Article

Dataset on *Insilico* approaches for 3,4-dihydropyrimidin-2(1H)-one urea derivatives as efficient *Staphylococcus aureus* inhibitor

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**Abstract**

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. 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 was used as a screening tool for the studied compounds. The observed molecular compounds used in this work was also correlated to Lipinski rule of five and the developed QSAR model using selected descriptors from the optimized compounds was also examined for its predictability. Also, the observed molecular docking revealed the interaction between the studied complex.

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### Specification Table

| Subject                  | Computational Chemistry |
|--------------------------|-------------------------|
| Specific subject area    | Drug Design             |
| Type of data             | Developed QSAR Model Equation |
| How data were acquired   | Spartan 14, Pymol 1.7.4.4, MATLAB, Autodock tool 1.5.6, AutoVina 1.1.2, Discovery Studio 2017 |
| Data format              | Analysed data (Developed, Observed and Calculated) |
| Parameters for data collection | B3LYP, 6–31G**, Gretl, Pymol 1.7.4.4, Discovery studio 2017R, Autodock tool 1.5.6 and Autodock vina 1.1.2. |
| Description of data collection | Calculation and selection of Descriptors, QSAR (MLR, PLS, Genetic algorithm, Artificial Neural network, Prediction of new set of Drug-like molecule, Optimization (QCM), Molecular Docking |

### Data source location

Computational Chemistry Research Laboratory, Department of Pure and Applied Chemistry, Ladoke Akintola University of Technology, P.M.B. 4000, Ogbomoso, Oyo State, Nigeria

Data accessibility

The observed and calculated data can be accessed with the data article

1. **Value of the data**

   - Datasets obtained in this research will help the scientists to know the molecular descriptors which describe the anti- Staphylococcus aureus properties of 3,4-dihydropyrimidin-2(1H)-one Urea Derivatives.
   - Data in this research will reveal the contribution of each calculated descriptor in the developed QSAR model.
   - It also helps in predicting library of efficient drug-like compounds via the developed QSAR model.
   - The ability of each observed compounds to inhibit Staphylococcus aureus via docking can also be understood.

2. **Data description**

   The molecular compounds used in this work were displayed in Table 1. In this work, sixteen molecular compounds were subjected to density functional theory via B3LYP with the standard 6–31G** basis set for optimisation and the obtained molecular descriptors were reported for further investigation. 3,4-dihydropyrimidin-2(1H)-one Urea derivatives was extracted from the work done by Mukesh, 2015 [1].
Table 1
The Schematic diagram of 3,4-dihydropyrimidin-2(1H)-one urea derivatives [1].

| S. No | R         | Structure |
|-------|-----------|-----------|
| A1    | 2-F       | ethyl 4-(4-(3-(2-fluorophenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate |
| A2    | 2-Cl      | ethyl 4-(4-(3-(2-chlorophenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate |
| A3    | 2-CF₃     | ethyl 4-(4-(3-(2-(trifluoromethyl)phenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate |
| A4    | 2-OCF₃    | ethyl 1,4,5,6-tetrahydro-2-methyl-6-thioxo-4-(4-(3-(2-(trifluoromethoxy)phenyl)ureido)phenyl)pyridine-3-carboxylate |
| A5    | 2-F, 6-CH₃| ethyl 4-(4-(2-fluoro-6-methylphenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate |
| A6    | 2-F, 6-CF₃| ethyl 4-(4-(2-fluoro-6-(trifluoromethyl)phenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate |
| A7    | 2-Cl, 6-CH₃| ethyl 4-(4-(3-(2-chloro-6-methylphenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate |
| A8    | 2-Cl, 6-F | ethyl 4-(4-(3-(2-chloro-6-fluorophenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate |
| A9    | 3-CF₃     | ethyl 4-(4-(3-(2-(trifluoromethyl)phenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate |
| A10   | 3-Cl, 4-F | ethyl 4-(4-(3-(3-chloro-4-fluorophenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate |
| A11   | 3,5-F     | ethyl 4-(4-(3,5-difluorophenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate |
| A12   | 3,4-CH₃   | ethyl 1,4,5,6-tetrahydro-2-methyl-4-(4-(3-(3,4-dimethylphenyl)ureido)phenyl)-6-thioxopyridine-3-carboxylate |
| A13   | 4-F, 3-CH₃| ethyl 4-(4-(3-(4-fluoro-3-methylphenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate |
| A14   | 4-isopropyl| ethyl 1,4,5,6-tetrahydro-2-methyl-4-(4-(3-(4-propylphenyl)ureido)phenyl)-6-thioxopyridine-3-carboxylate |
| A15   | 4-CF₃     | ethyl 4-(4-(4-(3-(2-(trifluoromethyl)phenyl)ureido)phenyl)-1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate |
| A16   | 4-OCH₃    | ethyl 1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylate |

Table 2 reveal the calculated molecular descriptors via density functional theory [2]. Series of calculated molecular parameter obtained were highest occupied molecular orbital ($E_{\text{HOMO}}$), lowest unoccupied molecular orbital energy ($E_{\text{LUMO}}$), band gap, molecular weight, Log P, Area, Ovality, polar surface area, polarisability, hydrogen bond donor (HBD), hydrogen bond acceptor (HBA) and number of rotatable bonds. Further investigation was conducted using Lipinski rule of five so as to determine the drug-likeness of the studied drug-like compounds [3].

Table 3 showed the developed QSAR model using the calculated molecular descriptors using back propagation neural network (BPNN) via MATLAB software [4,5]. The developed QSAR model involved molecular weight, volume, polarisability, $E_{\text{HOMO}}$ and Log P. This set of descriptors were chosen because they best described anti- Staphylococcus aureus activities of compounds used.
Table 2
Calculated molecular descriptors from 3,4-dihydropyrimidin-2(1H)-one urea derivatives.

| E_{HOMO}(eV) | E_{LUMO}(eV) | BG(eV) | MW(amu) | LogP | AREA(A^2) | VOL(A^3) | OVALITY | PSA(A^2) | Pol | HBD | HBA | PIC |
|-------------|-------------|-------|--------|------|----------|----------|---------|---------|-----|-----|-----|-----|
| A1*         | −5.76       | −1.35 | 4.41   | 428.49 | 2.32     | 438.04   | 411.06  | 1.64    | 71.73| 73.68| 4   | 7   | −1 |
| A2          | −5.87       | −1.4  | 4.47   | 444.94 | 2.72     | 442.77   | 418.99  | 1.64    | 67.75| 74.31| 4   | 7   | −1 |
| A3          | −5.86       | −1.42 | 4.44   | 478.5  | 3.08     | 460.51   | 437.19  | 1.65    | 66.84| 73.79| 4   | 7   | −1.39 |
| A4*         | −5.78       | −1.39 | 4.39   | 494.49 | 3.12     | 475.18   | 447.02  | 1.68    | 75.79| 76.6 | 4   | 8   | −1.47 |
| A5          | −5.78       | −1.4  | 4.38   | 442.52 | 2.8      | 452.32   | 498.41  | 1.65    | 69.13| 75.09| 4   | 7   | −1.77 |
| A6          | −5.85       | −1.41 | 4.44   | 496.49 | 3.24     | 467.22   | 428.41  | 1.66    | 69.88| 76.2 | 4   | 7   | −1.74 |
| A7          | −5.79       | −1.39 | 4.4   | 458.97 | 3.2      | 463.74   | 442.23  | 1.66    | 69.38| 75.84| 4   | 7   | −1.6 |
| A8          | −5.86       | −1.4  | 4.46   | 462.93 | 2.87     | 452.19   | 437.74  | 1.66    | 71.2 | 74.76| 4   | 7   | −1.81 |
| A9          | −5.83       | −1.42 | 4.41   | 476.5  | 3.08     | 465.2    | 451.46  | 1.67    | 69.02| 75.84| 4   | 7   | −1.6 |
| A10         | −5.81       | −1.43 | 4.38   | 462.93 | 2.87     | 450.04   | 450.89  | 1.65    | 69.04| 74.73| 4   | 7   | −1.77 |
| A11         | −5.84       | −1.4  | 4.44   | 466.48 | 2.47     | 439.84   | 452.18  | 1.64    | 68.97| 73.96| 4   | 7   | −1.95 |
| A12*        | −5.57       | −1.42 | 4.15   | 438.55 | 3.13     | 467.3    | 424.58  | 1.67    | 69.12| 76.24| 4   | 7   | −1.95 |
| A13*        | −5.61       | −1.42 | 4.19   | 442.52 | 2.8      | 454.02   | 437.74  | 1.65    | 69.13| 75.15| 4   | 7   | −1.81 |
| A14*        | −5.59       | −1.4  | 4.19   | 452.58 | 3.48     | 489.49   | 423.94  | 1.7     | 69.12| 77.76| 4   | 7   | −1.92 |
| A15*        | −5.85       | −1.4  | 4.45   | 475.5  | 3.09     | 464.25   | 414.63  | 1.67    | 68.92| 75.82| 4   | 7   | −1.3 |
| A16*        | −3.35       | −1.41 | 3.94   | 440.52 | 2.03     | 459.04   | 441.91  | 1.66    | 76.05| 75.55| 4   | 8   | −1.17 |

Note: BG: Bond gap; Vol: Volume; MW: molecular weight; LogP: Lipophilicity; PSA: polar surface area. Pol: Polarizability. HBD: Hydrogen bond Donor; HBA: Hydrogen bond Acceptor; PIC: negative log of inhibition concentration (IC50).

