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To cite this article: Ganesan Mahendran & Ramachandran Vijayan (2018) Neuropharmacological and molecular docking studies of xanthones from Swertia corymbosa, Journal of Receptors and Signal Transduction, 38:2, 166-177, DOI: 10.1080/10799893.2018.1458875

To link to this article: https://doi.org/10.1080/10799893.2018.1458875

Published online: 16 Apr 2018.

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Neuropharmacological and molecular docking studies of xanthones from Swertia corymbosa

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ABSTRACT
Anxiety represents a public health problem consistently found to be the most prevalent class of mental disorders among people of all ages. Xanthones possess many biological properties, including neuroprotective, antioxidant or antidepressant-like. In this study, we aimed to investigate anxiolytic-like anti-depressant and anticonvulsant properties of isolated xanthones from Swertia corymbosa. We evaluated anxiolytic-like activity of compounds 1–3 in the mouse elevated plus maze (EPM) and open field test (OF). We examined the influence on locomotor activity in mouse to determine if the effect observed in the actophotometer specific. We used step-through rotarod tests to evaluate the motor function and muscle grip. Compounds 1–3 significantly induced an increase in the number of entries into open arms and a decrease in time spent into closed arms at the dose of 50 mg/kg body weight (BW). The compounds also induced increase of rearing and decrease grooming at the doses of 25 and 50 mg/kg BW during the OF test. In addition, compounds induced a significant increase of time taken to enter at the center of the experimental set at the dose of 50 mg/kg BW during the open field test. The compounds 1–3 significantly delayed the onset as well as decreased the pentylenetetrazole and isoniazid-induced seizure tests. Compound 3 pretreatment significantly improved survivals in pentylenetetrazole and isoniazid-induced seizure tests. In silico studies reveal its possible mechanism of action shed on light to develop novel drugs against CNS disorders.

ABBREVIATIONS: CNS: central nervous system; GABA: y-aminobutyric acid; SRIs: serotonin reuptake inhibitors; SNRIs: serotonin-norepinephrine reuptake inhibitors; MAOIs: monoamine oxidase inhibitors

1. Introduction
Anxiety, depressants and antipsychotics disorders are widespread, disabling conditions have been recognized with life-time prevalence and are one of the most common mental disorders [1,2]. Anxiety represents a public health problem consistently found to be the most prevalent class of mental disorders among people at all ages and is associated with a considerable burden of disease, suicide, physical co-morbidity, high economic cost that significantly reduces the quality of life for the patient [1]. The neurobiology of anxiety and epilepsy involve the neurotransmitter y-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the mammalian central nervous system (CNS). Reduction in CNS inhibition is associated with the excessive activity which is experienced as anxiety or in severe cases, epileptic seizures [3]. A therapeutic approach to counter this exacerbated neuronal activity is to increase GABA levels in the brain.

Currently, the treatment for controlling anxiety and reducing stress is monitored by serotonin reuptake inhibitors (SRIs) serotonin-norepinephrine reuptake inhibitors (SNRIs) and monoamine oxidase inhibitors (MAOIs), benzodiazepines are prescribed drugs which have adverse side effects on patients [2,4]. Benzodiazepines act as positive allosteric modulators via a subpopulation of y-amino butyric acid receptors (GABA_A) increasing chloride channel opening [5]. In the brain, GABA is the principal inhibitory neurotransmitter in the mammalian CNS and plays an important role in different physiological phenomena including epilepsy, sleep, anxiety, memory formation and reward [6]. Accordingly, GABA inhibitory inter-neurons function via GABA_A receptor subtypes that are involved in mediating behavior [7].

In our ongoing search for natural neuropharmacological agents, the methanolic extract of Swertia corymbosa was found to possess CNS disorders inhibitors [8]. Swertia, one of the biggest genera of the family Gentianaceae with ~170 species [9] has been found to be a prolific source of xanthones, flavonoid and triterpenoids, of which xanthones are the most abundant [9]. Phenolic constituents from Swertia species have been reported to possess various biological activities, including anti-inflammatory, antibacterial, antioxidant, and anti-HIV properties. Recently, we reported the isolation, structural elucidation and anti-diabetic activity and anti-inflammatory properties of compounds from of S. corymbosa [10,11].

