IRSTI 31.21.15; 31.27.51 https://doi.org/10.26577/IJBCh2024v17.i2.10

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(Received 23 November 2024; received in revised form 4 December 2024; accepted 6 December 2024)

Enhanced compound selection using holistic virtual screening for gatifloxacin analogues to overcome dysglycemic effects

Abstract. Gatifloxacin, a fluoroquinolone-class antibacterial agent, is effective but has been associated with dysglycemic side effects, leading to the withdrawal of its oral formulation. Patients treated with gatifloxacin have shown notable decrease blood glucose level and after four days of treatment there will be increases in blood glucose levels. To mitigate this issue, novel gatifloxacin derivatives were designed and assessed for their efficacy and safety through in silico molecular docking studies. The derivatives aim to prevent dysglycemia by blocking human pancreatic alpha-amylase (PDB ID: 5TD4). These modifications are hypothesized to retain antibacterial effectiveness while minimizing blood glucose fluctuations. Using AutoDock, molecular docking of gatifloxacin and its derivatives with α -amylase (PDB ID: 5TD4) revealed binding energies, with gatifloxacin exhibiting a binding interaction of -7.1 Kcal/mol; meanwhile derivatives i) Gati I = -9.0 Kcal/mol, ii) Gati-II showed -8.2 Kcal/mol; iii) Gati III -8.5 Kcal/mol; iv) Gati IV = -9.3 Kcal/mol; v) Gati V = -8.9 Kcal/mol; vi) Gati VI = -7.6 Kcal/mol; Acarbose = -13.8 Kcal/mol. Unlike gatifloxacin, these derivatives demonstrated stronger binding interactions with 5TD4, potentially reducing dysglycemic risks. This study contributes to design the targeted antibacterial agents that minimize dysglycemia-related complications, thus enhancing clinical outcomes.
Key words: AUTODOCK, gatifloxacin, gatifloxacin derivatives, PDB ID: 5TD4, α-amylase, dysglycemic activity.

Introduction

Antibiotics are indispensable in virtually all modern medicine. The antibiotic era revolutionized the treatment of infectious diseases worldwide. Gatifloxacin is nothing but the synthetic broad-spectrum antibacterial scaffold possessing 8-methoxyfluoroquinolone [1]. As a quinolone antibiotic, gatifloxacin belongs to the fourth generation of fluoroquinolones [2]. It was first made available by Bristol-Myers Squibb in 1999 as Tequin® to treat respiratory tract infections. Gatifloxacin can be administered in oral, ophthalmic, or various aqueous solution forms for intravenous therapy [3,4].

Moreover, Allergan sells it under the Zymar® brand name as eye drops in the market for conjunctivitis. Gatifloxacin functions as an antibacterial agent by inhibiting bacterial enzymes namely topoisomerase II, and topoisomerase IV. Besides, DNA gyrase II also eradicate the bacteria growth. The mechanism is totally based on binding to DNA gyrase, an enzyme that permits the untwisting requisite to copy one DNA double helix into two, thus preventing bacterial DNA replication [5,6]. Notably, the medication exhibited 100-fold greater affinity for bacterial DNA gyrase than for human DNA gyrase. This broad-spectrum antibiotic is effective against not only gram-positive but also gram-negative bacteria [7]. These are useful in only for infections that are clearly caused by bacteria or that have been proven to be so [8].

Due to the substantial number of reports of adverse events pertaining to gatifloxacin-associated dysglycemia, there was a higher frequency of hyper- and hypoglycemic episodes in gatifloxacin-treated patients than in those receiving macrolide antibiotics [9]. Hence, the FDA withdrew approval for the use of gatifloxacin-containing non-opthalmic products. Therefore, gatifloxacin oral formulations (200 mg and 400 mg tablets) were banned due to dysglycemic conditions in India almost 2011 [10]. Gatifloxacin-associated dysglycemia events were reported in clinical studies, cohort episodes, case control trails, and post-marketing surveillance. However, in the case of oral formulation of gatifloxacin, hypoglycemia occurred in the first two days and hyperglycemia occurred 3-6 days after the administration of gatifloxacin. The onset of hyperglycemia occurs 3 to

10 days after the initiation of treatment, but this can be rectified by discontinuation of gatifloxacin therapy within 24 hours [11].

According to a literature survey, the reason behind dysglycemia has not been revealed. But the mechanism behind gatifloxacin's dysglycemic effects involves deregulation of key enzymes in glucose metabolism.

However, theoretically, dysglycemic events occur due to the targeted enzymes, namely α-amylase and α-glucosidase [12]. The salivary glands produce ptyalin, which is α-amylase. It's a metalloenzyme made of calcium that helps with digestion. From the exocrine cells of the pancreas, acinar cells secrete, produce, and transfer pancreatic amylase into the intestine. It plays a pivotal role by cleaving the internal α 1-4 glycosidic bonds of polysaccharides and hydrolyzing them into small-chain dextrins, namely glucose and maltose [13]. This allows the two important surface binding sites on the same face as the active site. It has been demonstrated that a second site with a tryptophan residue that a malto-oligosaccharide wraps around has a significant impact on soluble starch binding and hydrolysis, while the first site, which has two aromatic residues, is in charge of attachment to starch granules. Further, absorption of glucose single units facilitates through GLUT-1 and GLUT-2 transporters into the circulation system. Thus, affinity of gatifloxacin derivatives towards protein PDB ID: 5TD4 was assessed through molecular docking.

Consequently, the synthesis of gatifloxacin derivatives aims to mitigate dysglycemia while retaining the antibiotic's efficiency and potency. In this way, virtual screening of all six derivatives was carried out by selecting the protein PDB ID:5TD4 from the Protein Data Bank belongs to pancreatic α-amylase [14]. These derivatives may offer improved safety profiles and therapeutic benefits [15]. However, it is essential to conduct rigorous studies to validate the effectiveness and safety of these methods. The targeted modification of the chemical framework of gatifloxacin explored variations that overcome the deregulation of blood glucose level [16]. It is therefore hypothesized that gatifloxacin ester derivatives will be synthesized, with some bulky groups occupying the third position.

As per the literature review, plant isolated constituents namely quercetin, bergenin, kaempherol, betasitosterol, stigmasterol and lanosterol lower the blood glucose level and act as dibegon. This moiety act as carriers for all gatifloxacin derivatives. Phytosterol administration can enhance insulin circulation by promoting insulin secretion from pancreatic β-cells, thereby decreasing sugar level in circulation system [17]. Isolated lanosterol also exhibits glucose-lowering properties [18]. Stigmasterol may reduce intestinal glucose absorption and activate glycolytic and glycogenic processes, leading to decreased glycogenolysis and gluconeogenesis pathways [19].

