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Synthesis and anticonvulsant activity of new 3'-aryl-7 -bromo-spiro[[1]benzothiophene-3,2'-[1,3]thiazolidine] -2,4'-dione derivatives

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ABSTRACT

Two series of spiro[[1]benzothiophene-3,2'-[1,3]thiazolidine]-2,4'-diones 5a-e and 6a-e were synthesized, characterized and evaluated for anticonvulsant activity. Reaction of [1]benzothiophene-2,3-dione (3) with certain arylamines afforded the corresponding Schiff bases 4a-e. Cyclization of 4a-e with thioglycolic or thiolactic acids brought about the target spiro compounds 5a-e and 6a-e respectively. Spectral data, IR and ^{1}H-NMR proved that the structure of the spiro compounds 5a-e and 6a-e might be in a mixture of two forms or derivatives of [1,3]thiazolidinone and / or hydroxy[1,3]thiazole. The final compounds were tested for their anticonvulsant activity.

Key words: Anticonvulsant activity, epilepsy, drug therapy.

INTRODUCTION

Epilepsy, characterized by the periodic and unpredictable occurrence of seizures, is the most prevalent neurological disorder affecting approximately 50 millions people worldwide, with almost 90% of these people being in developing countries.[1] Despite of the development of several new anticonvulsants, the main drawback related with its management is associated with the fact that about one-third of patients do not respond well to current multiple drug therapy.[2-7]Even the new generation of antiepileptic drugs (AEDs) causes sizable side effects as ataxia, diplopia, mental dulling and hepatotoxicity.[8-10] These limitations with conventional antiepileptic drugs, demand the need for new AEDs with better safety, lower toxicity, and higher efficiency in difficult-control patients.

It is well known that numerous derivatives with anticonvulsant activity contain 5-, 6-heterocycle rings, one or two carbonyl groups, as well as an aromatic system.[11-13] Certain publications reported the anticonvulsant activity of thiophene-containing derivatives.[14-17] Recently available AEDs like tiagabine[14], etizolam[15] and brotizolam[16] contain thiophene moiety in their structure as an active pharmacophore. On the other hand, thia-azaheterocycles have attracted a considerable attention because of their biological and pharmacological activities.[18] Literature reported that arylidine derivatives of condensed 4-thiazolidinone have been found to be better medicinal agents than the parent 4-thiazolidinones. Besides, condensed 4-thiazolidinones are better anticonvulsants than their thiazole counterparts. [17]

Following these findings, our attention has been focused on a group of spirobenzothiophene-thiazolidinone derivatives (5a-e) and (6a-e). All the title compounds comprised four pharmacophoric elements that are necessary for good anticonvulsant activity.[19] These elements are present in many currently used antiepileptic drugs. These are hydrophobic domain A, hydrogen bonding domain HBD, electron donor moiety D, and distal hydrophobic domain R, (Fig. 1).

EXPERIMENTAL

All melting points were determined on a Stuart apparatus and are uncorrected. IR spectra were determined as KBr discs on Shimadzu IR 435 Spectrophotometer and values are represented in cm^{-1}. ^{1}H-NMR spectra were carried out using a Varian Gemini 200 MHz Spectrophotometer and Varian Mercury-300 (300 MHz) Spectrophotometer using TMS as internal standard. Chemical shift values are recorded in ppm on ä scale, Microanalytical Center, Cairo University, Egypt. Mass spectra were recorded on a GCMP-QP1000EX Mass spectrometer, Microanalytical Center, Cairo University, Egypt. Elemental analyses were carried out at the Microanalytical Center, Cairo University, Egypt. Progress of the reactions was monitored by TLC using TLC sheets precoated with UV florescent silica gel Merck 60 F 254 and were visualized using UV lamp.

7-Bromo[1]benzothiophen-3(2H)-one[20,21](1), 7-bromo-2-[(4-(dimethylamino) phenylimino] -[1]benzothiophen-3(2H)-one[22](2) and 7-bromo[1]benzothiophene-2,3-dione[23] (3) were prepared as reported.

7-Bromo-3-(arylimino)[1]benzothiophen-2(3H)-ones 4a-e

An equimolar mixture of **3** and an appropriate aromatic amine (0.001 mol each) in absolute ethanol (25 ml) and 3 drops of glacial acetic acid was heated under reflux for 5h. After cooling, the precipitated solid was filtered and crystallized from petroleum ether (60-80 °C).

7-Bromo-3-(phenylimino)[1]benzothiophen-2(3H)-one (4a)

Yield: 85%; mp: 158-160 °C. IR (KBr, cm^{-1}): 3055 (C-H aromatic), 1678 (C=O), 1597 (C=N). ^{1}H-NMR (DMSO-d_6, 200 MHz): 6.45-7.38 (m, 5H, Ar-H); 7.49 (dd, 1H, C_5-H); 7.66 (d, 1H, C_4-H); 8.07 (d, 1H, C_6-H). MS (EI) m/z (% rel. Int.): 317(2.62, $M^{+\cdot}$), 319 (2.83, M+2). Anal. Calcd for $C_{14}H_8BrNOS$ (Mwt 318.19): C, 52.85; H, 2.53; N, 4.40, Found: C, 52.63; H, 2.30 ; N, 4.87.

