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Design, synthesis and evaluation of Schiff bases & thiazolidinone derivatives for anticonvulsant activity

[1]Nikhil Batra*, [2]Shikha Batra, [3]Badri Prakash Nagori

[1,2,3,]Pharmacy Wing, Lachoo Memorial College of Science and Technology, Affiliated to Jai Narain Vyas University, Jodhpur, Rajasthan, India.

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ABSTRACT

A series of 2-oxo-N'-phenylmethylidene-2H-chromene-3-carbohydrazides and their thiazolidinone derivatives were designed on the basis of pharmacophoric distance mapping study of well established anticonvulsant drugs. In another computational study, pharmacokinetic parameters of designed compounds were predicted using Molinspiration Online Property Calculation Toolkit. Structures of all the compounds were confirmed by spectroscopical data. Compounds were evaluated for neurotoxicity by rotorod test. Anticonvulsant activity of test compounds was evaluated by maximal electroshock seizure (MES) animal model of seizures. Test compounds CS-6 and CST-6 were found to possess potent anticonvulsant activity and served as the prototype molecules of the series.

INTRODUCTION

The spectrum of disorders of the brain is large, covering hundreds of either the mental or neurological disorders (Gustavsson, 2011). Epilepsy is one of the most common serious neurological conditions that occur due to either primary genetic abnormalities or as a consequence of a variety of metabolic and structural disorders of the brain (Christopher *et al.,* 2010). It is characterized by recurrent episodes of sensory, motor or autonomic phenomena with or without loss of consciousness (Viteri *et al.,* 2010). This disease is estimated to affect over 60 million people worldwide (Neligan and Sander, 2013) and in the general population, 4-10 per 1000 people have active epilepsy (Viteri *et al.,* 2010). In India, the prevalence rate of epilepsy varies between 4.15 and 7.03 per 1000 population (Das *et al.,* 2007).

Several consequences of epilepsy contribute to the mediocre quality of life in subjects with epilepsy, including worry about seizures, functional impairment, educational handicap, difficulties with relationships and depression (Allain *et al.,* 2007). In addition, the side effects like drowsiness, ataxia, blurred vision & diplopia associated with current antiepileptic drugs (AEDs) may contribute to poor quality of life (Allain *et al.,* 2007; Ali *et al.,* 2012). Despite ongoing development of several new antiepileptic drugs (AEDs) over the past two decades approximately 40 % of patients with epilepsy exhibit resistance to pharmacotherapy and the development of Pharmaco-Resistant Epilepsy (PRE) exacts an enormous toll on patients and their families, while the loss of employment potential and cost of medical care has a substantial impact on society (Alexopoulos, 2013). Furthermore, there is currently no drug available which prevents the development of epilepsy. Thus, there are three important goals with reference to this disease: (1) Better understanding of basic mechanisms of the processes leading to epilepsy, thus allowing to create therapies aimed at the prevention of epilepsy in patients at risk; (2) improved understanding of biological mechanisms of pharmaco-resistance, allowing to develop drugs for reversal or prevention of resistance; and (3) development of disease-modifying therapies, inhibiting the progression of epilepsy (Loscher, 2002).

Schiff bases represent an important class of organic compounds owing to their wide range of biological activities and industrial applications. They are characterized by the presence of azomethine group and formed by the condensation of primary amines with aldehydes or ketones. Schiff bases derived from various heterocycles have been reported to possess a variety of

* *Corresponding Author*
E-mail: nikhilpharmacy@yahoo.com
Mobile: 098280-80833; Fax: 0291-2431820

biological activities including anticancer (Singh *et al.,* 2007; Hranjec *et al.,* 2011; Hu *et al.,* 2012), antioxidant (Chinnasamy *et al.,* 2010; Zhang *et al.,* 2011; Zhang *et al.,* 2013), antiglycation (Khan *et al.,* 2009), antimicrobial (Khanmohammadi *et al.*,2008; Amin *et al.,* 2012; Mange *et al.,* 2013), antimalarial (Kalkanidis *et al.,* 2002), and antiviral activities (Krishnan *et al.,* 2010; Sriram *et al.,* 2006). Apart from these pharmacological activities, Schiff bases of different heterocycles are also found to exhibit CNS activities (Sameem *et al.,* 2012; Chaubey and Pandeya, 2012; Pandeya and Rajput 2012; Saravanan *et al.*,2012; Shaquiquzzaman *et al.,* 2012; Thomas *et al.*,2011; Tripathi *et al.*,2011; Chinnasamy *et al.*,2010; Shingalapur *et al.,* 2010; Bahar and Yusuf 2010; Karakurt *et al.,* 2010; Bhat and Al-Omar 2010; Kulandasamy *et al.*,2009; Azam *et al.,* 2009; Sharma *et al.*,2009, Verma *et al.,* 2004; Yogeeswari *et al.,* 2004; Sridhar *et al.,* 2002).

