Chemistry Africa
https://doi.org/10.1007/s42250-020-00202-y

ORIGINAL ARTICLE

In-Silico Study on Anti-bacteria and Anti-fungal Activities of 3,4-Dihydropyrimidin-2(1*H*)-One Urea Derivatives

Abel Kolawole Oyebamiji[1,2] · **Banjo Semire**[2]

Received: 1 August 2020 / Accepted: 4 November 2020

Abstract
The menace caused by fungi amidst human being and in the world at large is colossal. Their increasing rate of causing havoc has drawn the attention of scientist to developing efficient drug-molecules in order to cure these diseases. In this work, sixteen molecular compounds were studied with aim of investigating the non-bonding interaction between the studied compounds and the receptors using the following software Spartan 14 (optimization), Pymol (for treating downloaded protein), Autodock Tool (for locating binding site in the downloaded protein and for converting ligand and receptor to.pdbqt format from.pdb format), Auto dock vina (for docking calculation) and discovery studio (for viewing the non-bonding interaction between the docked complexes) so as to observe anti-*e-coli* and anti-1,4α-demethylase properties of 3,4-dihydropyrimidin-2(1*H*)-one urea derivatives. The calculated parameters such as E_{HOMO} energy, E_{LUMO} energy, Dipole moment, log P, HBD and HBA which described anti-*e-coli* and anti-1,4α-demethylase properties of 3,4-dihydropyrimidin-2(1*H*)-one Urea Derivatives were observed. This showed that all the studied compounds have potential anti-*e-coli* and anti-1,4α-demethylase activities. Also, the calculated binding affinity showed that compound **4** and **3** possess better ability to inhibit *e-coli* and 1,4α-demethylase better than other studied compounds. More so, ADMET properties of five selected compounds were determined and it was observed that the ADMET properties obtained for the selected compounds were similar to the ADMET properties of the standards used in this work.

Keywords In-silico · Fungi · 3,4-dihydropyrimidin-2(1H)-one urea · DFT · Docking

1 Introduction

The continuous design and development of drugs has reduced mortality and morbidity rate globally. Growing resistance by fungi and bacteria to drugs has led to incessant and increasing rate of death [1]. Many researchers have reported that several antibiotics are becoming ineffective and this has prompted scientists all over the world to searching out lasting solution via medicinal plant and synthesized compounds to combat this menace [2]. Therefore, the need to design and develop efficient anti-fungi and anti-bacterial drugs has drawn the attention of scientist over the years [3].

Bacteria are numerous organisms which usually exist among human being [4–6]. They are composed of great area of prokaryotic microorganisms. They are very small in size and they cannot be seen except it is placed under lenses [7]. Bacteria have series of shapes (Sphere, rod and spiral) [8]. As reported by Georgiana et al. [9] some bacteria strains are pathogenic in nature and they have been reported to be responsible for several infections such as urinary tract infection, biliary tract infection, wound infections etc [10, 11]. Infections from bacteria have been regarded has one of the frontline cause of death globally and due to this, it is important that patients with infections from bacterial receives urgent treatment [12].

14α-demethylase is a vital protein for ergosterol's biosynthesis in fungi and it is a major target for drug-like molecules [13]. It is a vital enzyme that helps in converting lanosterol to lower molecules. It exists in several organisms and most especially in fungi where it acts as an intermediary in membrane absorptivity [14]. Fungal infection has also become cause of death among immune compromised human being.

✉ Banjo Semire
bsemire@lautech.edu.ng

[1] Department of Basic Sciences, Adeleke University, P.M.B. 250, Ede, Osun State, Nigeria

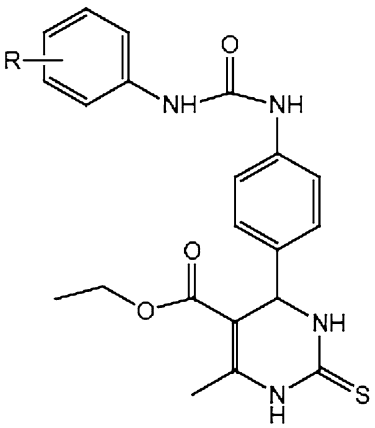
[2] Computational Chemistry Research Laboratory, Department of Pure and Applied Chemistry, Ladoke Akintola University of Technology, P.M.B. 4000, Ogbomoso, Oyo State, Nigeria

Published online: 01 December 2020

As reported by many researchers, several drug-like compounds such as voriconazole, echinocandins, ketoconazole, amphotericin B and nikkomycin have been used to combat fungi activities in human [15]. Despite all these efforts put in place by scientists to end fungi activities in human, the rate at which it operates keep increasing [16, 17]. According to Warrilow et al. [18], Sterol 1,4-α-demethylase was classified to be cytochrome P450 superfamily and it was observed to be one of the vital agent to synthesized ergosterol fungi. It also acts as an agent that biologically synthesized cholesterol in mammals.

Dihydropyrimidine derivatives are crucial molecular compounds in medicinal world. Their pharmacological and biological features have greatly drawn the attention of several scientists globally. Dihydropyrimidine derivatives could be used as antiviral, antibacterial, antifungal, antihypertensive and anticancer agents [19–22]. 3,4-Dihydropyrimidin-2-(1*H*)-one was first synthesized using Biginelli reaction and this was first accomplished in 1893 and several biological properties were reported by many researchers [23, 24]. Also, several scientists reported that N1-substituted Dihydropyrimidine derivatives possess more improved pharmacological activity [25–27]. In this work, sixteen molecular compounds were theoretically studied with the aim of observing the molecular descriptors responsible for anti- *E-coli* and anti-1,4α-demethylase activities of 3,4-dihydropyrimidin-2(1*H*)-one Urea Derivatives and developing efficient QSAR model to predict the biological activities of the studied compounds as well as observing biological interaction present between the studied compounds and *E coli* (PDB ID: 5r1r) [28] as well as 1,4α-demethylase (PDB ID: 3juv) [29] via docking study.

