

Original Research Paper

β -Naphthalene Incorporated Thiazole-5-Carboxamides/Thiazole -5- Ketones: Design, Synthesis and Anticonvulsant Screening against Two Seizure Models

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Abstract: A bunch of β -naphthalene incorporated thiazole-5-carboxamides/thiazole -5- ketones (**7a-7o** & **8a-8e**) were prepared by reacting 4-methyl-2-(naphthalen-2-yl)thiazole-5-carbonyl chloride with appropriate amines. Structures of all the compounds were explained by elemental analysis, FT-IR, ¹H NMR and mass spectral data. The compounds were evaluated for their anticonvulsant activity employing MES and chemoshock (scPTZ) seizure tests. Neurotoxicity was also assessed. Majority of these compounds exhibited significant activity against both animal models; however, compounds **7e**, **7j**, **7n** and **8c** displayed promising activity and could be considered as leads for further investigations.

Keywords: Thiazole, MES, scPTZ, Anticonvulsant Activity

Introduction

Epilepsy is a group of neurological conditions which has characteristics of epileptic seizures (Chang and Lowenstein, 2003; Robert *et al.*, 2014). Epileptic seizures are episodes that can differ from brief and nearly unnoticeable to long periods of forceful shaking. In the brain, epilepsy causes unusual release of neurotransmitters due to which the electrical working of brain gets disturbed prompting muscle spasm, nausea, convulsions and loss of consciousness (Al-Otaibi, 2019). It can be triggered by brain injuries, tumours, high fevers or strokes. In a substantial number of epilepsies, hereditary factor also plays an important role in the development of seizures.

Approximately 65 million people in the world are impacted by various types of epilepsy (Thurman *et al.*, 2011). The occurrence of epilepsy and other seizure related disorders in Saudi population was assessed approximately 0.65% (Al-Rajeh *et al.*, 2001). The lacks of single fundamental mechanism in case of epilepsy and, the multi-factorial origin of the disease create much more difficulty in developing new antiepileptic drugs. Furthermore, treatment of various epilepsies and particularly the partial one, which is the most common type, present a continuous headache to the drug developers. The typical antiepileptic drugs comprise phenobarbital, phenytoin, carbamazepine and valproic acid have been existing in several European countries since 1960s (Hess, 1985). All these currently

accessible antiepileptic drugs have neurological toxicity and idiosyncratic side effects (Brodie, 1990). The search for new antiepileptic compounds with more selectivity and lower toxicity is uninterruptedly an area of investigation for medicinal chemists. The important and highly effective approach to treat epilepsy is the identification of new targets through better understanding of molecular mechanisms of epilepsy.

In the last two decades, several new naphthalene analogues were synthesized for antiepileptic screening. The first naphthalene derivative developed as an antiepileptic agent was nafimidone. Nafimidone, a derivative of imidazole was discovered in early eighties, having structurally different class with exclusive properties. Till now, studies have revealed that nafimidone is a potent anticonvulsant than phenytoin. But the problems with the drug are huge in terms of its toxicity and low potency. The drug inhibits carbamazepine and phenytoin metabolism which in turn, leads to severe toxicity. Considering nafimidone as lead, various analogues of nafimidone or similar compounds were synthesized in recent years (Fig. 1; I, II, III and IV) and promising anticonvulsant results were observed with less toxicity (Karakurt *et al.*, 2001; 2006; 2010; 2012; Ozdemir *et al.*, 2014). The optimization of nafimidone is continued in the hope that the potent and less toxic nafimidone derivative will usher a new era of antiepileptic drug development.

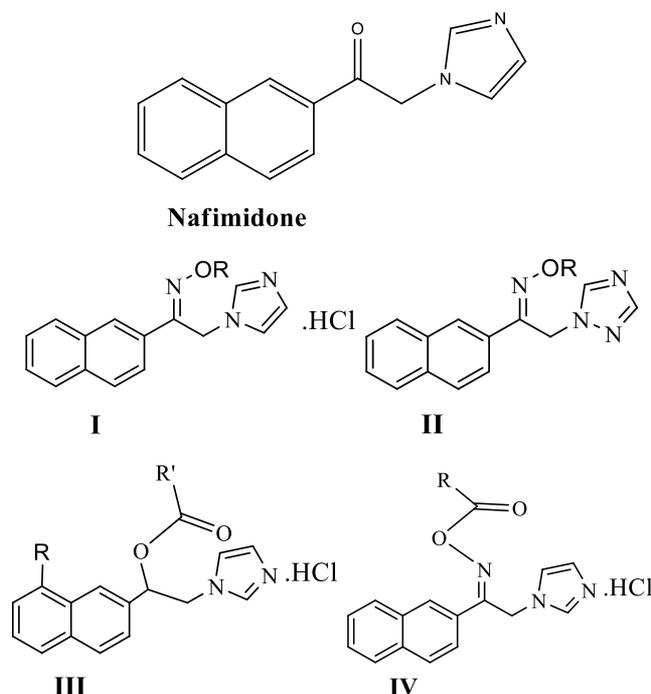


Fig. 1: Recently synthesized promising antiepileptic agents

In our study, β -naphthalene incorporated thiazole-5-carboxamide derivatives were aimed on the basis of structural similarities with nafimidone. Furthermore, the imidazole moiety of nafimidone was replaced with thiazole ring with the expectation to improve the bioactivity since thiazole possessed neuroprotective as well as antiseizure activity (Koufaki *et al.*, 2007; Amin *et al.*, 2008). The presence of sulfur moiety in the thiazole ring may facilitate the drugs to cross the Blood Brain Barrier (BBB) due to lipophilic nature and exhibit more anticonvulsant activity.

To understand the possible mode of action of substituted naphthalenyl-thiazole derivatives at the molecular level, we carried out molecular docking simulations studies of synthesized molecules (7a-7o&8a-8e) at the GABA aminotransferase catalytic ligand binding site. For the validation of docking parameters, the rosmarinic acid, a well-known gamma amino butyric acid (GABA) transaminase inhibitor was docked at the catalytic site of protein and the root-mean-square deviation (RMSD) between co-crystal and docked pose was found to be 0.255 Å (less than 2 Å).

Experimental

Chemical Synthesis

The melting points were determined in open capillary tubes in a Hicon melting point device and

are not changed. Elemental analysis was performed on a Vario-EL III CHNOS- Elemental analyzer and the results were within $\pm 0.4\%$ of the theoretical values of elements. The Fourier Transform Infrared (FTIR) spectra were documented in KBr pellets on a Jasco FT/IR 410 spectrometer and the values were attributed in inverse centimeter (ν_{\max} - cm^{-1}). The ^1H NMR spectra were taken on a Bruker model dpx 300 (300 MHz) NMR spectrometer and chemical shifts (δ) are presented in part per million (ppm) from the peak of Tetramethylsilane (TMS) which is used as reference standard. Mass spectra were taken on a Bruker Ion trap (Esquire 3000) mass spectrophotometer. The consistency of the compounds was checked by Thin Layer Chromatography (TLC) on silica gel G (Merck) coated plates by using toluene: Ethyl acetate: Formic acid (5:4:1) as solvent system. The TLC spots were visualized by using iodine chamber and UV lamp. Lipophilicity (Log P) was measured using ACD lab software version 12.0. The docking simulations study of synthesized compounds was performed using Maestro, version 9.4 implemented from Schrodinger software suite. The protein structure for docking study was obtained from protein data bank (PDB ID: 1OHW) and prepared by eliminating solvent, adding hydrogen and further energy minimization was achieved in the presence of bound ligand using protein preparation software. The ligands were sketched in 3D format using build panel and

were prepared for docking, making use of Ligprep application. Docking of title compounds were performed using Glide extra-precision (XP) mode, with up to three poses saved per molecule.

