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Research Article

Synthesis, Quantum mechanical calculation and *in silico* screening of novel hydrazone derivatives as Mycobacterium tuberculosis enoyl reductase inhibitors

J R Tulasi[1*], N. Swathi[2] and T Durga Snehitha[1]

[1]*Department of Pharmaceutical Chemistry, Sir Cr Reddy College of Pharmaceutical Sciences, Eluru 534007*
[2]*Departmant of Pharmaceutical Chemistry, Gokaraju Rangaraju College of Pharmacy, Hyderabad*

Abstract

A series of novel benzo hydrazide derivatives were synthesized and benzoylated. The compounds were purified and characterized by IR, NMR, Mass spectral studies. Drug likeliness assessment conferred all compounds obeying rule of thumb. Binding energy calculation revealed compounds having electron donating groups having high HOMO values (BS9, BS10, SB9, SB10). Structure based drug design was performed for 48 structures having various heterocyclic moieties, INH, and 10 compounds which are reported in literature as active Inh A inhibitors.

Docking and scoring study unravels that our compounds were having 1-5 H-bonding interactions with Tyr158, Ile95, Ile194, Pro 193 H_2O 856, 502, 563, and 552. Hydrophobic interactions of compounds were found to be with Ala157, Gly96, Ile215, Leu218, Met103, Tyr158, Phe97, Pro156, Ser123 and Iys165. All the compounds have good docking score compared to INH. *In vitro* anti oxidant activity by nitric oxide scavenging assay was also performed and the results inferred compounds having good docking score are having good activity. The compounds having electron donating groups are having good activity.

Keywords: Inh A, Hydrazide derivatives, enoyl reductase inhibitors, Docking, Benzoylation.

1. Introduction

Tuberculosis (TB), caused by infection with *Mycobacterium tuberculosis*, kills over 2 million people per year, with between 1 billion and 2 billion people latently infected worldwide (World Health Organization, 2002). Not only has the unfortunate synergy between TB and HIV increased the already high human life toll, but also the emergence of multidrug resistant strains, which are both difficult and very costly to treat, poses an additional public health hazard and further roadblock in effective control of the disease and development of antimycobacterial agents [1,2]. So there remains as much need for new drug discovery.

Isoniazid is a prodrug, the catalase-peroxidase-activated isoniazid, binds to the *inhA* gene product enoyl-ACP reductase of fatty acid synthase II, which converts D^2-unsaturated fatty acids to saturated fatty acids in the mycolic acid biosynthetic pathway [1,2]. A range of radicals are also produced by KatG activation of isoniazid, including nitric oxide, which has shown to be important in the action of another antimycobacterial prodrug [3] Literature review concluded that in order to obtain new derivatives of INH with low toxicity and excellent bio availability derivatisation should be directed towards increasing the lipophilicity of the compound, and preventing N-acetylation of the drug [4]. Present study concerns in docking 48 compounds against enoyl acp reductase and synthesizing high docking score derivatives.

2. Material and Methods

2.1 General

All the chemicals and reagents were purchased from Merck, Sd fine chem. Ltd, Himedia, SRL. All the solvents and starting materials were purified by standard methods. Melting points were determined in DBK programmed melting point apparatus and expressed in ^oC. Reactions were monitored by TLC using aluminium

* Correspondence Info
J R Tulasi
Department of Pharmaceutical Chemistry,
Sir Cr Reddy College of Pharmaceutical Sciences Eluru 534007
E mail: tulasi_jampana@yahoo.com

backed plates coated with silica gel 60 (MERCK). The chromatograms were visualized under UV light (254 nm) and stained with iodine. The IR spectra were recorded on schimadzu FT-IR affinity spectrophotometer using DRS-8000 and expressed in cm^{-1}. ^1H NMR spectra was recorded on a Bruker Ac-80 MHz, Avance 400 MHz NMR spectrophotometer. The chemical shifts were reported as parts per million (δ ppm), using tetramethyl silane as internal standard. The solvents used for NMR are DMSO and $CDCl_3$. Mass spectrum was recorded on Apex mass spectrum system. The spectral characterization was done by referring to the basic principles provided in text books. Quantum mechanical calculations for the synthesized compound were done on Argus lab 4.0.1. Druglikeliness was performed in molinspiration of cheminformatics and ALOGPS 2.1. Docking was performed using Schrodinger 2010 (maestro 9.1) on Dell Precision T-1500 workstation (Intel(R) Core(TM) i7 CPU 860 @ 2.80 GHz 2.79 GHz; 12.0 GB Ram, 1 TB Hard disk). The *In vitro* Antioxidant activity was determined using Schimadzu UV-Visible spectrophotometer

2.2 Experimental work

2.2.1 General procedure for synthesis of Benzohydrazide

2.2.1.1 Conventional Method

The mixture of methyl benzoate (1.35 mL, 0.01mol) and hydrazine hydrate (0.58 mL, 0.012 mol) was taken in a flat bottomed flask and refluxed for 2 h[5,6]. The reaction mixture was cooled at room temperature, white precipitate was obtained. It was filtered and washed thoroughly with water [7,8].

