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Synthesis, characterization, drug likeliness and biological activity of imidazopyridine derivatives as anti-tubercular agents

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Tuberculosis is a global threat that is in urgent need for new molecules. In the same perspective, Imidazopyridine derivatives have been synthesized against target ATP synthase. It is an important enzyme that provides energy for the cell to use through the synthesis of adenosine triphosphate (ATP). ATP is the most commonly used "energy currency" of cells from most organisms. Bedaquiline that primarily targets ATP now is most effective in treatment of tuberculosis. All synthesized molecules pass Lipinski rule of 5 and are non-substrate of CYP450 enzymes. They didn't portray significant anti-tubercular activity.

Keywords: Tuberculosis, imidazopyridine, ATP synthase, Lipinski rule of 5, ADME-T

Tuberculosis (TB) is one of the deadliest diseases in the world. *Mycobacterium tuberculosis* or Koch Bacillus, an obligate aerobic bacterium responsible for Tuberculosis in humans (TB)[1]. Other causative agent in this *M. tuberculosis* complex are *M. bovis*, *M. africanum*, *M. canetti* and *M. microti*[2]. The current chemotherapy regimen advised by WHO for drug-susceptible TB consists of a 2 month intensive phase, constituting four drugs administration (isoniazid, pyrazinamide, rifampicin and ethambutol), followed by a continuous phase of 4 months treatment with two drugs (commonly isoniazid and rifampicin) to which the *Mycobacterium tuberculosis* isolate had shown *in vitro* susceptibility during the intensive phase[3]. This disease has taken a new shape, more dreadful then previous by its resistance towards conventional drugs *i.e*. isoniazid and rifampicin in shape of Multi drug resistant tuberculosis (MDR-TB) and also with Extensive drug resistant tuberculosis (XDR-TB) which have resistance toward at least three of the six classes of second-line antituberculosis drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine and *para*-aminosalycilic acid)[4]. To combat MDR-TB and XDR-TB and to rapidly changing breakneck form of TB *i.e*. totally or extremely drug resistant TB (XXDR-TB) new agents from different classes came forward. In XXDR-TB, patients are resistant not only to first line drugs but also for second line of drugs[5].

These enzymes are membrane proteins that perform energetically various processes like folding and degrading proteins, the initiation of replication, DNA repair, and the transport of substances. This can be effective therapeutic target because the gene expression profiles of the P-type ATPases in Mtb facing toxic substances and under both latent infection and active disease, their roles in virulence and their structural divergence from human P-type ATPases[6]. An enzyme holing a key role in growth of *Mycobacterium tuberculosis*, utilized both by fermentable and non-fermentable carbon sources[8]. The ATP production involves energy stored in a transmembrane electrochemical potential difference of a coupling ion[9].

Structurally, the mycobacterial F0F1-ATPase comprises of F0 (membrane embedded) portion with a1b2c10–15 subunits and a F1 (hydrophilic) portion consisting of a3b3de[7]. Proton (H^+) migration through F0 triggers the rotation of rotary ring formed by oligomeric subunits 'c' which is coupled to the rotation of the 'c' subunit resided within the (ab)3 hexamer of F1.

In the present work we synthesized, characterized and evaluated various analogues of Imidazopyridine as antitubercular agents.

Results and Discussion

Chemistry

Imidazopyridine scaffold is known for its action on different diseases like Necopidem in Anxiolytics,

Bamaluzole in Anticonvulsant, Fadrozole in Breast cancer and many more (Table I). This scaffold also proven its efficiency in combating tuberculosis with its derivative Q203[11,15]. This derivative is currently under clinical trial. Its novel mode of action is through blocking ATP production involved in the energy metabolism of *M. tuberculosis*[10]. This scheme includes one pot two step reaction (GBBR and post cyclisation) (Scheme I).

Groebke-Blackburn-Bienaymé multicomponent reaction

It is a Multi Component Reaction involving 3 components *viz*., Amino pyridine, Aldehydes and 1-(2,2-dimethoxyethyl)-2-isocyanobenzene which was refluxed in dioxane. The above reaction mixture was then undergone post cyclization using TFA and DCM[12-14] (Scheme II).

