Research Article **ISSN: 2349 – 7106**

Asian Journal of Research in Chemistry and Pharmaceutical Sciences

Journal home page: www.ajrcps.com

DESIGN, ADME PROFILING AND MOLECULAR DOCKING SIMULATION OF NEW ISONIAZID - SCHIFF BASE ANALOGS AS MtKasB INHIBITORS

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ABSTRACT

A combinatorial library of 99 novel isoniazid Schiff base analogs has been designed virtually from isoniazid (INH) and various aliphatic and aromatic β-ketoesters. Absorption, distribution, metabolism, and excretion (ADME) properties of all the newly designed isoniazid-Schiff base analogs have been evaluated *in-silico* using Swiss ADME tool to predict the key physiochemical, pharmacokinetic, drug-likeness and medicinal chemistry properties. None of the compounds violated Lipinski's rule of five and thus presenting the possible use of the designed libraries for developing compounds with drug-like properties. Among the series, 16 INH-Schiff bases showed zero lead-likeness violation and 35 entries with acceptable one violation and found to have good oral bioavailability. Molecular docking simulations were accomplished for the selected 16 Schiff bases with Beta-ketoacyl Acyl Carrier Protein Synthase II (MtKasB) (PDB code: 2GP6) of *Mycobacterium tuberculosis*. The rule-based method for lead-likeness and the molecular docking studies represents a set of 7 isoniazid - Schiff bases as an optimal choice to initiate lead optimization with enhanced drug like properties. This *in-silico* investigation enlightens on identifying promising new hits as chemotherapeutic inhibitors against *Mycobacterium tuberculosis* with improved efficacy.

KEYWORDS

ADME, Cheminformatics, Drug design, Isoniazid Schiff Base, Molecular docking and Tuberculosis.

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INTRODUCTON

Tuberculosis, also known as 'white plaque'[1], is an infectious disease caused by several species of *mycobacteria*, collectively termed the *tubercle bacilli*[2]. The World Health Organization reported tuberculosis as one of the world's fatal and contagious diseases[3]. Globally, 9.6 million new cases of TB were reported in 2014 among which 5.4

million men, 3.2 million women and 1.0 million children and 12% were HIV-positive. Worldwide, about 1.5 million deaths, were reported, besides 400,000 deaths due to co-infection with HIV[4]. Two types of fatty acid synthases (FAS) are present in Mycobacteria[5]. The first type, FAS-I performs *de novo* synthesis of fatty acids[6], while the second type, FAS-II is essential to convert fatty acyl chains of medium length to precursors of lengthy chain (C(56)) in mycolic acids[7]. The *M. tuberculosis* beta-ketoacyl acyl carrier protein synthase (ACP) II MtKasB is an enzyme which involves in mycobacterial elongation in FAS-II type. Hence, these enzymes are considered as potential targets in identifying novel anti-tubercular drugs[8].

Schiff bases are one of the important classes of organic compounds which have many interesting properties and extensive applications in medicinal, agricultural, pharmaceutical fields and material science[9,10]. The Schiff bases and their complexes are reported for their potent biological activities such as antimicrobial, antibacterial, antifungal, anti-inflammatory, anticonvulsant, antitumor, antiproliferative, antioxidant activities[11-14] and as potent anti-tubercular agents[15-16]. Isonicotinic acid hydrazide (INH) is the cornerstone of treatment for drug-susceptible TB and it is also widely used to treat latent *M.Tb* infection[17]. Indeed, INH has become the single most researched anti tubercular agent potent enough to kill the *M. tuberculosis*. Schiff base derivatives containing isoniazid moiety have been recently reported to exhibit better anti-tubercular activity[18,19].

The early information regarding physiological, pharmacokinetics and toxicity profile of compounds for lead optimization and drug discovery has been on a great demand[20]. The early prediction of ADME properties in the drug designing phases considerably diminishes the fraction of pharmacokinetics-related failure in the clinical trials[21]. Our hypothesis is to design a chemical library of Schiff base analogs containing isoniazid moiety in the structure. Isoniazid being a frontier drug in the treatment of tuberculosis, the incorporation of this pharmacophore in the Schiff base skeleton could greatly enhance the pharmacological efficiency particularly the anti-mycobacterial activity.

COMPUTATIONAL METHODS

A series of 99 new INH-Schiff bases (Figure No.1) has been virtually designed and subjected to a theoretical *in-silico* ADME prediction study using the web tool, Swiss ADME. Physiochemical, pharmacokinetics, lipophilic, drug-likeness and medicinal properties of all the 99 entries based on various descriptors have been assessed.

A molecular sketcher based on Chem Axon's Marvin JS (http://www.chemaxon. com) was used to draw the 2D structure of the molecules to be analyzed. The 2D structures of the designed chemical library have been converted to canonical SMILES format and used to compute the ADME properties in the Swiss ADME tool.

Molecular Docking Study with MtKasB

Molecular docking studies were carried using the Auto Dock Tools (version 1.5.6) and Auto Dock docking programs (version 4.2.5.1) based on the genetic algorithm (GA) method. The X-ray Crystal Structure of *M. tuberculosis* Beta-ketoacyl Acyl Carrier Protein Synthase II (MtKasB) (PDB code: 2GP6) was downloaded from the protein data bank (http://www.rcsb.org./pdb). The chemdraw structures of the compounds were converted into energy optimized PDB format by Chem 3D 17.0. The receptor (MtKasB) and ligand PDB files were refined using Auto Dock Tools. The protein was bounded in a grid box with dimensions of 110 × 110 × 110 grid points along x × y × z directions with 0.375 Å spacing. AutoDock recorded the results of docking as extension file 'dlg'. Based on the docking scores of each pose, the lowest energy conformer was selected as the best binding mode. Chimera 1.11.2 and PyMOL v0.990 molecular graphics softwares were used to visualize the docking conformations.

RESULTS AND DISCUSSION

Physicochemical properties

The physicochemical properties of a drug have a significant impact on the pharmacokinetic and metabolic fate in the body. The results observed

from Table No.1 show that the molecular weight of all the compounds lies between 205.2 and 472.3 and thus follow one of the criteria of Lipinski rule of five. The Schiff base compounds 4g, 4f, 7c-7g have more than 10 rotational bonds and rest of the other tested compounds possess less than 10 rotatable bonds and hence satisfies a criterion for oral bioavailability.

