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In-silico Studies on 3,4-dihydropyrimidin-2(1H)-one Urea Derivatives (3,4-DPU) as Efficient Hydrolase Inhibitor *down regulating Staphylococcus aureus*

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ABSTRACT

The danger caused by *S. aureus* in the world at large is colossal and this has drawn the attention of researchers to designing effective dug-like compounds to combat this disease. Series of anti- *Staphylococcus aureus were studied via quantum chemical method and several molecular descriptors were obtained which were further used to develop QSAR model using back propagation neural network method using MATLAB. The developed QSAR model was observed to be predictive. Also, the inhibition concentration obtained for the proposed compound **1, 2** and **3** showed their ability to inhibit more than the modelled compounds as well as other proposed compounds (**4, 5** and **6**). More so, the molecular interaction observed between* 3,4-dihydropyrimidin-2(1H)-one Urea Derivatives and *Staphylococcus aureus* Sortase (PDB ID Code: **2kid**) via docking study was used as a screening tool for the studied compounds; thus, **A3, 3 (**Proposed Compound**)** and **4** (Proposed Compound) proved to be more effective. The studied molecular compounds used in this work proved to be effective since they obey Lipinski rule of five and the developed QSAR model using selected descriptors from the optimized compounds was predictive. Also, the studied molecular docking revealed the interaction between the studied complex; thus, **A3, 3 (**Proposed Compound**)** and **4** (Proposed Compound) inhibited efficiently than other studied compounds.

Keywords: 3,4-dihydropyrimidin-2(1H)-one Urea, *Staphylococcus aureus, DFT, QSAR, Docking, inhibitor*

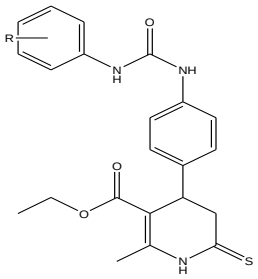
1. INTRODUCTION

The continuous threat posed by *Staphylococcus aureus in the world at large has increased the eagerness of scientists in designing and developing more efficient anti-bacterial agents [1,2]. Staphylococcus aureus has been a cause of death in many nations and in controlling this dreaded bacterial has claimed huge amount of money in both developing and developed countries [3]. According to Lowy, 1998, resistance to anti-Staphylococcus aureus* agents has made *S. aureus to be an important pathogen among other bacteria [4]. More so, the enzyme produces by S. aureus (Sortases) helps in fastening protein that reside on the surface of cell to the cell wall [5].*

3,4-Dihydropyrimidin-2-(1H)-one derivatives are vital heterocyclic compounds. The synthesis of 3,4-Dihydropyrimidin-2-(1H)-one via Biginelli reaction was first achieved in 1893 by an Italian chemist called Pietro Biginelli [6]) and they are reported to have several biological importance such as anti-bacterial, antihypertensive, anti-viral and anti-cancer activities [7-12]. Atwal *et al*., 1991, reported that 3,4-dihydropyrimidin-2-(1H)-one derivatives possess calcium channel blocker activity [13].

Thus, this work is aimed at investigating the efficiency of descriptors obtained from optimized 21 sets of 3,4-dihydropyrimidin-2(1H)-one urea derivatives in developing efficient QSAR model and exploring the molecular interaction between the studied compounds and *Staphylococcus aureus* Sortase (PDB ID Code: **2kid**) [14]).

The names of the studied compounds are:
ethyl 4-(4-(3-(2-fluorophenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate (**A1**),
ethyl 4-(4-(3-(2-chlorophenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate (**A2),**
ethyl4-(4-(3-(2-(trifluoromethyl)phenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate (**A3),**
ethyl1,4,5,6-tetrahydro-2-methyl-6-thioxo-4-(4-(3-(2-(trifluoromethoxy)phenyl)ureido)phenyl)pyridine-3-carboxylate(**A4),**
ethyl 4-(4-(3-(2-fluoro-6-methylphenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate (**A5),**
ethyl4-(4-(3-(2-fluoro-6-(trifluoromethyl)phenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate (**A6),**
ethyl 4-(4-(3-(2-chloro-6-methylphenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate (**A7),**
ethyl 4-(4-(3-(2-chloro-6-fluorophenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate (**A8),** ethyl 4-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate (**A9),**
ethyl4-(4-(3-(3-chloro-4-fluorophenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate (**A10),**
ethyl 4-(4-(3-(3,5-difluorophenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate (**A11),**
ethyl 1,4,5,6-tetrahydro-2-methyl-4-(4-(3-(3,4-dimethylphenyl)ureido)phenyl)-6-thioxopyridine-3-carboxylate (**A12),**
ethyl 4-(4-(3-(4-fluoro-3-methylphenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate (**A13),**
ethyl 1,4,5,6-tetrahydro-2-methyl-4-(4-(3-(4-propylphenyl)ureido)phenyl)-6-thioxopyridine-3-carboxylate(**A14),**
ethyl 4-(4-(3-(4-(trifluoromethyl)phenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate (**A15),**
ethyl 1,4,5,6-tetrahydro-4-(4-(3-(4-methoxyphenyl)ureido)phenyl)-2-methyl-6-thioxopyridine-3-carboxylate (**A16)**



