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Docking, synthesis, and characterization of novel heterocyclic ring system and their evaluation for mGlu8 receptor agonist as anticonvulsant agents

Sindiya D Naik[a], Sachin K Chandavarkar*[b], Shilpa S Tawade[a], Sunil G Shingade[c], Mahesh B Palkar[d] & Shivalingrao N Mamle Desai[a]

[a] Department of Pharmaceutical Chemistry, PES's Rajaram and Tarabai Bandekar College of Pharmacy, Farmagudi, Goa 403 401, India

[b] Department of Pharmacognosy, ASPM College of Pharmacy, Sangulwadi, Dist. Sindhudurg 416 810, India

[c] Department of Pharmaceutical Chemistry, SSP's V P College of Pharmacy, Madkhol, Dist. Sindhudurg 416 510, India

[d] Department of Pharmaceutical Chemistry, KLEU's College of Pharmacy, Hubli 580 031, India

E-mail: chandsachin@gmail.com; smamledesai@rediffmail.com

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This research work involves the synthesis of a series of substituted 1-(4-methoxy-1-phenyl/methyl-2-thioxo-1,2-dihydroquinolin-3-yl)ethanone [IVa/b(1-5)] derivatives by dimerization at third position and evaluation of their anticonvulsant activity. The starting material 3-acetyl-4-hydroxy-1-phenyl/methylquinolin-2(1*H*)-one **Ia/b** has been treated with P_4S_{10}:Al_2O_3 to yield compound 1-(4-hydroxy-1-phenyl/methyl-2-thioxo-1,2-dihydroquinolin-3-yl)ethanone (**IIa/b**). Compound **II**a/b has been methylated to yield compound 1-(4-methoxy-1-phenyl/methyl-2-thioxo-1,2-dihydroquinolin-3-yl)ethanone (**III**a/b) which, on condensation with ketones forms dimers giving the title compounds **IVa-b** (**1-5**). All the synthesized compounds are satisfactorily characterized by spectral data. The *in silico* pharmacophore modeling of the title compounds has been performed using Molegro Virtual Docker (MVD-2007 software and mGlu8 is the target and *in vivo* anticonvulsant activity by phenylenetetrazole (PTZ) induced convulsion method. The results of docking have revealed that the synthesized compounds exhibit well-conserved hydrogen bonds with one or more amino acid residues in the active pocket of metabotropic glutamate receptor mGluR8 complexed with (S)-3,4-dicarboxyphenylglycine (DCPG) (PDB ID:6E5V)LY341495 antagonist (PDB ID: 3MQ4). The MolDock Score of compound 2,6-bis(4-methoxy-1-phenyl-2-thioxo-1,2-dihydroquinolin-3-yl)hepato-2,5-dien-4-one (**IVa-1**) has been found to be −141.617. The *in vivo* anticonvulsant activity results show that compound 2,6-bis(4-methoxy-1-phenyl-2-thioxo-1,2-dihydroquinolin-3-yl)hepato-2,5-dien-4-one (**IVa-1**), 2,7-bis(4-methoxy-1-phenyl-2-thioxo-1,2-dihydroquinolin-3-yl)octa-2,6-dien-4,5-dione (**IVa-2**), 2,6-bis(4-methoxy-1-methyl-2-thioxo-1,2-dihydroquinolin-3-yl)hepato-2,5-dien-4-one (**IVb-2**) and (2E,6E)-2,6-bis(4-methoxy-1-phenyl-2-thioxo-1,2-dihydroquinolin-3-yl) cyclohexanone (**IVb-4**) have been found to be most potent against pentylenetetrazole induced convulsion.

Keywords: Quinolin-2(1*H*)-one, anticonvulsant, mGlu8 receptor, phenylenetetrazole

Epilepsy is the most prevalent neurological disorder affecting more than 0.5% of world population[1]. Epilepsy is highest among children younger than 5 years and elderly older than 65 years of age[2]. Most of the drugs ex. valproic acid, phenytoin, carbamazepine, are effective against newly diagnosed seizure disorders and effectiveness hampers after prolonged exposure. These drugs are also been associated with toxic effects like sedation, ataxia, weight loss (Topiramate), weight gain (Sodium veloproate), hepatotoxicity, tertogenesis, life threatening skin rashes and aplastic anemia[3-7].