2.2.1.2 Microwave Method

The mixture of methyl benzoate (1.35 mL, 0.01 mol) and hydrazine hydrate (0.583 mL, 0.012 mol) was taken in a 100 mL beaker and was refluxed at 350 W for 2 min, then 1 mL of ethanol was added and the reaction mixture was subjected to microwave irradiation for one more minute at 500 W[9,10]. The resulting white precipitate was washed thoroughly with water and dried. It was further recrystallized from ethanol.

2.2.2 General procedure for synthesis of benzohydrazide Schiff bases (SB1-SB10)

2.2.2.1 Conventional Method

A mixture containing a aryl or heteroaryl ketone (0.01 mol) and benzohydrazide (2.72 g, 0.02 mol) were taken in a 100 mL flat bottomed flask. To this anhydrous sodium acetate (4.92 g, 0.06 mol) and ethanol (20 mL) was added and then refluxed for 2-3 h[11,12]. The reaction mixture was cooled to room temperature to obtain solid product. The compound was filtered by vaccum filteration and washed thoroughly with water followed by ether. A similar procedure was adopted for obtaining compounds SB1-SB10.

2.2.2.2 Microwave Method

Benzohydrazide (1.36 g, 0.01 mol) was added to a solution containing aryl or heteroaryl ketone (0.01 mol) in ethanol (30 mL) and glacial acetic acid (2 drops). The reaction mixture was subjected to irradiation at 350 W. The reaction progress was checked by TLC and found to be completed in 2-3 min.[9,10] After the completion of reaction the reaction mixture was cooled, filtered and washed thoroughly with water. The compound was recrystallized by ethanol.

2.2.3 General procedure for the synthesis of N^1-benzoylated benzohydrazide Schiff base (BS1, BS6, BS10)

The Schiff bases SB1, SB6, SB10 (0.01 mol) was dissolved in 10 mL of dichloromethane and the reaction mixture was taken in a flat bottomed flask, to which an equimolar amount of benzoyl chloride (1.16 mL, 0.01 mol) was added slowly with stirring for 0.5 h and refluxed at 60-70^{0}C for 2-4 h. The crude products were separated out by evaporating dichloromethane. The compound was washed thoroughly with water and recrystallized from methanol [13].

2.3 Drug likeliness

The Lipinski parameters were calculated by using online software Molinspiration of cheminformatics and ALOGPS2.1. The structures of the molecules were drawn using java editor of the respective softwares and the drug likeliness parameters were calculated and tabulated in Table No 3.

2.4 Binding energy calculation

The structure of the compounds was drawn using Marwin sketch and hybridization is changed in Argus lab 4.0.1. The 3D structures of the compounds were geometry optimized using Austin model-1 (AM1) semi-empirical QM method [23]. The Highest Occupied Molecular Orbital (HOMO) and Lowest Occupied Molecular Orbital (LUMO) energy values were estimated using Hamiltonian Parameterized method 3 (PM3) and closed shell Restricted Hartree – Fock - Single Consistent Field (RHF-SCF) methods [14,15]. HOMO and LUMO surfaces were

visualized using a contour value of 0.05 in opaque mode using blue and red for positive and negative phase of the orbital in space. The estimated values of the energies of the tested compounds were given in the table no 4.

2.5 Docking in Schrodinger maestro 9.1.

2.5.1 Protein preparation

1) The crystal structure of the *Mycobacterium tuberculosis enoyl reductase* (Inh A) (PDB ID: 2H7M) has been downloaded from RCSB protein data bank.
2) All bonds in the structure were assigned, including het groups (Het groups include ligands, metal ions, and cofactors) were added to all atoms in the structure, Selenomethionines were converted (MSE) to methionines (MET), a Prime refinement was performed to place and optimize the missing side chains and missing loops[16-21].
3) The water molecules 502, 552, 563, 856 which were found to be important for ligand protein interaction during preliminary docking studies were retained in the protein and were subjected to pre-process [16-21].
4) Ionization states were generated at P^H of 7±4 and the protein chain having lowest penalty was selected.
5) The pre-processed protein was subjected to energy minimization using user defined OPLS_2005. The protein was then saved as *mae file.

2.5.2 Ligand preparation

Ligprep option was used to convert input 2D or 3D structures into corresponding low energy 3D structures. The ionization states for the ligands were generated at a PH 7±2 and Desalt was performed to remove any extra molecules or counter ions [16-21].

2.5.3 Receptor grid generation

Receptor grid generation was done with scaling factor 1 and partial cut off charge 0.25.A grid box of 20*20*20 A^0 around the co-crystallized ligand was generated.

2.5.4Ligand docking and scoring

GLIDE docking was done on XP extra precision mode with flexible docking. Docking simulations was performed in (Intel(R) Core(TM) i7 CPU 860. The compounds docked by XP were ranked based on affinity with the protein and were studied in terms of glide score (G score), LipophilicEvdW, HBond, Rotational penalty.

