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DESIGN, SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NOVEL INDOLE DERIVATIVES AS ANTI TUBERCULAR AGENTS

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ABSTRACT
The aim is to design and synthesize some novel heterocyclic analogues such as indole derivatives which will prove to be effective against Mycobacterium tuberculosis. The objectives are Design of *Glutamine synthetase* inhibitors by docking studies using Autodock ® software, Prediction of *Insilico* Drug likeness by Molinspiration® software, Insilico Toxicity Assessment done by OSIRIS® software, Laboratory synthesis of chosen compounds with top Docking Scores, Characterization of the synthesized compounds by TLC, Melting point, IR Spectroscopy, H1 NMR Spectroscopy, LC-Mass Spectrometry. Evaluation of *In-vitro* anti -tubercular activity of the synthesized compoundsby (MABA). The present study deals with A series of Schiff bases of isatin derivatives were designed, docked, synthesized and evaluated against Glutamine synthetase 1 enzyme which is critical for the survival and growth of MTB.The Minimum Inhibitory Concentration of the synthesized compounds ranges from 50-1.6µg/ml. The work concludes that the Compounds Compounds PK2 and PK4 showed activity at 1.6 µg/ml concentrations which are comparable to the activity of the standard drugs Pyrazinamide, Streptomycin, Ciprofloxacin which are active at 3.125µg/ml,6.25µg/ml,3.125µg/ml concentrations.Further, structural refinement of the synthesized compounds is expected to yield promising molecules against the pathogen MTB.

KEYWORDS: Synthesis, Characterization, Biological Evaluation, Novel Indole Derivatives.

INTRODUCTION
Tuberculosis (TB) is an airborne infectious disease caused by organisms of the Mycobacterium tuberculosis complex. Although primarily a pulmonary pathogen, M. tuberculosis can cause disease in almost any part of the body. Infection with M. tuberculosis can evolve from containment in the host, in which the bacteria are isolated within granulomas (latent TB infection), to a contagious state, in which the patient will show symptoms that can include cough, fever, night sweats and weight loss. Only active pulmonary TB is contagious. In many low-income and middle-income countries, TB continues to be a major cause of morbidity and mortality, and drug-resistant TB is a major concern in many settings. Although several new TB diagnostics have been developed, including rapid molecular tests, there is a need for simpler point-of-care tests.

The study of heterocyclic compounds has become a major topic today as most of the natural compounds are essentially heterocyclic compounds. Among the heterocycles, indole-based compounds have immense applications in the field of pharmaceuticals, agrochemicals, dyestuff, *etc.*[1] Indole derivatives are widely used as anti-inflammatory[2], anti-microbial, anti-viral, anti-cancer, antirheumatoidal, anti-HIV, and anti-tumor drugs, as well as corrosion inhibitors, copolymers and sanitizers.[3-12] Compounds like 2-aroylindole[13], 2,3-diarylindole[13], 2-aryl-3-arylcarbonylindole[13], indole-3-carbinol[14], di-indol-3-yl disulfides[15], and hetero-annulated indole derivatives[16] have an indole ring which possesses potential anti-cancer properties. M. Fadaeinasab *et al.* reported that the indole alkaloid Reflexin A, extracted from *Rauwolfia reflexa*, possesses anti-cancer properties against HCT-116 cancer cells.[17] Recently, Z.-X. He *et al.* synthesized new thiosemicarbazone-indole derivatives having anti-cancer properties and low toxic effects.[18] H. Hu *et al.* designed twelve new substituted indole-2-carbohydrazide derivatives and found that some of them possessed high

anti-cancer activity and inhibitory effect on CDK9 while others showed moderate or little such activities.[19] 5-substituted indole derivatives.[20]

The aim is to design and synthesize some novel heterocyclic analogues such as indole derivatives which will prove to be effective against Mycobacterium tuberculosis. The objectives are Design of *Glutamine synthetase* inhibitors by docking studies using Autodock ® software, Prediction of *Insilico* Drug likeness by Molinspiration® software, *Insilico* Toxicity Assessment done by OSIRIS® software, Laboratory synthesis of chosen compounds with top Docking Scores, Characterization of the synthesized compounds by TLC, Melting point, IR Spectroscopy, H1 NMR Spectroscopy, LC-Mass Spectrometry. Evaluation of *In-vitro* anti - tubercular activity of the synthesized compounds by (MABA).

