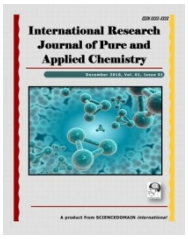

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Uses of 2-Amino-5,6-dihydro-4*H*-cyclopenta [*b*] thiophene-3-carbonitrile in the Synthesis of Heterocyclic Compounds with Anticonvulsant, Behavioral and CNS Antidepressant Activities

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ABSTRACT

The reaction of the cyclopenta[*b*]thiophene derivative 3 with phenylisothiocyanate4 gave thiourea derivative 5. The latter was reacted with the active methylene reagents 2a, b and 7 to give pyrimidine derivatives 6a, b and 8. N-Acylation of compound 3 was achieved *via* its reaction with acetic anhydride 9 to give the acetyl derivative 10. Compound 10 was utilized as a key for the synthesis of different heterocyclic compounds, where arylidene derivative 12 was obtained *via* its reaction with benzaldehyde11 and thienopyridone derivative 13 was obtained *via* its intramolecular cyclization using basic catalysis. Finally treatment of 10 with different activated carbonitriles2a, b or with hydrazine derivatives 15a, b afforded thienopyridone derivatives 14a,b and thienopyrimidine derivatives 17a,b, respectively. The newly synthesized compounds were tested for anticonvulsant, behavioral and CNS antidepressant activities.

Keywords: Thiophene; pyrimidine; pyridine; anticonvulsant; behavioral; CNS antidepressant activities.

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1. INTRODUCTION

Sulphur containing heterocycles paved the way for the active research in the pharmaceutical chemistry. Nowadays benzothiophene derivatives in combination with other ring systems have been used extensively in pharmaceutical applications such as antiallergic (Connor et al., 1992), analgesic (Wardkhan et al., 2008), anti-inflammatory (Mohammed et al., 2009) and Ocular hypotensive activities (Graham et al., 1989). Raloxifene a drug based on benzo[*b*]thiophene has been approved by the U.S Food and Drug Administration for the prevention and treatment of osteoporosis associated with woman postmenopausal (Jones et al., 1984; Jordan et al., 2003). On the other hand thiazoles bearing 1, 2, 4-triazole ring are very well known to exhibit powerful antimicrobial activity (Isloor et al., 2009). Also derivatives of 1,3,4-thiadiazoles have been synthesized as anticonvulsant agents (Rajak et al., 2009). Moreover some 1,2,4-triazolo[3,4-b][1,3,4]thiadiazines are associated with diverse pharmacological activities (Karabasanagouda et al., 2007; Prasad et al., 1989; El-Dawy et al., 1983; Farghaly et al., 2006; Badr et al., 2011).

Moreover, nitrogen-containing heterocycles including pyrimidine and pyridine are known to have a wide spectrum of biological and pharmacological activities. Thus many synthetic pyrimidines are considered as pharmacophores interfering with the synthesis and function of nucleic acids such as 5-FU the antitumor agent (Goette, 1981). Among other drugs containing pyrimidine moiety is antiepileptic phenobarbital (Kwan et al., 2004) and the powerful antimalaria drug is pyrimethamine in the combination formula with sulfadoxine (Ashley et al., 2006) Furthermore, several alkaloids containing the dihydropyrimidinone unit like batzelladine alkaloids have been found to be potent HIV gp120-Human CD4 binding inhibitors (Snider et al., 1996; Patil et al., 1995).

On the other hand, pyridine derivatives are also of great biological and medicinal importance. Biologically, pyridine ring is found in vitamin B family. Furthermore, synthesized pyridine derivatives exhibited various types of biological activities such as antibacterial (Foks et al., 2005), antimycobacterial (Kumar et al., 2009), analgesic and antiparkinsonian (Abdel-Latif et al., 2007), anticonvulsant (Subudhi et al., 2009) and antitumoral (Cocco et al., 2007). In the view of the above findings and as continuation of our efforts directed towards the synthesis of new heterocyclic compounds with expected biological activities (Mohareb et al., 2008), we herein report the synthesis of some new cyclopenta[*b*]thiophene derivatives containing pyrimidine and pyridine moieties and the screening of their anticonvulsant, behavioral and CNS antidepressant activities. The structures of the newly synthesized compounds were assigned using IR, NMR, ^{13}CNMR and Mass spectrometry techniques.

2. MATERIALS AND METHODS

All melting points are uncorrected. IR spectra were recorded for (KBr) discs on a PyeUnicam SP-1000 spectrophotometer.^{1}H-NMR and ^{13}C NMR spectrum were measured on a Varian EM-390-200 MHz in CD_3SOCD_3 as solvent using TMS as internal standard and chemical shifts are expressed as δ. Mass spectra were recorded on Kratos (75e-v) Ms Equipment (Germany). Analytical data were obtained from the Micro Analytical Data Unit at Cairo University, Giza, Egypt. Synthetic pathways are presented in Schemes 1-2 and the pharmacological data are indicated through Tables 1, 2 and 3.

2.1 Synthesis

2.1.1 2-Amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carbonitrile (3)

The titled compound 3 obtained *via* the reaction of malononitrile with Cyclopentanone and elemental sulfur according literature (Wang et al., 2010).

2.1.2 1-(3-Cyano-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-2-yl)-3-phenyl- thiourea (5)

To a solution of 2-amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carbonitrile(3) (1.5 g, 9.13×10^{-3}mol) in 1,4-dioxane (80 mL), phenylisothiocyanate(4) (1.24 g, 9.13×10^{-3}mol) and 0.5 mL of triethylamine were added. The reaction mixture was refluxed for 2.5 h then allowed to cool to room temperature and poured on ice / water mixture containing few drops of HCl. The formed precipitate was filtered off and recyrstallized.

Grey crystals from ethanol yield 69.34%, 1.90 g, m.p. 223-226ºC. IR (KBr): υ/cm^{-1}= 3491-3338 (2 NH), 3056 (CH aromatic), 2887 (CH_2), 2225 (CN), 1641 (C=C), 1204-1190 (C=S). ^{1}HNMR (DMSO) δ = 2.20-2.35 (m, 6H, $3CH_2$), 7.32-7.45 (m, 5H, C_6H_5), 8.26, 8.46 (2s, 2H, 2NH). ^{13}C NMR δ = 22.0, 26.9, 32.6 (3 CH_2), 116.0 (CN), 120.3, 120.5, 122.9, 124.2, 125.9, 129.0, 137.0, 139.9, (thiophene C, C_6H_5), 180.1 (C=S). Calcd for $C_{15}H_{13}N_3S_2$ (299.41): C, 60.17; H, 4.38; N, 14.03; S, 21.42%. Found: C, 60.34; H, 4.42; N, 14.11; S, 21.68%. MS (relative intensity) m/z: 299 (M^+, 20%), 207 (40%), 163 (100), 92(76%).

