Research article

Theoretical calculations of molecular descriptors for anticancer activities of 1, 2, 3-triazole-pyrimidine derivatives against gastric cancer cell line (MGC-803): DFT, QSAR and docking approaches

Rhoda Oyeladun Oyewole a, Abel Kolawole Oyebami jia,b, Banjo Semire a,*

a Department of Pure and Applied Chemistry, Faculty of Pure and Applied Sciences, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria
b Department of Basic Sciences, Adeleke University, P.M.B. 250, Ede, Osun State, Nigeria

ARTICLE INFO

Keywords:
Theoretical chemistry
1, 2, 3-triazole-pyrimidine derivatives
Human gastric cancer cells (MGC-803)
Anticancer
Molecular descriptors
Ligand conformations

ABSTRACTS

This work used quantum chemical method via DFT to calculate molecular descriptors for the development of QSAR model to predict bioactivity (IC50 - 50% inhibition concentration) of the selected 1, 2, 3-triazole-pyrimidine derivatives against receptor (human gastric cancer cell line, MGC-803). The selected molecular parameters were obtained by B3LYP/6-31G**. QSAR model linked the molecular parameters of the studied compounds to their cytotoxicity and reproduced their observed bioactivities against MGC-803. The calculated IC50 tailored the observed IC50 and greater than standard compound, 5-fluorouracil, suggesting that the developed QSAR model reproduced the observed bioactivity. Statistical analyses (including R2, CV. R2 and R2gave 0.950, 0.970 and 0.844 respectively) revealed a very good fitness. Molecular docking studies revealed the hydrogen bonding with the amino acid residues in the binding site, as well as ligand conformations which are essential feature for ligand-receptor interactions. Therefore, the methods used in this study are veritable tools that can be employed in pharmacological and medicinal chemistry researches in designing better drugs with improve potency.

1. Introduction

Globally, cancer kills within few months of diagnosis and over a million cases of death nowadays were resulted from cancer, thus posing serious burdens to the public (Song et al., 2017; Perez-Castillo et al., 2018; Ismail et al., 2019). Gastric cancer (GC) remains a common global malignancy with the second highest incidence and mortality rate of cancer diseases (Perez-Castillo et al., 2018; Ismail et al., 2019). Stomach cancer has been ranked 5th most common cancer globally, with diagnosed cases of 952,000 in 2012 and 723,000 deaths (WHO, 2014; Mustafa et al., 2017). Mostly, GC are gastric carcinoma and gastric antrum cancer, while the occurrence of gastroesophageal junction carcinoma is on the gradual increase. Analysis of the onset ages revealed that the occurrence of GC increases gradually among the youths (Li et al., 2015; Sun et al., 2015; Lee et al., 2017) and occurs twice as common in males than females (Mustafa et al., 2017), because estrogen probably protects women against the development of this form (Chandannos and Lagergren, 2008; Mustafa et al., 2017). Generally, GC patients are known to exhibit three high and three low characteristic features, this makes the incidence, metastasis and mortality rate to be significantly high (Ismail et al., 2019). To worsen the case, the early diagnosis and radical resection rates with five years survival rate are considerably low (Wu et al., 2015). Though, the exact causes of GC remain unclear, its pathogenesis is the same as that of other malignant tumors such as multistep and multifactorial comprehensive diseases (Song et al., 2017). Universally, GC cases are often categorized into early- and advanced-stages (Song et al., 2017; Sitarz et al., 2018). Early-stage GC are limited to the mucosa or sub-mucosa, irrespective of the lesion size and the presence of lymph node metastasis. While the cancer that extends beyond the sub-mucosa stage to invade the gastric muscular layer is regarded as middle GC, whereas, when tumors infiltrate beyond or into the subserosa to the nearby organs or metastasizes, they are defined as the advanced GC Song et al. (2017). This stage includes intermediate and advanced tumors. The treatment strategies and effectiveness are determined by the stages of the tumor. If for instance, the early GC patient undergoes radical surgery followed by chemotherapy, and the postoperative 5-years, then the rate of survival is 90%; thus, making the therapeutic effects of early GC acceptable (Song et al., 2017).

Realizing that successful treatment of cancer patients remains serious concerns and/or challenges for the researchers worldwide. Thus,
theoretical calculations of molecular descriptors as well as simulations of drug-like molecules with protein receptors are essentials for the prediction of the bioactivity and potency/efficacy of such molecules (Chill et al., 2003; Pogorzelska et al., 2015; Elshakre et al., 2020). Also, knowing the stable conformation, binding free energy and nonbonding interactions of the drug-like molecule in the active gouce of the protein receptor will help in understanding the pharmacokinetic of the drug interactions in the system (Slezd and Callisch, 2018; Marquina et al., 2019; Melge et al., 2019). Consequently, the role of computational chemist is not left out in the development of QSAR model that correlates molecular descriptors of the drug/drug like molecule to its bio-activity as well as simulating the drug-receptor interactions (docking) which govern kinetic mechanisms (Prachayasititkul et al., 2015; Gupta et al., 2018; Perez-Castillo et al., 2018).

Computational tools have gained tremendous significance in drug discoveries and design processes (Baldi, 2010; Ismail et al., 2019; Elshakre et al., 2020). Computational chemistry approach is often employed routinely for the study of drug-receptor complexes in atomic details and in calculating the properties of small-molecular drug candidates (Adedirin et al., 2018; Bello et al., 2018; Elshakre et al., 2020). Tool from information sciences and statistics are progressively important for organizing and managing the huge biological and chemical activity databases which are now possess by most pharmaceutical companies, so as to make the optimum use of these databases (Perez-Castillo et al., 2018). The most fundamental goal in using computer aided drug design is the prediction of various properties of drug, e.g. binding affinity to a certain target is necessary for biological activity (Ma et al., 2010; Vasaikar et al., 2016; Cruz-Monteagudo et al., 2017; Perez-Castillo et al., 2018). The principal benefit of this technique is that those properties can be predicted even before the candidates’ drug molecules are synthesized (Alam and Khan, 2017; Elshakre et al., 2020).

