Molecular Docking, Synthesis of Novel Schiff Base 1, 3-Thiazine Compounds from 3-Methoxy Chalcone and Evaluation of Their Anxiolytic Activity

SONU1*, GIRENDRA KUMAR GAUTAM2, ARUN KUMAR MISHRA3, BABY RABIYA PARVEEN3, RAJAT SAINI2 and HARPREEET SINGH1

1Faculty of Pharmacy, School of Pharmaceutical Sciences, IFTM University, Moradabad 244102, India.
2Department of Pharmaceutical Chemistry, Shri Ram College of Pharmacy, Muzaffarnagar 251001, India.
3Faculty of Pharmacy, Pharmacy Academy, IFTM University, Moradabad, 244102, India.
*Corresponding author E-mail: katariasonu376@gmail.com

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ABSTRACT

As they represent a sizable class of naturally occurring and synthetic chemicals with potent biological activity in the pharmaceutical and biological fields, 1, 3 Thiazine heterocycles are of great interest. The goal of this project was to create the Schiff base. 3-Methoxychalcone derivative of 1,3-thiazine. TLC, IR, 1HNMR, 13C NMR, each mass calculation were accustomed to identify the compositions of recently created targeted substances. Using an Elevated plus maze, the test compounds (B1–11) were examined for their ability to reduce anxiety. The most effective CNS medications were B1 and B8 compounds.

Keywords: Chalcone, Schiff base 1, 3-thiazine derivative, Anxiolytic, Computational studies.

INTRODUCTION

Research in organic, pharmaceutical, analytical, and medicinal chemistry has been rapidly exchanged thanks to heterocyclic molecules. In the pharmaceutical industry, the structures of the top 200 branded medications contain heterocyclic fragments in more than 75% of cases.1 It was discovered that 1,3-thiazines are six-membered heterocyclic rings that include sulfur and nitrogen, is a potential pharmacophore, and are rather stable in other compounds with significant medical applications, for eg, chlormezanone (used as a muscle relaxant and as an anxiolytic).2 Results from studies using thiazine derivative moiety have revealed a variety of biological and pharmacological characteristics, including anticonvulsant,3 antibacterial,4 COX-2 inhibitors,5 NSAID,6 anticancer,7-8 antidiabetic,9 anesthetic,10 and other actions. Over the world, treating bacterial infections provides a substantial therapeutic challenge. Due to the fact that this tendency has been shifting, it is necessary to design new anxiety medications with distinctive structural properties that can vary from the effects of the current anxiety drugs. Moreover, the thiazine nucleus had a pharmacophore of chlormezanone, which has
a key position in anti-anxiety research. In order to obtain a powerful anti-anxiety drug, new 1,3-thiazine derivatives have been synthesized due to the rapid development of anxiety resistance towards existing molecules. The process in the current study uses the synthesis of chalcone to a variety of substituted benzaldehydes and 3-Methoxyacetophenone (Claisen-Schmidt condensation reaction). The starting material for the synthesis of fresh Schiff base thiazines was chalcone derivatives.

**MATERIALS AND PROCEDURE**

**Materials**
Thiourea, 3-methoxyacetophenon, sodium hydroxide, and different substituted benzaldehydes were acquired from AB Fine Chemicals for the current study project (Nasik, India). Alprazolam, which was employed as a reference medication, was purchased from Local Market. All of the additional chemicals and solvents were provided by CDH. All of the chemicals were analytical grade and had been cleaned up before usage.

**General procedure**
The uncorrected melting range of the synthesized complexes was resolute using the unbolt capillary system. With a Perkin Elmer 2400 instrument, the IR graphic representation of synthetic substances was captured on potassium bromide discs. Using a Bruker Advance Neo spectrophotometer and °H NMR uses tetramethylsilane as an inner degree and °13CNMR spectra of the produced compounds were captured in CDCl3. In ppm (δ), all chemical shift values are recorded. In SAIF, P.U., Punjab, India, synthetic substances underwent spectroscopic analysis.

To track the development of the reactions, silica gel G thin-layer chromatography (TLC) was employed, and spots were seen in an iodine chamber. The Elevated plus maze approach will be used to pharmacologically evaluate the target drugs for antianxiety efficacy.

