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Molecular docking, synthesis and anticonvulsant activity of some novel 3-(2-substituted)-4-oxothiazolidine-3-yl)-2 -phenylquinazoline-4(3*H*)-ones

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Abstract

As the therapeutic potential of quinazolinone and thiazolidinone is well mentioned in literature for their versatile biological activities, their related toxicological profiles cannot be ignored. So, the purpose of this study is to synthesize 3-(2-substituted)-4-oxothiazolidine-3-yl)-2-phenylquinazoline-4(3*H*)-ones **(3a–3k)** and evaluate them as anticonvulsant agents. Novel series of **3a–3k** were synthesized and their structures elucidated on the basis of elemental and spectral analyses. A hybrid scaffold containing quinazolinone and thiazolidinone moieties was synthesized to get the title compounds, and their *in vivo* anticonvulsant activities were performed by maximal electro-shock (MES) induced convulsion model at a dose of 25 mg/kg body weight. Six compounds, **3b, 3c, 3d, 3e, 3f** and **3i,** were found to have significant anticonvulsant activities with their durations of tonic hind limb extension ranging from 13.117 to 16.450 s and animal protection from 83 to 100%. The results were compared with the standard. All compounds exhibited good binding energies ranging from −5.15 to −6.13 kcal/mol with sodium channel IIA inactivation gate (PDB ID: 1BYY) in molecular docking study; amongst them, **3d** has shown significant binding energy of −6.13 kcal/mol. The obtained result showed that biologically active compounds could be used as a template for future design, optimization and investigation for producing more active analogs.

Keywords Synthesis · 4-oxothiazolidine · Quinazoline-4(3*H*)-ones · Epilepsy · Anticonvulsant activity · Molecular docking

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Introduction

Epilepsy is a syndrome of various cerebral disorders of the central nervous system (CNS) is characterized by paroxysmal, excessive, and hypersynchronous discharges of large numbers of neurons [1, 2]. It affects a large section of the population (45–100 million people) worldwide [3, 4]. The poor tolerability and reported side effects of the antiepileptic drugs have affected the quality of life of the epilepsy patients [5, 6]. Therapeutic failure in 20–25% of patients and serious side effects of the available antiepileptic drugs have stimulated intensive research on novel antiepileptic drugs [7–10].

The quinazolinone nucleus and its derivatives have been found to be effective as antihypertensive [11–13], anti-inflammatory [14], antihyperglycemic [15], anticancer [16], antimalarial [17, 18], neuroprotective [19] and anticonvulsant [20, 21] agents. The presence of a substituted aromatic ring at position 3 of quinazolinone is a necessary requirement for the CNS depression and anticonvulsant activities of such derivatives as methaqualone, ethaqualone and mecloqualone (Fig. 1) [22]. Medicinal chemists over the years have substituted different heterocyclic rings at position 3 of 4(3*H*)-quinazolinone to get potent CNS acting drugs [21]. Literature searches reveal that 4-oxo thiazolidine derivatives exhibit antitubercular [23], cytotoxic [24], anti-inflammatory [25, 26] and anticonvulsant [27] activities. Therefore, in the present study, 2-substituted thiazolidinone moiety was connected to position 3 of the quinazolinone ring, as the combination of different pharmacophores in one frame may lead to significant anticonvulsant agents. Stabilization of the sodium channel IIA inactivation gate may be useful in disrupting prolonged neuronal seizure discharge, and has been an important target for a number of anticonvulsant drugs [28].

In the present work, compounds (**3a–3k)** were synthesized by stirring 3-amino-2-phenylquinazoline-4(3*H*)-one with substituted aromatic aldehydes using thioglycolic acid (TGA) and N, N-dicyclohexylcarbodiimide (DCC) in N, N-dimethyl formamide (DMF) as a solvent. The purity and completion of the reaction was monitored by using thin layer chromatography (TLC). All the synthesized compounds were characterized by spectral (IR, ^{1}H NMR, MS) and elemental analyses. A series of 3-(2-substituted)-4-oxothiazolidine-3-yl)-2-phenylquinazoline-4(3*H*)-ones (**3a–3k)** were evaluated for their anticonvulsant activity with the maximal electroshock (MES) test using Swiss albino mice.

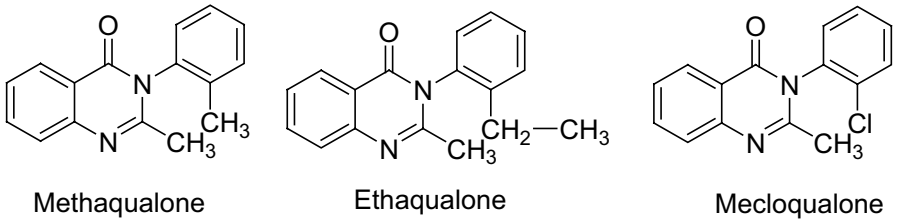


Fig. 1 Quinazolinone derivatives as potential CNS depressant agents [22]

A docking program, such as AutoDock, when used prior to experimental screening, can be a powerful computational filter to reduce labor and cost needed for the development of effective medicinal compounds [29]. Molecular docking studies were executed against 3D crystal structure of sodium channel IIA inactivation gate (PDB ID: 1BYY).

Experimental

Materials and methods

All the chemicals used for synthesis were of laboratory reagent (LR) and analytical reagent (AR) grade procured from Sigma-Aldrich, Sisco Research Laboratories (SRL), SD fine chemicals (India). To monitor the reactions as well as to establish the identity and purity of reactants and products, TLC was performed on pre-coated silica gel G plates (0.2 mm thickness, Merck, India) using chloroform : ethyl acetate (7 : 3) as a solvent system; the spots were visualized by exposure to iodine vapors or ultra-violet (UV) light cabinet (254 nm). Melting points were determined in open capillary tubes and are uncorrected. Infrared (IR) spectra of synthesized compounds were recorded on a Fourier-transform infrared (FT-IR) spectrophotometer (Shimadzu 8400-S) using potassium bromide (KBr) as an internal standard. ^{1}H nuclear magnetic resonance (NMR) spectra were measured on NMR (500 MHz) spectrometer (Bruker, India) in dimethyl sulfoxide (DMSO-d_6) and $CDCl_3$ and chemical shifts (δ) values were given in parts per million (ppm), downfield from tetramethyl silane (TMS) as an internal standard. Mass spectra were measured on a high-resolution mass spectrometer (HRMS) (Bruker, India). The elemental analyzer was used for elemental (C, H and N) analyses and results obtained were within ±0.4% of the theoretical values. The three-dimensional structure of the sodium channel IIA inactivation gate (PDB ID: 1BYY) was selected from the RCSB Protein Data Bank, which contains information about experimentally determined protein structures. CS ChemDraw Ultra 8.0 was used for ligand preparation. AutoDock 1.5.6 was used for molecular docking studies. Discovery Studio 3.5 visualizer was employed for visualization and further analyses of results.