7-Bromo-3-[(2-ethylphenyl)imino][1] benzothiophen-2(3H)-one (4b)

Yield: 65%; mp: 142-143 °C. IR (KBr, cm^{-1}): 3062 (C-H aromatic), 2927, 2870(C-H aliphatic), 1681(C=O), 1585(C=N). ^{1}H-NMR (DMSO-d_6, 200 MHz): 1.19 (t, 3H, CH_3), 2.59 (q, 2H, CH_2), 6.32-7.18 (m, 4H, Ar-H); 7.31-7.35 (m, 1H, C_5-H); 7.61 (d, 1H, C_4-H); 7.98 (d, 1H, C_6-H). Anal. Calcd for $C_{16}H_{12}BrNOS$ (Mwt 346.24): C, 55.50; H, 3.49; N, 4.05**,** Found: C, 55.45; H, 3.65; N, 4.42.

7-Bromo-3-[(4-methylphenyl)imino][1] benzothiophen -2(3H)-one (4c)

Yield: 62%; mp: 175-176 °C. IR (KBr, cm^{-1}): 3045(C-H aromatic), 2955, 2850(C-H aliphatic), 1680(C=O), 1604(C=N). ^{1}H-NMR (DMSO-d_6, 200 MHz): 2.23 (s, 3H, CH_3), 6.49 (d, 2H, Ar-H); 6.82 (d, 2H, Ar-H); 7.48 (dd, 1H, C_5-H); 7.64 (d, 1H, J=8Hz, C_4-H); 8.04 (d, 1H, C_6-H). MS (EI) m/z (% rel. Int.): 331(4.06, $M^{+\cdot}$), 333 (4.28, M+2). Anal. Calcd for $C_{15}H_{10}BrNOS$ (Mwt 332.22): C, 54.23; H, 3.03; N, 4.22 , Found: C, 54.02; H, 2.96; N, 4.45.

7-Bromo-3-[(4-methoxyphenyl) imino] [1] benzothiophen-2(3H)-one (4d)

Yield: 70%; mp: 165-166 °C. IR (KBr, cm^{-1}): 3032 (C-H aromatic), 2962, 2835 (C-H aliphatic), 1681(C=O), 1597(C=N). ^{1}H-NMR (DMSO-d_6, 200 MHz): 3.79 (s, 3H, OCH_3), 6.58-7.15 (m, 4H, Ar-H); 7.46 (dd, 1H, C_5-H); 7.63 (d, 1H, C_4-H); 8.03 (d, 1H, C_6-H). Anal. Calcd for $C_{15}H_{10}BrNO_2S$ (Mwt 348.21): C, 51.74; H, 2.89; N, 4.02 , Found: C, 51.55; H, 3.05 ; N, 4.35.

7-Bromo-3-[(1-naphthalen-1-yl)imino][1] benzothiophen-2(3H)-one (4e)

Yield: 72%; mp: 180-182 °C. IR (KBr, cm^{-1}): 3055 (C-H aromatic), 1693 (C=O), 1577(C=N). ^{1}H-NMR (DMSO-d_6, 200 MHz): 6.60-7.60 (m, 7H, Ar-H); 7.77 (dd, 1H, C_5-H); 7.98 (d, 1H, C_4-H); 8.12 (d, 1H, C_6-H). MS (EI) m/z (% rel. Int.): 367(1.08, $M^{+\cdot}$), 369 (0.89, M+2). Anal. Calcd for $C_{18}H_{10}BrNOS$ (Mwt 368.25): C, 58.71; H, 2.74; N, 3.80 , Found: C, 58.54; H, 2.86; N, 4.12.

3'-Aryl-7-bromo-2H-spiro[[1]benzothiophene-3,2'-[1,3]thiazolidine]-2,4'-diones and / or 3'-Aryl-7-bromo-4'-hydroxy-2H,3'H-spiro[[1] benzothiophene-3,2'-[1,3]thiazol]-2-ones 5a-e

An equimolar mixture of the appropriate **4a-e** and thioglycolic acid (0.001 mol each) in toluene (25 ml) was heated under reflux using Dean-Stark water separator until the theoretical amount

of water had been collected (H" 10h). The solvent was distilled off under reduced pressure, ethanol (10 ml) was added, and the precipitated crystalline solid was filtered and recrystallized from ethanol.

