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Design, Molecular Docking Of Noval Thiosemicarbazide Based Piperazine Derivatives

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ABSTRACT: Thiosemicarbazide is a white crystalline powder and is odorless. This material is used as a reagent for ketones and certain metal for photography. Thiosemicarbazide are of considerable interest because of their chemistry to form stable chilates with essential metal ions and potentially beneficial biological activities, such as antitumor, antibacterial, antiviral, and antimalarial. Individually thiosemicarbazide show varied pharmacological activities such as, anticancer, antimicrobial, antifungal, anticonvulsant, antimalarial, analgesic and anti-inflammatory. Thiosemicarbazone aldehydes and keto-acids possess have antimicrobial, antiviral and anti-cancer activity and are inhibitors of the synthesis of DNA. Objective: To Design the thiosemicarbazide based piperazine derivatives, characterized by binding energy. Methods: The molecular property prediction of all the designed compounds by using Lipinski's rule of 5, PASS, OSIRIS molecular property explorer, Mol soft, Docking software's. Results: All the compounds shows the good binding affinity All the compounds obeys the Lipinski's rule, non-toxic, drug likeness and more active and shows the good binding affinities when compared with the standard drug(Ciprofloxacin). The compound IIIe more potent and IIIc equipotent when compared with standard drug (Ciprofloxacin). Conclusion: The compounds IIIe and IIIc shows the good results in the molecular property prediction

Key words: Thiosemicarbazide, piperazine, Ciprofloxacin, Molecular docking, 2XDTS.

I. INTRODUCTION

Thiosemicarbazone aldehydes and ketoacids possess have antimicrobial, antiviral and anti-cancer activity and are inhibitors of the synthesis of DNA. Thiosemicarbazide are of considerable interest because of their chemistry to form stable chilates with essential metal ions and potentially beneficial biological activities, such as antitumor, antibacterial, antiviral and antimalarial.Individually mannich bases and thiosemicarbazide show varied pharmacological activities such as, anticancer, antimicrobial, antifungal, anticonvulsant, antimalarial, analgesic and anti-inflammatory.[(1)]

Thiosemicarbazides are the valuable starting compounds used for the synthesis of azoles. Thiosemicarbazides are important compounds having a variety of applications.They have shown activities like anticancer, anti- HIV, antimalarial, antifungal, and antibacterial.[(2)]

After 40 years of long wait, approval of Bedaquiline, a quinoline based drug for treating multi drug resistant TB have gained momentum to investigate various quinoline derivatives as antimycobacterial agents . Previously we reported that 2-substiuted dihydroquinolones exhibit potential antitubercular activity against H37RV. Also recent reports suggested that the groups like morpholine, piperazine helps improving pharmacological properties. Our continued interest in developing new antimycobacterial agents led to hybridization of 2-(thiophenyl) dihydroquinolines with morpholine, thiomorpholine, or N-substituted piperazines in one molecular platform to generate a new scaffold for biological evaluation. We herein report an efficient synthesis and evaluation of novel dihydroquinoline derivatives 7a-p in excellent yields. Screening all sixteen new compounds for in vitro activity against Mycobacterium tuberculosis H37Rv resulted in two compounds 7f and 7p (MIC: 1.56 mg/mL) as most potent ant tubercular agents.

Piperazine is a cyclic compound that has hetero atoms such as N, O and S as members of its ring having medicinal importance, Piperazine is such a medicinally important heterocyclic nucleus which consists of a six-member ring containing two nitrogen atoms at opposite positions in the ring. A novel series of substituted phenyl acetamide piperazine derivatives . The antimicrobial activities for all the synthesized compounds were evaluated against Gram-positive bacteria (Staphylococcus

