Asian Journal of Pharmaceutical Education and Research
Vol -13, Issue-3, July- September 2024
ISSN:2278 7496

REVIEW ARTICLE Impact Factor: 7.014

A REVIEW ON DERIVATIVES OF ESCITALOPRAM

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Received 12 June. 2024; Revised 15 June. 2024; Accepted 21 June. 2024, Available online 10 July. 2024

Cite this article as: Niingo AN, Bhanja M, Nanda N, Tiwari S. A review on derivatives of Escitalopram. Asian Journal of Pharmaceutical Education and Research. 2024; 13(3):44-52.

https://dx.doi.org/10.38164/AJPER/13.3.2024.44-52

ABSTRACT

Depression is a major public concern and a leading cause of disability worldwide. The World Health Organization (WHO) lists depression as the leading cause of illness in the world, with an estimated 300 million individuals affected worldwide contributing to worldwide disability. Not only is depression ubiquitous and widespread, but it also has the potential to be fatal; depression is thought to be a contributing factor in 90% of suicides. Psychiatric medications known as antidepressants are currently among the most often prescribed drugs for treating various forms of depression, among the most often prescribed medications is escitalopram. While there is disagreement among researchers regarding both their benefits and drawbacks with the exception of selective serotonin reuptake inhibitors (SSRI) escitalopram, the main issue with antidepressant use is the development of serious adverse reactions, including acts of suicide and ideas. Research has shown that escitalopram is superior to other SSRIs in treating severe depression because it acts faster (depressive symptoms subside after 1-2 weeks as opposed to 3-5 weeks) and causes fewer adverse effects. Owing to the significance of escitalopram discussed earlier a collection of 44 derivatives of escitalopram structures has been suggested by us; some of these structures likely exhibit markedly enhanced antidepressant efficacy when compared to the original drug.

Keywords: Escitalopram, Depression, Derivatives, Serotonin transporter.

INTRODUCTION

Escitalopram belongs to the class of selective serotonin reuptake inhibitors. It has been used in the treatment of severe depression and sometimes anxiety disorders. This substance raises serotonin levels in neuronal synapses by inhibiting serotonin (5-HT). It works by attaching to the allosteric, or principal, binding site on the serotonin transporter (SERT), which is also the site to which endogenous 5-HT binds, escitalopram increases serotonergic activity and inhibits serotonin from being reabsorbed into the presynaptic neuron [1].

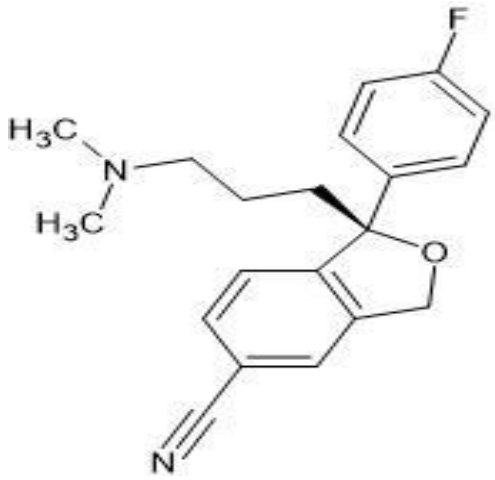


Fig 1.1 Escitalopram

A multitude of processes in human psychology and physiology, including mood, appetite, sleep, and sexual drive, are regulated by the serotonergic system.The 5-HT transporter SERT is one of the primary modulators of synaptic 5-hydroxytryptaminergic transmission [2]. The synaptic signal is terminated by SERT, which facilitates the reuptake of released 5-HT into the presynaptic terminal. Additionally, the procedure makes sure that the intracellular 5-HT stores are refilled. The physiological significance of SERT in 5-HT signaling is supported by the fact that medications that target SERT are used to treat a wide range of illnesses, including neuropathic pain, depression, anxiety, and obsessive-compulsive disorder. Among the most often prescribed selective 5-HT reuptake inhibitors (SSRIs) is escitalopram [3].

Issues with antidepressants

The main issue with antidepressant use nowadays, is the severe side effects that were previously discussed with the exception of the SSRI escitalopram, particularly the induction of suicidal behavior and ideas. Research has shown that escitalopram is superior to other SSRIs in treating severe depression because it acts faster (depressive symptoms subside after 1-2 weeks as opposed to 3-5 weeks) it also has fewer adverse effects [4]. Furthermore, escitalopram manufacturer Lundbeck's meta-analysis of a clinical trials database revealed no evidence that the medication would cause suicidal behavior in patients with major depressive disorder and anxiety disorders in comparison to a placebo; on the contrary, suicidal thoughts were significantly reduced in the escitalopram group [5].

