THINK INDIA JOURNAL

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

Computer-Aided Drug Discovery Against *Mycobacterium Tuberculosis* Using *In-Silico* Method

Amir Dar, Joginder Singh and Vikas Kaushik

Department of Bioinformatics, School of Bio-engineering and Bio-sciences, Lovely Professional University, Punjab, India

Corresponding Author E-mail: vikas.14664@lpu.co.in

Abstract

There are numbers of chemical compounds having antibacterial properties and some of the synthetic and natural compounds have proven anti-tuberculosis activity with greater efficacy and less toxicity. We have selected some of the compounds from the literature and tried to analyse their effectiveness and other ADME properties. So the selected compounds are listed below for further analysis. Now the steps which we have followed for the analysis of different compounds are listed below in the procedural flow chart form.

Introduction

Tuberculosis (TB) malady is caused by bacillus *Mycobacterium tuberculosis*, shares similarities with protozoal infection and HIV. The World Health Organization estimates that common fraction of the world's population is severely affected with *M. tuberculosis*. With 1.5 million deaths each year, it is the foremost fatal world killer. UN World Health Assembly adopted the new post-2015 world TB planning. This "EnD TB" designing sets extremely bold targets: to decrease TB victims by 95% and scale back new incidents by 90% between 2015 to 2035 and set to make sure that no family is burdened with harmful expenses because of TB. For the very first time, world ambition isn't simply to manage TB, however to eliminate it from the society. The development of drug-resistant cases in TB patients is usually related to failure to complete the lengthy treatment of chemotherapy. Drug-susceptible TB is treated with rifampicin (RIF), isoniazid (INH), ethambutol and pyrazinamide for 2 months followed by 4 months of RIF and NIH, whereas treatment of multi-drug-resistant (MDR) TB can

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

require up to 2 years of chemotherapy with possible damaging side effects. Medicine that kills *M. tuberculosis* more fast while also preventing the development of drug resistance may shorten chemotherapy considerably multiple drug resistance for tuberculosis are resistant to isoniazid and rifampicin. These are the frontline drugs for the treatment of tuberculosis. In 2015 it was found in a survey that 480,000 fresh cases of multiple drug-resistant patients [1]. The main reason behind the increase in multiple drug resistance is delayed diagnosis and treatment and the current drug therapy fails to treat it. The treatment for tuberculosis is long six to twelve months. While patients with drug resistance require treatment up to 24 months which in turn affect the other processes and has side effects. The drugs are administered in combination and when they are given for so long poor compliance, high cost and increase in drug resistance are observed. There is a need for the modification of drugs which high efficacy without side effects and drug resistance against *M. tuberculosis* [2].

Natural products for the treatment

Some of the compounds are under trials which can give better results than rifampicin, bedaquiline, delamanid have recently given approval against multiple drug résistance. The research is focussing completely on drug discovery to a specific target based on molecular genetics. This strategy has not yet become successful because the inhibitory action by the enzymes does not always correlate with the killing of bacteria [3]. Nowadays, there is a great outcome of natural product treatment using stereochemistry and other techniques. Phenazines are aromatic compounds produced in dye industries and by a bacteria acitinobacteria. This compound is involved in redox reactions and competitive, symbiotic interactions. These are inhibitory molecules showing antibacterial and antifungal activities [4]. Riminophenazines are under trials for the treatment of tuberculosis and are isolated from lichens. It has been found that they have great potential against tuberculosis. The number of riminophenazine related derivatives has been taken for analysis and leadership development for enhancing the activity and decreasing the lipophilicity [5, 6]. Piperidines are heterocyclic compounds used predominantly for the production of pharma products. It is extracted from black pepper and is also present in some other plants and coves a wide range of pharmaceutical drugs such as opioids, vasodilators etc. There are a number of derivatives of this compound which can be used for some specific treatment, for example, SQ609, BTZ043, PBTZ169, CPZEN-45 etc [7, 8]. Thiolactomycin inhibits the synthesis of bacterial fatty acids having huge drug spectrum and was isolated for anti-tuberculosis. It was found that it blocks mycolic acid