S. No	R
A1	2-F
A2	2-Cl
A3	2-CF_3
A4	2-OCF_3
A5	2-F, 6-CH3
A6	2-F, 6-CF_3
A7	2-Cl, 6-CH3
A8	2-Cl, 6-F
A9	3-CF_3
A10	3-Cl, 4-F
A11	3,5-F
A12	3,4-CH_3
A13	4-F, 3-CH3
A14	4-isopropyl
A15	4-CF_3
A16	4-OCH_3

Figure 1: The Schematic diagram of 3,4-dihydropyrimidin-2(1H)-one urea derivatives [1]

2. METHODOLOGY

Sixteen inhibitors were optimized using density functional theory with B3LYP/6-31G** via Spartan 14 and series of descriptors were obtained. The obtained descriptors were used in developing QSAR model using ordinary least square method via Gretl and Back propagation neural network (BPNN) via MATLAB. The developed QSAR model were validated using cross validation (CVR^2) (equation 1) and Adjusted R^2 (Equation 2). The optimized 3,4-dihydropyrimidin-2(1H)-one urea derivatives were computationally docked against *Staphylococcus aureus* Sortase (PDB ID Code: **2kid**) using Discovery Studio 2017 R2, AutoDockTools-1.5.6 and AutoDock Vina software. This inhibition constant could be calculated using equation 3.

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$$CV.R^2 = 1 - \frac{\sum(Y_{obs} - Y_{cal})^2}{\sum(Y_{obs} - \bar{Y}_{obs})^2} \text{----------(1)}$$

The R^2 adjusted could be calculated using equation (2)

$$R_a^2 = \frac{(N-I)\times R^2 - P}{N-1-P} \text{----------(2)}$$

$$K = e^{-\Delta G/RT} \text{.....(3)}$$

3. RESULT AND DISCUSSION

3.1 Molecular Descriptors and QSAR Modelling

The obtained descriptors from the studied drug-like molecules via density functional theory method were investigated by considering Lipinski's rule of five (Molecular Weight (MW) ≤ 500, Hydrogen Bond Donor (HBD) ≤ 5, Hydrogen Bond Acceptor (HBA) ≤ 10 and Lipophilcity (Log P) ≤ 5) [15]. From Table 1, it was observed that all the studied compounds agreed well with the Lipinski's rule of five and this proved that the studied compounds possess drug-like properties.

Furthermore, the obtained descriptors were used to develop QSAR model (Equation 4) using BPNN via MATLAB. It was observed that the predicted inhibition coefficient (IC_{50}) agreed well with the observed inhibition coefficient (IC_{50}) (Table 2). This shows the effectiveness of the developed model to be predictive and it was also confirmed via the test set (*). Also, the developed QSAR model was validated by considering adjusted R^2, $CV.R^2$, P-Value, R^2, MSE and this proved the effectiveness of the developed QSAR model to be predictive (Equation 1). Furthermore, Figure 2 and Table 2 revealed the closeness between the experimental IC_{50} and the calculated IC_{50}.

Table 1: Calculated molecular descriptors from 3,4-dihydropyrimidin-2(1H)-one urea derivatives

