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In silicon anti tubercular and pharmacokinetics studies of picolin derivatives bearing sulphonamide and carboxamide moieties

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ABSTRACT

Picoline degradation appears to be mediated primarily by bacteria, with the majority of isolates belonging to the Actinobacteria. 3-Methylpyridine degrades more slowly than the other two isomers, likely due to the impact of resonance in the heterocyclic ring. This work is aimed at investigating the antitubercular activity of some selected sulphonamide derivatives. The sulphonamide derivatives used in this study were designed following the success of pyridines rings, sulphonamides and carboxamides in the Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka. The results showed that all the hypothetical compounds have good binding against the target proteins. When compared with the reference, the reported compounds showed good binding affinity ranging from -7.2 to -10.9 kcal/mol for PKnB and -7.8 to -12.2 kcab/mol for Kat U compared to - 4.8 kcal/mol and -7-8 kcal/mol of Bedaquiline and Refampicin for PKnB and -8.3 kca/Jmol and -9.1 kcallmol for Kat G respectively which is the reference.

Keywords:In silicon, anti tubercular, pharmacokinetics, picolin derivatives and carboxamide moieties.

INTRODUCTION

Picoline refers to three different methyl pyridine isomers, all with the chemicalFormula C_6H_7N and a molar mass of 93.13 g mol^{-1} All three are colorless liquids at room 1tperature and pressure, with a characteristic smell similar to pyridine [1,2,3]. They are miscible with Later and most organic solvents. Picolines exhibit greater volatility and are more slowly degraded than their carboxylic d counterparts [4,5,6]. Volatilization is much less extensive in soil than water, owing to sorption of te compounds to soil clays and organic matter [7,8]. Picoline degradation appears to be mediated primarily by bacteria, with the majority of isolates belonging to the Actinobacteria. 3-Methylpyridine degrades more slowly than the other two isomers, likely due to the impact of resonance in the heterocyclic ring. Like most simple pyridine derivatives, the picolines contain more nitrogen than is needed for growth of microorganisms and excess 1atrogen is generally excreted to the environment as ammonium during the degradation process [9,10]. In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex [11,12]. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using, for example, scoring functions. Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small mo1ecule ligands to the appropriate target binding site. Characterization of the binding behavior plays an important role in rational design of drugs as well as to elucidate fundamental biochemical processes [13,14]. It is also known as PK. It is a

branch of pharmacology that determines the fate of substances administered into a living organism. The substances of interest include xenobiotics such as: pharmaceutical drugs, food additive, cosmetic ingredients, pesticides. Pharmacokinetics deals with how the living organism affects the drug whereas pharmacodynamics deals with how drugs affect the living organism. Pharmacokinetic properties of chemicals are affected by the route of administration and the dose of administered drug. These may affect the absorption rate [15,16,17]. Models have been developed to simplify conceptualization of the zany processes that take place in the interaction between an organism and a chemical substance. Tuberculosis (TB) is an infectious disease caused by the bacterium Mycobacterium riberculosis (MTB) (Tuberculosis Fact Sheet N° 104, 2016). Tuberculosis generally affects the lungs, but can also affect other parts of the body. Most infections do not have symptoms, in which case it is known as latent tuberculosis. About 10% of latent infections progress to active disease which, if left untreated, kills about half of those infected. The classic symptoms of active (Tuberculosis Fact Sheet N° 104, 2016). TB are a chronic cough with blood-containing sputum, fever, night sweats, and weight loss Tuberculosis is spread through the air when people who have active TB in their lungs cough, spit, speak, or sneeze [18,19]. People with latent TB do not spread the disease. Active infection occurs more often in people with HIV/AIDS and in those who smoke (Tuberculosis Fact Sheet N° 104, 2016). General signs and symptoms include fever, chills, night sweats, loss of appetite, weight loss, and fatigue [20]. Significant nail clubbing may also occur [21]. Prevention of TB involves screening those at high risk, early detection and treatment of cases, and vaccination with the bacillus Calmette-Guérin vaccine [22]. Treatment requires the use of multiple antibiotics over a long period of time (Tuberculosis Fact Sheet N° 104, 2016). Sulfonamides is the basis for several groups of drugs. The original antibacterial sulfonamides are synthetic antimicrobial agents that contain the sulfonamide group. Some sulfonamides are also devoid of antibacterial activity example: the anticonvulsant sultiame. The sulfonylureas and thiazide diuretics are newer drug groups based on the antibacterial sulfonamides [8]. Sulfonamides are therefore bacterio static and inhibit growth and multiplication of bacteria. Sulfonamides are used to treat allergies, antitubercular as well as antifungal and antimalarial functions. The moiety is also present in other medications that are not antimicrobials and some COX-2 inhibitors. An example of sulfonamide used as an antitubercular agentwasTrimethoprim/sulfamethoxazole (TMP/SMX). Because of the toxicity of the sulfones and the sulfonamides [9] and because isoniazid (INH) and streptomycin were stronger antituberculous drugs [10] both groups of drugs were abandoned for the treatment of tuberculosis in the early 195 Os, and their use was basically forgotten. They are derivatives of carboxylic acids in which an amine group (-NH2) replaces the -OH group of carboxylic acids [8]. They have the ability to bond strongly to themselves, at other amide sites down the chain, or different chains with amides through hydrogen bonding between the oxygen and hydrogen from the NH group elsewhere to form very strong intermolecular bonds. An example of carboxamide used as an antitubercular agent was pyraxin-2-carboxamide. They were used as first line antituberculosis medication, but is used only in combination with other antituberculosis medications such as isoniazid or rifampin [13]. The antituberculosis agents are a diverse group of drugs; the only similarity among the antituberculosis agents is that they are used to treat Mycobacterium tuberculosis. Not only does each agent exhibit a unique mechanism of action, adverse reactions are diverse and numerous.