Present clinically used antiepileptic drugs act by inducing prolonged inactivation of the Na^+ channels by blocking Ca^{+2} channel currents or by increasing Cl^- conductance at $GABA_A$ receptors Ex. benzodiazepines, barbiturates[8].

Glutamate Receptors

The neurotransmitter glutamate(Glu) mediate most of the fast excitatory transmission that control all brain functions especially learning and memory processes[9]. Excessive glutamergic neurotransmission is understood to be one of the primary metabolic or pathological reason behind the etiology of numerous types of epilepsy[10]. Glu can also activate G-Protein coupled metabotropic receptors(mGluRs) leading to inhibiting and excitatory effects. G-Protein Coupled Receptors (GPCRs) are the largest family of receptors having an extracellular N-terminal domain, an intracellular C-Terminal domain, seven α- helical transmembrane segments and an intraceullar loop that binds to G-proteins to produce second messanger signals. Metabotopic glutamate receptors (mGluR) are

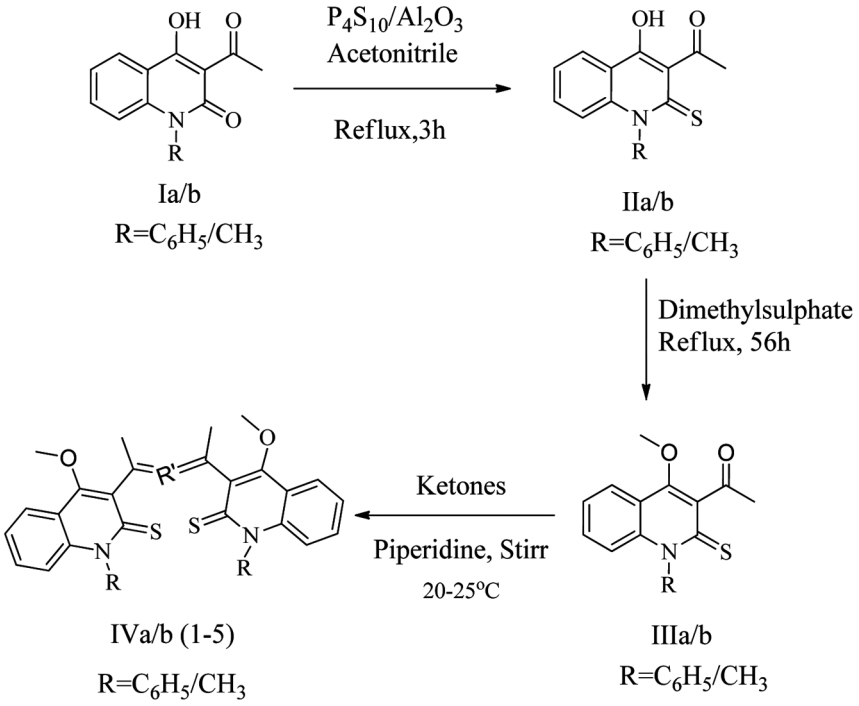
the G-Protein coupled receptors (GPCRs) controlling excitatory synapses. mGluRs are classified into three groups differentiated by their sequence homology, second messenger effects and pharmacology. The postsynaptic Group I (mGluR1 and mGluR5) receptors control excitatory neurotransmission, instead Group II (mGluR2 and mGluR3) and Group III metabotopic glutamate receptors (mGluR4 and mGluR7 and mGluR8) are located presynaptically and their activation reduces glutamate release. Many reporters identified mGlu group II and III agonists are the targets for novel antiepileptic agents[11-14]. Literature also reveals the novel group III mGlu receptor agonist (1S,3R,4S)-1-aminocyclopentane-1,2,4-tricarboxylic acid (ACPT-1) has a high affinity for mGlu8 receptor and shows potent anticonvulsant activity[15].

Quinolin-2-one is an important ring system present in alkaloids of Rutaceae family Ex. flindersine, dictamine, walerthione A, B,C, *etc*. Also synthetic derivatives of quinolin-2-one are of wide clinical impotance *viz*. aripiperazole, brespriprazole as antischizoprenic, careolol as an β-blocker in ophthalmic preparation, rebapimide as an antiulcer drug[16,17].