The prediction of topological polar surface area (TPSA) parameter helps to understand the passive molecular transport of drug molecules[22]. It is evident from the Table No.1 that the entire set of the compound library was found to be polar with TPSA values ranging between 71 $Å^2$ and 131 $Å^2$. Among the 99 compounds, 6e, 6f, and 6g had the highest TPSA (130.3 $Å^2$), whereas, the compound 8a had the lowest TPSA (71.4 $Å^2$). In drug discovery schemes focusing on oral administration, high solubility will favor complete absorption and the poor solubility limits the absorption of the drug in the gastrointestinal tract[23]. Table No.1 suggests that all the 99 tested compounds have good to moderate water solubility, the Log S value being between −1 and −5.6 and thus could facilitate good oral adsorption. It is observed that the compounds with the bulky substituents $-C_6H_5$, $-OCH_3$, $-OC_2H_5$, $-OC_6H_5$ are 'moderately soluble' and the rest are 'good soluble'.

Pharmacokinetics Properties

Interestingly, all the designed Schiff base molecules were observed with high intestinal absorption as shown in Table No.1 and hence could permeate quite easily across the intestinal lining and available for the cell membrane. Drugs that act in the central nervous system (CNS) need to pass over the blood-brain barrier (BBB) to reach their molecular target. However, little or no BBB permeation might be required for drug molecules with a peripheral target, so as to avoid central nervous system side effects[24]. The blood-brain barrier (BBB) permeation expresses the relative affinity of the drug for the blood or brain tissue. It is observed from Table No.1 that all the 99 INH-Schiff bases, without exception were predicted to have no blood-brain barrier penetration and hence, the peril of CNS side effects is expected to be absent. A major role of P-glycoprotein (P-gp) is to defend the central nervous system from xenobiotics[25]. The predicted result elucidates that majority of the INH-Schiff bases are substrates of P-gp and no Schiff base induce phospholipidosis. On the other hand, compounds 3e, 3f, 6a-g and 7e, 7f are non-substrate of P-gp and hence, expected to induce phospholipidosis due to the presence of 2–OH and 2-OCH_3 on the phenyl ring respectively.

The superfamily of cytochromes P450 (CYP) is significant in drug elimination through metabolic biotransformation[26]. Inhibition of these isoenzymes is certainly a major cause of pharmacokinetics-related drug-drug interactions[27] leading to toxic or other unwanted adverse effects due to the lower clearance and accumulation of the drug or its metabolites[28]. The results from Table No.1 show that all the INH-Schiff base compounds are found to be non-inhibitors of isoenzyme CYP2D6, except 4g, 7d, and 7g and therefore the side effect (i.e., liver dysfunction) may be absent. However, the -Cl, $-OC_6H_5$ and 2,4-OCH_3 substituted INH-Schiff bases are predicted to be metabolized by CYP1A2, CYP2C19, CYP2C9, CYP3A4 with a fewer exceptions. Entries 4g and 7g having phenoxy and methoxy substituents respectively are assessed to be inhibitors to all the 5 isoforms of CYP. The more negative the log Kp (with Kp in cm/s), the less skin permeant is the molecule[29]. The log Kp measurements of all the tested compounds are found to be within the limits (−8.0 to −1.0).

BOILED-Egg model

The Brain Or Intestinal EstimateD permeation method (BOILED-Egg) is an intuitive graphical method to accurately predict the passive human gastrointestinal absorption (HIA) and brain permeability (BBB). This classification model relies on the descriptors: WLOGP and TPSA values, for computing lipophilicity and corresponding polarity of small molecules[30]. As shown in Figure No.2 and No.3, the egg-shaped classification plot includes the yolk (i.e. the physicochemical space for highly probable brain permeation) and the white (i.e. the physicochemical space for highly probable passive absorption by the gastrointestinal tract). The outside

grey region stands for molecules with properties implying predicted low absorption and limited brain penetration[31]. From the BOILED –Egg plots (Figure No.2 and No.3), it has been observed that 11 compounds are found to be P-gp substrates indicated by the blue dots and also, all the 99 INH-Schiff bases were spotted in the white yolk attributed to highly probable HIA absorption. This is in accordance with the values obtained from Table No.1.

Lipophilicity and Drug-likeness

The coefficient log P determines the hydrophobic and hydrophilic nature of compounds. The outcome from Table No.2 shows that the log P values of all designed Schiff base libraries were found to be within the limits, i.e. between −0.7 and +5.0 and hence, are predicted to have good permeability and oral absorption. Drug-likeness evaluates qualitatively the probability of a molecule to become an oral drug candidate in regard to bioavailability.

Rule-of-five by Lipinski

As per Lipinski's rule-of-five[32], candidate violating none or less than one of the following four criteria is likely to be developed as a prospective oral drug. The criteria are as follows: log P (octanol-water partition coefficient) ≤5, molecular weight ≤500, number of hydrogen bond acceptors ≤10 and number of hydrogen bond donors ≤5. In this investigation, none of the INH-Schiff base compounds has violated Lipinski's rule of five (Table No.2) and thus showing the possible utility of series for developing the compound with drug-like properties. The Abbot Bioavailability Score[33] (BAS) is a semi-quantitative rule-based score relying on total charge, TPSA, and violation to the Lipinski filter which defines four classes of compounds with probabilities of 11%, 17%, 56% or 85%. All the designed drug molecules are found to have a bioavailability score of 55 and displaying a likelihood of being an oral drug candidate.

Bioavailability Radar

The drug-likeness of a molecule can be rapidly assessed from the Bioavailability Radar (Figure No.4). The pink colored zone is the suitable physiochemical space for oral bioavailability and the radar plot of the molecule has to fall entirely in the zone to be considered drug-like[34]. The pink area represents the optimal range of each property: LIPO (Lipophilicity): -0.7 < XLOGP 3 < +5.0; SIZE: 150 g/mol < MW < 500 g/mol; POLAR (polarity): 20Å^2< TPSA < 130Å^2; INSOLU (Insolubility): 0 < Log S (ESOL) < 6; INSATU (Insaturation): 0.25 < Fraction of Csp3 < 1; FLEX (Flexibility): 0 < Num. rotatable bonds < 9. From the Swiss ADME prediction output, it is evident that about 55 percent of compounds have the optimal range of all the six properties, enabling them to be considered to possess proficient chemotherapeutic potentials.

Medicinal Chemistry

PAINS (for pan assay interference compounds or promiscuous compounds) are substances possessing sub-structures which show false response with biologically potent output irrespective of the protein receptor[35]. Brenk alert is a structural alert which warns about allegedly toxic, metabolically unstable, chemically reactive fragments present in the structure[36]. The Table No.2 shows that none of the Schiff bases returns any PAINS alert and 1 Brenk alert universally for all the hits except for the compounds with chloro substituent. The synthetic accessibility (SA) score is normalized between 1 (easy synthesis) and 10 (very difficult synthesis). The SA scores for all the candidates in the library were found be less than 4 and hence possess good feasibility to synthesize.

