In Silico Screening and Pharmacological Evaluation of Fluoroquinolones: Lead-Optimization Studies

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Abstract

Fluoroquinolones are broad-spectrum antibiotics regularly used to treat eyes, urinary tracts, and respiratory infections. Transcriptional regulator (TcaR) enzyme plays an important role in the formation of biofilms in *Staphylococcus epidermidis*. These biofilms are important for the protection of bacteria from the host immune system. By using computer-aided drug design techniques, we investigate the molecular interactions and pharmacological properties of selected fluoroquinolones on *Staphylococcus epidermidis* TcaR. We identified the hit molecules through molecular docking and pharmacological evaluation of the selected dataset on TcaR. The hit molecules were used as the leads for further optimization studies to design novel pharmacophore analogs against *Staphylococcus epidermidis* TcaR. The newly designed lead-optimized molecules have shown good binding energies and fitness scores with improved pharmacological properties.

Introduction

Fluoroquinolones are potential antibiotic drugs of both Gram-negative and positive bacteria: they could be used to treat respiratory and urinary tract infections (Leshner et al., 1962; Robson 1992). The first synthetic quinolone, nalidixic acid, was discovered in 1962 by Leshner et al. Later, a fluorine atom was introduced in the basic skeleton of quinolone at R6 position which led to the development of fluoroquinolones (Belal et al., 1999; Ma et al., 2009). Fluoroquinolones have a broad spectrum of biological activities such as an antibiotic (topoisomerase II inhibitor, DNA gyrase, and DNA topoisomerase IV) (Wise et al., 1983; Wentland et al., 1984; Miyamoto et al., 1990; Hosaka et al., 1992; Hong et al., 1997), antifungal (Schmeling et al., 1996), antiviral, and anti-HIV (Oriana et al., 2008) activities. Also, Fluoroquinolones can be used for treating *Mycobacterium tuberculosis* as a part of multi-drug medication (Chhabra et al., 2012). Nowadays, fluoroquinolones have been predominantly used to control diseases caused by plant pathogenic fungi and bacteria (Huang 2004). In the last two decades, several antibiotic fluoroquinolones have been designed, developed, and commercialized: for example, ciprofloxacin, moxifloxacin (Wise et al., 1983), genifloxacin (Hong et al., 1997), norfloxacin (Koga et al., 1980), and sparfloxacin (Miyamoto et al., 1990). Unfortunately, many bacteria such as Gram-positive bacteria (*Staphylococcus aureus* and *Staphylococcus epidermidis*), Gram-negative bacteria (*Campylobacter* organisms) and *Mycobacterium tuberculosis* develop resistance to these drugs (Appelbaum et al., 2000). Recently, the rates of fluoroquinolone resistance in *Campylobacter* species have been significantly increased and exceeded 85% (Sproston et al., 2018). In order to overcome this drug resistance, it is urgently desired to design and develop novel pharmacophore analogs of fluoroquinolones with enhanced pharmacological properties and binding affinities to a specific target protein/enzyme. The evaluation of binding affinity between ligands and the selected target protein would facilitate the synthesis of the most promising compounds (Drlica et al., 2014; Ferreira et al., 2015).

Herein, by using the computer-aided drug design techniques, we investigate the molecular interactions and pharmacological analyses (physicochemical properties, ADMET) of the selected fluoroquinolones on *S. epidermidis*, which frequently instigates infection in immunocompromised people or those after

mutilation to the epithelium. Predicting the binding affinity of the ligand to a specific target is an important step of the drug design process. Molecular docking is a successful technique to identify the best conformation of a ligand to the specific target (Ferreira et al., 2015). We performed a molecular docking analysis of the selected dataset by utilizing two well-known docking programs: Genetic Optimization for Ligand Docking (GOLD) (Jones et al., 1997) and AutoDock vina (Trott et al., 2010). The pharmacological analysis of the selected dataset revealed that they have some toxic properties such as irritant, tumorigenic and low drug-likeness (DL) scores. Hence, we have designed new structural/pharmacophore analogs with enhanced DL scores. We further performed a molecular docking analysis on the specific target, *S. epidermidis* transcriptional regulator (TcaR). The TcaR plays an important role in the biofilm production of bacteria which is essential for bacteria to protect themselves from the host immune system and thereby to improve their resistance to antibiotic chemotherapy (Stewart et al., 2001). The biofilm tolerance is of major clinical significance, because the most of the bacterial infections involves the formation of biofilm (Fux et al., 2005). The present molecular docking results revealed that the designed molecules have a good binding affinity with the specific target *S. epidermidis* TcaR.

Computational Details And Methodology

We took a set of fourteen fluoroquinolones having antibacterial inhibitory activities (Ravi Kumar et al., 2014) (**Table S1**) against *Staphylococcus epidermis* for the present *in silico* analysis. The molecular structures of the dataset were constructed and energetically minimized by utilizing the molecular mechanics (MM+) force field executed in Hyperchem software (Hypercube 2007, <http://www.hyper.com/>).

We carried out the pharmacological analysis on the dataset to reveal structural characteristics (H-bond donors/acceptors, lipophilicity, molecular weight, volume, topological polar surface area), physicochemical, and ADMET properties. The molecules satisfying Lipinski's rule of five (Lipinski 2004) have a good bioavailability in the metabolic process of the organism and therefore are more likely to be eligible for oral medications. The pharmacological analysis of these molecules was carried out by using Molinspiration (<http://www.molinspiration.com/>) and OSIRIS property explorer (Mabkhot et al., 2016) online tools.

In the molecular docking studies on *Staphylococcus epidermidis* TcaR (PDB ID: **3KP4**), we predicted the molecular interaction between ligand and target protein by using well-validated docking programs: GOLD and AutoDock vina. The ligand-target complex results, analysis, and interaction images were generated by using Discovery studio visualization software (Discovery Studio visualizer 2012, <http://www.accelrys.com/>). The crystal structure of *Staphylococcus epidermis* TcaR was retrieved from the RCSB Protein databank (<http://www.rcsb.org>) at a resolution of 2.84 Å and the active site analysis was done by using SPDBV Software (Guex et al., 2006).

Results And Discussions

SAR and ADMET analysis

We performed the *in silico* analysis of 14 molecules to understand their structural features required to interact with the selected target by using ADMET and binding affinity prediction tools. We calculated the physicochemical and ADMET properties of the selected dataset by using Molinspiration and Osiris property explorer. All molecules satisfied Lipinski's rule of five and have shown positive enzyme inhibitor constant but the DL scores were very poor (Table 1 and 2). The poor DL scores represented that these molecules are highly toxic and not a good pharmacophore. We therefore moved to design novel pharmacophore analogs with improved pharmacological properties.

Table 1
Calculated SAR properties of the dataset obtained from the Molinspiration program.

Molecules	TPSA ^a	natoms	M.Wt ^b	nON ^c	nOHNH ^d	n rotb ^e	Volume	Enzyme inhibitor
7a	109.08	26	364.33	8	2	5	303.06	0.22
7b	99.84	25	348.33	7	2	5	294.07	0.24
7c	99.84	26	362.36	7	2	5	310.88	0.24
7d	99.84	27	376.38	7	2	5	327.46	0.19
7e	126.15	31	434.42	9	2	8	372.23	0.09
7f	128.52	35	478.48	9	3	6	407.13	0.21
7g	111.87	26	363.35	8	3	5	306.48	0.24
7h	103.08	27	377.37	8	2	5	323.42	0.22
7i	123.31	29	407.40	9	3	7	348.48	0.19
7j	128.86	32	441.42	10	2	6	369.95	0.21
7k	103.08	33	453.47	8	2	7	395.07	0.17
7l	103.08	32	439.44	8	2	6	378.26	0.15
7n	99.84	27	376.38	7	2	5	327.68	0.23
7o	154.96	30	420.40	10	5	6	353.57	0.13
7p	137.14	29	406.37	9	3	6	337.90	0.19
^a Topological polar surface area; ^b Molecular weight; ^c Number of H-bond donors; ^d Number of H-bond acceptors; ^e Number of rotatable bonds								

Table 2
Physicochemical parameters and drug-likeness properties of the dataset obtained from the Osiris program

Molecules	clogP	Solubility	Drug likeness Score	Overall drug Score
7a	-0.72	-2.47	-5.52	0.45
7b	0.10	-3.09	-4.91	0.44
7c	0.44	-3.36	-6.41	0.43
7d	0.71	-3.52	-3.32	0.43
7e	1.02	-3.98	-4.94	0.37
7f	1.51	-4.08	-2.27	0.37
7g	-2.93	-2.33	-4.06	0.46
7h	-1.54	-1.97	-0.53	0.61
7i	-2.06	-1.76	-1.14	0.54
7j	-0.31	-3.08	-1.41	0.48
7k	-0.12	-3.29	-1.45	0.46
7l	0.89	-3.81	-1.02	0.47
7n	0.79	-3.63	-8.91	0.41
7o	-1.72	-3.34	-7.91	0.24
7p	-0.56	-2.99	-4.12	0.43

Molecular Docking Analysis

We have performed molecular docking simulations on *S. epidermidis* TcaR to understand the enzyme-ligand interaction at the molecular level and to find a suitable orientation of each ligand within the active site. The fitness scores obtained from the GOLD program were high for active molecules when compared to those of least active and inactive molecules. In the docking results of the selected dataset, the fitness scores and binding energies did not correlate with the inhibitory activity of the molecules whereas the hydrophilic character (H-bond score) of molecules played an essential role and also exhibited a good correlation with their inhibitory activities. The most active molecules 7a, 7b, and 7g have shown the highest protein-ligand H-bonding scores 6.27, 6.73, and 6.40, fitness score of 56.33, 57.47, and 56.90, and binding energies of -8.7, -9.0, and -9.2 kcal/mol (Table 3) respectively. The inactive molecules had low

protein-ligand H-bonding scores except molecule 7o. Accordingly, a significant correlation has been found between the protein-ligand H-bond score and the inhibitory activity for the selected dataset.

Table 3
Molecular docking results of selected dataset against *S. epidermidis* TcaR

Molecules	Binding Energy (kcal/mol)	Fitness score	S(hb_ext) ^a	S(vdw_ext) ^b	S(vdw_int) ^c
7a	-8.7	56.33	6.27	45.78	-12.89
7b	-9.0	57.47	6.73	44.81	-13.19
7c	-8.9	61.30	2.01	49.34	-8.53
7d	-9.3	59.35	3.52	50.67	-13.84
7e	-8.3	60.04	6.09	52.25	-12.65
7f	-9.6	58.97	1.94	51.08	-13.22
7g	-9.2	56.90	6.40	47.19	-14.39
7h	-8.7	58.52	3.01	50.26	-22.09
7i	-8.8	61.34	2.70	54.17	-15.85
7j	-9.7	61.63	4.68	52.34	-15.01
7k	-8.5	62.09	2.26	55.70	-16.26
7l	-7.6	60.19	4.72	51.96	-15.98
7n	-4.3	58.06	4.76	47.51	-12.02
7o	-9.2	59.58	5.97	51.99	-17.88
7p	-9.2	57.13	6.04	51.89	-16.03
^a Protein-ligand H-bond scores; ^b Protein-ligand van der Waals scores; ^c Intramolecular van der Waals strain within the ligand					

The binding interactions of the active molecules 7a, 7b, and 7g with the target protein are shown in Figures 1, 2, and 3, respectively. The two carboxyl groups of molecule **7a** had five H-bond interactions with ARG110 (H-bond length (BL) 2.61 Å, 2.60 Å), GLU13 (BL 2.28 Å), and ASN20 (BL 2.44 Å, 2.55 Å). In molecule **7a**, the π cloud of quinolone ring involved in two π - π stacked interactions (BL 3.74 Å, 3.97 Å) and two π -cation interactions (BL 4.10 Å, 3.74 Å) with HIS42 residue, and the Pyrone ring showed one π -Alkyl interaction with ALA38 (BL 4.41 Å), and one carbon-hydrogen bond interaction with GLN61 (BL 2.88 Å). Similarly, molecule **7b** had five H-bond interactions with ARG110 (BL 2.63 Å), GLU13 (BL 2.84 Å), ASN17 (BL 2.97 Å), and ASN20 (BL 2.54 Å, 2.57 Å). Two carboxylic acid groups and one keto group were

involved in these H-bond interactions. The π cloud of quinolone ring has shown two π - π stacked interactions (BL 3.86 Å, 4.00 Å) and two π -cation interactions (BL 3.82 Å, 4.28 Å) with HIS42 residue, and the substituent pyrrole ring was involved in π -Alkyl interactions with VAL63 (BL 5.45 Å), and ALA38 (BL 4.17 Å). The keto group, two carboxyl groups, and six-membered piperazine ring of molecule **7g** have shown eight H-bond interactions with ARG110 (BL 2.61 Å, 2.33 Å), ASN45 (BL 2.62 Å), GLU13 (BL 2.39 Å), ASN17 (BL 2.61 Å), ASN20 (BL 2.49 Å, 2.72 Å), and GLU61 (BL 2.06 Å). The π cloud of the quinolone ring was involved in two π - π stacked interactions (BL 3.88 Å, 3.95 Å) and one π -cation interaction (BL 3.66 Å) with HIS42 residue. The present molecular docking analysis is helped us to understand how each substituent affects the binding affinity with the target.

Lead Optimization Studies

The initial pharmacological analysis of the selected dataset has shown poor DL properties. Therefore, we have carried out lead optimization studies by considering the most active inhibitors (7a, 7b, and 7g) as leads to develop novel molecules with improved pharmacological properties. We designed forty new pharmacophore analogs (Figure S1) by substituting various functional groups at different positions (1st, 6th, and 7th) of the basic skeleton of quinolone. Also, we analyzed the importance of each substituent and how the substituent enhances their medicinal values in the basic skeleton by using the *in silico* tools.

SAR and ADMET analysis of designed molecules

The physicochemical properties and *in silico* drug-relevant properties of designed molecules are summarized in **Tables S2 and S3**. The designed molecules satisfied Lipinski's rule of five, a rule of thumb to evaluate the drug-likeness of a molecule. The lipophilicity values of the designed molecules were less than five. The number of the H-bond donors and acceptors were not more than five and 10, respectively. The molecular weight was less than five hundred Dalton. The designed molecules have shown a positive enzyme inhibition constant, signifying that the molecules act as enzyme inhibitors.

The molecules of our design have shown significantly higher DL scores (except Mol37 to Mol40 over the selected dataset. The positive DL scores (4.83 to 7.20) of these molecules confirm that these pharmacophore analogs qualify as potential commercial drugs. Molecules Mol36, Mol35, Mol32, Mol24, and Mol33 have shown the highest DL scores of 7.20, 6.86, 6.37, 6.34, and 6.33, respectively. Interestingly, the *in silico* ADMET predictions indicated that the loss of one -COOH group (at 1st position) and the substitution of fluorine with chlorine can increase the DL properties and reduce the toxicity risks comparatively.

Molecular Docking Analysis of designed molecules

As per the docking results, all the designed molecules have shown good fitness scores (<50) (Table S4) against the target. In the selected dataset, the H-bond score has shown a very good correlation with the inhibitory activity. Therefore, molecules Mol1, Mol2, Mol4, Mol9, Mol17, Mol24, Mol34, and Mol35 with the highest H-bond scores were taken to be the most active inhibitors of the target.

We have drawn in Figure 4 the binding conformation of the best candidate molecule Mol34 in the active site of *S. epidermis* TcaR. The molecule (binding energy of -10.6 kcal/mol, H-bond score of 7.98, and fitness score of 62.95) took a conformation that fits well in the entire groove of the binding site of *S. epidermis* TcaR. The carboxyl and keto groups of Mol34 played a significant role in the binding by forming three H-bond interactions with the active site residues. The carboxyl group had one H-bond interaction with the ARG110 (BL 2.48 Å) and the keto group had two H-bond interactions with ASN20 (BL 2.71 Å, 2.06 Å). We observed two π - π stacked interactions with HIS42 (BL 4.79 Å, 4.22 Å) and several hydrophobic π -alkyl interactions with VAL63 (BL 4.89 Å), ALA67 (BL 4.53 Å), ALA38 (BL 5.12 Å, 3.75 Å), ALA24 (BL 4.34 Å, 3.36 Å), and LEU27 (BL 5.15 Å). In addition, Mol34 formed a π -cation interaction with ARG71 (BL 3.97 Å) and C-H interaction with ASN20 (BL 3.47 Å).

Conclusion

We completed a comprehensive *in silico* analysis to design and develop novel pharmacophores of fluoroquinolones with improved pharmacological properties and binding affinities. By utilizing a series of computational approaches, we identified the hit molecules against *S. epidermis* TcaR for a selected dataset. All the molecules of the dataset have satisfied Lipinski's rule of five but their drug-like scores were very poor. Hence, we have carried out the structure-based lead optimization of selected active molecules (7a, 7b, and 7g) to design and develop novel pharmacophore analogs with enhanced pharmacological properties, binding affinities, and docking scores. We have designed a total of 40 molecules and considered them for the *in silico* analysis. Among 40 molecules designed, five molecules namely Mol4, Mol9, Mol24, Mol34, and Mol35 have shown positive enzyme inhibitor value, good drug-like scores, and the highest H-bond scores along with good binding affinities. The designed molecules are considered to be the best antibacterial inhibitors of *S. epidermidis* TcaR over the selected dataset.

Declarations

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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Figures

Figure 2

Molecular docking conformation of molecule **7b** in the active site of *S. epidermis* TcaR. Drawn as broken lines (green: H-bond; pink: π - π stacked; orange: π - cation; light pink: alkyl) are the molecular interactions between molecule and protein active site.

Figure 3

Molecular docking conformation of molecule **7g** in the active site of *S. epidermis* TcaR. Drawn as broken lines (green: H-bond; pink: π - π stacked; orange: π - cation; light pink: alkyl) are the molecular interactions between molecule and protein active site.

Figure 4

Molecular docking conformation of Mol34 in the active of *S. epidermis* TcaR. Drawn as broken lines (green: H-bond; pink: π - π stacked; orange: π -cation; light pink: alkyl) are the molecular interactions between molecule and target active site.

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