2.6 Pharmacological activity

2.6.1Nitric oxide scavenging assay

To 100 µM of test or standard compound dissolved in 1 mL of di methyl sulphoxide, 1mL of sodium nitroprusside (10 mM) in phosphate buffer was added and incubated at 37^0C for 150 min. Then to the reaction mixture 1mL of Griess reagent was added and the absorbance was measured at 546 nm [22,23]. The experiment was performed in duplicate and the average of both was taken. Then the scavenging ability was expressed as a percentage and was calculated using the following formula.

$$\%\, Scavenging = \frac{A_c - A_s}{A_c} \times 100$$

Whare as As = the absorbance of the test sample Ac = the absorbance of the control.

3. Results and discussion

13 compounds were synthesized, purified and characterized by IR, NMR, and mass.

1) The benzohydrazide Schiff basess were synthesized by both conventiolal and microwave to see the influence of microwave reaction in yield and purity. A slight improvement in yield and purity of some compounds was observed.the data was tabulated in table no1
2) Drug likeliness characterization indicated all the compounds obeying Lipinski's rule of five and veber's rule of less than 10 rotatable bonds. TPSA of all compounds is also less than 120 A^0 as observed from table no 3.
3) The quantum mechanical calculation indicated the greater homo values for electron donating substituents and large fall in lumo values for electron accepting substituents. The lower GAP (BS6, BS10) values in table no 4 indicated high binding capability [26,27] which was in agreement in docking results.
4) All compounds have good binding capacity compared to standard drug INH (-6.26 Kcal/mol) except SB10. Some of the compounds like SB9, BS8, BS9, BS10, SB9, SB7 have score better than all test series compounds especially BIH (-8.09 Kcal /mol) which was reported in literature as equipotent active as INH and better activity than Ethambutol, Rifampicin and Ciprofloxacin.data was tabulated in table no 5 for training series compound and table no 6 for test set of compounds.

5) The hydrogen bonding interactions are formed by pyridyl nitrogen, ketogroups, amide NH, and Hydrogen bond forming substituents at para positin of phenyl ring with Tyr 158, Ile 95, Ile194, Pro193 and water molecules 502, 552, 563, 856 . All the compounds were buried in hydrophobic pocket created by mainly 13 amino acids Ala 157, Gly96, Gly104, Ile215, Leu218, Lys 165, Met103, Met 155, Met199, PHe97, Pro156, Ser123, and Tyr 158 shown in figure no 11.
6) The *invitro* Anti oxidant activity by nitric oxide scavenging assay of the synthesized compounds as depicted in table no7 shows that the compounds having electron donating groups (OH, OCH_3 at para position observed to have better activity comparable to standards INH and ascorbic acid.

Spectral data of synthesized compounds [24,25]

N^1-(1-phenyl ethylidene) benzohydrazideSB1

IR bands (ν cm^{-1})3192.9 (NH amide), 3028.24 (Ar C-H str), 1659 (C=O str), 1609 (C=N str), 1548.84 (C=C str). **^{1}H NMR (δ)** 9 (s, 1H, NH), 7.3-8 (m, 10H, ArH), 2.36 (s, 3H, CH_3) **Mass (m/z)** 239 (M+1), 237 (M-1).

***N^1*-(1-(4-chlorophenyl) ethylidene) benzohydrazideSB2**

IR bands (ν cm^{-1})3248.13 (NH amide), 3062.96 (Ar C-H str), 1690 (C=O str), 1600.9 (C=N str), 1558.84 (C=C str), 688.59 (C-Cl str), 829.39 (Ar CH bend).

***N^1*-(1-(4-bromophenyl) ethylidene) benzohydrazide SB3**

IR bands (ν cm^{-1})3253.91 (NH amide), 3032.10 (Ar C-H str), 1645.28 (C=O str), 1602.85 (C=N str), 1558.48 (C=C str), 561.29 (C-Br str), 1485.19 (CH_3 bend), 827.46 (Ar CH bend).**^{1}H NMR (δ)**11 (s,1H,NH), 7.5-7.8 (m,5H,ArH), 7.8-7.924 (d,2H,ArH), 7.29-7.27 (d,2H,ArH), 2.36 (s,3H, CH_3).

***N^1*-(1-(3-nitrophenyl) ethylidene) benzohydrazide SB4**

IR bands (ν cm^{-1})3261.63 (NH amide), 3022.45 (Ar C-H str), 1651.07 (C=O str), 1643.35 (C=N str), 1558.48 (C=C str), 1504.48 (C-NO_2 str), 1348.24 (CH_3 bend), 738.74 (Ar CH bend).

***N^1*-(1-(4-hydroxyphenyl) ethylidene) benzohydrazideSB5**

IR bands (ν cm^{-1})3304.06 (OH str), 3205.69 (NH amide), 3057.17 (Ar C-H str), 1656.85 (C=O str), 1606.70 (C=N str), 1512.19 (C=C str), 1226.73 (C-O str), 1309.67 (OH bend),

***N^1*-(1-(thien-2-yl)ethylidene) benzo hydrazideSB6**

IR bands (ν cm^{-1})3197.98 (NH amide), 3059.10 (Ar C-H str), 1645.28 (C=O str), 1600.92 (C=N str), 1537.27 (C=C, 1280.73), (C-S str), 700.16 (Ar CH bend).

