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Insilico pharmacological evaluation of dibenzosuberenone derivatives as antidepressant

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Abstract

A new drug takes a long time and is expensive to introduce. By using *insilico* drug design, you can save time and money. Utilizing computational software, a novel Schiff's base Dibenzosuberenone derivative was designed and molecular docking studies were performed using autodock software. To predict Absorption, Distribution, Metabolism, Excretion, and Molecular Properties of Dibenzosuberenone derivatives, *insilico* screening was performed. It should be examined how its Dibenzosuberenone derivatives interact with specific targets. The Dibenzosuberenone derivatives were successfully identified as targets in this study.

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Introduction

The new drug development is important for the pharmaceutical field. Because of the developing of new diseases, the resistance of the drug, and drugs having various side effects. A new approach is using in silico methods to develop new drugs by using various software. In silico methods, which are widely used in drug development, have significantly reduced both the cost and the time required. In silico drug discovery is based on the identification of the active target and the ligand [1].

Dibenzosuberenone is a good starting point for many biologically active compounds. l The 5-dibenzosuberenone through different modes of functionalization of the tricyclic structure. On the central "seven-membered ring," a carbonyl ring or two double bonds modify the structure of dibenzosuberenone.

Schiff's bases play an important role in pharmaceutical drug preparation. Schiff's bases are formed from primary amines and carbonyl compounds. An organic compound with the azomethine group (C = N) is referred to as a Schiff base.Schiff bases accompanying these reactions have been found to have biological activity, which is why they have been used to treat a variety of diseases. Dibenzosuberenone was used with amine compounds to design new molecules.The Schiff bases of dibenzosuberenone derivatives are new pharmaceutical entities [2-7].

Methodology

Drug design

The drug was designed using ChemSketch software. X-ray crystallography or NMR spectroscopy plays a crucial role in the structure-based drug design process. A medicinal chemist may use interactive graphics and intuition to design candidate drugs predicted to bind with high affinity and selectivity to the biological target based on its structure. The development of new drug entities may also be automated using various computational procedures [8-10].

Molecular Property Prediction

By using molinspiration, in silico molecular prediction was conducted on the new compounds. The properties such as logP, molecular weight, H-bond donors, H-bond acceptors, and rotatable bonds were assessed [11-13].

Molecular Docking Studies

A docking programme such as MGL Tools is used to automate the docking process. A ligand is usually a molecule that binds to a receptor (target) in a way that is most beneficial to the receptor (target). A rigid docking mode and a flexible docking mode are available. In docking, molecules are positioned, conformed, and oriented to fit perfectly into the target structure. When two molecules form an intermolecular complex, molecular docking determines how they are arranged. A ligand is typically a small molecule that binds to proteins. A binding site is an area of a protein where compounds are formed. Binding can take place in a variety of mutual conformations [14-17].

Autodock

Procedure

The automatic docking procedure Autodock 4.2.6 determines whether ligands interact with biomacromolecular targets. In this study, a serotonin transporter with a validated experimental structure was used as a target (PDB ID: 6AWO). Through the combination of rapid grid-based energy evaluation and efficient torsional freedom search, AutoDock accomplishes these goals. AutoDock typically provides reproducible docking results for ligands that have approximately 10 flexible bonds when using the Lamarckian

Genetic Algorithm and an empirical free energy scoring function. Protein and ligand starting structures impact docking results in a significant way [18-20].

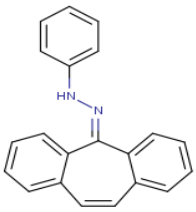
ADME Prediction

ChemSketch was used to draw the structures of all compounds. A Swiss ADME server is used for uploading the structures. Using the Swiss ADME server, the molecular sketcher import icon is clicked, a new window opens for selecting the structure, and then it is exported to SMILES. A further set of parameters was entered by pressing the icon "run" [21-22].

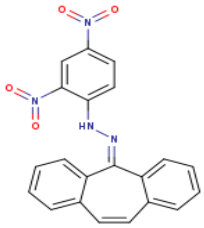
Results & Discussion

Drug Design

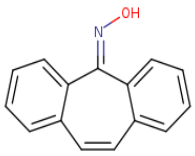
The ligands were drawn in chemsketch software and assigned to each compound with the appropriate 2D orientation. Smile Translator is used to convert the ligands into PDP format [23 & 24].



