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DESIGN, IN-SILICO AND ADMET STUDIES OF TRIAZOLE BEARING QUINOLONE MOLECULAR HYBRIDS AS ANTIMICROBIAL AGENTS

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ABSTRACT

Antimicrobial resistance is a global public health problem that threaten our ability to treat bacterial infections effectively. Micro-organisms that are treated with anti-microbial drugs increase their fitness against these drugs by acquiring and expressing resistance genes and spread these genes to other microorganisms through Darwinian selection. In order to have a compound that is effective against these microorganisms, we have designed a new series of compounds that are hybrids of two different pharmacophores which are previously known to be effective against these microorganisms. The new hybrids will be having synergistic effect and resistance development will be slow. The designed compounds were compared with the reference drug ciprofloxacin. Eighteen different hybrids were made out of which 3 compounds shows good binding affinity with DNA gyrase (PDB ID: 1AJ6). The compound QT12 was having highest affinity towards DNA gyrase (-7.1 kcal/mol) which was higher than the affinity of reference drug ciprofloxacin (-6.7 kcal/mol). The compound QT5 and QT6 were having affinity of -7.0 kcal/mol which was also higher than the reference drug. Further the ADMET studies of the compound QT5, QT6 and QT12 were also done using computational methods.

KEYWORDS: Antimicrobial resistance, quinolone, triazole, antibacterial.

INTRODUCTION

1.1 Antimicrobial Resistance

Antimicrobial resistance is a global public health problem that endanger our ability to treat bacterial infections effectively. Many infectious pathogens that could formerly be treated

successfully with any of several medication classes have developed resistance, typically to a wide range of antibiotics.

Antibiotic resistance is usually caused by antibiotic destruction or modification, target alterations (target replacement, target site mutations, target site enzymatic alterations, target site protection, target overproduction, or target bypass), and decreased antibiotic accumulation due to decreased permeability and/or increased efflux. Antibiotic resistance could also be the result of a bacterial cell's worldwide adaptability.

There is an urgent need to find new ways to deal with antibacterial resistance. A new strategy is used in this study in which new hybrids were designed by combining two different heterocyclic rings that were known to be effective against microorganisms. Quinolone and triazole moieties were used to make hybrids.

1.2 Quinolone

Quinolones are antimicrobials having a skeleton of 4-oxo-1,4-dihydroquinolone. Quinolones target bacterial type IIA topoisomerases, DNA gyrase, and topo IV, trapping these enzymes at the DNA cleavage stage and preventing strand re-joining, causing chromosomal topology to be disrupted. As a result, the DNA replication machinery becomes stuck at the blocked replication forks, causing DNA synthesis to be inhibited and bacteriostasis to occur. Quinolone-induced cell death is linked to the production of double-stranded DNA breaks (DSBs), which leads to chromosome fragmentation and an increase in reactive oxygen species (ROS).

DNA gyrase is the major target of the quinolone molecule. Gyrase is a heterotetrameric enzyme comprised of two GyrA and two GyrB subunits that works as a type IIA topoisomerase. Gyrase's activity is required for DNA super helicity control, bacterial replication, transcription and elongation.

1.3 Triazole

Triazoles are synthetic compounds with three nitrogen atoms in the five membered azole ring.

Antifungal triazoles block the ergosterol biosynthesis pathway by inhibiting 14--demethylase, an enzyme that removes the methyl group from precursor sterols at position C-14. ERG11 is the name of the gene that codes for the 14-lanosterol demethylase enzyme in yeast (Erg11p).

The inhibition of this enzyme causes an accumulation of abnormal sterol intermediates (14--methyl sterols) on the fungal surface, halting fungal development.

1.4 Hybridisation of molecules

Hybrid molecules are chemical entities that have two or more structural domains with separate biological functions and dual activities, implying that they behave as two or more pharmacophores. In comparison to parent medications, hybrid molecules have the ability to overcome drug cross resistance, broaden the biological spectrum, minimise toxicity, and improve efficacy. Combining 1,2,4-triazole with other antibacterial pharmacophores could result in new candidates that are highly effective against both drug-sensitive and drug-resistant bacteria. Quinolones are common antibacterial pharmacophores. As a result, quinolone hybridization with 1,2,4-triazole is likely to yield excellent antibacterial compounds.

2. MATERIALS AND METHODS

2.1 Preparation of receptors

3-D structure of DNA Gyrase was downloaded from PDB (protein data bank) (PDB ID: 1A6) in pdb format. Before starting the with the docking process, the receptor preparation was done by removing water molecules and the ligand already complexed with the DNA gyrase in the pdb file. Polar hydrogens were added and charges were computed and then the file was saved in pdbqt format using Autodock 4.2 Software.

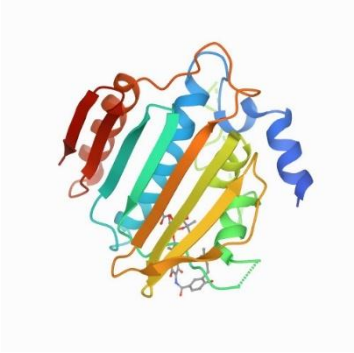


Figure 1: Crystal Structure of DNA Gyrase.

2.2 Preparation of ligands

Several quinolones and triazole compounds were downloaded from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in sdf format. The files were converted in pdb format by using OpenBabel software. The hybrids were designed and made in Chem Sketch software

and saved in mol format. These files were then changed in pdb format using OpenBable software. All the pdb files were changed in pdbqt format to make the ligands ready for docking process by using Autodock 4.2 Software.

2.3 Molecular Docking

Prior to the docking process, the preparation of the target proteins or receptors and ligands was done. Docking was done using Autodock 4.2 software using Genetic Algorithm as the Search Parameters. Blind docking was done with the target receptor. Full molecule was covered in the gid box. The results were analysed by using Autodock and Discovery studio visualiser and Pymol softwares. Several parameters were investigated using SwissADME and pkCSM- Pharmacokinetics web tools.

3. RESULTS AND DISCUSSION

3.1 Binding structures of Different quinolone molecules with DNA gyrase.

Figure 2: Compound quinolone (Q1) docked with DNA gyrase.

Both the rings of the compound were making pi-pi interactions with the phenylalanine amino acid and oxygen is making a hydrogen bond with arginine amino acid of DNA gyrase.

Figure 3: Methylquinolone (Q2) docked with DNA gyrase.

Both the rings of the compound were making pi-sigma interactions with the Isoleucine amino acid. The oxygen and the methyl group were making carbon-hydrogen bonds with proline and glutamic acid respectively.

