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Design and synthesis of 2-(1, 3-dioxoisoindolin-2-yl)-*N*-(4-oxo-2-substitutedthiazolidin-3-yl) acetamide derivatives as potential anticonvulsant agents

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ABSTRACT

A series of 2-(1,3-dioxoisoindolin-2-yl)-*N*-(4-oxo-2-substitutedthiazolidin-3-yl) acetamide derivatives were designed and synthesized using appropriate synthetic route, keeping in view the structural requirement of pharmacophore and evaluated for anticonvulsant activity and CNS depressant activities in mice. The synthesized derivatives were examined in the maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (sc-PTZ) induced seizure and neurotoxicity screens and were also evaluated for behavioral activity. All the tested compounds showed protection against MES test indicative of their ability to inhibit the seizure spread.

1. Introduction

Epilepsy, being one of the most common and serious neurological disorder is characterized by recurrent seizures which results from a temporary electrical disturbance of the brain due to an imbalance between excitatory and inhibitory neurotransmitters. About one third of the patients do not respond well to current multiple drug therapy [1,2]. Phenytoin, carbamazepine, lamotrigine, sulfamate and topiramate are recent antiepileptic drugs which have been clinically effective against different types of seizures [3].

The improvement in the treatment of epilepsy over the past decade is mainly associated with the development of new antiepileptic drugs, taking advantage of the pharmacophoric requirement specifically on a single target [4–6]. In the present work, our objective was to design and synthesize new compounds having dioxoindolin moiety coupled with thiazolidinone nucleus via amide linkage with the hope to get compounds with enhanced bioactivity. Thus, novel, 2-(1,3-dioxoisoindolin-2-yl)-*N*-(4-oxo-2-substitutedthiazolidin-3-yl) acetamide derivatives were synthesized as antiepileptic drugs that shares similar mode of action on neuronal sodium channels as phenytoin [7]. Our work also highlights the distance mapping and matching of the synthesized compounds with the help of the given model. All the synthesized titled compounds comprised of the essential pharmacophoric elements that are necessary for good anticonvulsant activity as suggested by Unverferth et al. [8], which are indicated by rectangles in Fig. 1. The essential structural features which could be responsible for an interaction with the active site of voltage-gated sodium channels were a hydrophobic unit (R), an electron donor (D) group, and a hydrogen donor/acceptor (HBD) unit [9]. Microwave assisted synthesis of title compounds was carried out as it gives reduced pollution, reduced reaction time, increased reaction rate; yield enhancement, cleaner and greener eco friendly synthetic protocol [10].

2. Chemistry

The synthetic protocols employed for the synthesis of 2-(1,3-dioxoisoindolin-2-yl)-*N*-(4-oxo-2-substitutedthiazolidin-3-yl) ace-tamide derivatives **6**(**a**–**p**) are presented in Scheme 1. The 2-(1,3-dioxoisoindolin-2-yl) acetohydrazides were obtained via reaction of 2-(1,3-dioxoisoindolin-2-yl) acetic acid with hydrazine hydrate in presence of *N*,*N*′- dicyclohexyl carbodiimide (DCC).

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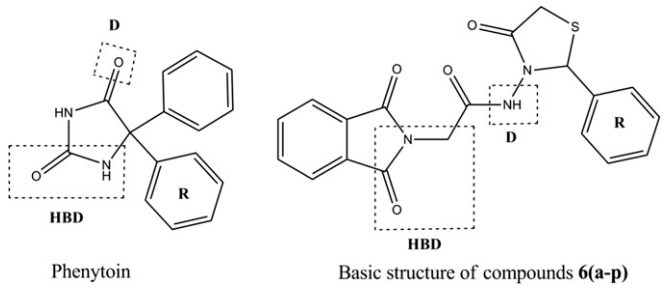


Fig. 1. Structures of sodium channel modulators. The essential structure elements for the pharmacophore of Unverferth are indicated by rectangles.

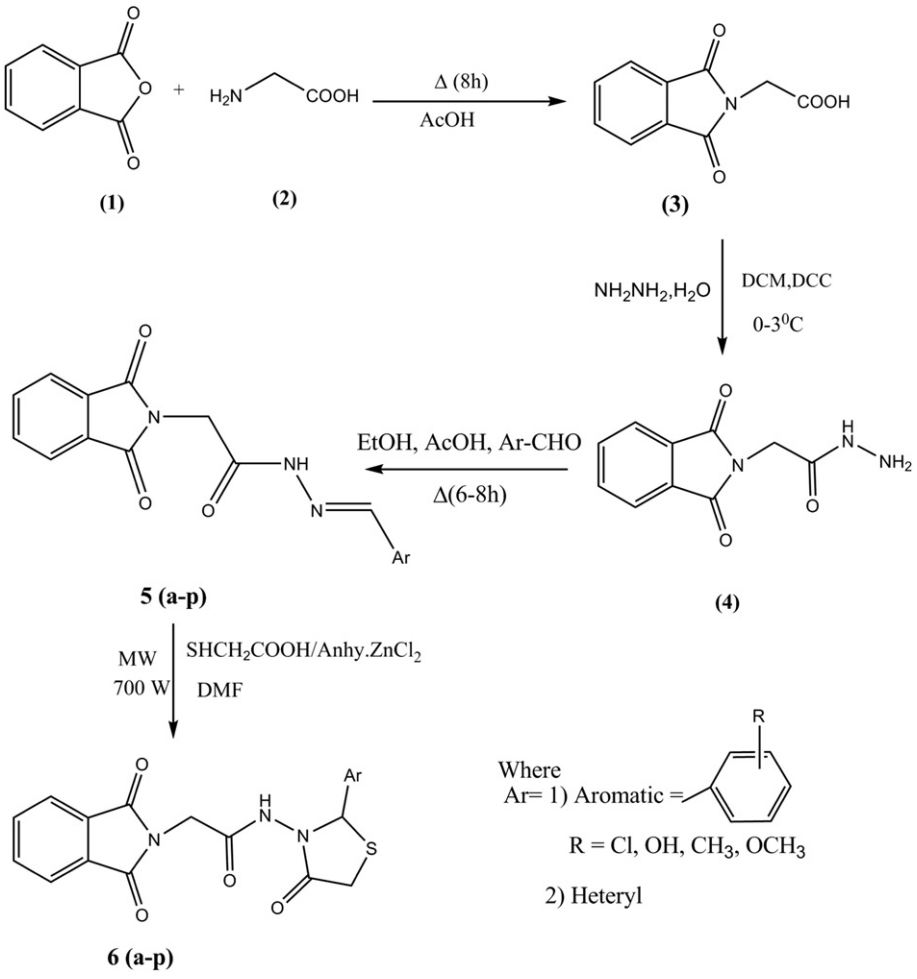
The 2-(1,3-dioxoisoindolin-2-yl) acetohydrazide when reacted with various substituted aromatic/heteryl aldehydes gave N-substituted benzylidene/methylene-2-(1,3-dioxo isoindolin-2-yl) acetohydrazides **5**(**a**–**p**), which upon reaction with thioglycolic acid under microwave irradiation in DMF for about 10–12 min (700 W), gave 2-(1,3-dioxoisoindolin-2-yl)-*N*-(4-oxo-2-substitutedthiazolidin-3-yl) acetamide derivatives **6**(**a**–**p**). The purity of the synthesized compounds was checked by TLC and melting points were determined in open capillary tubes on a Buchi 530 melting point apparatus and are uncorrected. The assignments of the structures were based on elemental and spectral data. The physical data of the synthesized compounds are presented in Table 1. The data obtained from IR, ^{1}H NMR, Mass and elemental analysis data confirmed the proposed structures.