In the present investigation a dimer of substituted 1-(4-methoxy-1-phenyl/methyl-2-thioxo-1,2-dihydroquinolin-3-yl)ethanone were synthesised and mGluR8 agonist activity was performed to know antiepileptic activity of the derivatives.

Result and Discussion

The starting material for the synthesis of title compounds was prepared following the literature[18-20]. The starting material 4-hydroxy-1-methyl/phenyl-3-acetylquinolin-2(1*H*)-one was subjected to thionation using phosphorous pentasulfide in presence of aluminium oxide as a catalyst. Thionated compound was subjected to *O*-methylation of hydroxyl group to avoid keto-enoltautomerism at 3rd and 4th position, might have been interfered with crossed aldol condensation reaction. Compound IIIa/IIIb further reacted with different ketones by crossed aldol condensation to yield title compounds in a manner as shown in Scheme I. The physical data the title compounds are shown in Table I. The spectral characterization of selective representative structure was satisfactorily performed by UV, IR, ^{1}H NMR and ^{13}C NMR spectroscopy and by Mass spectral data. The molecular docking study was performed using Molegro Virtual Docker 2007 (version 6.0). Many have shown good binding to mGluR8 receptor in comparison to ligand and standard drug. The Mol Dock score of the title compounds are shown in



Scheme I

Table I — List of the synthesized derivatives and their physical data

Compd	R	R_1	Mol. Formula	Mol. Wt.	m.p. (ºC)	Yield (%)	λ_{max}	R_f Value
IVa-1	C_6H_5-	CH-CO-CH	$C_{39}H_{32}N_2O3S_2$	640.81	>300	65.22	232.7	0.67
IVa-2	C_6H_5-	CH-CO-CO-CH	$C_{40}H_{32}N_2O_4S_2$	668.82	>300	68.25	231.6	0.67
IVa-3	C_6H_5-	$CHCH_2(CO)CH_2CH$	$C_{41}H_{34}N_2O_3S_2$	666.85	>300	60.16	235.8	0.73
IVa-4	C_6H_5-	$CH(CH_2)_3COCH$	$C_{42}H_{36}N_2O_3S_2$	680.88	>300	58.84	233.1	0.72
IVa-5	C_6H_5-	$CHCH_2(CO)_2\ CH_2CH$	$C_{42}H_{36}N_2O_4S_2$	696.88	>300	62.01	229.4	0.75
IVb-1	CH_3-	CH-CO-CH	$C_{29}H_{28}N_2O_3S_2$	516.67	>300	51.75	236.7	0.76
IVb-2	CH_3-	CH_2-CO-CO-CH	$C_{30}H_{28}N_2O_4S_2$	544.68	>300	53.54	234.09	0.77
IVb-3	CH_3-	$CHCH_2(CO)CH_2CH$	$C_{31}H_{30}N_2O_3S_2$	542.71	>300	45.21	236.09	0.88
IVb-4	CH_3-	$CH(CH_2)_3COCH$	$C_{32}H_{32}N_2O_3S_2$	556.74	>300	61.65	230.44	0.89
IVb-5	CH_3-	$CHCH_2(CO)_2\ CH_2CH$	$C_{32}H_{30}N_2O_4S_2$	570.72	>300	66.04	236.90	0.93

Table II — Results of the molecular docking study showing MolDock Scores of target compounds

Name	MolDock score	Rerank score	H Bond
IVa-1	−141.617	−102.141	−7.5
IVa-2	−120.241	−15.833	−2.5
IVa-3	−107.622	−60.5549	−0.06391
IVa-4	−111.881	−51.4096	−6.76057
IVa-5	−94.4933	−70.1609	−7.86196
IVb-1	−115.194	−49.785	−1.05641
IVb-2	−97.1308	−55.7571	−1.77508
IVb-3	−126.335	−34.8722	−4.78532
IVb-4	−134.099	−16.5003	−2.5
IVb-5	−112.230	−102.015	−22.3947
Active Ligand (DCPG)	−133.79	−103.287	−26.1403
Diazepam	−84.3509	−68.1236	−7.01865

Table II and graphical pictures in Figure 1 and Figure 2 A-G. The anticonvulsant activity was performed using pentylenetetrazole (PTZ) induced convulsions and many compounds IVa-1, Iva-2, IVb-1 and IVb-4 have shown protection for convulsions compared to that of standard drug diazepam. Mol dock score of the active compounds are matching with biological active compounds and indicating mGluR8 agonstic activity.

