A DFT-Based QSAR and Molecular Docking Studies on Potent Anti-Colon Cancer Activity of Pyrazole Derivatives

Abel Kolawole Oyebamiji[1]

[1] Ladoke Akintola University of Technology

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Abstract

Pyrazolederivatives have been described as a group of compounds with various biological activities including anticancer effect. Therefore, a set of twenty Pyrazole based compounds which had been previously shown to be active against human colon cancer cell (HT29) are use in the study. These compounds were optimized using Density Functional Theory (DFT) for the calculations of molecular descriptors that related the bioactivity of these compounds to their structures. The developed quantitative structure activity relation (QSAR) was validated, and it showed the reliability and acceptability of the model. The in silico simulations were carried out on the twenty Pyrazole based compounds with colon cancer cell line, HT29 (PDB ID: 2N8A) using Autodock vina software. The docked complexes were validated and enumerated based on the AutoDock Scoring function to pick out the best inhibitors based on docked Energy. The analysis of the ligand-receptor complexes showed that H-bonds played a prominent role in the binding and posed stability of the ligand in the ligandreceptor complexes. The binding free energy, Î?”G calculated ranged from - 6.10 kcal/mol â??” 8.20 Kcal/mol.

Index terms— pyrazole derivatives, DFT-QSAR, molecular docking.

1 Introduction

ancer is not a contagious neither infectious disease, but it has become a second leading cause of death worldwide and travels from one end to the other via bloodstream within the body system 1,2 . It can be caused by both external and internal factors, e.g. tobacco, infectious organisms, chemicals, and radiation are for outside while inherited mutations, hormones, and immune conditions for internal factor. Moreover, all of these factors may work together or in series to start or enhance carcinogenesis 3 . The cure for cancer remain surgery, chemotherapy and radiation therapy and adult, as well as, children can be affected. However, cases of children having cancer are limited 4 .

Colon cancer as a worldwide known health problem forays more than a million people every year, which has been the cause of death to over 600,000 people 5 . It is found to be the usual cause of death in comparison to other types of cancer that exist **??**,7 . Several features that may cause an increment in colon cancer risks comprise diet, diabetes, aging, obesity, genomic instability, etc. Over the last half-century, the United States Food and Drug Administration (USFDA) has approved more than one hundred drugs for clinical treatment of cancers. Nevertheless the search for new and/or improved chemical compounds as potential anticancer agents continues with the hope that better efficacy and more manageable adverse side effects of pharmaceutical drugs may be achieved. Molecular modeling, screening and mimicking of natural compound derivatives have been among several drug discovery approaches to rationally design and modified structures that may confer a better therapeutic index 8 or that can cure cancer in the human race 9 .

Among such compounds are pyrazole and its derivatives, pyrazoles are class of heterocyclic compounds used for the development of drugs, and they have attracted the attention of several researchers due to their extensive biotic actions such as anticancer 10 , antifungal 11 , antiviral 12 , antiinflammatory 14,15 . More so, pyrazole derivatives

such as Pyrazolopyrimidine and pyrazolo [4,3-d]pyrimdin-7-one perform some pharmacological activities which can never be put aside in the medical world, for example as antihypertensive 15 , antiviral 16,17 , tuberculostatic 18 , herbicidal agents 19 , antileishmanial 20 and treatment of heart diseases 21 . Therefore, the structural features of the Pyrazoles have been recognized as vital parameters due to their bioactivity as therapeutic aids. Several pyrazoles have been commercialized such as omeprazole, Albendazole, mebendazole, candesartan, telmisartan, astemizole [22][23][24] .

Quantitative Structural Activity Relationship (QSAR) as a statistical model embroils the relationship between physicochemical parameters of a chemical compound to its biological activity 25 . It has attracted vast usefulness for linking molecular evidence with biotic activities and many other physicochemical properties as well as its helpfulness for drug design, discovery, and development 26 . QSAR helps in the prediction of toxicity of materials in bulk system, for instance, drug-like compounds and are very useful in case of the classic chemicals [27][28][29][30] .

The use of molecular descriptors calculated from quantum chemical methods for development of QSAR models has been described to be sufficient for generating comprehensive QSAR. Thus the use of quantum chemical descriptors has countless potential [31][32][33][34] .

Molecular docking studies divulge information on the interaction between the drug-like compound known as a ligand and an enzyme/receptor through recognizing the active positions within the enzyme along with the binding energy calculation 34 . In molecular docking, scoring is a statistical way of predicting the strength of the interactions which are non-covalent in between a ligand and a receptor. Therefore, the calculations of interaction energy can be offered in the form of "dock score" 35 .

Consequently, in this research, twenty pyrazole derivatives with known anti-colon cancer activities 21 as displayed in Figure **??** were optimized using Density Functional Theory (DFT) method so as to obtain molecular descriptors for the compounds. These **??** b). Thus, the major objectives of this work are: (i) to calculate molecular descriptors with the use of quantum chemical method via Density Functional Theory (DFT), (ii) to develop QSAR model which probe into biological activity of the studied compounds, and (iii) to calculate the free energy of interactions (binding affinity, Î?"G) of the ligand with the receptor in the binding site through molecular docking.