	HOMO	LUMO	BG	MW	LogP	AREA	OVALITY	PSA	Pol	HBD	HBA	PIC
A1*	-5.76	-1.35	4.41	428.49	2.32	438.04	1.64	71.73	73.68	4	7	-1
A2	-5.87	-1.4	4.47	444.94	2.72	442.77	1.64	67.75	74.31	4	7	-1
A3	-5.86	-1.42	4.44	478.5	3.08	460.51	1.65	66.84	75.79	4	7	-1.39
A4*	-5.78	-1.39	4.39	494.49	3.12	475.18	1.68	75.79	76.6	4	8	-1.47
A5	-5.78	-1.4	4.38	442.52	2.8	452.32	1.65	69.13	75.09	4	7	-1.77
A6	-5.85	-1.41	4.44	496.49	3.24	467.22	1.66	69.88	76.2	4	7	-1.74
A7	-5.79	-1.39	4.4	458.97	3.2	463.74	1.66	69.38	75.84	4	7	-1.60
A8	-5.86	-1.4	4.46	462.93	2.87	452.19	1.66	71.2	74.76	4	7	-1.81
A9	-5.83	-1.42	4.41	478.5	3.08	465.2	1.67	69.02	75.84	4	7	-1.60
A10	-5.81	-1.43	4.38	462.93	2.87	450.04	1.65	69.04	74.73	4	7	-1.77
A11	-5.84	-1.4	4.44	446.48	2.47	439.84	1.64	68.97	73.96	4	7	-1.95
A12*	-5.57	-1.42	4.15	438.55	3.13	467.30	1.67	69.12	76.24	4	7	-1.95
A13*	-5.61	-1.42	4.19	442.52	2.8	454.02	1.65	69.13	75.15	4	7	-1.81
A14	-5.59	-1.4	4.19	452.58	3.48	489.49	1.7	69.12	77.76	4	7	-1.92
A15	-5.85	-1.4	4.45	478.5	3.09	464.25	1.67	68.92	75.82	4	7	-1.30
A16*	-5.35	-1.41	3.94	440.52	2.03	459.04	1.66	76.05	75.55	4	8	-1.17

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IC_{50} = -2209.75 - 0.0380508(MW) - 4.15718(Vol) + 51.7411(Pol) - 21.4175(HOMO) + 1.03509 (LogP) ----------(4)
N= 16, F = 13.36, P < 0.0001, R^2 = 0.930, Adjusted R^2 = 0.860, C.VR^2 = 0.999, MSE = 0.005

Table 2: Correlation between the observed IC_{50} and predicted IC_{50}

	PIC_{50}	BPNN	Residue
A1*	*5.0132*	4.988758	0.024442
A2	*5.0132*	4.986026	0.027174
A3	*4.6020*	4.59819	0.00381
A4*	*4.5228*	4.495399	0.027401
A5	*4.2218*	4.202829	0.018971
A6	*4.2596*	4.256674	0.002926
A7	*4.3979*	4.389545	0.008355
A8	*4.1870*	4.170594	0.016406
A9	*4.3979*	4.369175	0.028725
A10	*4.2218*	4.192853	0.028947
A11	*4.0457*	4.040972	0.004728
A12*	*4.0457*	4.016582	0.029118
A13*	*4.1870*	4.158285	0.028715
A14	*4.0705*	4.055939	0.014561
A15	*4.6989*	4.674892	0.024008
A16*	*4.8239*	4.819643	0.004257

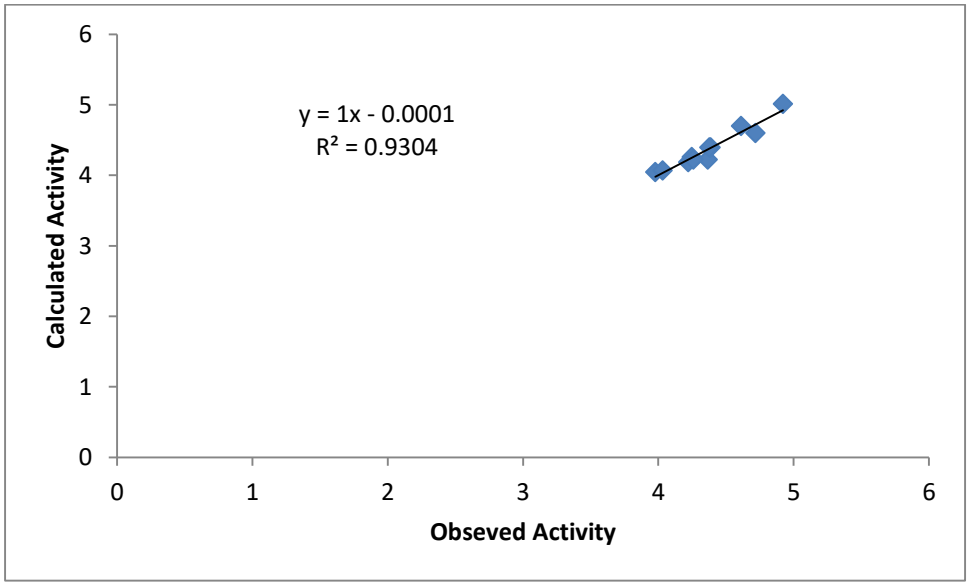
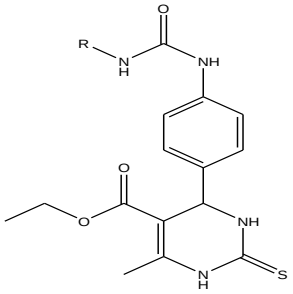


Figure 2: Graphical representation showing the correlation between calculated activity and observed activity

