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In Silico Molecular Docking Studies On Novel Analogues Of Diphenyl Phosphonates As Dna Gyrase Inhibitors For Tuberculosis.

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ABSTRACT

Tuberculosis (TB) is caused by the bacteria Mycobacterium tuberculosis that most often affect the lungs. Tuberculosis is a curable and preventable disease. Drug-susceptible TB disease is treated with a standard 4-month or 6-month course of four antimicrobial drugs. TB is spread from person to person through the air. When people with lung TB, cough, sneeze or spit, they propel the TB germs into the air. A person needs to inhale only a few of these germs to become infected. DNA gyrase (topoisomerase II) and the other topoisomerases (I and III) play a crucial role in maintaining the nucleoid structure and the compact supercoiled domains of the chromosome. The DNA GYRASE enzyme plays a very important role in the Mycobacterium tuberculosis. These enzymes help with the winding and unwinding of the DNA that occurs during replication and transcription. Tuberculosis DNA gyrase is thus a validated target for anti- tubercular drug discovery; its inhibition results in high mycobactericidal activity. Inhibitors of this enzyme are also active against non-replicating, persistent mycobacteria, which might be important for shortening the duration of TB therapy. The mechanism of inhibition can be related to the catalytic mechanism of DNA GYRASE action or include mechanism unrelated to stearic blockage of the active site or its neighbourhood. DNA GYRASE inhibitor drugs block the action of this enzymes. In this study, we have selected analogues of Cyclic DiphenylPhosphonates as DNA gyrase Inhibitors.In silico docking studies were carried out using BIOVIA Discovery Studio. The results showed that most of the chemical compounds binds effectively with DNA GYRASE enzyme. Among the docked compounds, the compound 18, compound 24, shows higher – cdocker energy and -cdocker interaction energy than the standard drug whereas the other analogues showed comparatively lower scores. This study will be the basement support for the synthesis of more substituted compounds or molecules with similar structure towards the tuberculosis therapy.

KEYWORDS: Tuberculosis, DNA GYRASE enzyme, Cyclic DiphenylPhosphonates , analogues, molecular docking.

I. INTRODUCTION:

Tuberculosis (TB) is an ancient disease that has affected mankind for more than 4,000 years. [1] It is a chronic disease caused by the bacillus Mycobacterium tuberculosis. TB usually affects the lungs but it can also affect other parts of the body, such as brain, intestines, kidneys, or the spine. Symptoms of TB depend on where in the body the TB bacteria are growing. In the cases of pulmonary TB, it may cause symptoms, such as chronic cough, pain in the chest, hemoptysis, weakness or fatigue, weight loss, fever, and night-sweats. It spreads from person to person through air, when a person with active TB disease coughs or sneezes and someone else inhales the expelled droplets, which contain TB bacteria.[2] Infections are among the major causes of human morbidity and mortality. The pharmaceutical industry is unable to keep up with the growing need for effective novel antibacterial drugs.The main reason for this situation is the rapid bacterial adaptation to antibiotics, which results in resistance development after antibacterial drugs are introduced into clinical use. Antibiotic resistance has been deemed as one of the most threats to global public health by the World Health Organization. [3]The increasing amount of genomic and molecular information is the basis for understanding higher-order biological

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systems, such as the cell and the organism, and their interactions with the environment, as well as for medical, industrial and other practical applications.[4]

Bacterial DNA gyrase, a type II DNA topoisomerase found in all bacteria, is a proven target for antibacterial chemotherapy. It is the only type II enzyme to retain its historical name. In contrast to other type II topoisomerases, DNA gyrase is the only enzyme that is capable of actively underwinding (i.e., negatively supercoiling) the double helix.[5][6]DNA gyrase was the first type II topoisomerase to be discovered and was first reported in 1976.DNA gyrase play a crucial role in maintaining the nucleoid structure and the compact supercoiled domains of the chromosome. This enzyme helps with the winding and unwinding of the DNA that occurs during replication and transcription. So here we have selected DNA gyrase. DNA gyrase is thus a validated target for antitubercular drug discovery; its inhibition results in high mycobactericidal activity. Inhibitors of this enzyme are also active against non-replicating, persistent mycobacteria, which might be important for shortening the duration of TB therapy. DNA gyrase has long been known as an attractive target for antibacterial drugs. Two classes of antibiotics have clinically validated DNA gyrase as a viable target quinolones and aminocoumarins. Fluoroquinolones inhibit DNA gyrase by interfering with the DNA cleavage/resealing function of the enzyme It is one of the most extensively researched and verified targets for the creation of novel antibacterial therapies. This enzyme is a good target for the development of antibacterial therapeutics with selective toxicity due to its lack in the mammalian organism and its critical function in the bacterial DNA replication cycle. Gyrase A and Gyrase B are the two subunits that make up the catalytically active heterotetrameric enzyme (i.e. A2B2). While the B subunit (DNA gyrase B) has ATPase activity and supplies enough energy for the DNA supercoiling, the A subunit is responsible for breaking and rejoining the double DNA strand. DNA gyrase is an essential bacterial enzyme that catalyses the ATP-dependent negative supercoiling of double-stranded closed-circular DNA. Gyrase belongs to a class of enzymes known as topoisomerases that are involved in the control of topological transitions of DNA. Tuberculosis DNA gyrase is thus a validated target for anti-tubercular drug discovery. Inhibitors of this enzyme are also active against non-replicating mycobacteria, which might be important for the eradication of persistent organisms.[7][8]

Molecular Docking is an effective and competent tool for insilico screening. Docking is a computational procedure of searching for an appropriate ligand that fits both energetically and geometrically the protein's binding site. In other words, it is a study of how two or more molecules e.g. ligand and protein, fit together.Molecular docking has become an increasingly important tool for drug discovery. In this review, we present a brief introduction of the available molecular docking methods, and their development and applications in drug discovery. The relevant basic theories, including sampling algorithms and scoring functions, are summarized. [9]Molecular docking has been proved very efficient tool for novel drug discovery for targeted protein. Among different types of docking, protein-ligand docking is of special interest, because of its application in medicine industry. Protein-ligand docking refers to search for the accurate ligand conformationswithin a targeted protein when the structure of proteins is known. The main objective of molecular docking is to attain ligandreceptorcomplex with optimised conformation and with the intention of possessing less binding free energy.[10] Characterization of the binding behavior plays an importantrole in rational design of drugs as well as to elucidate fundamental biochemical processes.Molecular docking research focuses on computationally simulating the molecular recognition process. It aims to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized.[10][11] Docking combined with a scoring function can be used to quickly screen large databases of potential drugs in silico to identify molecules that are likely to bind to protein target of interest.[12][13]The aim of the current study is focused on determining the binding effectiveness and potent compounds of various Diphenylphosphonate analogues against the DNA gyrase enzyme.

Material and Methods

ChemDraw software 20.1.1.125 (PerkinElmer Informatics, Inc., USA), OpenBabel 2.4.1.software (Openeye scientific, New Mexico.), BIOVIA Discovery Studio 2020 v20.1.0.19295 (Dassault system, San Diego, CA, USA).

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Molecular Docking Study

The two dimensional (2-D) structures of all molecules were drawn using ChemDraw software 20.1.1.125 and saved in .cdx format. The interactions between all molecules and protein DNA gyrase (PDB ID: 1KZN) [14] [9]. All drugs structures were converted to .sdf MDL MOL format from .cdx file using OpenBabel 2.4.1. Software (Openeye scientific, New Mexico.) as single file. Ligand preparation was performed by minimizing energy for docking. DNA gyrase (PDB ID: 1KZN) was downloaded and prepared. The preparation of protein was based on selection of chain containing amino acids for respective co-crystal (CLOROBIOCIN) for chain A and water molecules were removed. After protein preparation, binding site was defined with co-crystal. The prepared ligands were docked against prepared protein with CDOCKER inbuilt algorithm using BIOVIA Discovery Studio 2020. The interactions resulted in binding energy (kcal/mol), 2D and 3D interactions between respective ligand and protein [15].

