Docking-based Screening of Ficus religiosa Phytochemicals as Inhibitors of Human Histamine H2 Receptor

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ABSTRACT

Background: Ficus religiosa L. is generally known as Peepal and belongs to family Moraceae. The tree is a source of many compounds having high medicinal value. In gastrointestinal tract, histamine H2 receptors have key role in histamine-stimulated gastric acid secretion. Their over stimulation causes its excessive production which is responsible for gastric ulcer. Objective: This study aims to screen the range of phytochemicals present in F. religiosa for binding with human histamine H2 and identify therapeutics for a gastric ulcer from the plant. Materials and Methods: In this work, a 3D-structure of human histamine H2 receptor was modeled by using homology modeling and the predicted model was validated using PROCHECK. Docking studies were also performed to assess binding affinities between modeled receptor and 34 compounds. Molecular dynamics simulations were done to identify most stable receptor-ligand complexes. Absorption, distribution, metabolism, excretion, and screening was done to evaluate pharmacokinetic properties of compounds. Results: The results suggest that seven ligands, namely, germacrene, bergaptol, lanosterol, Ergost-5-en-3beta-ol, α-amyrin acetate, bergapten, and γ-cadinene showed better binding affinities. Conclusion: Among seven phytochemicals, lanosterol and α-amyrin acetate were found to have greater stability during simulation studies. These two compounds may be a suitable therapeutic agent against histamine H2 receptor. Key words: Absorption, distribution, metabolism, excretion, and toxicity, docking, histamine H2 receptor, homology modeling, molecular dynamic simulation

SUMMARY

• This study was performed to screen antulcer compounds from F. religiosa. Molecular modeling, molecular docking and MD simulation studies were performed with selected phytochemicals from F. religiosa. The analysis suggests that Lanosterol and α-amyrin may be a suitable therapeutic agent against histamine H2 receptor. This study facilitates initiation of the herbal drug discovery process for the antulcer activity.

INTRODUCTION

Herbs have been the important source of medicine in India since long. Medicinal plants have therapeutic properties due to the presence of various complex chemical substances of different compositions, which are formed as secondary plant metabolites in one or more parts of them. They are conventionally used due to their as therapeutic properties against diabetes,[1] cardiac diseases,[2] tuberculosis,[1] liver diseases,[4] asthma, cough-respiratory disorders,[5] and several other diseases.[6-13] A peptic ulcer is a major cause of mortality in many countries. With the ever developing interest in natural medicine, many plants have been identified and reported to be useful in treating and managing ulcer. A peptic ulcer occurs in that part of the gastrointestinal tract which is unprotected to gastric acid and pepsin, i.e., the duodenum and stomach. The etiology of peptic ulcer is not clearly known. It probably occurs due to an imbalance between the aggressive (pepsin, acid, bile and Helicobacter pylori)[14] and the defensive (bicarbonate secretion and gastric mucus prostaglandins, nitric oxide innate resistance of the mucosal cells) factors.[15] An understanding of the control of gastric acid secretion and mechanism will elucidate the targets of antisecretory drug action.

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Histamine plays an important role in a variety of pathophysiological conditions. Histamine exerts its biological effects by binding to and activating four different separate rhodopsin-like G protein-coupled receptors-histamine H1, H2, H3, and H4. Each of the histamine receptors has a functional response, but their mechanism is different from each other. Histamine H2 receptors primarily stimulate gastric acid secretion. H2 antagonists are also reported to be used in the clinical treatment of peptic ulceration.[12,13]

Ficus religiosa is a native Indian tree and commonly known as Peepal which belongs to the family Moraceae.[19] The preliminary phytochemical screening of different parts of F. religiosa plant such as bark, leaves, fruit, and seed has shown the presence of different chemicals of therapeutic value as shown in Table 1;[20-26] The studies on anti-ulcer (ulcer-preventive) effects of F. religiosa phytochemicals have shown positive results.[27-31]

In the current study, the structure of human histamine H2 receptor was modeled, molecular docking, and molecular dynamics (MD) simulation were performed between modeled histamine H2 receptor and F. religiosa phytochemicals. Phytochemicals were studied for their absorption, distribution, metabolism, excretion (ADME) properties. This work emphasizes on examining the binding interactions of human histamine H2 receptor with F. religiosa phytochemicals against gastric ulcer.