Table 1. Compound names of studied 1, 2, 3-triazole-pyrimidine hybrids system obtained from Figure 1.

| Compound | R₁ | R₂ | R₃ | Compound Name |
|----------|----|----|----|----------------|
| L₁       | p-OCH₃ | o-Cl | H  | 2-(1-(2-chlorobenzyl)-1H-1, 2, 3-triazol-4-yl)(methylthio)-4-((4-(methoxyphenyl)amino)-6-phenylpyrimidine-5-carbonitrile. |
| L₂       | m-CF₃ | o-Cl | H  | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-phenyl-6-(3-(trifluoromethyl)phenyl)amino) pyrimidine-5-carbonitrile. |
| L₃       | o-Cl | o-Cl | H  | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-((2-chlorophenyl)amino)-6-phenylpyrimidine-5-carbonitrile. |
| L₄       | p-Cl | o-Cl | H  | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-((4-chlorophenyl)amino)-6-phenylpyrimidine-5-carbonitrile. |
| L₅       | m-Cl | o-Cl | H  | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-((3-chlorophenyl)amino)-6-phenylpyrimidine-5-carbonitrile. |
| L₆       | o-OCH₃ | o-Cl | H  | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-((2-methoxyphenyl)amino)-6-phenylpyrimidine-5-carbonitrile. |
| L₇       | m-CH₃ | o-Cl | H  | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-phenyl-6-(3-(tolylamino)pyrimidine-5-carbonitrile. |
| L₈       | m-NO₂ | o-Cl | H  | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-((3-nitrophenyl)amino)-6-phenylpyrimidine-5-carbonitrile. |
| L₉       | o-F  | o-Cl | H  | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-((2-fluorophenyl)amino)-6-phenylpyrimidine-5-carbonitrile. |
| L₁₀      | p-F  | o-Cl | H  | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-((4-fluorophenyl)amino)-6-phenylpyrimidine-5-carbonitrile. |
| L₁₁      | o-CH₃ | o-Cl | H  | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-phenyl-6-(3-(tolylamino)pyrimidine-5-carbonitrile. |
| L₁₂      | o-F  | p-CH₃ | H  | 4-((2-fluorophenyl)amino)-2-((1-(4-methylbenzyl)-1H-1, 2, 3-triazol-4-yl) methylthio)-6-phenylpyrimidine-5-carbonitrile. |
| L₁₃      | p-CH₃ | p-CH₃ | H  | 2-(1-(4-Methylbenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-phenyl-6-(p-tolylamino)pyrimidine-5-carbonitrile. |
| L₁₄      | o-Cl | p-CH₃ | H  | 4-((2-fluorophenyl)amino)-2-((1-(4-methylbenzyl)-1H-1, 2, 3-triazol-4-yl) methylthio)-6-phenylpyrimidine-5-carbonitrile. |
| L₁₅      | p-CH₃ | o-Cl | H  | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-phenyl-6-(p-tolylamino)pyrimidine-5-carbonitrile. |
| L₁₆      | p-CH₃ | o-Cl | p-CH(CH₃)₂ | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-((4-isopropylphenyl)-6-(p-tolylamino)pyrimidine-5-carbonitrile. |
| L₁₇      | o-OCH₃ | o-Cl | p-CH(CH₃)₂ | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-((4-isopropylphenyl)-6-(p-tolylamino)pyrimidine-5-carbonitrile. |
| L₁₈      | p-CH₃ | o-Cl | p-CH₃ | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-(p-tolyl)-6-(p-tolylamino)pyrimidine-5-carbonitrile. |
| L₁₉      | p-CH₃ | o-Cl | m, p, m-triOCH₃ | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-(p-tolylamino)-6-(3, 4, 5-trimethoxyphenyl)pyrimidine-5-carbonitrile. |
| L₂₀      | p-CH₃ | o-Cl | p-Cl | 2-(1-(2-Chlorobenzyl)-1H-1, 2, 3-triazol-4-yl) (methylthio)-4-((4-chlorophenyl)amino)-6-(p-tolylamino)pyrimidine-5-carbonitrile. |
Pyrimidine containing sulfa drugs are classified on the basis of substitution and the classification with the respective example of drug is as follows. Monosubstituted and disubstituted sulfa drugs include sulfadimidine (sulfamethazine), sulfamerazine, sulfamethyldiazine, methyldiazine and sulfadiazine. Trisubstituted sulfa drugs are sulfadoxine, sulfadimethoxine, sulfamethomidine, sulfosomidine, sulfamethoxine, and sulfacytine. Sulfadoxine which has a half-life of 7–9 days was used for malarial prophylaxis (White, 1996). Pyrimidinones scaffolds represent the class of a heterocyclic compounds that possess noteworthy pharmacological efficiencies (Sharma et al., 2014; Fumagalli et al., 2017; El-Shahawi and El-Ziaty, 2017; Rogerio et al., 2018). For example: antiviral (Choi et al., 2000; Parveen et al., 2010), anti-HIV (McGuigan et al., 2000; Pontikis et al., 2000), anti-bacterial (Palanki et al., 2000) and anticancer (Martin et al., 2000; Curtin et al., 2004; Rostom et al., 2009; Conejo-García et al., 2011).

**Table 2.** Selected molecular parameters obtained by B3LYP/6-31G** for anticancer.

| Comp | HOMO | LUMO | BG | SE | \(\eta\) | \(\mu\) | MW | Ovality | Log P |
|------|------|------|----|----|-------|------|----|---------|-------|
| L1   | -5.57| -1.99| 3.58| -44.98| 1.79  | -3.78| 540.051| 1.73   | 6.25  |
| L2   | -6.25| -2.04| 4.21| -26.52| 2.105 | -4.145| 578.022| 1.74   | 7.3   |
| L3   | -6.03| -1.85| 4.18| -35.28| 2.09  | -3.94 | 544.47  | 1.71   | 6.94  |
| L4   | -5.94| -1.92| 4.02| -33.58| 2.01  | -3.93 | 544.47  | 1.72   | 6.94  |
| L5   | -6.08| -1.98| 4.1| -32.3| 2.05  | -4.03 | 544.47  | 1.71   | 6.94  |
| L6   | -5.71| -1.93| 3.78| -40.76| 1.89  | -3.82 | 540.051 | 1.72   | 6.25  |
| L7   | -6.16| -1.95| 4.21| -44.86| 2.105 | -4.055| 524.052 | 1.71   | 6.87  |
| L8   | -6.14| -2.01| 4.13| -54.69| 2.065 | -4.075| 557.038 | 1.72   | 6.02  |
| L9   | -6.21| -2.04| 4.17| -33.81| 2.085 | -4.125| 528.015 | 1.68   | 6.54  |
| L10  | -5.91| -1.93| 3.98| -30.05| 1.99  | -3.92 | 528.015 | 1.7    | 6.54  |
| L11  | -5.88| -1.9| 3.98| -32.44| 1.99  | -3.89 | 524.052 | 1.71   | 6.87  |
| L12  | -6.08| -1.94| 4.14| -38.16| 2.07  | -4.01 | 503.634 | 1.72   | 6.79  |
| L13  | -6.08| -1.96| 4.12| -33.14| 2.06  | -4.02 | 524.052 | 1.71   | 6.87  |
| L14  | -5.81| -1.9| 3.91| -34.87| 1.955 | -3.855| 524.052 | 1.71   | 6.87  |
| L15  | -5.68| -1.71| 3.97| -31.22| 1.985 | -3.695| 566.133 | 1.78   | 8.1   |
| L16  | -5.83| -1.93| 3.9| -27.49| 1.95  | -3.88 | 566.133 | 1.77   | 8.1   |
| L17  | -5.85| -1.99| 3.86| -38.92| 1.93  | -3.92 | 538.07  | 1.75   | 7.35  |
| L18  | -5.79| -2.06| 3.73| -40.61| 1.865 | -3.925| 614.13  | 1.81   | 6.49  |
| L19  | -5.95| -2.02| 3.93| -38.49| 1.965 | -3.985| 558.497 | 1.75   | 7.42  |
| L20  | -5.96| -2.18| 3.78| -39.98| 1.89  | -4.07 | 602.948 | 1.74   | 7.69  |