***Synthesis of 3-(2-Substituted)-4-oxothiazolidin-3yl)-2-phenyluinazolin-4(3H)-one* (3a–3k)** 0.01 mol of *3-amino-2-phenylquinazolin-4(3H)-one* was added to 25 ml of DMF. To this, different aromatic aldehydes (0.012 mol) were added. The reaction mixture was stirred under ice cold condition for 5 min, followed by addition of thioglycolic acid (0.02 mol). After 5 min, DCC (0.012 mol) was added to the reaction mixture at 0 °C and the reaction mixture was stirred for 5 h. The resulting mixture was filtered to remove the insoluble product of dicyclohexylurea. To the filtrate, 25 ml of cold water was added; product was filtered and recrystallised from acetone.

***3-(4-Oxo-2-phenylthiazolidin-3-yl)-2-phenylquinazolin-4(3H)-one* (3a)** Mol. Wt: 399.46; Yield: 79%; mp: 216–218 °C; IR (KBr) cm^{-1}: 1653.05 (C=O str in amide),

1311.64 (C=N str), 1282.71 (N–N str), 3063.06 (C–H str in arom), 1595.18 (C=O str in thiazolidinone), 1444.73 (C–N str), 752.26 (C–S–C str); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.31–7.42 (m, 5H, phenyl of thiazolidinone), 7.42–7.53 (m, 5H, phenyl), 7.53–7.57 (m, 3H, heterocyclic arom), 7.60 (d, $J = 5$ Hz, 1H, arom near C=O), 3.71 (s, 2H, CH_2 of thiazolidinone), 3.47 (s, 1H, CH of thiazolidinone); MS: *m/z* 399 (M); Anal. Calcd. for $C_{23}H_{17}N_3O_2S$: C, 69.15; H, 4.29; N, 10.52. Found: C, 68.94; H, 4.28; N, 10.54.

3-(2-(4-Hydroxyphenyl)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3H)-one **(3b)** Mol. Wt: 415.46; Yield: 72%; mp: 198–200 °C; IR (KBr) cm^{-1}: 1645.33 (C=O str in amide), 1315.50 (C=N str), 1282.71 (N–N str), 3053.42 (C–H str in arom), 1599.04 (C=O str in thiazolidinone), 1442.80 (C–N str), 702.11 (C–S–C str), 1369.50 (O–H str in phenol); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 7.06 (dd, 4H, phenyl of thiazolidinone), 7.64–7.65 (m, 3H, heterocyclic arom), 7.92 (d, $J = 5$ Hz, 1H, heterocyclic arom near C=O), 7.59–7.63 (m, 5H, phenyl), 2.73 (s, 2H, CH_2 of thiazolidinone), 2.51 (s, 1H, CH of thiazolidinone), 10.01 (s, 1H, -OH); MS: *m/z* 416 (M + 1); Anal. Calcd. for $C_{23}H_{17}N_3O_3S$: C, 66.49; H, 4.12; N, 10.11. Found: C, 66.27; H, 4.10; N, 10.13.

3-(2-(4-Methoxyphenyl)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3H)-one **(3c)** Mol. Wt: 429.49; Yield: 79%; mp: 250–252 °C; IR (KBr) cm^{-1}: 1651.12 (C=O str in amide), 1305.85 (C=N str), 3026.41 (C–H str in arom), 1637.62 (C=O str in thiazolidinone), 1442.80 (C–N str), 1174.69 (N–N str), 750.33 (C–S–C str), 1257.63 (C–O str in arylalkyl), 2956.97 (C–H str in alkyl); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 7.15 (dd, 4H, phenyl of thiazolidinone), 7.65–7.66 (m, 3H, heterocyclic arom), 7.96 (d, $J = 5$ Hz, 1H, heterocyclic arom near C=O), 7.28–7.62 (m, 5H, phenyl), 2.52 (s, 2H, CH_2 of thiazolidinone), 3.35 (s, 1H, CH of thiazolidinone), 3.82 (s, 3H, –OCH_3); MS: *m/z* 430 (M + 1); Anal. Calcd. for $C_{24}H_{19}N_3O_3S$: C, 67.12; H, 4.46; N, 9.78. Found: C, 67.02; H, 4.45; N, 9.82.

3-(2-(4-Nitrophenyl)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3H)-one **(3d)** Mol. Wt: 444.46; Yield: 75%; mp: 222–224 °C; IR (KBr) cm^{-1}: 1656.91 (C=O str in amide), 1334.78 (C=N str), 3061.13 (C–H str in arom), 1597.11 (C=O str in thiazolidinone), 1444.73 (C–N str), 1269.20 (N–N str), 761.91 (C–S–C str), 1519.96 (Ar–NO_2 str); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 7.29 (d, $J = 5$ Hz, 2H, phenyl of thiazolidinone), 7.92 (d, $J = 5$ Hz, 2H, phenyl of thiazolidinone), 7.64–7.67 (m, 3H, heterocyclic arom), 7.96 (d, $J = 5$ Hz, 1H, heterocyclic arom near C=O), 7.30–7.62 (m, 5H, phenyl), 2.51 (s, 2H, CH_2 of thiazolidinone), 3.38 (s, 1H, CH of thiazolidinone); Mass: *m/z* 445 (M + 1); Anal. Calcd. for $C_{23}H_{16}N_4O_4S$: C, 62.15; H, 3.63; N, 12.61. Found: C, 61.95; H, 3.64; N, 12.58.