***N^1*-(1-(furan-2-yl)ethylidene) benzo hydrazideSB7**

IR bands (ν cm^{-1})3238.48 (NH amide), 3039.81 (Ar C-H str), 1687.71 (C=O str), 1647.21 (C=N str), 1517.98 (C=C str), 1278.81 (C-O str), 750 (Ar CH bend).

***N^1*-(1-(4-aminophenyl) ethylidene) benzohydrazideSB8**

IR bands (ν cm^{-1})3321.48 (NH_2 str), 3026.31 (Ar C-H str),1645 (C=O str), 1603 (C=N str),1573.91 (C=C str), 1317.38 (NH_2 bend), 852.54 (Ar CH bend).

***N^1*-(1-(4-methoxyphenyl) ethylidene) benzohydrazideSB9**

IR bands (ν cm^{-1})3194.12 (NH amide), 3053.45 (Ar C-H str),1690 (C=O str), 1605 (C=N str),1556.5 (C=C str), 1184.29 (C-O str), 1446.6 (CH_3 bend), 833.25 (Ar CH bend).

***N^1*-(1-(4-ethoxyphenylamino) ethylidene) benzohydrazideSB10**

IR bands (ν cm^{-1})3309.98 (NH str), 3190.28 (NH amide), 3074.53 (Ar C-H str), 1653 (C=O str), 1606.70 (C=N str),1510.25 (C=C str), 1311.599 (CH_3 bend), 837.11 (Ar CH bend).**^{1}H NMR (δ)**9.88 (s,1H,NH), 6 (s,1H,NH), 7.48-7.44 (m,5H,ArH), 7.25-7.28 (d,2H,ArH), 7.3-7.39 (d,2H,ArH), 3.4-3.7(t,2H,CH_2), (q,3H, CH_3), 2.238 (s,3H, CH_3).

N-benzoyl-*N^1*-(1- phenylethylidene) benzo hydrazide BS1

IR bands (ν cm^{-1})3053.32 (Ar C-H str), 1670.35 (C=O str),1629.85 (C=N str), 1523.76 (C=C str), 1485.19 (CH_3 bend), 802.39 (Ar CH bend). **^{1}H NMR (δ)** 7.4-7.9 (m, 15H, ArH), 2.36 (s, 3H, CH_3)

N-benzoyl-*N^1*-(1-(thien-2-yl)ethylidene) benzohydrazide BS6

IR bands (ν cm^{-1})3053.32 (Ar C-H str), 1689.64 (C=O str),1629.85 (C=N str), 1537.27 (C=C str),1288.45 (C-S str), 705.95 (Ar CH bend). **^{1}H NMR (δ)** 8.76 (d,2H,ArH), 7.79-7.87 (d,2H,ArH), 7.7-7.65 (d,1H,ArH), 7 (t,1H,ArH),6.6-6.5 (d,1H,ArH), 2.31 (s,3H, CH_3).

N-benzoyl-*N^1*-(1-(4-ethoxy phenylamino)ethylidene) benzo hydrazide BS10

IR bands (ν cm^{-1})3309.98 (NH str), 3074.53 (Ar C-H str), 1653 (C=O str), 1606.70 (C=N str), 1510.25 (C=C str), 1311.599 (CH_3 bend), 837.11 (Ar CH bend).**^{1}H NMR (δ)**6.08 (s,1H,NH), 7.45-7.49 (m,5H,ArH), 7.29-7.26 (d,2H,ArH), 7.39-7.41 (d,2H,ArH), 3.58-3.69(t,2H,CH_2), 2.42 q,3H, CH_3), 2.238 (s,3H, CH_3).**Mass(m/z)**401.2 ($M+H^+$)

