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ARTICLE

Theoretical Bioevaluation of 1,2,4-Thiadiazole-1,2,4-triazole Derivatives *via* Molecular Modelling Approach

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ABSTRACT

Breast cancer still remains one of the precarious ailments among humans globally. The vulnerability of this ailment in homeopathic world remains colossal and this has drawn the attention of seasoned researchers to find lasting solution to this hazard. Therefore, 10 novel 1,2,4-thiadiazole-1,2,4-triazole derivatives were studied so as to explore their anti-breast cancer activities. The studied compounds were optimized using Spartan 14 and the QSAR study was executed by using Gretl and MATLAB. Also, docking study was observed using 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). The selected descriptors were used to developed effective QSAR model and it was observed that the developed QSAR model using artificial neural network (ANN) predicted better than the prediction made by multiple linear regression (MLR). More so, the calculated binding affinity revealed that compound **g** (-11.4 kcal/mol) possess ability to inhibit 3α-hydroxysteroid dehydrogenase type 3 (PDB ID: 4xo6) than other studied compounds as well as etoposide (Standard).

KEYWORDS

1,2,4-Thiadiazole, 1,2,4-Triazole, Breast cancer, QSAR, DFT.

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INTRODUCTION

Cancer as a dreaded disease still remains one of the dangerous diseases that troubles both young and adult globally [1]. The position taken by cancer among the most dangerous diseases that cause death in the world remains the second [2-4]. According to report by several researchers, over 65% of the cancer related death in the world could be traced to under-developed and developing countries [5,6]. Molina *et al.* [7] reported that early detection of cancer in human being and apt treatment *via* surgery or radiation or chemotherapy could cure cancer.

Furthermore, breast cancer which has become a major threat to women globally has drawn the attention of many researchers [8]. Helmrich *et al.* [9] and Keogh *et al.* [10] revealed the degree at which breast-cancer increases to be very high and it has also been observed that almost 95% of women have moderately

growing risk of breast cancer. Thus, an enhancement in designing and development of drug-like molecules with anti-breast cancer properties has increased the rate of survival among many women with breast cancer in the world [11]. The part played by three nitrogen present in heterocyclic compounds in drug design like 1,2,4-triazoles and 1, 2, 3-triazoles cannot be overemphasized. As reported by Kaur *et al*. [12] and Kapron *et al.* [13], the nitrogen present in triazole possesses the ability to form hydrogen bond targeting apt site thereby enhancing its toxicological and pharmacological features. Triazole derivatives have been linked with therapeutic activities such as antioxidant [14], anti-inflammatory [15,16], tubulin inhibitors [17], analgesics [18,19], anticancer [20], diuretics [21], antimicrobial [22,23].

Likewise, thiadiazole is a five-membered ring with vast therapeutic activities [24]. As reported by many researchers, thiadiazole derivatives possess several biological activities such as antioxidant, anti-inflammatory, central nervous system (CNS) depressant, antibacterial, analgesic, anticancer, molluscicidal, antidiabetic, antihypertensive and antitubercular activities, diuretic [25-34]. In this work, QSAR model was developed using molecular descriptors with anti-breast cancer obtained from the studied hybrid to predict the observed biological activities as well as the molecular interaction between the investigated 1,2,4-thiadiazole-1,2,4-triazole derivatives and breast cancer cell line (MCF-7) (PDB ID: 4xo6) [35].