3. Pharmacology

The new derivatives obtained by the above mentioned procedure were undertaken for the anticonvulsant studies by the anticonvulsant drug development (ADD) program protocol [11,12]. The profile of anticonvulsant activity was established after i.p. injections into mice and evaluated in the maximal electroshock (MES), subcutaneous pentylenetetrazole (sc-PTZ) and neurotoxicity screens, using doses of 30, 100 and 300 mg/kg at 0.5 h and 4 h time intervals. These data are presented in Table 2. The compounds were also evaluated for their CNS behavioral activity in mice using actophotometer at dose level of 30 mg/kg at 0.5 h and 4 h time intervals. The results are presented in Table 3.

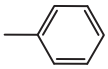
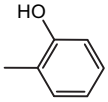
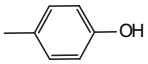
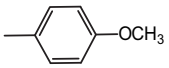
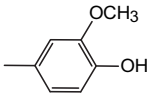
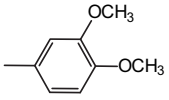
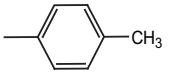
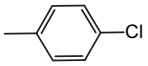
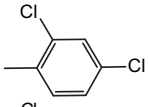
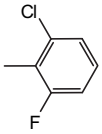
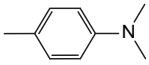
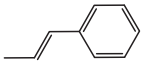
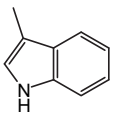
4. Computational parameter

The pharmacophore pattern studies in which distance between the various groups postulated as essential for anticonvulsant activity were done on the 3D optimized structures using ACD freeware 3D viewer 8.04 version. The results are presented in Table 4. Along with this *C* log *P* for synthesized compounds were calculated by using Pallas demo version 3112 which was then



Scheme 1. Synthetic protocol for titled compounds.

Table 1
Physical data 2-(1,3-Dioxoisoindolin-2-yl)-*N*-(4-oxo-2-substitutedthiazolidin-3-yl) acetamide derivatives **6**(**a**–**p**).

Compounds	Ar	Yield (%)	Melting point (o C)	Molecular formula (M.W.)	R_f
6a		87	218–220	$C_{19}H_{15}N_3O_4S$ (381)	0.62
6b		88	234–238	$C_{19}H_{15}N_3O_5S$ (397)	0.61
6c		95	198–200	$C_{19}H_{15}N_3O_5S$ (397)	0.65
6d		85	290–292	$C_{20}H_{17}N_3O_5S$ (411)	0.66
6e		92	268–270	$C_{20}H_{17}N_3O_6S$ (427)	0.55
6f		87	284–286	$C_{21}H_{19}N_3O_6S$ (441)	0.68
6g		92	244–246	$C_{20}H_{17}N_3O_4S$ (395)	0.56
6h		95	250–252	$C_{19}H_{14}ClN_3O_4S$ (415)	0.65
6i		94	318–320	$C_{19}H_{13}Cl_2N_3O_4S$ (449)	0.64
6j		91	294–296	$C_{19}H_{13}ClFN_3O_4S$ (433)	0.44
6k		89	262–264	$C_{21}H_{20}N_4O_4S$ (424)	0.59
6l		93	256–258	$C_{21}H_{17}N_3O_4S$ (407)	0.43
6m		84	232–234	$C_{17}H_{13}N_3O_5S$ (371)	0.46
6n		90	190–192	$C_{17}H_{13}N_3OS_2$ (387)	0.54
6o		87	236–238	$C_{18}H_{14}N_4O_4S$ (382)	0.55
6p		85	270–272	$C_{21}H_{16}N_4O_4S$ (420)	0.62

Solvent of re crystallization was ethanol; Eluants used in TLC were petroleum benzene: methanol (8:2) for all compounds.

Table 2
Anticonvulsant and neurotoxicity screening of compounds.

Compounds	MES screen		Sc PTZ screen		Neurotoxicity screen	
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
6a	100	100	100	300	30	30
6b	100	100	–	–	100	100
6c	30	100	–	–	300	300
6d	100	100	–	–	300	300
6e	30	100	300	300	–	–
6f	300	300	100	300	–	–
6g	30	30	100	300	–	–
6h	300	300	300	–	300	–
6i	–	30	100	100	300	–
6j	100	100	300	300	–	–
6k	300	300	300	300	–	–
6l	300	300	300	–	–	–
6m	100	–	–	–	–	–
6n	–	100	–	–	–	100
6o	100	300	–	–	–	–
6p	300	300	300	–	–	–
Phenytoin	30	30	×	×	100	100
Sodium Valproate	×	×	300	–	–	–

a Doses of 30, 100 and 300 mg/kg of the compound were administered and the protection and neurotoxicity measured after 0.5 and 4 h. The figures indicate the minimal dose required to cause protection or neurotoxicity in 50% or more of the animals. The dash (–) indicates the absence of anticonvulsant activity or neurotoxicity. × denotes not tested.

compared with the experimental log *P* data of these compounds. The results are presented in Table 5.