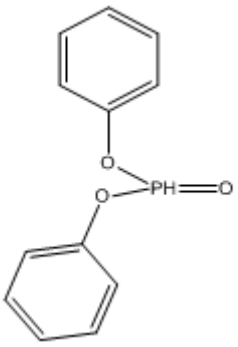
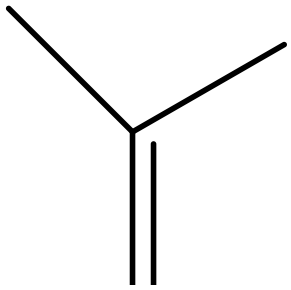
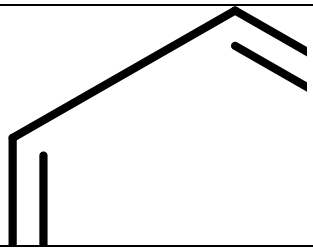


Fig1 :Pharmacophore

TABLE 1: STRUCTURES OF PROPOSED ANALOGUES OF DIPHENYL PHOSPHONATES

Docked Molecules	IUPAC Name	Structures
Standard molecule	CLOROBIOCIN	
M 1	Diphenyl (1-chloro-1,2,3,4-tetrahydropyridin-3- yl) phosphonate	

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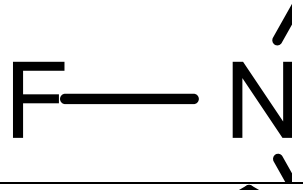
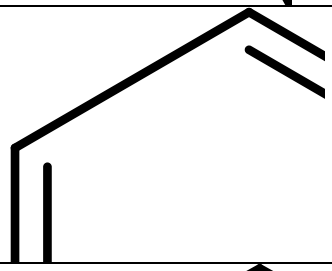
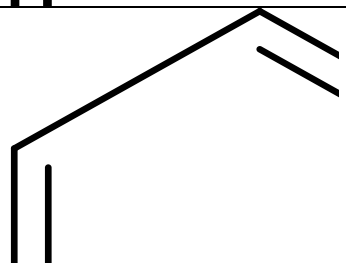
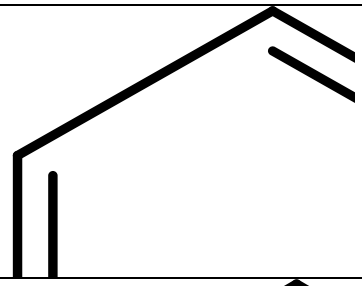
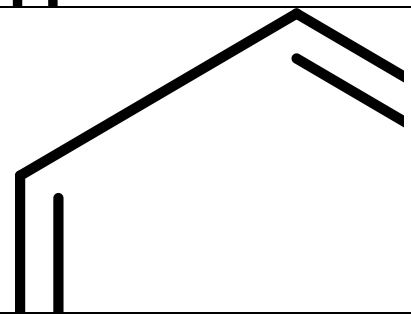
M 2	Diphenyl (1-fluoro-1,2,3,4-tetrahydropyridin-3-yl) phosphonate	
M 3	Diphenyl (1-amino-1,2,3,4-tetrahydropyridin-3-yl) phosphonate	
M 4	Diphenyl (1-bromo-1,2,3,4-tetrahydropyridin-3-yl) phosphonate	
M 5	Diphenyl (1-hydroxy-1,2,3,4-tetrahydropyridin-3-yl)phosphonate	
M 6	3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridine-1-carboxylic acid	

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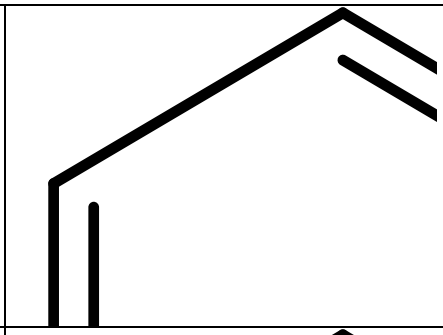
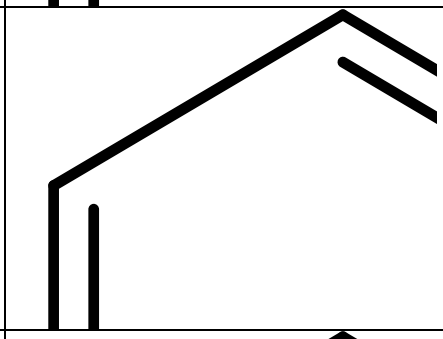
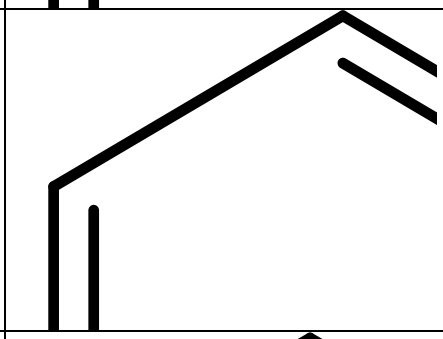
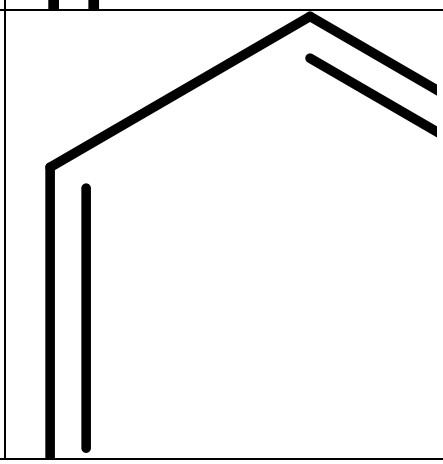
M 7	Diphenyl (1-sulfanyl-1,2,3,4-tetrahydropyridin-3-yl)phosphonate	
M 8	Diphenyl (1-methyl-1,2,3,4-tetrahydropyridin-3-yl)phosphonate	
M 9	Diphenyl (1-cyano-1,2,3,4-tetrahydropyridin-3-yl)phosphonate	
M 10	2-{[3-(diphenoxyphosphoryl) -1,2,3,4-Tetrahydropyridin-1-yl] amino}acetic acid	

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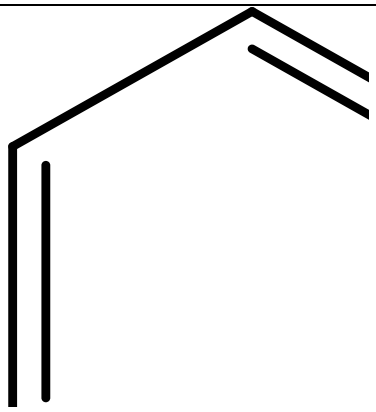
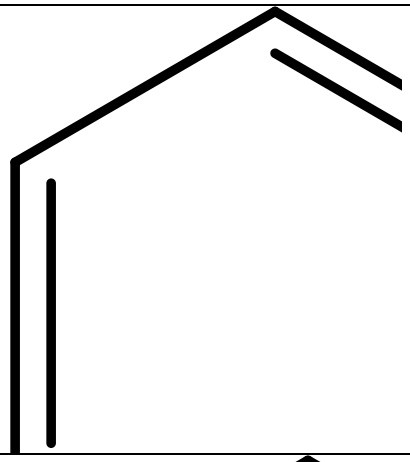
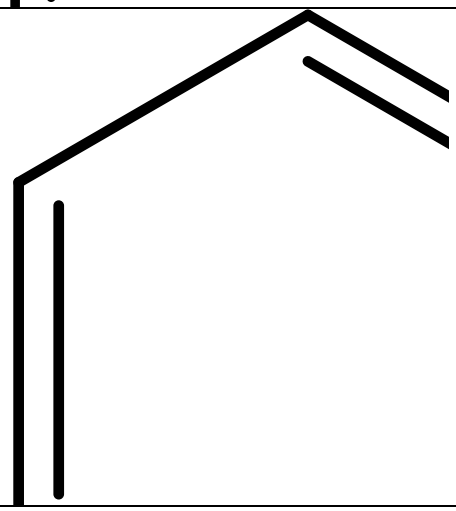
M 11	2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}propanoic acid	
M 12	2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}-3-hydroxypropanoic acid	
M 13	2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}-3-sulfanylpropanoic acid	