Table 1 Schematic structure of 3,4-dihydropyrimidin-2(1H)-one urea derivatives



1	2-F
2	2-Cl
3	2-CF_3
4	2-OC_6H_5
5	2-F, 6-CH_3
6	2-F, 6-CF_3
7	2-Cl, 6-CH_3
8	2-Cl, 6-CF_3
9	2-Cl, 5-CF_3
10	2-Cl, 4-CF_3
11	2-Cl, 6-F
12	3-CF_3
13	3-Cl, 4-F
14	4-isopropyl
15	4-CF_3
16	4-OCH_3

2 Materials and Methods

2.1 Optimization, QSAR and Docking Studies

In this present study, 2D structure of sixteen molecular compounds (Table 1) were accomplished using CHEMDRAW ultra 8.0 version and were optimized using density functional theory with 6-31G* (B3LYP) as basis set via Spartan'14 [30–34]. The studied compounds were optimized so as to generate descriptors that describe anti-1,4α-demethylase and anti-bacteria activities. In this work, series of molecular descriptors were calculated and eleven electronic descriptors were selected and were used for QSAR study. Also, quantitative structural activities relationship (QSAR) models (Eq. 1 for *Ecoli* and Eq. 2 for 1,4α-demethylase) were developed using selected electronic descriptors using Gretl software so as to predict the observed bioactivity of the studied compounds. The observed IC_{50} was used as dependent variable and the calculated descriptors were used as independent variables and the descriptors used were carefully selected so as to avoid multi-collinearity. Correlation coefficient (R^2), adjusted R^2, P value, mean square error (MSE) were observed in developing the QSAR model.

The optimised molecular compounds were subjected to docking to calculate binding affinity for individual studied compound and observe the non-bonding interaction existing between the complexes. The software used were Pymol (for treating downloaded protein by removing other foreign compounds downloaded together with the protein), Autodock Tool (for locating binding site in the downloaded protein and for converting ligand and receptor to.pdbqt format from.pdb format), Auto dock vina (for docking calculation) and discovery studio (for viewing the non-bonding interaction between the docked complexes). The grid box (dimension and centre) were: center (X = − 5.942, Y = 94.018, Z = 24.16) and size (X = 98, Y = 90, Z = 74) for *E coli* (PDB ID: 5r1r): and center (X = − 82.519, Y = 25.442, Z = − 5.492) and size (X = 74, Y = 58, Z = 96) for fungi (PDB ID: 3juv). The spacing was set to be 1.00 Å.

$$IC_{50} = -3695.81 - 22.3862(E_{HOMO}) + 29.0752(E_{LUMO}) - 1.41228(LogP) - 7.21692(Vol) - 0.0737399(PSA) + 89.4820(Pol) - 2.24656(NOR) \quad (1)$$

$R^2 = 0.821$, $AdjR^2 = 0.665$, $P < 0.0001$, F value = 5.25, MSE = 0.019862

$$IC_{50} = -2020.78 - 13.5155(E_{HOMO}) + 17.4543(E_{LUMO}) - 1.44899(LogP) - 3.92066(Vol) + 48.7551(Pol) - 1.90451(NOR) \quad (2)$$

$R^2 = 786$, $AdjR^2 = 0.643$, $P < 0.0001$, F value = 5.514, MSE = 0.020969

2.2 ADMET Properties

Phsyicochemical and Absorption, Distribution, Metabolism, Excretion and the Toxicity properties of the studied molecular compounds were studied via admetSAR (http://lmmd.ecust.edu.cn/admetsar1) [35]. Many properties were put in to consideration such as Human Intestinal Absorption (HIA), Blood Brain Barrier, Ames test, Caco-2 cell permeability.

3 Result and Discussion

3.1 Molecular Descriptors

The calculated molecular descriptors obtained from optimized studied compounds are highest occupied molecular orbital energy (E_{HOMO}), lowest unoccupied molecular orbital energy (E_{LUMO}), polarizability, dipole moment, hydrogen bond acceptor, energy band gap, area, volume, polar surface area, Log P, hydrogen bond donor (Table 2). In this study, the role of dipole moment as one of the molecular non-bonded interaction in drug design cannot be over emphasized [35, 36]. As reported by Oyewole et al. [37], as well as Oyebamiji et al. [38], molecular compound with high dipole moment value is expected to have anomalous property. As shown in Table 2, all the studied compounds can act as potential and fungal and antibacterial agent.

Also, calculated E_{HOMO} was obtained from the optimized 3,4-dihydropyrimidin-2(1*H*)-one Urea derivatives so as to determine their ability to release electron to the neighbouring compound [39, 40]. As shown in Table 2, compound **16** possess better ability to release electron to the nearby compounds and it is expected to inhibit more than other studied compounds. Also, the calculated E_{LUMO} gotten from the studied molecules reveal their tendency to receive electron from the nearby molecules [41, 42]; thus, compound **13** possess higher ability to receive electron from nearby compounds than other studied ligands.

Table 2 Calculated molecular parameters from 3,4-dihydropyrimidin-2(1*H*)-one Urea Derivatives

Mol	E_{HOMO}	E_{LUMO}	BG	MW	LogP	VOLUME	PSA	Pol	HBD	HBA	NOR
1	−5.76	−1.35	−4.41	428.49	2.32	411.06	71.73	73.68	4	7	3
2	−5.87	−1.4	−4.47	444.94	2.72	418.99	67.75	74.31	4	7	3
3	−5.86	−1.42	−4.44	478.5	3.08	437.19	66.84	75.79	4	7	3
4	−5.61	−1.36	−4.25	502.6	3.18	498.41	74.02	80.8	4	8	4
5	−5.78	−1.4	−4.38	442.52	2.8	428.41	69.13	75.09	4	7	3
6	−5.85	−1.41	−4.44	496.49	3.24	442.23	69.88	76.2	4	7	3
7	−5.79	−1.39	−4.4	458.97	3.2	437.74	69.38	75.84	4	7	3
8	−5.85	−1.36	−4.49	512.94	3.64	451.46	69.35	76.93	4	7	3
9	−5.95	−1.4	−4.55	512.94	3.64	450.89	67.99	76.87	4	7	3
10	−5.85	−1.39	−4.46	512.94	3.64	452.18	71.65	77	4	7	3
11	−5.86	−1.4	−4.46	462.93	2.87	424.58	71.2	74.76	4	7	3
12	−5.83	−1.42	−4.41	478.5	3.08	437.74	69.02	75.84	4	7	3
13	−5.81	−1.43	−4.38	462.93	2.87	423.94	69.04	74.73	4	7	3
14	−5.59	−1.4	−4.19	452.58	3.48	460.82	69.12	77.76	4	7	3
15	−5.85	−1.4	−4.45	478.5	3.09	437.54	68.92	75.82	4	7	3
16	−5.35	−1.41	−3.94	440.52	2.03	432.77	76.05	75.55	4	8	3

BG band gap, *MW* Molecular weight, *LogP* lipophilicity, *PSA* polar surface area, *HBD* hydrogen bond donor, *HBA* hydrogen bond acceptor, *NOR* number of rings

Other descriptors obtained are Molecular Weight, Hydrogen Bond Donor, Hydrogen Bond Acceptor and Log P; all these descriptors were found to fall within the standard range (molecular weight ≤ 500, hydrogen bond donor ≤ 5, Hydrogen bond acceptor ≤ 10 and Log P ≤ 5) except compound **4**, **8**, **9** and **10** with higher molecular weight. This showed that all the studied compounds possess drug potential.

