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Identification of Antimycobacterial Lead Molecules through *In Silico* Screening of Molecular Properties and Bioactivity Score of Imidazopyridines

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ABSTRACT

In silico studies were conducted on 6-chloro-1H-imidazo[4,5-b]pyridine derivatives to select the best possible drug candidates based on drug properties and bioactivity score of the compounds. 6-chloro-1H-imidazo[4,5-b]pyridine derivatives were subjected to predict bioactivity prediction and drug likeness score on the basis of Lipinski's rule through molinspiration cheminformatics software. Isoniazid was used as reference standard for comparing the molecular properties and bioactivity score. The results of new 6-chloro-1H-imidazo[4,5-b]pyridine derivatives were compared with Isoniazid to check the prospective of the optimized compounds. The best possible drug candidates were reported after comprehensive analysis on predicted cLogP, solubility, molecular weight, Topological Molecular Polar Surface Area (TPSA), drug-likeness, drug score properties and bioactivity score for different targets like G-protein-coupled Receptors (GPCR), ion channel, kinase, nuclear receptor, protease and enzymes. All the derivatives are found to be biologically important molecules with desirable molecular properties for drug likeness and possess good enzyme inhibitor activity. Thus these derivatives are considered to the best drug candidates for inhibition of mycobacterium tuberculosis synthetase. All the derivatives have not found to violate Lipinsiki's rule and shows significant bioactivity score when comparing to isoniazid. Thus these derivatives have emerged as a promising anti-tuberculosis lead molecule.

Keywords: 6-Chloro-1H-imidazo[4,5-b]pyridine derivatives, Bioactivity score, Antituberculosis, Molinspiration

INTRODUCTION

Tuberculosis (TB), a disease caused by *Mycobacterium tuberculosis* kills around 1.7 million people every year despite the availability of effective chemotherapy for more than half a century [1]. The emergence of Multiple Drug-resistant (MDR), Extensive Drug-Resistant (XDR) strains, and its association with HIV has severely affected the fight against TB [2]. *M. tuberculosis* glutamine synthetase, a key enzyme required for nitrogen metabolism and mycobacterial cell-wall biosynthesis, has emerged as a potential target for *M. tuberculosis* [3-6].

Lead compounds play an essential role in drug design and development as it possesses the desired pharmacological properties. The computational studies are being applied to select the possible best lead candidates based on the assessments of various important drug-relevant and biological properties of compounds through *in silico* methods to reduce the failure rate during the drug discovery process [7]. Oral bioavailability is considered as an important parameter for the development of highly effective therapeutic agents.

Certain properties of the lead compound should be taken into consideration such as Lipinski's rule of five. According to Lipinski's ''rule of five'', a candidate molecule is more likely to have good membrane permeability i.e. orally active, if the molecular weight is under 500 g/mol, the partition coefficient (log P) is less than 5, there are not more than 5 hydrogen bond donors (OH and NH groups), there are not more than 10 hydrogen bond acceptors (notably N and O) and number of violation less than 4 [8].

Pyridine is found to be very versatile molecule and have a large number of biological activities including antiviral, anticancer, antimicrobial, antidiabetic, antitubercular as well as newer biological activities such as antidote, antileishmanial, antioxidant, antichagasic, antithrombin, and anticoagulant along with most of the traditional biological activities were also reported [9]. In order to select the best drug candidates for anti-tuberculosis to inhibit the mycobacterial gluthamine synthethase enzyme, the 6-chloro-1H-imidazo[4,5-b]pyridine derivatives were designed to predict drug properties and bioactivity score using Molinspiration tools.

MATERIALS AND METHODS

The structures of 6-chloro-1H-imidazo[4,5-b]pyridine derivatives were selected from the literature M. Taha et al. They were drawn using online Molinspiration software for the calculation of molecular properties and bioactivity scores. The molecular properties and bio-activity scores of the all the twenty five compounds were compared with Isoniazid, to identify the potential lead compounds.

The predicted results were compared with the results of isoniazid to interpret the effectiveness of the compounds. Isoniazid (INH), also known as isonicotinyl hydrazine, is an organic compound used as a first-line drug in the prevention and treatment of TB. It has a simple structure containing two essential components required for the high inhibiting activity i.e., a pyridine ring and a hydrazide group [10].

Molecular property

Molecular properties such as s MiLogP, Total Polar Surface Area (TPSA), number of hydrogen bond donors and acceptors, molecular weight, number of atoms, number of rotatable bonds etc., of 6-chloro-1H-imidazo[4,5-b]pyridine derivatives were calculated using molinspiration tools. The values were given in Table 1. LogP measure molecular hydrophobicity, which affects drug absorption, bioavailability, drug-receptor interactions, metabolism of molecules, as well as their toxicity [11].