Synthesis of Naphthalene-2-Carbonitrile (2)

To a mixture of hydroxylamine hydrochloride (0.515 mol) and sodium formate (0.687 mol) in formic acid (anhydrous, 300 mL), 2-naphthaldehyde (0.343 mol) was mixed and the reaction blend was heated to 100°C for almost eight hours. After completion of reaction, the reaction mixture was cooled down to about 40°C and water was mixed. The reaction blend was cooled to about 25°C and agitated for about 1 h. The solid precipitated was strained, washed with water and dehydrated. The solid was then dissolved in acetone at about 50°C and water was mixed slowly over a time of about 30 min. The mixture was cooled to about 25°C and again agitated for about 1 h. The solid thus collected was strained, washed with acetone and water (1:1) mixture and dehydrated to obtain the title product.

Synthesis of Naphthalene-2-Carbothioamide (3)

To a suspension of sodium hydrosulfide (NaSH) (hydrate, 70% w/w) (11.98 g, 0.150 mol) and MgCl₂·6 H₂O (15.20 g, 0.075 mol) in DMF (100 mL), 2-nitrile naphthalene (0.075 mol) was added. The reaction blend was agitated at 20°C for 18 h and progress of reaction was checked on TLC. On finishing point of the reaction, the mixture was added in water (200 mL). The precipitated solid was washed with water and then agitated in 1N HCl (200 mL) for 20 min. After filtration and washing with water, the product was crystallized from toluene and hexane, obtaining the title compound, as a yellow solid. Yield: 79%, mp: 144°C.

Synthesis of Ethyl 4-Methyl-2-(Naphthalen-2-yl)Thiazole-5-Carboxylate (4)

Naphthalene-2-carbothioamide (0.069 mol) was dissolved in EtOH (130 mL) and to this, ethyl-2-chloroacetoacetate (9.5 mL, 11.30 g, 0.069 mol) was added. The reaction blend was refluxed for 16 hours. When the starting compound was completely finished, the reaction blend was cooled to room temperature and the product was strained. Crystal formation of intermediate was done from ethanol, obtaining a white solid at the bottom of the container. Yield: 71%; m.p.: 185°C, ¹H-NMR (300 MHz, DMSO-*d*₆): δ 2.66 (s, 3H, CH₃), 1.34 (t, 3H, CH₂CH₃), 4.32 (q, 2H, CH₂CH₃), 7.62-7.65 (m, 2H, Ar-H), 7.89-7.93 (m, 2H, Ar-H), 8.04-8.07 (m, 2H, Ar-H), 8.32 (s, 1H, Ar-H); ESI-MS *m/z* 297.08 (M⁺), 253.98, 226.17

4-Methyl-2-(Naphthalen-2-yl)Thiazole-5-Carboxylic Acid (5)

Thiazole-5-Carboxylic Acid (5)

To a mixture of ethanol (25 ml) and THF (05 ml) containing ethyl 4-methyl-2-(naphthalen-2-yl)thiazole-5-carboxylate (compound **4**, 0.01 mol), 2 ml of 1N NaOH was mixed and content was refluxed for 8 hr. After the reaction is complete the mixture was checked by TLC, the solvent was removed under evaporation and the residue was neutralized by 1N HCl to pH 2-3. The precipitated solid was strained, washed with water and crystal formation was done from aqueous ethanol. Yield: 68%; m.p.: 154°C; ¹H-NMR (300 MHz, DMSO-*d*₆): δ 2.65 (s, 3H, CH₃), 7.65-7.68 (m, 2H, Ar-H), 7.86-7.90 (m, 2H, Ar-H), 8.05-8.08 (m, 2H, Ar-H), 8.35 (s, 1H, Ar-H), 10.56 (s, 1H, COOH); ESI-MS *m/z* 269.05 (M⁺), 253.92, 226.26.

Synthesis of 4-Methyl-2-(Naphthalen-2-yl)Thiazole-5-Carbonyl Chloride (6)

To a mixture of 4-methyl-2-(naphthalen-2-yl)thiazole-5-carboxylic acid (compound **5**) (0.02 mol) in dry toluene in 50 ml RBF, thionyl chloride (0.06 mol) was added. The resulting blend was refluxed for about 4 hour. The status of the reaction was checked by TLC using TEF as solvent system. At the end of the reaction the extra thionyl chloride was eliminated by distillation under low pressure. The crude acyl chloride was obtained and crystal formation was done from ethanol. Yield: 72%; m.p.: 174°C, ¹H-NMR (300 MHz, DMSO-*d*₆): δ 2.64 (s, 3H, CH₃), 7.69-7.72 (m, 2H, Ar-H), 7.87-7.91 (m, 2H, Ar-H), 8.02-8.06 (m, 2H, Ar-H), 8.30 (s, 1H, Ar-H); ESI-MS *m/z* 289.01 (M+2), 287.02 (M⁺), 254.15, 226.12.

General Method for Synthesis of Compounds (7a-7o; 8a-8e)

To a solution of appropriate amine (52.0 mmol) in dry pyridine (50 ml) at room temperature, a solution of 4-methyl-2-(naphthalen-2-yl)thiazole-5-carbonyl chloride (compound **6**) (50.0 mmol) in dehydrated acetone (50 mL) was mixed. After the addition, the reaction blend was constantly agitated for 4-6 h. The status of the reaction was checked by TLC using TEF (5:4:1) as solvent system. At the end of the reaction, crude mixture was added into ice water (100 mL). The precipitate collected was agitated, washed with cold water and dehydrated to obtain desired compound. The crystal formation of the compound was done from methanol or ethanol. Figure 2 describes the synthetic scheme of the title compounds **7a-7o** and **8a-8e**.