2.1.3 2-(6-Amino-1-(3-cyano-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-2-yl)-4-imino-3-phenyl-3,4-dihydropyrimidin-2(1*H*)-ylidene)malononitrile (6a)

To a solution of compound 5 (0.2 g, 6.68×10^{-4}mol) in 1,4-dioxane (30 mL) containing triethylamine (0.5 mL), malononitrile(2a) (0.05 g, 6.68×10^{-4}mol) was added. The resulting reaction mixture was heated under reflux for 3 h, cooled and poured on ice / water mixture containing few drops of HCl. The formed precipitate was filtered off and recyrstallized.

Pale brown crystals from ethanol yield 55.5%, 0.149 g, m.p. 290-293ºC. IR (KBr): υ/cm^{-1} = 3474-3433 (NH_2, NH), 3058 (CH aromatic), 2895 (CH_2), 2225-2220 (3CN), 1660 (exocyclic C=N), 1644 (C=C). ^{1}HNMR (DMSO) δ = 2.18-2.34 (m, 6H, $3CH_2$), 4.47 (s, 2H, NH_2), 5.99 (s, 1H, pyrimidine H-5), 7.23-7.35 (m, 5H, C_6H_5), 8.33 (s, 1H, NH). ^{13}C NMR: δ = 22.2, 26.5, 33.7 (3 CH_2), 115.9, 116.2, 117.5 (3 CN), 124.3, 125.6, 126.9, 129.2, 134.5, 140.9, 143.2, 146.2 (thiophene C, C_6H_5, pyrimidine C), 172.3 (C=NH). Calcd for $C_{21}H_{15}N_7S$(397.46): C, 63.46; H, 3.80; N, 24.67; S, 8.07%. Found: C, 63.59; H, 3.94; N, 24.88; S, 8.12%.

2.1.4 Ethyl 2-(6-amino-1-(3-cyano-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-2-yl)-4-oxo-3-phenyl-3,4-dihydropyrimidin-2(1*H*)-ylidene)-2-cyanoacetate (6b)

To a solution of compound 5 (0.2 g, 6.68×10^{-4}mol) in 1,4-dioxane (30 mL) containing triethylamine (0.5 mL), ethyl cyanoacetate(2b) (0.08 g, 6.68×10^{-4}mol) was added. The resulting reaction mixture was heated under reflux for 2 h, cooled and poured into ice/water mixture containing few drops of HCl. The formed precipitate was filtered off and recyrstallized.

Yellow crystals from ethanol yield 39.99%, 0.12 g, m.p. 263-266ºC. IR (KBr): υ/cm^{-1}= 3466-3430 (NH_2), 3053 (CH aromatic), 2977, 2890 (CH_3, CH_2), 2223, 2221 (2CN), 1687-1684 (2CO), 1644 (C=C). ^{1}HNMR (DMSO) δ = 1.15 (t, 3H, J = 7.08 Hz, CH_3), 2.23-2.36 (m, 6H,

$3CH_2$), 4.23 (q, 2H, J = 7.08 Hz, CH_2), 4.44 (s, 2H, NH_2), 5.90 (s, 1H, pyrimidine H-5), 7.23-7.38 (m, 5H, C_6H_5).^{13}C NMR: δ = 18.9 (CH_3), 22.6, 26.9, 33.0 (3 CH_2), 59.8 (CH_2), 115.6, 117.2 (2 CN), 122.0, 123.4, 125.2, 127.3, 132.8, 138.3, 140.9, 144.7 (thiophene C, C_6H_5, pyrimidine C), 172.8 (C=O). Calcd for $C_{23}H_{19}N_5O_3S$(445.49): C, 62.01; H, 4.30; N, 15.72; S, 7.20%. Found: C, 62.29; H, 4.41; N, 15.77; S, 7.42%.

2.1.5 2-(6-Methyl-4-oxo-3-phenyl-2-thioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5,6-di- hydro-4*H*-cyclopenta[*b*]thiophene-3-carbonitrile (8)

To a solution of compound 5 (0.4 g,1.34×10^{-3}mol) in 50 mL of 1,4-dioxane containing triethylamine (0.5 mL) as a catalyst, ethyl acetoacetate (7) (0.18 g, 1.34×10^{-3}mol) was added and the reaction mixture heated under reflux for 2 h, cooled and poured on ice water containing few drops from HCl, and the formed precipitate was filtered out.

Dark brown crystals from ethanol yield 46.7%, 0.229 g, m.p. 198-201ºC. IR (KBr): υ/cm^{-1}= 3060 (CH aromatic), 2977, 2893 (CH_3, CH_2), 2220 (CN), 1684 (CO), 1644 (C=C), 1208-1190 (C=S). ^{1}HNMR (DMSO) δ = 2.19-2.32 (m, 6H, $3CH_2$), 2.88 (s, 3H, CH_3), 5.99 (s, 1H, pyrimidine H-5), 7.27-7.32 (m, 5H, C_6H_5). ^{13}C NMR: δ = 18.6 (CH_3), 21.8, 25.9, 32.8 (3 CH_2), 116.9 (CN), 122.8, 124.9, 127.6, 130.6, 134.3, 138.4, 156.2 (thiophene C, C_6H_5, pyrimidine C), 163.4 (C=O), 179.9 (C=S). Calcd for $C_{19}H_{15}N_3OS_2$ (365.47): C, 62.44; H, 4.14; N, 11.50; S, 17.55%. Found: C, 62.66; H, 4.37; N, 11.69; S, 17.29%.

2.1.6 N-(3-Cyano-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-2-yl) acetamide (10)

To a solution of (3) (2.5 g, 0.015 mol) in glacial acetic acid (60 mL), acetic anhydride (9) (1.56 g, 0.015 mol) was added so that the ratio of acetic acid to acetic anhydride is 5:1. The reaction mixture was then refluxed for 3 h, cooled, then poured on ice-water and the formed precipitate was filtered out.