Despite this apparent medicinal value, the psychopharmacological effects of xanthones from S. corymbosa have not been extensively characterized. Thus, the goal of the present study was to screen the psychopharmacological activities of xanthones through established animal models. Rates were given xanthenes compounds and then were subjected to
evaluate the psychomotor, sedative-hypnotic, anxiolytic and anticonvulsant effects of a substance. Finally, molecular modeling study [12,13] was employed to understand the structural features and the key active site residues involved in the molecular interactions with the anti-epileptic and anxiolytic receptors. We also observed the structural changes of the receptors active sites upon drug binding provides insights into the biological interactions may help in the development of potential drugs against psychiatric disorders.

2. Material and methods

2.1. Plant material and isolation

The extraction and isolation of 1,2,8-trihydroxy-6-methoxy xanthone (1), 1,8-dihydroxy-2,6-dimethoxyxanthone (2) and 1,2, dihydroxy-6-methoxyxanthone-8-O-β-D-xylopyranosyl (3) from S. corymbosa was performed according to Mahendran et al. [10,11].

2.2. Animals

Young male albino Swiss mice (18–25 g) and Wistar albino rats (150–200 g) were obtained from the Animal Centre, Department of Pharmacology, Nandha College of Pharmacy and Research Institute. Animals were housed in groups of five per cage (40 × 32 × 17 cm) at a controlled room temperature (22 ± 2°C) and humidity (60–80%) under a 12–12h light–dark cycle. All the studies conducted were approved by the Institutional Animal Ethics Committee of Nandha College of Pharmacy and Research Institute, Department of Pharmacology, and the approval number was 688/02/C/CPCSEA. All efforts were made to minimize animal suffering and to reduce the number of animals used.

2.3. Drugs and chemicals

Diazepam (DZP; Direc-2, Sun Pharmaceutical Industries Ltd., Mumbai, India), Pentyleneetetrazole (PTZ; HiMedia, Mumbai, India) Isoniazid (S.D. Fine Chemicals) were employed. Compounds were dissolved in 0.5% CMC (Carboxy Methyl Cellulose).

2.4. Behavioral tests

2.4.1. Elevated plus maze

Anxiolytic-like activity of compounds (1–3) was measured using the elevated plus maze (EPM) test. EPM was performed as reported earlier [14]. Briefly, Control animals were given a single diazepam was administered via intraperitoneal (i.p.) in a dose of 2 mg/kg 30 min before behavioral tests. Experimental animals were given at the dose of 0.5% saline 30 min before behavioral tests. 0.5% CMC with Compounds (1–3) were administered orally within a dose range of 25 and 50 mg/kg 60 min before the animals were submitted to behavioral evaluation based on the scheduled duration of the treatment. After treatment animals were individually placed at the center of the plus maze with their nose pointing to one of the enclosed arms and observed for 5 min [8]. The number of passes and the time spent in the open and closed arms was recorded during 5 min. After each test, the maze was cleaned with 70% ethanol.

2.4.2. Open field test

The arena was used to assess the exploratory activity of the animal over a 5 min period after the orally administration of compounds 1–3. The open field apparatus is made up of white plywood and measuring 56 × 72 × 36 cm. The entire apparatus was painted black and 6 mm thick white lines divided the floor onto 16 square of identical dimension. The number of squares crossed (with all four paws) and rearing (vertical exploratory activity) containing the parameters were recorded and analyzed as indicative of locomotor behavior. The number of squares crossed, the average speed, the number of entries and distance traveled within the center zone plus the number of entries and distance traveled in the peripheral zone. After 30 min of treatment, the animals were placed, one at a time, in the center of the field for quantification of the number of crossings with four legs (spontaneous locomotor activity), number of self-cleaning behavior (grooming) and the number of lifting (rearing) without abutting the wall during the period of 5 min [15].