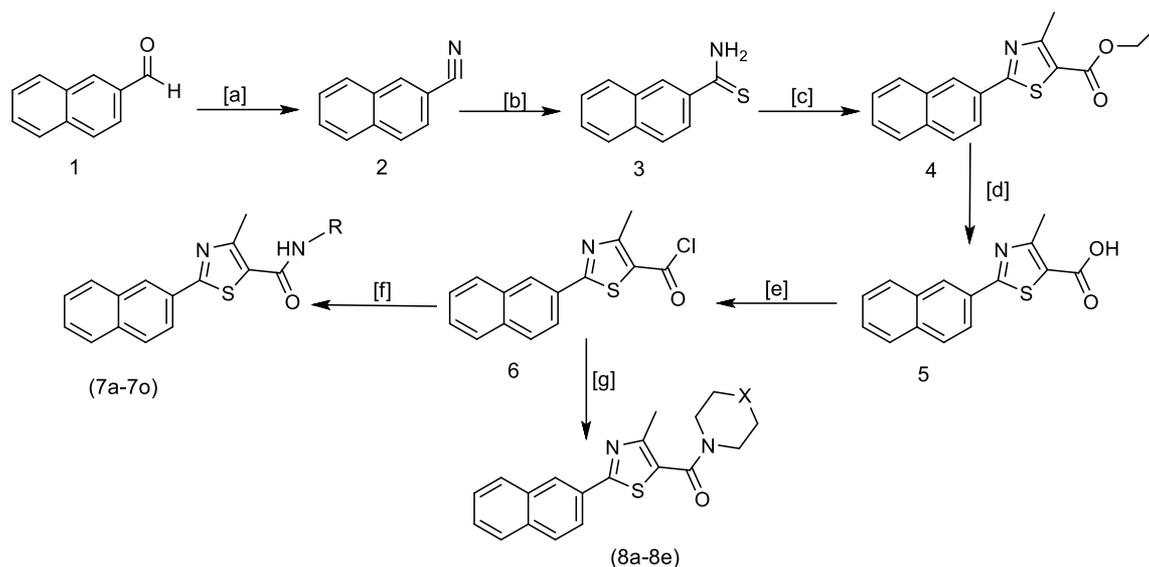


Fig. 2: Synthesis of the title compounds (**7a-o** & **8a-e**); Reagents and conditions: [a] NH_2OH , HCl , $\text{HCOONa}/\text{HCOOH}$, [b] NaSH , MgCl_2 , [c] $\text{CH}_3\text{COCHClCOOC}_2\text{H}_5/\text{ethanol}$ [d] $\text{THF}/\text{C}_2\text{H}_5\text{OH}$, NaOH/HCl , [e] SOCl_2 , [f] $\text{ArNH}_2/\text{Pyridine}$ [g] $\text{HNC}_4\text{H}_8\text{X}$ **7a**: $\text{R} = \text{C}_6\text{H}_5$, **7b**: $\text{R} = 4\text{CH}_3\text{-C}_6\text{H}_4$ -, **7c**: $\text{R} = 4\text{Cl-C}_6\text{H}_4$ -, **7d**: $\text{R} = 4\text{F-C}_6\text{H}_4$ -, **7e**: $\text{R} = 4\text{Br-C}_6\text{H}_4$ -, **7f**: $\text{R} = 4\text{NO}_2\text{-C}_6\text{H}_4$ -, **7g**: $\text{R} = 4\text{OCH}_3\text{-C}_6\text{H}_4$ -, **7h**: $\text{R} = 4\text{OH-C}_6\text{H}_4$ -, **7i**: $\text{R} = 3\text{Cl,4F-C}_6\text{H}_3$ -, **7j**: $\text{R} = 3,4\text{-diCl-C}_6\text{H}_3$ -, **7k**: $\text{R} = 2\text{OH-C}_6\text{H}_4$ -, **7l**: $\text{R} = 2\text{F-C}_6\text{H}_4$ -, **7m**: $\text{R} = 2\text{CH}_3\text{-C}_6\text{H}_4$ -, **7n**: $\text{R} = 4\text{NH}_2\text{SO}_2\text{-C}_6\text{H}_4$ -, **7o**: $\text{R} = \text{Cyclohexyl-}$, **8a**: $\text{X} = \text{CH}_2$, **8b**: $\text{X} = \text{O}$, **8c**: $\text{X} = \text{S}$, **8d**: $\text{X} = \text{NCH}_3$, **8e**: $\text{X} = \text{NCH}_2\text{Cl}$

4-Methyl-2-(Naphthalen-2-yl)-N-Phenylthiazole-5-Carboxamide (**7a**)

Yield: 65%; mp: 157°C, LogP: 5.33, FT-IR ν_{max} (cm^{-1} , KBr pellets): 3378 (NH), 1687 (C = O), 1623 (C = C), 1590 (C = N). $^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ 2.64 (s, 3H, CH_3), 7.08-7.11 (m, 1H, Ar-H), 7.51 (d, 2H, Ar-H, $J = \text{Hz}$), 7.58-7.62 (m, 4H, Ar-H), 7.87-7.91 (m, 2H, Ar-H), 8.05-8.08 (m, 2H, Ar-H), 8.34 (s, 1H, Ar-H), 12.67 (s, 1H, CONH); ESI-MS m/z 344.10, 253.95, 226.19. Anal. Calcd for $\text{C}_{21}\text{H}_{16}\text{N}_2\text{OS}$: C, 73.23; H, 4.68; N, 8.13. Found: C, 73.44, H, 4.69; N, 8.17.

4-Methyl-2-(Naphthalen-2-yl)-N-p-Tolylthiazole-5-Carboxamide (**7b**)

Yield: 59%; mp: 174°C, LogP: 5.79, FT-IR ν_{max} (cm^{-1} , KBr pellets): 3367 (NH), 1680 (C = O), 1626 (C = C), 1593 (C = N). $^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 7.25 (d, 2H, Ar-H, $J = \text{Hz}$), 7.54-7.59 (m, 4H, Ar-H), 7.89-7.92 (m, 2H, Ar-H), 8.09-8.11 (m, 2H, Ar-H), 8.30 (s, 1H, Ar-H), 12.44 (s, 1H, CONH); ESI-MS m/z 358.11, 253.91. Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{OS}$: C, 73.71; H, 5.06; N, 7.82. Found: C, 73.50; H, 5.08; N, 7.87.

N-(4-Chlorophenyl)-4-Methyl-2-(Naphthalen-2-yl)Thiazole-5-Carboxamide (**7c**)

Yield: 68%; mp: 168°C, LogP: 6.12, FT-IR ν_{max} (cm^{-1} , KBr pellets): 3363 (NH), 1688 (C = O), 1623 (C = C), 1589 (C = N). $^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ 2.66

(s, 3H, CH_3), 7.42 (d, 2H, Ar-H, $J = \text{Hz}$), 7.57-7.60 (m, 2H, Ar-H), 7.74-7.73 (m, 2H, Ar-H, $J = \text{Hz}$), 7.85-7.90 (m, 2H, Ar-H), 8.10-8.13 (m, 2H, Ar-H), 8.36 (s, 1H, Ar-H), 12.57 (s, 1H, CONH); ESI-MS m/z 380.09 ($\text{M}+2$), 378.06 (M^+), 254.09, 226.69. Anal. Calcd for $\text{C}_{21}\text{H}_{15}\text{ClN}_2\text{OS}$: C, 66.57; H, 3.99; N, 7.39. Found: C, 67.73; H, 7.97; N, 7.43.

N-(4-Fluorophenyl)-4-Methyl-2-(Naphthalen-2-yl)Thiazole-5-Carboxamide (**7d**)

Yield: 72%; mp: 140°C, LogP: 5.78, FT-IR ν_{max} (cm^{-1} , KBr pellets): 3370 (NH), 1690 (C = O), 1628 (C = C), 1596 (C = N). $^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ 2.65 (s, 3H, CH_3), 7.26 (d, 2H, Ar-H, $J = \text{Hz}$), 7.57-7.64 (m, 4H, Ar-H), 7.87-7.92 (m, 2H, Ar-H), 8.06-8.10 (m, 2H, Ar-H), 8.33 (s, 1H, Ar-H), 12.51 (s, 1H, CONH); ESI-MS m/z 362.09, 254.15, 226.30. Anal. Calcd for $\text{C}_{21}\text{H}_{15}\text{FN}_2\text{OS}$: C, 69.59; H, 4.17; N, 7.73. Found: C, 69.33; H, 4.19; N, 7.77.