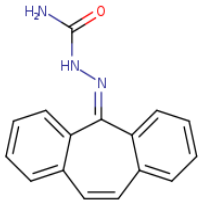
Compound -1



Compound-2



Compound-3



Compound-4

Calculation On Molecular Properties

The molecular properties were calculated using molecular inspiration. Lipinski's rule of five describes it. Molecule weight, hydrogen bond donor, hydrogen bond acceptor, and log P make up these five properties.[25].

TableNo:1Molecular properties of designed compounds and reference drug

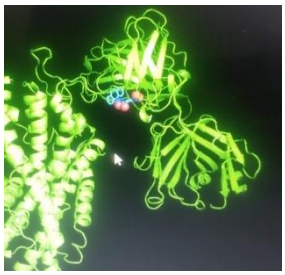
Compound name	M.W (G/Mol)	Donor-hydrogen bonds	Acceptors-hydrogen bonds	Log P	No.of.violation
compound-1	296.37	1	1	4.66	nil
compound-2	386.36	1	5	3.78	nil
compound-3	221.25	1	2	3.19	nil
compound-4	263.29	2	2	2.48	nil
Amitriptyline	277.40	0	1	4.36	nil

Molecular Docking Studies

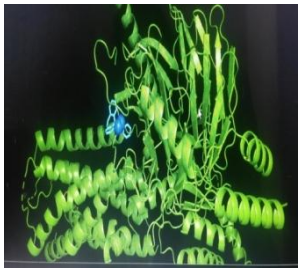
An auto-dock program was used to perform molecular docking studies efficiently.[26] Ligants bind to protein, and their binding energy has been calculated. Compound 2 has the highest protein binding energy.[28&29]. The protein is docked with all four ligands, and the results are,

Table No: 2 Molecular docking result of designed compounds and reference drug

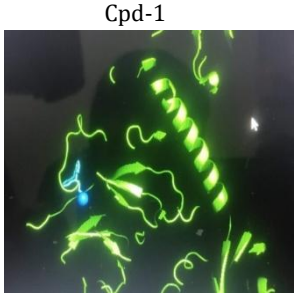
Compound name	Docking interaction	(-) Binding energy (kcal mol−1)
1	6AWO	-7.37
2	6AWO	-8.31
3	6AWO	-6.72
4	6AWO	-7.13
Amitriptyline	6AWO	-6.61



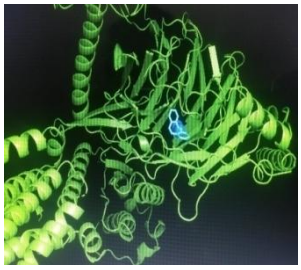
Cpd-1



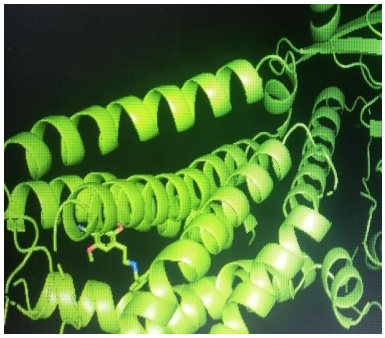
Cpd -2



Cpd-3



Cpd -4



Cpd -5

ADME Prediction

The ADME properties of the compounds and the reference drug amitriptyline were predicted using the SWISS ADME server, [30] and the results are recorded in Table.no.3

TableNo: 3 ADME properties of designed compounds and reference compound

COMPOUND NAME	M/W (g/mol)	HBA	HBD	TPSA	CONSENSUS Log Po/w	MR	GI	BBB	P-gp	Lipinski	Bioavailability	PAINS	BRENK
1	296.37g/mol	1	1	24.39 Å	4.66	96.90	high	yes	no	Yes*	0.55	0	0
2	386.36g/mol	5	1	116.03 Å	3.78	114.54	low	no	no	Yes*	0.55	0	1
3	221.52g/mol	2	1	32.59 Å	3.19	68.80	high	yes	no	Yes*	0.55	0	2
4	263.29g/mol	2	2	67.48 Å	2.48	78.98	high	yes	no	Yes*	0.55	0	0
Amitriptyline	277.40	1	0	3.24 Å	4.36	90.96	high	yes	no	Yes**	0.55	1	0