2.5. Anticonvulsant activity

2.5.1. Pentyleneetetrazole-induced convulsion test

PTZ-induced convulsions intraperitoneal injection of PTZ (60 mg/kg i.p.) was given to eight groups of mice (n = 6/group) pretreated 30 min prior with varying doses of compounds (25 and 50 mg/kg), saline (10 ml/kg) and diazepam (5 mg/kg). The latency to tonic–clonic convulsions was noted in all groups. The onset and duration of tonic convulsion and time to death for each mouse were recorded. Mice that do not convulse within 30 min of PTZ injection were considered protected [16,17]. Compounds and diazepam-treated groups were compared with a control group in order to find out the significant anticonvulsant effect.

2.5.2. Isoniazid-induced convulsions

In this test, isoniazid (INH) (250 mg/kg, i.p.) was used to induce for seizure. Animals in different groups were separately treated orally with compounds 1–3 at doses of 25 and 50 mg/kg and distilled water (10 ml/kg). The standard group received diazepam (5 mg/kg) 30 min before injection of isoniazid. The onset and duration of convulsion and time to death for each mouse were recorded. Mice that do not convulse within 30 min of isoniazid injection were considered protected [18].

2.5.3. Maximal electroshock-induced convulsions

The animals were divided into five groups, each group comprised six rats. Different groups were treated with distilled water (10 ml/kg), diazepam (5 mg/kg) and compounds 1–3 at doses of 25 and 50 mg/kg. Thirty minutes later, convulsions
were induced by electroconvulsometer. A 60 Hz current of 150 mA for 2 s was supplied on the ear electrodes [19]. The animal was observed for the occurrence of tonic hind-limb extension.

2.6. Assessment of sedative activity

2.6.1. Spontaneous motor activity

The locomotor activity was executed according to the method of Adnaik et al. [20]. The movement of the animal crossings a beam of light falling on a photocell which was recorded [8]. Subsequently, the animals were divided into eight groups, each consisting of six animals. Different groups were treated with distilled water (10 ml/kg), diazepam (2 mg/kg) and compounds 1–3 at doses of 25 and 50 mg/kg body weight (BW). After 60 min, the rat was kept again in the actophotometer for observing the activity for 10 min [20].

2.7. Neurotoxicity by rotarod performance

The equipment of rotarod was used to evaluate motor coordination produced by drugs in animals [21]. The mice were trained before the experiment to acquire the capacity to remain for 300 s on a diameter rod, rotating at 20 rpm. Three trials were enough for the animals to learn this task. Forty-eight mice were divided into eight groups; each group comprised six rats. Different groups were treated with distilled water (10 ml/kg), diazepam (2 mg/kg) and compounds 1–3 at doses of 25 and 50 mg/kg BW. Then, the animals were placed in rotating bar and were observed for a period of five minutes. The difference between the fall-off time of the mice before and after treatment was considered as an index of muscle relaxation [21,22].