MATERIALS AND METHODS

Drug design is referred to as rational drug design, which is an inventive process of finding newer drug molecules based on the knowledge of a biological target.[67] The drug is an organic small molecule that activates or inhibits the function of a biomolecule such as protein, which in turn results in a therapeutic benefit to the patient. Drug design involves the design of molecules that are complementary in shape and charge to the biomolecular target with which they interact and will bind to it.

TYPES OF DRUG DESIGN

There are two major types of drug design.
Ligand-based drug design
Structure-based drug design

LIGAND-BASED

Ligand-based drug design (or indirect drug design) depends upon the knowledge of other molecules that bind to the biological target of interest (protein). The other molecules may be used to derive a pharmacophore model that offers the minimum necessary structural characteristics a molecule must possess in order to bind to the target.

STRUCTURE-BASED

Structure-based drug design (or direct drug design) depends upon the knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy. If an experimental structure of a target is not available, it may be possible to create a homology model of the target based on the experimental structure of a related protein.

TARGET ENZYME: *GLUTAMINE SYNTHETASE* I

The crystal structure of the enzyme was downloaded from the Protein Data Bank (An Information Portal to Biological Macromolecular Structures) (PDB id – 3zxr). The target enzyme *glutamine synthetase I* from *Mycobacterium tuberculosis*, is one of the key enzymes involved in GLUTAMINE SYNTHESIS, which is critical for the survival and growth of Mycobacterium tuberculosis.

BINDING SITE IDENTIFICATION

Binding site identification is an important step in structure based drug design. Location of the binding site is trivial, if the structure of the target or a sufficiently similar homolog is determined in the presence of a bound ligand. However, there may be unoccupied allosteric binding sites that may be of interest. Furthermore, it may be only apoprotein (protein without ligand) structures are available and the reliable identification of unoccupied sites that have the potential to bind ligands with high affinity is non-trivial.

Molecular Docking by AUTODOCK ®

AutoDock ® 4.2.5.1 is a software for predicting the interaction of ligands with biomacromolecular targets. In any docking scheme, two conflicting requirements must be balanced: the desire for a robust. The current version of AutoDock, using the Lamarckian Genetic Algorithm and empirical free energy scoring function, typically will provide reproducible docking results for ligands with approximately 10 flexible bonds. The quality of any docking results depends on the starting structure of both the protein and the potential ligand. The protein and ligand structure need to be prepared to achieve the best docking results. The following steps are employed

1. Protein preparation.
2. Ligand preparation.
3. Receptor grid generation.
4. Ligand docking (screening)

Preparation of Protein

- Read molecule from the file (allows reading of PDB coordinatefiles.)
- Edit -Charges – Compute Gasteiger (for arbitrarymolecules)
- Edit – Hydrogen –Merge non polar.
- Save as. pdbinAutoDockfolder.

Preparation of Ligand

- Ligand –Input from file
- Ligand – Torsion –choose torsion: Rotatable bonds are shown in green, and non- rotatable bonds are shown in red. Bonds that are potentially rotatable buttreated as rigid, such as amide bonds and bonds that are made rigid by the user, are shown in magenta.
- Ligand – Torsion –set number of torsion: sets the number of rotatable bonds in the ligand by leaving the specified number of bonds asrotatable.
- Ligand – Output – save as pdbqt in AutoDock folder

Grid preparation

- Grid – Macromolecule -open (open the pdb file thet has beensavedand then save it in pdbqt extension in AutoDock folder)

- Grid – Set map types –open ligand : tools to define the atom types for the grids that will be calculated
- Grid – Grid box – launches interactive commands for setting the grid dimensions and center (Set dimension of 60: 60:60 – Center :center on macromolecule)
- File – Close savingcurrent
- Grid – Output – save as .gpf(grid parameterfile)

Preparation of Docking Parameters

- Docking –macromolecules – set rigid filename
- Docking – ligand –open
- Docking –search parameters – genetic algorithm parameters : this command open a panel for setting the parameters used by each of the search algorithms, such as temperature schedules in simulated annealing and mutation/crossover rates in genetic algorithms.
- Docking – docking parameters: opens a panel for setting the parameters used during the docking calculation, including options for the random number generator, options for the force field, step sizes taken when generating new conformations, and out put options.
- Docking- output –Lamarkian GA –save as .dpf (docking parameterfile)
- Open command prompt [autodock4.exe –p a.dpf –la.dlg]

Visualization / Interpretation of Docking

- Analysis –Docking – open .dlg (docking log file)file
- Analysis – macromolecule open
- Analysis – Confirmation –Play and Play ranked by energy: Play- will use the order of conformations as they were found in the docking calculations, and Play Ranked By Energy will order the conformations from lowest energy to highest energy.
- Analysis – Load : Information on the predicted interaction energy is shown at the top, and individual conformations
- Analysis – Docking – show interaction: specialized visualization to highlight interactions between the docked conformation of the ligand and the receptor.