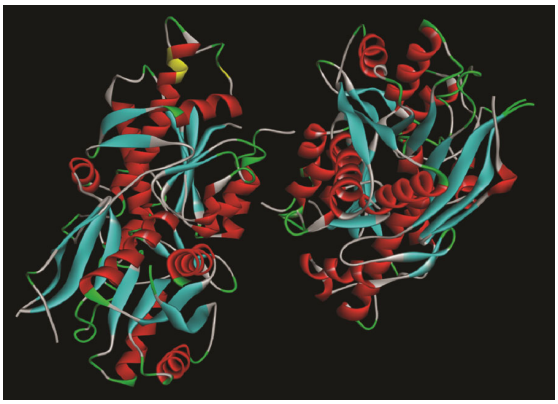


Figure 1 — Structure of human mGlu8 receptor amino terminal domain in complex with (S)-3,4-Dicarboxyphenylglycine (DCPG) obtained from protein data bank with the PDB ID:6E5V

Experimental Section

Chemicals used for the synthesis were purchased from Molychem (Mumbai) and SD-Fine Chem Ltd. (Mumbai). All the reagents and solvents were of laboratory grade. The reactions were monitored by Thin Layer Chromatography (TLC) using precoated plates. Melting Points of the synthesized compounds were determined by Thiele's melting point apparatus and are uncorrected. The UV-Visible absorbance was recorded on Shimadzu UV-Visible Spectrophotometer 1800. Fourier Transform Infrared (FTIR) spectra were recorded on SHIMADZU IR AFFINITY-1 spectrophotometer by KBr disc method. The ^{1}H NMR and ^{13}C NMR were recorded on Bruker Avance II 400 NMR spectrometer using deuterated dimethylsulfoxide (DMSO-d_6) as the solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed as delta (δ) values in parts per million (ppm). The Mass spectra (MS) were recorded on Waters, Q-TOF Micromass. *In-silico* molecular docking study was carried out on the synthesized derivatives using Molegro Virtual Docker2007 (version6.0).

