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Research Article

IN-SILICO DESIGNING AND SCREENING OF QUINAZOLINEDIONE SULFONAMIDE DERIVATIVES AS ANTIBACTERIAL AGENTS: A DOCKING APPROACH

***Ajeet[1], Mansi Verma[2], Sangeeta Rani[3] and Arvind Kumar[1]**
[1]Department of Pharmaceutical Chemistry and Drug Design, S. D. College of Pharmacy and Vocational Studies, Muzaffarnagar 251001, India
[2]Department of Pharmacology, S. D. College of Pharmacy and Vocational Studies, Muzaffarnagar-251001, U.P., India
[3]Department of Pharmacognosy, S. D. College of Pharmacy and Vocational Studies, Muzaffarnagar-251001, U.P., India
**Author for Correspondence*

ABSTRACT
The purpose of present work is to design derivatives of Quinazolinedione sulfonamide, anti-bacetrial agents with the help of computing software and docking procedures. Quinazolinediones are fluoroquinolone-like inhibitors of bacterial gyrase and sulfonamides have highest powerful antibacterial activity, so, a hybrid of these two agents has been designed and 10 molecules have been developed by *in-silico* means. Molecular docking approaches are routinely used in modern drug design to help understand drug-receptor interaction. This work has been performed with the help of Chemdraw Ultra 7.0, AutoDock Vina. For the studies Bacillus subtilis lipase A, E-coli primosomal protein and heterodimeric hexaprenyl diphosphate synthase has been taken. Results reveals that the protein-ligand interaction energy of derivatives S2 was -5.9 Kcal/mol which is much closer to standard drug (CID no. 4539) as -6.2 Kcal/mol when the derivatives were treated with Bacillus subtilis lipase A. But, exciting results have been found with treating the derivatives with E-coli primosomal protein, and heterodimeric hexaprenyl diphosphate synthase.

Keywords: *Quinazolinedione Sulfonamide; Docking; Bacillus Subtilis Lipase A; E-Coli Primosomal Protein; Heterodimeric Hexaprenyl Diphosphate Synthase*

INTRODUCTION
Antibiotic resistance is a growing public health concern due to the continual emergence of bacterial strains that demonstrate multidrug resistance. Successful traditional therapies are failed to be effective, and clinicians are now switching to newer agents as a strategy to treat life-threatening infections. Consequently, the quinzolinediones, represent as antibacterial class, are filling an unmet medical need. (Ellsworth, 2006)

Quinazolinones is considered as an important chemical synthesis of various physiological significance and pharmacological utility. Quinazolinones are a large class of active chemical compounds exhibiting a broad spectrum of biological activities in animals as well as in humans (Rajput, 2012).

Quinazolinediones are fluoroquinolone-like inhibitors of bacterial gyrase and DNA topoisomerase IV. Earlier work with killing by quinolones revealed that only a subset of quinolone-class agents can kill cells when protein synthesis is blocked (Malik, 2011).

More advanced studies revealed that modified sulfonamides also showing high to moderate antibacterial activity. Aliphatic sulfonamides have highest powerful antibacterial activity for Gram (-) bacteria than Gram (+) and antibacterial activity decreases as the length of the carbon chain increases. Also, novel macrocyclic bis-sulfonamides showed antimicrobial activities.

Due to the broad applicability of sulfonamides, it is desirable to find some effective methods for their synthesis. Therefore, the synthesis of these compounds is of continuing interest. To date many synthetic methods have been reported (Kołaczek, 2014).

On studying the above mentioned literature about the antibacterial behavior of Quinazolinediones and sulfonamides promoted us to theoretically develop their combined moieties and screen them by the means of *in-silico* resources.

Rational drug design helps to facilitate and fasten the drug designing process, which involves various methods to identify novel compound, out of them one method is the docking of molecules with the receptor (Sharma, 2011).

Docking procedures allows virtually screening a data-base of compounds and predict the strongest binder based on various scoring functions. It gives way in which two molecules such as drugs and an enzyme receptor fit together and dock to each other well (Shiva, 2010; Ajeet, 2012; Ajeet, 2013a).

Molecular docking techniques are used in modern drug design to help understand drug–receptor interaction. It has been shown in the literature that these computational procedures can strongly support and help the design of new, more potent drugs by revealing the mechanism of drug–receptor interaction (Shiva, 2010; Ajeet, 2012; Ajeet, 2013a).