**Synthesis of 1-(3-Methoxy-phenyl)-4-methylene-hepta-2,5-dien-1-one (chalcone1b for C2)**
Equimolar amounts of benzaldehyde and 3-methoxy acetophenone were mixed in pure alcohol (0.02 mol), and 10% NaOH solution (25 mL) was poured in while being stirred dropwise. The action was then permitted to continue for 3–4 h before being stopped overnight. To obtain the outcome, the chemical processing fusion was then submerged in frosty water for a whole night. The final product was created by recrystallizing the crude product from ethanol.

**Scheme 1. Synthesis of Schiff base thiazine derivatives (B1-B11)**
Synthesis of thiazine compound (C2)

In an ethanolic 10% NaOH solution, chalcone (1b) and thiourea were dissolved in an equimolar amount and 2-3 h of stirring at room hotness. The retort fusion was mixed continuously for 1 h after being refluxed for 4 hours. To get the result, in an ice-water bath, the retort fusion was stand overnight. The obtained product underwent filtering, dried and purified from alcohol to produce the resulting product.

General Procedure Synthesis Schiff base of Thiazine derivatives (B1-B11)

The volume was lowered by up to 25% after an equimolar mixture of substituted benzaldehyde and thiazine derivative (C2) were dissolved in Glacial acetic acid. In order to produce the desired result, The mixture for the reaction was left overnight. The end product was obtained by filtering, washing, and recrystallizing the resultant precipitate from ethanol, and the reaction's completeness was verified by TLC.

Thiazine compound (C2)

Characterization: White solid; Yield: 80%; 267-268°C. Elemental analysis of C_{19}H_{21}N_{3}OS Calcd. (found) %: C, 67.23; H, 6.24; N, 12.38; O, 4.71; S, 9.45. IR (KBr, \(\nu_{\text{max}}, \text{cm}^{-1}\)): 1617 (Ar-H, stretching), 3551 (str, NH amide), 1636 (C=N, stretching in ring), 1026 (CO, stretching in ring), 2861 (O-CH₃, stretching in ring), 832 (CH=CH p-disub-Aromatic). 1H NMR (500 MHz, CDCl₃) \(\delta\): 3.78 (s, 3H, -OCH₃), 6.50 (s, 2H, NH₂), 5.58 (s, CH, thiazine), 6.01 (s, 1H, CH), 6.88-7.43 (m, 9H, Ar-H). 13C NMR (100 MHz, CDCl₃) \(\delta\): 129.42 (C1,), 115.04 (C2), 113.55 (C4), 118.26 (C8), 68.65 (C9), 129.43 (C17, C18), 126.03 (C16, CH₂), 55.44 (OCH₃), Mass: m/z: (M+) 297.01, (M+1) 298.02.

Benzylidene-[4-(3-methoxy-phenyl)-6-phenyl-4H-[1,3]thiazin-2-ylimino]-methyl-pheno-phenol (B2)

Characterization: White solid; Yield: 82%; m. p. 320-321°C. Elemental analysis of C_{24}H_{20}N_{2}O_{2}S Calcd. (found) %: C, 74.97; H, 5.24; N, 7.29; O, 4.16; S, 8.34. IR (KBr, \(\nu_{\text{max}}, \text{cm}^{-1}\)): 1635 (Ar-H, stretching), 3238 (str, Ar-OH), 1618 (C=N, stretching in ring), 1089 (CO, stretching in ring), 2875 (O-CH₃, stretching in ring), 834 (CH=CH p-disub-Aromatic). 1H NMR (500 MHz, CDCl₃) \(\delta\): 3.77 (s, 3H, -OCH₃), 8.63 (s, 1H, CH=N), 5.68 (s, 1H, thiazine), 5.93 (s, 1H, CH), 6.83-7.90 (m, 14H, Ar-H). 13C NMR (100 MHz, CDCl₃) \(\delta\): 160.45 (N=C), 129.01 (C1,), 115.62 (C2), 111.68 (C4), 118.23 (C8), 63.24 (C9), 130.11 (C17, C18), 117.24 (C19) 126.03 (C20), 130.34 (C25, C29), 100.80 (C27), 131.11 (C26, 28), 55.44 (OCH₃), Mass: m/z: (M+) 400.06, (M+1) 401.08.

