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Research Article

SYNTHESIS AND DOCKING STUDIES OF SCHIFF BASES DERIVED FROM 4-AMINOPYRIDINE

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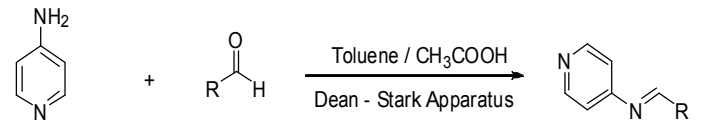
ABSTRACT
A Schiff base is a compound with a functional group that contains a carbon-nitrogen double bond with the nitrogen atom connected to aryl or alkyl group. In the present study, schiff bases were synthesized using 4-amino pyridine and different aldehydes, after assessing the drug likeliness properties. The structure of synthesised compounds were characterized by IR, NMR and Mass spectroscopic techniques. Docking studies were carried out for the schiff bases derived from 4-amino pyridine using Molegro Virtual Docker and protein beta-ketoacyl acyl carrier protein synthase II (mtKasB) enzyme was selected as the target for *M. tuberculosis*. The results of docking study was compared with the standard drug isoniazid and the significant results were obtained.
Key Words: Schiff Base, 4-aminopyridine, antitubercular agent, Lipinski's rule, docking

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*. It is the second leading cause of death from an infectious disease worldwide. India is among the twenty two high burden countries for incidence of TB.[1] The first line drugs involved in the treatment of TB are isoniazid, rifamycin (rifampin, rifapentine), pyrazinamide, ethambutol and streptomycin. The second line treatment for tuberculosis are ethionamide, cycloserine and capreomycin. But due to the multi-drug resistance developed by the bacillus these drugs are proved to be losing efficacy and re occurrence of the disease is seen in many cases. Schiff base derived from aromatic aldehydes have arouse the researchers interest because of its varied use in biological as antimicrobial[2,4] and antitubercular agent[3,4] analytical and inorganic field. It forms complexes with transition metals which have antibacterial, antiviral, anti-insecticidal and anti-tumor activities.[5,6] These complexes act as catalysts in various chemical reactions.[6] Since both nitrogen based heterocyclic ring system and schiff bases are useful in anti-tubercular activity combining both nitrogen heterocyclic ring and Schiff base could have a synergistic effect and help to overcome the resistivity problem of present antitubercular agents. Hence, an attempt was made to synthesise schiff bases from 4-aminopyridine.

Synthesis of schiff base



Scheme 1: Synthetic route for the preparation of Schiff base

4- Amino Pyridine — **1**
Aldehyde, R = Alkyl or Aryl — **2 a- j**
Schiff Base — **3 a-j** (10 Derivatives)

On review of literature, it has been observed that Abdel-Latif et al., have reported only one example from the proposed series i.e., schiff base derived from salicyladehyde and 4-aminopyridine and it was futher used for the preparation of complexes with various metals.[7]

EXPERIMENTAL

Drug Likeliness

Druglikeness may be defined as a complex balance of various molecular properties and structure features which determine whether particular molecule is similar to the known drugs.[8] These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and of course presence of various pharmacophoric features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others. One of the criteria that a molecule should possess to have drug like properties is to follow Lipinski Rule of Five. According to this rule a molecule should have following characteristics: (Table 1)
In the online tool of Molsoft[9,10] the structures of the Schiff bases were drawn and the drug likeness and molecular properties were calculated.

4-amino pyridine **1** and aldehydes **2a-j** (Table 2) were taken in equimolar concentration and dissolved in toluene. To this catalytic amount of glacial acetic acid was added. The mixture was refluxed under Dean Stark conditions till the complete utilisation of the reactants. The progress of the reaction was monitored by TLC using ethylactetate and chloroform (4:6) as solvent system.
After the completion of the reaction the solvent was distilled off. The crude sample was purified by column chromatography using Pet. ether and ethylacetate as the

solvent system. The purified compounds were characterized by FT-IR, ^{1}H NMR and Mass Spectroscopic techniques.

Docking studies

Docking is a method which predicts the preferred orientation of a molecule to a protein target in order to predict the affinity and activity of the small molecule towards the target. The PDB format of the protein beta-ketoacyl acyl carrier protein synthase II (mtKasB) enzyme (PDB ID- 2GP6) was downloaded from protein data bank.[11] Molegro Virtual Docker was the tool used for docking. The protein was imported in the work space and water molecules were removed. Cavities were detected and depending on this, particular constraint was created, within which docking takes place. The ligand was imported and docking was done by selecting various standard parameters.

