THEORETICAL STUDIES ON PYRAZOLE DERIVATIVES AS ANTI-BREAST CANCER AGENTS: DFT, QSAR AND DOCKING METHODS

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Pyrazole derivatives as anti-cancer agents were observed using Density functional theory (DFT), Quantitative Structure Activity Relation (QSAR) and docking method. The molecular descriptors obtained from DFT were used to develop QSAR model so as to predict their cytotoxicity. Therefore, the predicted IC50 obtained from modeled QSAR fitted well the experimental IC50. Also, the calculated molecules were docked against breast cell line and the molecular binding energy which resulted from the interaction showed the level of their affinity.

Key words: Pyrazole derivatives, DFT, QSAR, Docking.

INTRODUCTION

The breast cancer as the second leading cause of death throughout the world, is still the most frequently identified cancer in women. Recently, it was estimated that 252,710 women were diagnosed of this malignant neoplasia and death of 40,610 women were reported by American Cancer Society (Breast Cancer Facts & Figures, 2017-2018). Despite the substantial developments made to cure early breast cancer, medical defies still remain (Oyebamiji and Semire, 2016a; Bayani et al 2017). The possible risk factors in breast cancer are gender, family history, genetics, and age (Aghaee et al 2012). The possible available cures for breast cancer comprise chemotherapy, radiation therapy, surgery, hormonal therapy, or combination therapy (Oyebamiji and Semire, 2016b; Jemal et al 2011). Therefore, many research works have concentrated on the area of drug resistance so as to enhance cancer chemotherapy (Gottesman, 2002; Harris et al 2000).

Pyrazole contains an unsaturated five membered ring with two nitrogen atoms which are adjacent to each other. Although many heterocyclic moieties like imidazole, coumarin, benzimidazole, quinazoline etc. are associated with pharmacological activities (Dahiya and Kumar, 2008; Dahiya et al 2008; 2010; Dahiya and Mourya, 2013; Dahiya and Pathak, 2007) but due to the interested biological activities like anticancer (Balbi et al 2011), antifungal (Prakash et al 2008), analgesic (Pereira et al 1998), antiviral (Storer et al 1999), pyrazoles have attracted the attention of the researchers. The pyrazole moiety has other significant role such as, arylpyrazole derivatives with anti-HIV ability and pyrazole-3-carboxamide derivatives with anti-CB1 cannabinoid capacity (Genin et al 2000; Ruiu et al 2003). Also, in crop protection chemistry, pyrazole derivatives have numerous uses.

Quantitative structural activity relationship (QSAR) models are very valuable regression simulations in the biological sciences analysis (Oyebamiji and Semire, 2016c; Sharma et al 2016; Agarwal et al 2015a; 2015b; Bansal et al 2011). It is an arithmetic model which link...
physicochemical parameters of a chemical compound to its biological activity (Hansch, 1969). Thus, the development of a good and effective QSAR model is a function of higher quality data and the choice of descriptors. Docking as a developing vital scheme for drug discovery is a key device in computer-based drug design (Sharma et al. 2011; Balasubramanian and Vijaya Gopal, 2012; Jain et al. 2013; Sharma and Kumar, 2014). It helps in the understanding of the interaction between the molecular compounds and the enzymes by identifying the suitable active gouge in enzyme. In docking study, the strength of the contact which is in statistical form between the molecular compounds and the enzymes can be calculated and presented as dock score (Taylor et al. 2002). Present research work comprises of twenty synthesized molecules (Hafez et al. 2016), as shown in Figure 1. These compounds which were optimized using density functional theory (DFT) via 6-31G (d,p) basis set, were vetted against MCF-7 (human breast cancer) cell line so as to obtain molecular parameters.

![Chemical structures of synthesized molecules](image)

