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Original Research Article

Synthesis, Anticonvulsant Activity and *In silco* Studies of Schiff Bases of 2-Aminothiophenes via Guanidine-Catalyzed Gewald Reaction

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Abstract

Purpose: *To synthesize Schiff bases of 2-aminothiophenes and evaluate their anticonvulsant activity and in silco properties*

Methods: *2-Amino-N-o-tolyl-5,6-dihydro-4H-cylcopenta[b]thiophene-3-carboxamide was synthesized using 1,1,3,3-tetramethylguanidine lactate as a basic catalyst and by microwave irradiation. 2-substitued-o-tolyl-5,6-dihyro-4H-cylcopenta[b]thiophene-3-carboxamide was prepared by reacting with different substituted aromatic aldehydes. The synthesized compounds were characterized by Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance spectroscopy (^{1}H NMR) and mass spectrometry (MS) while their anticonvulsant activity was screened against maximum electroshock-induced seizure (MES), and pentylenetetrazole-induced seizure (PTZ) against phenytoin and diazepam as reference standards. Molecular docking (in silico) studies were performed using 4-aminobutyrate-aminotransferase in order to predict possible protein-ligand interactions.*

Results: *Among the 21 synthesized compounds,* ***2b, 2d, 2f, 2k, 2m, 2n*** *and* ***2o*** *showed good to moderate activity against MES and PTZ-induced convulsions. Compounds* ***2b, 2d, 2f, 2k*** *and* ***2m*** *exhibited lower activity against PTZ than against MES model while compounds* ***2n*** *and* ***2o*** *afforded greater protection against PTZ than against MES model. In silico results also revealed maximum binding affinity to GABA-AT protein which was higher than other compounds*

Conclusion: *The synthesized compounds showed potent anticonvulsant activity. Molecular docking results should give an insight into how further modification of lead compound can be carried out for higher inhibitory activity.*

Keywords: *Ionic liquid, 2-Aminothiophenes, Anticonvulsant, In silco studies, Molecular docking.*

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INTRODUCTION

Thiophene scaffold have a variety of biological activities such as antitubercular [1], antioxidant [2], anti-HIV-PR inhibitors [3], antimicrobial [4], multitargeted kinase inhibition [5], A_1 adenosine receptor allosteric enhancement [6]. Of Several approaches for the synthesis of 2-aminothiophenes have been reported including the use of microwave assisted synthesis [7], synthesis from thiomorpholides [8], coupling reaction [9], solid support [10], base-induced inter- and intra-molecular C-S and C-C bond

formation [11] and ultrasonication [12]. Ionic liquids (ILs) have attracted attention for green organic synthesis because of their unique physical and chemical properties such as non-volatility, non-flammability, thermal stability, recyclability and controlled miscibility. Synthesis using ionic liquid has great advantages including easy workup, milder reaction and high yields. Molecular docking studies have been performed on synthesized compounds with gamma-aminobutryic acid aminotransferase (GABA-AT) in order to identify possible binding conformations of the ligand. [13]. The aim of the present research was to study some Schiff bases for anticonvulsant activity and ligand docking with gamma-aminobutryic acid aminotransferase in order to identify possible binding conformations. By performing molecular docking studies, one can identify possible binding conformations of ligands, and the data obtained would be very helpful to achieve further modification of lead for greater inhibitory activity.

EXPERIMENTAL

Melting point was determined using an electrochemical thermal apparatus (IA 9100 Digital melting point apparatus) and were uncorrected. FT-IR spectra were recorded on a Perkin Elmer FT-IR spectrometer. ^{1}H NMR spectra were obtained with Bruker Spectrometer (400 MHz) in $CDCl_3$ (deuterated chloroform) and DMSO (dimethyl sulfoxide) using tetramethyl-silane (TMS) as an internal standard. Mass spectra were obtained with LC-MSD Trap-SL 2010 A Schimadzu. All the compounds were synthesized according to the scheme in Figure 1.

Synthesis of 2-cyano-N-o-tolylacetamide(1): A mixture of o-toluidine (0.01 mol) and ethylcyanoacetate (0.655 mol) was heated at 180^{0}C in a microwave (Raga Scientific Microwave system model RG31L) at 2450 MHZ for 5 min. The reaction mixture was left at room temperature overnight. The solid obtained was separated, washed with ethanol, dried and recrystallized from acetone:water mixture.

Synthesis of 2-amino-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide under microwave irradiation(2): A mixture of cyclopentanone (0.04 mol), 2-cyano-N-o-tolylacetamide (0.04 mol), sulphur(0.04 mol), ionic liquid (1.5 g), ethanol (15 ml) were placed in a volumetric flask and stirred for 5 min. The reaction mixture was placed in a microwave at 100 W for 3 min. The progress of the reaction was monitored by thin layer chromatography (TLC) Water (10 ml) was added during which reddish brown crystals were separated. The preciptated product was filtered under suction. Ionic liquid was recovered by removing water under reduced pressure stored in a desicator for its reuse.

General procedure for synthesis of 2-substituted N-o-tolyl-5,6-dihydro-4H-cyclo-penta[b]thiophene-3-carboxamide under conventional heating (2): A mixture of 2-amino-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (0.02 mol) and appropriately subtituted aryl aldehydes/ketones (0.02 mol) was dissolved in ethanol in the presence of catalytic amount of glacial acetic acid (1ml) by heating under reflux for 5 h. The reaction mixture was cooled overnight, the separated solid was filtered washed with isopropyl alcohol and recrystallized

General procedure for synthesis of 2-substitutedN-o-tolyl-5,6-dihydro-4H cyclo penta[b]thiophene-3-carboxamide under microwave irradiation(2): A mixture of 2-amino-N-o-tolyl-5,6-dihydro-4H-cyclopen-ta[b]thiophene-3-carboxamide (0.02 mol) and appropriately subtituted aryl aldehydes/ketones (0.02 mol) was added to acidic alumina (1 g) at room temperature. The reaction mixture was mixed, allowed to adsorb on acidic alumina, dried and kept inside the alumina bath and irradtiated at 750 W for 30 s. The reaction mixture was cooled, the product extracted with ethyl acetate, concentrated and cooled. The solid product was separated filtered, washed thoroughly with water and recrystallized from dimethyl formaamide.