3.2 QSAR Study

The developed QSAR models (Eqs. 1 and 2) which comprises of selected descriptors were used to predict observed inhibition concentration (IC_{50}) for Ecoli and 14α-demethylase. E_{HOMO}, E_{LUMO}, LogP, Vol, PSA, Pol, NOR for ECOLI and E_{HOMO}, E_{LUMO}, LogP, Vol, Pol, NOR (14α-demethylase) have played a serious role in predicting biological activities of 3,4-dihydropyrimidin-2(1*H*)-one urea derivatives. As shown in Eq. 1, decreasing E_{HOMO}, LogP, Volume, PSA, and NOR as well as increasing E_{LUMO} and polrizability enhanced the anti-ecoli activity of,4-dihydropyrimidin-2(1*H*)-one Urea Derivatives. Also, decreasing E_{HOMO}, LogP, Volume, and NOR as well as increasing E_{LUMO} and polrizability improved the anti-14α-demethylase activity of,4-dihydropyrimidin-2(1*H*)-one Urea Derivatives (Eq. 2). As shown in Table 3, the predicted IC_{50} were closer to the observed IC_{50}, this show the efficiency of the developed QSAR model (Figs. 1 and 2). Also, it was observed that the lower the calculated residual, the closer the predicted IC_{50} to the experimental IC_{50}.

3.3 Molecular Docking Results

The optimized compounds were subjected to docking studies via discovery studio, autodock tool, autodock vina and pymol software. Docking studies was carried out on the studied compounds so as to observe the non-bonding interaction present between 3,4-dihydropyrimidin-2(1*H*)-one urea derivatives and *E coli* (PDB ID: 5r1r) as well as 1,4α-demethylase (PDB ID: 3juv). In order to ascertain the authenticity of the employed docking method, the docking method was validated by re-docking the native ligand into the active site of 1,4α-demethylase (PDB ID: 3juv) so as to detect the likeness between the re-docked compound with best conformation to the posture of the native molecule (Fig. 3). Hence, the detected comparison as well as the root mean square deviation (RMSD) which occurs between the re-docked native molecule and the native ligand was closer to 1; therefore, this verified the reliability of the employed docking method.

All the studied compounds are very active against *E coli* and fungi as shown in Table 4. Compound **3** and **4** with −8.9 kcal/mol and −8.4 kcal/mol proved to be better than other studied compounds as anti-14α-demethylase and anti-*e-coli* respectively. As shown in Table 4, the standard compounds i.e. amoxylin and fluconazole have a lower binding affinity compared to the binding affinity obtained for each of the studied 3,4-dihydropyrimidin-2(1*H*)-one urea derivative. In this work, all the studied compounds possess potential ability to inhibit *E-coli* and 1,4α-demethylase than the standard used and as shown in Figs. 4 and 5 urea parts of the studied compounds showed no interaction with the studied protein. More so, the residues involve in the interaction between the studied compounds and the *E coli* (PDB

Table 3 Observed and Predicted inhibition concentration (IC_{50}) for Ecoil and 14α-demethylase

	E. coli	Predicted IC_{50}	Residual	14α-demethylase	Predicted IC_{50}	Residual
1	5.0132	5.0206	−0.0074	5.0132	5.0836	−0.0704
2	5.0132	4.9014	0.1118	5.0132	4.7429	0.2703
3	4.8239	4.7401	0.0838	4.6020	4.5386	0.0634
4	4.4559	4.4559	0.0000	4.3979	4.3979	0.0000
5	4.5228	4.4845	0.0383	4.3010	4.5069	−0.2059
6	4.3979	4.6713	−0.2734	4.2596	4.5756	−0.3160
7	4.2596	4.1934	0.0662	4.3976	4.2236	0.1740
8	4.2218	4.3089	−0.0871	4.2218	4.2723	−0.0505
9	4.0969	4.2295	−0.1326	4.2218	4.2351	−0.0133
10	4.6020	4.3346	0.2674	4.4559	4.3386	0.1173
11	4.0705	4.1356	−0.0651	4.3979	4.4137	−0.0158
12	4.6989	4.4126	0.2863	4.6020	4.4145	0.1875
13	4.0705	4.2377	−0.1672	4.0969	4.2609	−0.1640
14	4.2596	4.2881	−0.0285	4.0457	4.0613	−0.0156
15	5.0132	5.0888	−0.0756	4.8239	4.8284	−0.0045
16	4.8239	4.8408	−0.0169	5.0132	4.9698	0.0434

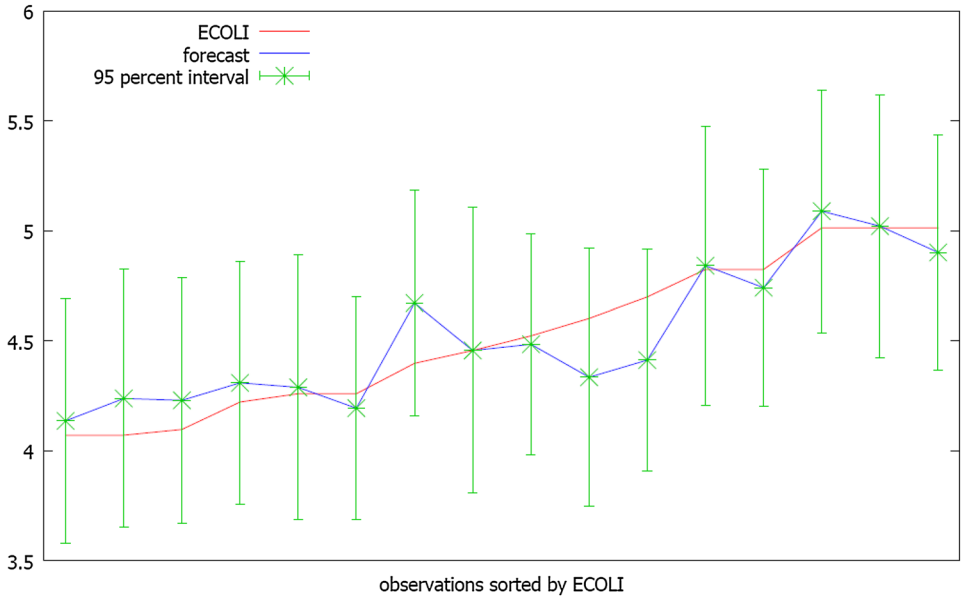


Fig. 1 Graph showing correlation between the predicted and observed IC_{50} (ECOLI)