This paper presents the design and synthesis of Schiff bases (2-oxo-N'-phenylmethylidene-3,4-dihydro-2*H*-chromene-3-carbohydrazides) & thiazolidinone derivatives and their evaluation for anticonvulsant activity. Structures of compounds were characterized using IR, ^{1}H-NMR and Mass spectroscopy and anticonvulsant activity was evaluated by maximal electroshock seizure (MES) animal model. The rotorod assay was performed in mice to evaluate the neurotoxicity of synthesized compounds.

MATERIAL AND METHODS

ACD/ ChemSketch (Product 12.01), Accelrys Discovery Studio Version 2.1, Argus Lab 4.0 Mark Thompson Planaria Software LLC and Molinspiration Online Property Calculation Toolkit were used for computational studies. For synthesis of titled compounds, starting chemicals and solvents were procured from chemical suppliers and were of laboratory grade. Melting points were determined by open capillary method and uncorrected. The purity of compounds and progress of the reactions were checked by TLC using silica gel-G as adsorbent. IR spectra were recorded on Bruker ATR Spectrometer. 1H-NMR spectra were recorded on Brucker 400 MHz NMR spectrometer; chemical shifts are given in δ values (ppm) using TMS as an internal standard and deuterated dimethylsulphoxide (DMSO) was used as solvent. Mass spectra were recorded on Micromass spectrometer.

Pharmacophoric distance mapping

This study was performed to correlate the structural requirements of well known and structurally different anticonvulsant drugs with the titled compounds. Earlier studies had identified that the existence of a lipophilic aryl ring, an electron donor group and hydrogen bonding domain are essential for anticonvulsant activity as also evidenced by well established anticonvulsant drugs like phenytoin, mephobarbital, carbamazepine or lamotrigine which fulfil these demands. Two dimensional modelling and SAR studies of potential anticonvulsant agents proposed four essential pharmacophoric elements for anticonvulsant activity. These elements include at least one aryl group which acts as a lipophilic domain, one or two electron donor atoms and/or an NH group in a special spatial arrangement which acts as a hydrogen bonding domain and a hydrophobic centre (Dimmock and Pandeya, 1995; Pandeya *et al.,* 2000; Unverferth *et al.,* 1998).

All the titled compounds were confirmed for the presence of pharmacophoric elements that were found to be essential for good anticonvulsant activity in earlier studies and also present in well established and structurally different anticonvulsant drugs (Fig 1). Pharmacophoric distance mapping study of seven established anticonvulsant drugs (phenytoin, mephobarbital, carbamazepine, gabapentin, progabide, ralitoline and zonisamide) and titled compounds was carried out to confirm that whether the titled compounds fulfil the requirements of pharmacophore when compared to the average distances among the essential elements present in established anticonvulsant drugs (Figure 2).

Structures of selected anticonvulsant drugs were drawn using ChemSketch and energy minimization was performed by applying CHARMm force field using Discovery Studio 2.1. Distances among the essential elements were determined using Argus Lab 4.0 Mark A. Thompson Planaria Software LLC and average distances & distance ranges for these elements were calculated (Table 1). Distances among the pharmacophoric elements of designed Schiff bases and thiazolidinone derivatives were also determined by following the same procedure and compared with the distance ranges of anticonvulsant drugs.

Prediction of pharmacokinetic parameters

Another computational study of titled compounds was performed for prediction of pharmacokinetic parameters such as percentage absorption (% ABS), Topological Polar Surface Area (TPSA) (Ertl *et al.,* 2000), Molecular Weight (MW), Molecular Volume (MV), number of rotational bonds (n-ROTB), number of hydrogen bond donors (n-OHNH) & number of hydrogen bond acceptors (n-ON) and violations of Lipinski's rule of five (Lipinski *et al.,* 2001) were calculated using online available Molinspiration Property Calculation Toolkit (Available at: http://www.molin spiration. com) (Table 2). Percentage absorption was calculated by % ABS = 109 - (0.345 X TPSA) (Zhao *et al.,* 2002).

Synthesis of Schiff bases and thiazolidinone derivatives

Schiff bases and thiazolidinone derivatives were synthesized in below mentioned steps and scheme is presented in Figure 3.

Step 1: Synthesis of ethyl-2-oxo-2H-chromene-3-carboxylate (1)

Salicylaldehyde (1.22 g, 0.01 mol) and diethylmalonate (1.6 g, 0.01 mol) were taken in 250 ml RBF and dissolved in 150 ml of absolute ethanol to give clear solution. 2 ml of piperidine was added to this solution and refluxed on water bath for 5-6 hrs. Completion of reaction was monitored by TLC. After completion of reaction, reaction mixture was concentrated to half of the volume and allowed to cool. Then this mixture was poured onto crushed ice and stirred well. Solidified product (1) was filtered out and crystallized from ethanol to give white shiny crystals.

Compound was found to be TLC pure (toluene: ethyl acetate: formic acid, 5:4:1, v/v/v); m.p. 121-122°C; Yield: 92%; IR (ATR) cm^{-1}: 1760 (C=O, ester), 1651(CO, coumarin), 1197 (C-O).