These molecular compounds include 4-amino-3-(4-chlorophenyl)-1H-pyrazol‐5-yl - (3,5-dimethyl-1H-pyrazol-1-yl) derivatives) methanone Aa,b, 2-[(4-amino-3- (4-chloro phenyl)- 1H -pyrazol-5-yl) carbonyl]- 5-methyl-2,4-dihydro-3H-pyrazol-3-one B, 1-[(4-amino-3-(4-chlorophenyl-1H-pyrazol-5-yl)carbonyl) pyrazolidine-3,5-dione C, 3-(4-chlorophenyl)-5-(1,3,4-oxa/thiadiazol-2yl) -1H- pyrazol-4-amine D dab, 6-amino-3-(4-chloro phenyl)-5-methyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one E, 4-amino-3-(4-chlorophenyl)-N’-[aryl methylidene]-1H-pyrazole-5-carbonylhydrazide F a,d, 3-(4-chlorophenyl)-5-methyl-1,6-dihydro-7H-pyrazolo [4,3-
investigate its biological activities (Pourbasheer et al. 2009). Multiple linear regression method, a frequent statistical procedure used in making QSAR model was used to realize this. Furthermore, the validation of the developed QSAR model was achieved by observing some statistical equations like cross validation ($R^2$) and adjusted $R^2$ as shown in equation 1:

$$CV. R^2 = 1 - \frac{\sum (\text{obs} - \text{calc})^2}{\sum (\text{obs} - \text{obs})^2}$$

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

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

**Docking and scoring**

The receptor used [MCF-7 (PDB: 1HI7)] (Williams et al. 2001) was downloaded from protein data bank and it was treated using discovery studio. Also, the ligand and the treated enzyme were both converted to the format (pdbqt) acceptable by autodockvina via autodock tool. Then the docking calculation was carried out by autodockvina which was stirred by Darwinian evolution theory to be repeated optimization method (Rani et al. 2014).

**RESULTS AND DISCUSSION**

**Molecular descriptors**

Solvation energy, weight, hydrophobicity (Log P), volume (V), Area, polar surface area (PSA), ovality, dipole moment (DM), heteroatoms (average of Mulliken charges on all heteroatoms), HOMO, and LUMO energies were the molecular descriptors calculated for this study. The highest occupied molecular orbital (HOMO) were $-5.54eV, -5.66eV, -5.87eV, -6.58eV, -5.74eV, -5.66eV, -5.96eV, -5.84eV, -6.07eV, -5.56 eV, -5.99eV, -6.23eV, -5.91eV, -5.91eV, -5.88eV, -6.18eV, -5.79eV, -5.73eV, -5.7eV for compounds $A_s$–$N_b$ respectively. Similarly, the lowest unoccupied molecular orbital (LUMO) energy were $-1.66eV$ for $A_s$, $-1.85eV$ for $A_b$, $-1.6eV$ for $B$, $-1.94eV$ for $C$, $-1.41eV$ for $D_a$, $-1.8eV$ for $D_b$, $-1.36eV$ for $E$, $-0.82eV$ for $F_a$, $-1.65eV$ for $F_b$, $-1.8eV$ for $F_c$, $-1.44eV$ for $F_d$, $-1.31eV$ for $G$, $-2.09eV$ for $H$, $-2.09eV$ for $I$, $-1.99eV$ for $J$, $-1.45eV$ for $K$, $-1.89eV$ for $L$, $-1.41eV$ for $M$, $-1.24eV$ for $N_a$, $-1.3eV$ for $N_b$.

Furthermore, HOMO together with LUMO provides substantial qualitative facts about the molecular excitation properties (Bouachraine et
al 2009; Yang et al 2005). In this research work, no correlation between HOMO as well as LUMO and bioactivity of pyrazole was detected. Also, the band gap which is basically the relics of energy series that are not enclosed by band (Harisson, 1966), are 3.98eV, 3.81eV, 4.27eV, 4.64eV, 4.33eV, 3.86eV, 4.6eV, 5.02eV, 4.33eV, 4.27eV, 4.12eV, 4.68eV, 4.14eV, 3.82eV, 4.39eV, 4.43eV, 4.29eV, 4.38eV, 4.49eV and 4.4eV for Aa–Nb as displayed in Table 1. It is believed that, the band gap would play a significant part that can’t be ignored, because lower band gap brings about easier excitation together with better proficiency of a compound to donate an electron(s) to the adjoining molecules; however, as observed in this research, there is no effective correlation between the band gap and biological activities of pyrazole derivatives. Furthermore, calculated Log P reveals the abilities of molecular compounds to relax in non-aqueous solution (Abass et al 2011). Thus, problem may likely arise, if the administered molecules have Log P to be greater than 5 (Meanwell, 2011). The calculated Log P are 0.07 for Aa, -0.06 for Aa, -1.01 for B, -1.52 for C, 0.26 for Da, 0.83 for Da, 0.15 for E, 0.6 for Fc, 0.62 for Fc, 2.02 for Fc, 1.34 for Fc, 0.1 for G, 1.55 for H, 1.67 for I, 1.83 for J, 0.76 for K, 0.15 for L, -0.96 for M, 0.09 for Na, 1.49 for Nb, therefore, the molecules used in this work are proficient in term of lipophilicity. Moreover, the calculated dipole moment are 5.26 Debye, 3.33 Debye, 6.35 Debye, 2.54 Debye, 3.51 Debye, 3.76 Debye, 4.23 Debye, 5.19 Debye, 1.68 Debye, 1.81 Debye, 2.91 Debye, 4.11 Debye, 2.26 Debye, 4.67 Debye, 0.76 Debye, 6.68 Debye, 3.02 Debye, 4.84 Debye, 4.68 Debye, 4.39 Debye for Aa–Nb respectively; and this explains the product of the charge degree as well as the distance of separation between the charges (McMurry and Fay, 2004). Therefore, in term of dipole moment, most of the ligands are likely to have firm non-bonded interactions with the receptor, only for Aa, B and Fc that are beyond the accepted range (3 to 5 kJ/mol) (Lewis and Broughton, 2002). The heteroatom, ovality, area, and volume were also calculated in this research work (Table 1).