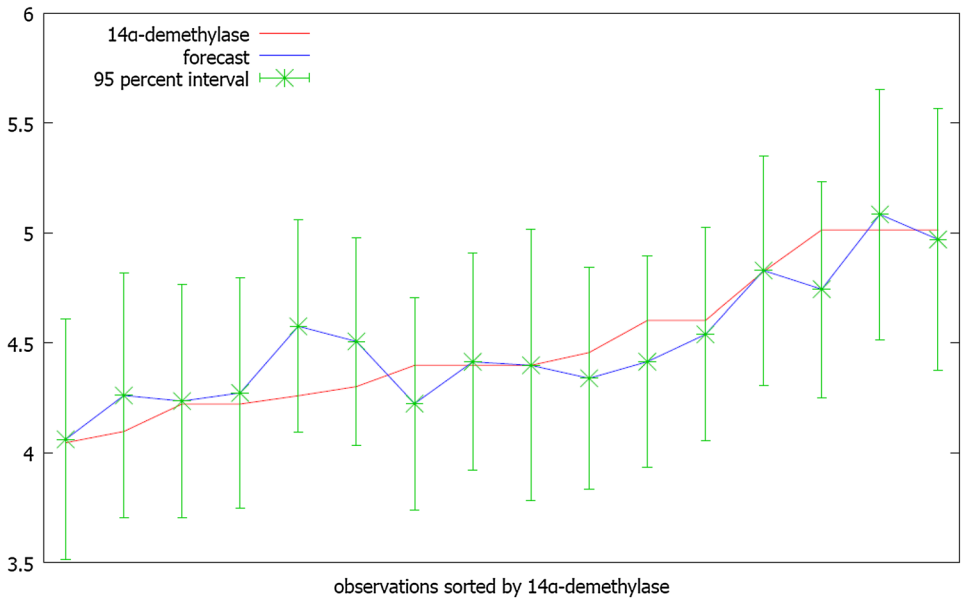


Fig. 2 Graph showing correlation between the predicted and observed IC_{50} (14α-demethylase)

ID: 5r1r) as well as 1,4α-demethylase (PDB ID: 3juv) were displayed in Figs. 4 and 5.

3.4 ADMET Properties Prediction of selected Compounds that Describe Anti-e-coli Activities of 3,4-Dihydropyrimidin-2(1H)-One Urea Derivatives

Table 4 Show the ADMET properties of selected compounds with more efficient binding affinity than other studied compounds as well as amoxicillin (**3, 4, 8, 9** and **12**) via admetSAR server. According to Khaled et al., [43], it was reported that drug-molecules that have higher human intestinal absorption value tends to absorb well. Thus, as displayed in Table 4, the value obtain for human intestinal absorption (HIA) for all the studied compounds fell within the same range and they were lower compare to the value obtain for amoxicillin (Standard). Also, the blood brain barrier value for the selected compounds fall within the same ranges shown in Table 4. The observed P-glycoprotein (non-substrate and non-inhibitor) reported for all the selected molecules were similar to the amoxicilin. AMES was observed so as to determine the level of mutagenicity; thus, all the

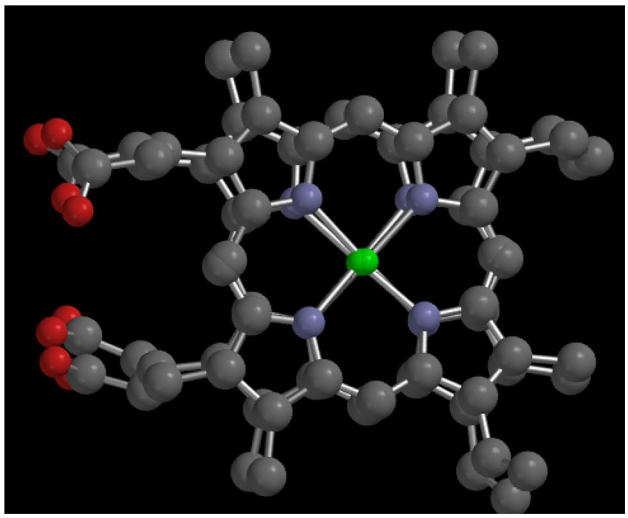


Fig. 3 Overlay of native drug-like compounds over re-docked drug compound

Table 4 Calculated binding affinity

	Binding affinity (*E coli*) (kcal/mol)	Binding Affinity (1,4α-demethylase) (kcal/mol)
1	−7.2	−7.5
2	−7.0	−7.5
3	−7.4	−8.9
4	−8.4	−7.2
5	−6.5	−6.9
6	−7.3	−7.7
7	−6.8	−7.5
8	−7.5	−7.7
9	−7.8	−7.1
10	−6.9	−8.6
11	−7.0	−7.5
12	−7.5	−7.4
13	−7.1	−7.5
14	−6.5	−7.4
15	−7.2	−7.9
16	−6.8	−7.6
Amoxicillin	−6.5	–
Fluconazole	–	−6.5

Compounds with better efficiency are indicated in bold

selected compounds were negative and this correlated with the standard (Amoxicilin). More so, the selected compounds were not carcinogenic and it also agreed with the standard (Table 5). The calculated cytochrome P450 showed that it could be inhibited by some of the studied compounds.

