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Research Article

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Theoretical Studies on 1,2,3-Triazole-Pyrimidine-Urea Hybrids against Type 3 of 3α-Hydroxysteroid Dehydrogenase Reducing Breast Cancer Cell Growth

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ABSTRACT

Anti-breast cancer activity of eleven synthesized molecules was studied using computational approach. The molecular descriptors which describe the anti-breast cancer activities of the studied compounds were optimized using B3LYP/6-31+G via Spartan 14 and the obtained descriptor were EHOMO (eV), ELUMO (eV), dipole moment (Debye), log P, molecular weight (amu), HBA, HBD, Vol and Ovality. Furthermore, the calculated descriptors played a serious role in developing QSAR model for predicting observed inhibition concentration (IC_{50}) using Gretl for multiple linear regression (MLR) and MATLAB software packages for BPNN. The developed model proved to be effective and predictive; nevertheless, BPNN-QSAR model predicted more efficiently than MLR. Furthermore, molecular docking studied on 1,2,3-triazole-pyrimidine-urea Hybrids and type 3 of 3α-Hydroxysteroid Dehydrogenase (PDB ID: 4xo6) brought about nine conformation each and it was observed that compounds have the highest tendency to inhibit that other studied compounds.*

Keywords: 1,2,3-Triazole-pyrimidine-urea; DFT; 3α-Hydroxysteroid dehydrogenase; Breast cancer; QSAR; Docking

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INTRODUCTION

Breast cancer remains one of the prominent causes of death among women globally [1]. The threat posing by this malignant neoplasa seems to be increasing on a daily basis [2]. According to Keogh *et al*., [3], over 90% of women in the world have abstemiously increased threat of breast cancer. Providentially, the rate of survival among the

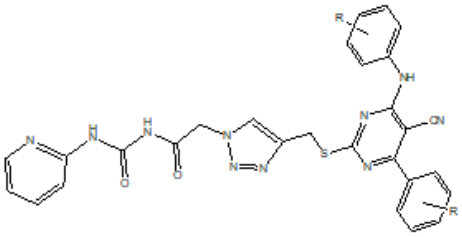
patient with breast cancer keeps increasing and this could be attributed to advancement in drug designing and development [4].

Type 3 of 3*α*-Hydroxysteroid Dehydrogenase is an imperative enzyme in which its role in androgen breakdown cannot be underestimated [5]. In the prostate, the inactivation of androgens could be catalysed by 3*α*-Hydroxysteroid Dehydrogenase *via* transformation of 5*α*-dihydrotestosterone to 3*α*-androstanediol [6]. Also, series of 3*α*-Hydroxysteroid Dehydrogenase have been identified in human body to be a serious enzyme in sex act [7]. Also, Bo *et al*., [6], revealed that overpowering type 3 of 3*α*-Hydroxysteroid Dehydrogenase automatically subdue MCF-7 cells growth.

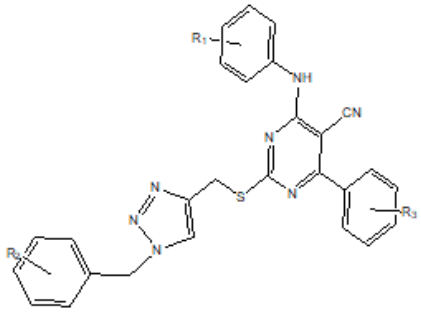
Several derivatives of triazole and pyrimidine have been reported to have series of importance in Medicinal world. These compounds have been reported by many researchers to have series of biological importance like analgesics, anti-inflammatory, antioxidant, anticancer, and diuretics [8-16]. Therefore, hybrids of both triazole and pyrimidine are expected to possess more efficient biological importance than either of the two compounds.

Increasing concern of scientists to develop a predicting technique for cytotoxicities before the synthesis in recent times is becoming alarming. Thus, Quantitative Structure-Activity Relationship (QSAR) searches info linking chemical structure to biological and other activities by developing a QSAR model [17].