Pale brown crystals from ethanol yield 81.21%, 2.55 g, m.p. 128-131ºC. IR (KBr): υ/cm^{-1}= 3478-3312 (NH), 2988 (CH_3), 2890 (CH_2), 2221 (CN), 1686 (CO), 1646 (C=C).^{1}HNMR (DMSO) δ = 2.24-2.35 (m, 6H, $3CH_2$), 2.79 (s, 3H, CH_3), 8.66 (s, 1H, NH). ^{13}C NMR: δ = 23.0 (CH_3), 24.8, 27.8, 30.6, (3 CH_2), 116.0 (CN), 128.6, 130.6, 133.6, 138.9 (thiophene C), 170.3 (C=O). Calcd for $C_{10}H_{10}N_2O$ S(206.268): C, 58.23; H, 4.89; N, 13.58; S, 15.55%. Found: C, 58.32; H, 4.95; N, 13.74; S, 15.64%.

2.1.7 N-(3-Cyano-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-2-yl)-3-phenyl-acrylamide (12)

Compound 10(0.16 g, 7.76×10^{-4}mol) was dissolved in 30 mL of 1,4-dioxane and 0.5 mL of piperidine was added. Benzaldehyde(11) (0.08 g, 7.76×10^{-4} mol) was then added and the whole reaction mixture was heated under reflux for 2 h and then poured on some water containing ice and a few drops of HCl. Suction filtration was then used to collect the coagulated precipitate.

Brown crystals from ethanol yield 50.6 %, 0.111 g, m.p. 239-242ºC. IR (KBr): υ/cm^{-1}= 3487-3420 (NH), 3057 (CH aromatic), 2895 (CH_2), 2227 (CN), 1689 (CO), 1645 (C=C). ^{1}HNMR (DMSO) δ = 2.22-2.38 (m, 6H, $3CH_2$), 5.24, 5.29 (2d, 2H, J= 2.38 Hz, CH=CH), 7.33-7.46 (m, 5H, C_6H_5), 8.54 (s, 1H, NH). ^{13}C NMR: δ = 24.3, 27.5, 32.9 (3 CH_2), 110.8, 114.9 (CH=CH), 116.4 (CN), 121.6. 124.5, 128.5, 130.6, 133.8, 138.5 (thiophene C, C_6H_5), 170.0 (C=O). Calcd for $C_{17}H_{14}N_2OS$(294.37): C, 69.36; H, 4.79; N, 9.52; S, 10.89 %. Found: C, 69.43; H, 5.02; N, 9.74; S, 10.99 %.

2.1.8 4-amino-1,5,6,7-tetrahydro-2*H*-cyclopenta[4,5]thieno[2,3-*b*]pyridin-2-one (13)

Compound 10(0.3 g, 1.46×10^{-3}mol) was dissolved in 40 mL of 1,4-dioxane and 0.5 mL of triethylamine was added, then subjected to heat under reflux for 3 h aiming to form the cyclized product. The liquid was then poured on water and ice and a few drops of HCl were added to enhance precipitate formation and the latter was then collected by filtration.

Brown crystals from ethanol yield 39.5%, 0.119 g, m.p. 263-266ºC. IR (KBr): υ/cm^{-1}= 3492-3321 (NH_2, NH), 3052 (CH aromatic), 2884 (CH_2), 1692 (CO), 1647 (C=C).^{1}HNMR (DMSO) δ = 2.24-2.36 (m, 6H, $3CH_2$), 6.07 (s, 1H, pyridine H-3), 5.21 (s, 2H, NH_2), 8.46 (s, 1H, NH),.^{13}C NMR: δ = 24.9, 28.2, 32.8 (3 CH_2), 126.9, 128.6, 130.9, 138.8, 140.6, 148.9 (thiophene C, pyridine C), 170.8 (C=O). Calcd. for $C_{10}H_{10}N_2OS$(206.26): C, 58.23; H, 4.89; N, 13.58; S, 15.55%. Found: C, 58.39; H, 4.99; N, 13.76; S, 15.72%.

2.1.9 2-(4,6-Diamino-2-oxopyridin-1(2*H*)-yl)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene -3-carbonitrile (14a)

To a solution of compound 10(0.25 g, 1.21×10^{-3}mol) in 30 mL of ethanol, malononitrile(2a) (0.08 g, 1.21×10^{-3}mol) and 0.5 mL of triethylamine were added. The reaction mixture has been subjected to heat under reflux for 3 h, after which it was added to a mixture of ice, water containing few drops of HCl, the obtained precipitate collected by filtration.

Brown crystals from ethanol yield 48.7%, 0.161 g, m.p. >300ºC. IR (KBr): υ/cm^{-1}= 3472-3330 ($2NH_2$), 3056 (CH aromatic), 2880 (CH_2), 2220 (CN), 1689 (CO), 1649 (C=C).^{1}HNMR (DMSO) δ = 2.22-2.35 (m, 6H, $3CH_2$), 4.82, 5.30 (2s, 4H, $2NH_2$), 6.09, 6.13 (2s, 2H, pyridine H-3, pyridine H-5). ^{13}C NMR: δ = 24.3, 27.9, 33.4 (3 CH_2), 115.9 (CN), 122.4, 128.9, 132.9, 133.6, 136.4, 139.2, 140.6, 145.3, 158.5 (thiophene C, pyridine C), 168.9 (C=O). Calcd for $C_{13}H_{12}N_4OS$(272.33): C, 57.34; H, 4.44; N, 20.57; S, 11.77%. Found: C, 57.41; H, 4.59; N, 20.69; S, 11.83%.

2.1.10 2-(6-Amino-4-hydroxy-2-oxopyridin-1(2*H*)-yl)-5,6-dihydro-4*H*-cyclopenta[*b*] thiophene-3-carbonitrile (14b)

To a solution of compound10(0.5 g, 2.43×10^{-3}mol) in ethanol (60 mL) containing 0.5 mL of triethylamine, ethyl cyanoacetate(2b) (0.28 g, 2.43×10^{-3}mol) was added, the reaction mixture was heated under reflux for 2 h, then poured on some water containing HCl (a few drops) and the obtained precipitate collected by filtration.