7-Bromo-3'-phenyl-2H-spiro[[1]benzothiophene-3,2'-[1,3]thiazolidine]-2,4'-dione and / or 7-Bromo-3'-phenyl-4'-hydroxy-2H,3'H-spiro[[1]benzothiophene-3,2'-[1,3]thiazol]-2-one (5a)

Yield: 58%; mp: 184-185 °C. IR (KBr, cm^{-1}): 3421 (OH), 3065 (C-H aromatic), 2950, 2850 (C-H aliphatic), 1681, 1668 (2C=O). ^{1}H-NMR (DMSO-d_6, 200 MHz): 3.88 (br.s, 1H, C_2-H_a); 4.50 (br.s, 1H, C_2-H_b); 7.00-7.22 (m, 5H, Ar-H); 7.28-7.38 (m, 1H, C_5'-H); 7.46 (d, 1H, C_4'-H); 7.60 (d, 1H, C_6'-H); 9.88 (br.s., less than 1H, OH, D_2O exchangeable). MS (EI) m/z (% rel. Int.): 391(0.13, $M^{+\cdot}$), 393 (0.17, M+2). Anal. Calcd for $C_{16}H_{10}BrNO_2S_2$ (Mwt 392.29): C, 48.99; H, 2.57; N, 3.57, Found: C, 49.15; H, 2.30; N, 3.22.

7-Bromo-3'-[(2-ethylphenyl)-2H-spiro[[1]benzothiophene-3,2'-[1,3]thiazolidine]-2,4'-dione and/or 7-Bromo-3'-(2-ethylphenyl)-4'-hydroxy-2H,3'H-spiro[[1]benzothiophene- 3,2'-[1,3]thiazol]-2-one (5b)

Yield: 50%; mp: 198-200 °C. IR (KBr, cm^{-1}): 3433 (OH), 3055 (C-H aromatic), 2923, 2835 (C-H aliphatic), 1682, 1666 (2C=O). ^{1}H-NMR (DMSO-d_6, 200 MHz): 1.17 (t, 3H, CH_3), 2.56 (q, 2H, CH_2); 3.79 (br.s, 1H, C_2-H_a); 4.35 (br.s, 1H, C_2-H_b); 7.07-7.24 (m, 4H, Ar-H); 7.31-7.35 (m, 1H, C_5'-H); 7.47 (d, 1H, C_4'-H); 7.58 (d, 1H, C_6'-H); 9.34 (br.s., less than 1H, OH, D_2O exchangeable). Anal. Calcd for $C_{18}H_{14}BrNO_2S_2$ (Mwt 420.34): C, 51.43; H, 3.36; N, 3.33, Found: C,51.22; H, 3.15; N, 3.45.

7-Bromo-3'-[(4-methylphenyl)-2H-spiro[[1]benzothiophene-3,2'-[1,3]thiazolidine]-2,4'-dione and / or 7-Bromo-3'-(4-methylphenyl)-4'-hydroxy-2H,3'H-spiro[[1] benzothiophene-3,2'-[1,3]thiazol]-2-one (5c)

Yield: 65%; mp: 202-203 °C. IR (KBr, cm^{-1}): 3445 (OH), 3055 (C-H aromatic), 2923, 2852 (C-H aliphatic), 1684, 1665 (2C=O). ^{1}H-NMR (DMSO-d_6, 200 MHz): 2.34 (s, 3H, CH_3); 3.98 (br.s, 1H, C_2-H_a); 4.53 (br.s, 1H, C_2-H_b); 7.02-7.21 (m, 5H, 4Ar-H and C_5'-H); 7.43 (d, 1H, C_4'-H); 7.64 (d, 1H, C_6'-H); 10.35 (br.s., less than 1H, OH, D_2O exchangeable). Anal. Calcd for $C_{17}H_{12}BrNO_2S_2$ (Mwt 406.32): C, 50.25; H 2.98; N, 3.45, Found: C, 50.10; H, 3.34; N, 3.85.

7-Bromo-3'-[(4-methoxyphenyl)-2H-spiro[[1]benzothiophene-3,2'-[1,3]thiazolidine]-2,4'-dione and / or 7-Bromo-3'-(4-methoxylphenyl)-4'-hydroxy-2H,3'H-spiro[[1] benzothiophene-3,2'-[1,3]thiazol]-2-one (5d)

Yield: 75%; mp: 185-186 °C. IR (KBr, cm^{-1}):): 3450 (OH), 3100 (C-H aromatic), 2916, 2835 (C-H aliphatic), 1680, 1662 (2C=O). ^{1}H-NMR (DMSO-d_6 300 MHz): 3.79 (s, 3H, OCH_3); 3.85 (br.s, 1H, C_2-H_a); 4.20 (br.s, 1H, C_2-H_b); 6.85-7.28 (m, 5H, 4Ar-H and C_5'-H); 7.47 (d, 1H, C_4'-H); 7.58 (d, 1H, C_6'-H); 9.86 (br.s., less than 1H, OH, D_2O exchangeable). Anal. Calcd for $C_{17}H_{12}BrNO_3S_2$ (Mwt 422.32): C, 48.35; H 2.86; N, 3.32, Found: C, 48.56; H, 2.98; N,3.48.