5. Results and discussions

A series of novel 2-(1,3-dioxoisoindolin-2-yl)-*N*-(4-oxo-2-substitutedthiazolidin-3-yl) acetamide derivatives **6**(**a**–**p**) were obtained under microwave irradiation in good yield and require shorter reaction times, the solvent used in conventional synthesis of thiazolidinones is benzene, which is carcinogenic and hence avoided in present investigation. All the synthesized compounds were evaluated for anticonvulsant activity and have shown promising anticonvulsant activities.

5.1. Anticonvulsant activity

All the tested compounds showed protection against MES test indicative of their ability to inhibit the seizure spread. Compounds **6c**, **6e** and **6g** showed protection against the MES model at 30 mg/kg and compounds **6a**, **6b**, **6d**, **6j**, **6m** and **6o** showed protection at dose level of 100 mg/kg while compounds **6f**, **6h**, **6k**, **6l** and **6p** showed protection at dose level of 300 mg/kg after 0.5 h. Compounds **6g** and **6i** showed protection against the MES model at 30 mg/kg and compounds **6a**, **6b**, **6c**, **6d**, **6e**, **6j** and **6n** showed protection at dose level of 100 mg/kg while compounds **6f**, **6h**, **6k**, **6l**, **6o** and **6p** showed protection at dose level of 300 mg/kg at 4 h. The compound **6g** showed activity both at 0.5 h and 4 h period at dose level of 30 mg/kg indicating the compound to be more effective and long acting. Similarly compound **6c** and **6e** were also found to be more effective but short acting as 4 h protection requires the dose of 100 mg/kg. The compounds **6a**, **6b**, **6d** and **6j** showed activity both at 0.5 h and 4 h period at dose level of 100 mg/kg indicating that compounds are effective and long acting. The compounds **6f**, **6h**, **6k**, **6l** and **6p** showed activity both at 0.5 h and 4 h period at dose level of 300 mg/kg indicating that compounds are less potent and long acting. The compounds **6i** showed activity at dose level of 30 mg/kg and **6n** showed activity at dose level of 100 mg/kg only at 4 h indicating that compounds have sustained release activity. The compound **6m** showed activity only at 0.5 h indicating that compound has rapid onset and shorter duration of action.

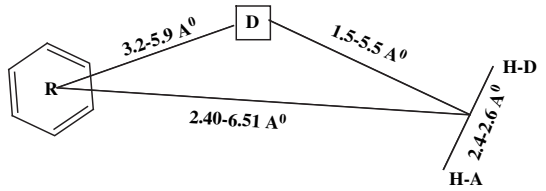
Most of the compounds were found to be active in the sc PTZ test, a test used to identify compounds that elevate seizure threshold. The Compounds **6a**, **6f**, **6g** and **6i** showed activity at a dose of 100 mg/kg while, compounds **6e**, **6h**, **6j**, **6k**, **6l**, and **6p** showed activity at dose of 300 mg/kg at 0.5 h. The Compounds **6i** showed activity at a dose of 100 mg/kg while **6a**, **6e**, **6f**, **6g**, **6j** and **6k** showed activity at dose of 300 mg/kg at 4 h. No compounds were found active at dose level of 30 mg/kg. The compounds **6e**, **6j** and **6k** have shown activity at 300 mg/kg at 0.5 h and 4 h indicating that these compounds have moderate activity. The compounds **6a**, **6f** and **6g** were found to be potent with rapid onset and intermediate duration of action. The compounds **6b**, **6c**, **6d**, **6m**, **6n** and **6o** showed absence of activity at all dose level while, compounds **6h**, **6l** and **6p** found to be active with short duration of action.

Table 3
Behavioral study of compounds using Actophotometer.

Compounds	Activity score using actophotometer			% Decrease in locomotor activity	
	Control (24 h before)	Post treatment[a]		0.5 h	4 h
		0.5 h	4 h		
6a	116.40 ± 7.24	58.20 ± 9.37	41.60 ± 10.67	50.00(↓)	64.26(↓)
6b	188.36 ± 4.28	126.88 ± 5.46	118.82 ± 6.34	32.63(↓)	36.91(↓)
6c	120.68 ± 2.72	38.16 ± 8.84	68.37 ± 12.34	68.37(↓)	43.34(↓)
6d	327.17 ± 12.37	316.51 ± 6.60	278.30 ± 10.18	3.25(↓)	14.93(↓)
6e	160.74 ± 1.36	99.44 ± 9.94	148.98 ± 13.24	38.13(↓)	7.31(↓)
6f	167.29 ± 2.25	133.41 ± 3.64	120.54 ± 4.84	20.25(↓)	27.95(↓)
6g	118.20 ± 5.28	87.54 ± 12.24	37.64 ± 6.68	25.94(↓)	68.16(↓)
6h	112.20 ± 5.73	55.16 ± 18.34NS	94.10 ± 7.46	50.83(↓)	16.13(↓)
6i	165.88 ± 7.33	60.15 ± 2.64	123.49 ± 8.78	63.73(↓)	25.55(↓)
6j	144.32 ± 1.60	126.98 ± 5.64	100.75 ± 5.52	12.01(↓)	30.18(↓)
6k	289.00 ± 11.16	260.71 ± 13.54NS	161.58 ± 3.24	9.78(↓)	44.08(↓)
6l	267.50 ± 14.85	252.34 ± 9.55	89.59 ± 8.88	5.66(↓)	66.50(↓)
6m	262.00 ± 19.41NS	248.51 ± 6.35	231.48 ± 9.82	5.14(↓)	11.64(↓)
6n	142.22 ± 3.45	52.56 ± 4.87	40.20 ± 5.46	63.04(↓)	71.73(↓)
6o	148.37 ± 0.92	121.61 ± 5.32	112.74 ± 5.58	18.03(↓)	24.01(↓)
6p	122.88 ± 3.26	110.65 ± 10.25	91.12 ± 6.64	9.95(↓)	25.84(↓)
Phenytoin	119.33 ± 17.43	78.87 ± 16.66	97.17 ± 13.49	33.90(↓)	18.57(↓)
Diazepam[b]	210.43 ± 10.22	56.42 ± 13.30	119.23 ± 5.98	73.18(↓)	43.33(↓)

[a] Each value represents the mean ± SEM significantly different from the control at $p < 0.05$, NS denotes not significant at $p < 0.05$ (Student's *t* test), locomotor activity score was measured for 10 min.
[b] The compound was tested at dose level of 4 mg/kg (i. p.).

