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MOLECULAR DOCKING, VALIDATION AND PHARMACOKINETIC PREDICTION OF SOME DESIGNED PYRAZOLE DERIVATIVES AGAINST DNA GYRASE

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ABSTRACT

Pyrazoles are biologically important derivatives for various pharmacological activities. The study aims to evaluate the potency of designed pyrazole derivatives for theiranti-bacterial activity against the active site of bacterial DNA gyrase using autodock4.2.6. The three-dimensional crystal structure of the DNA gyrase (PDB Id: 4URM) was retrieved from the RCSB Protein Data Bank (PDB), the amino acid residues interacting with co-crystallized ligand were used as active site. The compounds 1c and 3c with respective binding energy of -9.12kcal/mol (Ki 948.07nM) and 8.12 kcal/mol (Ki 706.03nM) were ranked top as bacterial DNA gyrase inhibitors. The interacting amino acid residues were visualized using Discovery Studio 3.5 to elucidate the 2-dimensional and 3-dimensional interactions. The study was validated by i) re-docking the designed ligands with DNA gyrase ii) docking decoy ligands to DNA gyrase. The ligands that showed low binding energy were further predicted for and pharmacokinetic properties and Lipinski's rule of 5 and the results are tabulated and discussed.

Keywords: Molecular Docking, Validation, Pharmacokinetic Prediction Pyrazole Derivatives, Dna Gyrase

1. INTRODUCTION:

DNA topoisomerases are enzymes that bring about changes in the topology of DNA i.e. they can interconvert relaxed and supercoiled forms of DNA **[1, 2]**. They play a crucial role in controlling the physiological function of the genome and in DNA processes of replication, transcription recombination repair and chromosome decondensation **[3, 4]**. Hence these enzymes serve as attractive targets for designing new antibacterial drugs. Topoisomerase inhibitors act as an obstacle to the ligation step in the microbial (gram positive and gram negative) cell cycle, generating single and double stranded breaks that damage the integrity of the genome leading to apoptosis (cell death) in the proliferating cell **[5]**. DNA gyrase is a type IIA topoisomerase belonging to gyrase, heat-shock protein 90 (Hsp 90) histidine kinase MutL (GHKL), protein kinases and the DNA mismatch repair protein MutL (Mismatch from replication recognized by mutL)) family of enzymes. These enzymes are associated with many fundamental biological processes that involve DNA- they are involved in segregation of DNA after replication, initiation of DNA replication and gene expression **[8]**. It is one of the most investigated and validated targets for the development of new antibacterial agents. Its absence in the mammalian organism and its crucial role in the bacterial DNA replication cycle makes this enzyme a suitable target for the development of antibacterial drugs with selective toxicity. It comprises of two subunits-gyrase A and gyrase B that together form the catalytically active heterotetrameric enzyme (i.e. A2B2). The role of the A subunit is breakage and reunion of the double DNA strand, while the B subunit (DNA gyrase B) possesses the ATPase activity, providing a sufficient amount of energy for the DNA supercoiling **[6–9]**. DNA gyrase being a highly appealing drug target, a large number of inhibitors have been synthesized and characterized with quinolones and aminocoumarins being the most widely studied compounds **[10]**.

Currently, the 6-fluoroquinolones class of compounds are the only DNA gyrase inhibitors used in clinical practice. The quinolones create restriction in the process of re-joining double-strand breaks in DNA while aminocoumarins and cyclothialidines (cyclic peptides) block the ATPase activity of DNA gyrase **[11, 12]**. In addition to the above compounds, two proteinaceous poisons, microcin B17 and CcdB block Escherichia coli gyrase in a manner similar to that of quinolones. Most of these inhibitors fall into two groups based on their site of action and mechanism of inhibition: inhibitors such as

fluoroquinolones, CcdB and microcin B17 affect the cleavage–religation step, while coumarins and cyclothialidines prevent ATP hydrolysis **[13]**. Despite the potency of existing drugs, several bacterial strains becoming resistant to the current therapeutic regimen have emerged. DNA gyrase is a validated target for the development of antimicrobial drugs hence synthesis of novel gyrase inhibitors is a highly active research area. This review also summarizes the current strategies utilized for discovery and synthesis of new chemical scaffolds as potential DNA gyrase inhibitors.