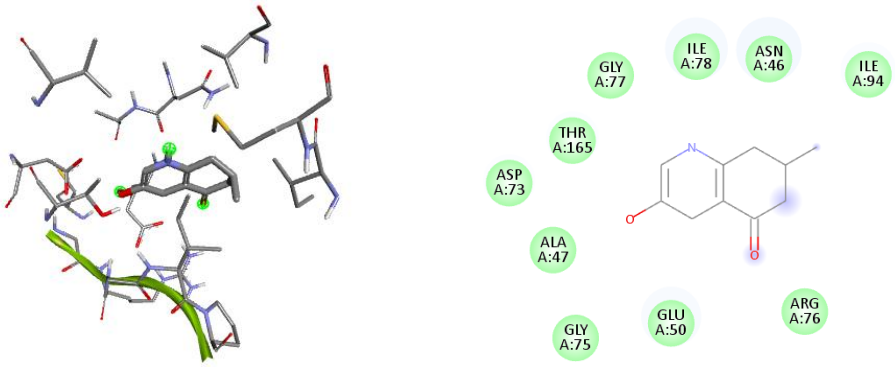


Figure 4: Hydroxymethylquinolone (Q3) docked with DNA gyrase.

The compound is involved in vander waals interactions with Isoleucine, asparagine, glycine, threonine, aspartic acid, alanine, glutamic acid and arginine amino acids.

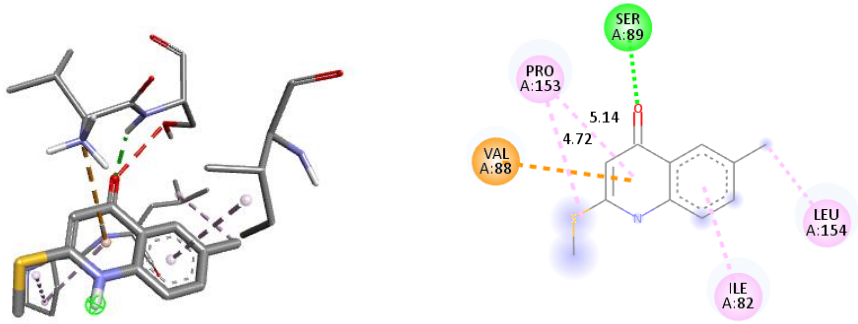


Figure 5: Methylthioquinolone (Q4) docked with DNA gyrase.

The benzene ring of the compound is involved in pi-alkyl interactions with leucine and isoleucine amino acids. The pyridine ring is involved in pi-cation and pi-alkyl interactions with proline and valine amino acids. The oxygen forms a hydrogen bond with serine amino acid.

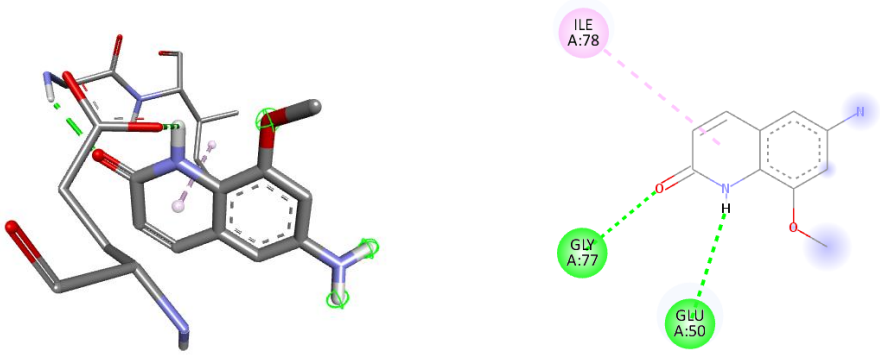


Figure 6: 6-amino-8-methoxyquinolone (Q5) docked with DNA gyrase.

The hydrogen attached with the nitrogen of the pyridine ring and the oxygen are making hydrogen bonds with glutamic acid and glycine respectively. The pyridine ring is also involved in pi-alkyl interactions with isoleucine amino acid.

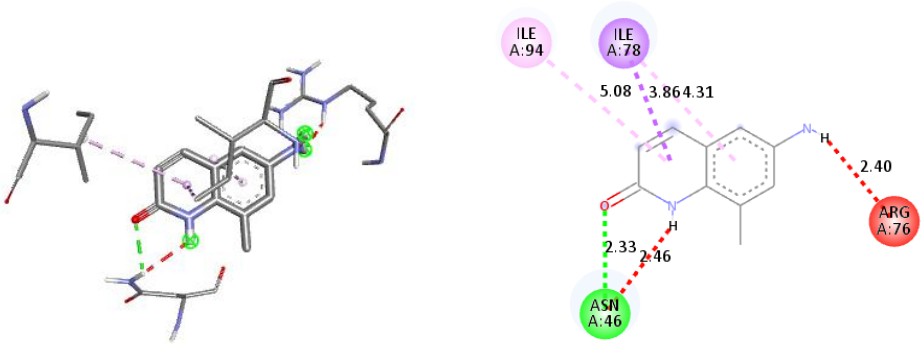


Figure 7: 6-amino-8-metylqunilone (Q6) docked with DNA gyrase.

The benzene ring is involved in pi-alkyl interactions with isoleucine and the pyridine ring is involved in pi-alkyl interactions with isoleucine and also pi-sigma interactions with isoleucine amino acid. The oxygen is involved in making a hydrogen bond with asparagine amino acid. Two donor-donor bonds were also made between the compound and arginine and asparagine.

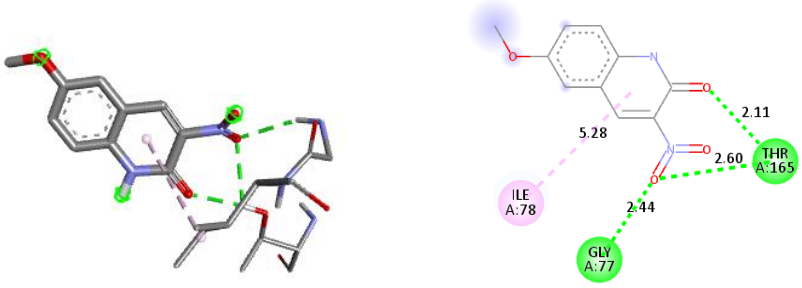


Figure 8: 6-methoxynitroquinolone (Q7) docked with DNA gyrase.

The pyridine ring is involved in pi-alkyl interactions with isoleucine amino acid. The oxygen of nitro group makes two hydrogen bonds with glycine and threonine amino acids. The other oxygen attached directly with the pyridine ring also makes a hydrogen bond with threonine amino acid.