Insilico Toxicity Assessment Osiris®

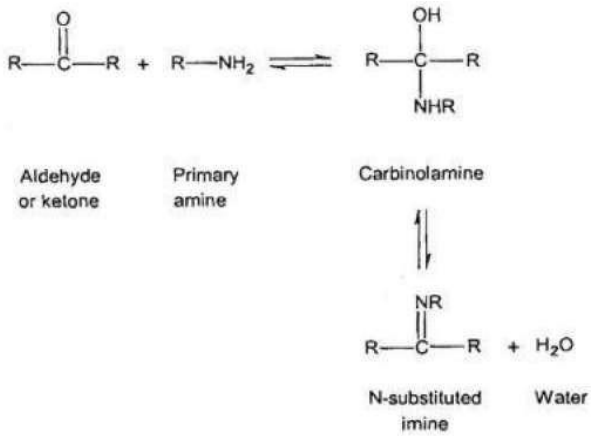
- *Insilico* toxicity Assessment for the molecules were predicted by using OSIRIS®, a JAVA based online tool.
- The tool predicts toxicity related parameters such as Mutagenicity, Tumorogenicity, Skin Irritancy and the effects on reproduction.
- The prediction is based the fragment contribution group present in thestructure of the molecule.
- Properties with high risks of undesired effects are shown in red color. Whereasa green color indicates drug-conform behavior.

Prediction of Drug Likeness (Molinspiration®)

- The designed and docked molecules were screened *insilico* using MOLINSPIRATION® software to evaluate drug likeness.
- It is the online software available for the calculation of important molecular properties such as log P, polar surface area, number of hydrogen bond donors and acceptors., etc.

Synthetic Scheme

The selected compounds with top docking score were selected for synthesis according to the scheme given below.



Procedure

Equimolar quantities of ketone (0.01mol) and Para-substituted amine (0.01mol) are added into 20mL of absolute ethanol and 5mL of glacial acetic acid is added to it. Reaction mixture is refluxed for 24hrs at 60ºC. Completion of reaction is confirmed by TLC. The product obtained was filtered and dried. Recrystallisation is done by using ethanol.

Characterization Physical Evaluation

1. Physical properties of the synthesized compounds are evaluated, such as

- Color
- Nature
- Solubility
- Molecular weight
- Molecular formula
- Melting point

2. Further the synthesized compounds are characterized by the following Spectroscopic and Spectrometric methods such as

- IR Spectroscopy by ABB MB 3000-PH FTIR spectrometer using KBrpellets.
- ^{1}H-NMR Spectrometry by 500 MHZ BrukerTopSpin using DMSO
- LC-MS by AGILANT technologies 6230B Time Of Flight(TOF)

Evaluation of Anti Tubercular Activity

MICROPLATE ALAMAR BLUE ASSAY (MABA) is performed to evaluate the *invitro* anti tubercular activity.

Procedure

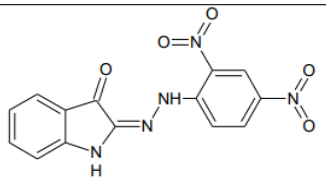
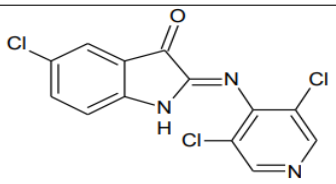
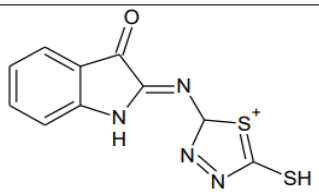
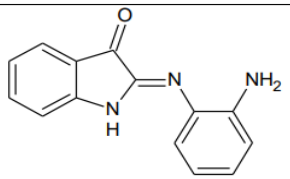
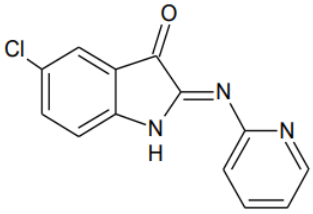
- *The anti mycobacterial activity of compounds were assessed against M. tuberculosis using* microplate Alamar Blue assay (MABA).
- This methodology is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method.
- Briefly, 200µl of sterile de-ionized water was added to all outer perimeter wells of sterile 96 wells plate to minimized evaporation of medium in the test wells during incubation.
- The 96 wells plate received 100 µl of the Middle brook 7H9 broth and serial dilution of compounds were made directly on plate.
- The final drug concentrations tested were 100 to 0.2µg/ml. Plates were covered and sealed with parafilm and incubated at 37°C for five days.
- After this time, 25µl of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 was added to the plate and incubated for 24hrs.
- A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. The MIC was defined as lowest drug concentration which prevented tsshe color change from blue to pink.