Evaluation of anticonvulsant activity

Male albino Swiss mice, weighing 20 - 25 g, were used to study the effect of the synthesized compounds on MES- and PTZ-induced seizures. Female animals were excluded because of the fact that estrous cycle could influence their activity threshold. They were procured from National Institution of Nutrition; Hyderabad and had free access to balanced food and water *ad libitium* Prior to experimentation, the animals were allowed a week time to acclimatize to laboratory conditions. However, food, but not water, was withdrawn 8 h before and during the experiments.

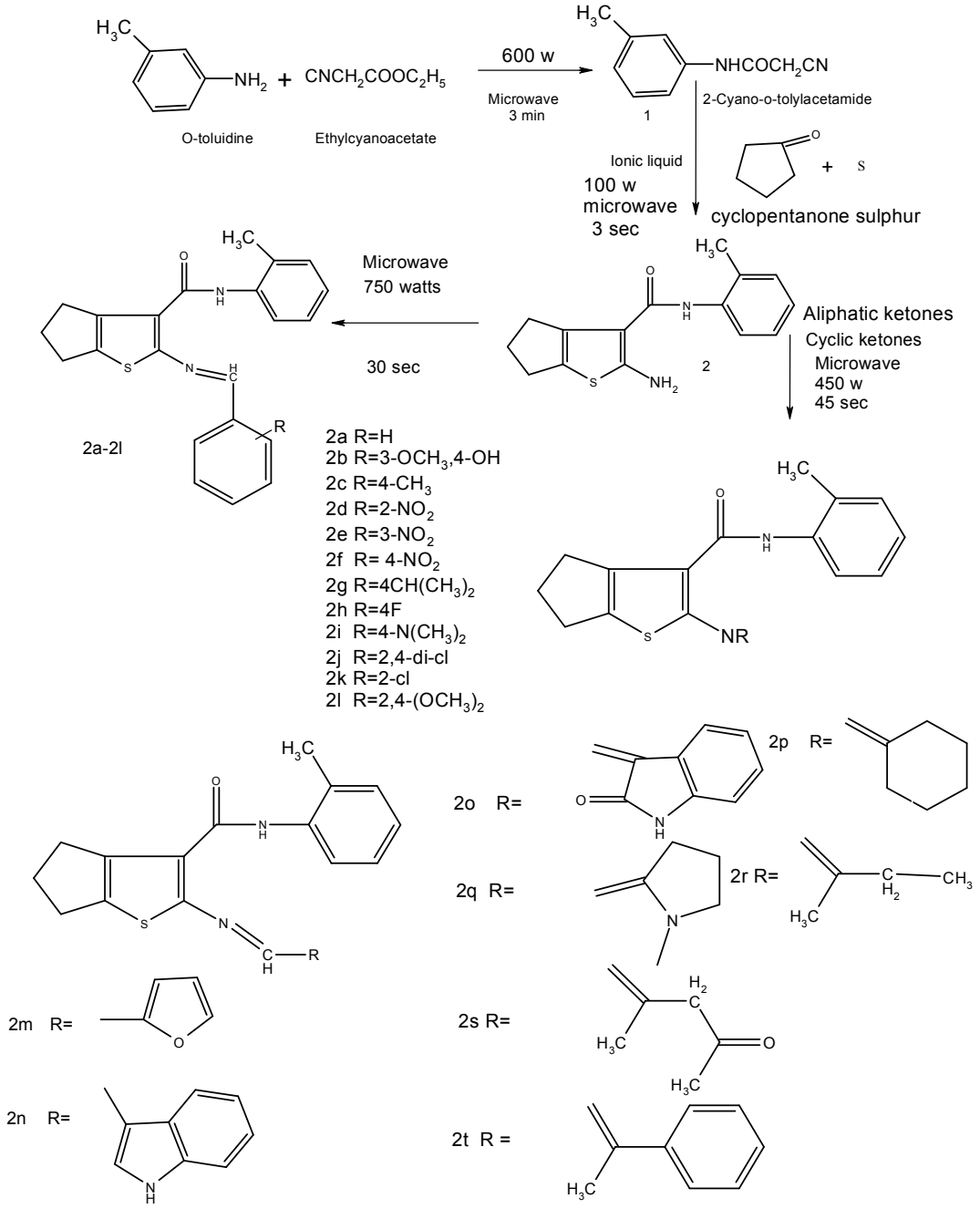

Figure 1: Synthesis of 2-substituted- N- o-tolyl-5, 6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide

Animal experiments were performed in accordance with the institutional guidelines for animal experimentation[14]. Institutional animal ethical permission was obtained from Malla Reddy College of Pharmacy **(**ref no. 1217/a/08/CPCSEA**)** which is affiliated to Osmania University, prior to the animal studies. All the protocols and the experiments were conducted in strict compliance according to ethical principles and guidelines the animals received due care according to the criteria outlined in the "Guide for the Care and Supervision of Experiments on Animals" prepared of the National Academy of Sciences and published by National Institutes of Health, USA.

Maximal electroshock-induced seizure test

Seizure was induced by maximal electroshock in albino mice (n=6)with the aid of an electroconvulsiometer (EC 01,Orchid Scientifics) by passing a current of 45 mA for 0.2 s using ear clip electrodes. The duration of different phases of seizures was noted [15].

Pentylenetetrazole-induced seizure test

Albino mice (n = 6) were treated with test prior to subcutaneous injection of PTZ (80 mg/kg), The mice were observed for clonic and tonic convulsions and 24 hr mortality. The mice were observed for onset of convulsion up to 30 min after PTZ administration.

***In silco* studies**

A set of 21 different ligands were drawn using Chemsketch, (11.0 ACD labs) while geometrical optimization was carried out with LigPrep.2.5 (Schrodinger Suite 2011). Using this tool, a single low energy 3D structure was obtained for each ligand and different conformers obtained during ionization of the ligands using EPIK module which generates ionization states in the pH range of 7 ± 2. The molecular properties of the minimized ligands were studied using QIKPROP module 2.5 Schrodinger suite 2011 which predict absorption, distribution, metabolism and excretion (ADME, Quiprop version 3.4, Schrodinger Suite 2011) [16].

Ligand protein interaction of 2-aminosubstituted thiophenes with GABA-AT was studied by docking GLIDE-XP. The protein structure was retrieved from the protein data bank server (PDB entry 1OHV, (http://www.rcsb.org/pdb/home/home.do). The structure of the protein was corrected by adding hydrogen and removing water moieties with force field OPLS-2005, i.e., optimized potentials for liquid simulations. The active site was identified by SITEMAP tool. Receptor grid generation was carried out using glide; the ligands were docked by employing XP mode and they were docked flexibly. Best pose was selected based on E-model energy and docking score from glide (glide score) was entirely based on Chem score. It also includes a steric-clash term, and adds polar terms featured by Schrödinger to correct electrostatic mismatches [17,18].