Figure **??**: The schematic structures of the pyrazole derivatives, the compounds were numbered as used in [20] II.

2 Computational Details a) Ligand optimization and molecular descriptors

The equilibrium geometries for the twenty optimized at Density Functional Theory (DFT). The use of DFT method entails three-parameter density functional, which comprises Becke's gradient exchange correction 37 and the Lee, Yang, Parr correlation functional (i.e., B3LYP) 38 . The accuracy of DFT calculations depends on the particular functional chosen and basis sets. However, 6-31G** basis set has been found to be appropriate for the confirmation search and calculation of drug-like compounds 39 . Therefore 6-31G** basis set was used in this work. Also, the optimized compounds were used to calculate molecular parameters/descriptors that described the bioactivity (IC 50) of the compounds. The optimized molecular structures were used for the docking study to estimate the binding affinity of the compounds to the colon cancer cell line, HT29 receptor (PDB ID: 2N8A). The optimization of the compounds was carried out using quantum chemical software Spartan '14 by wavefunctionInc 40 . (S = 1/?) eV -1 Electro negativity [µ = 1/2 (E HOMO -E LUMO)] eV Nucleophilicity (? = µ 2 /2?) eV DM P HOMO LUMO SE (N+N)/2 BD ? S µ ?

3 b) Data processing and QSAR modeling

Furthermore, the chosen calculated parameters were engaged to develop quantitative structure-activity relationship (QSAR) model to link the bioactivity to the calculated molecular descriptors obtained from the studied compounds 41 . This was achieved using multiple linear regression (MLR) method which is a recurrent statistical technique used in developing QSAR model. MLR and correlation analyses were carried out by the statistics software SPSS 13.0 version. Before MLR analysis, the person correlation table was used to examine collinearity among the descriptors (r > 0.90). The descriptors with higher correlation with the dependent variable (IC 50] were retained, and the others were removed from the descriptor data matrix. The remaining descriptors were used to construct the MLR model, by the stepwise method. Moreover, the QSAR model was validated using some statistical equations such as cross validation (R 2) and adjusted R 2 . Cross validation is a mathematical method which oversees the reliability of QSAR model that can be used for a set of facts as shown in equation 1.CV. R 2 = 1 ? ?(? obs ?? cal) 2 ?(? obs ?? obs) 2 (1)

The adjusted R 2 could be calculated using equation (2)R a 2 = (N?I)×R 2 ?P N?P?1 (**2**)

where N is number of observations (compounds), p is number of descriptors, Also, for a good model, the standard error of estimate (s) of a set of data should be low, and this is defined as follows:?? = ? ?(?? ?????? ??? ??????) 2 ??????1 (3)

To judge the overall significance of the regression coefficients, the variance ratio (F) which is the ration of regression mean square to deviations mean square can be defined as follows:

The F value has two degrees of freedom: p, N ? p ? 1. The computed F value of a model should be significant at $p < 0.05$; thus for overall significance of the regression coefficients, the F value should be high.

4 c) Molecular Docking and binding affinity

The downloaded HT29 receptor (PDB ID: 2N8A 42) from protein data bank was treated i.e., removal of water molecules, ligand, and cofactors from the receptor with the use of discovery studio. Then, both the receptor and ligand were converted to the acceptable format (pdbqt) for AutoDockvina programme. The grid dimension used for all the 2N8A protein was are 50 × 40 ×40 Å (grid size) with point separated by 1.000 Å (grid-point spacing). The docking was done using autodock vina which was inspired by Darwinian evolution theory to be iterative optimization method 43 which involves search Algorithm. At the completion of the docking runs, ligand showing different conformations known as Binding modes were obtained with their respective binding affinity. The stable pattern was assumed to be the one with the lowest binding affinity and was taken for post-docking analysis using Edupymol version 1.7.4.4.

5 III.

Result and Discussion a) QSAR modeling The molecular descriptors calculated for the twenty pyrazole compounds served as independent variables, while the observed inhibitory actions (IC 50, µM) against cancer cells line as the dependent variable in the development of QSAR model via multiple linear regression (MLR). These molecular descriptors used for QSAR model were displayed in Tables 2 and 3. In QSAR study, the quality of a model is evaluated by its fitting and prediction abilities; however, for a model to be acceptable, its predictability power is of paramount important. Therefore, Pearson's matrix was used for the selection of suitable descriptors for the QSAR study (Table 4). The selected descriptors were used to build a linear QSAR model to understand how multiple linear regression (MLR) equations can explain the structural key points correlating to differential behavior in bioactivity against colon cancer cell (HT29) as shown in equation 4. This model was validated statistically by using the squared fitting factor (R 2), cross validation (CV.R 2), adjusted fitting factor (adj R 2) and variation ratio (F). The developed model was very robust in predicting satisfactory the experimental values. The high values of F, R 2 , CV.R 2 and adj R 2 as shown in Table 5 indicated that the models are statistically acceptable and also have good external predictability 44,45 . The calculated R 2 is 0.9564; this revealed a reasonable fitness, and it also uncovered the efficiency of the model as displayed in equation 4. The value for CV.R 2 was calculated to be 0.9542 which is greater than 0.5 (standard) 46 , and this showed the reliability and acceptability of the model as well as the adjusted R 2 with 0.9247 which was greater than 0.6 (Table 5) IC

