Inhibiting Activity of 1,2,3-Triazole-Pyrimidine-Urea Hybrids Against Esophageal Cancer: Theoretical Approach

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Abstract - 29 derivatives of 1,2,3-Triazole-Pyrimidine-Ureawere investigated for anti- Esophageal Cancer activities. Several molecular descriptors such as E_{HOMO}(eV), E_{LUMO} (eV), dipole moment (Debye), log P, molecular weight (amu), HBA, HBD, Vol and Ovality were obtained from the optimized compounds via B3LYP/6-31+G*. In addition, the QSAR model was developed using Gretl software and series of statistical analysis were calculated. The developed QSAR model was predictive and this was proved via Table 1. Furthermore, molecular docking study was executed with Esophageal cancer cell line (PDB ID: 2leo); it was observed that A17 with binding energy of -9.1 kcal/mol possess ability to inhibit than other studied compounds.

Keywords: 1,2,3-triazole-pyrimidine hybrids, DFT, QSAR, Molecular docking

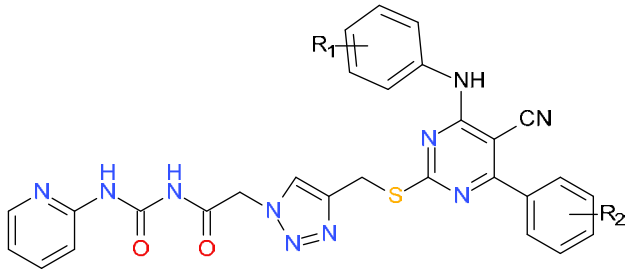
1. Introduction

Esophageal cancer as a deadly type of cancer remains one of the top five (5) severest cancers worldwide [1]. Yubin *et al*., 2019 and Fichter *et al*., 2014 reported that esophageal squamous-cell carcinoma and esophageal adenocarcinoma are the major two types of esophageal cancer [2,3]. Esophageal cancer can be influenced by the following factors: genetics, body composition, obesity and ethnicity. Also, several factors that are lifestyles-based like smoking, diet, taking of alcohol as well as ecological factors such as disclosure to chemical compounds can be responsible for the cause of esophageal cancer [4,5]. The treatment for esophageal cancer remain poor and the cure for this malignant disease is still a serious threat to medicinal world [6,7].

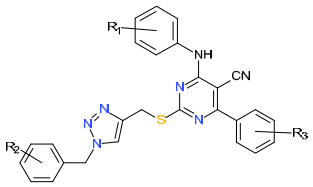
The role played by heterocycles in drug design and development is very important. 1,2,3-Triazole-Pyrimidine-Urea Hybrids comprises of two active parent structures i.e. triazole and pyrimidine. Triazole derivatives and pyrimidine derivatives have been reported to have several biological activities such as antimicrobial [8, 9], anticancer [10], antioxidant [11], anti-inflammatory [12, 13], diuretics [14] and analgesics [15, 16]. Thus, the effectiveness of both triazole and pyrimidine have drawn the attention of researchers to their as hybrids for more effectiveness.

Moreover, seventeen molecular compounds (**A1**-**A17**)obtained from Ma *et al.,* 2015 and twelve compounds (A18-A29) gotten from the work done by Ma et al., 2014 were matched together for the purpose of this study (Figure 1) [17-18]. The selected compounds were shown in Figure 1.

Thus, this research is aimed at developing operational QSAR models via multiple linear regression (MLR) method using obtained molecular descriptors from 1,2,3-triazole-pyrimidine hybrids and also examine the non-bonding relationship between 1,2,3-triazole-pyrimidine Hybrids and Esophageal cancer cell line(**PDB ID: 2leo**) [19] via molecular docking.