*Comp: compound, HOMO: highest occupied molecular orbital, LUMO: lowest unoccupied molecular orbital, BG: band gap, SE: solvation energy, \(\eta\): chemical hardness, \(\mu\): chemical potential, MW: molecular weight, LogP: hydrophobicity, DM: dipole moment.*
Lopez-Cara et al., 2011; Jin et al., 2011; Zhu et al., 2013; Morales et al., 2014). Abdel-Mohsen et al. (2010) reported the potent antitumor agent and cytotoxic activity of benzimidazole pyrimidine conjugate. The study of 1, 2, 3-triazole moiety combined with pyrimidine derivatives is a new hybrid system that remains an unexplored research field in the area of theoretical/computation chemistry. Despite a notable success of the 1, 2, 3-triazole and pyrimidine as good anti-cancer activity, its theoretical investigations still remain unexplored and emergent area. Also, developing a new drug still remains major challenge, time consuming and cost intensive processes. Owing to the enormous expenses or failure of most candidate drugs found in the market, their developments presently face liability such as possible side effects, in addition to their therapeutic properties. This makes the computational approach a hot topic and novel method due to its ability to speed up and assist drug design processes (Kumari et al., 2017). Therefore, this research aimed at calculating the molecular descriptors for anticancer activities of 1, 2, 3-triazole-pyrimidine hybrids using quantum chemical method and calculations of binding free energy via molecular docking. This was limited to the use of DFT and to develop QSAR model that correlates molecular descriptor with bio-activities of the 20 molecules from 1, 2, 3-triazole-pyrimidine hybrids reported by Ma et al. (2014) and finally, to calculate binding free energies of the stable conformation for the ligand-receptor complexes.

2. Materials and methods

The major materials used for this work were software (Spartan 14 for quantum chemical calculations, Gretl for QSAR modeling, Discovery studio 4.1 for preparation of both ligand and receptor, Autodock

| Compd | DM  | PSA  | Area | HBD | HBA | POLAR | Volume | HET | NOR |
|-------|-----|------|------|-----|-----|--------|--------|-----|-----|
| L1    | 3.55| 63.812| 539.77| 0   | 8   | 82.62  | 518.87 | 10  | 5   |
| L2    | 4.02| 56.96 | 545.26| 0   | 7   | 82.85  | 523.59 | 12  | 5   |
| L3    | 6.63| 55.694| 524.23| 0   | 7   | 81.36  | 505.1  | 10  | 5   |
| L4    | 5.18| 57.679| 526.97| 0   | 7   | 81.44  | 505.6  | 10  | 5   |
| L5    | 6.5 | 58.249| 525.32| 0   | 7   | 81.4   | 505.41 | 10  | 5   |
| L6    | 3.68| 61.257| 538.28| 0   | 8   | 82.85  | 518.63 | 10  | 5   |
| L7    | 5.9 | 58.608| 529.33| 0   | 7   | 81.74  | 509.93 | 9   | 5   |
| L8    | 2.65| 104.593| 536.28| 1   | 10  | 82.49  | 518.83 | 12  | 5   |
| L9    | 3.21| 57.413| 510.17| 0   | 7   | 80.62  | 495.92 | 10  | 5   |
| L10   | 3.3 | 58.468| 515.43| 0   | 7   | 80.7   | 496.34 | 10  | 5   |
| L11   | 2.33| 57.185| 526.95| 0   | 7   | 81.76  | 509.43 | 9   | 5   |
| L12   | 4.89| 58.158| 532.64| 0   | 7   | 82.13  | 514.41 | 8   | 5   |
| L13   | 4.05| 57.194| 527.18| 0   | 7   | 81.73  | 509.47 | 9   | 5   |
| L14   | 2.54| 56.777| 528.95| 0   | 7   | 81.8   | 509.77 | 9   | 5   |
| L15   | 5.34| 57.236| 589.15| 0   | 7   | 86.26  | 564.87 | 9   | 5   |
| L16   | 1.82| 56.239| 585.25| 0   | 7   | 86.23  | 564.33 | 9   | 5   |
| L17   | 3.95| 59.366| 552.15| 0   | 7   | 83.33  | 528.51 | 9   | 5   |
| L18   | 1.5 | 77.827| 616.19| 0   | 10  | 88.46  | 591.33 | 12  | 5   |
| L19   | 6.99| 58.575| 548.48| 0   | 7   | 82.94  | 523.81 | 10  | 5   |
| L20   | 1.65| 57.663| 551.29| 0   | 7   | 83.34  | 528.32 | 10  | 5   |

*PSA: polar surface area, HBD: hydrogen bond donor, HBA: hydrogen bond acceptor, HET: heteroatoms, NOR: number of organic residues.

Figure 3. The correlation between observed and predicted IC$_{50}$ for MGC-803.
exchange correlation (Becke, 1993) and the Lee, Yang, Parr correlation three parameters density functional which includes Becke’s gradient, standard 6-31G** (d, p) basis set. The DFT method used consists of the

2.3. Quantum chemical method

(displayed iteratively until new equilibrium geometry is reached which is
during this process, atoms, bond length and bond angle of the molecules
searching for the equilibrium or minimum energy of conformation.

Table 1 . The standard drug used was 5-
twenty (20) derivatives (take from Ma et al. (2014) as presented in

2.3. Quantum chemical method

The equilibrium geometries for the 1, 2, 3-triazole-pyrimidine hy-
broids (Table 1) used in this study were optimized using DFT with the
standard 6-31G** (d, p) basis set. The DFT method used consists of the three parameters density functional which includes Becke’s gradient, exchange correlation (Becke, 1993) and the Lee, Yang, Parr correlation functional (i.e. B3LYP) (Yang et al., 2005). The choice of the selected

Table 4. Experimental and predicted IC50 for MGC-803.

| Mol  | Predicted | Observed |
|------|-----------|----------|
| L1   | 11.59     | 7.56     |
| L2   | 24.44     | 22.83    |
| L3   | 5.48      | 4.64     |
| L4   | 3.30      | 5.85     |
| L5   | 6.72      | 15.82    |
| L6   | 5.90      | 5.80     |
| L7   | 24.34     | 16.15    |
| L8   | 43.07     | 43.07    |
| L9   | 9.18      | 7.58     |
| L10  | 4.75      | 8.74     |
| L11  | 13.05     | 7.28     |
| L12  | 56.60     | 64.00    |
| L13  | 22.74     | 17.28    |
| L14  | 1.03      | 7.19     |
| L15  | 66.59     | 64.00    |
| L16  | 60.19     | 64.00    |
| L17  | 27.66     | 24.44    |
| L18  | 29.38     | 30.75    |
| L19  | 19.00     | 18.54    |
| L20  | 16.14     | 15.63    |

(autodock tool 1.5.6 and autodock vina 1.1.2) for docking and bonding energy evaluation and pymol 1.7.4.4 for molecular visualization).