2.8. Molecular modeling studies

Four [anti-epileptic (PDB: 3DOW) and serotonin] and anxiolytic (PDB: 1BL8 and 4F12) proteins were selected as targets for docking studies. Anti-epileptic and anxiolytic protein 3D structures were downloaded from the Protein Data Bank. Serotonin (5HT1A) receptor structure has not been crystallized so far. Serotonin-5HT1A from the human sequence (P08908) was retrieved from the Uniprot database (www.uniprot.org). Sequence database search was performed with blast tool in NCBI (www.ncbi.nlm.nih.gov/blast) to identify the known homologous structures from the Protein Data Bank. The coordinates of chimera protein of human 5-hydroxytryptamine receptor-1B and Escherichia coli soluble cytochrome b562 (PDB: 4IAR) were selected as a template to construct the serotonin-5HT1A structure through homology modeling using MODELLER version 9.19 (University of California San Francisco, San Francisco, CA, USA) [23]. The quality of the model was assessed using PROCHECK (EMBL-EBI, Hinxton, Cambridgeshire, UK) to confirm the quality of the stereochernomy of the protein structure [24]. The chemical structure of the isolated compounds and commercial compound were drawn using ChemSketch, version 2015.1 (Advanced Chemistry Development, Inc., Toronto, ON, Canada) (www.acdlabs.com/chemsketch/). All the structures were prepared for docking in SYBYLx 1.2 (Tripos International, St. Louis, MO) by removing the crystallized water molecules, by adding the missing hydrogen atoms and by extracting the ligand. Ligand atom types were assigned according to the Tripos force-field (Tripos International). The binding site was defined by a 10 Å radius sphere around the active center of the pocket using LIGSITE (Germany) [25]. Docking [26] was performed with GOLD 5.1 software (The Cambridge Crystallographic Data Centre, Cambridge, UK) based on genetic algorithm and Auto-Dock, version 4.2 (Molecular Graphics Laboratory, La Jolla, CA, USA) [27] was using the Lamarckian Genetic Algorithm (LGA) with default settings. The AutoDock LGA is a major improvement on the Genetic Algorithm, and both genetic methods are much more efficient on Empirical Binding Free Energy Function than Monte Carlo simulated annealing (SA) method. Docking poses were evaluated and ranked according to the Gold Score. Drug score (pc1664.pharmazie.uni-marburg.de/drug-score/) has been used to calculate based on knowledge-based potentials derived from the observed atom-pair interactions. Results were visualized by PyMOL (Schrodinger, LLC, New York City, NY, USA) and diazepam [28] was used as a reference compound in the docking studies.

2.9. Statistical analysis

Data were analyzed using SPSS Statistics 16.0 software (IBM Corporation, Chicago, IL, USA). Statistical analyses were carried out using one-way analysis of variance (ANOVA) and comparison of means between groups was carried out using Tukey’s post hoc and Newman–Keuls’ post hoc analysis. All data are expressed as mean ± standard error and mean± standard deviation (p < .05, p < .01 and p < .001 were considered significant).

3. Results

3.1. EPM test

The results are summarized in Figure 1(a,b). In the EPM test, the animals treated with a 2 mg/kg dose of diazepam and compounds 1–3 at doses of 25 and 50 mg/kg showed a significant increase in the number of entries and length of stay in the open arms when compared to the control group. We observed that a significant decrease in the time spent in the closed arms at these compounds doses and diazepam compared with control. Also there was an increase in the number of entries into the open arms at all compounds doses and diazepam, but only the value for compounds the dose of 50 mg/kg was significant (p < .001) compared to control (Figure 1).

3.2. Open field test

The results are summarized in Figure 2. In the open field test, there was a decrease in the number of crossings (Locomotor) and groomings and more frequent rearings of diazepam-treated mice compared to the control group. The
animals receiving compounds 1–3 at doses of 25 and 50 mg/kg showed significantly reduction in the number of crossings and groomings.

3.3. Anticonvulsant

3.3.1. Pentylenetetrazole-generalized seizure model
Anticonvulsant effects of compounds 1–3 on PTZ-induced convulsions are shown in Figure 3. The compounds 1 and 3 administered orally at the dose of 50 mg/kg exhibited significant anticonvulsant effects as evident by significantly (p < .01, p < .001, respectively) increased seizure latency respectively. No significant effects were observed at a dose of 25 mg/kg (Figure 3(a)). Newman-Keuls’ post hoc test indicated a statistical significant reduction in the duration of clonic convulsions by the compound 1 and 3 at 50 mg/kg used (p < .01 at 50 mg/kg of compound 1; p < .001 at 50 mg/kg of compound 3) (Figure 3(b)). Standard antiepileptic drug i.e. diazepam (5 mg/kg) was also showed complete protection against PTZ-induced seizures as evidenced by the significantly (p < .001) enhanced seizure latency and reduced duration of convulsions compared to saline treated mice. As shown in Figure 3(c), compound 3 (50 mg/kg) protected 66.66% of mice against the convulsion. No deaths were recorded with diazepam and the compound 3 at 50 mg/kg showed 66.66% compared with control in which 100% mortality was recorded.