HBA: Hydrogen bond acceptors; HBD-Hydrogen bond donors; MR-Molar Refractivity; TPSA- Topological Polar Surface Area; GI-Gastro-intestinal; BBB: Blood brain barrier; P-GP: P-Glycoprotein; *Average of five Prediction; **1 violation: MLOGP> 4.15 PAINS- Pan-Assay Interference compounds; MW: Molecular weight;

Conclusion

Designed the new molecules from the dibenzosuberenone nucleus. The design compounds possess the Lipinski rule. The compounds were studied using molecular docking, and compound-2 had a lower binding energy than the others. Based on the comprehensive virtual screening done for ADMET profiling of dibenzosuberenone derivatives, it has been concluded that these molecules should be synthesized, characterized, and evaluated pharmacologically in the future based on the predicted values of physicochemical descriptors.

Acknowledgement

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Takashi Fujiwara, Steric structure–activity relationship of cyproheptadine derivatives as inhibitors of histone methyltransferase Set7/9. Bioorganic & Medicinal Chemistry 24(2016) 4318–4323.
2. Stana, A.New Thiazolyl-Triazole Schiff Bases: Synthesis and Evaluation of the Anti-Candida Potential. Molecules 2016, 21, 1–19.
3. Mahadev N. Kumbar,1 Ravindra R. Kamble, Design and Microwave Assisted Synthesis of Coumarin Derivatives as PDE Inhibitors International Journal of Medicinal Chemistry Volume 2016, Article ID 9890630, 16 pages.
4. Singh, A., Srinivasan, A.K., Chakrapani, L.N. and Kalaiselvi, P., 2019. LOX-1, the common therapeutic target in hypercholesterolemia: a new perspective of antiatherosclerotic action of aegeline. Oxidative medicine and cellular longevity, 2019.
5. Ter Laak AM, Van Drooge MJ, Timmerman H, Donné-Op den Kelder GM.QSAR andmolecular modelling studies on histamine H1-receptor antagonists. Quantitative structureactivity relationships (2008); 11 (3):348 – 363.
6. Yamamoto T, Niwa S, Iwayama S, Koganei H, Fujita S, Takeda T, et al.Discovery, structure-activity relationship study, and oral analgesic efficacy of cyproheptadinederivatives possessing N-type calcium channel inhibitoryactivity. Bioorg Med Chem. (2006);14(15):5334.
7. Honda M., Nishida T., Ono H. Tricyclic analogs cyclobenzaprine, amitriptyline andcyproheptadine inhibit the spinal reflex transmission through 5-HT2 receptors. Eur JPharmacol. (2003);458 (1-2):91-99.
8. Ke-Liang Guo, Design, Synthesis and Bioevaluation of Substituted Phenyl Isoxazole Analogs as Herbicide SafenersJournal of Agricultural and Food Chemistry, (2020).
9. Singh, A., Gowtham, S., Chakrapani, L.N., Ashokkumar, S., Kumar, S.K., Prema, V., Bhavani, R.D., Mohan, T. and Sathyamoorthy, Y.K., 2018. Aegeline vs Statin in the treatment of Hypercholesterolemia: A comprehensive study in rat model of liver steatosis. Functional Foods in Health and Disease, 8(1), pp.1-16.
10. Shah, J. Design, Synthesis and Evaluation of Benzotriazole Derivatives as Novel Antifungal Agents. Bioorg. Med. Chem. Lett. 2015, 25, 3730–3737.
11. Khedr, M. Design, Synthesis, and In Vitro Antifungal Screening of (Z)-Substituted-Propenoic Acid Derivatives with Potent Broad-Spectrum Antifungal Activity. Drug Des. Devel. Ther. 2015, 4501–4513.
12. Singh, A., Kumar, A. and Kalaiselvi, P., 2018. Aegeline, targets LOX1, the receptor for oxidized LDL to mitigate hypercholesterolemia: a new perspective in its anti-atherosclerotic action. Free Radical Biology and Medicine, 128, p.S41.
13. W. Hamaguchi, "Design and synthesis of novel benzimidazole derivatives as phosphodiesterase 10A inhibitors with reduced CYP1A2 inhibition," Bioorganicand Medicinal Chemistry, vol. 21, no. 24, pp. 7612–7623, 2013.