The rule-based method for lead-likeness, aids the medicinal chemist to identify the appropriate molecule for initiating lead optimization. Interestingly, INH-Schiff bases 8c, 8d, 8e, 8h, 8i, 9b, 9h, 9i, 10a, 10b, 10h, 10i, 12a, 12b, 12h and 12i were found to have zero violation for lead-likeness and these molecules (Figure No.5), therefore, are considered to be suitable for initiating lead optimization. Besides, 35 compounds with one violation are also found to satisfy the criteria for oral bioavailability as evident from the radar representations (Figure No.4).

Molecular docking studies with MtKasB receptor

The 16 INH-Schiff bases selected based on the ADME profiling were docked into the active site of the MtKasB. The results of the docking are shown in Table No.3. All the Schiff bases were bound deeply into the active site of the receptor (Figure No.6). The predicted active residues consisted of amino acids such as Tyr 144, Met 145, Gly 116, Gly 114, Gly 406, Asn 147, Ala 118, Ala 169, Leu 115, Val 141, Val 348, Pro146, His 408, Cys 170, Phe 205, Phe 206, Phe 405, Gln 142. The possible key hydrophobic interactions were detected by compounds 8c, 8e, 8h, 8i, 9b, 10a and 10h with active site residues (Gly 406, Met 145, Asn 147, Val 167, Tyr 144, Ser 117, Phe 209, Asn 147, Gly 406, Ala 169 and Gly 114 may play a vital role in interaction profile of the mentioned INH-Schiff bases (Figure No.7).

The residues Phe 209, Ser 110, Tyr 144, Leu 115, Gln 142 make π-interactions with the N- atom of the pyridine ring. The results from Table No.3 indicate that the compounds 8d, 9h, 10a, 10i, 12a, 12b, 12h and 12i have relatively higher binding energy and found to have lesser affinity for binding with targeted protein and consequently would show weak inhibition effect to the organism. The lower the relative binding energy, the more effective is the binding affinity between the ligand molecules and the receptor. The Schiff bases 8c, 8e, 8h, 8i, 9b, 10a and 10h were found to possess relatively lower binding energy values (Table No.4) indicating their higher affinity to the target site.

The protein-ligand interactions of the compounds with the targeting enzymes were established with 2D-representations (Figure No.8) using Ligplot plus programme. The hydrogen bond interaction between the docked compounds and receptor active sites were calculated and displayed in Table No.4. Significantly, compound 8d displays 4 hydrogen bonds with residues Thr 165, Val 167, Glu 175 and Arg 179. The important residues Tyr 144 and Ser 117 were found to involve in 3 hydrogen bonding interactions with compound 8i. The attained results from molecular docking simulations emphasize that the interaction between the INH-Schiff bases and the target protein was conquered by strong hydrogen bonding, hydrophobic forces and π-interactions. The docking study thus, propose the following compounds 8c, 8e, 8h, 8i, 9b, 10a and 10h among the 16 virtual hits as the most promising analogs predicted to bind to the MtKasB receptor with stronger binding affinity.

Table No.1: Physiochemical and Pharmacokinetics properties prediction of selected INH –Schiff Bases

S.No	ENTRY	R^1	R^2	Physiochemical Properties				Pharmacokinetics Properties					
				MW	#RB	TPSA ($Å^2$)	ESOL Class	GIA	BBB P	Pgp S	CYP^1	CYP^2	log Kp (cm/s)
1	8c	C_2H_5	H	263.3	7	80.65	SOL	High	No	No	No	No	-7.00
2	8d	C_6H_5	H	311.3	7	80.65	SOL	High	No	No	Yes	No	-6.75
3	8e	OCH_3	H	265.3	7	89.88	V.SOL	High	No	No	No	No	-7.68
4	8h	Cl	H	269.7	6	80.65	SOL	High	No	No	No	No	-7.19
5	8i	OH	H	251.2	6	100.9	V.SOL	High	No	No	No	No	-7.98
6	9b	CH_3	CH_3	263.3	7	80.65	SOL	High	No	No	No	No	-7.00
7	9h	Cl	CH_3	283.7	7	80.65	SOL	High	No	No	No	No	-7.01
8	9i	OH	CH_3	265.3	7	100.9	V.SOL	High	No	No	No	No	-7.80
9	10a	H	C_2H_5	263.3	7	80.65	V.SOL	High	No	No	No	No	-7.09
10	10b	CH_3	C_2H_5	277.3	7	80.65	SOL	High	No	No	No	No	-6.77
11	10h	Cl	C_2H_5	297.7	7	80.65	SOL	High	No	No	No	No	-6.79
12	10i	OH	C_2H_5	279.3	7	100.9	V.SOL	High	No	No	No	No	-7.58
13	12a	H	*t*- C_4H_9	277.3	7	80.65	SOL	High	No	No	No	No	-7.05
14	12b	CH_3	*t*- C_4H_9	291.4	7	80.65	SOL	High	No	No	No	No	-6.73
15	12h	Cl	*t*- C_4H_9	311.8	7	80.65	SOL	High	No	No	No	No	-6.75
16	12i	OH	*t*- C_4H_9	293.3	7	100.9	V. SOL	High	No	No	No	No	-7.54

MW- Molecular Weight, #RB - No. of Rotatable bonds, TPSA – Topographic Polar Surface Area, Cons. Log P- Consensus Log P, ESOL - Water Solubility, SOL-Soluble, M.SOL- Moderately Soluble, V.SOL-Very Soluble, GIA – Gastro Intestinal Absorption, BBB P- Blood-Brain Barrier Permeability, PgpS - Permeability glycoprotein Substrate, CYP1 - CYP2C9 inhibitor, CYP2 - CYP2D6 inhibitor, log Kp (cm/s) - Skin permeant

Table No.2: Drug likeness and Medicinal Chemistry properties of selected INH –Schiff Bases