4-{[6-(3-Methoxy-phenyl)-4-phenyl-4H-[1,3] thiazin-2-imino]-methyl}-phenol (B3)

Characterization: Light yellowish solid; Yield: 82%; m. p. 320-321°C. Elemental analysis of C_{24}H_{19}ClN_{2}OS Calcd. (found) %: C, 68.81; H, 4.57; Cl, 4.16; S, 8.34. IR (KBr, \(\nu_{\text{max}}, \text{cm}^{-1}\)): 1615 (Ar-H, stretching), 1635 (C=N, stretching in ring), 1038 (CH=CH p-disub-Aromatic). 1H NMR (500 MHz, CDCl₃) \(\delta\): 3.77 (s, 3H, -OCH₃), 8.69 (s, 1H, CH=N), 5.68 (s, 1H, thiazine), 5.93 (s, 1H, CH), 6.83-7.59 (m, 14H, Ar-H). 13C NMR (100 MHz, CDCl₃) \(\delta\): 160.57 (N=C), 129.01 (C1,), 118.26 (C8), 63.24 (C9), 130.11 (C17, C18), 117.24 (C19) 126.03 (C20), 130.34 (C25, C29), 100.80 (C27), 131.11 (C26, 28), 55.44 (OCH₃), Mass: m/z: (M+) 400.04, (M+1) 401.07.

(3-Chloro-benzylidene)-[6-(3-methoxy-phenyl)-4-phenyl-4H-[1,3] thiazin-2-ylimino]-methyl-phenol (B4)

Characterization: Light yellowish solid; Yield: 82%; m. p. 320-321°C. Elemental analysis of C_{24}H_{19}ClN_{2}OS Calcd. (found) %: C, 68.81; H, 4.57; Cl, 4.16; S, 8.34. IR (KBr, \(\nu_{\text{max}}, \text{cm}^{-1}\)): 1615 (Ar-H, stretching), 1635 (C=N, stretching in ring), 1038 (CH=CH p-disub-Aromatic). 1H NMR (500 MHz, CDCl₃) \(\delta\): 3.77 (s, 3H, -OCH₃), 8.69 (s, 1H, CH=N), 5.68 (s, 1H, thiazine), 5.93 (s, 1H, CH), 6.83-7.59 (m, 14H, Ar-H). 13C NMR (100 MHz, CDCl₃) \(\delta\): 160.57 (N=C), 129.01 (C1,), 118.26 (C8), 63.24 (C9), 130.11 (C17, C18), 117.24 (C19) 126.03 (C20), 130.34 (C25, C29), 100.80 (C27), 131.11 (C26, 28), 55.44 (OCH₃), Mass: m/z: (M+) 400.04, (M+1) 401.07.
Characterization: Yellowish solid; Yield: 82%; m.p. 324–325°C. Elemental analysis of C_{24}H_{19}BrN_{2}O_{3}S. Calc. (found)%: C, 62.31; H, 4.13; Br, 17.27; N, 6.05; O, 3.45; S, 6.92. IR (KBr, cm\(^{-1}\)):
- 1191 (CH=CH p-disub-Aromatic).
- 1619 (Ar-H, stretch.), 1637 (C=N, stretch. in ring), 1025 (CO, stretching in ring), 848 (O=CH, stretching in ring), 815 (CH=CH p-disub-Aromatic).

1H NMR (500 MHz, CDCl\(_3\))
- 3.78 (s, 3H, -OCH\(_3\)), 8.69 (s, 1H, CH=N), 5.68 (s, 1H, thiazine), 5.94 (s, 1H, CH), 6.83–8.25 (m, 13H, Ar-H). 13C NMR (100 MHz, CDCl\(_3\))
- 159.32 (N=C), 129.01 (C1,), 117.24 (C2), 111.68 (C4), 118.23 (C8), 63.24 (C9), 129.42 (C17, C18), 117.18 (C19) 126.05 (C16, 20), 130.11 (C25, 29), 100.88 (C27), 133.43 (C26, 28), 55.44 (OCH\(_3\)).
  Mass: m/z: (M\(^+\)) 429.02, (M\(^+\)\(^{+}\)) 430.06 (B7).
calcd. (found)%: C, 72.44; H, 5.35; N, 6.76; O, 7.72; S, 7.74. IR (KBr, νmax, cm⁻¹): 1616 (Ar-H, stretching), 1644 (C=N, stretching in the ring), 1010 (CO, stretching in the ring), 2858 (O-CH₃, stretching in the ring), 850 (CH=CH p-disub-Aromatic).