Table 4
Distance range between the essential structure elements R, D & HBD.



Compounds	R-HD	R-D	D-HBD
Phenytoin	3.58	3.77	2.21
Carbamazepine	5.09	4.87	4.06
Lamotrigine	6.44	3.41	4.45
Diazepam	4.79	4.82	1.49
Lead moiety of **6**(**a**–**p**)	6.18	5.62	3.83

Distances calculated for 3D optimized structures using ACD freeware 3D viewer 8.04 version.

In neurotoxicity screening, compounds **6e**, **6f**, **6g**, **6j**, **6k**, **6l**, **6m**, **6o** and **6p** did not show neurotoxicity in the maximum administered dose (300 mg/kg). The compounds **6a** showed neurotoxicity at dose 30 mg/kg, while **6b** showed neurotoxicity at dose 100 mg/kg. The remaining compounds were found to be less neurotoxic as compared to phenytoin.

In behavioral activity using actophotometer, the compounds **6b**, **6d**, **6f**, **6g**, **6j**, **6k**, **6l**, **6m**, **6o** and **6p** showed no behavioral despair effect when compared to phenytoin at 0.5 h. The compounds **6e**, **6d**, **6h** and **6m** showed no behavioral despair effect when compared to phenytoin at 4 h. Compounds **6e** and **6h** showed decreased locomotor activity in the 0.5 h interval but no significant effect on behavioral despair was observed during 4 h time period when compared to phenytoin. All other compounds were found to decrease behavioral activity of the animals when compared to phenytoin. All compounds showed no behavioral despair effect when compared to diazepam at 0.5 h. The compounds **6b**, **6d**, **6e**, **6f**, **6h**, **6i**, **6j**, **6m**, **6o** and **6p** showed no behavioral despair effect when compared to diazepam at 4 h. All other compounds were found to show decreasing behavioral activity of the animals when compared to diazepam. From experimental Log *P* determination it was observed that most of the compounds are having Log *P* values between 1.5 and 2.7, sufficient value for crossing of BBB, therefore these compounds are showing promising anticonvulsant activity.

Table 5
C log *P* for synthesized compounds.

Compounds	Experimental Log *P*	Theoretical Log $P_{combined}$ value
6a	2.23	1.62
6b	1.46	1.23
6c	2.40	1.23
6d	1.97	1.49
6e	1.31	1.10
6f	2.78	1.37
6g	2.97	2.11
6h	3.21	2.18
6i	2.54	2.73
6j	3.79	2.33
6k	2.84	1.90
6l	3.65	2.13
6m	1.13	0.23
6n	2.15	1.60
6o	1.25	0.28
6p	1.59	1.16

Theoretical Log $P_{combined}$ was calculated by using Pallas demo version 3112.

5.1.1. SAR

As observed through data analysis, the compound with electron releasing groups are highly effective but compound **6g** with p–CH_3 substitution at aromatic ring was found to be most effective in both the models and also possess long duration of action. Thus overall conclusion suggests that the whole moiety can be interpreted as the lead molecule from this data. In sc-PTZ induced seizers among the tested compounds **6i**, having dichloro phenyl substituent was found to be highly effective having rapid onset and long duration of action. When aromatic ring was replaced by heterocyclic rings like furan, thiophene, pyridine and indol, the anticonvulsant activity was altered in both the models and has exhibited less significant effect. Compounds having –OCH_3, –OH, substituents on aromatic ring have shown better activity.

During the study most of the synthesized derivatives were more effective in the MES test, and the MES test is known to be sensitive to sodium channel inhibitors (e.g. Phenytoin), which suggested that tested compounds may inhibit voltage-gated ion channels (particularly sodium channels).

5.2. Computational parameter

5.2.1. Distance mapping

The present work involves the correlation of the structural requirement of well known and structurally different anticonvulsant compounds with the titled compounds. The presence of at least one aryl (R) unit, one or two electron donor (D) atoms, and a hydrogen bond acceptor/donor unit (HBD) are structural requirement for anticonvulsant activity. The essential structural features which could be responsible for an interaction with the active site of voltage-gated sodium channels were a hydrophobic unit (R), an electron donor (D) group, and a hydrogen donor/acceptor (HBD) unit. In the present study, four well-known and structurally different compounds with anticonvulsant activity i.e. phenytoin, carbamazepine, lamotrigine and diazepam were selected. In an initial study, calculations on the basis of molecular mechanics, with the force field based on CHARMM parameterization [13] were performed to obtain an overview on their minimum energy conformation. Table 4 shows the distances between the various groups postulated as essential for anticonvulsant action. Now it was interesting to evaluate whether the synthesized compounds 2-(1,3-dioxoisoindolin-2-yl)-*N*-(4-oxo-2-substitutedthiazolidin-3-yl) acetamide **6**(**a**–**p**) reflected the conditions of the derived pharmacophore model. Our analysis of the distance relationship showed that the titled compounds fulfill the essential demands of pharmacophore when compared with other standard anticonvulsants.

5.2.2. Log P determination

Some of the active compounds showed dependence of biological activity on lipophilic character in a congeneric series. For several classes of CVS active substances, Hansch and Leo found that BBB penetration is optimal when the log *P* values are in the range of 1.5–2.7, with the mean value of 2.1 [14,15]. In this study, we attempted to correlate the anticonvulsant activity of congeners with their combined calculated Log *P* value, CLOGP. As observed some of the experimental values were in good agreement with the theoretical values. Some of the compounds like **6a**, **6c**, **6d**, **6g**, **6i**, **6k**, **6n** have shown dependence of biological activity on lipophilic character in congeneric series.

