Saudi Journal of Medical and Pharmaceutical Sciences **ISSN 2413-4929 (Print)**
Scholars Middle East Publishers **ISSN 2413-4910 (Online)**
Dubai, United Arab Emirates
Website: https://saudijournals.com/

Synthesis and Anticonvulsant Activity (*Chemo-Shock*) of Some Potent Benzoxazole Semicarbazone Derivatives as GABA-Agonist

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Original Research Article

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Article History
Received: 02.07.2018
Accepted: 22.07.2018
Published: 30.07.2018

DOI:
10.36348/sjmps.2018.v04i07.015

Abstract: A series of novel semicarbazone derivatives (BS1-22) of (2*E*)-2-[2-(1, 3-benzoxazol-2-ylsulfanyl)-1-phenylethylidene] hydrazinecarboxamide have been prepared. The structural conformation of the newly synthesized compounds has been established by elemental analysis, spectral analysis and melting point studies. Compounds BS1, BS3, BS9, BS10, BS11, and BS21 have been subjected to anticonvulsant screening by chemo-shock models. In the series, compounds BS9, BS10, and BS11 showed most potent result while compounds BS1, BS3, and BS21 were showing moderate results than standard drug.
Keywords: Benzoxazole, Semicarbazone, Chemo-shock, Anticonvulsant.

INTRODUCTION

Gamma-aminobutyric acid (GABA) is a neurotransmitter that sends chemical messages through the central nervous system and it is also involved in regulating communication between brain cells. GABA is widely distributed throughout the CNS; early GABAergic drugs had very generalized effects on CNS function. The development of better selective agents has led to the identification of at least two distinct classes of GABA receptor, GABA-A, and GABA-B. They differ in their pharmacological, electrophysiological and biochemical properties. Benzoxazole ring is the most common heterocycles in medicinal chemistry. Previous reports represents that substituted benzoxazole possess diverse biological activities including antibiotic [1], antimicrobial [2-6] antiviral**,** [7] topoisomerase 1 and 2 inhibitors [8] and antitumor activities [9-10].

In the last few years, differents 2-substituted benzoxazole derivatives were studied extensively for their antitumor, antiviral, & antimicrobial activities as non-nucleoside topoisomerase I inhibitor, HIV-1 reverse transcriptase &/or DNA gyrase inhibitors. For Example, the antibiotic Calcimycin, which includes a 2-substituted benzoxazole ring in its molecular structure, is very active against Bacillus cereus, *Bacillus megaterium & Micrococcus lutes***.**

The benzoxazole derivatives, 3-(4, 7-dichlorobenzoxazole2-yl methyl amino)-5-ethyl-6-methyl-pyridin-2(1H)-one was found to be an effective non-nucleoside selective HIV-1 reverse transcriptase inhibitor. A combined therapy of Zidovudine with above compound showed marked decrease of viremia in some primary HIV-infected patients [11-13].

Recent observation suggested that the substituted benzimidazole, benzoxazole, benzothiazoles & related fused heterocycles indicated potential antitumor, antiviral & antibiotic activities as the new topoisomerase 1 inhibitor, HIV-1 reverse transcriptase inhibitors &/or potent DNA gyrase inhibitors with lower toxicities in the chemotherapeutic approaches [14-16].

We report here the synthesis, anticonvulsant activity and neurotoxicity of a new series of semicarbazone derivatives BS (1-22), derived from substituted 1, 3-benzoxazole-2-thiol as starting material with the objectives of considering possible anticonvulsant activity by chemo shock methods.

MATERIALS AND METHODS

Experimental procedure

Chemistry

The chemicals were purchased by the commercial vendors and were used further without purification. The reactions were monitored and the purity of the compounds was checked by Thin Layer Chromatography (TLC). Silica

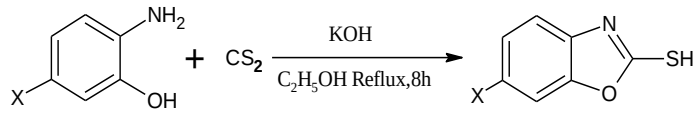
gel 60 was used for TLC. Detecting agents used (for TLC) was iodine vapors. All the melting points were measured in open capillaries on Jindal melting point apparatus. Yields were calculated after recrystallization. IR spectrum were recorded on Perkin-Elmer FT-IR RXI spectrophotometer. ^{1}H NMR was recorded on Bruker DPX-200 (operating at 200 MHz for ^{1}H), spectrometer using $CDCl_3$ as a solvent. Tetramethylsilane (0.00 ppm) used as an internal standard in ^{1}H NMR. Elemental analysis was performed on Vario EL-III analyzer.