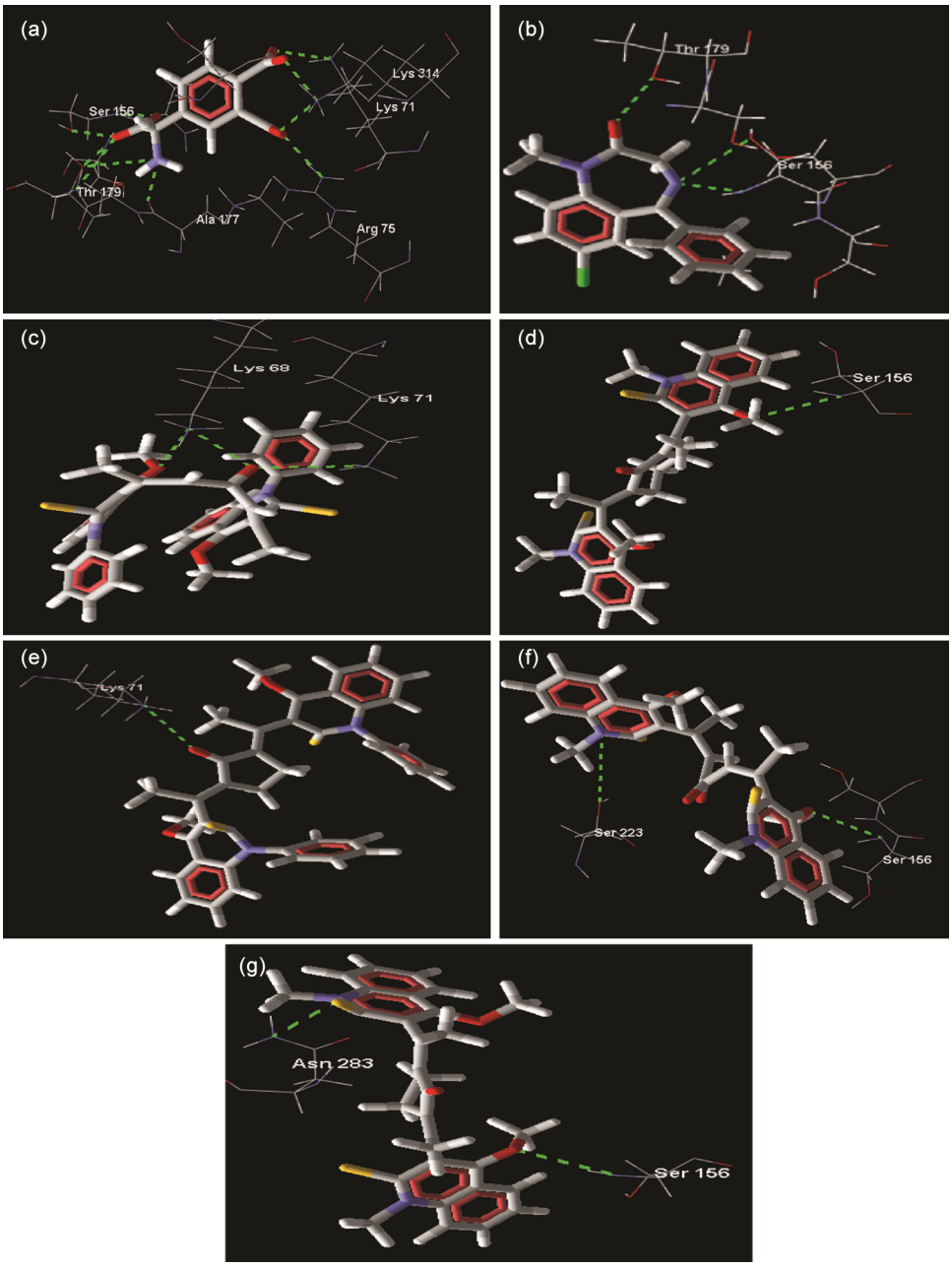


Figure 2 — Hydrogen bonding interactions of best poses of representative compounds with amino acid residues at the active site of protein human mGlu8 receptor amino terminal domain in complex with (S)-3,4-Dicarboxyphenylglycine (DCPG) (**A**) DCPG (active ligand) (**B**) Diazepam; (**C**) IVa-1; (**D**) IVb-4; (**E**)IVa-3; (**F**) IVb-2, (**G**) IVb-3.

Synthesis

Synthesis of 1-(4-hydroxy-1-phenyl/methyl-2-thioxo-1,2-dihydroquinolin-3-yl)ethanone (IIa/b)

Compound4-hydroxy-1-methyl/phenyl-3-acetylquinolin-2(1*H*)-one (Ia/Ib) was subjected to thionation by stirring with phosphourspentasulfide in presence of aluminium oxide as a catalyst using acetonitrile as a solvent. The resultant viscous liquid was then extracted with hexane or diethylether, crude solid was obtained after removal of solvent using IKA make rotaevoporator, recryalllised using toluene as solvent.

Synthesis of 1-(4-methoxy-1-phenyl/methyl-2-thioxo-1,2-dihydroquinolin-3-yl)ethanone (IIIa/b)

O-Methylation of compound **IIa/b** was performed by refluxing with dimethylsulphate and potassium carbonate in acetone for 48-56 hours. Solvent was removed by evaporation, reddish brown solid

obtained was washed with water, filtered and recrystallized using ethanol.

Synthesis of substituted 1-(4-methoxy-1-phenyl/ methyl-2-thioxo-1,2-dihydroquinolin-3-yl) ethanone [IVa/b (1-5)]

Compound IIIa and IIIb were divided into two portions, the first portion was vigorously stirred mechanically using piperdine base and aqueous ethanol as solvent at temperature of 20-25°C for 20 minutes. And the second half was added slowly and further stirred for 30 minutes. Filtered and washed with water to remove alkali and recrystallized with ethanol.