MATERIALS AND METHOD

Docking

Molecular docking techniques are used in modern drug design to help understand drug–receptor interaction. It has been shown in the literature that these computational procedures can strongly support and help the design of new, more potent drugs by revealing the mechanism of drug–receptor interaction.

Rational drug design helps to facilitate and speedup the drug designing process, which involves variety of methods to identify novel compound, out of them one method is the docking of the drug molecule with the receptor.

The therapeutic action of the clinical drug will be effective when the biochemical pathway of the enzyme can be exploited (Ajeet, 2012; Ajeet, 2013a; Ajeet, 2013b; Ajeet, 2013c).

Docking procedures allows virtually screening a data-base of compounds and predict the strongest binder based on various scoring functions (Ajeet, 2012; Ajeet, 2013a; Ajeet, 2013b; Ajeet, 2013c).

Receptor

Bacillus subtilis lipase A, E-coli primosomal protein, heterodimeric hexaprenyl diphosphate synthase.

Docking Tool

Here docking has been performed with AutoDock docking software. It is virtual screening software for computational drug discovery that can be used to screen libraries of compounds against potential drug targets.

It enables medicinal chemists to run virtual screening form any platform and helps users in every steps of this process from data preparation to job submission and analysis of the results (Ajeet, 2012; Ajeet, 2013a; Ajeet, 2013b; Ajeet, 2013c).

For performing docking, all receptors have been downloaded from NCBI website with PDB ID 1R4Z (Bacillus subtilis lipase A), 2CCZ (E-coli primosomal protein) and 3AQB (heterodimeric hexaprenyl diphosphate synthase), all the designed ligands have been docked with protein (receptor) with AutoDock software having its default settings.

Field Study Tool

Different fields like hydrophobic field, positive field (H-bond acceptors on a protein) and negative field (H-bond donors on a protein) in a molecule have been studied with the free trial version of TorchV10Lite software (TorchV10Lite, 2012).

RESULTS AND DISCUSSION

Designing and Optimization of Quinazolinedione Sulfonamide Derivatives

The Quinazolinedione sulfonamide derivatives (Figure 1) were designed and their energy minimization for highest stability was performed.

