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Molecular Docking Insights into Gatifloxacin Derivatives as Prospective Antidepressant Agents

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The current focus in drug discovery aims to identify promising therapeutic candidates for further research. Depression, a significant public health issue, is closely linked to low serotonin levels. Researchers are investigating novel antidepressant agents through chemical modifications and protein analysis. The various derivatives are assessed for their antidepressant activity through in silico molecular docking simulations by using AutoDock and ADME analysis. Autodock includes formation of PDBQT files, docking of converted ligands and protein forms, formation of 9 different positions of docked molecules results into binding score, 2D image and 3D images of same one. Docking studies reveal molecular interactions between biological macromolecules (8FSB) and ligands, with strong protein-ligand interactions potentially inhibiting the reuptake of serotonin at the post-synaptic nerve, thereby increasing serotonin availability and exerting antidepressant effects. Gatifloxacin derivatives demonstrated higher binding affinities with 8FSB, Gati I (-11.4 kcal/mol), Gati II (-11.1 kcal/mol), Gati III (-8.2 kcal/mol), Gati IV (-7.9 kcal/mol), Gati V (-9.5 kcal/mol), and Gati VI (-9.7 kcal/mol), all exceeding gatifloxacin (-6.9 kcal/mol). These findings suggest that gatifloxacin derivatives may serve as potent antidepressants of drug discovery lies in the synergistic use of in vitro and in vivo studies, leveraging technological advancements to develop safer and more effective therapies. The findings related to gatifloxacin derivatives highlight the potential of these approaches in identifying novel antidepressants, paving the way for further research and clinical trials.

Keywords: Antidepressant activity; AutoDock; Gatifloxacin; Gatifloxacin derivatives; PDB ID: 8FSB.

According to the World Health Organization (WHO), depression is one of the most common mental health disorders worldwide. Here, considering an alarming number of mental health patients, which may be three patients behind 20 persons or 5.3% people of all ages suffer from depression globally. [1] It is characterized by a protracted period of depression, loss of pleasure, or lack of interest in activities. [2] All depressive disorders are characterized by feelings of melancholy, emptiness, or irritability, together with physical and cognitive abnormalities that seriously impair the sufferer's ability to function. [3]

The etiology of major depressive disorder is multifactorial, viz. biological, environmental, and genetic, such as changes in brain chemistry, family history of depression, shifting social norms, stress or trauma exposure, social isolation, and family conflicts. [4,5] Despite these obstacles, a literature survey has found several factors linked to depression in young Indian adults. [6]

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The prime aim of treatment is antidepressants, a popular choice for depression, to relieve the symptoms of severe depression. [7] They are also used to stop suicidal thoughts and to relieve symptoms like anxiety, restlessness, and insomnia. [8] The way symptoms worsen over time and the likelihood of a relapse of depression will also determine how long treatment takes. Some people use antidepressants for a long time. [9]

Hence, researchers worldwide are actively seeking new antidepressant agents. One approach involves modifying existing medications chemically and analyzing medicated substances to identify potential antidepressant properties. [10] This strategy aims to enhance drug effectiveness and address unmet medical needs in treating depression. [11] Therefore, researchers pointed out, fluoroquinolone compound that is non-opthalmic gatifloxacin, which was banned due to an adverse-effects, namely dysglycemia. The new targeted gatifloxacin derivatives may act as good antidepressant drugs. [12]

Gatifloxacin is a monocarboxylic acid that is 4-oxo-1,4-dihydroquinoline-3-carboxylic acid. Cyclopropyl groups are substituted on the nitrogen of the compound, and fluoro, 3-methylpiperazin-1-yl, and methoxy groups are substituted at positions 6, 7, and 8, respectively. [13,14] As an antibiotic belonging to the fourth-generation fluoroquinolone family, gatifloxacin inhibits the bacterial topoisomerase type-II enzymes, just like other antibiotics in the family. It functions as an antimicrobial, an anti-infective. [15]

Notably, serotonin in the brain regulates the mood. It's often called the body's natural good or happy chemical. When serotonin is in the normal range, you feel more focused, emotionally stable, happier, and calmer. Serotonin is synthesized from a protein called tryptophan. Hence, serotonin is termed 5-HT (5-hydroxy tryptophan). Low serotonin levels in the brain cause depression, which is worse for health. [16]