EXPERIMENTAL

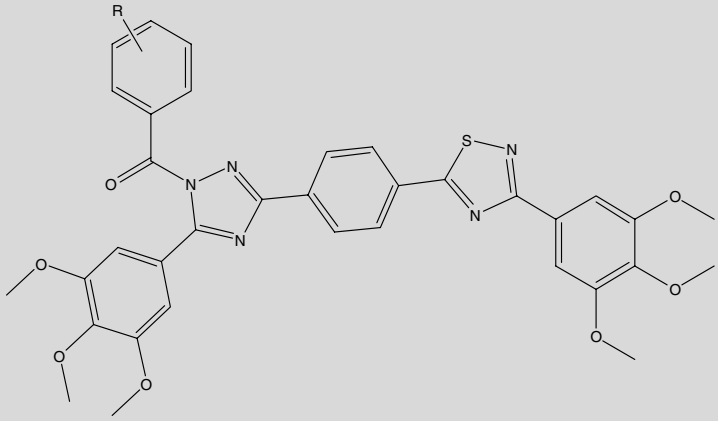
QSAR and molecular docking analysis: Ten molecular compounds (Table-1) with anti-breast cancer activities were adapted from the work carried out by Yazala *et al.* [36] and subjected to quantum chemical calculations *via* density functional theory (6-31G*) using Spartan 14 software [37,38]. Several descriptors were obtained which exposed the anti-breast cancer activities of 1,2,4-thiadiazole-1,2,4-triazole derivatives and few were selected out of the numerous descriptors obtained to develop quantitative structural activities relationship (QSAR) model (eqn. 1) so as to predict the observed biological activities of the studied ligands using multiple linear regression (MLR) (Gretl) and Artificial neural network (ANN) (MATLAB). More so, molecular interactions between the studied 1,2,4-thiadiazole-1,2,4-triazole derivatives and MCF-7 (PDB ID: 4xo6) [35] were studied by observing the binding affinity for individual compound, residues involved in the interaction as well as the type of non-bonding interaction that occur between the complexes.

$$IC_{50} = 656.891 + 104.448(E_{HOMO}) + 0.262031(PSA) - 0.0608408(VOL) + 11.9384(E_{LUMO}) - 0.875020(DM) \quad (1)$$

$F = 3.37$, $P < 0.0001$, $R^2 = 0.894$, Adjusted $R^2 = 0.629$, MSE = 0.521.

ADMET properties: Absorption, distribution, metabolism, excretion and the toxicity features of 2,4-thiadiazole-1,2,4-triazole derivatives were investigated using admet SAR (http://lmmd.ecust.edu.cn/admetsar1) [39]. The investigated ADMET properties were Blood-brain barrier, human intestinal absorption, Caco-2 permeability, P-glycoprotein substrate, P-glycoprotein inhibitor, renal organic cation transporter, subcellular localization, CYP450 2C9 substrate, CYP450 2D6 substrate, CYP450 3A4 substrate, CYP450 1A2 inhibitor, CYP450

TABLE-1
SEVERAL DESCRIPTORS VALUES OF 1,2,4-THIADIAZOLE-1,2,4-TRIAZOLE DERIVATIVES



	R	Observed IC_{50}	MLR	ANN	Binding affinity (kcal/mol)
a	H	3.57	3.27	3.54	-8.6
b	3,4,5-Trimethoxy	0.10	1.51	0.07	-9.6
c	3,5-Dimethoxy	1.12	-0.08	1.11	-8.8
d*	4-Methoxy	1.44	3.97	1.41	-8.6
e	4-Nitro	0.23	0.65	0.21	-9.3
f	3,5-Dinitro	5.66	5.38	5.65	-8.6
g	4-Chloro	1.02	1.45	1.01	-11.4
h*	4-Bromo	7.28	-0.55	7.26	-8.4
i	4-Cyano	1.27	0.83	1.24	-8.7
j	4-Methyl	5.94	5.89	5.91	-8.3
Etoposide	–	2.11	–	–	-9.1

*Denote test set

2C9 inhibitor, CYP450 2D6 inhibitor, CYP450 2C19 inhibitor, CYP450 3A4 inhibitor, CYP inhibitory promiscuity, human Ether-a-go-go-Related gene inhibition, AMES toxicity, carcinogens, fish toxicity, tetrahymena pyriformis toxicity, honey bee toxicity and biodegradation.

RESULTS AND DISCUSSION

Molecular descriptors and QSAR analysis: The studied molecular compounds were optimized using density functional theory (DFT) method and molecular descriptors obtained were highest occupied molecular orbital energy (E_{HOMO}), polar surface area (PSA), lowest unoccupied molecular orbital energy (E_{LUMO}), weight, lipophilicity (log P), volume (V), dipole moment (DM), ovality, area, hydrogen bond donor (HBD), Hydrogen bond acceptor (HBA) and the values are tabulated in Table-2.

According to Table-3, rational correlation was examined between the investigated variables (calculated descriptors). It was observed that IC_{50} fairly correlated with E_{HOMO} and E_{LUMO} by 0.544 and -0.677 respectively. Also, E_{HOMO} and E_{LUMO} are negatively correlated as well as polar surface area (PSA) and dipole moment are positively correlated.