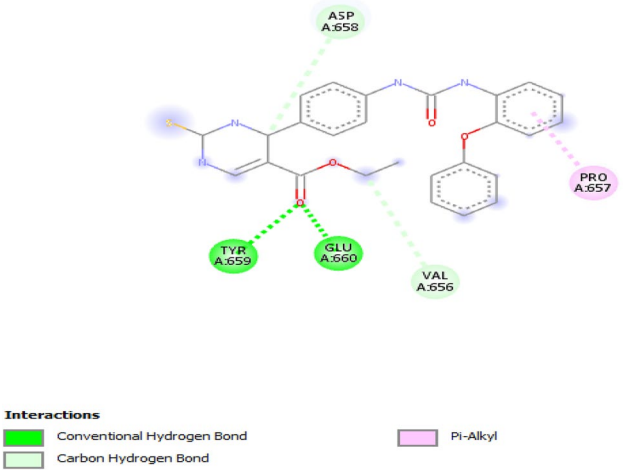


Fig. 4 Molecular interaction of compound **4** with 5r1r

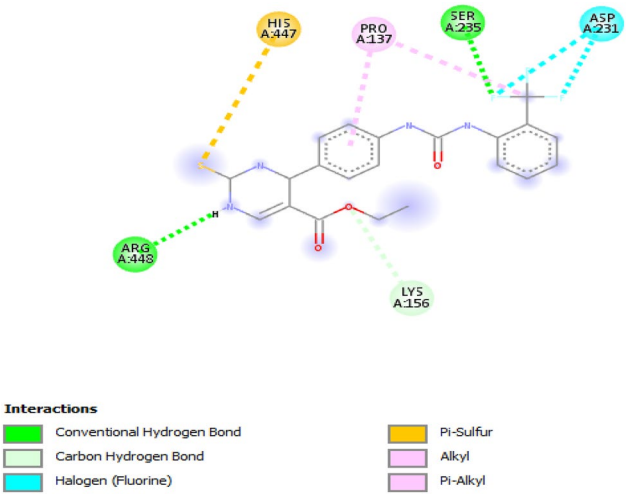


Fig. 5 Molecular interaction of compound **3** with 3juv

3.5 ADMET Properties Prediction of selected Compounds that Describe Anti-1,4α-Demethylase Activities of 3,4-Dihydropyrimidin-2(1*H*)-One Urea Derivatives

ADMET properties of best five (5) studied compounds (**3, 6, 8, 10** and **15**) with potential anti-1,4α-demethylase properties were considered. As shown in Table 5, HIA value obtained for the selected compounds were very closer to that of Fluconazole. AMES was observed so as to determine the level of mutagenicity; thus, all the selected compounds were negative and this correlated with the standard

Table 5 Predicted ADMET properties of selected compounds that describe *anti-e-coli* activities of 3,4-dihydropyrimidin-2(1H)-one urea derivatives

Mode	Compound **3**		Compound **4**		Compound **8**		Compound **9**		Compound **12**		Amoxylin	
	Result	Probability	Result	Probability	Result	Probability	Result	Probability	result	Probability	Result	Probability
Blood–Brain Barrier	BBB–	0.5083	BBB-	0.6045	BBB–	0.5304	BBB-	0.5113	BBB–	0.5236	BBB–	0.9967
Human Intestinal Absorption	HIA+	0.7561	HIA+	0.7564	HIA+	0.7399	HIA+	0.6005	HIA+	0.7588	HIA–	0.9008
Caco-2 Permeability	Caco2–	0.5495	Caco2–	0.5417	Caco2–	0.5446	Caco2–	0.5571	Caco2–	0.5540	Caco2–	0.8722
P-glycoprotein Substrate	Non-substrate	0.5584	Non-substrate	0.5789	Non-substrate	0.5646	Non-substrate	0.5308	Non-substrate	0.5501	Substrate	0.5741
P-glycoprotein Inhibitor	Inhibitor	0.7905	Inhibitor	0.6973	Inhibitor	0.8281	Inhibitor	0.7550	Inhibitor	0.6992	Non-inhibitor	0.9665
	Non-inhibitor	0.8553	Non-inhibitor	0.8403	Non-inhibitor	0.7650	Non-inhibitor	0.8230	Non-inhibitor	0.8477	Non-inhibitor	0.9968
Renal Organic Cation Transporter	Non-inhibitor	0.9243	Non-inhibitor	0.9150	Non-inhibitor	0.9317	Non-inhibitor	0.9298	Non-inhibitor	0.9264	Non-inhibitor	0.9636
Subcellular localization	Mitochondria	0.7611	Mitochondria	0.7507	Mitochondria	0.7582	Mitochondria	0.7627	Mitochondria	0.7544	Lysosome	0.4840
CYP450 2C9 Substrate	Non-substrate	0.7534	Non-substrate	0.7083	Non-substrate	0.7404	Non-substrate	0.7504	Non-substrate	0.7073	Non-substrate	0.8430
CYP450 2D6 Substrate	Non-substrate	0.8274	Non-substrate	0.8280	Non-substrate	0.8257	Non-substrate	0.8260	Non-substrate	0.8246	Non-substrate	0.8446
CYP450 3A4 Substrate	Non-substrate	0.5586	Non-substrate	0.5233	Non-substrate	0.5220	Non-substrate	0.5522	Non-substrate	0.5157	Non-substrate	0.5478
CYP450 1A2 Inhibitor	Inhibitor	0.5802	Inhibitor	0.5980	Inhibitor	0.5298	Inhibitor	0.5501	Inhibitor	0.5444	Non-inhibitor	0.9045
CYP450 2C9 Inhibitor	Inhibitor	0.6813	Inhibitor	0.6867	Inhibitor	0.7174	Inhibitor	0.6712	Inhibitor	0.6617	Non-inhibitor	0.9070
CYP450 2D6 Inhibitor	Non-inhibitor	0.8790	Non-inhibitor	0.8714	Non-inhibitor	0.8845	Non-inhibitor	0.8792	Non-inhibitor	0.8748	Non-inhibitor	0.9231
CYP450 2C19 Inhibitor	Inhibitor	0.7608	Inhibitor	0.7984	Inhibitor	0.7552	Inhibitor	0.7622	Inhibitor	0.7662	Non-inhibitor	0.9150
CYP450 3A4 Inhibitor	Non-inhibitor	0.6857	Non-inhibitor	0.6323	Non-inhibitor	0.5270	Non-inhibitor	0.6925	Non-inhibitor	0.6780	Non-inhibitor	0.8309
CYP Inhibitory Promiscuity	High CYP Inhibitory Promiscuity	0.9142	High CYP Inhibitory Promiscuity	0.9426	High CYP Inhibitory Promiscuity	0.9207	High CYP Inhibitory Promiscuity	0.9196	High CYP Inhibitory Promiscuity	0.9303	Low CYP Inhibitory Promiscuity	0.9767
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9884	Weak inhibitor	0.9803	Weak inhibitor	0.9874	Weak inhibitor	0.9953	Weak inhibitor	0.9927	Weak inhibitor	0.9996
	Non-inhibitor	0.6982	Non-inhibitor	0.7508	Non-inhibitor	0.6861	Non-inhibitor	0.6717	Non-inhibitor	0.6908	Non-inhibitor	0.8761

Table 5 (continued)

