Panacea Journal of Pharmacy and Pharmaceutical Sciences 2018:7(1);719-734

International Journal

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Panacea Journal of Pharmacy and Pharmaceutical Sciences

ISSN: 2349 7025

Original Research Article **Volume 7 Issue 1**

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NOVEL SCHIFF BASE 1, 3-THIAZINE DERIVATIVES

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Article history:

Received: 25th Feb 2018

Received in revised form: 6th March 2018

Accepted: 20th March 2018

Available online: 31st March 2018

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These author(s) have no conflict of interest to declare.

Abstract:

Although many active anticonvulsant drugs have since been developed, a disturbing co-occurrence with the use of present drugs as single agent has developed drug resistance. This has made use to investigate for new thiazine derivatives for finding more effective anticonvulsant agents. The present investigation, was designed a new series of 2-amino-4-phenyl-6H-1, 3-thiazine indolin-2-one derivatives (3a-j) were synthesized from 1,3-thiazine derivatives. In the beginning acetophenone which underwent Claisen-Schmidt condensation, was dissolved in ethanol and various substituted aromatic aldehydes were added in the presence basic media to afford chalcones (1a-j). Further these various chalcones were subjected to cyclocondensation with thiourea, in ethyl alcohol, catalyzed by aqueous potassium hydroxide to afford 1, 3-thiazine derivatives (2a-j). Now these 1,3-thiazine derivatives were refluxed with substituted isatin catalyzed by glacial acetic acid in ethanol to afford 2-amino-4-phenyl-6H-1,3-thiazine indolin-2-one derivatives (3a-j). The structures of the newly synthesized compounds have been characterized by their infrared spectroscopy, proton nuclear magnetic resonance, ^{13}Carbon nuclear magnetic resonance, mass spectral data and elemental analysis. These newly synthesized compounds were screened for their anticonvulsant activity. Anticonvulsant activity has been done by Maximal electroshock (MES) method and pentylenetetrazole (PTZ) induced method. These compounds were subjected to molecular property prediction, drug-likeness, lipophilicity and solubility parameters determination using Molinspiration, Osiris program was used for prediction of the toxicity.

Keywords: Claisen-Schmidt; 1,3-Thiazines; Schiff Base; Anticonvulsant activity

INTRODUCTION:

Thiazine derivatives are an important class of biologically active compounds was found in most of synthetic compounds. Animal models for seizures and epilepsy have played a fundamental role in advance our perceptive of basic mechanism underlying ictogenesis and epileptogenesis and have been instrumental in the innovation and preclinical expansion of novel antiepileptic drugs (AEDs). However, there is emergent apprehension that the efficacy of drug management of epilepsy has not substantially improved with the introduction of new AEDs, which, at least in part, may be due to the fact that the same straightforward screening models, i.e., the maximal electroshock seizure (MES) and pentylenetetrazole (PTZ) seizure tests, have been used as gatekeepers in antiepileptic drugs invention for more than 6 decades. It has been argued that these old models may identify only drugs that share characteristics with existing drugs, and are unlikely to have effect on noncompliant epilepsies. In fact, accumulating evidence with several novel AEDs, including levetiracetan, has shown that the MES and PTZ models do not identify all potential AEDs but as an alternative may fail to discover compounds that have great potential efficacy but work through mechanisms not tested by these awareness of the limitations of acute seizure models comes at a serious crossroad. To realize this objective the molecular mechanisms of the next generation of therapy must necessarily develop, to include targets that contribute to epileptogenesis and pharmacoresistance in relevant epilepsy models.

The heterocyclic compounds [1] which contain nitrogen, sulphur and oxygen possess an enormous significance in the field of medicinal chemistry. Thiazine derivative moiety showed diverse biological and pharmaceutical profiles such as anticonvulsant [2-3], analgesic, anti-inflammatory & ulcerogenic [4-5], antimicrobial [6-7], anticancer [8-10], anthelmintic [11], antidiabetic [12], antianxiety [13], psychotropic [14], antiviral [15], antitubercular [16], anesthetic [18], insecticidal and pesticidal [17], activities. In the present study we intended to synthesized some novel hydrophobic 1,3-thiazine derivatives for evaluating the anticonvulsant activity. Most of the anticonvulsant agents in therapy comprise a hydrophobic group with urea or urea like functionality (**Fig. 1**). Hydrophobicity assists the molecule to reach the brain by crossing blood brain barrier and also to interact with the target site via the hydrophobic interactions whereas the urea or ureas like functionality for the polar interactions. These structural features of

the existing drugs have become the rationale for designing novel anticonvulsant agent-containing hydrophobic substituted cyclohexyl portions along with polar thiourea moieties. We reported the synthesis of novel hydrophobic 1,3-thiazine derivatives containing electron withdrawing and electron-releasing substituents on the aryl and arylidene rings and without any modification on the thiourea portion to study the effect of such substitutions on anticonvulsant activity.