Table 3
Developed QSAR model for 3,4-dihydropyrimidin-2(1H)-one Urea derivatives.

| Equation          | F      | P-value | R^2  | Adj. R^2 | C.VR^2 | MSE  |
|-------------------|--------|---------|------|----------|--------|------|
| IC50 = −2209.75 - 0.3308508(MW) - 4.15718(Vol) + 51.7411(Pol) - 21.4175(EHOMO) + 1.03509(LogP) | 13.36  | P < 0.0001 | 0.930| 0.860    | 0.999  | 0.005|

Table 4
Correlation between the observed IC50 and predicted IC50.

| PIC50       | BPNN | Residue |
|-------------|------|---------|
| A1*         | 5.0132 | 4.988758 | 0.024422 |
| 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 |

* Test Set.

In this work than other calculated descriptors. The calculated correlation coefficient (R^2) for the developed QSAR model was 0.930. The developed QSAR model was validated by considering several parameters such as Adjusted R^2, Cross validation (C.VR^2), P-Value, F-Value. Also, the molecular compounds used were divided into two (Test set and Training set). The compounds used as training set were compound A2, A3, A5, A6, A7, A8, A9, A10, A11, A14, A15 and the compounds used as test set were A1, A4, A12, A13 and A16.
Fig. 1. Graphical representation showing the correlation between calculated activity and observed activity.

Table 5
Structure for proposed compounds with the biological activities.

| R     | IC<sub>50</sub> |
|-------|-----------------|
| CH<sub>3</sub> | 1.23           |
| CH<sub>3</sub>F | 1.56           |
| CHF<sub>2</sub> | 2.06           |
|                  | 22.89          |
|                  | 11.29          |
|                  | 12.09          |

Therefore, table 4 reveal the effectiveness of the developed model shown in Table 3. Also, correlation between the observed and the predicted inhibition concentration was displayed in Fig. 1. More so, five (5) molecular compounds were proposed and the IC<sub>50</sub> were predicted using the developed QSAR model (Table 5).
Table 6
Interactions between 3,4-dihydropyrimidin-2(1H)-one Urea Derivatives and Staphylococcus aureus sortase (PDB ID: 2kid).

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

Proposed Compounds

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

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) [6] were displayed in Table 6. The residues involved in the interaction were displayed in SI.

More so, the interaction between the proposed compounds and Staphylococcus aureus sortase (PDB ID Code: 2kid) were displayed in Table 6. The molecular interaction between the molecular compounds used and the receptor were displayed in SII.

3. Experimental design, materials, and methods

In this work, series of vital materials (Software) were used to accomplish this research [7]. Spartan’14 was used to optimised 3,4-dihydropyrimidin-2(1H)-one Urea derivatives studied in this work. The density functional theory used for the optimisation was achieved using three-parameter B3LYP that comprises Becke’s gradient exchange correction [8,9], Lee, Yang, as well as Parr correlation functional [10]. It was through this that several molecular descriptors were obtained to develop QSAR model using BPNN via MATLAB software. Also, docking was accomplished using pymol 1.7.4.4 software. It was used for treating (removal of foreign compounds) downloaded Staphylococcus aureus Sortase (PDB ID Code: 2kid) from protein data bank (www.rcsb.org). Also, the treated Staphylococcus aureus Sortase (PDB ID Code: 2kid) was subjected to autodock tool 1.5.6 so as to locate the binding sites in the receptor and convert the receptor as well as the ligand to the format which will acceptable by autodock vina 1.1.2 that will do the docking calculation. The use of autodock tool 1.5.6 require the use of commands in order to accomplish the docking calculation; to execute the calculation, vina –config conf.txt
–log.txt was used. Also, vinasplit –input out.pdbqt was used to split the calculated binding affinity according to the energy of each conformation. The observed grid box was as follows: centre \((X = 0.677, Y = 0.25, Z = -1.245)\) and size \((X = 64, Y = 52, Z = 56)\).

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**Declaration of Competing Interest**

The authors declare that they have no conflict of interest.

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**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dib.2020.106195.

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