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ORIGINAL ARTICLE

Sulfonamide derivatives of thiazolidin-4-ones with anticonvulsant activity against two seizure models: synthesis and pharmacological evaluation

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Abstract

A series of 4-thiazolidinones bearing a sulfonamide group (**4a–w**) were prepared by cyclizing various 5-bromo-2-methoxy-*N*′-[(1*E*)-arylmethylene/arylethylidene]benzenesulfonohydrazides. All the compounds were characterized by IR, ^{1}H NMR, and elemental analysis. The compounds were tested for their anticonvulsant activity utilizing MES and scPTZ animal models. The majority of the compounds exhibited significant activity against both animal models; however, compounds **4c**, **4m**, and **4o** displayed promising activity and could be considered as leads for further investigations.

Keywords: *thiazolidin-4-ones; sulfonamides; anticonvulsant activity*

Introduction

Epilepsy is a common chronic neurological disorder that is characterized by recurrent unprovoked seizures[1]. Different types of epilepsy are not based on a single underlying mechanism but are multifactorial in origin. It has been postulated that these seizures are transient signs and/or symptoms due to abnormal, excessive, or synchronous neuronal activity in the brain[2]. In a considerable number of epilepsies, genetic or familial disposition also plays an important role in seizure precipitation. Epilepsy is usually controlled but not cured with medication, and the literature reveals that over 30% of people with epilepsy do not have seizure control, even with the best available medications[3,4]. Thus, the search for new anticonvulsant drugs continues to be an active area of investigation in medicinal chemistry.

Antiepileptic drugs belong to many different chemical classes of compounds[5,6]. The most common structural elements of the older generation of clinically active antiepileptic drugs derived from hydantoins, oxazolidinediones, succinimides, and glutarimides can be defined as a nitrogen-containing heteroatomic system bearing one or two phenyl rings and at least one carbonyl group[7,8]. Moreover, several sulfonamide/sulfamate derivatives (acetazolamide, topiramate, zonisamide, etc.) have already been in clinical use, and the anticonvulsant effects of these or related sulfonamides are probably due to CO_2 retention followed by inhibition of red-cell and brain enzymes[9–12].

Previously we have reported several heterocyclic compounds showing considerable anticonvulsant activity[13–15]. In the course of our investigations on heterocyclic moieties aimed at developing newer anticonvulsants, a number of sulfonamides incorporating thiazolidin-4-ones have been synthesized and evaluated for anticonvulsant activity. The presence of sulfur in the sulfonamide as well as thiazolidin-4-one moieties of the titled compounds was expected to increase the lipophilicity, consequently elevating drug concentration in the brain.

All the synthesized compounds showed the four pharmacophoric elements (Figure 1) that are necessary for good anticonvulsant activity as suggested by Pandeya *et al.*[16]. These elements are present in many currently used antiepileptic drugs. They are the hydrophobic domain (A), hydrogen bonding domain (HBD), electron donor moiety (D), and distal hydrophobic domain (C). The attachment of a second aryl ring designated as the distal ring to the proximal aryl ring to increase the van der Waals bonding at the binding site and to increase potency has also been reported[17]. The present work further gives impetus to these observations.

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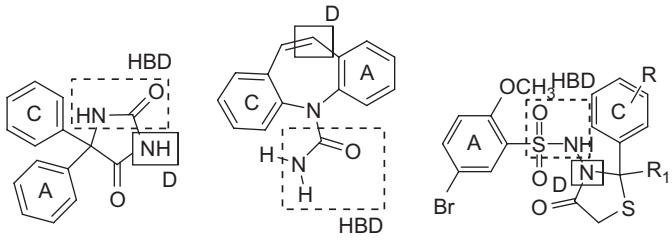


Figure 1. Anticonvulsant agents showing required pharmacophoric elements.

Distance mapping of the synthesized compounds was also performed with the help of the given model.

Materials and methods

Chemistry

Melting points were taken in open capillary tubes and are uncorrected. ^{1}H nuclear magnetic resonance (NMR) spectra (400 MHz) were recorded on a Bruker model DRX 400 NMR spectrometer in dimethylsulfoxide (DMSO)-d_6 using tetramethylsilane (TMS) as internal standard. Infrared (IR) spectra were recorded on a Bio-Rad FTS 135 spectrometer using a KBr pellet. Elemental analysis was performed using a Vario EL III CHNS analysis system (Elementar, Germany). Thin layer chromatography (TLC) was carried out using silica gel 60 F_{254} plates (Merck). All the chemicals and solvents used were obtained from Merck.

*General procedure for the synthesis of titled compounds (**4a–w**)*

*5-Bromo-2-methoxybenzenesulfonyl chloride (**1**)* *p*-Bromoanisole (0.10 mol, 18.7 g) was gradually added to chlorosulfuric acid (3 mol, 20 mL) at 0°C with constant stirring. The reaction mixture was left for 1 h at room temperature and then poured on crushed ice to give a white powder.

*5-Bromo-2-methoxybenzenesulfonohydrazide (**2**)* The sulfonyl chloride (**1**) (0.03 mol, 10 g) treated with hydrazine hydrate (98%, 3 mol, 6 mL) in aqueous ethanol (10 mL) at 0°C was set aside overnight at 0°C. The hydrazide was obtained as a white powder.

