32, and 68.60 % increase in immobility period as compare to control. Carbamazepine (standard drug) showed 58.63 % increase in the immobility time (**Table 2**). At a specific binding site, the putative binding site theory used to postulate the interaction of anticonvulsant compounds, and interaction of molecule with the protein[22-23**]**(**Figure 2**).

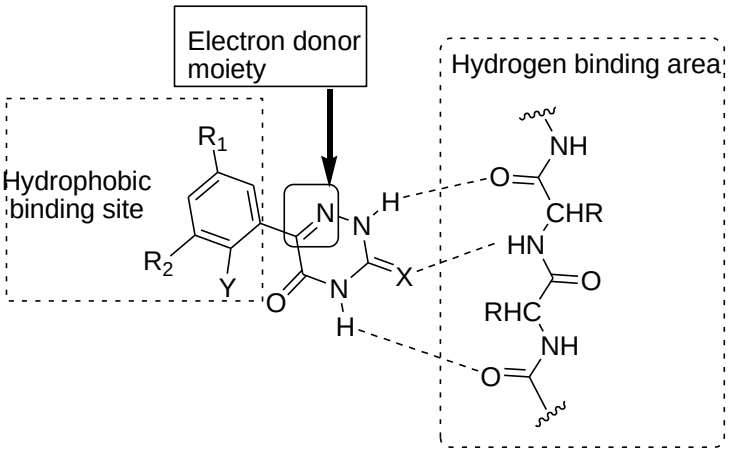
Computational study showed that all titled compounds showed great % ABS ranging from 81.87 to 87.76% (**Table 3**). No compounds violate Lipinski's parameters. Compounds (**5a-j**) with a positive druglikeness (2.44-5.66) and drug-score (0.17-0.87) values were similar or even better than antiepileptic drugs (**Table 4**). Compounds **5b**, **5d**, **5f**, **5h**, and **5j** showed only mutagenic and reproductive effective toxicities while compounds **5a**, **5c**, **5e**, **5g**, and **5i** does not showed any such type of toxic effects.

Figure 1: Structures of proposed general pharmacophore model of the designed compounds.



5a-j (Y= Cl)

Figure 2: Proposed binding interactions of the designed compounds using putative binding site theory.



5a-j (Y= Cl)

Scheme 1 for synthesis of compounds 5a-j.

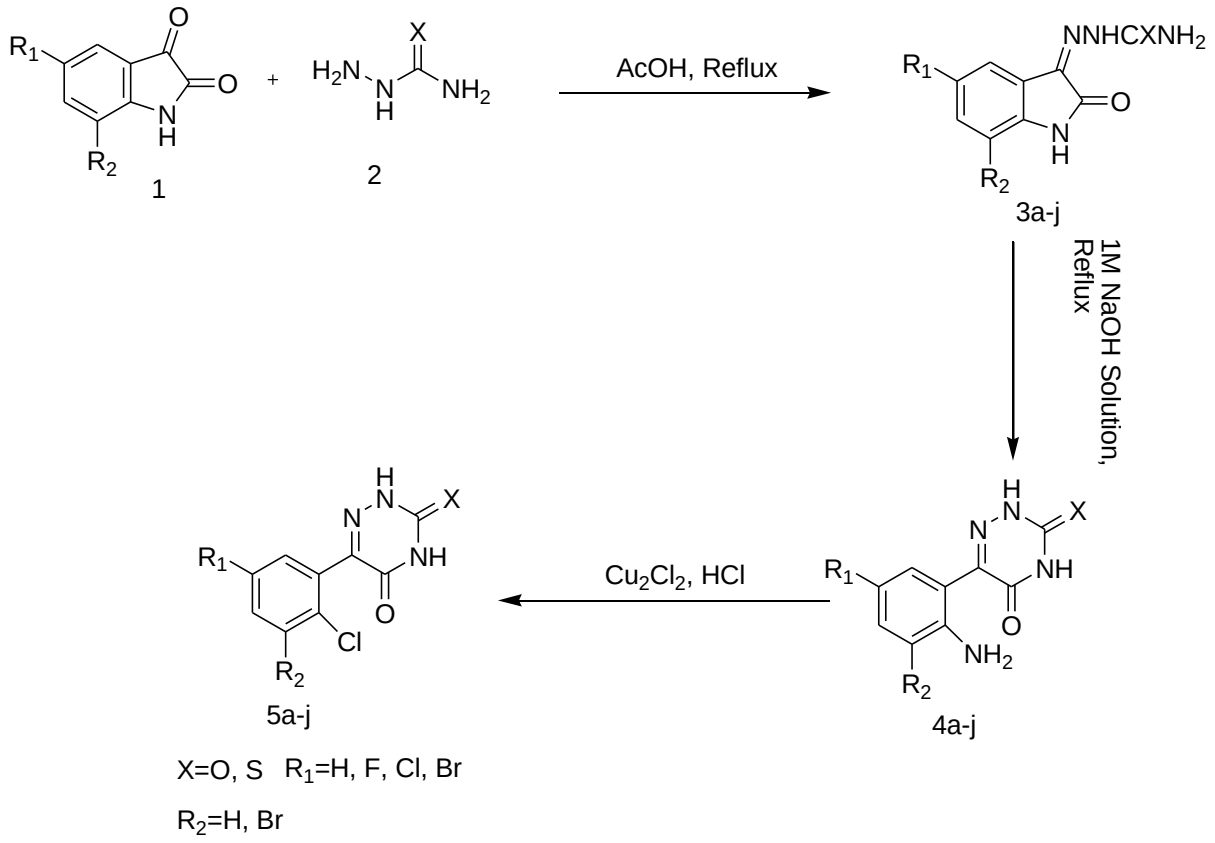


Table 1: Anticonvulsant and motor impairment screening of synthesized compounds (5a-j) using maximal electroshock seizure and rotarod models