Mechanically, quercetin lowers serum glucose levels primarily through its antioxidant effects and modulation of hepatic gene expression. By blocking α-glucosidase activity *in vitro*, quercetin also lowers blood sugar levels [20]. It has been discovered that isolated kaempferol inhibits α-amylase and α-glucosidase, which further reduces glucose [21].

The association of ligand-protein paired complexes and their potential interaction sites are investigated in the field of drug development using silico docking. Molecular modelling has been shown to be an effective technique for creating novel gatifloxacin drug candidates by comparing the interactions of active medications with those of ligand molecules when they become embedded inside proteins (PDB ID: 5TD4) (Figure 1) [22].

Figure 1 – Binding topology of 5TD4

PDB ID: 5TD4 is named as Human pancreatic α-amylase enzyme, which is a starch binding site; presented in Table 1.

Table 1 – Macromolecular content

Classification	Hydrolase
Organism(s)	*Homo sapiens*
Molecule	Pancreatic alpha-amylase
Chains	A, B, C, D, E, F
Sequence length	496
Expression system	*Komagataella pastoris*
Method	X-RAY DIFFRACTION
Resolution	2.30A^{o}
Structure weight	59.66 kDa
Atoms count	4,352
Model residues count	496
Deposited residues count	496
Unique protein chain	6

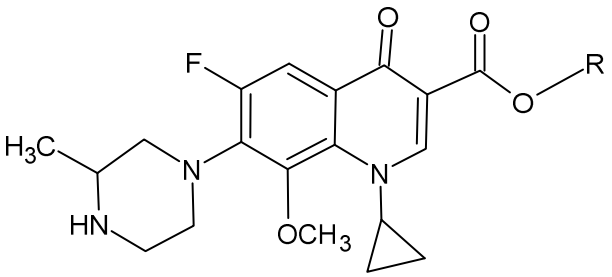
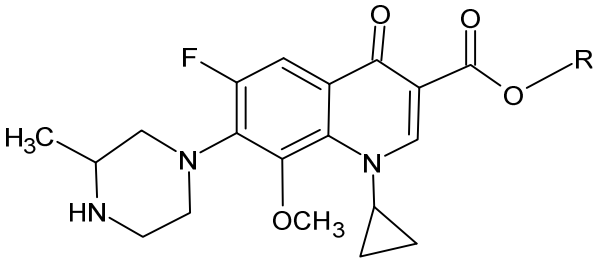
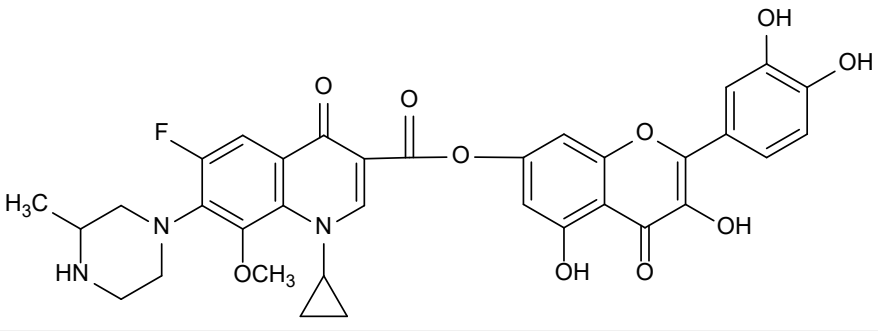
It includes D300N variant complexed with an octaose substrate.

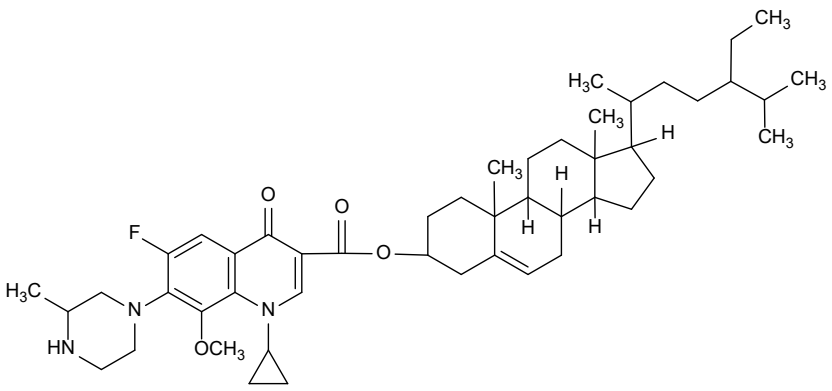
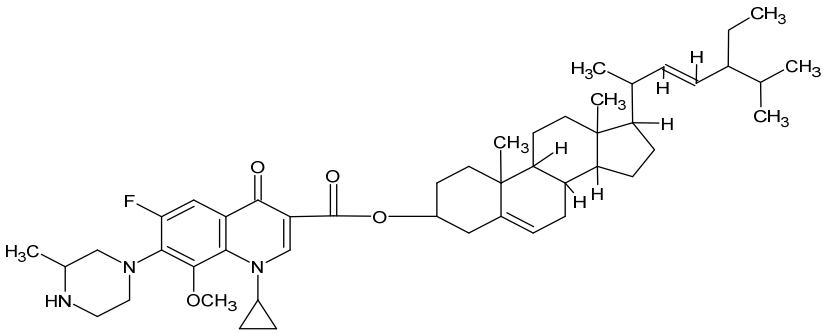
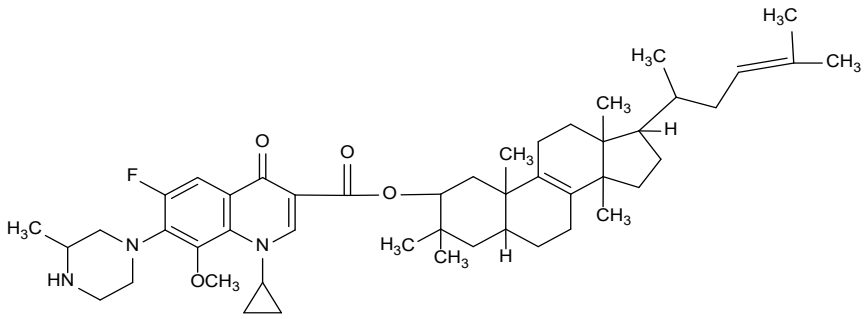
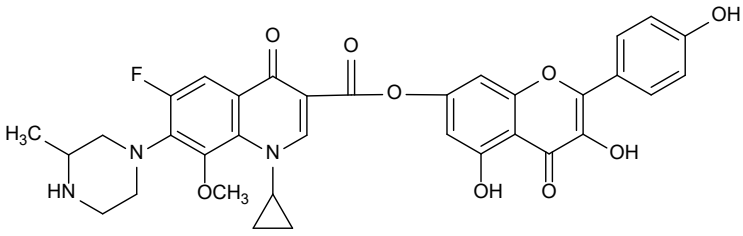
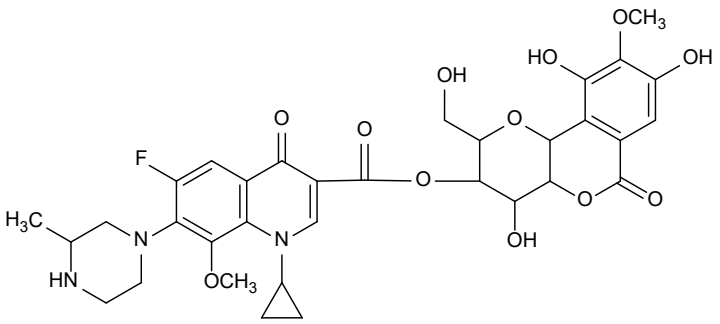
Materials and methods