At the molecular level, the presynaptic membrane synthesizes and secretes serotonin, reaching into the synapse where available serotonin binds to the serotonin receptor present on the synaptic membrane. Under no more conditions, SLC6A4 allows reabsorption of serotonin in the presynaptic membrane and also brings the Cl- and K+ into extracellular space. The selective serotonin reuptake inhibitors inhibit the reuptake by blocking the SLC6A4 transporter, resulting in more serotonin available to bind the post-synaptic membrane. [17,18]

These modifications in gatifloxacin include the conversion of the third carboxylic group of gatifloxacin into an ester group. Further, this ester group is fused with quercetin [21], â-sitosterol [22], stigmasterol [23], lanosterol, kaempherol, and bergenin [24], which reflects anti-depessant activity as per the literature survey.

So, the rationale of hypothesized derivatives was screened for anti-depressant activity through molecular docking simulation. Therefore, it will be beneficial to synthesize particular derivatives that showed the best binding energy with respective proteins also based on drug likeliness property. [25] Thus, hypothesized drug entities are claimed for anti-depressant activity. This research highlights the potential effect of developing more effective antidepressants, which could significantly improve treatment outcomes for individuals suffering from depression. Also, higher binding energies of these derivatives suggest enhanced antidepressant potential compared to gatifloxacin, warranting further exploration for clinical development.

MATERIAL AND METHODS

Molecular docking allows the availability of three-dimensional macromolecular structures, which enables a diligent inspection of the binding site topology. This computational approach indicated sequence alignment, residue network interaction, binding energy. This different docking softwares were downloaded like

a. ACDLabs202121_ChemSketchFree_Install
b. Avogadro-1.2.0n-win32
c. BIOVIA_2021.DS2021Client
d. Getintopc.com-PerkinElmer_ChemOffice_Suite_v21.0.0.28
e. Mgltools_win32_1.5.7_Setup
f. PYMOL-2.5.2-Windows-x86_64

This fundamental process was initiated by targeting desirable protein from data bank.

Protein selection

Prior to docking, researcher identified appropriate proteins from the Protein Data Bank, based on lower A° value. The initial phase involved

by considering the completeness of their data and their correlation with relevant enzymes to produce pharmacological effects. The interested protein was downloaded from protein data bank, PDB ID: 8FSB relevant to anti-depressive activity. [26]

Initialize the ligand for docking

Chemdraw

The ligand structure was generated by using ChemDraw software. We selected the 'structure' option from the toolbar, performed a 'check structure' to identify and then applied '3D cleanup'. The resulting structure was saved as 'Ligand' in MDL Molfile (*mol) format."

Pymol

This process involved opening the saved ligand, selecting the 'file' option, and choosing 'Export structure' as 'Export molecule.' This action led to an output window where the file was saved once more, this time in the 'BIOVIA discovery file' format.[27]

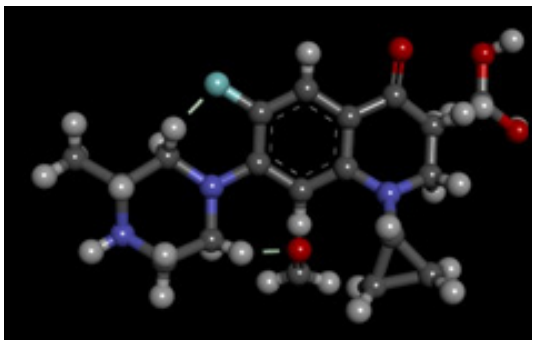


Fig. 1. Gatifloxacin structure

Protein Design

The process involved opening the downloaded protein in BIOVIA. From the 'Chemistry' option on the toolbar, polar hydrogen groups were added. As a result, it showed strong binding affinity, specificity and binding topology with ligand. Simultaneously, ligand groups and heteroatoms were removed from side windows. By right-clicking, amino acid attributes were copied to the configuration file. Finally, the modified protein was saved as 'Protein' in the BIOVIA discovery file format, specifically in the 'Protein Data Bank File' format. [28]

Docking

AutoDock 1.5.7 is a widely used in receptor-ligand docking simulation program. The docked protein was consequently saved as PDBQT files. The PDBQT files of protein and ligand were formed to showcase protein -ligand docking score. It explores different interaction positions. Specifically, it identifies up to 9 distinct ligand-protein interaction sites by analyzing the main docking folder using specific commands. The first command was vina.exe -help, then second command was vina.exe —config config.txt —log log.txt, it gave binding affinity score. The last command was vina_split.exe —input ligand.out. pdbqt which unveiled 9 possible interactions of protein-ligand complex.

