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Research Article

Design, Synthesis, Pharmacological Evaluation and DFT Investigation of New Bioactive Unsymmetrical Bi-Functional Ligand

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Abstract

Compounds with more than one bioactive motif become of great interest. In this regard, a new tridentate 1,2-unsymmetrical ligand consists of flexible and rigid bioactive arms spaced by benzene ring in an ortho position designed to form a bifunctional molecule. The 2-((3-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl)benzonitrile (PPMB) synthesized under phase transfer reaction and characterized using 1H-NMR and mass spectroscopy and studied as potent kinase inhibitors. Theoretically, the molecule structure was investigated at the B3LYP/6-311++G(d,p) level of theory in the gas phase and revealed that all bond lengths and bond angles within the accepted limit. The frontier molecular orbitals (FMO) energies (HOMO and LUMO), energy gap, dipole moment, chemical softness and chemical hardness were calculated. Pharmacologically, the ligand activity was investigated in silico using SWISS ADME. Furthermore, the compound was docked into the transforming growth factor (TGF) beta type I receptor kinase active site to evaluate the ability of ligand as a kinase inhibitor.

Keywords: DFT, pyrazolyl-pyridine, physiochemical, properties molecular docking, bioactive molecules, unsymmetrical ligands

INTRODUCTION

Significant attention in recent years has been received in the design and synthesis of heterocyclic organic molecules containing nitrogen or nitrile group, specifically in medicinal chemistry.[1–3]This kind of compounds is often essential for all fields of chemistry and medicinal chemistry research. However, nitriles are a common group in nature, also working as intermediates for synthetic various functional groups such as amine, tetrazoles and others.[4] The N-heterocyclic compounds with terminal nitrile group have gained great attention in drug discovery as a nitrile group is chemically less reactive than aldehydes.[5] Furthermore, it can form a hydrogen bonding (HB) acceptor between the terminal nitrile nitrogen and amino acids or water-mediated interactions with protein backbones.[6] The HB can be investigated using crystallographic data retrieved from the Cambridge Structural Database (CSD) and *via* computational chemistry.[7,8] Most pharmaceuticals containing aromatic molecules nitrile are the inhibitors of aromatase, such as Anastrazole[9] or Letrozole[10], which are used for the treatment of estrogen-dependent breast cancer, type 2 diabetes, and osteoporosis.[11,12] However, millions of bioactive compound containing nitrile group are recorded in the database.[13] Pyridine is an example of heterocyclic molecules, which has one nitrogen atom present in many natural products[14,15] and exhibits tremendous applications in the medicinal fields.[16,17] In medicinal chemistry, many drugs and pesticides designed based on pyridine due to its pH sensitivity.[17] Pyrazole is an example of a five-member ring of an N-heterocyclic molecule that has two nitrogen atoms showed a broad range of pharmacological and biological activities.[18,19] The fusing of the 2-pyridyl ring with 3-pyrazole cycle produces hybrid N-heterocyclic organic molecules 3-(2-pyridyl)pyrazole, used widely in coordination chemistry as ligands containing two active biological moieties used widely in medicinal chemistry and drug design.[20] The reaction of terminal alkynes and organic azides in the presence of Cu(I)-catalyzed "click chemistry" produced new N-heterocyclic molecules containing three nitrogen atoms, namely 1, 4-disubstituted 1, 2, 3-triazoles. The Huisgen 1, 3-dipolar cycloaddition reaction of organic azides and alkynes has gained considerable attention in recent years due to their potent biological properties.[21] Additionally, click chemistry is interested in a much different research field and is used increasingly in the biomedical field and is considered a good synthetic tool of pharmacological drugs.[22] Also, 1,2,3-triazoles can be connected to 2-pyridyl to form 2-(2H-1,2,3-triazol-4-yl)pyridine (Ts). The Ts working as ligands in coordination chemistry and could be attached to aromatic pendant molecules to produce a new class of ligands (Figure 1). In medicinal chemistry 2-(2H-1,2,3-triazol-4-yl)pyridine can be combined with Quinoline to form hybrid molecules TsQu with potent biological activity.[23] TsQu compounds have many Applications in medicinal chemistry including cancer, malaria, tuberculosis and others. Another example is Pteridines which is a class of N-heterocyclic compound containing two different N-heterocyclic rings and present in a wide range of the living organism. Pteridine has many applications in medicines as anticancer, antiviral, antibacterial and diuretic drugs as well as an essential role in growth processes and the metabolism of the one-carbon unit as cofactors in enzyme catalysis and biological coloration.[23] Transforming growth factor-b (TGF-b) has been assumed to be involved in several diseases, including inflammation, fibrosis, cancer, asthma, and cardiovascular disease. The complex function of this cytokine, which mediates pathways connecting the regulation of gene response and DNA transcription factors, is dependent upon the activation of type I (TbR-I) and type II (TbR-II) receptors, transmembrane-spanning proteins containing serine/threonine kinase domains.[2] Inhibition of such domains with bifunctional inhibitors would be expected to interrupt downstream signal transduction and possibly deliver palliative effects on diseases modulated *via* TGF-b.[24–29]