4. PROPOSED NOVEL DRUG-LIKE MOLECULES

In this work, effective drug-like compounds were designed based on the parent structure of the compounds studied in this research. The names of the proposed compounds are
ethyl 1,2,3,4-tetrahydro-6-methyl-4-(4-(3-methylureido)phenyl)-2-thioxopyrimidine-5-carboxylate **(1);**
ethyl 4-(4-(3-(fluoromethyl)ureido)phenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidine-5-carboxylate **(2);**
ethyl 4-(4-(3-(difluoromethyl)ureido)phenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidine-5-carboxylate **(3);**
ethyl 4-(4-(3-(furan-2-yl)ureido)phenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidine-5-carboxylate **(4);**
ethyl 1,2,3,4-tetrahydro-6-methyl-4-(4-(3-(thiophen-2-yl)ureido)phenyl)-2-thioxopyrimidine-5-carboxylate **(5);**
ethyl 4-(4-(3-(1H-pyrrol-2-yl)ureido)phenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidine-5-carboxylate **(6)**

The ability of each of the designed compounds was shown via calculated inhibition concentration (IC_{50}) using the developed QSAR model equation 1.



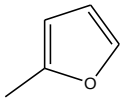
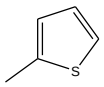
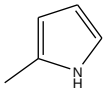
	R	IC_{50}
1	CH_3	1.23
2	CH_2F	1.56
3	CHF_2	2.06
4		22.89
5		11.29
6		12.09

Figure 3: Structure for proposed compounds with the biological activities

The predicted inhibition concentration is 1.23, 1.56, 2.06, 22.89, 11.29 and 12.09 for compound **1-6** respectively. This shows the effectiveness and the reliability of the developed model (QSAR-BPNN) and as shown in Table 3, compounds **1-3** have higher inhibition concentration than the model compounds used in this work.

4.1 Molecular Docking

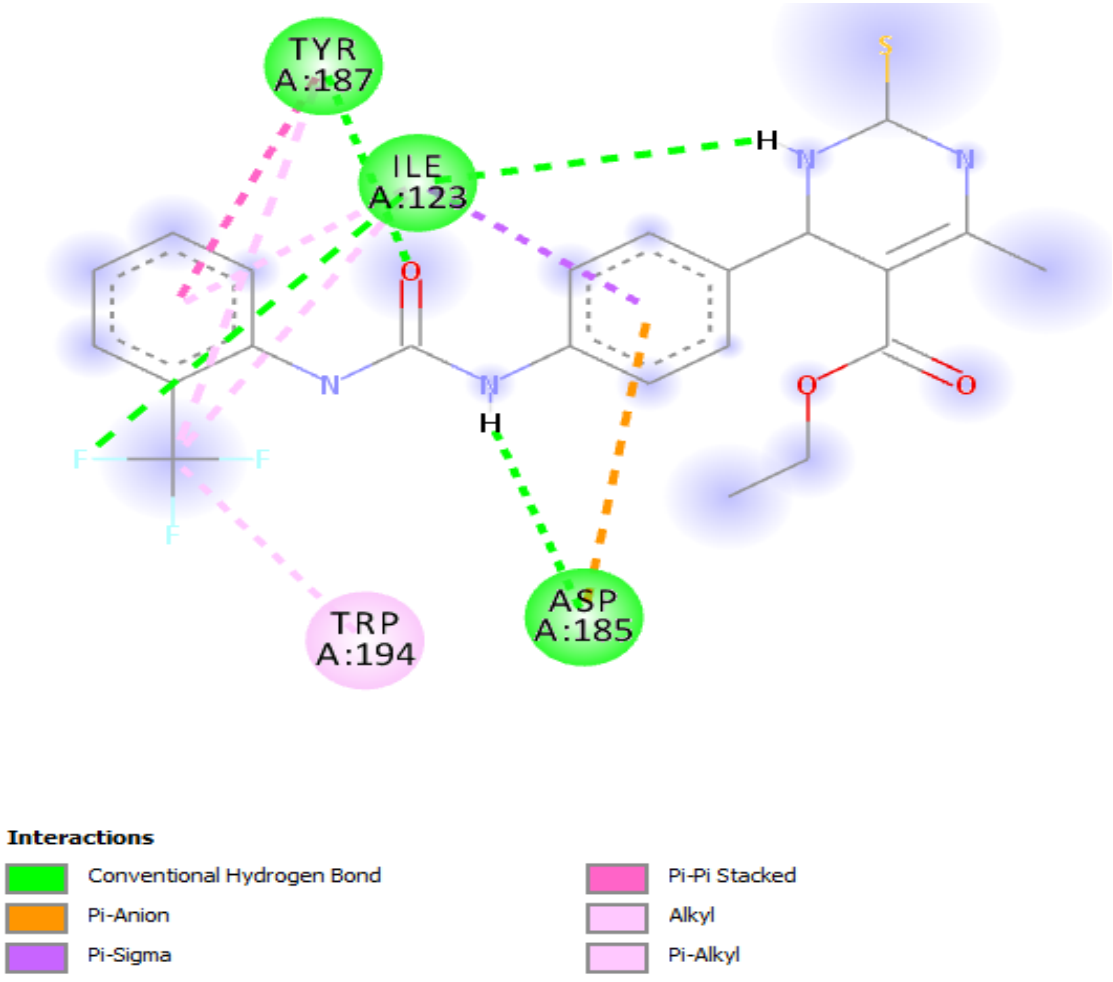
Series of 3,4-dihydropyrimidin-2(1H)-one Urea Derivatives were docked against *Staphylococcus aureus* sortase and the binding affinity, inhibition constant as well as amino residues observed in the interaction between 3,4-dihydropyrimidin-2(1H)-one Urea Derivatives and *Staphylococcus aureus* sortase (PDB ID Code: **2kid**) were displayed in Table 4. According to Oyebamiji *et al*., 2018 molecular compound with lower value of binding affinity is assumed to have ability to inhibit more than other studied compounds [16]; therefore, ethyl 4-(4-(3-(2-(trifluoromethyl)phenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate (**A3)** proved to have more ability to inhibit than other studied 3,4-dihydropyrimidin-2(1H)-one Urea Derivatives as well as Cephalexin (Standard).