SYNTHESIS OF BENZOXAZOLE DERIVATIVES

Procedure for the synthesis of 1, 3-benzoxazole-2-thiol (1) [17]:

Substituted aminophenol (5 gm; 0.05 mol) was dissolved in ethanol (50 ml), and potassium hydroxide (6 gm) was added to the above reaction mixture with stirring, after that carbon disulfide (20 ml) was also added to the above reaction and the whole content of the reaction mixture was refluxed for 8 hr. The reaction mixture was concentrated in vacuum, and 5N aqueous hydrochloric acid (18 ml) and ethyl acetate (100 ml) was added to the reaction mixture residue. The organic layer washed with water (100 ml) and dried over $MgSO_4$. Substituted 1, 3-benzoxazole-2-thiol 1 was obtained as pale brownish solid and used further without purification.

Scheme 1:



Substituted aminophenol

X= -H, Cl

1,3-Benzenoxazole-2-thiol

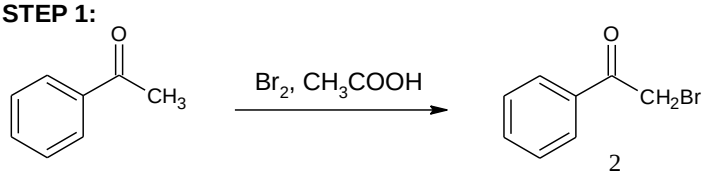
(1)

Procedure for the synthesis of 2-(1, 3-benzoxazol-2-ylsulfanyl)-1-phenylethanone (3)

This procedure involves two steps. In step 1, acetophenone (5 ml) and chloroform (25 ml) were taken in round bottom flask and in a separate beaker bromine (2.2 ml) was taken in 10 ml of chloroform then bromine solution was added gradually in acetophenone solution with stirring and cooling on the ice bath. The bromine color disappeared quickly although very little hydrogen bromide gas was evolved from the reaction mixture. On evaporation greenish color concentrated solution of phenacyl bromide, 2 was obtained. Further in step 2, the equimolar quantity of substituted 1, 3-benzoxazol-2-thiol 1 and phenacyl bromide 2 was taken in round bottom flask in presence of anhydrous potassium carbonate in dry acetone and whole reaction mixture was refluxed for 12 hr. The reaction mixture was cooled and the separated solid substituted-2- (1, 3-benzoxazol-2-ylsulfanyl)-1-phenylethanone 3 was filtered and recrystallized by using ethanol.

Scheme 2:

STEP 1:

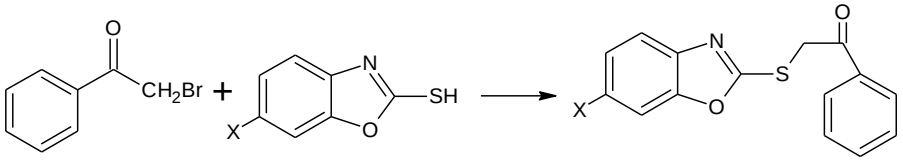


Acetophenone

2

Phenacyl bromide

STEP 2:



2

1

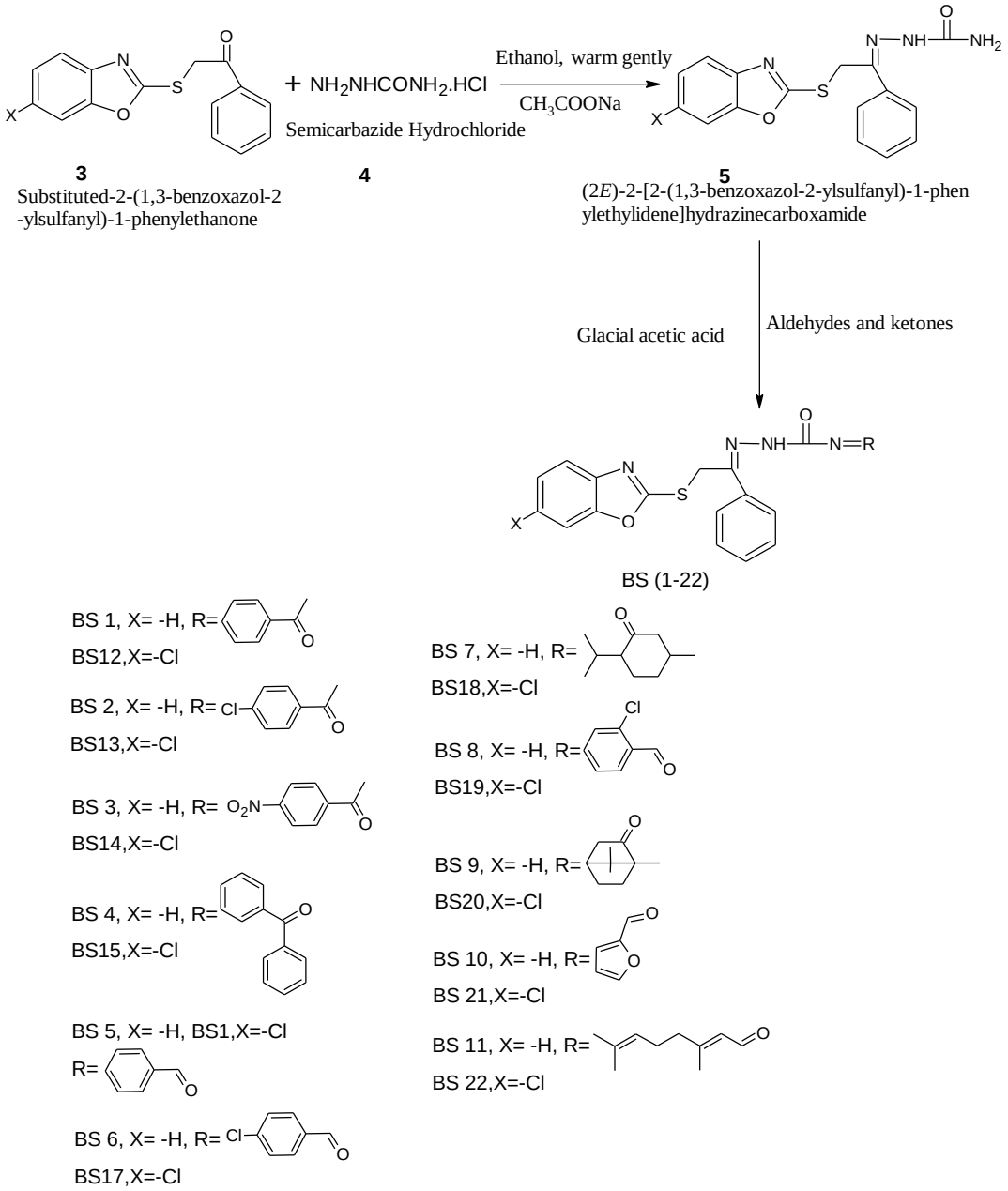
3

Substituted-2-(1,3-benzoxazol-2-ylsulfanyl) -1-phenylethanone

Procedure for the synthesis of (2*E*)-2-[2-(1, 3-benzoxazol-2-ylsulfanyl)-1-phenylethylidene] hydrazinecarboxamide followed by their semicarbazones (5)

Added semicarbazide hydrochloride (1gm) and anhydrous sodium acetate (0.9 gm) or (1.25 gm of crystalline acetate) in 5 ml of distilled water and heated gently until a clear solution 4 was obtained. After that solution of substituted 2-(1,3-benzoxazol-2-ylsulfanyl)-1-phenylethanone 3 (1gm) in 5 ml of rectified spirit/ethanol was added to solution 4 and warmed then mixed the solution gently on the water bath for 15 minutes. Substituted (2*E*)-2-[2-(1, 3-benzoxazol-2-ylsulfanyl)-1-phenylethylidene] hydrazinecarboxamide 5 was obtained which was further treated with different aldehydes and ketones to synthesize their semicarbazone derivatives which rapidly crystallized whilst the solution was still being heated. Finally cooled, filtered off the product and washed with water, drained and recrystallized with ethanol and dried at room temperature, the product obtained as colorless solid.

Scheme 3:



Characterization of the newly synthesized compounds BS (1-22)

BS1

IR (KBr, cm^{-1}): 3155(NH), 3150(Ar. C-H), 1625(C=N), 1515(Ar. C=C), 1630 (C=O), 689 (C-S); ^1H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 2.35 (3H, s), 3.91 (2H, s), 4.8(1H, s), 7.20-7.56 (8H, m), 7.71-7.80 (6H, m); anal. calcd. for,

$C_{24}H_{20}N_4O_2S$ (428.5062) (%): found= C(67.10), H(4.30), N(13.01), calculated = C(67.27), H (4.70), N (13.07), MS (m/z,%): 429.22 (M^++1)

BS2

IR (KBr, cm^{-1}): 3155(NH), 3150(Ar. C-H), 1625(C=N), 1515(Ar. C=C), 1638 (C=O), 695 (C-S); ^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 2.37 (3H, s), 3.92 (2H, s), 4.6(1H, s), 7.21-7.40 (5H, m), 7.45-8.56 (8H, m), anal. calcd. for, $C_{24}H_{19}ClN_4O_2S$ (462.9512) (%): found= C(62.12), H(4.01), N(12.14): calculated = C(62.27), H(4.14), N(12.10); MS (m/z,%): 463.80 (M^++1)

BS3

IR (KBr, cm^{-1}): 3155(NH), 3150(Ar. C-H), 1625(C=N), 1515(Ar. C=C), 1645 (C=O), 700 (C-S); ^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 2.40 (3H, s), 3.93 (2H, s), 4.9(1H, s), 7.22-7.42 (5H, m), 7.54-8.33 (8H, m), anal. calcd. for, $C_{24}H_{19}N_5O_4S$ (473.5037) (%): found= C(60.76), H(4.12), N(14.52): calculated = C(60.88), H(4.04), N(14.79); MS (m/z,%): 474.42 (M^++1)