7-Bromo-3'-[(1-naphthalen-1-yl)-2H-spiro[[1]benzothiophene-3,2'-[1,3]thiazolidine]-2,4'-dione and / or 7-Bromo-3'-[(1-naphthalen-1-yl)-4'-hydroxy-2H,3'H-spiro[[1] benzothiophene-3,2'-[1,3]thiazol]-2-one (5e)

Yield: 52%; mp: 220-221 °C. IR (KBr, cm^{-1}): 3400 (OH), 3110 (C-H aromatic),2935, 2845 (C-H aliphatic), 1685, 1668 (2C=O). ^{1}H-NMR (DMSO-d_6, 200 MHz): 3.66 (br.s, 1H, C_2-H_a); 4.35 (br.s, 1H, C_2-H_b); 6.89-8.12 (m, 10H, Ar-H); 9.46 (br.s., less than 1H, OH, D_2O exchangeable). MS (EI) m/z (% rel. Int.): 441(18.26, $M^{+\cdot}$), 443 (17.25, M+2). Anal. Calcd for $C_{20}H_{12}BrNO_2S_2$ (Mwt 442.35): C, 54.30; H 2.73; N, 3.17, Found: C, 54.00; H, 2.84; N, 3.35.

3'-Aryl-7-bromo-5'-methyl-2H-spiro[[1]benzothiophene-3,2'-[1,3]thiazolidine]-2,4'-diones and/or 3'-Aryl-7-bromo-4'-hydroxy-5'-methyl-2H,3'H-spiro[[1]benzothiophene-3,2'-[1,3]thiazol]-2-ones 6a-e

An equimolar mixture of the appropriate **4a-e** and thiolactic acid (0.001 mol each) in toluene (25 ml) was heated under reflux using Dean-Stark water trap until the theoretical amount of water had been collected (H" 10 h). The solvent was distilled off under reduced pressure, ethanol (10 ml) was added, and the precipitated crystalline solid was filtered and recrystallized from ethanol.

7-Bromo-5'-methyl-3'-phenyl-2H-spiro[[1]benzothiophene-3,2'-[1,3]thiazolidine]-2,4'-dione and / or 7-Bromo-4'-hydroxy-5'-methyl-3'-phenyl-2H,3'H-spiro[[1]-benzothiophene-3,2'-[1,3]thiazol]-2-one (6a)

Yield: 65%; mp: 210-211°C. IR (KBr, cm^{-1}): 3400 (OH), 3150 (C-H aromatic), 2924, 2850 (C-H aliphatic), 1681, 1664 (2C=O). ^{1}H-NMR (DMSO-d_6, 200 MHz): 2.50 (s, 3H, CH_3); 4.14 (br. s, 1H, C_2-H); 7.00-7.28 (m, 5H, Ar-H); 7.30-7.38 (m, 1H, C_5'-H); 7.45 (d, 1H, C_4'-H); 7.66 (d, 1H, C_6'-H); 10.02 (br.s., less than 1H, OH, D_2O exchangeable). MS (EI) m/z (% rel. Int.): 405(0.13, $M^{+\cdot}$), 407 (0.30, M+2). Anal. Calcd for $C_{17}H_{12}BrNO_2S_2$ (Mwt 406.32): C, 50.25; H 2.98; N, 3.45, Found: C, 50.02; H, 2.66; N, 3.65.

7-Bromo-3'-[(2-ethylphenyl)-5'-methyl-2H-spiro[[1]benzothiophene-3,2'-[1,3]thiazolidine]-2,4'-dione and/or 7-Bromo-3'-(2-ethylphenyl)-4'-hydroxy-5'-methyl-2H,3'H-spiro[[1]benzothiophene-3,2'-[1,3]thiazol]-2-one (6b)

Yield: 55%; mp: 220-221 °C. IR (KBr, cm^{-1}): 3350 (OH), 3110 (C-H aromatic),, 2955, 2850 (C-H aliphatic), 1683, 1666 (2C=O). ^{1}H-NMR (DMSO-d_6, 200 MHz): 1.17 (t, 3H, CH_3); 2.56 (q, 2H, CH_2); 2.68 (s, 3H, CH_3); 3.40 (br. s, 1H, C_2-H); 7.07-7.20 (m, 4H, Ar-H); 7.32-7.35 (m, 1H, C_5'-H); 7.48 (d, 1H, C_4'-H); 7.58 (d, 1H, C_6'-H); 10.00 (br.s., less than 1H, OH, D_2O exchangeable). Anal. Calcd for $C_{19}H_{16}BrNO_2S_2$ (Mwt 434.37): C, 52.54; H 3.71; N, 3.22, Found: C, 52.13; H, 3.50; N, 3.14.