Table 1: PARAMETERS OF LIPINSKI RULE OF FIVE

Molecular weight	Less than equal to 500 daltons
Hydrogen bond donor	Less than equal to 5
Hydrogen bond acceptor	Less than equal to 10
cLogP	Less than equal to 5

Table 2:THE ALDEHYDES USED FOR SYNTHESIS

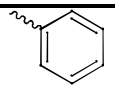
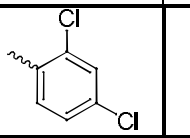
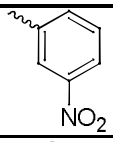
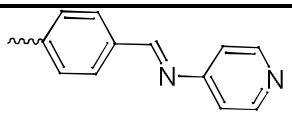
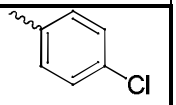
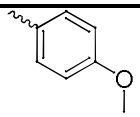
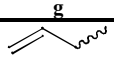
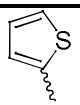
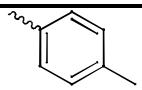
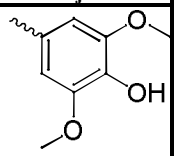
Compound	**a**	**b**	**c**	**d**	**e**
R					
Compound	**f**	**g**	**h**	**i**	**j**
R					

Table 3: RESULTS OF LIPINSKI RULE OF FIVE

Schiff base	Mol weight	HBA	HBD	clogP	Drug likeliness
3a	182.08	2	0	2.01	-1.05
3b	250.01	2	0	3.59	**0.26**
3c	227.07	4	0	2.01	-1.15
3d	286.12	4	0	2.15	-0.74
3e	216.05	2	0	2.7	-0.66
3f	212.09	3	0	2.06	-0.72
3g	146.08	2	0	1.58	-1.16
3h	188.04	3	0	1.69	-1.00
3i	196.10	2	0	2.47	-1.16
3j	258.10	5	1	1.67	**-0.46**

TABLE 4: PHYSICAL DATA OF SYNTHESIZED COMPOUNDS

Compound	Molecular formula	Mol. Weight	Color	% Yield	M.P. (°C)
3a	$C_{12}H_{10}N_2$	182	Pale white	65%	55-60
3b	$C_{12}H_8N_2Cl_2$	250	Brown	54%	45-50
3c	$C_{12}H_9N_3O_2$	227	Yellow	77%	70-75
3d	$C_{13}H_{10}N_2O$	210	Light yellow	78%	70-75
3e	$C_{12}H_9ClN_2$	217	Light yellow	71%	70-75
3f	$C_{13}H_{12}N_2O$	212	Light yellow	63%	130
3g	$C_9H_{10}N_2$	146	Yellow	69%	103
3h	$C_{10}H_8N_2S$	188	Light yellow	81%	117-120
3i	$C_{13}H_{12}N_2$	196	Light yellow	88%	100-105
3j	$C_{14}H_{14}N_2O_3$	258	Yellow	46%	75-85

TABLE 5: DOCKING SCORES

Compound	Docking_Score
Isoniazid	-40.57
3a	-51.8335
3b	-59.9791
3c	-66.5138
3d	**-67.5261**
3e	-66.3002
3f	-65.0913
3g	-58.6932
3h	-64.7491
3i	-64.6875
3j	-53.6883

RESULTS AND DISCUSSION

Drug Likeliness

The proposed Schiff bases fulfill the Lipinski rule of five (Table 3) and for instance, clogP value of the compounds ranging from 1.67 to 3.59, which are less than 5. Hence, it is anticipated that they may possess drug like property.

It has been observed that the compounds **3b**, **3j** showed relatively good drug likeliness score value and hence drug like properties. Further, all the proposed molecules were synthesized and docking study was carried out.

Physico Chemical Parameters of Compounds

Melting points, percentage yield of the synthesised compounds were measured and reported in Table 4.