QSAR study *via* multiple linear regression: As shown in eqn. 1, five (5) molecular descriptors were selected and used to develop QSAR model in order to obtain a better prediction of the observed inhibition concentration (IC_{50}). The molecular compound were divided into two (raining set and test set). The training set was used in developing the QSAR model which was used for predicting biological activity of molecules. However, the selected compounds used as test set did not undergo any process in developing QSAR model. Thus, the test set confirmed the dependability of the developed QSAR model. Also, the obtained calculated statistical parameters using multiple linear regression (MLR) are correlation coefficient (R^2), adjusted correlation coefficient (Adj R^2), P-value, mean square error (MSE) and the correlation coefficient (R^2) obtained using MLR showed the efficiency of the developed QSAR model and this was proved *via* the predicted inhibition efficiency using MLR (Fig. 1). As reported by Taourati *et al.* [40] developed QSAR model can also be approved reliable when the calculated correlation coefficient (R^2) is higher than the mean squared errors (MSE); therefore, the developed QSAR model *via* MLR method proved to be efficient in predicting the observed inhibition concentration (IC_{50}) [40]. Moreover, even distribution in Fig. 2 revealed the predictability of the devel-oped QSAR model thereby resulted to closeness between the predicted IC_{50} and observed IC_{50}.

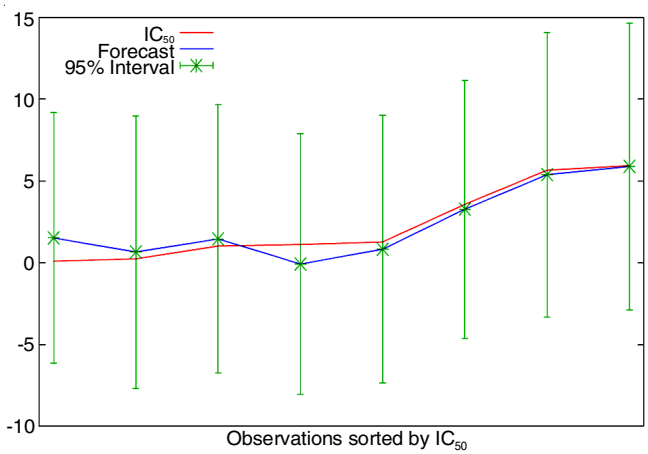


Fig. 1. Correlation between the predicted and observed IC_{50} (MLR)

QSAR study *via* artificial neural network (ANN): The role played by machine learning method *via* artificial neural network in predicting cytotoxicity of molecular compounds cannot be overemphasized [41]. Its predicting power has been reported to be reliable and the result obtained using ANN as shown in Table-1 proved it dependability. The calculated correlation coefficient (R^2) (0.999) is a proof that the employed ANN method possess the ability to predict than MLR; therefore, this showed that ANN possess the ability to develop QSAR model with effective predicting capability.

TABLE-2
CALCULATED MOLECULAR DESCRIPTORS

	E_{HOMO}	E_{LUMO}	DM	MW	AREA	VOL	PSA	OVALITY	POL	HBD	HBA
a	-5.88	-2.43	7.66	623.646	608.08	584.88	121.493	1.80	88.01	3	12
b	-5.89	-2.44	8.56	713.724	695.76	666.13	141.095	1.89	94.60	3	15
c	-5.90	-2.40	7.16	711.752	705.99	675.28	134.632	1.90	95.33	3	14
d	-5.88	-2.35	8.14	653.672	636.07	611.25	128.242	1.83	90.13	3	13
e	-5.91	-3.04	8.94	668.643	632.71	606.19	160.470	1.83	89.87	3	15
f	-5.93	-3.16	9.81	713.640	659.33	627.96	199.918	1.86	91.66	3	18
g	-5.91	-2.40	5.76	658.091	622.40	597.76	121.789	1.81	89.04	3	12
h	-5.91	-2.43	7.16	702.542	626.42	602.22	121.203	1.82	89.40	3	12
i	-5.91	-2.46	9.75	648.656	628.04	603.83	136.858	1.82	89.54	3	13
j	-5.66	-3.96	8.87	637.673	609.29	599.56	120.940	1.77	89.61	3	12