In this research, a new N-heterocyclic compound with specific features was designed, synthesized and characterized, and its chemical, pharmaceutical and biological activities were evaluated theoretically. The molecule-based on the combination of two different bio-active groups. The bi-functional molecules consist of 3-(2-pyridyl)pyrazole connected to a methyl-benzyl group and one more bio-functional group, which is nitrile.

EXPERIMENTAL AND METHODS

General details

All commercially available chemicals and solvents were purchased from commercial sources and used without further purification. 3-(2-pyridyl)pyrazole compound was prepared according to the published method.[30] ^{1}H NMR spectra were recorded on Bruker AVI-400 spectrometers.

Preparation of 2-((3-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl) benzonitrile (PPMB)

A mixture of 2-(chloromethyl)benzonitrile (0.5 g, 3.29 mmol), 3-(2-pyridyl)pyrazole (0.477 g, 3.29 mmol), aqueous NaOH (1.31g, 3.29 mmol), and tetrahydrofuran (THF) (60 mL) was heated at reflux with stirring for 20 h. After cooling, the organic layer was extracted, washed with water, and then dried over $MgSO_4$. Removal of the solvent in vacuo, the residue purified *via* passage through silica eluted with ethyl acetate to afford white powder. EI-MS: m/z 260 (100%). ^{1}H NMR (400MHz, $CDCl_3$): δ 5.44 (2H, s; CH2), 6.55 (1H, d; pyrazoly H4), 7.14 (1 H, d; pyridyl H5), 7.15 (1H, d; phenyl H3), 7.383 (1H, d; phenyl H5), 7.528(1H, d; phenyl H4), 7.695(1 H, td; pyridyl H4), 7.763 (1 H, d; pyridyl H3), 7.836 (1H, d; phenyl H6), 8.009 (1H, m; pyrazolyl H5), 8.59 (1H, dd; pyridyl H6).

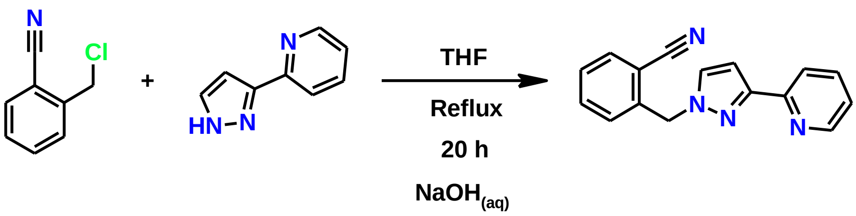
Computational details

All calculations were conducted using Gaussian 09 software.[31] Full geometry optimization was performed at B3LYP/6-311++G** levels of theory, and this was followed by frequency calculation to ensure that the structure is minima with no imaginary frequency noted. The B3LYP method is formed by combining Becke's three-parameter hybrid functional15 and the LYP semi-local correlation function.[32] Chemical hardness and chemical softness were calculated according to the method described.[33] Physicochemical properties and bioactivity were estimated using SwissADME (http://www.swissadme.ch). Molecular docking was carried out using molecular operative environment software [34] the procedure was followed according to the published method.[35]

