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*Original Research Article*

# *In silico* Investigation on Isatin (1H-indole-2,3-dione) Derivatives as Potential Anti-Tumor Necrosis Factor-Alpha

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ABSTRACT

The role played by tumor necrosis factor-alpha (TNF-α) in advancing cancer has drawn the attention of many researchers. Thus, Isatin(1H-Indole-2,3-Dione) derivatives have been explored to curb this dreaded cancer-causing agent via semi-empirical (PM6) method. In order to obtain the descriptors that describe anti-tumor necrosis factor-alpha, the quantitative structure-activity relationship (QSAR) and molecular docking methods were used in this study. The ability of the studied compounds to acts as a drug were evaluated using Lipinski rule of five. The selected descriptors were used to develop QSAR model, which proved to be predictive, and this was confirmed and validated by considering the squared correlation coefficient ($R^2$=0.89), adjusted squared correlation coefficient (adj. $R^2$=0.89), cross validation (CV $R^2$=0.87). The docked compounds **9**, **14,** and **16** against tumor necrosis factor-alpha (TNF-α) with -6.5 kcal/mol proved to be effective than other studied compounds as well as the referenced drug. Also, the correlation between the selected descriptors and calculated binding affinity was examined. It was observed that the plot of Log P against binding affinity obeyed $0.5 \leq x \leq 1$, which showed that Log P contributed to inhibitory activities of the studied compounds against tumor necrosis factor-alpha.

***Keywords***: Cancer, Binding Affinity, B3LYP, Molecular docking, Inhibitory activity.

## Introduction

The unique role of tumor necrosis factor-alpha (TNF-α) in advancing cancer in human has drawn the attention of many researchers over the years.[1] It comprises of a pleiotropic cytokine and has power to normalize several biological actions.[2] According to Li *et al.*, 2018, it was considered as the most comprehensively investigated cytokine,[3] and a series of signal activities within the cellular could be attributed to TNF-α.[4] More so, targeting TNF-α with small molecules in down-regulating cancer is an efficient therapeutic method that has drawn the attention of many researchers in the past few decades.[5-7] Currently, many derivatives of 1H-indole-2,3-dione have been observed by many scientists to possess anti-microbial, anti-cancer, antimicrobial, antiviral, antioxidant, tumor suppressor and anti-tubercular activities.[8-9] The 1H-indole-2,3-dione derivatives have been reported to be rich in bioactive constituents, and this could also be attributed to the stability of the indole nucleus[10]. Isatin(1H-indole-2,3-dione) was observed to be originated from various sources such as plants, mammals, and organisms, etc.,[11,12] and a series of chemically reactive functional groups were observed to be contained by isatin(1H-indole-2,3-dione). [13-15]

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Several challenges such as protein-protein interface and flexibility of proteins have been attributed to molecular docking study. This is based on its capacity to enhance the relationship between any studied pharmacophore and enzyme by identifying the suitable binding sites in the studied enzyme (receptor).[16] Also, the calculated binding affinity between the studied complexes could be expressed as dock score since the docking score helps to predict the power of the interactions that are non-covalent between complexes after docking.[17] Thus, this work is aimed at identifying the descriptors with efficient anti-tumor necrosis factor-alpha (TNF-α) activities of the studied isatin(1H-indole-2,3-dione) derivatives and developing valid 2D and 3D quantitative structure-activity relationship (QSAR) models using efficient descriptors obtained from the studied compounds. The study also investigates the non-bonding interactions existing between isatin(1H-indole-2,3-dione) derivatives and tumor necrosis factor α (PDB ID: 2az5).[18] Our discoveries may open door for the design and development of library of efficient pyrimidine-based drug-like compounds as potential anti-cancer agents.