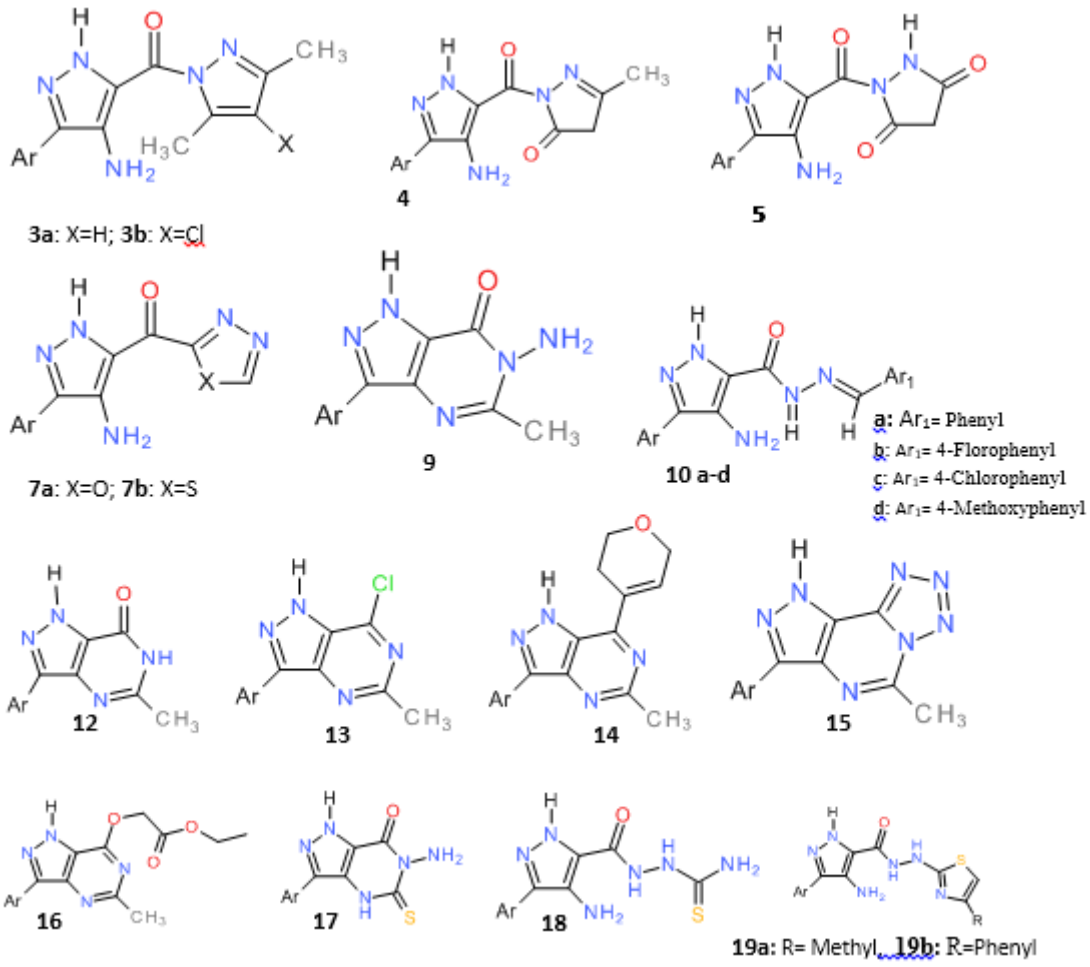
The QSAR model contained eight descriptors in different combinations; each descriptor with either positive or negative coefficient attached to it. However, the magnitudes of the coefficients as well as, the values of descriptors have significant roles in deciding the overall biological activity of the molecule. The descriptors with negative coefficients in the model were very significant because they contributed towards increasing the value of the biological activity of anti-colon cancer agents. Therefore, the descriptors with a negative coefficients were most significant followed by descriptors with low weight positive coefficients and lastly the parameters with high weight positive coefficients. The predicted anti-colon cancer activity of the ligands using the QSAR model as well as deviation from the experimental values was displayed in Table 6 and graphically presented in Figures 2 and 3. Observed IC 50 (?M)

Predicted IC 50 (?M) The molecular docking studies were performed on the twenty pyrazole derivatives together with colon cancer cells line (PDB ID: 2N8A) 42 obtained from protein data bank. This was achieved with the use of several software such as Discovery studio, Autodock tool, Autodock vina and Pymol as post-dock software. Docking of each compound was carried using autodock vina and conformations obtained varies in number but ranged from 8 -15 conformations for compounds 3a-19b. The structure with lowest binding energy (i.e., highest negative free energy of binding, Î?"G) in each docking simulation was taken to be most stable and analyzed for detailed interactions using Discovery Studio Visualizer4.0 software. Docking simulations can be understood by comparing the values of the free energy of binding (Gibbs energy, Î?"G) of the ligands to the protein receptor. Î?"G is an indicator to show the stability interaction between ligand and receptor, and it can be used to explain the strength of binding energies of different docking conformation 47, **??**8 .