N-(4-Bromophenyl)-4-Methyl-2-(Naphthalen-2-yl)Thiazole-5-Carboxamide (**7e**)

Yield: 66%; mp: 159°C, LogP: 6.50, FT-IR ν_{max} (cm^{-1} , KBr pellets): 3368 (NH), 1683 (C = O), 1620 (C = C), 1592 (C = N). $^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ 2.66 (s, 3H, CH_3), 7.32 (d, 2H, Ar-H, $J = \text{Hz}$), 7.62-7.67 (m, 4H, Ar-H), 7.88-7.91 (m, 2H, Ar-H), 8.06-8.10 (m, 2H, Ar-H), 8.36 (s, 1H, Ar-H), 12.62 (s, 1H, CONH); ESI-MS m/z 424.04 ($\text{M}+2$), 422.01 (M^+), 253.86, 226.08. Anal. Calcd for $\text{C}_{21}\text{H}_{15}\text{BrN}_2\text{OS}$: C, 59.58; H, 3.57; N, 6.62. Found: C, 59.76; H, 3.59; N, 6.60.

4-Methyl-2-(Naphthalene-2-yl)-N-(4-Nitrophenyl) Thiazole-5-Carboxamide (7f)

Yield: 70%; mp: 175°C, LogP: 5.42, FT-IR ν_{\max} (cm⁻¹, KBr pellets): 3370 (NH), 1679 (C = O), 1618 (C = C), 1596 (C = N). ¹H-NMR (300 MHz, DMSO-d₆): δ 2.67 (s, 3H, CH₃), 7.62-7.68 (m, 4H, Ar-H), 7.86-7.93 (m, 2H, Ar-H), 8.05-8.12 (m, 4H, Ar-H), 8.34 (s, 1H, Ar-H), 12.60 (s, 1H, CONH); ESI-MS m/z 389.08, 254.20, 226.22. Anal. Calcd for C₂₁H₁₅N₃O₃S: C, 64.77; H, 3.88; N, 10.79. Found: C, 64.48; H, 3.89; N, 10.85.

N-(4-Methoxyphenyl)-4-Methyl-2-(Naphthalen-2-yl) Thiazole-5-Carboxamide (7g)

Yield: 59%; mp: 180°C, LogP: 5.28, FT-IR ν_{\max} (cm⁻¹, KBr pellets): 3362 (NH), 1683 (C = O), 1622 (C = C), 1591 (C = N). ¹H-NMR (300 MHz, DMSO-d₆): δ 2.65 (s, 3H, CH₃), 3.89 (s, 3H, CH₃), 7.05-7.08 (d, 2H, Ar-H, J = Hz), 7.67-7.72 (m, 4H, Ar-H), 7.83-7.86 (m, 2H, Ar-H), 8.09-8.12 (m, 2H, Ar-H), 8.36 (s, 1H, Ar-H), 12.63 (s, 1H, CONH); ESI-MS m/z 374.11, 226.30. Anal. Calcd for C₂₂H₁₈N₂O₂S: C, 70.57; H, 4.85; N, 7.48. Found: C, 70.72; H, 4.86; N, 7.53.

N-(4-Hydroxyphenyl)-4-Methyl-2-(Naphthalen-2-yl) Thiazole-5-Carboxamide (7h)

Yield: 62%; mp: 149°C, LogP: 4.59, FT-IR ν_{\max} (cm⁻¹, KBr pellets): 3366 (NH), 1689 (C = O), 1620 (C = C), 1597 (C = N). ¹H-NMR (300 MHz, DMSO-d₆): δ 2.64 (s, 3H, CH₃), 7.00-7.03 (d, 2H, Ar-H, J = Hz), 7.64-7.70 (m, 3H, Ar-H), 7.88-7.91 (m, 2H, Ar-H), 8.03-8.06 (m, 2H, Ar-H), 8.32 (s, 1H, Ar-H), 9.30 (s, 1H, OH), 12.69 (s, 1H, CONH); ESI-MS m/z 360.09, 254.12, 226.34. Anal. Calcd for C₂₁H₁₆N₂O₂S: C, 69.98; H, 4.47; N, 7.77. Found: C, 69.70; H, 4.45; N, 7.81.

N-(3-Chloro-4-Fluorophenyl)-4-Methyl-2-(Naphthalen-2-yl) Thiazole-5-Carboxamide (7i)

Yield: 75%; mp: 188°C, LogP: 7.02, FT-IR ν_{\max} (cm⁻¹, KBr pellets): 3373 (NH), 1684 (C = O), 1619 (C = C), 1594 (C = N). ¹H-NMR (300 MHz, DMSO-d₆): δ 2.65 (s, 3H, CH₃), 7.44-7.49 (m, 2H, Ar-H), 7.63-7.66 (m, 2H, Ar-H), 7.85-7.90 (m, 3H, Ar-H), 8.06-8.09 (m, 2H, Ar-H), 8.37 (s, 1H, Ar-H), 12.58 (s, 1H, CONH); ESI-MS m/z 398.02 (M+2), 396.05 (M⁺), 254.04, 226.15. Anal. Calcd for C₂₁H₁₄ClFN₂O₂S: C, 63.55; H, 3.56; N, 7.06. Found: C, 63.74; H, 3.58; N, 7.13.

N-(3, 4-Dichlorophenyl)-4-Methyl-2-(Naphthalen-2-yl) Thiazole-5-Carboxamide (7j)

Yield: 73%; mp: 195°C, LogP: 7.13, FT-IR ν_{\max} (cm⁻¹, KBr pellets): 3370 (NH), 1681 (C=O), 1622 (C=C), 1592 (C=N). ¹H-NMR (300 MHz, DMSO-d₆): δ 2.67 (s, 3H, CH₃), 7.59-7.67 (m, 4H, Ar-H), 7.83-7.87

(m, 2H, Ar-H), 8.00-8.06 (m, 3H, Ar-H), 8.34 (s, 1H, Ar-H), 12.60 (s, 1H, CONH); ESI-MS m/z 416.05 (M+4), 414.07 (M+2) 412.02 (M⁺), 253.90, 226.25. Anal. Calcd for C₂₁H₁₄Cl₂N₂O₂S: C, 61.02; H, 3.41; N, 6.78. Found: C, 61.25; H, 3.42; N, 6.83.

N-(2-Hydroxyphenyl)-4-Methyl-2-(Naphthalen-2-yl) Thiazole-5-Carboxamide (7k)

Yield: 61%; mp: 163°C, LogP: 5.34, FT-IR ν_{\max} (cm⁻¹, KBr pellets): 3368 (NH), 1687 (C = O), 1623 (C = C), 1597 (C = N). ¹H-NMR (300 MHz, DMSO-d₆): δ 2.64 (s, 3H, CH₃), 7.09-7.15 (m, 3H, Ar-H), 7.64-7.73 (m, 4H, Ar-H), 7.86-7.90 (m, 2H, Ar-H), 8.03-8.07 (m, 2H, Ar-H), 8.36 (s, 1H, Ar-H), 12.64 (s, 1H, CONH); ESI-MS m/z 360.07, 254.31, 226.10. Anal. Calcd for C₂₁H₁₆N₂O₂S: C, 69.98; H, 4.47; N, 7.77. Found: C, 69.76; H, 4.49; N, 7.72.