Table 1. The calculated molecular descriptors from the compounds Aa–Nb for anti-breast cancer

| MOL | HOMO | LUMO | BG | DM | S.E | | μ | GN | H | N+N |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Aa  | -5.54 | -1.66 | 3.98 | 5.26 | -0.01289 | 3.6 | -1.94 | 0.5227 | -1.0204 | -0.758 |
| Aa  | -5.66 | -1.85 | 3.81 | 3.33 | -0.01208 | 3.755 | -1.905 | 0.4832 | -1.0111 | -0.758 |
| B   | -5.87 | -1.6 | 4.27 | 6.35 | -0.02134 | 3.735 | -2.135 | 0.6102 | -0.9578 | -0.705 |
| C   | -6.58 | -1.94 | 4.64 | 2.54 | -0.03482 | 4.26 | -2.455 | 0.7074 | -0.938 | -0.709 |
| Da  | -5.74 | -1.41 | 4.33 | 3.51 | -0.02187 | 3.575 | -2.165 | 0.6556 | -0.9172 | -0.795 |
| Db  | -5.66 | -1.8 | 3.86 | 3.76 | -0.01747 | 3.73 | -1.93 | 0.4993 | 0.2134 | -0.798 |
| E   | -5.96 | -1.36 | 4.6 | 4.23 | -0.01815 | 3.66 | -2.3 | 0.7227 | -1.0292 | -0.81 |
| Fa  | -5.84 | -0.82 | 5.02 | 5.19 | -0.01575 | 3.33 | -2.51 | 0.946 | -0.9988 | -0.736 |
| Fb  | -5.84 | -1.65 | 4.33 | 1.68 | -0.01442 | 3.815 | -2.165 | 0.6143 | -1.489 | -0.735 |
| Fc  | -6.07 | -1.8 | 4.27 | 1.81 | -0.01671 | 3.935 | -2.135 | 0.5792 | -0.9649 | -0.753 |
| Fd  | -5.56 | -1.44 | 4.12 | 2.91 | -0.01841 | 3.5 | -3.1275 | 1.3973 | -0.9946 | -0.736 |
| G   | -5.99 | -1.31 | 4.68 | 4.11 | -0.01977 | 3.65 | -2.34 | 0.7501 | -1.0293 | -0.801 |
| H   | -6.23 | -2.09 | 4.14 | 2.26 | -0.01402 | 4.16 | -2.07 | 0.515 | -0.9957 | -0.826 |
| I   | -5.91 | -2.09 | 3.82 | 4.67 | -0.01784 | 4 | -1.91 | 0.456 | -0.345 | -0.853 |
| J   | -5.91 | -1.99 | 4.39 | 0.76 | -0.01789 | 4.185 | -2.195 | 0.5756 | -0.4787 | -0.848 |
| K   | -5.88 | -1.45 | 4.43 | 6.68 | -0.01861 | 3.665 | -2.215 | 0.6693 | -0.7108 | -0.836 |
| L   | -6.18 | -1.89 | 4.29 | 3.02 | -0.02548 | 4.035 | -2.145 | 0.5701 | -0.7108 | -0.781 |
| M   | -5.79 | -1.41 | 4.38 | 4.84 | -0.03355 | 3.6 | -2.19 | 0.6661 | -1.3475 | -0.792 |
| Na  | -5.73 | -1.24 | 4.49 | 4.68 | -0.02043 | 3.485 | -2.245 | 0.7231 | -1.0347 | -0.743 |
| Nb  | -5.7 | -1.3 | 4.4 | 4.39 | -0.02085 | 3.485 | -2.2 | 0.6914 | -0.7948 | -0.742 |