2.1. Quantum chemical software (Spartan)

Spartan 14 is a molecular modeling environment that is well-known for its equity, flexibility, ease of use and a tool for exploring organic, bio-organic, inorganic and organic chemistry through molecular mechanics and quantum chemical calculations, together with an array of graphical model for conveying the results of those calculations. It is also employed for molecular orbital calculations as well as wide ranges of graphical models with a full range of molecular mechanism, semi-empirical method, DFT and a section of wave function based on the important post-hartree fork model (Desai et al., 2001).

2.2. Minimization and optimization

In this research, 1, 2, 3-triazole-pyrimidine hybrids (Figure 1) were used to perform quantum calculations for molecular descriptors, QSAR model and docking simulation. The compounds (Figure 1) consist of twenty (20) derivatives (take from Ma et al. (2014) as presented in

2.2. Minimization and optimization

In this research, 1, 2, 3-triazole-pyrimidine hybrids (Figure 1) were used to perform quantum calculations for molecular descriptors, QSAR model and docking simulation. The compounds (Figure 1) consist of twenty (20) derivatives (take from Ma et al. (2014) as presented in

2.2. Minimization and optimization

In this research, 1, 2, 3-triazole-pyrimidine hybrids (Figure 1) were used to perform quantum calculations for molecular descriptors, QSAR model and docking simulation. The compounds (Figure 1) consist of twenty (20) derivatives (take from Ma et al. (2014) as presented in

2.3. Quantum chemical method

The equilibrium geometries for the 1, 2, 3-triazole-pyrimidine hybrids (Table 1) used in this study were optimized using DFT with the standard 6-31G** (d, p) basis set. The DFT method used consists of the three parameters density functional which includes Becke’s gradient, exchange correlation (Becke, 1993) and the Lee, Yang, Parr correlation functional (i.e. B3LYP) (Yang et al., 2005). The choice of the selected

Table 4. Experimental and predicted IC50 for MGC-803.

| Mol  | Predicted | Observed |
|------|-----------|----------|
| L1   | 11.59     | 7.56     |
| L2   | 24.44     | 22.83    |
| L3   | 5.48      | 4.64     |
| L4   | 3.30      | 5.85     |
| L5   | 6.72      | 15.82    |
| L6   | 5.90      | 5.80     |
| L7   | 24.34     | 16.15    |
| L8   | 43.07     | 43.07    |
| L9   | 9.18      | 7.58     |
| L10  | 4.75      | 8.74     |
| L11  | 13.05     | 7.28     |
| L12  | 56.60     | 64.00    |
| L13  | 22.74     | 17.28    |
| L14  | 1.03      | 7.19     |
| L15  | 66.59     | 64.00    |
| L16  | 60.19     | 64.00    |
| L17  | 27.66     | 24.44    |
| L18  | 29.38     | 30.75    |
| L19  | 19.00     | 18.54    |
| L20  | 16.14     | 15.63    |

(autodock tool 1.5.6 and autodock vina 1.1.2) for docking and bonding energy evaluation and pymol 1.7.4.4 for molecular visualization).

2.1. Quantum chemical software (Spartan)

Spartan 14 is a molecular modeling environment that is well-known for its equity, flexibility, ease of use and a tool for exploring organic, bio-organic, inorganic and organic chemistry through molecular mechanics and quantum chemical calculations, together with an array of graphical model for conveying the results of those calculations. It is also employed for molecular orbital calculations as well as wide ranges of graphical models with a full range of molecular mechanism, semi-empirical method, DFT and a section of wave function based on the important post-hartree fork model (Desai et al., 2001).

2.2. Minimization and optimization

In this research, 1, 2, 3-triazole-pyrimidine hybrids (Figure 1) were used to perform quantum calculations for molecular descriptors, QSAR model and docking simulation. The compounds (Figure 1) consist of twenty (20) derivatives (take from Ma et al. (2014) as presented in

2.3. Quantum chemical method

The equilibrium geometries for the 1, 2, 3-triazole-pyrimidine hybrids (Table 1) used in this study were optimized using DFT with the standard 6-31G** (d, p) basis set. The DFT method used consists of the three parameters density functional which includes Becke’s gradient, exchange correlation (Becke, 1993) and the Lee, Yang, Parr correlation functional (i.e. B3LYP) (Yang et al., 2005). The choice of the selected

functional and basis sets was attributed to the accuracy of DFT calculations. The sufficiency of polarized split-valence 6-31G** (d, p) basis sets have been demonstrated for the calculated of the excited properties of ligands (Jacquemin et al., 2008); this (i.e. 6-31G** (d, p) basis set) was therefore employed in this study. Frequency calculations were carried out at the same levels of the theory in order to characterize the stationary points as local minima and none of the optimized molecules has imaginary frequency. The molecules under study were designed to generate molecular descriptors that described the bioactivity (IC50) and binding affinity upon docking of the molecules with receptors (Table 1).

DFT is very useful in providing chemical descriptors such as chemical hardness (η), electronegativity (χ), softness (S), electrophilicity index (μ) and local Fukui function indices. Zhou and Navangul (1990) reported the principle of maximum hardness (absolute hardness) η, for an N-electron system with total energy E and η are defined as:

where IE is the vertical ionization energy which is approximated as -EHOMO and EA for the vertical electron affinity, denoted as -ELUMO (Koopmans, 1934). The global softness is the inverse of chemical hardness 

The electron affinity can also be used in combination with ionization energy to give electronic chemical potential, µ as shown in Eq. (2). The negative of electron affinity (-χ) was defined by Parr and Pearson (Zhou and Navangul, 1990), as the characteristic of electronegativity of molecules:

The global electrophilicity index, ω, was introduced by Parr et al. (1999); this can be calculated using the electronic chemical potential, μ and chemical hardness, η, as

As shown in the definition, this index measured the propensity of a species to accept electrons. Domingo (2002) proposed that high nucleophilicity and electrophilicity of heterocycles corresponded to the opposite extreme of the scale of global reactivity indexes. A good and more reactive nucleophile is characterized by a lower value of μ, ω, and in the opposite, a good electrophile was characterized by a high value of μ, ω.

2.4. Molecular descriptors

The molecular descriptors selected for this research were based on electronic properties of the studied compounds. These descriptors were the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO), HOMO-LUMO band gap, softness, chemical hardness, chemical potential, dipole moment, solvation energy, global nucleophilicity, log P, Ovality, area volume, polar surface area (PSA) and polarizability.