Brown crystals from ethanol yield 34.5%, 0.231 g, m.p. 295-298ºC. IR (KBr): υ/cm^{-1}= 3561-3341 (OH, NH_2), 3056 (CH aromatic), 2884 (CH_2), 1690 (CO), 1644 (C=C), 2220 (CN).^{1}HNMR (DMSO) δ = 2.22-2.37 (m, 6H, $3CH_2$), 4.52 (s, 2H, NH_2), 6.07, 6.10 (2s, 2H, pyridine H-3, pyridine H-5), 9.44 (s, 1H, OH). ^{13}C NMR: δ = 24.0, 27.6, 32.2 (3 CH_2), 115.2 (CN), 112.7, 125.7, 131.3, 133.6, 140.1, 142.4, 163.5 (thiophene C, pyridine C), 168.8 (C=O). Calcd for $C_{13}H_{11}N_3O_2S$(273.31): C, 57.13; H, 4.06; N, 15.37; S, 11.73%. Found: C, 57.38; H, 4.37; N, 15.48; S, 11.67%.

2.1.11 1-(2-Methylcyclopenta[4,5][thieno[2,3-*d*]pyrimidin-4(3*H*)-ylidene)-hydrazone (17a)

Compound 10(0.25 g, 1.21×10^{-3}mol) was dissolved in 30 mL of ethanol. Hydrazine hydrate (15a) (0.06 g, 1.21×10^{-3}mol) was then added and the whole mixture refluxed for 3 h and

then poured on some water containing ice and a few drops of HCl. Suction filtration was then used to collect the coagulated precipitate.

Brown crystals from ethanol yield 46.3%, 0.125 g, m.p. 193-196ºC. IR (KBr): υ/cm^{-1}= 3484-3312 (NH_2, NH), 2968, 2880 (CH_3, CH_2), 1662 (exocyclic C=N), 1646 (C=C). ^{1}HNMR (DMSO) δ = 2.25-2.39 (m, 6H, 3CH_2), 3.07 (s, 3H, CH_3), 4.55 (s, 2H, NH_2), 8.93 (s, 1H, NH). ^{13}C NMR: δ = 20.8 (CH_3), 24.3, 27.8, 30.2 (3 CH_2), 124.8, 127.6, 130.6, 138.9, 141.4, 143.0, 155.3 (thiophene C, pyridine C), 158.8, 160.7 (2 C=N). Calcd for $C_{10}H_{12}N_4S$(220.29): C, 54.52; H, 5.49; N, 25.43; S, 14.56%. Found: C, 54.79; H, 5.65 N, 25.67; S, 14.72%.

2.1.12 1-(2-Methylcyclopenta[4,5][thieno[2,3-*d*]pyrimidin-4(3*H*)-ylidene)-phenylhydrazone (17b)

Compound 10(0.25 g, 1.21×10^{-3}mol) was dissolved in 30 mL of ethanol. Phenyl hydrazine (15b) (0.13 g, 1.21×10^{-3}mol) was then added and the whole mixture was refluxed for 3.5 h and then poured on some water containing ice and a few drops of HCl. Suction filtration was then used to collect the coagulated precipitate.

Brown crystals from ethanol yield 61.8%, 0.222 g, m.p. 158-161ºC. IR (KBr): υ/cm^{-1}= 3461-3311 (2NH), 3056 (CH aromatic), 2982, 2884 (CH_3, CH_2), 1663 (exocyclic C=N), 1648 (C=C).^{1}HNMR (DMSO) δ = 2.22-2.37 (m, 6H, 3CH_2), 3.05 (s, 3H, CH_3), 7.31-7.38 (m, 5H, C_6H_5), 8.44, 8.74 (2s, 2H, 2NH). ^{13}C NMR: δ = 22.8 (CH_3), 24.6, 27.3, 30.6 (3 CH_2), 118.8, 119.4, 120.6, 122.2, 124.3, 126.9, 132.8, 136.6, 142.6, 143.9, 155.3 (thiophene C, pyridine C, C_6H_5), 158.5, 162.8 (2 C=N). Calcd for $C_{16}H_{16}N_4S$(296.39): C, 64.84; H, 5.44; N, 18.90; S, 10.82%. Found: C, 64.98; H, 5.51; N, 18.76; S, 10.92%.

2.2 Biological Activity

2.2.1 Pharmacological results for synthesized compounds

2.2.1.1 Pharmacology

Anticonvulsant evaluation of the newly synthesized products was done by the anticonvulsant drug development (ADD) program protocol (Dimmock et al., 1995, Rajak et al., 2009). The profile of anticonvulsant activity was established after i.p. injection by the MES pattern test and the subcutaneous pentylenetetrazole (scPTZ) seizure threshold test. Minimal motor impairment was measured by the rotorod (neurotoxicity, NT) test using doses of 30, 100 and 300 mg/kg at two different time intervals. Male albino mice (CF-1 strain or Swiss, 18-25 g) and rats (Sprague-Dawley or Wistar, 100-150 g) were used as experimental animals. The tested compounds were suspended in polyethylene glycol 400.

2.2.1.2 Anticonvulsant screening

Initially all the compounds were administered i.p. in a volume of 0.01 ml/g body weight for mice and 0.004 ml/g body weight for rats at doses of 30, 100, 300 mg/kg to two to four animals. Activity was established using the MES and scPTZ tests and these data are presented in Table 1.

Table 1. Anticonvulsant activity and minimal motor impairment of the synthesized compounds

Comp. No.	Intraperitoneal injection in mice[a]					
	MES[b] screen		scPTZ[c] screen		Neurotoxicity screen[d]	
	0.5h	4h	0.5h	4h	0.5h	4h
3	100	300	300	-	100	-
5	100	300	300	-	-	-
6a	100	-	300	-	100	300
6b	100	300	-	-	100	-
8	-	-	300	100	-	300
10	100	300	300	-	-	-
12	-	-	-	100	100	-
13	100	-	300	-	100	300
14a	100	300	-	100	-	300
14b	-	-	100	300	-	300
17a	-	-	300	-	-	-
17b	100	300	-	-	100	-
Phenytoin[e]	30	30	-	-	100	100
Ethosuximide[e]	-	-	100	300	-	-

[a]Doses of 30, 100 and 300 mg/kg were administered. The values in the table indicate the minimum dose whereby bioactivity was demonstrated in half or more of the mice. The animals were examined 0.5 and 4 h after the injections were made; the symbol (-) indicates the absence of activity at maximum dose administered (300 mg/kg).

[b]Maximal electroshock test; [c]Subcutaneouspentylenetetrazole test; [d]Neurotoxocity screening (rotorod test); [e]Data from Refs. (Dimmock et al., 1995; Rajak et al., 2009).