The poses of the lowest conformation of each ligand were examined based on Î?"G, and interaction of the ligand with the 2N8A protein structure in ligandreceptor complex. The free binding energy (Î?"G) calculated for the docked twenty pyrazole derivatives ranged from -6.10 kcal/mol (ligand 7a) to -8.20 kcal/mol (ligand 19b) as displayed in Table 7. The interaction of ligand with the 2N8A protein structure was discussed by of H-bonding between the ligand and the receptor molecule as shown in Figure 4. Analysis of the ligandreceptor complex showed that H-bonds played a prominent role in the binding and posed stability of the ligand in the ligand-receptor complex; thus affect the potency/function of biological molecules. The number of H-bonds present in the ligand-protein complex as well as H-bonds distances was shown in Table 7 IV.

6 Conclusion

In this study, the quantum chemical method via density functional theory (DFT) method was used for calculation of molecular descriptors relating to the anticancer activity of pyrazole derivatives. The QSAR analysis revealed the efficiency of the model developed using multiple linear regression (MLR), and that the QSAR model replicated the observed bioactivities of the studied compounds against colon cancer cells line (ID: 2N8A). Furthermore, the simulated molecular docking predicted stable conformations of the drug-like molecules (Pyrazolederiatives) in the active gouge of the receptor. Also, the binding energy as well as, nature of electrostatic interactions of the ligands in the ligandreceptor complexes were obtained for the twenty compounds. [1]



4

Figure 1: compounds are 4 -

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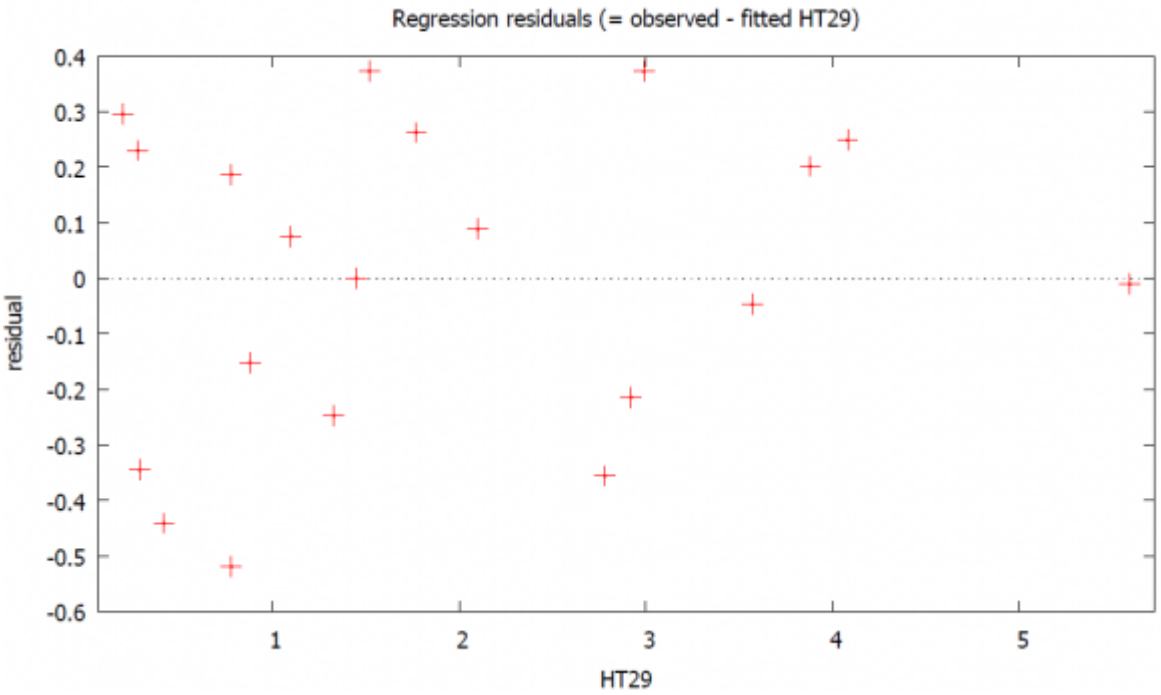
Regression residuals (= observed - fitted HT29)
residual
HT29
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
1
2
3
4
5

Figure 2:

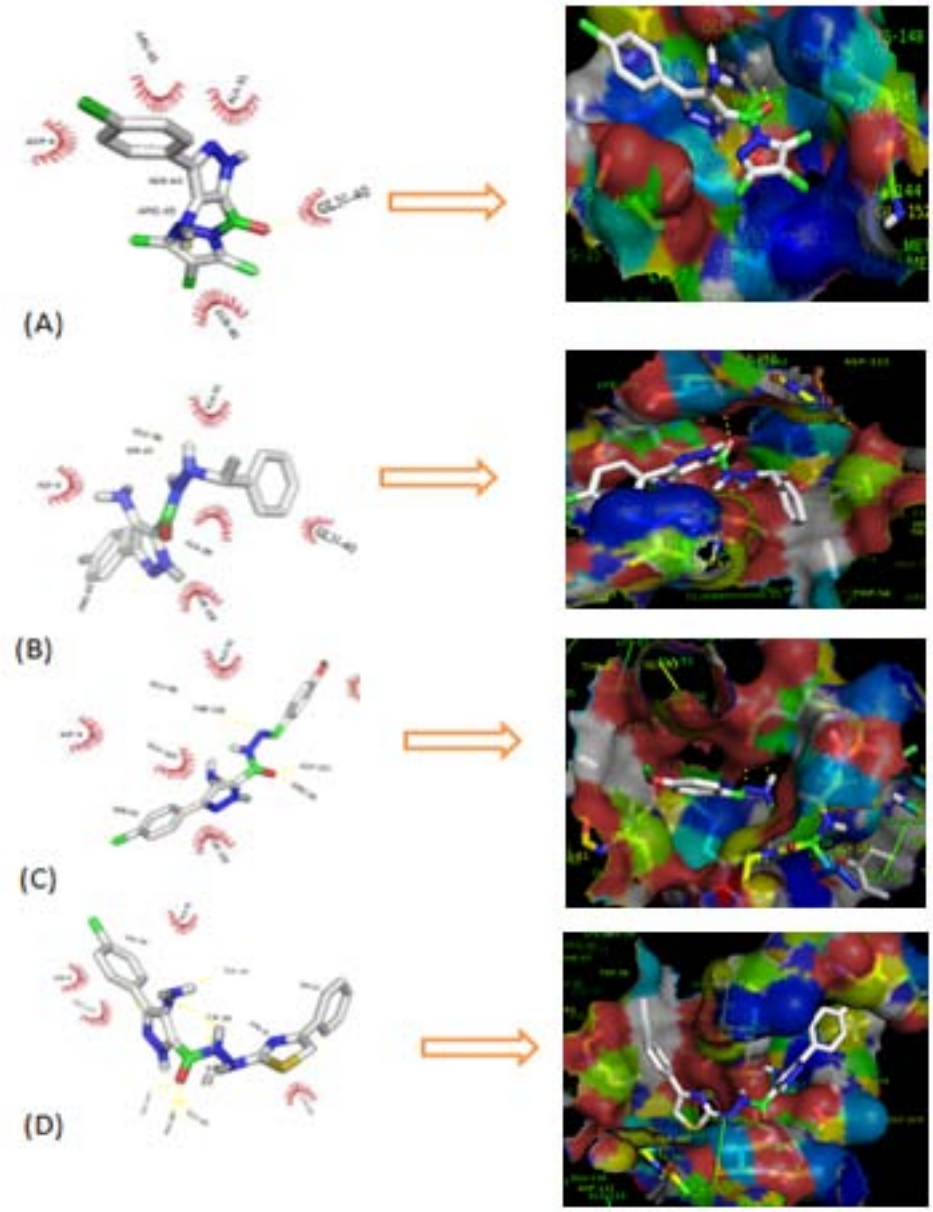

Figure 3:

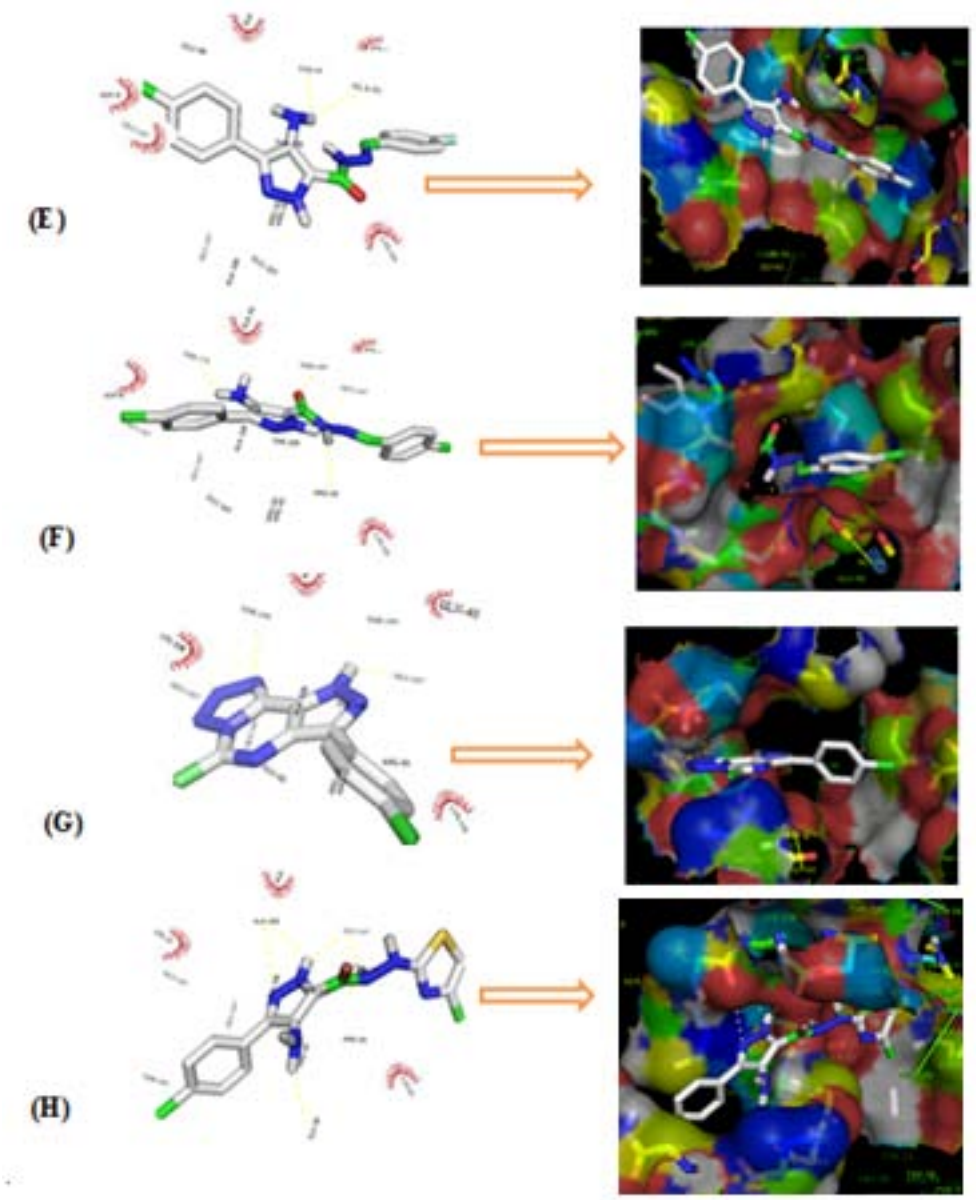

Figure 4:

1

Descriptors	Symbol	Abbreviation
Quantum	Molecular dipole moment	
chemical	Molecular polarizability	
descriptors	Highest occupied molecular orbital, eV	
	Lowest unoccupied molecular orbital, eV	
	Solvation energy (au)	

Figure 5: Table 1 :

2

MOL	HOMO	LUMO	BG	DM	SE (au)	(N+N)/2 Het	?	µ	?
3a	-5.54	-1.66	3.98	5.26	-0.01389	-0.379	3.600	-1.940	0.5227
3b	-5.66	-1.85	3.81	3.33	-0.01208	-0.379	3.755	-1.905	0.4832
4	-5.87	-1.60	4.27	6.35	-0.02134	-0.353	3.735	-2.135	0.6102
5	-6.58	-1.94	4.64	2.54	-0.03482	-0.355	4.260	-2.455	0.7074
7a	-5.74	-1.41	4.33	3.51	-0.02187	-0.398	3.575	-2.165	0.6556
7b	-5.66	-1.80	3.86	3.76	-0.01747	-0.399	3.730	-1.930	0.4993
9	-5.96	-1.36	4.60	4.23	-0.01815	-0.405	3.660	-2.300	0.7227
10a	-5.84	-0.82	5.02	5.19	-0.01575	-0.368	3.330	-2.510	0.9460
10b	-5.84	-1.65	4.33	1.68	-0.01442	-0.368	3.815	-2.165	0.6143
10c	-6.07	-1.80	4.27	1.81	-0.01671	-0.377	3.935	-2.135	0.5792
10d	-5.56	-1.44	4.12	2.91	-0.01841	-0.368	3.500	-3.128	1.3973
12	-5.99	-1.31	4.68	4.11	-0.01977	-0.401	3.650	-2.340	0.7501
13	-6.23	-2.09	4.14	2.26	-0.01402	-0.413	4.160	-2.070	0.5150
14	-5.91	-2.09	3.82	4.67	-0.01784	-0.427	4.000	-1.910	0.4560
15	-5.91	-1.99	4.39	0.76	-0.01789	-0.424	4.185	-2.195	0.5756
16	-5.88	-1.45	4.43	6.68	-0.01861	-0.418	3.665	-2.215	0.6693
17	-6.18	-1.89	4.29	3.02	-0.02548	-0.391	4.035	-2.145	0.5701
18	-5.79	-1.41	4.38	4.84	-0.03355	-0.396	3.600	-2.190	0.6661
19a	-5.73	-1.24	4.49	4.68	-0.02043	-0.372	3.485	-2.245	0.7231
19b	-5.70	-1.30	4.40	4.39	-0.02085	-0.371	3.485	-2.200	0.6914

Figure 6: Table 2 :

3

H	0.294	0.294	0.296	0.300	0.285	0.282	0.292	0.292	0.294	0.295	0.293	0.294	0.292	0.277	0.297	0.287	0.300
HET	4 2 6	2 6	3 7	3 8	2 6	2 6	2 5	3 6	3 6	3 6	3 7	1 4	1 4	1 5	1 6	1 6	3 7
HBD																	
HBA																	
NHBI	1.012	1.011	1.010	1.010	1.008	1.008	1.008	1.010	1.010	1.010	1.010	1.008	1.008	1.006	1.008	1.007	1.009
NNBI	1.322	1.322	1.320	1.329	1.333	1.334	1.345	1.329	1.334	1.336	1.333	1.345	1.354	1.352	1.352	1.351	1.339
Log P	0.07 63.21	- 10.06	- 1.01	- 1.52	0.26 74.59	0.83 64.53	- 70.15	0.60 88.83	1.62 79.20	2.02 79.11	1.34 86.23	0.10 56.31	1.55 37.70	1.67 42.72	1.83 68.58	0.76 64.47	0.15 74.92
PSA	64.57	63.22	85.75	100.07	58.95	59.82	72.74	66.90	66.94	67.71	68.82	59.33	59.98	65.70	60.37	64.95	60.23
Pol		65.69	63.71	62.61			60.29										
Ova	1.48	1.51	1.48	1.46	1.39	1.40	1.42	1.55	1.45	1.55	1.57	1.39	1.40	1.47	1.40	1.52	1.41
MOL	3a	3b	4	5	7a	7b	9	10a	10b	10c	10d	12	13	14	15	16	17
MW	315.76	450.20	917.73	619.70	261.67	277.73	275.69	941.80	257.77	374.23	169.81	260.68	479.13	326.78	285.69	332.74	293.7
Vol	297.32	310.90	287.79	275.32	229.28	238.68	246.62	329.28	327.84	337.13	350.35	235.01	241.38	311.07	246.93	303.52	244.9