View docking result

Finally, affinity was recorded in the form of kcal/mol and displayed in AutoDock window. The table showed binding energy, lower bound and upper bound root mean square deviation of

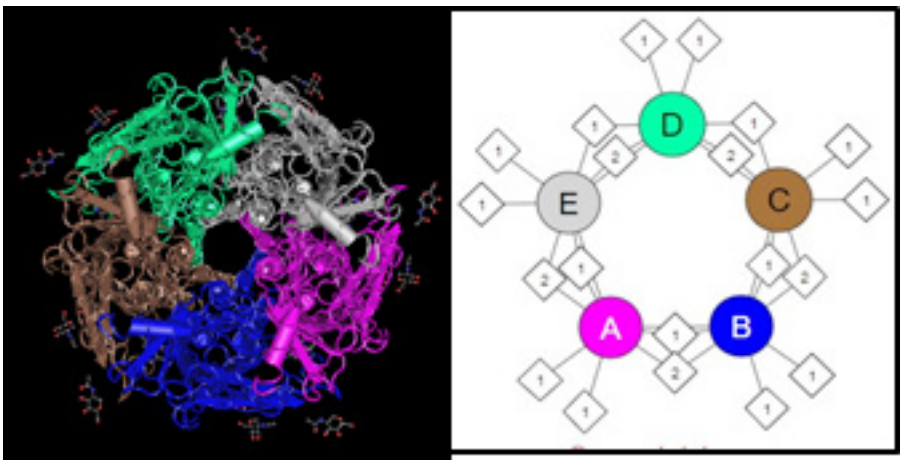


Fig. 2. PDB ID: 8FSB

different 9 positions. So, these 9 positions were dragged into BIOVIA and positions were assessed for H bond interactions. It exhibited depicted conformations with 2 D and 3 D images. The 2D images displayed the pi-pi stacking, covalent bond, vander wall forces, H bond, electrostatic bond and hydrophobic interactions. [29]

RESULT AND DISCUSSION

The emphasis on identifying promising therapeutic candidates underscores the interdisciplinary approach, can facilitate faster progress through methodologies such as in silico docking simulations and ADME. The use of in silico molecular docking simulations is a powerful tool in providing insights into the binding affinities of gatifloxacin derivatives to the target protein 8FSB. All derivatives showed a free binding energy score by binding with amino acids of targeted proteins at a specific distance. The reported binding energies in Table 5 indicate that these derivatives have significantly higher binding affinities than gatifloxacin itself, suggesting enhanced potential for therapeutic efficacy.

The link between low serotonin levels and depression is well-established, supporting the rationale for targeting serotonin availability in therapeutic strategies. The role of the serotonin reuptake inhibitor further justifies the investigation of compounds that can inhibit its binding of serotonin at the synaptic nerve, leading to increased serotonin levels in the brain. The promising in silico results highlight the need for further exploration, including in vitro and in vivo studies to assess the efficacy, safety, and pharmacokinetics of gatifloxacin derivatives. This progression is essential to open avenues for whether these

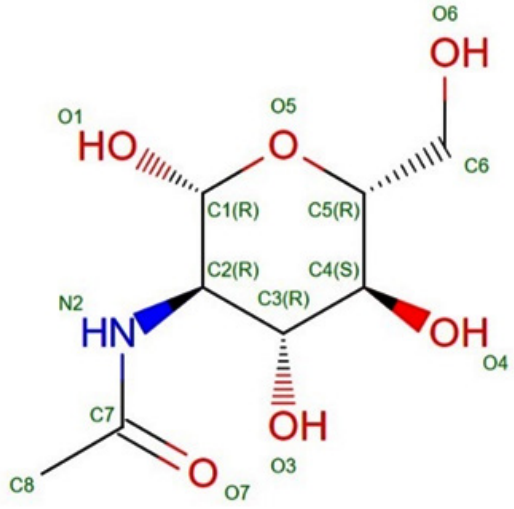


Fig. 3. NAG - acetamido-2-deoxy-beta-D-glucopyranose: (C8H15NO6)