RESULTS AND DISCUSSION

Chemistry

The reaction of 2-(chloromethyl)benzonitrile with 3-(2-pyridyl)pyrazole (Scheme 1) under phase transfer reaction resulted in 2-((3-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl) benzonitrile (PPMB) with two different types of functional groups: (i) chelating bidentate unit; pyrazolyl-pyridine and (ii) environmental sensitive group which is nitrile. The well-known 3-(2-pyridyl)pyrazole chelating bidentate unit has been extensively used in coordination chemistry to form complexes with transition M(II) in differential geometry.[36] Moreover, pyridine[15] and pyrazolyl moieties have become a central theme of research due to their attractive pharmacological and biological activities such as antibacterial, antimicrobial and antidiabetic.(19) The cyanide group's unique structural feature is its directionality as having a linear shape (sp hybridized C atom). The cyanide group with one direction of coordination has been used to form complexes with a soft metal cation.[37] also enable them to fit readily into protein-binding site sub-pockets by forming hydrophobic interactions similar to halogen atoms.[7] The coordination sites of the ligand connected in O-position, which is closed together Scheme 1. The ligand structure was confirmed using ^{1}HNMR and EI-mass spectroscopy.



Scheme 1: Synthesis conidiation for the PPMB.

Density functional theory (DFT)

The compound was optimized at B3LYP/6-311++G** and the selected structural parameters were reported in Table 1. The dihedral angle between N12-C13-C16-N19 was 20.62, indicating that this moiety of the compound is not planar (Figure 1), which is a good indicator for better solubility and low crystal packing.

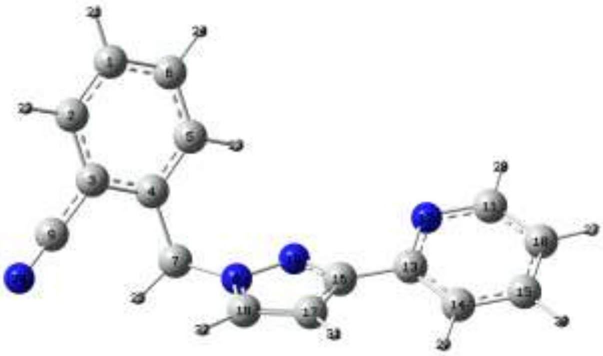


Figure 2: Optimized structure of PPMB at B3LYP/6-311++G(d,p) levels with atomic numbering.

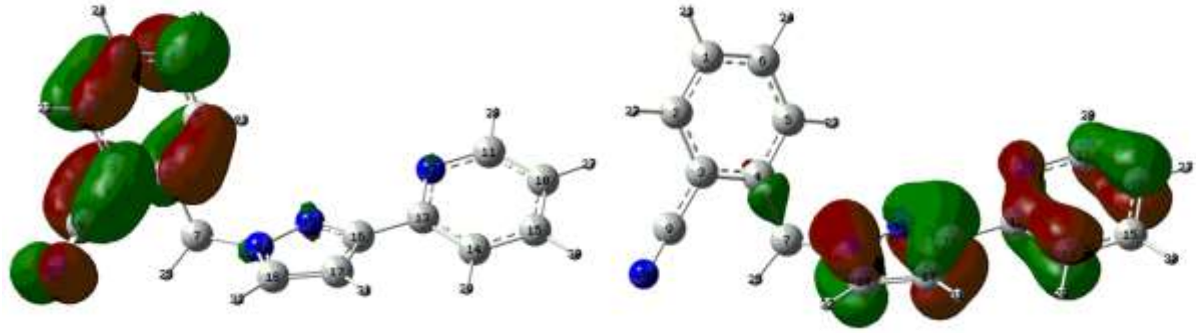
Table 1: Selected bond lengths and bond angle at B3LYP/6-311++G(d,p) of the ligand