2.1.1.3 Behavioral testing

The title compounds (100 mg/kg) were screened for their behavioral effect using cytophotometer (Biossier et al., 1965) at 30 min and 1 h after drug administration. The behavior of animals inside the photocell was recorded as a digital score. Increased scores suggest good behavioral activity. Percentage decrease in locomotor activity is calculated with the help of activity score of control (24 h prior) and score after 1 h of drug treatment. Mean values were taken for the calculations. The control group animal was administered with PEG 400. The observations are presented in Table 2.

2.1.1.4 CNS antidepressant activity

The forced swim pool method described earlier (Porsolt et al., 1978) was followed; Wistar rats were placed in chamber (diameter 45 cm, height 20 cm) containing water up to a height of 15 cm at 25 ± 2ºC. Two swim sessions were conducted: an initial 15 min pretest following by a 5 min test session 24 h later. The animals were oral drug administrated (100 mg/kg) with the test compound 30 min before the test session. The period of immobility (passive floating without struggling, making only those movements which are necessary to keep its head above the surface of water) during the 5 min test period was measured. The results are presented in Table 3.

Table 2. Behavioral study of the synthesized compounds

Comp. no.[a]	Activity score[b]			
	Control (24 h prior)	Post-treatment		
		After 0.5 h	After 1h	% Inhibition
3	590.23± 1.29	422.48 ±2.38	360.49± 1.22	39
5	524.43 ± 1.52	413.62 ± 1.83	402.05 ± 1.62	23
6a	539.51 ± 2.52	432.88 ± 2.69	399.05 ± 0.82	26
6b	489.78 ± 2.73	408.44 ± 0.89	374.09 ± 2.22	24
8	444.94 ± 2.69	421.05 ± 1.83	399.54 ± 2.03	10
10	569.52 ± 1.32	411.52 ± 2.72	319.25 ± 1.73	44
12	480.42 ± 2.55	395.37 ± 2.28	378.40 ± 1.09	21
13	489.07 ± 1.84	437.62 ± 2.83	275.94 ± 0.94	44
14a	588.37 ± 2.91	492.22 ± 1.89	377.94 ± 2.23	36
14b	466.43 ± 1.52	433.62 ± 1.83	312.05 ± 0.62	33
17a	429.22 ± 1.63	408.38 ± 0.78	360.22 ± 2.37	16
17b	488.49 ± 0.96	395.46 ± 1.42	359.73 ± 2.55	26
Phenytoin[c]	646.40 ± 31.12	549.02 ± 12.32	207.42 ± 30.11	64

[a]The compounds were tested at a dose of 100 mg/kg i.p.
[b]Each score represents the means ± SEM of six mice significantly different from the control score at p < 0.05 and NS at p > 0.05 denotes not significant.
[c]Tested at 30 mg/kg p.o.

Table 3. CNS study on the synthesized compounds by forced swim pool test

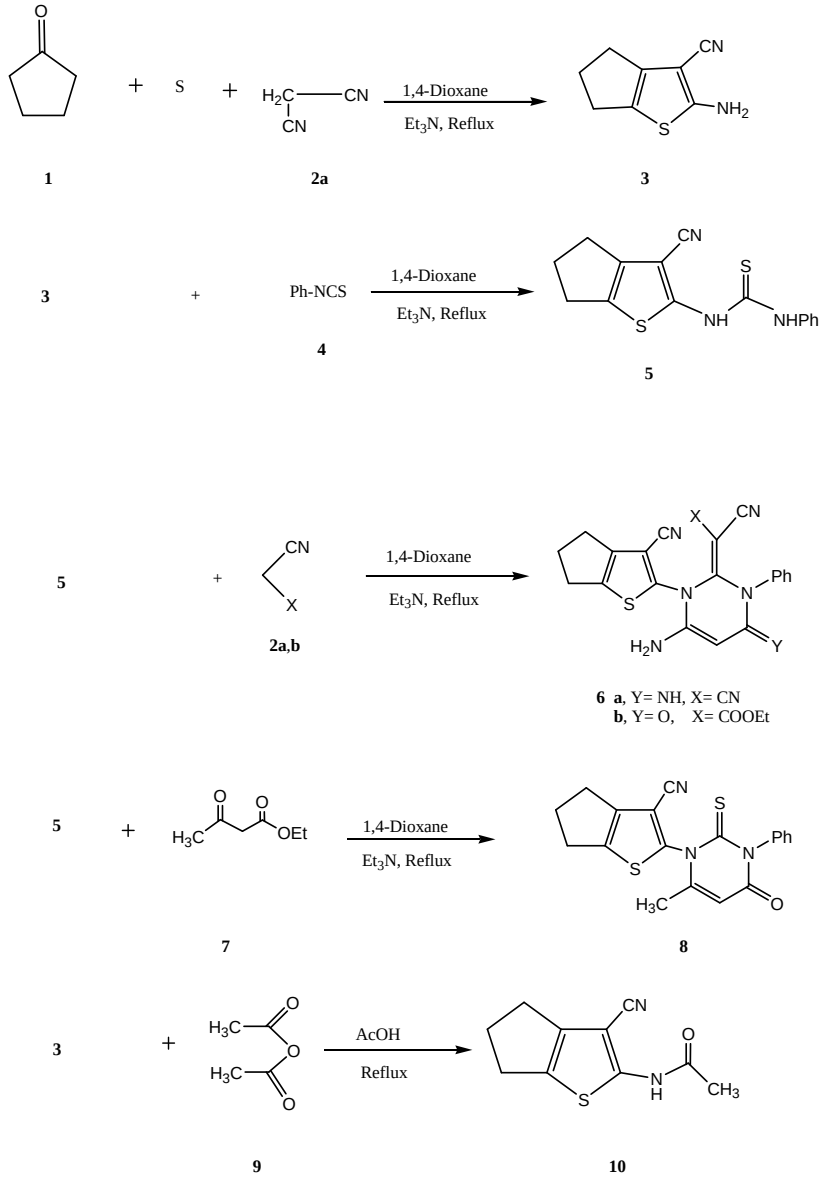
Comp. no.[a]	Immobility time[b] (s)	
	Control (24 h prior)	Post-treatment (after 1 h)
3	67.77± 6.92	89.37±8.28
5	117.32 ± 12.98	122.36 ± 13.16
6a	115.11 ± 13.88	160.51 ± 14.84
6b	78.12 ± 16.98	103.23 ± 3.27
8	66.36 ± 6.88	96.54 ± 8.52
10	70.42 ± 6.03	105.72 ± 7.93
12	130.42 ± 16.06	184.82 ± 18.09
13	137.32 ± 12.48	172.36 ± 23.16
14a	111.73 ± 5.91	185.83 ± 18.93
14b	124.94 ± 3.28	187.91 ± 9.41
17a	62.32± 18.42	93.83±4.91NS
17b	117.01 ± 20.37	132.69±7.24
Carbamazepine[c]	138.82±15.09	240.30± 14.10

[a]The compounds were tested at a dose of 100 mg/kg (oral).
[b]Each value represents the means SEM of six rats significantly different from the control at p < 0.05 and NS denotes not significant at p < 0.05 (Student's t-test).
[c]Tested at 30 mg/kg (i.p.).