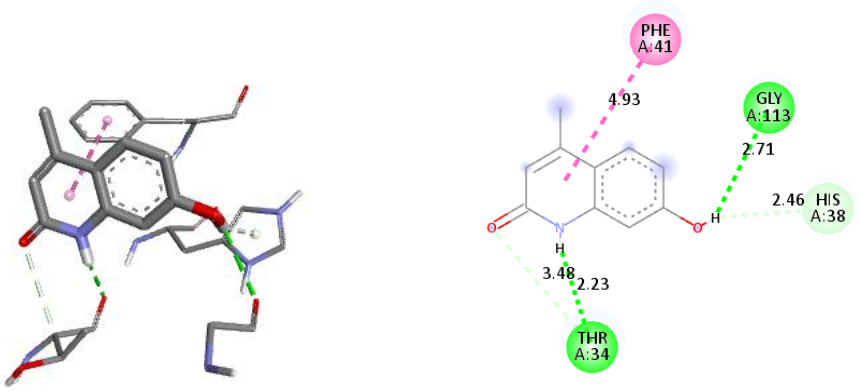


Figure 9: 7-hydroxy-4-methylquinolone (Q8) docked with DNA gyrase.

The pyridine ring is involved in pi-pi interactions with phenylalanine. The hydrogen of yhe hydroxy group makes a hydrogen bond with glycine and a carbon hydrogen bond with histidine. The hydrogen attached to nitrogen also makes a hydrogen bond with threonine amino acid.

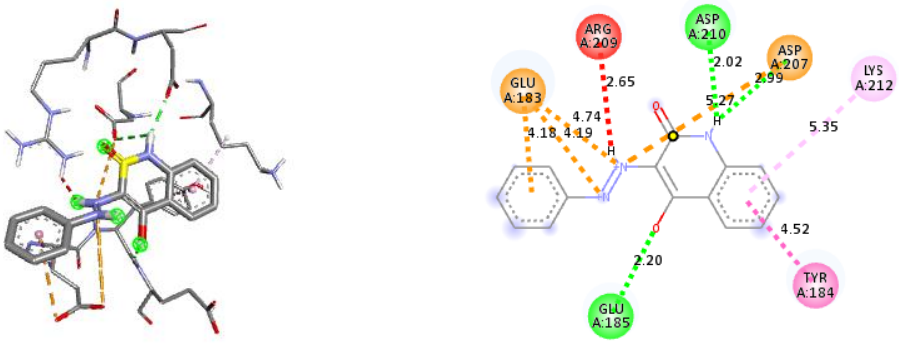


Figure 10: 4-Hydroxy-3-(phenylazo)-2-quinolone (Q9) docked on DNA gyrase.

The pyridine ring of the quinolone nucleus is involved in pi-pi interactions with lysine and tyrosine. The attached phenyl ring and both nitrogen of azo bond makes pi-anion interactions with glutamic acid and aspartate amino acid. The oxygen of the hydroxy group and the hydrogen of the amine group of the pyridine ring makes hydrogen bond with glutamic acid and aspartate amino acid respectively.

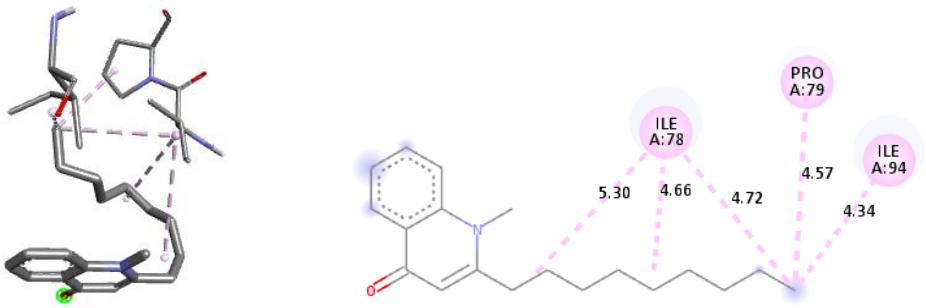


Figure 11: 1-Methyl-2-nonylquinolin-4-one (Q10) docked with DNA gyrase.

The alkyl chain attached to the 2nd position on the pyridine ring is involved in making alkyl bonds with isoleucine and proline amino acids.

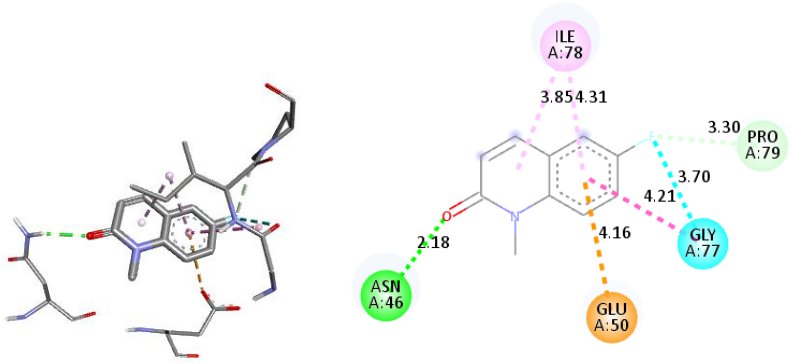


Figure 12: 1-methyl-6-fluoroquinolone (Q11) docked with DNA gyrase.

Both the rings are involved in making pi-alkyl bonds with isoleucine amino acid. The benzene ring is involved in pi-anion interactions with glutamic acid. The halogen in the molecule is having interactions with glycine and proline. The oxygen of the ketone group forms a hydrogen bond with asparagine amino acid.

The binding affinity of compounds Q1 to Q11 is shown in table 7.1 in kcal/mol.

Table 1: Binding affinities of different quinolone compounds(Q1-Q11).

S.no		Ligand	Affinity(kcal/mol)
1	Q1	Quinolone	-4.8
2	Q2	Methylquinolone	-5.3
3	Q3	Hydroxymethylquinolone	-5.7
4	Q4	Methylthioquinolone	-4.9
5	Q5	6-amino-8-methoxyquinolone	-5.6
6	Q6	6-amino-8-metylqunilone	-6.0
7	Q7	6-methoxynitroquinolone	-5.4
8	Q8	7-hydroxy-4-methylquinolone	-5.4
9	Q9	4-Hydroxy-3-(phenylazo)-2-quinolone	-6.5

10	Q10	1-Methyl-2-nonylquinolin-4-one	-5.2
11	Q11	1-methyl-6-fluoroquinolone	-5.5

3.2 Binding structures of Different triazole molecules with DNA gyrase

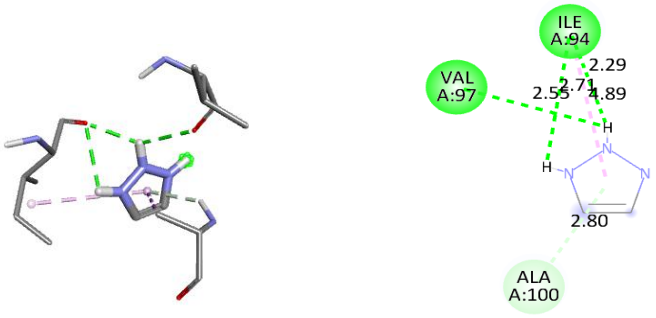


Figure 13: Triazole docked with DNA gyrase.