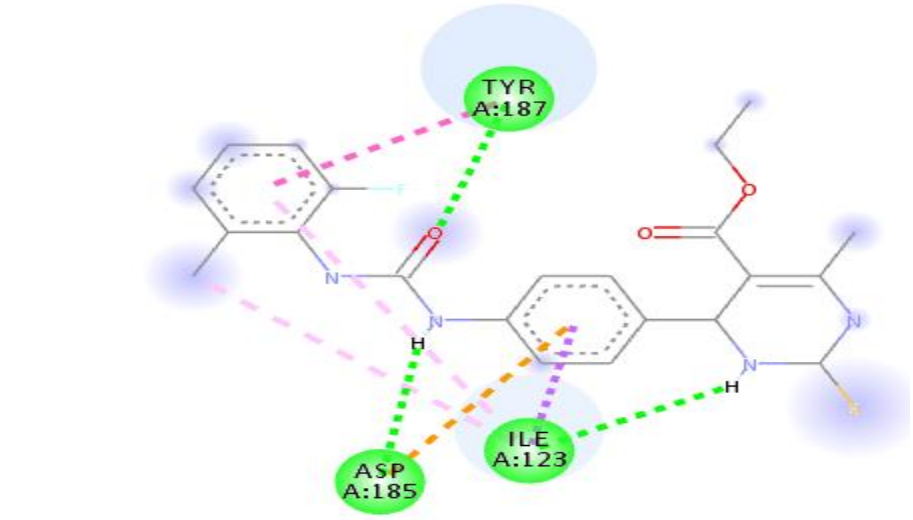
More so, the interaction between the proposed compounds and *Staphylococcus aureus* sortase (PDB ID Code: **2kid**) were displayed in Table 4 and it was observed that all the proposed compounds except compound **A5** possess the ability to inhibit than Cephalexin which was used as standard. Compound **3** and **4** proved to have higher tendency to inhibit *Staphylococcus aureus* sortase than other proposed compounds (Figure 5).

Table 4: Interactions between 3,4-dihydropyrimidin-2(1H)-one Urea Derivatives and *Staphylococcus aureus* sortase (PDB ID Code: 2kid)

Comp	Scoring (kcal/mol)	K (μM)	Amino Acid Residues
A1	-7.2	1.89748 x 10^5	THR-121, TYR-187, ASP-185, ILE-123
A2	-6.9	1.14354 x 10^5	VAL-168, TRP-194, VAL-166, ARG-197, HIS-120
A3	-7.6	3.72744 x 10^5	TYR-187, ILE-123, ASP-185, TRP-194
A4	-7.3	2.24640 x 10^5	THR-121, ILE-123, TYR-187, ASP-185
A5	-7.4	2.65947 x 10^5	TYR-187, ASP-185, ILE-123
A6	-6.9	1.14354x10^5	TYR-187, THR-121, ILE-123, TRP-194, PHE-122
A7	-6.3	4.1534 x 10^4	ASP-186, ASP-185, ILE-123
A8	-7.2	1.89748 x 10^5	TYR-187, ILE-123, ASP-185
A9	-7.4	2.65947 x 10^5	TYR-187, ASP-185, ILE-123
A10	-6.8	9.6593 x 10^4	TYR-187, TRP-194, ASP-185, ILE-1123
A11	-6.9	1.14354 x 10^5	ARG-197, VAL-168, THR-164, ASP-165, TRP-194, HIS-120
A12	-7.5	3.14849 x 10^5	TYR-187, ASP-185, ILE-123
A13	-7.2	1.89748 x 10^5	TRP-194, TYR-187, ILE-123, ASP-185
A14	-7.4	2.65947 x 10^5	ILE-123, TYR-187
A15	-7.4	2.65947 x 10^5	PRO-91, ALA-92, THR-93, ILE-199, ILE-182, VAL-168, ARG-197
A16	-7.0	1.35382 x 10^5	ASP-185, ILE-123, TYR-187
Cephalexin	-5.7	1.5085 x 10^4	ILE-123; ASP-185; ASP-186; TYR-187