3.3.2. Isoniazid-induced convulsions
As shown in Figure 4, compounds 1–3 (25 and 50 mg/kg) and diazepam (5 mg/kg) significant effect (p < .01, p < .001) on the onset of latency and duration of convulsion, death and protection. The duration of convulsion was significantly reduced by the compound 3 at 50 mg/kg compared with control. No deaths were recorded with diazepam and the compound 3 at 50 mg/kg compared with control in which 100% mortality was recorded. At compounds 1 and 2 dose of 50 mg/kg, mortality was 33.33 and 40%, respectively (Figure 4(c)).

3.3.3. Maximal electroshock-induced convulsions
Compounds 1–3 (25 and 50 mg/kg) and diazepam (5 mg/kg) did not elicit significant effect (p > .01) on the onset of convulsion and duration (Figure 5). Contrary to the effect of diazepam and compounds 1–3 at all other doses, the compounds at the dose of 50 mg/kg significantly reduced the duration of convulsion compared with control.

3.4. Measurement of locomotor activity
In actophotometer reading, isolated compounds 1–3 treated were dose dependently reduced (Table 1).

3.5. Rotarod performance
Table 2 showed that the effects of compounds 1–3 from S. corymbosa in the rotarod performance which was used to evaluate motor coordination and muscle gripping effects. The present result revealed that after administration of compounds 1–3 (25 and 50 mg/kg) significantly increased grip and fall on time when compared to control. All the compounds treated animals retained on the rotating rod 197.42 ± 5.46, 196.16 ± 7.16 and 285.35 ± 7.58, respectively at 50 mg/kg as shown in Table 2 indicate compounds to be devoid of neurotoxicity.

3.6. Homology modeling
The target sequence of serotonin was compared with the related family for identity and similarity using BLAST. In the results of BLAST against PDB, the chimera protein of human 5-hydroxytryptamine receptor-1B and E. coli soluble cytochrome b562 (PDB: 4IAR), showed a moderate level of sequence similarity and the identity of serotonin protein with 42.25%. Three-dimensional structure of serotonin was predicted by homology model building (Figure 6) [23]. The geometry of the serotonin model was then evaluated with Ramachandran plot calculations computed with the PROCHECK (EMBL-EBI, Hinxton, Cambridgeshire, UK) program [24]. This revealed that the backbone phi and psi dihedral angles of serotonin are 88.6, 9.4 and 2.0% of the residues are located within the most favorable, additionally allowed, and generously allowed regions, respectively of the Ramachandran plot (Figure 7). Ramachandran plot analysis confirms that the stability of residues is found to be in the core regions of the serotonin structure to be highly reliable for further docking simulation studies. LIGSITE program [25] was used to search the protein-binding sites by locating cavities in the protein structure. Through comparing the conserved residues in the family of well-studied protein and combining the in silico search results,
Figure 2. Effect of the compounds 1–3 on open field test in mice. (a) Latency and time taken to enter central compartment. (b) Locomotion. (c) Grooming and rearing. Control (vehicle): normal water. The data represent the mean ± SE (n = 6). *p < .01, **p < .001 significantly different compared to control.

Figure 3. Effect of isolated compounds 1–3 on PTZ-induced seizures in mice. (a) Onset/latency of seizure. (b) Duration of seizures. (c) Percentage of mortality and protection. Control (vehicle): normal water. The data represent the mean ± SE (n = 6). *p < .01, **p < .001 significantly different compared to PTZ-induced seizure control.
the binding sites of anxiolytic and antiepileptic proteins were predicted. Those results were used to guide the following docking experiment [29].

3.7. Molecular docking

Based on the behavior studies, compound 3 was observed to be a potent inhibitor showing inhibitory effect on behavior studies in mice. We speculate the antioxidant activity of compound 6 might be due to the presence of the free 4'-OH group. To gain more insight on the mode of interaction and binding affinity of compounds 1–3 from *S. corymbosa* along with known standard inhibitor diazepam has been investigated by molecular docking studies [12,13] with monoaminergic, serotoninergic, noradrenergic and GABA receptors. All the three compounds were docked into the active site of anxiolytic and antiepileptic receptors and adopted a unique binding confirmation. These three compounds bind deeply into the pocket and stabilization of the active site occurs through several electrostatic, van der Waals and hydrogen bonding interactions. We have calculated the binding constants of angiolytic (PDB: 1BL8 and 4F12) and anti-epileptic (3D0W and seratonin) receptors with the compounds (diazepam, compound 1, compound 2 and compound 3) and incorporated in Table 3. Docked structures further clearly demonstrates that the relative binding energy of compound 3 for the structures has been found to be 64.4 (Goldscore) and −105 (Drugscore) with serotonin receptor,