2.5. Multiple linear regressions

Multiple linear regression analysis (MLR) is used to examine the relationship between two or more independent variables and one dependent variable. MLR has been a veritable method used to investigate the correlation between biological activity and physicochemical properties of a set of bioactive compounds. It describes how a y-variable relates to two or more x-variables (or transformations of x-variables). The software used in this research work was Grelt which helped in generating equation which be expressed as:
where $X$ is the regressor (also called the predictor or independent variable), $Y$ is the response (also called the dependent variable), $\alpha$ and $\beta$ are parameters that describe the relationship between $X$ and $Y$, and the term $\varepsilon$ represents the error model (the errors are also referred to as residuals) (Rob, 2014). Therefore, $R^2$ was considered for the linearity and efficiency of the analysis.

Tolerance and variance inflation factor (V.I.F) were examined for the validity of the analysis. The highest correlation of independent variables with dependent variable was chosen for deriving the QSAR model. The statistical values, multiple correlation coefficients ($r$), standard error(s), cross validation $R^2$ and standard error of prediction were used to evaluate the QSAR models. Several combinations of independent variables which obey the necessary rules for the validity of analysis were added in order to optimize the statistical values. The best model derived from the MLR

$$Y = \alpha + \beta X + \varepsilon$$  \hspace{1cm} (4)
analysis was used to predict the inhibitory activity of the 1, 2, 3-triazole-pyrimidine derivatives considered. To avoid self-correlation between the variables used for the derivation of QSAR model, the tolerance and V. I. F. rules were strictly adhered to. Figure 2 shows the various steps involved in QSAR modeling process.

2.6. Validation of QSAR model

The statistical equations were used to validate the QSAR model. The cross validation ($R^2$), Adjusted $R^2$, Chi-square, standard error, Root Mean Square Error (RMSE) and F-test were considered in this study. Cross-validation governed how reliable a QSAR model could be used for a particular set of data (Puzyn et al., 2010). It was also employed as an analytic instrument to estimate the prognostic control of an equation. Therefore, it was estimated using Eq. (5).

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

The $R^2$ adjusted could be calculated using Eq. (6)

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

Thus, QSAR model is considered prognostic, if $R^2_{adj} > 0.6$. $R^2$ is a statistical measure of how close the data are to the fitted regression line. It is also known as the coefficient of determination, or the coefficient of multiple determinations for multiple regressions. The implication is that the closer the $R^2$ value to 1 (unity), the better fits it is. Thus, the higher the $R^2$ value, the better the model fits the data.

Figure 5. Transparent view of docked complexes showing ligand-receptor interactions in the binding pocket for the compounds L2, L5, L7, L8, L12-L13 against MGC-803 using Pymol.
2.7. Molecular docking and binding energy evaluation

Molecular interactions are in several forms including protein-nucleic acid, enzyme substrate, protein-protein, drug protein and drug nucleic acid. They play imperative role in several essential biological processes, like cell regulations, gene expression controls, enzyme inhibitions, signal transduction, transport, antibody-antigen recognitions, and even the assemblies of multi-domain proteins. These types of interactions mostly bring about formations of stable protein–protein or protein-ligand complexes that are necessary to carry out their biological functions. Therefore, molecular docking helps in predicting the conformation of receptor-ligand complexes, the specific receptors of interest (usually proteins or nucleic acid molecules) was gotten from the protein data bank (www.proteindatabank.com) and the ligands are the molecules (Alejandra et al., 2013).

2.8. Discovery studio

Discovery studio is software for simulating molecules; it was developed and distributed by acceryls. It has a strong academic collaboration programmes that supports scientific researches (Young, 2001). Also, it is used in preparing (i.e. removal of water molecule and any other residues apart from the desired compound) the ligand and the receptor before subjecting them to docking using autodock tool software.

2.9. Autodock

Autodock tool was designed to simulate how small a molecule, such as substrate or drug candidate bind to receptor of known 3D structures. This helps to locate the active binding site (active gorge) in the receptor. In this work, Autodock vina was used, it is a novel generation of docking software from the molecular graphic laboratory (Trott and Olson, 2010). It achieves noteworthy improvement in the average accuracies of the binding mode predictions. It does not require the choose of atom type(s) and pre-calculated grid map (Morris et al., 2009). Instead, it calculates the grid internally; for the atom type that is needed, and does that virtually instantly (Eswar et al., 2006). The following commands are required to achieve the desired goals; vina –config conf.txt –log log.txt to do the calculation and vinasplit –input out.pdbqt to split the result in the order of scoring. Finally, Pymol, a post docking software was used to view the conformation and hydrophobic interactions of the ligands with the receptors.

Figure 6. Transparent view of docked complexes showing ligand-receptor interactions in the binding pocket for the compounds L15-L20 against MGC-803 using Pymol.
Table 5. Interaction among residues of drugs and SACM.

| Mol | Binding Energy (kcal/mol) | IC50 (μM) | H-Bond Between Amino Acid and Drug | Distance of H-Bond Between Amino Acid and Drug (Å) |
|-----|--------------------------|-----------|-----------------------------------|-----------------------------------------------|
| L1  | -0.7                     | 7.56      | THR-72, LIG:N                     | 2.7                                           |
| L2  | -0.9                     | 22.83     |                                   |                                               |
| L3  | -10.0                    | 4.64      | (i) GLU-52, LIG:N (ii) GLU-52, LIG:N (iii) GLU-52, LIG:N | 2.8, 3.1, 2.8 |
| L4  | -10.2                    | 5.85      | (i) THR-23, LIG:N (ii) SER-21 LIG:N | 1.9, 1.6                                      |
| L5  | -9.8                     | 15.82     |                                   |                                               |
| L6  | -9.2                     | 5.8       |                                   |                                               |
| L7  | -10.1                    | 16.15     | (i) GLU-52, LIG:N (ii) GLU-52, LIG:N | 2.5, 2.8                                      |
| L8  | -10.2                    | 43.07     | (i) TYR-38, LIG: H (ii) TYR-93, LIG:O (iii) TYR-34, LIG:O (iv) TYR-34, LIG:O (v) SER-91, LIG:O (vi) SER-91, LIG:N | 1.9, 2.7, 2.8, 3.1, 2.7, 2.2 |
| L9  | -9.6                     | 7.58      | (i) SER-36, LIG:N (ii) TYR-38, LIG:H | 2.7, 2.1                                      |
| L10 | -9.7                     | 8.74      |                                   |                                               |
| L11 | -10.3                    | 7.28      |                                   |                                               |
| L12 | -9.0                     | 64        | (i) TYR-34, LIG:N (ii) SER-91, LIG:N | 3.3, 3.0                                      |
| L13 | -8.7                     | 17.28     | TYR-34, LIG:N                     | 2.2                                           |
| L14 | -10.0                    | 7.19      | ASP-87 LIG:N                      | 3.0                                           |
| L15 | -9.4                     | 64        |                                   |                                               |
| L16 | -9.3                     | 64        |                                   |                                               |
| L17 | -10.3                    | 24.44     | GLN—40, LIG: N                   | 3.5                                           |
| L18 | -8.0                     | 30.75     | (i) THR-19, LIG: O (ii) SER-2.3, LIG: O (iii) SER-11, LIG:O | 1.5, 2.3, 2.3 |
| L19 | -3.2                     | 18.54     | SER-91, LIG:N                     | 1.0                                           |
| L20 | -10.0                    | 15.63     | (i) THR-72, LIG: N (ii) THR-19, LIG: N (iii) THR-19, LIG:N | 1.5, 2.0, 2.5 |
| 5-Fu| -4.2                     | 7.69      |                                   |                                               |