Spectral Data

2, 6-dimethoxy-3-[(pyridin-4-ylimino)methyl]phenol (3j)

Yellow solid; Yield 46%; M.P. 75-85˚C; **IR (KBr)** 1672.28 (C=N), 3284.77 (OH), 1537.42 (C=C ring stretch), 1332.81(C-O); **^{1}H NMR** (400MHz, $CDCl_3$) δ 7.43, 7.1282 (Ar-H, s), 6.45- 6.46 (PyH, d, *J*=5.12Hz), 8.3114 (N=CH-Ar, s), 3.94-3.94 (O-CH_3-Ar, s); **MS** m/z= calculated=258.2; observed=257.2

***N*-(pyridin-4-yl)but-2-en-1-imine (3g)**

Yellow solid; Yield 71%; M.P. 103˚C; **IR (KBr)** 1616.35 (C=N), 1566.20 (C=C ring stretch); **^{1}H NMR** (400MHz, $CDCl_3$) δ 7.89-6.98 (Ar-H), 8.32 - 8.31 (N=CH, d, *J*=4.4Hz), 2.37 (C-CH_3, s).

1-(4-chlorophenyl)-*N*-(pyridin-4-yl)methanimine (3e)

Light yellow solid; Yield 71%; M.P. 70-75˚C; **IR (KBr)** 771.53 (C-Cl), 1602.85 (C=N)

***N*-(pyridin-4-yl)-1-(thiophen-2-yl)methanimine (3h)**

Light yellow solid; Yield 81%; M.P. 117-120˚C; **IR (KBr)** 1600.92 (C=N), 3002.13 (C-H stretch), 1504.48 (C=C ring stretch)

Docking Score

According to the docking studies, the best docking score was obtained for the ligand **3d** (Table 5). Further, it is noteworthy that all the synthesised compounds have showed better docking score when compared to standard drug Isoniazid.

CONCLUSION

The objective of this work was to synthesize Schiff bases derived from 4-amino pyridine using various aldehydes. The proposed Schiff bases were first evaluated for drug likeliness. When it was confirmed that the molecules possess drug likeliness they were synthesized using toluene as solvent and under Dean Stark conditions. The structure of the purified products was confirmed by characterization by FT-IR, ^{1}H NMR and Mass spectroscopic techniques. In docking studies it was observed that **3d** showed the best docking score. Hence, the results showed that Schiff bases derived from 4-amino pyridine have the ability to act as antitubercular drug and in future invitro screening will be done to validate the in silico results.

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REFERENCES

1. WHO Report 2011- Global Tuberculosis Control Available from - http://www.who.int/tb/publications/global_report/en/ [cited 2012 Apr 12].
2. Aysen, D. M., Birol, O., Bedrettin, M.; Synthesis and antibacterial activity of schiff base derivatives, *Int. J. Drug. Dev. Res.,* 2010, 2(1), 102-107.
3. Rajasekaran, A., Periasamy, M., Venkatesan, S.; Synthesis, characterization and biological activity of some novel azetidinones, *J. Dev. Biol. Tissue Eng.,* 2010, 2(1), 5-13.
4. Ilango, K., Arunkumar, S.; Synthesis, Antimicrobial and Antitubercular Activities of Some Novel Trihydroxy Benzamido Azetidin-2-one Derivatives, *Trop. J. Pharm. Res.,* 2011, 10 (2), 227-232.
5. Nath, P., Dhumwad, S. D.; Synthesis, Characterization and Antimicrobial studies of Co(II), Ni(II), Cu(II) and Zn(II) complexes derived from a Schiff base of 2-[(4-Methyl-2-oxo-*2H*chromen-7-yl)oxy]acetohydrazide with 3-formyl-2-hydroxy quinoline and 3-formyl-2-mercapto quinoline, *J. Chem. Pharm. Res.,* 2012, 4(1), 851-865.
6. Kumar, S., Dhar, D. N., Saxena, P.N.; Applications of metal complexes of Schiff bases-A review, *J. Sci. Ind. Res.,* 2009, 68, 181-187.
7. Abdel-Latif, S. A., Hassib, H. B., Issa, Y. M.; Studies on some salicylaldehyde Schiff base derivatives and their complexes with Cr(III), Mn(II), Fe(III), Ni(II) and Cu(II), *Spectrochim. Acta A: Mol. Biomol. Spectroscopy*, 2007, 67(3-4), 950-957.
8. Nagalakshmi, G., Maity, T. K., Maiti B. C; Synthesis, Characterization and Antiproliferative Activity of Some Novel 2-(substitutedphenyl)-5-methyl-3-(pyridin-4-yl)-1,3-thiazolidin-4-ones, *Int. J. Pharm. Tech. Res.*, 2011, 3(2), 707-718.
9. http://www.molinspiration.com [cited 2012 Apr 12].
10. http://www.molsoft.com [cited 2012 Apr 12].
11. http://www.rcsb.org/pdb/explore/explore.do?structureId=2GP6 [cited 2012 Apr 12].

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