Our present research work is about to identify a potent DNA Gyrase inhibitor other than fluro quinolones as a potential new chemical scaffold. In the present study various pyrazole derivatives have been designed and their DNA gyrase inhibitory activity was assessed by molecular docking studies. Later, the docking was validated by two methods like redocking and docking with decoy ligands. Various pharmacokinetic properties and drug likeliness properties are also assessed for the designed derivatives.

2. Materials and methods

Several softwares, tools and webservers were used in the present study at different steps are: Chemsketch **[14]**, AutoDock 4.2.6 **[15]**, MGLTools 1.5.4, Discovery Studio 3.5 **[16]**, Openbable **[17]** and SwissADME **[18]**.

2.1. System information

The following were the system properties with which the study was conducted. Processor: Intel CORE i3-7100U CPU @ 2.40 GHz processor, system memory: 4 GB RAM, system type: 64-bit operating system, Windows 10 as Operating System.

2.2. Ligand preparation

The designed pyrazole derivatives were drawn by using chemsketch free ware and are saved in mol format. Later the ligands were converted to pdb format by using openbable software. However, the co-crystalised ligand (kibdelomycin) was also docked with DNA Gyrase to compare.

2.3. Protein preparation

The 3-dimensional structure of DNA Gyrase (PDB Id: 4URM) belonging to the class of Topoisomerase –II was retrieved from the Protein Data Bank database (https://www.rcsb.org/) **(Figure 1)**. The structure of protein consists of alpha helices, beta sheets and turns/loops which are represented in various colours. The protein was in a complex with aninhibitor kibdelomycin. Water molecules, inhibitor, and other heteroatoms from the protein removed using Discovery studio and used for docking.

2.4. Determining the active site

The active site is the target for an enzyme's inhibition. The active site amino acid

residues of the protein DNA Gyrase was predicted by estimating the amino acids that are interacting with the co crystallised ligand. The amino acid residues prediction was done by viewing the 2d interaction diagram of the co crystallised ligand in Discovery studio and then it was compared with the data available in the RCSB data base. Only after this step, molecular docking was succeeded.

Table 1: Structure of the designed pyrazole derivatives

S. No.	Ligand	R1	R2	R3
1	1a	H	CH_3	CH_3
2	2a	C_6H_5	CH_3	CH_3
3	3a	$C_6H_4(NO_2)_2$	CH_3	CH_3
4	1c	H	$CHCHC_6H_5$	$CHCHC_6H_5$
5	2c	C_6H_5	$CHCHC_6H_5$	$CHCHC_6H_5$
6	3c	$C_6H_4(NO_2)_2$	$CHCHC_6H_5$	$CHCHC_6H_5$
7	1e	H	OCH_3	CH_3
8	2e	C_6H_5	OCH_3	CH_3
9	3e	$C_6H_4(NO_2)_2$	OCH_3	CH_3