*5-Bromo-2-methoxy-N'-[(1E)-arylmethylene/arylethylidene] benzenesulfonohydrazides (**3a–w**)* To the hydrazide (**2**) (0.11 mol) in glacial acetic acid (5 mL) ethanol (10 mL) was added and refluxed with aromatic aldehydes and ketones (0.11 mol) for 5–8 h. The reaction mixture was cooled to room temperature and kept overnight. The solid collected was washed with methanol, dried in open air, and recrystallized from methanol to get the hydrazones (**3a–w**).

*5-Bromo-2-methoxy-N-(2-alkyl-4-oxo-2-aryl-1,3-thiazolidin-3-yl)benzenesulfonamides (**4a–w**)* A mixture of hydrazones (**3a–w**) (0.01 mol) and thioglycolic acid (0.01 mol) in 25 mL dioxane was taken in a round-bottomed flask. To this solution a pinch of zinc chloride was added and the reaction mixture was refluxed for 8–10 h. The mixture was then poured on crushed ice and the solid so obtained was filtered, washed with water, dried in air, and recrystallized from dioxane.

*5-Bromo-2-methoxy-N-(2-methyl-4-oxo-2-phenyl-1,3-thiazolidin-3-yl)benenesulfonamide (**4a**)* IR (KBr) cm^{-1}: 3458 (N-H), 3024 (C-H), 1723 (C=O), 1312 (NH-SO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 2.01 (s, 3H, CH_3), 3.74 (s, CH_2-thia.), 3.83 (s, 3H, OCH_3), 7.04–7.06 (d, 1H, Ar-H), 7.23–7.67 (m, 5H, Ar-H), 7.89–7.91 (d, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 10.57 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-N-[2-(2-hydroxyphenyl)-2-methyl-4-oxo-1,3-thiazolidin-3-yl]-2-methoxy benzenesulfonamide (**4b**)* IR (KBr) cm^{-1}: 3237 (O-H), 3236 (N-H), 3019 (C-H), 1683 (C=O), 1319 (NH-SO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 2.00 (s, 3H, CH_3), 3.65 (s, CH_2-thia.), 3.81 (s, 3H, OCH_3), 7.00–7.08 (m, 3H, Ar-H), 7.14 (s, 1H, OH), 7.49–7.63 (m, 2H, Ar-H), 7.89–7.91 (d, 1H, Ar-H), 8.07 (s, 1H, Ar-H), 9.87 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-N-[2-(3-hydroxyphenyl)-2-methyl-4-oxo-1,3-thiazolidin-3-yl]-2-methoxy benzenesulfonamide (**4c**)* IR (KBr) cm^{-1}: 3450 (O-H), 3447 (N-H), 2961 (C-H), 1716 (C=O), 1302 (NH-SO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 1.98 (s, 3H, CH_3), 3.69 (s, CH_2-thia.), 3.78 (s, 3H, OCH_3), 6.67–6.73 (m, 1H, Ar-H), 7.04–7.06 (d, 1H, Ar-H), 7.23 (s, 1H, Ar-H), 7.35–7.41 (m, 1H, Ar-H) 7.89–7.91 (d, 1H, Ar-H), 8.03 (s, 1H, Ar-H), 8.23 (s, 1H, OH) 9.79 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-N-[2-(4-hydroxyphenyl)-2-methyl-4-oxo-1,3-thiazolidin-3-yl]-2-methoxy benzenesulfonamide (**4d**)* IR (KBr) cm^{-1}: 3546 (OH), 3543 (N-H), 2919 (C-H), 1769 (C=O), 1308 (NH-SO_2); ^{1}H NMR (DMSO-d_6) δppm: 2.03 (s, 3H, CH_3), 3.71 (s, CH_2-thia.), 3.80 (s, 3H, OCH_3), 7.07-7.09 (d, 1H, Ar-H), 7.10–7.12 (d, 2H, Ar-H), 7.54–7.56 (d, 2H, Ar-H), 7.82–7.84 (d, 1H, Ar-H), 8.09 (s, 1H, Ar-H), 9.84 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-N-[2-(2,4-dihydroxyphenyl)-2-methyl-4-oxo-1,3-thiazolidin-3-yl]-2-methoxy benzenesulfonamide (**4e**)* IR (KBr) cm^{-1}: 3439 (O-H), 3435 (N-H), 2998 (C-H), 1669 (C=O), 1311 (NH-SO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 2.00 (s, 3H, CH_3), 3.72 (s, CH_2-thia.), 3.81 (s, 3H, OCH_3), 6.45 (s, 1H, Ar-H), 7.04–7.15 (m, 5H, Ar-H and 2 × OH), 7.88–7.90 (d, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 9.91 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-2-methoxy-N-[2-(2-methoxyphenyl)-2-methyl-4-oxo-1,3-thiazolidin-3-yl] benzenesulfonamide (**4f**)* IR (KBr) cm^{-1}: 3316 (N-H), 3053 (C-H), 1719 (C=O), 1318 (NH-SO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 2.01 (s, 3H, CH_3), 3.69 (s, CH_2-thia.), 3.84 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 6.69–7.21 (m, 5H, Ar-H), 7.83–7.85 (d, 1H, Ar-H), 8.12 (s, 1H, Ar-H), 10.21 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-2-methoxy-N-[2-(3-methoxyphenyl)-2-methyl-4-oxo-1,3-thiazolidin-3-yl] benzenesulfonamide (**4g**)* IR (KBr) cm^{-1}: 3428 (N-H), 3037 (C-H), 1673 (C=O), 1301 (NH-SO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 2.01 (s, 3H, CH_3), 3.70 (s, CH_2-thia.), 3.81 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3) 7.04–7.06 (d, 1H, Ar-H), 7.23–7.67 (m, 5H, Ar-H), 7.81–7.83 (d, 1H, Ar-H), 8.06 (s, 1H, Ar-H), 10.18 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-2-methoxy-N-[2-(4-methoxyphenyl)-2-methyl-4-oxo-1,3-thiazolidin-3-yl] benzenesulfonamide (**4h**)* IR (KBr) cm^{-1}: 3433 (N-H), 2942 (C-H), 1659 (C=O), 1307 (NH-SO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 1.94 (s, 3H, CH_3), 3.76 (s, CH_2-