TABLE-3
PEARSON'S CORRELATION FOR SELECTED CALCULATED MOLECULAR DESCRIPTORS

	IC_{50}	E_{HOMO}	PSA	VOL	E_{LUMO}	DM
IC_{50}	1.000					
E_{HOMO}	0.544	1.000				
PSA	0.191	-0.435	1.000			
VOL	-0.356	-0.239	0.229	1.000		
E_{LUMO}	-0.677	-0.763	-0.203	0.268	1.000	
DM	0.312	0.098	0.587	-0.012	-0.455	1.000

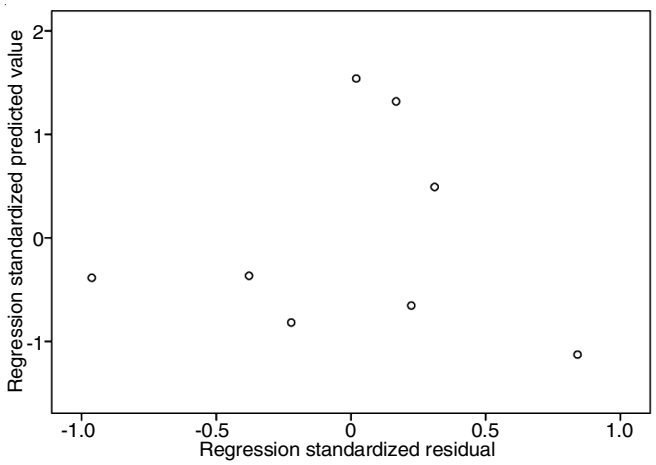


Fig. 2. Standardized predicted value against standardized residual (MLR)

Molecular docking analysis: The employed docking method was validated by re-docking the native ligand into the active gouge of MCF-7 (PDB ID: 4xo6) in order to observe the similarity between the re-docked ligand with best conformation to the posture of the native molecule (Fig. 3). Therefore, the observed similarity and the root mean square deviation (RMSD) between the re-docked native molecule and the native ligand were nearer to 1; hence, this proved the dependability of the molecular docking method used. Therefore, the studied compounds were subjected to docking study so as to observe the non-bonding interaction between the studied 1,2,4-thiadiazole-1,2,4-triazole derivatives and 3α-hydroxy-steroid dehydrogenase type 3 (PDB ID: 4xo6). It was observed that three compounds (**b**, **e** and **g**) acted better than the standard (etoposide) as shown in Table-1. This showed that the addition of 3,4,5-trimethoxy (compound **b**), 4-nitro (compound **e**) and 4-chloro (compound **g**) enhanced the activity of the studied parent compound and helped it biological activity than etoposide (standard). As show in Table-1, compound **g** possesses better ability to inhibit than other studied compounds as well as the standard (etopiside) (Fig. 4). The residues and the type non-bonding interaction involve in the studied interactions are shown in Table-4.

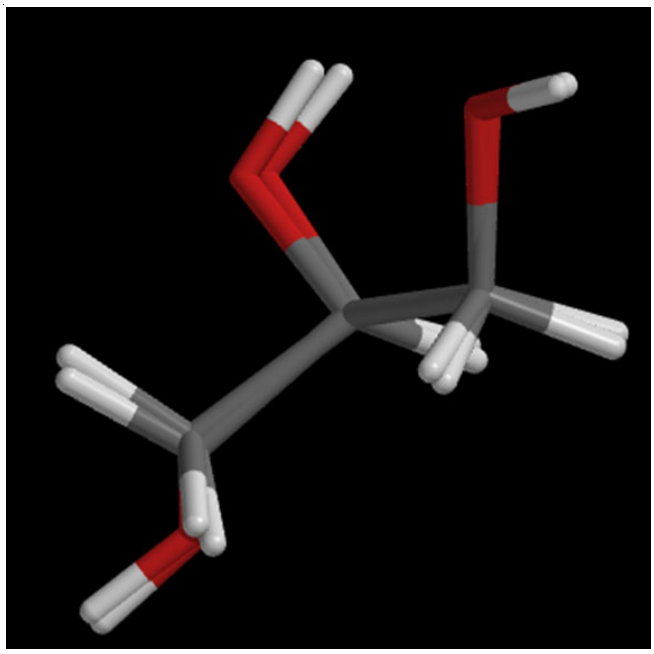


Fig. 3. Overlay of native drug-like compounds over re-docked drug compound

ADMET properties of selected compounds describing the anti-breast cancer activities of 2,4-thiadiazole-1,2,4-triazole derivatives: The ADMET properties investigated were blood-brain barrier, human intestinal absorption, Caco-