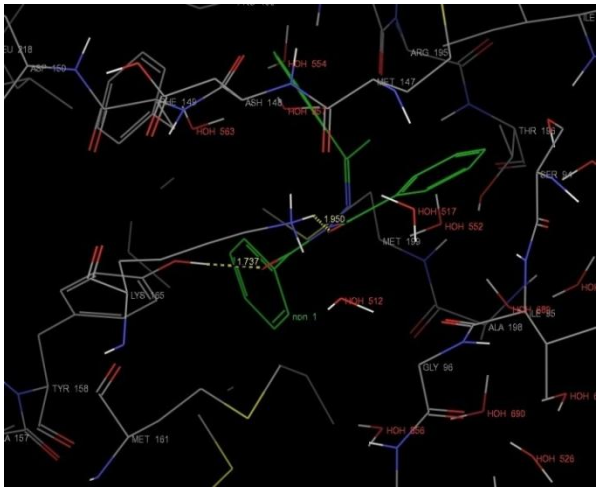

Figure no. 1 Hydrophillic interactions of BS1

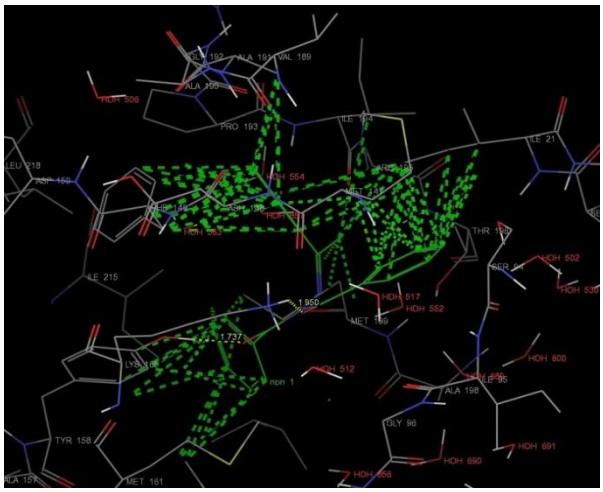

Figure no 2 hydrophobic interactions of BS1

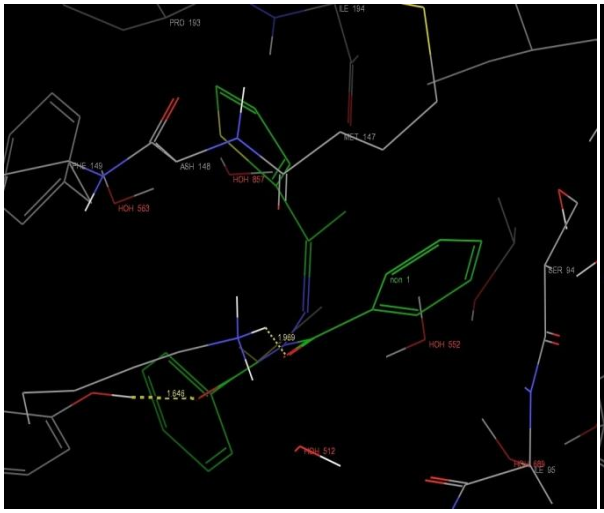

Figure no. 3 Hydrophillic interactions of BS6

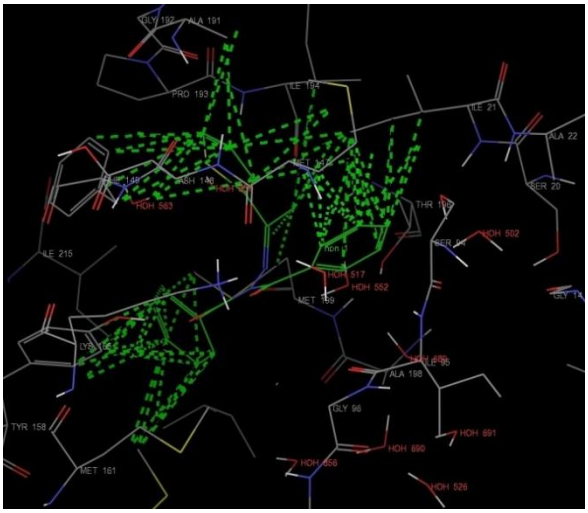

Figure no 4 hydrophobic interactions of BS6

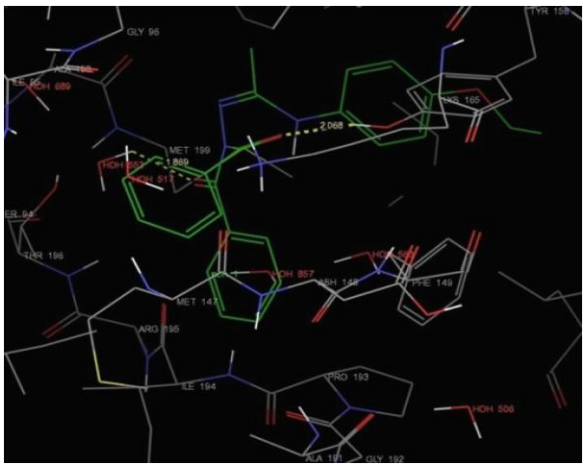

Figure no.5 Hydrophillic interactions of BS10

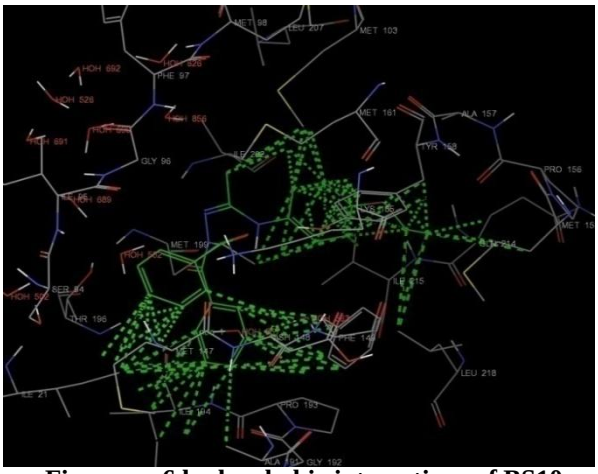

Figure no 6 hydrophobic interactions of BS10

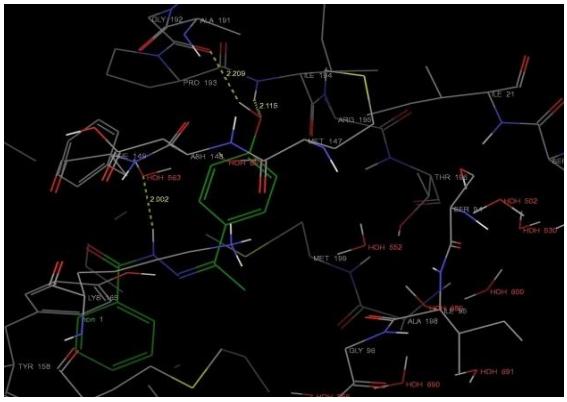