Compounds	R_1	R_2
A1	*p*-Cl	*p*-$CH(CH_3)_2$
A2	*m*-Cl	*p*-$CH(CH_3)_2$
A3	*m*-NO2	*p*-$CH(CH_3)_2$
A4	*o*-F	*p*-$CH(CH_3)_2$
A5	*p*-OCH3	*p*-$CH(CH_3)_2$
A6	*p*-CH3	*p*-$CH(CH_3)_2$
A7	*o*-CH_3	*p*-$CH(CH_3)_2$
A8	*m*-CH_3	*p*-$CH(CH_3)_2$
A9	*o*-OCH_3	*p*-$CH(CH_3)_2$
A10	*o*-OH	*p*-$CH(CH_3)_2$
A11	*p*-$CH(CH_3)_2$	*p*-$CH(CH_3)_2$
A12	*p*-$CH(CH_3)_2$	*p*-CH_3
A13	*p*-OCH_3	*p*-CH_3
A14	*o*-OCH_3	*p*-CH_3
A15	*p*-CH_3	*p*-Br
A16	*m*-CF_3	*p*-Br
A17	*p*-CH_3	*p*-Cl



	R_1	R_2	R_3
A18	*p*-OCH_3	*o*-Cl	H
A19	*p*-Cl	*o*-Cl	H
A20	*o*-OCH_3	*o*-Cl	H
A21	*m*-CH_3	*o*-Cl	H
A22	*o*-CH_3	*o*-Cl	H
A23	*o*-Cl	*p*-CH_3	H
A24	*p*-CH_3	*o*-Cl	*p*-$CH(CH_3)_2$
A25	o-OCH3	*o*-Cl	*p*-$CH(CH_3)_2$
A26	*p*-CH3	*o*-Cl	p-CH_3
A27	*p*-CH3	*o*-Cl	*m,p,m*-triOCH_3
A28	*p*-CH3	*o*-Cl	*p*-Cl
A29	*p*-CH3	*o*-Cl	*p*-Br

Figure 1: The schematic structures of 1,2,3-Triazole-Pyrimidine-Urea Hybrids derivatives

2. Methodology

Optimization of 1, 2, 3-triazole-pyrimidine derivatives using Density functional theory method at B3LYP with 6-31+G* as basis set was calculated in water using Spartan 14 software [20]. The descriptors obtained from the optimization of the studied compounds were used for QSAR development in order to predict the inhibition concentration (IC_{50}) of the studied compounds. The obtained descriptors are E_{HOMO}, E_{LUMO}, band gap (eV), Ovality, dipole moment (Debye), log P, and molecular weight (amu). The developed QSAR model for multiple linear regression was achieved by using Gretl [21].

Furthermore, the developed QSAR model was validated by calculating squared correlation coefficient (R^2), cross validation ($CV.R^2$) (equation 1), adjusted squared correlation coefficient R^2_{adj},(equations 2) and p-value [22]. More so, docking study with accurate distance and dimension were observed to study the non-bonding interaction between the studied ligands and receptor.

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

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

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

3. Results and Discussion

3.1. DFT and QSAR Studies

The optimization of 29 sets of 1,2,3-Triazole-Pyrimidine-Urea Hybrids generated series of effective molecular descriptors which were used in the development of quantitative structural activities relationship model as shown in equation 3. As shown in Table 1, the comparison between the predicted inhibition concentration and the observed inhibition concentration proved the effectiveness of the developed QSAR model.

According to Eslam *et al*., 2014 and Oyebamiji *et al*., 2016, a developed QSAR model can be considered predictive when the calculated squared correlation (R^2) is greater than 0.5; therefore, the developed QSAR model is predictive (Equation 3) [23, 24]. The model developed in this work was also validated by considering many statistical analysis such as cross validation ($CV.R^2$) (Standard ≥ 0.5), adjusted squared correlation (R^2_a) (Standard ≥ 0.6), F value, P-value. The calculated $CV.R^2$ and R^2_a proved that the model developed possesses the ability to predict well since they are greater than the standard. More so, the calculated F and P-values showed the prognostic ability of the developed QSAR model.