Molecular Docking Study

A pharmacophore model of the title compounds were built for rational design of novel anticonvulsant agents and mGluR8 receptor was the target. *In silico* molecular docking study of the title compounds were carried out using Molegro Virtual Docker (MVD) 2007 (version 6.0). The selected molecules were built using Chemdraw 12.0.2. The 2D structures were then converted into energy minimized 3D structures, which were saved as MDL MolFile (.mol2). The coordinate file and crystal structure of human mGlu8 receptor amino terminal domain in complex with (S)-3,4-dicarboxyphenylglycine (DCPG) (PDB ID:6E5V) were obtained from the RCSB-PDB website. The protein file was prepared by the removal of water molecules, addition of polar hydrogens, and removal of other bound ligands. The site at which binding of the complexes of agonist occurs was selected as the active site for docking of the test derivatives. The docking protocol was carried out for synthesized compounds with MVD-2007 (version 6.0) software using the standard operating procedure. The MolDock scores and the hydrogen bonding of the test compounds were compared with those of (S)-3,4-dicarboxyphenylglycine (DCPG) (active ligand) and diazepam; taken as reference standard for the study.

The site at which the known DCPG agonist binds with the target protein was selected as the active site domain. It is lined with amino acid residues such as Lys 68, Lys71, Lys314, Ser156, Thr179, Arg75 and Ala177, *etc*. Hence to identify other residual interactions of the tested compounds, a grid box (include residues within a 15.0 A radius) large enough to accommodate the active site was constructed. Since DCPG is a known agonist, the centre of this site was considered as the centre of search space for docking.

Docking of the synthesized compounds with human mGlu8 receptor amino terminal domain in complex with (S)-3,4-Dicarboxyphenylglycine (DCPG) domain exhibited well conserved hydrogen bonding with the amino acid residues at the active site. The MolDock scores of the test compounds ranged from -94.4933 to -141.617 while that of DCPG agonist was -133.79. Diazepam was used as the reference standard for comparison of efficiency and exhibited MolDock score of -84.3509. Most of the designed molecules exhibited MolDock score higher than that exhibited by diazepam; with compound 2,6-bis(4-methoxy-1-phenyl-2-thioxo-1,2-dihydroquinolin-3-yl)hepato-2,5-dien-4-one**(IVa-1)**having a highest MolDock score of -141.617. The best poses of test derivatives exhibiting the most promising hydrogen bonding are shown in Figure 2. Hydrogen bonding was observed between –O of C=O of **IVa-1** derivative with -NH of Lys71 and Lys68, -O of methoxy group showed interaction with –NH of Lys68. Compound **IVb-4** with MolDock score -134.099 showed hydrogen bonding with methoxy oxygen forming bond with –NH of Ser156. Compound **IVa-3** with MolDock score -107.622 showed hydrogen bond with oxygen of cyclopentanone ring with –NH of Lys71. Compound **IVb-3** and **IVb-2** with MolDock score -126.335 and -97.1308 respectively also exhibited hydrogen bonding interaction of methoxy oxygen with –NH of Ser156. These results show that the novel quinol-2(1*H*)-one derivatives IVa-1 and IVb-4 possess higher affinity than active ligand and standard drug diazepam towards the active site of the target protein while test derivatives IVa-3, IVb-2 and IVb-3 possess higher affinity towards active site than standard drug diazepam.

Anticonvulsant Activity

The animal experiment was conducted by the approval of Institutional Animal Ethics Committee vide letter No. 1659/PO/Re/S/12CPCSEA dtd. 14.11.2018. Acute oral toxicity study was carried out as per OECD Guidelines 423 Acute Toxic Class Method for 14 days. Male albino mice of either sex weighing 25-30g were used as experimental animals. Test compounds were suspended in tween80 for PTZ

screening. The animals were maintained at an ambient temperature 22 ± 1°C, in groups of six per cage under standard laboratory conditions.