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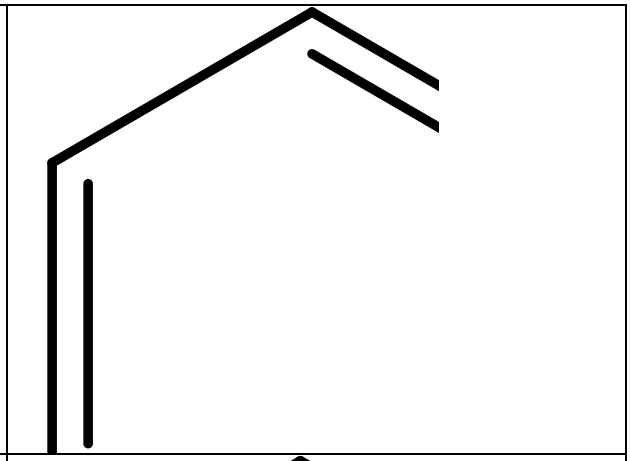
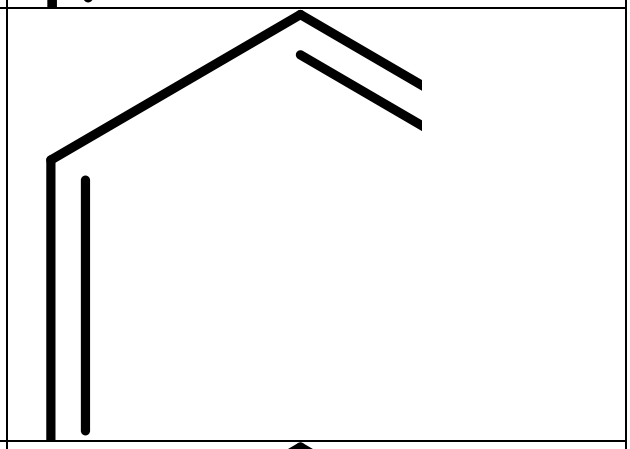
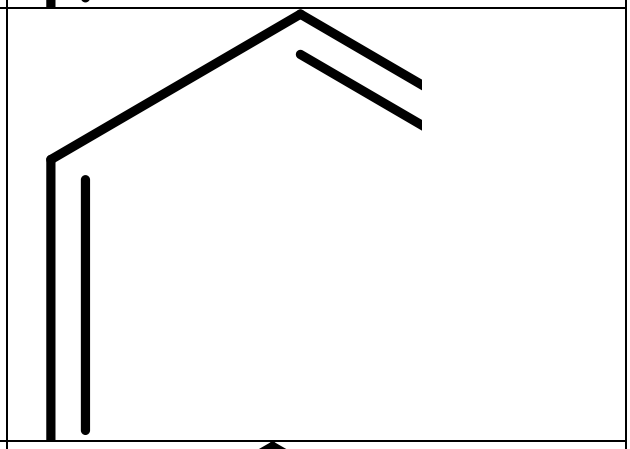
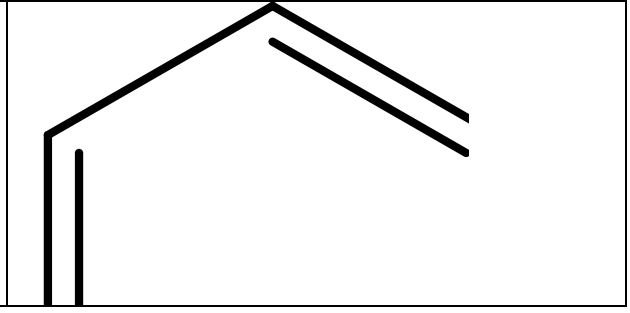
14	2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}-3-methylbutanoic acid	
M 15	2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}-4-methylpentanoic acid	
M 16	2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}-4-(methylsulfanyl)butanoic acid	
M 17	1-[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]pyrrolidine-2-carboxylic acid	

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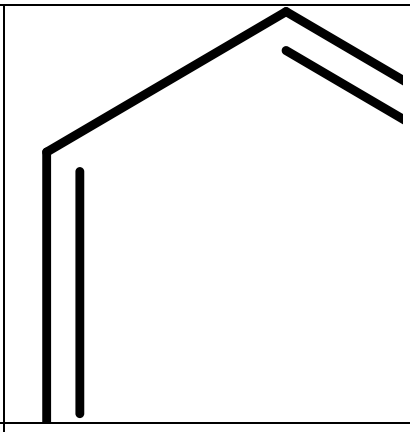
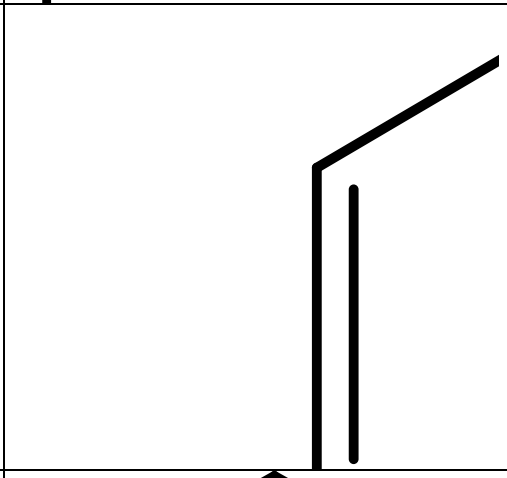
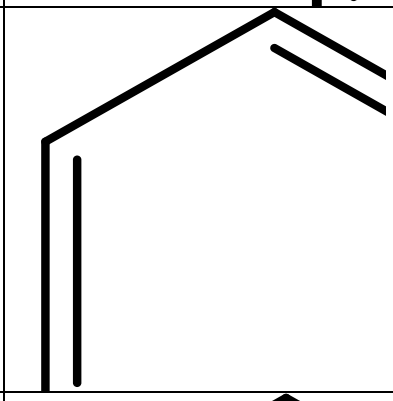
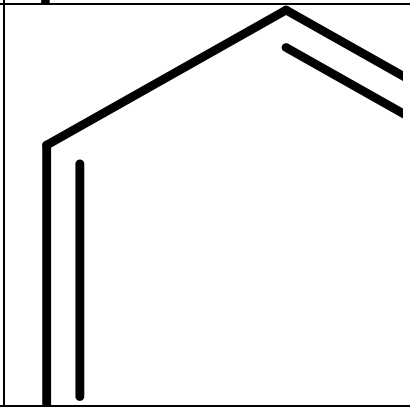
M 18	2-{[3-(diphenoxyphosphoryl)-1,2,3,4- Tetrahydropyridin-1-yl]amino}-3-(4-hydroxyphenyl)propanoic acid	
M 19	5-carbamimidamido-2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}pentanoic acid	
M 20	6-amino-2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}hexanoic acid	
M 21	2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}-3-(1H-imidazol-4-yl)propanoic acid	

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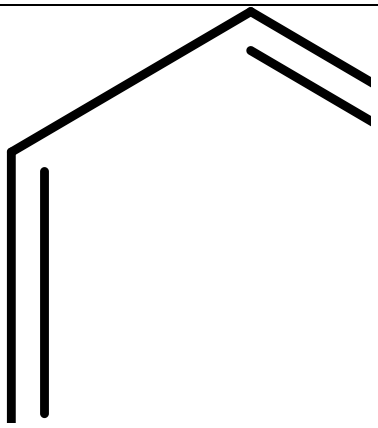
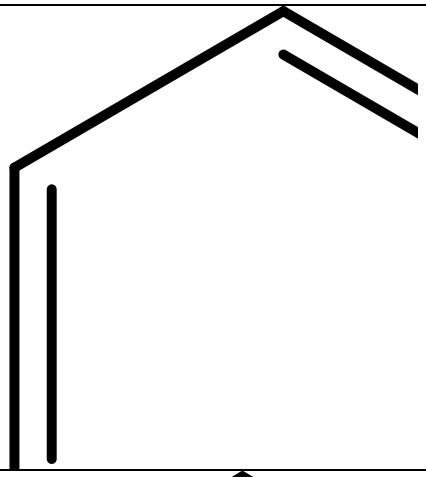
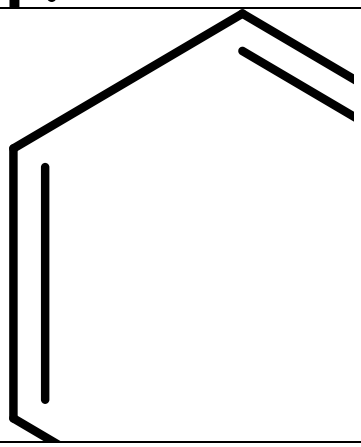
M 22	2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}pentanedioic acid	
M 23	2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}-3-hydroxybutanoic acid	
M 24	2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}-3-(1H-indol-3-yl)propanoic acid	