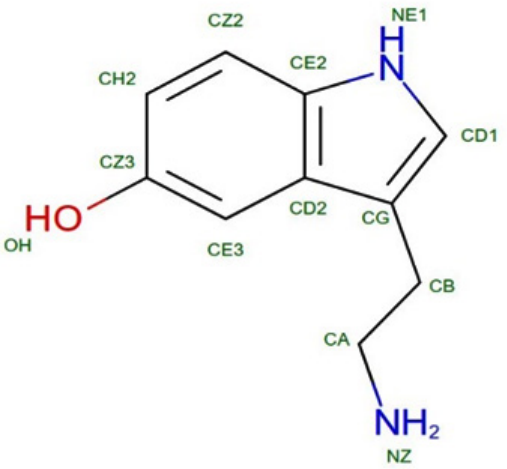


Fig. 4. SRO - SEROTONIN: (C10H12N2O)

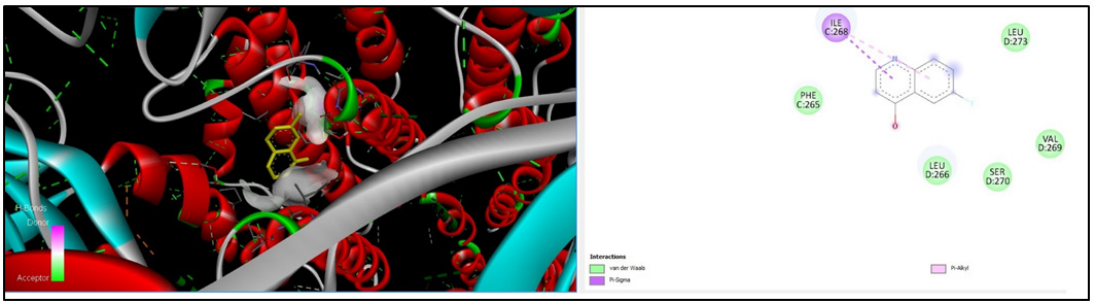


Fig. 5. Gati I: 8FSB

Fig. 6. Gati II: 8FSB

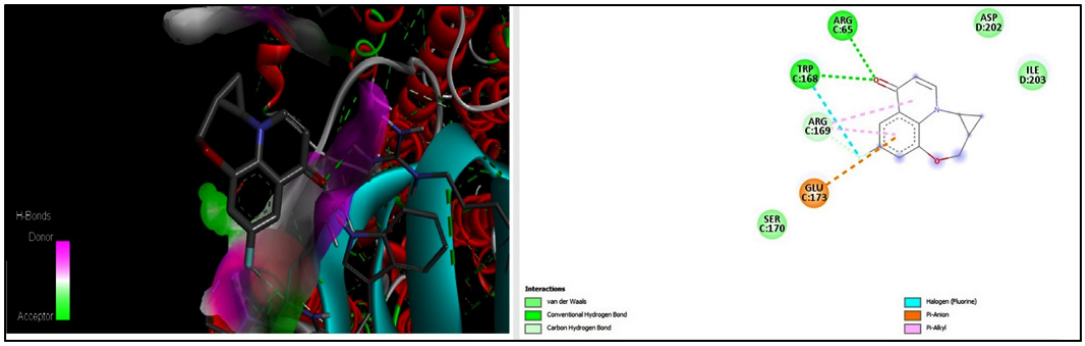


Fig. 7. Gati III: 8FSB

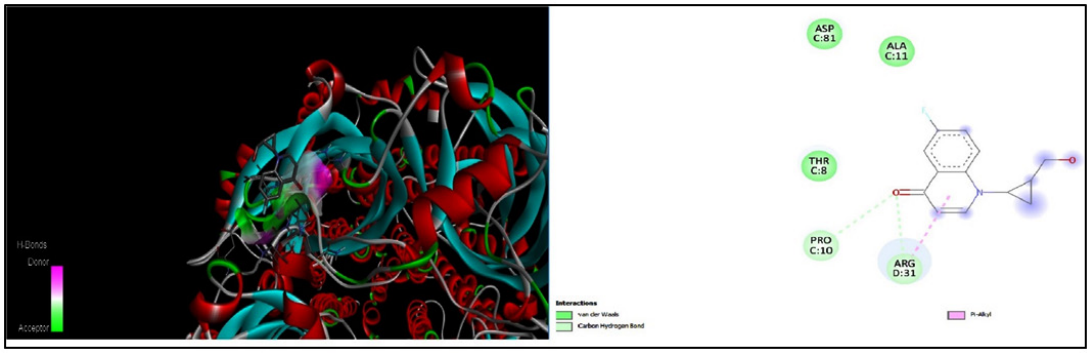


Fig. 8. Gati IV: 8FSB

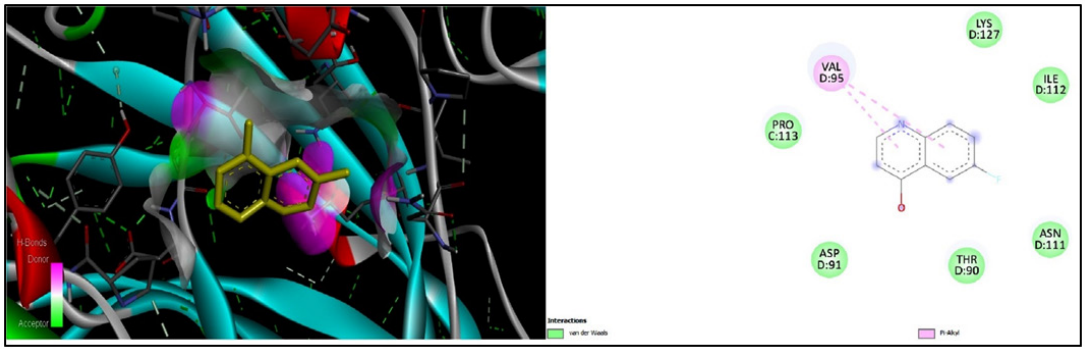


Fig. 9. Gati V: 8FSB

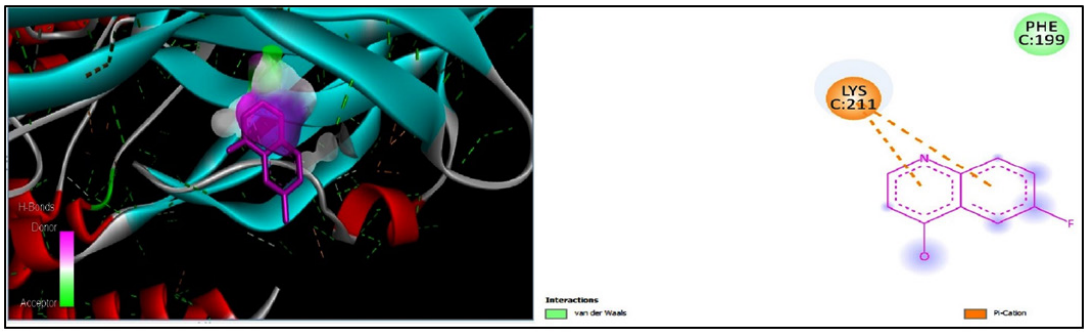


Fig. 10. Gati VI: 8FSB

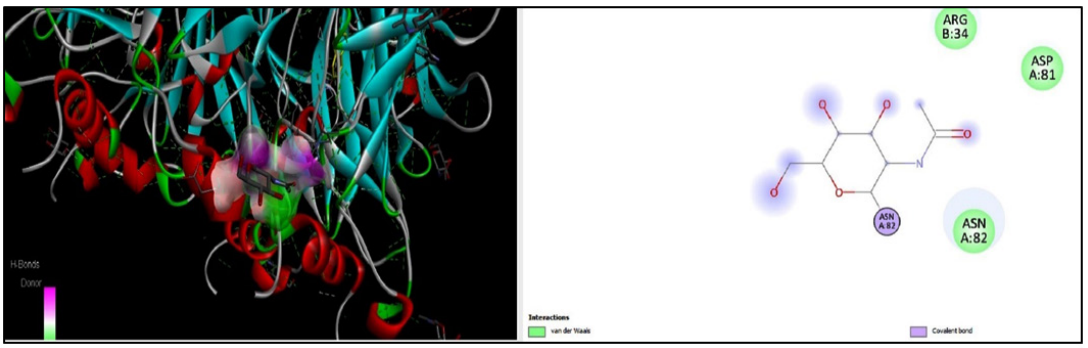


Fig. 11. Gatifloxacin: 8FSB

Table 1. Macromolecular content

Sr. no.	Name of Protein	8FSB
1.	Classification	Transport protein
2.	Organism(s)	Mus musculus
