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Review Article

Mini Review on Anti-Tubercular Activity of Thioridazine on Basis of Molecular Docking Studies

Mohammad Asif[1]* and Md Tauquir Alam[2]

[1]*Department of Pharmaceutical Chemistry, Himalayan Institute of Pharmacy Research, Dehradun, India*

[2]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Northern Border University, Saudi Arabia*

***Corresponding Author:** Mohammad Asif, Department of Pharmaceutical Chemistry, Himalayan Institute of Pharmacy Research, Dehradun, India.

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Abstract

Thioridazine (TZ) is a drug that has been used for over 35 years as a psychoactive drug, is now potentially utilized in combination with certain anti-tubercular (anti-TB) drugs to cure Multi Drug Resistant (MDR), Extensively Drug Resistant (XDR) and Totally Drug Resistant (TDR) tuberculosis (TB). This study explores the possible reasons for its anti-TB activity by molecular docking procedure. Molecular docking studies were performed on seventeen enzymes from different mechanisms were docked to study the binding affinity of TZ on the active sites of various *Mycobacterium tuberculosis* (*Mtb*) enzymes in an effort to increase the understanding of the action of TZ as an anti-TB drug. The enzyme CmaA2-Cyclopropane mycolic acid synthase (PDB id: 1KPI) scored lowest binding energy which means the greater stability of the Thioridazine's ability to bind to the receptor. MmaA2 (1TPY), InhA (2NSD) and PknG (2PZI) enzymes of *Mtb* gave the best G-scores. The docking study results revealed that TZ may act by more than one possible mechanism to exert anti-tubercular activity against MDR-TB, XDR-TB and TDR-TB.

Keywords: Thioridazine; Molecular Docking; Enzymes; Binding Energy; MDR-TB; XDR-TB

Introduction

The World Health Organization (WHO) declared Tuberculosis (TB) is a global public health emergency in 1993 and it is still continues to be a major global health problem. Globally in 2012, an estimated 450,000 people developed Multi Drug Resistant (MDR-TB) and there were an estimated 170,000 deaths from MDR-TB also there was reported cases of Extensively Drug Resistant (XDR) and Totally Drug Resistant (TDR) tuberculosis (TB). On an average, about 9.6% of MDR-TB cases have converted to XDR-TB [1]. A study of the use of Thioridazine (TZ) as salvage therapy in 4 Indian patients with XDR-TB (near total drug resistance to current therapy) with advanced disease. They found the drug to be done well tolerated, even in the malnourished and ill patient. It also led to clinical progress in 3 of the 4 patients [2]. The TZ, a neuroleptic drug, which is less toxic than chlorpromazine (CPZ), kills intracellular *Mtb* isolates that are resistant to two or more antibiotics. The TZ shows anti-TB effects *in-vitro* and *in-vivo* mouse models [3]. The TZ is effective when used in combination with antibiotics to which the initial *Mtb* was resistant. Because TZ is cheap, it should be used in therapy of XDR-TB and TDR-TB patients in economically poor population [4,5] and TZ in the treatment regimen on a 'compassionate' basis. The TZ in patients with XDR-TB who have exhausted all available drug options [6]. The TZ may be patented for its "new use". New drugs for treatment of TB, most notable MDR-TB and XDR-TB, are urgently needed; phenothiazines and their targets should be exploited for this use [7]. This study explore the possible mechanism of action of TZ by molecular docking studies. Though TZ was found to act through efflux pump mechanism, still it was not well explored [8].