3-(2-(3-Hydroxyphenyl)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3H)-one **(3e)** Mol. Wt: 415.46; Yield: 77%; mp: 230–232 °C; IR (KBr) cm^{-1}: 1728.28 (C=O str in amide), 1340.57 (C=N str), 3059.20 (C–H str in arom), 1662.69 (C=O str in thiazolidinone), 1444.73 (C–N str), 1265.35 (N–N str), 700.18 (C–S–C str),

1166.97 (O–H str in phenol); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 6.85–6.93 (m, 4H, phenyl of thiazolidinone), 7.60–7.63 (m, 3H, heterocyclic arom), 7.92 (d, $J=5$ Hz, 1H, heterocyclic arom near C=O), 7.12–7.21 (m, 5H, phenyl), 2.51 (s, 2H, CH_2 of thiazolidinone), 3.36 (s, 1H, CH of thiazolidinone), 9.67 (s, 1H, –OH); MS: *m/z* 416 (M + 1); Anal. Calcd. for $C_{23}H_{17}N_3O_3S$: C, 66.49; H, 4.12; N, 10.11. Found: C, 66.27; H, 4.13; N, 10.07.

3-(2-(3-Nitrophenyl)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3H)-one **(3f)** Mol. Wt: 444.46; Yield: 78%; mp: 232–234 °C; IR (KBr) cm^{-1}: 1687.77 (C=O str in amide), 1338.64 (C=N str), 3059.20 (C–H str in arom), 1620.26 (C=O str in thiazolidinone), 1446.66 (C–N str), 1298.14 (N–N str), 744.55 (C–S–C str), 1587.47 (Ar–NO_2 str); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 7.91–7.97 (m, 4H, phenyl of thiazolidinone), 7.62–7.66 (m, 3H, heterocyclic arom), 7.79 (d, $J=5$ Hz, 1H, heterocyclic arom near C=O), 7.31–7.61 (m, 5H, phenyl), 2.51 (s, 2H, CH_2 of thiazolidinone), 3.36 (s, 1H, CH of thiazolidinone); MS: *m/z* 445 (M + 1); Anal. Calcd. for $C_{23}H_{16}N_4O_4S$: C, 62.15; H, 3.63; N, 12.61. Found: C, 62.03; H, 3.64; N, 12.56.

3-(2-(4-(Dimethylaminophenyl)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3H)-one **(3g)** Mol. Wt: 442.53; Yield: 70%; mp: 210–212 °C; IR (KBr) cm^{-1}: 1620.26 (C=O str in amide), 1309.71 (C=N str), 3037.99 (C–H str in arom), 1579.75 (C=O str in thiazolidinone), 1440.87 (C–N str), 1242.20 (N–N str), 819.77 (C–S–C str), 2926.11 (C–H str in alkyl); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 6.78 (d, $J=5$ Hz, 2H, phenyl of thiazolidinone), 7.57 (d, $J=5$ Hz, 2H, phenyl of thiazolidinone), 7.95–7.97 (m, 3H, heterocyclic arom), 8.0 (d, $J=5$ Hz, 1H, heterocyclic arom near C=O), 7.61–7.66 (m, 5H, phenyl), 2.51 (s, 2H, CH_2 of thiazolidinone), 3.34 (s, 1H, CH of thiazolidinone), 5.58 (s, 6H, –CH_3); MS: *m/z* 443 (M + 1); Anal. Calcd. for $C_{25}H_{22}N_4O_2S$: C, 67.85; H, 5.01; N, 12.66. Found: C, 67.75; H, 4.99; N, 12.63.

3-(2-(3-Chlorophenyl)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3H)-one **(3h)** Mol. Wt: 433.91; Yield: 80%; mp: 245–247 °C; IR (KBr) cm^{-1}: 1683.16 (C=O str in amide), 1310.75 (C=N str), 3069.80 (C–H str in arom), 1698.70 (C=O str in thiazolidinone), 1442.50 (C–N str), 1245.50 (N–N str), 735.20 (C–S–C str), 750.52 (C–Cl str in arom); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 7.13–7.42 (m, 4H, phenyl of thiazolidinone), 7.82–7.92 (m, 3H, heterocyclic arom), 7.96 (d, $J=5$ Hz, 1H, heterocyclic arom near C=O), 7.52–7.65 (m, 5H, phenyl), 2.51 (s, 2H, CH_2 of thiazolidinone), 3.93 (s, 1H, CH of thiazolidinone); MS: *m/z* 434 (M + 1); Anal. Calcd. for $C_{23}H_{16}ClN_3O_2S$: C, 63.66; H, 3.72; N, 9.68. Found: C, 63.43; H, 3.71; N, 9.72.

3-(2-(3,4-Dimethoxyphenyl)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3H)-one **(3i)** Mol. Wt: 459.52; Yield: 79%; mp: 282–284 °C; IR (KBr) cm^{-1}: 1660.15 (C=O str in amide), 1316.86 (C=N str), 3060.53 (C–H str in arom), 1640.72 (C=O str in thiazolidinone), 1444.80 (C–N str), 1180.59 (N–N str), 720.44 (C–S–C str), 1259.65 (C–O str in arylalkyl), 2950.88 (C–H in alkyl); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 6.93–7.05 (m, 3H, phenyl of thiazolidinone), 7.62–7.65 (m, 3H, heterocyclic arom), 7.90 (d, $J=5$ Hz, 1H, heterocyclic arom near C=O), 7.23–7.60 (m, 5H,

phenyl), 2.55 (s, 2H, CH_2 of thiazolidinone), 3.37 (s, 1H, CH of thiazolidinone), 3.98 (s, 6H, $–OCH_3$); MS: *m/z* 460 (M + 1); Anal. Calcd. for $C_{25}H_{21}N_3O_4S$: C, 65.34; H, 4.61; N, 9.14. Found: C, 65.10; H, 4.60; N, 9.11.

3-(2-(2-Chlorophenyl)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3H)-one **(3j)** Mol. Wt: 433.91; Yield: 78%; mp: 248–250 °C; IR (KBr) cm^{-1}: 1686.36 (C=O str in amide), 1320.76 (C=N str), 3070.82 (C–H str in arom), 1696.60 (C=O str in thiazolidinone), 1446.53 (C–N str), 1280.50 (N–N str), 736.20 (C–S–C str), 748.62 (C–Cl str in arom); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 7.29–7.44 (m, 4H, phenyl of thiazolidinone), 7.87–7.93 (m, 3H, heterocyclic arom), 7.96 (d, $J = 5$ Hz, 1H, heterocyclic arom near C=O), 7.45–7.65 (m, 5H, phenyl), 2.55 (s, 2H, CH_2 of thiazolidinone), 3.65 (s, 1H, CH of thiazolidinone); MS: *m/z* 434 (M + 1); Anal. Calcd. for $C_{23}H_{16}ClN_3O_2S$: C, 63.66; H, 3.72; N, 9.68. Found: C, 63.40; H, 3.72; N, 9.66.