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aureus, Streptococcus pyrogenes) and Gram-negative bacteria (Escherichia coli, Pseudomonas aeruginosa). The antibacterial activity was evaluated using Ciprofloxacin as a standard drug.Nitrogen heterocycles remain an attractive topic for small molecular drug design and discovery. Among all heterocycles, piperazines, the six-member nitrogen-containing heterocyclic ring, are certainly an established important pharmacophore in medicinal chemistry. For example, the piperazine moiety is present in the core structure of many important commercial fluoroquinoline antibiotics such as: Norfloxacin, Ciprofloxacin, Gatifloxacin, Grepafloxacin, Sparfloxacin, and Levofloxacin Of particular significance is the fact that combining the piperazine moiety with other heterocyclic ring systems, such as tetrazole, has resulted in new antifungal agents. Such prior studies have clearly identified the potential use of piperazine derivatives as important pharmacophore.[3] Piperazine derivatives have played important role in improving the potency of antibacterial drugs. Ciprofloxacin (CPX) is a piperazine containing fluoroquinolone antibiotic and exerts its action by the inhibition of bacterial DNA gyrase. Extensive structure activity relationship (SAR) has shown that carboxylic acid and carbonyl groups at C-3 and C-4 are essential for DNA gyrase inhibiting activity [4] Piperazine moiety contains two nitrogen atoms at two opposite positions of a sixmember heterocyclic ring. Polar nitrogen atoms increase the favorable interactions of piperazine with macromolecules. It has the ability to cross the blood brain barrier (BBB) due to its lipophilic nature, and is useful in various diseases, such as Alzheimer's disease, psychosis, and depression. Many potent marketed drugs like flfluphenazine, cinnarizine, flflunarizine, lomerizine, ciprofloxacin, indinavir, etc., have a piperazine moiety. Piperazine derivatives have shown significant pharmacological potent marketed drugs like fluphenazine, cinnarizine, flunarizine, lomerizine, ciprofloxacin, indinavir, etc., have a piperazine moiety[5]. Piperazine derivatives have shown significant activities, such as anti-tuberculosis, anti-inflflammatory, antiviral, as Central Nervous System (CNS) pharmacological activities, such as anti-tuberculosis, antiinflammatory, antiviral, as Central Nervous System (CNS) agents, anticancer, as cardioprotective agents, and antidiabetic.[6]

DOCKING

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 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.[7]

The associations between biologically relevant molecules such as protein, peptides, nucleic acids, carbohydrates and lipids, play a central role in signal transduction. Furthermore, the relative orientation of the two interacting partners may affect the type of signal produced (e.g. agonism vs antagonism). Therefore, docking is useful for predicting both the strength and type of signal produced.

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 molecule 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.

II. LIPINSKI RULE

Designed molecules(5) were subjected to Lipinski filtration to predict their molecular properties. Online softwere (super computer IIT Delhi) site was used. Molecules that satisfied Lipinski rule of five were selected for further investigation.[8,9]

Molecular docking studies were performed by using AUTODOCK 4.0 on the filtered non-toxic, safe molecules at the active site of crystal structure of thiosemicarbazide and piperazine targeted enzyme DNA gyrase(2XCT)

CHEMICALS:Chemicals for designed molecule were thionyl chloride, Ethanol, Dichloro methane, dimethyl formamide, tryethyl amine, methanol, chloroform.