In contemporary drug discovery, virtual screening serves as a crucial foundation and plays a vital role in identifying potential lead compounds. Finding the ideal ligand arrangement and placement within a receptor's binding site is the goal of molecular docking. In order to compute docking scores, AutoDock Vina was utilized to handle flexible ligands, giving priority to conformations and binding interactions that resembled those of the co-crystallized ligand.

Table 2 includes a list of the six gatifloxacin derivative structures.

Table 2 – Gatifloxacin scaffolds

Gatifloxacin	
Gatifloxacin derivatives	
Gati-I	

Gati-II	
Gati-III	
Gati-IV	
Gati-V	
Gati-VI	

The following steps were performed on Autodock:

Three-dimensional macromolecular structures are made available through molecular docking, a technique allowing for careful examination of the binding region topology. Downloading various software packages was the first step in these docking procedures namely [23,24].

i. ChemDraw
ii. Pymol
iii. Bioviadiscovery
iv. Autodock 1.5.7
v. Mgltools 1.5.7 [25,26].

Based on the protein's lower resolution, the data's completeness, and the target enzyme accountable for pharmacological activity, the appropriate proteins were chosen from the Protein Data Bank. The selected proteins were downloaded as PDB ID:5TD4 dysglycemic activity [27].

1. Preparation of 3D Ligands:

a. ChemDraw software:

The ChemDraw software was used to draw ligand, and 'structure' tab was selected, which is available on the toolbar. Then I clicked on the 'check structure' and 'clean up' structures for errors if present, and finally clicked on '3D cleanup'. Thus, in MDL – output format, an established structural unit was verified in the form of "Ligand."

b. Pymol:

The verified ligand was opened, and the "file" and "Export structure" options were selected as the "Export molecule." The outcome window that resulted contained the same file stored in the "BIOVIA discovery file" format as "Ligand" [28].

2. Preparation of Protein:

a. BIOVIA:

The "Chemistry" option in the toolbar was used to open the downloaded protein and add polar hydrogen groups. The side window was simultaneously cleared of the heteroatoms and ligand groups. The modified protein has been stored as "Protein" as part of the "BIOVIA discovery file" in the "Protein Data Bank File" format, and amino acid attributes were copied to the configuration file on the right. [29].

3. AutoDock 1.5.7:

In addition to helping to dock ligands and proteins, AutoDock also predicts binding affinities for potential interactions by converting proteins and ligands into PDBQT files. Nine distinct positions of ligand and protein interactions were obtained by commanding the main docking folder's toolbar: dock. vina.exe.cmd–help (1st command), dock.vina.exe--configconFiguretext--loglog.text (2nd command), and dock.vina_split.text.exe--inputligand.9out (3rd command). pdbqt. Lastly, the affinity was recorded in Kcal/mol. After dragging these nine positions into BIOVIA, the locations where Hydrogen-bond stacking with amino acids took place were examined. The results were verified by 2D image, 3D image, and H-bond interactions [30].

Results and discussion

This research work focused on different gatifloxacin building blocks as a good antibacterial scaffold that possesses less impact on blood glucose level. We designed six derivatives, namely Gati I to Gati VI, and analyzed their binding interaction with key targeted protein (5TD4) to understand their safety and efficacy profiles.

The parent gatifloxacin exhibited an affinity energy of -7.6 Kcal/mol towards this protein, indicating a strong interaction. Gatifloxacin exhibited condition based dysglycemia like hypoglycemia or hyperglycemic episodes. Hence, this study aimed to tweak its chemical structure, hoping to retain its antibacterial properties while overcoming its dysglycemic effects. The affinity energies of these derivatives were tested against the protein identified PDB ID: 5TD4. The derivatives showed reduced binding affinities: Gati I: -9.0 Kcal/mol; Gati II: -8.2 Kcal/mol; Gati III: -8.5 Kcal/mol; Gati IV: -8.9 Kcal/mol; Gati V: -8.9 Kcal/mol; Gati VI: -7.6 Kcal/mol. These lower binding affinities suggested that all derivatives interact more strongly with the 5TD4 protein compared to the parent gatifloxacin. The above increased affinity energies are reflecting minimum changes on blood glucose level than gatifloxacin treatment. Therefore, we are able to synthesize gatifloxacin derivatives in antibacterial armory by reducing the potential risk of blood glucose disturbance. Docking simulations of all the derivatives were carried out with PDB ID: 5TD4 for dysglycemic activity. The binding interactions gave 2D and 3D images, linked amino acids with H-bond interactions to ligands, and docking scores (Table 3, Figure 2).

Here, Gati I disclosed a potential target of 5TD4 and an affinity energy of -9.0 Kcal/mol (1st binding pose). Additionally, the 2nd binding pose had a -8.7 Kcal/mol affinity energy, and the lower and upper bound root square mean derivations were 30.528 and 34.969, respectively. The linked amino acids are Glu A:78, ARG A:20, VAL A:366, ARGA:72, GLY A:365, and ILEA:367 (Table 4, Figure 3).