Therefore, eleven molecular compounds were studied in this work with the aim of designing and developing QSAR model and examining the observed non-bonding interactions (binding affinity, hydrophilic interactions and hydrophobic interactions) between these studied compounds (Figure 1) and type 3 of 3*α*-Hydroxysteroid Dehydrogenase for possible reduction of breast cancer growth [18,19].



R^1	R^2
m-CF_3	*p*-$CH(CH_3)_2$
m-CF_3	*m,p,m*-triOCH_3
m-CF_3	*p*-CH_3
m-CF_3	*p*-Br



R^1	R^2	R^3
p-OCH_3	*o*-Cl	H
o-Cl	*o*-Cl	H
p-Cl	*o*-Cl	H
o-OCH_3	*o*-Cl	H
o-F	*o*-Cl	H
o-CH_3	*o*-Cl	H
p -CH_3	*o*-Cl	H

Figure 1. The schematic structures of 1,2,3-triazole-pyrimidine-urea Hybrids derivatives [18,19]

METHODOLOGY

Eleven molecular compounds were studied and optimized using quantum chemical methods *via* Spartan 14 software [20]. The obtained descriptors played effective role in developing QSAR model (equation 4) by using Gretl and Matlab R2015a and the predicted inhibition concentration revealed the effectiveness of the developed model. Also, the developed model was validated by considering correlation coefficient (R), cross validation (CVR^2) (Equation 1), adjusted correlation coefficient (R^2_{adj}) ($Equation$ 2), P-value. More so, interactions observed between the studied ligand and 3α-Hydroxysteroid Dehydrogenase type 3 (PDB ID: **4xo6**) [6] were studied *via* molecular docking. The inhibition constant was calculated using equation 3.

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

The R_2 adjusted could be calculated using equation (2)

$$\boldsymbol{R^2_a = \frac{(N-I)\times R^2 - P}{N-1-P}} \quad \textbf{(2)}$$

$$\boldsymbol{K = e^{-\Delta G/RT}} \quad \textbf{(3)}$$

RESULTS AND DISCUSSION

QSAR Study

The obtained molecular descriptors (highest occupied molecular orbital energy (E_{HOMO}), lowest unoccupied molecular orbital energy (E_{LUMO}), solvation energy, Dipole Moment (DM), weight, ovality, hydrophobicity (Log P), Volume (V), Area, Polar Surface Area (PSA)) using quantum chemical method were used to developed QSAR model. As shown in Table 1, it was observed that the developed model used to predict for Multiple Linear Regression (MLR) *via* Gretl software proved to be effective and reliable; however, the prediction made by back propagation nueral network (BPNN) using Matlab R2015a proved to be slightly more effective than the prediction made by using MLR. Thus, the prediction made by using MLR and BPNN were very closer to the experimental and this showed the efficiency of the developed model (Equation 4) (Figures 2 and 3). Also, the prediction were validated by considering cross validation ($CV.R^2$) and adjusted R^2 (R^2_{adj}) and these supported the efficiency of the developed models claimed in this work.

IC_{50} = -1730.27 - 10.2988(E_{HOMO}) - 0.0915933(DM) + 42.4947(POLARI) - 3.44514(VOL) + 15.2774(E_{LUMO}) - 8.92142(OVALITY) (4)

N=11, F=15.17277, P<0.0001, R^2=0.957, R^2_{adj}=0.894, $CV.R^2$=0.996, MSE=1.205