Step 2: Synthesis of 2-oxo-2H-chromene-3-carbohydrazide (2)

Ethyl-2-oxo-2H-chromene-3-carboxylate (1.9g, 0.01mol) and hydrazine hydrate (1 ml, 0.01 mol) were dissolved in 150 ml of absolute ethanol and refluxed on water bath for 8-10 hrs. Completion of reaction was monitored by TLC. After cooling, reaction mixture was poured into ice cold water. Solidified product was filtered out and crystallized from ethanol to give yellow crystals. Compound was found to be TLC pure (toluene: ethyl acetate: formic acid, 5:4:1, v/v/v); m.p. 138-140°C; Yield: 87%; IR (ATR) cm-1: 3348 (1° NH2), 3278 (2° NH), 1688 (C=O, amide), 1598 (CO, coumarin).

Step 3: General procedure for synthesis of Schiff Bases (CS-1 to CS-9)

2-oxo-2H-chromene-3-carbohydrazide (0.01 mol) and an aromatic aldehyde (0.01 mol) were dissolved in 200 ml of absolute ethanol. 0.2 ml of glacial acetic acid was added to this reaction mixture and refluxed on water bath for 10-12 hrs. Completion of reaction was monitored by TLC. The mixture was then cooled and poured onto crushed ice. Separated solids were filtered, dried and crystallized from ethanol to give light yellow to pale yellow coloured compounds.

CS-1: Yellow solid, crystallized from ethanol, yield 76%, m.p. 146-148°C, IR (ATR) cm^{-1}: 3284 (2° NH), 1690 (C=O, amide), 1602 (CO, coumarin), 1473-1560 (C=N str); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.98-7.87 (m, Ar-H), 9.00 (s, 1H, =NNH), 8.80 (s, 1H, CH=N), 5.75 (s, 1H, C-4 of coumarin); Mass: m/z 292 (M^+).

CS-2: Yellow solid, crystallized from ethanol, yield 67%, m.p. 154-157°C, IR (ATR) cm^{-1}: 3243 (2° NH), 1698 (C=O, amide), 1605 (CO, coumarin), 1443-1516 (C=N str); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.97-7.87 (m, Ar-H), 9.38 (s, 1H, =NNH), 8.81 (s, 1H, CH=N), 5.56 (s, 1H, C-4 of coumarin); Mass: m/z 337 (M^+).

CS-3: Yellow solid, crystallized from ethanol, yield 68%, m.p. 154-156°C, IR (ATR) cm^{-1}: 3264 (2° NH), 1693 (C=O, amide), 1599 (CO, coumarin), 1444-1558 (C=N str); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.87-7.87 (m, Ar-H), 9.18 (s, 1H, =NNH), 8.92 (s, 1H, CH=N), 5.57 (s, 1H, C-4 of coumarin).

CS-4: Light yellow solid, crystallized from ethanol, yield 71%, m.p. 154-156°C, IR (ATR) cm^{-1}: 3287 (2° NH), 1695 (C=O, amide), 1622 (CO, coumarin), 1445-1517 (C=N str); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.87-7.77 (m, Ar-H), 9.37 (s, 1H, =NNH), 8.72 (s, 1H, CH=N), 5.77 (s, 1H, C-4 of coumarin).

CS-5: Light yellow solid, crystallized from ethanol, yield 70%, m.p. 150-153°C, IR (ATR) cm^{-1}: 3223 (2° NH), 1698 (C=O, amide), 1605 (CO, coumarin), 1443-1516 (C=N str); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.89-7.79 (m, Ar-H), 9.08 (s, 1H, =NNH), 8.85 (s, 1H, CH=N), 5.79 (s, 1H, C-4 of coumarin); Mass: m/z 326 (M^+).

CS-6: Pale yellow solid, crystallized from ethanol, yield 72%, m.p. 151-154°C, IR (ATR) cm^{-1}: 3242 (2° NH), 1690 (C=O, amide), 1602 (CO, coumarin), 1445-1517 (C=N str); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 7.31-7.79 (m, Ar-H), 9.05 (s, 1H, =NNH), 8.82 (s, 1H, CH=N), 5.91 (s, 1H, C-4 of coumarin).

CS-7: Yellow solid, crystallized from ethanol, yield 77%, m.p. 158-160°C, IR (ATR) cm^{-1}: 3144 (2° NH), 1690 (C=O, amide), 1600 (CO, coumarin), 1444-1517 (C=N str); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.94-7.70 (m, Ar-H), 8.99 (s, 1H, =NNH), 8.73 (s, 1H, CH=N), 5.41 (s, 1H, C-4 of coumarin), 2.49 (s, 3H, methyl); Mass: m/z 306 (M^+).