The ring makes pi-donor hydrogen bond with alanine and the hydrogens attached with 1,2-Nitrogen makes hydrogen bonds with isoleucine and valine amino acids. The ring also makes a pi-sigma interaction with isoleucine.

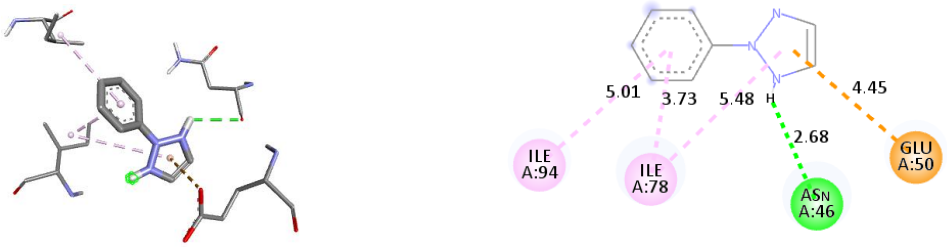


Figure 14: 2-Phenyl-2H-1,2,3-triazole docked with DNA gyrase.

Both the rings are involved in pi-alkyl interactions with isoleucine amino acids. The triazole ring makes pi-anion interactions with glutamic acid. The hydrogen at position 1 makes a hydrogen bond with asparagine amino acid.

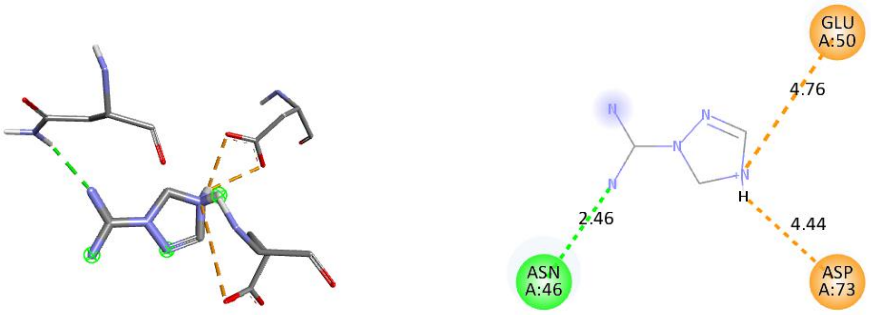


Figure 15: 1,2,4-Triazole-Carboxamidine docked with DNA gyrase.

The conjugated nitrogen makes a hydrogen bond with asparagine. The nitrogen at 4th position makes salt bridge and attractive charges with aspartate and glutamic acid.

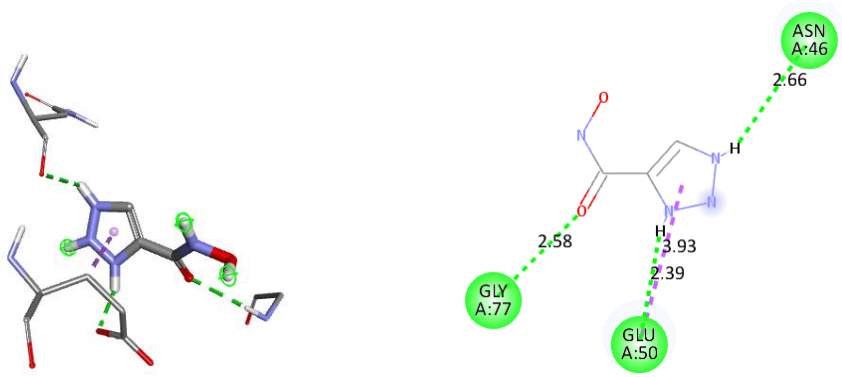


Figure 16: N-Hydroxy-triazole-4-carboxamide docked with DNA gyrase.

The triazole ring is involved in pi-sigma interactions with glutamic acid. Hydrogen at position 1 and 3 makes a hydrogen bond with asparagine and glutamic acid. The oxygen also makes a hydrogen bond with glycine.

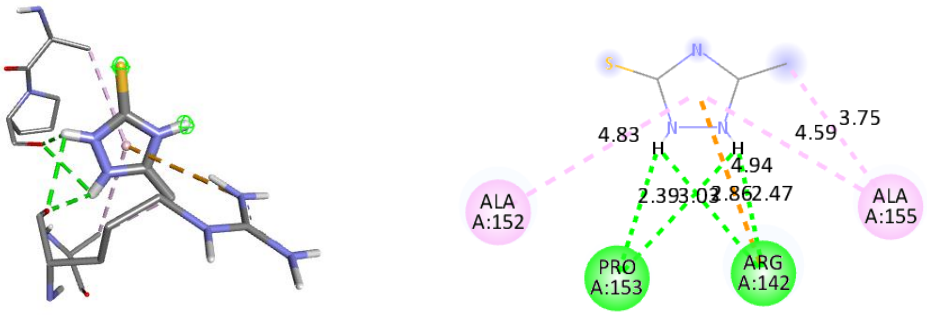


Figure 17: 5-Methyl-4H-1,2,4-triazole-3-thiol docked with DNA gyrase.

The triazole ring and the methyl group at 5th position are involved in pi-alkyl interactions with alanine amino acid. The ring also has pi-cation interaction with arginine. The hydrogens at 1st and 2nd position makes hydrogen bond with proline and arginine.

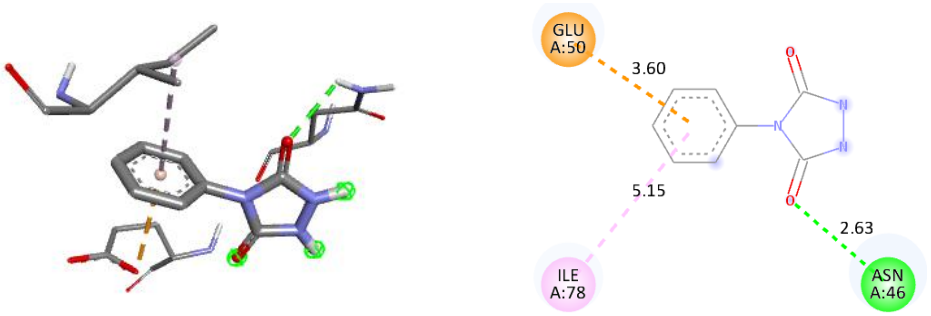


Figure 18: 4-Phenyl-1,2,4-triazoline-3,5-dione docked with DNA gyrase.