BS4

IR (KBr, cm^{-1}): 3155(NH), 3150(Ar. C-H), 1625(C=N), 1515(Ar. C=C), 1640 (C=O), 690 (C-S); ^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 3.91 (2H, s), 4.4(1H, s), 7.14-7.51 (10H, m), 7.52-7.72 (4H, m), 7.79-7.94 (5H, m), anal. calcd. for, $C_{29}H_{22}N_4O_2S$ (490.5755) (%): found= C(70.14), H(4.32), N(11.27): calculated = C(71.00), H(4.52), N(11.42); MS (m/z,%): 491.50 (M^++1)

BS5

IR (KBr, cm^{-1}): 3155(NH), 3150(Ar. C-H), 1625(C=N), 1515(Ar. C=C), 1650 (C=O), 710 (C-S); ^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 3.95 (2H, s), 4.6(1H, s), 7.22-7.80 (10H, m), 8.03-8.31 (4H, m), 9.81 (1H, s), anal. calcd. for, $C_{23}H_{18}N_4O_2S$ (414.4796) (%): found= C(66.73), H(4.21), N(13.23): calculated = C(66.65), H(4.38), N(13.52); MS (m/z,%): 415.32 (M^++1)

BS6

IR (KBr, cm^{-1}): 3155(NH), 3150(Ar. C-H), 1625(C=N), 1515(Ar. C=C), 1650 (C=O), 710 (C-S); ^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 3.94 (2H, s), 4.8(1H, s), 7.22-7.57 (8H, m), 7.72-7.83 (5H, m), 9.83 (1H, s), anal. calcd. for, $C_{23}H_{17}ClN_4O_2S$ (448.9246) (%): found= C(61.33), H(3.56), N(12.37): calculated = C(61.54%), H(3.82%), N(12.48%); MS (m/z,%): 449.90 (M^++1)

BS7

IR (KBr, cm^{-1}): 3155(NH), 3150(Ar. C-H), 1625(C=N), 1515(Ar. C=C), 1645 (C=O), 715 (C-S); ^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 0.92 (3H, d), 0.95-1.04 (6H, d), 1.31-1.43 (2H, dd), 1.52-1.91 (2H,dd), 2.01-2.25 (2H, d), 2.26-2.42 (2H, dd), 2.63 (1H, ddd), 3.94-3.96 (2H,s), 4.7(1H, s), 7.25-7.48 (5H, m), 7.58 (4H, m), anal. calcd. for, $C_{26}H_{30}N_4O_2S$ (462.6070) (%): found= C(67.31), H(6.44), N(12.02): calculated = C(67.50), H(6.54), N(12.11); MS (m/z,%): 463.52 (M^++1)

BS8

IR (KBr, cm^{-1}): 3155(NH), 3150(Ar. C-H), 1625(C=N), 1515(Ar. C=C), 1635 (C=O), 705 (C-S); ^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 3.93 (2H, s), 4.5(1H, s), 7.21-7.55 (8H, m), 7.56-7.90 (5H, m), 9.83 (1H, s), anal. calcd. for, $C_{23}H_{17}ClN_4O_2S$ (448.9246) (%): found= C(61.41), H(3.78), N(12.53): calculated = C(61.54), H(3.82), N(12.48); MS (m/z,%): 449.82 (M^++1)

BS9

IR (KBr, cm^{-1}): 3155(NH), 3150(Ar. C-H), 1625(C=N), 1515(Ar. C=C), 1580 (C=O), 725 (C-S); ^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 0.94 (6H, s), 1.29 (3H, s), 1.43-1.86 (4H, m), 2.41-2.63 (3H, dd), 3.92-3.91 (2H, s), 4.3(1H, s), 7.21-8.49 (9H, m), anal. calcd. for, $C_{26}H_{28}N_4O_2S$ (460.5911) (%): found= C(67.73), H(6.09), N(12.10): calculated = C(67.80), H(6.13), N(12.16); MS (m/z,%): 461.32 (M^++1)

BS10

IR (KBr, cm^{-1}): 3155(NH), 3150(Ar. C-H), 1625(C=N), 1515(Ar. C=C), 1608 (C=O), 720 (C-S); ^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 3.90 (2H, s), 6.72 (1H, dd), 4.6(1H, s), 7.21-7.45 (5H, m), 7.55-7.63 (4H, m), 7.67-8.31 (3H, m), 9.74 (1H, s), anal. calcd. for, $C_{21}H_{16}N_4O_3S$ (404.4417) (%): found= C(62.24), H(3.87), N(13.64): calculated = C(62.36), H(3.99), N(13.85); MS (m/z,%): 405.42 (M^++1)