TPSA characterizes the transport properties of a drug such as intestinal absorption, bioavailability, blood brain barrier penetration etc. TPSA of drug molecules is <160 Å. Number of rotatable bonds is a simple topological parameter that measures molecular flexibility and is considered to be a good descriptor of oral bioavailability of drugs [12,13].

Table 1: Molecular property of 6-chloro-1H-imidazo[4,5-b]pyridine derivatives

Compound ID	Compound name	MiLogP	TPSA	N atoms	Molecular weight	n ON	nO HNH	N violations	nrotb	volume
1A	4-(6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)benzene-1,2-diol	2.50	82.03	18	261.67	5	3	0	1	205.69
2A	4-(6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)benzene-1,3-diol	2.70	82.03	18	261.67	5	3	0	1	205.69
3A	3-(6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)benzene-1,2-diol	2.71	82.03	18	261.67	5	3	0	1	205.69
4A	3-(6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)phenol	2.97	61.80	17	245.67	4	2	0	1	197.67
5A	2-(6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)-4-methoxyphenol	3.23	71.04	19	275.69	5	2	0	2	223.22
6A	2-(6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)phenol	3.20	61.80	17	245.67	4	2	0	1	197.67
7A	4-(6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)phenol	2.99	61.80	17	245.67	4	2	0	1	197.67
8A	6-chloro-2-(pyridin-4-yl)-1H-imidazo[4,5-b]pyridine	2.18	54.47	16	230.66	4	1	0	1	185.50
9A	6-chloro-2-(3-chlorophenyl)-1H-imidazo[4,5-b]pyridine	4.12	41.58	17	264.12	3	1	0	1	203.19
10A	6-chloro-2-(2-chlorophenyl)-1H-imidazo[4,5-b]pyridine	4.10	41.58	17	264.12	3	1	0	1	203.19
11A	6-chloro-2-(4-chlorophenyl)-1H-imidazo[4,5-b]pyridine	4.15	41.58	17	264.12	3	1	0	1	203.19
12A	2-(6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)-5-methoxyphenol	3.23	71.04	19	275.69	5	2	0	2	223.22
13A	6-chloro-2-(pyridin-2-yl)-1H-imidazo[4,5-b]pyridine	2.32	54.47	16	230.66	4	1	0	1	185.50
14A	6-chloro-2-(pyridin-3-yl)-1H-imidazo[4,5-b]pyridine	2.40	54.47	16	230.66	4	1	0	1	185.50
15A	6-chloro-2-(3-fluorophenyl)-1H-imidazo[4,5-b]pyridine	3.61	41.58	17	247.66	3	1	0	1	194.58
16A	6-chloro-2-(2-fluorophenyl)-1H-imidazo[4,5-b]pyridine	3.58	41.58	17	247.66	3	1	0	1	194.58
17A	6-chloro-2-(2-methylphenyl)-1H-imidazo[4,5-b]pyridine	3.87	41.58	17	243.70	3	1	0	1	206.21
18A	6-chloro-2-(4-methylphenyl)-1H-imidazo[4,5-b]pyridine	3.92	41.58	17	243.70	3	1	0	1	206.21
19A	6-chloro-2-(3-methylphenyl)-1H-imidazo[4,5-b]pyridine	3.89	41.58	17	243.70	3	1	0	1	206.21
20A	6-chloro-2-(4-nitrophenyl)-1H-imidazo[4,5-b]pyridine	3.43	87.40	19	274.67	6	1	0	2	212.99
21A	6-chloro-2-(3-nitrophenyl)-1H-imidazo[4,5-b]pyridine	3.40	87.40	19	274.67	6	1	0	2	212.99
22A	6-chloro-2-(4-fluorophenyl)-1H-imidazo[4,5-b]pyridine	3.63	41.58	17	247.66	3	1	0	1	194.58
23A	6-chloro-2-(3,4-dimethoxyphenyl)-1H-imidazo[4,5-b]pyridine	3.12	60.04	20	289.72	5	1	0	3	240.74
24A	6-chloro-2-(2,6-dimethoxyphenyl)-1H-imidazo[4,5-b]pyridine	3.49	60.04	20	289.72	5	1	0	3	240.74
25A	6-chloro-2-(3-methoxyphenyl)-1H-imidazo[4,5-b]pyridine	3.50	50.81	18	259.70	4	1	0	2	215.20
Standard	Isoniazid	-0.97	68.01	10	137.14	4	3	0	1	122.56

Table 2: Bioactivity scores of the 6-chloro-1H-imidazo[4,5-b]pyridine derivatives