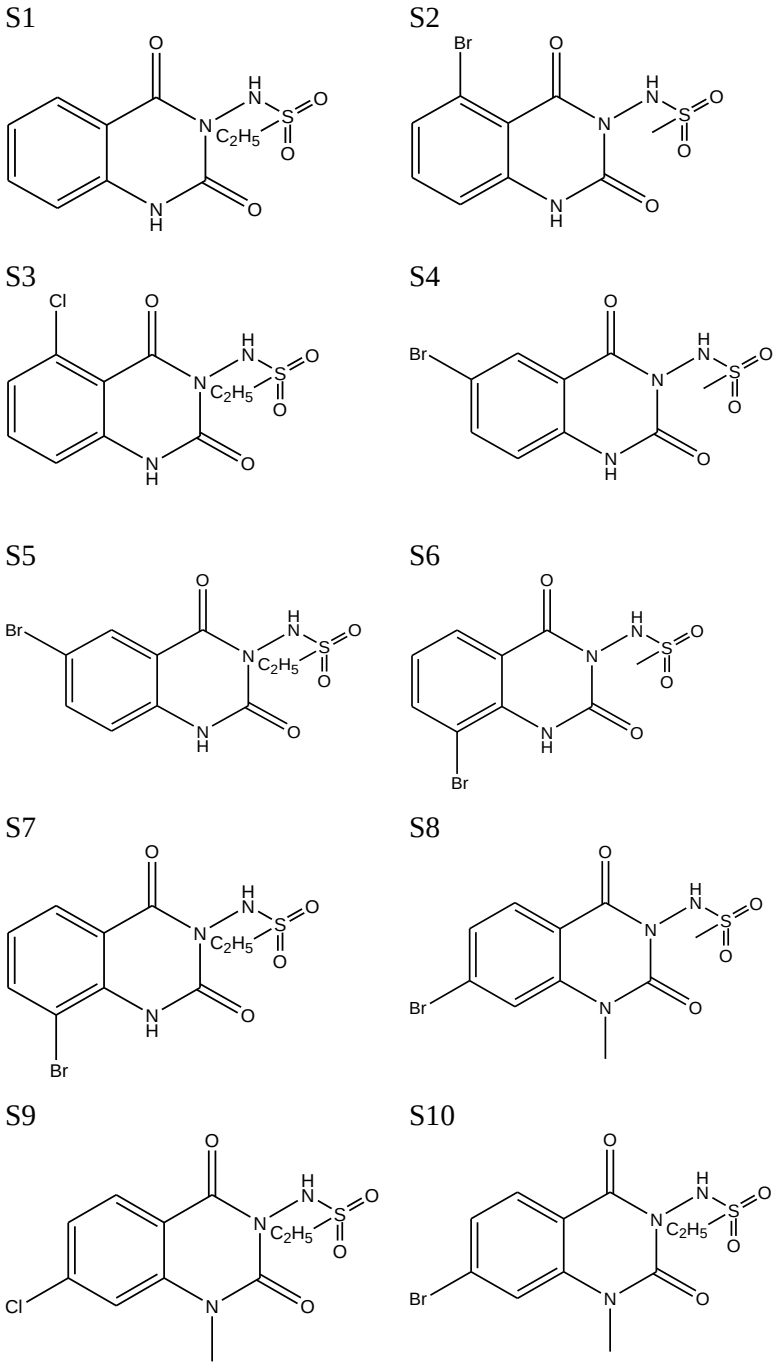


Figure 1: Chemical structures of the designed derivatives

Docking results

Binding Site Analysis

The experimental analysis of binding site shows that His 3, Asn 174, Asn 98, Asn 4, Gln 121, Lys 69, Ser 24, Asn 166, Lys 35, Ser 32 and Leu 173 could be the catalytic site residue present in the structure of 1R4Z (Bacillus subtilis lipase A).

The experimental analysis of binding site shows that Ser 79, Gln 45, Arg 44, Cys 80, Gln 49, Lys 82, His 26, Ser 55, His 81, Cys 80 and His 93 could be the catalytic site residue present in the structure of 2CCZ (E-coli primosomal protein).

The experimental analysis of binding site shows that Asp 152, Asn 155, Asn 234, Asp 88, Lys 22, Pro 19, Tyr 156, Pro 157 and Ser 159 could be the catalytic site residue present in the structure of 3AQB (heterodimeric hexaprenyl diphosphate synthase).

Docking Studies of Derivatives with 1R4Z (Bacillus Subtilis Lipase A).

The protein-ligand interaction affinities were given by AutoDock Vina for best pose of derivatives. The best pose ligand-protein interaction affinity of all 10 designed molecules was found to be as -5.6, -5.9, -5.6, -5.5, -5.5, -5.7, -5.7, -5.8, -5.8 and -5.8 Kcal/mol with 3, 4, 3, 4, 2, 4, 3, 3, 3 and 4 hydrogen bonds respectively. Here, negative values for interaction energy would reflect the positive docking approach. Other binding details are given in table 1 and docking images are given in Figure 2.

Table 1: Docking results of derivatives with 1R4Z (Bacillus subtilis lipase A)

Receptor	Ligand	Affinity (Kcal/mol)	H-bonds	H- Binding Ligand			H- Binding Receptor			
				Element	Atom No.	Type	Residue	Element	Atom No.	Type
IR4Z	S1	-5.6	3	O	11	Acceptor	His 3	N	00	Donor
				O	16	Acceptor	Asn 174	N	1305	Donor
				O	10	Acceptor	Asn 98	N	736	Donor
	S2	-5.9	4	O	10	Acceptor	Asn 4	N	10	Donor
				N	08	Acceptor	Asn 98	N	736	Donor
				O	18	Acceptor	Asn 4	N	17	Donor
				N	14	Donor	Asn 4	O	16	Acceptor
	S3	-5.6	3	O	11	Acceptor	Asn 4	N	17	Donor
				N	06	Donor	Gln 121	O	894	Acceptor
				O	10	Acceptor	Asn 98	N	736	Donor
	S4	-5.5	4	O	10	Acceptor	Lys 69	N	522	Donor
				O	17	Acceptor	Lys 69	N	522	Donor
				O	17	Acceptor	Asn 4	N	17	Donor
				O	11	Acceptor	Asn 4	N	17	Donor
	S5	-5.5	2	O	11	Acceptor	Asn 4	N	10	Donor
				O	10	Acceptor	Asn 98	N	736	Donor
	S6	-5.7	4	N	06	Donor	Ser 24	O	156	Both
				O	10	Acceptor	Ser 24	O	156	Both
				O	17	Acceptor	Asn 166	N	1245	Donor
				O	11	Acceptor	Asn	N	1245	Donor