TABLE-4
RESIDUES INVOLVED IN THE INTERACTION

	Residues involved in the interactions	Types of Non-bonding interaction involved
a	ASN-105, ARG-101, HIS-53, VAL-128, ALA-27, GLU-224, TRP-227, TRP-86, VAL-54	Conventional hydrogen bond, Pi-Cation, Pi-Sigma, Pi-Pi, Pi-Alkyl
b	LYS-131, LEU-306, HIS-222, TYR-216, TYR-55, TYR-24, TRP-227, VAL-54, VAL-128	Conventional hydrogen bond, Carbon hydrogen bond, Pi-Sigma, Pi-Pi Stacked, Pi-Pi T-Shaped, Pi-Alkyl
c	PRO-30, GLU-28, PRO-26, LYS-270, HIS-222, SER-221, LEU-219, LEU-236, VAL-29	Van der waals, Conventional hydrogen bond, Carbon hydrogen bond, Pi-Cation, Pi-Anion, Pi-Sigma, Amide-Pi Stacked, Pi-Alkyl
d	TRP-227, PRO-226, TYR-24, TRP-86, ARG-101, ASN-105, ASN-56, VAL-128, HIS-53, GLU-224, ALA-27	Conventional hydrogen bond, Carbon hydrogen bond, Pi-Cation, Pi-Anion, Pi-Donor Hydrogen bond, Pi-Sigma, Pi-Pi T-Shaped, Pi-Alkyl
e	VAL-128, ALA-27, VAL-54, TYR-54 LEU-306, HIS-222, TYR-55, ASP-50	Carbon hydrogen bond, Pi-Cation, Pi-Pi Stacked, Pi-Pi T-Shaped, Pi-Alkyl
f	ASN-56, LYS-31, VAL-54, VAL-128, ILE-129. LYS-131	Conventional hydrogen bond, Unfavourable Acceptor-Acceptor, Pi-Sigma, Pi-Alkyl
g	VAL-29, PRO-26, TYR-24, HIS-222, HIS-117, ASN-167, TYR-216, SER-221, LEU	Conventional hydrogen bond, Carbon hydrogen bond, Pi-Cation, Pi-Sigma, Pi-Pi Stacked, Pi-Pi T-Shaped, Amide-Pi Stacked, Alkyl, Pi-Alkyl
h	ASP-112, PHE-15, CYS-7, LYS-4, GLN-6, TYR-5, ASP-78, GLU-77, ILE-79	Conventional hydrogen bond, Pi-Anion, Pi-Sulfur, Pi-Pi Stacked, Pi-Pi T-Shaped, Pi-Alkyl
i	ILE-42, ASP-2, GLN-6, VAL-281, GLU-285, GLN-282, LYS-249, ARG-250	Conventional hydrogen bond, Carbon hydrogen bond, Unfavourable Acceptor-Acceptor, Pi-Cation, Pi-Anion, Pi-Sigma.
j	PHE-284, LYS-4, TYR-5, CYS-7	Conventional hydrogen bond, Pi-sulfur, Pi-Pi Stacked, Pi-Alkyl
Etoposide	LEU-219, HIS-222, SER-221, ASN-280, GLN-279, PRO-252, ARG-276, LYS-270	Van der waals, Conventional hydrogen bond, Amide-Pi Stacked, Alkyl, Pi-Alkyl