3. RESULTS AND DISCUSSION

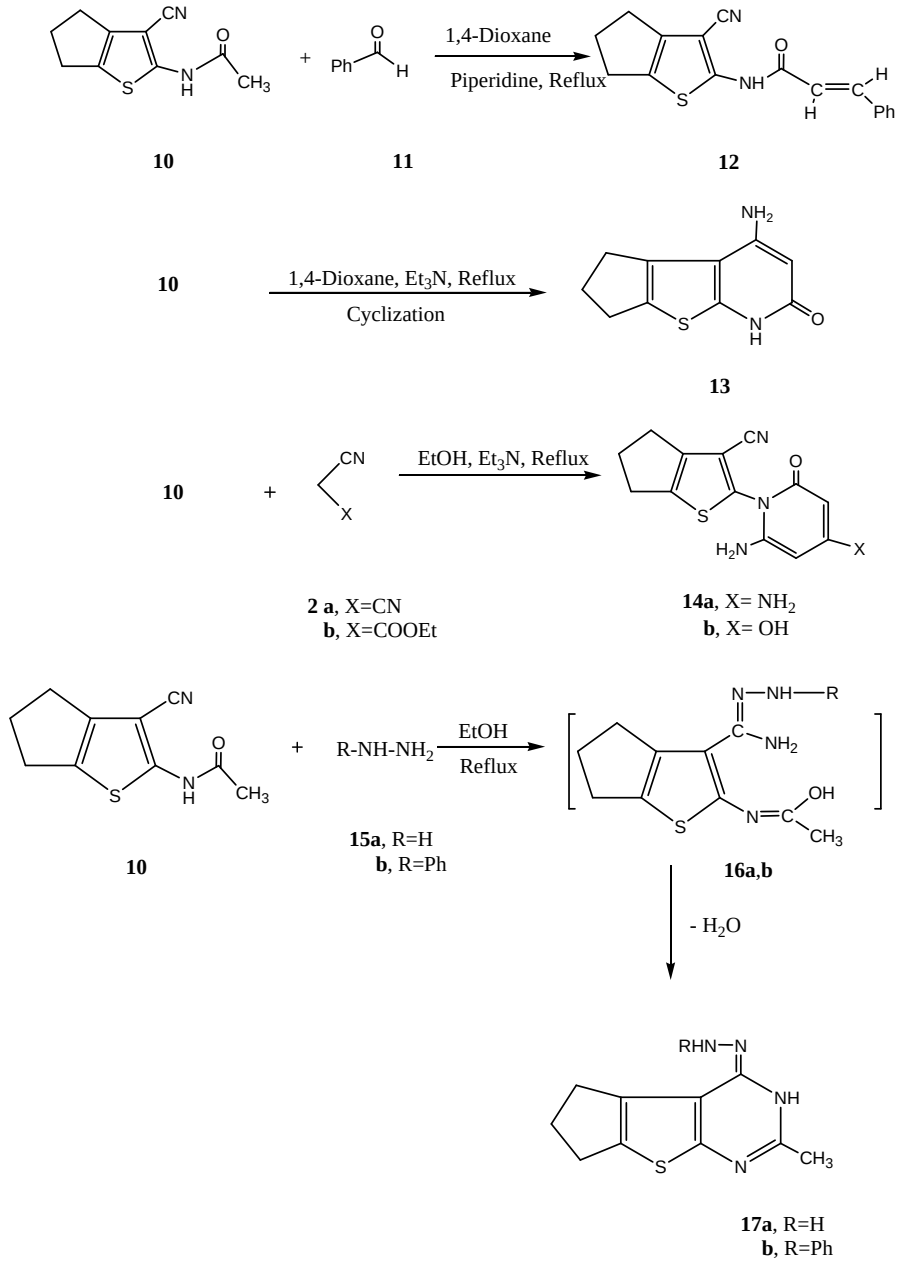
The reaction of 3 with phenyl isothiocyanate produced N-Phenylthiourea derivative 5 similar formation described before (Mohareb et al., 2012) which was allowed to react with different active nitriles namely malononitrile2a and ethyl cyanoacetate2b to afford the pyrimidine

derivatives 6a and 6b, respectively. On the other hand reaction of 3 with ethyl acetoacetate 7 yielded pyrimidine derivative8. The proposed structure for the compound 8 is based on the analytical and spectral data. Thus the ^{1}HNMR spectrum showed a multiplet at δ=2.19-2.32 corresponding to the hydrogens of the three (CH_2) groups in the cyclopentene moiety, singlet at δ=2.88 corresponding to the three hydrogens of (CH_3), a singlet at δ = 5.99 corresponding to one hydrogen in pyrimidine ring, a multipletat δ=7.27-7.32 corresponding the five hydrogens in phenyl group. Heating of cyclopenta[*b*]thiophenederivative**3** in a mixture of acetic anhydride 9 and acetic acid yielded the N-Acetyl derivative 10 (Scheme 1).



Scheme 1. Synthesis of compounds 3-10

The produced amide derivative 10 was subjected to a series of reactions. First, it was allowed to react with benzaldehyde11 in the presence of a catalytic amount of piperidine to give the *E*- isomer of the benzal derivative 12. Second, it was cyclized when heated in 1,4-dioxane in presence of few drops of triethylamine to give the fused pyridine derivative 13. Third, it was allowed to react with cyanomethylene reagents, namely malononitrile2a and ethyl cyanoacetate2b and afforded the pyridine derivatives 14a,b, respectively (scheme 2). Structure assignment for the latter pyridines was based on analytical and spectral data.