thia.), 3.72 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 7.06–7.08 (d, 1H, Ar-H), 7.23–7.25 (d, 1H, Ar-H) 7.56–7.59 (d, 1H, Ar-H), 7.87–7.89 (d, 1H, Ar-H), 8.01 (s, 1H, Ar-H), 9.51 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-2-methoxy-N-[2-(2,4-dimethoxyphenyl)-2-methyl-4--oxo-1,3-thiazolidin-3-yl]benzenesulfonamide(**4i**)* IR(KBr) cm^{-1}: 3435 (N-H), 2998 (C-H), 1715 (C=O), 1319 ($NH-SO_2$); ^1H NMR (DMSO-d_6) δ ppm: 1.94 (s, 3H, CH_3), 3.53 (s, 3H, OCH_3), 3.69 (s, 2H, CH_2-thia.), 3.78 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 6.62 (s, 1H, Ar-H), 6.78–6.80 (d, 1H, Ar-H), 7.01–7.03 (d, 1H, Ar-H), 7.47–7.49 (d, 1H, Ar-H), 7.83–7.95 (d, 1H, Ar-H), 8.05 (s, 1H, Ar-H), 9.38 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-2-methoxy-N-[2-(3,4-dimethoxyphenyl)-2-methyl-4-oxo-1,3-thiazolidin-3-yl] benzenesulfonamide (**4j**)* IR (KBr) cm^{-1}: 3428 (N-H), 3052 (C-H), 1722 (C=O), 1315 ($NH-SO_2$); ^1H NMR (DMSO-d_6) δ ppm: 1.98 (s, 3H, CH_3), 3.70 (s, 6H, 2 × OCH_3), 3.73 (s, 2H, CH_2-thia.), 3.81 (s, 3H, OCH_3), 7.00–7.11 (m, 4H, Ar-H), 7.82–7.84 (d, 1H, Ar-H), 7.96 (s, 1H, Ar-H), 9.41 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-N-[2-(2-chlorophenyl)-2-methyl-4-oxo-1,3-thiazolidin-3-yl]-2-methoxy benzene sulfonamide (**4k**)* IR (KBr) cm^{-1}: 3437 (N-H), 2983 (C-H), 1719 (C=O), 1310 ($NH-SO_2$); ^1H NMR (DMSO-d_6) δ ppm: 2.05 (s, 3H, CH_3), 3.76 (s, 2H, CH_2-thia.), 3.82 (s, 3H, OCH_3), 7.08–7.10 (d, 1H, Ar-H), 7.29–7.53 (m, 4H, Ar-H), 7.89–7.91 (d, 1H, Ar-H), 8.09 (s, 1H, Ar-H), 10.46 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-N-[2-(3-chlorophenyl)-2-methyl-4-oxo-1,3-thiazolidin-3-yl]-2-methoxy benzene sulfonamide (**4l**)* IR (KBr) cm^{-1}: 3376 (N-H), 3055 (C-H), 1689 (C=O), 1306 ($NH-SO_2$); ^1H NMR (DMSO-d_6) δ ppm: 2.03 (s, 3H, CH_3), 3.73 (s, 2H, CH_2-thia.), 3.84 (s, 3H, OCH_3), 7.07–7.09 (d, 1H, Ar-H), 7.16–7.54 (m, 4H, Ar-H), 7.93–7.95 (d, 1H, Ar-H), 8.13 (s, 1H, Ar-H), 10.39 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-N-[2-(4-chlorophenyl)-2-methyl-4-oxo-1,3-thiazolidin-3-yl]-2-methoxy benzene sulfonamide (**4m**)* IR (KBr) cm^{-1}: 3453 (N-H), 2978 (C-H), 1712 (C=O), 1305 ($NH-SO_2$); ^1H NMR (DMSO-d_6) δ ppm: 2.07 (s, 3H, CH_3), 3.78 (s, 2H, CH_2-thia.), 3.87 (s, 3H, OCH_3), 7.01–7.03 (d, 1H, Ar-H), 7.58–7.60 (d, 2H, Ar-H), 7.69–7.71 (d, 2H, Ar-H), 7.92–7.94 (d, 1H, Ar-H), 8.16 (s, 1H, Ar-H), 10.47 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-N-[2-(2,4-dichlorophenyl)-2-methyl-4-oxo-1,3-thiazolidin-3-yl]-2-methoxy benzenesulfonamide (**4n**)* IR (KBr) cm^{-1}: 3438 (N-H), 2982 (C-H), 1719 (C=O), 1314 ($NH-SO_2$); ^1H NMR (DMSO-d_6) δ ppm: 2.05 (s, 3H, CH_3), 3.76 (s, 2H, CH_2-thia.), 3.85 (s, 3H, OCH_3), 7.05–7.07 (d, 1H, Ar-H), 7.40–7.42 (d, 1H, Ar-H), 7.90–7.92 (d, 1H, Ar-H), 7.95 (s, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 8.21–8.23 (d, 1H, Ar-H), 10.53 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-N-[2-(4-bromophenyl)-2-methyl-4-oxo-1,3-thiazolidin-3-yl]-2-methoxy benzene sulfonamide (**4o**)* IR (KBr) cm^{-1}: 3445 (N-H), 3051 (C-H), 1689 (C=O), 1318 ($NH-SO_2$); ^1H NMR (DMSO-d_6) δ ppm: 2.03 (s, 3H, CH_3), 3.77 (s, 