6. Conclusion

By choosing proper experimental conditions we have been able to synthesize 2-(1,3-dioxoisoindolin-2-yl)-*N*-(4-oxo-2-substitutedthiazolidin-3-yl) acetamide derivatives in good yields and

investigate for anticonvulsant and CNS depressant activities with the hope of discovering new structure leads serving as potential anticonvulsant agents. SAR studies revealed the critical role of *p*–CH_3 substituent on aryl group in the target compounds like **6g** that showed promising activity. Compounds **6c**, **6e** and **6g** showed significant activity in MES screen model. Compounds **6a**, **6e**, **6f** and **6i** have exhibited significant activity when compared with standard in sc PTZ model. Some of the synthesized compounds exhibited lesser CNS depression and neurotoxicity compared to clinically effective drug. In conclusion compound **6g** can be further optimized and developed as a lead molecule.

7. Experimental protocols

7.1. Chemistry

All reagents and solvents were used as obtained from the supplier or recrystallized/redistilled unless otherwise noted. Infrared (IR) and proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded for the compounds on JASCO FTIR (PS 4000) using KBr pallet and Brucker Advance II (400 MHz) instruments, respectively. Chemical shifts are reported in parts per million (ppm), using TMS as an internal standard. All exchangeable protons were confirmed by the addition of D_2O. Elemental analyses (C, H, and N) were undertaken with a Shimadzu's FLASHEA112 analyzer and all analyses were consistent with theoretical values (within ±0.5%) unless indicated. The homogeneity of the compounds was monitored by ascending thin layer chromatography (TLC) on silica gel-G (Merck) coated aluminum plates, visualized by iodine vapor.

*7.1.1. General procedure for the preparation of N-substituted benzylidene/methylene-2-(1,3-dioxo isoindolin-2-yl) acetohydrazides **5**(**a**–**p**)*

2-(1,3-Dioxoisoindolin-2-yl) acetic acid **(3)** was obtained by the reaction of phthalic acid anhydride **(1)** (0.05 mol) with glycine **(2)** (0.05 mol) [16]. Equimolar quantities of 2-(1,3-dioxoisoindolin-2-yl)acetic acid **(3)** (0.03 mol) and hydrazine hydrate (99%) (0.03 mol) were condensed in the presence of DCC (0.03 mol) in dichloromethane, by stirring at ice-cold conditions (0–3 °C) for 6–8 h [17]. Equimolar quantities of 2-(1,3-dioxoisoindolin-2-yl) acetohydrazide **(4)** (0.03 mol) and different substituted aromatic aldehydes and heterocyclic aldehydes (0.03 mol) were refluxed in ethanol for 6–8 h, in presence of glacial acetic acid (0.06 mol). Products were recrystallized with ethanol. The other compounds **5**(**a**–**p**) were prepared similarly by treating with corresponding aldehydes [18].

*7.1.2. General procedure for the preparation of 2-(1,3-dioxoisoindolin-2-yl)-N-(4-oxo-2-substitutedthiazolidin-3-yl) acetamide derivatives **6**(**a**–**p**)*

In an Erlenmeyer flask the mixture of compounds **5**(**a**–**p**) (0.01 mol), thioglycolic acid (0.01 mol) and anhydrous zinc chloride (0.004 mol) was taken in DMF (20 ml). The reaction mixture was irradiated inside a synthetic microwave oven for about 10–12 min (700 W). After completion of reaction, mixture was poured into ice-cold water. The solid product formed was filtered, dried and recrystallized from ethanol.

*7.1.2.1. 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-N-(4-oxo-2-phenyl-thiazolidin-3-yl) acetamide **6a**.* IR (KBr, ν_{max} in cm^{-1}): 3335 (N–H of amide), 3012 (C–H of aromatic), 2886 (C–H of alkyl), 1770 C=O of thiazolidinone), 1720, 1715 C=O of Phthalimide), 1680 C=O of amide), 1605 (C···C of aromatic), 1315 (C–N), 1285 (N–N), 736 (C–S–C); ^{1}H NMR (DMSOd_6, 400 MHz) δ ppm: 4.03 (s, 2H, CH_2 of thiazolidinone ring), 4.87 (s, 2H, –N–CH_2), 5.95 (s, 1H, –N–CH–Ar), 6.94–7.79 (m, 9H, Ar–H), 8.61 (s, 1H, –CONH, D_2O exchangeable); MS *m*/*z*: 382 (M+1); Anal. Calcd. for $C_{19}H_{15}N_3O_4S$: C, 59.84; H, 3.93; N, 11.02. Found: C, 59.86; H, 3.93; N, 11.01.

*7.1.2.2. 2-(1, 3-dioxo-1,3-dihydro-isoindol-2-yl)-N-[2-(2-hydroxy-phenyl)-4-oxo-thiazolidin-3-yl] acetamide **6b**.* IR (KBr, ν_{max} in cm^{-1}): 3450 (OH), 3335 (N–H of amide), 3152 (C–H of aromatic), 2876 (C–H of alkyl), 1770 C=O of thiazolidinone), 1725, 1718 C=O of Phthalimide), 1640 C=O of amide), 1608 (C···C of aromatic), 1310 (C–N), 1288 (N–N), 716 (C–S–C); ^{1}H NMR (DMSOd_6, 400 MHz) δ ppm: 3.85 (s, 2H, CH_2 of thiazolidinone ring), 4.87 (s, 2H, –N–CH_2), 5.42 (s, 1H, OH) 5.92 (s, 1H, –N–CH–Ar), 6.94–7.79 (m, 8H, Ar–H), 8.64 (s, 1H, –CONH, D_2O exchangeable); MS *m*/*z*: 398 (M+1); Anal. Calcd. for $C_{19}H_{15}N_3O_5S$: C, 57.43; H, 3.77; N, 10.57. Found: C, 57.45; H, 3.78; N, 10.55.

*7.1.2.3. 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-N-[2-(4-hydroxy-phenyl)-4-oxo-thiazolidin-3-yl] acetamide **6c**.* IR (KBr, ν_{max} in cm^{-1}): 3446 (OH), 3328 (N–H of amide), 3150 (C–H of aromatic), 2776 (C–H of alkyl), 1775 C=O of thiazolidinone), 1725, 1720 C=O of Phthalimide), 1642 C=O of amide), 1610 (C···C of aromatic), 1315 (C–N), 1278 (N–N), 720 (C–S–C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 3.80 (s, 2H, CH_2 of thiazolidinone ring), 4.97 (s, 2H, –N–CH_2), 5.49 (s, 1H, OH) 5.90 (s, 1H, –N–CH–Ar), 6.94–7.79 (m, 8H, Ar–H), 8.74 (s, 1H, –CONH, D_2O exchangeable); MS *m*/*z*: 398 (M+1); Anal. Calcd. for $C_{19}H_{15}N_3O_5S$: C, 57.43; H, 3.77; N, 10.57. Found: C, 57.44; H, 3.77; N, 10.56.