The phenyl ring makes pi-anion interactions with glutamic acid and pi-alkyl interactions with isoleucine. One of the oxygens of the ketone group makes hydrogen bond with asparagine amino acid.

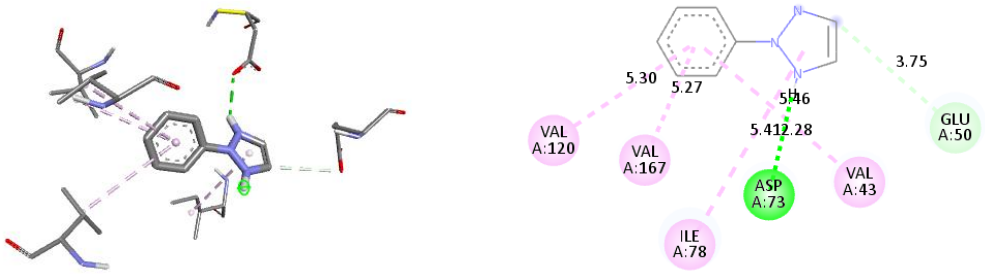


Figure 19: 2-Phenyl-2H-1,2,3-triazole docked with DNA gyrase.

The phenyl ring is involved in pi-alkyl interactions with valine and triazole ring with isoleucine. The carbon in the triazole ring makes a carbon-hydrogen bond with glutamic acid. The nitrogen at position 1st or 3rd makes a hydrogen bond with aspartic acid.

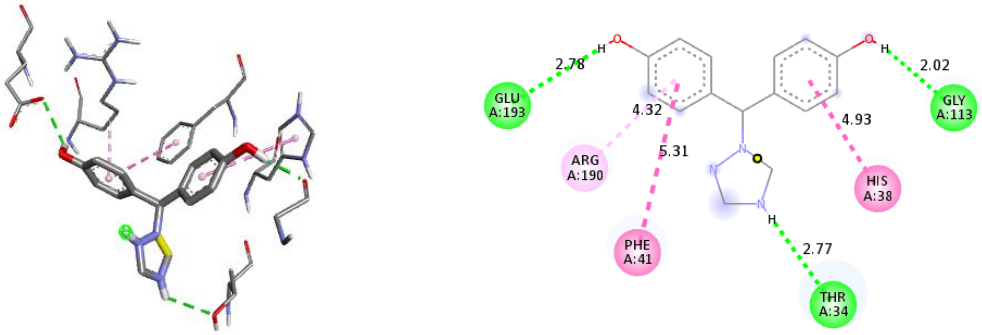


Figure 20: 1-[Bis-(4-hydroxyphenyl) methyl]-1H- [1,2,4] triazole docked with DNA gyrase.

One of the phenyl rings is involved in pi-pi interactions with histidine and the other one is involved in pi-pi interactions with phenylalanine and pi-alkyl interactions with arginine. Both the hydroxy groups make hydrogen bonds with glutamic acid and glycine. The nitrogen at 4th position in the triazole ring makes a hydrogen bond with threonine amino acid.

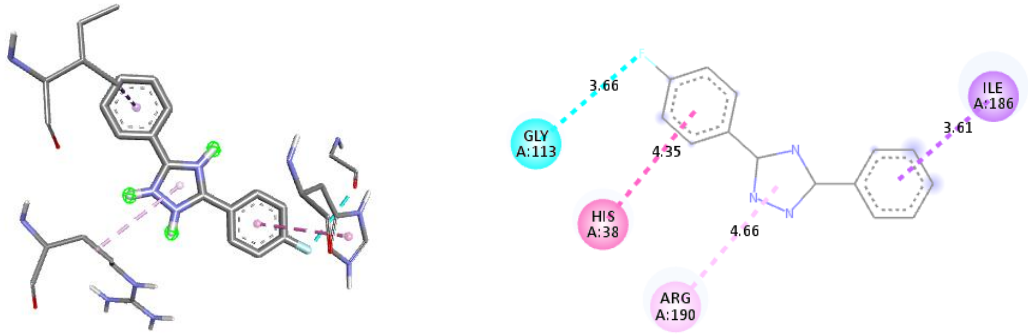


Figure 21: 3-(4-Fluorophenyl)-5-phenyl-4H-1,2,4-triazole docked with DNA gyrase.

The halogen fluorine has interactions with glycine. The phenyl ring at 3rd position has pi-pi interactions with histidine and the one at 5th position has pi-sigma interactions with isoleucine. The triazole ring is also involved in pi-alkyl interactions with arginine.

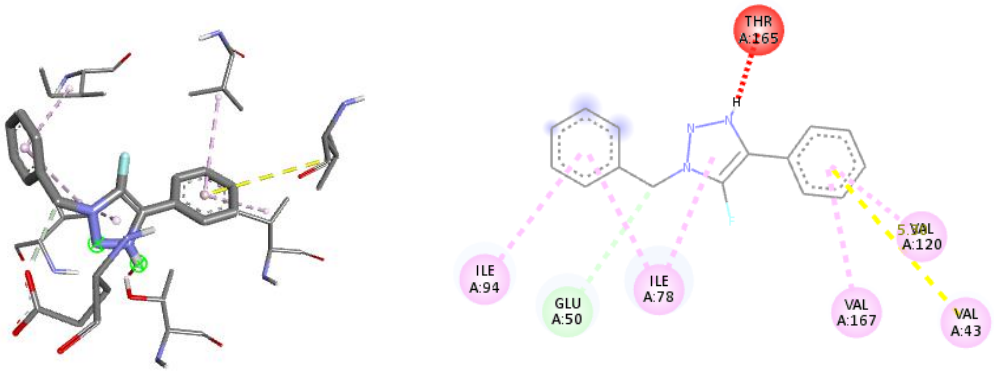


Figure 22: 1-Benzyl-4-phenyl-5-fluoro-1H-1,2,3-triazole docked with DNA gyrase.