N-(2-Fluorophenyl)-4-Methyl-2-(Naphthalen-2-yl) Thiazole-5-Carboxamide (7l)

Yield: 69%; mp: 145°C, LogP: 5.30, FT-IR ν_{\max} (cm⁻¹, KBr pellets): 3373 (NH), 1689 (C = O), 1629 (C = C), 1607 (C = N). ¹H-NMR (300 MHz, DMSO-d₆): δ 2.67 (s, 3H, CH₃), 7.12-7.19 (m, 3H, Ar-H), 7.67-7.70 (m, 2H, Ar-H), 7.86-7.92 (m, 3H, Ar-H), 8.09-8.12 (m, 2H, Ar-H), 8.35 (s, 1H, Ar-H), 12.60 (s, 1H, CONH); ESI-MS m/z 362.09, 253.99, 226.14. Anal. Calcd for C₂₁H₁₅FN₂O₂S: C, 69.59; H, 4.17; N, 7.73. Found: C, 69.74; H, 4.18; N, 7.78.

4-Methyl-2-(Naphthalen-2-yl)-N-o-Tolylthiazole-5-Carboxamide (7m)

Yield: 64%; mp: 139°C, LogP: 5.79, FT-IR ν_{\max} (cm⁻¹, KBr pellets): 3361 (NH), 1684 (C = O), 1620 (C = C), 1595 (C = N). ¹H-NMR (300 MHz, DMSO-d₆): δ 2.24 (s, 3H, CH₃), 2.64 (s, 3H, CH₃), 7.08-7.10 (m, 1H, Ar-H), 7.35-7.41 (m, 3H, Ar-H), 7.64-7.68 (m, 2H, Ar-H), 7.84-7.87 (m, 2H, Ar-H), 8.05-8.09 (m, 2H, Ar-H), 8.37 (s, 1H, Ar-H), 12.68 (s, 1H, CONH); ESI-MS m/z 358.11, 253.68, 226.47. Anal. Calcd for C₂₂H₁₈N₂O₂S: C, 73.71; H, 5.06; N, 7.82. Found: C, 73.85; H, 5.04; N, 7.88.

4-Methyl-2-(Naphthalen-2-yl)-N-(4-Sulfamoyl-Phenyl) Thiazole-5-Carboxamide (7n)

Yield: 76%; mp: 201°C, LogP: 4.14, FT-IR ν_{\max} (cm⁻¹, KBr pellets): 3373 (NH), 1692 (C = O), 1625 (C = C), 1570 (C = N). ¹H-NMR (300 MHz, DMSO-d₆): δ 2.02 (s, 2H, NH₂), 2.48 (s, 3H, CH₃), 7.37-7.39 (d, 2H, Ar-H, J = Hz), 7.62-7.64 (d, 2H, Ar-H, J = Hz), 7.80-7.93 (m, 4H, Ar-H), 7.98-8.0 (d, 2H, Ar-H, J = Hz), 8.27 (s, 1H, Ar-H), 9.30 (s, 1H, CONH); ESI-MS m/z 423.50, 254.28, 226.33. Anal. Calcd for C₂₁H₁₇N₃O₃S₂: C, 59.56; H, 4.05; N, 9.92. Found: C, 59.43; H, 4.03; N, 9.96.

N-(Cyclohexyl)-4-Methyl-2-(Naphthalene-2-yl)
Thiazole-5-Carboxamide (**7o**)

Yield: 67%; mp: 178°C, LogP: 5.63, FT-IR ν_{\max} (cm⁻¹, KBr pellets): 3365 (NH), 1680 (C = O), 1623 (C = C), 1598 (C = N). ¹H-NMR (300 MHz, DMSO-d₆): δ 1.39-1.45 (m, 6H, 2xCH₂), 1.81-1.89 (m, 4H, 2xCH₂), 2.66 (s, 3H, CH₃), 7.66-7.69 (m, 2H, Ar-H), 7.82-7.89 (m, 4H, Ar-H), 8.04-8.07 (m, 2H, Ar-H), 8.36 (s, 1H, Ar-H), 12.61 (s, 1H, CONH); ESI-MS *m/z* 350.15, 253.89, 226.40. Anal. Calcd for C₂₀H₂₀N₂O₂S: C, 71.97; H, 6.33; N, 7.99. Found: C, 71.76; H, 6.35; N, 8.04.

4-Methyl-2-(Naphthalene-2-yl) Thiazol-5-yl)
(Piperidin-1-yl) Methanone (**8a**)

Yield: 80%; mp: 170°C, LogP: 4.15, FT-IR ν_{\max} (cm⁻¹, KBr pellets): 1677 (C = O), 1624 (C = C), 1589 (C = N). ¹H-NMR (300 MHz, DMSO-d₆): δ 1.65-1.72 (m, 6H, 3xCH₂), 2.64 (s, 3H, CH₃), 3.68-3.72 (m, 4H, 2xCH₂), 7.68-7.70 (m, 2H, Ar-H), 7.88-7.91 (m, 2H, Ar-H), 8.07-8.10 (m, 2H, Ar-H), 8.38 (s, 1H, Ar-H); ESI-MS *m/z* 336.13, 254.21, 225.97. Anal. Calcd for C₂₀H₂₀N₂O₂S: C, 71.40; H, 5.99; N, 8.33. Found: C, 71.52; H, 5.95; N, 8.37.

[4-Methyl-2-(Naphthalen-2-yl) Thiazol-5-yl]
(Morpholin-4-yl) Methanone (**8b**)

Yield: 78%; mp: 183°C, LogP: 2.60, FT-IR ν_{\max} (cm⁻¹, KBr pellets): 1679 (C = O), 1621 (C = C), 1592 (C = N). ¹H-NMR (300 MHz, DMSO-d₆): δ 2.64 (s, 3H, CH₃), 3.62-3.65 (m, 4H, 2xCH₂), 3.70-3.76 (m, 4H, 2xCH₂), 7.65-7.68 (m, 2H, Ar-H), 7.86-7.90 (m, 2H, Ar-H), 8.10-8.13 (m, 2H, Ar-H), 8.35 (s, 1H, Ar-H); ESI-MS *m/z* 338.11, 253.91, 226.09. Anal. Calcd for C₁₉H₁₈N₂O₂S: C, 67.43; H, 5.36; N, 8.28. Found: C, 67.48; H, 5.39; N, 8.32.