S.No	ENTRY	LIPOPHILICITY					DRUGLIKENESS						MEDICINAL CHEMISTRY			
		I Log P	X LogP	W Log P	M LogP	Cons. Log P	No. of Violations					BAS	#alerts		Lead likeness	SA
							L	G	V	E	M		PAINS	Brenk		
1	8c	1.37	1.27	1.4	0.68	1.32	0	0	0	0	0	0.55	0	1	0	3.19
2	8d	2.8	2.04	2.1	1.46	2.23	0	0	0	0	0	0.55	0	1	0	3.34
3	8e	1.8	0.33	0.4	-0.4	0.63	0	0	0	0	0	0.55	0	1	0	3.29
4	8h	1.92	1.07	1	0.41	1.2	0	0	0	0	0	0.55	0	2	0	3.13
5	8i	1.55	-0.2	-0.3	-0.7	0.18	0	0	0	0	0	0.55	0	1	0	3.07
6	9b	1.94	1.28	1.4	0.68	1.43	0	0	0	0	0	0.55	0	1	0	3.25
7	9h	1.76	1.44	1.4	0.68	1.45	0	0	0	0	0	0.55	0	2	0	3.31
8	9i	1.29	0.16	0.1	-0.4	0.42	0	0	0	0	0	0.55	0	1	0	3.26
9	10a	1.6	1.15	1.5	0.68	1.37	0	0	0	0	0	0.55	0	1	0	2.79
10	10b	2.57	1.72	1.8	0.95	1.82	0	0	0	0	0	0.55	0	1	0	3.35
11	10h	2.08	1.87	1.8	0.95	1.78	0	0	0	0	0	0.55	0	2	0	3.41
12	10i	1.93	0.59	0.5	-0.1	0.81	0	0	0	0	0	0.55	0	1	0	3.36
13	12a	2.22	1.33	1.9	0.95	1.71	0	0	0	0	0	0.55	0	1	0	2.9
14	12b	2.75	1.9	2.2	1.2	2.07	0	0	0	0	0	0.55	0	1	0	3.46
15	12h	2.32	2.05	2.1	1.2	2.04	0	0	0	0	0	0.55	0	2	0	3.51
16	12i	2.17	0.78	0.9	0.15	1.07	0	0	0	0	0	0.55	0	1	0	3.47

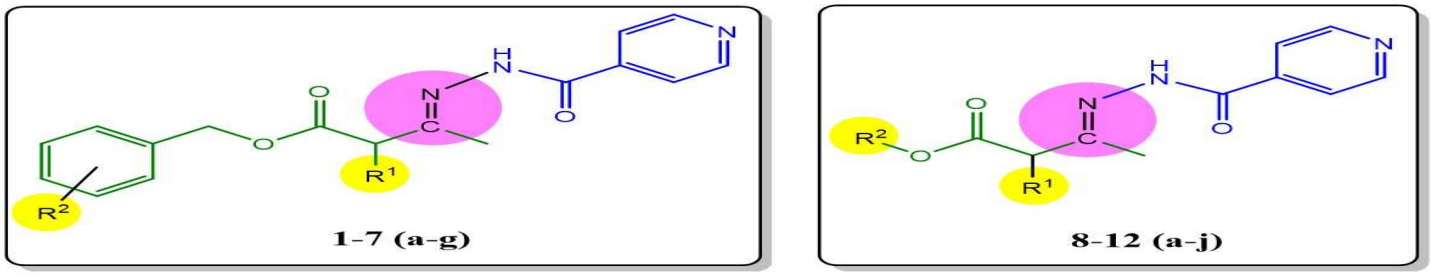
Cons. LogP – Consensus LogP, L- Lipinski, G- Ghose, V- Veber, E- Egan, M- Muegge Rule, BAS- Bioavailability Score, SA– Synthetic Accessibility

Table No.3: Docking results of the INH-Schiff Bases with MtKasB (PDB ID: 2GP6)

S.No	Compound	Final intermolecular energy (kcal mol−1)		Total (1)	Final total internal Energy (kcal mol^{-1}) (2)	Torsional free energy (kcal mol^{-1}) (3)	Unbound system's Energy (kcal mol^{-1}) (4)	Estimated free energy of binding [(1)+(2)+(3)−(4)] (kcal mol^{-1})
		Vd W + H bond + dissolving energy	Electrostatic energy					
1	8c	-5.15	+0.85	-4.30	-0.73	+1.79	0.00	-3.24
2	8d	+13.25	+0.91	+14.16	-0.48	+1.79	0.00	+15.47
3	8e	+0.48	1.90	-0.72	+1.79	+1.79	0.00	-0.83
4	8h	-2.56	0.51	-2.05	-1.65	+1.49	0.00	-2.22
5	8i	-2.52	+0.49	-2.04	-1.12	+1.79	0.00	-1.37
6	9b	-4.17	+0.05	-4.12	-0.23	+1.49	0.00	-2.86
7	9h	+0.43	-0.09	0.34	1.52	+1.49	0.00	+3.35
8	9i	-3.27	+0.05	-3.22	-1.10	+1.79	0.00	-2.52
9	10a	+2.29	+0.06	+2.38	-0.19	+1.79	0.00	+3.98
10	10b	-3.55	-0.09	-3.65	-0.76	+1.79	0.00	-2.61
11	10h	-1.78	+0.03	-1.75	-0.43	+1.79	0.00	-0.39
12	10i	-0.59	+0.08	-0.51	-1.09	+2.09	0.00	+0.49
13	12a	+4.53	-0.15	+4.38	+2.09	+1.79	0.00	+8.26
14	12b	+5.32	0.00	+5.32	+7.64	+1.79	0.00	+14.75
15	12h	+3.83	+0.04	+3.87	+4.13	+1.79	0.00	+9.79
16	12i	+6.65	-0.07	+6.58	+3.21	+2.09	0.00	+11.88

Table No.4: Possible key hydrogen bonds between the INH-Schiff bases and MtKasB target

S.No	Compound	Ligand	Receptor	Bond distance (Å)
1	8c	C_{10}-OH	N(Asn147)	2.81
2	8e	C_{11}-OH	S (Cys170)	2.91
3	8h	C_4-OH	N (Thr165)	2.78
			N (Val167)	3.23
			O (Glu175)	2.75
		C=N	N (Arg179)	2.66
4	8i	INH C=O	N (Ser117)	3.14
		C=N	O (Tyr144)	2.77
		C_9-OH	O (Tyr144)	2.88
5	10a	N (pyridine ring) C_9-OH	N (Gln142)	2.97
			S (Cys170)	3.02
6	10h	C_{10}-OH	N (Asn147)	2.76



	a	b	c	d	e	f	g	h	i	J
R_1 =	H	CH_3	C_2H_5	C_6H_5	OCH_3	OC_2H_5	OC_6H_5	-	-	-
R_2 in	**1=** 2-H; **2**= 2-Cl; **3**= 2-OH; **4**=2-OCH_3; **5**=2,4-Cl; **6**=2,4-OH; **7**=2,4-OCH_3									
R_1 =	H	CH_3	C_2H_5	C_6H_5	OCH_3	OC_2H_5	OC_6H_5	Cl	OH	$CH_2C_6H_5$
R_2 in	**8=** H; **9**= CH_3; **10**= C_2H_5; **11**=*i*- C_4H_9; **12**=*t*- C_4H_9									