2H, CH_2-thia.), 3.86 (s, 3H, OCH_3), 7.09–7.11 (d, 1H, Ar-H), 7.64–7.66 (d, 2H, Ar-H), 7.96–7.98 (d, 1H, Ar-H), 8.00–8.02 (d, 1H, Ar-H), 8.15 (s, 1H, Ar-H), 10.37 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-N-[2-(2-nitrophenyl)-2-methyl-4-oxo-1,3-thiazolidin-3-yl]-2-methoxy benzene sulfonamide (**4p**)* IR (KBr) cm^{-1}: 3419 (N-H), 2998 (C-H), 1710 (C=O), 1321 ($NH-SO_2$); ^1H NMR (DMSO-d_6) δ ppm: 2.17 (s, 3H, CH_3), 3.72 (s, 2H, CH_2-thia.), 3.85 (s, 3H, OCH_3), 7.13–7.15 (d, 1H, Ar-H), 7.56–7.87 (m, 4H, Ar-H), 7.93–7.95 (d, 1H, Ar-H), 8.17 (s, 1H, Ar-H), 10.71 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-N-[2-(3-nitrophenyl)-2-methyl-4-oxo-1,3-thiazolidin-3-yl]-2-methoxy benzene sulfonamide (**4q**)* IR (KBr) cm^{-1}: 3431 (N-H), 2984 (C-H), 1715 (C=O), 1319 ($NH-SO_2$); ^1H NMR (DMSO-d_6) δ ppm: 2.09 (s, 3H, CH_3), 3.75 (s, 2H, CH_2-thia.), 3.87 (s, 3H, OCH_3), 7.09–7.11 (d, 1H, Ar-H), 7.76–7.80 (t, 1H, Ar-H), 7.90–7.92 (d, 1H, Ar-H), 8.04–8.19 (m, 3H, Ar-H), 8.31 (s, 1H, Ar-H), 10.69 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-N-[2-(4-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-methoxy benzenesulfonamide (**4r**)* IR (KBr) cm^{-1}: 3438 (N-H), 2997 (C-H), 1718 (C=O), 1315 ($NH-SO_2$); ^1H NMR (DMSO-d_6) δ ppm: 2.06 (s, 3H, CH_3), 3.79 (s, 2H, CH_2-thia.), 3.84 (s, 3H, OCH_3), 7.07–7.09 (d, 1H, Ar-H), 7.91–7.93 (d, 1H, Ar-H), 7.95–7.97 (d, 2H, Ar-H), 8.19 (s, 1H, Ar-H), 8.32–8.34 (d, 1H, Ar-H), 10.73 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-2-methoxy-N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl) benzenesulfonamide (**4s**)* IR (KBr) cm^{-1}: 3443 (N-H), 2988 (C-H), 1712 (C=O), 1306 ($NH-SO_2$); ^1H NMR (DMSO-d_6) δ ppm: 3.67 (s, 2H, CH_2-thia.), 3.80 (s, 3H, OCH_3), 6.25 (s, 1H, CH-thia.), 7.05–7.07 (d, 1H, Ar-H), 7.30–7.52 (m, 5H, Ar-H), 7.85–7.97 (d, 1H, Ar-H), 7.97 (s, 1H, Ar-H), 8.19 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-2-methoxy-N-[2-(2-methylphenyl)-4-oxo-1,3-thiazolidin-3-yl]benzene sulfonamide (**4t**)* IR (KBr) cm^{-1}: 3419 (N-H), 2971 (C-H), 1718 (C=O), 1311 ($NH-SO_2$); ^1H NMR (DMSO-d_6) δ ppm: 2.58 (s, 3H, CH_3), 3.63 (s, 2H, CH_2-thia.), 3.79 (s, 3H, OCH_3), 6.16 (s, 1H, CH-thia.), 7.02–7.60 (m, 5H, Ar-H), 7.85–7.87 (d, 1H, Ar-H), 7.94 (s, 1H, Ar-H), 8.15 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-2-methoxy-N-[2-(3-methylphenyl)-4-oxo-1,3-thiazolidin-3-yl]benzene sulfonamide (**4u**)* IR (KBr) cm^{-1}: 3426 (N-H), 2985 (C-H), 1689 (C=O), 1317 ($NH-SO_2$); ^1H NMR (DMSO-d_6) δ ppm: 2.33 (s, 3H, CH_3), 3.65 (s, 2H, CH_2-thia.), 3.82 (s, 3H, OCH_3), 6.29 (s, 1H, CH-thia.), 6.99–7.32 (m, 5H, Ar-H), 7.82–7.84 (d, 1H, Ar-H), 7.91 (s, 1H, Ar-H), 8.21 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-2-methoxy-N-[2-(4-methylphenyl)-4-oxo-1,3-thiazolidin-3-yl]benzene sulfonamide (**4v**)* IR (KBr) cm^{-1}: 3429 (N-H), 2991 (C-H), 1701 (C=O), 1320 ($NH-SO_2$); ^1H NMR (DMSO-d_6) δ ppm: 2.29 (s, 3H, CH_3), 3.68 (s, 2H, CH_2-thia.), 3.76 (s, 3H, OCH_3), 6.21 (s, 1H, CH-thia.), 7.05–7.07 (d, 1H, Ar-H), 7.21–7.23 (d, 2H, Ar-H), 7.59–7.61 (d, 2H, Ar-H) 7.85–7.87 (d, 1H, Ar-H), 7.96 (s, 1H, Ar-H), 8.13 (s, 1H, NH, D_2O exchangeable).