PTZ Method

The phenylenetetrazole (PTZ) test primarily identifies compounds that raise seizure threshold. The PTZ a dose of 85 mg/kg by intraperitoneal route (i.p) was administered. This produces clonic and tonic seizures lasting for a period of at least five seconds in 97 percent of animals tested. Animals were divided into twelve groups, six animals in each group. Mice of either sex weighing between 20-30g were fasted 12h prior to the experiment. Solutions of test derivatives were administered orally at dose level of 100 mg/kg to test groups (group3-group12) and standard group (group 2) received diazepam at dose level 5mg/kg by i.p route, 45 min later PTZ was administered intraperitoneally (i.p) at dose level of 85mg/kg and animals were observed over a 30 min period. Latency to clonic and tonic seizure and survival of mice in the observed time period indicated the compounds ability to abolish the effect of pentylenetetrazole on seizure threshold. Control group (group1) received PTZ at dose of 85mg/kg by i.p route, the results were compared with control group are given in Table III. It was observed that there were significant variations ($^{***}p<0.001$) in latency time to clonic and tonic convulsions between the treated and control groups. Dunnett's method revealed that derivatives IVa-1, IVa-2, IVb-1 and IVb-4 at dose of 100 mg/kg antagonised seizure elicited by pentylenetetrazole in mice and there was significantly increased latency period to clonic and tonic convulsion and showed 83% protection as compared to control. The dimmers formed by the acetone, 2,3-butadione have exhibited higher protection for tonic and clonic seizure. The rational of *in-silico* design matches with *in-vivo* biological activity.

Table III — Result of anticonvulsant activity of title compounds

Compd	Latency to clonic (in min)	Latency to tonic (in min)	% Protection
Control	3.187± 0.3029	3.338±0.2909	00
Diazepam	9.440± 0.2291***	14.00±0.1647***	83
IVa-1	8.370± 0.4215***	11.60±1.028***	83
IVa-2	8.458± 0.5863***	11.09±1.011***	83
IVa-3	3.552± 0.4051^{ns}	4.345±0.4913^{ns}	33.33
IVa-4	3.575± 0.6964^{ns}	8.938±0.3507***	50
IVa-5	2.832± 0.4126^{ns}	2.872±0.4260^{ns}	16.66
IVb-1	7.580± 0.4353***	10.31±1.001***	83
IVb-2	7.120± 0.08046***	7.173±0.4413***	66.66
IVb-3	4.082± 0.2824^{ns}	4.212±0.3319^{ns}	16.66
IVb-4	9.485± 0.5081***	10.42±0.6304***	83
IVb-5	3.755± 0.5388^{ns}	6.620±0.2295**	33

Results of PTZ Method

The synthesized compounds were characterized by spectral analysis. Spectral data of representative compounds is presented herewith.

Spectral data 1-(4-hydroxy-1-phenyl-2-thioxo-1,2-dihydroquinolin-3-yl)ethanone (II-a):

IR (KBr, cm^{-1}): 3269.34 (broad band of -OH); 3005.10, 2945.30 (aromatic C-H stretch); 2883.58 (aliphatic C-H stretch); 1658.85(-C=O acetyl); 1213.23 (-C=S).

Spectral data of 1-(4-hydroxy-1-methyl-2-thioxo-1,2-dihydroquinolin-3-yl)ethanone (II-b):

IR (KBr, cm^{-1}): 3290.56 (broad band of -OH); 3005.10, 2945.30 (aromatic C-H stretch); 2887.44; (aliphatic C-H stretch); 1656.85 (C=O acetyl; 1242.16 (-C=S).

Spectral data of 1-(4-methoxy-1-phenyl-2-thioxo-1,2-dihydroquinolin-3-yl)ethanone (III-a):

IR (KBr, cm^{-1}): 3055.24, 3010.88 (aromatic C-H stetch); 2974.23, 2899.01 (aliphatic C-H stretch); 1654.92 (-C=O acetyl); 1213.23 (-C=S); 1265.30 (C-O). ^{1}H NMR (DMSO-d_6, δ ppm): 7.64-6.53 (m, 9H, Ar-H), 3.40 (s, 3H, -OCH_3); 2.51 (s, 3H, -$COCH_3$).