Figure No.1: Structure of designed INH- Schiff Base chemical library

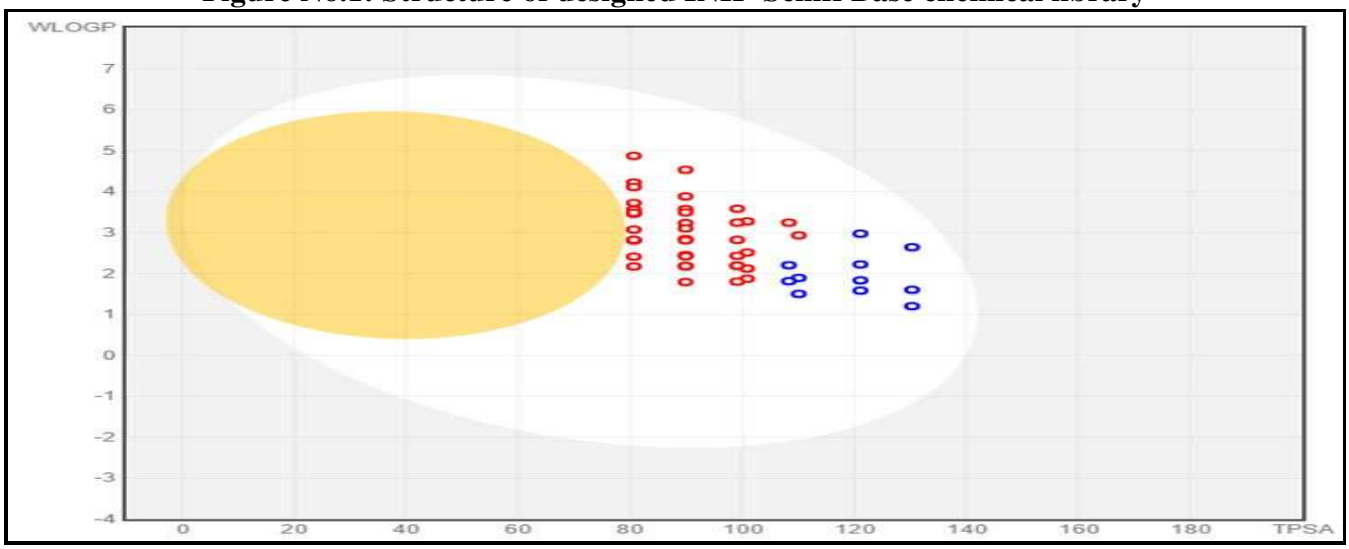


Figure No.2: BOILED-Egg representation of INH-Schiff Bases (1a-7g) Legends: Yellow: BBB, White: HIA, Blue dots: PGP+, Red dots: PGP-

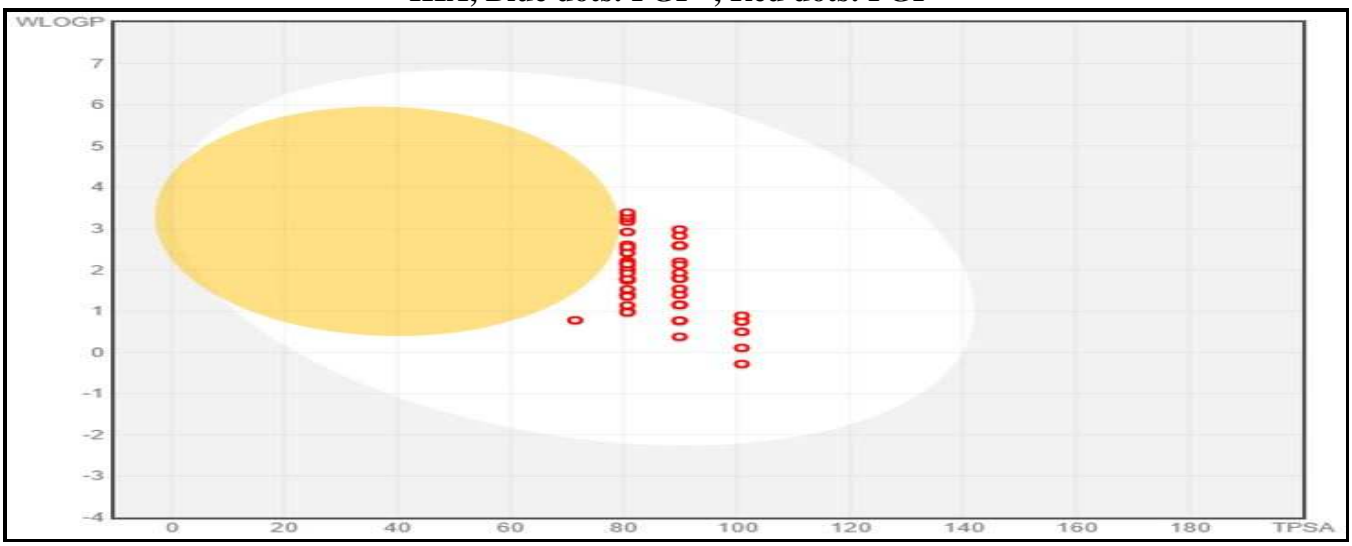


Figure No.3: BOILED-Egg representation of INH-Schiff Bases (8a-12j)