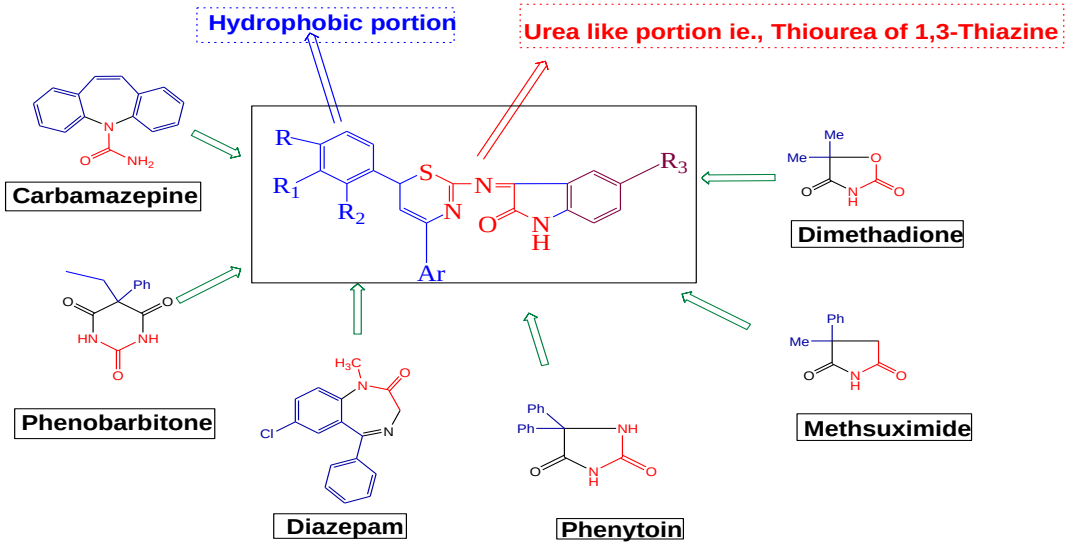

Fig. 1. *Design of hydrophobic group linked 1,3-thiazine analouges for their anticonvulsant activity. Hydrophobic portion shown in blue where as polar urea or urea like portion in red.*

MATERIAL AND METHODS

Experimental section

Chemistry

Melting points were determined by open glass capillary method and are uncorrected. IR spectra

(KBr) were recorded on a Perkin Elmer 1720X FT–IR spectrometer as potassium bromide pellets. IR spectrophotometer, ^{1}H NMR spectra were recorded on a Bruker WM-40 C (400 MHz) FT spectrometer in DMSO-d_6 All NMR spectra used tetramethylsilane as the internal standard and were run in deuterated solvents. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz using the same solvent and internal reference. Mass spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic carbon,

hydrogen and nitrogen analyzer. All chemicals used were reagent grade and were used as received without further purification. Silica gel-G was for TLC. Thin layer chromatography (TLC) was carried out on Merck 5735 Kiesel gel 60 F_{254} fluorescent plates.

Experimental part chemical synthesis

General procedure for the synthesis of chalcones (1a-j)

Acetophenone (0.1M) was dissolved in ethanol (50 ml) and aromatic aldehydes (0.1M) added and then add aqueous sodium hydroxide solution (40%, 10 ml) to the above solution. Then the reaction mixture was stirred mechanically at room temperature for about 2-8 hrs and kept overnight. The solid separate was filtered and washed with ice cold water. The crude product was recrystallized with ethanol acetic acid mixture. The α, β-unsaturated carbonyl group, characteristic of a chalcone[18], were usually appear as a prominent stretching peaks generally fall between 1620-1750 cm-1, a relatively unique part of the IR spectrum. The region at which other absorption bands appear depends on the type of aromatic and heteroaromatic rings as well as the substituents present on these ring system. 1b) UV (λmax): 320 nm; IR (KBr, Cm^{-1}): 1d) 1641(C=O), 1586, 1438(Ar), 1127(C-Cl), 826(C=C).