QSAR model
Multiple linear regression method was used to make QSAR analysis so as to explore the structural activity relationship of 20 pyrazole derivatives with anti-cancer ability. Therefore, 15 parameters were involved in making the model for the prediction of highly fitted IC50. The developed equation is shown in equation 3.
Thus, the developed model was used to predict and the results are displayed in Table 2. Also the correlation between predicted and observed IC50 are presented in Figure 2. This exposed the efficacy of the modeled equation as shown in equation 3 by predicting the IC50.

\[
pIC50 = -15997.4 - 137.209(\text{HOMO}) + 144.997(\text{LUMO}) - 76.1468(\text{BG}) - 0.672815(\text{DM}) - 447.602(\text{SE}) - 12.1672(\text{GN}) + 3.06587(\text{HET}) - 0.340542(\text{MW}) - 0.520499(\text{AREA}) - 24.0735(\text{VOL}) + 24.7665(\text{N+N})
\]

Table 2. Regression result for anti-colon cancer activity

|     | Predicted IC50 | Observed IC50 | Predicted IC50 | Observed IC50 |
|-----|----------------|---------------|----------------|---------------|
| Aa  | 1.43           | 1.45          | Fd             | 3.84          |
| Ab  | 0.81           | 0.78          | G              | 1.52          |
| B   | 2.42           | 2.54          | H              | 1.54          |
| C   | 3.51           | 3.75          | I              | 0.92          |
| Da  | -0.27          | 0.1           | J              | 0.21          |
| Db  | -0.09          | 0.09          | K              | 3.76          |
| E   | 1.05           | 1.62          | L              | 1.33          |
| Fa  | 5.61           | 5.52          | M              | 4.32          |
| Fb  | 2.00           | 2.01          | N              | 0.96          |
| Fc  | 3.11           | 3.24          | N              | 0.22          |

![Fig. 2. The calculated predicted IC50 against the observed IC50](image)

**QSAR model validation**

The major expediency of QSAR models is not only their capacity to replicate observed IC50 and confirm them using their fitting power (R^2); however, it is primarily their potential for predictive use. Therefore, the modeled QSAR validation was observed by considering R^2, CV.R^2 and adjusted R^2. The calculated R^2 is 0.962; which reveal an equitable fitness as well as the efficacy of the model as shown in equation 3. Also, the calculated CV.R^2 was 0.999 ({> 0.5} (standard)) (Ponce et al 2004) and this showed the reliability and acceptability of the model as well as the adjusted R^2 with 0.823 which is greater than 0.6 (standard). Thus, the Qsar model would be predictive. Furthermore, the plot of residual for the predicted IC50 against the observed IC50 is displayed in Figure 3 and it was observed that the plot did not show any reasonable inaccuracy. This is because the residuals propagation at the two sides of zero is indiscriminate.

![Fig. 3. The residuals versus observed IC50](image)

**Molecular docking studies**

Docking studies were carried out using Discovery Studio (Discovery Studio version 2.5, 2009), autodock tool, autodockvina and pymol. The protein used was MCF-7 with PDB ID: 1HI7 (Williams et al 2001). The ligands were simulated and resulted to different conformations for individual molecular compound. The calculated binding affinity are -4.7 Kcal/mol, -4.1 Kcal/mol, -4.2 Kcal/mol, -4.7 Kcal/mol, -4.2 Kcal/mol, -5.0 Kcal/mol, -5.1 Kcal/mol, -5.9 Kcal/mol, -4.8 Kcal/mol, 29.7 Kcal/mol, 33.7 Kcal/mol, 32.3 Kcal/mol, -5.8 Kcal/mol, -4.0 Kcal/mol.
Kcal/mol, -4.6 Kcal/mol, -4.9 Kcal/mol, -4.4 Kcal/mol, -4.8 Kcal/mol, -4.7 Kcal/mol, -4.2 Kcal/mol, -1.9 Kcal/mol for Aa–Nb. As shown in Table 3, some of the compounds (Da, Db, E, and G) acted very well as an anti-cancer agent. Moreover, highest binding energy conformation (i.e. conformation with more negative value) is presumed to be the best (i.e. Conformation with more negative value will require only small amount of energy to bind with the active site of the receptor). Therefore, as per the result, compound G (-5.8) was found to be the best inhibitor among other pyrazole derivatives studied in this research work (Table 3) because it shows maximum docked energy (in term of negativity). The interaction between the ligand and the receptor of the few compounds with higher docking result is displayed in Figure 4.

