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STUDIES IN DESIGNING OF DAPSONE DERIVATIVES AS POTENTIAL MYCOBACTERIUM LEPRAE ENOYL ACYL REDUCTASE INHIBITORS IN SILICO APPROACH

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Abstract: The present work describes the docking between designed dapsone derivatives against leprosy. The dock score of dapsone is found to be comparable with designed diaminodiphenyl sulfone derivatives. The Van der waals forces, hydrogen bonding, hydrophilic interactions, were found between designed dapsone derivatives with Ile16, Ser20, Ile21, Ser94, Gly 96,Phe149, Met155, Met161, Tyr158, Ile194, Thr196, Met199, Trp222. ADME properties of diaminodiphenyl sulfone derivatives are in range.

Keywords: Antileprosy, Blind docking,2NTV, Sulfone derivatives, Dapsone, ADME.

Introduction: Infection with the mycobacterium leprae causes leprosy[i] Leprosy is also known as Hansen's Disease.[ii] Leprosy is a chronic, curable infectious disease mainly causing skin lesions and nerve damage and it can affect the eyes, nose, and muscles. Each year millions of living beings get affected by mycobacterium leprosy globally.[ii iii] The world health organisation (WHO) recommends combinatorial therapy or multidrug therapy[iv] (MDT) to combat leprosy. Currently, dapsone, rifampicin and clofazimine are used for treatment of leprosy.[v] Multi drug resistance[vi] is developed in mycobacterium leprae.
Hence there is a need to develop new drugs to cure leprosy.
Sulphone derivatives are known for anticancer[vii], antimalarial[viii], antibacterial[ix], antifungal[x] activities. Hence we decided to design new sulfone derivatives against leprosy.
In current work, we have docked a series of sulfone derivatives against leprosy using CB dock[xi]. The ADME properties were calculated.

Experimental functions:
Materials and Methods
Hardware Molecular docking studies described herein were performed on Acer ASPIRE i5 Laptop (Intel® Core™ i5-processor) running Windows 11 Operating System.

Docking studies

Docking between dapsone derivatives and mycobacterium leprae InhA protein were performed on CB Dock web server. Mycobacterium leprae InhA proteins were downloaded from www.rcsb.org. PDB ID 2NTV used for docking [xii].

Ligands Preparation

Chemdraw software used to draw dapsone derivatives and saved in *.sdf* file format.
SWISS ADME Web server[xi] used to calculate ADME properties.

Target identification

Acyl carrier protein synthesizes fatty acids which provides energy to living organisms while in bacteria, the associated substrates of acyl carrier protein along with monofunctional enzymes synthesizes fatty acids.[xiii] Thus there is a different pathway for synthesis of fatty acids in living organisms and in bacteria. Thus interfering in the bacterial pathway for synthesis of fatty acids will be a suitable target for inhibiting protein.[xii-xiii]

Results and Discussions:

Dapsone- antileprosy drug was docked against enoyl acyl reductase (PDB ID:2NTV) and found interaction with the active site of binding pocket[xii]

In present work again, we did docking of dapsone against enoyl acyl reductase using PDB ID 2NTV. Dapsone shows a dock score of -7.8 while designed dapsone derivatives show dock score more than dapsone. (**Table 01).** The addition of heterocycle in dapsone molecule results in slight increase in docking score upto 9.7, whereas addition of substituted phenyl group results in increase of dock score upto 11.9.

The dapsone show hydrogen bonding, hydrophilic interaction, lipophilic interaction and Van der waals forces with Gly14,Ile15,Ile16,Gly40,Phe41,Arg43,Leu63,Asp64,Val65,Gln66, Ser94,Ile95,Gly96,Ile122.[xii-xiv]

The designed dapsone derivatives show interaction with amino acids of active site of binding pocket of enoyl acyl reductase enzyme.[xii] The addition of heterocyclic rings like furyl, thiophenyl ring or substituted phenyl groups show similar type of amino acid interaction.[xii-xiv] This indicates designed compounds have potential enoyl acyl reductase characteristics in silico. The ADME properties are listed in table 02