IC_{50} = 28.7486 -5.02708 (E_{LUMO}) -0.0560142(Vol) + 3.11803(HBD) + 0.00190041(Energy)----------(3)

N= 29, F = 13.70, P < 0.0001, R^2 = 0.695, R^2_{adj} = 0.644, C.VR^2 = 0.898, MSE = 9.568

Table 1: Observed IC_{50} and predicted IC_{50}

	Observed IC_{50}	Predicted IC_{50}	Residual
1	11.17	7.61	3.56
2	13.26	7.61	5.65
3	31.31	31.34	-0.03
4	15.51	8.69	6.82
5	5.42	7.32	-1.90
6	6.70	8.05	-1.35
7	7.23	7.68	-0.45
8	7.32	8.10	-0.78
9	8.96	7.68	1.28
10	7.38	11.55	-4.17
11	2.49	5.81	-3.32
12	7.45	8.11	-0.66
13	5.87	9.62	-3.75
14	7.85	9.60	-1.75
15	7.92	6.13	1.79
16	2.96	4.75	-1.79
17	13.07	10.12	2.95
18	7.96	8.31	-0.35
19	1.42	8.69	-7.27
20	9.67	8.73	0.94
21	15.57	9.08	6.49
22	9.74	9.19	0.55
23	11.22	9.41	1.81
24	5.08	5.63	-0.55
25	3.58	5.32	-1.74
26	4.65	7.88	-3.23
27	5.85	3.89	1.96
28	7.54	7.73	-0.19
29	3.09	3.61	-0.52

3.3. Molecular Docking

The tendency of molecular compounds to inhibit receptor can be calculated using docking method [25]. According to Oyebamiji *et al*., 2019, ligand-receptor interaction with lowest binding affinity describes the molecules with propensity to inhibit the studied receptor [25]. As shown in Table 2, compound 17 with lowest binding affinity is agreed to inhibit more than other studied compounds and the residues involved in the interaction were displayed in Figure 2 as well as the complex form between compound 17 and Esophageal cancer cell line **(2leo)** was presented in Figure 2.

Table 2: Interactions between 1,2,3-Triazole-Pyrimidine-Urea Hybrids Derivatives and receptor (2leo)

	Scoring **(kcal/mol)**
A1	-8.1
A2	-7.7
A3	-8.5
A4	-8.2
A5	-8.6
A6	-8.3
A7	-8.2
A8	-7.5
A9	-8.0
A10	-7.4
A11	-7.7
A12	-8.9
A13	-8.5
A14	-7.9
A15	-8.2
A16	-7.2
A17	-9.1
A18	-6.9
A19	-8.2
A20	-6.7
A21	-8.1
A22	-7.1
A23	-6.9
A24	-8.5
A25	-7.4
A26	-7.7
A27	-7.6
A28	-8.4
A29	-8.4