Compound ID	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1A	0.21	0.27	0.44	-0.65	-0.36	0.42
2A	0.20	0.19	0.39	**-0.61**	-0.36	0.40
3A	0.25	0.14	0.39	-0.79	**-0.26**	0.47
4A	0.18	0.29	0.41	-0.70	-0.42	0.41
5A	0.14	0.08	0.35	-0.66	-0.37	0.33
6A	0.12	0.18	0.30	-0.82	-0.43	0.37
7A	0.18	0.29	0.37	-0.71	-0.40	0.40
8A	0.10	0.28	0.40	-1.09	-0.49	0.35
9A	0.12	0.21	0.30	-0.91	-0.46	0.32
10A	0.16	0.15	0.32	-0.88	-0.42	0.29
11A	0.12	0.22	0.29	-0.93	-0.44	0.31
12A	0.15	0.07	0.34	-0.63	-0.36	0.32
13A	0.28	0.48	0.56	-1.17	-0.29	0.52
14A	0.12	0.30	0.45	-1.09	-0.46	0.40
15A	0.17	0.22	0.39	-0.83	-0.43	0.31
16A	0.15	0.30	0.39	-1.03	-0.48	0.30
17A	0.13	0.12	0.34	-0.89	-0.49	0.28
18A	0.06	0.11	0.24	-0.95	-0.51	0.23
19A	0.09	0.13	0.28	-0.90	-0.47	0.26
20A	0.00	0.13	0.19	-0.85	-0.47	0.18
21A	0.01	0.12	0.23	-0.84	-0.47	0.20
22A	0.13	0.20	0.36	-0.88	-0.46	0.30
23A	0.16	0.09	0.41	-0.67	-0.33	0.28
24A	0.27	0.11	0.37	-0.61	-0.28	0.36
25A	0.10	0.11	0.33	-0.81	-0.44	0.27
Standard	-1.39	-1.45	-1.05	-2.33	-1.23	-0.66

Bio-activity scores

The bioactivity scores of all derivatives towards G-protein-coupled Receptors (GPCR) ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitors were given in Table 2. Bioactivity of the compounds was decided based on the bioactivity score. If bioactivity score is >0, it is an active compound while <-5.0 is an inactive compound and range between -5.0-0.0 is moderately active compounds [14].

RESULTS AND DISCUSSION

Molecular property of the 6-chloro-1H-imidazo[4,5-b]pyridine derivatives

All the twenty five 6-chloro-1H-imidazo[4,5-b]pyridine derivatives obeyed the Lipinski's rule of five and showed good drug likeness scores. MiLogP values of these compounds were found to be <5 which lies in range of 2.18-4.15 indicated their good permeability across the cell membrane. Drug likeness property was found to be higher in compound 8A (MiLog P 2.18) than other compounds.

All the compounds were found to have TPSA in range of 41.58-87.40 which is well below 160$\AA^2$ and their molecular weight were less than 500. Number of hydrogen bond donors (<5), hydrogen bond acceptors (<10), were found to be within Lipinski`s limit. All the screened compounds were flexible (<5 rotatable bonds) and found to have and n-violations=0.b).

Bioactivity scores of the 6-chloro-1H-imidazo[4,5-b]pyridine derivatives

For different human receptors GPCR, ion channel, kinase, nuclear receptor, protease and enzymes bioactivity scores were calculated for the reference compound and new compounds. The bioactivity scores of the twenty five 6-chloro-1H-imidazo[4,5-b]pyridine derivatives compounds revealed that all the compounds were found to be highly bioactive (>0) towards GPCR ligands, ion channel modulator, kinase inhibitor and enzyme inhibitor compared to Isoniazid. Since these compounds are active as enzyme inhibitor, therefore it is believed that these drug candidates able to inhibit the *M. tuberculosis* gluthamine synthetase.

The most promising compound was identified as 13A for which bioactivity score of 0.28, 0.48, 0.56 and 0.52 was obtained for GPCR ligands, ion channel modulator, kinase inhibitor and enzyme inhibitor respectively. The nuclear receptor ligand and protease inhibitor property for all the compounds were found to be moderately active (<0). Among the moderately active compounds, compound 2A has the highest value (-0.61) for nuclear activity whereas compound 3A (-0.26) for protease inhibitor.

CONCLUSION

It can be concluded that all the derivatives are biologically important molecules with desirable molecular properties for drug likeness and possess significant enzyme inhibitor activity. Therefore the entire derivatives are considered to be the best drug candidates for inhibiting *M. tuberculosis* synthetase. Compound 13A, 6-chloro-2-(pyridin-2-yl)-1H-imidazo[4,5-b]pyridine has emerged as most promising anti-tuberculosis lead molecule, as it shows higher bioactivity score in comparison to standard drug isoniazid.

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