Statistical analysis

The data are expressed as mean ± standard error of mean (SEM). One-way analysis of variance (ANOVA) followed by Tukey multiple comparison test was carried out with Graph Pad Prism software (version 3.0). Differences between means were considered significant at $p < 0.01$.

RESULTS

Compound 2b with 4-hydroxy-3-methoxy substitution showed good activity compared to control and standard, while compounds 2m, 2n and 2o with heterocyclic ring system such as furan, indole and isatin, showed moderate activity against maximum electroshock-induced seizure (MES). In the case of pentylene tetrazole-induced seizure, compounds 2b, 2e, 2f, 2o and 2q with substitutions 4-Hydroxy-3-methoxybenzylideneamino,3-nitrobenzylidene-amino, 4-nitrobenzylideneamino, -(2-oxoindolin-3-ylideneamino, 1-methylpyrrolidin-2-ylidene-amino substitution at 2-amino-N-o-tolyl-5,6-dihydro-4H-Cyclopenta[b]thiophene-3-carboxa-mide produced greater reduction in the duration of convulsion than control but lower than the reference standard. All the synthesized compounds showed lower protection against PTZ-induced seizure than diazepam (reference standard).

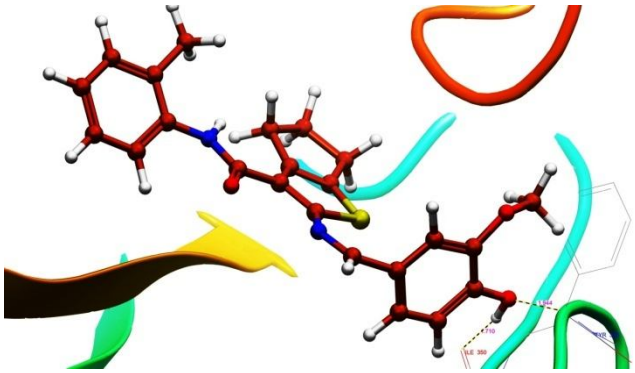

Figure 2: Interaction of compound 2b with the receptor. *Docking score of compound 2b was -7.01 interacting with the protein residues Ile 350 and Tyr 348*

Flexible docking of all the synthesized compounds was carried out at the active site of GABA-AT. The results reveal that eleven compounds are capable of binding to the active site of the receptor amino acid, Tyr 348; this predicts favorable interaction with protein residues that exhibit hydrophobic and hydrophilic interactions. Protein ligand interaction results indicate that protein residue, such as TYR 348, is the common amino acid that interacted with most of the ligands and other residues such as GLY 104, LEU 103, THR 132, PRO 344, and ILE 350, and that they also participate in the formation of hydrogen bonds. Compounds 2b, 2e, 2f, 2o and 2q with 4-hydroxy-3-methoxy substitution showed the highest docked score of 7.01, and were more tightly bound to the active site of GABA-AT than other compounds. The phenyl ring and carbonyl moiety of amide in compound 2b displayed good interactions at the active site. The best ligand protein interactions are shown in Figure 2. These observations provide a good basis for the estimation of the inhibitor activity of these compounds. Compounds 2c, 2g, 2m, 2n and 2s with 4-methylbenzylideneamino , 4-isopropylbenzylideneamino, furan-2-ylmethyl-eneamino, 1H-indol-3-yl-methyleneamino, 4-oxopentan-2-ylideneamino at 2-amino-N-o-tolyl-

5,6-dihydro-4H-Cyclopenta[b]thiophene-3-carboxamide did not demonstrate any hydrogen bond interactions may be responsible for the low docking score.

2-cyano-N-o-tolylacetamide(1):
Yield (%):75 , Colour: light pinkish crystals, Mol.wt:174, R_f value: 0.77, Mp (^{0}C): 143-144; IR (KBr, Cm^{-1}): 3268(NH), 3052 (Ar-H) ,2260(C-N), 1663(C=O); ^{1}H NMR($CDCl_3$, δ ppm): 2.32(,3H,CH_3), 4.01(d,2H,CH_2), 7.14(d,2H,Ar-H), 7.24(d,2H,Ar-CH);Mass (m/z):175$[M]^+$. Anal. Calcd.for $C_{10}H_{10}N_2O$: C(68.95); H(5.79); N(16.08). Found:C(68.85);H(5.68); N(15.89).

2-amino-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide(2):
Yield(%): 81, Colour: reddish brown crystals Mol.wt: 272, R_f value: 0.47, Mp (^{0}C): 148-150; IR (KBr, Cm^{-1}): 3429(NH_2), 3313(NH), 3021(Ar-H), 1628(C=O);^{1}H NMR ($CDCl_3$, δ ppm): 2.30 (s, 3H, CH_3), 2.4(m,2H,CH_2), 2.7(t,2H,CH_2), 6.2(s,2H,NH_2), 7.03-7.08(t,3H,Ar-H), 7.18-7.29(m,3H,Ar-H), 7.96-7.99(d,1H,NH);Mass: (m/z):273$[M]^+$. Anal.Calcd. for $C_{15}H_{16}N_2OS$: C (66.15); H (5.92); N(10.29). Found: C(66.09); H(5.90); N(10.32).

2-(bezylideneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2a):
Yield (%): 57, colour: light greenish crystals, Mol.wt:360, R_f value: 0.44, Mp (^{0}C): 109-110; IR (KBr, Cm^{-1}): 3365 (NH), 3065 (Ar-H), 1569(N=CH), 1668(C=O); ^{1}H NMR($CDCl_3$, δppm): 2.27(s,3H,CH_3), 2.36-2.45(t,2H,CH_2), 2.89-2.93(t,2H,CH_2), 3.12-3.17(t,2H,CH_2), 7.07-7.12(t,1H,Ar-H), 7.21-7.23(t,2H,Ar-H), 7.52(t,3H,Ar-H), 7.80-7.82(d,2H,Ar-H), 7.91-7.93(d,1H, Ar-H), 8.54(s,N=CH), 10.41(s,1H,NH);Mass(m/z):361$[M]^+$.Anal.Calcd.for $C_{22}H_{20}N_2OS$:C (73.30); H (5.59); N (7.77).Found: C(73.12); H (5.49); N (7.78).