					r	166			
	S7	-5.7	3	O	18	Acceptor	Asn 98	N	736	Donor
				O	10	Acceptor	Asn 98	N	736	Donor
				O	11	Acceptor	Asn 4	N	17	Donor
	S8	-5.8	3	O	18	Acceptor	His 3	N	00	Donor
				O	18	Acceptor	Lys 35	N	250	Donor
				O	17	Acceptor	Ser 32	O	222	Both
	S9	-5.8	3	O	18	Acceptor	Lys 35	N	250	Donor
				O	18	Acceptor	His 3	N	00	Donor
				O	17	Acceptor	Ser 32	O	222	Both
	S10	-5.8	4	O	11	Acceptor	Asn 4	N	17	Donor
				O	11	Acceptor	Asn 4	N	4	Donor
				N	14	Donor	Leu 173	O	1293	Acceptor
				O	10	Acceptor	Asn 98	N	736	Donor

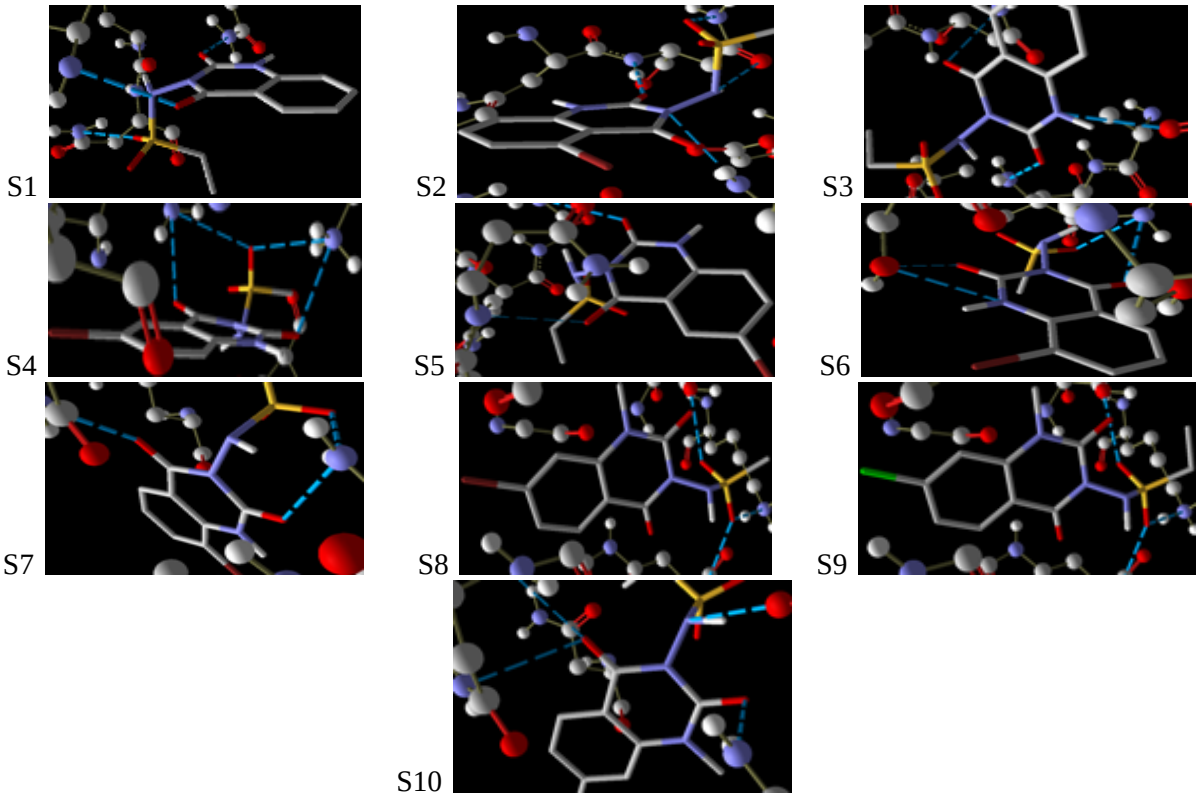


Figure 2: Docked images of derivatives with 1R4Z (Bacillus subtilis lipase A)

Docking Studies of Derivatives with 2CCZ (E-Coli Primosomal Protein)

The best pose ligand-protein interaction affinity of all 10 designed molecules was found to be as -5.9, -6, -6.2, -6.4, -6.1, -5.8, -6.1, -6.2, -6.3 and -6.3Kcal/mol with 3, 2, 6, 3, 3, 2, 3, 3, 2 and 3 hydrogen bonds respectively. Other binding details are given in table 2 and docking images are given in Figure 3.