Atoms	Bond lengths(Å)	Atoms	Bond angle(°)
C1-C2	1.387	C2-C1-C6	119.8
C1-C6	1.395	C2-C1-H21	119.8
C1-H21	1.084	C1-C2-C3	119.9
C2-C3	1.405	C1-C2-H22	120.8
C2-H22	1.083	C6-C1-H21	120.4
C3-C4	1.408	C1-C6-C5	120.4
C3-N8	1.432	C1-C6-H24	120
C4-C5	1.397	C3-C2-H22	119.3
C4-C7	1.519	C2-C3-C4	120.6
C5-C6	1.392	C15-C16-H29	120.5
C5-H23	1.084	C17-C16-N15	124
C6-H24	1.084	C16-C17-H30	120.2
C16-H29	1.087	C17-C18-H31	121.6
C14-N15	1.343	C17-C18-C19	118.9
C14-C19	1.403	C18-C17-H30	120.8
C11-C14	1.475	N15-C16-H29	115.8
C18-C19	1.389	C14-N15-C16	118.2
C19-H32	1.083	N15-C14-C19	121.9

Table 2 shows the electronic properties calculated based on frontier molecular orbitals (FMOs) of the molecule. The HOMO and LUMO considered as outermost orbital filled and first empty innermost orbital unfilled by electrons, respectively.[38] Moreover, indicate the chemical reactivity and area of chemical reactivity. HOMO and LUMO can detect the electrophilic and nucleophilic attached location. However, the difference between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbitals as (LUMO) indicates the molecular stability and photophysical properties.[38] Figure 2 shows the calculated HOMO-LUMO orbital based on the used parameters. The characterizations of molecules, such as their ability to accept electrons and their electron donation ability, play an important role in chemistry. The HOMO and LUMO behave as electron donor and electron acceptor, respectively.[39] So, some molecular characterizations can be discussed based on Frontier Molecular Orbitals' values (FMOs) see Table 2. The energy gap values can indicate the stability of molecules were calculated from the difference between the HOMO and LUMO;(40) for molecule, the calculated energy gap is 4.67 eV. The reactivity of molecules was investigated on the chemical hardness.[41] The synthesized ligand has been recorded η=4.67 eV. The relationship between the softness (S), first ionization potential (I) and electron affinity (A) can be expressed as $S = 1/\eta$; where the maximum softness (S = zero; minimum value) means no energy change of associated with disproportionation reaction ($S+S \rightarrow S^{+}+S^{-}$).[21] The softness (S) calculated the value of the molecule recorded 0.21 eV^{-1}.

Table 2: Calculated electronic properties of PPMB at B3LYP/6-311++G(d,p) level.

Property	Value
Energy (a.u)	-836.114
Dipole moment (Debye)	2.96
E_{HOMO} (eV)	-1.87
E_{LUMO} (eV)	-6.54
E_g (eV)	4.67
Ionization potential (I)	6.54
Electron affinity (A)	1.87
Electronegativity (χ)	4.20
Global chemical hardness (η)	4.67
Electronic chemical potential (μ)	-4.20
Global electrophilicity index (ω)	1.89
Chemical softness (S)	0.21



LUMO HOMO

Figure 3: Frontier orbitals of PPMB obtained at B3LYP/6-311++G(d,p)

Pharmaceutical study

The physiochemical study was carried out using the SWISS ADME predictor.[42] SWISS ADME is a free web tool to evaluate small molecules' pharmacokinetics, drug-likeness, and medicinal chemistry friendliness. The properties like molecular weight less than 500 g/mol, less than five hydrogen bond donors, less than ten hydrogen bond acceptors and less than ten rotatable bonds were chosen as criteria while selecting molecules to be synthesized.[43] Traditionally, the synthesized molecule has been a small molecule that falls within Lipinski's rule of five (i.e., a molecule with a molecular mass less than 500 Da) 260.29 g/mol. To obey the role of five, it should no more than five hydrogen bond donors, no more than ten hydrogen bond acceptor. Generally, the synthesized molecule presented 3 number of H-bond acceptor with no number of H-bond donor. Another significant physiochemical parameter is the octanol-water partition coefficient. The log *P* should not > 5. The present result provided a reasonable lipophilicity limit. The physicochemical properties of small molecular drugs significantly impact their BBB permeability, primarily via passive diffusion. Lipinski's "rule of five", five key physicochemical parameters (molecular weight, lipophilicity, polar surface area, and hydrogen bonding) require optimization to improve BBB permeability by passive diffusion.[44] Generally in 2-((3-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl) benzonitrile TPSA was >70 about 54.50 Å^2 , had high GIT absorption and BBB penetration. Another important pharmacokinetics section is predicted if those molecules enzyme-inhibitors for certain cyp450 enzymes. Synthesized molecule resulted in inhibition of CYP2D6 AND CYP3A4 enzymes. The assessment of synthetic accessibility (SA) of a lead candidate plays a significant role in the lead discovery,[45] in the presented data molecule gives 2.50 within the SA limit.