*5-Bromo-N-{2-[4-(dimethylamino)phenyl]-4-oxo-1,3-thiazolidin-3-yl}-2-methoxy benzene sulfonamide (**4w**)* IR (KBr) cm^{-1}: 3464 (N-H), 2983 (C-H), 1712 (C=O), 1323 ($NH-SO_2$); ^1H NMR (DMSO-d_6) δ ppm: 3.06 (s, 6H, 2 × CH_3), 3.58 (s, 2H, CH_2-thia.), 3.74 (s, 3H, OCH_3), 6.19 (s, 1H, CH-thia.),

6.73–6.75 (d, 2H, Ar-H) 7.07–7.09 (d, 1H, Ar-H), 7.21–7.23 (d, 2H, Ar-H), 7.85–7.87 (d, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 8.07 (s, 1H, NH, D_2O exchangeable).

Pharmacology

Anticonvulsant activity

The investigations were conducted on Swiss albino mice of either sex (25–30 g). Food and water were withdrawn prior to the experiments. All the compounds **(4a–w)** were dissolved in polyethylene glycol. Initially all compounds were administered intraperitoneally (ip) at doses of 30, 100, and 300 mg/kg to mice. Activity was established using the maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) tests according to the protocol of the Antiepileptic Drug Development Program (ADD), Epilepsy Branch, National Institute of Health, Bethesda, MD, USA[18,19].

MES test Mice were prescreened 24 h beforehand by delivering a maximal electroshock of 50 mA, 60 Hz, and 0.2 s duration by means of corneal electrodes. A drop of 0.9% sodium chloride was instilled in each eye prior to application of the electrodes in order to prevent death of the animal. The abolition of the hind-limb tonic extensor component of the seizure in half or more of the animals was defined as protection.

scPTZ test The scPTZ test utilized a dose of pentylenetetrazole 70 mg/kg. This produced clonic seizures lasting for a period of at least 5 s. The test compounds were administered at the three graded doses, i.e. 30, 100, and 300 mg/kg ip. At the anticipated time, the convulsant was administered subcutaneously. Animals were observed over a 30 min period. The absence of clonic spasm in half or more of the animals in the observed time period indicated a compound's ability to abolish the effect of pentylenetetrazole on the seizure threshold.

Toxicity studies

Neurotoxicity The minimal motor impairment was measured in mice by the rotarod test[20]. The mice were trained to stay on an accelerating rotarod of diameter 3.2 cm that rotated at 10 rpm. Neurotoxicity was indicated by the inability of the animal to maintain equilibration on the rod for at least 1 min in each of three trials. The dose at which 50% of the animals were unable to balance themselves and fell off the rotating rod was determined.

Ethanol potentiation test Mice were treated with the test compound and 1 h later with ethanol 2.5 g/kg ip. This dose of ethanol did not induce a lateral position in the control animals. The number of animals that were in the lateral position after receiving ethanol in each group was determined[21].