General procedure for the synthesis of 2-amino-4-phenyl-6H-1,3-thiazine derivatives(2a-j)

Different chalcones (0.01M) dissolved in ethanol (25 ml) were added to thiourea (0.01M). To this aqueous potassium hydroxide solution (0.02M) was added (prepared from KOH in small amount of distilled water). The reaction mixture was refluxed for 3-4 hrs, cooled, diluted with water and acidified with conc. HCl. Then the product was filtered, dried and recrystallized from ethanol. Physical and spectral data of the synthesized compounds.6-(4-methoxyphenyl)-4-phenyl-6H-1,3-thiazin-2-amine [19]. (2b). UV (λmax): 338.50 nm; **IR** (KBr, Cm^{-1}): 3422(-NH_2 Str, Amine), 3075(-CH Str, benzene), 2975(-OCH_3 Str, aliphatic), 2879(-CH Str, Thiazine), 2385(-C-S-C Str, Thiazine), 1707(C=O Str), 1693(C=O Str), 1565(C=N Str), 1178(C-N Str). **^{1}H NMR** (DMSO, δ ppm)**:** 8.13-8.12(2H, Ar-NH_2), 7.75-7.55(10H, Ar-H), 5.27 (1H, Thiazine-CH), 3.49-3.42(3H, -OCH_3). **Mass (EI-MS): m/z=** 296(M), 297(M + 1), 295(M -1).

General procedure for the synthesis of 2-amino-4-phenyl-6H-1,3-thiazine, indolin-2-one derivatives[19] (3a-j)