## Materials and Methods

*Computational Details*

*Ligand Preparation via Quantum chemical method*

Thirty-six (36) isatin(1H-indole-2,3-dione) derivatives obtained from the work experimentally carried out by Boukarai *et al*., 2015[19] were modeled using CHEMDRAW ultra 12.0 to ascertain the accuracy of the modeled structure before subjecting it to Spartan 14[20, 21] for optimization using semi-empirical (PM6) as basis set. Several biochemical descriptors such as the highest occupied molecular orbital energy ($E_{HOMO}$), lowest unoccupied molecular orbital energy ($E_{LUMO}$), bandgap (BG), dipole moment (DM), molecular weight (MW),

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lipophilicity (LogP), ovality, polar surface area (PSA), polarizability, hydrogen bond donor (HBD), and hydrogen bond acceptor (HBA) were obtained from the optimized molecular compounds in order to investigate the anti-tumor necrosis factor-alpha (TNF-α) of the studied isatin(1H-indole-2,3-dione) derivatives. The IUPAC name of the studied compounds is presented in Table 1.

*Quantitative Structure-activity Relationship (QSAR) Study*
*QSAR Study Using Combined Electronic and Geometric Descriptors*
The optimized compounds, which brought about a series of descriptors, were divided into two sections (training set (80%) and test set (20%)) using the Kennard stone algorithm method via Dataset Division GUI 1.2 software.[22] The descriptors used to develop the QSAR model from the training set were composed of electronic and geometric descriptors using material studio software for the purpose of validity and reliability (Equation 1).

$IC_{50}$ = 0.006745608(MW) + 36.697004105(C6-C5) - 49.928827432----------(1)

$R^2$ = 0.89, Adj $R^2$ = 0.89, CV.$R^2$ = 0.87, Significance-of-regression F-value = 118.83071100, Critical SOR F-value (95%) = 4.45536700

*QSAR Validation Evaluation*
Five statistical factors were investigated so as to confirm the validity and reliability of the developed model. The considered statistical factors were squared correlation coefficient ($R^2$), adjusted squared correlation coefficient (Adj.$R^2$), cross-validation squared correlation coefficient (CV.$R^2$), Significance-of-regression F-value, and Critical SOR F-value (95%). According to Oyebamiji *et al*., 2021, the squared correlation coefficient ($R^2$) alone cannot be statistically used to adjudge the validity and reliability of any QSAR model; thus, validation of the quantitative structure-activity relationship (QSAR) model is highly crucial[23].

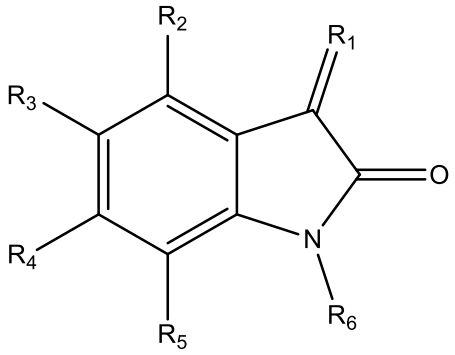
*Preparation of Studied Receptor (tumor necrosis factor-alpha (TNF-α))*
Tumor necrosis factor-alpha (TNF-α) (PDB ID: 2az5) was obtained from the protein data bank (http://www.rcsb.org). The downloaded receptor was treated by removing small molecules and water molecules that were present with the desired protein for the purpose of having only protein for docking study using Pymol 1.7.4.4 software. The treated receptor was subjected to autodock tool software so as to locate the binding site in the studied receptor, and the respective calculated value for the centre and size in X, Y and Z directions were -26.567, 65.935, and 41.94 for the centre as well as 48, 48 and 52 for size. Autodock vina was used for docking calculation to obtain binding affinity between the studied complexes.

## Results and Discussion

*Calculated Descriptors from Isatin(1H-indole-2,3-dione) Derivatives*
In this work, several descriptors were obtained from the optimized studied compounds. As shown in Table 2, the ability of the studied compounds to act as drugs was investigated using the Lipinski rule of five (Molecular weight ≤500 amu; Log P≤ 5; HBD≤ 5; HBA≤ 10). It was observed that 94.44% of the studied compounds completely satisfied the Lipinski rule of five, while 5.56% of the studied compounds were observed not to conform to Lipinski rule of five. Thus, thirty-four (34) studied isatin(1H-indole-2,3-dione) derivatives showed the ability to act as a drug-like compound while the weight for two of the studied compounds was beyond the standard value for drug. Other calculated descriptors were presented in the supplementary file (Supp 1).