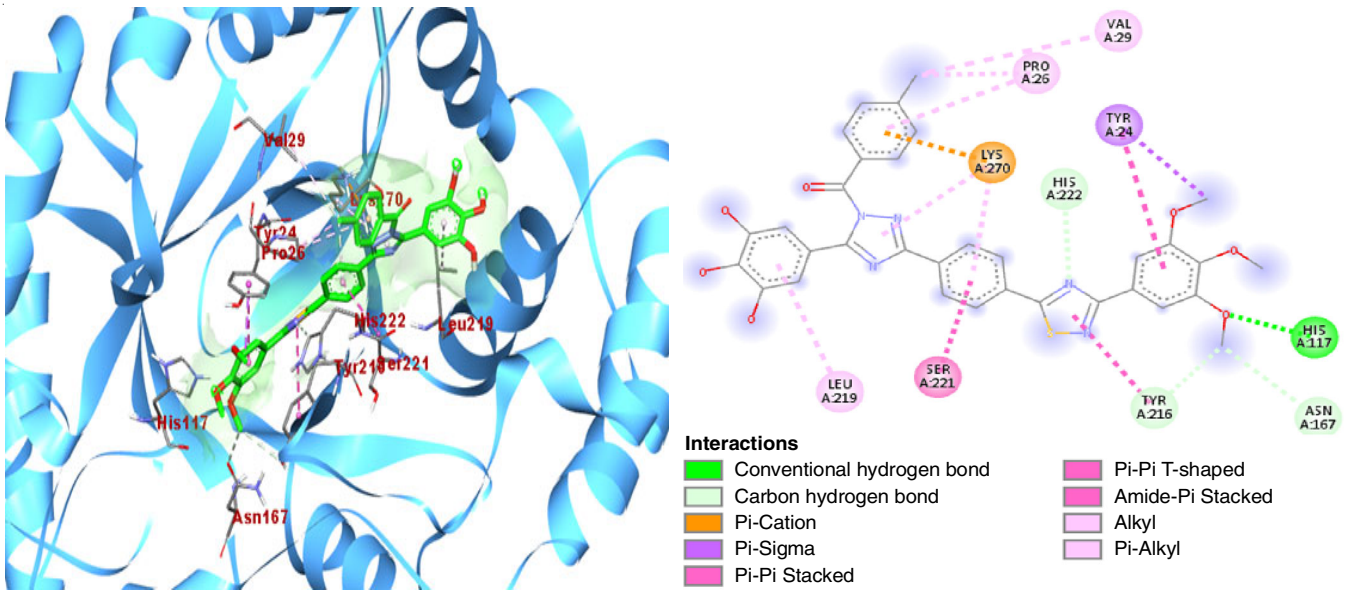


Fig. 4. Residual interactions between compound **g** and 3α-hydroxysteroid dehydrogenase type 3

2 permeability, P-glycoprotein substrate, P-glycoprotein inhibitor, renal organic cation transporter, subcellular localization, CYP450 2C9 substrate, CYP450 2D6 substrate, CYP450 3A4 substrate, CYP450 1A2 inhibitor, CYP450 2C9 inhibitor, CYP450 2D6 inhibitor, CYP450 2C19 inhibitor, CYP450 3A4 inhibitor, CYP inhibitory promiscuity, human Ether-a-go-go-Related gene inhibition, AMES toxicity, carcinogens, fish toxicity, tetrahymena pyriformis toxicity, honey bee toxicity and biodegradation. It was discovered that the selected compounds have better tendency to be absorbed in human intestine that the standard used, since higher human intestinal absorption value denote better efficiency in human intestinal absorption of drug. The obtained blood brain barrier value for the selected compounds were within the same range as shown in Table-5 and the calculated P-glycoprotein (non-inhibitor) for the selected compounds was similar to etoposide

TABLE-5
PREDICTED ADMET PROPERTIES OF SELECTED COMPOUNDS THAT DESCRIBE ANTI-BREAST CANCER ACTIVITIES OF 2,4-THIADIAZOLE-1,2,4-TRIAZOLE DERIVATIVES