7-Bromo-5'-methyl-3'-[(4-methylphenyl)-2H-spiro[[1]benzothiophene-3,2'-[1,3]thiazolidine]-2,4'-dione and / or 7-Bromo-4'-hydroxy-5'-methyl-3'-(4-methylphenyl)-2H,3'H-spiro[[1]benzothiophene-3,2'-[1,3]thiazol]-2-one (6c)

Yield: 74%; mp: 208-209 °C. IR (KBr, cm^{-1}): 3421 (OH), 3047 (C-H aromatic), 2920, 2850 (C-H aliphatic), 1682, 1660 (2C=O). ^{1}H-NMR (DMSO-d_6 , 200 MHz): 2.28, 2.50 (2s, 6H, $2CH_3$); 3.88 (br. s, 1H, C_2-H); 6.98-7.25 (m, 5H, 4Ar-H and C_5'-H); 7.44 (d, 1H, C_4'-H); 7.65 (d, 1H, C_6'-H); 10.12 (br.s., less than 1H, OH, D_2O exchangeable). MS (EI) m/z (% rel. Int.): 419(59.16, $M^{+\cdot}$), 420 (11.64, M+H). Anal. Calcd for $C_{18}H_{14}BrNO_2S_2$ (Mwt 420.34): C, 51.43; H 3.36; N, 3.33, Found: C, 51.22; H, 3.55; N, 3.48.

7-Bromo-3'-[(4-methoxyphenyl)-5'-methyl-2H-spiro[[1]benzothiophene-3,2'-[1,3]thiazolidine]-2,4'-dione and / or 7-Bromo-4'-hydroxy-3'-(4-methoxylphenyl)-5'-methyl-2H,3'H-spiro[[1]benzothiophene-3,2'-[1,3]thiazol]-2-one (6d)

Yield: 72%; mp: 218-220 °C. IR (KBr, cm^{-1}): 3430 (OH), 3122 (C-H aromatic), 2918, 2855 (C-H aliphatic), 1681, 1660 (2C=O). ^{1}H-NMR (DMSO-d_6, 300 MHz): 2.30 (s, 3H, CH_3); 3.56 (br. s, 1H, C_2-H); 3.79 (s, 3H, OCH_3); 6.59-6.95(m, 4H, Ar-H); 7.00-7.25 (m, 1H, C_5'-H); 7.47 (d, 1H, C_4'-H); 7.60 (d, 1H, C_6'-H); 10.00 (br.s., less than 1H, OH, D_2O exchangeable). Anal. Calcd for $C_{18}H_{14}BrNO_3S_2$ (Mwt 436.34): C, 49.55; H 3.23; N, 3.21, Found: C, 49.21; H, 3.65; N, 3.09.

7-Bromo-5'-methyl-3'-[(1-naphthalen-1-yl)-2H-spiro[[1]benzothiophene-3,2'-[1,3]thiazolidine]-2,4'-dione and / or 7-Bromo-4'-hydroxy-5'-methyl-3'-[(1-naphthalen-1-yl)-2H,3'H-spiro[[1]benzothiophene-3,2'-[1,3]thiazol]-2-one (6e)

Yield: 70%; mp: 225-226 °C. IR (KBr, cm^{-1}): 3429 (OH), 3053 (C-H aromatic), 2924, 2852 (C-H aliphatic), 1681, 1668 (2C=O). ^{1}H-NMR (DMSO-d_6, 200 MHz): 2.50 (s, 3H, CH_3); 3.36 (br. s, 1H, C_2-H); 6.63-7.65 (m, 8H, 7Ar-H and C_5'-H); 7.77 (d, 1H, C_4'-H); 7.99 (d, 1H, C_6'-H); 9.96 (br.s., less than 1H, OH, D_2O exchangeable). Anal. Calcd for $C_{21}H_{14}BrNO_2S_2$ (Mwt 456.38): C, 55.27; H 3.09; N, 3.07, Found: C, 55.12; H, 3.29; N, 2.95.

Biological studies

All test compounds 5a-e and 6a-e were investigated on various animal models including phenobarbitone sleeping time and strychnine-induced convulsions in mice.

Phenobarbitone- induced sleeping time

Adult albino mice of either sex weighing 25-30 g were randomly allocated to the control and test groups (6 animals per group). Test groups were treated with compounds 5a-e and 6a-e, (2 mg/kg i.p.). Phenobarbitone sodium (40 mg/kg, i.p.) was administered 30 min later. The control group received 10 ml/kg normal saline, i.p. 15 min before phenobarbitone (40 mg/kg, i.p.). For positive control group; phenobarbitone (40 mg/kg, i.p.) was administered 15 min after chlorpromazine hydrochloride (cpz) (1 mg/kg, i.m.).[24] Onset of sleep was taken as the time when mice accepted the

