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Molecular docking study and anticonvulsant activity of synthesized 4-((4,6-dimethyl-6H-1, 3-thiazin-2-yl)phenylsulfonyl)urea/thiourea derivatives

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KEYWORDS

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Drug likeness

Abstract A new series of 1-(4-substitutedphenyl)-3-(4-(4,6-dimethyl-6H-1,3-thiazin-2-yl)phenylsulfon-yl)urea/thiourea (**3a–l**) derivatives were synthesized and screened for anticonvulsant activity by maximal electro shock (MES) and pentylenetetrazole (PTZ) induced convulsant model. All the derivatives were evaluated for neurotoxicity measures by rotarod method. Structures of synthesized compounds were established by spectroscopic techniques and elemental analysis. Pharmacological results were justified by the data obtained from the molecular docking studies along with the drug likeness and drug scores. From the experimental results, compounds **3a**, **3b** and **3c** were found to be significantly effective. Out of these the chloro substituted derivative 1-(4-(4,6-dimethyl-6H-1,3-thiazin-2-yl)phenylsulfonyl)-3-(4-hydroxyphen-yl)urea (**3c**) was the most active convulsion protective compound. From the evaluation results it was concluded that the sulfonylurea series is better and safer than the sulfonylthiourea for anticonvulsant activity.

1. Introduction

Convulsion is neurological disorder that leads the recurrent neuronal firing from the cortical neurons (Henry, 2012). Due to overproduction of nerve impulses there is transitory loss of consciousness and other symptoms related to brain dysfunction. This bursting activity occurs from the prolonged depolarization of neuronal membrane due to opening of voltage gated Na^+ channels which initiate the action potentials repeatedly (Köhling, 2002). Voltage gated sodium channel is the target for various cyclic anticonvulsant drugs i.e. phenytoin, carbamazepine, lamotrigine (Lipkind and Fozzard, 2010) and phenobarbitals (Rajak et al., 2010). This idea use to explore to develop some other tricyclic compounds along with some other basic structural characteristics like an aryl hydrophobic binding site (A), hydrogen bonding domain

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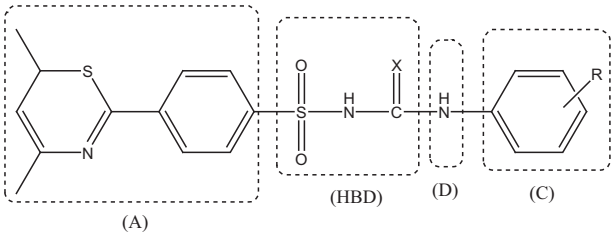
(HBD), hydrophobic-hydrophilic site controlling the pharmacokinetic properties (C) and an electron donor group (D) for efficient anticonvulsant activity (Rajak et al., 2010). In the earlier study sulfonylurea pharmacophoric model reported significant anticonvulsant activity (Thakur et al., 2015). Besides the anticonvulsant activity sulfonylurea reported for hypoglycemic (Zhang et al., 2009), antitumor (Samanta et al., 2004), cytotoxic (Zhang et al., 2010), antimalarial (León et al., 2007) and antifungal (Chen et al., 2015) activities in which the respective protein molecules were target for binding to exert the activity.

Here in the present work some new thiazine containing sulfonylurea and sulfonylthiourea derivatives have been prepared along with the mentioned structural requirements for efficient anticonvulsive effect.



Sulfonylurea share structural features which closely resemble established molecule already in use as anticonvulsant viz. phenytoin, carbamazepine, Phenobarbitals, etc. These also contain sulfonamide moiety which show anticonvulsive properties as acetazolamide and topiramate (Masereel et al., 2002).

In silico (docking) study is the best way to develop mechanism base molecules, which could identify more precisely the bonding requirements in structure with targeted protein molecule. Here for anticonvulsant study open voltage gated sodium channel is chosen as the target protein for docking study to find its binding affinity to the test molecule by comparing with standard drug molecule (Iman et al., 2015).

2. Material and methods

The chemicals used for the experimental work were procured from Qualigens, Fine Chemicals Mumbai and CDH (P) Ltd. New Delhi. The ranges of melting point of synthesized compounds were measured by open capillary method and are uncorrected. The progress and completion of reactions were determined by thin layer chromatography using Silica gel G (E. Merck) using acetonitrile and methanol (60:40) as mobile phase. Detection of elements in synthesized compounds was carried out on Carlo Erba EA 1108 elemental analyser. KBr pellets of test compounds were used for taking IR spectra on FTIR spectrophotometer (JASCO), ^{1}H NMR spectra were taken in DMSO (TMS as internal standard) on a Bruker Advance (400 MHz) NMR spectrophotometer using and mass spectra was taken on SHIMADZU-2010 AT.