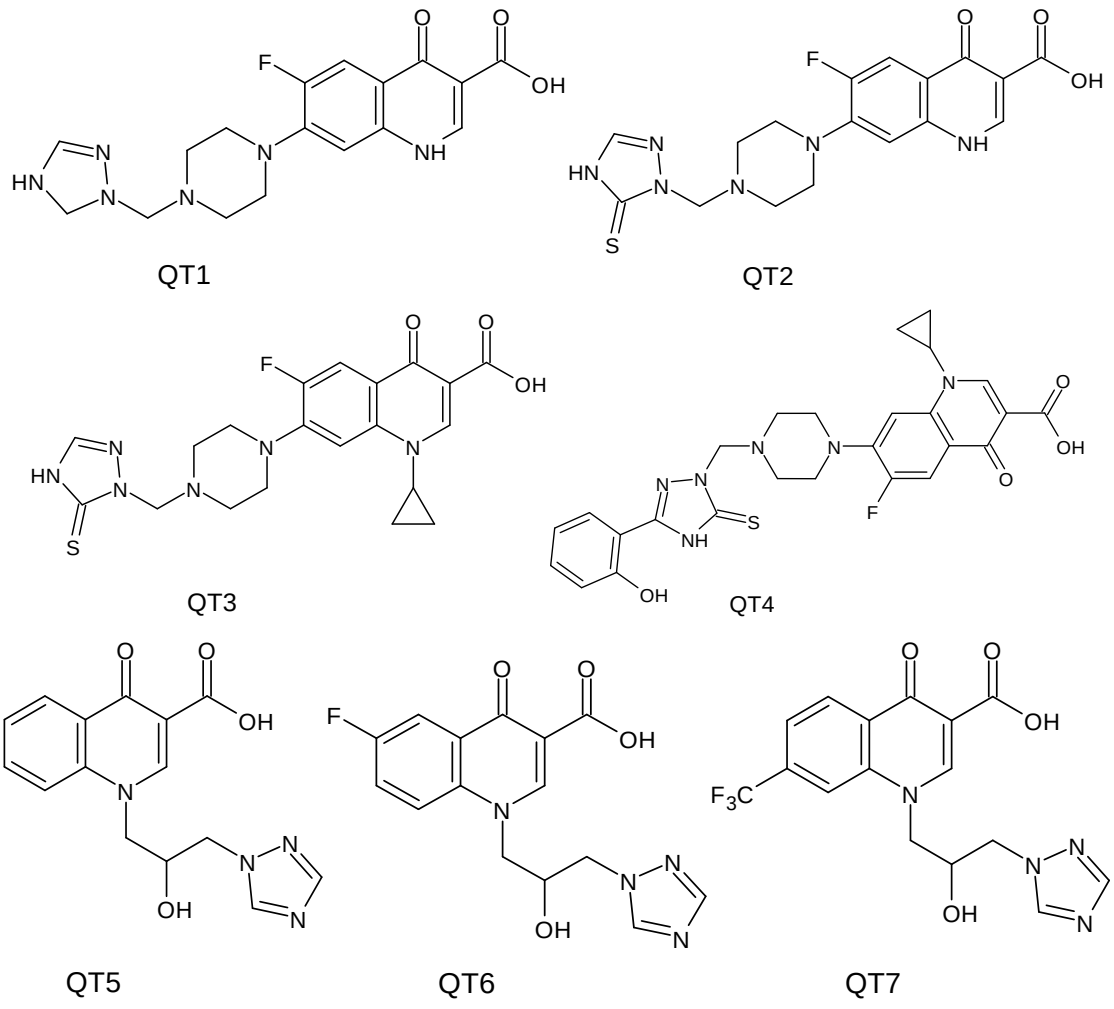
The phenyl ring at position 4 is involved in pi-alkyl interactions with valine and the phenyl ring at position 1 is involved in pi-alkyl interactions with isoleucine. The CH_2 group at position 1 makes a carbon hydrogen bond with glutamic acid. The nitrogen at position 3rd also has unfavorable donor-donor interaction with threonine. The triazole ring is also involved in pi-alkyl interactions with isoleucine.

The binding affinity of compounds T1 to T10 is shown in table 2 in kcal/mol.

Table 2: Binding affinities of different triazole compounds(T1-T10).

S.no		Ligand	Affinity(kcal/mol)
1	T1	Triazole	-3.7
2	T2	2-Phenyl-2H-1,2,3-triazole	-4.9
3	T3	1,2,4-Triazole-Carboxamidine	-3.9
4	T4	N-Hydroxy-triazole-4-carboxamide	-5.5
5	T5	5-Methyl-4H-1,2,4-triazole-3-thiol	-3.1
6	T6	4-Phenyl-1,2,4-triazoline-3,5-dione	-5.6
7	T7	2-Phenyl-2H-1,2,3-triazole	-6.0
8	T8	1-[Bis-(4-hydroxyphenyl)methyl]-1H-[1,2,4]triazole	-6.2
9	T9	3-(4-Fluorophenyl)-5-phenyl-4H-1,2,4-triazole	-6.5
10	T10	1-Benzyl-4-phenyl-5-fluoro-1H-1,2,3-triazole	-7.2

Different triazole-quinolone hybrids were made according to the affinities from table 1 and 2 and from the SAR studies of quinolone and triazole compounds. The compounds QT1 to QT18 were made that are shown in figure 23.