14. Arnott, J.The Influence of Lipophilicity in Drug Discovery and Design. Expert Opin. Drug Discov.2012, 7, 863–875.
15. Konatham Teja Kumar Reddy, & M. Akiful Haque. (2022). Develop and validate a highly sensitive method for the estimation of Molnupiravir in rat plasma by high-performance liquid chromatography-tandem mass spectroscopy and its application to pharmacokinetic studies. *Journal of Pharmaceutical Negative Results*, 28–34. https://doi.org/10.47750/pnr.2022.13.S01.0
16. Konatham Teja Kumar Reddy, Penke Vijaya Babu, Rajinikanth Sagapola, & Peta Sudhakar. (2022). A REVIEW OF ARTIFICIAL INTELLIGENCE IN TREATMENT OF COVID-19. *Journal of Pharmaceutical Negative Results*, 254–264. https://doi.org/10.47750/pnr.2022.13.S01.31
17. Sultan, M.A.; Almansour, A. Synthesis, theoretical studies and molecular docking of a novel chlorinated tetracyclic:(Z/E)-3-(1, 8-dichloro-9, 10-dihydro-9, 10-ethanoanthracen-11-yl) acrylaldehyde. J. Mol. Struct. 2017, 1150, 358–365.
18. Singh, A., 2022. Role of microbial metabolites in cardiovascular and human health. In Microbiome, Immunity, Digestive Health and Nutrition (pp. 137-148). Academic Press.
19. Morris, G. AutoDock4 and AutoDockTools4: Automated Docking with Selective Receptor Flexibility. J. Comput. Chem. 2009, 30, 2785–2791.
20. Konatham Teja Kumar Reddy, Kumaraswamy Gandla, Penke Vijaya Babu, M Vinay Kumar Chakravarthy, Pavuluri Chandrasekhar, & Rajinikanth Sagapola. (2022). A CRITICAL REVIEW ON BIOANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF FEW ONCOLOGY DRUGS BY USING LC-MS-MS. Journal of Pharmaceutical Negative Results, 16–27. https://doi.org/10.47750/pnr.2022.13.S01.03
21. Reddy, K. T. K., & Haque, M. A. (2022). Bioanalytical method development and validation of atrasentan in human plasma using verapamil as internal standard by liquid chromatography coupled with tandem mass spectrometry. International Journal of Health Sciences, 6(S8), 625–638. https://doi.org/10.53730/ijhs.v6nS8.10470
22. Singh, A., 2022. Hyperlipidemia in cardiovascular health and digestion. In Nutrition and Functional Foods in Boosting Digestion, Metabolism and Immune Health (pp. 141-150). Academic Press.
23. Mujeeb A. Sultan Synthesis, Molecular Docking, Drug likeness Analysis, and ADMET Prediction of the Chlorinated Ethanoanthracene Derivatives as Possible Antidepressant Agents. Appl. Sci. 2020, 10, 7727.
24. S. Vilar, E. Quezada, "Design, synthesis, and vasorelaxant and platelet antiaggregatory activities of coumarin–resveratrol hybrids," Bioorganic and MedicinalChemistry Letters, vol. 16, no. 2, pp. 257–261, 2006.
25. Shiv Chandra Singh, A., Yu, A., Chang, B., Li, H., Rosenzweig, A. and Roh, J.D., 2021. Exercise Training Attenuates Activin Type II Receptor Signaling in the Aged Heart. Circulation, 144(Suppl_1), pp.A14259-A14259.
26. Paolo Grieco,Design and Microwave-Assisted Synthesis of Novel Macrocyclic Peptides Active at Melanocortin Receptors: Discovery of Potent and Selective hMC5R Receptor Antagonists J. Med. Chem. (2008), 51, 2701–2707.
27. Konatham Teja Kumar Reddy et.al High Performance Liquid Chromatography for The Simultaneous Estimation of Anti-Ulcer Drugs in Pharmaceutical Dosage Form, journal of Positive School Psychology, Vol. 6, No. 9, 4524-452
28. Roh, J., Hill, J.A., Singh, A.,Valero-Muñoz, M. and Sam, F., 2022. Heart failure with preserved ejection fraction: heterogeneous syndrome, diverse preclinical models. Circulation Research, 130(12), pp.1906-1925.
29. Reddy KTK, Haque MA. Development and Validation of a High Throughput Lc-Ms/MS Method for Quantitation of Ipilimumab in Human Plasma. International Journal of Pharmaceutical Quality Assurance. 2022;13(3):303-307
30. Teja Kumar Reddy Konatham et al, A Systematic Review on Method Development and Validation of Few Antiviral Drugs by Using RP-HPLC. Ijppr.Human, 2021; Vol. 21 (3): 651-661.
31. W. Hamaguchi, "Design and synthesis of novel benzimidazole derivatives as phosphodiesterase 10A inhibitors with reduced CYP1A2 inhibition," Bioorganicand Medicinal Chemistry, vol. 21, no. 24, pp. 7612–7623, 2013.
32. Boini, K.M., singh, A. and Koka, S.S., 2021. Gut Microbial Metabolite Trimethylamine N-oxide Enhances Endoplasmic Reticular Stress and Promotes Endothelial Dysfunction. Circulation, 144(Suppl_1), pp.A14071-A14071.
33. Nayana Adhikari, Microwave assisted synthesis, docking and antimalarial evaluation of hybrid PABA-substituted 1,3,5-triazine derivatives, J.HeterocyclicChem. 2020; 1–11.wileyonlinelibrary.com/journal/jhet.
34. Teja Kumar Reddy Konatham, M. Anuradha (2020), a stability indicating method development and validation of Telmisartan and Nifedipine in pure form using RP-HPLC. International Journal of Pharmaceutical, Biological and Chemical Sciences, 9(3): 36-44
35. T. J. T. Josna, N. R. N. Rajesh, K. N. S. K. Naga Sindhura, K. H. R. K. Hema Ravali, N. U. J. N. Uma Jyothi, and V. N. G, "incidence and prevalence of various psychiatric disorders in psychiatric department of teaching based hospital ongole: a prospective observational study", *Int J Indig Herb Drug*, pp. 11-24, Aug. 2020.
36. Teja Kumar Reddy Konatham, Satyanarayana Reddy K., Anuradha Manipogo, a Review on viruses that originated from china; Sars, mers and covid-19 World Journal of Pharmaceutical Research, Vol 9, Issue 5, 2020, 2010-2015.