2-(4-hydrox-3-methoxybenzylideneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide(2b):
Yield (%): 68%, colour: dark brown crystals, Mol.wt:406, R_f value: 0.68, Mp (^{0}C): 190-191; IR (KBr, Cm^{-1}): 3450(C-OH), 3264(NH), 2947(Ar-H), 1650(C=O), 1570(N=CH), 1257(Ar-OCH_3); ^{1}H NMR ($CDCl_3$, δ ppm): 2.28(s,3H,CH_3), 2.38-2.4(t,2H,CH_2), 2.82-2.92(m,3H,OCH_3), 3.10-3.15(t,2H ,CH_2), 3.96 (s,1H,OH), 3.79(s,1H,CH_2), 7.07-7.10(t,1H,Ar-H), 7.18-7.22(m,2H,Ar-H), 7.34-7.36(t,2H,Ar-H), 7.41-7.43(m,1H,Ar-H), 7.86-7.89(d,1H,Ar-H), 8.42(s,1H,N=CH), 10.45(s,1H,NH); Mass (m/z):407$[M]^+$. Anal. Calcd.for $C_{23}H_{22}N_2O_3S$: C(67.96); H(5.46); N(6.89). Found :C(67.90); H(5.43); N(6.86).

2-(4-methylbenzylideneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2c):
Yield (%):54, colour: light brownish crystals, Mol.wt:406, R_f value: 0.70, Mp (^{0}C): 130-132; IR (KBr, Cm^{-1}): 3240(NH), 3077(Ar-H), 2925(CH of CH_3), 1671(C=O str), 1584(N=CH);^{1}H NMR ($CDCl_3$, δ ppm): 2.27(m, 3H, CH_3), 2.42-2.44(d, 4H, CH_2), 2.55-2.62(d,4H,CH_2), 2.84-2.97(m,3H,CH_3), 7.07-7.23(m,4H,Ar-H),7.28-7.34(d,1H,Ar-H), 7.70-7.72(d,1H,Ar-H), 7.76-7.79(d,1H,Ar-H), 7.88-7.93(d,1H,Ar-H),8.51 (s,1H,N=CH), 10.44(S,1H,NH); Mass (m/z): 375$[M]^+$. Anal.Calcd. for $C_{23}H_{22}N_2OS$: C(73.76); H(5.92); N(7.48).Found :C(73.69); H(5.88); N(7.45).

2-(2-nitrobenzylideneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2d):
Yield (%):66, colour: light brownish crystals, Mol.wt:405, R_f value: 0.75, Mp (^{0}C): 128-130; IR (KBr , Cm^{-1}): 3285(NH), 3059(Ar-H), 1664(C=O), 1588(N=CH), 1340(NO_2);^{1}H NMR ($CDCl_3$, δ ppm): 2.12(s,3H,CH_3), 2.37-2.47(m,,2H,CH_2), 2.90-2.95(t,2H,CH_2), 3.13-3.18(t,2H,CH_2), 7.16-7.29(m,,2H,Ar-H), 7.72-7.82(m,3H,Ar-H), 7.96-7.97(d,2H,Ar-H), 8.06-8.18(s,1H,Ar-H), 9.02(s,1H,N=CH), 10.23(S,1H, NH) ;Mass (m/z):406$[M]^+$. Anal.Calcd. for $C_{22}H_{19}N_3O_3S$:C(65.17); H(4.72); N(10.36). Found C(65.20);H(4.69);N(10.32).

2-(3-nitrobenzylideneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2e):
Yield (%): 55, colour: dark brown crystals, Mol.wt:405, R_f value: 0.56, Mp (^{0}C): 140-142; IR (KBr, Cm^{-1}): 3250(NH), 3021(Ar-H),1656(C=O),1588(N=CH),1340(NO_2); ^{1}H NMR ($CDCl_3$, δ ppm). 1.3(s,1H,CH_3), 2.37-2.5(d,,2H,CH_2), 2.7(d,2H,CH_2), 4.2(q,2H,CH_2), 7.06-7.09(m,2H,Ar-H), 7.64-7.68(t,3H,Ar-H), 7.80-(d,2H,Ar-H), 8.01(s,1H,Ar-H-), 9.2(s,1H, N=CH), 10.12(s,1H,NH) ;Mass (m/z):406$[M]^+$. Anal.Calcd.for $C_{22}H_{19}N_3O_3S$:C(65.17); H(4.72); N(10.36). Found: C(65.20); H(4.69); N(10.32).

2-(4-nitrobenzylideneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2f):
Yield (%):59, colour: light brown crystals, , Mol.wt:405, R_f value:0.62 Mp (^{0}C): 189-190; IR (KBr,Cm^{-1}): 3299(NH), 3122(Ar-H), 1631(C=O), 1345(NO_2); ^{1}H NMR ($CDCl_3$, δ ppm), 1.6(s,3H,CH_3), 2.4(s,2H,CH_2), 2.50(s,1H,CH_2), 4.1(q,2H,CH_2), 6.9(s,1H,Ar-H), 7.1(t,3H,Ar-H), 7.2(s,3H,Ar-H), 7.4(d,1H,Ar-H), 8.6(s,1H,N=CH), 11.0(s,1H,NH);Mass (m/z):406$[M]^+$. Anal.Calcd.

for $C_{22}H_{19}N_3O_3S$:C(65.17); H(4.72); N(10.36). Found: C(65.20); H(4.69);N(10.32).

2-(4-isopropylbenzylideneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2g):

Yield (%):59, colour: dark brown crystals, Mol.wt:402, R_f value: 0.50 Mp (^{0}C): 105-106; IR (KBr, Cm^{-1}): 3295(NH), 3040(Ar-H), 2971(Ali-CH), 1645(C=O), 1583(N=CH), 1366 ((CH_3)$_2$);^{1}H NMR ($CDCl_3$, δ ppm): 1.26-1.29(d,6H,(CH_3)$_2$), 2.29(s,1H,CH_3), 2.37-2.45(t,2H,CH_2), 2.84-3.01(m,1H,CH), 3.12-3.16(t,2H,CH_2), 7.22-7.40(m,5H,Ar-H), 7.73-7.75(d,2H,Ar-H), 7.88-7.91 (d,1H,Ar-H),8.50(s,1H,N=CH), 10.47(s,1H,NH); Mass (m/z):403[M]$^+$. Anal.Calcd. for $C_{25}H_{26}N_2OS$:C(74.59); H(6.51); N(6.96).Found: C(74.52);H(6.52);N(6.98).