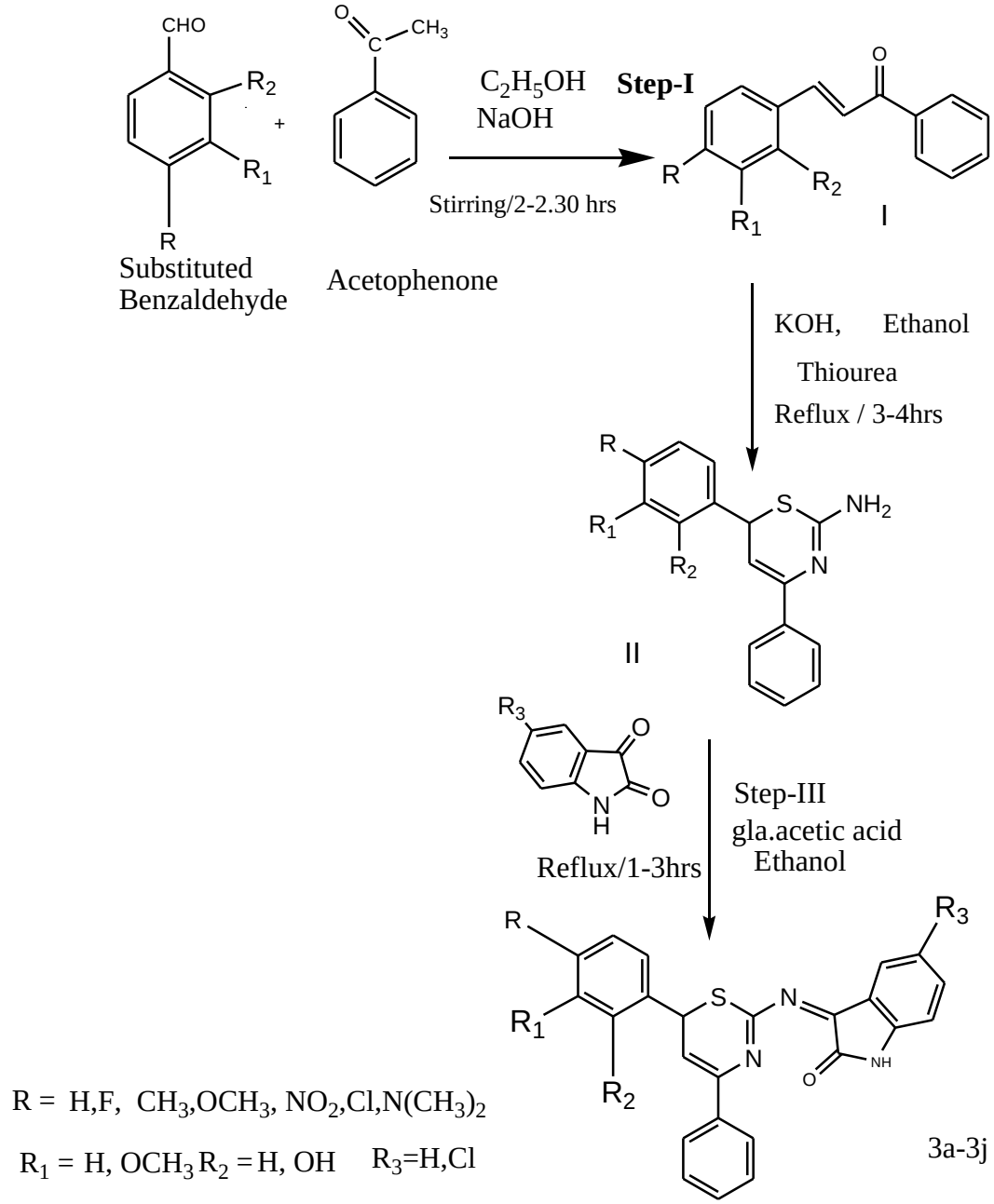

Fig.2. Scheme of work for the title compounds

1,3-thiazine derivatives (compound 2 , 0.01 mol) were taken in a mixture of isatin (0.01 mol) and glacial acetic acid (5 ml) and ethanol(30 ml) then the reaction mixture were under refluxed for 3 hrs. The progress of the reaction has been monitored by TLC (Hexane: Ethyl acetate, 1:4, v/v). Then reaction mixture was cooled to room temperature. A solid residue was obtained, which was filtered, dried and washed with

hexane and recrystallized with methanol to afford analytically pure respective compounds from 3a-3j as crystalline solids.

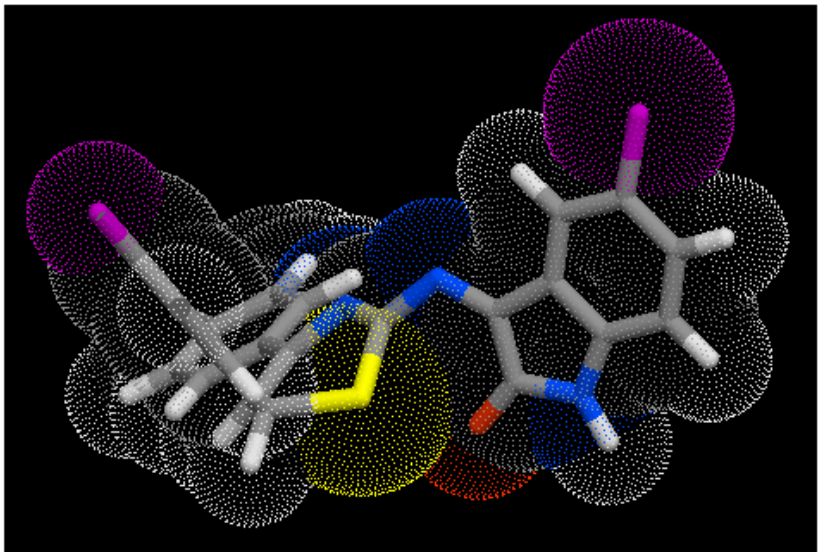

Fig. 3: 3 Dimensional (3D) structural representation of 3h molecule

Spectral data of the synthesized compounds

(Z)-5-chloro-3-(6-(3,4-dimethoxyphenyl)-4-phenyl-6H-1,3-thiazin-2-ylimino) indolin-2-one(3a).

IR (KBr, cm^{-1}): 3498(-NH *Str*), 3017(-CH *Str*), 2972(-OCH_3 *Str*), 2892(-CH *Str*), 2314(-C-S-C *Str*), 1730(C=O *Str*), 1558(C=N *Str*), 1144(C-N *Str*), 1095(C-Cl *Str*). ^{1}HNMR (DMSO-d_6, δ ppm): 11.85(1H, -NH), 7.81-6.89(12H, Ar-H), 4.28(1H, methine-CH), 3.25-3.01(6H, -OCH3). ^{13}C-NMR (DMSO ppm):170.41, 152.74, 143.55, 142.16, 137.11, 136.63, 132.81, 131.42, 123.78, 122.04, 120.90, 111.57, 110.10, 60.20, 53.40. MS (EI-MS) m/z: 489(M), 490(M + 1), 488(M -1).

(Z)-5-chloro-3-(4-phenyl-6-p-tolyl-6H-1,3-thiazin-2-ylimino)indolin-2-one(3d).

