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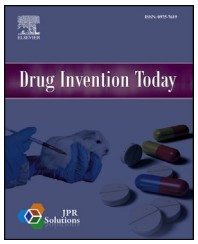

Original Article

Synthesis of indazole substituted-1,3,4-thiadiazoles and their anticonvulsant activity

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ABSTRACT

Objectives: To synthesize a new series of indazole substituted-1,3,4-thiadiazole derivatives **7(a-l)** and test the anticonvulsant activity against maximal electroshock (MES) seizure model in male Wistar rats.

Methods: New compounds were synthesized by the reaction of indazole substituted-1,3,4-thiadiazoles with various sulfonyl chlorides. The purity of the compounds was confirmed on the basis of their elemental analysis. Chemical structures of all the new compounds were established by ^{1}H NMR and mass spectral data. Anticonvulsant study was done by MES seizure model and rotorod method was employed to determine the neurotoxicity.

Results: All the compounds were synthesized in good yield. Out of twelve compounds, **7b** and **7d** are found to be most potent of this series. The same compounds showed no neurotoxicity at the maximum dose administered (100 mg/kg).

Conclusions: The results obtained justify the usage of these compounds from their promising anticonvulsant activity. Further studies are needed to fully characterize the toxicity and the mechanisms involved with the anticonvulsant activity and neurotoxicity of these compounds.

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1. Introduction

The word epilepsy usually describes a group of common chronic neurological disorders characterized by recurrent unprovoked seizures due to excessive neuronal firing or synchronous neuronal activity in the brain.[1,2] Seizures may vary from the briefest lapses of attention or muscle jerks to severe and prolonged convulsions.[3] The maximal electroshock (MES) test is a predictor of compounds that are active against grand mal seizures.[4] The anticonvulsant drug design is based on the presumption that while at least one phenyl or similar aromatic group in close proximity to two electron donor atoms in the compound is required for the activity in MES.[5] Several new drugs such as vigabatrin, lamotrigine, gabapentin, tiagabine, felbamate, topiramate, fosphenytoin and levetiracetam have appeared on the market, the development of new agents, particularly compounds effective against complex partial seizures, remains a major focus of antiepileptic drug research.[6]

Indazole and their derivatives display interesting biological properties and powerful pharmacological activities, such as

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antibacterial and antifungal activities.[7] Thiadiazoles exhibit a broad spectrum of biological effectiveness such as anti-parkinsonism,[8] anti-histaminic[9] and anti-asthmatic.[10] Thiazolidin-4-one derivatives are also known to exhibit diverse bioactivities such as anti-convulsant,[11] antidiarrheal,[12] anti-histaminic,[13] anti-diabetic,[14] cardioprotective,[15] and anti-cancer.[16] Similarly, 2,5-disubstituted-1,3,4-thiadiazoles are also display wide spectrum of anticonvulsant[17] activity. The therapeutic importance of these rings are prompted us to develop selective molecules in which a substituent could be arranged in a pharmacophore pattern to display higher pharmacological activities. In the present study, a series of new indazole substituted-1,3,4-thiadiazole derivatives **7(a–l)** have been synthesized and their anticonvulsant effects are determined through maximal electroshock (MES) seizure test.

2. Materials and methods

2.1. Chemistry

Melting range was determined by Veego Melting Point VMP III apparatus. Elemental analyses were recorded on VarioMICRO superuser V1.3.2 Elementar. ^{1}H NMR spectra was recorded on Bruker DRX-500 spectrometer at 400 MHz using DMSO-d_6 as solvent and TMS as an internal standard. Mass spectral data were obtained by LC/MSD Trap XCT. Silica gel column chromatography was performed using Merck 7734 silica gel (60–120 mesh) and Merck-made TLC plates.

2.1.1. *Synthesis of 1,3,4-thiadiazol-amine (2)*

Thiosemicarbazide (**1**, 25.0 g, 0.2743 mol) was taken in 100 mL formic acid and the reaction mixture was stirred at room temperature for 1 h. Cool the reaction mass and 100 mL conc. hydrochloric acid was added. Reaction completion was monitored by TLC. Cool the reaction mass to 0 °C and basified with ammonium hydroxide solution. The solid formed was filtered, washed with water and dried to yield the above compound as off white solid (Yield: 22.75 g, 82%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.21 (s, br, 2H), 9.31 (s, 1H). MS (ESI) *m/z*: 102.14.

2.1.2. *Synthesis of 5-bromo-1,3,4-thiadiazol-2-amine (3)*

To a stirred solution of **2** (40.0 g), sodium acetate (64.89 g) in 200 mL acetic acid (4.0 vol) at 10 °C, bromine was added drop wise (37.92 g). The reaction mass was stirred at room temperature for 3 h. The reaction mass was concentrated to syrup and basified with saturated sodium bicarbonate solution. The compound was extracted with ethyl acetate and the ethyl acetate layer was washed with water followed by brine, dried over sodium sulphate and concentrated to syrup. The crude syrup was crystallized using ethyl acetate to yield the above compound as off white solid (Yield: 53.4 g, 75%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.21 (s, br, 2H). MS (ESI) *m/z*: 181.10.