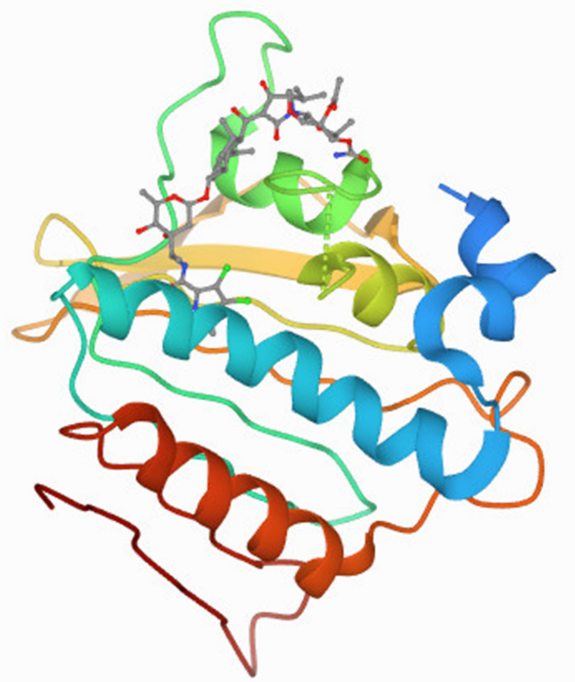

Figure 1: Structure of DNA Gyrase(4URM) along with its co-crystallised ligand

Table 2: Active site residues of DNA gyrase

S. No.	Amino acid	Residue Number		S. No.	Amino acid	Residue Number
1	ILE	51		14	ALA	98
2	ASN	54		15	VAL	101
3	SER	55		16	ILE	102
4	ASP	57		17	VAL	105
5	GLU	58		18	LEU	106
6	VAL	79		19	HIS	107
7	ASP	81		20	ALA	108
8	ARG	84		21	GLY	109
9	ILE	86		22	GLY	110
10	PRO	87		23	LYS	111
11	GLY	91		24	SER	128
12	LYS	93		25	THR	173
13	MET	94		26	ILE	175

2.5. Molecular docking using AutoDock 4.2.6

AutoDock 4.2.6 was downloaded from 'The Scripps Research Institute' official website (http://autodock.scripps.edu/) along with other supporting software viz., Python 3.8.2 and MGLTools 1.5.4. Docking of ligands and DNA Gyrase was performed indigenously by docking 'one ligand at a time to the protein' manually using AutoDock 4.2.6 **[19]**. It is free and considered one of the most reliable software for molecular docking by the scientific community **[20]**.

2.5.1. Initializing and preparation of PDBQT files

Before docking, the starting directory was set to the desired folder. The processed protein molecule was imported into the AutoDock 4.2.6 workspace. The polar hydrogen atoms were added; the Kollman charges were computed for the protein. The protein was then saved in PDBQT format that was then used as the target. The ligand was imported into the workspace; the polar hydrogen atoms were added; the Gasteiger charges were computed; the torsion tree was defined by choosing the root; the number of rotatable bonds was identified and saved in PDBQT format. The ligand and protein were imported in PDBQT format into the workspace for further simulation process.

2.5.2. Grid parameters

Assigning the grid parameters is the most important step in molecular docking since it navigates the ligand to the binding site of the DNA gyrase. Grid spacing was set to 0.400 Å. Centre grid box values were set to x 8.182, y -1.187, and z 61.448. The number of grid points along the x, y, and z dimensions was set as 60 X 60 X 60 respectively. These parameters were set to cover the entire 3-dimensional active site of the DNA Gyrase. The output was saved in the grid parameter file (GPF) file format.

2.5.3. Running AutoGrid and AutoDock

The AutoGrid was executed by providing the AutoGrid executable and GPF files as input and converted to the grid log file

(GLG). The grid was then launched. After the successful execution of AutoGrid, the genetic algorithm was set to default and is as follows: i) the number of GA runs: 100; ii) population size: 150; iii) the number of energy evaluations: 2.5 million (2.0 Å clustered tolerance); and iv) the number of generations: 27000. The Lamarckian genetic algorithm was used and the output was saved in docking parameter file (DPF) file format. The AutoDock was executed by providing the AutoDock executable and DPF files as input, converted to the docking log file (DLG) and docking was launched. The final DLG file contained essential details viz., top ten free binding energy energies for every run and inhibitory constant. The results were analyzed; ranked based on their binding energies; saved in PDBQT format; the lowest binding energy complex was saved in PDB format for further analysis.

2.6. Visualizing interactions

Discover Studio 3.5 from Biovia, was used to visualize and study the 2-dimensional, 3-dimensional, and surface annotation of ligand interaction with the protein

2.7. Docking validation

The docking procedure was validated using two methods viz.,

2.7.1. Re docking:

The ligands from the lowest binding energy complex ofprotein / ligand were removed and re-docked into the active site using AutoDock 4.2.6 **[21]**. It was done manually by opening the protein/ligand complex in discovery studio, removing the inhibitor heteroatoms from, and pasting it into a new molecular window and saved as an inhibitor in PDB file format. The same protocol including the grid parameters was unchanged in the process. It was done to ensure the ligands binds exactly to the active site cleft and must show less deviation compared to the actual co-crystallized complex. After completion of redocking the rootmean square deviation (RMSD) of the ligands was retrieved from DLG file.