3-(2-(4-Fluorophenyl)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3H)-one **(3k)** Mol. Wt: 417.46; Yield: 70%; mp: 220–222 °C; IR (KBr) cm^{-1}: 1682.46 (C=O str in amide), 1318.86 (C=N str), 3075.82 (C–H str in arom), 1698.65 (C=O str in thiazolidinone), 1448.63 (C–N str), 1285.70 (N–N str), 726.40 (C–S–C str), 1050.60 (C–F str in arom); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 7.22 (d, $J = 5$ Hz, 2H, phenyl of thiazolidinone), 7.29 (d, $J = 5$ Hz, 2H, phenyl of thiazolidinone), 7.64–7.81 (m, 3H, heterocyclic arom), 7.84 (d, $J = 5$ Hz, 1H, heterocyclic arom near C=O), 7.44–7.62 (m, 5H, phenyl), 2.51 (s, 2H, CH_2 of thiazolidinone), 3.35 (s, 1H, CH of thiazolidinone); MS: *m/z* 418 (M + 1); Anal. Calcd. for $C_{23}H_{16}FN_3O_2S$: C, 66.17; H, 3.86; N, 10.07. Found: C, 65.97; H, 3.84; N, 10.04.

Pharmacology

Anticonvulsant activity was determined by maximal electro-shock (MES) induced convulsion test using albino mice of either sex weighing 25–30 g of body mass. The animals were divided into different groups (control, test and standard) containing six animals each. The animals were housed in standard polypropylene cages under standard laboratory conditions (12:12 h light/dark cycle at 25 ± 3 °C). They had free access to standard commercial diet and water. The ethical guidelines for the investigation of animals used in experiments were followed in all tests.

Maximal electro-shock (MES) induced convulsions

In this test, the mice were subjected to 50 mA alternating current from a convulsiometer for 0.2 s through a pair of electrodes attached to each ear. The duration of tonic hind limb extensor phase and the number of animals protected from convulsions were noted. In this study, the animals were administered 25 mg/kg dose of the test drugs and standard drug phenytoin. The test and standard drug compounds were suspended in 0.1% carboxy methyl cellulose (CMC) and administered intraperitoneally 30 min prior to testing. The control group animals, instead, received the 10 mg/kg vehicle (0.1% CMC). A complete abolition of tonic hind limb extension

was considered as 100% protection. The ability to prevent this feature was considered as an indication of anticonvulsant activity.

Statistical analysis

The results were expressed as mean ± SEM; n represents the number of animals. Data obtained from pharmacological experiments were analyzed with one-way analysis of variance (ANOVA) followed by Dunnett's t-test. A *P*-value of less than 0.001 was considered statistically significant.

Molecular docking study

Protein preparation

The 3D crystal structure of the sodium channel IIA inactivation gate with PDB ID: 1BYY [30] was obtained from the Brookhaven Protein Data Bank (PDB; http://www.rcsb.org/pdb). and hydrogens were added. The receptor file was converted to the pdbqt format, which is pdb plus 'q' charges and 't' AutoDock type. To confirm the AutoDock types, polar hydrogens should be present, whereas non-polar hydrogens and the lone pair should be merged; each atom should be assigned Gasteiger partial charges.

Ligand design

The structure of ligands is one of the most important determinants for successful docking, thus pre-analysis of the ligand structures is most important. The drugs' like properties of ligands were confirmed by manually applying the Lipinski's Rule of Five and used for the further studies. ChemDraw Ultra 8.0 (Cambridge Soft.com 100 Cambridge park drive, Cambridge, MA, 02140, USA) was used to draw the structure of the ligands (**3a**–**3k**). The ligands were cleaned in 2D and further in 3D by addition of explicit hydrogens and the gradient optimization function of MarvinSketch 5.8.1 (Chemaxon Ltd; http://www.chemaxon.com). Original states of ionization were retained and chiralities were determined from the 3D structures. All the structures were written in Tripos mol2 file format. AutoDock requires that ligands give partial atomic charges and AutoDock atom types for each atom; it also needs a description of rotatable bonds in the ligands. AutoDock depends upon the concept of a tree in which the rigid core of the molecule is 'root' and flexible parts are 'branches' that extends from the root. This set consists of united atoms, aromatic carbons in a cycle, aliphatic carbons, hydrogen bonded nitrogen, polar hydrogens and directly hydrogen bonded oxygen, among others, each with partial charges. Therefore pdbqt format was used for ligands, which were recognized by AutoDock. The torsional degree of freedom is used in calculating the change in free energy caused by loss of a torsional degree of freedom upon binding; in AutoDock 1.5.6,

the torsional degree of freedom value for the ligand is the total number of rotatable bonds in the ligand.

Molecular docking simulations

AutoDock allows fully flexible modeling of specific portions of the protein, in a manner similar to that of ligands [31, 32]. Prior to the actual docking run, AutoGrid 1. 5. 6 was introduced to pre-calculate grid maps of interaction energies of various atom types [33, 34]. In the present study, the binding site was selected based on the amino acid residues, which were involved in binding with sodium channel IIA inactivation gate obtained from Protein Data Bank with ID 1BYY. Therefore the grid was centered at the region including amino acid residues (GLU1492, LYS1502) that surround the active sites. In the procedure of docking, a grid map with $60 \times 60 \times 60$ points, a grid spacing of 0.375 Å were used and the maps were centered on the ligand binding sites with centers $x = 5.669$, $y = 5.401$ and $z = -1.697$. An affinity grid was calculated for each type of atom in the substrate, typically carbon, oxygen, nitrogen and hydrogens, as well as a grid of electrostatic potential, using point charge of +1 as the probe [35, 36]. The Lamarckian Genetic Algorithm (LGA) based on an optimization algorithm [37] was used to find the conformers with lowest binding energy. The docking task was finally performed by two commands: (i) autogrid4. exe –p 1BYY.gpf –l 1BYY.glg and (ii) autodock4.exe –p ligand.dpf –l ligand.dlg. The results of molecular docking studies were obtained in dlg files in the form of estimated free energy bindings (kcal/mol) and inhibition constant *(Ki* in μM) at 298.15 K temperature. The dlg file was then converted into the pdbqt format. For visualization and analyses of docking results, Discovery Studio Visualizer version 3.5 was used, which explored hydrogen, hydrophobic and van der Waals contacts.