Figure 7: Table 3 :

4

HT29	HT29	HOMO	LUMO	BG	DM	SE	N+N/2HET	CP	CH	GN	MW	VOL	OVA	LOGP	PSA	POL	NNBL	NHBL
HOMO	1.000	0.306	0.633	0.428	0	0.274	-	-		0.423	0.283	0.295	0.456	-	0.524	0.288	-	0.240
LUMO	0.000	1.000	0.947	0.520	0.370	0.152	0.434	0.191		0.230	0.285	0.365	0.419	0.292	0.033	0.372	0.095	0.221
BG	1.000	0.000	1.000	0.349	0.506	0.372	0.320	0.005	-	0.567	0.195	0.272	0.414	0.049	0.483	0.258	-	0.135
DM		0.655	0.102	-	2	0.219	-		0.828	0.397	-	-	0.078	-	0.482	-	0.463	-
SE		1.000	0.000	0.028	0.060	0.448	-			0.039	0.044	0.027	0.303	0.199	0.081	0.047	-	0.013
N+N/2HET				-	-	-		0.888	-		0.044	0.130	0.061	-	-	0.128	0.331	-
CP				0.342	0.173	0.472	-			0.111	0.125	0.233	0.501	0.266	0.631	0.240	0.031	0.074
CH				-	1.000	0.092	0.235			0.356	0.533	0.499	-	-	0.672	0.494	-	0.098
GN				0.064		0.229	-			-	-	-	0.349	0.375	-	-	0.245	0.787
MW				1.000		-	0.596			0.970	0.225	0.272	-	0.587	0.459	0.262	0.078	-
VOL						0.343	-			-	-	-	0.484	-	-	-	-	0.137
OVA						1.000	0.177			0.482	0.274	0.365	0.442	0.434	0.325	0.360	0.861	-
LOGP							-			1.000	0.284	0.355	0.913	0.018	0.439	0.347	0.044	0.202
PSA							0.284				1.000	0.973	0.921	0.101	0.392	0.973	0.454	0.174
POL							0.283					1.000	1.000	0.015	0.311	1.000	-	0.402
NNBL							1.000							0.257	0.457	0.918	0.137	0.380
NHBL														0.299	-	0.304	-	0.386
HHET4r														0.152	0.488	0.300	0.422	-
HBD														1.000	1.000	1.000	-	0.334
HBA																	0.394	0.435
																	-	0.381
																	0.446	-
																	0.488	0.802
																	-	1.000
																	0.580	
																	-	
																	0.395	
																	1.000	

Figure 8: Table 4 :

5

N	p	R 2	CV.R 2	R 2	adj	s	F
20	8	0.9564	0.9542	0.9247		0.4141	30.168

Figure 9: Table 5 :

6

Comp	Observed	Predicted	Residual	Comp	Observed	Predicted	Residual
3A	1.45	1.45	-0.00	10D	3.57	3.05	0.52
3B	1.10	1.57	-0.47	12	0.78	0.54	0.24
4	2.78	2.53	0.25	13	1.52	1.23	0.29
5	2.99	2.82	0.17	14	0.88	0.96	-0.08
7A	0.28	-0.26	0.54	15	0.29	0.70	-0.41
7B	0.20	0.31	-0.11	16	3.88	3.86	0.02
9	1.77	2.19	-0.42	17	1.33	1.24	0.09
10A	4.08	4.16	-0.08	18	5.59	5.65	-0.06
10B	2.10	2.18	-0.08	19A	0.42	1.09	-0.67
10C	2.92	2.83	0.09	19B	0.78	0.62	0.16

Figure 10: Table 6 :

7

Year 2018
17

Figure 11: Table 7 :

[Likewise] , Likewise . (ligand 12receptor complex presented two H-bonds)

[] , 10.7537/marsnys09061610. 9 p. .

[Inca ()] , *Inca* 2008. 628. INCA -Institutonacional de câncerAções de prevençãoprimáriaesecundária no controle do câncer. Rio de Janeiro

[Eur J Med ()] , *Eur J Med* Chem2008. 43 p. 435.