In vitro GABA-transminase inhibition assay

Since several sulfonamide derivatives have already been found to show anticonvulsant activity due to CO_2 retention followed by inhibition of red-cell and brain enzymes, the most active compounds were tested *in vitro* against the γ-aminobutyric acid-transaminase (GABA-T) enzyme and the inhibition was assessed. The GABA-T enzyme was isolated from *Pseudomonas fluorescens* using a method described earlier[22]. The assay was performed for a 4 h time period according to the standard protocol[23].

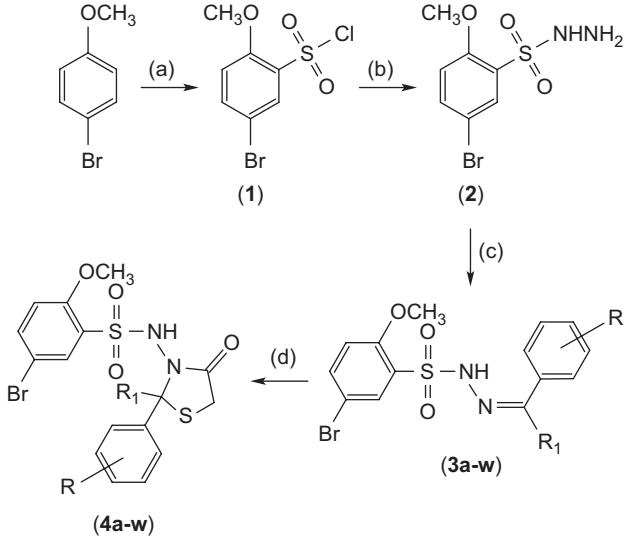
Distance mapping

In conformational analysis of the older-generation clinically active anticonvulsant drugs such as phenytoin, carbamazepine, lamotrigene, rufinamide, remacemide, and phenobarbitone, a molecular model was suggested on the basis of molecular dynamics distance estimations[24]. According to these, an electron donor (D) should be at a distance of 3.2–5.1 Å from an aryl ring or any other hydrophobic unit (C) and 3.9–5.5 Å from the hydrogen bonding domain (HBD). For the molecular mechanics calculations, the ACD/Chemsketch/3-D viewer version 2.0 program was used to employ the CHARMM force field[8].

Results and discussion

Chemistry

The synthetic pathway giving access to the titled compounds **(4a–w)** is illustrated in Scheme 1. The synthesis of 5-bromo-2-methoxybenzenesulfonyl chloride **(1)** involved a reaction between *p*-bromoanisole and chlorosulfuric acid. In the subsequent step, 5-bromo-2-methoxybenzenesulfonohydrazide **(2)** was synthesized by the treatment of compound **1** with hydrazine hydrate. The aromatic aldehydes and ketones were refluxed with compound **2** in glacial acetic acid, yielding 5-bromo-2-methoxy-*N*'-[(1*E*)-arylmethylene/arylethylidene]benzenesulfonohydrazide **(3a–w)**. In the last step, compounds **3a–w** were cyclized in the presence of zinc chloride to afford the final compounds **4a–w**. The physicochemical parameters of all the synthesized compounds are given in Table 1.



Scheme 1. Synthetic route to the titled compounds **4a–w**. Reagents and conditions: (a) $HClSO_4$, 0°C; (b) $NH_2NH_2.H_2O$, 0°C, ethanol; (c) CH_3COOH, $RCOR_1$, reflux; (d) $HSCH_2COOH$, $ZnCl_2$, reflux.

Table 1. Physical characterization data of compounds **4a–w**.

Compound	R	R_1	Mol. formula	% Yield	Mp (°C)	R_f[a]	Log P[b]
4a	H	CH_3	$C_{17}H_{17}BrN_2O_4S_2$	75	165	0.74	2.88
4b	2-OH	CH_3	$C_{17}H_{17}BrN_2O_5S_2$	62	162	0.70	2.14
4c	3-OH	CH_3	$C_{17}H_{17}BrN_2O_5S_2$	69	158	0.79	2.14
4d	4-OH	CH_3	$C_{17}H_{17}BrN_2O_5S_2$	62	163	0.81	2.14
4e	2,4-OH	CH_3	$C_{17}H_{17}BrN_2O_6S_2$	65	142	0.84	1.42
4f	2-OCH_3	CH_3	$C_{18}H_{19}BrN_2O_5S_2$	74	175	0.73	2.79
4g	3-OCH_3	CH_3	$C_{18}H_{19}BrN_2O_5S_2$	69	168	0.76	2.79
4h	4-OCH_3	CH_3	$C_{18}H_{19}BrN_2O_5S_2$	70	163	0.64	2.79
4i	2,4-OCH_3	CH_3	$C_{19}H_{21}BrN_2O_6S_2$	56	135	0.75	2.59
4j	3,4-OCH_3	CH_3	$C_{19}H_{21}BrN_2O_6S_2$	63	148	0.78	2.61
4k	2-Cl	CH_3	$C_{17}H_{16}BrClN_2O_4S_2$	78	155	0.69	3.47
4l	3-Cl	CH_3	$C_{17}H_{16}BrClN_2O_4S_2$	71	178	0.65	3.47
4m	4-Cl	CH_3	$C_{17}H_{16}BrClN_2O_4S_2$	68	150	0.68	3.47
4n	2,4-Cl	CH_3	$C_{17}H_{15}BrCl_2N_2O_4S_2$	63	159	0.72	4.08
4o	4-Br	CH_3	$C_{17}H_{16}Br_2N_2O_4S_2$	78	137	0.87	3.65
4p	2-NO_2	CH_3	$C_{17}H_{16}BrN_3O_6S_2$	74	167	0.84	2.61
4q	3-NO_2	CH_3	$C_{17}H_{16}BrN_3O_6S_2$	79	169	0.81	2.61
4r	4-NO_2	H	$C_{17}H_{16}BrN_3O_6S_2$	70	176	0.76	2.61
4s	H	H	$C_{16}H_{15}BrN_2O_4S_2$	76	138	0.53	2.33
4t	2-CH_3	H	$C_{17}H_{17}BrN_2O_4S_2$	68	149	0.64	2.79
4u	3-CH_3	H	$C_{17}H_{17}BrN_2O_4S_2$	63	142	0.60	2.79
4v	4-CH_3	H	$C_{17}H_{17}BrN_2O_4S_2$	66	135	0.68	2.79
4w	4-$N(CH_3)_2$	H	$C_{18}H_{20}BrN_3O_4S_2$	73	109	0.90	2.44