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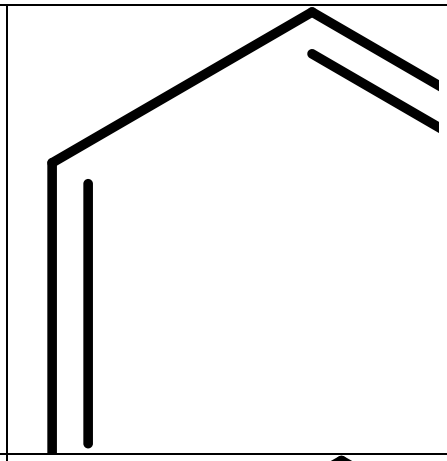
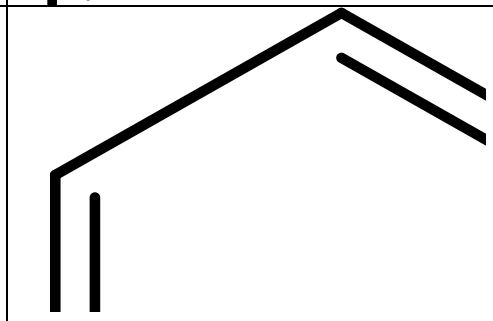
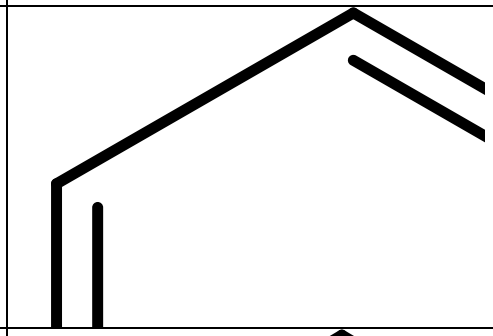
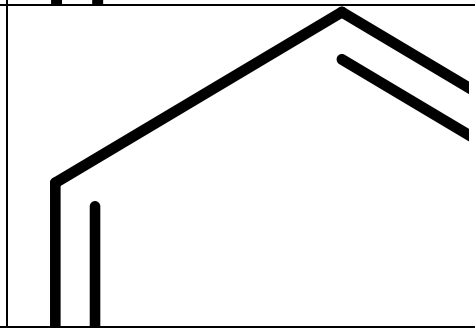
M 25	2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}-3-phenylpropanoic acid	
M 26	Diphenyl {1-[(aminooxy)methyl]-1,2,3,4-tetrahydropyridin-3-yl}phosphonate	
M 27	Diphenyl [1-(aminomethyl)-1,2,3,4-tetrahydropyridin-3-yl]phosphonate	
M 28	Diphenyl (1-ethyl-1,2,3,4-tetrahydropyridin-3-yl)phosphonate	

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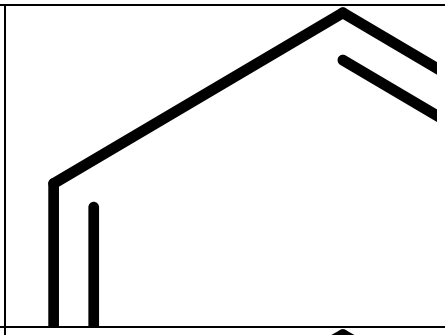
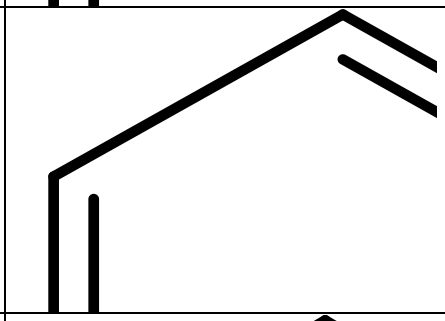
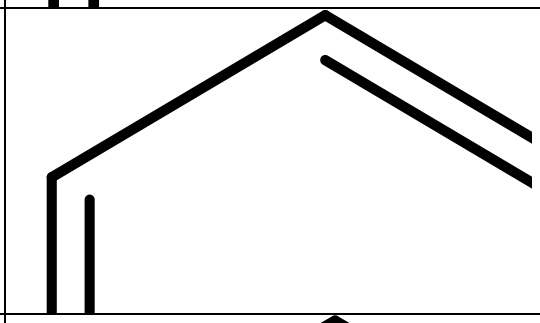
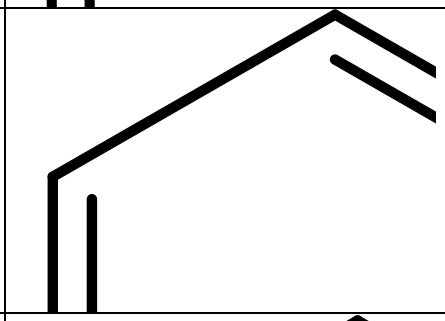
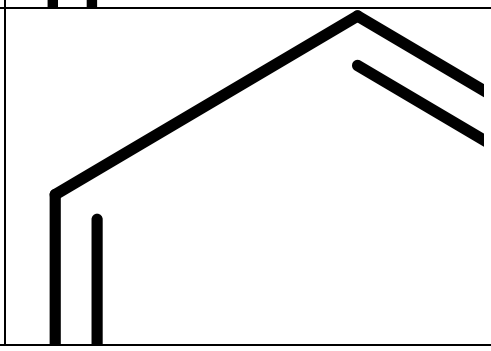
M 29	Diphenyl (1-nitro-1,2,3,4-tetrahydropyridin-3-yl)phosphonate	
M 30	Diphenyl [1-(trifluoromethyl)-1,2,3,4-tetrahydropyridin-3-yl]phosphonate	
M 31	Diphenyl (1-acetamido-1,2,3,4-tetrahydropyridin-3-yl)phosphonate	
M 32	Diphenyl (1-methoxy-1,2,3,4-tetrahydropyridin-3-yl)phosphonate	
M 33	Diphenyl (1-acetyl-1,2,3,4-tetrahydropyridin-3-yl)phosphonate	

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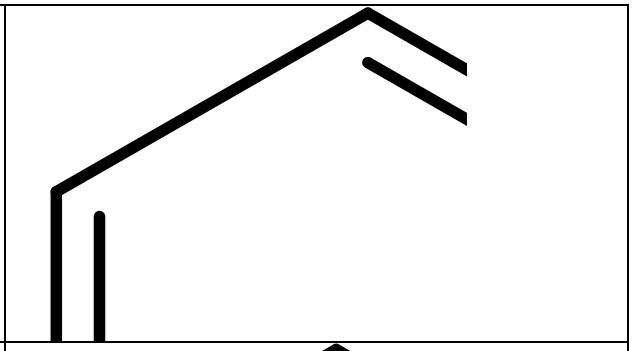
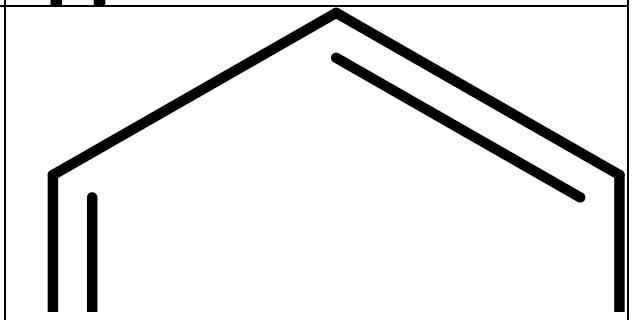
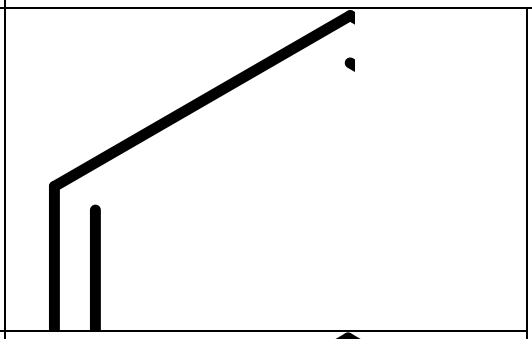
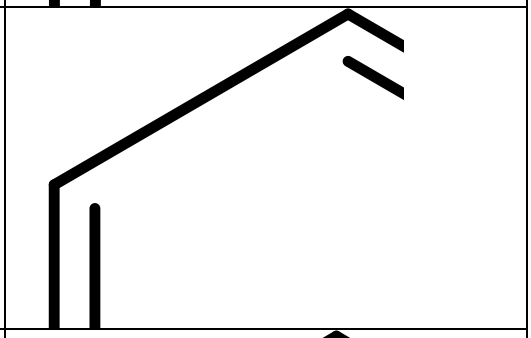
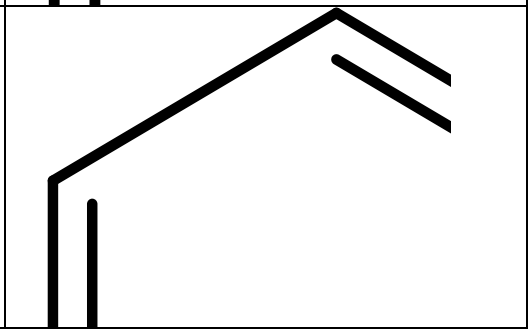
M 34	Amino diphenyl phosphate	
M 35	2-ethylhexyl diphenyl phosphate	
M 36	Diphenylphosphonate	
M 37	Diphenyl (propan-2-yl)phosphonate	
M 38	Diphenyl (4-methylphenyl)phosphonate	