Results and discussion

Target compounds **(3a–3k)** were synthesized according to Scheme 1 by a two-component reaction using *3-amino-2-phenylquinazolin-4(3H)-one*, substituted aromatic aldehydes, TGA and DCC in *N*, *N*-dimethyl formamide as a solvent. The reaction mixture was stirred for 5 h. This reaction proceeds with initial formation of imine (the nitrogen of the amino group attacks the carbonyl carbon of the aldehydes) and a

3-amino-2-phenylquinazolin-4(3H)-one

Substituted aromatic aldehydes

3-(2-substituted)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3*H*)-one **(3a-3k)**

Scheme 1 Synthesis of target compounds (**3a**–**3k**)

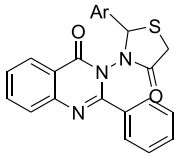
nucleophilic attack of thiol on imino carbon followed by intramolecular cyclization by the loss of water. *N*, *N*′-dicyclohexyl carbodiimide (DCC) was used as a dehydrating agent to accelerate the intramolecular cyclization, resulting in faster reaction and improved yields [38, 39]. All the target compounds were identified and confirmed by physical and spectral data. In general, IR (KBr) spectra displayed the C=O peak in cyclic amide at 1620.26–1728.28 cm^{-1}. The other characteristic peaks, such as C=O stretching of thiazolidinone, C-H stretching of the aromatic ring, C=N and C–S–C stretching, were observed at 1579.75–1698.70 cm^{-1}, 3026.41–3075.82, 1305.85–1340.57 cm^{-1} and 700.18–819.77 cm^{-1} , respectively. In the nuclear magnetic resonance (^{1}H NMR) spectra, the signals of the respective protons of the target compounds were confirmed on the basis of their chemical shift (δ ppm) values. The spectra showed CH_2 protons of thiazolidinone as a singlet at 2.51–3.71 ppm and aromatic protons as a multiplet at 7.12–7.61 ppm. In the mass spectra of synthesized compounds, the molecular ion was evident and its mass was measured. From physical, spectral and elemental analysis data, all the target compounds were in conformity and structures were envisaged.

All the synthesized *3-(2-substituted)-4-oxothiazolidin-3yl)-2-phenyluinazolin-4(3H)-one* **(3a–3k)** derivatives were assessed manually against Lipinski's Rule of Five [40]. Lipinski's Rule of Five states that for a chemical compound to be a successful oral drug, it should fall within following criteria: (i) Number of hydrogen bond donors (sum of OHs and NHs) should be ≤ 5, (ii) Number of hydrogen bond acceptors (sum of Os and Ns) should be ≤ 10, (iii) Its molecular weight should be ≤ 500, (iv) Its ClogP value should be ≤ 5. All the synthesized compounds were found within the limits of the parameters described by the Lipinski *et al*. (Table 1). Anticonvulsant activity of each of the synthesized compounds **(3a–3k)** was investigated by the MES model [41] and the results are shown in Table 2. According to the results of the experiment, it was observed that compounds **3b**, **3c**, **3d**, **3e**, **3f** and **3i** with substituted *p*-hydroxy, *p*-methoxy, *p*-nitro, *m*-hydroxy, *m*-nitro and 3,4-dimethoxy derivatives showed significant anticonvulsant activities at dose 25 mg/kg. Compounds **3b**, **3d**, **3f** and **3i** demonstrated 100% protection, considered an indication of anticonvulsant activity.

Analyzing the anticonvulsant activities of synthesized compounds **3b**, **3c**, **3d**, **3e**, **3f** and **3i** the structure-activity relationship (SAR) reveals that presence of electron withdrawing groups such as -NO_2 at *p*- and *m*- position increases the anticonvulsant activity. Also the presence of electron rich groups such as –OH, –OCH_3 shows significant anticonvulsant activity. The compounds **3c, 3e, 3h**, **3j**, **3k** with substituted *m*-chloro, *o*-chloro and *p*-fluoro derivatives exhibited moderate anticonvulsant activity with 83% protection, and other compounds **3a** with substituted *3,4*-dimethyl amino and **3g** derivatives had 67% protection with poor anticonvulsant activity.

To predict possible binding interactions, the proposed ligands (**3a–3k**) were docked into the sodium channel IIA inactivation gate by using AutoDock 1.5.6. Sulfur present in the thiazolidinone ring is an isostere of the nitrogen of Phenytoin containing an imidazolidine-2,4-dione ring, because in nitrogen and sulfur peripheral layers of electrons can be considered identical. [42, 43]. Phenytoin shows anticonvulsant activity by acting as voltage-gated sodium channel blocker [44, 45]. Hence, for the anticonvulsant activity, the 3D crystal structure of the

Table 1 Calculation of various descriptors for proposed *3-(2-substituted)-4-oxothiazolidin-3yl)-2-phenyluinazolin-4(3H)-one* (**3a**–**3k**) according to Lipinski's Rule of Five



(**3a-3k**)