Note. Elemental analyses for C, H, and N were within ±0.4% of the theoretical values.
[a]Solvent system used was toluene/ethyl acetate/formic acid (5:4:1).
[b]Log P was calculated using ACD lab version 8.0.

All the synthesized compounds were well characterized by elemental analysis and spectroscopic data. In IR spectra, absorption bands for N-H, O-H, C-H, C=O, and NH-SO_2 were found in the regions 3544–3236, 3055–2919, 1769–1659, and 1323–1301 cm^{-1}, respectively. The ^1H NMR spectra showed a distinct singlet at δ values 3.79–3.58 ppm assigned for CH_2-thiazolidinones. Various singlets, doublets, triplets, and multiplets were found in aromatic zones. A singlet at δ values ranging from 10.73 to 8.07 ppm was assigned to N-H attached to the phenyl ring.

Pharmacology

Anticonvulsant evaluation of compounds **4a–w** in mice utilizing MES and scPTZ models is summarized in Table 2 together with the neurotoxicity and ethanol potentiation data. To obtain information about undesired side effects, the highly and moderately active compounds were subjected to neurotoxicity (rotorod) and ethanol potentiation tests.

Preliminary evaluation of all the synthesized compounds was performed against two well-established seizure models, namely MES and scPTZ. All the compounds showed encouraging anticonvulsant activity. Compounds **4c**, **4m**, and **4o** were found to be highly active against the MES test at a dose level of 30 mg/kg at 0.5 h time interval, indicative of their ability to prevent seizure spread at a relatively low dose. Compounds that exhibited moderate protection against the MES model at 100 mg/kg included **4b**, **4d**, **4e**, **4j**, **4k**, **4l**, **4q**, **4s**, and **4w,** at 0.5 h. Thus, the majority of the compounds showed encouraging anticonvulsant activity at the 0.5 h interval, indicating rapid onset and shorter duration of action.

In the chemoshock investigation, those compounds that exhibited considerable activity in the MES test were chosen for scPTZ study. Compounds **4d**, **4e**, **4m**, and **4w** were found to be active after 0.5 h of drug administration at a dose of 100 mg/kg.

In neurotoxicity studies, ethanol potentiation and rotorod tests were employed to estimate the undesired effects such as sedation and ataxia produced by the compounds. The ethanol potentiation test was performed in parallel with the rotorod test to investigate the neurotoxic effects of the compounds, by inducing a lateral position in the animals. Compounds **4b**, **4e**, **4j**, **4k**, **4o**, **4q**, and **4w** showed an interaction with ethanol, thereby potentiating the effect of ethanol, whereas compounds **4c**, **4d**, **4l**, **4m**, and **4s** did not interact with ethanol. In the rotorod test, compounds **4c**, **4e**, **4j**, **4o**, **4q**, and **4w** were less neurotoxic, and the rest of the compounds did not exhibit neurotoxicity.

The correlation of lipophilicity (log P) and *in vivo* anticonvulsant activity as well as neurotoxicity was established and found to be non-linear. The lipophilicity of highly active compound **4c** was found to be minimum (log P = 2.14), whereas the other highly active compounds **4m** (log P = 3.47) and **4o** (log P = 3.65) were moderately lipophilic. Paradoxically, the least active compound **4n** showed high lipophilicity (log P = 4.08). Variable results were found between neurotoxicity and lipophilicity data.

Table 2. Anticonvulsant and neurotoxicity data of compounds **4a–w**.