2.7.2. Decoy ligands:

Ligands similar to our designed ligands were obtained from DUD-E online server (http://dude.docking.org/) **[22]** and docked against the active site of DNA Gyrase. Decoys are compounds that are similar in physical properties with respect to the reference ligand that might not bind effectively to a protein. 25 such decoys for each designed ligand were used to validate the docking procedure. It was done to enhance ligand enrichment, which is essential to assess the docking procedure and to eliminate false positives.

These were done to validate the docking procedure to ensure the accuracy of docking algorithm.

2.8. Pharmacokinetic properties and Lipinski's rule of 5

Pharmacokinetic properties are essential in determining the absorption, distribution, metabolism, and excretion of drug molecules. This prediction was done using SwissADME (http://www. swissadme.ch/) **[23-26]**. Lipinski's oral drug likeliness properties were predicted using the following i) Molecular weight (<500 Daltons), ii) Number of hydrogen bond donors (<5), iii) Number of hydrogen bond acceptors (<10), iv) Log P (<5), and v) Molar refractivity (<140) **[27-28]**. The toxicity properties of ligands were assessed through the ProtoxII (https://tox-new.charite.de/protox_II/) web server. The pharmacokinetic properties were predicted for all the ligands.

3. RESULTS AND DISCUSSION

Details of ligands with best conformations are listed in **Table 2**. From the work, the designed pyrazole derivatives have shown good DNA gyrase inhibitory activity. The 2D interaction diagram drawn from discovery studio shows significant interaction with receptor residues in the present study. Out of the designed compound 2C had the best binding conformation with the protease with a binding energy of 9.12 kcal/mol followed by 3c and 1cwith 8.17 and 8.03 kcal/mol respectively **(Table 3)**. Lesser the binding energy, the greater the binding efficiency, hence augmented inhibition.

The compound 2c interacted with 10 amino acid residues in the active site of the protease with 1 hydrogen bondwithin 1.85 Å with amino acid residues ASN 54 **(Figures 2 and 3)**. Greater the number of hydrogen bonds, the higher the binding efficiency and inhibition **[29]**. Inspite of lesser number of hydrogen bonds ligand 2c shown best docking score in comparision with the control ligand and other designed ligands. **Figure 4** denotes the surface image active site cleft of the DNA gyrase with 2c bound to it. The in-silico study predicted an inhibition constant (Ki) value of 207.26 nM. Inhibition constant value is the half-maximum inhibition of an enzyme by a chemical compound and is used to estimate the potential of substrate/inhibitor in enhancing/inhibiting the biological and function of enzymes **[30]**. Compounds with an inhibition constant less than 100 mM are considered to be potential inhibitors whereas inhibition constant greater than 100 mM are non-potent inhibitors **[31]**. Ligand 3c has interacted with 12 amino acid in the active site. Apart from this, Ligand 1c interacted with 10 aminoacids while both has formed one hydrogen bond with inhibitory constant of 706.03 nM and 948.07 nM at 298.15 K **[32]**.

3.1. Docking validation

3.1.1. Re-docking and superimposition

The re-docking was done to examine the docking procedure and efficiencies. The

same methodology that was used previously was used in the re-docking process. The peptide inhibitor bound exactly to the active site with good binding energy of 8.32 kcal/mol. ILE 51, ASN 54, GLU 58, ASP57, ALA 61, ARG 84, ILE 86, PRO 87, ARG 144, THR 173 and ILE 175 are the interacting amino acids (Data not shown) in the active site pocket. The RMSD ranged between 0.26 to 4.29 Å and found that ligands interacted with the same amino acids as that of the previous. RMSD values were shown in **Table 4**.