AIM OF THE RESEARCH

This work is aimed at investigating the antitubercular activity of some selected sulphonamide derivatives.

MATERIALS AND METHODS

METHODOLOGY

The sulphonamide derivatives used in this study were designed following the success of pyridines rings, sulphonamides and carboxamides in the Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka.

ANTITUBERCULAR CHEMOTHERAPY

Docking studies were carried out between the test compounds and a novel antitubercular protein target, protein kinase B (PknB) and Kat G. The compounds were screened for antitubercular activity as follows.

COLLECTION OF 3D TARGET PROTEIN-LIGAND COMPLEX STRUCTURE

The X-ray structure of the protein-ligand complex a co-crystallized inhibitor, Pknl3 and Kat G were retrieved from an online protein data bank (www.rcsb.org).

TREATMENT OF THE 3D TARGET PROTEIN-LIGAND COMPLEX STRUCTURE

The 3D target protein-ligand structure was treated using MOE software as follows: For the complex, the co-crystallized water molecules and small molecules was deleted. The retained protein-ligand complex was protonated using the protonate 3D procedure implemented in MOE. The protonated complex was then energy minimized in order to remove atomic clashes, using the Merck Molecular (MMFF94) Force field101 until a gradient of 0.001 kcal/mol was attained. The chains with missing amino acid residues in the middle of the chain were deleted, together with their bound ligands.

GENERATION OF 3D STRUCTURES OF THE TEST COMPOU1IDS

The 3D structures of the sulfonamide derivatives were generated using the molecular builder interface implemented in MOE and energy minimized to gradient of 0.001 kcal/mol.

DOCKING PROTOCOL VALIDATION

The docking protocol was validated by re-docking the co-crystallized ligand into the binding site of the protein in different grid dimensions using Autodock 4.1. The grid points in x-, y-, and z-axes and the distance between two connecting grid points which gave the dimension with least root-mean- square-deviation (RMSD) value was retained and therefore, used for the docking studies.

DOCKING STUDIES

After validation of the molecular docking protocol and scoring predictability with cocrystallized ligand (positive control), virtual screening (docking) of the test compounds was performed against PknB using AutoDock4.1 by docking the test compounds toward the binding site of the co-crystallized native ligand, using the methods, grid box centroids and dimensions obtained in the validation phase.

OBSERVING PREDICTED BINDING PATTERN

Accerlyl's Discovery Studio Visualizer 2016 was used to observe the AutoDock l predicted binding patterns of the best test compounds and the binding sites of the targetprotein.