Table 2: Docking studies of derivatives with 2CCZ (E-coli primosomal protein)

Receptor	Ligand	Affinity (Kcal/mol)	H-bonds	H- Binding Ligand			H- Binding Receptor			
				Element	Atom No.	Type	Residue	Element	Atom No.	Type
2CCZ	S1	-5.9	3	O	10	Acceptor	Ser 79	O	634	Both
				N	06	Donor	Gln 45	O	363	Acceptor
				O	17	Acceptor	Arg 44	N	359	Donor
	S2	-6	2	O	10	Acceptor	Arg 44	N	359	Donor
				O	17	Acceptor	Ser 79	O	634	Both
	S3	-6.2	6	O	17	Acceptor	Arg 44	N	359	Donor
				O	18	Acceptor	Arg 44	N	359	Donor
				O	11	Acceptor	Arg 44	N	359	Donor
				O	11	Acceptor	Arg 44	N	358	Donor
				O	10	Acceptor	Ser 79	O	634	Both
				N	06	Donor	Cys 80	O	638	Acceptor
	S4	-6.4	3	O	10	Acceptor	Gln 49	N	402	Donor
				O	18	Acceptor	Gln 49	N	402	Donor
				O	17	Acceptor	Lys 82	N	646	Donor
	S5	-6.1	3	O	10	Acceptor	Ser 79	O	634	Both
				O	18	Acceptor	Arg 44	N	359	Donor
				N	06	Donor	Gln 45	O	363	Acceptor
	S6	-5.8	2	O	10	Acceptor	Arg 44	N	359	Donor
				O	17	Acceptor	Ser 79	O	634	Both

S7	-6.1	3	O	17	Acceptor	Gln 49	N	402	Donor
			O	10	Acceptor	Gln 49	N	394	Donor
			N	06	Donor	Gln 49	O	397	Acceptor
S8	-6.2	3	O	17	Acceptor	His 26	N	221	Donor
			O	11	Acceptor	Ser 55	O	458	Both
			N	14	Donor	Ser 55	O	458	Both
S9	-6.3	2	O	11	Acceptor	His 81	N	641	Donor
			O	11	Acceptor	Cys 80	S	640	Donor
S10	-6.3	3	O	17	Acceptor	His 26	N	221	Donor
			N	06	Acceptor	Ser 55	O	458	Both
			O	10	Acceptor	His 93	N	730	Donor