IR (KBr, cm^{-1}): 3450(-NH Str), 3103(-CH Str), 2956(-CH_3 Str), 2775(-CH Str), 2391(-C-S-C Str), 1696(C=O Str), 1520(C=N Str), 1127(C-N Str), 1070(C-Cl Str). ^{1}HNMR (DMSO-d_6, δ ppm): 12.85(1H,-NH), 8.65-6.83(12H, Ar-H), 3.32(1H, methine-CH), 2.32(3H, -CH_3). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 168.48, 147.57, 144.41, 136.60, 132.81, 130.00, 123.78, 122.84, 121.91, 120.57, 111.74, 110.93, 108.74, 60.80, 44.74, 40.19. MS (EI-MS) m/z: 443(M), 444(M + 1), 442(M -1).

(Z)-5-chloro-3-(6-(4-methoxyphenyl)-4-phenyl-6H-1,3-thiazin-2-ylimino)indolin-2-one(3e).

IR (KBr, cm^{-1}): 3343(-NH Str), 3063(-CH Str), 2973(-CH_3 Str), 2827(-CH Str), 2333(-C-S-C Str), 1695(C=O Str), 1579(C=N Str), 1166(C-N Str), 1023(C-Cl Str). ^{1}HNMR (DMSO-d_6, δ ppm): 12.86(1H,-NH), 7.40-6.83(13H, Ar-H), 4.34(1H, methine-CH), 3.90-3.71(3H, -OCH_3). MS (EI-MS) m/z: 459(M), 460(M + 1), 458(M -1).

(Z)-5-chloro-3-(6-(2-hydroxyphenyl)-4-phenyl-6H-1,3-thiazin-2-ylimino)indolin-2-one(3g)

IR (KBr, cm^{-1}): 355(-OH *Str*, Ar-OH), 3400(-NH *Str*), 3093(-CH *Str*), 2939(-CH *Str*), 2383(-C-S-C *Str*), 1732(C=O *Str*), 1590(C=N *Str*), 1127(C-N *Str*), 1096(C-Cl *Str*). ^{1}HNMR DMSO-d_6, δ ppm): 12.65(1H,-NH), 7.92-6.91(13H, Ar-H), 5.32(1H, -OH), 4.00(1H, methine-CH). MS (EI-MS) m/z: 445(M), 446(M + 1), 444(M -1).

(Z)-3-(6-(4-chlorophenyl)-4-phenyl-6H-1,3-thiazin-2-ylimino)indolin-2-one (3i).

IR (KBr, cm^{-1}): 3420(-NH *Str*), 3027(-CH *Str*), 2902(-CH *Str*), 2302(-C-S-C *Str*), 1682(C=O *Str*), 1539(C=N *Str*), 1155(C-N *Str*), 1051(C-Cl *Str*). ^{1}HNMR (DMSO-d_6, δ ppm): 12.85(1H,-NH), 7.81-6.54(14H, Ar-H), 4.20(1H, methine-CH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 162.42, 144.46, 137.14, 136.63, 132.81, 130.30, 123.78, 122.32, 121.30, 120.57, 110.10, 109.78, 62.28, 43.34, 41.90. Calculated analysis for: $C_{24}H_{16}ClN_3OS$: C, 67.05; H, 3.75; Cl, 8.25; N, 9.77; O, 3.72; S, 7.46. Found: C: 61.54; H: 6.13; N: 12.36; S: 6.73. MS (EI-MS) m/z: 429(M), 430(M + 1), 428(M -1).

PHARMACOLOGICAL ACTIVITY

Experimental animals

Swiss mice of either sex, 8-10 weeks old, weighing about 25-30g were used in experiment. Animals were housed in polypropylene cages maintained under standard condition (12 hours light / dark cycle; 25 ± 3^0C, 45-65% humidity) and had free access to standard rat feed (Hindustan Liver Ltd., India) and water *adlibitum*. All the animals were acclimatized to laboratory provision for a week before commencement of experimentation; The experimental protocol for the pharmacological screening was done in accordance with the guidelines were reviewed and accepted by an Institutional Animal Ethics Committee (CPCSEA No: 1292/ac/09/CPCSEA) prior to the initiation of the experiment.