CS-8: Yellow solid, crystallized from ethanol, yield 74%, m.p. 156-159°C, IR (ATR) cm^{-1}: 3193 (2° NH), 1691 (C=O, amide), 1596 (CO, coumarin), 1361-1516 (C=N str); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.95-7.77 (m, Ar-H), 11.54 (s, 1H, -OH), 8.98 (s, 1H, =NNH), 8.38 (s, 1H, CH=N), 5.48 (s, 1H, C-4 of coumarin); Mass: m/z 308 (M^+).

CS-9: Yellow solid, crystallized from ethanol, yield 79%, m.p. 159-162°C, IR (ATR) cm^{-1}: 3258 (2° NH), 1693 (C=O, amide), 1627 (CO, coumarin), 1445-1517 (C=N str); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.88-7.77 (m, Ar-H), 9.37 (s, 1H, =NNH), 8.72 (s, 1H, CH=N), 5.78 (s, 1H, C-4 of coumarin); Mass: m/z 293 (M^+).

Step 3: General procedure for synthesis of thiazolidinone derivatives of Schiff Bases (CST-1 to CST-9)

Equimolar quantities of different Schiff bases (0.005 mol) and merceptoacetic acid (0.005 mol) were refluxed in DMF for 8 hrs in the presence of catalytic amount of anhydrous zinc chloride. Completion of reaction was monitored by TLC. The mixture was then cooled and poured onto crushed ice. Separated solid was filtered, dried and crystallized from ethanol to give yellow to orange brown coloured compounds.

CST-1: Light yellow solid, yield %, m.p. 161-162°C, IR (ATR) cm^{-1}: 3169 (2° NH), 1615 (C=O, amide), 1565 (CO of coumarin and thiazolidinone); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.98-7.87 (m, Ar-H), 9.00 (s, 1H, NH-N), 5.16 (s, 1H, C-4 of coumarin), 2.72 (s, C-2 of thiazolidinone), 2.32 (s, C-4 of thiazolidinone); Mass: m/z 366 (M^+).

CST-2: Brown solid, yield %, m.p. 162-164°C, IR (ATR) cm^{-1}: 3260 (2° NH), 1613 (C=O, amide), 1566 (CO of coumarin and thiazolidinone); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.98-7.87 (m, Ar-H), 9.01 (s, 1H, NH-N), 5.12 (s, 1H, C-4 of coumarin), 2.72 (s, C-2 of thiazolidinone), 2.32 (s, C-4 of thiazolidinone); Mass: m/z 411 (M^+).

CST-3: Pale yellow solid, yield %, m.p. 162-164°C, IR (ATR) cm^{-1}: 3243 (2° NH), 1689 (C=O, amide), 1604 (CO of coumarin and thiazolidinone); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.80-7.69 (m, Ar-H), 8.97 (s, 1H, NH-N), 5.12 (s, 1H, C-4 of coumarin), 2.67 (s, C-2 of thiazolidinone), 2.29 (s, C-4 of thiazolidinone).

CST-4: Yellow solid, yield %, m.p. 164-165°C, IR (ATR) cm^{-1}: 3360 (2° NH), 1613 (C=O, amide), 1566 (CO of coumarin and thiazolidinone); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.99-7.69

(m, Ar-H), 8.92 (s, 1H, NH-N), 5.12 (s, 1H, C-4 of coumarin), 2.67 (s, C-2 of thiazolidinone), 2.29 (s, C-4 of thiazolidinone).

CST-5: Yellow solid, yield %, m.p. 158-161°C, IR (ATR) cm^{-1}: 3185 (2° NH), 1704 (C=O, amide), 1613 (CO of coumarin and thiazolidinone); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.92-7.69 (m, Ar-H), 8.87 (s, 1H, NH-N), 5.12 (s, 1H, C-4 of coumarin), 2.67 (s, C-2 of thiazolidinone), 2.30 (s, C-4 of thiazolidinone); Mass: m/z 400 (M^+).

CST-6: Pale yellow solid, yield %, m.p. 158-160°C, IR (ATR) cm^{-1}: 3352 (2°NH), 1678 (C=O, amide), 1594 (CO of coumarin and thiazolidinone); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.96-7.69 (m, Ar-H), 9.21 (s, 1H, NH-N), 5.13 (s, 1H, C-4 of coumarin), 2.71 (s, C-2 of thiazolidinone), 2.35 (s, C-4 of thiazolidinone).

CST-7: Yellow solid, yield %, m.p. 164-166°C, IR (ATR) cm^{-1}: 3360 (2° NH), 1613 (C=O, amide), 1566 (CO of coumarin and thiazolidinone); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.94-7.70 (m, Ar-H), 8.99 (s, 1H, NH-N), 5.33 (s, 1H, C-4 of coumarin), 2.71 (s, C-2 of thiazolidinone), 2.38 (s, C-4 of thiazolidinone), 2.15 (s, 3H, CH_3); Mass: m/z 380 (M^+).