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

along with fatty acids. It shows activity against some resistant strains but lost its efficiency against mycobacterium tuberculosis strains having mutation with Kasa G269S. Also, showing the good response of anti-Tb, some other relative compounds have been synthesized and screened for lead discovery [9]. Lipiarmycin A3 is an inhibitor for RNA polymerase synthesis in bacteria approved by food and drug agency. It showed better results of anti-tuberculosis H37RV strain invitro without showing any cross-resistance. It binds to separate RNA polymerase. It has great drug potential but the issue is it contradicts with the approved DMET properties [10]. Using genome sequencing mmpL3, drpE1, qcrB are targeted on the membrane, mmpl3 is a membrane transporter present in the outer membrane and is responsible for the transport of trehalose to membrane for the synthesis of mycolic acid [11].

The given guidelines for patients with multiple drug resistance should receive treatment for longer duration and should be given at least five medicines which include pyrazinamide and four core line medicines. one from A, one from group B and two from C, and D2 and D3 sometimes added for prescription of total five [12]. Drug discovery for anti-tuberculosis from natural products and it has been found that many natural products extracted are having antimicrobial properties. The complexity in isolation and structure of natural products hinders the process of drug discovery for example triterpenes having more than 10 chiral carbons in the structure [13]. The challenges in developing drugs against tuberculosis are because of its pathogenicity and very complex biological structure, the second challenge which hinders is screening and selection of safe compounds which shows high potency and obeys other properties and rule to qualify as a drug molecule and other challenge is resistance against the drugs [14].

PXR is a receptor expressed in the liver and intestines and helps in the elimination of some antibiotics. Its response is ligand-dependent and regulates a number of activities. Its activation regulates a large number of genes. The model organisms used for the analysis of PXR is mouse because of its activity and relation with the huge network of genes. It has great clinical application because it responds to drug-drug interactions, multiple therapies of drug regimes in HIV, tuberculosis has become the main reason for the interaction of a drug with a drug. Rifampicin is used in high dosages, and it activates the PXR response. Due to heavy dosages now the resistance has developed which needs to be reduced. The docking pattern and the energy minimization principle results can be helpful in reducing drug resistance because the ligand molecule that has been used for the stimulation of PXR is naturally occurring chemical compound and will help in eliminating the rifampicin therapy.

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

Improvement in drugs will reduce the multiple drug resistance especially use of natural compounds which will not affect the other pathways in the body [15]. In the present study, we have explored the possibility of a potent solution against M.Tb.

Methodology

Determination of chemical compounds from the literature having Anti-tuberculosis activity

⇩

Isolation of structures of these compounds with smile format

⇩

A ccomplete study of properties of these compounds using swiss ADME and PUBCHEM

⇩

Creating a tabulated form of all the properties

⇩

Isolation of receptor sequence from SwissProt and use multidrug receptor transporter receptor (ITASSER)

⇩

After obtaining the structure of receptor and ligand molecules, patch dock was used for the docking process and the results of docking/docking score are listed in table 7.

Result and Discussion

Table 1 Showing different chemical properties of compounds having anti-tuberculosis properties

Molecules	MW	TSPA	Consensus Log P	Ali Log S	Ali Class	GI absorption
Oxazolidinones	87.08	38.33	-0.05	-0.07	Highly Soluble	High
Pyrrole	67.09	15.79	0.7	-0.62	Highly Soluble	high
Linezolid	337.35	71.11	1.26	-1.76	Highly Soluble	high
Delamanid	534.48	103.8	3.79	-7.57	poorly soluble	low
Dehydrocostus lactone	230.3	26.3	2.98	-2.82	Soluble	high
Costunolide	232.32	26.3	2.97	-2.27	Soluble	high
Psedopetroxazole	309.45	26.03	5.31	-6.8	Poorly soluble	high
Tryptanthrin	248.24	51.96	2.16	-2.77	Soluble	high
Cyclodepsipeptide	747.83	229.8	3.59	-10.91	Insoluble	low