Figure no. 6 Hydrophillic interactions of SB5

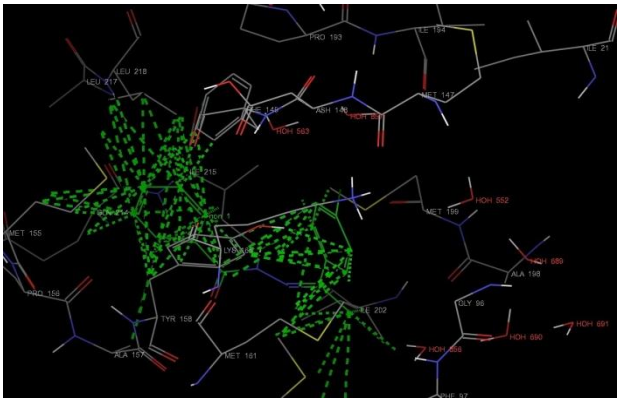

Figure no 7 hydrophobic interactions of SB1

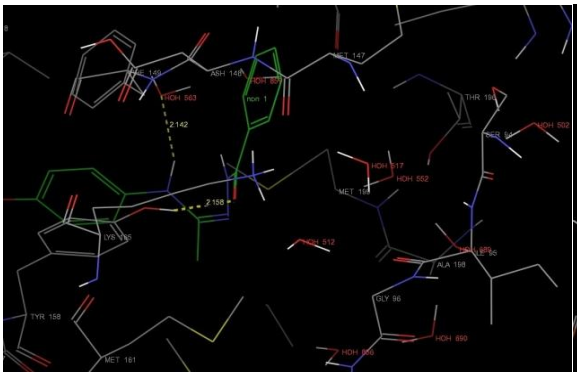

Figure no. 9 Hydrophillic interactions of SB10

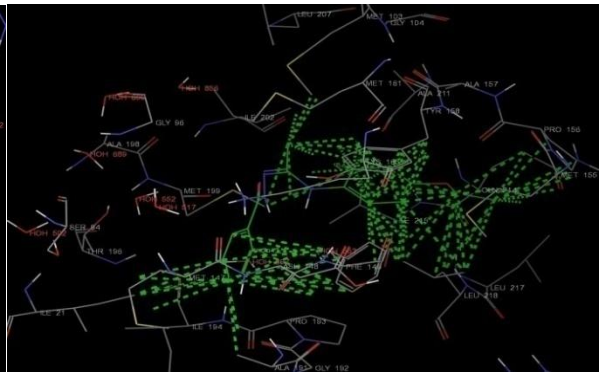

Figure no 10 hydrophobic interactions of SB10

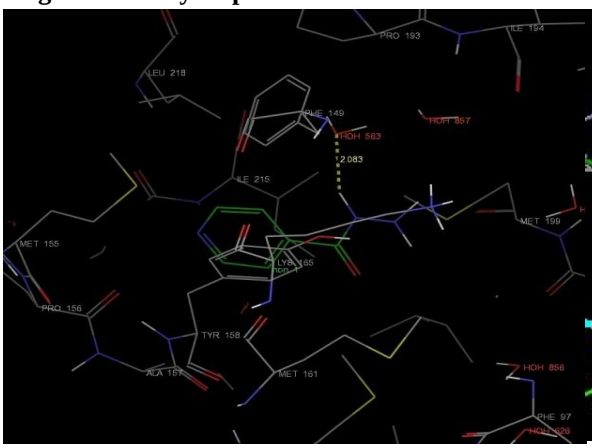

Figure no10. Hydrophilic interaction of INH

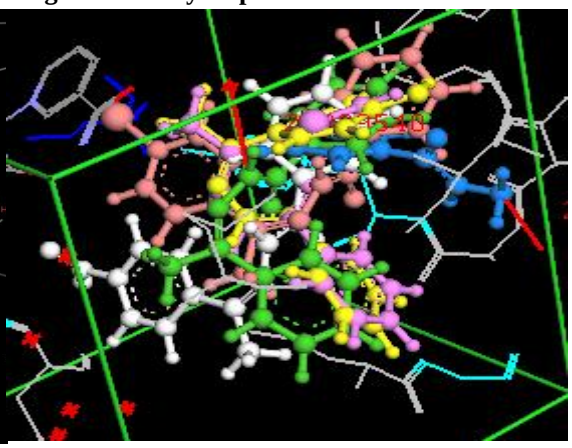

Figure no.11 Stacking photo of INH (blue)

Table No 1: Physical and analytical data of synthesized compounds (SB1-SB10).