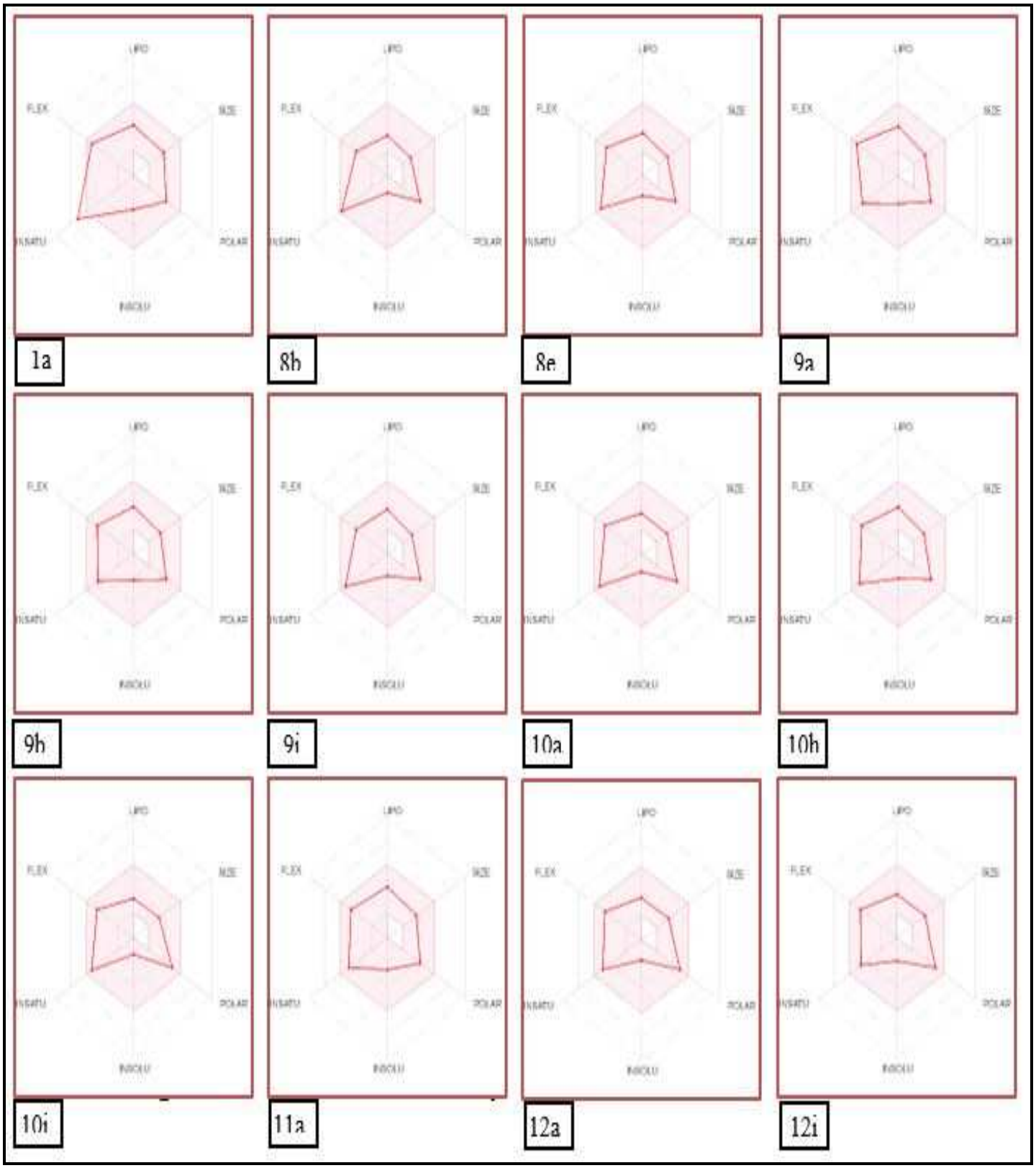


Figure No.4: Bioavailability Radar of selected INH- Schiff Bases

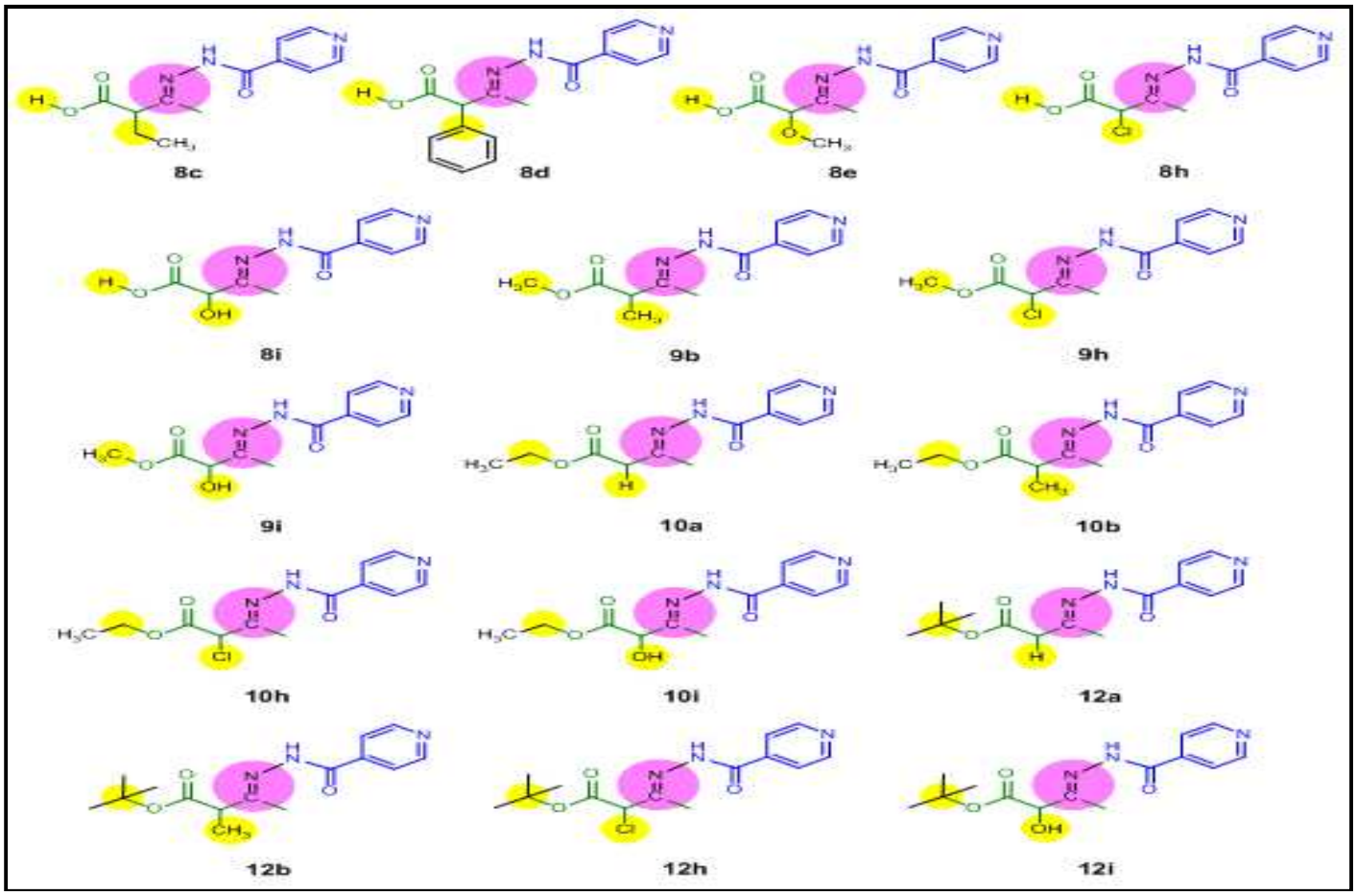


Figure No.5: Structure of INH-Schiff bases with zero lead-likeness violations

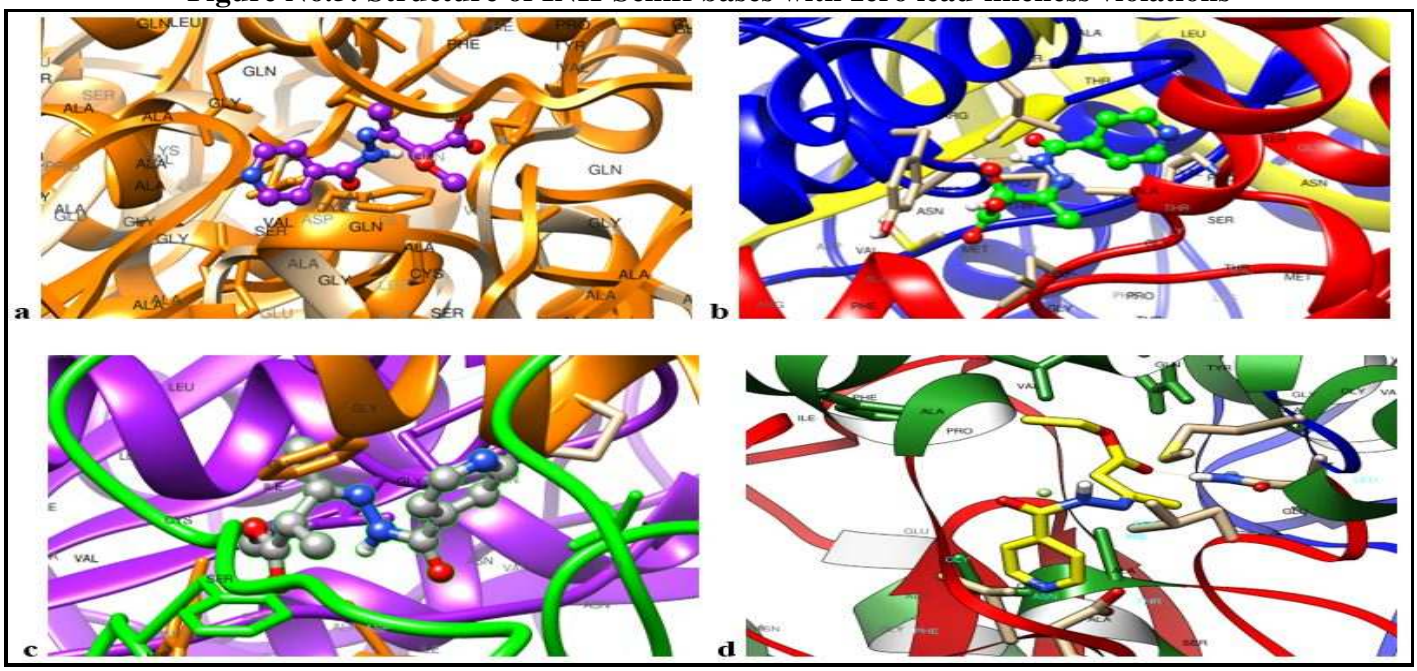