CST-8: Light yellow, yield %, m.p. 155-157°C, IR (ATR) cm^{-1}: 3324 (-OH), 1608 (C=O, amide), 1516 (CO of coumarin and thiazolidinone); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.94-7.70 (m, Ar-H), 11.12 (s, 1H, -OH), 8.96 (s, 1H, NH-N), 4.96 (s, 1H, C-4 of coumarin), 2.70 (s, C-2 of thiazolidinone), 2.35 (s, C-4 of thiazolidinone); Mass: m/z 382 (M^+).

CST-9: Orange brown solid, yield %, m.p. 149-152°C, IR (ATR) cm^{-1}: 3226 (2° NH), 1615 (C=O, amide), 1568 (CO of coumarin and thiazolidinone); ^{1}H-NMR (400 MHz, DMSO- d_6) δ ppm: 6.94-7.70 (m, Ar-H), 9.16 (s, 1H, NH-N), 5.22 (s, 1H, C-4 of coumarin), 2.74 (s, C-2 of thiazolidinone), 2.41 (s, C-4 of thiazolidinone); Mass: m/z 367 (M^+).

Pharmacology

Evaluation of anticonvulsant activity and neurotoxicity of synthesized compounds were undertaken by the established procedures and had been approved by the Institutional Animal Ethical Committee (Reg.No.541/02/C/CPCSEA).

Neurotoxicity

Rotorod test was performed to test the neurotoxicity of test compounds (Krall *et al.*, 1978). Albino mice were firstly trained to stay on an accelerating rotorod of rotorod apparatus having six compartments (Model: 2195-D; Make: HICON, Grover Enterprises, Delhi). Rotorod was set to rotate at ten revolutions per minute. Trained animals were given *i.p.* injection of the test compounds in doses of 30, 100 and 300 mg/ kg and monitored for overt signs of minimal muscular impairment (MMI) or minimal neurological impairment (MNI). Neurotoxicity was indicated by inability of the animals to maintain equilibrium on the rod for at least one minute in each of the three trials.

Maximal Electro Shock (MES) model

MES model is the best-validated preclinical model for predicting the effective of compounds against generalized tonic clonic seizures or grand mal type of epilepsy. It permits evaluation of the ability of a test substance to prevent the seizure spread through neural tissues (Swinyard and Kupferberg 1985; Castel-Branco *et al.*, 2009)

In this model, adult Albino rats of Wistar strain of either sex weighing 180-200 gm were used. The animals were divided into five groups (control, standard and three groups receiving test compounds) and each group comprised of six rats. Animals of test groups were pre-treated with *i.p.* injection of three different doses (30, 100 and 300 mg/kg body weight) of test compounds suspended in 0.5 % aqueous methyl cellulose solution. Phenytoin sodium was used as a standard drug which was given in the dose of 30 mg/kg by *i.p.* to the animals of standard group which were observed for 100% protection against the induced convulsions. Control group received only 0.5 % aqueous methyl cellulose suspension.

The seizures were induced by electroconvulsiometer (Model: KI-9531; Make: Swastika Electric and Scientific Works, Ambala Cant, Haryana). Animals were subjected to electroshock by delivering the current of 150 mA through ear electrodes for a period of 0.2 seconds and observed for convulsive responses at 0.5 and 4.0 hours from the time of administration of substances. Different stages of convulsions *i.e.* the tonic flexion (towards the upper extremities), tonic extensor phase (extension of lower extremities), clonic convulsions (intermediate jerking of limbs), stupor (unconsciousness) and recovery or death were observed for each animal and time of hind limb tonic extensor phase was noted down in seconds and average time of each group for phase was converted into % protection (Table 3) by below mentioned formula:

$$\% \text{ Protection} = \frac{(\text{Control} - \text{Test}) \times 100}{\text{Control}}$$

Anticonvulsant activity of test compounds was assessed by reduction or absence of hind limb tonic extensor phase of the seizure. The % protection observed at 0.5 hour from the time of administration of test compounds was used to calculate the Effective Median Doses (ED_{50} values) for each test compound. Biological activity data were converted into negative logarithmic molar concentration of Effective Median Doses (pED50) using $pED50 = - \log (ED50 \times 10^{-6})$ formula.

RESULT AND DISCUSSION

Pharmacophoric distance mapping study revealed that the designed Schiff bases and thiazolidinone derivatives fulfil the requirements of pharmacophore for having anticonvulsant activity as the distances among the pharmacophoric elements of synthesized compounds were found to be in the distance ranges of established anticonvulsant drugs. Another computational study - prediction of pharmacokinetic parameters indicated that the synthesized compounds exhibited good percentage of absorption ranging from 65.73 to 84.28 and not a single compound violated

the Lipinski's rule of five. On the basis of these computational studies, it was decided to synthesize the designed compounds and to evaluate them for anticonvulsant activity.