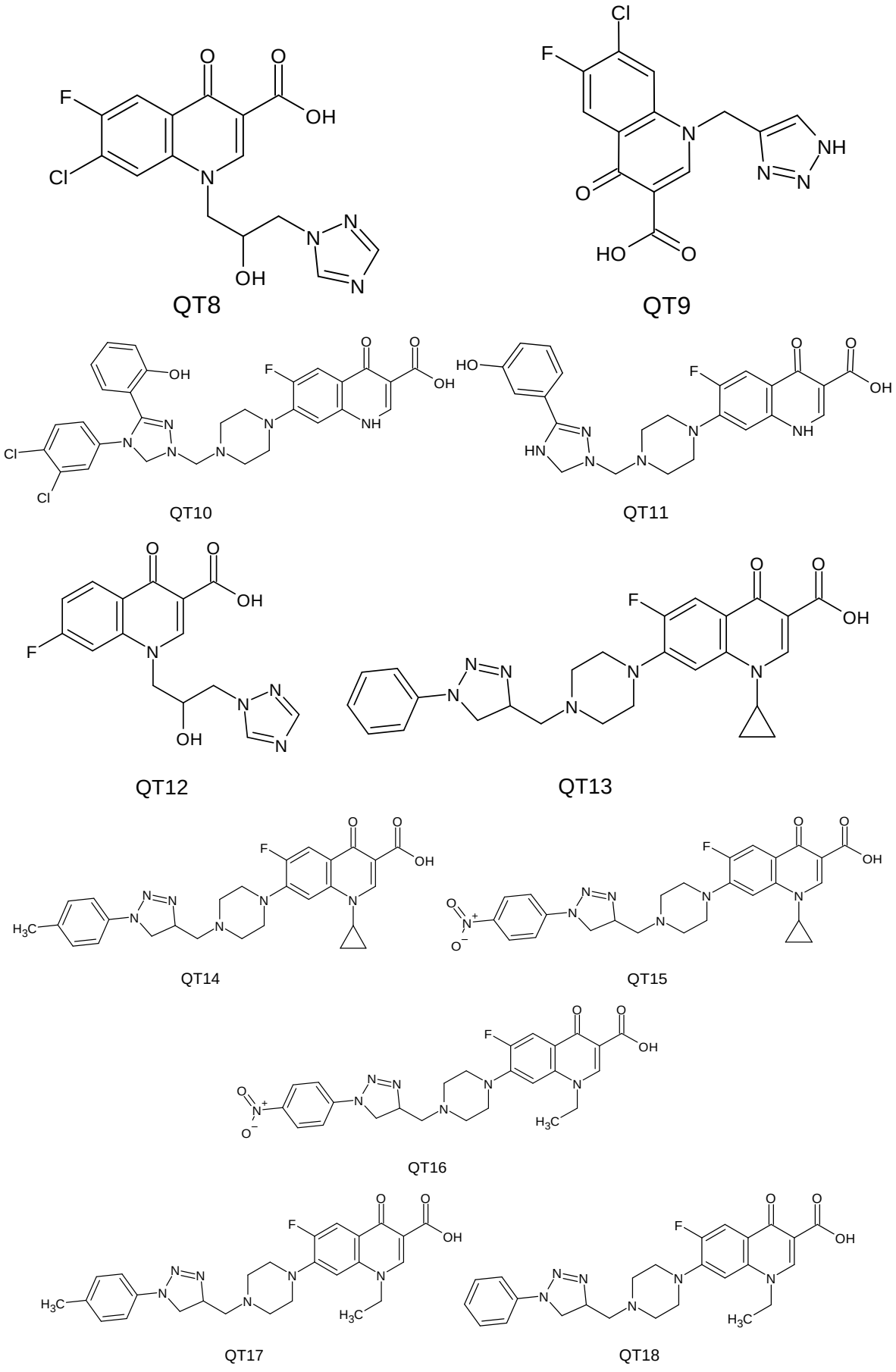


Figure 23: Quinolone-triazole hybrids (QT1-QT18).

3.3 Binding structures of different quinolone-triazole hybrids with DNA gyrase

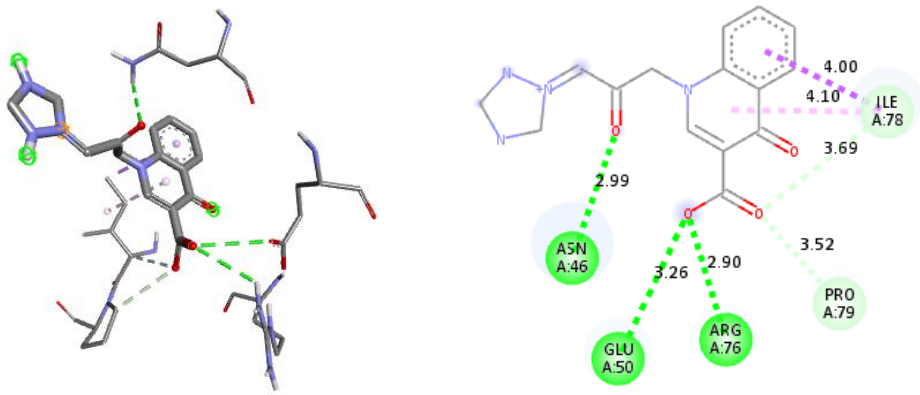


Figure 24: Compound QT5 docked with DNA gyrase.

The benzene ring in the quinolone nucleus is involved in pi-sigma interactions with isoleucine and the pyridine ring is involved in pi-alkyl interactions with isoleucine. The carboxylic acid group makes carbon-hydrogen bond with proline and isoleucine. The hydroxy group makes two hydrogen bonds with arginine and glutamic acid. The oxygen of the ketone group also forms a hydrogen bond with asparagine amino acid.

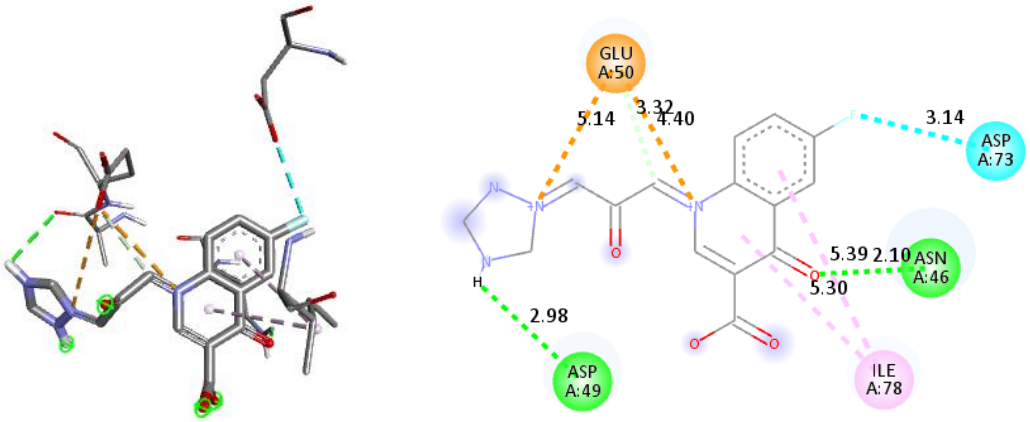


Figure 25: Compound QT6 docked with DNA gyrase.

The halogen fluorine has interactions with aspartic acid. Both the rings of the quinolone nucleus have pi-alkyl interactions with isoleucine. The nitrogen at 4th position and the oxygen of the ketone group of quinolone nucleus makes hydrogen bonds with aspartic acid and asparagine respectively. The nitrogen of triazole ring and quinolone ring has interactions with glutamic acid.

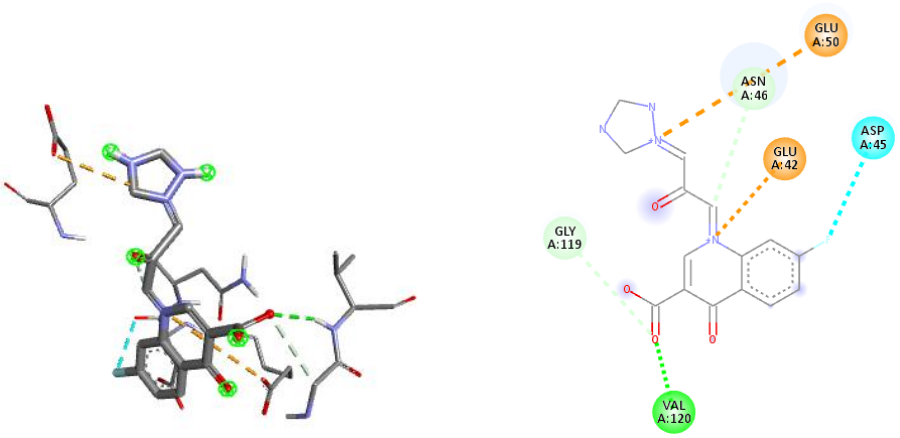


Figure 26: Compound QT12 docked with DNA gyrase.