¹H NMR (500 MHz, CDCl₃): 3.77 (s, 6H, -OCH₃), 8.66 (s, 1H, CH=N), 5.68 (s, 1H, thiazine), 5.93 (s, 1H, CH), 6.83-8.66 (m, 13H, Ar-H). ¹³C NMR (100 MHz, CDCl₃): 159.36 (N=C), 129.01 (C1), 117.24 (C2), 114.98 (C4), 118.23 (C8), 63.24 (C9), 130.21 (C17, C18), 117.24 (C19), 126.05 (C16, 20), 131.10 (C25, 29), 100.88 (C26), 55.34 (OCH₃), Mass: m/z: (M⁺) 400.06, (M⁺1) 401.08.(B10).

(4-Methoxy-benzylidene)-[6-(3-methoxy-phenyl)-4-phenyl-4H-[1,3]thiazin-2-yl]amine (B11)

Characterization: Brown solid Yield; 82%; m.p. 332-333°C. Elemental analysis of C₂₅H₂₂N₂O₂S calcd. (found)%: C, 72.44; H, 5.35; N, 6.76; O, 7.72; S, 7.74. IR (KBr, νmax, cm⁻¹): 1600 (Ar-H, stretching), 1644 (C=N, stretching in ring), 1010 (CO, stretching in ring), 2859 (O-CH₃, stretching in ring), 850 (CH=CH p-disub-Aromatic). ¹H NMR (500 MHz, CDCl₃): 3.77 (s, 6H, -OCH₃), 8.69 (s, 1H, CH=N), 5.68 (s, 1H, thiazine), 5.93 (s, 1H, CH), 6.83-8.69 (m, 13H, Ar-H). ¹³C NMR (100 MHz, CDCl₃): 160.35 (N=C), 129.01 (C1), 117.24 (C2), 114.98 (C4), 118.23 (C8), 63.24 (C9), 130.21 (C17, C18), 117.24 (C19), 126.05 (C16, 20), 131.10 (C25, 29), 100.88 (C26), 55.34 (OCH₃), Mass: m/z: (M⁺) 414.06, (M⁺1) 415.05. (B11).

Molecular Modeling Studies

Studies on the separated chemicals’ molecular docking, the isolated compounds (B1–B11) were docked with the target protein Human Gamma-aminobutyric Acid (GABAA) (PDB ID: 4COF) in this work. Using Auto Dock Vina4.2 (MGLtools 1.5.7), It was determined through molecular docking studies how the test medicines would likely bind to the targeted anxiolytic proteins. Binding force (kcal per mol), bond lengths of hydrogen and a graphic demonstration of feasible modeling locations are among the results of the docking computation. ChemDraw 16.0 were worn to display the arrangements of the products (B1–B11) in the suitable 2D inclinations. ChemDraw3D extreme was worn to reduce the power of the compounds/ligands. When the energy of the ligand molecules was decreased, AutoDock Vina was used to run the docking simulation. Using the protein data database, the receptor protein molecules’ crystal structures were discovered (PDB file). The intricate synchronizes of the arrangements, which contained hydrated particles and other grains are what gave rise to the better resolution. A protein preparation technique with default settings was used to prepare the proteins. With Auto Processing of intention Protein wallet Auto Dock 4.2, the object protein wallet was created via departure the correlated deposit (eradicate hydrated atom and coaspects) with the protein wallet (MGL tools 1.5.7). The visual punter boundary software was altered such that the lattice box for the molecular modeling simulation, which has a dimension of 60, 60, 64, and 0.377 points, encompasses the macromolecule’s region of interest. Using the docking technique of AutoDock Vina, It was calculated how much energy the protein and ligand might potentially bind with. PyMOL and Discovery Studio Visualizer choose the configurations with the least favourable attaching energies among the intention molecule of proteins and chemicals in order to study the dealings between the intention Protein and molecule. The interrelating deposits and H-bonds are revealed as stick displayed, although the drug is represented by different colors.