2-(4-fluorobenzylideneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2h):

Yield (%): 80, colour: lemon yellow crystals, Mol.wt:378, R_f value: 0.76, Mp (^{0}C): 165-166__ ; IR (KBr, Cm^{-1}): 3292(NH), 3070(Ar-H), 1666(C=O), 1587(N=CH), 1229(C-F); ^{1}H NMR ($CDCl_3$, δ ppm):2.25(S,3H,CH_3),2.36-2.45(m,2H,CH_2),2.88-2.93(t,2H,CH_2),3.12-3.16(t,2H,CH_2), 7.23(m,5H,Ar-H),7.79-7.84(t,2H,Ar-H),7.90-7.93(d,1H,Ar-H),8.5(s,1H, N=CH),10.31(s,1H,NH); (m/z):379[M]$^+$. Anal.Calcd.for $C_{22}H_{19}FN_2OS$: C(69.82); H(5.06); N(7.40):Found: C(69.80); H(5.08); N(7.38).

2-(4-(dimethylamino)bezylideneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2i):

Yield (%):62, colour: dark reddish crystals, Mol.wt:403, R_f value:0.50, Mp (^{0}C): 160-161;IR (KBr, Cm^{-1}): 3219(NH), 3024(Ar-H), 2906(CH Of CH_3), 1660(C=O), 1584 (N=CH); ^{1}H NMR ($CDCl_3$, δ ppm): 2.29(s, 3H, CH_3), 2.36-2.40(t,2H,CH_2), 2.86-2.91(t,4H,CH_2), 3.10-3.15(s,6H,(CH_3)$_2$), 6.92-6.95(d,2H,Ar-H), 7.06-7.11(t,1H,Ar-H), 7.20-7.23(t,2H,Ar-H), 7.73-7.71(d,2H,Ar-H), 7.88-7.91(d,1H,Ar-H), 8.4(S,1H,N=CH), 10.51(s,1H,NH); Mass (m/z):404[M]$^+$. Anal.Calcd.for $C_{24}C_{25}N_3OS$: C(71.43); H(6.24); N(10.41). Found:C(71.35); H(6.14); N(10.11).

2-(2,4-dichlorobenzylideneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2j):

Yield (%):57, colour: light brown crystals, Mol.wt:428, R_f value:0.77, Mp (^{0}C): 180-182. IR (KBr, Cm^{-1}): 3178(NH), 3036(Ar-H), 1661(C=O), 1575(N=CH); ^{1}H NMR ($CDCl_3$, δ ppm):2.18(s,1H,CH_3), 2.39-2.49(m,2H,CH_2), 2.83-2.88(t,2H,CH_2), 2.92-2.97(t,2H,CH_2), 7.30-7.39(m,4H,Ar-H),7.48-7.49(S,1H,Ar-H),7.86-7.96(m,2H,ArH),9.54(s,1H,N=CH),10.41(s,1H,NH);Mass(m/z):429[M]$^+$, 431[M]$^{+2}$. Anal.Calcd. for $C_{22}H_{18}Cl_2N_2OS$: C(61.54);H(4.23); N(6.52).Found: C(61.49);H(4.18);N(6.56).

2-(2-chlorobenzylideneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2k):

Yield (%):70, colour: dark brown crystals, Mol.wt:394, R_f value: 0.73, Mp (^{0}C): 208-210; IR (KBr, Cm^{-1}): 3290(NH), 3070(Ar-H), 1671(C=O), 1553(N=CH); ^{1}H NMR ($CDCl_3$, δ ppm): 2.21(s,3H,CH_3), 2.36-2.46(m,2H,CH_2), 2.89-2.94(t,2H,CH_2), 3.13-3.17(t,3H,CH_2), 7.06-7.11(t,1H,Ar-H), 7.18-7.42(m,3H,Ar-H), 7.44-7.48(s,1H,Ar-H), 7.91-7.99(m,2H,Ar-H), 8.95(s,1H,Ar-H), 10.32(S,1H,N=CH), 10.49(s,1H,NH); Mass(m/z):395[M]$^+$, 397[M]$^{+2}$. Anal.Calcd. for $C_{22}H_{19}ClN_2OS$:C(66.91);H(4.85);N(7.09).Found: C(66.85);H(4.88);N(7.14).

2-(2,4-dimethoxybenzylideneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2l):

Yield (%):55, colour: Apple green crystals, Mol.wt:420, R_f value:0.59, Mp (^{0}C): 142-144; IR (KBr, Cm^{-1}): 3178(NH), 3036(Ar-H), 1661(C=O), 1575(N=CH), 1269(Ar-OCH_3);^{1}H NMR ($CDCl_3$, δ ppm): 2.17(s,2H,CH_2), 2.28-2.31(s,2H,CH_3), 2.40(s,2H,CH_2), 2.43-2.46(m,3H,OCH_3),2.83-.96(m,3H,OCH_3), 3.11-3.16(t,2H,CH_2), 7.29-7.42(m,6H,Ar-H), 7.85-7.88(s,1H,Ar-H), 8.44(S,1H,N=CH), 9.86(s,1H,NH);Mass (m/z):421[M]$^+$. Anal.Calcd. for $C_{24}H_{24}N_2O_3S$:C(68.55);H(5.75);N(6.66).Found :C(68.45);H(5.69);N(6.58).

2-(furan-2-ylmethyleneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2m):

Yield (%):71, colour: light green crystals, Mol.wt:350, R_f value: 0.64, Mp (^{0}C): 138-140; IR (KBr, Cm^{-1}): 3287(NH), 3057(Ar-CH Str), 1669(C=O Str), 1587(N=CH- str); ^{1}H NMR ($CDCl_3$, δ ppm): 2.35-2.44(m, 4H, CH_2), 2.83-2.97(m,3H,CH_3), 3.12-3.17(t,2H,CH_2), 6.99(d,1H, Ar-H), 7.05(t,1H,Ar-H), 7.20(t,2H,Ar-H), 7.33(s,1H,Ar-H), 7.62(s,1H,Ar-H), 8.05(d,1H,Ar-H), 8.25(s,1H,N=CH), 10.64(s,1H, NH); Mass (m/z):351[M]$^+$. Anal.Calcd. for $C_{20}H_{18}N_2O_2S$: C(68.55);H(5.18);N(7.99).Found:C(69.12);H(5.05);N(7.86).