Acute toxicity study

The toxicity study was determined in mice by modified method of Lorke [21]. OECD guidelines no. 423 was used for the present oral acute toxicity [22] study. Mice fasted for 16 hrs were indiscriminately divided into groups of 6 mice per group and were orally administered with the synthesized compounds in doses 5, 50 100, 250, 500, 1000 & 2000 mg/kg. The animals were observed for 1 hr after the dosing and further there were daily observed for 14 days for the signs of autonomic and neurological toxicities. The mice were found safe at all the given doses i.e. there were no signs of toxicity or mortality even at 2000 mg/kg. Hence 2000mg/kg was selected as safer dose and 1/10th of 2000 mg/kg i.e. 200 mg/kg was selected for our *in vivo* studies.

Biological Screening

The newly synthesized compounds (3a-3j) were screened to evaluate their anticonvulsant activity. Beginning screening was performed with 200mg/kg of each compound given intraperitoneally after electrical induction of convulsions with maximal electroshocks (MES) [16]. The MES induced model has been used to identify anticonvulsants that are functionally similar to diazepam and activity in this model appear to be highly predictive of the ability to protect against generalized tonic-clonic seizures. The anticonvulsant activity of the newly synthesized compounds was compared to that of diazepam as the reference standard drug at the dose of 10mg/kg.

Anticonvulsant assessment: Electrically-induced seizures

In the electrically-induced seizure model, the Maximal electroshock (MES) method described previously by Swinyard was employed. In short, tonic convulsions of the hind extremities of the rats were induced by passing alternating electrical current of 50 Hz and 150 mA for 0.2 sec through corneal electrodes. The animals were divided randomly into 12 groups containing 6 animals each. Group I served as control group containing normal saline; groups II served as reference standard drug containing diazepam 10mg/kg, injected i.p 15 minutes prior to MES convulsions. 3a, 3b, 3c 3d, 3e, 3f, 3g, 3h, 3i & 3j served as test groups treated with test compounds with dose of 200 mg/kg per oral, respectively administered 1 hour prior to the induction of convulsions. In MES test, values represents number of rats protected divided by number of rats tested. Maximal electroshock produced hind limb tonic extension seizures (HLTE) in rats. The onset of

seizures in seconds, numbers of animals died and percentage mortality is recorded in all groups of rats. The results are represented in table no.1.

Table.1. Maximal Electroshock with single dose by MES in Rats

Entry	Dose in mg/kg	Quantal protection	Mean on set of seizures(seconds)	Mean recovery time (minute)	% of animals protected	% of mortality
3a	200	5/6	6.53± 0.35*	3.51±0.74*	83	16
3b	200	5/6	4.73±0.49	6.46±0.15	83	16
3c	200	5/6	4.79±0.32	5.27±0.10	83	16
3d	200	5/6	5.15±0.73	6.73±0.11	83	16
3e	200	5/6	4.36±0.18	5.92±0.35	83	16
3f	200	5/6	3.12±0.25	6.68±0.16	83	16
3g	200	5/6	3.25±0.96	6.54±0.91	83	16
3h	200	5/6	6.38±0.13*	3.72±0.38*	83	16
3i	200	5/6	6.58±0.36*	3.34±0.49*	83	16
3j	200	5/6	6.71±0.54*	3.29±0.72*	83	16
Control	**-**	0/6	2.21±1.73	-----	0	100
Diazepam	10	6/6	---------	---------	100	0

"Values are expressed as mean ± SEM of each group (n=6) and are significant when done ONE-WAY ANOVA with followed by Dunnett's multiple comparison test. * p <0.05 when compared with disease control."

Pentylenetetrazole (PTZ) Induced Seizures

In PTZ induced seizure model, standard antiepileptic drug diazepam (10 mg/kg) and epilepsy inducer pentylenetetrazole (PTZ) was dissolved in normal saline. Albino mice weighing around 20-25 g were used for the present study. The mice were acclimatized for 30 days under standard laboratory conditions i.e room temperature: 23+28 ^{0}C; relative humidity: 60+5 %; illumination: 12 h light/dark cycles and freely accessed to food and water *adlibitum*. The animals were divided into 12 groups of six mice in each group. All groups were treated subcutaneously with PTZ at dose of 85 mg/kg body weight one hour after test compounds administration and 15 minutes after diazepam treatment. Standard group mice received diazepam injection intraperitoneally at a dose of 10 mg/kg body weight. Synthesized compounds (3a-3j) were administered to test groups of mice at a dose [23] of 200 mg/kg. The parameters that were measured are as follows, onset of seizures in seconds, number of animals died and percentage mortality. Results are expressed by using statistical analysis by Mean ± SEM and analyzed by analysis of variance (ANOVA) with dunnett's multiple comparison tests. Results were considered significant at $p < 0.05$ and their results are summarized in **Table 2**.