BS11
IR (KBr, cm^{-1}): 3155(NH), 3150(Ar. C-H), 1625(C=N), 1515(Ar. C=C), 1612 (C=O), 710 (C-S); ^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 1.52-1.55 (6H, s), 1.97 (3H, s), 2.10 (2H, s), 2.44 (2H, t), 3.93 (2H, s), 4.9(1H, s), 5.21 (1H, t), 6.33 (1H, d), 7.21-7.44 (5H, m), 7.58-8.32 (4H, m), 9.22 (1H, d), anal. calcd. for, $C_{26}H_{28}N_4O_2S$ (460.5911) (%): found= C(67.55), H(6.07), N(12.11): calculated = C(67.80), H(6.13), N(12.16); MS (m/z,%): 461.52 (M^++1)

BS12
IR (KBr, cm^{-1}): 3158(NH), 3152(Ar. C-H), 1621(C=N), 1510(Ar. C=C), 1620 (C=O), 690 (C-S); ^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 2.39 (3H, s), 3.97 (2H, s), 7.29 (1H, t), 7.40-7.58 (5H, m), 7.78 (1H, tt), 7.87 (1H, dd), 7.99 (1H, dd), 8.08 (2H, dd), 8.37 (2H, d), anal. calcd. for, $C_{24}H_{19}ClN_4O_2S$ (462.9512) (%): found= C(62.16), H(4.06), N(12.09): calculated = C(62.27), H(4.14) N(12.10); MS (m/z,%): 463.90 (M^++1)

BS13
IR (KBr, cm^{-1}): 3151(NH), 3156(Ar. C-H), 1612(C=N), 1521(Ar. C=C), 1635 (C=O), 698 (C-S); ^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 2.40 (3H, s), 3.96 (2H, s), 7.29 (1H, t), 7.45 (2H, d), 7.50-7.58 (3H,m), 7.81 (2H, d), 7.87 (1H, d), 7.99 (1H, d), 8.37 (2H, d), anal. calcd. for, $C_{24}H_{18}Cl_2N_4O_2S$ (497.3963) (%): found= C(57.72), H(3.33), N(11.14): calculated = C(57.95), H(3.65), N(11.26); MS (m/z,%): 498.29 (M^++1)

BS14
IR (KBr, cm^{-1}): 3156(NH), 3136(Ar. C-H), 1632(C=N), 1533(Ar. C=C), 1640 (C=O), 709 (C-S);^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 2.43 (3H, s), 3.97 (2H, s), 7.29 (1H, t), 7.45 (2H, d), 7.55 (1H, d), 7.87 (1H, d), 7.99 (1H, d), 8.06 (2H, d), 8.13 (2H, d), 8.38 (2H, d), anal. calcd. for, $C_{24}H_{18}ClN_5O_4S$ (507.9488) (%): found= C(56.35), H(3.52), N(13.27): calculated = C(56.75%), H(3.57%), N(13.79%); MS (m/z,%): 508.72 (M^++1)

BS15
IR (KBr, cm^{-1}): 3142(NH), 3131(Ar. C-H), 1652(C=N), 1528(Ar. C=C), 1656 (C=O), 715 (C-S);^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 3.98 (2H, s), 7.29 (1H, t), 7.40-7.59 (7H,m), 7.72-7.82 (2H,t), 7.85-7.95 (3H,dd), 7.92 (2H, dd), 7.99 (1H, dd), 8.37 (2H, dd), anal. calcd. for, $C_{29}H_{21}ClN_4O_2S$ (525.0206) (%): found= C(66.14), H(4.11), N(10.56): calculated = C(66.34), H(4.03), N(10.67); MS (m/z,%): 526.01 (M^++1)

BS16
IR (KBr, cm^{-1}): 3138(NH), 3142(Ar. C-H), 1658(C=N), 1535(Ar. C=C), 1606 (C=O), 705 (C-S);^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 3.96 (2H, s), 7.29 (1H, t), 7.40-7.58 (5H, m), 7.78 (1H, t), 7.87 (1H, d), 7.99 (1H, d), 8.06 (2H, d), 8.37 (2H, d), 9.83 (1H, s), anal. calcd. for, $C_{23}H_{17}ClN_4O_2S$ (448.9246) (%): found= C(61.37), H(3.70), N(12.23): calculated = C(61.54), H(3.82), N(12.48); MS (m/z,%): 449.72 (M^++1)

BS17
IR (KBr, cm^{-1}): 3130(NH), 3122(Ar. C-H), 1632(C=N), 1531(Ar. C=C), 1626 (C=O), 716 (C-S);^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 3.96 (2H, s), 7.29 (1H, t), 7.40-7.58 (5H, m), 7.80 (2H, d), 7.87 (1H, d), 7.99 (1H, d), 8.37 (2H, d), 9.81 (1H, s), anal. calcd. for, $C_{23}H_{16}Cl_2N_4O_2S$ (483.3697) (%): found= C(57.14), H(3.23), N(11.54): calculated = C(57.15), H(3.34), N(11.59); MS (m/z,%): 484.30 (M^++1)