Mode	Compound **3**		Compound **4**		Compound **8**		Compound **9**		Compound **12**		Amoxylin	
	Result	Probability	Result	Probability	Result	Probability	Result	Probability	result	Probability	Result	Probability
AMES Toxicity	Non AMES toxic	0.6397	Non AMES toxic	0.6410	Non AMES toxic	0.6508	Non AMES toxic	0.6381	Non AMES toxic	0.6368	Non AMES toxic	0.9099
Carcinogens	Non-carcinogens	0.7102	Non-carcinogens	0.6973	Non-carcinogens	0.6901	Non-carcinogens	0.7107	Non-carcinogens	0.6826	Non-carcinogens	0.5439
Fish Toxicity	High FHMT	0.9961	High FHMT	0.9973	High FHMT	0.9962	High FHMT	0.9951	High FHMT	0.9962	High FHMT	0.9725
Tetrahymena Pyriformis Toxicity	High TPT	0.9914	High TPT	0.9944	High TPT	0.9947	High TPT	0.9932	High TPT	0.9951	High TPT	0.7245
Honey Bee Toxicity	Low HBT	0.7487	Low HBT	0.7543	Low HBT	0.7217	Low HBT	0.7357	Low HBT	0.7450	Low HBT	0.6935
Biodegradation	Not ready biodegradable	1.0000	Not ready biodegradable	1.0000	Not ready biodegradable	1.0000	Not ready biodegradable	1.0000	Not ready biodegradable	1.0000	Not ready biodegradable	0.9606

(fluconazole). Other ADMET properties were reported in Table 6.

4 Conclusion

The unceasing design and development of drugs to cure infections from bacteria and fungi increases nowadays and this has reduced the rate of mortality and morbidity globally. Therefore, study of anti-*e-coli* and anti-1,4α-demethylase properties of 3,4-dihydropyrimidin-2(1H)-one Urea Derivatives was observed in this work using density functional theory as well as molecular docking software (Pymol, Autodock Tool, Auto dock vina and discovery studio). The descriptors which revealed the anti-*e-coli* and anti-1,4α-demethylase were clearly identified to be E_{HOMO}, E_{LUMO}, LogP, Vol, PSA, Pol, NOR and E_{HOMO}, E_{LUMO}, LogP, Vol, Pol, NOR respectively using multiple linear regression method. The obtained molecular descriptors described well anti-*e-coli* and anti-1,4α-demethylase properties of 3,4-dihydropyrimidin-2(1*H*)-one urea derivatives. Also, compound **4** and **3** were observed to inhibit *e-coli* and 1,4α-demethylase better than other studied compounds and it was observed that every part of the studied compounds interacted with the studied proteins except the urea part of the compounds. More so, ADMET properties of five selected compounds were determined and it was observed that they were correlated to the standards used in this work. Therefore, the developed QSAR model will in help in designing and developing more efficient drug like compounds.

Acknowledgements We are grateful to Computational Chemistry Research Laboratory, Department of Pure and Applied Chemistry, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria for the computational resources and Mrs E.T. Oyebamiji for the assistance in the course of this study.

Funding This research received no external funding.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Akintelu SA, Erazua EA, Folorunso AS (2019) Theoretical and experimental investigations on the antibacterial activities of Garcinia Kola seed. J Chem Pharm Res 11(2):38–44
2. Larbi ZN, Farida S, Hocine L, Ahmed O, Joice GNW, Filippo M (2020) Chemical composition and antibacterial activity of essential oils from the algerian endemic *Origanum glandulosum* Desf against Multidrug-Resistant Uropathogenic *E. coli*

Table 6 Predicted ADMET properties of selected compounds that describe anti-1,4α-demethylase activities of 3,4-dihydropyrimidin-2(1H)-one urea derivatives

Mode	Compound **3**		Compound **6**		Compound **8**		Compound **10**		Compound **15**		Fluconazole	
	Result	Probability	Result	Probability	Result	Probability	Result	Probability	Result	Probability	Result	Probability
Blood–Brain Barrier	BBB–	0.5083	BBB–	0.5113	BBB–	0.5304	BBB–	0.5236	BBB+	0.5255	BBB+	0.9382
Human Intestinal Absorption	HIA+	0.7561	HIA+	0.6005	HIA+	0.7399	HIA+	0.7588	HIA+	0.8164	HIA+	0.9894
Caco-2 Permeability	Caco2–	0.5495	Caco2–	0.5571	Caco2–	0.5446	Caco2–	0.5540	Caco2–	0.5643	Caco2+	0.8867
P-glycoprotein Substrate	Non-substrate	0.5584	Non-substrate	0.5308	Non-substrate	0.5646	Non-substrate	0.5501	Non-substrate	0.5849	Non-substrate	0.6008
P-glycoprotein Inhibitor	Inhibitor	0.7905	Inhibitor	0.7550	Inhibitor	0.8281	Inhibitor	0.6992	Inhibitor	0.7548	Non-inhibitor	0.8782
	Non-inhibitor	0.8553	Non-inhibitor	0.8230	Non-inhibitor	0.7650	Non-inhibitor	0.8477	Non-inhibitor	0.6972	Non-inhibitor	0.9004
Renal Organic Cation Transporter	Non-inhibitor	0.9243	Non-inhibitor	0.9298	Non-inhibitor	0.9317	Non-inhibitor	0.9264	Non-inhibitor	0.9298	Non-inhibitor	0.6461
Subcellular localization	Mitochondria	0.7611	Mitochondria	0.7627	Mitochondria	0.7582	Mitochondria	0.7544	Mitochondria	0.7408	Mitochondria	0.8498
CYP450 2C9 Substrate	Non-substrate	0.7534	Non-substrate	0.7504	Non-substrate	0.7404	Non-substrate	0.7073	Non-substrate	0.7291	Non-substrate	0.7898
CYP450 2D6 Substrate	Non-substrate	0.8274	Non-substrate	0.8260	Non-substrate	0.8257	Non-substrate	0.8246	Non-substrate	0.8249	Non-substrate	0.9116
CYP450 3A4 Substrate	Non-substrate	0.5586	Non-substrate	0.5522	Non-substrate	0.5220	Non-substrate	0.5157	Non-substrate	0.5551	Non-substrate	0.5650
CYP450 1A2 Inhibitor	Inhibitor	0.5802	Inhibitor	0.5501	Inhibitor	0.5298	Inhibitor	0.5444	Inhibitor	0.5483	Non-inhibitor	0.6312
CYP450 2C9 Inhibitor	Inhibitor	0.6813	Inhibitor	0.6712	Inhibitor	0.7174	Inhibitor	0.6617	Inhibitor	0.6493	Non-inhibitor	0.5497
CYP450 2D6 Inhibitor	Non-inhibitor	0.8790	Non-inhibitor	0.8792	Non-inhibitor	0.8845	Non-inhibitor	0.8748	Non-inhibitor	0.8862	Non-inhibitor	0.8090
CYP450 2C19 Inhibitor	Inhibitor	0.7608	Inhibitor	0.7622	Inhibitor	0.7552	Inhibitor	0.7662	Inhibitor	0.7833	Inhibitor	0.5320
CYP450 3A4 Inhibitor	Non-inhibitor	0.6857	Non-inhibitor	0.6925	Non-inhibitor	0.5270	Non-inhibitor	0.6780	Non-inhibitor	0.7530	Non-inhibitor	0.8196
CYP Inhibitory Promiscuity	High CYP Inhibitory Promiscuity	0.9142	High CYP Inhibitory Promiscuity	0.9196	High CYP Inhibitory Promiscuity	0.9207	High CYP Inhibitory Promiscuity	0.9303	High CYP Inhibitory Promiscuity	0.9218	Low CYP Inhibitory Promiscuity	0.5240
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9884	Weak inhibitor	0.9953	Weak inhibitor	0.9874	Weak inhibitor	0.9927	Weak inhibitor	0.9966	Weak inhibitor	0.8229
	Non-inhibitor	0.6982	Non-inhibitor	0.6717	Non-inhibitor	0.6861	Non-inhibitor	0.6908	Non-inhibitor	0.6751	Non-inhibitor	0.6614