Table 3 – Docking score with 5TD4 (Kcal/mol)

Sr. No.	Compounds	Affinity energy	Number of H-bond
1.	Gati I	-9.0	6
2.	Gati II	-8.2	2
3.	Gati III	-8.5	1
4.	Gati IV	-9.3	4
5.	Gati V	-8.9	3
6.	Gati VI	-7.6	2
7.	Gatifloxacin	-7.1	3
8.	Acarbose	-13.8	1

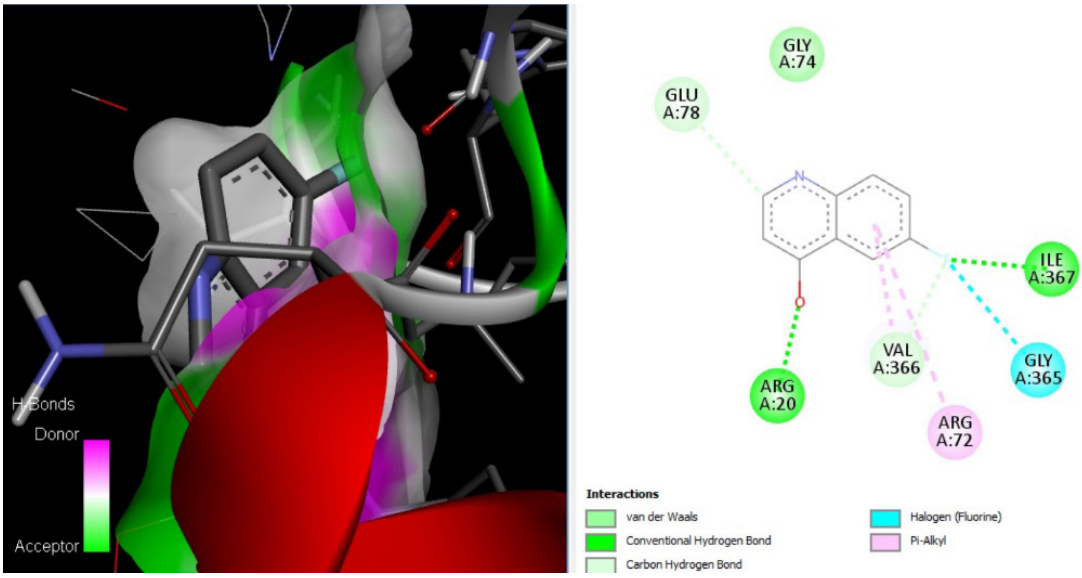


Figure 2 – 2D, 3D images – Gati I (PDB ID: 5TD4)

Table 4 – Docking score with binding interactions of Gati-I

Derivative	Binding energy (Kcal/mol)	Ligand	Linked amino acid	Distance	Type of interaction
Gati-I	-9.0	C atom of Pyridine	GLU A:78	1.89642	H bond
		O atom of pyridine ring	ARG A:20	3.02626	H bond
		Benzene ring	VAL A: 366	1.76012	H bond
		Benzene ring	ARG A:72	1.89824	H bond
		F atom	GLY A: 365	1.99998	H bond
		F atom	ILE A:367	3.36772	H bond

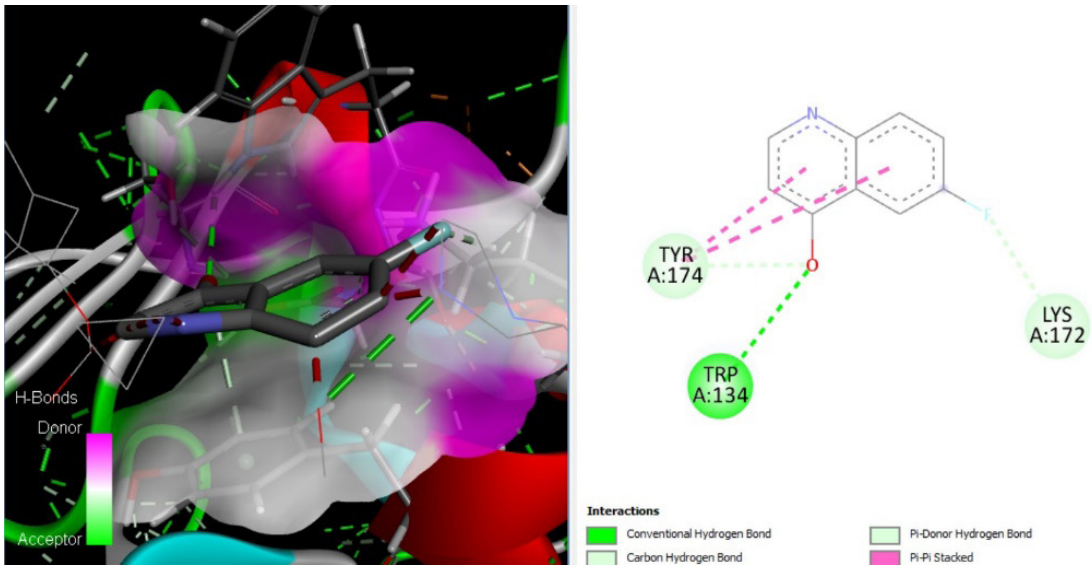


Figure 3 – 2D, 3D images – Gati II (PDB ID: 5TD4)

The second derivative, Gati II, had 1.093 and 1.770 distances from the lower & upper bounds limits (root square mean deviation), respectively, and showed binding affinities of -8.2 Kcal/mol (1st binding pose) and -8.1 Kcal/mol (2nd binding pose). The amino acids CYS A:70 and CYS A:115 demonstrated the predominant proteins' affinity energy for ligands (Table 5, Figure 4).

Table 5 – Docking score with binding interactions of Gati II

Derivative	Binding energy (Kcal/mol)	Ligand	Linked amino acid	Distance	Type of interaction
Gati-II	-8.2	Pyridine ring	CYS A:70	1.86493	Hydrophobic bond
		F atom	CYS A:115	1.93467	H bond

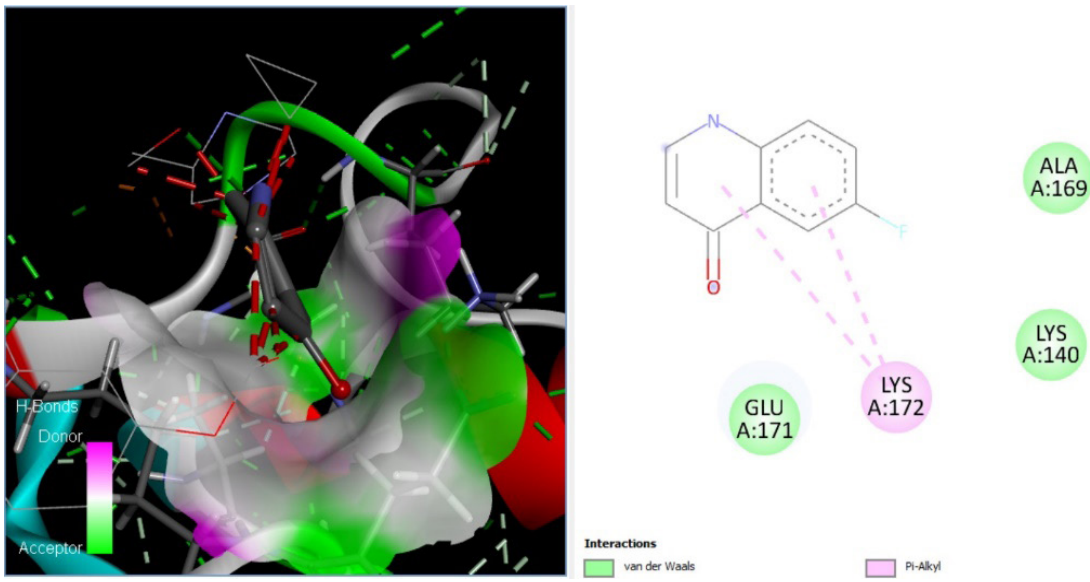


Figure 4 – 2D, 3D images – Gati III (PDB ID: 5TD4)

The free binding energy was estimated using the interaction between the 5TD4 protein and Gati III. The docking score was -8.5 Kcal/mol for the first binding pose and -8.4 Kcal/mol for the second binding pose, according to the lower bound (1.065) and upper bound (1.496) root mean square deviations. The ligand was docked onto protein sites by LYS A:172 (Table 6, Figure 5).

Table 6 – Docking score with binding interactions of Gati-III

Derivative	Binding energy (Kcal/mol)	Ligand	Linked amino acid	Distance	Type of interaction
Gati-III	-8.5	Benz pyrimidine ring	LYS A:172	2.52343	H bond

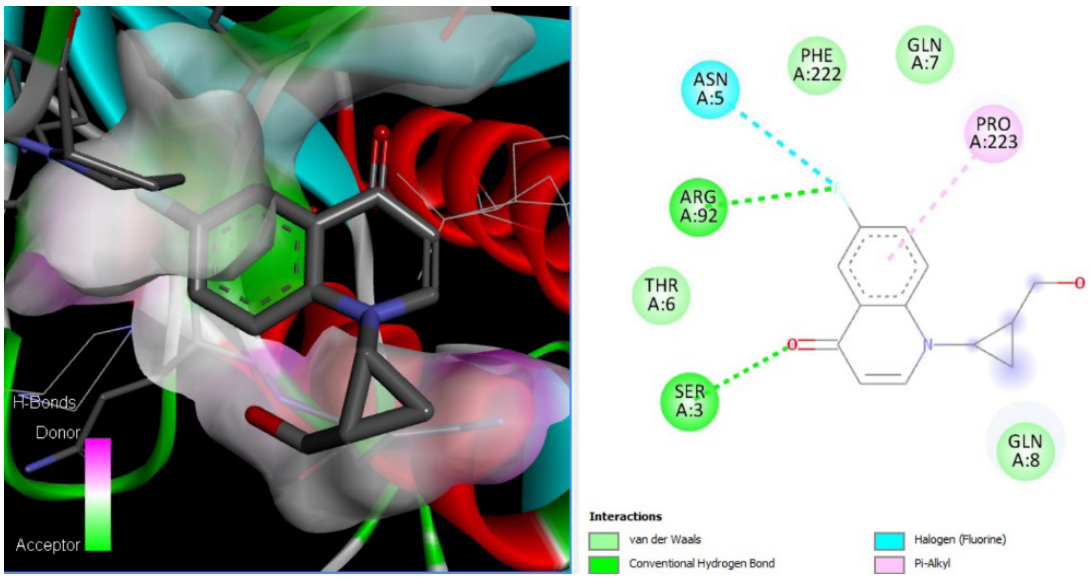


Figure 5 – 2D, 3D images – Gati IV (PDB ID: 5TD4)

Gati IV exhibited an affinity energy of -9.3 Kcal/mol in the primary binding pose and -9.3 Kcal/mol in the secondary pose, with corresponding root mean square deviations (RMSD) of 1.839 Å (lower) and 2.368 Å (upper). Potential interacting amino acid residues include ASN A:5, ARG A:92, SER A:3, and PRO A:223 (Table 7, Figure 6).

Table 7 – Docking score with binding interactions of Gati IV

Derivative	Binding energy (Kcal/mol)	Ligand	Linked amino acid	Distance	Type of interaction
Gati-IV	-9.3	F atom	ASN A:5	3.01834	H bond
		F atom	ARG A:92	3.24961	H bond
		O atom of ketone	SER A:3	2.95887	H bond
		Benzene ring	PRO A:223	2.98123	H bond

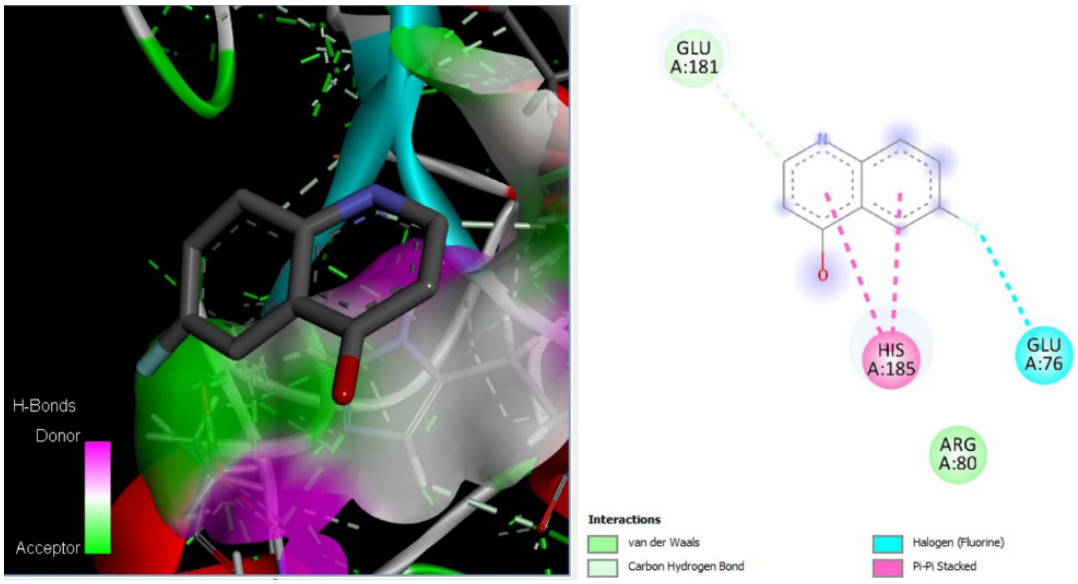


Figure 6 – 2D, 3D images – Gati V (PDB ID: 5TD4)