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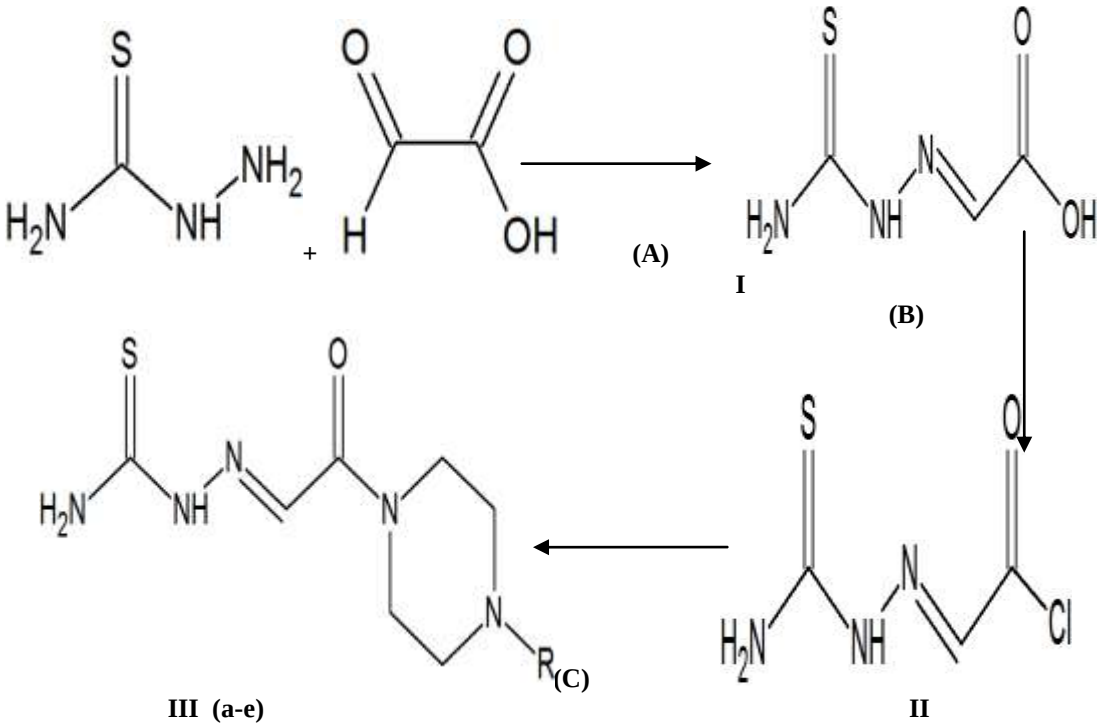
III. SCHEME



IIIa	-H
IIIb	$-CH_3$,
IIIc	$-COCH_3$
IIId	$-COC_6H_5$
IIIe	$-CH_2C_6H_5$

Reactions and conditions:
A= Glyoxalic acid stirring for 1hr.
B= $SOCl_2$, DCM, DMF reflux for2 hrs.
C=DCM, Et_3N, Piperazine reflux for8 hrs.

PHYSICAL DATA

Table-1

Compound Code	HBD	HBA	Mass	LogP	Molar refractivity
IIIa	4	4	215	-2.7	68.2
IIIb	3	4	229	-1.38	72.2
IIIc	3	4	257	-1.7	89.7
IIId	3	4	305	-1.1	95.6
IIIe	3	4	319	1.32	98.4

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PASS PREDICTION

Pa	Pi	Activity
0,766	0,004	Antimycobacterial
0,750	0,004	Antituberculosic
0,721	0,010	Nucleotide metabolism regulator
0,704	0,009	Antiviral (Poxvirus)
0,669	0,004	Antineoplastic (melanoma)
0,688	0,044	Nootropic
0,617	0,005	Thiol protease inhibitor
0,585	0,004	Antineoplastic (brain cancer)

*Pa-probability of activity, Pi-probability of inactive[10]

Molecular properties of the designed molecules by Molesoft (version3.7-2)

Table-2

Compound code	M.Wt	HBA	HBD	MlogP	M.logS	M.Vol	S.C
IIIa	215	4	4	-0.93	70.40	232.28	0
IIIb	229.10	4	3	-0.80	61.92	239	0
IIIc	257	4	3	-1.19	75.63	266.77	0
IIId	319	4	3	0.25	74.90	321.84	0
IIIe	309	4	3	0.67	61.98	313.22	0

*****HBD-Hydrogen bond donor, HBA-Hydrogen bond acceptor, S.C nomber of stereo centers, MlogP-Molecular logP, MlogS-MolecularlogS, M.Vol-Molar Volume**.**