Table 3. Binding affinity of Autodockvina of 1HI7 enzymes

| Mol | Affinity (Kcal/mol) | H-Bond between amino acid and drug | Distance |
|-----|---------------------|-----------------------------------|----------|
| Aa  | -4.7                | (i) PHE-34, LIG: H (ii) PHE-34, LIG:O (iii) PHE-34, LIG:O | 2.1, 3.2, 2.2 |
| Ab  | -4.1                | (i) ASP-35, LIG: O (ii) PHE-34, LIG: N (iii) PHE-34, LIG: N | 3.0, 3.2, 2.7 |
| B   | -4.2                | PHE-34, LIG: H | 24 |
| C   | -4.7                | CYS-32, LIG: O | 3.3 |
| Da  | -5.0                | PHE-34, LIG: N (i) PHE-34, LIG: H | 2.1, 2.2 |
| Db  | -5.1                | PHE-34, LIG: N | 2.1 |
| D   | -5.9                | THR-49, LIG: H (ii) THR-49, LIG: N (iii) THR-49, LIG: N | 2.7, 2.0, 2.3 |
| Fa  | -4.8                | PHE-34, LIG: N | 3.4 |
| Fb  | 29.7                | PHE-34, LIG: N (i) PHE-34, LIG: N | 2.5, 2.0 |
| Fc  | 33.7                | ASP-35, LIG: N (ii) VAL-9, LIG: O (iii) VAL-9, LIG: N | 3.4, 2.8, 2.6 |
| Fd  | 32.3                | VAL-9, LIG: N (i) VAL-9, LIG: O (ii) ASP-35, LIG: N | 2.5, 2.5, 3.2 |
| G   | -5.8                | PRO-47, LIG: N (i) THR-49, LIG: N (ii) THR-49, LIG: N (iii) THR-49, LIG: N | 3.2, 2.2, 2.0, 2.7 |
| H   | -4.0                | (i) ASP-35, LIG: N (ii) ASP-35, LIG: H | 3.3, 2.2 |
| I   | -4.6                | PHE-34, LIG: N (i) PHE-34, LIG: H | 3.2, 2.0 |
| J   | -4.9                | GLU-13, LIG: N (ii) GLN-15, LIG: H (iii) GLN-15, LIG: N | 3.4, 3.2, 2.7 |
| K   | -4.4                | Cys-32, LIG: O (ii) PHE-34, LIG: O (iii) PHE-34, LIG: O (iv) PHE-34, LIG: H (v) PHE-34, LIG: N | 3.2, 2.1, 3.6, 2.4, 3.2 |
| L   | -4.8                | ARG-14, LIG: O (i) THR-8, LIG: H | 2.6, 2.5 |
| M   | -4.7                | THR-49, LIG: H (i) GLU-5, LIG: H | 2.3, 2.1 |
| Na  | -4.2                | PHE-34, LIG: O (ii) PHE-34, LIG: O (iii) PHE-34, LIG: H (iv) ASP-35, LIG: N | 2.1, 3.2, 2.4, 3.5 |
| Nb  | -1.9                | - | - |

CONCLUSION
In present work, the result obtained via quantum chemical method (DFT) and QSAR (MLR) showed how effective the methods employed are and also revealed the potential of pyrazole derivatives as anti-cancer agent. The model obtained from QSAR reproduced the observed IC50 using multiple linear regression via Gretl software. Also, in drug designing, the role played by the interaction between the ligand and the receptor are very crucial, therefore, the ligands simulated in this research work predicted stable conformations of the drug-like molecules (Pyrazole derivatives) in the active site of the enzyme. Thus, the binding affinity of the interaction was acquired and compound G exhibited a better binding affinity.
Fig. 4. Binding interactions for: (a) D_a (b) D_b (c) E and (d) G with 1HI7.

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