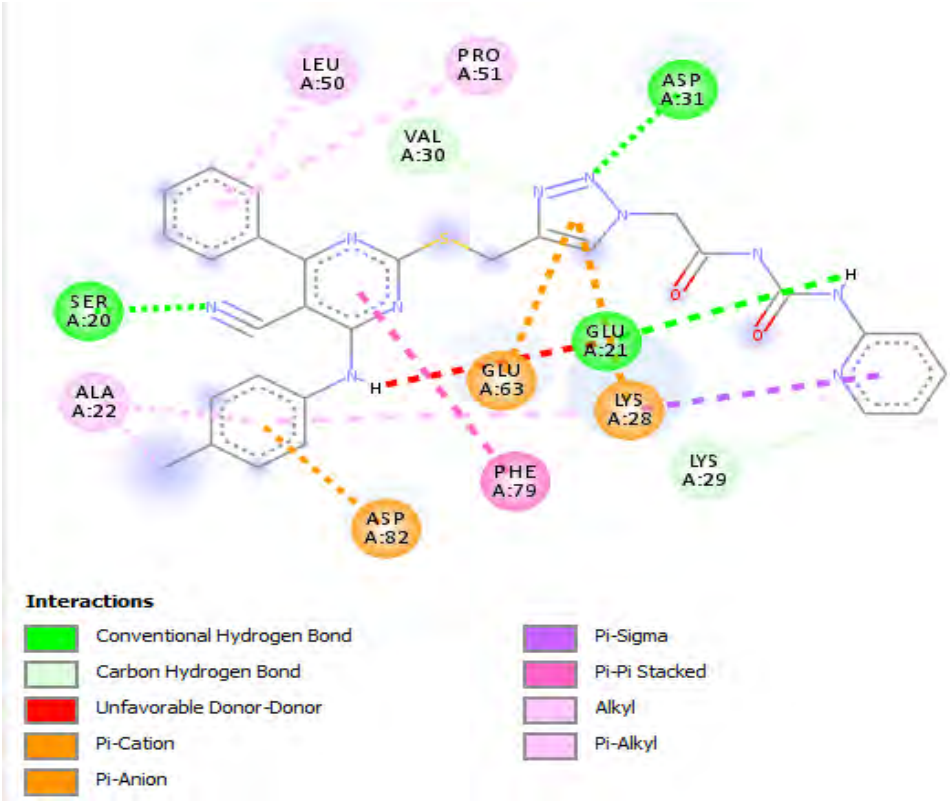


Figure 2: Interactions of **A17** with the residue in the active gouge of esophageal cancer cell line (2leo).

4. Conclusion

Biological activity of derivatives of1,2,3-triazole-pyrimidine-urea hybridswere investigated via calculation of electronic descriptors using density functional theory method via 6-31+G(d,p) basis set, development of QSAR model to predict the cytotoxicity of the observed inhibition concentration and observation of the interactions between the studied ligands and the receptor. Molecular descriptors obtained from the optimized molecular compounds, which processes anti- Esophageal cancer properties were selected for QSAR studies. In addition, the developed QSAR model was prognostic and the observed non-bonding interaction revealed the studied compound with highest binding affinity to the receptor. Thus, compound **A17** inhibited more effectively than other compounds.

Reference

[1] Z. Fengli, and Z. Mei.Oleuropein inhibits esophageal cancer through hypoxic suppression of BTG3 mRNA. Food & Function,2019, 10(2):978-985. doi: 10.1039/c8fo02223b.DOI: 10.1039/c8fo02223b.
[2] J.Yubin, L.Yichen, X.Nina, D.Tingting, W.Liyuan, H.Rui, L.Ling, Y.Chunhongand C.Xiaoguang.Cryptotanshinone inhibits esophageal squamous-cell carcinoma in vitro and in vivo through the suppression of STAT3 activation. OncoTargets and Therapy, 2019, 12: 883–896.
[3] C.D.Fichter, V.Gudernatsch, C.M.Przypadlo, et al. ErbB targeting inhibitors repress cell migration of esophageal squamous cell carcinoma and adenocarcinoma cells by distinct signaling pathways. J Mol Med. 2014, 92(11):1209–1223.
[4] F.L.Huang and S.J.Yu. Esophageal cancer: Risk factors, genetic association, and treatment, Asian J. Surg 2018, 41: 210–215.
[5] Y.Lin, Y.Totsuka, B.Shan, C.Wang, W.Wei, Y.Qiao, S.Kikuchi, M.Inoue, H.Tanaka. and Y. He.Esophageal cancer in high-risk areas of China: research progress and challenges, Ann. Epidemiol.2017, 27: 215–221.
[6] W.Chen Cancer statistics: updated cancer burden in China. Chin. J. Cancer Res. =Chung-kuo yen cheng yen chiu. 2015, 27: 1
[7] S.Ohashi et al. Recent advances from basic and clinical studies of esophageal squamous cell carcinoma. Gastroenterology 2015;149: 1700–1715.
[8] N.K.Basu,F.LRose. S-triazolopyridazines: synthesis as potential therapeutic agents. J. Chem. Soc., 1963, 5660.
[9] M.A.El-Dawy, A.B.Hozzoa. Potential Broad Spectrum Anthelmintics IV: Design, Synthesis, and Antiparasitic Screening of Certain 3,6-Disubstituted- (7H) -s -triazolo- [3,4-b][1,3,4]thiadiazine Derivatives. J. Pharm Sci., 1983,72: 45.
[10] A.Mishra, K.Srivastava, R.Tripathi, S.K.Puri, S.Batra. Search for new pharmacophores for antimalarial activity. Part III: synthesis and bioevaluation of new 6-thioureido-4-anilinoquinazolines. Eur. J. Med. Chem., 2009, 44: 4404e4412.
[11] J.Wu, L.Hu, Y.Du, F.Kong, Y.Pan. Prognostic role of LSD1 in various cancers: evidence from a meta-analysis.OncoTargetsTher., 2015, 8: 2565e2570
[12] F.Lazrak, E.M. Essassi, Y.KandriRodi,K.Misbahi,M.Pierrot. Synthese De Nouveaux Systemes Condenses Renfermant Le 1,2,4-Triazole, La 1,3-Thiazine, La 1,3-Thiazepine Et La 1,3,5,7-Dithiadiazocine.Phosphorus, Sulfur, and Silicon, 1792, 004: 1799-1808.
[13] F.Lazrak, N.H.Ahabchane, A.Keita, E.M.Essassi, M.Pierrot. Synthesis and crystal structure of 3-methoxycarbonyl-5-methyl-1-p-tolyl-1,2,4-triazolo [3,4-c]-1,2,4-triazole. Indian Journal of Chemistry – Section B Organic and Medicinal Chemistry, 2002,41(4): 821-825.
[14] H.Kumar,A.S.Javed,A.S.Khan,M.Amir.1,3,4-Oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid: synthesis and preliminary evaluation of biological properties. Eur J Med Chem, 2008, 43: 2688-2698.