RESULTS

Activity Prediction

More than 150 compounds were docked against the enzyme Glutamine synthetase I using AUTODOCK® tools 4.2.5.1 software. The molecules with good docking score and good interactions were synthesized and characterized.

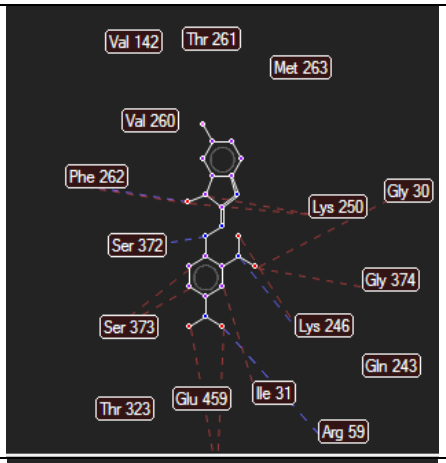
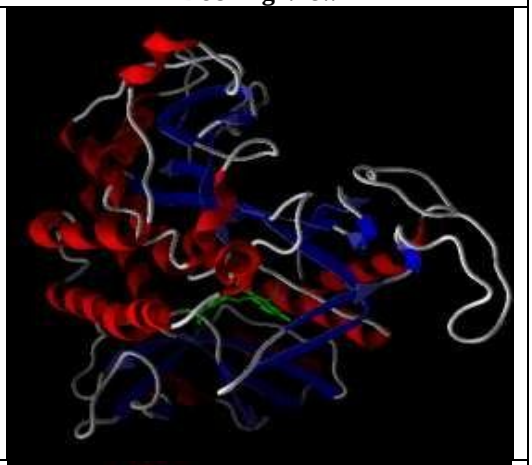
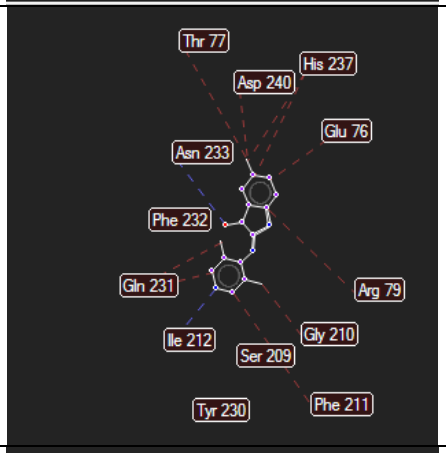
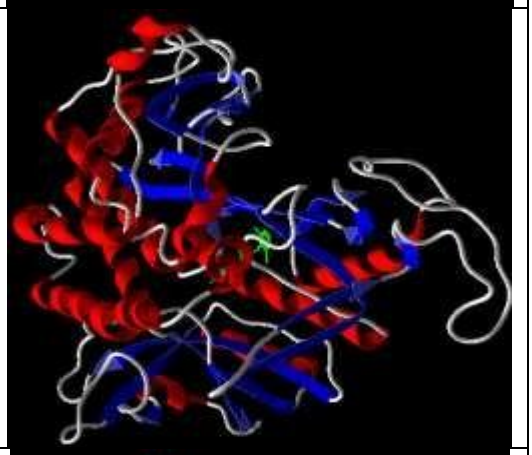
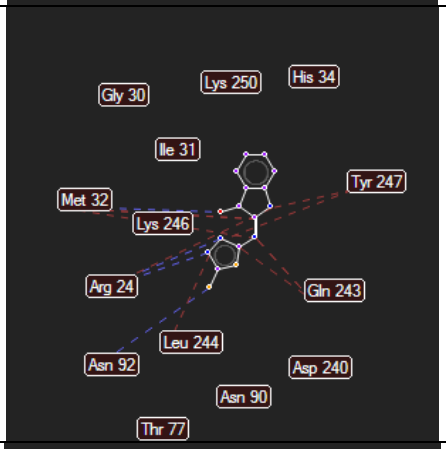
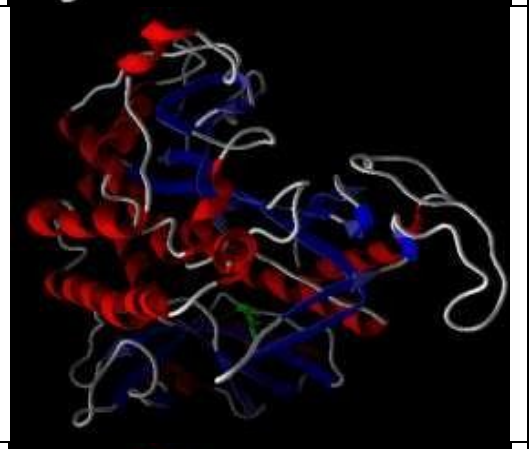
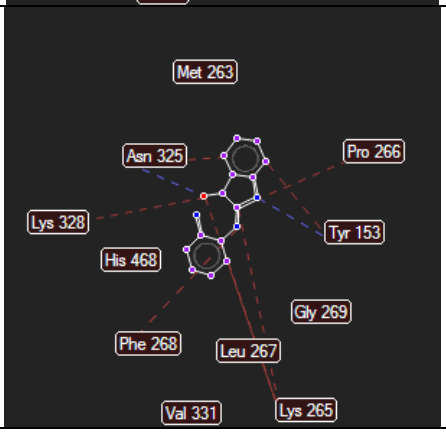
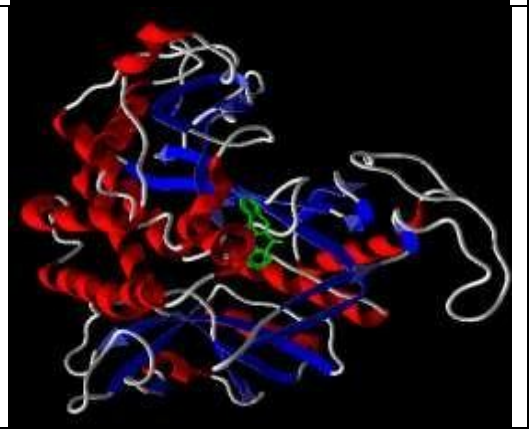
Table 1: the selected molecules with docking score are mentioned below.