Compound	No. of H-bond donors	No. of H-bond acceptors	CLogP	Molecular weight	Lipinski violation
3a	0	5	4.32	399.46	0
3b	1	6	3.65	415.46	0
3c	0	6	4.24	429.49	0
3d	0	8	4.06	444.46	0
3e	1	6	3.65	415.46	0
3f	0	8	4.06	444.46	0
3g	0	6	4.48	442.53	0
3h	0	5	5.00	433.91	0
3i	0	7	3.98	459.52	0
3j	0	5	5.00	433.91	0
3k	0	5	4.46	417.46	0

sodium channel IIA inactivation gate with PDB ID 1BYY (Fig. 2) was selected from the Protein Data Bank. The sodium channel IIA inactivation gate has a helix structure with a length of 11 amino acid residues including GLU1492, LYS1495, MET1490 PHE1489 and LYS1502. The grid was centered at the region including amino acid residues (GlU1492, LYS1502) that surround the active sites as shown in Fig. 3. The results were expressed in terms of estimated free binding energies (kcal/mol) and estimated inhibition constants *(Ki* in μM) as shown in Table 3. Molecular docking studies indicated that estimated free energy of binding of docked ligand ranged between − 5.15 and − 6.13 (kcal/mol), while their estimated inhibition constants (*Ki*) were found between 32.00 and 166.94 μM. The interacting amino acid residues were found to be GLU1492, MET1490, PHE1489 and LYS1495. Further analyses of results showed that *p*-nitro substituted derivatives of **3d** shown the highest affinity towards sodium channel IIA inactivation gate, with interacting amino acid residues MET1490, LYS1495 and additionally PHE1489. In contrast, *p*-fluoro substituted derivative **3k** shown moderate affinity and un-substituted phenyl derivative **3a** was found to have the least affinity towards sodium channel IIA inactivation gate, with interacting amino acid residues like MET1490, LYS1495 and PHE1489. The docking results were compared

Table 2 Anticonvulsant activity of compounds (**3a**–**3k**) using Maximal electro-shock (MES) induced convulsion model

Group	Dose (mg/kg)	Duration of Tonic Hind Limb Extension Phase (Sec.) (Mean ± SEM)	Animals protected (%)
Normal control (normal saline)	10 ml/kg	25.516 ± 0.5163	0
3a	25 mg/kg	18.976 ± 0.3588	67
3b	25 mg/kg	15.128 ± 0.4776*	100
3c	25 mg/kg	15.542 ± 0.4908*	83
3d	25 mg/kg	13.117 ± 0.3578*	100
3e	25 mg/kg	16.450 ± 0.5527*	83
3f	25 mg/kg	13.226 ± 0.4117*	100
3g	25 mg/kg	18.406 ± 0.5074	67
3h	25 mg/kg	17.262 ± 0.4547	83
3i	25 mg/kg	14.538 ± 0.3684*	100
3j	25 mg/kg	17.441 ± 0.3266	83
3k	25 mg/kg	17.165 ± 0.4109	83
Standard (Phenytoin)	25 mg/kg	6.412 ± 0.4364*	100

$n = 6$ in each group

*$P < 0.001$ compared against the control group

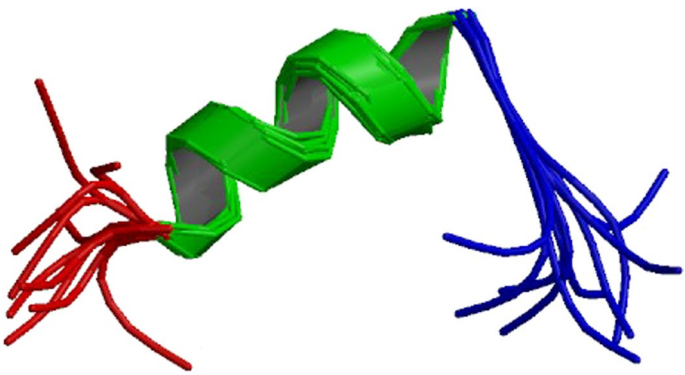


Fig. 2 1BYY: Sodium Channel IIA Inactivation Gate

with standard phenytoin with binding energy −4.56 kcal/mol and interacting amino acid residues such as GLU1492, MET1490, PHE1489 and LYS1495. Docking of most active **3d**, moderate active **3k**, least active **3a** and standard phenytoin in 1BYY sodium channel IIA inactivation gate are shown in Figs. 4, 5, 6 and 7.

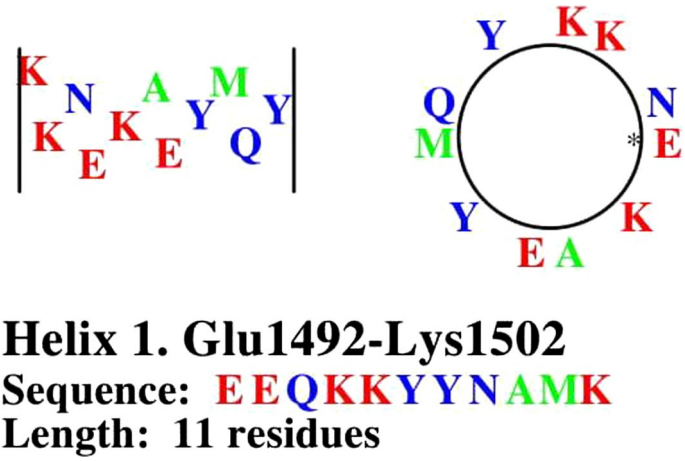


Fig. 3 Helix 1 Structure of Sodium Channel IIA Inactivation Gate

Table 3 Molecular docking analysis results of *3-(2-substituted)-4-oxothiazolidin-3yl)-2-phenyluinazolin-4(3H)-one* (**3a**–**3k**)

Compound	Binding Energy (kcal/mol)	Inhibition constant (*Ki*, μM)	No. of hydrogen bonds involved	Interacting atoms of the protein
3a	− 5.15	166.94	1	MET1490
3b	− 5.88	48.82	1	MET1490
3c	− 5.79	56.54	2	MET1490, LYS1495
3d	− 6.13	32.00	2	MET1490, LYS1495
3e	− 5.65	71.95	2	MET1490, LYS1495
3f	− 5.97	42.23	1	LYS1495
3g	− 5.29	133.21	1	MET1490
3h	− 5.33	123.05	1	MET1490
3i	− 5.97	42.07	2	MET1490, LYS1495
3j	− 5.31	128.69	1	LYS1495
3k	− 5.36	117.23	1	MET1490
Phenytoin (Standard)	− 4.56	456.92	1	GLU1492

Conclusion

A series of eleven novel *3-(2-substituted)-4-oxothiazolidin-3yl)-2-phenyluinazolin-4(3H)-ones* **(3a–3k)** were synthesized in this study. Synthesized compounds were characterized by physical as well as spectral data including IR, ^{1}H NMR, mass spectra and elemental analysis. Their anticonvulsant activities were evaluated using the maximal electro-shock (MES) induced convulsion model. Six compounds, **3b**, **3c**, **3d, 3e**, **3f** and **3i**, possess significant anticonvulsant activity, and