2-(1H-indol-3-yl)methyleneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2n):

Yield (%):69, colour: dark yellow crystals, Mol.wt:399, R_f value: 0.54, Mp (^{0}C): 180-182; IR (KBr, Cm^{-1}): 3430,3223(NH),1655(C=O),1612(C=O , indole),1588(N=CH); ^{1}H NMR (DMSO, δ ppm): 2.05(s,3H,CH_3), 2.27-2.37(m,2H,CH_2), 2.83-2.88(s,2H,CH_2), 2.95-2.97(s,2H,CH_2), 6.80-6.85(t,1H,Ar-H), 7.09-7.26(m,4H,Ar-H), 7.49-7.52(d,1H,Ar-H), 7.67-7.70(d,1H,Ar-H), 7.91-7.94(d,1H, Ar-H),8.26-8.27(s,1H,Ar-H),8.80(s,1H, N=CH),10.61(s,1H,NH), 12.15(s,1H,NH indole); Mass (m/z):400[M]$^+$. Anal.Calcd. for $C_{24}H_{21}N_3OS$:C(72.15);H(5.30);N(10.52).Found: C(72.20);H(5.18);N(10.32).

2-(2-oxoindolin-3-ylideneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2o):

Yield (%):32, colour: dark reddish crystals, Mol.wt:401, R_f value:0.83, Mp (^{0}C): 149-150; IR (KBr, Cm^{-1}): 3296(NH), 3042(Ar-H), 1666(C=O), 1606(C=O, isatin), 1589(N=CH);^{1}H NMR (DMSO, δ ppm): 2.30(s,3H,CH_3), 2.45-2.52(t,2H,CH_2), 2.79(s,2H,CH_2), 2.87-2.95(s,2H, CH_2), 7.15-7.22(m,7H,Ar-H), 7.43(s,1H,Ar-CH), 8.00(s,1H,NH), 11.75(s,1H,lactam);Mass (m/z): 402[M]$^+$. Anal.Calcd.for$C_{24}H_{21}N_3O_2S$: C(69.37); H(5.09); N(10.11).Found: C(68.37); H (4.10); N (10.15).

2-(cyclohexylideneamino)-N- o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2p):

Yield (%):58, colour: dark brown amorphous powder , Mol.wt:352, R_f value:0.65 Mp (^{0}C): 102-103; IR (KBr, Cm^{-1}): 3298(NH), 3056(Ar-H), 2930(Alip-CH), 1630(C=O),1573(C=N);^{1}H NMR ($CDCl_3$, δ ppm): 2.15(s,3H,CH_3), 2.37-2.30(m,6H,CH_2), 2.43-2.57(m,2H,CH_2), 2.83-3.08(m,6H,CH_2), 3.41(S,2H,CH_2),7. 19-7.23(m,4H, Ar-H), 8.02(N=CH), 11.79(s,1H, NH);Mass (m/z):351[M]$^-$. Anal.Calcd. for $C_{22}H_{26}N_2OS$: C(72.09); H(7.15);N(7.64). Found: C(73.01); H(7.25); N(7.62).

2-(1-methylpyrrolidin-2-ylideneamino)-N- o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2q):

Yield (%):49, colour: dark brown amorphous powder, Mol.wt:353, R_f value:0.69, Mp (^{0}C): 138-139; IR (KBr in Cm^{-1}): 3313(NH), 2929(Ar-H), 1628(C=O),1572(C=N),1341(C-N);^{1}H NMR ($CDCl_3$, δ ppm): 1.13 (s,3H,NCH_3), 2.34 (S,3H,CH_3), 4.0(d,2H,CH_2), 2.5(d,2H,CH_2), 2.8(d,2H,CH_2), 7.96(s,1H,NH), 7.27(m,4H,Ar-CH); Mass (m/z):354[M]$^+$. Anal.Calcd. for $C_{21}H_{25}N_3OS$: C(68.63); H(6.86); N(11.43).Found :C(68.43);H(6.74);N(11.89).

2-(butan-2-ylideneamino)-N-o-tolyl-5,6-dihydro-4H-Cyclopenta[b]thiophene-3-carboxamide(2r):

Yield (%):71 colour:Ash coloured crystals, Mol.wt:326, R_f value:0.60, Mp (^{0}C): 115-117; IR (KBr in Cm^{-1}): 3314(NH), 2904(Ar-H), 2843(CH str in CH_3), 1628(C=O Str), 1571(C=N Str); ^{1}H NMR ($CDCl_3$, δ ppm): 1.4(t,6H,CH_3), 2.4(m,3H,CH_3), 2.9(m,4H,CH_2), 4.3(m,4H,CH2), 9.57(s,NH,1H), ,8.44(d,1H,Ar-H), 8.02(d,1H,Ar-H), 7.7(t,1H,Ar-H), 7.54(t,1H,Ar-H); Mass (m/z):327[M]$^+$. Anal.Calcd.for $C_{19}H_{22}N_2OS$:C(69. 90); H(6.79); N(8.58). Found: C(68.54); H(6.53); N(8.12).

2-(4-oxopentan-2-ylideneamino)-N-o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide(2s):

Yield (%):55, colour:light brown crystals, Mol.wt:354, R_f value:0.71, Mp (^{0}C): 120-122; IR (KBr in Cm^{-1}): 3314(NH), 3056(Ar-H), 2850(CH-Str in CH_3), 1628(C=O), 1571(C=N); ^{1}H NMR ($CDCl_3$, δ ppm): 1.2(t,6H,CH_3), 1.6(s,3H,CH_3), 2.5(t,6H,CH_2), 4.1(m,2H,CH_2), 6.83(d,1H,Ar-H),7.0(t,1H,CH),7.12(t,1H,Ar-H),7.32(s,1H,d), 10.5(s,1H,NH); Mass (m/z):355[M]$^+$. Anal.Calcd. for $_{20}H_{22}N_2O_2S$:C(67.77);H(6.26);N(7.90).Found: C(66.15), H(5.89); N(7.14).

2-(1-phenylethylideneamino)-N- o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide (2t):

Yield (%):60, colour:dark brown crystals, Mol.wt:375, R_f value: 0.59 Mp (^{0}C): 124-125;IR (KBr in Cm^{-1}). 3315(-NH), 2923(Ar-H), 2851(Alip-CH_2),1628(C=O Str),1571(C=N Str);^{1}H NMR ($CDCl_3$, δ ppm).1.8(s,3H,CH_3), 2.1(s,3H,CH_3) , 2.60(m,2H,CH_2), 2.92(t,2H,CH_2), 2.4(t,2H,CH_2), 7.0(m,5H,Ar-H), 7.32(d,1H,Ar-H), 7.45(s,1H,Ar-H), 7.65(m,2H,Ar-H),8.45(s,1H,NH); Mass (m/z):376[M]$^+$. $C_{23}H_{22}N_2OS$:C(73.76);H(5.92); N(7.48).Found C(72.87);H(5.46);N(7.12).