5	-9.0	-10.0	0.26	0.29
6	-9.3	-10.1	0.28	0.30
7	-7.2	-8.4	0.27	0.32
8	-7.4	-8.6	0.29	0.34
9	-9.6	-10.8	0.30	0.33
10	-10.9	-11.5	0.27	0.29
11	-10.9	-108	0.25	0.25
12	-8.8	-9.5	0.24	0.26
13	-9.6	-10.7	0.26	0.29
14	-10.7	-10.6	0.30	0.30
15	-7.2	-7.8	0.27	0.30
16	-7.4	-9.1	0.27	0.33
17	-7.5	-9.2	0.25	0.31
18	-8.0	-9.4	0.30	0.36
19	-9.1	-10.5	0.23	0.26
20	-7.8	-9.4	0.23	0.28
21	-7.9	-8.7	0.23	0.26
22	-7.4	-9.0	0.23	0.28
23	-7.7	-8.3	0.30	0.33
24	-9.6	-8.2	0.40	0.34
Bedaquiline	-4.8	-8.3		
Rifanipicin	-7.8	-9.1		

Table 1 is the result of the in silica studies using PKnB and Kat U as target. The results showed that all the hypothetical compounds (table 1) have good binding against the target proteins. When compared with the reference, the reported compounds showed good binding affinity ranging from -7.2 to -10.9 kcal/mol for PKnB and -7.8 to -12.2 kcal/mol for

K at U compared to - 4.8 kcal/mol and -7-8 kcal/mol of Bedaquiline and Refampicin for PKnB and -8.3 kcal/mol and -9.1 kcal/mol for Kat G respectively which is the reference.