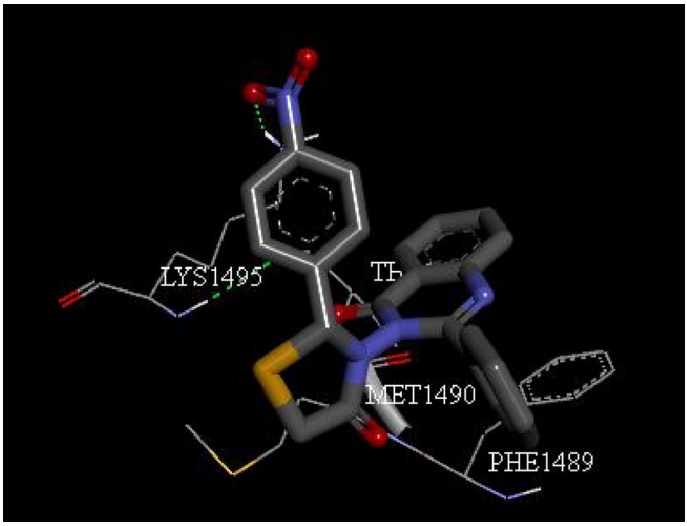


Fig. 4 Docking of most active compound **3d** (Binding energy − 6.13 kcal/mol) in sodium channel IIA inactivation gate (PDB ID: 1BYY)

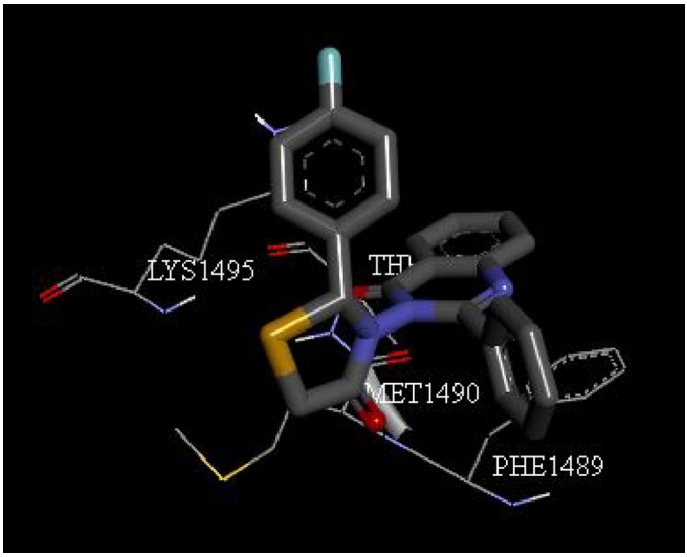


Fig. 5 Docking of moderate active compound 3 k (Binding energy − 5.36 kcal/mol) in sodium channel IIA inactivation gate (PDB ID: 1BYY)

lower activity as compared to the standard drug. The compounds were administered intraperitoneally at the dose of 25 mg/kg and compared with control ($P < 0.001$). Binding energies ranging from − 5.15 to − 6.13 kcal/mol were found for all synthesized compounds when subjected to molecular docking study with

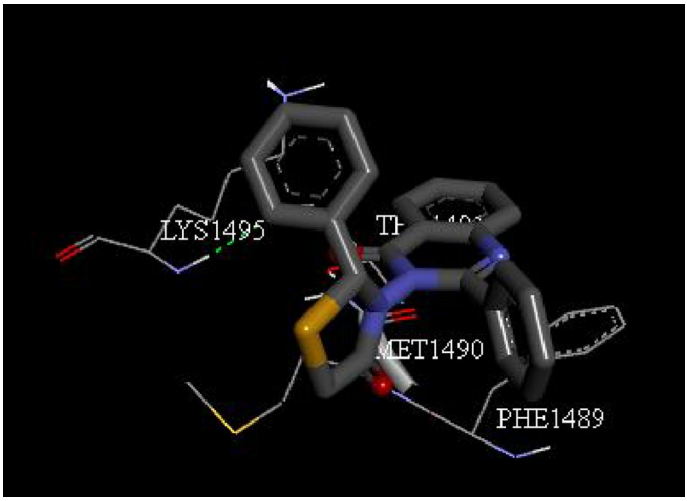


Fig. 6 Docking of least active compound **3a** (Binding energy −5.15 kcal/mol) in sodium channel IIA inactivation gate (PDB ID: 1BYY)

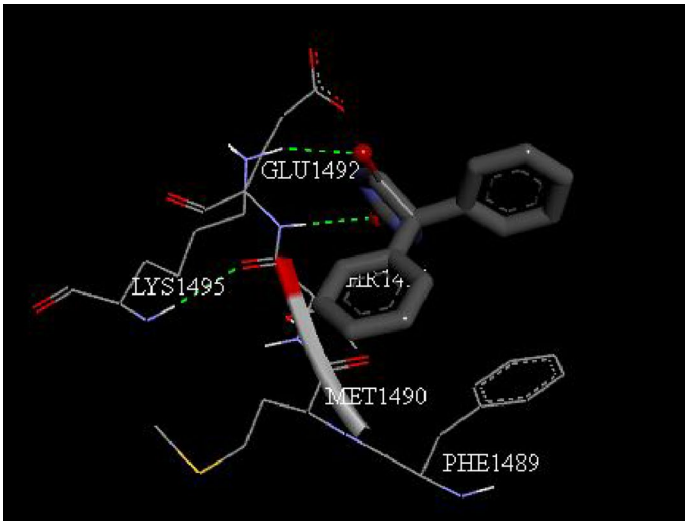


Fig. 7 Docking of phenytoin (Binding energy −4.56 kcal/mol) in sodium channel IIA inactivation gate (PDB ID: 1BYY)