Table.2. Anticonvulsant effect of synthesized compounds (3a-3j) by using PTZ induced model convulsions in mice

Compound	Dose in mg/kg	No. of animals treated	Onset of seizures (sec)	No. of animals died	% mortality
3a	200	6	6.72± 0.12*	0	0
3b	200	6	4.27±0.73	2	33.33
3c	200	6	4.82±0.79	2	33.33
3d	200	6	4.72±0.61	2	33.33
3e	200	6	4.12±0.15	2	33.33
3f	200	6	3.52±0.58	2	33.33
3g	200	6	3.73±0.12	2	33.33
3h	200	6	6.21±0.18*	1	16.66
3i	200	6	6.74±0.29*	0	0
3j	200	6	5.92±0.51	1	16.66
Control	-	6	2.16±0.56	6	100
Diazepam	10	6	-	0	0

"Values are expressed as mean ± SEM of each group (n=6) and are significant when done ONE-WAY ANOVA with followed by Dunnett's multiple comparison test. * $p < 0.05$ when compared with disease control."

Estimation of toxicity, lipophilicity and drug score profiles

Actelion developed OSIRIS property explore applet that draws chemical structures and simultaneously calculates on-the-fly various drug-relevant properties, using a fragment-based approach, whenever a structure is valid. The predicted values are shown both as numbers and are coded in colors. The applet predicts log P, solubility and drug-likeness, estimated as proportion of fragments in drugs and various commercially available chemicals.

Table-3: Computationally predicted toxicity risks, lipophilicity and drug score of the title compounds

Entry	Clog P*	Drug score	M.wt	Toxicity risk**
3a	4.9	0.32	489	Negative
3b	5.1	0.19	472	Negative
3c	5.2	0.09	476	Negative
3d	5.5	0.31	443	Negative
3e	5.0	0.34	459	Negative
3f	4.9	0.37	445	Negative
3g	4.9	0.37	445	Negative
3h	5.2	0.33	447	Negative
3i	5.2	0.35	429	Negative
3j	4.4	0.43	425	Negative
3k	4.6	0.41	413	Negative
3l	5.1	0.28	463	Negative

Calculated octanol/water partition coefficients, * Indicating C log P values calculated for the lipophilicity, ** Indicating the mutagenicity, tumorigenicity, irritancy and reproductive effects.

Osiris program was used for forecast of the toxicity of the newly synthesized compounds [24]. The prediction relies on a substructure give the impression of being for route determining the occurrence frequency of any fragment (constructed and core fragments) within any of toxicity classes. The drug score combines C log P, molecular weight and toxicity risks in one handy value that may be used to referee the compounds overall potential to meet the necessities for a drug. Osiris program was used for prediction of the C log P of synthesized compounds. C log P is a well established

parameter to determine the hydrophilicity of the synthesized compounds. Compounds show reasonable probability of being well absorbed, when they have C log P value around 5.0. All the synthesized 1,3-thiazine scaffold derivatives have showed low Insilco possible toxicity risks. From the obtained data, it was observed that all compounds have revealed C log P around 5.0 indicating that the synthesized compounds could be potential drug candidates. prediction of C log P, drug score and toxicity for 1,3-thiazine scaffolds derivatives are prearranged in table 3 and almost all the compounds possess good values of drug score, C log P, and stumpy probable toxicity risks as revealed by computational in silico studies.