Table 6 (continued)

Mode	Compound **3**		Compound **6**		Compound **8**		Compound **10**		Compound **15**		Fluconazole	
	Result	Probability	Result	Probability	Result	Probability	Result	Probability	Result	Probability	Result	Probability
AMES Toxicity	Non AMES toxic	0.6397	Non AMES toxic	0.6381	Non AMES toxic	0.6508	Non AMES toxic	0.6368	Non AMES toxic	0.6250	Non AMES toxic	0.5480
Carcinogens	Non-carcinogens	0.7102	Non-carcinogens	0.7107	Non-carcinogens	0.6901	Non-carcinogens	0.6826	Non-carcinogens	0.6843	Non-carcinogens	0.7298
Fish Toxicity	High FHMT	0.9961	High FHMT	0.9951	High FHMT	0.9962	High FHMT	0.9962	High FHMT	0.9957	High FHMT	0.7896
Tetrahymena Pyriformis Toxicity	High TPT	0.9914	High TPT	0.9932	High TPT	0.9947	High TPT	0.9951	High TPT	0.9926	High TPT	0.8590
Honey Bee Toxicity	Low HBT	0.7487	Low HBT	0.7357	Low HBT	0.7217	Low HBT	0.7450	Low HBT	0.6830	Low HBT	0.8709
Biodegradation	Not ready biodegradable	1.0000	Not ready biodegradable	1.0000	Not ready biodegradable	1.0000	Not ready biodegradable	1.0000	Not ready biodegradable	1.0000	Not ready biodegradable	1.0000

Isolates. Antibiotics 9:29. https://doi.org/10.3390/antibiotics9010029

3. Gwatkin DR, Rustein S, Johnson K, Pande RP, Wagstaff A (2000) Socioeconomic differences in health, nutrition and population. World Bank, Health, Population and Nutrition Group, Washington DC
4. Oyebamiji AK, Semire B (2018) DFT-QSAR and Docking Studies of 2-[5-(aryloxymethyl)-1,3,4-oxadiazol-2-ylsulfanyl]acetic acids Derivatives against *Bacillus subtilis*. Der Pharma Chemica 10(3):135–139
5. Backhed F, Ley R, Sonnenburg J, Peterson D, Gordon J (2005) Science 307:1915–1920
6. Fauci AS, Zerhouni EA (2005) Science 308:49
7. Maloy S, Schaechter M (2006) The era of microbiology: a golden phoenix. Int Microbiol 9(1):1–7
8. Fredrickson JK, Zachara JM, Balkwill DL, Kennedy D, Li SM, Kostandarithes HM, Daly MJ, Romine MF, Brockman FJ (2004) Geomicrobiology of high-level nuclear waste-contaminated vadose sediments at the Hanford site, Washington state. Appl Environ Microbiol 70(7):4230–4241
9. Georgiana N, Isabela MN, Octavian TO, Anca U, Dragos PM, Anca Z, George MN, Denisa M (2017) Molecular docking and screening studies of new natural sortase a inhibitors. Int J Mol Sci 18:2217. https://doi.org/10.3390/ijms18102217
10. Zhang Y, Zhang J, Chen W, Angsantikul P, Spiekermann KA, Fang RH, Gao W, Zhang L (2017) Erythrocyte membrane-coated nanogel for combinatorial antivirulence and responsive antimicrobial delivery against *Staphylococcus aureus* infection. J Control Release 263:185–191
11. Gilmore MS, Clewell DB, Ike Y, Shankar N (2014) Enterococci: from commensals to leading causes of drug resistant infection. Massachusetts Eye and Ear Infirmary, Boston
12. Nobuo W, Kirill K, So N, Junko ST, Meiko T, Yukiko K, Satomi M, Toru I, Hiromichi A, Sadaki I, Tadashi I, Shigeaki I (2018) Detection of pathogenic bacteria in the blood from sepsis patients using 16S rRNA gene amplicon sequencing analysis. PLoS ONE 13(8):e0202049. https://doi.org/10.1371/journal.pone.0202049
13. Becher R, Wirsel SG (2012) Fungal cytochrome P450 sterol 14alpha-demethylase (CYP51) and azole resistance in plant and human pathogens. Appl Microbiol Biotechnol 95(4):825–840. https://doi.org/10.1007/s00253-012-4195-9 (**PMID: 22684327**)
14. Daum G, Lees ND, Bard M, Dickson R (1998) Biochemistry, cell biology and molecular biology of lipids of *Saccharomyces cerevisiae*. Yeast 14(16):1471–1510
15. Nafiz ÖC, Ulviye AÇ, Begüm NS, Serkan L, Büşra K, Yusuf Ö, Zafer AK, Ali SK et al (2017) Synthesis, molecular docking studies, and antifungal activity evaluation of new benzimidazole-triazoles as potential lanosterol 14α-demethylase inhibitors. J Chem 2017:15
16. Tang H, Zheng C, Lv J et al (2010) Synthesis and antifungal activities in vitro of novel pyrazino [2,1-a] isoquinolin derivatives. Bioorg Med Chem Lett 20(3):979–982
17. Ghabbour HA, Qabeel MM, Eldehna WM, Al-Dhfyan A, Abdel-Aziz HA (2014) Design, synthesis, and molecular docking of 1-(1-(4-chlorophenyl)-2-(phenylsulfonyl)ethylidene)-2-phenylhydrazine as potent nonazole anticandidal agent. J Chem 2014
18. Warrilow AG, Josie EP et al (2013) Azole affinity of sterol 14α-demethylase (CYP51) enzymes from *Candida albicans* and *Homo sapiens*. Antimicrob Agents Chemother 57(3):1352–1360
19. Lal J, Gupta SK, Thavaselvam D, Agarwal DD (2012) Design, synthesis, synergistic antimicrobial activity and cytotoxicity of 4-aryl substituted 3, 4-dihydropyrimidinones of curcumin. Bioorg Med Chem Lett 22(8):2872–2876
20. Wan J-P, Pan Y (2012) Recent advance in the pharmacology of dihydropyrimidinone. Mini Rev Med Chem 12(4):337–349