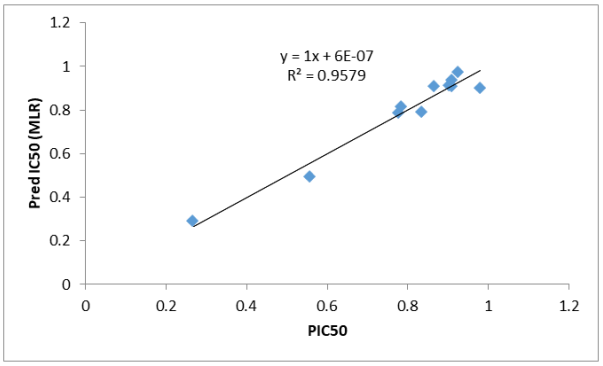


Figure 2. Graphical illustration of Predicted IC_{50} *via* MLR and observed activity

Table 1. Calculated and Experimental IC_{50} values

	PIC	MLR	BPNN
1	0.935507	0.907475	0.907001
2	0.910624	0.901625	0.902344
3	0.786751	0.775482	0.769193
4	0.49276	0.557581	0.470222
5	0.905796	0.864109	0.877017
6	0.290035	0.267348	0.285876
7	0.814248	0.784004	0.809769
8	0.790285	0.833185	0.765064
9	0.906335	0.908087	0.899029
10	0.900367	0.978932	0.889868
11	0.974051	0.924424	0.965476

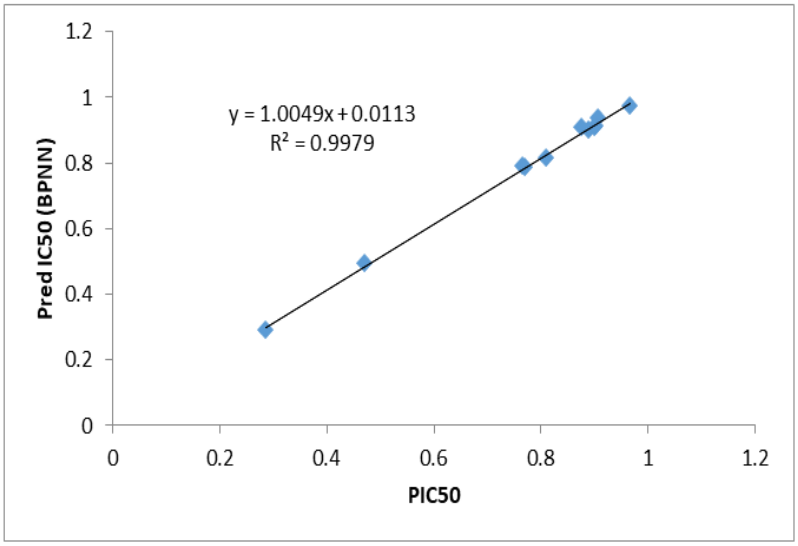


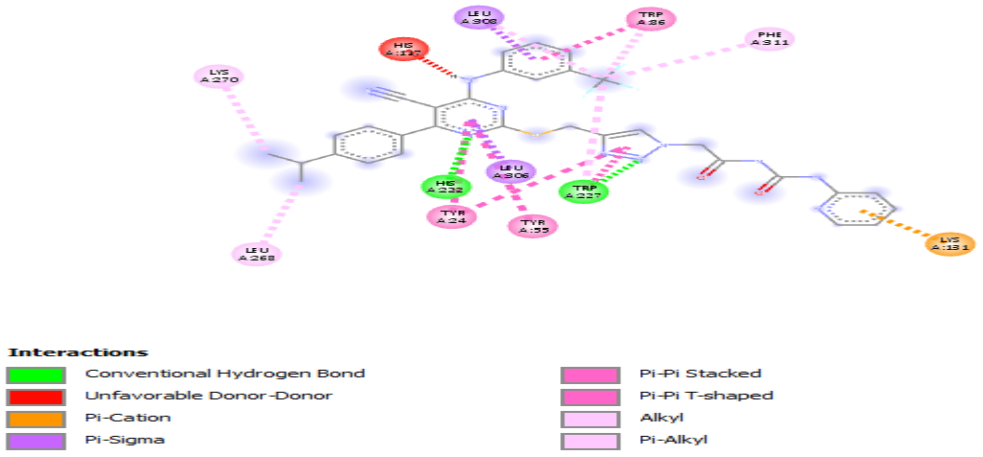
Figure 3. Graphical illustration of Predicted IC_{50} *via* BPNN and observed activity