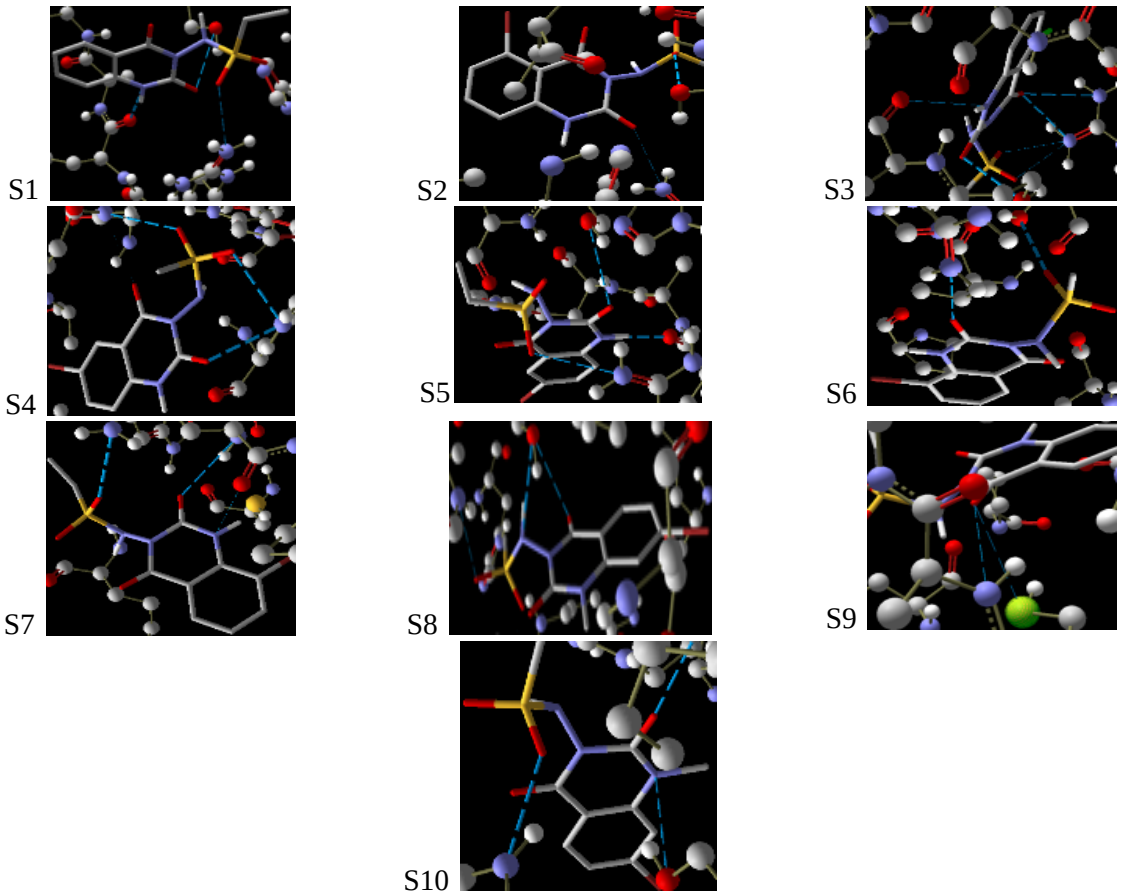


Figure 3: Docked images of derivatives with 2CCZ (E-coli primosomal protein)

Docking Studies of Derivatives with 3AQB (Heterodimeric Hexaprenyl Diphosphate Synthase)

The best pose ligand-protein interaction affinity of all 10 designed molecules was found to be as -6.4, -6.8, -6.2, -6.4, -7, -7.1, -6.3, -6.3, -6.9 and -6.4Kcal/mol with 2, 2, 4, 3, 4, 4, 2, 3, 4 and 1 hydrogen bonds respectively. Other binding details are given in table 3 and docking images are given in Figure 4.

Table 3: Docking studies of derivatives with 3AQB (heterodimeric hexaprenyl diphosphate synthase)

Receptor	Ligand	Affinity (Kcal/mol)	H-bonds	H- Binding Ligand			H- Binding Receptor			
				Element	Atom No.	Type	Residue	Element	Atom No.	Type
	S1	-6.4	2	N	13	Donor	Asp 152	O	1180	Acceptor
				O	10	Acceptor	Asn 155	N	1240	Donor
	S2	-6.8	2	N	14	Donor	Asp 152	O	1180	Acceptor
				O	10	Acceptor	Asn 155	N	1240	Donor
	S3	-6.2	4	O	10	Acceptor	Asn 234	N	1854	Donor
3AQB				O	18	Acceptor	Asn 234	N	1854	Donor
				O	17	Acceptor	Asn 234	N	1854	Donor
				N	14	Donor	Asp 88	O	701	Acceptor
	S4	-6.4	3	O	18	Acceptor	Lys 22	N	208	Donor
				N	14	Donor	Pro 19	O	174	Acceptor
				O	17	Acceptor	Tyr 156	O	1223	Both
	S5	-7	4	N	06	Donor	Asp 152	O	1209	Acceptor
				O	10	Acceptor	Asn 155	N	1240	Donor
				N	14	Donor	Pro 157	O	1227	Acceptor
				O	18	Acceptor	Ser 159	O	1243	Both
	S6	-7.1	4	N	06	Donor	Asp 152	O	1209	Acceptor
				O	10	Acceptor	Asn 155	N	1240	Donor
				N	14	Donor	Pro 157	O	1227	Acceptor
				O	18	Acceptor	Ser 159	O	1243	Both

	S7	-6.3	2	O	18	Acceptor	Tyr 156	O	1252	Both
				O	10	Acceptor	Tyr 156	O	1252	Both
	S8	-6.3	3	O	17	Acceptor	Tyr 156	O	1252	Both
				N	14	Donor	Tyr 156	O	1252	Both
				O	10	Acceptor	Tyr 156	O	1252	Both
	S9	-6.9	4	O	18	Acceptor	Lys 22	N	208	Donor
				O	11	Acceptor	Lys 22	N	208	Donor
				N	14	Donor	Pro 19	O	174	Acceptor
				O	17	Acceptor	Tyr 156	O	1223	Both
	S10	-6.4	1	O	17	Acceptor	Tyr 156	O	1252	Both