[4-Methyl-2-(Naphthalen-2-yl) Thiazol-5-yl]
(Thiomorpholin-4-yl)Methanone (**8c**)

Yield: 83%; mp: 191°C, LogP: 3.48, FT-IR ν_{\max} (cm⁻¹, KBr pellets): 1685 (C = O), 1626 (C = C), 1600 (C = N). ¹H-NMR (300 MHz, DMSO-d₆): δ 2.64 (s, 3H, CH₃), 3.62-3.65 (m, 4H, 2xCH₂), 3.70-3.76 (m, 4H, 2xCH₂), 7.65-7.68 (m, 2H, Ar-H), 7.86-7.90 (m, 2H, Ar-H), 8.10-8.13 (m, 2H, Ar-H), 8.35 (s, 1H, Ar-H); ESI-MS *m/z* 354.12, 254.21, 226.09. Anal. Calcd for C₁₉H₁₈N₂O₂S₂: C, 64.38; H, 5.12; N, 7.90. Found: C, 64.45; H, 5.18; N, 7.95.

[4-Methyl-2-(Naphthalen-2-yl) Thiazol-5-yl]
(4-Methylpiperazin-1-yl) Methanone (**8d**)

Yield: 76%; mp: 136°C, LogP: 3.06, FT-IR ν_{\max} (cm⁻¹, KBr pellets): 1684 (C = O), 1624 (C = C), 1597 (C = N). ¹H-NMR (300 MHz, DMSO-d₆): δ 2.28 (s, 3H, NCH₃), 2.35-3.38 (m, 4H, 2xCH₂), 2.64 (s, 3H, CH₃), 3.36-3.39 (m, 4H, 2xCH₂), 7.66-7.69 (m, 2H, Ar-H), 7.84-7.87 (m, 2H, Ar-H), 8.06-8.09 (m, 2H, Ar-H), 8.33 (s, 1H, Ar-H); ESI-MS *m/z* 351.14, 254.16, 225.90.

Anal. Calcd for C₂₀H₂₁N₃O₂S: C, 68.35; H, 6.02; N, 11.96. Found: C, 68.41; H, 6.08; N, 11.91.

[4-Methyl-2-(Naphthalen-2-yl) Thiazol-5-yl]
(4-Chloromethylpiperazin-1-yl) Methanone (**8e**)

Yield: 85%; mp: 148°C, LogP: 3.45, FT-IR ν_{\max} (cm⁻¹, KBr pellets): 1680 (C = O), 1621 (C = C), 1591 (C = N). ¹H-NMR (300 MHz, DMSO-d₆): δ 2.45-2.53 (m, 7H, CH₃ and 2xCH₂), 3.22-3.29 (m, 4H, 2xCH₂), 7.56-7.71 (m, 2H, Ar-H), 7.79-7.96 (m, 2H, Ar-H), 8.03-8.10 (m, 2H, Ar-H), 8.33 (s, 1H, Ar-H); ESI-MS *m/z* 324.14 (M+2), 322.11 (M⁺), 253.91, 226.13. Anal. Calcd for C₂₀H₂₀ClN₃O₂S: C, 62.25; H, 5.22; N, 10.89. Found: C, 62.19; H, 5.29; N, 10.94.

Anticonvulsant Screening

The pharmacological screening of all the title compounds was performed according to the standard procedure specified by the epilepsy branch of the National Institute of Neurological Disorders and Stroke (Kupferberg, 2001).

Male albino mice (Swiss) of 25-30 g were used as investigational animal. Title compounds were suspended in PEG 200 for MES and scPTZ evaluation. The animals were kept at an ambient temperature 22±1°C, in groups of six per cage under standard laboratory condition and permitted to free access to food and water (Krall *et al.*, 1978; Clark *et al.*, 1984).

Maximal Electroshock Seizure Test (MES Test)

Test compounds were delivered as an intraperitoneal (*i.p.*) injection at dose of 30, 100 and 300 mg/kg body weight and the anticonvulsant potential was measured after 0.5 h and 4 h intervals of administration. Maximal electroshock seizures were caused in mice by delivering 60Hz, 50 mA electrical stimuli for 0.2 s via ear clip electrodes. Abolition of hind limb tonic extensor component of the seizure in half or more of the animals is termed as protection.

Subcutaneous Pentylenetetrazole Seizure Test (scPTZ)

The scPTZ primarily pinpoints compounds that elevate seizure threshold. The sc PTZ test employs a dose of pentylenetetrazol (85 mg/kg). This yields clonic seizures lasting for a period of at least five seconds in 97 percent (CD₉₇) of animals tested. Solutions of test compounds were administered intraperitoneally at dose level of 30, 100 and 300 mg/kg. At the estimated time of testing (0.5 h and 4.0 h), the convulsant (PTZ) was administered subcutaneously and animals were observed over a 30 min period. Abolition of clonic seizure in half or more of the animals in the observed time period designated a compound's ability to eliminate the effect of pentylenetetrazol on seizure threshold.

In vitro GABA-Transaminase Inhibition Assay

As docking study demonstrated that these compounds are binding with gamma aminotransferase enzyme, the most active compounds were screened *in vitro* against the γ -amino Butyric Acid-Transaminase (GABA-T) enzyme and the inhibitory activity was evaluated. The GABA-T enzyme was isolated from *Pseudomonas fluorescens* using a method described previously (Scott and Jakoby, 1958). The assay was performed for a 4 h time period according to the standard procedure (Lippert *et al.*, 1977).

Neurotoxicity Screening

The minimal motor damage was measured in mice by the rotarod test. The mice were skilled to hold on speeding up rotarod of diameter 3.2 cm that rotates at 10 Revolutions Per Minute (RPM). Neurotoxicity was designated by the inability of the animal to withstand equilibration on the rod for at least one minute in each of the three experiments. The dose at which 50% of the animals qualified to balance themselves and fell off the rotating rod was determined (Dunham and Miya, 1957).

Ethanol Potentiation Test

Mice were subjected with the minimum test compound (30 mg/kg body weight) and 1 h later with ethanol 2.5 g kg⁻¹ip. This dose of ethanol did not bring lateral position in the control animals. The number of animals that were in the lateral position after getting ethanol in each group was determined (Clerici and Pocar, 2001).

Results and Discussion

Chemistry

The structures of synthesized analogues were identified by elemental analysis, FT-IR, ¹H NMR and mass spectral data. FT-IR spectrum revealed four bands for NH, C = O and C = C and C = N at 3378-3348 cm⁻¹, 1692-1677 cm⁻¹, 1629-1618 cm⁻¹ and 1607-1570 cm⁻¹ respectively. The ¹H NMR of **7a-7o** confirmed presence of NHC = O group exhibiting chemical shift (δ) in the range of 12.69-9.30 with broad singlet shape and splitting, exchangeable with D₂O while the same peak was found absent in the compounds **8a-8e**. The physical and chemical data for newly synthesized analogues are presented supplementary material.

Anticonvulsant Activity

The preliminary evaluation of the titled compounds **7a-7o** and **8a-8e** were evaluated for anticonvulsant activity utilizing the predictable animal models and the neurotoxicity was assessed by rotorod test method. Of these, the MES and scPTZ seizure models exemplify the most widely used screening models in the search for new anticonvulsant agents. Data are presented "Table 1" after the 0.5 and 4 h time intervals at the dose level of 30, 100

and 300 mg/kg body weight of the animals. Phenytoin and carbamazepine were used as the standard drugs for the comparison.

The synthesized compounds **7e**, **7j**, **7n** and **8c** showed anticonvulsant potential at the dose level of 30 mg/kg after 0.5 h against the seizure spread indicating rapid onset but shorter duration of action except **8c**. Compound **8c** displayed protection after 0.5 h and 4 h signifying quick onset and long duration of action.