Scheme 2. Synthesis of compounds 12-17a,b

Finally, also compound 10 was allowed to react with hydrazine hydrate 15a andphenyl hydrazine 15b to give pyrimidine derivatives 17a, and 17b,supposedly through the formation of the intermediates 16a and 16b, respectively (scheme 2). Similar to hydrazones being reported in literature via similar mechanism $RNHNH_2$ with CN compounds to give amidrazones (Aggarwal et al., 2011; Garfunkle et al., 2008). The proposed structures for compounds 17a, b were consistent with analytical and spectral data. Thus the ^{1}HNMR spectrum of 17a, for example, showed a multiplet at δ 2.25-2.39 corresponding to the methylene groups' protons in the cyclopentene moiety, and three singlets at δ 3.07, δ 4.55 and δ 8.93 corresponding to the protons of methyl group, the NH_2 and NH group of the pyrimidine ring, respectively.

The preliminary results of the semicarbazones in the mouse i.p. MES, scPTZ and neurotoxicity screens are presented in Table 1, along with data of clinically used drugs. Most of the compounds were active in the MES and scPTZ tests at a dose of 100 and 300 mg/kg, indicative of their ability to prevent seizure spread and possible interaction with glycine receptors too. At a dose of 100mg/kg, compounds that showed protection in half or more of the tested mice in MES screen were 3 (0.5, 4h), 5 (0.5h, 4h), 6b (0.5 h, 4h), 10 (0.5, 4h), 14a (0.5 h, 4h) and 17b (0.5h, 4h). Only compounds 3 (300 mg/kg, 0.5h) and 5 (300 mg/kg, 0.5h), 6a (300 mg/kg, 0.5h), 8 (300 mg/kg, 0.5h), 10 (300 mg/kg, 0.5h), 13 (300 mg/kg, 0.5h) and 17a (300 mg/kg, 0.5h) showed protection in the scPTZ test. Compounds 3, 5, 6b, 10, 12,17a, and did not show any neurotoxicity in the maximum dose administrated (300mg/kg). Compounds 3, 6a, 6b, 12, 13 and 17b revealed neurotoxicity at a dose of 100mg/kg compared to the standard drugs.

From the results in table 2 only three compounds 3, 10 and 13showed inhibition more than 38% decrease in locomotors after 1 h of compound administration. Compound 8was the least potent and compounds 10 and 13 were the most potent in the prepared series, it may be the presence of NHCO group together with the thiophene moiety showed higher activity.
From Table 3 it is clear that all compounds were found to exhibit potent CNS antidepressant activity as indicated by increased immobility time. The most active compounds are 12,14a and 14b. However, the least active compounds are 3, 6b, 8, 10 and 17a. Comparing 6a and 6b one can say that the presence of CN group in 6a together with the C=N moiety showed higher activity than that of 6b with the COOEt and C=O groups. On the other hand comparing compounds 17a and 17b, it is obvious that 17a with the hydrazono N-H group has lower activity than that of 17b with the N-phenylhydrazono group.

4. CONCLUSION

In this work cyclopenta[*b*]thiophene derivatives were synthesized and screened for their anticonvulsant, behavioral and CNS antidepressant activities. Among the synthesized compounds 3, 6a, 6b, 12, 13 and 17b revealed neurotoxicity at a dose of 100mg/kg compared to the standard drugs. On the other hand, compounds 12, 14a and 14b showed the maximum CNS antidepressant activity as indicated by increased immobility time.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

Abdel-Latif, N. A., Sabry, N.M., Mohamed, A.M., Abulla, M.M. (2007). Synthesis, analgesic, and antiparkinsonian profiles of some pyridine, pyrazoline and thiopyrimidine derivatives. Monatshefte fur Chemie, 138, 715–724.

Aggarwal, R., Kumar, V., Kumar, R., Singh. S.P. (2011). Approaches towards the synthesisof 5-aminopyrazoles. Beilstein J Org Chem., 7, 179-197.

Ashley, E., McGready, R., Proux, S., Nosten, F. (2006). Review Malaria. Travel Medicine and Infectious Disease, 4, 159–173.

Badr, S.M., Barwa, R.M. (2011). Synthesis of some new[1,2,4]triazol[3,4-b][1,3,4]thiadiazines and [1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles starting from 5-nitro-2-furoic acid and evaluation of their antimicrobial activity. Bioorg. Med. Chem., 1, 19(15), 4506-4512.

Boissier, J.R., Simon, P. (1965). Action de la caféinesur la motilitéspontanée de la souris. Arch. Int. Pharmacodyn. Ther., 158(1), 212–221.

Cocco, M.T., Congiu, C., Lilliu, V., Onnis V.(2007). Synthesis and in vitro anti mtumoralactivity of new 3,5-dicyanopyridine derivatives. Bioorg. Med. Chem., 15(4), 1859-1867.

Connor, D.T., Cetenko, W.A., Mullican, M.D., Sorenson R.J., Unangst, P.C., Weikert, R.J., Adolphson, R.L., Kennedy, J.A., Thueson, D.O., Wright, C.D., Conroy, M.C. (1992). Novel benzothiophene-, benzofuran- and naphthalenecarboxamidotetrazoles as potential antiallergy agents. J. Med. Chem., 35, 958-965.

Dimmock, J.R., Pandey, S.N., Quail, J.W., Pugazhenthi, U., Allen, T.M., Kao, G.Y., Balzarini, J., DeClercq, E. (1995). Evaluation of the semicarb- azones, thiosemicarb-azones and bis-carbohydrazones of some aryl alicyclic ketones for anticonvulsant and other biological properties. Eur. J. Med. Chem., 30, 303-314.

El-Dawy, M.A., Omar, A.M.M.E., Hazzaa, A.I. (1983).Potionalbroad spectrum anthlementics IV: Design, synthesis and antiparasitic screening of certain 3,6-di-substituted-(7*H*)-s-triazolo-[3,4-b][1,3,4]thiadiazine derivatives. J. Pharm. Sci., 72, 45– 50.

Farghaly, A., De Clercq, E., El-Kashef, H. (2006). Synthesis and antiviral activity of novel[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles, [1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazines and [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines. Arkivoc(X), 137-151.