SAMPLE CODE	STRUCTURE	DOCKING SCORE
PK1		-7.56
PK2		-7.1
PK3		-6.57
PK4		-5.83
PK5		-5.7

Docking View and Interaction of The Docked Molecules with The Aminoacids

AUTODOCK® 4.2.5.1 tools performs a complete systemic search of the conformations, orientations and position of a compound in the defined binding siteand eliminates unwanted poses using scoring and energy optimization. The best poses were selected on the basis of the scoring function and the quality of pose orientation within the active site of the aminoacids.

Table 2: Interaction of the molecules with amino acids and docking view.

Samplecode	Interaction with theAmino Acid	Docking View
PK1		
PK2		
PK3		
PK4		

VARIANTS

Prediction of Drug Toxicity (Insilico)

In-silico toxicity assessment for the chosen molecules were predicted by using OSIRIS®, a JAVA based online tool.

The tool predicts toxicity related parameters such as Mutagenicity, Tumourogenicity, Skin Irritancy and Teratogenicity apart from other toxicities.

The prediction is based on the fragment contribution group present in the structure of the molecule.

Properties with high risks or undesired effects are shown in red color. Green colour shows drug conform behavior.

PREDICTION OF DRUGLIKENESS

The designed molecules were screened *insilico* using MOLINSPIRATION® software to evaluate drug likeness. It is an online software available for the calculation of important molecular properties such as log P, polar surface area, number of hydrogen bond donors acceptors and number of rotatable bonds. In an attempt to improve the predictions of drug likeness, the rules have spawned many extensions. They are given below:

- Partition coefficient log P, range from -0.4 to +5.6
- Molar refractivity from 40 to130
- Molecular weight from 180 to500 daltons.
- Number of atoms from 20 to 70
- Not more than 5 hydrogen bond donors and 10 hydrogen bond acceptors

Characterization

The selected compounds were synthesized, recrystallised and purified by usingethanol.

JUSTIFICATION OF PURITY OF SYNTHESIZED COMPOUNDS

Melting point

The melting points of the synthesized compound were determined by one end open capillary method. Sharp melting point indicated that the synthesized compounds werepure.