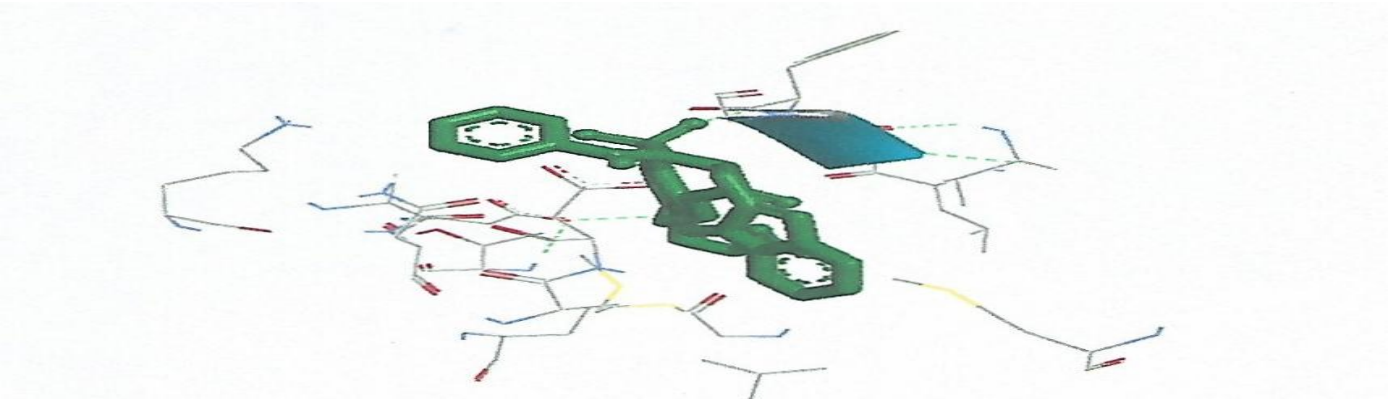

Figure 1: Docking Test compound 10 against Kat G

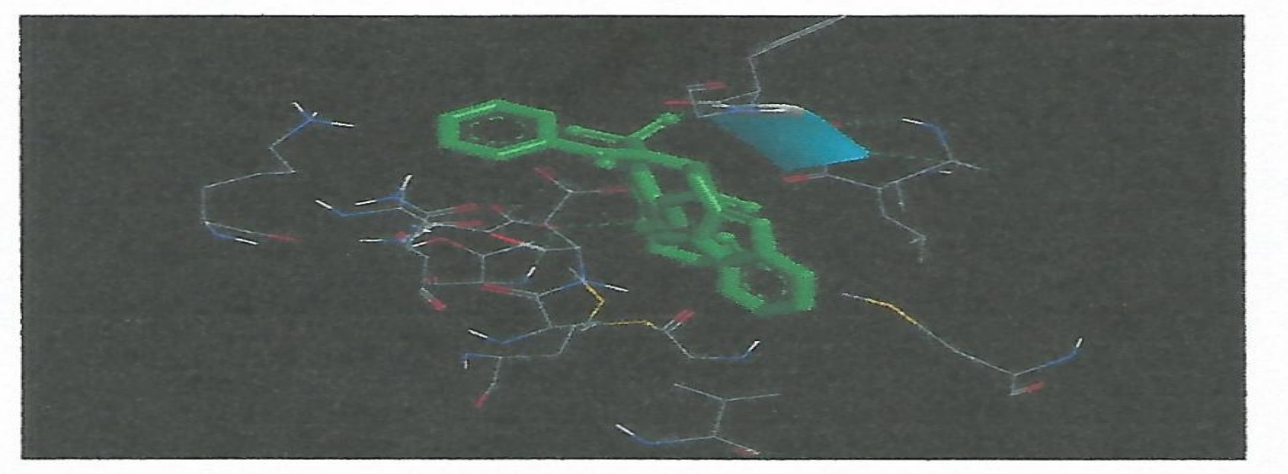

Figure 2: 3D Docking test compound 10 against Kat U