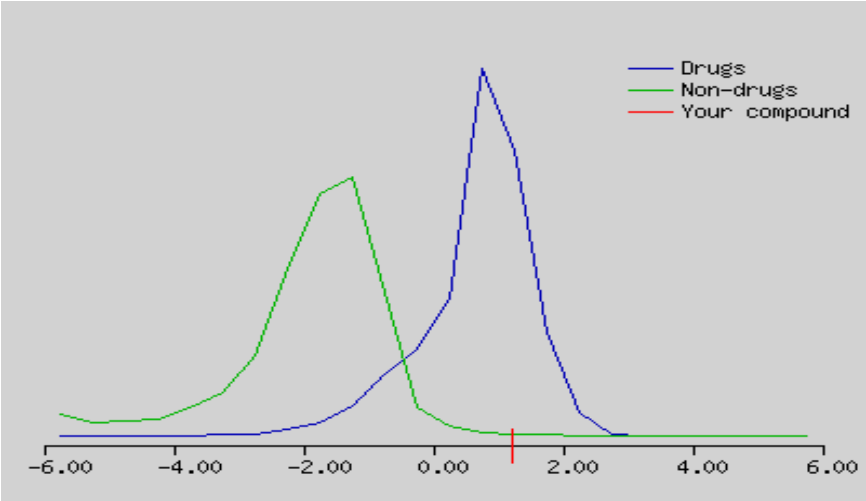

Fig.4. Drug-likeness model score graph of 3j & Non toxic fragment

RESULTS AND DISCUSSION

Chemistry: The conventional method base-catalyzed Claisen- Schmidt condensation followed by Schiff base reaction lead to the synthesis of target compounds. Purification of the synthesized compounds was done by recrystallization employing methanol as solvent. The structural characterization of the compounds was done with the help of spectroscopic studies including IR, proton NMR, 13C NMR, MS and elemental analysis. The spectral data of the synthesized compounds was in accordance with the anticipated structures. The infrared spectra of these compounds give away characteristic –C=O stretching at 1640-1720 cm^{-1}, C=N stretching at 1520-1558 cm^{-1}, and C=C stretching at 1450-1530 cm^{-1}, respectively. The additional C-N stretching at 1144-1166 cm^{-1}, and NH stretching at 3343-3420 cm^{-1}, 3010-3060 cm^{-1}, stretching had established the incidence

of aromatic ring systems. The proton NMR spectra of the synthesized compounds were done by dissolving the compounds in DMSO and two diagnostic doublets in the spectrum around δ 6.6-7.8 and δ 8.8-12.6 ppm for aromatic and NH, respectively, confirmed the formation and other protons exhibited additional resonance signals typically present in each compound. The 13C NMR spectrum of the compounds publicized the characteristic signals around δ 152-172(C-1), 122-130(C-2), 132-143(C-3), and 60-50(C-5). The molecular ion peak in the mass spectrum further depicts the formation of thiazines. The elemental analysis results were within ±5% of the calculated values.

Biology

In MES induced convulsions model in rats it was found that compounds 3a, 3h, 3i and 3j exhibited significant antiepileptic activity by delaying onset of convulsions (6.53± 0.35, 6.38±0.13, 6.58±0.36, 6.71±0.54 seconds) when compared to control (2.21±1.73 seconds) and showing a quick recovery (3.51±0.74, 3.72±0.38, 3.34±0.49, 3.29±0.72 seconds) when compared to control rats (no recovery).

In PTZ induced convulsions model in mice onset of seizures and percentage mortality was used to evaluate antiepileptic potential. It was found that synthesized compounds 3a, 3h, 3i exhibited significant anticonvulsant activity by delaying the onset of seizures (6.72± 0.12, 6.21±0.18, 6.74±0.29 seconds) when compared to control mice(2.16±0.56 seconds). Similarly synthesized compounds 3a, 3h, and 3i exhibited significant anticonvulsant activity by reducing the percentage mortality (0%, 16.66%, and 0%) when compared to control group mice (100%). The other compounds carrying different electron withdrawing and electron releasing substituent were also found to be somewhat potent. In addition a combination of electron withdrawing and releasing groups on the phenyl ring or hetero aryl rings can be synthesized and tested with a hope to get promising anticonvulsant agents.

CONCLUSION

It can be concluded from the study that the anticonvulsant effects of the Structure-activity relationships (**Fig. 1)** based on the above results suggests that 1,3-thiazine scaffolds fused with hydrophobic substituted cyclohexyl portion is essential for the activity. The substituted aryl and arylidene moieties at positions 4th and position8th play

a crucial role in the activity. In particular it was found that if these rings are substituted with electron releasing hydrophobic groups like methoxyl and alkyl groups are essential for the activity. If more number of such groups are present, there is a greater increase in the potency. Presence of hydrophilic hydroxyl groups on the aromatic rings has reduced the activity.

Acknowledgement

The authors extend his appreciation to the management, Vignan Institute of Pharmaceutical Sciences Hyderabad Telangana India for encouragement and for providing the required facilities to carry out this research work. The authors are also thankful to IICT and SIPRA labs Hyderabad for providing mass, NMR spectral data and elemental analysis.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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How to cite this article:

Ravindar Bairam, and Srinivasa Murthy Muppavarap;* Synthesis, characterization and biological evaluation of some novel schiff base 1, 3-thiazine derivatives, *Panacea Journal of Pharmacy and Pharmaceutical Sciences 2018:7(1); 719-734.