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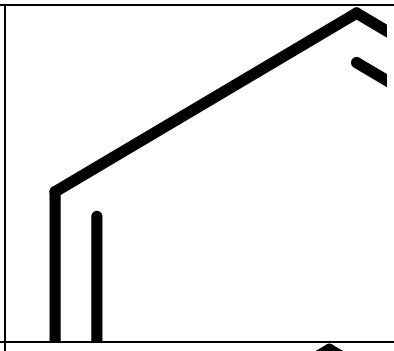
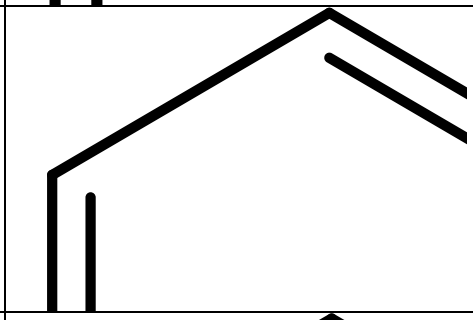
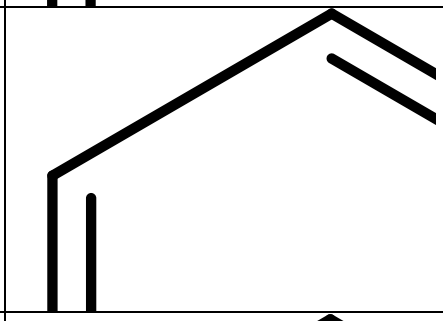
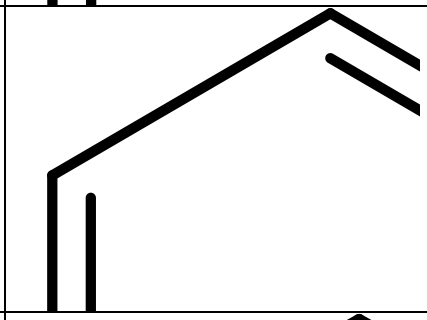
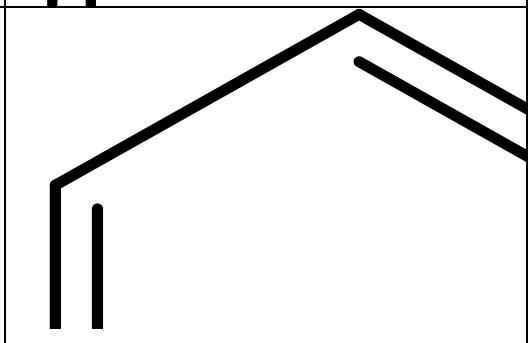
M 39	Diphenyl methylphosphonate	
M 40	Diphenyl (1,2-dihydroxypropyl)phosphonate	
M 41	Diphenyl (1-amino-2-methylpropyl)phosphonate	
M 42	Diphenyl (aziridin-1-yl)phosphonate	
M 43	Diphenyl (thiomorpholin-4-yl)phosphonate	

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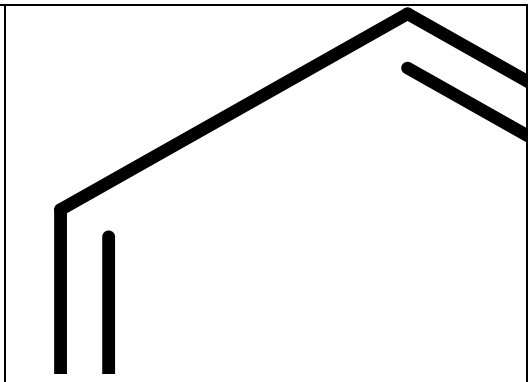
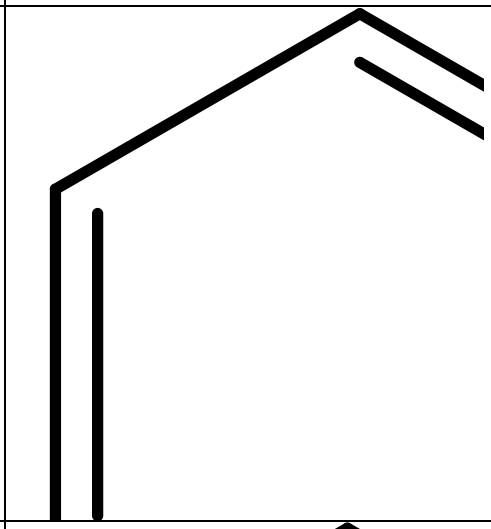
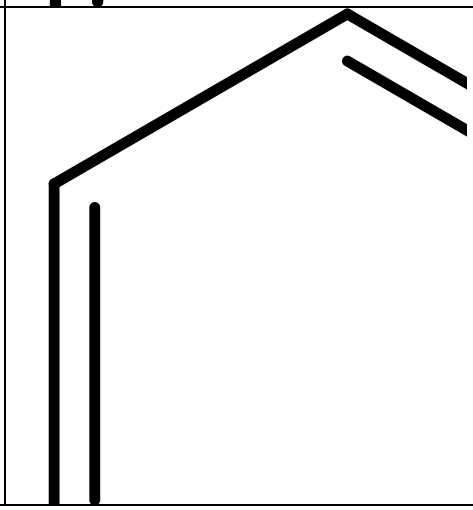
M 44	Diphenyl {3-[methoxy(methyl)amino]-2-oxopropyl}phosphonate	
M 45	2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}-3-methylpentanoic acid	
M 46	4-carbamoyl-2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}butanoic acid	

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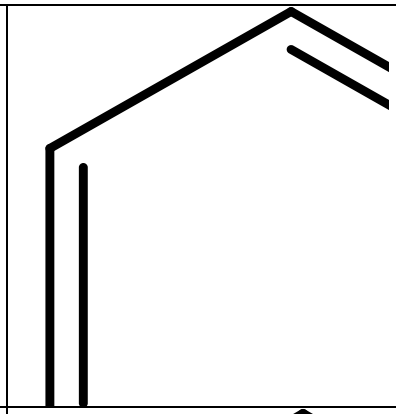
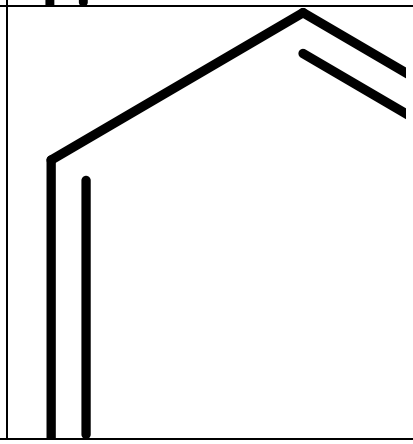
M 47	3-carbamoyl-2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}propanoic acid	
M 48	2-{[3-(diphenoxyphosphoryl)-1,2,3,4-tetrahydropyridin-1-yl]amino}butanedioic acid	

II. RESULTS AND DISCUSSION:

Standard (Clorobiocin) and the proposed 48 molecules were docked against the target DNA gyrase. Among the various docked compounds, molecule 18 and molecule 24 showed good binding energy, shorter bond length and potential affinity towards the target. The larger bond distances may lead to unstable protein-ligand complex, shorter bond length is stable. The binding energy values for the interaction of amino acids of DNA gyrase (PDB ID : 1KZN) and atoms or functional groups of co crystal (Clorobiocin), molecule 24 and molecule 18 were -144.463 (kcal/mol), -110.739 (kcal/mol) and -97.6299 (kcal/mol) respectively. The nature of the bond, bond length and the interaction between the atoms or functional groups of the standard and potential molecules with the amino acids in the target is elaborated in the Table 2.