Physicochemical Properties

Physicochemical properties similar to molecular weight (MW), molecular refractivity (MR), polar surface area (PSA), partition coefficient (log Po/w), and the number of rotatable bonds in a molecule count of specific atom types, hydrogen bond acceptors and donors counts are represented in Table 3. The values are calculated with SwissADME.[42] Drug-likeness can be expected as an excellent balance between molecular parameters that affect pharmacodynamics and pharmacokinetics of molecules, affecting their absorption, distribution, metabolism, and excretion (ADME) in the human body.[37] Additionally, from Lipinski's rule, the molecular weight of drugs should be (<500). Our compound's molecular mass was 260.29g/mol, which makes it easy to cross membranes, transport, absorbed and diffused compared with heavy molecules Table 3. Molecular refractivity (MR) is a significant parameter to identify the steric factor. It is classically selected as an easy measure of the volume working either by a single atom or a group of atoms.[46] The molecular refractivity (MR) value was 75.92 Table3. An additional important parameter is that PSA is calculated using the fragmental technique called topological polar surface area (TPSA), considering sulfur and phosphorus as polar atoms. That is an essential useful parameter used for estimation properties of drug transport. Polar surface area is a sum of polar atoms surfaces (commonly nitrogen, oxygen, and attached hydrogens) in a drug. This parameter has been observed to associate very well with the human blood-brain barrier penetration, bioavailability, and intestinal absorption. Lipinski, Ghose and Veber rules say that topological polar surface area (TPSA) < 140 Å2.[47] The determination of PSA in a classical way has some disadvantages such as time-consuming, due to the necessity to create a reasonable 3D molecular geometry and detect the surface itself. In addition, calculations need particular software to produce the 3D molecular structures and to detect the surface.[48] Topological polar surface area (TPSA) is noticed by SwissADME is fast and easy.[32]Total polar surface area (TPSA) is showed to be (54.50 Å) Table 3 (<140 Å limit), nearly related to the hydrogen bonding potential of a compound. The partition coefficient between n-octanol and water (log Po/w) is the common property for Lipophilicity calculation. It has a crucial section in SwissADME because of the vital importance of this physicochemical parameter for pharmacokinetics drug discovery.[49] Numerous computational techniques for log Po/w determination were developed with diverse performance on various chemical groups. General practice is using numerous predictors to select the best accurate method for a given chemical group or to create consensus determination. The models after the predictors must be as different as possible to increase the estimation accuracy through consensus log Po/w.[38] It seems that the lipophilicity is potentially related to toxicity, which is in agreement with the observation that lipophilic binding is non-specific, whereas polar binding is related to the specificity and therefore selectivity. It is proof that the toxicity is significantly higher for compounds with a log Po/w exceeds 5 and a topological polar surface area (TPSA) < 75 Å2.[39] The log Po/w value of the compound is showed to be (2.23) that are below 5 follows Lipinski's rule of five. The synthesized compound is likely to have adequate hydrophilicity as well as adequate lipophilicity. This shows that the compound will have reasonable permeability across cell membranes. Soluble molecules have greatly simplified numerous drug development actions, mainly the ease of management and formulation.[40] Furthermore, for drug discovery methods of oral administration, solubility is one main property affecting absorption.[41] As well as, a drug designed for parenteral treatment has to be great water-soluble to deliver an adequate amount of active ingredient in the small volume from the pharmaceutical dosage form.[50] The number of hydrogen bond acceptors and donors (HBA, HBD) for our compound which is smaller than 5 for hydrogen donors, also for hydrogen acceptors smaller than 10 and the number of rotatable bonds was 3 as represented in Table 3, thus the compound obeys Lipinski s rule for drug-likeness and orally bioactive.