Mode	Compound **b**		Compound **e**		Compound **g**		Etoposide	
	Result	Probability	Result	Probability	Result	Probability	Result	Probability
Blood-Brain Barrier	BBB-	0.8074	BBB-	0.7977	BBB-	0.8024	BBB-	0.9609
Human intestinal absorption	HIA+	0.9697	HIA+	0.9577	HIA+	0.9759	HIA+	0.8360
Caco-2 permeability	Caco2-	0.5584	Caco2-	0.5653	Caco2-	0.5739	Caco2-	0.5234
P-glycoprotein substrate	Non-substrate	0.5730	Non-substrate	0.6280	Non-substrate	0.5769	Substrate	0.7019
P-glycoprotein Inhibitor	Non-inhibitor	0.8444	Non-inhibitor	0.7827	Non-inhibitor	0.8835	Non-inhibitor	0.8005
	Non-inhibitor	0.9355	Non-inhibitor	0.9304	Non-inhibitor	0.9264	Non-inhibitor	0.8381
Renal organic cation transporter	Non-inhibitor	0.9289	Non-inhibitor	0.9481	Non-inhibitor	0.9217	Non-inhibitor	0.8412
Subcellular localization	Mitochondria	0.6911	Mitochondria	0.6466	Mitochondria	0.6636	Mitochondria	0.7431
CYP450 2C9 Substrate	Non-substrate	0.5491	Non-substrate	0.5668	Non-substrate	0.5607	Non-substrate	0.8228
CYP450 2D6 Substrate	Non-substrate	0.8107	Non-substrate	0.8171	Non-substrate	0.8146	Non-substrate	0.9116
CYP450 3A4 Substrate	Non-substrate	0.5091	Substrate	0.5087	Substrate	0.5373	Substrate	0.6134
CYP450 1A2 Inhibitor	Non-inhibitor	0.6233	Non-inhibitor	0.6687	Non-inhibitor	0.6540	Non-inhibitor	0.9045
CYP450 2C9 Inhibitor	Non-inhibitor	0.5298	Inhibitor	0.5234	Inhibitor	0.5759	Non-inhibitor	0.6884
CYP450 2D6 Inhibitor	Non-inhibitor	0.8561	Non-inhibitor	0.8407	Non-inhibitor	0.8532	Non-inhibitor	0.8392
CYP450 2C19 Inhibitor	Non-inhibitor	0.6182	Non-inhibitor	0.5223	Inhibitor	0.5061	Non-inhibitor	0.5290
CYP450 3A4 Inhibitor	Non-inhibitor	0.6886	Inhibitor	0.6075	Non-inhibitor	0.7196	Non-inhibitor	0.8309
CYP inhibitory promiscuity	Low CYP Inhibitory Promiscuity	0.6130	High CYP Inhibitory Promiscuity	0.7338	High CYP Inhibitory Promiscuity	0.5337	High CYP Inhibitory Promiscuity	0.5576
Human ether-a-go-go-related gene inhibition	Weak inhibitor	0.9970	Weak inhibitor	0.9923	Weak inhibitor	0.9958	Weak inhibitor	0.9847
	Non-inhibitor	0.5938	Non-inhibitor	0.5838	Non-inhibitor	0.5527	Non-inhibitor	0.8734
AMES Toxicity	Non AMES toxic	0.6289	Non AMES toxic	0.5139	Non AMES toxic	0.6404	Non AMES toxic	0.9132
Carcinogens	Non-carcinogens	0.8472	Non-carcinogens	0.8055	Non-carcinogens	0.7730	Non-carcinogens	0.9325
Fish toxicity	High FHMT	0.9850	High FHMT	0.9864	High FHMT	0.9954	High FHMT	0.9815
Tetrahymena pyriformis toxicity	High TPT	0.9880	High TPT	0.9904	High TPT	0.9942	High TPT	0.9918
Honey bee toxicity	Low HBT	0.7149	Low HBT	0.7298	Low HBT	0.7717	High HBT	0.6868
Biodegradation	Not ready biodegradable	0.9565	Not ready biodegradable	0.9789	Not ready biodegradable	0.9947	Not ready biodegradable	0.9467

(Standard). Also, the selected 1,2,4-thiadiazole-1,2,4-triazole derivatives were observed not to be carcinogenic and this was similar to the reported obtained for the standard used. Furthermore, the observed cytochrome P450 revealed that it could be inhibited by some of the selected 1,2,4-thiadiazole-1,2,4-triazole derivatives.

Conclusion

In summary, the anti-breast cancer properties of 1,2,4-thiadiazole-1,2,4-triazole derivatives were studied *via* density functional theory method, Gretl software (QSAR model), docking software (Pymol, Autodock Tool, Auto dock vina and discovery studio) and Gromacs for molecular dynamics simulation. The calculated descriptors obtained from optimization of 1,2,4-thiadiazole-1,2,4-triazole derivatives were screened and the selected descriptors were used to develop efficient QSAR model for effective prediction. The predicted IC_{50} by MLR and ANN were observed to be closer to the experiment al IC_{50}. However, the prediction made by ANN was observed to be closer to the experimental inhibition concentration (IC_{50}) than the prediction made by MLR. The non-bonding interaction between the studied ligands and 3α-hydroxysteroid dehydrogenase type 3 (PDB ID: 4xo6) were investigated and it was observed that compound **g** possess better inhibiting ability to inhibit 3α-hydroxysteroid dehydrogenase type 3 than other studied compounds. Hence, the developed QSAR model will help in developing effective drug molecules.

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