TABLE 2: INTERACTION RESULTS FOR DOCKING STUDIES OF THE STANDARD AND POTENTIAL MOLECULES

Interaction	Binding Energy (kcal/mol)	Interacting amino acids and atoms	Nature of Bond	Bond length(Å)
1KZN-Cocrystal CLOROBIOCIN	-144.463	ASN/A: 46 and 5th position OH of 2,2 dimethyl oxane ring.	Hydrogen Bond	1.95 and 2.86
		ASP/A: 73 and H of methyl pyrrole ring.	Hydrogen Bond	1.96
		ARG/A: 136 C=O of 2-oxo-2Hchromen-7-yl)oxy] ring.	Alkyl Bond	1.97
		PRO/A: 79 and 2-oxo-2Hchromen-7-yl)oxy] ring.	Alkyl Bond	4.60 and 5.49

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		ILE/A: 90 methyl group of oxane ring.	Alkyl Bond	4.02
		VAL/A: 167 and H of methyl pyrrole ring.	Alkyl Bond	5.39
		VAL/A: 71 and CH_3 of methyl pyrrole ring.	Alkyl Bond	4.37
		ALA/A: 47 and H of methyl pyrrole ring and methyl in methyl pyrrole ring.	Alkyl Bond	4.32 and 4.46
		ARG/A: 76 and 2-oxo-2Hchromen-7-yl)oxy] ring.	Pi Cation	4.91 and 5.43
1KZN-MOLECULE Diphenoxyphosphoryl (-1,2,3,4-tetrahydropyridin-1-yl amino}-3-(4-hydroxyphenyl)propanoic acid	-97.6299	ASN/A: 46 and H of 1,2,3,4tetrahydropyridin-1-yl amino ring.	Hydrogen Bond	2.78
		ALA/A: 96 and OH of 4hydroxyphenyl ring.	Hydrogen Bond	2.09
		GLU/A: 50 H of 1,2,3,4tetrahydropyridin-1-yl amino ring.	Hydrogen Bond	2.68
		PRO/A: 79 –O of diphenoxyphosphoryl ring.	Hydrogen Bond	2.56
		ILE/A: 90 of hydroxyphenyl ring.	Alkyl Bond	4.71
		ILE/A:78 of 1,2,3,4tetrahydropyridin-1-yl amino ring.	Alkyl Bond	4.97
		ARG/A:136 of diphenoxyphosphoryl ring.	Pi Cation	4.31
1KZN-MOLECULE Diphenoxyphosphoryl (-1,2,3,4tetrahydropyridin-1-yl amino]-3-(1H-indol-3yl)propanoicacid	-110.739	ASN/A: 46 and –NH of 1,2,3,4-tetrahydropyridin-1-yl amino ring.	Hydrogen Bond	2.29
		ASP/A: 49 and –OH of 1Hindol-3-yl)propanoicacid.	Hydrogen Bond	1.99
		ARG/A: 76 and –O of diphenoxyphosphoryl ring.	Hydrogen Bond	2.90
		GLU/A: 50 and 1,2,3,4tetrahydropyridin ring.	Hydrogen Bond	2.48
		PRO/A: 79 and	Hydrogen	2.65
		diphenoxyphosphoryl ring.	Bond	
		ILE/A:78 and tetrahydropyridin ring.	Alkyl Bond	4.74
		ILE/A:90 and 1H-indol ring and diphenoxyphosphoryl ring.	Alkyl Bond	4.33 and 4.19 and 5.44

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		ALA/A:86 and diphenoxyphosphoryl ring.	Alkyl Bond	5.41

TABLE 3:BINDING ENERGIES OF ALL PROPOSED STRUCTURAL ANALOGUES

Name	Visible	Tagged	Visibility Locked	Binding Energy	CDOCKER_ENERGY	CDOCKER_INTERACTION_ENERGY
M24	No	No	No	**-110.739**	37.2655	50.4208
M18	No	No	No	**-97.6299**	37.4815	43.8713
M11	No	No	No	**-88.0013**	32.0201	40.9319
M35	No	No	No	**-84.3862**	40.1892	35.431
M10	No	No	No	**-83.8267**	33.3277	42.0369
M22	No	No	No	**-81.4587**	36.9936	45.1102
M17	No	No	No	**-80.7267**	15.8097	44.5767
M46	No	No	No	**-79.6799**	36.8147	47.6684
M12	No	No	No	**-77.7852**	33.7097	41.7569
M19	No	No	No	**-75.7196**	36.8612	41.38
M45	No	No	No	**-75.0845**	32.6397	44.3096
M16	No	No	No	**-74.4617**	30.635	44.5479
M21	No	No	No	**-71.2443**	36.1886	46.1064
M38	No	No	No	**-70.8127**	26.7856	32.5771
M15	No	No	No	**-70.7009**	37.6626	45.2282
M13	No	No	No	**-68.2369**	33.451	42.6848
M27	No	No	No	**-67.3319**	26.7424	35.8539
M41	No	No	No	**-66.7563**	27.6983	28.6142
M31	No	No	No	**-65.3051**	26.4077	39.5265
M47	No	No	No	**-64.397**	32.4826	36.4856
M36	No	No	No	**-61.8855**	13.2219	25.0822
M23	No	No	No	**-61.6811**	30.2301	40.4489
M28	No	No	No	**-61.3977**	25.0356	35.3721
M4	No	No	No	**-60.3064**	22.153	32.7238
M2	No	No	No	**-55.4996**	18.7246	29.3888
M6	No	No	No	**-53.4774**	25.2212	34.3011
M14	No	No	No	**-52.9746**	32.7579	43.0139
M1	No	No	No	**-52.6619**	22.6008	33.097
M25	No	No	No	**-51.6252**	33.6061	40.7493
M43	No	No	No	**-49.1354**	21.8769	29.9137
M37	No	No	No	**-48.4525**	26.1048	26.6226
M3	No	No	No	**-48.1899**	22.4329	32.7271
M33	No	No	No	**-47.1488**	24.8975	34.8378
M7	No	No	No	**-46.7204**	19.1637	29.4622

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M32	No	No	No	**-44.7538**	24.1603	32.8243
M29	No	No	No	**-42.5084**	19.6157	33.9592
M39	No	No	No	**-42.4032**	22.194	25.5504
M5	No	No	No	**-41.6085**	23.3227	33.9375
M48	No	No	No	**-38.5954**	42.0457	42.1312
M26	No	No	No	**-37.7394**	24.56	35.6351
M44	No	No	No	**32.4925**	37.422	36.5127
M40	No	No	No	**-31.9729**	22.6558	30.5718
M8	No	No	No	**-26.4893**	19.7041	29.5512
M9	No	No	No	**-24.4124**	19.6205	30.4618
M42	No	No	No	**-23.4466**	-64.4561	26.7739
M30	No	No	No	**-2.2237**	19.3107	30.9372
M34	No	No	No	**5.3422**	26.863	29.1163
M20	No	No	No	**8.3393**	34.9725	42.4261