Code No.	R_1	R_2	X	MES[a]		Motor Impairment[a]	
				0.5h	4.0h	0.5 h	4.0 h
5a	H	H	O	300	100	-	-
5b	H	H	S	-	-	-	300
5c	F	H	O	300	-	-	-
5d	F	H	S	-	-	-	-
5e	Cl	H	O	-	100	-	-
5f	Cl	H	S	-	-	-	300
5g	Br	H	O	-	100	-	-
5h	Br	H	S	30	100	-	-
5i	Br	Br	O	100	100	-	-
5j	Br	Br	S	100	100	-	-
Control				-	-	-	-
Phenytoin[b]				30	30	100	100
Carbamazepine[b]				30	100	100	300

[a]Doses of 30, 100, and 300 mg/kg were administered to albino mice through intra-peritoneal (i.p.) route. The numbers in the table indicate the minimum dose whereby bioactivity was displayed in half or more of mice. The animals were examined 0.5 and 4 h after the drug administration. The dash (-) indicates an absence of activity at maximum dose administered (300 mg/kg). [b]Data for Carbamazepine and Phenytoin, used as standard drugs, were obtained from the references[4, 24].

Table 2: Data of CNS depressant activity of the selected compounds (5h, 5i, and 5j) performed in mice using forced swim test.

Compound	Duration of immobility(sec) (mean ± SEM)	% Increased of immobility
5h	77.67±1.53	46.43
5i	79.73±1.12	50.32
5j	89.43±2.27	68.60
Carbamazepine	84.14±1.33	58.63
Control	53.04±2.47	-

The compounds were tested at a dose of 100 mg/kg (i.p.). Each value represents the mean ± SEM of six mice. The CNS depressant effect was compared with respect to standard drug. *$p < 0.0001$. Data was analyzed by unpaired student's *t* test.

Table 3: Pharmacokinetic parameters important for good oral bioavailability of compounds 5a-j.

Code No.	R_1	R_2	X	% ABS	TPSA (A^2)	n-ROTB	MW	MV	miLogP	n-OHNH donors	n-ON acceptors	Lipinski's violations
Rule				-	-	-	<500	-	<5	<5	<10	<1
5a	H	H	O	81.877	78.616	1	223.619	172.77	1.091	2	5	0
5b	H	H	S	87.766	61.545	1	239.687	181.648	1.433	2	4	0
5c	F	H	O	81.877	78.616	1	241.609	177.701	1.23	2	5	0
5d	F	H	S	87.766	61.545	1	257.677	186.579	1.573	2	4	0
5e	Cl	H	O	81.877	78.616	1	258.064	186.306	1.745	2	5	0
5f	Cl	H	S	87.766	61.545	1	274.132	195.184	2.087	2	4	0
5g	Br	H	O	81.877	78.616	1	302.515	190.655	1.876	2	5	0
5h	Br	H	S	87.766	61.545	1	318.583	199.533	2.218	2	4	0
5i	Br	Br	O	81.877	78.616	1	381.411	208.54	2.613	2	5	0
5j	Br	Br	S	87.766	61.545	1	397.479	217.419	2.955	2	4	0
Lamotrigine				77.70	90.722	1	256.096	192.632	2.040	4	5	0
Phenytoin				88.92	58.196	2	252.273	223.886	2.178	2	4	0
Carbamazepine				92.43	48.028	0	236.274	215.083	2.840	2	3	0

% ABS, percentage of absorption, TPSA, topological polar surface area, n-ROTB, number of rotatable bonds, MW, molecular weight, MV, molecular volume, n-OHNH, number of hydrogen bond donors, n-ON, number of hydrogen bond acceptors, miLogP, logarithm of compound partition coefficient between n-octanol and water.

Table 4: Druglikeness, drug-score and in silico toxicity risks of titled compounds 5a-j.

Code No.	R_1	R_2	X	Drug likeness	Drug-Score	Mutagenic	Tumorigenic	Irritant	Reproductive Effective
5a	H	H	O	5.66	0.87	1	1	1	1
5b	H	H	S	4.61	0.31	3	1	1	3
5c	F	H	O	3.97	0.83	1	1	1	1
5d	F	H	S	2.89	0.29	3	1	1	3
5e	Cl	H	O	5.66	0.28	1	3	1	3
5f	Cl	H	S	4.60	0.17	3	3	1	3
5g	Br	H	O	3.52	0.75	1	1	1	1
5h	Br	H	S	2.44	0.26	3	1	1	3
5i	Br	Br	O	3.92	0.29	3	1	1	3
5j	Br	Br	S	2.87	0.21	3	1	1	3
Phenytoin				4.20	0.19	3	3	1	3
Carbamazepine				2.80	0.23	3	1	1	3
Lamotrigine				-0.88	0.51	1	1	1	1

Toxic (3), Less Toxic (2), No Toxic (1)

4. Conclusion

It was revealed from present study that anticonvulsant activity of tested compounds may be due to presence of adequate halogens i.e. F, Cl and Br which provides adequate lipophilicity and binding at receptor site. No compounds were violate Lipinski's parameters and also fit as potentially promising agents for epilepsy therapy. Currently, much attention has been focused on 6(2-Chloro 3,5-substituted phenyl)-1,2,4-triazine ring, which has useful structure for molecular exploration and for development of bioactive molecules and hence would become a useful tool in treatment of epilepsy in near future.

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