The nitrogen at position 1 of triazole ring and the nitrogen of quinolone ring has attractive charges with glutamic acid. The halogen fluorine has interactions with aspartic acid. The carboxylic acid group makes a carbon-hydrogen bond with glycine and the oxygen makes a hydrogen bond with valine. The carbon attached to the nitrogen of the quinolone ring also made a carbon-hydrogen bond with asparagine amino acid.

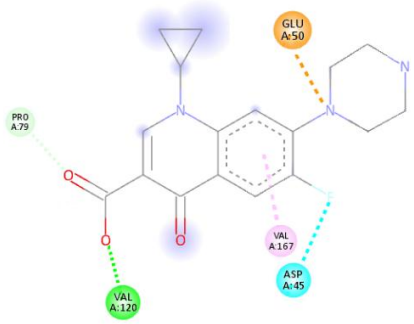


Figure 27: Binding of the reference drug (ciprofloxacin) with DNA gyrase

Table 3: Binding affinities of different triazole-quinolone hybrids (QT1- QT18) and ciprofloxacin.

S.no	Quinolone/triazole hybrids	Affinity(kcal/mol)
1	Qt1	Result not obtained
2	Qt2	Result not obtained
3	Qt3	Result not obtained
4	Qt4	Result not obtained
5	**Qt5**	**-7.0**
6	**Qt6**	**-7.0**
7	Qt7	Result not obtained
8	Qt8	Result not obtained
9	Qt9	Result not obtained
10	Qt10	Result not obtained

11	Qt11	Result not obtained
12	**Qt12**	**-7.1**
13	Qt13	Result not obtained
14	Qt14	Result not obtained
15	Qt15	Result not obtained
16	Qt16	Result not obtained
17	Qt17	Result not obtained
18	Qt18	Result not obtained
19	**Ciprofloxacin**	**-6.7**

The reference drug, ciprofloxacin, was docked on the DNA gyrase and the drug shows a binding affinity of -6.7 kcal/mol. The oxygen atom makes a hydrogen bond with valine and the other oxygen is involved in carbon hydrogen bond with proline amino acid. The halogen(fluorine) is involved in interactions with aspartic acid. The benzene ring is involved in interactions with valine and the nitrogen atom of the ring attached with the benzene ring has attractive charges with glutamic acid.

Out of the 18 hybrid compounds that were formed only 3 compounds were docked to the target molecule (QT5, QT6 and QT12). Furthermore, the ADME properties of these compounds were found by SwissADME software. The ADME properties these compounds are shown in table below.

Table 4: Physicochemical Properties of compound QT5, QT6, QT12 and ciprofloxacin according to swissADME.

S.No	Physicochemical Properties	QT5	QT6	QT12	Ciprofloxacin
1	Formula	C15H14N4O4	C15H13FN4O4	C15H13FN4O4	C17H18FN3O3
2	Molecular weight	314.30 g/mol	332.29 g/mol	332.29 g/mol	331.34 g/mol
3	Num. heavy atoms	23	24	24	24
4	Num. arom. heavy atoms	15	15	15	10
5	Fraction Csp3	0.20	0.20	0.20	0.41
6	Num. rotatable bonds	5	5	5	3
7	Num. H-bond acceptors	6	7	7	5
8	Num. H-bond donors	2	2	2	2
9	Molar Refractivity	81.57	81.53	81.53	95.25
Solubility properties					
1	Lipophilicity (Log Po/w)	0.49	0.75	0.85	1.10
2	Water Solubility	Soluble	Soluble	Soluble	Highly Soluble
Pharmaco					

kinetics					
1	GI absorption	High	High	High	High
2	BBB permeation	No	No	No	No
3	Log K_p (skin permeation)	-7.45 cm/s	-7.49 cm/s	-7.49 cm/s	-9.09 cm/s
Drug likeness					
1	Lipinski	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation
2	Ghose	Yes	Yes	Yes	Yes
3	Veber	Yes	Yes	Yes	Yes
4	Egan	Yes	Yes	Yes	Yes
5	Muegge	Yes	Yes	Yes	Yes
6	Bioavailability Score	0.56	0.56	0.56	0.55
Medicinal Chemistry					
1	Lead likeness	Yes	Yes	Yes	Yes
2	Synthetic accessibility (1=very easy; 10=very difficult)	2.84	2.89	2.97	2.51

Table 5: ADMET predicted values of compound QT5, QT6, QT12 and ciprofloxacin according to pkCSM.

ADMET Predicted Values.						
Property	**Model Name**	**QT5**	**QT6**	**QT12**	**ciprofloxacin**	**Unit**
Absorption	Water Solubility	-3.391	-3.609	-3.598	-2.336	Numeric (Log mol/L)
Absorption	Intestinal absorption (Human)	53.446	57.632	54.595	92.859	Numeric (% Absorbed)
Absorption	Skin Permeability	-2.733	-2.734	-2.734	-2.773	Numeric (Log kp)
Distribution	BBB Permeability	-0.908	-1.131	-1.142	-0.506	Numeric (Log BB)
Toxicity	Hepatotoxicity	Yes	Yes	Yes	Yes	Categorical (Yes/No)
Toxicity	Skin Sensitisation	No	No	No	No	Categorical (Yes/No)

4. CONCLUSION

From the list of designed compounds, compound **QT5,QT6** and **QT12** has good binding affinities of -7.0, -7.0 and -7.1 respectively. These compounds have greater binding affinities than that of any of the quinolone or triazole analogues. Moreover, the reference drug, **ciprofloxacin**, has a binding affinity of -6.7 with the selected protein i.e., DNA gyrase (PDB ID: 1AJ6). The compound QT12 was binding at the same binding site as that of the reference drug. The 2D structure of the binding of the hybrid compounds and the reference drug were obtained from Discovery Studio Visualiser. The compound QT12 and the reference drug, both are making a hydrogen bond with the Val120 of the DNA gyrase binding site. The nitrogen atom of both the compound also have same binding with Glu50. The fluorine atom of both the compound have attractive charges with Asp45. By these results it is clear that the

compound QT12 and the reference drug are having the same binding site on DNA gyrase. The ADMET properties of the designed compounds are also comparable to reference drug.

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6. Conflict of Interest

The Authors declared no conflict of interests.

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