3. Results and discussion

3.1. Calculated molecular properties of compounds L1-L20 used for testing anticancer property

In this work, several calculated molecular parameters including solvation energy, weight, hydropobicity (LogP), volume (V), area, polar surface area (PSA), ovality, dipole moment (DM), heteroatoms (average of Mulliken charges on all heteroatoms), HOMO, and LUMO energies were obtained as shown in Tables 2 and 3. The HOMO and LUMO are very important parameters which give convincing qualitative details about the excitation features of modeled compounds (Bouachrine et al., 2009, Yang et al., 2005, and Semire et al., 2012). As expected, the HOMO and LUMO energies along with the band gap energies of the compounds L1-L20 played essential role in binding the molecular compounds to the enzymes. Thus, the magnitude of these parameters determines the extent of nonbonding interactions such as hydrogen bonding and hydrophilic interactions between the receptor and ligand. The calculated HOMO and LUMO values for Compounds L1-L20 are presented in Table 2. High values of HOMO energy are indication of enhanced ability of the ligand to donate electron to the neighboring compounds (Oyebamiji and Semire, 2016a). Whereas, the lower values of LUMO energy imply that the studied molecular compounds have the ability to receive electrons from the neighboring compound which has the ability to donate electron (Oyebamiji and Semire, 2016a,b).

The calculated band gaps obtained by ground-state properties, from which the band gap is estimated from the energy difference between the LUMO and HOMO (Curioni et al., 1998; Hay, 2002) are presented in Table 2. The band gaps are essentially left-over energy ranges that are not concealed by any band as a result of the finite widths of the energy bands (Table 2). The lower the band gap, the better the capacity of a compound to donate electron to the neighbouring molecules. Thus, based on aforementioned facts, band gap played an important role in protein–ligand interaction between bioactivity of the studied drug-like compounds. Moreover, the calculated Log P reveals the capacity of the drug-like molecule to melt in lipophilic (non-aqueous) solutions. Drug-like compounds need this to infuse through several biological membranes. Lipophilicity is classically measured as the distributions of the molecules between the aqueous and non-aqueous phases and it shows the cytotoxicity of ligands (Khaled et al., 2011). The calculated Log P values are shown in Table 2 showing that the compounds L1-L20 were not effective in term of lipophilicity when considered the value of Meanwell (2011). The value obtained in this study are slightly higher than the Log P value of 5 reported by Meanwell (2011). This suggest that the Log P is not enough to validate effectiveness of the compounds under this study in term of lipophilicity.

Furthermore, the solvation energy (SE) was calculated using SM5.4 model based on semi-empirical (AM1) wave functions (Liu and Zou, 2006; Oyebamiji and Semire, 2016a,b). The SE consists of the summation of two terms which are: the required energy for creating a...
cavity in the solvent (water) and the energy of the electrostatic interactions between the solvent and the solute once the solute/molecule is placed in the cavity (Oyebamiji and Semire, 2016a). The equilibrium geometries as well as spectra and any property derived from the wave function are unaffected by SM5.4 model for SE calculation (Hehre, 2003). The SIs for compound L1-L20 are presented in Table 2. L8 was observed to be better in term of SE, since high value of SE adds to the drug resistance (Lowrey et al., 1997).

More so, DM which is the product of the charge at both ends of the dipole of the molecule and the distance between the charge of molecules were calculated as reported in Table 3. Moreover, the rare features of every single molecule studied was believed to be a function of larger value of DM (Debenedetti, 2003). The natures of non-bonded interactions are very critical in the relationship between ligand and the enzyme in which DM affects. The values established for DM of molecular compounds falls between 3 and 5 kJ/mol ( David and Howard, 2002). This implies that almost all DM values obtained in this study fall within the accepted range except the value for L3, L4, L5, L7, L15 and L19 which are just slightly greater than 5 by only <2 suggesting their fairly acceptability as shown in Table 3. Therefore, all compounds having their values within the expected range should be stout in non-bonded interactions with the enzymes. Also, every molecular descriptor that was calculated was reviewed, in order to check if any relationship with bioactivity (IC50) could be observed.

3.2. QSAR model for human gastric cell line (MGC-803) using multiple linear regressions (MLR)

The use of QSAR brings about the proficient way of procuring a whole set of values, and this has nothing to do with the need of performing costly laboratory experiments. Also, in drug design and medicinal chemistry, QSAR is one of the treasured implements and most essential areas in chemometric which are comprehensively used (Hansch et al., 1990; Manly et al., 2001; Pourbasheer et al., 2010; Prachayasititkul et al., 2014, 2015). In this study, thirteen calculated descriptors (Eq. 7) were employed in the development of QSAR model which were used against human gastric cell line. The developed QSAR model related the activities of the studied compounds to their biological activities and this showed the effectiveness of the equation generated via the model as shown in Eq. (7).

Moreover, the calculated IC50 tailored the observed IC50 as presented in Figure 3 which means that the developed QSAR model reproduced the observed bioactivity of the studied compounds. Thus, the combination of selected calculated descriptors as shown in Eq. (7) were observed to act well as anti-gastric cancer activity of the studied compounds. Furthermore, the QSAR model equation using thirteen descriptors for evaluation MGC-803 as shown in Eq. (7) was employed to determine the values CV.R2 and R2. The statistical analyses of R2, CV.R2 and R2 (obtained from Eqn. 7) were 0.950, 0.970 and 0.844 respectively revealing a very good fitness. Table 4 presents the observed and predicted IC50 for MGC 803. By comparison, the observed and predicted are well correlated with only little negligible differences in some cases. However, while some predicted values were not perfectly correlated with the observed values, did not in any way imply their inactivity against MGC-803, rather, indicated their less activities, ranging from moderate to good activity.