Moreover, compounds **7b**, **7d**, **7g**, **7h**, **7k** and **8d** exhibited MES protection at the dose level 100 mg/kg at 0.5 h, but after 4 h these analogues had displayed protection at dose level 300 mg/kg indicating rapid onset and short duration of action. The other compounds either did not exhibit any protection or showed activity at a dose of 300 mg/kg which is not significant enough to consider them for other future investigations. As previously discussed only those analogues were selected for anti PTZ screening which had displayed a significant anti MES activity. Therefore, compounds **7b**, **7d**, **7e**, **7g**, **7h**, **7i**, **7j**, **7k**, **7n** and **8d** were screened for anti PTZ activity. Analogues **7h**, **7i**, **7j** and **8c** showed potential at 100 mg/kg dose after 0.5 h. Out of these, two analogues notably **7h** and **7i** showed potential even after 4 h at an increased dose of 300 mg/kg. The overall outcomes suggested the quick onset of these analogues and short duration of action in anti PTZ potential. A few compounds for example **7b**, **7d** and **7g** showed very less anti PTZ activity and therefore, insignificant to mention.

When we correlate anticonvulsant data with lipophilicity (log P) data, it is quite obvious that the lipophilicity is not the only factor which diktats the anticonvulsant activity. Therefore, compound **7e** (log P = 6.50) and **7j** (log P = 7.13) showed high activity against MES. But the other two highly active compounds **7n** and **8c** showed low lipophilicity (log P values are 4.14 and 3.4 respectively). Log P values of the titled analogues are shown in supplementary material.

The four most active compounds (**7e**, **7j**, **7n** and **8c**) were subjected to *in vitro* GABA-T inhibition assay to establish the mechanism involved in the anticonvulsant potential of the title analogues. The GABA-transaminase enzyme has been found to be accountable for the metabolism of GABA and therefore, inhibition of the enzyme will cause in an elevated amount of GABA in various brain parts. The results of the assay are offered in "Table 2". All four analogues were observed to inhibit the GABA-T enzyme at the 4 h time period. Compound **7d** was found to inhibit GABA-T almost throughout the time periods, but the full inhibition shown by **7d** was 20% at 4 h. Compound **7n** inhibited the enzyme at 1 h and maximum inhibition (12%) was detected at 4 h. Compound **7j** demonstrated second maximum inhibition amongst these compounds. It displayed inhibition at 2 h and continued to inhibit the enzyme considerably throughout the time periods. Compound **8c** exhibited less enzyme inhibition and maximum inhibition was witnessed at 4 h (11%).

Table 1: Anticonvulsant and neurotoxicity screen data of compounds (**7a-o**; **8a-e**)

	MES screening		scPTZ screening		Neurotoxicity screen		^a Ethanol Potentiation
	0.5 h	4.0 h	0.5 h	4.0 h	0.5 h	4.0 h	
7a	300	(—)	X	X	X	X	X
7b	100	300	300	(—)	(—)	(—)	(—)
7c	(—)	300	X	X	X	X	X
7d	100	300	(—)	300	(—)	(—)	(—)
7e	30	100	300	(—)	100	300	(+)
7f	300	(—)	X	X	X	X	X
7g	100	300	300	(—)	(—)	(—)	(—)
7h	100	300	100	300	(—)	(—)	(—)
7i	100	(—)	100	300	300	(—)	(+)
7j	30	300	100	(—)	(—)	(—)	(—)
7k	100	300	(—)	(—)	(—)	(—)	(—)
7l	(—)	300	(—)	(—)	X	X	X
7m	(—)	(—)	(—)	300	X	X	X
7n	30	300	(—)	(—)	(—)	(—)	(—)
7o	(—)	300	(—)	(—)	X	X	X
8a	(—)	(—)	X	X	X	X	X
8b	300	(—)	X	X	X	X	X
8c	30	30	100	(—)	(—)	(—)	(—)
8d	100	300	(—)	300	(—)	(—)	(+)
8e	300	300	X	X	X	X	X
Phenytoin	30	30	(—)	(—)	100	100	X
Carbamazepine	30	100	100	300	100	300	X

30, 100 and 300 mg/kg body weight doses of the title analogues were delivered and the protection and neurotoxicity were estimated after 0.5 and 4h. The figures pointed out the lowest dose required to show protection or neurotoxicity in 50% or more of the animals. The dash (—) represents the absence of anticonvulsant potential or neuro-motor impairment. X represents not tested. ^aEthanol potentiation test: (+), half or more animals passed the test; (—), half or more animals failed the test. X represents not tested.

Table 2: *In vitro* GABA-transaminase inhibition evaluation of selected compounds

Compd. No.	Percentage inhibition of GABA-T ^a				
	0.5 h	1.0 h	2.0 h	3.0 h	4.0 h
Control	—	—	—	—	—
7e	—	08	12	15	20
7j	—	—	9	13	18
7n	—	5	8	10	12
8c	—	—	—	7	11

^a*In vitro* enzyme inhibition was performed at a dose of 500 μM for each compounds

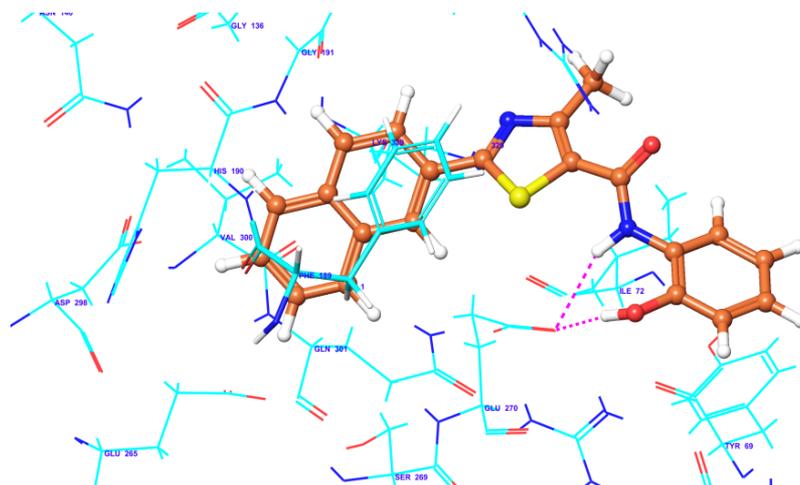


Fig. 3: Highest ligand scoring compound with catalytic domain of GABA aminotransferase protein