**MATERIALS AND METHODS**

**Tertiary structure prediction**

Molecular modeling of human histamine H2 receptor was performed using (Modeller 9.15) by homology modeling approach.[32] The sequence for the histamine H2 receptor isoform 2 (Homo sapiens) (Ref. Seq: NP_071640.1) was taken from database of NCBI.[33] The NCBI histamine H2 receptor sequence database contains protein sequences and their encoding regions derived from the nucleotide sequences. The sequence of histamine H2 receptor with GI: 13435405 were selected for three-dimensional (3D) model development that contains 359 amino acid residues with molecular weight 39967 Daltons. Suitable templates were searched with basic local alignment search tool against the Protein Database.[34,35] On the basis of similarity search, four structures (2VT4, 2Y00, 4BVN, and 5A8E) from PDB were considered templates for modeling. Five 3D models were generated with different Discrete Optimized Potential Energy (DOPE)-scores featuring the accuracy of prediction [Figure 1]. Stereochemical quality of a protein structure and overall geometry was analyzed using PROCHECK server[36] and also produced a Ramachandran plot [Table 2 and Figure 2].

**Ligand preparation**

Ligprep was used for the preparation of ligands as shown in [Figure 3].[37] We obtained the initial ligand from PubChem database[38] and PDBchem in Structure Data Format. Without performing pre-docking filtering all structures were included and generated low energy 3D conformers with satisfactory bond lengths and angles for each two-dimensional structure. Optimized potential liquid simulation (OPLS2005) force field was used by Ligprep.[39] All possible protoners (protonation states) and ionization states were computed for the respective ligand using Ionizer at a pH 7.4. The obtained structures were used for analysis. We obtained the initial ligand from PubChem database[38] and PDBchem in Structure Data Format. Without performing pre-docking filtering all structures were included and generated low energy 3D conformers with satisfactory bond lengths and angles for each two-dimensional structure. Optimized potential liquid simulation (OPLS2005) force field was used by Ligprep. All possible protoners (protonation states) and ionization states were computed for the respective ligand using Ionizer at a pH 7.4. The obtained structures were used for analysis.

**Table 1: List of phytochemicals in Ficus religiosa**

| Parts of plant | Phytochemicals | References |
|----------------|----------------|------------|
| Bark           | Lanosterol, bergapten, stigmasterol, bergapten, β-sitosterol, lupen-3-one, β-sitosterol-d-glucoside (phytosterolin) Vitamin K1, wax | [20-22] |
| Leave          | Stigmasterol, campesterol, isofucosterol, lupeol, tannic acid, serine, isoleucine, aspartic acid, glycine, threonine, alanine, proline, tryptophan, tryosine, methionine, valine leucine, n-nonacosane, n-hentriecontane, hexacosanol, n-octacosan | [23,24] |
| Fruit          | Asgaragine, unduecane, tetradeacene, trideace, (e)-β-ocimene, alooaromadendrene, a-thujeneβ-pinene, a-pinene, limonene, a-terpinene, dindrolasnine, aromadendrene, dindrolasnine α-ylangene, α-copene, β-bourbonene, β-caryophyllene, a-trans-bergamotene, a-humulene, germacrene, bicyclogermacrene, γ-cadinene, δ-cadinene | [25,26] |
| Seed           | Alamine, tyrosine, threonine | [25] |