Code	Conventional method			Microwave method			R_f [a]
	Time	Yield (%)	m. r (^{0}C)	Time (min)	Yield (%)	m. r. (^{0}C)	
SB1	15 min	96	149-151	1	93	149-151	0.56
SB2	30 min	92	197-198	2	94	197-198	0.69
SB3	1 h	92	206-207	2	92.6	206-207	0.75
SB4	1 h	90	186-187	2	93	184-186	0.54
SB5	1 h	92	228-229	2	93	223-225	0.4
SB6	2 h	85	165-167	3	76	167	0.52
SB7	2 h	82	138-139	3	89	136-137	0.39
SB8	1 h	91	186-187	2	93.6	185-187	0.25
SB9	1 h	90	160-162	2	93.4	159-160	0.63
SB10	1h	90	169	2	95	169-170	0.65

R_f: retention factor ; m. r. : melting range ; a = toluene: ethyl acetate (7:3)

Table No. 2: Physical and analytical data of synthesized compounds (BS1,BS6,BS10).

Code	Physical state	R_f [b]	m.r (^{0}C)	Yield (%)
BS1	Yellow solid	0.71	214-215	56
BS6	Yellow solid	0.69	148-150	51
BS10	Yellow solid	0.5	245-247	55

R_f: retention factor b = toluene : ethyl acetate (6:4).

Table 3: Drug likeliness profile of synthesized compounds

Comp code	M.wt	M.V	TPSA	CLogP	ALog P	HBA	HBD
SB1	238.29	226.6	41.5	3.012	3.37±0.57	3	1
SB2	272.73	240.19	41.5	3.69	3.98±0.56	3	1
SB3	317.19	244.54	41.5	3.82	4.11±0.62	3	1
SB4	283.2	249.99	87.28	2.971	3.29±0.53	6	1
SB5	254.3	234.7	61.7	2.51	3.10±0.45	4	2
SB6	244.3	217.3	41.5	2.91	3.09±0.41	3	1
SB7	228.25	208.22	54.6	2.27	2.51±0.48	4	1
SB8	253.3	237.94	67.5	2.088	2.69 ±0.48	4	3
SB9	252.32	243.22	41.5	3.46	3.32±0.55	3	1
BS1	342.39	317.43	49.7	4.29	4.35±0.86	4	1
BS6	348.427	308.14	49.7	4.18	4.07±0.95	4	1
BS10	359.38	321.29	82.86	2.51	2.92±0.55	5	1

M.wt : Molecular weight; M.V: Molar volume; TPSA : Topological polar surface area; HBA : Hydrogen bond acceptor; HBD : Hydrogen bond donors; No.v : Number of violations.

Table No. 4: HOMO, LUMO, GAP, Binding energies of synthesized compounds, test set and standards

S.No	Comp code	HOMO	LUMO	GAP	Binding energy(Kcal/mol)
1	INH	-9.65	-0.85	8.8	-7.09
2	SB1	-8.95	-0.56	8.39	-11.6
3	SB2	-9.05	-0.74	8.31	-11.1
4	SB3	-9.07	-0.75	8.32	-
5	SB4	-9.49	-1.77	7.72	-10.6
6	SB5	-9.11	-0.55	8.56	-11.26
7	SB6	-8.99	-0.88	8.11	-11.24
8	SB7	-8.904	-0.53	8.374	-8.83
9	SB8	-8.32	-0.22	8.1	-11.05
10	SB9	-9.08	-0.54	8.54	-10.32
11	BS1	-9.5	-0.67	8.83	-13.0054
12	BS6	-9.14	-1.01	8.13	-11.559
13	BS10	-8.84	-0.55	8.29	-13.114
14	A1	-8.65	-0.73	7.92	-9.192
15	A2	-8.77	-0.8	7.97	-8.55
16	A3	-8.57	-0.71	7.86	-8.06
17	A4	-8.6	-0.88	7.72	-7.28
18	A5	-8.66	-0.84	7.82	-10.34
19	BIH	-8.65	-0.73	7.92	-10.37

HOMO: energy of Highest occupied molecular orbital; LUMO: energy of lowest un occupied molecular orbital; GAP: energy difference between HOMO and LUMO.

Table No 5: Schrodinger scoring parameters and *in vitro* minimum inhibitory concentration values reported in literature for test compounds and standarads

Comp code	G Score	Lipophilic Evd W	H Bond	Rot Penal	MIC MTB-H37Rv ($\mu M * 10^{-3}$)
A1	-8.38	-4.18	-1.44	0.23	11
A2	-7.2	-4.13	-0.7	0.23	12
A3	-8.1	-3.01	-1.18	0.29	11
A4	-6.59	-3.52	0	0.24	20
A5	-6.92	-3.33	-0.29	0.39	52
A6	-7.46	-3.65	-0.52	0.31	12
BIH	-8.09	-4.02	-1.08	0.38	4.9
INH	-6.26	-2.35	-0.7	0	2.04
etambutol					15.31
rifampicin					9.4
ciprofloxacin					0.24

[#] GScore: glide score; Hbond: hydrogen bonding term; RotPenal : Rotatable bond penalty; LipophilicEvdW: Lipophilic term derived from hydrophobic grid potential.