TLC

Precoated aluminum TLC plates were used. Solutions of the reactants and products were prepared by dissolving them in methanol. Appearance of a single spot not corresponding to the parent compounds confirms the purity of the synthesized Compounds.

Rf values of the synthesized compounds varies from the parent compounds indicates that the reaction was completed.

Table 3: Rf values of the synthesized compounds.

S.No	Compound Code	Mobile Phase	Rf Value
1	PK1	HEXANE:ETHYLACETATE(7:3)	0.63
2	PK2	HEXANE:ETHYLACETATE(7:3)	0.71
3	PK3	HEXANE:ETHYLACETATE(7:3)	0.78
4	PK4	HEXANE:ETHYLACETATE(7:3)	0.69
5	PK5	HEXANE:ETHYLACETATE(7:3)	0.75

Table 4: Physical Data of The Synthesized Compounds.

S.NO	Compoud Name	Molecular Foumula	Molecular Weight	% Yield	Melting Point
1	PK1	C14H9N5O5	327.25	85	164-166°C
2	PK2	C13H6Cl3N3O	326.56	80	154-156°C
3	PK3	C10H6N4OS2	262.31	72	158-160°C
4	PK4	C14H11N3O	237.25	80	180-182°C

LC-MS

Liquid Chromatography – Mass Spectrometry is used to determine the purity and mass of the synthesized to compounds.

Table 5: Molecular weight determined by mass spectrometry.

S.No	Sample Code	Actual Mass	Calculated Mass
1	PK1	327.25	325
2	PK2	326.56	325.05
3	PK3	262.31	264.80
4	PK4	237.25	234.20
5	PK5	257.67	253.80

BIOLOGICAL EVALUATION

Microplate Alamar Blue Assay [Maba]

The compounds were evaluated for their invitro antitubercular activity by the MABA method. Strains used: Mycobacterium tuberculosis H37RV strains.

The standard drugs used are: Pyrazinamide-3.125µg/ml. Streptomycin-6.25µg/ml. Ciprofloxacin 3.125µg/ml.

Table 6: The MABA report of the synthesized compounds were tabulatedbelow.

S. No.	Sample	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.12 µg/ml	1.6 µg/ml	0.8 µg/ml
1	PK1	S	S	R	R	R	R	R	R
2	PK2	S	S	S	S	S	S	S	R
3	PK3	S	S	R	R	R	R	R	R
4	PK4	S	S	S	S	S	S	S	R
ss5	PK5	S	S	R	R	R	R	R	R

Table 7: Comparative study of docking score with MABA report.

Compound name	Docking score Kcal/mol	MABA (biological activity)(µg/ml)
PK1	-7.56	50
PK2	-7.1	1.6
PK3	-6.57	50
PK4	-5.83	1.6
PK5	-6.39	50
PYRAZINAMIDE	-4.69	3.125
CIPROFLOXACIN	-6.45	3.125

SUMMARY

Glutamine synthetase I enzyme is the critical enzyme for the survival and growth for Mycobacterium tuberculosis is chosen as the potential drug target. Molecules were designed and docked against Glutamine synthetase I enzyme 3ZXR protein using Autodock® 4.2.1 software. Molecules with good docking score were screened for insilico toxicity by using OSIRIS® software and evaluation of drug likeness by MOLINSPIRATION software. The selected compounds were synthesized and labeled as PK1, PK2, PK3, PK4, PK5. Purity of the synthesized compounds were justified by its sharp melting point and TLC. Further the synthesized compounds were characterized by IR, LC-MS, H^1NMR. Biological evaluation is done by MICROPLATE ALAMAR BLUE ASSAY Compounds PK2 and PK4 showed activity at 1.6 µg/ml concentrations which are comparable to the activity of the standard drugs Pyrazinamide, Streptomycin, Ciprofloxacin which are ctive at 3.125µg/ml, 6.25µg/ml,3.125µg/ml concentrations.

CONCLUSION

The present study deals with A series of Schiff bases of isatin derivatives were designed, docked, synthesized and evaluated against Glutamine synthetase 1 enzyme which is critical for the survival and growth of MTB. The Minimum Inhibitory Concentration of the synthesized compounds ranges from 50-1.6µg/ml. The work concludes that the Compounds Compounds PK2 and PK4 showed activity at 1.6 µg/ml concentrations which are comparable to the activity of the standard drugs Pyrazinamide, Streptomycin, Ciprofloxacin which are active at 3.125µg/ml,6.25µg/ml,3.125µg/ml concentrations. Further, structural refinement of the synthesized compounds is expected to yield promising molecules against the pathogen MTB.

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