Figure No.6: Molecular docked models of selected INH-Schiff bases 8e (b), 8h (c), 8i (d), 9b (e) and 10h (g) positioned within the hydrophobic packet of MtKasB receptor

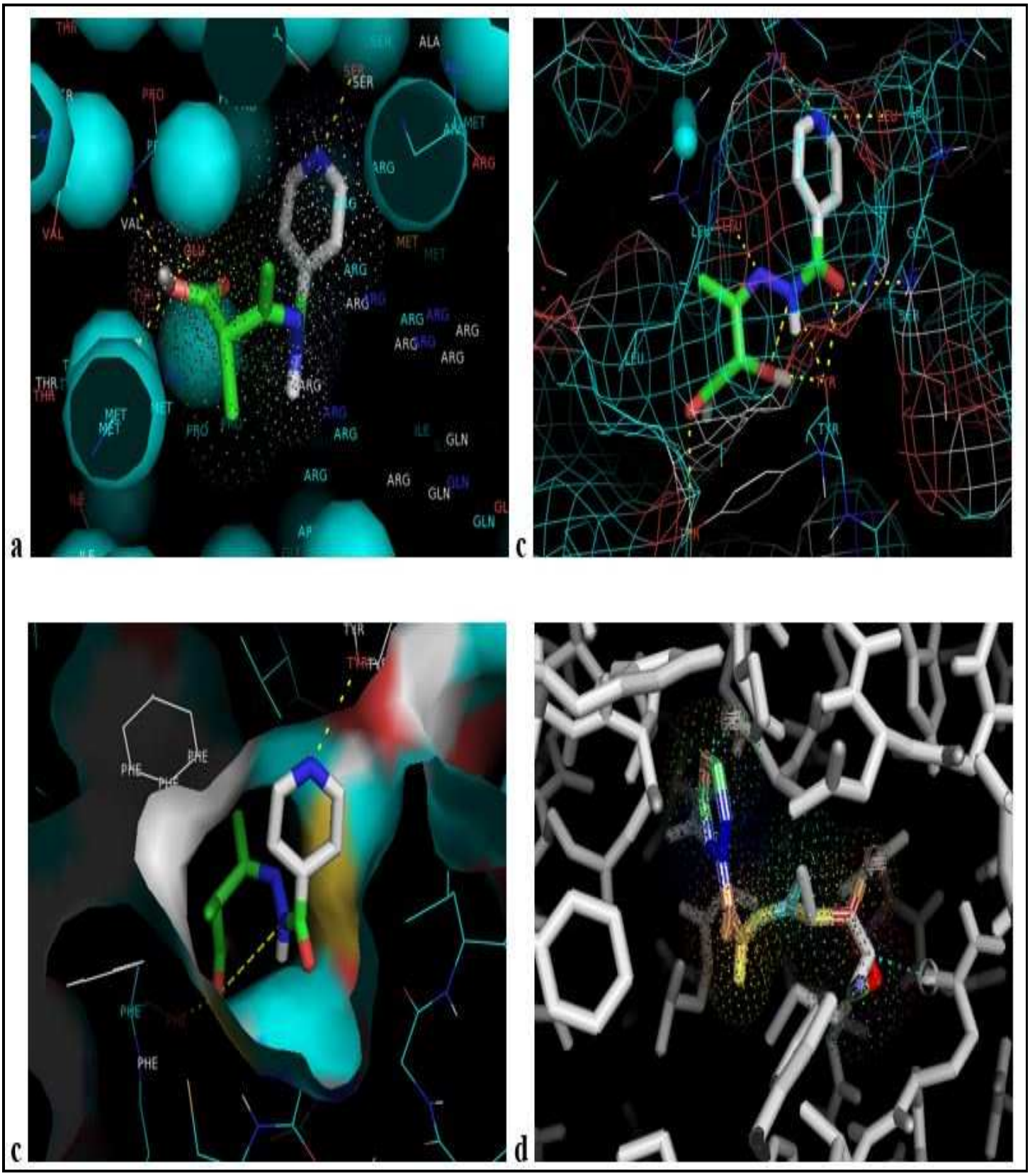


Figure No.7: Docking poses of the compounds 8h (a), 8i (b), 9b (c) and 10h (d)