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

Pyrithione	127.16	57.25	1.12	-1.27	Highly Soluble	High
1,4 azainole	168.89	12.03	-0.17	0.42	Highly Soluble	low
Quinoline	129.16	12.89	2.08	-1.93	Highly Soluble	high

Table 2 Physiochemical properties of anti-tuberculosis compounds using SwissADME

Molecule	Ali Log S	Ali Class	GI absorption	BBB permeant
Ethambutol	-0.82	Very Soluble	High	No
Pyrazinamide	-0.37	very soluble	High	No
Streptomycin	1.67	Highly soluble	Low	No
Buthionine sulfoximine	-1.34	Very soluble	High	No
Dequalinium chloride	-10.06	Insoluble	High	No
Moxifloxacin	-1.94	Very soluble	High	No
Sulfathiazole	-2.16	Soluble	High	No
Miconazole	-6.27E+00	Poorly soluble	High	No
Nialamide	-2.2	Soluble	High	No
Lomefloxacin	-0.29	very soluble	High	Yes
Fleroxacin	-1.18	very soluble	High	Yes
Doxycycline	-2.02	Soluble	Low	No
Aconiazide	-3.83	Soluble	High	No
Clina floxacin chloride	-2.63	Soluble	High	No
Sparfloxacin	-1.78	Very soluble	High	No
Semicarbazide	2.43	highly soluble	High	No
Benzothiazole	-2.5	Soluble	High	Yes
Terizidone	-1.48	very soluble	High	No
Cyclodecyne	-2.76	Soluble	Low	Yes
Camphor	-2.27	Soluble	High	Yes
Artemisinin	-3.69	Soluble	High	Yes

Table 3 Activity analysis of anti-tuberculosis compounds using SwissADME

Molecule	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor
Ethambutol	No	No	No	No
Pyrazinamide	No	No	No	No
Streptomycin	Yes	No	No	No
Buthionine sulfoximine	No	No	No	No
Dequalinium chloride	Yes	No	No	No
Moxifloxacin	Yes	No	No	No
Sulfathiazole	No	No	No	No
Miconazole	No	Yes	Yes	yes
Nialamide	Yes	No	No	No
Lomefloxacin	Yes	No	No	No
Fleroxacin	Yes	No	No	No
Doxycycline	No	No	No	No
Aconiazide	No	No	No	No

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

Clina floxacin chloride	Yes	No	No	No
Sparfloxacin	Yes	No	No	No
Semicarbazide	No	No	No	No
Benzothiazole	No	Yes	No	No
Terizidone	No	No	No	No
Cyclodecyne	No	No	No	No
Camphor	No	No	No	No
Artemisinin	No	Yes	No	No

Table 4 Activity analysis of anti-tuberculosis compounds using SwissADME

Molecule	CYP2D6 inhibitor	CYP3A4 inhibitor	Lipinski #violations
Ethambutol	No	No	0
Pyrazinamide	No	No	0
Streptomycin	No	No	3
Buthionine sulfoximine	No	No	0
Dequalinium chloride	No	No	2
Moxifloxacin	Yes	No	0
Sulfathiazole	No	No	0
Miconazole	Yes	Yes	1
Nialamide	No	No	0
Lomefloxacin	No	No	0
Fleroxacin	No	No	0
Doxycycline	No	No	1
Aconiazide	No	No	0
Clinafloxacin chloride	No	No	0
Sparfloxacin	Yes	No	0
Semicarbazide	No	No	0
Benzothiazole	No	No	0
Terizidone	No	No	0
Cyclodecyne	No	No	1
Camphor	No	No	0
Artemisinin	No	No	0