2.1.3. *Synthesis of tert-butyl-4-(5-amino-1,3,4-thiadiazole-2-yl)piperazine-1-carboxylate (4)*

To a stirred solution of **3** (25.0 g, 0.1388 mol), potassium carbonate (57.57 g, 0.4165 mol) in dimethyl formamide (250 mL) and mano boc piperazine (31.03 g, 0.1666 mol) were added and stirred the reaction mass for 10 h at room temperature. The reaction mass was quenched into ice water (2.0 L), stirred at room temperature for 1 h. Solid formed was filtered and dried. The crude compound was purified by column chromatography on silica gel (60–120 mesh size) using ethyl acetate and hexanes as eluent (5–10% EtoAc in hexane) (Yield: 33.6 g, 85%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.41 (s, 9H), 3.10 (t, J = 4.80 Hz, 4H), 3.77 (t, J = 5.16 Hz, 4H), 4.21 (s, 2H). MS (ESI) *m/z*: 286.03.

2.1.4. *Synthesis of tert-butyl-4-(5-(1-methyl-1H-indazole-3-carboxamido)-1,3,4-thiadiazol-2-yl)piperazine-1-carboxylate (5)*

To a stirred solution of **4** (15.0 g, 0.0525 mol) in dichloromethane (250 mL), triethyl amine (15.95 g, 0.1576 mol), 1-methyl-1H-indazole-3-carboxylic acid (11.09 g, 0.063 mol) and TBTU (20.23 g, 0.1051 mol) were added. The reaction mass was stirred at room temperature for 12 h. The reaction mass was washed with saturated bicarbonate solution followed by 1.0 N HCl, water and brine. The organic layer was dried over sodium sulphate, concentrated to syrup and crystallized using dichloro methane to yield the above compound as off white solid (Yield: 19.81 g, 85%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.48 (s, 9H), 3.50 (t, J = 4.84 Hz, 4H), 3.59 (t, J = 5.10 Hz, 4H), 4.18 (s, 3H), 7.31 (t, J = 7.80 Hz, 1H), 7.48 (t, J = 7.60 Hz, 1H), 7.76 (d, J = 8.52 Hz, 1H), 8.07 (d, J = 8.16 Hz, 1H), 12.25 (s, 1H). MS (ESI) *m/z*: 444.5.

2.1.5. *Synthesis of 1-methyl-N-(5-(piperazine-1-yl)-1,3,4-thiadiazole-2-yl)-1H-indazole-3-carboxamide hydrochloride (6)*

To a stirred solution of **5** (15 g, 0.0338 mol) in 1,4 dioxane at 0–5 °C, 4 N HCl in dioxane (60.0 mL) was added. The reaction mixture was stirred at room temperature for 10 h, filtered the solid. Solid was triturated with diethyl ether, filtered and washed with diethyl ether, packed in air tight container to yield the above compound as pale yellow hygroscopic solid (12.7 g, 90%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.19 (t, J = 4.83 Hz, 4H), 3.71 (t, J = 5.12 Hz, 4H), 4.19 (s,3H), 7.36 (t, J = 7.11 Hz, 1H), 7.52 (t, J = 7.86 Hz, 1H), 7.82 (d, J = 8.52 Hz, 1H), 8.14 (d, J = 8.10 Hz, 1H), 9.46 (s, 2H). MS (ESI) *m/z*: 344.05.

2.1.6. *General procedure for the synthesis of indazole substituted-1,3,4-thiadiazole derivatives 7(a-l)*

To a mixture of **6** (1.0 eq) and triethyl amine (4.5 eq) in dichloromethane (10 volume), substituted sulphonyl chloride (2.4 eq) was added at 5–10 °C and stirred at room temperature for 12 h. Reaction completion was confirmed through TLC. The reaction mixture was poured in to separating funnel washed with water followed by brine solution, dried over anhydrous sodium sulphate and concentrated to syrup. Crude syrup was purified by crystallization using ethyl acetate to yield the thiadiazole substituted sulfonamide as off white to pale yellow solids.

2.1.6.1. 1-Methyl-N-(5-(4-((2-nitro-4-(trifluoromethyl)phenyl) sulfonyl)piperazine-1-yl)-1,3,4-thiadiazole-2-yl)-1H-indazole-3-carboxamide (7a). Yield: 75% (White solid); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.43 (t, J = 4.84 Hz, 4H), 3.58 (t, J = 5.06 Hz, 4H), 4.19 (s, 3H), 7.35 (t, J = 7.44 Hz, 1H), 7.52 (t, J = 7.84 Hz, 1H), 7.80 (d, J = 8.52 Hz, 1H), 8.15 (d, J = 8.16 Hz, 1H), 8.26 (d, J = 8.64 Hz, 2H), 8.65 (s, 1H), 12.25 (s, 1H). MS (ESI) *m/z*: 595.5. Anal. Calcd. for $C_{22}H_{19}F_3N_8O_5S_2$: C, 44.29; H, 3.21; N, 18.78; Found: C, 44.34; H, 3.31; N, 18.86%.

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