3.3. Docking studies for human gastric cancer cell line (MGC-803)

Docking studies aimed at observing the interactions between ligand and the receptor to ascertain the precise configuration of the studied molecules in the course of receptor. In addition, it usually employs to predict the affinity of the ligand towards the protein (Harsha, 2011; Gupta et al., 2018). Therefore, in this present study, twenty compounds denoted as L1-L20 were docked against human gastric cell line; MGC-803 (PDB ID: 5ACM). The docking simulations performed on the compounds L1 to L20 were presented in Figures 4, 5, and 6. Table 5 is showing the interactions among residues of drugs and 5ACM obtained from the protein data bank. This showed that all compounds exhibited related binding energy (Table 5). The binding energies of compounds L1-L20 ranges from −3.2 to −10.3 kcal/mol and the distance of H-bond between amino acid and drug ranges from 1.0 to 3.3 Å (Table 5).

Whereas, the corresponding inhibition efficiency (IC50) of the compounds L1-L20 ranges from 4.64 μM to 64 μM. However, based on the existing fact that the compound(s) with low IC50 within ≤10 μM gives a better activity against the selected receptor (Walsky et al., 2006; Abdel-Mohsen et al., 2010; Zheng et al., 2013; Ma et al., 2014). This suggests that compounds L1, L3, L4, L6, L9-L11, L14 were perfectly aligned within the ≤10 μM range of the literature value while L12, L15 and L16 showed the highest IC50 and less activity. This, however, did not suggest a non-activity of the compounds which their IC50 were slightly higher or far greater than the 10 μM range.

Comparing the 8 compounds with better activity (Figure 4), the compound L3 with the lowest IC50 values (i.e. 4.64 μM) exhibited excellent activity against human gastric cancer cell line (MGC-803) under the study. This significant activity than the other compounds was ascribed to its charge at the ortho position (R1 = ortho-CI). This further implies that compound L3 have more potency with about 14-fold higher than L12, L15 and L16 which both possess the same IC50 values of 64 μM. Whereas, in comparison with the standard (5-fluorouracil denoted as 5-Fu) a well-known anticancer drug (Zheng et al., 2013) which was used in the experimental work by Ma et al. (2014), L3 was about 2-fold potent than 5-Fu which have IC50 value of 7.69 μM (Table 5). This observation could be the influence of polarizability of chloride atom on the ortho-position of L3. Although, majority of these compounds bearing a 1, 2, 3-triazole–pyrimidine hybrids exhibited moderate to good potency with IC50 values in the range of 4.64–64 μM. However, compounds L1-L11, L13, L17-L20 were more potent considering their IC50 values which are lower than L12, L15-L16, though they both possess IC50 values in the single- or double-digit micromolar (μM) ranges. Similar findings were reported by Walsky et al. (2006); Abdel-Mohsen et al., 2010; Zheng et al. (2013); Ma et al. (2014).

This study further examined the compounds with the best IC50 and binding energy based on the lowest IC50 of all the compounds presented in Table 5. Based on this, eight compounds including, L1, L3, L4, L6, L9-L11 and L14 were therefore selected as the best compounds (Figure 4) with the lowest IC50 in the single-digit micromolar (μM) range and their corresponding binding energies as presented Table 5. These were further compared by dockiing the standard compound (5-Fu) which is one of the anticancer drugs already in the market, in order to determine the potency of the eight (8) selected compounds. Here, it was observed that the compounds gave excellent inhibition properties against MGC-803 than the reference compound 5-Fu, due to their higher binding free energies than 5-Fu (with binding energy of -4.2 kcal/mol (Adejoro et al., 2016).
However, the correlation between binding energy and IC\textsubscript{50} of the eight selected compounds is shown in Figure 7 which is in the order of increasing IC\textsubscript{50} and decreasing binding energy. According to Table 5, comparing the binding energies with the standard, the best selected compounds were in the order of L3 > L6 > L14 > L11 > L1 > L9 > 10 > 5-Fu. The analysis of the docked complex (as shown in Figure 4) revealed the relationships between binding energy and IC\textsubscript{50} (presented in Figure 7), implying the conformation of the ligand in the active gouge of the receptor. The binding interactions that occurred in-between the ligand and the receptor were displayed in Table 5. This suggests hydrogen bond and electrostatic relationship that further explained the hydrophobic interactions (as a result of non-polar residue interaction). The docked complexes of compounds L3 revealed a minimum free binding energy in terms of negativity as displayed in Table 5 and Figures 4 and 5 implying the binding pores and interactions of the complex and ligand. This result was in good agreement with the findings of Adejoro et al. (2016). The best conformation in each ligand-receptor complex with minimum free energy of interaction and inhibition efficiency was taken as shown in Table 5 and Figure 4. This was assumed to be correlated with IC\textsubscript{50} and binding energy in each docking.

4. Conclusion

The part played by triazole-pyrimidine hybrid in the clinical world as anti-cancer cannot be over emphasized. Quantum chemical method, quantitative structural activities relationship model and molecular docking approaches were used in the correlation of the activities of selected triazole-pyrimidine hybrid to their activities. In the QSAR evaluation, the statistical validation, multiple correlation coefficients (r), standard error(s), cross validation R\textsuperscript{2} and standard error of prediction were used. Therefore, the best model derived from the analysis was employed in the prediction of the IC\textsubscript{50} of the considered triazole-pyrimidine derivatives. Docking studies were performed to assess the effectiveness of triazole-pyrimidine hybrid attached to active residues of MGC-803.

The results obtained showed that quantum chemical calculations via DFT calculations of molecular parameters in building QSAR model linked the molecular parameters of the studied compounds to their cytotoxicity. The developed QSAR models exposed the responsibility taken by several calculated descriptors to link the electronic properties of the molecules to their bioactivities and the QSAR model reproduced the observed bioactivities of these compounds against MGC-803. Finally, the molecular docking studies help to know that hydrogen bonded with the amino acid residues in the binding site, and also, the essentiality of the ligand conformations as the significant features for ligand-receptor binding.

Declarations

Author contribution statement

Rhoda Oyetadun Oyewole: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.
Abel Kolawole Oyebamiji: Contributed reagents, materials, analysis tools or data.
Banjo Semire: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

The authors acknowledge the Department of Pure and Applied Chemistry, Faculty of Pure and Applied Sciences, LAUTECH Ogbomoso, Oyo State, Nigeria for the platform to carry out this research and also appreciate Dr. Adegoke Adesina Kayode for the assistance in data interpretation and presentation.