Molecular property prediction by OSIRIS property explorer (version-2)

Table-3

Compound code	ClogP	Solubility	M .w	TPSA	Drug likeness	Drug score
IIIa	-1.45	-0.69	215	114.8	5.92	0.98
IIIb	-1.2	-0.32	229	100	0.92	0.98
IIIc	-1.14	-0.61	257	123.1	0.57	0.97
IIId	0.3	-1.78	319	123	9.67	0.93
IIIe	0.22	-1.65	305	106	9.51	0.94

*ClogP- Calculated logP, TPSA-Topological polar surface area, MW-molecular weight.

DOCKING STUDIES: Resultsrevealed that both the ligands (IIId&IIIe) exhibited greater affinity than ciprofloxacin for 2XCT.Ligand IIIe exhibited hydrogen bond, interacted with aminoacids N-ARG1366,ARG1370and has shown highest affinity with 2XCT with a binding energy(-5.87ΔG) of Kcal/Mol.

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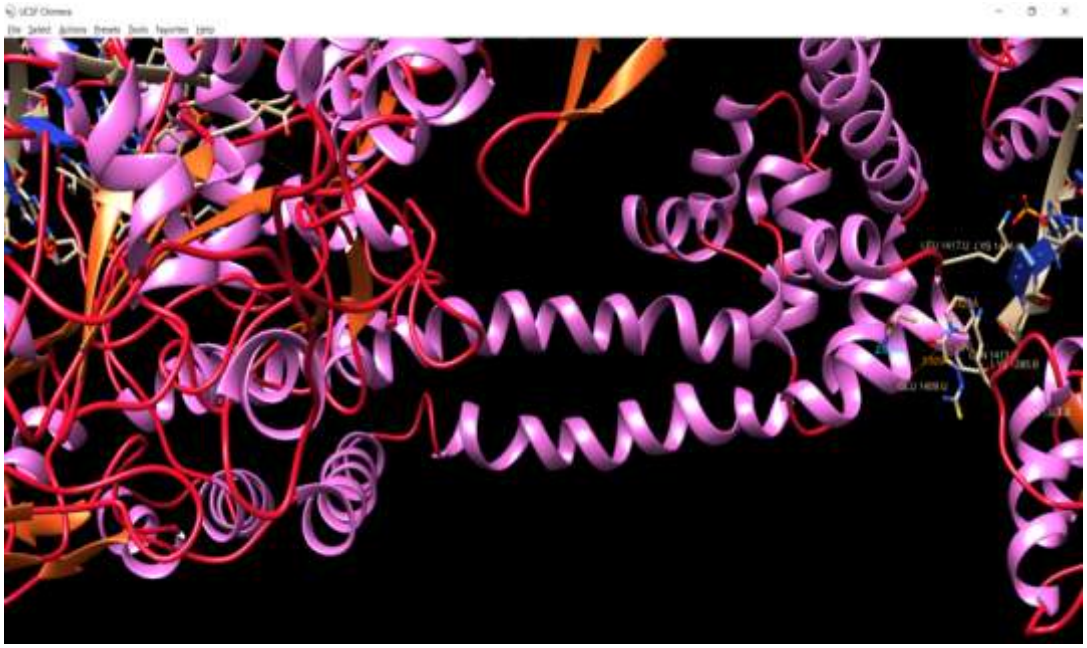

Fig.10: Docking interaction of compound IIIa with the active site of 2XCT

Fig.11: Docking interaction of compound IIIc with the active site of 2XCT

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Fig.12: Docking intesraction of Ciprofloxacin with the active site of 2XCT