3.	Molecule	5-hydroxytryptamine receptor 3A
4.	Chains	A, B, C, D, E
5.	Sequence Length	553
6.	Expression System	Spodoptera frugiperda
7.	Method	Electron spectroscopy
8.	Resolution	2.75 A^0
9.	Total Structure Weight	315.95 kDa
10.	Atom Count	16,640
11.	Modelled Residue Count	1,975
12.	Deposited Residue Count	2,765
13.	Unique protein chains	1

Table 2. Chemical composition of 8FSB

Chain	Length	Residues	Atoms				
			Total	C	N	O	S
A, B, C, D, E	553	395	3273	2156	535	573	9

Table 3. Structure of Gatifloxacin derivatives

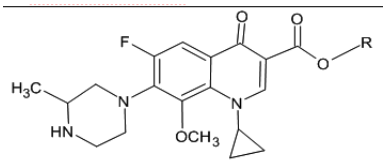
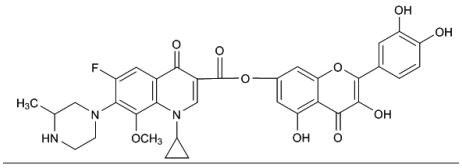
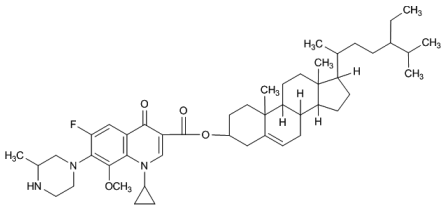
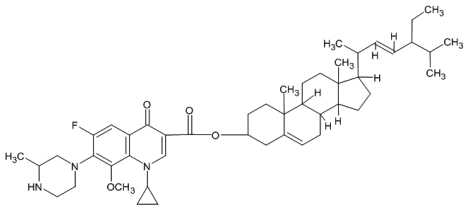
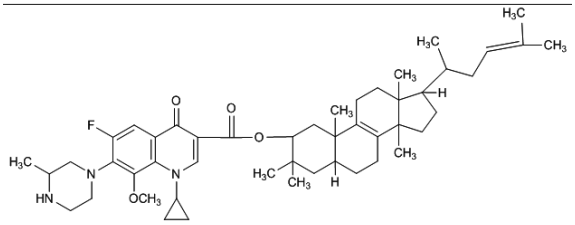
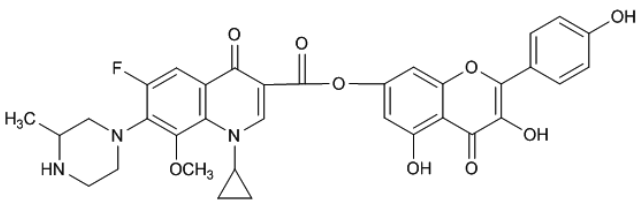
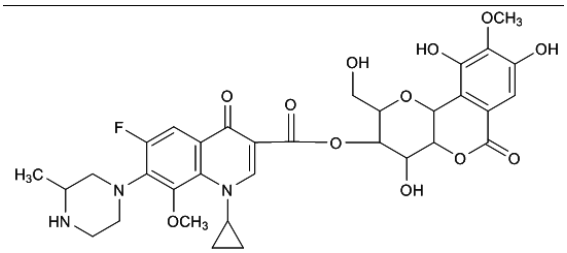
Sr. no.	Basic structure of derivatives	
		
1.	Gati I	
2.	Gati II	
3.	Gati III	
4.	Gati IV	
5.	Gati V	
6.	Gati VI	

Table 4. Docking score

Sr. no.	Compound	8FSB	
		Free binding energy (kcal/mol)	No. of H-bond interaction
1.	Gati I	-11.4	2
2.	Gati II	-11.1	0
3.	Gati III	-8.2	6
4.	Gati IV	-7.9	3
5.	Gati V	-9.5	2
6.	Gati VI	-9.7	2
7.	Gatifloxacin	-6.9	0

compounds can translate from laboratory findings to clinical success.