Designed Schiff bases and thiazolidinone derivatives were synthesized and characterized on the basis of their M.P., R_f values, IR, ^{1}H NMR and MASS spectra. Synthesized compounds were evaluated for neurotoxicity by rotorod test in mice and were found to be safe as no overt signs of MMI or MNI were observed. Then these compounds were evaluated for anticonvulsant activity by MES model in Albino rats and were found to possess the mentioned activity. Test compounds CS-6 and CST-6 provided considerable protection against seizures and considered as the prototype molecules of the series and their ED_{50} values were found to be lesser than 150 µmol/kg. Test compounds CS-7, CS-8, CST-1, CST-4, CST-5 and CST-7 provided good protection against seizures, ED_{50} values were found to be lesser than 200 µmol/kg and considered as the compounds possessing good activity. Test compound CST-9 was found to be the least active compound of the series with the highest ED_{50} value. Observed activity of test compounds CS-6, CS-7, CS-8, CST-5, CST-6 and CST-7 can be correlated with their good absorption profile and calculated optimum log p values. On comparison of activities of CST-1, CST-2, CST-3 and CST-4, it was observed that the presence of nitro group at para position is more suitable than the ortho and meta positions. But, on comparison of activities of CST-1 and CST-4, it was found that the presence of nitro group even at para position provided the lesser active compound than the compound without nitro group on aryl ring indicating that the presence of nitro group is responsible for reduction in anticonvulsant activity. Results of biological activity of CS-6 and CST-6 indicated that the presence of chloro group at para position of aryl ring in synthesized compounds is the most suitable place for observing highest activity. However, presence of methyl & hydroxy groups in Schiff bases and presence of nitro, chloro and methyl groups in thiazolidinone derivatives also provided good activity. Test compounds CS-5 and CS-6 both possessed the electron withdrawing chloro group but CS-6 possessing this group at para position was found to be more potent than CS-5 possessing same the group at ortho position indicating para position as the appropriate position for electron withdrawing groups.

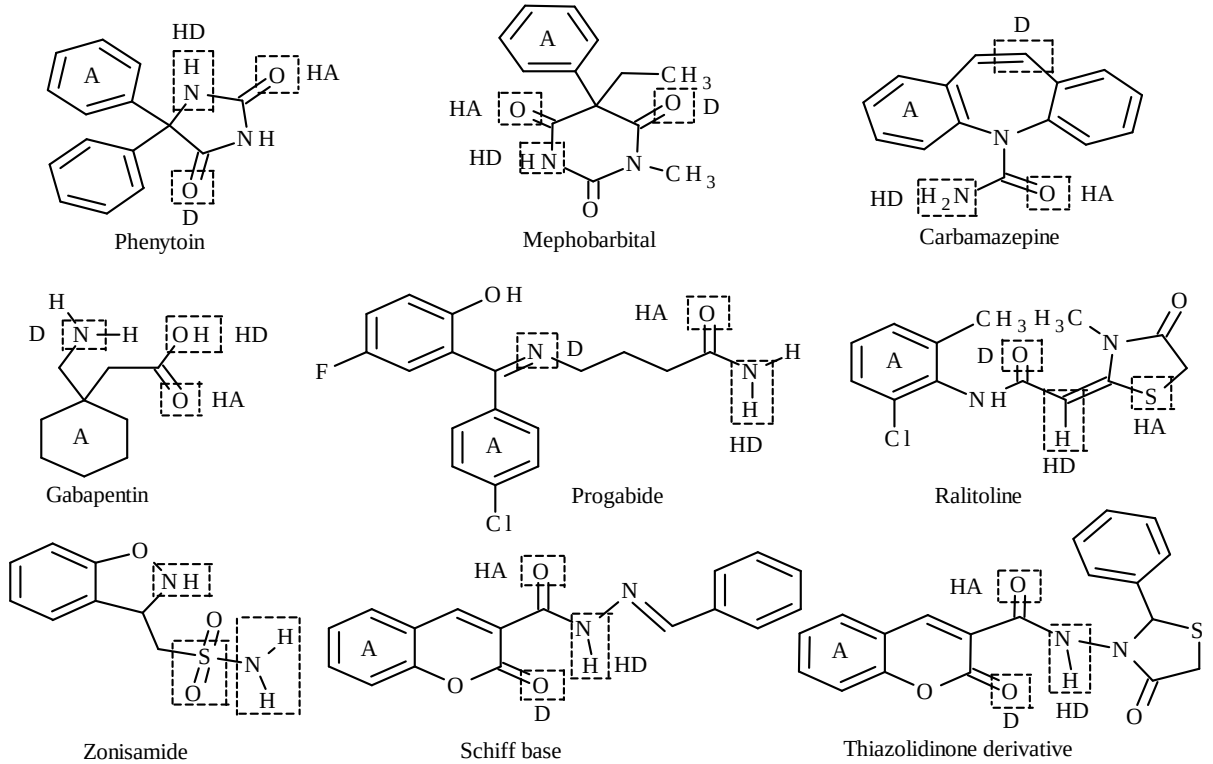

Fig. 1: Pharmacophoric pattern of anticonvulsant drugs and titled compounds showing the presence of pharmacophoric elements.