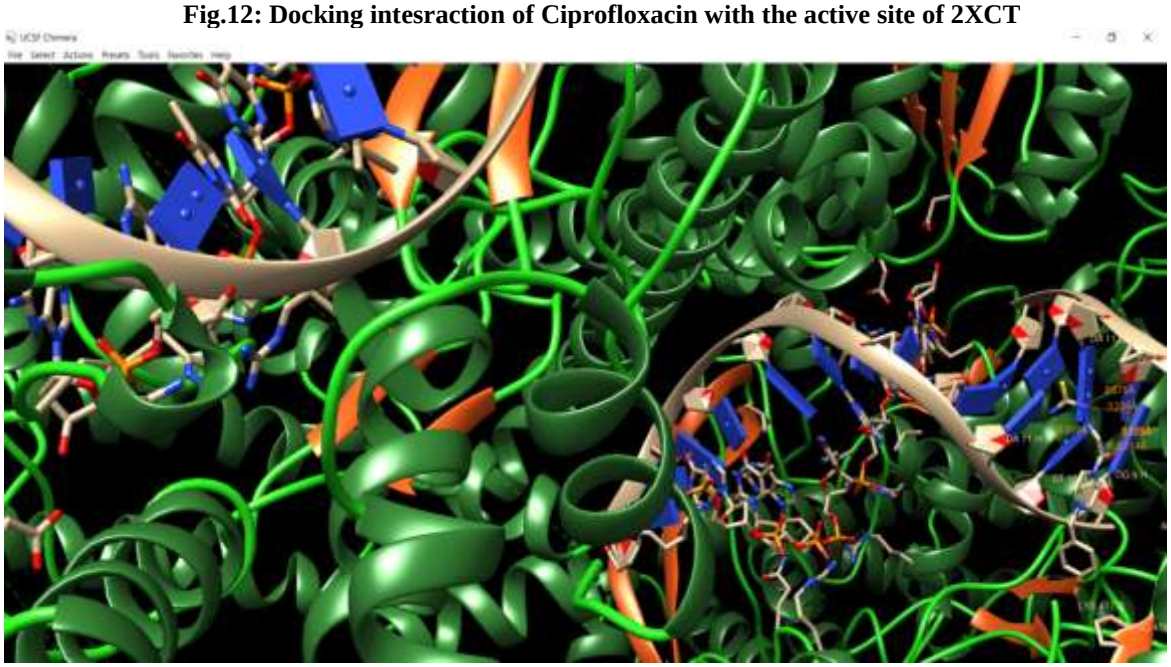

Fig.13: Docking interaction of compound IIIe with the active site of 2XCT

Molecular docking interactions and their binding energy of compounds (IIIa-IIIe) with 2XCT.

Table-4

S.NO	Compound Code	Binding energy(ΔG) (Kcal/Mol)	No. of **'H'** bonds
1	IIIa	-5.28	3H
2	IIIb	-5.09	2H
3	IIIc	-5.59	10H
4	IIId	-3.61	4H
5	IIIe	-5.87	6H
6	Std(Ciprofloxacine)	-5.68	14H

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Molecular docking interactions and their binding Amino acids of compounds (IIIa-IIIe) with 2XCT.

Table-5

Compound code	Amino acids	No. of `H' bonds
IIIa	LYS1413, N-GLN1413(3.42A^o),GLN1412	3H
IIIb	LYS1421, LEU1432(2.87A^o)	2H
IIIc	LYS1451, LEU1448,N-TYR1454, ARG1377,N-LYS,(3.008A^o) ALA1374,TYR, N-GLU,NH_2GLDN-LYS.	10H
IIId	ARG1328,GLU1532	4H
IIIe	LEU1448,TRP1573(3.675A^o)	6H
Std(Ciprofloxacin)	LYS1373,NZ-UNL(3.177A^o)	14H

CONCLUDION

DOCKING STUDIES: Resultsrevealed that both the ligands (IIId&IIIe) exhibited greater affinity than ciprofloxacin for 2XCT.Ligand IIIe exhibited hydrogen bond, interacted with aminoacids N-ARG1366,ARG1370and has shown higest affinity with 2XCT with a binding energy(-5.87ΔG) of Kcal/Mol.

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