Molecular docking study

Several derivatives of 1,2,3-triazole-pyrimidine-urea hybrids derivatives were docked against 3*α*-Hydroxysteroid Dehydrogenase type 3 (PDB ID: 4xo6) to identify the non-bonding interactions existing between the studied ligands and receptor. The interactions which were considered are hydrogen bonding, hydrophobic interaction (pi-pi, pi-alkyl, pi-aryl, pi-cation, pi-anion and pi-sigma) as shown in Figure 4. In this work, it was observed that compound 1 possess ability to inhibit 3*α*-Hydroxysteroid Dehydrogenase type 3 than other studied compounds since the highest the binding affinity (in term of negative) the better the efficiency [20,21]. The residues involved between compound **1** and **4xo6** are LYS-270, HIS-117, LEU-308, TRP-86, PHE-311, LYS-131, TRP-227, TYR-55, TYR-24, LEU-306, HIS-222, LEU-268 (Figure 4) (Table 2).

Table 2. Interactions between 1,2,3-triazole-pyrimidine-urea hybrids Derivatives and receptor (4xo6)

	Binding Affinity (kcal/mol)	K_i (μM)	Amino Acid Residue
1	-12.80	2.41×10^9	LYS-270, HIS-117, LEU-308, TRP-86, PHE-311, LYS-131, TRP-227, TYR-55, TYR-24, LEU-306, HIS-222, LEU-268.
2	-8.80	2.82×10^6	GLN-6, ALA-44, VAL-281, GLU-285, ARG-278, SER-1, ASP-2, GLN-6
3	-11.00	1.15×10^8	PRO-26, VAL-29, TYR-272, ALA-25, HIS-222, SER-217, LYS-270, LEU-306, TYR-55, TYR-216, THR-23, TYR-24, ALA-218, LEU-219, SER-221, GLY-220, HIS-117, LEU-268, GLY-22, ALA-269, ARG-2233, VAL-234, LEU-235, LEU-236
4	-9.80	1.52×10^7	ILE-129, HIS-222, LEU-306, TRP-227, TYR-55, VAL-128, TYR-24, VAL-54, HIS-53, LYS-31, ASN-56, ALA-27
5	-10.90	9.78×10^7	VAL-128, TRP-227, SER-217, HIS-222, LEU-308, HIS-117, LEU-306, TYR-24, VAL-54
6	-9.90	1.80×10^7	PRO-26, HIS-222, TYR-55, TYR-216, SER-217, LEU-306, LYS-270, ALA-253, ARG-276, LEU-219
7	-10.40	4.20×10^7	ARG-276, LEU-219, ALA-253, LEU-268, TYR-216, HIS-222, LYS-270
8	-10.60	5.89×10^7	HIS-222, TYR-55, LEU-306, ALA-27, TRP-227, LEU-308, PHE-118, TRP-86, HIS-117, TYR-216
9	-11.10	1.37×10^8	TYR-55, TRP-227, LEU-306, HIS-222, VAL-54, ALA-27, VAL-128, HIS-117, TRP-86, LEU-308, PHE-118, ASN-167
10	-10.50	4.98×10^7	ARG-276, PRO-26, TYR-216, LEU-268, LYS-270, ALA-218, LEU-219, ALA-253
11	-10.90	9.78×10^7	LYS-270, ALA-253, LEU-219, ARG-276, ALA-218