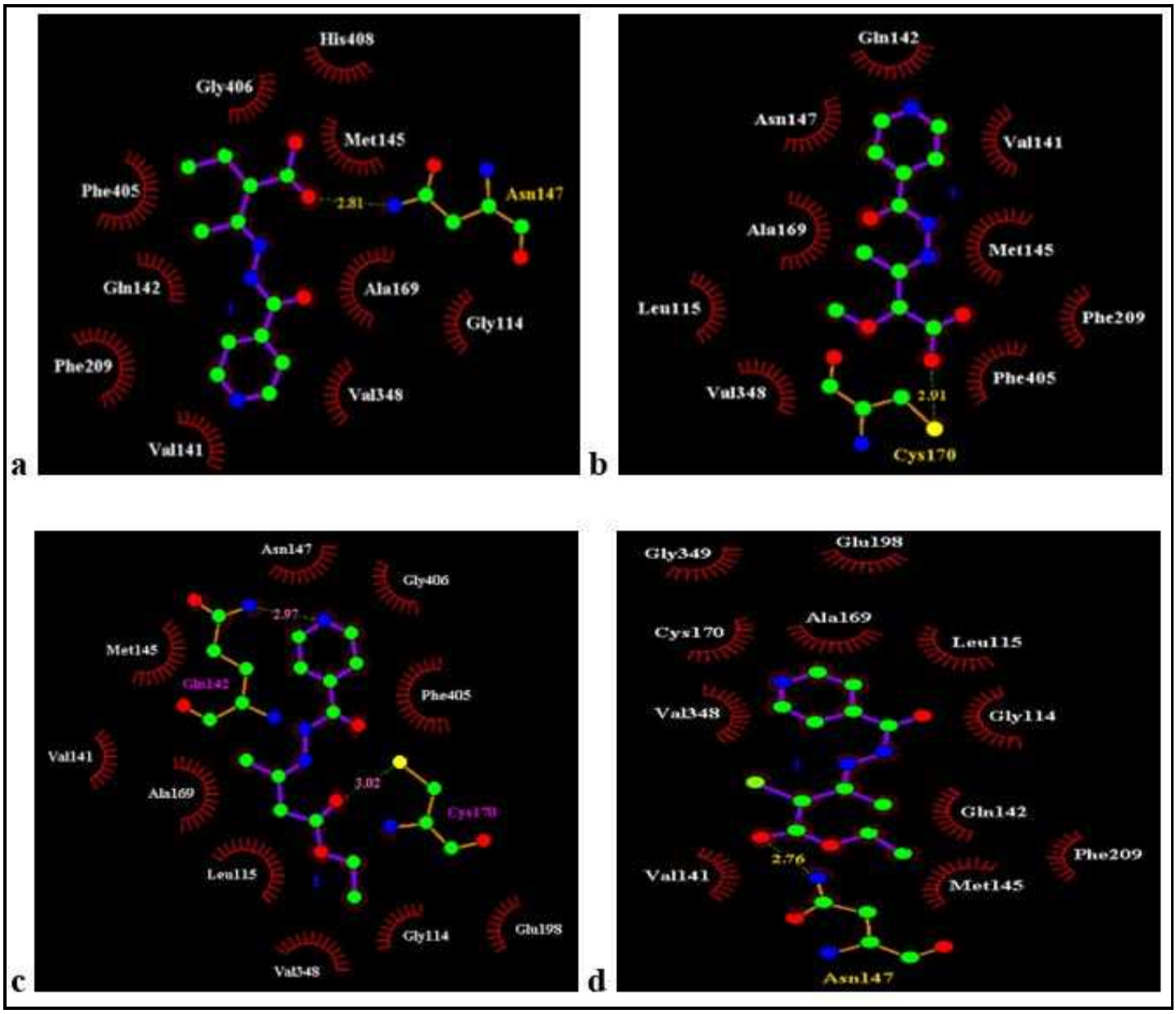


Figure No.8: Two-dimensional representation of H-bonding interactions of the compounds 8c (a), 8e (b), 10a (c) and 10h (d) with the targeting enzymes

CONCLUSION

A series of 99 INH-Schiff base derivatives is designed and subjected to *in-silico* assessment of ADME properties using Swiss ADME tool. The entire sets of compounds are polar with good to moderate water solubility and are therefore expected to have good oral absorption and bioavailability. The predicted gastro-intestinal absorption was displayed high and could assess the absence of toxicity at CNS level, due to non-permeation across the blood-brain barrier. All the newly designed molecules were predicted as non-inhibitors of isoenzyme CYP2D6 except the compounds 4g, 7d and 7g. A large number of the entries are found to be non-substrate for P-glycoprotein and they are non-inducers of phospholipidosis. The log P values of all designed Schiff base compounds were found to be optimal and hence, are predicted to have good permeability and oral absorption. None of the compounds

investigated has violated the Lipinski rule of five and the oral bioavailability is found to be universal. Among the series, 16 INH-Schiff bases showed zero lead-likeness violation and 35 entries with acceptable one violation and thus, satisfy the criteria for oral bioavailability. These 16 INH-Schiff bases with zero lead-likeness violation were further studied for molecular docking into the active site of the MtKasB receptor. Most of the docked compounds were found to possess good interaction deep inside the receptor sites and exhibited bonding and non-bonding interactions with the active residues of the receptor. The Schiff bases 8c, 8e, 8h, 8i, 9b, 10a and 10h displayed stronger binding affinity to the MtKasB and could act as a potent inhibitor against the organism. The proposed set of 7 INH-Schiff bases optimized by virtual ADME screening and molecular simulation methods may represent optimal choice of building blocks as better chemotherapeutic agent against *Mycobacterium tuberculosis*. This study, nevertheless could help the medicinal chemists to spotlight the focus on this chemical space towards the discovery of antimycobacterial drugs with elevated inhibitory potencies.

ACKNOWLEDGEMENT

The authors would like to thank and acknowledge the SIB - Swiss Institute of Bioinformatics (www.sib.swiss) and Chem Axon Ltd. (www.chemaxon.com) for providing computational resources.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Shabeer T K *et al*. Design, ADME profiling and molecular docking simulation of new isoniazid - schiff base analogs as MtKasB inhibitors, *Asian Journal of Research in Chemistry and Pharmaceutical Sciences,* 6(1), 2018, 20-34.