Proposed Compounds			
1	-5.8	1.7859 x 10^4	GLN-64; LYS-71; VAL-72; GLY-147; LYS-62; ASN-148
2	-6.3	4.1534 x 10^4	LYS-162; ASP-165; ALA-92; ALA-104; LEU-169; ILE-182; ALA-118
3	-6.5	5.8213 x 10^4	ASP-165; THR-164; LYS-162; PRO-163; ALA-92; ALA-104; LEU-104; LEU-169; ILE-182; ALA-118
4	-6.5	5.8213 x 10^4	TYR-187; THR-121; PHE-122
5	-5.6	1.2742 x 10^4	ILE-65; PRO-89
6	-6.3	4.1534 x 10^4	ASP-185; THR-121; TYR-187; TRP-194; PHE-122

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ASP
A:185
ILE
A:123
H
H


Interactions
Conventional Hydrogen Bond
Pi-Anion
Pi-Sigma
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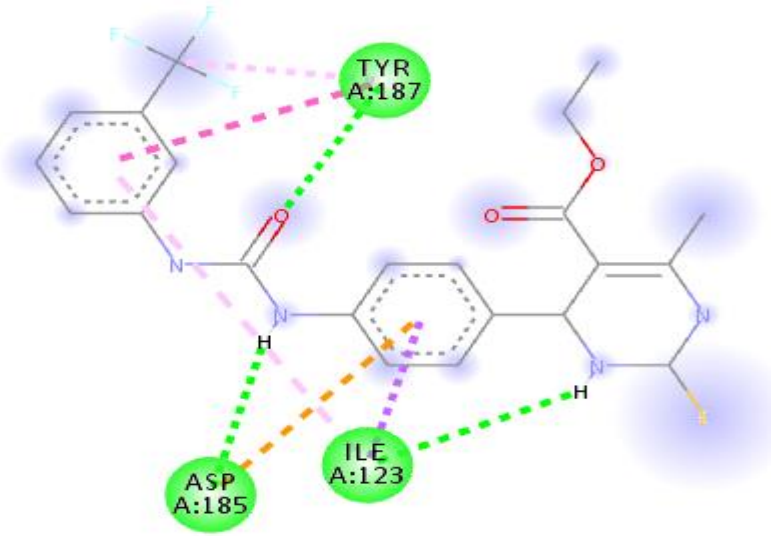
Alkyl
Pi-Alkyl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Interactions
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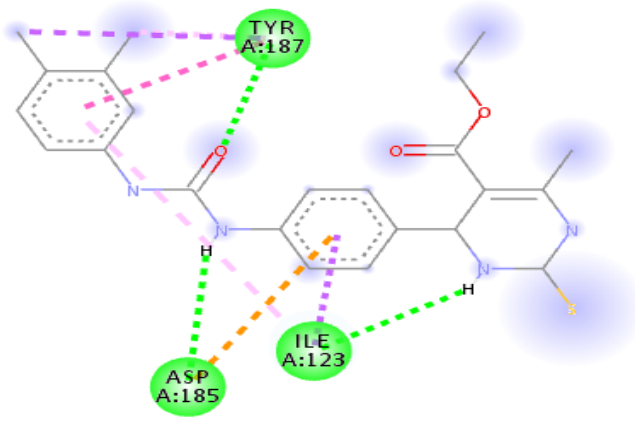
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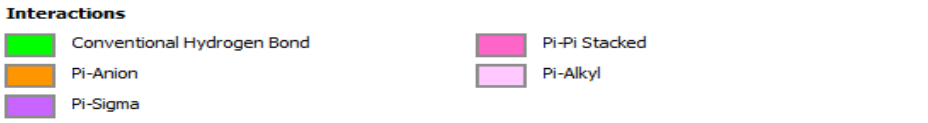
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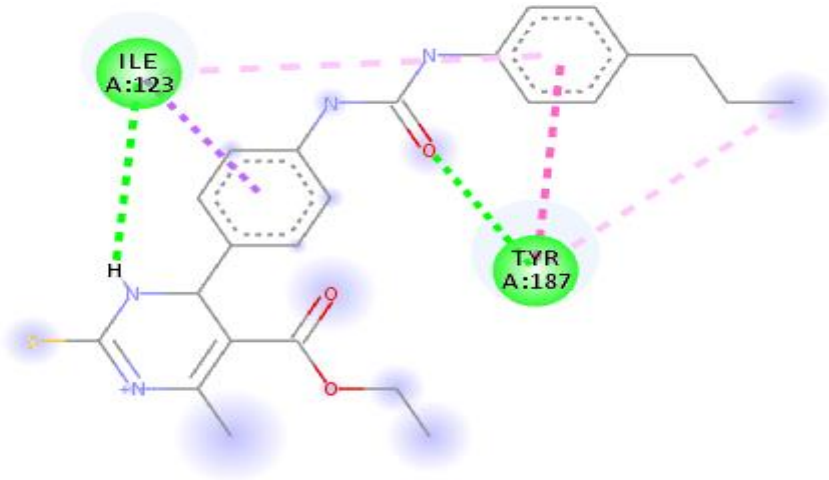
Pi-Anion
Pi-Sigma
Pi-Pi Stacked
Pi-Alkyl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A:123
TYR
A:187