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[However] '(H-amino group of pyrazole ring) and ALA-89/LIG:H (hydrogen of N-H of pyrazole ring). Two H-bonds were observed in docked complex of ligand 10b and receptor; THR-88/LI G: H (H-amino group of pyrazole ring) and ALA-91/LIG:H (hydrogen of N-H of pyrazole ring). For ligand 10c, five H-bonds were observed via THR-176/LIG:H (hydrogen of N-H of carboxamide'. However . GLU-107/LIG:H. *one H-bond was observed between LYR-47 and LIG:N (amino group of pyrazole ring); whereas two H-bonds for 7b with*, (GLU-107/LIG:H (H-amino group of pyrazole ring), GLU-107/LIG:H (hydrogen of N-H of pyrazole ring), GLU-107/LIG: O (Carbonyl oxygen of pyrimidinone). Others were ALA-89/LIG: O (Carbonyl oxygen of pyrimidinone. hydrogen of N-H of pyrazole ring), GLU-107/LIG:O (pyrazole-carbonyl oxygen) and ARG-65/LIG:O (pyrazole-carbonyl oxygen)

[Lig:O (ii Gly-111 Lig:O (iii Thr-109 Lig:H (iv Glu-107 Lig:H (v) Glu-107 Lig: N] '(i) MET-38, LIG: H (ii) GLN-40, LIG:H (i) 2.4 (i) 2.3 9 -6.8 (i) THH-109, LIG:N (ii) GLU-107, LIG:H(iii) GLU-107, LIG:H (iv) GLU-107, LIG: O (v) ALA-89, LIG: O (vi) ILE-64 LIG: O (vii) ILE-64, LIG: H (i) 3.0 (ii) 2.9 (iii) 2.1 (iv) 3.4 (v) 3.2 (vi) 3.6 (vii) 2.5 10a -7.4 (i) THR-109'. LIG: H (i) 3.3 (ii) 2.1 (iii) 2.7 (iv) 2.0 10b -7.2 (i) THR-88. *H (i) 2.8 (ii) 2.5 10c -7.2 (i) THR-176, LIG: H (ii) THR-109, LIG: H (iii) GLU-107, LIG:H (iv) GLU-107*,) Lig:O (ii, Gly-111,) Lig:O (iii, Thr-109,) Lig:H (iv, Glu-107, Lig:H (v) Glu-107, Lig: N (ed.) (LIG: H, (ii) ALA-91, LIG) (LIG: O (ii) THR-109. LIG:H (i) 3.3 (ii) 2.2 13 -6.4 MET-38, LIG:H (i) 2.2 14 -7.0 (i) ASP-6, LIG: H (ii) THR-109, LIG:H (i) 2.4 (ii) 2.5 15 -7.3 (i) GLU-107, LIG:H (ii) THR-109, LIG: N (iii) THR-109, LIG: N (iv) LYS-108, LIG: N (v) LYS-108, LIG: N (i) 2.5 (ii) 2.0 (iii) 2.7 (iv)

[Lig:H (ix Ala-89 Lig:H (x) Glu-107 Lig:H (xi Glu-107 Lig: H (i) 3.5] '(ii) 2.5 (iii) 2.2 (iv) 2.1 (v) 2.2 (vi) 2.6 (vii) 2.4 (viii) 2.5 (ix) 2.5 (x) 2.5 (xi) 2.8 19a -7.2 (i) ALA-106'. LIG: H (viii) GLU-90. *LIG: O (ii) THR-109, LIG:O (iii) LYS-108, LIG: O (iv) GLU-107, LIG:H (v) GLU-107*,) Lig:H (ix, Ala-89, Lig:H (x) Glu-107,) Lig:H (xi, Glu-107, Lig: H (i) 3.5 (ed.) (LIG:N (ii) GLU-90,LIG:H (iii) GLU-90. LIG: H (i) 2.3 (ii) 2.8 (iii) 2.0 (iv) 2.9 (v) 2.4 (vi) 2.5 (vii) 2.5 (viii) 2.0)

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[LYS-108/LIG: N (one of N of triazolyl ring) and LYS-108/LIG: N (one of N of triazolyl ring). Moreover, one H-bond was observe 'LYS-108/LIG: N (one of N of triazolyl ring) and LYS-108/LIG: N (one of N of triazolyl ring). Moreover, one H-bond was observed for ligand 16-receptor complex viaLYS-47/LIG:O(carboxylic-group) with Hbond distance of 2.4 Å; whereas for ligand 17-receptor complex, six H-bonds were detected. The H-bonds were ALA-89/ LIG:H (hydrogen of N-H of pyrazole ring'. GLU-107/LIG:H. */LIG:H (hydrogen of N-H of pyrazole ring) with the distance of 2.4 Å and THR-109/LIG:H (hydrogen of N-H of pyrazole ring) with of distance 2.5 Å. Also, for ligand 15, five H-bonds were identified through GLU-107/LIG:H (hydrogen of N-H of pyrazole ring*, First ketonic-group of pyrimidine-dione ring ; Second Ketonic-group of pyrimidinedione ring ; First ketonic-group of pyrimidine-dione ring (THR-109/LIG: N (N of N-H of pyrazole ring). hydrogen of N-H of pyrazole ring) and THR-109/LIG:N (N of N-H of pyrazole ring)

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