*7.1.2.4. 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-N-[2-(4-methoxy-phenyl)-4-oxo-thiazolidin-3-yl] acetamide **6d**.* IR (KBr, ν_{max} in cm^{-1}): 3335 (N–H of amide), 3012 (C–H of aromatic), 2886 (C–H of alkyl), 1775 C=O of thiazolidinone), 1722, 1715 C=O of Phthalimide), 1660 C=O of amide), 1615 (C···C of aromatic), 1318 (C–N), 1270 (N–N), 1214 (O–CH_3) 736 (C–S–C); ^{1}H NMR (DMSOd_6, 400 MHz) δ ppm: 3.85 (s, 3H, O–CH_3), 4.03 (s, 2H, CH_2 of thiazolidinone ring), 4.87 (s, 2H, –N–CH_2), 5.95 (s, 1H, –N–CH–Ar), 6.94–7.79 (m, 8H, Ar–H), 8.61 (s, 1H, –CONH, D_2O exchangeable); MS *m*/*z*: 412 (M+1); Anal. Calcd. for $C_{20}H_{17}N_3O_5S$: C, 58.39; H, 4.13; N, 10.21. Found: C, 58.40; H, 4.13; N, 10.20.

*7.1.2.5. 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-N-[2-(4-hydroxy-3-methoxy-phenyl)-4-oxo-thiazolidin-3-yl] acetamide **6e**.* IR (KBr, ν_{max} in cm^{-1}): 3457 (OH), 3345 (N–H of amide), 3152 (C–H of aromatic), 2876 (C–H of alkyl), 1770 C=O of thiazolidinone), 1728, 1713 C=O of Phthalimide), 1640 C=O of amide), 1615 (C···C of aromatic), 1313 (C–N), 1288 (N–N), 1215 (O–CH_3), 716 (C–S–C); ^{1}H NMR (DMSOd_6, 400 MHz) δ ppm: 3.32 (s, 3H, O–CH_3), 3.85 (s, 2H, CH_2 of thiazolidinone ring), 4.87 (s, 2H, –N–CH_2), 5.42 (s, 1H, OH), 5.92 (s, 1H, –N–CH–Ar), 6.94–7.79 (m, 7H, Ar–H), 8.64 (s, 1H, –CONH, D_2O exchangeable); MS *m*/*z*: 428 (M+1); Anal. Calcd. for $C_{20}H_{17}N_3O_6S$: C, 56.20; H, 3.98; N, 9.83. Found: C, 56.22; H, 3.94; N, 9.85.

*7.1.2.6. N-[2-(3,4-dimethoxy-phenyl)-4-oxo-thiazolidin-3-yl]-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl) acetamide **6f**.* IR (KBr, ν_{max} in cm^{-1}): 3349 (N–H of amide), 3150 (C–H of aromatic), 2896 (C–H of alkyl), 1765 C=O of thiazolidinone), 1733, 1728 C=O of Phthalimide), 1644 C=O of amide), 1616 (C···C of aromatic), 1316 (C–N), 1298 (N–N), 1242, 1215 (O–CH_3), 706 (C–S–C); ^{1}H NMR (DMSOd_6, 400 MHz) δ ppm: 3.32–3.45 (s, 6H, O–CH_3), 3.83 (s, 2H, CH_2 of thiazolidinone ring), 4.80 (s, 2H, –N–CH_2), 5.90 (s, 1H, –N–CH–Ar), 6.94–7.79 (m, 7H, Ar–H), 8.69 (s, 1H, –CONH, D_2O exchangeable); MS *m*/*z*: 442 (M+1); Anal. Calcd. for $C_{21}H_{19}N_3O_6S$: C, 57.14; H, 4.30; N, 9.52. Found: C, 57.18; H, 4.29; N, 9.50.

7.1.2.7. 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-N-(4-oxo-2-p-tolyl-thiazolidin-3-yl) acetamide ***6g***. IR (KBr, ν_{max} in cm^{-1}): 3335 (N–H of amide), 3110 (C–H of aromatic), 2956 (C–H_3), 2883 (C–H of alkyl), 1785 C=O of thiazolidinone), 1725, 1720 C=O of Phthalimide), 1705 C=O of amide), 1635 (C···C of aromatic), 1405 (C–N), 1280 (N–N), 725 (C–S–C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 2.30 (s, 3H, CH_3), 4.13 (s, 2H, CH_2 of thiazolidinone ring), 4.55 (s, 2H, –N–CH_2), 5.90 (s, 1H, –N–CH–Ar), 6.94–7.79 (m, 8H, Ar–H), 8.68 (s, 1H, –CONH, D_2O exchangeable); MS *m/z*: 396 (M+1); Anal. Calcd. for $C_{20}H_{17}N_3O_4S$: C, 60.75; H, 4.30; N, 10.63. Found: C, 60.90; H, 4.30; N, 10.61.

7.1.2.8. N-[2-(4-chloro-phenyl)-4-oxo-thiazolidin-3-yl]-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl) acetamide ***6h***. IR (KBr, ν_{max} in cm^{-1}): 3545 (N–H of amide), 3152 (C–H of aromatic), 2876 (C–H of alkyl), 1755 C=O of thiazolidinone), 1720, 1715 C=O of Phthalimide), 1642 C=O of amide), 1626 (C···C of aromatic), 1320 (C–N), 1284 (N–N), 825 (Ar–Cl), 716 (C–S–C); ^{1}H NMR ($DMSOd_6$, 400 MHz) δ ppm: 3.97 (s, 2H, CH_2 of thiazolidinone ring), 4.79 (s, 2H, –N–CH_2), 5.89 (s, 1H, –N–CH–Ar), 7.74–8.06 (m, 8H, Ar–H), 8.08 (s, 1H, –CONH, D_2O exchangeable); MS *m/z*: 416 (M+1); Anal. Calcd. for $C_{19}H_{14}ClN_3O_4S$: C, 54.93; H, 3.37; N, 10.12. Found: C, 54.86; H, 3.33; N, 10.14.