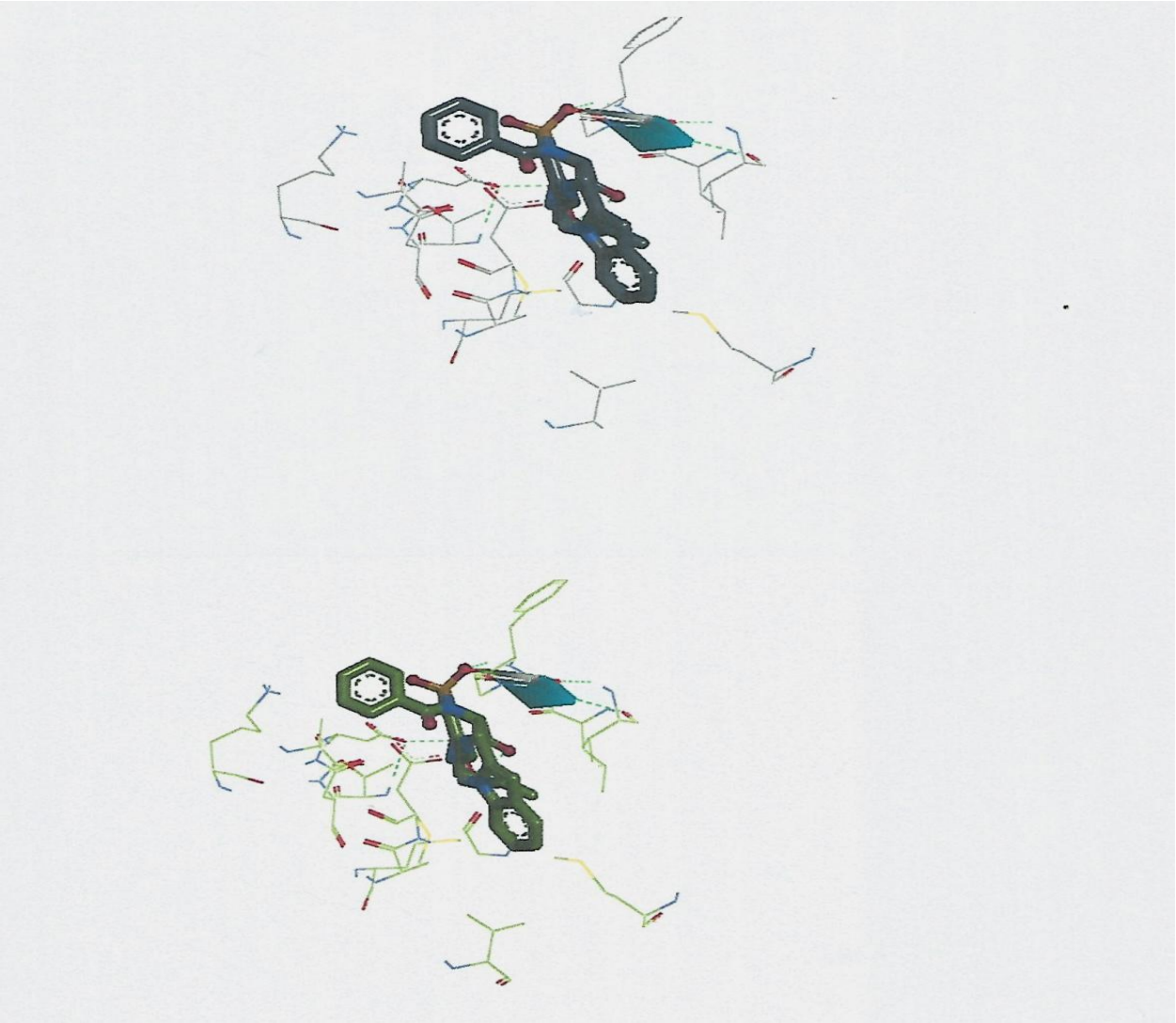

Figure 3: Binding pose pretheted by AutoDock4 for Test compound 10 against antitubercular Target Protein Binding Site