BS18
IR (KBr, cm^{-1}): 3136(NH), 3142(Ar. C-H), 1644(C=N), 1552(Ar. C=C), 1642 (C=O), 710 (C-S);^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 0.93 (3H, d), 0.97-1.02 (6H,d), 1.37-1.93 (4H,d), 2.05-2.29 (2H,d), 2.29-2.46 (2H,d), 2.65 (1H, d), 3.97-3.98 (2H,s), 7.29 (1H, d), 7.45 (2H, d), 7.55 (1H, d), 7.87 (1H, d), 7.99 (1H, d), 8.38 (2H, d), anal. calcd. for, $C_{26}H_{29}ClN_4O_2S$ (497.0520) (%): found= C(62.67), H(5.40), N(11.20): calculated = C(62.83), H(5.88), N(11.27); MS (m/z,%): 498.02 (M^++1)

BS19
IR (KBr, cm^{-1}): 3126(NH), 3122(Ar. C-H), 1634(C=N), 1542(Ar. C=C), 1602 (C=O), 716 (C-S);^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 3.96 (2H, s), 7.24-7.64 (7H, m), 7.87 (1H, d), 7.99 (1H, d), 8.10 (1H, s), 8.37 (2H, d), 9.82 (1H, s), anal. calcd. for, $C_{23}H_{16}Cl_2N_4O_2S$ (483.3697) (%): found= C(57.06), H(3.23), N(11.45): calculated = C(57.15), H(3.34), N(11.59); MS (m/z,%): 484.32 (M^++1)

BS20
IR (KBr, cm^{-1}): 3135(NH), 3133(Ar. C-H), 1644(C=N), 1522(Ar. C=C), 1622 (C=O), 701 (C-S);^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 0.93 (6H, s), 1.29 (3H, s), 1.42-1.86 (4H,m), 2.44-2.66 (3H,d), 3.97-3.98 (2H,s), 7.29 (1H, t), 7.45 (2H, d), 7.55 (1H, d), 7.87 (1H, d), 7.99 (1H, d), 8.38 (2H, d), anal. calcd. for, $C_{26}H_{27}ClN_4O_2S$ (495.0361) (%): found= C(63.12), H(5.32), N(11.24): calculated = C(63.08), H(5.50), N(11.32), S(6.48); MS (m/z,%): 496.02 (M^++1)

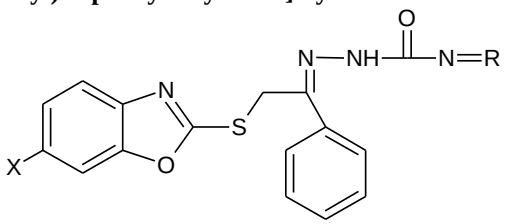
BS21

IR (KBr, cm^{-1}): 3131(NH), 3135(Ar. C-H), 1640(C=N), 1515(Ar. C=C), 1608 (C=O), 716 (C-S);^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 3.96 (2H, s), 6.78 (1H, d), 7.29 (1H, t), 7.45 (2H, d), 7.55 (1H, d), 7.62 (1H, d), 7.67 (1H, d), 7.87 (1H, d), 7.99 (1H, d), 8.37 (2H,d), 9.77 (1H, s), anal. calcd. for, $C_{21}H_{15}ClN_4O_3S$ (438.8868) (%): found= C(57.42), H(3.30), N(12.53): calculated = C(57.47), H(3.44), N(12.77); MS (m/z,%): 439.81 (M^++1)

BS22

IR (KBr, cm^{-1}): 3140(NH), 3125(Ar. C-H), 1624(C=N), 1530(Ar. C=C), 1628 (C=O), 702 (C-S);^{1}H NMR (300 MHz, $CDCl_3$, ppm, δ): δ 1.53-1.54 (6H, s), 1.99 (3H, s), 2.11 (2H, t), 2.47 (2H, t), 3.96 (2H, s), 5.23 (1H, t), 6.39 (1H, d), 7.29 (1H, t), 7.45 (2H, d), 7.55 (1H, d), 7.87 (1H, d), 7.99 (1H, d), 8.37 (2H, d), 9.28 (1H, d), anal. calcd. for, $C_{26}H_{27}ClN_4O_2S$ (495.0361) (%): found= C(63.04), H(5.36), N(11.27): calculated = C(63.08), H(5.50), N(11.32); MS (m/z,%): 496.02 (M^++1)

Table-1: Physicochemical properties of novel semicarbazone derivatives BS (1-22) of (2*E*)-2-[2-(1, 3-benzoxazol-2-ylsulfanyl)-1-phenylethylidene] hydrazinecarboxamide.