*QSAR Studies Using Combined Electronic and Geometric Descriptors*
Two sets of descriptors were obtained from the optimized compounds to develop the efficient and valid QSAR model (Equation 1). The two sets of obtained descriptors used in developing QSAR model were employed in order to achieve more predictive QSAR model. The optimized ligands were divided into training sets (70%) and test sets (30%). The calculated descriptors obtained from the studied compounds classified under the training set were screened.

**Table 1:** Studied Isatin (1H-indole-2,3-dione) Derivatives




| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ |
|---|---|---|---|---|---|---|
| **A1** | O | H | Br | H | Br | $H_2CCH{=}CH_2$ |
| **A2** | O | H | Br | H | Br | $H_2CCH_2OCH_3$ |
| **A3** | O | H | Br | H | Br | $H_2CCH_2CH(CH_3)_2$ |
| **A4** | O | H | Br | H | Br | $H_2CC_6H_5$ |
| **A5** | O | H | Br | H | Br | $H_2CC_6H_4CH_3$b |
| **A6** | O | H | Br | H | Br | $H_2CC_6H_4OCH_3$b |
| **A7** | O | H | Br | H | Br | $H_2CC_6H_4OCH_3$c |
| **A8** | O | H | Br | H | Br | $H_2CC_6H_4NO_2$b |
| **A9** | O | H | Br | H | Br | $H_2CC_6H_4NO_2$d |
| **A10** | O | H | Br | H | Br | $H_2CC_6H_4$Clb |
| **A11** | O | H | Br | H | Br | $H_2CC_6H_4$Brb |
| **A12** | O | H | Br | H | Br | $H_2CC_6H_4$Ib |
| **A13** | O | H | Br | H | Br | $H_2CC_6H_4CF_3$b |
| **A14** | O | H | H | Br | H | $H_2CC_6H_4CF_3$b |
| **A15** | O | H | Br | H | Br | $H_2CC_6H_4COOCH_3$b |
| **A16** | O | H | Br | H | Br | $H_2CCH{=}CHC_6H_5$ |
| **A17** | O | H | H | H | H | H |
| **A18** | O | Br | H | H | H | H |
| **A19** | O | H | F | H | H | H |
| **A20** | O | H | I | H | H | H |
| **A21** | O | H | NO2 | H | H | H |
| **A22** | O | H | OCH3 | H | H | H |
| **A23** | O | H | Br | H | Br | H |
| **A24** | O | H | I | H | I | H |
| **A25** | O | H | Br | H | NO2 | H |
| **A26** | O | H | Br | Br | Br | H |
| **A27** | N-C6H5 | H | H | H | H | H |
| **A28** | O | H | H | H | H | $CH_3$ |
| **A29** | O | H | Br | H | Br | $H_2$CCH2C6H5 |
| **A30** | O | H | Br | H | Br | $H_2CCH_2C_6H_4$Brc |
| **A31** | O | H | Br | H | Br | $H_2CCH_2C_6H_4$Brb |
| **A32** | O | H | Br | H | Br | $H_2CCH_2C_6H_4OCH_3$c |
| **A33** | O | H | Br | H | Br | $H_2CCH_2C_6H_4OCH_3$b |
| **A34** | O | H | Br | H | H | $CH_2COC_6H_4$Brc |
| **A35** | O | H | Br | H | Br | $CH_2COC_6H_4$Brb |
| **A36** | O | H | Br | H | Br | $CH_2COC_6H_4OCH_3$b |