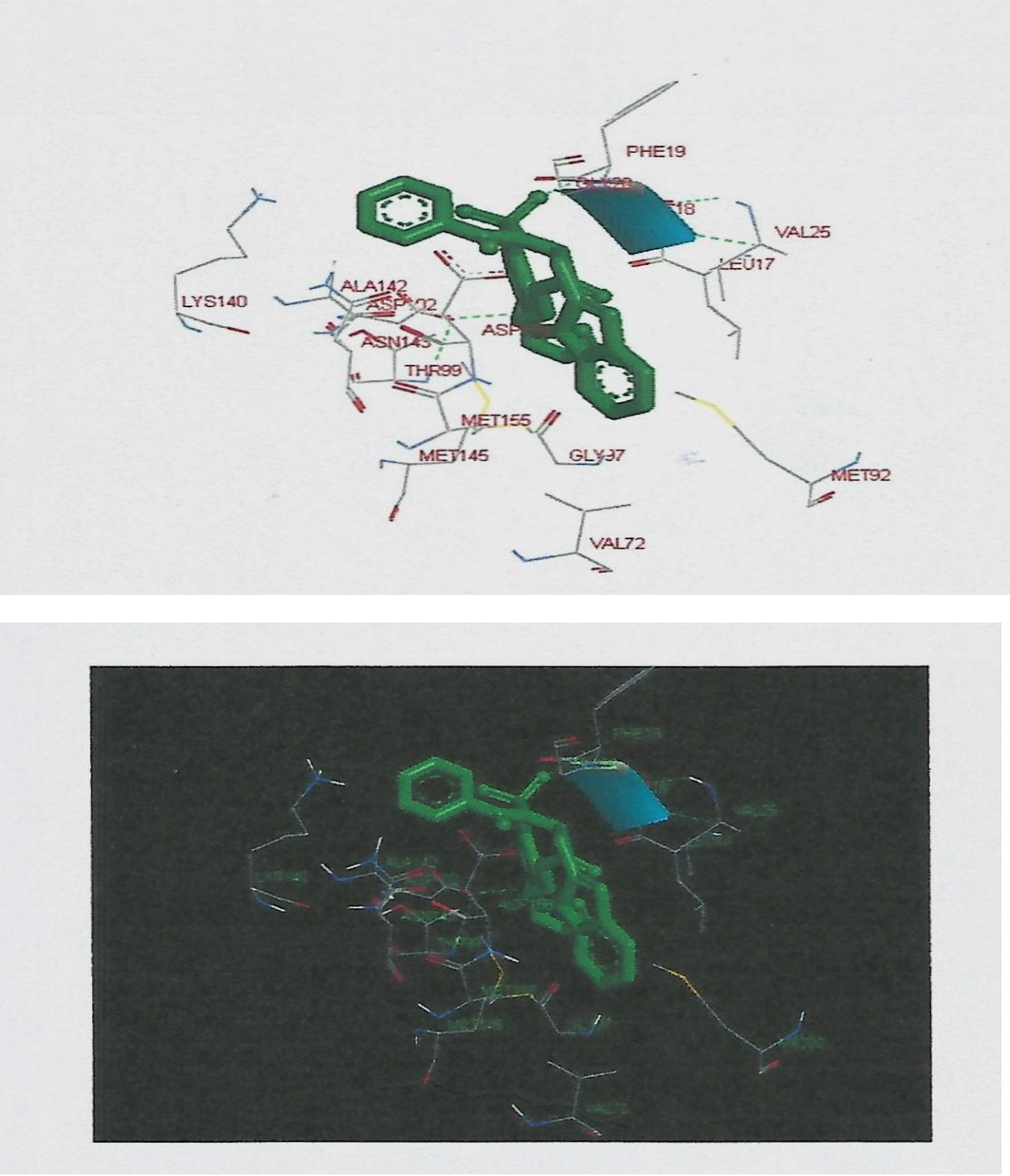

Figure 4: Binding pose predicted by AutoDock4 for Test compound 10 against antitubercular Target Protein Binding Site