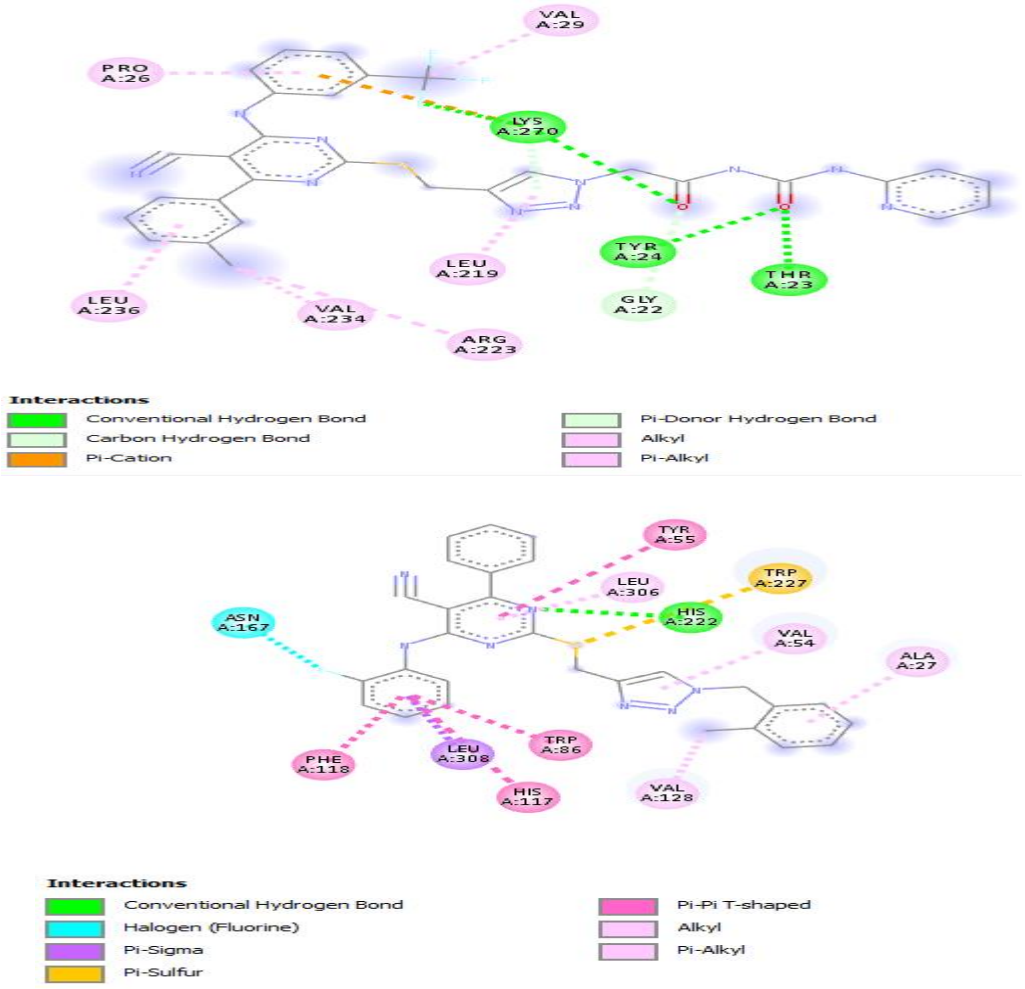


Figure 4. Binding interaction of compound 1, 3 and 9 with 4xo6

CONCLUSION

Cytotoxicity of Eleven (11) 1,2,3-triazole-pyrimidine-urea hybrids Derivatives were studied using Quantum chemical method and the molecular descriptors obtained were used to develop QSAR model to predict the observed inhibition concentration (IC_{50}) *via* Gretl. The model established for both MLR and BPNN predicted well and proved to be proficient. Also, the difference between the predicted IC_{50} for both MLR and BPNN was very slight; however, the prediction made by using BPNN was more accurate than the prediction made using MLR. More so, the docking study was observed to reveal the binding interaction between the studied compounds and the receptor. Thus, compound 1 inhibited more effectively than other compounds.

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