3.1.2. Docking decoy ligands

Decoy are compounds similar to the active ligands in physical properties like molecular weight, log P values, topological surface area, hydrogen bond donors, etc. **[33]**. But chemically different from them. This is based on the fact to overcome false positives and enhancing ligand enrichment **[34]**. Decoy ligands are assumed that they do not bind to the target molecule **[35]** because the chemical properties are the ones that influences the interactions between a ligand and a target, physical similarities have nothing to do with **[36]**. This is an easy technique to assess the protocol and efficiency of the AutoDock 4.2.6 software. Docking a decoy ligand to a target must show high binding energy in comparison with the re-docked complex to prove the docking efficiency. A total of 225 decoy ligands similar to the designed pyrazole derivatives were retrieved from the DUD-E web server along with binding energies of best 15 are reported in **Table 6**, their binding energies remained between -5.375 to -0.77 kcal/mol **(Table 6)**. All decoy ligands showed high binding energy compared to the re-docked complex compared to the re-docked complex (8.32 kcal/mol). Only a negligible quantity of decoy was found to have greater binding affinity than the re-docked complex, hence this confirms the docking efficiency and protocol.

3.2. Pharmacokinetic prediction and lipinski's rule of 5

Pharmacokinetic and Lipinski properties of the designed pyrazole derivatives were predicted, studied, and tabulated **(Tables 7–9)**. It is clear that except none of the derivatives have violated the Lipinski rule.

All the designed pyrazole derivatives satisfied their properties according to Lipinski's rule of 5 **(Table 6)**. Lipinski rule is considered one of the essential criteria to predict the oral drug likeliness of a drug **[37]**. To enhance the predictions of drug likeliness, Ghose, Veber, Egan, and Muegge filters have been used in the study. 3a, 1c and 3e with bioavailability scores of 0.55 are the compound that satisfied all the rules used to predict the drug likeliness. However, these lead molecules upon in-vitro, in-vivo, and clinical trials, can be administered through other routes of drug

administration namely, intravenous, intranasal, intraperitoneal, and subcutaneous. None of the drugs are either immunotoxic or cytotoxic. Every compound is hepatotoxic except 2a and 2c if administered above prescribed limits.

3.3. Pharmacokinetics

Pharmacokinetics of the designed pyrazole derivatives are reported in **Table 9**. All of these drugs were carcinogenic. No drugs inhibited the cytochromes. The Lipinski's rule of 5 is one the essential criteria for oral drug likeliness, that was not satisfied by all the designed pyrazole derivatives. All the designed obeyed the Lipinski, Veber and Egan, where as compounds 1a, 2c 3c and 1e didn't satisfied Gosh & 1a, 2a, 2c, 1e and 2e disobeyed Muegge filters. All the designed derivatives except 3c shown high GI absorption where as compounds 1a, 2a, 1c, 1e and 2e are prone to cross blood brain barrier.

Table 3: interactions of designed ligands with amino acids at the active site

Ligand	P_I-Alkyl bond	Alkyl	P_I Sigma bond	No of H Bonds	Docking Score	Inhibition Constant(Ki)
control	———	ILE B:102,ALA B:98,VAL B:101,ARG B:84,ILE B:175,LYS B:93	ILE B:86,	5+1	-8.19	1.01 nM
1a	VAL B:79	ILE B:175	ILE B:51	2+1	-4.17	875.68 µM
2a	ILE B:86,ILE B:175,ILE B:51,VAL B:79	-----	THR B:173	2+1	-5.83	81.55 µM
3a	-------	ARG C:200	------	3	-6.04	27.69 µM
1c	ILE B:86,ARG B:84	---------	-----	1	-8.03	948.07 nM
2c	ILE B:51,ILE B:175,PRO B:87 , ALA B:61	----------	-----	1	-9.12	207.26 nM
3c	ILE B:86,ILE B:175,ILE B:51	---------	THR B:173,PRO B:87,ALA B:61	1	-8.17	706.03 nM
1e	--------	ARG C:200	-----	3	-4.10	868.87 µM
2e	VAL B:79,ILE B:175	VAL B:79,ILE B:175	ILE B:51	2	-5.62	72.44 µM
3e	ILE B:86	ILE B:86	-----	5+1	-5.05	107.94 µM