Table No 6: Scrodinger scoring parameters of synthesized compounds

Comp code	G Score	Lipophilic Evd W	H Bond	Rot Penal	Electro	Sitemap
SB1	-7.05	-3.12	-0.36	0.26	-0.34	-0.62
SB2	-6.52	-3.03	0	0.21	-0.17	-0.62
SB3	-6.44	-2.92	0	0.16	-0.2	-0.62
SB4	-6.32	-3.04	0	0.29	-0.13	-0.47
SB5	-6.42	-3.97	-1.63	0.35	-0.38	-0.12
SB6	-6.52	-3.04	-0.34	0.25	-0.29	-0.63
SB7	-7.72	-3.16	-1.11	0.28	-0.52	-0.24
SB8	-6.25	-2.89	0	0.35	-0.32	-0.52
SB9	-6.64	-2.8	-0.43	0.32	-0.27	-0.55
SB10	-8.73	-5.09	-1.18	0.44	-0.64	-0.09
BS1	-7.65	-3.36	-1.02	0.21	-0.61	-0.02
BS6	-7.42	-3.32	-1	0.2	-0.66	-0.05
BS10	-8.68	-4.86	-1.03	0.31	-0.67	0

[#] GScore: glide score; Hbond: hydrogen bonding term; RotPenal: Rotatable bond penalty; LipophilicEvdW: Lipophilic term derived from hydrophobic grid potential; Electro: Electrostatic rewards; Sitemap: SiteMap ligand/receptor non-H bonding polar/hydrophobic and hydrophobic/hydrophilic complementarity terms.

Table No.7: Absorbances and %scavenging of synthesized compounds by nitric oxide method

#	Comp.code	A_s (A^0)	% Scavenging
1	SB1	1.349	55
2	SB2	1.262	57.91
3	SB3	1.731	42.25
4	SB4	1.768	41.03
5	SB5	1.216	59.46
6	SB6	1.217	59.43
7	SB7	1.07	64.3
8	SB8	1.07	64.3
9	SB9	1.175	60.82
10	SB10	1.195	60.153
11	BS1	1.01	66.4
12	BS10	1.07	64.3
13	BIH	1.26	56.4
14	Ascorbic acid	0.990	66.8
15	INH	1.195	60.153

Ac: the absorbance of the control (2.999); As: the absorbance of the test sample.

Table No 8 Hydrophilic and Hydrophobic interactions of some high scored compounds.

S. No	Comp. Code	Interacting Residues	
		Hydrophilic	**Hydrophobic**
1	Sb1	-	Met 103, Phe149 (π-π), Met155, Ala157, Tyr 158, LEU 207, Leu218.(figure no.8)
2	SB5	NH-H_20 563(2.002), OH-Ile 194 (2.115).(figure no7)	Ile21, Met 103, Phe149, Ala157, Tyr 158, Met161, Ile 194, Met199, LEU 207.
3	SB7	-	Met 103, Phe149, Met155, Pro156, Ala157, Tyr 158, Ala191, and Leu218.
4	SB10	C=O-Tyr158 (2.158), NH- H_20 563(2.142).(figure no.9)	Ile21, Met 103, Phe149, Met155, Tyr 158, Met161, Ile 194, Met199, LEU 207.(figure no.10)
5	BS1	C=O-Tyr158 (1.737), C=O-Lys165 (1.95).shown in figure no1	Ile21, Met 103, Met147, Phe149, Tyr 158, Val189.(figure no2)
6	BS6	C=O-Tyr158 (1.646), C=O-Lys165 (1.969).(figure no.3)	Ile21, Met 103, Met147, Phe149, Tyr 158, Ala 191, Ile194.(figure no.4)
7	BS10	C=O- H_20 552(1.869), C=O-Tyr158 (2.068).(figure no.5)	Ile21, Met 103, Phe149, Tyr 158,Met161, Ala 191.(figure no.6)
8	BS1	C=O-Tyr158 (1.737), C=O-Lys165 (1.95).	Ile21, Met 103, Met147, Phe149, Tyr 158, Val189.
9	INH	NH- H_20 563(2.083).(figure no.10)	Met103,Tyr158.

4. Conclusion

In conclusion the compounds Schiff bases and their benzoylated derivatives were in silico predicted as good binding Inh A inhibitors.The increased lipophilicity of the compounds may also help in blocking the N acetylation. The future scope of work is to synthesize some more derivatives and screen the good scoring compounds as potent anti tubercular agents.

Conflicts of interest: The authors declare that they have no conflicts of interest concerning this article.

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