21. Wan J-P, Liu Y (2010) Synthesis of dihydropyrimidinones and thiones by multicomponent reactions: strategies beyond the classical Biginelli reaction. Synthesis 23:3943–3953
22. Narahari SR, Reguri BR, Gudaparthi O, Mukkanti K (2012) Synthesis of dihydropyrimidinones via Biginelli multi-component reaction. Tetrahedron Lett 53(13):1543–1545
23. Japp FR, Klingemann FI (1891) Ethylic phenanthroxylene-acetoacetate. J Chem Soc Trans 59:1–26
24. Atwal KS, Swanson BN, Unger SE, Floyd DM, Mereland S, Hedberg A, O'Reilly BC (1991) Dihydropyrimidine calcium channel blockers. 3. 3-Carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarboxylic acid esters as orally effective antihypertensive agents. J Med Chem 34:806
25. Min W, Shun Z, Hong XJ, Hao HZ (2019) Green synthesis and structural characterization of novel N1-substituted 3,4-dihydropyrimidin2(1*H*)-ones. Green Process Synth 8:230–234
26. Singh K, Arora D, Poremsky E, Lowery J, Moreland RS (2009) Eur J Med Chem 44:1997–2001
27. Zalavadiya P, Tala S, Akbari J, Joshi H (2009) Arch Pharm Chem Life Sci 342:469–475
28. Persson AL, Eriksson M, Katterle B, Potsch S, Sahlin M, Sjoberg BM (1997) A new mechanism-based radical intermediate in a mutant R1 protein affecting the catalytically essential Glu441 in Escherichia coli ribonucleotide reductase. J Biol Chem 272:31533–31541
29. Strushkevich N, Usanov SA, Park HW (2010) Structural basis of human CYP51 inhibition by antifungal azoles. J Mol Biol 397:1067–1078
30. Oyebamiji AK, Abdulsalami IO, Semire B (2020) Dataset on *Insilico* approaches for 3,4-dihydropyrimidin-2(1*H*)-one urea derivatives as efficient *Staphylococcus aureus* inhibitor. Data in Brief 32:106195
31. Adegoke RO, Oyebamiji AK, Semire B (2020) Dataset on the DFT-QSAR, and docking approaches for anticancer activities of 1, 2, 3-triazole-pyrimidine derivatives against human esophageal carcinoma (EC-109). Data Brief 31:105963
32. Semire B, Oyebamiji AK, Odunola OA (2020) Electronic properties' modulation of D–A–A via fluorination of 2-cyano-2-pyran-4-ylidene-acetic acid acceptor unit for efficient DSSCs: DFT-TDDFT approach. Sci Afr 7:e00287
33. Semire B, Oyebamiji AK, Odunola OA (2017) Tailoring of energy levels in (2Z)-2-cyano-2-[2-[(E)-2-[2-[(E)-2-(p-tolyl) vinyl]thieno[3,2-b]thiophen-5-yl]vinyl]pyran-4-ylidene]acetic acid derivatives via conjugate bridge and fluorination of acceptor units for effective D–p–A dye-sensitized solar cells: DFT–TDDFT approach. Res Chem Intermed 43:1863–1879
34. Oyebamiji AK, Fadare OA, Semire B (2020a) Hybrid-based drug design of 1,2,3-triazolepyrimidine-hybrid derivatives: Efficient inhibiting agents of mesenchymal–epithelial transition factor reducing gastric cancer cell growth. J Chem Res 44(5–6):277–280
35. Jie S, Feixiong C, You X, Weihua L, Yun T (2010) Estimation of ADME properties with substructure pattern recognition. J Chem Inf Model 50:1034–1041
36. David FLL, Howard BB (2002) Molecular binding interactions: their estimation and rationalization in QSARs in terms of theoretically derived parameters. Sci World J 2:1776–1802
37. Oyewole RO, Oyebamiji AK, Semire B (2020) Theoretical calculations of molecular descriptors for anticancer activities of 1, 2, 3-triazole-pyrimidine derivatives against gastric cancer cell line (MGC-803): DFT QSAR and docking approaches. Heliyon 6:e03926
38. Oyebamiji KA, Semire B (2016) Studies of 1, 4-dihydropyridine derivatives for anti-breast cancer (MCF-7) activities: combinations of DFT-QSAR and docking methods. N Y Sci J 9(6):58–66
39. Oyebamiji AK, Fadare OA, Semire B (2020b) Anti-gastric cancer activity of 1,2,3-triazolo[4,5-d]pyrimidine hybrids (1,2,3-TPH): QSAR and molecular docking approaches. Heliyon 6:e03561
40. Oyebamiji AK, Tolufashe GF, Semire B (2020) Inhibition study on anti-type 3 of 3 α-hydroxysteroid dehydrogenase activity against 1,2,3-triazolo[4,5-D]pyrimidine derivatives: molecular modelling approach. Sci Afr 8:e00444
41. Oyebamiji AK, Semire B (2020) In vitro biological estimation of 1,2,3-triazolo[4,5-d]pyrimidine derivatives as anti-breast cancer agent: DFT, QSAR and docking studies. Curr Pharm Biotechnol 21:70–78
42. Abdul-Hammed M, Semire B, Adegboyega SA, Oyebamiji AK, Olowolafe TA (2020) Inhibition of cyclooxygenase-2 and thymidylate synthase by dietary sphingomyelins: insights from DFT and Molecular docking studies. Phys Chem Res 8(2):296–310
43. Mebarka O, Salah B, Khaled L, Ismail D, Houmam B (2018) Molecular docking studies and ADMET properties of new 1.2.3 triazole derivatives for anti-breast cancer activity. J Bionanosci 12:1–11