Table 5 Druglikliness of anti-tuberculosis compounds using SwissADME

Molecule	Bioavailability Score	PAINS #alerts	Leadlikeness #violations
Ethambutanol	0.55	0	2
Pyrazinamide	0.55	0	1
Streptomycin	0.17	0	2
Buthionine sulfoxamine	0.55	0	1
Dequalinium chloride	0.17	0	3

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

Moxifloxacin	0.55	0	1
Sulfathiazole	0.55	0	0
Miconazole	0.55	0	2
Nialamide	0.55	0	1
Lomifloxacin	0.55	0	1
Fleroxacin	0.55	0	1
Doxycycline	0.11	0	1
Aconiazide	0.5	0	0
Clinafloxacin chloride	0.55	0	1
Sparfloxacin	0.55	0	1
Semicarbazide	0.55	0	1
Benzothiazole	0.55	0	1
Terizidone	0.55	0	0
Cyclodecyne	0.55	0	1
Camphor	0.55	0	1
Artemisinin	0.55	0	0

Table 6 List of compounds selected for drug designing with smile format

Chemical name	**Smiles**
2-Oxazolidinones	C1COC(=O)N1
Pyrrole	C1=CNC=C1
Linezolid	CC(=O)NCC1CN(C(=O)O1)C2=CC(=C(C=C2)N3CCOCC3)F
Delamanid	CC1(CN2C=C(N=C2O1)[N+](=O)[O-])COC3=CC=C(C=C3)N4CCC(CC4)OC5=CC=C(C=C5)OC(F)(F)F
Dehydrocostus lactone	C=C1CCC2C(C3C1CCC3=C)OC(=O)C2=C
Costunolide	CC1=CCCC(=CC2C(CC1)C(=C)C(=O)O2)C
Psedopetroxazole	CC1CCC2C(CC(C3=C2C1=C4C(=C3C)N=CO4)C=C(C)C)C
Tryptanthrin	C1=CC=C2C(=C1)C(=O)N3C4=CC=CC=C4C(=O)C3=N2
Cyclodepsipeptide	CCC(C)C1C(=O)NC(C(=O)C(C(=O)OC(C(=O)OC(C(C(=O)OC(C(=O)O1)C)NC(=O)C2=C(C(=CC=C2)NC=O)O)C)CC(C)C)(C)C)CC(C)C
Pyrithione	C1=CC(=S)N(C=C1)O
1,4 azainole	C1=C[In]=CN1
Quinoline	C1=CC=C2C(=C1)C=CC=N2
Thujone	O=C1[C@H](C)[C@@H]2[C@](C(C)C)(C1)C2
Artemisinin	O=C3O[C@@H]4O[C@@]1(OO[C@@]42[C@@H](CC1)[C@H](C)CC[C@H]2[C@H]3C)C

Receptor information:

UniProt: P9WJX9

Docking results of the compounds which we have selected from the literature on the basis of antimicrobial /antitubercuosis activity.

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

Table 7 docking results using different ligand molecules against *Mycobacterium tuberculosis* having membrane receptor (UniProt: P9WJX9), a multidrug efflux transporter

Chemical Names	Score	Area	ACE
4-azainole	2040	217.00	-90.59
Cyclodepsipeptide	4160	481.30	-196.22
Delamanid	4714	523.00	-165.36
Psedoperaxazole	2532	273.90	-126.73
Pyrithiones	1954	213.70	-100.15
Pyrrole	2978	334.80	-116.49
Linezolid	4912	592.60	-280.65
Artemisin	4372	498.20	-191.84
Thujone	3326	368.70	-129.44
Aconiazide	5164	601.60	-248.60
Costunolide	4666	548.70	-550.53
2-oxalodizanone	4232	518.40	-181.17
Dehydrocostus lactone	6294	744.90	-129.59