37. Konda RK. Brief description of Clinical Case study formats: a basic review. Journal of Case Studies and Case Reports. 2022 Apr 30:24-6.
38. A. Bekhit and T. Abdel-Aziem, "Design, synthesis and biological evaluation of some pyrazole derivatives as antiinflammatory- antimicrobial agents," Bioorganic and MedicinalChemistry, vol. 12, 2004 no. 8, pp. 1935–1945,.
39. Jiang, Y. Synthesis, In Vitro Evaluation and Molecular Docking Studies of New TriazoleDerivatives as Antifungal Agents. Bioorg. Med. Chem. Lett. 2011, *21*, 4471–4475.
40. T. J. T. Josna, S. R. SK. Rizwana, and G. G.V.Nagaraju, "Case Study On Depression", *Int J Indig Herb Drug*, pp. 1-3, Aug. 2019.
41. Konatham Teja Kumar Reddy and Kumaraswamy Gandla. Novel Vesicular Drug Delivery Systems Proniosomes. Pharm Res 2022, 6(3): 000272.
42. Gabriel Marc1, Anca Stana, 3,5-Disubstituted Thiazolidine-2,4-Diones:Design, Microwave-Assisted Synthesis, Antifungal Activity, and ADMET Screening, Society for Laboratory Automation and Screening. SLAS Discovery1–8 2018.