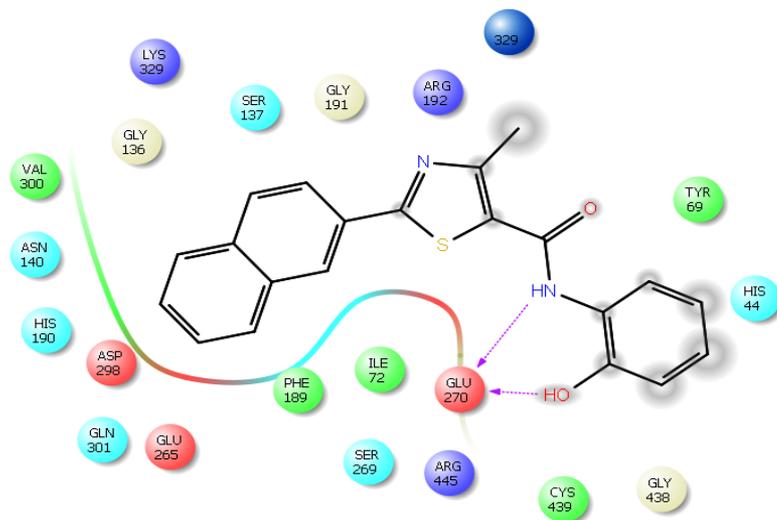


Fig. 4: Lig-plot: Highest ligand scoring compound 7k with catalytic domain of GABA aminotransferase protein

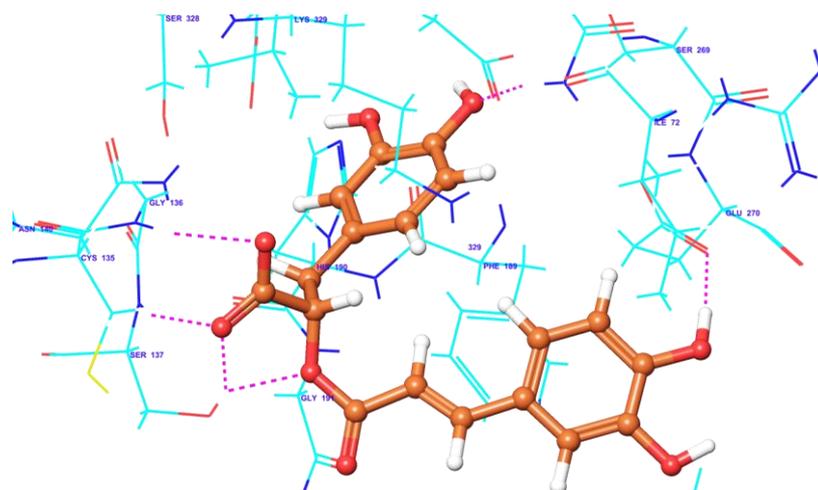


Fig. 5: Binding pose of rosmarinic acid (standard) with GABA aminotransferase protein

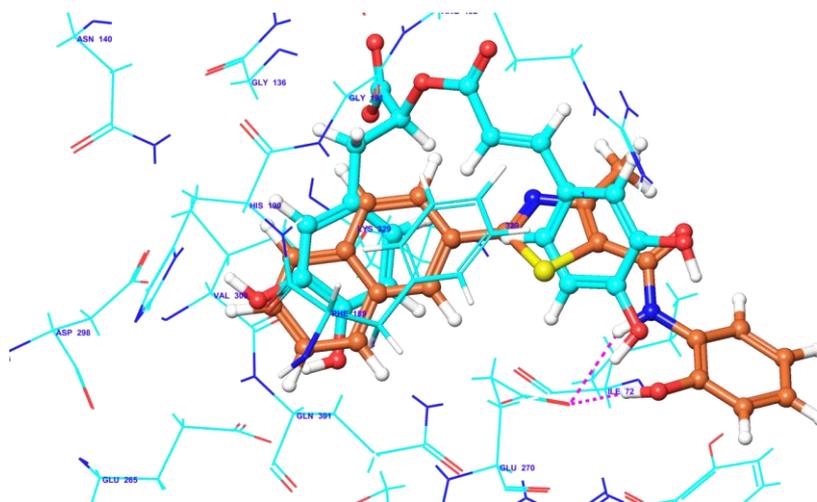


Fig. 6: Superimposition of rosmarinic acid (cyan) with highest ligand scoring compound (grey).

Only those compounds were selected for neurotoxicity screening, which had shown good to moderate anticonvulsant activity.

Compound **7e** showed considerable neuro-motor impairment at a dose of 100 mg/kg in the rotorod test, whereas compound **7i** showed neurotoxicity at an increased dose of 300 mg/kg. The rest of the compounds did not show any neuro-motor impairment in rotorod test. Compounds **7e**, **7i** and **8d** showed an interaction with motor system, due to which they potentiated the effect of ethanol inducing the lateral position to the animals. The rest of the analogues did not display any interaction with ethanol at minimum dose of 30 mg/kg (Table 1).

We performed molecular docking on synthesized compounds **7a-7o** & **8a-8e** against GABA aminotransferase and the docking studies revealed a common binding orientation of all the synthesized compounds in the catalytic binding pocket of GABA aminotransferase. Figure 3 shows highest ligand scoring compound with catalytic domain of GABA aminotransferase protein.

Log plot of highest ligand scoring analogue **7k** with catalytic domain of GABA aminotransferase protein is offered in Fig. 4.

Binding pose of rosmarinic acid (standard) with GABA aminotransferase protein has been presented in Fig. 5. Figure 6 shows superimposition of rosmarinic acid (cyan) with highest ligand scoring compound (grey).

The binding pose of compound (**7k**) has been compared with the standard co-crystal ligand which is bonded with GABA aminotransferase protein. The thiazole moiety of the compound indirectly plays a significant role in binding with the amino acid. The nitrogen atom of amino group is involved in hydrogen bonding interactions with amino acid residue Glu270 and 2-hydroxy substitution on phenyl ring forms hydrogen bonding with Glu270 at the catalytic site (Fig. 3-6). Hydrophobic amino acids Gly438, Cys439, Arg445, Ile72, Phe189, Glu265, Gln301, Asp298, His190, Asn140 and Val300 appeared as a cup like structure (Fig. 3-6). In addition, the naphthalene moiety shows hydrophobic interaction with GABA amino transferase protein PHE189, VAL300, HIS190 and GLN301 amino acid residues. It was also observed that ortho substitution in phenyl moiety of **7k** gives better interaction with backbone of GABA aminotransferase protein. The hydrogen bonding interaction may probably cause the inhibition of GABA aminotransferase enzyme.

Conclusion

β -Naphthalene incorporated thiazole-5-carboxamides/thiazole -5- ketones were synthesized and evaluated for their anticonvulsant activity utilizing MES and scPTZ animal models. Neuro-motor impairment was assessed by rotorod and ethanol potentiation methods.

Majority of these compounds exhibited significant activity against both animal models; however, compounds **7e**, **7j**, **7n** and **8c** emerged as highly active. These highly potent analogues did not show any sign of neuromotor impairment when they were subjected to rotorod and ethanol potentiation tests. Docking analysis and GABA-transaminase inhibitory assay suggested the mechanism of action of these analogues. All these experimental data revealed that these compounds might serve as lead candidates for further design and development of anticonvulsant agents with low toxicity and high efficacy.

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Author's Contributions

Mohammed Faiz Arshad: Designed the concept of this work and contributed in all sections.

Faisal Al-Otaibi: Performed antiepileptic activity of the title compounds.

Gulam Mustafa: Performed docking studies and partly contributed in synthesis of the title compounds.

Saad Shousha: Contributed in toxicity evaluation.

Abdulrahman Alshahrani: Contributed in characterization of the title compounds and also contributed in synthetic work.

Conflict of Interest

The authors affirm that there is no conflict of interest concerning the publication of this work.

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