S.N	Compound code	Molecular Formula	Molecular Wt.	m.p.(°C)	Rf	Yield (%)	Solubility in DMSO
1	BS-1	$C_{24}H_{20}N_4O_2S$	428.5062	260-262	0.72	62	Soluble
2	BS-2	$C_{24}H_{19}ClN_4O_2S$	462.9512	271-273	0.81	55	Soluble
3	BS-3	$C_{24}H_{19}N_5O_4S$	473.5037	280-282	0.85	48	Soluble
4	BS-4	$C_{29}H_{22}N_4O_2S$	490.5755	268-270	0.68	66	Soluble
5	BS-5	$C_{23}H_{18}N_4O_2S$	414.4796	275-277	0.37	65	Soluble
6	BS-6	$C_{23}H_{17}ClN_4O_2S$	448.9246	288-290	0.52	72	Soluble
7	BS-7	$C_{26}H_{30}N_4O_2S$	462.6070	198-200	0.60	40	Soluble
8	BS-8	$C_{23}H_{17}ClN_4O_2S$	448.9246	190-192	0.90	49	Soluble
9	BS-9	$C_{26}H_{28}N_4O_2S$	460.5911	202-204	0.76	66	Soluble
10	BS-10	$C_{21}H_{16}N_4O_3S$	404.4417	210-212	0.65	65	Soluble
11	BS-11	$C_{26}H_{28}N_4O_2S$	460.5911	206-208	0.56	78	Soluble
12	BS-12	$C_{24}H_{19}ClN_4O_2S$	462.9512	264-266	0.42	72	Soluble
13	BS-13	$C_{24}H_{18}Cl_2N_4O_2S$	497.3963	277-279	0.74	61	Soluble
14	BS-14	$C_{24}H_{18}ClN_5O_4S$	507.9488	292-294	0.45	67	Soluble
15	BS-15	$C_{29}H_{21}ClN_4O_2S$	525.0206	263-265	0.58	59	Soluble
16	BS-16	$C_{23}H_{17}ClN_4O_2S$	448.9246	258-260	0.78	67	Soluble
17	BS-17	$C_{23}H_{16}Cl_2N_4O_2S$	483.3697	268-270	0.64	52	Soluble
18	BS-18	$C_{26}H_{29}ClN_4O_2S$	497.0520	220-222	0.52	73	Soluble
19	BS-19	$C_{23}H_{16}Cl_2N_4O_2S$	483.3697	190-192	0.88	56	Soluble
20	BS-20	$C_{26}H_{27}ClN_4O_2S$	495.0361	195-197	0.39	42	Soluble
21	BS-21	$C_{21}H_{15}ClN_4O_3S$	438.8868	221-223	0.55	48	Soluble
22	BS-22	$C_{26}H_{27}ClN_4O_2S$	495.0361	230-232	0.84	66	Soluble

Biological Evaluation

Anticonvulsant Screening

Animals

For anticonvulsant screening albino mice of either sex weighing between 20- 25 g were used. The animals were kept in large spacious hygienic animal cages during the study. The animals were provided standard commercial diet and water and were kept in properly cleaned rooms maintained at 22± 1^{0}C with 12 h light dark cycle. The animals were divided into three groups of 7 animals each: Group I: Control group (distilled water treated). Group II: Test group (were dissolved in polyethylene glycol (PEG-400) and 30, 100, 300 mg/kg *i.p.* doses), Group III: Standard group, reference drug (Diazepam, 10 mg/kg *i.p*, Diazepam, 30 mg/kg *i.p.*). All the drugs were administered 30 minutes before to the

administration of strychnine (1 mg/kg, *i.p.*) thiosemicarbazide (20 mg/kg, *s.c.*) and isoniazid (INH) (300 mg/kg, *s.c.*). The anticonvulsant screening of the final compounds was performed according to the protocols of the anticonvulsant drug development (ADD) program [18].

Procedure

Strychnine Induced Model

Mice of either sex with a weight of 25-30 g were treated with the test compounds or the standard (diazepam 10 mg/kg *i.p.*) by oral or intraperitoneal administration. Controls received the vehicle only, 30-minute before treatment with a subcutaneous dose of 1mg/kg strychnine, and test compounds in doses 30, 100; 300 mg/kg *i.p.* was injected. The incidence of tonic seizures, clonic seizures, and death or recovery was recorded after 0.5 hr, 1hr, 2hr, & 4hr time interval respectively [19].

Thiosemicarbazide Induced Model

Albino mice of either sex having a weight of 25-30 gm were treated with the test compounds or the standard drug (diazepam 10 mg/kg *i.p.*) by the oral or intraperitoneal route of drug administration. Controls received the vehicle only, 30-minutes before treatment with a subcutaneous dose of 20 mg/kg thiosemicarbazide, test compounds in doses 30, 100, 300 mg/kg *i.p.* was injected. The appearance of clonic seizures, tonic seizures, and death or recovery was recorded after 0.5 hr, 1hr, 2hr, & 4hr time interval respectively [20, 21]. Not protected means death of the mice occurs at the mentioned time.

Isonicotinic Acid Hydrazide (INH) Induced Model

Albino mice of either sex having a weight of 25-30 g were treated with the test compounds or the standard drug (diazepam 30 mg/kg *i.p.*) by the oral or intraperitoneal route of drug administration. Controls received the vehicle only, 30 minute after *i.p.* treatment the animals were injected with a subcutaneous dose of 300 mg/kg isoniazid (INH). The appearance of clonic seizures, tonic seizures, and death or recovery was recorded after 0.5 hr, 1hr & 2hr time interval respectively [22].