![Figure 4](image)

Figure 4. Effect of isolated compounds 1–3 on INH-induced seizure in mice. (a) Latency of seizure. (b) Duration of seizures. (c) Percentage of mortality and protection. Control (vehicle): normal water. The data represent the mean ± SE (*n* = 6). *p < .01, **p < .001 significantly different compared to INH-induced seizure control.

![Figure 5](image)

Figure 5. Effect of isolated compounds on tonic seizures induced by maximal electroshock in mice. (a) Latency of seizure. (b) Duration of seizures. Control (vehicle): normal water. The data represent the mean ± SE (*n* = 6). *p < .01, **p < .001 significantly different compared to maximal electroshock-induced seizure control.
45.72 (Goldscore) and −156 (Drugscore) for GABA type A receptor, 73.68 (Goldscore) and −145 (Drugscore) for GABA type B receptor and 48.96 (Goldscore) and −132 (Drugscore) with KCSA receptor (Table 3). Compound 3 has the highest binding affinity in both anxiolytic and anti-epileptic receptors compared to compound 1, compound 2 and reference compound diazepam (Table 3) (Figures 8–11).

### 4. Discussion

Anxiety-related disorders frequently require a pharmacological approach as a first-line treatment, although, a number of unwanted side effects accompany the currently available therapeutic options [2]. Accordingly, the demand for substitute pharmacological agents is mounting. The aim of the present study was to evaluate the neuropharmacological profile of isolated compounds 1–3 in mice utilizing different anxiety, sedative, epilepsy and motor coordination tests. The EPM is a validated test for the assessment of anxiety in rodents, especially while addressing benzodiazepine-induced anxiolysis. This method may be employed not only for evaluating anxiolytic but also anxiogenic effects of pharmacological agents in rodents [2]. The results obtained with the EPM test showed an increase in the number of entries into and time spent in open arms for the mice receiving the compounds 1–3 of S. corymbosa, when compared with those of the control group; as well as a reduced the number of entries into, and time spent in closed arms as a reduced number of entries into and time spent in closed arms.

Anxiolytic effects of xanthones and its relatively good tolerability have been shown in numerous animal and human studies [30,31]. The increase in the activity in the open arms directly reflects a reduction of anxiety and the reduction in
Docking of anxiolytic (PDB: 1BL8 and 4F12) and anti-epileptic (3D0W and Seratonin) receptors with isolated compounds.

Table 3

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Taken together, in this part of the present research various mouse models of seizures were utilized to study anticonvulsant properties of isolated compounds 1–3. Noteworthy, these screening assays not only identified a novel anticonvulsant agent, but they also allowed predicting its efficacy against different types of seizures in humans [37]. The PTZ-induced seizures model is widely used to detect the anticonvulsant potential of tested compounds. PTZ is known to diminish the activity in the closed arms shows a decrease of stress. The presence of anxiolytic properties was confirmed in the OF test, where compounds increased the crossing at the dose of 50 mg/kg BW and decreased locomotion in the OF at the same dose. These effects observed in the OF suggest anxiolytic properties of the compounds. Bum et al. [32] and Rodgers et al. [33] showed that any compound which increases the crossing and reduces the locomotion produced under the conditions of stress that the OF imposes is anxiolytic. These anxiolytic effects could be mediated by compounds which could act as agonists of benzodiazepines and GABA on the benzodiazepines/GABA receptors; or as antagonists of N-methyl-D-aspartate (NMDA) on the NMDA receptors [34]. These anxiolytic properties could also result from the antagonism of the 5-hydroxytryptamine (5-HT) on its type 2 or type 3 receptors [35].