Foks, H., Pancehowska-Ksepko, D., Kedzia, A., Zwolska, Z., Janowiec, M., Augustvnowicz-Kopec, E. (2005). Synthesis and antibacterial activity of 1*H*-pyrazolo[3,4-b]pyrazine and –pyridine derivatives. II Farmaco., 60(6-7), 513-517.

Garfunkle, J., Ezzili. C., Rayl, T.J., Hochstatter, D.G., Hwang, I., Boger, D.L. (2008). Optimization of the central heterocycle of α-ketoheterocycle inhibitors of fatty acid amide hydrolase. J Med Chem., 51(15), 4392-4403.

Goette, D.K. (1981). Topical chemotherapy with 5-fluorouracil. Acad. Dermatol., 4, 633–649.

Graham, S.L., Shepard, K.L., Anderson, P.S., Baldwin, J.J., Best, D.B., Christy, M.E.,Freedman, M.B., Gautheron, P., Habecker, C.N. (1989). Topically active carbonic anhydrase inhibitors. 2. Benzo[b]thiophene sulfonamide derivatives with ocular hypotensive activity. J. Med. Chem., 32, 2548–2554.

Isloor, A.M., Kalluraya, B., Shetty, P. (2009). Regioselective reaction: Synthesis, characterization and pharmacological studies of some new Mannich bases derived from1,2,4-triazoles. Eur. J. Med. Chem., 44, 3784–3787.

Jones, C.D., Jevnikar, M.G., Pike, A.J., Peters, M.K., Black, L.J., Thompson, A.R., Falcone, J.F., Clements, J.A.(1984). Antiestrogens. 2. Structure-activity studies in a series of 3-aroyl-2-arylbenzo[b]thiophene derivatives leading to [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]-methanone hydrochloride (LY 156758), a remarkably effective estrogen antagonist with only minimal intrinsic estrogenicity. J. Med. Chem., 27, 1057–1066.

Jordan, V.C. (2003). Antiestrogens and selective estrogen receptor modulators as multifunctional medicines. 1. Receptor interactions. J. Med. Chem., 46, 883–908.

Jordan, V.C. (2003). Antiestrogens and selective estrogen receptor modulators as multifunctional medicines. 2. Clinical considerations and new agents. J. Med. Chem., 46, 1081–1111.

Karabasanagouda, T., Adhikari, A.V., Shetty, N.S. (2007). Synthesis and anti-micro bial activities of some novel 1,2,4-triazolo[3,4-b]1,3,4-thiadiazoles and 1,2,4triazolo[3,4-b]1,3,4thiadiazines carrying thioalkyl and sulphonylphenoxy moieties. Eur. J. Med. Chem., 42, 521-529.

Kumar, R.R., Perumal, S., Senthilkumar, P., Yogeeswari, P., Sriram, D. (2009). A facile synthesis and antimycobacterial evaluation of novel spiro-pyrido-pyrrolizines and pyrrolidines. Eur J Med Chem., 44, 3821–3829.

Kwan, P., Brodie, M.J. (2004). Phenobarbital for the treatment of epilepsy in the 21st century: a critical review. Epilpesia, 45(9), 1141-1149.

Mohamed, A.A.R., Shehab, M.A., El-Shenawy, S.M. (2009). Synthesis and biological evaluation of 5-substituted benzo[*b*]thiophene derivatives as anti-inflammatory agents. Monatsh Chem., 140, 445–450.

Mohareb, R.M., El-Sharkawy, K.A., Sherif, S.M. (2008). The reaction of β- -amino α, γ – dicyanocrotononitrile with acetophenone: Synthesis of pyridine, pyridazine and thiophene derivatives with antimicrobial activities. Acta Pharm., 58, 429–444.

Mohareb, R.M., Al-farouk, F.O. (2012). Anti-tumor and anti-leishmanial evaluations of novel thiophene derivatives derived from the reaction of cyclopentanone with elemental sulphur and cyano-methylene reagents. Organic Chem Current Res., 1(1), in press.

Patil, A.D., Kumar, N.V., Kokke, W.C., Bean, M.F., Freyer, A.J., De Brosse, C., Mai, S., Truneh, A., Carte, B. (1995). Novel alkaloids from the sponge *Batzella* sp.: Inhibitors of HIV gp120-Human CD4 Binding. J. Org. Chem., 60(5), 1182-1188.

Prasad, A.R., Ramalingam, T., Rao, A.B., Diwan, P.W., Sattur, P.B. (1989). Synthesis and biological evaluation of 3-aryloxyalkyl-6-aryl-7H-s-triazolo [3,4-b][1,3,4] thia-diazines. Eur. J. Med. Chem., 24, 199–201.

Prosolt, R.D., Anton, G., Blanet, N., Jalber, M. (1978). Behavioral despair in rats: a new animal model sensitive to antidepressant treatments. Eur. J. Pharmacol., 47, 379-391.

Rajak, H., Deshmukh, R., Aggarwal, N., Kashaw, S., Kharya, M.D., Mishra, P. (2009). Synthesis of novel 2,5-Di substituted 1,3,4-thiadiazoles for their potential anti-convulsant activity: pharmacophoric model studies. Arch. Pharm., 342, 456-461.

Snider, B.B., Chen, J., Patil, A.D., Freyer, A.J. (1996). Synthesis of the tricyclic portions of batzelladines A, B and D. Revision of the stereochemistry of batzel; ladines A and D. Tetrahedron Lett., 37(39), 6977-6680.

Subudhi, B.B., Panda, P.K., Swain, S.P., Sarangi, P. (2009). Synthesis, characterization and anticonvulsant activity evaluation of some 1,4-dihydropyridines and 3,5-(substituted)oxycarbonyl-1,4-dihydro-2,6-dimethyl-N-[2-(sulfamoyl phenyl amino)-acetyl]-4-(substituted)pyridines. Acta Poloniae Pharmaceutica–Drug Research, 66(2), 147-153.

Wang, T., Huang, X., Liu, J., Li, B., Wu Chen, J.K., Zhu, W.L., Xu, X.Y., Zeng, B.B. (2010). An efficient one-pot synthesis of substituted 2-aminothiophenesvia three-component Gewald reaction catalyzed by L-Proline. Syn Lett, 9, 1351-1354.

Wardakhan, W.W., Abdel-Salem, O.M.E., Elmegeed, G.A. (2008). Screening for anti depressant, sedative and analgesic activities of novel fused thiophene derivatives. Acta Pharm., 58, 1–14.