Table 1: Total Binding Affinities Energy (kcal.mol⁻¹) comparison between Alprazolam and the (B1-B11) Schiff base thiazine derivatives against the GABAA receptor

<table>
<thead>
<tr>
<th>Compound Code</th>
<th>Involved amino acid residues within 5 Å</th>
<th>Interaction Hydrogen bond</th>
<th>Total Binding Affinity Energy (kcal.mol⁻¹)</th>
<th>RMSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>Leu294, Leu297, Ala300, Phe301, Ile423, Phe431, Leu297</td>
<td>Leu297</td>
<td>-8.4</td>
<td>1.077</td>
</tr>
<tr>
<td>B2</td>
<td>Leu294, Leu297, Glu298, Leu423</td>
<td>Leu423</td>
<td>-8.2</td>
<td>3.433</td>
</tr>
<tr>
<td>B3</td>
<td>Phe291, Leu294, Phe301, Val430, Phe431</td>
<td>Leu294</td>
<td>-8</td>
<td>2.691</td>
</tr>
<tr>
<td>B4</td>
<td>Leu294, Leu297, Glu298, Leu423</td>
<td>Leu423</td>
<td>-8.3</td>
<td>2.182</td>
</tr>
<tr>
<td>B5</td>
<td>Leu294, Leu297, Glu298, Leu423, Trp426, Phe431</td>
<td>Leu423</td>
<td>-8</td>
<td>11.934</td>
</tr>
<tr>
<td>B6</td>
<td>Glu65, Ala88, Val93, Asp95, Thr96, Tyr97, Phe98, Ser104, Ile130, Ala88, Thr96</td>
<td>Alu88, Thr96</td>
<td>-7.8</td>
<td>50.286</td>
</tr>
<tr>
<td>B7</td>
<td>Leu294, Leu423, Trp426, Val430, Phe431</td>
<td>Leu294</td>
<td>-8.4</td>
<td>2.933</td>
</tr>
<tr>
<td>B8</td>
<td>Phe291, Leu294, Leu297, Glu298, Phe431, Leu423</td>
<td>Leu294</td>
<td>-8.3</td>
<td>4.652</td>
</tr>
<tr>
<td>B9</td>
<td>Phe291, Leu294, Phe301, Ile423, Val430</td>
<td>Leu294</td>
<td>-8.3</td>
<td>2.751</td>
</tr>
<tr>
<td>B10</td>
<td>Phe291, Leu294, Ile423, Trp426, Ser427</td>
<td>Leu294</td>
<td>-8.1</td>
<td>4.538</td>
</tr>
<tr>
<td>B11</td>
<td>Leu294, Phe301, Ile423, Trp426, Val430, Phe431, Ser427</td>
<td>Leu294</td>
<td>-8.1</td>
<td>11.806</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Leu294, Val430, Phe431</td>
<td>Leu294</td>
<td>-8.4</td>
<td>2.751</td>
</tr>
</tbody>
</table>
The separated compounds B1–B11 and Alprazolam's binding affinities with the protein GABAA receptor in the 2D images (1-12), respectively.
Biological Evaluation

Anxiolytic activity

Method of evaluating anxiety using an elevated plus maze

Albino Swiss mice with a bodyweight of 22 to 25 g were chosen from a collection group kept given complete food and water supply in the main animal house. Animals were kept in air-conditioned cages. The 15 rooms kept their temperature at zero degrees during the daylight hours. Each drug was utilized in freshly made solutions in 1% polyethylene glycol at a concentration of 5 mg/kg. On test days, each solution was newly made and injected intraperitoneal injection (i.p.) in a dose equal to 0.6 mL/22–25 g of mice body weight. The test drugs (5 mg/kg) or alprazolam (2 mg/kg, n=5) were administered to the experimental animals 60 min before to their assessment in the maze. Saline with 1% polyethylene glycol was administered to the control group. The raised plus maze device had an open canopy and two arms that were 15x4 cm² open and two arms that were 15x4x11 cm² closed. Each mouse was positioned on the platform in the middle, facing the unbolted part. Over a 5 min epoch, the quantity of entrances the integer of times into unbolted and wrapped parts, as well as the instance tired in unbolted parts, were write down. For each mouse, the proportion of entry into open arms was computed by multiplying (open/open+closed) by 100. Table 2 provides a summary of the elevated plus maze method results.