Table 3: Physiochemical properties for PPMB.

Property	**M.W.**	**MR**	**TPSA**	**clogP**	**IogS**	**nRotb**	**HBA**	**HBD**	**Bioavailability Score**
Value	260.29	75.92	54.50	2.23	-2.95	3	3	0	0.55

nRotb: number of rotatable bonds; HBD: number of hydrogen bond donor; HBA: number of hydrogen bond acceptor.

Pharmacokinetics

From the earlier consequences notice that our compound has physicochemical properties within the good range. Therefore, these considerations should be taken into respect as a manager for more screening examines against different targets: [Kinase inhibitor (KI), G-protein-coupled receptors (GPCR), Ion channel modulator (ICM), Protease inhibitor (PI), Enzyme inhibitor (EI) and Nuclear receptor ligand (NRL)] thus, by using SwissADME, the bioactivity of our compound was detected and noted in table 4. The pharmacokinetic properties of the compound are cautiously linked with its chemical structure, investigational information are stored in computer databases, also an enormous number of experimental clarifications are related to the chemical structural and physicochemical properties. These properties can be used to realize computer-assisted in silico collections.[51] Some estimates are important in the Pharmacokinetics section, evaluating individual ADME performances of the compound under improvement via the SwissADME. The estimates for passive human gastrointestinal absorption (GI Absorption) for the compound from the result **(Table 4)** observe that the compound has high GI Absorption. Furthermore, the blood-brain permeation barrier (BBB permeant) showed that the compound can cross BBB. The understanding around compounds existence substrate or non-substrate of the permeability glycoprotein (P-gp) suggested the main essential member between ATP-binding cassette transporters or ABC-transporters) is significant to evaluate active efflux molecules through cell membranes, for example from the gastrointestinal wall to the lumen or from the brain.[52] One main important role of P-gp is to defend the central nervous system (CNS) from xenobiotics. Significantly as well, P-gp is overexpressed in certain cancer cells and leads to drug resistance.[53]The compound is non-substrate of the permeability glycoprotein (P-gp) as represented in table 4. Another significant model is a multiple linear regression, that resolves at expecting the skin permeability coefficient (K_p). It is adapted from Potts and Guy,[54] who create K_p linearly related with lipophilicity and molecular size. The great negative the log K_p (with K_p in cm/s), the littler skin permeant is the compound. From results **(Table 4)** The compound has a high negative value is (-6.19) that is meaning it has low skin permeant.

Table 4: Pharmacokinetics for Atorvastatin and its Analogues.

Property	**GI Absorption**	**BBB permeant**	**P-gp substrate**	**Log K_p**
Value	High	Yes	No	-6.19

Abbreviations: human gastrointestinal absorption (GI Absorption), blood-brain permeation barrier (BBB permeant), glycoprotein (P-gp substrate), skin permeability coefficient (Log K_p).

Drug-likeness

"drug-likeness" assesses qualitatively the chance for a molecule to grow an oral drug with respect to bioavailability. Drug-likeness was recognized from physicochemical properties or chemical structural of development compounds classical enough to be measured oral drug-candidates. This information is frequently employed to reach filtering of small compound libraries to remove molecules with properties most probably incompatible with a suitable pharmacokinetics profile.[55]This SwissADME section be responsible for access to different rule-based filters, with various ranges of properties confidential of which the compound is distinct as drug-like. These filters often create from examines via main pharmaceutical corporations targeting to improvement the quality of their proprietary chemical groups. The Lipinski filter 'rule-of-five', the Ghose (Amgen), Veber (GSK) methods were applied from refs[56–59], respectively. Generally, when the bioactivity score is great, this will increase the possibility of the measured compound to be active. Therefore, a compound having bioactivity score more than 0.00 is most likely to have significant biological activities, while values -0.50 to 0.00 are predictable to be moderately active and if score is less than -0.50 it is supposed to be inactive. The bioavailability score of the ligand was higher than zero (0.55) Table 3, which suggest that it is bioactive.