Table. 1: Distances among the essential pharmacophoric elements (A, HA, D and HD) of anticonvulsant drugs and titled compounds.

Compounds	A-HA	A-HD	A-D	HA-HD	HA-D	HD-D
Phenytoin	5.43	3.64	4.20	2.26	4.50	3.51
Mephobarbital	4.15	4.64	3.73	2.23	4.76	4.01
Carbamazepine	5.79	5.35	3.64	2.17	4.04	4.34
Gabapentin	3.25	3.06	3.75	2.24	2.83	3.65
Progabide	4.25	5.93	3.06	2.25	3.16	3.54
Ralitoline	3.35	2.82	4.74	2.70	4.65	2.31
Zonisamide	4.46	4.26	3.34	1.71	3.68	3.64
Average Distance	4.38	4.24	3.78	2.22	3.94	3.57
(Range)	(3.25-5.79)	(3.64-5.93)	(3.06-4.74)	(1.71-2.70)	(2.83-4.76)	(2.31-4.34)
Schiff base	5.62	5.80	4.76	2.25	3.24	3.67
Thiazolidinone derivative	5.44	5.67	4.76	2.24	3.03	3.94

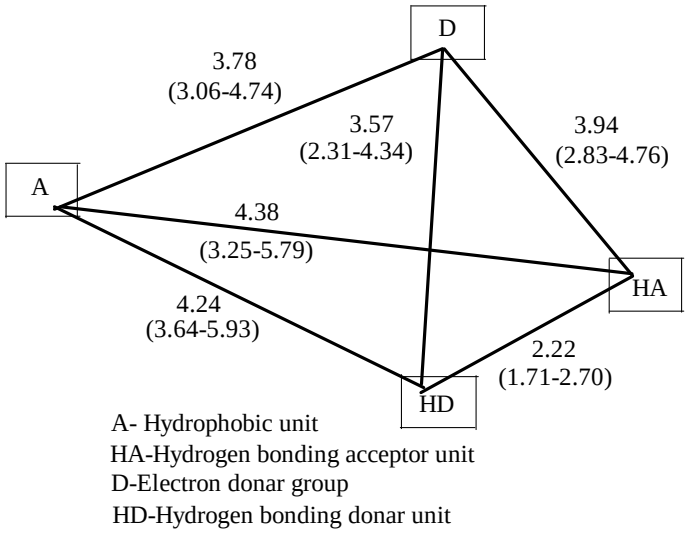

Fig. 2: Average distances and distance ranges for pharmacophoric elements of anticonvulsant drugs.