References

Abdel-Mohsen, H.T., Ragab, F.A.F., Ramla, M.M., El-Diwani, H.L., 2011. Novel benzimidazole pyrimidine conjugates as potent antitumor agents. Eur. J. Med. Chem. 45, 2336–2344.
Adeediri, O., Uzairu, A., Shallangwa, G.A., Abechi, S.E., 2018. QSAR studies on derivatives of quinoline-4(3H)-ones with anticonvulsant activities. J. Eng. Exact Sci JICE 4 (2).
Adejoro, I.A., Waheed, S.O., Adeboye, O.O., 2016. Molecular docking studies of Lonchocarpus cymenxes triterpenoids as inhibitors for malaria. J. Phys. Chem. Biophys. 6 (213).
Aher, N.G., Pare, V.S., Mishra, N.N., Kumar, A., Shukla, P.K., Sharma, A., Bhat, M.K., 2009. Synthesis and antifungal activity of 1, 2, 3-triazole containing flucanazole analogues. Bioorg. Med. Chem. Lett. 19, 759–763.
Ahmed, M., Razaq, H., Faisal, M., Siyal, A.N., Haider, A., 2017. Metal-free and azide-free synthesis of 1,2,3-triazoles derivatives. Synth. Commun. 47 (13), 1193–1200.
Alam, S., Khan, F., 2017. 3D-QSAR studies on Mastlinic acid analogs for Anticancer activity against Breast Cancer cell line MCF-7. Sci. Rep. 7, 6019, 1–13.
Alejandra, H., Aldo, Y., Victor, A., Hector, V., Claudia, M., 2013. Protein-Protein and Protein-Ligand Docking Chapter 3. In: Protein Engineering-Technology and Application, pp. 63–81.
Baldi, A., 2010. Computational approaches for drug design and discovery: an overview. Syst. Rev. Pharmaceut. Becke, A., 1993. Density functional thermochemistry. III. The role of exact exchange. J. Phys. Chem. 98, 5648–5652.
Bello, A.S., Uzairu, A., Shallangwa, G.A., Ibrahim, A., 2018. In-silico studies of some indole derivatives as anti-hepatitis drug. J. Eng. Exact Sci JICE 4 (2).
Bouchrane, M., Hamidi, M., Bouziane, S.M., Taoufik, H., 2009. Theoretical study on the structure and electronic properties of new materials based on thiopehen and oxadiazole. J. Chem. Res. 10, 29–37.
Chandannos, E., Lagergren, J., 2008. Oestrogen and enigmatic male predominance of gastric cancer. Eur. J. Canc. 44 (16), 2397. Chapter 1. 1. World Cancer Report (2014). World Health Organization.
Chill, J.H., Quadri, S.D., Levy, R., Schreiber, G., Anglister, J., 2003. The human type I interferon receptor: NMR structure reveals the molecular basis of ligand binding. Structure 11 (7), 791–802.
Choi, Y., Li, L., Grill, S., Gullen, E., Lee, C.S., Gumina, G., Tsuji, E., Cheng, Y.C., Chu, C.K., 2000. Structure-activity relationships of (E)-5-(2-bromovinyl)-uracil and related pyrimidine nucleosides as antiviral agents for Herpes viruses. J. Med. Chem. 43, 2538–2546.
Conejo-Garcia, A., Garcia-Rubino, M.E., Marchal, J.A., Núnez, M.C., Ramírez, A., Cimino, S., Garcia, M.A., Aranega, A., Gallo, M.A., Campos, J.M., 2011. Synthesis and anti cancer activity of (RS)-9-(2,3-dihydro-1,4-benzoxa heteroin-2-ylmethyl)- 9H-oxadiazole. J. Chem. Res. 10, 29–37.
David, F.L.L., Howard, B.B., 2002. Molecular binding interactions: their estimation and interpretations and presentation.
Conejo-Garcia, A., Garcia-Rubino, M.E., Marchal, J.A., Núnez, M.C., Ramírez, A., Cimino, S., Garcia, M.A., Aranega, A., Gallo, M.A., Campos, J.M., 2011. Synthesis and anti-cancer activity of (RS)-9-(2,3-dihydro-1,4-benzoxa heteroin-2-ylmethyl)- 9H-oxadiazole. J. Chem. Res. 10, 29–37.
Desai, B., Sureja, D., Naliapara, Y., Shah, A., Saxena, A., 2001. Synthesis and QSAR studies of 4-substituted phenyl-2,6-dimethyl-3,5-bis-N-(substituted phenyl)carbamoyl-1,4-dihydroquinoline-2,3-dione. J. Med. Chem. 47, 4905–4922.
David, F.I.L., Howard, B.B., 2002. Molecular binding interactions: their estimation and rationalization in QSARs in terms of theoretically derived parameters. Sci. World J. 2, 1777–1802.
Debenedetti, P., 2003. Condensed matter. J. Phys. (15), 1669–1670.
Demaray, J.A., Thuenen, J.E., Dawson, M.N., Suckich, S.J., 2008. Synthesis of triazoleoxadiazolidinones via a one-pot reaction and evaluation of their antimicrobial activity. Bioorg. Med. Chem. Lett. 18, 4868–4871.
Desai, B., Sureja, D., Naliapara, Y., Shah, A., Sarsena, A., 2001. Synthesis and QSAR studies of 4-substituted phenyl-2,6-dimethyl-3,5-bis-N-(substituted phenyl)carbamoyl-1,4-dihydroquinolines as potential antiinflammatory agents. Bioorg. Med. Chem. Lett. 9 (8), 1963–1968.
De-Simone, R., Chini, M.G., Bruno, I., Riccio, R., Mueller, D., Werz, O., Bifulco, G., 2011. Structure-based discovery of inhibitors of microosomal prostaglandin E2 synthase-1, 5-lipoxygenase and 5-lipoxygenase-activating protein: promising hits for the development of new anti-inflammatory agents. J. Med. Chem. 54, 1565–1575.

Heliyon 6 (2020) e03926
Sledz, P., Calfisch, A., 2018. Protein structure-based drug design: from docking to molecular dynamics. Curr. Opin. Struct. Biol. 48, 93–102.

Song, Z., Wu, Y., Yang, J., Yang, D., Fang, X., 2017. Progress in the treatment of advanced gastric cancer. Tumor Biol. 1–7.

Sun, Z., Wang, Q., Yu, X., et al., 2015. Risk factors associated with splenic hilar lymph node metastasis in patients with advanced gastric cancer in northwest China. Int. J. Clin. Exp. Med. 8, 21358–21364.

Trott, O., Olson, A., 2010. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. J. Comput. Chem. 31, 455–461.

Vasaikar, S., Bhatia, P., Bhatia, P.G., Chu Yaiw, K., 2016. Complementary approaches to existing target based drug discovery for identifying novel drug targets. Biomedicines 4.

Walsky, R.L., Astuccio, A.V., Obach, R.S., 2006. Evaluation of 227 drugs for in vitro inhibition of cytochrome P450 2B6. J. Clin. Pharmacol. 46.

Wang, X.L., Wan, K., Zhou, C.H., 2010. Synthesis of novel sulfanilamide-derived 1, 2, 3-triazoles and their evaluation for antibacterial and antifungal activities. Eur. J. Med. Chem. 45, 4631–4639.

White, N.J., 1996. The treatment of malaria. N. Engl. J. Med. 335 (11), 800–806. http://www.scopus.com/scopus/inward/record.url?eid=2-s2.0-0029792910&partnerID=K84CvKBR&rel=3.0.0&mdid=0134e84ce961c7db4e1b025106d2ebd.

World Health Organization, 2014. Chapter 1.1. World Cancer Report 2014. ISBN 9283204298.