[15] R.Gupta, A.KGupta, S.Paul. 1,3,4-Oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid: synthesis and preliminary evaluation of biological properties. Indian J. Chem., Sect. B, 2000,39: 847.
[16] MTMEl Wassimy, M.Abdel-Rahman, A.B.A.G.Ghattas, OAAAbdallah. Synthesis and reactions of n-chloromethyl-1,2,4-triazoles with sulfur and oxygen nucleophiles. Phosphorus, Sulfur& Silicon, 1992, 70: 99-108.
[17] M.Li-Ying, W.Bo, P.Lu-Ping, Z.Miao, W.Sai-Qi, Z.Yi-Chao, S.Kun-Peng, X.Deng-Qi, L.Hong-Min. Design and synthesis of novel 1,2,3-triazole-pyrimidine-urea hybrids as potential anticancer agents.Bioorganic & Medicinal Chemistry Letters, 2015, doi:http://dx.doi.org/10.1016/j.bmcl.2014.12.087.
[18] M.Li-Ying, P.Lu-Ping, W.Bo, Z.Miao, H.Biao, X.Deng-Qi,S.Kun-Peng, Z.Bao-Le, L.Ying, Z.En, L.Hong-Min. Design and synthesis of novel 1,2,3-triazole-pyrimidine hybrids as potential anticancer agents. European Journal of Medicinal Chemistry,2014, doi: 10.1016/j.ejmech.2014.08.010.
[19] Y.Feng, Y.Geng, T.Zhou, J.Wang.NMR structure note: human esophageal cancer-related gene 2.J.Biomol.Nmr. 2012,53: 65-70.
[20] Spartan 14, Wave function, INC, Irvine, CA (2015).
[21] http://gretl.sourceforge.net/
[22] M.Ghamali, S.Chtita, A.Ousaa, B.Elidrissi, M.Bouachrine, T.Lakhlifi,QSAR analysis of the toxicity of phenols and thiophenols using MLR and ANN.Journal of Taibah University for Science,2017, 11: 1-10.
[23] P. Eslam,A.Reza, R.G.Mohammad, N.Parviz, S.Javad. QSAR study of ACK1 inhibitors by genetic algorithm–multiple linear regression (GA–MLR). Journal of Saudi Chemical Society,2014, 18: 681–688.
[24] K.A.Oyebamiji and B.Semire,Studies Of 1, 4-Dihydropyridine Derivatives For Anti-Breast Cancer (MCF-7) Activities: Combinations Of DFT-QSAR And Docking Methods. New York Science Journal, 2016, 9(6).
[25] A.K.Oyebamiji and B.B.Adeleke. Theoretical Bio-significance Evaluation of Quinazoline Analogues, International Research Journal of Pure & Applied Chemistry, 2019, 18(1): 1-8.