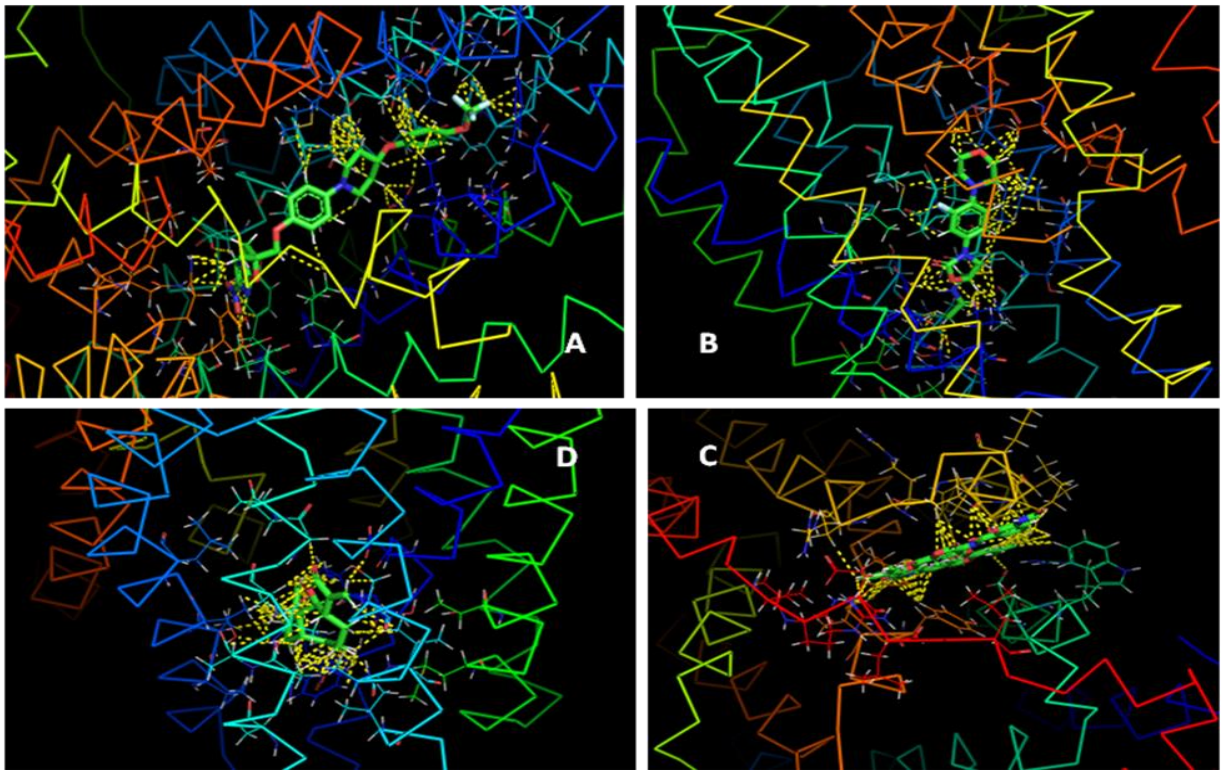

Fig 1. Showing docking results between membrane receptor efflux transporter and chemical ligands A. Dehydrocoustus lactone B. Delamanid C. Cyclodepsipeptide D. Coustunolide

Conclusions

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

Novel and highly efficient drug delivery methods and new drugs need to be designed for the treatment of tuberculosis and some other pathogenic bacteria. The screening of receptors and ligand molecules is going on, and there is a pipeline of drugs and vaccines under FDA trials which may lead to some improvement in drug therapy and reduce the level of multiple drug resistance and other factors like duration of treatment. Existence of chemical compounds in plants like flavonoids, terpenes, alkaloids etc. have shown efficient anti-tuberculosis activity and are being used traditionally in various parts of the world. So to eliminate drug resistance and reduce the pathogenicity of *M. tuberculosis* the new molecules need to be screened, and we have selected some of the compounds and perform some analysis and docking. Multiple strategies have been used to develop vaccines against water-borne diseases as such, and there is no vaccine available for the number of viral and bacterial diseases. Advancement in science and technology is revolutionising the clinical approaches for the treatment of various diseases. This work demonstrate the effectiveness of some compounds against M.Tb.