When depressed individuals were not taking medication, unpleasant responses were more common than when they were receiving antidepressant treatment. Treatment with nortriptyline was linked to weight gain (15%), constipation (33%), and dry mouth (74%). During escitalopram medication, yawning (16%), sleeplessness (36%), and diarrhea (9%), were more frequent. Nortriptyline withdrawal was predicted by

tiredness and urine issues. The cessation of escitalopram was predicted by diarrhea and decreased appetite. Even with the improved citalopram derivative, which is thought to have fewer negative effects than the other antidepressants, we can still develop better derivatives because they have negative side effects as well, although they are generally less severe than those of the other drugs [6].

Another problem is treatment failure, wherein, even in patients whose depression remitted acutely by clinical measures, the medication showed no relative improvement with acute treatment (controlling for time or repeated testing). This underscores the need for high binding and effective derivatives. We can obtain more and better derivatives from escitalopram if it is a superior derivative of citalopram[7-9].

Methodology as per review of literature

Screening of derivatives

Admetlab 2.0

Which is a website used for the methodical assessment of ADMET (absorption, distribution, metabolism, excretion and toxicity) qualities, together with various physicochemical properties and medicinal chemistry friendliness. Admetlab makes it possible to quickly and easily calculate and predict 17 physical characteristics, 13 medicinal chemistry measures, 23 ADME outcomes, 27 toxicity endpoints, and 8 toxicophore guidelines (751 substructures), which helps to identify lead compounds with potential for additional research [10,11].

This prediction is made because, in order for a new molecular entity to be developed into a medicine, it must meet several criteria, including having a positive pharmacokinetic profile that includes toxicity (ADMET) and the appropriate biological activity in addition to being safe and effective. Therefore, in order to improve the likelihood of compounds making it to the lead optimization stage, it is necessary to forecast the ADMET features early in the development process. Admetlab screens for the following admet properties; absorption, distribution, metabolism, excretion and toxicity [12-14].

Chemsketch

Chemsketch is a sketching program/software that makes drawing easier by including built-in templates, bonds that are limited to specific lengths and angles, and other features. It creates, sketches, and alters pictures of molecular structures. Moreover, it produces IUPAC names. This program also aid in the prediction of spectral data, and they can be used to create 3D structures [15,16]. To enhance visibility, the application has several sophisticated features that enable the molecules to spin and add color. It offers

several templates with images and functional groupings, allowing users to customize outputs produced by the program by adding text and utilizing additional tools [17-19].

Protein data bank

Developed in 1971, the Protein Data Bank is a computer-based archive for macromolecules. The Bank maintains partial bond connectivity and atomic coordinates in a standard format. The Bank's mission is to gather, standardize, and disseminate information from crystallographic research, including atomic coordinates. The Protein Data Bank contains structural variables and stages from macromolecule diffraction experiments alongside atomic coordinates and connectivity [20,21].

Our protein was obtained with the aid of the Protein Data Bank.

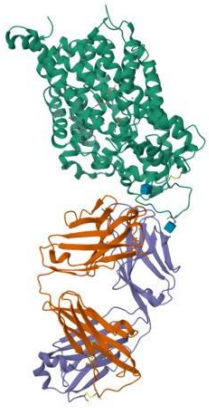


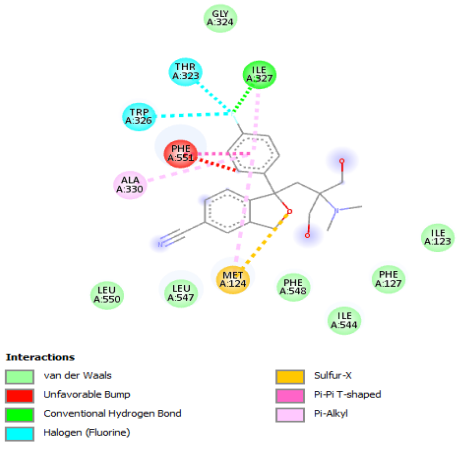
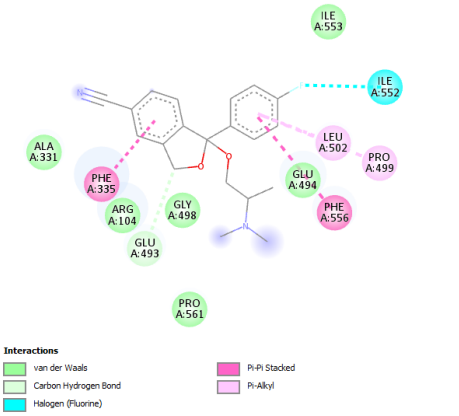
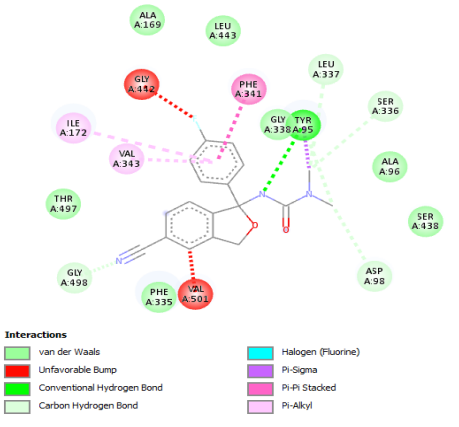
Fig 1 Protein 5i73