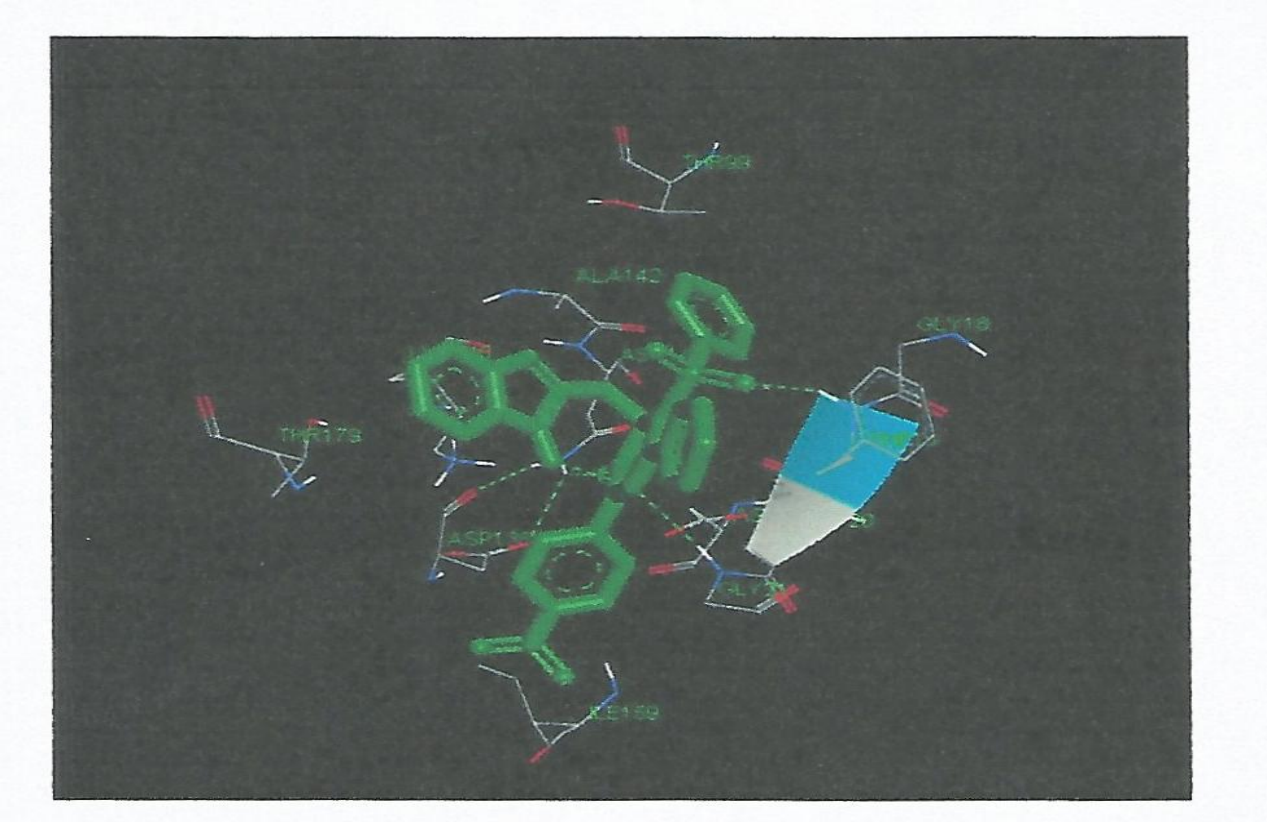

Figure 5: 3D Docking test compound 11 against PKnB

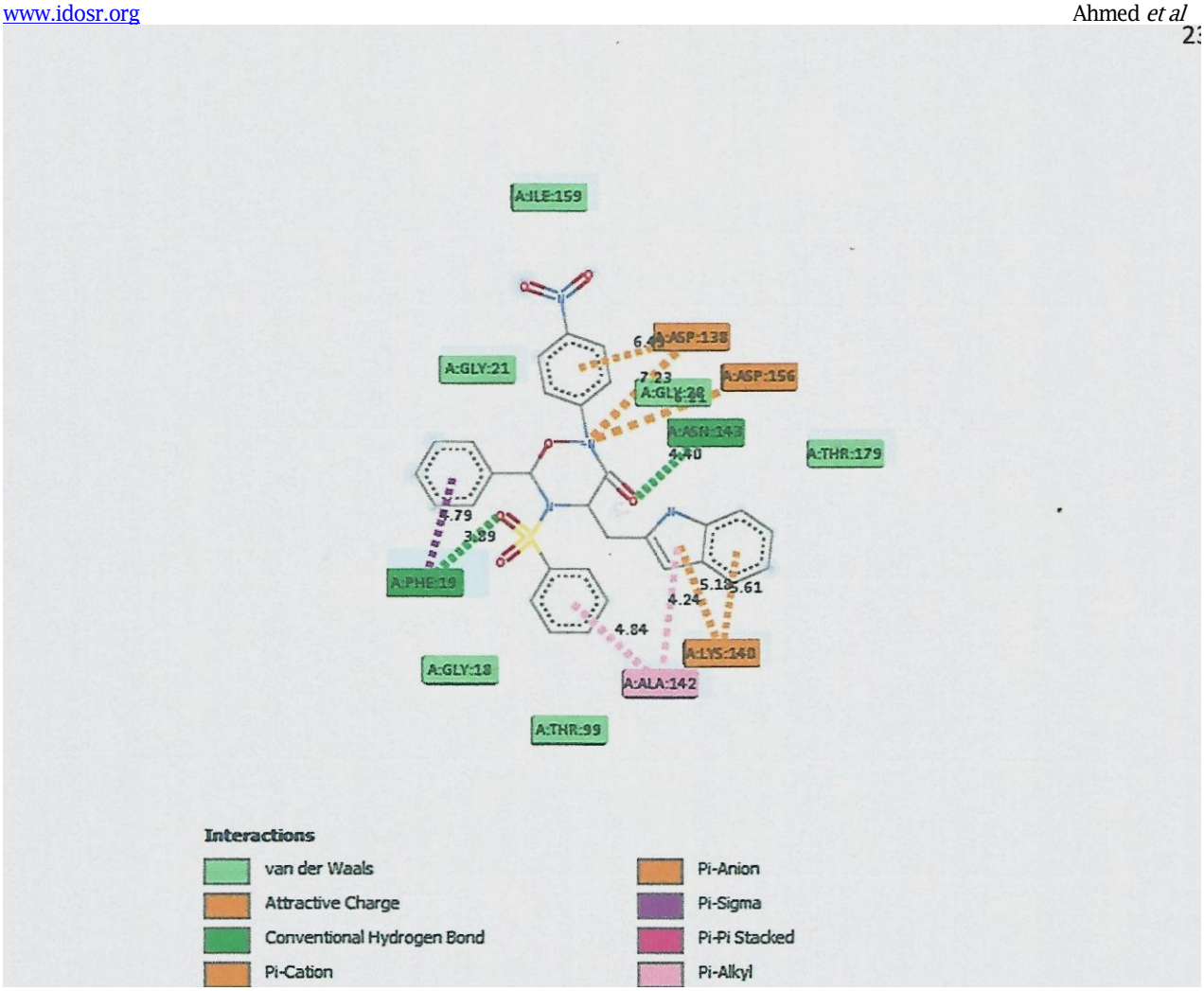

Fig 6: the interaction of ligands with the following amino acids: A:ILE:l59, A:GLY:21, A:PFIE:l9, A:GLY:1X, A:TFIR:99, A:ALA:142, A:LYS:140, A:THR:179, A:ASN:143, A:GLY:29, A:ASP:156, A:ASP:138.

In the development of new drug candidates intended for oral use, oral bioavailability and proper drug delivery are considered to play an important role [9,10]. The result of the pharmacokinetics studies of some 4-picoline derivative are given in the table below.