Molecular Docking

Docking procedures are widely used to discover the binding affinities of a sequences of ligands. In this reserach, to study the binding environment in which the inhibitor interacts within the type I receptor kinase. Due to its similarity with previously synthesized inhibitors,[60] PPMB was docked into the transforming growth factor (TGF) beta type I receptor kinase active site, the crystal structure of the protein was obtained from the protein data bank (PDB=1PY5), at a resolution of 2.3 Å. The protein active site consists of the following residuals Ser280, Ala230, Gly212, Leu340, Ile211, Gly286, Ser287, Val219, Lys232, Asp351, Leu260, Leu278, Ala350, and Glu245. The docking score was -6.72 kcal/mol Table 5, which is quite similar to the crystal inhibitor which was -7.50 kcal/mol, There was a particular noticeable interaction observed between compound and the binding site residue Gly212 to forms arene-hydrogen interaction with the pyridine ring of compound with distance 4.58Å It was also found that the Gly212 was able to form an H–pi stack interactions with -0.8 kcal/mol energy Figure 3. The ligand was not able to form any hydrogen bond with the residuals, the root-mean-squared-deviation (RMSD) between the predicted pose and those of the crystal one was also calculated.

Table 5: Receptor interactions and binding energies of PPMB and TGF-beta type I receptor kinase

Name	Docking score kcal/mol	RMSD_refine	Resiudals	Distance Å	Interation type
PPMB	-6.72	1.92	Gly212	4.58	H - π
			Asp351	2.12	H-bond
Rference	-7.50	0.84	His283	3.53	H-bond
			Lys232	2.88	H-bond

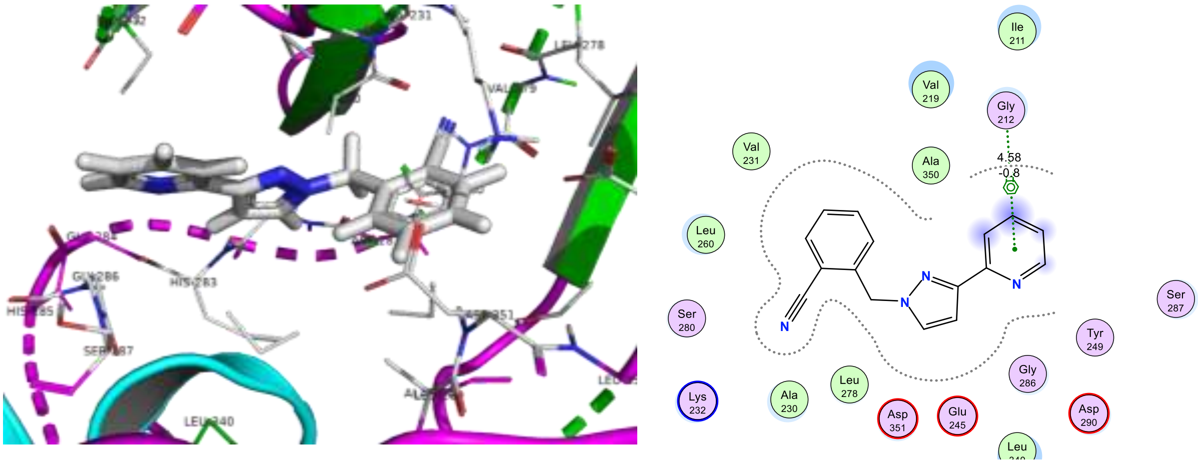


Figure 4: The 3D binding interactions and the 2D positioning of the PPMB inside the active site.

CONCLUSION

The fused compounds that consist of imidazole, triazole and others as a class of N-heterocyclic compounds and nitrile groups play an important role in the development of new potent drugs. The bioavailability score of the 1,2-unsymmetrical ligand revealed that the ligand may bioactive. However, docking of the newly designed and synthesized fused ligand that consists of bioactive motif revealed that there was a particular interaction between compound and Gly212 to forms arene-hydrogen interaction with the pyridine ring of the compound with distance 4.58Å; which may exhibit activity as a kinase inhibitor. Notably, the ligand was unable to form H-bonding of the residuals with the nitrogen atom of the CN group.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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