7.1.2.9. N–[2-(2,4-dichloro-phenyl)-4-oxo-thiazolidin-3-yl]-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl) acetamide ***6i***. IR (KBr, ν_{max} in cm^{-1}): 3545 (N–H of amide), 3159 (C–H of aromatic), 2873 (C–H of alkyl), 1755 C=O of thiazolidinone), 1710, 1702 C=O of Phthalimide), 1645 C=O of amide), 1620 (C···C of aromatic), 1321 (C–N), 1280 (N–N), 855, 825 (Ar–Cl), 695 (C–S–C); ^{1}H NMR ($DMSOd_6$, 400 MHz) δ ppm: 3.90 (s, 2H, CH_2 of thiazolidinone ring), 4.73 (s, 2H, –N–CH_2), 5.59 (s, 1H, –N–CH–Ar), 7.74–8.06 (m, 7H, Ar–H), 8.10 (s, 1H, –CONH, D_2O exchangeable); MS *m/z*: 450 (M+1); Anal. Calcd. for $C_{19}H_{13}Cl_2N_3O_4S$: C, 50.77; H, 2.89; N, 9.35. Found: C, 50.80; H, 2.89; N, 9.37.

7.1.2.10. N-[2-(2-chloro-6-fluoro-phenyl)-4-oxo-thiazolidin-3-yl]-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl) acetamide ***6j***. IR (KBr, ν_{max} in cm^{-1}): 3540 (N–H of amide), 3059 (C–H of aromatic), 2875 (C–H of alkyl), 1760 C=O of thiazolidinone), 1722, 1705 C=O of Phthalimide), 1643 C=O of amide), 1620 (C···C of aromatic), 1329 (Ar–F), 1311 (C–N), 1273 (N–N), 825 (Ar–Cl), 693 (C–S–C); ^{1}H NMR ($DMSOd_6$, 400 MHz) δ ppm: 3.91 (s, 2H, CH_2 of thiazolidinone ring), 4.70 (s, 2H, –N–CH_2), 5.49 (s, 1H, –N–CH–Ar), 7.74–8.06 (m, 7H, Ar–H), 8.54 (s, 1H, –CONH, D_2O exchangeable); MS *m/z*: 434 (M+1); Anal. Calcd. for $C_{19}H_{13}ClFN_3O_4S$: C, 52.65; H, 3.00; N, 9.69. Found: C, 52.69; H, 3.00; N, 9.67.

7.1.2.11. N-[2-(4-dimethylamino-phenyl)-4-oxo-thiazolidin-3-yl]-2-(1,3-dioxo-1,3-dihydro- isoindol-2-yl) acetamide ***6k***. IR (KBr, ν_{max} in cm^{-1}): 3295 (N–H of amide), 3145 (C–H of aromatic), 2885 (C–H of alkyl), 1755 C=O of thiazolidinone), 1733, 1725 C=O of Phthalimide), 1680 C=O of amide), 1615 (C···C of aromatic), 1308 (C–N), 1295 (N–N), 785 (C–S–C); ^{1}H NMR ($DMSOd_6$, 400 MHz) δ ppm: 1.50 (s, 6H, $N(CH_3)_2$), 4.24 (s, 2H, CH_2 of thiazolidinone ring), 4.82 (s, 2H, –N–CH_2), 5.90 (s, 1H, –N–CH–Ar), 6.90–7.79 (m, 8H, Ar–H), 8.69 (s, 1H, –CONH, D_2O exchangeable); MS *m/z*: 425 (M+1); Anal. Calcd. for $C_{21}H_{20}N_4O_4S$: C, 59.43; H, 4.71; N, 15.09. Found: C, 59.45; H, 4.70; N, 15.10.

7.1.2.12. 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-N-(4-oxo-2-styryl-thiazolidin-3-yl) acetamide ***6l***. IR (KBr, ν_{max} in cm^{-1}): 3335 (N–H of amide), 3012 (C–H of aromatic), 2886 (C–H of alkyl), 1770 C=O of thiazolidinone), 1720, 1715 C=O of Phthalimide), 1680 C=O of amide), 1630 (C–H = CH–Ar), 1605 (C···C of aromatic), 1315 (C–N), 1285 (N–N), 736 (C–S–C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 4.03 (s, 2H, CH_2 of thiazolidinone ring), 4.87 (s, 2H, –N–CH_2), 5.50–5.84 (m, 2H, CH = CH–Ar), 5.95 (s, 1H, –N–CH–Ar), 6.94–7.79 (m, 9H, Ar–H), 8.61 (s, 1H, –CONH, D_2O exchangeable); MS *m/z*: 408 (M+1); Anal. Calcd. for $C_{21}H_{17}N_3O_4S$: C, 61.91; H, 4.17; N, 10.31. Found: C, 61.94; H, 4.18; N, 10.28.

7.1.2.13. 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-N-(2-furan-2-yl-4-oxo-thiazolidin-3-yl) acetamide ***6m***. IR (KBr, ν_{max} in cm^{-1}): 3405 (N–H of amide), 3088 (C–H of aromatic), 2845 (C–H of alkyl), 1777 C=O of thiazolidinone), 1728, 1725 C=O of Phthalimide), 1681 C=O of amide), 1655 (C···C of aromatic), 1315 (C–N), 1282 (N–N), 1256 (C–O–C), 737 (C–S–C); ^{1}H NMR ($DMSOd_6$, 400 MHz) δ ppm: 3.62 (s, 2H, CH_2 of thiazolidinone ring), 4.83 (s, 2H, –N–CH_2), 5.95 (s, 1H, –N–CH–Ar), 7.0–7.94 (m, 7H, Ar–H), 8.08 (s, 1H, –CONH, D_2O exchangeable); MS *m/z*: 372 (M+1); Anal. Calcd. for $C_{17}H_{13}N_3O_5S$: C, 54.98; H, 3.50; N, 11.32. Found: C, 54.94; H, 3.48; N, 11.25.