Gati V displayed significant dysglycemic activity at the 5TD4 protein target. In the first binding pose with 5TD4, Gati V showed a free binding energy of -8.9 Kcal/mol. The second binding pose exhibited a free binding energy of -8.8 Kcal/mol, with root-mean-square deviation (RMSD) values of 20.097 Å (lower bound) and 23.664 Å (upper bound). Notably, Gati V interacts with the receptor protein through binding with residues GLU A:181, HIS A:185, and GLU A:76 (Table 8, Figure 7).

Gati VI demonstrated a binding energy of -7.6 Kcal/mol in its primary binding pose, indicating potential as a monoamine oxidase inhibitor. The secondary binding pose exhibited a binding affinity of -7.5 Kcal/mol, with root mean square deviations (RMSD) of 16.572 Å (lower bound) and 19.558 Å (upper bound). The interacting amino acid residues are GLU A:181 and HIS A:185 (Table 9, Figure 8).

At PDB ID: 5TD4, gatifloxacin demonstrated a less binding interaction with the same protein. In particular, when Gatifloxacin interacted with 5TD4, it showed a free binding energy of -7.1 Kcal/mol for the first binding pose. With a lower bound root-mean-square deviation (RSMD) of 1.562 and an upper bound of 2.149, the second pose yielded a binding energy of -7.0 Kcal/mol. Gatifloxacin interacts with the amino acids PRO A:228, LEU A:214, and LYS A:227 to bind to the receptor protein (Table 10, Figure 9).

Table 8 – Docking score with binding interactions of Gati V

Derivative	Binding energy (Kcal/mol)	Ligand	Linked amino acid	Distance	Type of interaction
Gati V	-8.9	C atom of pyrimidine ring	GLU A:181	2.75787	H bond
		Benzene ring	HIS A:185	2.32565	H bond
		F atom of benzene ring	GLU A:76	2.92036	H bond

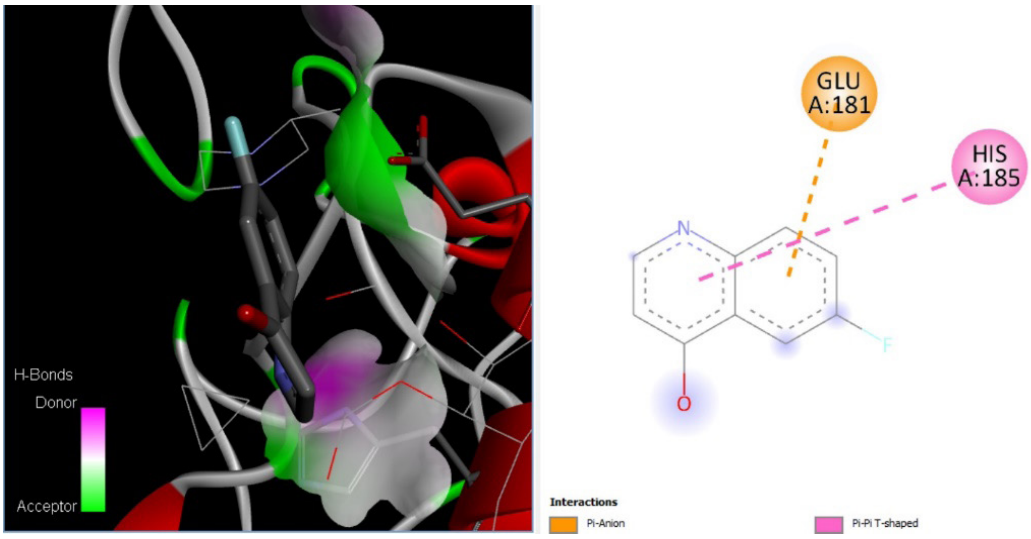


Figure 7 – 2D, 3D images – Gati VI (PDB ID: 5TD4)

Table 9 – Docking score with binding interactions of Gati VI

Derivative	Binding energy (Kcal/mol)	Ligand	Linked amino acid	Distance	Type of interaction
Gati VI	-7.6	Benzene ring	GLU A: 181	1.7	H bond
		F atom of benzene ring	HIS A: 185	2.0	H bond

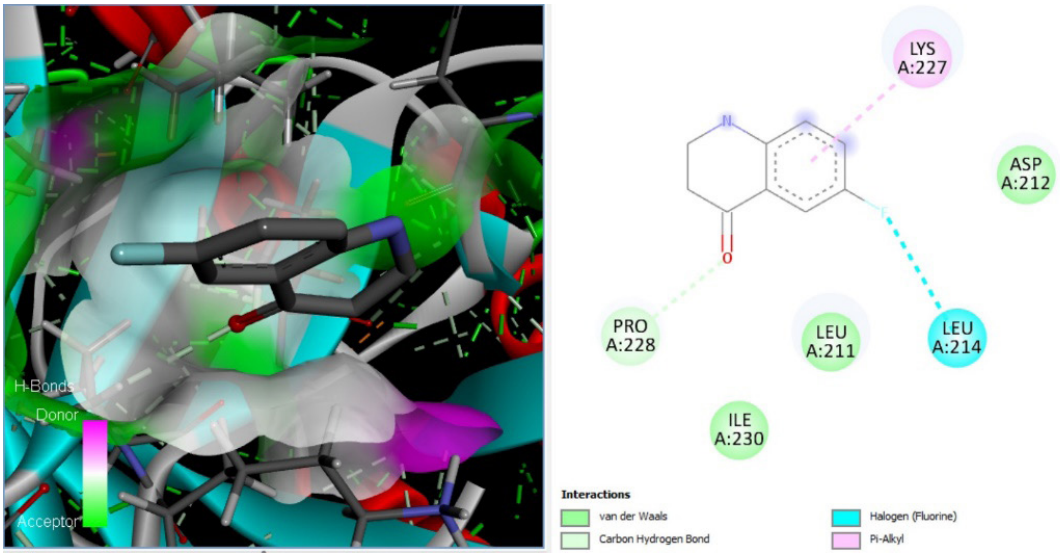


Figure 8 – 2D, 3D images – Gatifloxacin (PDB ID: 5TD4)