Interactions
Conventional Hydrogen Bond
Pi-Sigma
Pi-Pi Stacked
Pi-Alkyl

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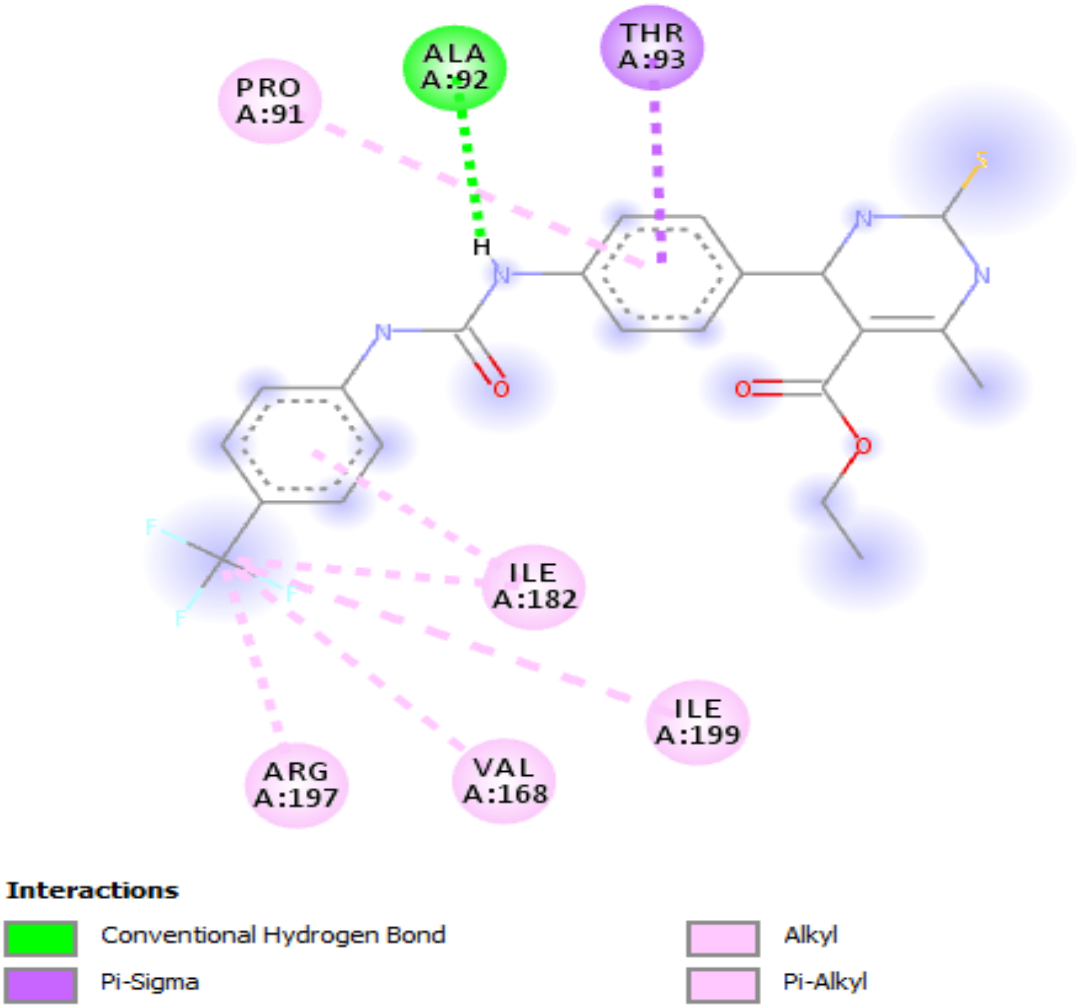

Figure 4: Molecular interaction of compound **A3, A5, A9, A12, A14** and **A15** with **2kid** respectively.