If gatifloxacin derivatives demonstrate the desired antidepressant effects in clinical trials, their introduction to the market could provide a new treatment option for depression, addressing an urgent public health need. This potential is especially relevant in light of the rising rates of depression globally, underscoring the importance of innovative therapeutic strategies.

Gati I exhibit a robust affinity for the protein with PDB ID: 8FSB for antidepressant activity. Specifically, Gati I demonstrated a free binding energy of -11.4 kcal/mol for first binding pose when interacting with 8FSB. The second pose gave -11.4 kcal/mol binding energy had lower bound root-mean-square deviation (RSMD) value is 16.724, while the upper bound RSMD value is 20.444. Notably, Gati I binds to the receptor protein by interacting with the ILE C:268 amino acid residue.

Here, Gati II displayed -11.1 kcal/mol (first binding pose) binding energy with potential targeted protein as Mono amino oxidase inhibitor. Also, second binding pose showed -11.0 kcal/mol binding affinity recorded lower bound and upper bound root square mean deviation is 2.3222, 3.614 respectively

Third derivative of Gatifoxacin namely Gati III indicated -8.2 kcal/mol (first binding pose), -7.9 kcal/mol (second binding pose) binding affinity which had -2.866, 4.471 distance from lower bound and upper bound root square mean deviation. The binding affinity was showed by key protein target with ligand through amino acids namely SER C:170, GLU C:173, ARG C:169, TRP C:168, ARG: C:65

The free binding energy was estimated by interlinking of 8FRX protein with Gati IV. The docking score was -8.5 kcal/mol for first binding pose and -7.9 kcal/mol for second binding pose interpreted with lower bound 8.084 and 24.268 upper bound root mean square deviation. The ligand was perfectly docked into sites of protein by PRO C:10, ARG D:31.

The Gati V showed -10.0 kcal/mol binding affinity for first pose and -9.5 kcal/mol having 1.720 and 2.970 lower and upper root mean square deviation. The possible interlinked amino acid – VAL D: 95

The Gati VI revealed -9.7 kcal/mol for first binding pose as well as -9.6 kcal/mol binding energy displayed root mean square deviation. (lower bound 7.205, upper bound 12.642). The linked amino acids – LYS C: 211.

The Gatifloxacin exhibited -6.9 kcal/mol binding energy for first and second binding pose. Simultaneously second pose recorded root mean square deviation. (lower bound-5.127, upper bound-7.338).

CONCLUSION

The current circumstances provided, lead identification and optimization have been only possible by computer-aided drug design. This high throughput screening tool is achieved successful insights for exploring the interaction of ligands with key protein. The docked derivatives stood out for their favorable binding with PDB ID: 8FSB via blocking the reuptake of 5HT at synapse. Gatifloxacin exhibits -6.9 kcal/mol binding energy with protein 8FSB. In stark contrast, all derivatives of gatifloxacin showed greater binding affinity than

gatifloxacin with targeted protein. Among that, Gati I and Gati II showed -11.4 kcal/mol and -11.1Kcal/mol respectively, which displayed greater protein binding affinity. Besides, remaining derivatives showed docking score namely Gati III -8.2 kcal/mol, Gati IV 7.9 kcal/mol, Gati V -9.5 kcal/mol and Gati VI has -9.7 kcal/mol. Hence, the predicted better anti-depressant activity of derivatives is perfectly ascribed H bond interactions, amino acid networking and binding affinity score. The above proposed chemical entity of gatifloxacin contains attached drug entity which is already proven for antidepressant activity.

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Conflict of Interest

The authors do not have any conflict of interest.

Data Availability Statement

All data generated or analysed during this study are included in this published article and will be made available on reasonable request to the corresponding author.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Author contribution's statement

PPM (Priyanka Prakash Majalekar) : has done docking study, collected required data and written manuscript as per author instructions; PJS (Pramodkumar Jaykumar Shirote) : has designed the hypothesis of research work, checked and reviewed thoroughly.

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