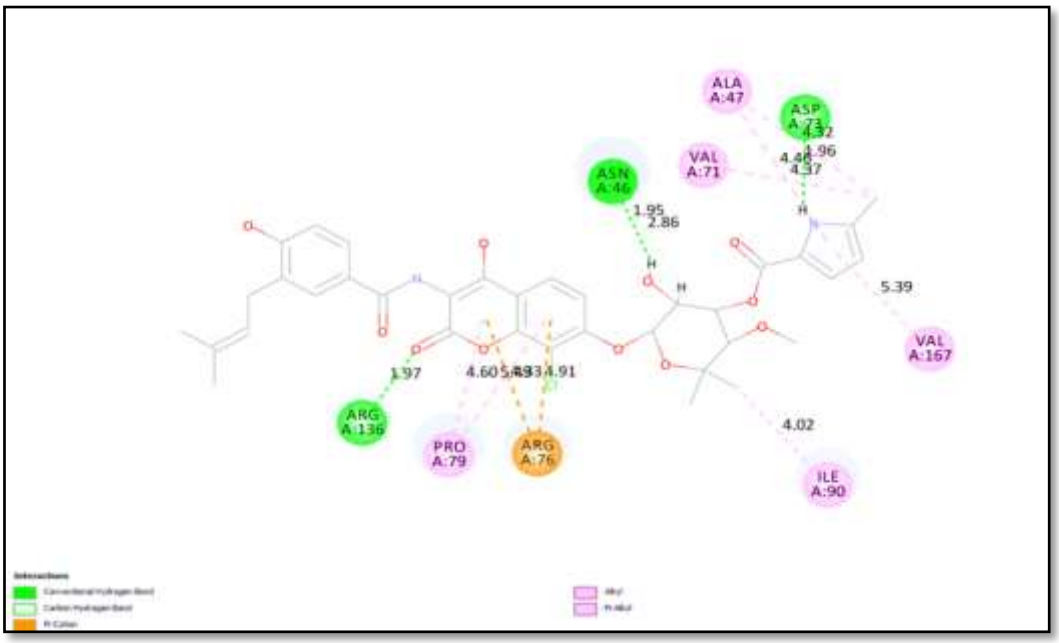

FIG2: 2D structure and interaction of functional groups of cocrystalclorobiocinwithamino acids of DNA GYRASE (PDB ID : 1KZN).

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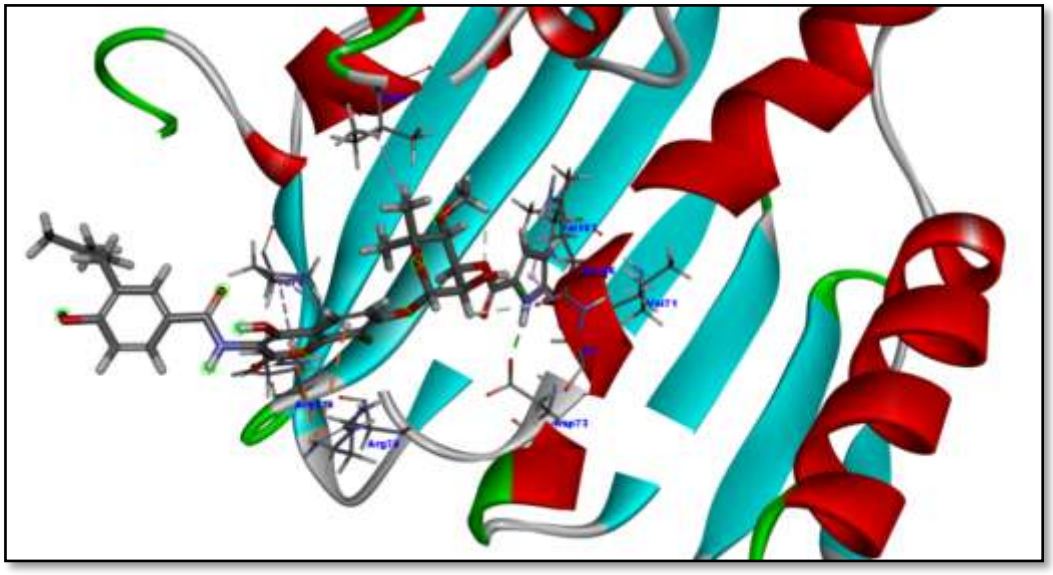

FIG3: 3D structure and interaction of cocrystalClorobiocin at the active site of DNA GYRASE (PDB ID : 1KZN).

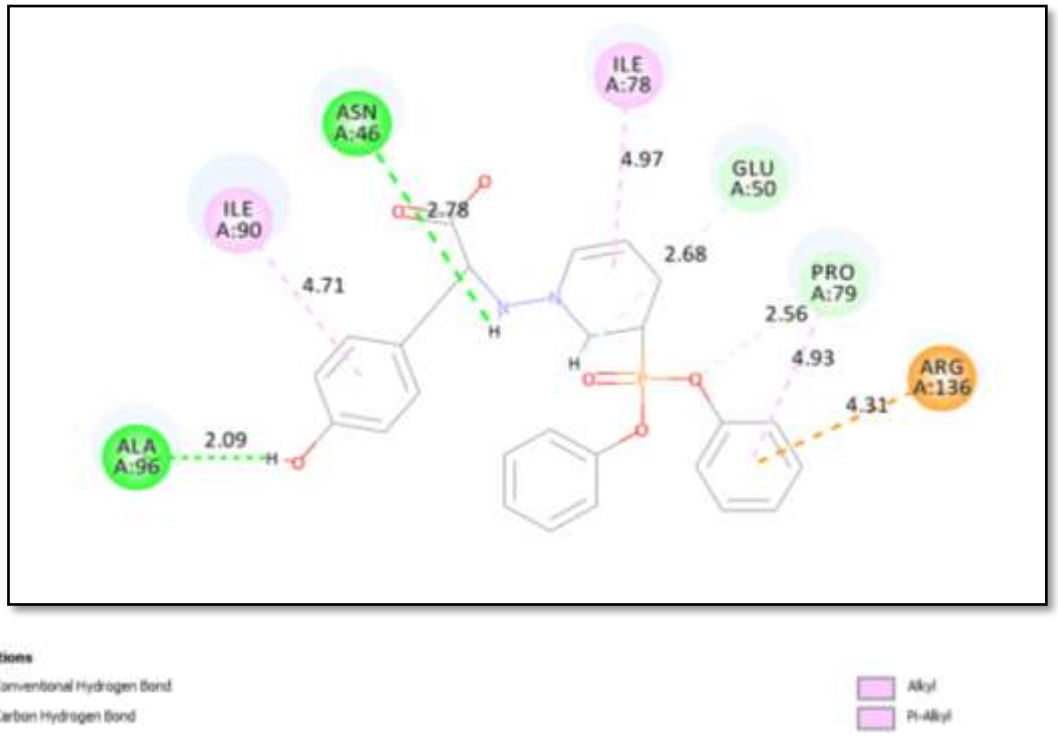

FIG4: 2D structure and interaction of 2-{[3-(diphenoxyphosphoryl(-1,2,3,4-tetrahydropyridin-1-yl amino}-3-(4-hydroxyphenyl) propanoic acid at the active site of DNA Gyrase (PDB ID : 1KZN).