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**Table 2:** Selected descriptors obtained from isatin(1H-indole-2,3-dione) derivatives

| | MW | LOG P | C6-C5 | HBD | HBA |
|---|---|---|---|---|---|
| **A1** | 344.99 | 0.80 | 1.438 | 0 | 3 |
| **A2** | 363.00 | -0.05 | 1.44 | 0 | 4 |
| **A3** | 375.06 | 1.68 | 1.441 | 0 | 3 |
| **A4** | 395.05 | 1.84 | 1.439 | 0 | 3 |
| **A5** | 409.07 | 2.33 | 1.442 | 0 | 3 |
| **A6** | 425.07 | 1.71 | 1.442 | 0 | 4 |
| **A7** | 425.07 | 1.71 | 1.441 | 0 | 4 |
| **A8** | 439.10 | 1.99 | 1.438 | 0 | 4 |
| **A9** | 440.04 | 1.87 | 1.441 | 0 | 6 |
| **A10** | 429.49 | 2.40 | 1.438 | 0 | 3 |
| **A11** | 473.94 | 2.67 | 1.442 | 0 | 3 |
| **A12** | 520.94 | 3.20 | 1.437 | 0 | 3 |
| **A13** | 463.04 | 2.76 | 1.437 | 0 | 3 |
| **A14** | 375.17 | 2.23 | 1.434 | 0 | 6 |
| **A15** | 453.08 | 1.66 | 1.438 | 0 | 4 |
| **A16** | 421.08 | 2.35 | 1.438 | 0 | 3 |
| **A17** | 147.13 | -0.40 | 1.431 | 1 | 3 |
| **A18** | 226.02 | -0.26 | 1.433 | 1 | 3 |
| **A19** | 165.12 | -0.93 | 1.431 | 1 | 3 |
| **A20** | 273.02 | 0.26 | 1.432 | 1 | 3 |
| **A21** | 192.13 | -1.09 | 1.437 | 1 | 6 |
| **A22** | 177.15 | -1.38 | 1.423 | 1 | 4 |
| **A23** | 304.92 | -0.13 | 1.429 | 1 | 3 |
| **A24** | 398.92 | 0.93 | 1.437 | 1 | 3 |
| **A25** | 271.02 | -0.96 | 1.44 | 1 | 6 |
| **A26** | 383.82 | 0.01 | 1.429 | 1 | 3 |
| **A27** | 222.24 | 1.72 | 1.433 | 1 | 3 |
| **A28** | 161.16 | -0.16 | 1.433 | 0 | 3 |
| **A29** | 409.07 | 2.12 | 1.438 | 0 | 3 |
| **A30** | 487.97 | 2.95 | 1.438 | 0 | 3 |
| **A31** | 487.97 | 2.95 | 1.438 | 0 | 3 |
| **A32** | 439.10 | 1.99 | 1.438 | 0 | 4 |
| **A33** | 439.10 | 1.99 | 1.438 | 0 | 4 |
| **A34** | 423.06 | 1.72 | 1.432 | 0 | 4 |
| **A35** | 501.95 | 1.85 | 1.404 | 0 | 4 |
| **A36** | 453.08 | 0.90 | 1.438 | 0 | 5 |

The selected descriptors were subjected to material studio using a genetic function algorithm (GFA) to develop QSAR model in order to predict the observed inhibition concentration ($IC_{50}$) from the screened and selected descriptors. Molecular weight (electronic descriptor) and C6-C5 (geometric descriptor) were selected and used to develop the model as shown in equation 1 and it was observed that the developed model which was made up of combined descriptors, proved to be efficient. The number of descriptors in the developed model obeyed the rule of ratio 1 to 4 of the total number of the studied compounds. The predicted $IC_{50}$ values were closer to the observed $IC_{50}$ value, and this was also confirmed via the residual values (Table 3 and Figure 1).