Neurotoxicity Screening

The activity of the drugs conflicting with motor coordination was checked by the rotarod test. The mice will train to stay on an accelerating rotarod that revolves at 6 revolutions per minute. Trained animals were given intraperitoneal injection of the test compounds in doses of 30, 100, 300 mg/kg. The rota-rod diameter was 3.2 cm. Neurotoxicity represented by the inability of the animal to maintain equilibrium on the rotarod for at least 1 min in each of three trials. The dose, at which the animals were unable to grasp the rotarod, will be determined. All the results were reported in the Table-1.

RESULTS AND DISCUSSIONS

The preparation of semicarbazone derivatives BS (1-22) were depicted in scheme 3. All the newly synthesized compounds were characterized by the IR, ^{1}H-NMR, mass and elemental analysis. In all the cases TLC of the products showed the single spot confirming the chromatogram for only one product. The physical properties of newly synthesized compounds BS (1-22) were shown in Table 1. Almost all the synthesized semicarbazones showed potent anticonvulsant activity. All the newly synthesized compounds comprise essential pharmacophoric requirements that are more important for better anticonvulsant activity as proposed by Dimmock *et al*., [23].

In the pharmacological study, from all the synthesized derivatives only compound BS1, BS3, BS9, BS10, BS11, and BS21 were found potent by using various chemical induced convulsion models viz strychnine, thiosemicarbazide and isonicotinic acid hydrazide (INH) to induced convulsion, diazepam was used as the standard drug, new derivatives were given at the dose of 30, 100, 300 mg/kg b.w. Anticonvulsant activity and neurotoxicity (NT) data for the BS (1-22) were given in Table-2 and many of the newly synthesized compounds showed better anticonvulsant activity.

All the compounds protect mice in Strychnine; thiosemicarbazide and isonicotinic acid hydrazide (INH) induced seizures at 30mg/kg at 0.5h except BS3 and BS21. Compound BS3 showed moderate activity in thiosemicarbazide induced model and no activity was observed in isonicotinic acid hydrazide (INH) induced model while BS21 was most potent in Strychnine induced model and showed mild activity in thiosemicarbazide and isonicotinic acid hydrazide (INH) induced models. Derivatives BS9, BS10, and BS11 were found most potent compounds in all the three models. Further, all the compounds exhibited no neurotoxicity in rotarod test up to a dose of 300mg/kg. All the newly synthesized compounds showed activity against chemo shock method which indicated their ability to prevent seizure spread.

Table-2: Anticonvulsant evaluation of newly synthesize semicarbazones BS (1-22) in the strychnine, thiosemicarbazide, and isonicotinic acid hydrazide (INH) induce models after intraperitoneal injection in mice.

Strychnine induced convulsion				Thiosemicarbazide induced convulsion			Isonicotinic acid hydrazide (INH) induced convulsion			Neurotoxicity screen	
Time to peak effect	**0.5 h**	**1 h**	**2 h**	**0.5 h**	**1 h**	**2 h**	**0.5 h**	**1 h**	**2 h**	**0.5h**	**4h**
Controls	-	-	-	-	-	-	-	-	-	-	-
Compound											
BS1	30	30	300	30	-	-	30	-	-	-	-
BS3	30	30	300	30	-	-	-	-	-	-	-
BS9	30	30	-	30	30	30	300	100	-	-	-
BS10	30	100	30	100	-	30	300	-	-	-	-
BS11	30	100	30	100	100	100	300	100	30	-	-
BS21	30	30	30	30	-	-	30	-	-	-	-
Diazepam(mg/kg)	10	10	10	10	10	10	30	30	30	-	-

Test compounds were suspended in polyethylene glycol (PEG) and doses of 30, 100, 300 mg/kg were administered through intraperitoneal *(i.p.*) injection in mice. The figures in the table represent the dose in mg/kg at which bioactivity was observed in a majority of the animals. The dash (-) line indicates the absence of activity at maximum dose administered (300 mg/kg).

CONCLUSION

We have attempted to design and synthesize novel semicarbazones BS (1-22) to exhibit anticonvulsant activity. The results obtained revealed that numbers of novel BS (1-22) derivatives effective in chemical induce (chemo-shock) model, compounds BS9, BS10 and BS11 were found most potent while BS1, BS3, and BS21 showing moderate activity. Therefore, these derivatives may possible to use as lead molecule for other biological activities also. Overall, the newly synthesized compounds emerged as more active and less neurotoxic derivatives.

ACKNOWLEDGMENTS

The author would like to express their obligation to the Director, Saroj Institute of Technology and Management, Lucknow, India, for providing necessary laboratory facilities during this project. Authors are also thanks to the head, sophisticated analytical instrumental facility department, Central Drug Research Institute (CDRI) for providing spectroscopic analysis facilities.

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