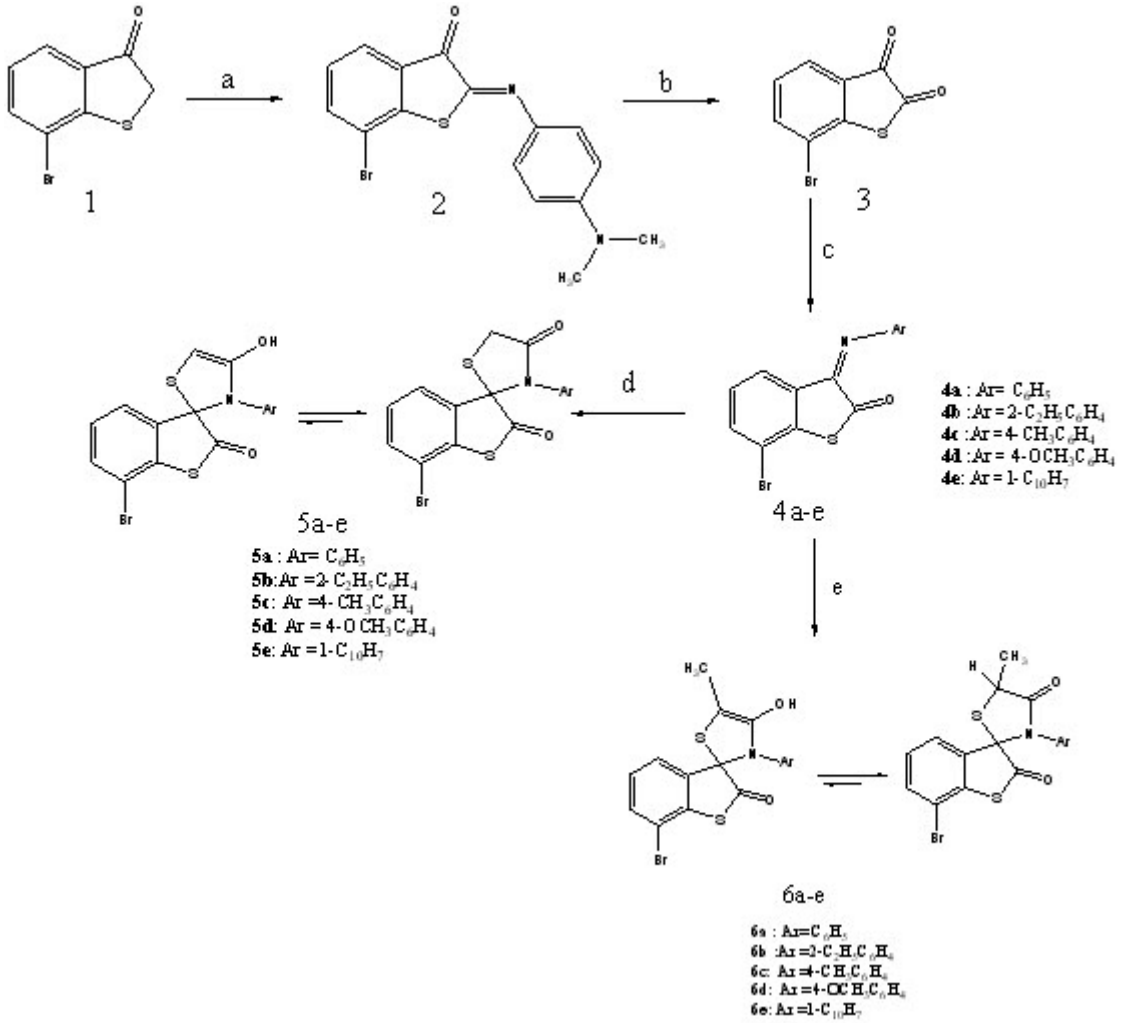
decubitodorsal position for three consecutive trials. Conversely, the duration was considered completed when mice did not accept the decubitodorsal position for three consecutive trials.[25]

Strychnine-induced seizures

Adult albino mice of either sex weighing 25-30 g were randomly allotted to the control and test groups (6 animals per group). The control mice were treated with strychnine sulphate (4 mg/kg, i.m.) 30 min after normal saline (10 ml/kg,i.p.). The positive control group of mice received strychnine sulphate (4 mg/kg, i.m.), 15 min after phenobarbitone sodium (40 mg/kg, i.p.).Test group of mice received test compounds **5a-e** and **6a-e**, i.p. 30 min before strychnine sulphate (4 mg/kg, i.m.). Onset to forelimb clonic and tonic seizures was recorded. Mice that did not show convulsions 30 min after strychnine administration were considered protected.[26]

RESULTS AND DISCUSSION

7-Bromo[1]benzothiophen-3(2H)-one (1) was previously reported.[20,21] Condensation of 1 with 4-nitroso-N,N-dimethylaniline afforded 7-bromo-2-[(4-(dimethylamino)phenylimino]-[1]benzothiophen-3(2H)-one (2).[22] 7-Bromo[1]benzothiophene-2,3-



Scheme 1: Reagents and conditions (a) 4-nitroso-N,N-dimethylanaline (b) HCl (c) $ArNH_2$/ethanol/ reflux 5h, (d) $HSCH_2COOH$/toluene/reflux/ 10th (e) $CH_3CH(SH)COOH$/toluene/reflux 10h

dione (3) was prepared by acid hydrolysis of 2, through a procedure previously reported for the synthesis of analogous compounds.[23] Condensation of 3 with a number of aromatic amines, gave Schiff bases 4a-e. Attention was next turned to preparation of the spiro targets 5a-e and 6a-e. Following a