Table 10 – Docking score with binding interactions of Gatifloxacin

Standard	Binding energy (Kcal/mol)	Ligand	Linked amino acid	Distance	Type of interaction
Gatifloxacin	-7.1	Benzene ring	PRO A:228	1.73673	H bond
		F atom	LEU A: 214	2.03383	H bond
		Benzene ring	LYS A:227	2.90897	H bond

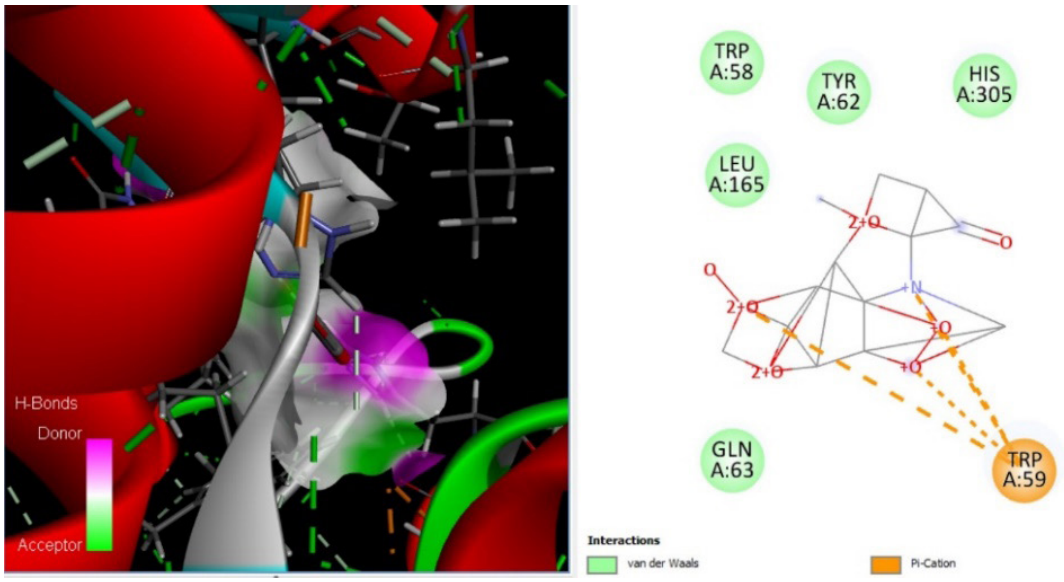


Figure 9 – 2D, 3D images – Acarbose (PDB ID: 5TD4)

At PDB ID: 5TD4, acarbose demonstrated strong dysglycemic action. In particular, while interacting with 5TD4, it showed an unrestrained binding power of -13.8 Kcal/mol for the initial binding position. With a lower limit of the root-mean-square deviation (RSMD) of 0.923 and an upper bound of 2.049, the second pose yielded an energy binding value of -13.6 Kcal/mol. Gatifloxacin interacts with the amino acid TRP A:59 to attach to the receptor protein (Table 11).

Table 11 – Docking score with binding interactions of Acarbose

Standard	Binding energy (Kcal/mol)	Ligand	Linked amino acid	Distance	Type of interaction
Acarbose	-13.8	Quaternary N atom	PRO A:228	1.73673	H bond

Conclusion

This discovery successfully enlighted that gatifloxacin derivatives (Gati I to Gati VI) contribute a maximum affinity energy towards the 5TD4 protein. The increased affinity energy is less significant to induce dysglycemic effects. Thus, finding gives a safer alternative to gatifloxacin, retaining antibacterial efficacy while minimizing the risk of adverse effects on blood glucose levels. So, this research encountered a promising avenue for developing improved antibacterial agents with enhanced safety profiles.

Acknowledgments

Deep sense of appreciation goes towards the research institution Appasaheb Birnale College of pharmacy, Sangli for offering the AUTODOCK molecular modelling program.

Conflict of interest

All authors are aware of the article's content and declare no conflict of interest.