**Table 3:** The observed and the predicted inhibition concentration ($IC_{50}$)

| | Observed $IC_{50}$ | Predicted $IC_{50}$ | Residual Values |
|---|---|---|---|
| **A1** | 5.18 | 5.16 | 0.01 |
| **A2*** | 5.46 | 5.36 | 0.09 |
| **A3** | 5.62 | 5.48 | 0.13 |
| **A4** | 5.94 | 5.54 | 0.39 |
| **A5** | 6.31 | 5.74 | 0.56 |
| **A6** | 5.74 | 5.85 | -0.11 |
| **A7*** | 5.75 | 5.81 | -0.06 |
| **A8** | 6.05 | 5.80 | 0.24 |
| **A9** | 5.64 | 5.91 | -0.27 |
| **A10** | 6.01 | 5.73 | 0.27 |
| **A11** | 6.2 | 6.18 | 0.01 |
| **A12** | 5.64 | 6.31 | -0.67 |
| **A13** | 6.10 | 5.92 | 0.17 |
| **A14** | 5.28 | 5.22 | 0.05 |
| **A15** | 5.92 | 5.89 | 0.02 |
| **A16** | 5.63 | 5.68 | -0.05 |
| **A17** | 3.25 | 3.57 | -0.32 |
| **A18*** | 3.67 | 4.18 | -0.51 |
| **A19** | 4.01 | 3.69 | 0.31 |
| **A20** | 4.27 | 4.46 | -0.19 |
| **A21** | 3.88 | 4.10 | -0.22 |
| **A22** | 3.38 | 3.48 | -0.10 |
| **A23** | 4.98 | 4.56 | 0.41 |
| **A24** | 5.11 | 5.49 | -0.38 |
| **A25*** | 3.59 | 4.74 | -1.15 |
| **A26** | 5.17 | 5.10 | 0.06 |
| **A27** | 4.12 | 4.15 | -0.03 |
| **A28** | 3.62 | 3.74 | -0.12 |
| **A29** | 6.11 | 5.60 | 0.50 |
| **A30** | 6.11 | 6.13 | -0.02 |
| **A31** | 6.06 | 6.13 | -0.07 |
| **A32** | 5.97 | 5.80 | 0.16 |
| **A33** | 5.63 | 5.80 | -0.17 |
| **A34*** | 5.20 | 5.47 | -0.27 |
| **A35** | 5.04 | 4.97 | 0.06 |
| **A36** | 5.27 | 5.89 | -0.62 |

*denote test set

The calculated $R^2$ was 0.89 and this proved the effectiveness of the developed model since the value for $R^2$ must be $0.5 \leq x \leq 1$. The reliability of the developed model was examined by considering the Adj.$R^2$ ($0.6 \leq x \leq 1$) and CV.$R^2$ ($0.5 \leq x \leq 1$). In this work, the calculated value for Adj.$R^2$ was 0.89 and 0.87 for CV.$R^2$; this showed that the developed model is valid and reliable in predicting the biological activities of isatin(1H-indole-2,3-dione) based compounds (Table 3).

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*Molecular docking studies of Isatin(1H-indole-2,3-dione) derivatives and tumour necrosis factor-alpha complexes*

The role played by each of the ligands in inhibiting tumor necrosis factor-alpha was further identified and investigated using a docking study. Thirty-six (36) compounds were docked against tumor necrosis factor-alpha, and the binding affinity, residues involved in the interactions, and type of non-bonding interactions involved were presented in Table 4. As shown in Table 3, all the studied compounds proved to possess a better ability to inhibit tumor necrosis factor-alpha than the referenced drug. Also, compounds 9, 14, and 16 were observed to have a higher tendency to inhibit the studied receptor than other studied compounds and the referenced drug. The residues involved in the interactions between compounds 9, 14 and 16 were Phe144, Lys 65, Gly24, Gln25; Gly121, Tyr119, Tyr59 and Tyr59, Tyr119 respectively.

*Correlation between the Calculated Descriptors and Binding Affinity*

The role played by an individual calculated descriptor in inhibitory activities of each ligand against the studied receptor (tumor necrosis factor-alpha) cannot be overemphasized. The descriptors obtained from optimized compounds is expected to contribute to the role played by the studied drug-like compound in the active site of the studied receptor. Therefore, the correlation between the calculated descriptors and calculated binding affinity has been explored to investigate the role of each descriptor in the binding activity of the isatin(1h-indole-2,3-dione) derivatives in the active site of tumor necrosis factor-alpha. The accepted range for the $R^2$ is $0.5 \leq x \leq 1$;[24] thus, $R^2$ for molecular weight (MW), C6-C5, hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) against calculated binding affinity were 0.4543, 0.0264, 0.4166 and 0.0059 respectively. This showed that MW, C6-C5, HBD and HBA show no correlation with the binding affinity except Log P with squared correlation coefficient ($R^2$) of 0.6954, which proved to show a better correlation with the calculated binding affinity. This also revealed the role of Log P in isatin (1h-indole-2,3-dione) derivatives in inhibiting tumor necrosis factor-alpha when docked into its active site (Figure 2-6).