**Table 2: Ramachandran plot statistics for the predicted model (Seq.B999900003)**

| Number of residues (%) |
|------------------------|
| Most favored regions (A, B, L) | 306 (92.7) |
| Additional allowed regions (a, b, l, p) | 19 (5.8) |
| Generously allowed regions (–a, –b, –l, –p) | 2 (0.6) |
| Disallowed regions (XX) | 3 (0.9) |
| Nonglycine and nonproline residues | 330 (100.0) |
| End-residues (excl. Gly and Pro) | 2 |
| Glycine residues | 16 |
| Proline residues | 11 |
| Total number of residues | 359 |

Based on an analysis of 118 structures of resolution of at least 2.0 Angstrom and R-factor no >20.0 a good quality model would be expected to have over 90% in the most favored regions (A, B, L).
of 7.4. Tautomeric states were incorporated for chemical groups with possible prototropic, tautomerism. Only the lowest energy conformer was kept for all ligands.

**Molecular docking of modeled protein with phytochemicals using GLIDE tool**

Flexible docking was performed using Schrödinger software (New York, USA). The docking calculations were performed using the Schrödinger software suite with default parameters and proteins were prepared using the Protein Preparation Wizard. Receptor grid was prepared with default parameters without any constraints. SiteMap was used for prediction and evaluation of binding sites. The eModel and glide scores were used to predict the binding affinity of docked structures using the SP and XP feature of GLIDE module implemented in the Schrödinger LLC.

**Functional assessment for absorption, distribution, metabolism, and excretion**

QikProp v4.4 was used for ADME prediction program which predicts physically significant descriptors and pharmaceutically related properties of organic molecules, either individually or in batches. Predicted significant ADME properties such as molecular weight (MW), donor hydrogen bond (HB), acceptor HB, QPlog, Po/w, % human oral absorption (HOA), the rule of five, central nervous system (CNS) were recorded. The predictions also included molecular properties, along with comparing a particular molecule’s properties with those of 95% of known drugs.

**Molecular dynamics simulations**

Gromacs version 5.1.2 was used to perform MD simulations for different protein-ligand complex. The AMBER03 force field was used to generate the topologies for the complex. Assigning of the protons to protein-ligand complex was performed automatically using the program pdb2gmx within the GROMACS package. Complex systems were solvated with the TIP3P water model in a triclinic box under the periodic boundary conditions using a distance of 1.2 nm from the protein to the surface of the box. To neutralize the system, the number of counterions used for the complex was 54 NA and 69 Cl ions, respectively. Each system was subjected to energy minimization using the steepest descent integrator without position restraints. Finally, a 5000 ps production run was performed under NPT conditions by removing position restraints.

Berendsen weak-coupling method was used for maintaining temperature and pressure of the system. Lennard-Jones potentials...
were used for van der Waals interactions, and electrostatic interactions were handled by particle-mesh Ewald electrostatics calculations with a cut-off for the real space term of 0.8 nm.\(^{[49]}\) The LINCS algorithm was used to constrain all the bonds.\(^{[50]}\) A 2 fs time step was applied, and 2 ps final coordinates were saved. Most of the analyses for simulation studies were performed using Gromacs in-built tools such as root-mean-square deviation (RMSD), solvent-accessible surface area (SASA), a number of hydrogen bond (NHB), and radius of gyration (Rg) calculations were performed using a least-squares fit.\(^{[51]}\) The production simulation was performed for 12 ns at 300 K. Xmgrace tool was used for graph plotting for all trajectory analysis.\(^{[52]}\) The MD trajectories were analyzed using gmx_rmsd, gmx_SASA, gmx_NHB, and gmx_gyration of GROMACS utilities to get the RMSD, SASA of each system, the Rg and NHB.