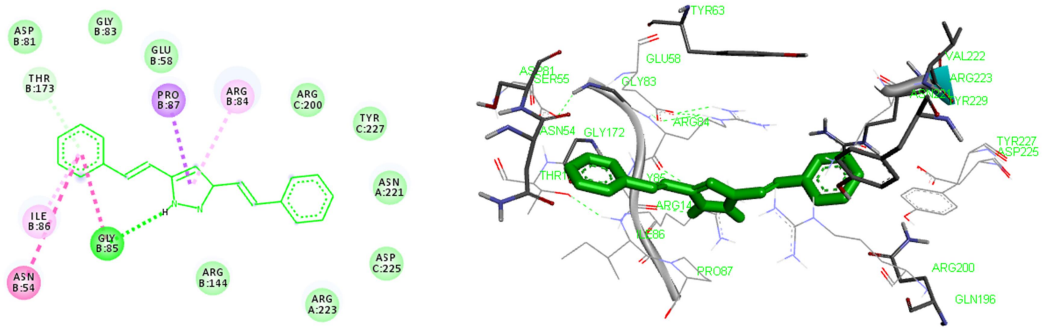

Figure 2: 2D and 3D diagram of compound 1c showing interactions with DNA Gyrase

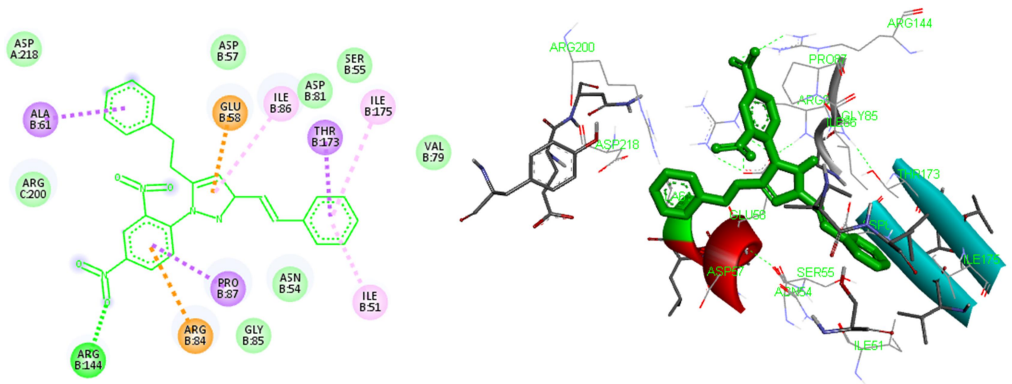

Figure 3: 2D and 3D diagram of compound 3c showing interactions with binding site at best pose