S. No.	Name of the enzyme (PDB ID)	G-Score (Kcal/mo)	Ref
A	Function (Lipid Metabolism)		
1.	CmaA-2 Cyclopropane Mycolic Acid Synthase (1KPI)	-9.5	[10]
2.	MmaA2-Methoxy Mycolic Acid Synthase 2 (1TPY)	-9.4	[11]
3.	InhA-NADH-Dependent Enoyl ACP (Acyl Carrier Protein) Reductase (2NSD)	-8.4	[12]
4.	FabH-(3-Oxo-acyl)-(Acyl Carrier Protein) ACP Synthase (1HZP)	-3.7	[13]
5.	MbtK-Lysine-N(Epsilon)-acyltransferase (1YK3)	-2.2	[14]
6.	FabD-Malonyl CoA- Acyl Carrier Protein transacylase (2QC3)	-3.8	[15]
7.	PcaA-Mycolic Acid (Cyclopropane) Synthase (1L1E)	-5.4	[16]
8.	DprE1-Decaprenylphosphoryl-B-D-Ribose 2′-Epimerase (4FDO)	-3.8	[17]
B	**Function (Intermediary Metabolism and Respiration)**		
9.	AdoK-Adenosine Kinase (2PKK)	-4.5	[18]
10.	GlnA1-Glutamine Synthetase (4ACF)	-6.0	[19]
11.	ThyX–Thymidylate Synthase (3GWC)	-2.0	[20]
12	TmK–Thymidylate Kinase (1G3U)	-3.8	[21]
C	**Function (Cell wall and Cell Processes)**		
13.	LdtB- L, D-Transpeptidase-2 (3VAE)	-6.4	[21]
14.	Mmr-Multi-Drug Resistant Protein (2IQ4)	-4.9	[22]
15.	Glf -UDP-Galactopyranose Mutase (1V0J))	-4.1	[23]
16.	EmbC-Arabinosyl-Indolyl Acetyl Inositol Synthase (3PTY)	-3.1	[24]
D	**Function (Regulatory Protein)**		
17.	PknG-Protein Kinase (2PZI)	-8.2	[25]

Table 1: Molecular docking results of Thioridazine from Glide [9].

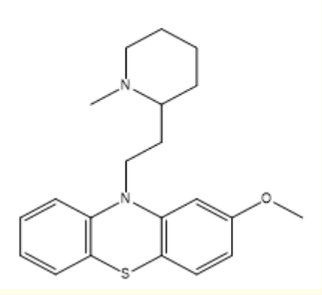

Figure 1: Thioridazine (Psychoactive and antitubercular drug).

Discussion

Comparative docking analysis of TZ with various pathophysiological enzymes responsible for TB is a reasonable method to study the TZ as a anti-TB drug. The TZ is reported for its efficacy towards TB in a curious mechanism, the docking results showed that it may act on other mechanisms possibly. The binding efficiency of the drug TZ with 17 pathophysiological enzymes (Table 1) and the G-Score have ranged between -3.1 to -9.5. The non-bonding interactions/hydrophobic region include the key amino acid residues like tyrosine (TYR), isoleucine (ILE), leucine (LEU) and phenylalanine (PHE) in top scored three enzymes against TZ. The TZ docked well with the enzymes Cyclopropane Mycolic Acid Synthase (lipid metabolism), Methoxy Mycolic Acid Synthase (lipid metabolism), NADH-Dependent Enoyl ACP (Acyl Carrier Protein) Reductase (lipid metabolism), and Protein Kinase-G (Regulatory Protein) with the G-Score of -9.5 Kcal/mol, -9.4 Kcal/mol, -8.4 Kcal/mol and -8.2 Kcal/mol respectively. This is an indication for an antidepressant drug TZ, against *Mtb* through an unusual mechanism has encouraged the study [9].

Conclusion

Thioridazine (TZ) as an antidepressant is reported to act by inhibiting the efflux pump mechanism. The docking studies indicated that it might be acting by inhibition of several enzymes notably Cyclopropane Mycolic Acid Synthase (lipid metabolism), Methoxy Mycolic Acid Synthase (lipid metabolism), NADH-Dependent Enoyl ACP (Acyl Carrier Protein) Reductase (lipid metabolism), and Protein Kinase-G (Regulatory Protein) with the G-Score of -9.5 Kcal/mol, -9.4 Kcal/mol, -8.4 Kcal/mol and -8.2 Kcal/mol respectively. So the Anti-TB activity of TZ is not because of Efflux pump mechanism but may be by more than one mechanism possibly. The computational studies also concluded that the novel approach on TZ derivatives may lead to newer and more effective anti-TB drugs.

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