**RESULTS AND DISCUSSION**

**Prediction of histamine H2 receptor**

The model (Seq.B99990003) of histamine H2 receptor isoform 2 (Homo sapiens) with the lowest DOPE score was selected for structure-based drug designing [Figure 4]. Stereo-chemical assessment of the predicted model shows that 92.7% of residues were in most favorable regions, 5.8% in allowed region, 0.6% in generously allowed regions, and 0.9% of the residues in disallowed regions [Table 3]. The selected protein models were found to be satisfactory for the calculated stereo-chemical parameters.

**Docking of phytochemicals with histamine H2 receptor**

Ligands were docked at the active site of the histamine H2 receptor which shows different respective docking score, Glide energy, Glide gscore, and Glide e-model [Table 4 and Figure 5]. The G-score and glide energy of the top seven ligands germacrene, bergaptol, lanosterol, Ergost-5-en-3beta-ol, α-amyrin acetate, bergapten, and γ-cadinene in the case of docking with histamine H2 receptor were found to be −5.838, −5.472, −5.423, −5.387, −5.255, −5.109, and −5.029, respectively [Table 5]. As well as the Glide-score, other parameters such as Glide energy, and the Glide E-model were also used for the evaluation of the docking results. Histamine H2 receptor complex has HB interactions between the ligand and the active site residues [Figures 6 and 7].

**Functional assessment for absorption, distribution, metabolism, excretion properties**

About all descriptors and properties were reported of which few important are given in [Table 6]. The predicted values of MW, %HOA and permeability for all conformers were good [Figure 8a and b]. The drug-like activity of the ligand molecule is characterized using ADME properties and can be used to focus lead optimization efforts to enhance the desired properties of a given compound. Lanosterol and α-amyrin acetate hits displayed the properties such as MW, donor HB, acceptor HB, QPlog, Po/w, % HOA, the rule of five and CNS within the permissible range.

**Molecular dynamics simulation**

On the basis of lowest glide energy docked complex were selected for MD simulation. α-amyrin acetate-complex, lanosterol-complex, and Ergost-5-en-3beta-ol-complex showed lowest glide energy −33.358, −28.686 and −26.468, respectively. The RMSD for α-amyrin acetate-complex was found to be approximate 0.6 nm and it showed a gradual decrease after ~9000ps. α-amyrin acetate-complex maintained an overall stability throughout 12,000 ps of simulation, lanosterol-complex was found to be approximate 0.3 nm and it showed a gradual decrease after ~6000 ps. Lanosterol-complex maintained an overall stability throughout 12000 ps of simulation an Ergost-5-en-3beta-ol-complex was found to be approximately 0.9 nm and it showed a gradual increase after ~7000ps. Ergost-5-en-3beta-ol-complex showed more fluctuation in comparison to α-amyrin acetate-complex and lanosterol-complex [Figure 9].

The Rg was also calculated for the α-amyrin acetate-complex, lanosterol-complex, and Ergost-5-en-3beta-ol-complex to assess the compactness of the complex structure. The Rg range of the α-amyrin acetate-complex structure is between 2.8 and 2.95 nm. From 0 to ~6000 ps, there is a continuous decrease in the Rg value and further
increased. Rg range of lanosterol-complex structure is between 2.73 and 2.93 nm. From 0 to ~6000 ps, there is a continuous increase in the Rg value and further decreased. Rg range of Ergost-5-en-3beta-ol-complex structure is between 2.65 to 2.86 nm. From 0ps to 12000ps obtained the reduced Rg range of lanosterol-complex structure was obtained.

The SASA was also calculated for the α-amyrin acetate-complex structure lies between 2.05 and 2.30 nm$^2$ and showed fluctuation increases and finally decreased [Figure 11]. The NHB of α-amyrin acetate-complex structure were obtained initially increased and after ~6000 ps reduced. The lanosterol-complex structure shows increased in number of HBs till 12,000 ps and Ergost-5-en-3beta-ol-complex structure showed decreased in the number of HB in comparison to α-amyrin acetate-complex and lanosterol-complex [Figure 12].