Spectral data of 1-(4-methoxy-1-methyl-2-thioxo-1,2-dihydroquinolin-3-yl)ethanone (III-b):

IR (KBr, cm^{-1}): 3080.32, 3045.60 (aromatic C-H stretch); 2943.37, 2885.51 (aliphatic C-H stretch); 1649.14 (-C=O acetyl); 1242.16 (-C=S); 1284.59 (C-O). ^{1}H NMR (DMSO-d_6, δ ppm): 8.10-7.30 (m, 4H, Ar-H), 3.55 (s, 3H, -OCH_3); 3.38 (s, 3H, -N-CH_3); 2.72 (s, 3H, -$COCH_3$).

Spectral data of 2,6-bis(4-methoxy-1-phenyl-2-thioxo-1,2-dihydroquinolin-3-yl)hepta-2,5-dien-4-one (IVa-1):

IR (KBr, cm^{-1}): 3074.53, 3053.32, 3010.88 (aromatic C-H stretch); 2918.30 (aliphatic C-H stretch); 1656.85 (-C=O acetyl); 1614.42 (-C=C stretch); 1265.30 (C-O stretch); 1215.15 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 7.95-7.18 (m,

18H, Ar-H), 6.50 (s, 2H, -C-CH) 3.55 (s, 6H, -OCH_3); 2.50 (s, 6H,=C-CH_3). MS: m/z = 642 (m+1 peak).

Spectral data of 2,7-bis(4-methoxy-1-phenyl-2-thioxo-1,2-dihydroquinolin-3-yl)octa-2,6-diene-4,5-dione (**IVa-2**):

IR (KBr, cm^{-1}): 3049.46, 3008.95 (aromatic C-H); 2879.72 (aliphatic C-H); 1654.92 (-C=O acetyl); 1614.42 (-C=C); 1265.30 (C-O); 1215.15 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 7.95-7.18 (m, 18H, Ar-H), 6.50 (s, 2H, -C-CH) 3.55 (s, 6H, -OCH_3); 2.50 (s, 6H,=C-CH_3). MS: m/z = 670 (m + 1).

Spectral data of 2,6-bis(4-methoxy-1-methyl-2-thioxo-1,2-dihydroquinolin-3-yl)hepta-2,5-dien-4-one (IVb-1):

IR (KBr, cm^{-1}): 3091.89, 3028.24 (aromatic C-H stretch); 2976.16, 2941.44 (aliphatic C-H stretch); 1651.07(-C=O acetyl); 1620.21 (-C=C stretch); 1284.59 (C-O); 1242.16 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 7.95-7.18 (m, 8H, Ar-H), 6.50 (s, 2H, -C=CH) 3.55 (s, 6H, -OCH_3); 3.40 (s, 6H,-N- CH_3) 2.50 (s, 6H,=C-CH_3).

Spectral data of 2,6-bis(1-(4-methoxy-1-methyl-2-thioxo-1,2-dihydroquinolin-3-yl)cyclohexanone (IVb-4):

IR (KBr, cm^{-1}): 3080.32, 3005.10 (aromatic C-H stretch); 2943.37, 2885.51 (aliphatic C-H stretch); 1649.14(-C=O acetyl); 1620.21 (-C=C stretch); 1282.66 (C-O); 1242.16 (C=S).

Spectral data of 2,5-bis(1-(4-methoxy-1-methyl-2-thioxo-1,2-dihydroquinolin-3-yl)cyclopentanone (IVb-3):

IR (KBr, cm^{-1}): 3091.89, 3028.24 (aromatic C-H stretch); 2976.16, 2941.44, 2889.37 (aliphatic C-H stretch); 1651.07 (-C=O acetyl); 1620.21 (-C=C stretch); 1284.59 (C-O); 1242.16 (C=S). ^{13}C NMR (DMSO-d_6, δ ppm): 197.93(1C, -C=O); 175.38 (2C, -C=S); 164.40 (2C, -C-O-CH_3); 155.98 (2C, -C-CH_3); 140.70 (2C, CH of cyclohexanone); 139.88-108.29 (14C, Ar-C); 62.41 (2C, -O-CH_3); 56.76 (2C, -N-CH_3); 33.39 (4C, -CH_2 of cyclohexanone); 27.98 (2C, -C-CH_3). MS: m/z = 544 (m+1).

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