	MES		scPTZ		Neurotoxicity		Ethanol
Compound	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	potentiation test[a]
4a	300	(–)	X	X	X	X	X
4b	100	300	300	(–)	(–)	(–)	(–)
4c	30	100	300	(–)	300	(–)	(+)
4d	100	300	100	300	(–)	(–)	(+)
4e	100	100	100	300	300	(–)	(–)
4f	300	(–)	X	X	X	X	X
4g	(–)	(–)	X	X	X	X	X
4h	300	300	X	X	X	X	X
4i	300	300	X	X	X	X	X
4j	100	300	(–)	(–)	300	(–)	(–)
4k	100	300	(–)	300	(–)	300	(–)
4l	100	(–)	300	300	(–)	(–)	(+)
4m	30	100	100	300	(–)	(–)	(+)
4n	300	300	X	X	X	X	X
4o	30	100	300	(–)	300	300	(–)
4p	300	(–)	X	X	X	X	X
4q	100	300	300	300	300	(–)	(–)
4r	300	(–)	X	X	X	X	X
4s	100	300	300	(–)	(–)	(–)	(+)
4t	300	300	X	X	X	X	X
4u	300	(–)	X	X	X	X	X
4v	(–)	300	X	X	X	X	X
4w	100	300	100	100	300	(–)	(–)
Phenytoin	30	30	(–)	(–)	100	100	X

Note. Doses of 30, 100, and 300 mg/kg were administered ip. The figures indicate the minimum dose whereby bioactivity was demonstrated in half or more mice. (–), absence of activity at maximum dose administered (300 mg/kg); (X) not tested.
[a]Ethanol potentiation test: (+), half or more animals passed the test; (–), half or more animals failed the test.

Table 3. *In vitro* GABA-transaminase inhibition assay of selected compounds.

	Percentage inhibition of GABA-T[a]				
Compound	0.5 h	1.0 h	2.0 h	3.0 h	4.0 h
Control	—	—	—	—	—
4c	5	8	10	10	12
4m	—	—	5	4	8
4o	—	10	15	18	30

[a]*In vitro* enzyme inhibition was carried out at a concentration of 500 µM for compounds.

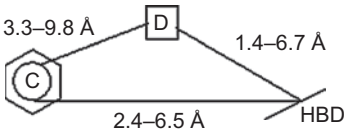
In vitro GABA-T inhibition assay

In our quest to understand the mechanism involved in the anticonvulsant activity of the titled compounds, the three most active compounds (**4c**, **4m**, and **4o**) were subjected to the *in vitro* GABA-T inhibition assay. The GABA-transaminase enzyme has been found to be responsible for the metabolism of GABA, and therefore inhibition of the enzyme will result in an increased concentration of GABA in different brain regions. The results of the assay are presented in Table 3. All three compounds were found to inhibit the GABA-T enzyme at the 4 h time period. Compound **4c** was found to inhibit GABA-T throughout the time points, but the maximum inhibition shown by **4c** was 12% at 4 h. Compound **4m** inhibited the enzyme at 2 h and maximum inhibition (8%) was observed at 4 h. Compound **4o** exhibited maximum inhibition among these compounds. It showed inhibition at 1 h and continued to inhibit the enzyme significantly throughout the time points. The maximum inhibition of 30% at 4 h indicates the promising nature of this compound.

Distance mapping

The present work further involved comparison of the structures of well known and structurally different compounds and the synthesized compounds. Comparison of the structures of the synthesized compounds and other molecules with anticonvulsant activity was performed to determine the structural elements essential for action. The compounds selected for this comparison have at least one aryl (C) hydrophobic domain, one electron donor (D), and a hydrogen bond acceptor/donor unit (HBD). In an initial study, molecular mechanics calculations using a force field based on CHARMM parameterization were performed to obtain an overview of their minimum conformation for bioactivity. Table 4 shows the distances between the various groups postulated as essential for anticonvulsant action. The

Table 4. Distance ranges between essential structural elements C, D, and HBD.



Compound	C–HBD[a]	C–D[a]	D–HBD[a]
Basic structure of compounds **4a–w**	3.379	2.419	1.452
Carbamazepine	6.517	3.931	5.554
Phenytoin	3.042	3.868	2.497
Lamotrigine	5.807	3.301	4.598
Zonisamide	4.058	5.651	6.729
Rufinamide	2.407	7.474	5.209
Dezinamide	4.481	5.909	2.948
Remacemide	3.211	9.811	6.635
Diazepam	4.793	4.827	1.497

[a]Distance calculated for 3D optimized structures using ACD/Chemsketch/3-D viewer version 2.0 program.

synthesized compounds were examined to check whether they reflected the conditions of the derived pharmacophore model. Analysis of the distance relationship showed that synthesized compounds **4a–w** fulfilled the essential demands of the pharmacophore when compared with other known anticonvulsant drugs. In the case of the titled compounds, the distances C–D, C–HBD, and D–HBD were in conformity with the distances for active anticonvulsant drugs.

Conclusions

The sulfonamide derivatives of thiazolidin-4-one exhibited remarkable anticonvulsant activity with lesser neurotoxicity against the two animal models. Compounds **4c**, **4m**, and **4o** were highly active in the MES test. In the scPTZ test, compounds **4m** and **4o** continued to be active, indicating the ability of these compounds to prevent more than one type of seizure. The anticonvulsant effects of these sulfonamide derivatives of 4-thiazolidinone are probably due to CO_2 retention followed by inhibition of red-cell and brain enzymes.

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Declaration of interest

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