The OF test also showed an increase of time taken in the center of the OF at the dose of 50 mg/kg and an increase of grooming at the doses of 25 and 50 mg/kg BW. As suggested by Augustsson et al. [36] the increase of grooming and time spent at the center show an increase in the locomotory activity and the level of exploration and consequently a decrease of anxiety. The compounds of S. corymbosa, induced a significant reduction of rearing in the OF at the doses of 25 and 50 mg/kg BW. According to Rodgers et al. [33] this reduction of rearing shows a decrease of the locomotory activity of the animals and could be explained by the sedative properties of the compounds. This result is similar to that obtained by Bum et al. [32] who showed that the decoction of Nauclea latifolia induces a spontaneous reduction of the locomotory activity of the mice. The sedative properties of compounds may be related to activating benzodiazepine and/or GABA receptors in the GABA receptor complex [33].

In addition to anticonvulsant studies, compounds 1–3 were also screened for its acute toxicity as well as its neurotoxicity. The compound was found to be free from acute toxicity i.e. percentage mortality, even though the animals were treated with the 10 time higher dose of the effective dose.
Figure 8. Docked conformation of compound 3 and diazepam with anxiolytic receptor, potassium channel from Streptomyces lividans (PDB: 1BL8).

Figure 9. Docked conformation of compound 3 and diazepam with anxiolytic GABA(B) receptor GBR2 (PDB: 4F12).
Figure 10. Docked conformation of compound 3 and diazepam with anti-epileptic GABA(A) receptor (PDB: 3DOW).

Figure 11. Docked conformation of compound 3 and diazepam with Serotonin 5HT1A model structure.
Antiepileptic effects of drugs are associated with various side effects, including muscle relaxation, ataxia, abnormal gait, sedation and reduced or inhibited righting reflexes in rodents, these effects are commonly termed as neurotoxic effects. These neurotoxic effects can be evaluated by using different pharmacological models like an inverted screen; actophotometer, chimney and rotarod test [38]. In the present study, locomotor count using actophotometer and rotarod test was used to determine neurotoxic effects. The compounds was found to be free from any neurotoxic signs in rotarod test as compared to the saline treated mice respectively. Whereas diazepam showed significant neurotoxic potential at 5 mg/kg, thus compounds observed to be safer anticonvulsant than diazepam.

Docking results further indicated that all three compounds are in close proximity reveals numerous electrostatic, van der Waals and hydrogen bonding interactions between the compounds-receptors complex and therefore exhibit biological activity (Figures 8–11). It has been evident that compounds binding to the receptors due to formation of several interactions, lowered the hydrophilicity that enhances the hydrophobicity to keep the protein ligand complex very stable. Our research findings clearly describe that all three compounds bounds well to anxiolytic and antiepileptic receptors systems are known to play major roles in major depression [39]. However, the GABA system also participates in the antidepressant actions of thiazole-BDZ such as ALP that, in addition to enhancing the release of serotonin (5-HT) in the hippocampus to produce antidepressant actions, may act by means of a GABAergic mechanism that is independent of the BDZ-site receptor [40].

5. Conclusion

In conclusion, the in silico and in vivo experiments study reveals that pharmacological properties of a novel and highly potent isolated compounds 1–3 of S. corymbosa were investigated. We proved that this compound 3 is more effective in mouse models of chemically induced seizures. It has also anxiolytic-like, antidepressant properties in vivo. In silico results are in good agreement with behavior studies. Noteworthy, at biologically active doses does not impair animal motor coordination, but it might cause locomoter deficits. Taken together, these compounds can be regarded as an interesting lead to clinical and further molecular studies are required to clarify the exact underlying protective mechanisms.

Disclosure statement

The authors declare no conflict of interest.

Funding

We thank Prof. S. Gourinath, School of Life Sciences, Jawaharlal Nehru University for critical comments while preparation of our manuscript. RV acknowledge the Department of Science and Technology for SERB National Post-Doctoral fellowship [Grant no. PDF/2016/001926].

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