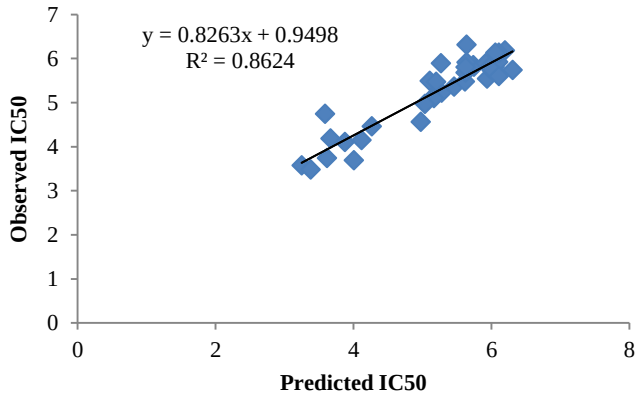


**Figure 1:** Correlation between observed $IC_{50}$ and predicted $IC_{50}$.

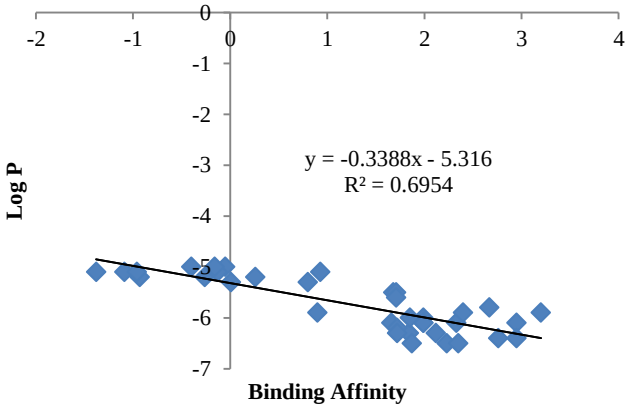


**Figure 2:** Correlation between Log P and calculated binding affinity.

**Table 4:** Calculated binding affinity and interactions between the studied complexes

| | Binding Affinity (kcal/mol) | Residues involved in the interactions | Types of Non-bonding interaction involved |
|---|---|---|---|
| **1** | -5.3 | Tyr59, Tyr151, Tyr119 | Conventional Hydrogen bond, Pi-Aklyl, Pi-Pi Stacked |
| **2** | -5.0 | Ile58, Tyr59 | Carbon Hydrogen Bond, Pi-Pi Stacked |
| **3** | -5.5 | Tyr151, Tyr119, Tyr59 | Conventional Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl |
| **4** | -6.3 | Tyr59, Tyr119 | Pi-Pi Stacked |
| **5** | -6.1 | Leu57, Ile155, Tyr59 | Pi-Pi Stacked, Pi-Alkyl, Alkyl |
| **6** | -5.5 | Tyr59 | Carbon Hydrogen Bond, Pi-Pi Stacked |
| **7** | -5.6 | Tyr59 | Pi-Pi Stacked |
| **8** | -6.0 | Tyr119, Tyr59 | Pi-Pi Stacked |
| **9** | -6.5 | Phe144, Lys 65, Gly24, Gln25 | Conventional hydrogen Bond, Pi-Pi T-shaped |
| **10** | -5.9 | Tyr59, Leu120, Tyr119 | Carbon Hydrogen Bond, Pi-Pi Stacked |
| **11** | -5.8 | Tyr59 | Pi-Pi Stacked |
| **12** | -5.9 | Tyr59, Tyr119, Leu120 | Carbon Hydrogen Bond, Pi-Pi Stacked |
| **13** | -6.4 | Ser60, Tyr59, Leu57, Tyr119, Tyr151 | Conventional Hydrogen Bond, Pi-Donor Hydrogen Bond, Pi-Pi Stacked, Pi-Pi T-shaped, Alkyl, Pi-Alkyl |
| **14** | -6.5 | Gly121, Tyr119, Tyr59 | Carbon Hydrogen Bond, Pi-Pi Stacked, Pi-Alkyl |
| **15** | -6.1 | Leu120, Gly121 | Carbon Hydrogen Bond, Pi-Pi Stacked |
| **16** | -6.5 | Tyr59, Tyr119 | Pi-Pi Stacked |
| **17** | -5.0 | Gly24, Gln25 | Conventional Hydrogen Bond |
| **18** | -5.2 | Gly24, Gln25 | Conventional Hydrogen Bond |
| **19** | -5.2 | Gln25, Gly24 | Conventional Hydrogen Bond |