Herbal drugs are known to have minimal or no side effects. Peptic ulcer is a common problem in old as well as young people. Histamine stimulated gastric acid secretion is a normal phenomenon, but excessive stimulation causes increased acid production which

Table 4: Inhibitory activity of phytochemicals on selected modeled structure

| Compound’s name | Entry ID | Docking score | Glide gscore | Glide energy | Glide emodel |
|-----------------|---------|---------------|--------------|--------------|--------------|
| Germacrene     | Structure 3D_CID_5317570.1 | -5.838         | -5.838       | -18.946      | -25.386      |
| Bergapten      | Structure 3D_CID_2355.1     | -5.109         | -5.109       | -24.886      | -32.547      |
| Lupeol         | Structure 3D_CID_259846.1   | -4.885         | -4.885       | -31.989      | -42.419      |
| Aromadendrene  | Structure 3D_CID_11095734.1 | -4.865         | -4.865       | -20.933      | -27.173      |
| α-humulene     | Structure 3D_CID_731701.1   | -4.836         | -4.836       | -31.706      | -41.361      |
| Dendrolasine   | Structure 3D_CID_22003145.1 | -4.861         | -4.861       | -23.571      | -29.727      |
| β-sitosterol    | Structure 3D_CID_731701.1   | -4.836         | -4.836       | -31.706      | -41.361      |
| Bicyclergumacerne | Structure 3D_CID_531347.1 | -4.776         | -4.776       | -22.211      | -28.615      |
| Alloroamadendrene | Structure 3D_CID_10899740.1 | -4.749        | -4.749       | -21.169      | -27.223      |
| β-bourbonene | Structure 3D_CID_324224.1 | -4.711         | -4.711       | -17.241      | -22.238      |
| δ-cadinene     | Structure 3D_CID_441005.1   | -4.988         | -4.988       | -18.788      | -23.9        |
| γ-cadinene     | Structure 3D_CID_222284.1 | -4.955         | -4.955       | -26.787      | -33.491      |
| δ-cadinene     | Structure 3D_CID_222284.1 | -4.955         | -4.955       | -26.787      | -33.491      |
| β-caryophyllene | Structure 3D_CID_5317570.1 | -4.617         | -4.617       | -18.828      | -24.043      |
| Isosucosterol   | Structure 3D_CID_5281326.1  | -4.537         | -4.537       | -19.698      | -25.173      |
| Ergostol        | Structure 3D_CID_6429302.1  | -4.376         | -4.376       | -17.659      | -21.979      |
| β-pinene       | Structure 3D_CID_14896.1   | -4.324         | -4.324       | -15.468      | -19.436      |
| α-pinene       | Structure 3D_CID_6654.1    | -4.246         | -4.246       | -15.328      | -19.234      |
| Lupeol acetate | Structure 3D_CID_92157.1   | -4.086         | -4.086       | -30.352      | -38.569      |
| Stigmasterol    | Structure 2D_CID_5280794.1  | -2.797         | -2.797       | -12.578      | -11.753      |
| β-oicinene     | Structure 3D_CID_5281533.1  | -2.691         | -2.691       | -14.96       | -17.027      |
| n-octacosan    | Structure 3D_CID_12408.1   | -1.957         | -1.957       | -20.49       | -22.97       |
| n-hentrietritanen | Structure 3D_CID_12410.1 | -1.197         | -1.197       | -10.166      | -11.087      |
| Tetradecane     | Structure 3D_CID_12389.1   | 1.233          | 1.233        | -20.714      | -17.351      |
| Tridecane      | Structure 3D_CID_12388.1   | 1.245          | 1.245        | -18.796      | -16.019      |
| Undecane       | Structure 3D_CID_14257.1   | 1.622          | 1.622        | -17.923      | -14.047      |