Table 1: Effect of test compounds 5a-e and 6a-e on phenobarbitone-induced sleeping time in mice

Treatment (mg/Kg)	Onset of sleep±S.E.M.(min)	Sleeping time±S.E.M.(min)
Control: saline (10ml/kg, i.p.)	7.2 ± 0.2	40.0 ± 0.6
5a	4.8 ± 0.2*	46.8 ± 0.4*
5b	4.1± 0.2*	48.2 ± 0.9*
5c	4.3 ± 0.2*	49.7 ± 0.3*
5d	4.0 ± 0.2*	50.7 ± 0.4*
5e	3.9 ± 0.2*	51.0 ± 0.3*
6a	4.2 ± 0.2*	48.5 ± 0.5*
6b	q5.5 ± 0.2*	44.5 ± 0.3*
6c	4.7 ± 0.2*	47.8 ± 0.5*
6d	4.5 ± 0.2*	48.0 ± 0.3*
6e	3.8 ± 0.2*	53.8. ± 0.3*
cpz (1mg/kg, i.m.)	3.4 ± 0.2*	57.4 ± 0.2*

* Significant P < 0.05 compared to control, ANOVA; n =6.

All values are expressed as mean ±S.E.M.

Data were analysed by non-parametric ANOVA followed by Dunnett's multiple comparison.

Table 2: Effect of test compounds 5a-e and 6a-e on strychnine-induced seizures in mice.

Treatment (mg/Kg)	Seizure onset ±S.E.M.(min)	
	Clonic	Tonic
Control: saline (10ml/kg, i.p.)	4.5 ± 0.2	5.1 ± 0.1
5a	8.5 ± 0.2*	4.2± 0.4*
5b	9.7 ± 0.3*	4.8. ± 0.2*
5c	6.8 ± 0.2*	4.5 ± 0.3*
5d	5.5 ± 0.2*	4.9 ± 0.5*
5e	9.3 ± 0.2*	5.7 ± 0.2*
6a	7.2 ± 0.2*	5.0 ± 0.4*
6b	6.5 ± 0.2*	4.5 ± 0.2*
6c	5.8 ± 0.3*	5.7 ± 0.3*
6d	6.5 ± 0.2*	4.7 ± 0.2*
6e	8.2 ± 0.2*	5.2. ± 0.3*
Phenobarbitone (40mg/kg, i.p.)	NC	NC

NC: no convulsions

* Significant P < 0.05 compared to control, ANOVA; n =6.

All values are expressed as mean ±S.E.M.

Data were analysed by non-parametric ANOVA followed by Dunnett's multiple comparison.

procedure similar to that of Joshi *et al*.,[27] the Schiff bases 4a-e were condensed with either thioglycolic acid or thiolactic acid in refluxing toluene with azeotropic removal of water to give the spiro compounds 5a-e and 6a-e respectively, Scheme 1. Structures of the synthesized compounds 4a-e, 5a-e and 6a-e have been confirmed on the basis of microanalytical and spectral studies. IR and ^{1}H-NMR spectral data showed existence of tautomerism in the spiro compounds 5a-e and 6a-e indicated by existence of an absorption band in the range of 3500- 3300 cm^{-1} (OH) and two carbonyl groups (1680-1660 cm^{-1}) in their IR specra. ^{1}H-NMR revealed characteristic chemical shifts agreed with their proposed structures and showed presence of less than one D_2O exchangeable proton at ä 9-10 ppm (tautomeric OH).

The anticonvulsant activities of the synthesized compounds were determined through the evaluation of phenobarbitone-induced sleeping time and the ability of the test compounds to protect mice against convulsions induced by strychnine. In summary, all test compounds have shown significant

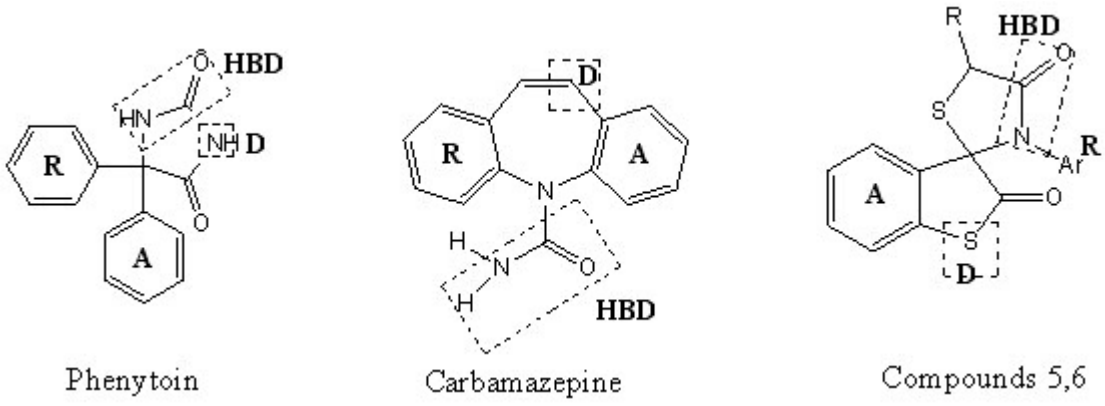


Fig. 1: Anticonvulsant agents showing the requried pharmacophoric elements

prolongation of phenobarbitone-induced sleeping time which indicates central nervous system depressant activity, as well as prolongation of both clonic and tonic seizure latency indicating appreciable anticonvulsant activity. Among the tested compounds, the naphthyl derivatives 5e and 6e were found to be the most effective in prolongation phenobarbitone-induced sleeping time as well as protection against strychnine-induced seizures.