7.1.2.14. 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-N-(4-oxo-2-thiophen-2-yl-thiazolidin-3-yl) acetamide ***6n***. IR (KBr, ν_{max} in cm^{-1}): 3325 (N–H of amide), 3108 (C–H of aromatic), 2852 (C–H of alkyl), 1780 C=O of thiazolidinone), 1733, 1721 C=O of Phthalimide), 1688 C=O of amide), 1659 (C···C of aromatic), 1311 (C–N), 1288 (N–N), 785, 737 (C–S–C); ^{1}H NMR ($DMSOd_6$, 400 MHz) δ ppm: 3.66 (s, 2H, CH_2 of thiazolidinone ring), 4.82 (s, 2H, –N–CH_2), 5.85 (s, 1H, –N–CH–Ar), 7.10–7.93 (m, 7H, Ar–H), 8.18 (s, 1H, –CONH, D_2O exchangeable); MS *m/z*: 388 (M+1); Anal. Calcd. for $C_{17}H_{13}N_3OS_2$: C, 52.71; H, 3.35; N, 10.85. Found: C, 52.84; H, 3.38; N, 10.80.

7.1.2.15. 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-N-(4-oxo-2-pyridin-3-yl-thiazolidin-3-yl) acetamide ***6o***. IR (KBr, ν_{max} in cm^{-1}): 3349 (N–H of amide), 3112 (C–H of aromatic), 2850 (C–H of alkyl), 1774 C=O of thiazolidinone), 1730, 1723 C=O of Phthalimide), 1678 C=O of amide), 1650 (C···C of aromatic), 1610 (C]N), 1301 (C–N), 1265 (N–N), 730 (C–S–C); ^{1}H NMR ($DMSOd_6$, 400 MHz) δ ppm: 3.15 (s, 2H, CH_2 of thiazolidinone ring), 4.22 (s, 2H, –N–CH_2), 5.13 (s, 1H, –N–CH–Ar), 7.12–7.90 (m, 8H, Ar–H), 8.13 (s, 1H, –CONH, D_2O exchangeable); MS *m/z*: 383 (M+1); Anal. Calcd. for $C_{18}H_{14}N_4O_4S$: C, 56.54; H, 3.66; N, 14.65. Found: C, 56.84; H, 3.68; N, 14.83.

7.1.2.16. 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-N-[2-(1H-indol-3-yl)-4-oxo-thiazolidin-3-yl] acetamide ***6p***. IR (KBr, ν_{max} in cm^{-1}): 3406 (N–H of indole), 3289 (N–H of amide), 3155 (C–H of aromatic), 2874 (C–H of alkyl), 1768 C=O of thiazolidinone), 1728, 1720 C=O of Phthalimide), 1689 C=O of amide), 1655 (C···C of aromatic), 1305 (C–N), 1263 (N–N), 732 (C–S–C); ^{1}H NMR ($DMSOd_6$, 400 MHz) δ ppm: 3.67 (s, 2H, CH_2 of thiazolidinone ring), 4.75 (s, 2H, –N–CH_2), 5.48 (s, 1H, –N–CH–Ar), 7.15–7.95 (m, 9H, Ar–H), 8.18 (s, 1H, –CONH), 11.5 (b, 1H, NH of indole, D_2O exchangeable); MS *m/z*: 421 (M+1); Anal. Calcd. for $C_{21}H_{16}N_4O_4S$: C, 60.00; H, 3.80; N, 13.33. Found: C, 60.09; H, 3.80; N, 13.35.

7.2. Pharmacology

Male Swiss albino mice (CF-1 strain, 20–30 g) were used as experimental animals. All the test compounds were suspended in 0.5% methyl cellulose in the case of MES and sc PTZ induced seizure models and 30% PEG 200 for behavioral activity at our lab. The animals were maintained at an ambient temperature of 25 ± 2 °C, in groups of five per cage under standard laboratory conditions, receiving standard laboratory chow and water ad libitum. A 12 h: 12 h light/dark cycle was maintained throughout the experimental studies. All the tests have been performed in accordance with the guidelines laid out by the Institutional Animal Ethics Committee.

7.2.1. Anticonvulsant screening

All the test compounds were administered intraperitoneally in a volume of 0.01 mL/g for mice at doses of 30, 100 and 300 mg/kg. Anticonvulsant activity was assessed after 30 min and 4 h of drug administration. The preliminary anticonvulsants (MES and sc PTZ) evaluations were done using reported procedures.

7.2.2. Neurotoxicity screening

Rotarod test has been performed to detect the minimal motor deficit in mice. Animals were divided into groups of 5 and trained to stay on an accelerating rotarod that rotates at 10 rpm. The rod diameter was 3.2 cm. Trained animals (able to stay on the rotarod for at least two consecutive trials of 90 s each) were given an i.p. injection of the test compounds at doses of 30, 100 and 300 mg/kg. Neurological deficit was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the three trials. The dose at which the animal fell off the rod was determined.

7.2.3. Behavioral activity

The activity was measured as digital score using actophotometer [19] with the ip administration of drug (30 mg/kg) to mice. The mice were placed in the box and the behavior was noted for 10 min. Further, the animals were treated with the drug and after 0.5 h and 4 h drug administration the animal were re-tested. The activity score was noted and based on these results, % decrease in locomotor activity was calculated.

7.3. Computational parameter

7.3.1. Distance mapping

In conformational analysis of the clinically effective anticonvulsant drugs such as phenytoin, carbamazepine, lamotrigine and diazepam, a molecular model was suggested on the basis of molecular dynamics distance estimations [20]. For the estimation of the molecular mechanics calculation of titled compounds, the ACD/3D viewer 8.04 version program was used for employing the CHARMM force field.

7.3.2. Log P determination

The partition coefficient between octanol and phosphate buffer was determined at room temperature [21]. 10 mL of octanol and 10 mL phosphate buffer were taken in a glass stoppered graduated tube and 5 mg of accurately weighed drug was added. The mixture was then shaken with the help of mechanical shaker for 24 h at room temperature and then transferred to a separating funnel and allowed to dynamic equilibrate for 6 h. The aqueous and octanol phase were separated and filtered through membrane filter and drug content in aqueous phase was analyzed by UV spectroscopy.

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