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| | | | |
|---|---|---|---|
| **20** | -5.2 | Gln25, Gly24 | Conventional Hydrogen Bond |
| **21** | -5.1 | Gln25, Gly24 | Conventional Hydrogen Bond |
| **22** | -5.1 | Gln25, Gly24 | Conventional Hydrogen Bond |
| **23** | -5.1 | Tyr59, Tyr151 | Conventional Hydrogen Bond, Pi-Pi Stacked |
| **24** | -5.1 | His15, Leu57, Tyr59, Tyr151 | Conventional Hydrogen Bond, Pi-Pi Stacked, Alkyl, Pi-Alkyl |
| **25** | -5.1 | Tyr59, Tyr151 | Conventional Hydrogen Bond, Unfavourable Donor-Donor, Pi-Pi Stacked |
| **26** | -5.3 | Tyr59, Tyr151 | Unfavourable Donor-Donor, Pi-Pi Stacked |
| **27** | -6.2 | Tyr 151, Tyr59 | Conventional Hydrogen Bond, Pi-Pi Stacked |
| **28** | -5.0 | Tyr 59, Tyr 151 | Conventional Hydrogen Bond, Pi-Pi Stacked |
| **29** | -6.3 | Tyr59, Leu120, Tyr119, Gly121 | Carbon Hydrogen Bond, Pi-Pi Stacked |
| **30** | -6.1 | Gly121, Tyr119, Tyr59 | Carbon hydrogen bond, Pi-Pi Stacked |
| **31** | -6.4 | Tyr119, Tyr59 | Pi-Pi Stacked |
| **32** | -6.1 | Tyr151, Tyr59, Leu120, Tyr119, Gly121 | Conventional Hydrogen Bond, Carbon hydrogen bond, Pi-Pi Stacked |
| **33** | -6.1 | Tyr119, Tyr59 | Pi-Pi Stacked |
| **34** | -6.3 | Tyr119, Leu120, Tyr59 | Carbon hydrogen bond, Pi-Pi Stacked |
| **35** | -6.0 | Gly121, Tyr119, Tyr59 | Carbon hydrogen bond, Pi-Pi stacked |
| **36** | -5.9 | Glu135, Leu26, Asn46 | Conventional Hydrogen Bond, Carbon hydrogen bond, Pi-Anion |
| **5-FU** | -4.3 | - | - |