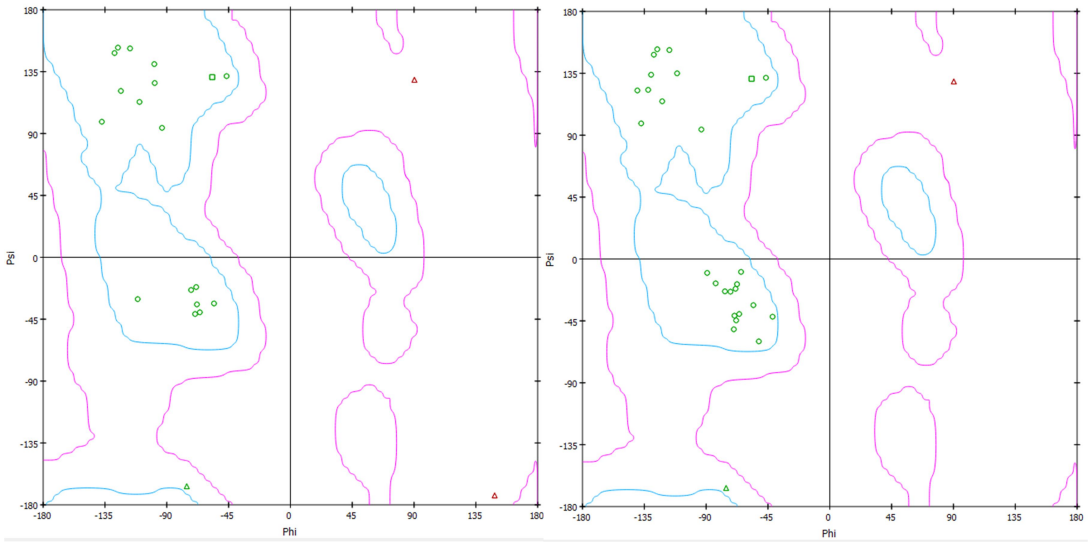

Figure 4: Ramachandran plot of DNA gyrase (4URM) showing amino acids interacting with ligand 1c and 3c

Table 4: Docking scores and RMSD of the redocked complexes

Derivative	Docking Score Kcal/mol (4URM)	Reference RMSD (Å)
1a	-4.37	1.12
2a	-5.76	0.48
3a	-4.85	1.06
1c	-7.48	4.29
2c	-8.20	2.26
3c	-8.32	0.41
1e	-4.11	1.60
2e	-5.54	0.26
3e	-6.79	2.48

Table 5: Docking scores of top 15 decoy ligands

S. No.	Smile	docking score
1	CC(C)c1cc2c(cc1)occ2CC(=O)Sc1ccc(Cl)cc1	-5.375
2	C=C(C)Cn1c(C)cn2c1nc1N(C)C(=O)N(C)C(=O)c12	-5.018
3	C[C@@H](CC)c1ccc(cc1)N1C(=O)c2ccccc2N=C1SCC=1N=C2SC=CN2C(=O)C=1	-4.973
4	Clc1cc(c(Cl)cc1)c1ccc(o1)[C@@H]1C(=C(C)N=C2S[C@@H](CC)C(=O)N21)C(=O)OCC	-4.903
5	CCOc1cccc2cc(oc21)C(=O)N(Cc1ccco1)c1nc2cc(C)cc(C)c2s1	-4.884
6	C[C@H]1CCCN(C1)S(=O)(=O)c1ccc(cc1)C(=O)/N=C1/Sc2cccc(F)c2N1CCC	-4.834
7	O=C(OCC)CN1c2c(cccc2S\C1=N/C(=O)c1ccc2CCCCc2c1)OC	-4.727
8	Clc1ccc(s1)C(=O)/N=C1\Sc2cc(C)cc(C)c2N1CC=C	-4.632
9	CC(=O)c1ccc(cc1)Oc1nn2nnnc2cc1	-4.595
10	Cc1n2c3c(nc2oc1C)N(C)C(=O)N(CC=C)C3=O	-4.559
11	CC[C@@H]1CC[C@H](C1)N1N=C(C)CC1=O	-4.511
12	O=C(OCC)[C@H](n1nnc2ccccc12)N1CCOCC1	-4.483
13	Fc1ccc(N[C@@H]2C[C@H](CCC2)CC)c(OCC)c1	-4.476
14	N#Cc1ccccc1Oc1nc(Cl)nc(n1)n1cncn1	-4.459
15	Cc1ccc(c(C)c1)C(=O)/N=C1\Sc2cc(ccc2N1CC#C)CC	-4.443

Table 6: Lipinski properties of ligands

Derivative	Lipinski rule of five (RO5)						Docking Score Kcal/mol (4URM)
	Mol.Wt (≤ 500 g/mol)	No. of H-ba (≤10)	No. of H-bd (≤5)	LogP value (≤5)	tPSA (Å)	% ABS	
1a	96.13	1	1	1.07	28.68	99.11	-4.17
2a	172.23	1	0	2.39	17.82	102.85	-5.83
3a	262.22	5	0	1.56	109.46	71.24	-6.04
1c	275.37	2	2	2.55	24.06	100.70	-8.03
2c	348.44	1	0	4.13	17.82	102.85	-9.12
3c	438.43	5	0	3.18	109.46	71.24	-8.17
1e	112.13	2	1	1.19	37.91	95.92	-4.10
2e	188.23	2	0	2.51	27.05	99.67	-5.62
3e	278.22	6	0	1.75	118.69	68.05	-5.05