References

1. Fish D., North D. (2001) Gatifloxacin, an advanced 8-methoxy fluoroquinolone. *Pharmacother.,* 21(1), pp. 35-59. https://doi.org/10.1592/phco.21.1.35.34440.
2. Kishii R., Takei M., Fukuda H., Hayashi K., Hosaka M. (2003) Contribution of the 8-methoxy group to the activity of gatifloxacin against type ii topoisomerases of streptococcus pneumonia. *J Antimicrob Agents and Chemother.,* 47(1), pp. 77-81. https://doi.org/10.1128/aac.47.1.77-81.2003.
3. Fung-Tomc J., Minassian B., Kolek B., Washo T., Huczko E., Bonner D. (2000) In vitro antibacterial spectrum of a new broad-spectrum 8-methoxy fluoroquinolone, gatifloxacin. *J Antimicrob Chemother.*, 45(40), pp. 437-446. https://doi.org/10.1093/jac/45.4.437.
4. Stein G. (2000) The methoxy fluroquinolones: Gatifloxacin and moxifloxacin. *J Infections Med.*, 17(8), pp. 564-570.
5. Franca S., Carvalho C. (2002) Effectiveness, safety and tolerability of gatifloxacin, a new 8- methoxy fluoroquinolone, in the treatment of outpatients with community-acquired pneumonia: a Brazilian study. *Braz J Infect Dis*., 6(4), pp. 157-163. https://doi.org/10.1590/S1413-86702002000400002.
6. Grasela D. (2003) Clinical pharmacology of gatifloxacin, a new fluoroquinolone. *Clin Infect Dis*., 31, suppl. 2, pp. S51-S58. https://doi.org/10.1086/314061.
7. Dubreuil L., Behra-Miellet J., Neut C., Calvet L. (2003) In vitro activity of gatifloxacin, a new fluoroquinolone, against 204 anaerobes compared to seven other compounds. *Clin Microb Infect.,* 9(11), pp. 1133-1138. https://doi.org/10.1046/j.1469-0691.2003.00773.x.
8. Jones R., Croco M., Pfaller M., Beach M., Kulger K. (1999) Antimicrobial activity evaluations of gatifloxacin, a new fluoroquinolone: contemporary pathogen results from a global antimicrobial resistance surveillance program (SENTRY, 1997). *Clinical Microb Infect.,* 5(9), pp. 540–546. https://doi.org/10.1111/j.1469-0691.1999.tb00432.x.
9. Cunha B. (1998) Quinolones: Clinical use and formulary considerations. *Adv Ther*., 15(5), pp. 277-287.
10. Gajjar D., Kollia G., Lacreta F. (2000) Effect of multiple- dose gatifloxacin or ciprofloxacin on glucose homeostasis and insulin production in patients with noninsulin-dependent diabetes mellitus maintained with diet and exercise. *Pharmacother*., 20(6Pt2), pp. 76-86. https://doi.org/10.1592/phco.20.8.76S.35182.
11. Note: Determination that TEQUIN (Gatifloxacin) was withdrawn from sale for Reasons of Safety Effectiveness by the Department of Health and Human Services, FDA (US), Docket no. FDA, 2006, 0081.
12. Kaur N., Kumar V., Nayak S., Wadhwa P., Kaur P., Sahu S. (2021) A-amylase as molecular target for treatment of diabetes mellitus: a comprehensive review. *Chem Biology and Drug Design*., 98(4), pp. 539-560. https://doi.org/10.1111/cbdd.13909.
13. Ben E., Asuquo A., Owo A. (2019) The role of serum alpha-amylase and glycogen synthase in the anti-diabetic potential of terminalia catappa aqueous leaf extract in diabetic wistar rats. *Asian J Res Med Pharm Sci*., 6(2), pp. 1-11. https://doi.org/10.9734/ajrimps/2019/v6i230096.
14. Butterworth P., Warren F., Ellis P. (2011) Human α-amylase and starch digestion: An interesting marriage. *Starch – Stärke*., 63(7), pp. 395-405. https://doi.org/10.1002/star.201000150.
15. Park-wyllie L., Juurlink D., Kopp A., Shah B., Stukel T., Stumpo C., Dresser L., Low D., Mamdani M. (2006) Outpatient gatifloxacin therapy and dysglycemia in older adults. *J New England Med.*, 354(13), pp. 1352. https://doi.org/61. 10.1056/NEJMoa055191.
16. Baker S., Hangii M. (2002) Possible gatifloxacin-induced hypoglycemia. *Annals of Pharmacother*., 36(11), pp. 1722-1726. https://doi.org/10.1345/aph.1A480.
17. Ponnulakshmi R., Shyamaladevi B., Vijayalakshmi P., Selvaraj J. (2016) In silico and in vivo analysis to identify the antidiabetic activity of beta sitosterol in adipose tissue of high fat diet and sucrose induced type-2 diabetic experimental rats. *Toxicol Mech Methods.,* 29(4), pp. 276-290. https://doi.org/10.1080/15376516.2018.1545815.
18. Bagri P., Ali M., Aeri V., Bhowmik M. (2016) Isolation and antidiabetic activity of new lanostenoids from the leaves of psidium guajava l. *Int J Pharm Sci.,* 8(9), pp. 14-18. http://dx.doi.org/10.22159/ijpps.2016v8i9.10425.
19. Wang J., Huang M., Yang J. (2017) Anti-diabetic activity of stigmasterol from soybean oil by targeting the GLUT4 glucose transporter. *Food Nutrition Res.,* 61(1), pp. 1-14. https://doi.org/10.1080/16546628.2017.1364117.
20. Bulea M., Abdurahmand A., Nikfara S., (2019) Antidiabetic effect of quercetin: A systematic review and meta-analysis of animal studies. *Food Chem Toxicol.,* 125, pp. 494-502. https://doi.org/10.1016/j.fct.2019.01.037.
21. Ibitoye O., Uwazie J., Ajiboye T. (2018) Bioactivity-guided isolation of kaempferol as the antidiabetic principle from Cucumis sativus L. fruits. *J Food Biochem.,* 42(3), pp. 1-7. https://doi.org/10.1111/jfbc.12479.
22. Cowen P., Browning M. (2015) What has serotonin to do with depression? *World Psychiatry*., 14(2), pp. 158-160. https://doi.org/10.1002/wps.20229.
23. Omran Z. (2024) Design, synthesis of new gatifloxacin derivatives as antibacterial activity. *J Res Chem.*, 5(1), pp. 19-27. https://doi.org/10.22271/reschem.2024.v5.i1a.112.
24. Sriram D., Fisher L., Yogeeswari P., Aubry A. (2006) Gatifloxacin derivatives: synthesis, antimycobacterial activities, and inhibition of Mycobacterium tuberculosis DNA gyrase. *Bioorgan Med letters.*, 16(11), pp. 2982-2985. https://doi.org/10.1016/j.bmcl.2006.02.065.
25. Mesaik M. (2010) Synthesis, characterization, antibacterial, antifungal, and immunomodulating activities of gatifloxacin derivatives. *Med Chem Res*., 19, pp. 1210-1221. https://doi.org/10.1016/j.molstruc.2010.01.036.

26. Mauro V., Maurı F., Saraiva A., Marcus V., Cristiane F., Vicenteb F., Lourenc M. (2007) Synthesis and antitubercular activity of lipophilic moxifloxacin and gatifloxacin derivatives. *Bioorgan Med Chem Letters.*, 17(20), pp. 5661-5664. https://doi.org/10.1016/j.bmcl.2007.07.073.

27. Forli S., Huey R., Pique M., Sanner M., Goodsell D., Olson A. (2016) Computational protein ligand docking and virtual drug screening with the AutoDock suite. *Natural Protocols.,* 11(5), pp. 905-919. https://doi.org/10.1038/nprot.2016.051.

28. Trott O., Olson A. (2010) AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. *J Computer Chem.,* 31(2), pp. 455-461. https://doi.org/0.1002/jcc.21334.

29. Seeliger D., Groot B. (2010) Ligand docking and binding site analysis with pymol and autodock/vina. *J Computer Aided Drug Design.,* 24, pp. 417-422. https://doi.org/10.1007/s10822-010-9352-6.

30. Desai K., Hajoori M., (2019) Molecular docking studies of novel nitrophenyl inhibitor against saldose reductase. *Int J Res Reviews.,* 6(2), pp. 92z-95z. https://doi.org/10.1371/journal.pone.0138186.

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