TABLE 2:Pharmacokinetic studies of 4-picoline derivatives

S/N	MW	MiLqgP	TPSA (A2)	HBA	HBD	NRB	Volume	ABS (%)	AMR	NAC	NA	LV
1.	423.49	3.40	96.44	7	1	6	367.21	75.73	122.7	0	30	0
2.	513.62	4.83	96.44	7	1	8	455.45	75.73	156.07	0	37	1
3.	552.66	5.29	112.23	8	2	8	484.43	70.28	167.93	0	40	2
4.	479.60	4.68	96.44	7	1	8	433.99	75.73	140.18	0	34	0
5.	479.60	4.65	96.44	7	1	8	433.99	75.73	138.81	0	34	0
6.	465.57	4.15	96.44	7	1	7	417.19	75.73	135.73	0	33	0
7.	375.45	1.48	99.60	7	2	4	324.45	74.63	97.32	0	26	0
8.	359.45	2.39	79.37	6	1	4	316.41	81.62	100.37	0	25	0
9.	454.46	2.92	142.26	10	1	7	373.99	59.92	121.64	0	32	0
10.	544.59	4.34	142.26	10	1	9	462.22	59.92	155.0	0	39	1
11.	583.63	4.80	158.06	11	2	9	491.20	54.47	166.86	0	42	1
S/N	MW	MiLqgP	TPSA (A2)	HBA	HBD	NRB	Volume	ABS (%)	AMR	NAC	NA	LV
12.	510.57	4.19	142.26	10	1	9	440.76	59.92	139.12	0	36	1
13.	510.57	4.16	142.26	10	1	9	440.76	59.92	137.75	0	36	1
14.	496.55	3.66	142.26	10	1	8	423.96	59.92	134.67	0	35	0
15.	406.42	0.99	145.42	10	2	5	331.23	58.83	99.31	0	28	0
16.	390.42	1.90	125.19	9	1	5	323.18	65.81	96.26	0	27	0
17.	409.47	2.96	96.44	7	1	6	350.65	75.73	119.21	0	29	0
18.	499.59	4.38	96.44	7	1	8	438.89	75.73	147.25	0	36	0
19.	538.63	4.84	112.23	8	2	8	467.87	70.28	159.99	0	39	1
20.	465.57	4.23	96.44	7	1	8	417.43	75.73	137.05	0	33	0

21.	465.57	4.20	96.44	7	1	8	417.43	75.73	136.37	0	33	0
22.	451.55	3.70	96.44	7	1	7	400.63	75.73	131.85	0	32	0
23.	361.42	1.03	99.60	7	2	4	307.89	74.63	97.65	0	25	0
24.	345.42	1.95	79.37	6	1	4	299.85	81.62	94.11	0	24	0

The test compounds were evaluated for drug-likeness (Lipinski's rule of five) using the Molinspiration online property calculation toolkit to establish a favorable pharmacokinetic (absorption, distribution, metabolism, excretion and toxicity) profile. The octanol-water partition coefficient (logP), Number of H-Bond acceptors (0 and N atoms), Number of H-Bond donors (OH and NH groups), Number of Rule of 5 violations (NV), Number of rotatable bonds (NRB), Topological polar surface area(TPSA), Absorption % (% ABS), Molecular volume (MV) and (NA) were calculated. The percentage of absorption was estimated using the equation: % ABS109-(0.345xTPSA), according to Zhao et al (2002). Polar surface area, together with lipophilicity, is an important property of a molecule in transport across biological membranes. Too high TPSA values give rise to a poor bioavailability and absorption of a drug. According to the above criterions, calculated percentages of absorption for compounds 1-24 ranged between 54 and 81%. The number of atoms (NA) ranged between 24 and 40, the octanol-water partition coefficient (logP) is between 1.03 to 5.29, hydrogen bond donors (HBD) varied between 1 to 2, hydrogen bond acceptor (HBA) ranged between 6 and 11, number of rotatable bond(NRB) are between 4 to 9, % absorption (%ABS) ranged from 54.47 through 70.28 to 81.62. The results presented in table 3 revealed that 6 tested compounds comply with Lipinski' s rule of 5 with non violating any one of the rules, where logP values ranged between 4.19 and 4.84 (<5), Molecular weight (MW) range 510.57—583.63 (>500), HBA range 6-11 (10), and HBD range 1-2 (<5), suggesting that these compounds would not be expected to cause problems with oral bioavailability. Moreover, all the tested compounds showed NRB values of 4-9 (1 0), indicating acceptable molecular flexibility with consequent expected good permeability and oral bioavailability. All the evaluated compounds showed TPSA range 96.44-158.06 A2 (<140 A2), indicating good permeability and transport of the compounds in cellular pa membrane. Furthermore, all the tested compounds exhibited a considerable % ABS range 54.47—8l.620/c, which is a designation of good bioavailability upon oral administration. It is be noted that TPSA is inversely proportional to %ABS.

CONCLUSION

In the present study, we developed novel chemical entities as potential antitubercular agents. The compounds showed good drug-likeness scores based on Lipinski's rule. Among the 24 compounds, compound 2, 10, 11, 12, 13 and 19 exhibited potent antitubercular activity. In the in silico studies, these test compounds showed minimum binding energy with PknB and KatG values as well as they showed not more than one violation to Lipinski rule of five. So the present study provides us insight for the further development of better antitubercular agents as PknB kinase B inhibitor.

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