References

1. Kurabachew, M., Lu, S. H., Krastel, P., Schmitt, E. K., Suresh, B. L., Goh, A., ... & Cynamon, M. (2008). Lipiarmycin targets RNA polymerase and has good activity against multidrug-resistant strains of *Mycobacterium tuberculosis*. *Journal of Antimicrobial Chemotherapy*, *62*(4), 713-719.
2. L Dudek, N., Perlmutter, P., Aguilar, I., P Croft, N., & W Purcell, A. (2010). Epitope discovery and their use in peptide based vaccines. *Current pharmaceutical design*, *16*(28), 3149-3157.
3. Laver, W. G., Air, G. M., Webster, R. G., & Smith-Gill, S. J. (1990). Epitopes on protein antigens: misconceptions and realities. *Cell*, *61*(4), 553-556.
4. Law, J. W. F., Ab Mutalib, N. S., Chan, K. G., & Lee, L. H. (2015). Rapid methods for the detection of foodborne bacterial pathogens: principles, applications, advantages and limitations. *Frontiers in microbiology*, *5*, 770.
5. Leinikki, P., Lehtinen, M., Hyöty, H., Parkkonen, P., Kantanen, M. L., & Hakulinen, J. (1993). Synthetic peptides as diagnostic tools in virology. In *Advances in virus research* (Vol. 42, pp. 149-186). Academic Press.
6. Leo, S., Gaïa, N., Ruppé, E., Emonet, S., Girard, M., Lazarevic, V., & Schrenzel, J. (2017). Detection of bacterial pathogens from broncho-alveolar lavage by next-generation sequencing. *International journal of molecular sciences*, *18*(9), 2011.

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

7. Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., Adair-Rohani, H., ... & Aryee, M. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The lancet*, *380*(9859), 2224-2260.
8. Lin, A. H., Murray, R. W., Vidmar, T. J., & Marotti, K. R. (1997). The oxazolidinone eperezolid binds to the 50S ribosomal subunit and competes with binding of chloramphenicol and lincomycin. *Antimicrobial agents and chemotherapy*, *41*(10), 2127-2131.
9. McSparron, H., Blythe, M. J., Zygouri, C., Doytchinova, I. A., & Flower, D. R. (2003). JenPep: a novel computational information resource for immunobiology and vaccinology. *Journal of chemical information and computer sciences*, *43*(4), 1276-1287.
10. Moraes, G. L., Gomes, G. C., De Sousa, P. R. M., Alves, C. N., Govender, T., Kruger, H. G., ... & Lameira, J. (2015). Structural and functional features of enzymes of Mycobacterium tuberculosis peptidoglycan biosynthesis as targets for drug development. *Tuberculosis*, *95*(2), 95-111.
11. Moreau, V., Granier, C., Villard, S., Laune, D., & Molina, F. (2006). Discontinuous epitope prediction based on mimotope analysis. *Bioinformatics*, *22*(9), 1088-1095.
12. Morris, G. E. (2005). Epitope mapping. In *Immunochemical Protocols* (pp. 255-267). Humana Press.
13. Neeland, M. R., Shi, W., Collignon, C., Taubenheim, N., Meeusen, E. N., Didierlaurent, A. M., & de Veer, M. J. (2016). The lymphatic immune response induced by the adjuvant AS01: a comparison of intramuscular and subcutaneous immunization routes. *The Journal of Immunology*, *197*(7), 2704-2714.
14. Nikaido, H. (2001, June). Preventing drug access to targets: cell surface permeability barriers and active efflux in bacteria. In *Seminars in cell & developmental biology* (Vol. 12, No. 3, pp. 215-223). Academic Press.
15. Organization WH Global tuberculosis report 2015:wwwwhoint/tb/publications/global-report/.