DISCUSSION

The compounds synthesized by both microwave and conventional method. 2-Amino-N- o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide was prepared by the reaction of 2-cyano-N-o-tolylacetamide with cyclohexanone, sulphur and ionic liquid. The IR spectrum of 2-cyano-N-o-tolylacetamide showed the presence of CN peak at 2260 cm^{-1} (C-N), disappearance of CN peak and formation of NH_2 peak at 3429 cm^{-1}, and thus confirmed the formation of 2-aminothiophenes when basic ionic liquids are used for synthesis. Ionic liquids are non-volatile, recylable, non-explosive, thermally robust. 2-Amino-N-tolyl-5,6-dihydro-4H- cyclopenta(b)

Table 1: Anticonvulsant activity of 2-(Substituted)-N- o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide on Maximum Electroshock induced convulsions(MES)

Group	Treatment	Flexion (s)	Extension (s)	Clonus (s)	Stupor (s)	Recovery (s)
I	Control	6.81±0.016	12.81±0.006	13.28±0.040	6.21±0.040	189.5
II	Phenytoin	4.83±0.001***	0.00±0.000***	8.31±0.0166***	0.98±0.016***	17.3
III	2	6.11±0.016*	11.8±0.018*	12.65±0.004*	5.72±0.007*	82.1
IV	2a	5.18±0.016***	3.83±0.021***	10.28±0.090***	4.88±0.007***	75.6
V	2b	1.78±0.116***	1.55±0.022***	1.11±0.030***	0.97±0.004***	68.3
VI	2c	4.21±0.006***	2.18±0.016***	4.40±0.036***	1.83±0.049***	70.3
VII	2d	2.71±0.060***	2.05±0.022***	1.93±0.021***	1.21±0.001***	69.5
VIII	2e	3.25±0.057***	2.76±0.017***	2.20±0.001***	1.81±0.009***	78.1
IX	2f	2.71±0.001***	2.24±0.006***	1.98±0.002***	1.46±0.021***	72.3
X	2g	3.92±0.002***	3.50±0.002***	8.75±0.150***	1.31±0.098***	69.5
XI	2h	3.85±0.006***	3.42±0.003***	8.32±0.076***	1.53±0.111***	78.1
XII	2i	5.62±0.004***	4.81±0.006***	8.02±0.014***	1.48±0.065***	72.3
XIII	2j	4.51±0.010***	3.33±0.008***	8.14±0.014***	1.23±0.084***	77.5
XIV	2k	2.85±0.009***	2.14±0.001***	5.80±0.001***	1.31±0.003***	89.2
XV	2l	3.28±0.030***	3.05±0.034***	8.23±0.156***	1.85±0.194***	87.8
XVI	2m	2.91±0.003***	2.51±0.006***	7.63±0.130***	0.95±0.011***	84.4
XVII	2n	2.68±0.003***	2.50±0.002***	7.63±0.055***	0.96±0.014***	92.0
XVIII	2o	2.23±0.042***	2.11±0.006***	7.31±0.030***	1.03±0.034***	72.0
XIX	2p	5.38±0.040***	3.81±0.065***	12.11±0.040***	5.73±0.017*	80.3
XX	2q	4.13±0.088***	3.81±0.065***	8.70±0.063***	2.45±0.143***	74.0
XXI	2r	4.83±0.034***	4.91±0.054***	10.46±0.147***	4.36±0.084***	89.0
XXII	2s	4.50±0.051***	4.33±0.666***	9.56±0.105***	4.41±0.130***	90.0
XXIII	2t	5.16±0.049***	4.81±0.054***	4.8±0.051***	4.63±0.135***	72.0

*Values are expressed as mean ± SEM for six animals; **p < 0.05, *p < 0.001 compared to control group; phenytoin dose: 25 mg/kg; test: 30 mg/kg*

Table 2: Anticonvulsant activity of 2-(Substituted)-N- o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide on pentylene tetrazole-induced convulsions (PTZ)

Group	Treatment	Onset of clonic convulsion (s)	Onset of tonic convulsion (s)	% Protection after 30 min	% Protection after 24 h
I	Control	47.1±0.108	6.21±0.040	0	0
II	Diazepam	0.00±0.000	0.00±0.000	100	100
III	2	17.4±0.084***	5.72±0.007*	66.66	33.33
IV	2a	15.1±0.036***	4.88±0.007***	50	16.66
V	2b	10.2±0.030***	2.07±0.002***	83.33	83.33
VI	2c	10.4±0.066***	1.83±0.049***	33.33	16.66
VII	2d	12.2±0.016***	1.23±0.080***	83.33	83.33
VIII	2e	13.8±0.018***	1.36±0.088***	83.33	50
IX	2f	12.0±0.033***	1.03±0.009***	83.33	83.33
X	2g	11.2±0.006***	1.31±0.098***	66.66	50
XI	2h	16.8±0.015***	1.53±0.111***	66.66	66.66
XII	2i	14.4±0.026***	1.48±0.065***	83.33	50
XIII	2j	11.1±0.005***	1.23±0.084***	66.66	33.33
XIV	2k	12.0±0.022***	1.31±0.107***	83.33	66.66
XV	2l	14.8±0.004***	1.85±0.194***	66.66	50
XVI	2m	9.98±0.009***	0.95±0.011***	83.33	83.33
XVII	2n	10.9±0.020***	0.96±0.014***	83.33	66.66
XVIII	2o	10.1±0.004***	1.03±0.034***	50	50
XIX	2p	24.2±0.002***	5.73±0.017*	50	50
XX	2q	9.83±0.168***	2.45±0.143***	83.33	83.33
XXI	2r	18.4±0.028***	4.36±0.084***	83.33	83.33
XXII	2s	16.8±0.080***	4.41±0.130***	83.33	66.66

*Values are expressed as mean ± SEM for six animals; ***p < 0.05, *p < 0.001 compared to control group;* diazepam dose: 5 mg/kg; dose of test compound: 30mg/kg

Table 3: ADME (absorption, distribution, metabolism, excretion) properties of 2-(Substituted)-N- o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide

Compound	CNS	QPlogP po/w	QPlogS	Qplog HERG	QPP Cacco	Qplog BB	QPP MDCK	Qplog Kp	Qlog Khsa	%Human oral absorption
2	0	3.443	-4.338	-4.637	1815.3	-0.196	1726.854	-2.017	0.33	100
2a	1	5.367	-6.001	-5.886	4539	0	3870.398	-0.487	0.882	100
2b	0	4.929	-5.902	-5.814	1676.2	-0.572	1349.691	-1.299	0.749	100
2c	0	5.72	-6.739	-5.963	4529.9	-0.016	3898.422	-0.675	1.058	100
2d	-1	4.495	-4.84	-5.455	1730.7	-0.588	1251.683	-1.101	0.531	100
2e	-1	4.341	-5.162	-5.547	735.63	-0.963	547.676	-1.907	0.575	100
2f	-2	4.311	-5.769	-6.004	442.98	-1.289	317.55	-2.372	0.624	100
2g	0	6.351	-7.415	-5.979	4539.5	-0.086	3865.438	-0.672	1.303	100
2h	1	5.659	-6.394	-5.782	4912.1	0.15	7718.86	-0.542	0.935	100
2i	0	5.801	-6.879	-5.965	4418.4	-0.096	3773.591	-0.686	1.044	100
2j	1	5.973	-6.512	-5.066	4798	0.321	10000	-0.816	1.004	100
2k	1	5.611	-6.131	-5.625	4608.2	0.067	5134.292	-0.542	0.962	100
2l	0	5.389	-5.706	-5.311	4700.1	-0.106	3831.542	-0.558	0.821	100
2m	1	4.917	-5.522	-5.797	4991.1	0.056	4574.05	-0.449	0.663	100
2n	0	5.516	-6.172	-5.806	3237.3	-0.147	2593.073	-0.743	0.992	100
2o	0	4.763	-6.15	-5.993	1163.5	-0.594	1028.937	-1.674	0.779	100
2p	0	5.458	-6.415	-5.031	3507.7	-0.109	3011.975	-1.346	1.045	100
2q	1	3.974	-4.281	-5.782	1086.2	0.383	933.207	-3.219	0.608	100
2r	0	5.154	-5.723	-4.882	4853.3	-0.015	4383.093	-0.991	0.827	100
2s	1	5.663	-6.216	-5.688	5253.6	0.063	4417.94	-0.451	1.007	100
2t	0	5.099	-5.772	-4.838	2927.7	-0.201	2878.586	-1.363	0.83	100

Table 4: Docking studies of 2-(Substituted)-N- o-tolyl-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxamide

Compound	Dock score	e model	No of bonds	Interacted protein residues	H-bond distance
2	-4.017	-36.112	2	Leu 130,Thr 132	1.825,2.017
2a	-3.288	-35.699	1	Tyr 348	2.101
2b	-7.01	-40.382	2	Ile 350,Tyr 348	1.710,1.944
2c	-4.341	-33.889	-	-	-
2d	-2.2981	-47.413	1	Ile 350	2.176
2e	-6.121	-42.201	4	Arg 343,Pro 344,Tyr 348	1.897,2.445,1.719,2.122
2f	-6.865	-45.184	4	Arg343,Pro 344,Tyr348	1.895,2.212,1.719,2.290
2g	-4.186	-42.744	-	-	-
2h	-4.425	-28.5822	1	Tyr 348	2.165
2i	-4.16	-39.696	1	Tyr 348	2.438
2j	-4.076	-37.851	1	Tyr 348	2.118
2k	-4.777	-29.547	1	Tyr 348	2.137
2l	-4.311	-36.503	1	Tyr348	2.386
2m	-3.574	-36.763	-	-	-
2n	4.398	-44.376	-	-	-
2o	-5.136	-54.835	1	Ile 350	1.947
2p	-4.353	-38.168	1	Tyr 348	2.077
2q	-5.878	-26.655	2	Tyr 348,Gly104	2.162,2.328
2r	-3.457	-41.757	2	Gly104,Leu 103	1.827,2.080
2s	-3.462	-37.648	-	-	-
2t	-5.636	-41.595	1	Tyr 132	1.917

'-' indicates compound did not interacting with protein residues that had not hydrogen bond

peak and formation of N=CH at 1569 Cm^{-1} which means that the compound is derivatized. thiophene-3-carboxamide was treated with different aldehydes to form Schiff bases, and the IR spectra showed the dissappearance of NH_2.

Inhibition of MES test indicates activity against generalized tonic-clonic (grand mal) and cortical focal seizures [19]. It permits evaluation of the capacity of a substance to prevent seizure spread through neural tissue. MES test is not suitable for the testing of drugs acting on Na^+ channels; the model is suitable for the evaluation of the majority of standard and newly developed anticonvulsant drugs, despite the fact that these drugs interact with other drug targets. In MES-induced convulsion model, reference drug, phenytoin (25 mg/kg) prevented the important tonic extensor phase of the tonic-clonc seizures, offered 100 % protection and produced tonic flexion convulsions, whereas compounds **2b, 2e, 2f, 2m, 2n, 2o, 2q** altered extensor phase duration and onset of clonus phase; probably due to the inhibition of high frequency action potential firing but the compounds did not totally abolish the various phases at 30mg/kg dose.

PTZ is a most frequently used substance as well as an acute experimental model in the preliminary screening to test potential anticonvulsant drugs. PTZ is a selective blocker of the chloride ionophore complexation to the $GABA_A$ receptor, and after repeated or single-dose administration, leads to a decrease in GABAergic function and to the stimulation and modification of density or sensitivity of different glutamate receptor subtypes in many brain regions [19]. The precise mechanism of the synthesized compounds is not clear, but *in silico* studies revealed that the action of the test substances was on the GABA mediated chloride channel.

CONCLUSION

A simple rapid, efficient synthesis of 2-aminothiophenes by introduction of amide linkage at 3rd position has been achieved by one-pot synthesis utilizing cost-effective guanidine-based ionic liquid. Recent advances in the synthesis of 2-aminothiophenes reveal imidazoles-based ILs is replaced by guanidine-based ionic liquid. Isolation is simple, without the need for chromatographic purification, and there is no loss of catalytic activity. The anticonvulsant activity of the synthesized compounds is moderate against screening models. The results of *in silco* studies reveal significant role of topological parameters in inhibiting GABA-AT while docking results reveal significant role of phenyl ring and terminal carboxamide in drug-receptor interaction.

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