Argus Lab

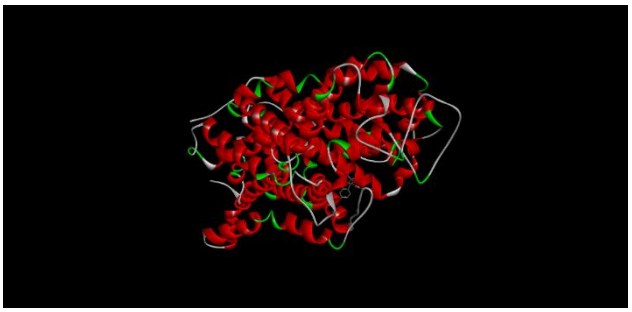
Molecular docking is the study of the fit between two or more molecular structures. It is employed to forecast a protein's interactions with ligands. It enables the prediction of the favored binding orientation of a ligand (or receptor) to another molecule (or both) when the two combine to create a stable complex. Molecular docking's scoring function can be used to forecast the energy profile (such as binding free energy), strength, and stability (such binding affinity and binding constant) of complexes based on information obtained from the preferred orientation of bound molecules [22,23]. Argus Lab is a software program designed for quantum computation, graphics, and molecular modeling. The building of molecular structures using basic molecular dynamics simulation, improving structure using basic generic force fields, and file processing for quantum chemical computation applications are all implemented by

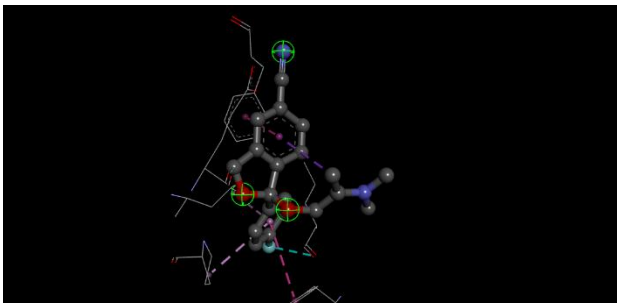
this application [24,25]. This application was used for protein-ligand interaction and Receptor-ligand interaction

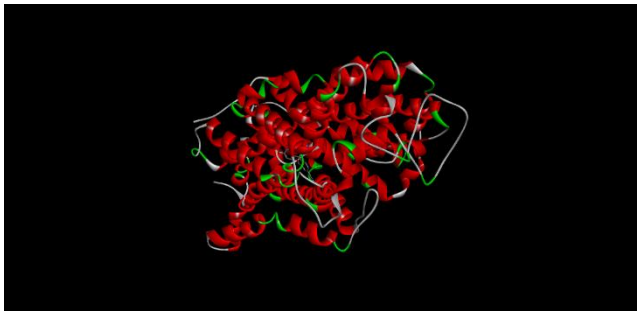
Table 1: Ligands interaction with binding energy and binding pose.

Sl. No	2D ligand interactions	Binding energy	Bonding pose
1		-10.4049 kcal/mol	132 final unique configurations
2		-10.3713 kcal/mol	128 final unique configurations
3		-10.7866 kcal/mol	126 final unique configurations

The interactions mentioned in a table above are displayed below:

1. 

2. 

3. 

CONCLUSION

We can create novel escitalopram compounds that may be employed as possible antidepressants thanks to the antidepressant activity at the SERT that is consistently anticipated as they all had a high binding energy and bonding pose. We believe that increasing the number of negative electrostatic interactions at the SERT active site and aiding in the escitalopram membrane crossing will result in a significant enhancement of the SERT antagonism activity. Therefore, we increased the number of hydrophobic and hydrophilic interactions with escitalopram by adding allyl, ethyl, i-propyl, propyl, and t-butyl substituents and halogen (F, Cl, Br), hydroxyl, nitro, methoxy, or amide substituents. These substances served as a recommendation for additional research in both clinical and molecular modeling.

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