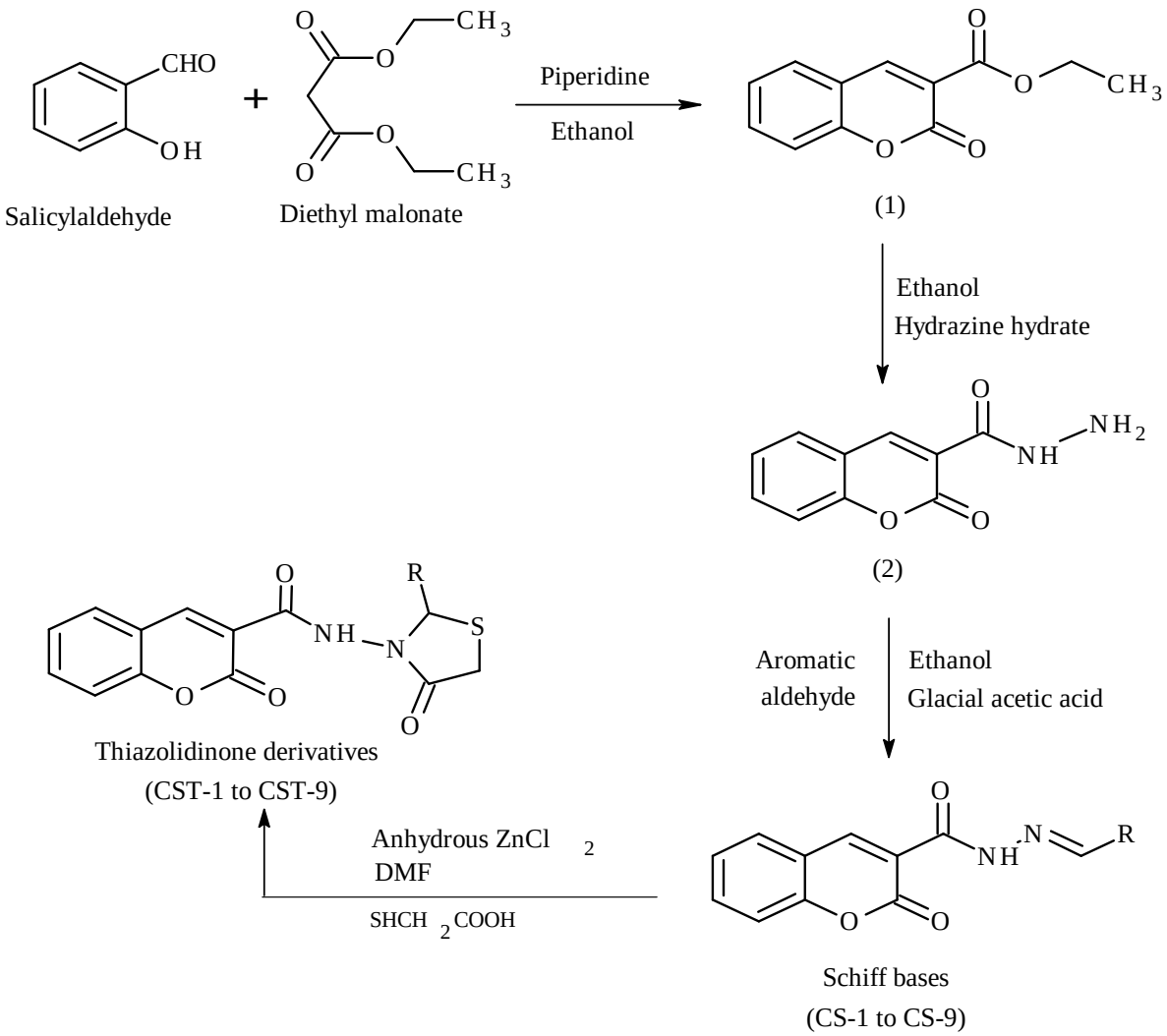

Fig. 3: Synthetic pathway for Schiff bases and thiazolidinone derivatives.

Table. 2: Pharmacokinetic parameters, number of violations of Lipinski's rule of five and miLog *P* of titled compounds.

Rule	-	-	-	<500	-	-	<5	<10	≤1	≤5
Code of compound	R	% ABS	TPSA (A^2)	MW	MV	n-ROTB	n-OHNH donors	n-ON acceptors	Lipinski's violation	miLog *P*
CS-1	$-C_6H_5$	84.28	71.67	292.29	254.64	3	1	5	0	3.10
CS-2	$2-NO_2C_6H_5$	68.47	117.49	337.29	277.97	4	1	8	0	3.01
CS-3	$3-NO_2C_6H_5$	68.47	117.49	337.29	277.97	4	1	8	0	3.03
CS-4	$4-NO_2C_6H_5$	68.47	117.49	337.29	277.97	4	1	8	0	3.06
CS-5	$2-ClC_6H_5$	84.28	71.67	326.73	268.17	3	1	5	0	3.73
CS-6	$4-ClC_6H_5$	84.28	71.67	326.73	268.17	3	1	5	0	3.78
CS-7	$4-CH_3C_6H_5$	84.28	71.67	306.32	271.20	3	1	5	0	3.55
CS-8	$4-OHC_6H_5$	77.30	91.90	308.29	262.65	3	2	6	0	2.62
CS-9	$-C_5H_5N$	79.83	84.56	293.28	250.48	3	1	6	0	1.81
CST-1	$-C_6H_5$	81.54	79.61	366.39	304.06	3	1	6	0	1.40
CST-2	$2-NO_2C_6H_5$	65.73	125.44	411.39	327.39	4	1	9	0	1.31
CST-3	$3-NO_2C_6H_5$	65.73	125.44	411.39	327.39	4	1	9	0	1.33
CST-4	$4-NO_2C_6H_5$	65.73	125.44	411.39	327.39	4	1	9	0	1.36
CST-5	$2-ClC_6H_5$	81.54	79.61	400.84	317.60	3	1	6	0	2.03
CST-6	$4-ClC_6H_5$	81.54	79.61	400.84	317.60	3	1	6	0	2.08
CST-7	$4-CH_3C_6H_5$	81.54	79.61	380.42	320.62	3	1	6	0	1.85
CST-8	$4-OHC_6H_5$	74.56	99.84	382.39	312.08	3	2	7	0	0.92
CST-9	$-C_5H_5N$	77.09	92.51	367.386	299.908	3	1	7	0	0.115

(% ABS, percentage of absorption; TPSA, topological polar surface area; MW, molecular weight; MV, molecular volume; n-ROTB, number of rotatable bonds; n-OHNH, number of hydrogen bond donors; n-ON, number of hydrogen bond acceptors).

CONCLUSION

Present study highlights the importance of the structural features responsible for the anticonvulsant activity. Schiff bases bearing electron donating groups like methyl and hydroxyl and thiazolidinone derivatives having nitro, chloro and methyl groups at para position found to exhibit good anticonvulsant activity against generalized tonic clonic seizures. Considering the structural activity relationships for this class of compounds and analyzing the contribution of different groups at different position to the anticonvulsant efficacy, we could speculate that the nature and position of substituents modulate the activity. The present work may guide the future development of potent and selective anticonvulsant drugs. However further studies on other species of animals with drug-induced epilepsy models is recommended, and comparison with other antiepileptic drugs in different species need to perform to fill the future need of model drug.

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