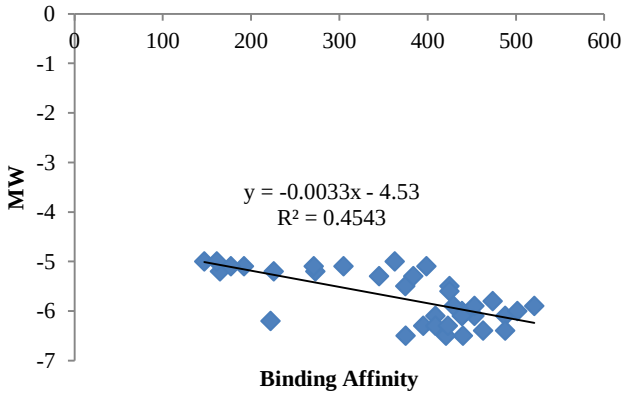


**Figure 3:** Correlation between molecular weight and calculated binding affinity.

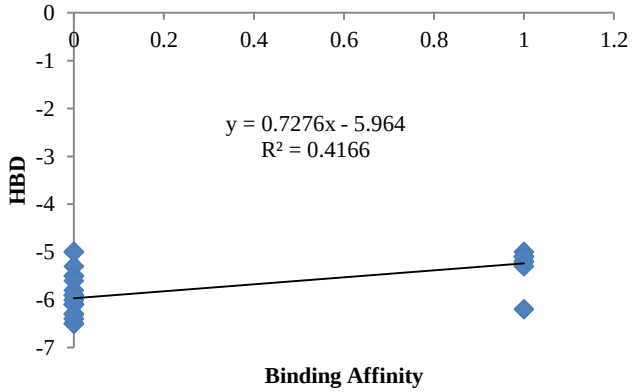


**Figure 5:** Correlation between HBD and calculated binding affinity.

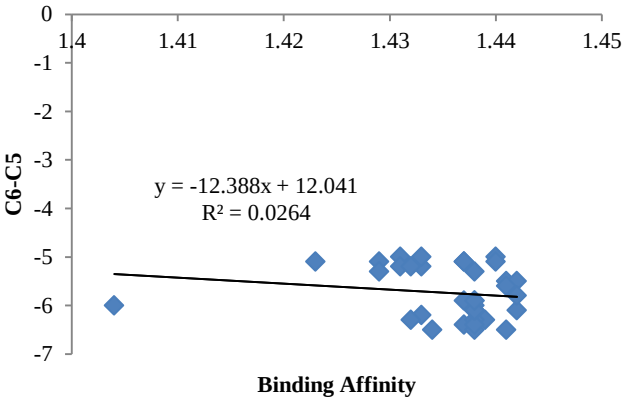


**Figure 4:** Correlation between C6-C5 and calculated binding affinity.

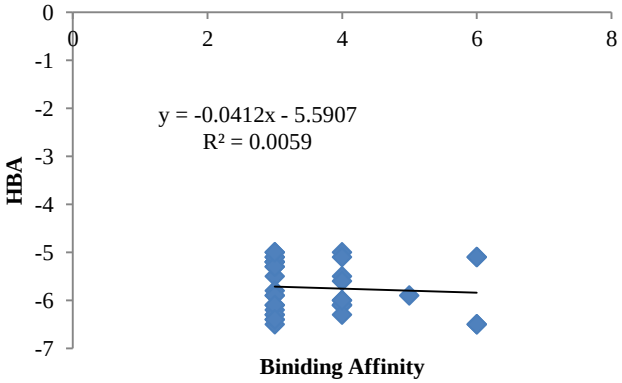


**Figure 6:** Correlation between HBA and calculated binding affinity.

## Conclusion

Tumor necrosis factor-alpha (TNF-α) with pleiotropic cytokine as one of its major component played a serious role in cancer development. Its operation keep advancing despite several efforts put in place by researchers to curb it action among human. Thus, in this work, thirty-six compounds were evaluated against tumor necrosis factor-alpha (TNF-α) via quantum chemical study, quantitative structure-activity relationship and molecular docking studies. The ability of the studied compounds to acts as a drug were evaluated using Lipinski rule of five and it was observed that all the studied compounds have the ability to act as a drug. The selected descriptors were used to develop QSAR model which proved to be predictive and this was confirmed and validated by considering squared correlation coefficient ($R^2$), adjusted squared correlation coefficient (adj. $R^2$), cross validation ($CVR^2$). The docked compound **9**, **14** and **16** against tumor necrosis factor-alpha (TNF-α) with -6.5 kcal/mol each proved to be effective than other studied compounds as well as the referenced drug. Also, the correlation between the selected descriptors and calculated binding affinity were examined and it was observed that plot of Log P against binding affinity obeyed $0.5 \leq x \leq 1$ which showed that Log P contributed to inhibitory activities of the studied compounds against tumor necrosis factor-alpha.

## Conflict of Interest

The authors declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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