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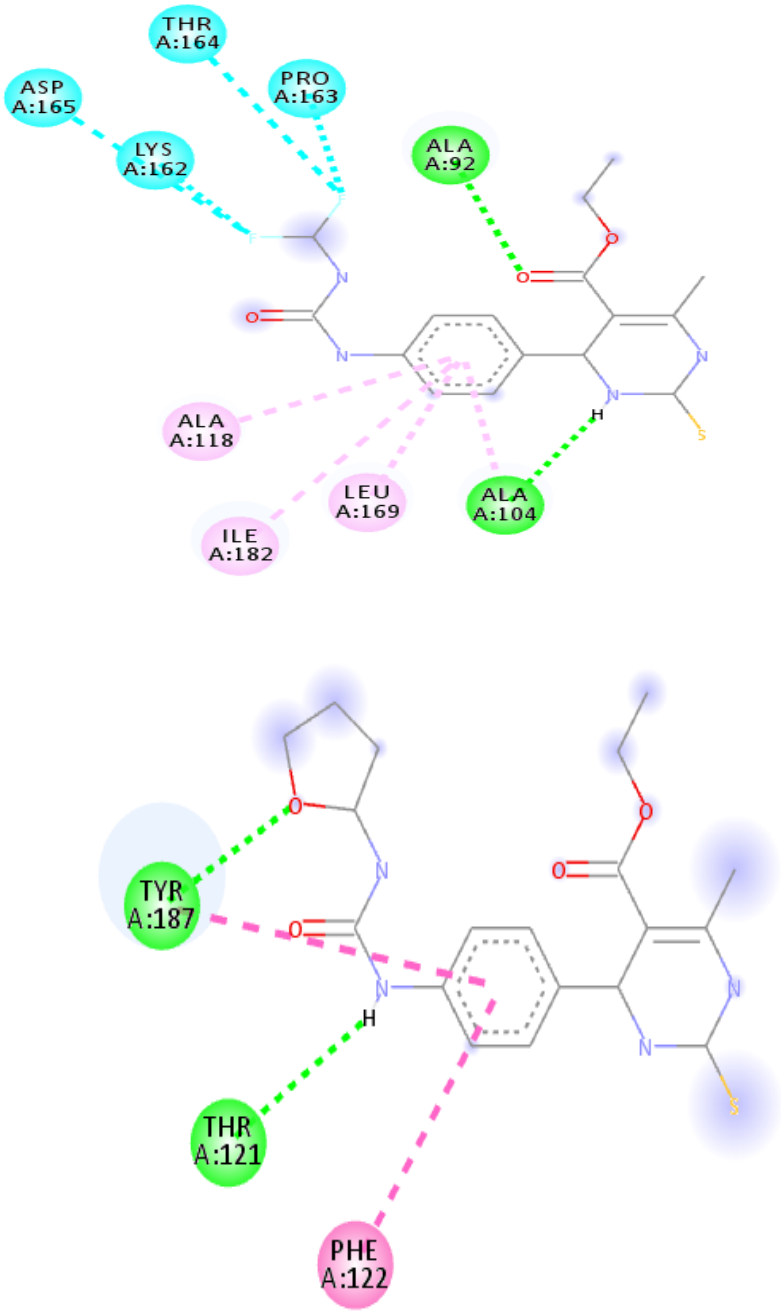

Figure 5: Molecular interaction of proposed compound **3** and **4** with **2kid**

5. CONCLUSION

The studied 16 molecular compounds optimized via density functional theory proved to be effective as drug-like compounds. Also, the selected descriptors from the optimized molecular compounds were used to develop effective QSAR model and this was confirmed through the predicted inhibition concentration (IC_{50}). The developed QSAR-BPNN model effectively predicted inhibition concentration for the proposed compounds. More so, the docking study between 3,4-dihydropyrimidin-2(1H)-one Urea Derivatives and *Staphylococcus aureus* sortase (PDB ID Code: **2kid**) revealed the interactions present in the complex; thus, **A3, 3 (**Proposed Compound**)** and **4** (Proposed Compound) inhibited efficiently than other studied compounds.

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