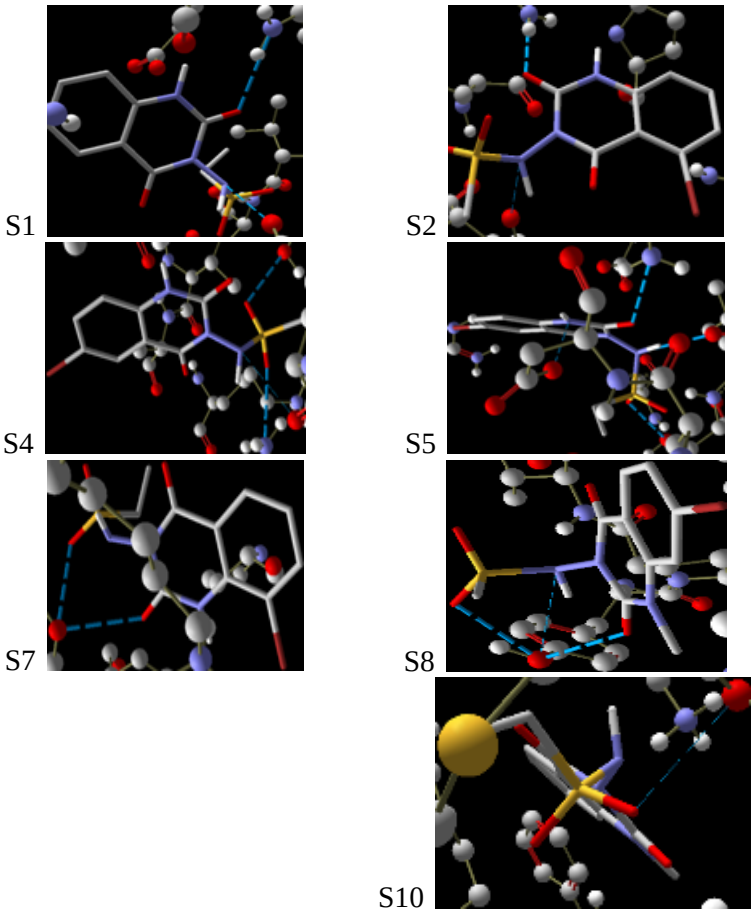


Figure 4: Docked images of derivatives with 3AQB (heterodimeric hexaprenyl diphosphate synthase)

Docking Studies of Norfloxacin (CID_4539) as Reference Drug

On docking analysis (Table 4 and Figure 5), the standard drug CID_4539 has been found to be docked with the protein PDB ID- 1R4Z (Bacillus subtilis lipase A), it forms 1 hydrogen bond with binding affinity of -6.2 Kcal/mol. On residue study, the amino acids GLN 29 was found to be significant. On the account of ligand here oxygen atom is significant in the binding, the type of binding found with acceptor bond, whereas a significant element in receptor binding is also oxygen.

The reference drug does not shows any bonding with the 2CCZ (E-coli primosomal protein) and 3AQB (heterodimeric hexaprenyl diphosphate synthase).

Table 4: Docking studies of Norfloxacin (CID_4539) as reference drug

Ligand	Receptor	Affinity Kcal/mol	H-bonds	H- Binding Ligand			H- Binding Receptor			
				Elem.	At. ID.	Type	Res.	Elem.	At.ID.	Type
CID_4539	1R4Z	-6.2	1	O	23	Both	GLN 29	O	193	Acceptor
	2CCZ	-6.1	0	-	-	-	-	-	-	-
	3AQB	-7.3	0	-	-	-	-	-	-	-