Table 2: Target compounds (B1-B11) showed anti-anxiety action by using an elevated plus maze-based approach

<table>
<thead>
<tr>
<th>Compound</th>
<th>Extended period</th>
<th>No of entries</th>
<th>% No of entries</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>78.52± 2.51</td>
<td>8.09± 0.36</td>
<td>47.38</td>
</tr>
<tr>
<td>B2</td>
<td>65.90 ± 2.36</td>
<td>7.59± 0.77</td>
<td>46.82</td>
</tr>
<tr>
<td>B3</td>
<td>63.62 ± 1.70</td>
<td>7.02± 0.44</td>
<td>44.29</td>
</tr>
<tr>
<td>B4</td>
<td>54.81± 2.21</td>
<td>3.65± 0.33</td>
<td>37.21</td>
</tr>
<tr>
<td>B5</td>
<td>50.07± 3.46</td>
<td>4.09± 0.7</td>
<td>40.72</td>
</tr>
<tr>
<td>B6</td>
<td>48.65± 4.67</td>
<td>3.39± 0.74</td>
<td>5.12</td>
</tr>
<tr>
<td>B7</td>
<td>61.66± 1.85</td>
<td>6.69± 0.70</td>
<td>41.09</td>
</tr>
<tr>
<td>B8</td>
<td>86.30± 0.60</td>
<td>10.51± 0.60</td>
<td>58.92</td>
</tr>
<tr>
<td>B9</td>
<td>79.44± 0.71</td>
<td>9.50± 0.76</td>
<td>57.98</td>
</tr>
<tr>
<td>B10</td>
<td>69.10± 2.04</td>
<td>8.72± 0.63</td>
<td>56.98</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>90.82± 2.32</td>
<td>9.97± 0.73</td>
<td>64.46</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>41.12 ± 3.42</td>
<td>202± 91</td>
<td>21.02</td>
</tr>
</tbody>
</table>

RESULT

Chemistry for synthesis

By following the steps in Scheme 1, all of the novel Schiff bases of thiazine derivatives (B1-B11) were successfully developed. through the use of infrared spectroscopy, fundamental study, 13C NMR, 1H NMR and molecular spectroscopy, the structures of all the lately created compounds were verified. Benzaldehyde and 3-methoxy acetoephone were combined in a Claisen-Schmidt Condensation reaction to create 1-(3-Methoxyphenyl)-4-methylene-hepta-2, 5-dien-1-one (chalcones 1b). Under constant stirring and reflux, compound 1b was cyclized with thiourea to produce a thiazine compound (C2). In ethyl alcohol, thiazine compound C2 reacted with various substituted benzaldehydes to produce a Schiff base 1, 3 thiazine derivatives (B1-B11).

Molecular model

Human Gamma-Aminobutyric acid (GABAA) (PDB ID:4COF) was the subject of a molecular docking investigation of target compounds (B1-B11) in relation to the reference medication Alprazolam. The target molecules (B1–B11) had lower docking scores on human gamma-aminobutyric acid, indicating that they could have more effective anxiolytic actions. B8, B1, B4, B9, and B2 were among the produced compounds that were most effective because they had the lowest docking scores for the human gamma-aminobutyric acid (GABAA) receptor.

DISCUSSION

Pharmacology

At a quantity of 5 mg per kg i.p., the elevated plus maze procedure was employed to assess the anxiolytic effects. Table 2 exhibits the anxiolytic activity results. Alprazolam was used as a common medication. B8 showed a significant amount of anxiolytic activity, whereas B1 showed the least amount. The findings indicated that the activity response was producing outcomes comparable to those of the docking research.

CONCLUSION

Novel Schiff bases thiazine derivatives (B1-B11) were synthesized by first creating...
1-(3-Methoxy-phenyl)-4-methylene-hepta-2, 5-dien-1-one (chalcones 1b) using a stirring Claisen-Schmidt Condensation reaction between benzaldehyde and 3-methoxy acetophenone compound 1b was exposed to a continuous stirring and reflux cyclization procedure to produce thiazine compound (C2). In glacial acetic acid and ethyl alcohol, the compound C2 interacted with several substituted benzoaldehydes to produce a Schiff base of derivatives of thiazine. According to experimental data, compound B8, whose benzaldehyde ring has one bromo group in 3-position has a notable effect. Overall, the 4COF enzyme is inhibited by the substance B8, which is a powerful antianxiety molecule for the treatment of anxiety, which may be related to the outcome of molecular docking. Alprazolam (LEU, PHE) and B8 (2D Image 8) (LEU, PHE) interaction residues for the 4COF receptor are identical, according to the research of docking results with regard to residues involved in amino acid interactions. The similarity between the interaction residues for alprazolam and B1 (2D Image 1) (LEU, PHE) for the 4COF receptor was also found.

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Conflict of interest

There are no competing interests, according to the authors.

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