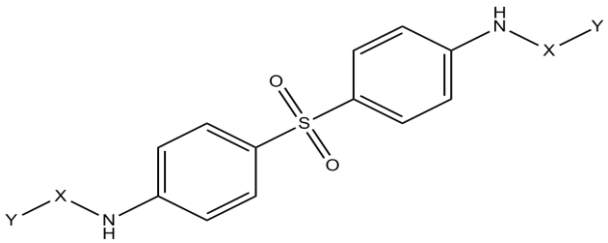

Table 01: Docking score of Dapsone derivatives

Sr No	Compound	X	Y	Dock score
1	Compound 1	C=O	Phenyl	-11.5
2	Compound 2	C=O	2-fluorophenyl	-11.9
3	Compound 3	C=O	3-fluorophenyl	-11.9
4	Compound 4	C=O	4-fluorophenyl	-11.7

5	Compound 5	C=O	2-cholorophenyl	-11.9
6	Compound 6	C=O	3-cholorophenyl	-11.9
7	Compound 7	C=O	4-cholorophenyl	-11.5
8	Compound 8	C=O	2-bromophenyl	-11.7
9	Compound 9	C=O	3-bromophenyl	-11.3
10	Compound 10	C=O	4-bromophenyl	-11.5
11	Compound 11	C=O	2-iodophenyl	-11.6
12	Compound 12	C=O	3-iodophenyl	-11.6
13	Compound 13	C=O	4-iodophenyl	-11.5
14	Compound 14	C=O	2-nitrophenyl	-11.7
15	Compound 15	C=O	4-nitrophenyl	-11.7
16	Compound 16	C=O	2-hydroxyphenyl	-11.3
17	Compound 17	C=O	3-hydroxyphenyl	-11.4
18	Compound 18	C=O	4-hydroxyphenyl	-11.4
19	Compound 19	C=O	Furan	-9.7
20	Compound 20	C=O	Thiophene	-9.6
21	Compound 21	Dapsone	_	-7.8
22	Compound 22	Clofazimine	_	-10.7

Table 02 ADME Properties

Compound	**H-bond acceptor**	**H-bond donor**	**Log P**	**Log S**	**GI absorption**	**BBB permeant**	**log Kp**	**Lipinski violations**
Compound 1	2	2	1.55	-2.54	High	No	-7.13	0
Compound 2	4	2	4.14	-6.36	High	No	-5.88	0
Compound 3	6	2	4.66	-6.43	Low	No	-6.05	1
Compound 4	6	2	4.83	-6.56	Low	No	-5.95	1

Compound 5	6	2	4.81	-6.56	Low	No	-5.95	1
Compound 6	4	2	5.08	-7.52	Low	No	-5.5	2
Compound 7	4	2	5.26	-7.65	Low	No	-5.41	2
Compound 8	4	2	5.26	-7.65	Low	No	-5.41	2
Compound 9	4	2	5.24	-7.65	Low	No	-5.95	2
Compound 10	4	2	5.43	-7.79	Low	No	-5.86	2
Compound 11	4	2	5.43	-7.79	Low	No	-5.86	2
Compound 12	4	2	5.31	-7.57	Low	No	-6.58	2
Compound 13	4	2	5.45	-7.57	Low	No	-6.58	2
Compound 14	4	2	5.5	-7.71	Low	No	-6.49	2
Compound 15	8	2	2.84	-7.79	Low	No	-6.76	2
Compound 16	8	2	2.91	-7.92	Low	No	-6.67	2
Compound 17	6	4	3.71	-7.81	Low	No	-5.66	0
Compound 18	6	4	3.39	-6.47	Low	No	-6.57	0
Compound 19	6	4	3.39	-6.47	Low	No	-6.57	0
Compound 20	6	4	3.41	-6.47	Low	No	-6.57	0

Conclusion: The docking study of dapsone derivatives show hydrogen bonding, hydrophilic interaction, lipophillic interaction or van der Waals forces with enoyl acyl reductase. This indicates designed dapsone derivatives have potential antileprosy characteristics in silico. The ADME properties reveals the drug likeness properties for designed compounds.

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