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REFERENCES

1. Fisher, R.; Boas, W. V. E.; Blume, W.; Elger, C.; Genton, P.; Lee, P.; Engel, *J. Epilepsia*, **46**: 470 (2005).
2. Schmidt, D.; Loscher, W. *Epilepsia* **46**: 858 (2005).
3. Jain, K. K., *Exp. Opin. Invest. Drugs* **9(4)**: 1 (2000).
4. Pevarello, P.; Bonsignori, A.; Caccia, C.; Amici, R.; McArthur, R.; Fariello, R.; Salvati, P.; Varasi, M. *Bioorg.Med. Chem. Lett.* **9**: 2521

(1999).
5. Villetti, G.; Bregola, G.; Bassani, F.; Bergamaschi, M.;Rondelli, I.; Pietra, C.; Simonato, M. *Neuropharmacology* **40**: 866 (2001).
6. Brodie, M. J.; Dichter, M. A. N. *Engl. J. Med. Chem*. **334**: 1583 (1996).
7. (a) White, H. S. *Epilepsia* **1999,** 40(Suppl. 5), S2; (b)White, H. S. *Epilepsia* **44**(Suppl. 7): 2 (2003).
8. Vamecq, J.; Bac, P.; Herrenknecht, C.; Maurois, P.;Delcourt, P.; Stables, J. *J. Med. Chem*. **43**, 1311 (2000).
9. Loscher, W.; Schmidt, D. *Epilepsy Res*. **50**: 3 (2002).
10. Greenwood, R. S. *Epilepsia* **41**: S42 (2000).
11. Edafiogho, I.O.; Scott, K.R. *Anticonvulsant, in: M.E. Wolff (Ed.),Burger's Medicinal Chemistry and Drug Discovery**/3, fifth ed.,Wiley, New York, , pp. 175-/260 (1996).
12. Perucca, E. *Br. J. Clin. Pharmacol*. **42**: 531 (1996).
13. Brodie, M.J. *Epilepsy Res.* **45**: 3 (2001).
14. Arroyo, S., Salas-Puig, J. *Rev. Neurol*. **32**: 1041 (2001).
15. Polivka, Z.; Holubek, J.; Svatek, E.; Metys, M. Protiva, *Collect. Czech. Chem. Commun.* **49**: 621 (1984).
16. Noguchi, H.; Kitazumi, K.; Mori, M.; Shiba, T. *J. Pharm. Sci.* **94**: 246 (2004).
17. Arya, K.; Dandia, A. *J. Fluorine Chem.* **128**: 224 (2007).
18. (a) Reifschneider, W.; Bisabari-Ershadi, B.; Dripps, J. E.; Bonron, J. B. U.S. Patent 5,075,293, 1991; Chem. Abstr. **116,** 129249f; (1991) (b) Rovnyak, G. C.; Narayanan, V. L.;Haugwitz, R. D. U. S. Patent 4,053,613; Chem. Abstr, **88**: 22892; (1978). (c) Ali, S.; Alam, M. Arch. Pharmacol.Res. **17**, 131 (1994).
19. Pandeya, S.N.; Yogeeswari, P.; Stables, J.P. *Eur. J. Med. Chem.* **35**: 879 (2000).
20. Guha S. K.; Mitra, A.K. *J. Ind. Chem. Soc.* **43**: 597 (1966).
21. Charles, E.D.; Frederick, G.M. *J. Chem. Soc.* 893 (1945).
22. Bezdrik, A.; Friedlander, P.; Kaeniger, P. *Ber.* 227 (1908).
23. Ashraf F. Zaher; Hanan M. Refaat; Omneya M. Khalil, *Bull. Fac. Pharm.Cairo Univ.* **47**(2): 69 (2009).
24. Mujumdar, A.M.; Naik, D.G.; Waghole, R.J.; Kulkarni, D. K.; Kumbhojkar M. S. *Pharmaceutical Biology*. **38**: 13-17 (2000).
25. Yemitan O.K.; Ajibade A.M.;, Adeyemi O. *Nigerian Journal of Neuroscience*. **4**: 33-40 (2001).
26. Rasilingam, D.; Duraisamy,S. Subramanian, R. *Bangladesh J Pharmacology***, 4**: 51-54 (2009).
27. Joshi, K. C.; Patni, R.; Chand, P. *Heterocycles,* **16**: 1555 (1981).