Table 5: Docking analysis of histamine H2 receptor with top seven screened with interacting residues

| Compound’s name | Entry ID | Glide gscore | Interacting residues |
|-----------------|---------|--------------|----------------------|
| Germacrene     | Structure 3D_CID_5317570.1 | -5.838         | Leu141, Ile145, Leu107, Ile142, Phe110, Met111, Leu114, Phe56, Cys118, Ser138, Asp115 |
| Bergapten      | Structure 3D_CID_5283637.1  | -5.387         | Phe110, Ile145, Leu107, Leu114, Ile142, Phe110, Met111, Ser138, Val130, Arg134, Leu129 |
| Lanosterol      | Structure 3D_CID_246983.1  | -5.423         | Val193, Leu107, Leu149, Ile145, Leu141, Ser138, Arg134, Val130, Val135, Tyr126, Leu52, Asp115, Phe56, Cys118, Met111, Leu114, Ile142, Phe110 |
| Ergost-5-en-3beta-ol | Structure 3D_CID_92842.1 | -5.255         | Leu107, Phe110, Met111, Ile142, Leu145, Leu141, Ser138, Phe56, Cys118, Asp115, Tyr126, Leu52, Asp115, Phe56, Cys118, Ser138, Met111, Arg134, Leu129 |
| α-amyrin acetate | Structure 3D_CID_92313.1  | -5.029         | Arg134, Val135, Ile137, Leu141, Ile142, Phe110, Ser138, Met111, Leu114, Phe56, Asp115, Leu52, Val130, Tyr126 |

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**Figure 7:** Human histamine H2 receptor in complex with \( \alpha \)-amyrin acetate. Hydrogen bonds have been shown in yellow dashed line.

**Figure 9:** Root-mean-square deviation graphs of respective entry IDs: (1) Structure3D_CID_92313, (2) Structure3D_CID_2355, (3) Structure3D_CID_5280371, (4) Structure3D_CID_5317570, (5) Structure3D_CID_5283637, (6) Structure3D_CID_92842, (7) Structure3D_CID_246983

contributes to peptic ulcer. Here, 34 compounds from *F. religiosa* were screened against the modeled structure of human histamine H2. Out of them, only seven compounds were found to have significantly high binding scores with the receptor. Absorption, distribution, metabolism, excretion, and toxicity (ADMET) screening was done after docking to ensure that any highly promising prospective drug is not skipped only due to insignificant violation of pharmacokinetic properties. Stability of the receptor and ligand complexes were re-assessed using MD simulations. Trajectory, Rg, and SASA analysis confirmed the docking results. Among seven phytochemicals lanosterol and \( \alpha \)-amyrin acetate were found to have greater stability. In addition, they were also in accordance with the ADMET rules. Apart from screening, docking, and MD simulation studies, the study helps in understanding the human histamine H2 and receptor interaction. The insights about the active site of the receptor will help in further analytics and investigations.

**CONCLUSION**

Molecular modeling, molecular docking, and MD simulation studies were performed with selected phytochemicals from *F. religiosa*. The analysis suggests that lanosterol, \( \alpha \)-amyrin acetate, and Ergost-5-en-3beta-ol form the most stable complex with human histamine H2 receptor. The MD shows lanosterol and \( \alpha \)-amyrin acetate have a relatively better binding affinity in comparison to others phytochemicals. Significantly, both compounds satisfy all the *In silico* parameters such as docking score, glide energy, ADME/Tox, and trajectories analysis. These two compounds may be a suitable therapeutic agent against histamine H2 receptor. This study facilitates initiation of the herbal drug discovery process for the antiulcer activity.
Table 6: Absorption, distribution, metabolism, excretion and toxicity properties of phytochemicals