Table 7: Drug likeliness of the designed pyrazole ligands with no of violations in the brackets

Derivative	Lipinski	Ghose	Veber	Egan	Muegge
1a	Yes	No(3)	Yes	Yes	No(1)
2a	Yes	Yes	Yes	Yes	No(1)
3a	Yes	Yes	Yes	Yes	Yes
1c	Yes	Yes	Yes	Yes	Yes
2c	Yes	No(1)	Yes	Yes	No(1)
3c	Yes	No(1)	Yes	Yes	No(1)
1e	Yes	No(3)	Yes	Yes	No(1)
2e	Yes	Yes	Yes	Yes	No(1)
3e	Yes	Yes	Yes	Yes	Yes

Table 8: Toxicity properties of the designed pyrazole ligands

S. No.	Compound	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity	Predicted LD50 mg/kg
1	1a	Active	Active	Inactive	Inactive	Inactive	1060
2	2a	Inactive	Active	Inactive	Active	Inactive	1300
3	3a	Active	Active	Inactive	Active	Inactive	1300
4	1c	Active	Active	Inactive	Active	Inactive	1760
5	2c	Inactive	Active	Inactive	Active	Inactive	1300
6	3c	Active	Active	Active	Active	Inactive	1310
7	1e	Active	Active	Inactive	Inactive	Inactive	1000
8	2e	Active	Active	Inactive	Inactive	Inactive	741
9	3e	Active	Active	Inactive	Active	Inactive	971

Table 9: Pharmacokinetics of the designed pyrazole derivatives

S. No.	Ligand	GI Absorption	BBB Permeation	P-GP Substrate	CYP Inhibitor	Skin Permeation (cm/s)
1	1a	High	Yes	No	No	-6.16
2	2a	High	Yes	No	No	-5.44
3	3a	High	No	No	No	-6.23
4	1c	High	Yes	No	No	-5.11
5	2c	High	No	No	No	-3.81
6	3c	Low	No	No	No	-4.60
7	1e	High	Yes	No	No	-6.33
8	2e	High	Yes	No	No	-5.60
9	3e	High	No	No	No	-6.40

4. CONCLUSION

Till today there is no perfect cure for multi drug resistant (MDR) bacterial disease, research ongoing in developing lead molecules and precursors that could act as potential antibacterial drugs against the disease. The motive of the present study was to discover pyrazole containing compounds that could be potential against MDR bacterial strains that can inhibit the bacterial DNA gyrase (PDB Id: 4URM), thereby decreasing the replication and viable count. Nine designed pyrazole derivatives were designed from the literature. The active site of the DNA gyrase was determined using the Discovery Studio. Molecular docking was done using AutoDock 4.2.6 along with supporting software and Discovery Studio 3.5 to elucidate the interactions between the ligands and protein. Out of nine compounds docked, the top three compounds with high binding energies were 2c (-9.12 kcal/mol)3c (-8.17 kcal/mol) and 1c (-8.03 kcal/mol)have shown potential to inhibit the bacterial DNA very effectively and the interactions were compared with co crystallised ligand.Pharmacokinetics and toxicity properties of designed compounds were studied and reported. On the whole, compound 1c of the designed pyrazole derivatives were found to be very potent antibacterial agents while inhibiting DNA gyrase, and also showed better drug likeliness properties and better pharmacokinetic properties, hence one could prevent the infections using these. This research could act as a road map for the discovery of compounds to treat multi drug resistant bacterial strains. Thus, in-silico studies provided rapid and comprehensive insights into results in screening a of compounds. Future studies will focus on the other proteins of resistant bacteria though in-silico studies.

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