a sodium channel IIA inactivation gate (PDB ID: 1BYY). Compound **3d** exhibited significant binding energy, −6.13 kcal/mol, when compared with others and standard phenytoin. The obtained result showed that active compounds could be used as a template for future design and investigation to produce more active analogs. However, these compounds should be optimized in order to increase their efficacy and potency.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. C. Wei, D. Wu, Z. Sun, K. Chai, Z. Quan, Med. Chem. Res. **19**, 925 (2009)
2. M. Gasior, R. Carter, S. Goldberg, J. Witkin, J. Pharrmacol. Exp. Ther. **282**, 543 (1997)
3. V. Alagarsamy, S. Govindaraj, Med. Chem. Res. **22**, 1711 (2013)
4. G. Bell, J. Sander, Seizure **10**, 306 (2002)
5. A. Seth, P. Sharma, A. Tripathi, P. Choubey, P. Srivastava, P. Tripathi, S. Shrivastava, Med. Chem. Res. **27**, 1206 (2018)
6. A. EI-Helby, R. Ayyad, H. Sakr, A. Abdelrahim, K. EI-Adl, F. Sherbiny, I. Eissa, M. Khalifa, J. Mol. Struct. **1130**, 333 (2017)
7. Z. Quan, C. Zhang, C. Yang, X. Deng, Med. Chem. Res. **21**, 3294 (2012)
8. B. Spear, Epilepsia **42**, 31 (2001)
9. H. Bootsma, L. Ricker, Y. Hekster, J. Hulsman, D. Lambrechts, M. Majoie, A. Schellekens, M. de Krom, A. Aldenkamp, Seizure **18**, 327 (2009)
10. G. Kennedy, S. Lhatoo, CNS Drugs **22**, 739 (2008)
11. S. Xue, J. McKenna, W. Shieh, O. Repic, J. Org. Chem. **69**, 6474 (2004)
12. D. Al-Shamary, M. Al-Alshaikh, N. Kheder, Y. Mabkhot, S. Badshah, Chem. Cent. J. **11**, 1 (2017)
13. M. Al-Alshaikh, D. Al-Shammary, F. El-Baih, Res. J. Chem. Environ. **17**, 48 (2013)
14. A. Alafeefy, A. Kadi, A. El-Azab, S. Abdel-Hamid, M. Daba, Arch. Pharm. (Weinheim) **341**, 377 (2008)
15. V. Ram, B. Farhanullah, A.Srivastava Tripathi, Bioorg. Med. Chem. **11**, 2439 (2003)
16. A. Al-Obaid, S. Abdel-Hamide, H. El-Kashef, A. Abdel-Aziz, A. El-Azab, H. Al-Khamees, H. El-Subbagh, Eur. J. Med. Chem. **44**, 2379 (2009)
17. L. Werbel, M. Degnan, J. Med. Chem. **30**, 2151 (1987)
18. Y. Kabri, N. Azas, A. Dumetre, Eur. J. Med. Chem. **45**, 616 (2010)
19. Y. Kim, H. Choi, J. Lee, Bioorg. Med. Chem. Lett. **18**, 6279 (2008)
20. S. Kashaw, V. Jatav, P. Mishra, N. Jain, J. Stable, Eur. J. Med. Chem. **44**, 4335 (2009)
21. V. Jatav, P. Mishra, S. Kahaw, J. Stable, Eur. J. Med. Chem. **43**, 1945 (2008)
22. A. El-Azab, E. Tahir, Bioorg. Med. Chem. Lett. **22**, 1879 (2012)
23. K. Babaoglu, M. Page, V. Jones, M. McNeil, C. Dong, J. Naismith, R. Lee, Bioorg. Med. Chem. Lett. **13**, 3227 (2003)
24. V. Gududuru, E. Hurh, J. Dalton, D. Miller, J. Med. Chem. **48**, 2584 (2005)
25. M. Vigorita, R. Ottana, F. Monforte, R. Maccari, A. Traovato, Bioorg. Med. Chem. Lett. **11**, 2791 (2001)
26. B. Goel, R. Tyagi, E. Bansal, N. Sinha, Eur. J. Med. Chem. **34**, 265 (1999)
27. N. Desai, A. Dodiya, A. Makwana, Med. Chem. Res. **21**, 2320 (2012)
28. A. Errington, T. Stohr, G. Lees, Curr. Top. Med. Chem. **5**, 15 (2005)
29. I. Batool, A. Saeed, I. Qureshi, S. Kalsoom, A. Razzaq, Res. Chem. Intermed. **42**, 1139 (2016)
30. C. Rohl, F. Boeckman, C. Baker, T. Scheuer, W. Catterall, R. Klevit, Biochemical **38**, 855 (1999)
31. M. Sharma, S. Suthar, V. Aggarwal, M. Chauhan, A. Sharma, S. Bansal, Med. Chem. Res. **24**, 1331 (2015)
32. G. Morris, R. Huey, W. Lindstrom, M. Sanner, R. Belew, D. Goodsell, A. Olson, J. Comput. Chem. **30**, 2785 (2009)
33. S. Bansal, B. Sinha, R. Khosa, Med. Chem. Res. **22**, 134 (2013)
34. P. Goodford, J. Med. Chem. **28**, 849 (1985)
35. S. Allison, R. Bacquet, J. McCammon, Biopolymers **27**, 251 (1998)
36. K. Sharp, R. Fine, B. Honig, Science **236**, 1460 (1987)

37. F. Solis, R.J.-B. Wets, Math. Oper. Res. **6**, 19 (1981)
38. A. Joseph, S. Suthar, V. Jaiswal, S. Lohan, S. Bansal, A. Chaudhary, A. Tiwari, A. Alex, Eur. J. Med. Chem. **63**, 589 (2013)
39. C. Kavitha, S. Basappa, K. Swamy, S. Mantelingu, M. Doreswamy, J. Sridar, K.Rangappa Prasad, Bioorg. Med. Chem. **14**, 2290 (2006)
40. C. Lipinski, F. Lombardo, B. Dominy, P. Feeney, Adv. Drug Deliv. Rev. **46**, 3 (2001)
41. R. Sharma, G. Misra, J. Sainy, S. Chaturvedi, Med. Chem. Res. **20**, 245 (2011)
42. E. LaVoie, G. Patani, Chem. Rev. **96**, 3147 (1996)
43. H. Erlenmeyer, M. Leo, Helv. Chim. Acta **15**, 1171 (1932)
44. H. Bolcskei, I. Tamawa, P. Kocsis, Med. Chem. Res. **17**, 356 (2008)
45. C. Kuo, Mol. Pharmacol. **54**, 712 (1998)