2.1. In silico studies

The docking study is performed to elucidate mode of binding of compound with the target site. The open pore Na^+ channel (retrieve from protein data bank, http://RCSB.org) was used as a target protein model based on homology of K^+ channel structure for docking studies of synthesized compounds (Iman et al., 2015). Chem Draw ultra 10.0 has been used for drawing the structure of synthesized compound and converted to .pdb format from .mol file for docking. To investigate the mode of binding and related interactions of the synthesized compounds with target, Argus Lab 4.0 docking software was used. The protein–ligand interaction study was carried out by pymol 1.3 software. The drug likeness and drug score were calculated by Osiris online software.

2.2. Synthesis

2.2.1. General procedure for the synthesis of 4,6-dimethyl-2-phenyl-6H-1,3-thiazine (*1*)

Compound **1** was synthesized according to the reported procedures (Thakur et al., 2015).

2.2.2. General procedure for synthesis of 4-(4,6-dimethyl-6H-1,3-thiazin-2-yl)benzene-1-sulfonyl chloride (*2*)

The chlorosulfonation of synthesized compound (**1**) was carried out using chlorosulfonic acid solution. Two separate equimolar (0.06 mol) solutions of compound **1** and chlorosulfonic acid were prepared in 1,4-dioxane (60 ml) with stirring at room temperature. Both the solutions were mixed together to produce a homogenous exothermic mixture by stirring at room temperature for half an hour. The resulting solution was added to the crushed ice for precipitation of compound **2**. The precipitated solid was filtered and recrystallized from ethanol. Yield 74% and m.p. 240–244 °C.

IR Vmax (KBr, in cm^{-1}): 1509–52 (Ar-C═C—), 1193 (C—N), 2360 (C—S—C), 1380 (C—CH_3), 1359 and 1177 (C—SO_2), 3058 (Ar—C—H); ^{1}H NMR (300 MHz, DMSO-d_6, δ): 5.60 (1H, d, C–H of thiazine), 3.46 (1H, m, CH-S of thiazine), 1.53 (3H, d, CH_3 of thiazine) 1.72 (3H, s, CH_3 of thiazine), 7.94–8.14 (4H, m, Ar-SO_2); FAB-MS (m/z): 301 [M^+].

2.2.3. General procedure for synthesis of 1-(4-substitutedphenyl)-3-(4-(4,6-dimethyl-6H-1,3-thiazin-2-yl) phenylsulfonyl)urea/thiourea (*3a–l*) (Samanta et al., 2004)

Substituted phenylurea/phenylthiourea (Robert and Smith, 1948) (0.15 mol) was dissolved in alkaline sodium hydroxide solution (2 N) in a flask. To the resultant solution, chlorosulfonyl derivative (compound 2) was added slowly with constant stirring and maintained at 70 °C in water bath. In order to keep the reaction mixture alkaline further sodium hydroxide solution was added and allowed to cool to the room temperature. The solution was filtered and acidified with hydrochloric acid for complete precipitation.

*2.2.3.1. 1-(4-(4,6-dimethyl-6H-1,3-thiazin-2-yl)phenylsulfonyl)-3-phenylurea (**3a**).* Yield 79% (yellowish brown fine crystals), m.p. 222–224 °C, IR Vmax (KBr, in cm^{-1}): 1286 (C—N), 2360 (C—S—C), 1326 and 1134 (SO_2N), 1672 (—C═O), 3064 (Ar—C—H), 3336 (—NH—); ^{1}H NMR (300 MHz, DMSO-d_6, δ): 5.68 (1H, d, C–H of thiazine), 3.31 (1H, m, CH-S of thiazine), 1.55 (3H, d, CH_3 of thiazine) 1.73 (3H, s, CH_3 of thiazine), 7.84–8.02 (4H, m, Ar-SO_2), 7.01–7.77 (5H, m, Ar), 6.02 (2H, s, —NH— of ureido); FAB-MS (m/z): 477 [M^+]; Anal. Calcd for $C_{19}H_{19}N_3O_3S_2$: