International Journal of Bioprocess & Biotechnological Advancements
IJBBA, 5(1): 144-150
www.scitcentral.com
ISSN: 2380-0259
Original Research Article: Open Access

In Silico Molecular Docking Study of Delafloxacin against 4MQT for the Treatment of Acute Bacterial Skin and Skin Structure Infections

Shamrat Kumar Paul[1], Pranta Ray[2], Md. Solayman Hossain[2], Abul Bashar Ripon Khalipha[2] and Muhammad Torequl Islam[2*]

[1]*Department of Biochemistry and Molecular Biology, Life Science School, Bangabandhu Sheikh Mujibur Rahaman Science and Technology University, Gopalganj-8100, Bangladesh*

[*2]*Department of Pharmacy, Life Science School, Bangabandhu Sheikh Mujibur Rahaman Science and Technology University, Gopalganj-8100, Bangladesh*

Received December 24, 2018; Accepted December 28, 2018; Published December 20, 2019

ABSTRACT

Infection occurring in the skin and its associated soft tissues such as loose connective tissue and mucous membranes is known as "Acute Bacterial Skin and Skin Structure Infection (ABSSSI)". Till 2008, ABSSSI is recognized as complicated skin and skin structure infection (cSSSI) and uncomplicated skin and skin structure infection (uSSSI). Delafloxacin (DLX), a fluoroquinolone antibiotic which is used to treat ABSSSI. In this study, we have seized Canonical SMILES of DLX from PubChem Compound Database of National Center for Biotechnology Information and predicted the targets using the method of "Shaping the interactive landscape of bioactive molecules" and retrieved 4EKK, 5T31, 2O5K, 3M1S, 4MQS and 4MQT protein crystal structures. The energy minimization of DLX was performed by Universal Force Field (UFF) using the steepest descent algorithm with 2000 iteration to obtain the optimized structures. To obtain the best binding energy there was used Autodock Vina docking protocol. The main structure of DLX was modified with $-CF_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CF_3$ and -Br groups. The DLX-CF_3 modified DLX showed binding energy -11.4 kcal/mol with protein 4MQT of muscarinic acetylcholine receptor M2 family compared to the main drug showed binding energy -9.7 kcal/mol with the same protein. All the modified drugs showed considerable Homo-Lumo, thermodynamic properties and pharmacokinetics properties. DLX containing trifluoromethane derivative will be the best inhibitor against muscarinic acetylcholine receptor M2 induced skin infection.

Keywords: ABSSSIs, Delafloxacin, Molecular modeling, Virtual screening, 4MQT

INTRODUCTION

Skin and skin structure infections (SSSIs) refer to a diverse collection of clinical infectious syndromes involving the layers of the skin and its associated underlying soft tissues, but excluding osseous tissue [1]. It is also known as skin and soft tissue infections (SSTIs). The US FDA used a modified definition previously in their 1998 draft guidance for industry was complicated skin and soft tissue infection (cSSTI) but cSSTI has been supplanted by the other term acute bacterial skin and skin structure infections (ABSSSIs), including wound infections, cellulitis and erysipelas and major cutaneous abscesses that involve a minimum surface area of 75 cm^2 [2].

Delafloxacin (DLX) is a novel fluoroquinolone that distinct from chemically currently marketed fluoroquinolones conferring a weakly acidic character to the molecule but with the absence of a protonatable substituent. This property of DLX results in enhanced bactericidal activity and increased intracellular penetration under acidic conditions which characterize the infectious milieu at a number of sites. The US Food and Drug Administration approved DLX for the treatment of ABSSSIs and it is unique in its balanced target enzyme inhibition [3]. DLX exhibits increased in vitro activity against a wide range of Gram-positive and -negative species and many fluoroquinolone-resistant strains such as

Corresponding author: Muhammad T Islam, Department of Pharmacy, Life Science School, Bangabandhu Sheikh Mujibur Rahaman Science and Technology University, Gopalgonj-8100, Bangladesh, Tel: +8801793726407; E-mail: mti031124@gmail.com

Citation: Paul SK, Ray P, Hossain MS, Khalipha ABP & Islam MT. (2019) *In Silico* Molecular Docking Study of Delafloxacin against 4MQT for the Treatment of Acute Bacterial Skin and Skin Structure Infections. Int. J. Biopro. Biotechnol. Advance, 5(1): 144-150.

methicillin-resistant *Staphylococcus aureus* (MRSA) [4] and Enterococci and it represents a promising option in the empirical and targeted treatment of ABSSSIs due to its favorable pharmacokinetic characteristics, the potential for sequential therapy and the wide spectrum of action both in hospital- and in community-based care [5].

The minimum inhibitory concentrations (MICs) demonstrated by DLX that are consistently three- to five-fold lower than comparator fluoroquinolones against Gram-positive organisms. It is due to its greater affinity for DNA gyrase compared with other fluoroquinolones. DNA gyrase acts onward of the replication fork and inhibits DNA replication more rapidly by removing positive supercoils than the interaction with topoisomerase IV [6]. The specific shape, size and polarity of DLX are responsible for its increased potency against Gram-positive bacteria [7]. The chemical structure of DLX **(Figure 1)** includes heteroaromatic ring at N1, the absence of a basic group at C7 and weak polarity defined by the chlorine atom at C8 and heteroaromatic ring at N1 increases the solvent accessible surface area, and collaboration between this large substituent and the weakly polar group at C8 is thought to influence the potency against quinolone-resistant Gram-positive bacteria [7] and C8 substitution could also reduce second-step resistance development in *S. aureus* [8,9] and the absence of a basic group at C7 gives DLX an anionic character at neutral pH [10].

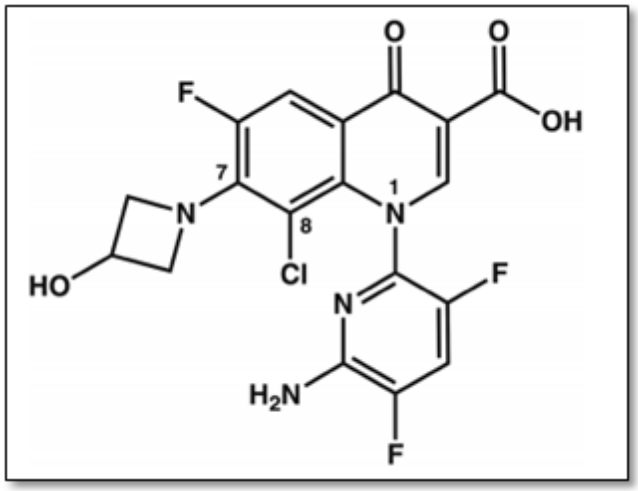

Figure 1. Chemical structure of delafloxacin ($C_{18}H_{12}ClF_3N_4O_4$).

In silico molecular and virtual screening are the best way to save time and cost for new drug discovery and design. In this study, we have identified DLX as the drug of choice to treat ABSSSIs [11], screening with the crystal structure of its targets against 4EKK, 5T31, 2O5K, 3M1S, 5OY4, 5CVX, 5DSG, 4MQS and 4MQT [12]. The target 4MQT, the human M2 muscarinic acetylcholine receptor has been investigated as the best one regarding to its selectivity [13]. We have employed the density functional theory to optimize DLX and its related compounds. Thermo-dynamic properties and frontier molecular orbitals of those drugs are also explored in details. Molecular docking calculation has been performed to understand the non-bonding interaction between the designed drugs with 4MQT of muscarinic acetylcholine receptor M2.

METHODOLOGY

Protein selection

We have retrieved target of DLX from Swiss target predictor [14] on the basis of probability we have chosen Glycogen synthase kinase-3 alpha (by homology), Glycogen kinase-3 beta, Muscarinic acetylcholine receptor M1, Muscarinic acetylcholine receptor M2 (by homology), Muscarinic acetylcholine receptor M4 (by homology). Using their Uniprot ID we retrieved protein crystal structures of 4EKK, 5T31, 2O5K, 3M1S, 4MQS and 4MQT.

Optimization of ligands

All calculations were carried out using Gaussian view 09 and Chem3DPro12.0 program packages **(Figure 2)** [15]. Initial three-dimensional geometry of chair forms of DLX was retrieved from the bound crystal structure of 4EKK, 5T31, 2O5K, 3M1S, 4MQS and 4MQT. The carbon-13 position of parent has -OH group that was modified with-CF_3, -OCH_3, -OCH_2CH_3, -OCH_2CF_3 and -Br functional groups. These structures were fully optimized by density functional theory [16].

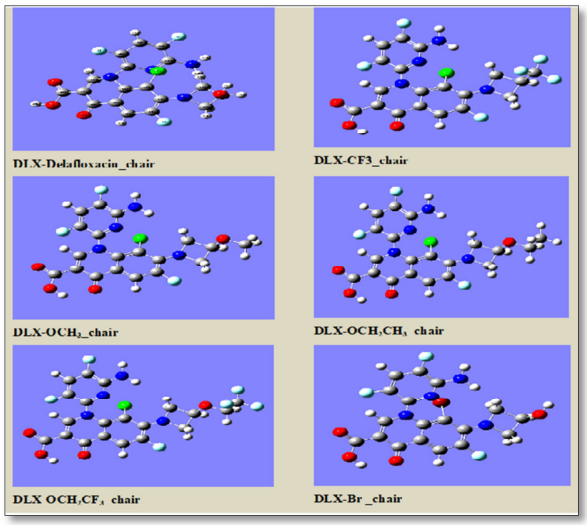

Figure 2. Preparation of ligand's (DLX) derivatives.

Binding site and docking analysis

The active binding pocket of DLX predicted by CASTp-having the highest pocket area [17]. The binding site residues predicted by CASTP for 4EKK, 5T31, 2O5K, 3M1S, 4MQS and 4MQT were used for grid generation. The docked pose of lowest binding free energy conformer with

the respective protein was analyzed using PyMOL Molecular Graphics System (version 1.7.4) [18].

Pharmacokinetic parameters

For the prediction of the data related to drug absorption, metabolism and carcinogenicity for DLX and its modified derivatives the AdmetSAR online database has been utilized [19]. Structure Data File (SDF) and the simplified molecular-input line-entry system (SMILES) strings were utilized throughout the generation process.

RESULTS AND DISCUSSION

HOMO-LUMO, gap, hardness and softness analyzes

HOMOs are the highest occupied molecular orbital and LUMOs are the lowest unoccupied molecular orbital. The chemical stability and kinetic of drug molecules are predicted by the energy gap between HOMO and LUMO [20]. The D-CF_3 showed lowest energy gap values and lowest hardness value and increased softness value that indicates that this drug has increased chemical reactivity. The frontier molecular orbital of DLX and DLX-OCH_3 showed in **Figure 3**. HOMO-LUMO, gap, hardness (η) and softness (S) values of the drugs calculated according to the following equation [18,21] were given in **Table 1**.

$$\eta = \varepsilon LUMO - \varepsilon HOMO/2 \quad (1)$$

$$S = 1/\eta \quad (2)$$

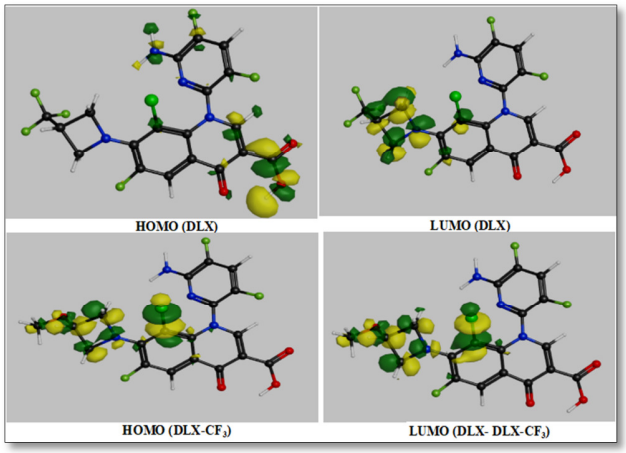

Figure 3. Frontier molecular orbitals of DLX and DLX-CF_3.

Table 1. HOMO-LUMO, gap, hardness and softness.

Molecules (Chair)	εHOMO	εLUMO	Gap	Hardness (η)	Softness
DLX	-7.871	-2.31	5.561	2.780	0.3596
DLX-OCH_3	-7.718	-1.226	6.492	3.246	0.308
DLX-OCH_2CH_3	-7.919	-2.305	5.614	2.807	0.3562
DLX-Br	-7.839	-0.746	7.093	3.546	0.5639
DLX- OCH_2CF_3	-6.641	-1.618	5.023	2.511	0.3981
DLX-CF_3	-4.222	-2.331	1.891	0.945	1.0576

Binding energy (kcal/mol) for ligand – 4 MQT (at chair form) systems obtained from docking

The ethers derivatives of DLX (DLX-CF_3) showed binding energy -11.4 (kcal/mol) with protein 4MQT compared to the main drug (DLX) that showed binding energy -9.7 (kcal/mol) with the same protein. The binding energy of ligand-proteins was given in **Table 2**.

Table 2. Free energy of binding values (kcal/mol) for ligand - 4MQT.

Proteins	DLX	DLX-CF_3	DLX-OCH_3	DLX-OCH_2CH_3	DLX-OCH_2CF_3	DLX-Br
4EKK	-8.7	-8.4	-8.1	-8.0	-8.0	-8.2
5T31	-8.8	-8.7	-8.7	-8.5	-8.3	-9.1
2O5k	-9.2	-8.7	-7.8	-8.4	-8.6	-7.4
3M1S	-7.2	-8.8	-8.2	-8.3	-8.8	-9.5
4MQS	-8.4	-8.1	-7.77	-7.8	-7.7	-8.5
4MQT	-9.7	-11.4	-10.9	-10.8	-10.4	-7.7

Selected non-covalent interactions between chair ligands DLX, DLX-CF_3 and 4MQT obtained by discovery studio

The hydrogen bond is observed in trifluoromethane derivative of DLX (DLX-CF_3) that is necessary for DNA structure in biology [22]. It is demonstrated that the binding affinity will increase in hydrogen bond distance lower than 2.3 Å [23]. Strong hydrogen bonds with ILE417 (1.92 Å) present in DLX-4MQT. In DLX-CF_3-4MQT, hydrogen bond occurred with ASN410 (2.79). A number of hydrophobic bonds are formed in the DLX-CF_3-4MQT complex **(Table 3)**. The binding site of ligand-proteins has been given in **Figure 4**.

Table 3: Selected non-covalent interactions among chair ligands DLX, DLX-OCH_3 and 4MQT.

Systems	Contacts	Bond distances (Å)	Systems	Contacts	Bond distances (Å)
DLX-4MQT	O…H(ILE417)	1.92	DLX-CF_3 - 4MQT	F…HD21 (ASN410)	2.79
	O…H (ALA414)	2.38		O…HD21 (ASN410)	2.94
	OH…H17 (TYR177)	2.70		O…HD22 (ASN410)	2.66
	Pi-Alkyl (ALA193)	3.61		Pi-Alkyl (TYR177)	5.24
	Pi-Alkyl (PRO198)	4.01		Pi-Alkyl (TYR177)	5.30
	O…H(ILE417)	1.92		F…HD21 (ASN410)	2.79

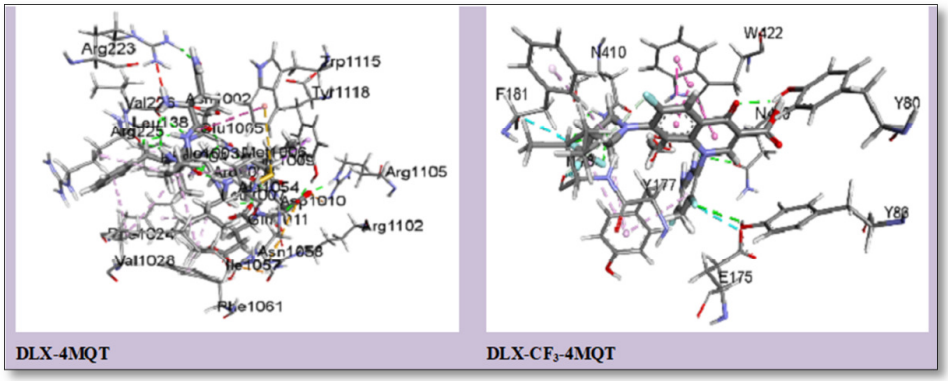

Figure 4. Binding sites of ligands-proteins.

Pharmacokinetic properties of DLX and its modified derivatives

The non-carcinogenic properties are predicted by AdmetSAR calculation for all the drugs. Thus, the drugs those are modified, expected to be safe for use. Generally, these kinds of drugs are capable to cross the blood-brain-barrier (BBB). The bioavailability of these drugs are expected to be improved, thus the drug metabolism and intestinal absorption will also be modified in a positive manner [24]. They are also P-glycoprotein inhibitors. The AdmetSAR values for these ligands were given in **Table 4**.

Table 4. AdmetSAR values of ligands.

Parameters	DLX	DLX-CF_3	DLX-OCH_3	DLX-OCH_2CH_3	DLX-OCH_2CF_3	DLX-Br
Blood brain barrier	0.764	0.618	0.814	0.650	0.509	0.787
Human intestinal absorption	0.983	0.998	0.984	0.988	0.974	0.975
Caco-2 permeability	0.526	0.561	0.533	0.566	0.575	0.530
P-glycoprotein inhibitor	0.960	0.975	0.940	0.8983	0.900	0.936
Human ether a-go-go-related (hERG) gene inhibition	0.965	0.962	0.958	0.929	0.920	0.977
Acute oral toxicity	0.658	0.625	0.675	0.684	0.660	0.654
Rat acute toxicity, LD_{50} (mol/kg)	2.325	2.299	2.651	2.682	2.649	2.920
Aqueous solubility	-3.501	-3.940	-3.465	-3.836	-3.991	-3.368
Carcinogenicity	No	No	No	No	No	No

MedChem Designer, admetSAR@LMMD, was used for ADMET analysis of the identified compound. According to MedChem Designer, In general, lipophilicity is the logarithm value of the partition coefficient P (logP) [25] between octanol and water (buffer), which explains the partition of the unionized (neutral) form of the compound, whereas logD describes the total partition of both the ionized and the unionized forms of the compound [26]. Compounds identified from ChEMBL showed logP value more than 5 indicating their lipophilic proprieties, whereas compound DLX7 showed low logP scores of 0.959 respectively, indicating their hydrophilic nature. MlogP (Moriguchi octanol-water partition coefficient) is well known and is traditionally used in QSAR model structure analysis [27]. It reveals the lipophilicity of a compound, which indicates the penetration of the compound from aqueous solutions to lipid-rich zones. Moriguchi's logP (MLogP) of greater than 4.15 suggests that the compound would be poorly absorbed [27]. The calculated MLogP of all compounds significantly less than 4.15, suggesting that these compounds would be easily absorbed **(Table 5)**.

Table 5. ADMET value by MedChem designer.

Parameters	DLX	DLX-CF_3	DLX-OCH_3	DLX-OCH_2CH_3	DLX-OCH_2CF_3	DLX-Br
MlogP	0.356	1.649	0.577	0.793	1.111	0.467
S+logP	1.227	2.477	1.864	2.225	2.194	1.147
S+logD	-0.414	0.908	0.284	0.683	0.752	-0.274
MWt	440.76	492.76	454.79	468.82	522.79	485.224

Toxicity predicted by PreADMET in **Table 6** suggesting that all the compounds having toxicity less than 1.0.

Table 6. Toxicity analysis by preADMET.

Parameters	DLX	DLX-CF_3	DLX-OCH_3	DLX-OCH_2CH_3	DLX-OCH_2CF_3	DLX-Br
algae_at	0.023	0.011	0.020	0.014	0.008	0.021
daphnia_at	0.052	0.035	0.045	0.032	0.017	0.042
medaka_at	0.006	0.002	0.004	0.002	0.001	0.004
minnow_at	0.002	0.001	0.001	0.001	0.001	0.002

Electronic structure of DLX and its modified derivatives

DLX has dipole moment 9.391 Debye and all modified drugs having stoichiometry, electronic energy, enthalpy, Gibbs free energy in Hartree and increased dipole moment in **Table 7**. DLX-OCH_3 and DLX-Br showed a large dipole moment that can lead to higher binding affinity against 4MQT.

Table 7. Stoichiometry, electronic energy, enthalpy, Gibbs free energy in Hartree and dipole moment (Debye) of DLX and its derivatives.

Name	Stoichiometry	Electronic Energy	Enthalpy (Hartee)	Gibbs free energy (Hartee)	Dipole moment (Debye)
DLX	$C_{18}H_{12}ClF_3N_4O_4$	-1962.65	0.339	0.258	9.391
DLX-CF_3	$C_{19}H_{11}ClF_6N_4O_3$	-2234.33	0.320	0.230	10.553
DLX-OCH_3	$C_{19}H_{14}ClF_3N_4O_4$	-2011.78	0.347	0.259	12.425
DLX-OCH_2CH_3	$C_{20}H_{16}ClF_3N_4O_4$	-2051.08	0.376	0.285	12.581
DLX-OCH_2CF_3	$C_{20}H_{13}ClF_6N_4O_4$	-2348.82	0.355	0.258	10.802
DLX-Br	$C_{18}H_{12}BrF_3N_4O_4$	-4084.02	0.317	0.231	13.055

CONCLUSION

In this *in silico* study, the binding affinity of the ether derivatives of delafloxacin (DLX-CF_3) showed binding energy -11.4 (kcal/mol) with protein 4MQT compared to the main drug (DLX) that showed binding energy -9.7 (kcal/mol) with the same protein with considerable modified pharmacokinetics, HOMO-LUMO, thermodynamics properties. Altogether, DLX-CF_3-4MQT is the best conformer as the target of the treatment of ABSSSIs.

ACKNOWLEDGEMENT

We are grateful to the Evergreen Scientific Research Center (http://www.esrc-bd.com) and Department of Pharmacy, Bagnabandhu Sheikh Mujibur Rahman Science and Technology University (BSMRSTU), Gopalgonj-8100, Bangladesh for supporting this study.

AUTHORS' CONTRIBUTION

ABRK- Idea generation, MSH and MTI- Drug design and report writing, SKP- Data collection and manipulation, PR- Data analysis and report writing. All authors read and approved the paper.

REFERENCES

1. May AK, Stafford RE, Bulger EM, Heffernan D, Guillamondegui O, et al. (2009) Treatment of complicated skin and soft tissue infections. Surg Infect 10: 467-499.
2. Almarzoky Abuhussain SS, Goodlet KJ, Nailor MD, Nicolau DP (2018) Optimizing skin and skin structure infection outcomes: Considerations of cost of care. Expert Rev Pharmacoecon Outcomes Res 18: 235-244.
3. Jorgensen SC, Mercuro NJ, Davis SL, Rybak MJ (2018) Delafloxacin: Place in therapy and review of microbiologic, clinical and pharmacologic properties. Infect Dis Ther 7: 197-217.
4. Bassetti M, Righi E, Pecori D, Tillotson G (2018) Delafloxacin: An improved fluoroquinolone developed through advanced molecular engineering. Future Microbiol 13: 1081-1094.
5. Righi E, Carnelutti A, Vena A, Bassetti M (2018) Emerging treatment options for acute bacterial skin and skin structure infections: Focus on intravenous delafloxacin. Infect Drug Resist 11: 479-488.

6. Nilius AM, Shen LL, Hensey-Rudloff D, Almer LS, Beyer JM, et al. (2003) *In vitro* antibacterial potency and spectrum of ABT-492, a new fluoroquinolone. Antimicrob Agents Chemother 47: 3260-3269.

7. Duffy EMDJ, Devito JA, Remy J, Burak E (2010) Delafloxacin chemical properties lead to increased potency against gram-positive pathogens, including quinolone-resistant pathogens II. In 50th Interscience Conference on Antimicrobial Agents and Chemotherapy.

8. Lu T, Zhao X, Li X, Drlica-Wagner A, Wang JY, et al. (2001) Enhancement of fluoroquinolone activity by C-8 halogen and methoxy moieties: Action against a gyrase resistance mutant of Mycobacterium smegmatis and a gyrase-topoisomerase IV double mutant of Staphylococcus aureus. Antimicrob Agents Chemother 45: 2703-2709.

9. Okumura R, Hirata T, Onodera Y, Hoshino K, Otani T, et al. (2008) Dual-targeting properties of the 3-aminopyrrolidyl quinolones, DC-159a and sitafloxacin, against DNA gyrase and topoisomerase IV: Contribution to reducing *in vitro* emergence of quinolone-resistant *Streptococcus pneumoniae*. J Antimicrob Chemother 62: 98-104.

10. Lemaire S, Tulkens PM, Van Bambeke F (2011) Contrasting effects of acidic pH on the extracellular and intracellular activities of the anti-gram-positive fluoroquinolones moxifloxacin and delafloxacin against *Staphylococcus aureus*. Antimicrob Agents Chemother 55: 649-658.

11. Pollack Jr CV, Amin A, Ford Jr WT, Finley R, Kaye KS, et al. (2015) Acute bacterial skin and skin structure infections (ABSSSI): Practice guidelines for management and care transitions in the emergency department and hospital. J Emerg Med 48: 508-519.

12. Moellering Jr RC (2011) Discovering new antimicrobial agents. Int J Antimicrob Agents 37: 2-9.

13. McCorvy JD, Roth BL (2015) Structure and function of serotonin G protein-coupled receptors. Pharmacol Ther 150: 129-142.

14. Lepak AJ, Andes DR (2016) *In vivo* pharmacodynamic target assessment of delafloxacin against *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Klebsiella pneumoniae* in the murine lung infection model. Antimicrob Agents Chemother 60: 4764-4769.

15. Bresler G, Tse D (2008) The two-user Gaussian interference channel: A deterministic view. Eur Trans Telecomm 19: 333-354.

16. Yang W, Ayers PW (2003) Density-functional theory. In Computational Medicinal Chemistry for Drug Discovery. CRC Press, pp: 103-132.

17. Grimme S, Ehrlich S, Goerigk L (2011) Effect of the damping function in dispersion corrected density functional theory. J Comput Chem 32: 1456-1465.

18. DeLano WL (2002) The PyMOL molecular graphics system. DeLano Scientific, Palo Alto, CA, USA. Available at: http://www.pymol.org

19. Cheng F, Li W, Zhou Y, Shen J, Wu Z, et al. (2012) admetSAR: A comprehensive source and free tool for assessment of chemical ADMET properties. J Chem Inf Model 52: 3099-3105.

20. Rahman A, Hoque MM, Khan MA, Sarwar MG, Halim MA (2016) Non-covalent interactions involving halogenated derivatives of capecitabine and thymidylate synthase: A computational approach. SpringerPlus 5: 146.

21. Pearson WR, Lipman DJ (1988) Improved tools for biological sequence comparison. Proc Natl Acad Sci 85: 2444-2448.

22. Jeffrey GA, Saenger W (2012) Hydrogen bonding in biological structures. Springer Science & Business Media.

23. Wade RC, Goodford PJ (1989) The role of hydrogen-bonds in drug binding. Prog Clin Biol Res 289: 433-444.

24. Kruijtzer CMF, Beijnen JH, Rosing H, ten Bokkel Huinink WW, Schot M, et al. (2002) Increased oral bioavailability of topotecan in combination with the breast cancer resistance protein and P-glycoprotein inhibitor GF120918. J Clin Oncol 20: 2943-2950.

25. McKim J, Schmieder P, Veith G (1985) Absorption dynamics of organic chemical transport across trout gills as related to octanol-water partition coefficient. Toxicol Appl Pharmacol 77: 1-10.

26. Manners CN, Payling DW, Smith DA (1988) Distribution coefficient, a convenient term for the relation of predictable physico-chemical properties to metabolic processes. Xenobiotica 18: 331-350.

27. Cheng T, Zhao Y, Li X, Lin F, Xu Y, et al. (2007) Computation of octanol-water partition coefficients by guiding an additive model with knowledge. J Chem Inf Model 47: 2140-2148.