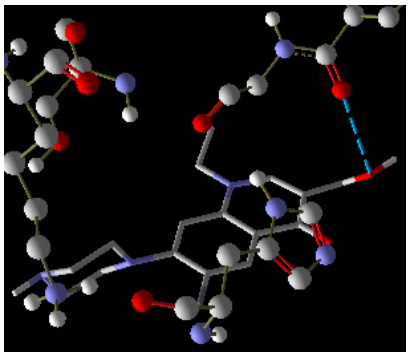


Figure 5: Docking image of Norfloxacin (CID_4539) with 1R4Z

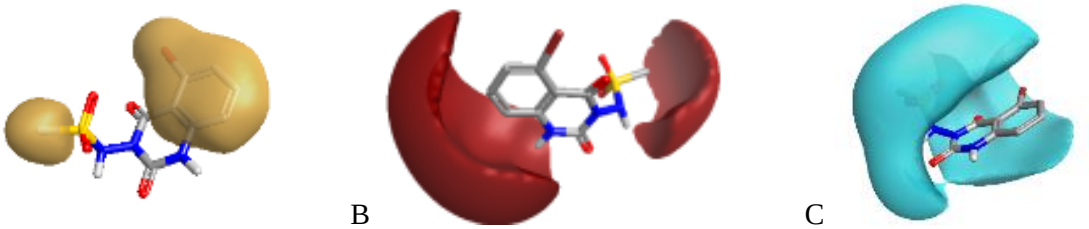
Key results

After studying the docking results, three derivatives have been selected as best derivative for each of the protein taken.

- S2 could be the lead molecule for inhibition of 1R4Z (Bacillus subtilis lipase A)
- S4 could be the lead molecule for inhibition of 2CCZ (E-coli primosomal protein)
- S6 could be the lead molecule for inhibition of 3AQB (heterodimeric hexaprenyl diphosphate synthase)

Different Field Study of the Lead Derivative Selected After Docking Procedures

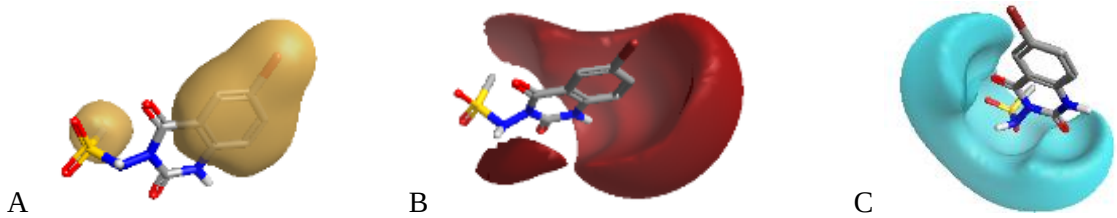
Hydrophobic field, positive field (H-bond acceptors on a protein) and negative field (H-bond donors on a protein) has been obtained for S2 (Pose bound with 1R4Z) and shown in Figure 6.



A B C

Figure 6: A-Hydrophobic field, B-positive field and C-negative field for S2 (Pose bound with 1R4Z)

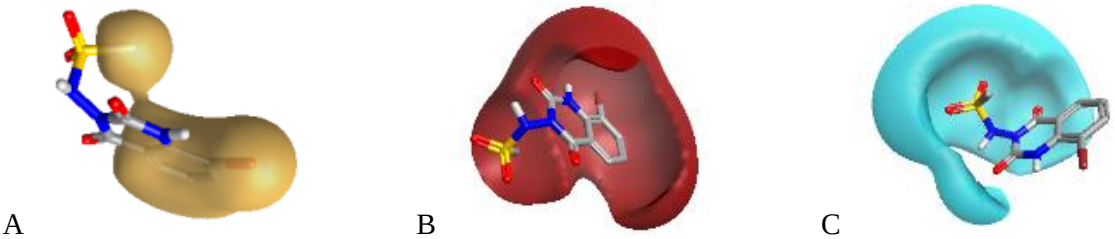
Hydrophobic field, positive field and negative field has been obtained for S4 (Pose bound with 2CCZ) and shown in Figure 7.



A B C

Figure 7: A-Hydrophobic field, B-positive field and C-negative field for S4 (Pose bound with 2CCZ)

Hydrophobic field, positive field and negative field has been obtained for S6 (Pose bound with 3AQB) and shown in Figure 8.



A B C

Figure 8: A-Hydrophobic field, B-positive field and C-negative field for S6 (Pose bound with 3AQB)

Conclusion

Computational study comprises of screening through docking of Quinazolinedione sulfonamide derivatives (S1-S10) proved them potential antibacterial agents. Although a systemic biochemical study is necessary to confirm the findings. On comparing the chemical structure of Quinazolinedione sulfonamide derivatives with norfloxacin, a pre-existing known anti-bacterial agent; there is no structural similarity have been found, except a concept of un-saturated and almost saturated fused rings. So, this could be concluded that the designed derivatives may lead to a novel class of anti-bacterial agents.

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