| PubChem CID | MW     | Donor HB | Acceptor HB | QPlog Po/w | Percentage human oral absorption | Rule of five | CNS |
|------------|--------|----------|-------------|------------|----------------------------------|-------------|-----|
| 12408      | 394.766| 0        | 0           | 15.583     | 100                              | 1           | 2   |
| 12409      | 408.793| 0        | 0           | 16.051     | 100                              | 1           | 2   |
| 12410      | 436.847| 0        | 0           | 17.171     | 100                              | 1           | 2   |
| 2355       | 216.193| 0        | 3.75        | 1.429      | 94.591                           | 0           | 0   |
| 6654       | 136.236| 0        | 0           | 3.615      | 100                              | 0           | 2   |
| 12388      | 184.364| 0        | 0           | 7.812      | 100                              | 1           | 2   |
| 12389      | 198.391| 0        | 0           | 8.365      | 100                              | 1           | 2   |
| 14257      | 156.311| 0        | 0           | 6.701      | 100                              | 1           | 2   |
| 14896      | 136.236| 0        | 0           | 3.505      | 100                              | 0           | 2   |
| 17868      | 136.236| 0        | 0           | 3.836      | 100                              | 0           | 2   |
| 73170      | 426.724| 1        | 1.7         | 6.947      | 100                              | 1           | 1   |
| 92157      | 468.762| 0        | 2           | 7.866      | 100                              | 1           | 1   |
| 92313      | 204.355| 0        | 0           | 5.49       | 100                              | 1           | 2   |
| 92842      | 468.762| 0        | 2           | 8.056      | 100                              | 1           | 1   |
| 222284     | 414.713| 1        | 1.7         | 7.393      | 100                              | 1           | 0   |
| 246983     | 426.724| 1        | 1.7         | 7.523      | 100                              | 1           | 2   |
| 259846     | 426.724| 1        | 1.7         | 7.055      | 100                              | 1           | 1   |
| 324224     | 204.355| 0        | 0           | 5.115      | 100                              | 1           | 2   |
| 440917     | 136.236| 0        | 0           | 3.991      | 100                              | 0           | 2   |
| 441005     | 204.355| 0        | 0           | 5.489      | 100                              | 1           | 2   |
| 441005     | 204.355| 0        | 0           | 5.489      | 100                              | 1           | 2   |
| 5280371    | 202.166| 1        | 3.75        | 0.996      | 84.961                           | 0           | 0   |
| 5281326    | 412.698| 1        | 1.7         | 7.373      | 100                              | 1           | 2   |
| 5281515    | 204.355| 0        | 0           | 5.037      | 100                              | 1           | 2   |
| 5281520    | 204.355| 0        | 0           | 5.133      | 100                              | 1           | 2   |
| 5281553    | 136.236| 0        | 0           | 4.425      | 100                              | 0           | 2   |
| 5283637    | 400.687| 1        | 1.7         | 7.06       | 100                              | 1           | 0   |
| 5315347    | 204.355| 0        | 0           | 5.077      | 100                              | 1           | 2   |
| 5315347    | 204.355| 0        | 0           | 5.077      | 100                              | 1           | 2   |
| 5317570    | 204.355| 0        | 0           | 5.427      | 100                              | 1           | 2   |
| 6429302    | 204.355| 0        | 0           | 5.195      | 100                              | 1           | 2   |
| 10899740   | 204.355| 0        | 0           | 5.058      | 100                              | 1           | 2   |
| 11095734   | 204.355| 0        | 0           | 5.134      | 100                              | 1           | 2   |
| 22003145   | 218.338| 0        | 0.5         | 4.419      | 100                              | 0           | 2   |

Permissible ranges for different parameters: Solute molecular weight (130.0/725.0); Donor HBs (0.0/6.0); Acceptor HBs (2.0/20.0); Percentage human oral absorption (±20%) (-25%; Poor, >80%; High); Lipinski rule of 5 - (maximum=4); Predicted CNS activity (- to ++) - +2 (inactive), +2 (active). QPlog Po/w: Predicted octanol/water partition coefficient; CNS: Central nervous system; HBs: Hydrogen bonds; MW: Molecular weight; +: CNS-active; -:CNS-inactive
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Conflicts of interest

There are no conflicts of interest.

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