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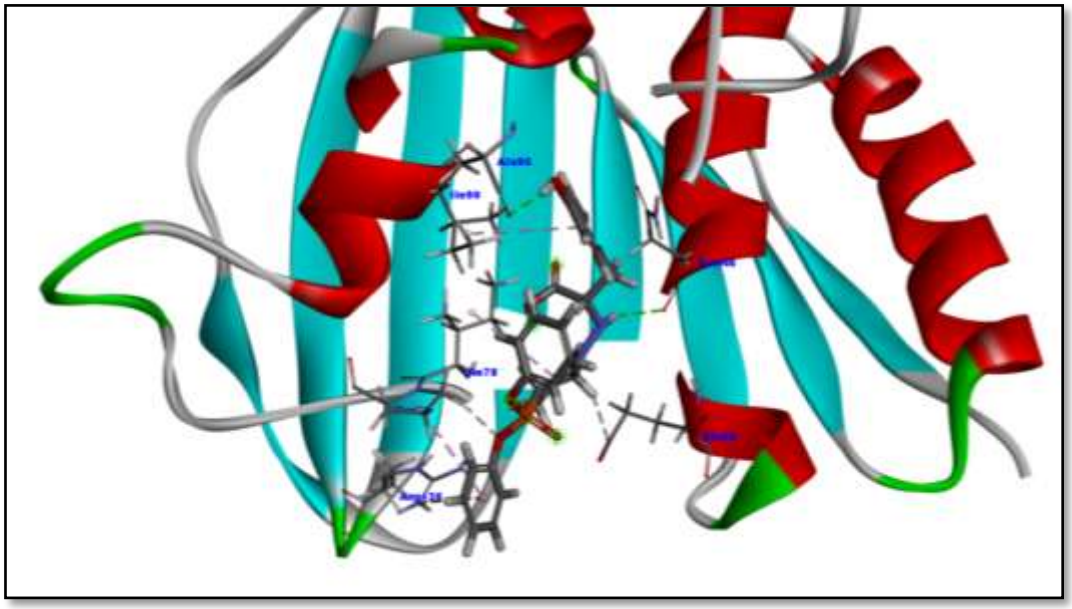

FIG5: 3D structure and interaction of 2-{[3-(diphenoxyphosphoryl(-1,2,3,4-tetrahydropyridin-1-yl amino}-3-(4-hydroxyphenyl)propanoic acid at the active site of DNA Gyrase (PDB ID : 1KZN).

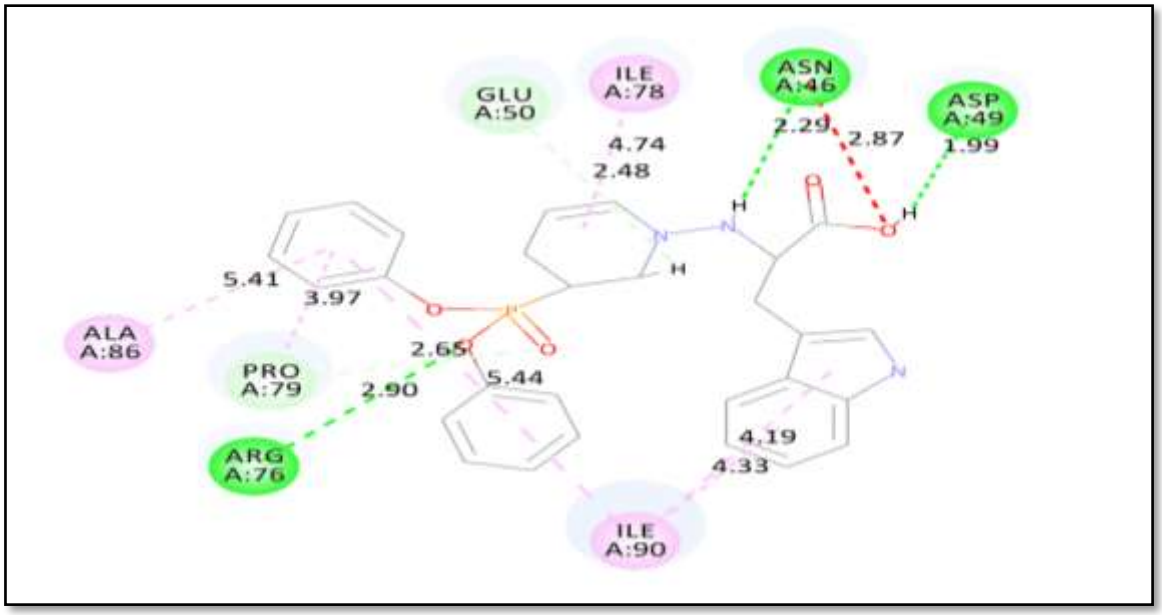

FIG6: 2D structure and interaction of 2-{[3-(diphenoxyphosphoryl(-1,2,3,4-tetrahydropyridin-1-yl amino]-3-(1H-indol-3-yl)propanoic acid at the active site of DNA Gyrase (PDB ID : 1KZN).

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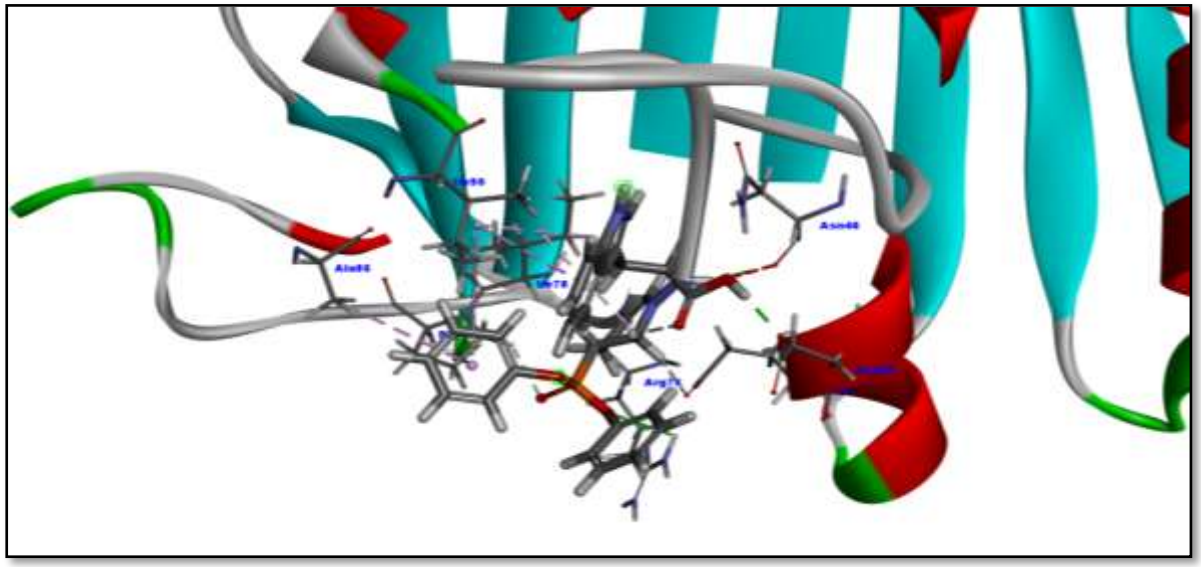

FIG7: 3D structure and interaction of 2-{[3-(diphenoxyphosphoryl(-1,2,3,4-tetrahydropyridin-1-yl amino]-3-(1H-indol-3-yl) propanoic acid at the active site of DNA Gyrase (PDB ID : 1KZN).

III. CONCLUSION

With the help of the extensive literature studies, we have selected DNA gyrase (PDB ID: 1KZN) as the tuberculosis target for finding out the binding effectiveness of the chemical molecules. By performing molecular docking study on various chemical molecules, we have understood that the chemical molecule M24 [2-{[3-(diphenoxyphosphoryl(-1,2,3,4-tetrahydropyridin-1-ylamino]-3(1H-indol-3-yl) propanoicacid] and molecule M18 [2{[3 (diphenoxyphosphoryl (1,2,3,4-tetrahydropyridin-1- yl amino}-3-(4-hydroxyphenyl) propanoic acid] were found to have good binding energy (kcal/mol) and hence good binding affinity against the target DNA GYRASE. This indicates that the compounds with substitutes in diphenylphosphonate chain having amino acid substitutes will have good interaction with the target DNA GYRASE. In future, designing of the chemical constituents having the pharmacophore similar to cyclic diphenylphosphonates or their derivatives with varying substituents in different position will be a good drug for anti-tubercular activity. This study will be the basement support for the synthesis of more substituted compounds or molecule with similar structure towards the tuberculosis therapy.

ACKNOWLEDGEMENT

We would like to specially thank Rajiv Gandhi University of Health Sciences in Bangalore, Karnataka-India for providing the Undergraduate Students Research Fund for carrying out this project.

LIST OF ABBREVIATIONS

DNA: Deoxyribonucleic acid
ASN: Asparagine
ASP: Aspartic acid
ARG: Arginine
PRO: Proline
ILE: Isoleucine
VAL: Valine
ALA: Alanine
GLU: Glutamic Acid
PDB: Protein Data Bank

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