Anti-Tubercular Activity

The synthesized compounds shown marginal activity towards ATP synthase. Compound 3-(1*H*-indol-1-yl)-2-(4-(methylthio)phenyl)imidazo[1,2-a]pyridine shown better activity among synthesized derivatives. It is observed that 2-(3-fluorophenyl)-3-(1*H*-indol-1-yl)imidazo[1,2-a]pyridine and 3-(1*H*-indol-1-yl)-2-(3-methoxyphenyl)imidazo[1,2-a]pyridine containing Fluoro and methoxy substitution on third position are effective anti-mycobacterial agents (Table II).

Drug Likeliness

Imdazopyridine derivatives were determined for Lipinski rule of 5. All molecules obey Lipinski rule of five. All derivatives have Mol.wt. less than 500, Hydrogen bond donor less than 5, Hydrogen bond Acceptor less than 10. Among the derivatives only compound 3-(1*H*-indol-1-yl)-2-(naphthalen-1-yl) imidazo [1,2-a]pyridine have log p value greater than 5.

ADME-T

The predicted Human intestinal absorption (HIA) for all compounds was greater than 95%. The compounds were found to be an inhibitor of CYP2C19, and CYP3A4 and non-substrate of CYP2D6. Moderate plasma protein binding was observed in the case of all the selected molecules.

The rodent carcinogenicity model based on data of the National Toxicology Program and US FDA of mice and rats for two years was used to predict the carcinogenicity.

Experimental Section

General Methods

Step-1: **Groebke-Blackburn-Bienaymé multicompo nent reaction**

To the solution of 2-aminopyridine (1.17 mmol) in dioxane, were added various substituted aldehydes (1.17 mmol), 1-(2,2-dimethoxyethyl)-2-isocyano benzene (0.78 mmol) and a catalytic amount of $ZnCl_2$ (5 mol%). The reaction mixture was refluxed for 5-6 hrs and the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, reaction mixture was cooled to room temperature, solvent was evaporated in rotavapour and without further purification put for next step.

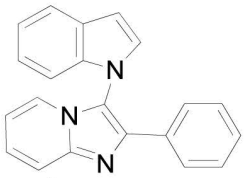
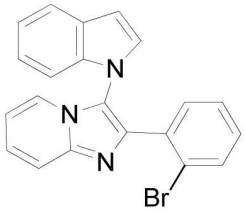
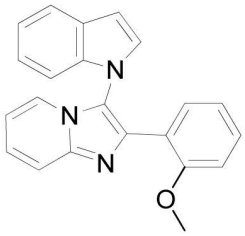
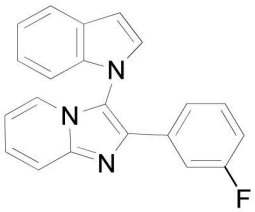
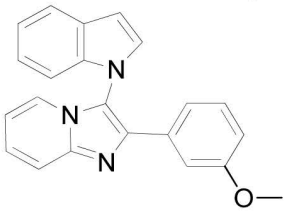
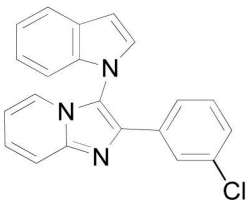
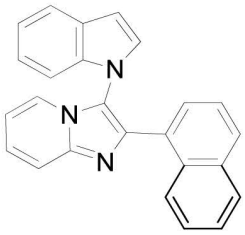
Step-2: **Post cyclisation (Indole formation)**

Dissolve the above reaction mixture in DCM and stirred at 0°C. TFA: DCM (1:1) was then added slowly at 0°C and allowed to stir for 4-5 hrs. After completion of the reaction, TFA was evaporated under vacuum, added 100 mL of water then extracted with DCM (3 X 100 mL) and washed with $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated under vacuum and the column chromatography of crude product over silica gel furnished title compounds.

3-(1*H*-Indol-1-yl)-2-phenyl imidazo[1,2-a]pyridine, 4a [$C_{21}H_{15}N_3$], No. of H 15: Solid (brown). m.p.161ºC. Yield 61%. R_f = 0.4 (40% Ethyl Acetate/ Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (2H, d, J = 1.32 Hz), 7.73-7.68 (2H, m), 7.36 (2H, t, J = 7.45 Hz), 7.29-7.19 (4H, m), 7.02-6.97 (2H, m), 6.88-6.84 (1H, m), 6.75-6.72 (1H, m), 6.23 (1H, d, J = 8.30 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.6, 139.2, 132.0, 128.6, 128.4, 127.7, 127.0, 124.9, 123.5, 122.7, 120.2, 119.1, 117.4, 114.0, 113.5, 112.1, 106.6; HRMS (ESI): MH^+ found 310.1337 requires 310.1339.

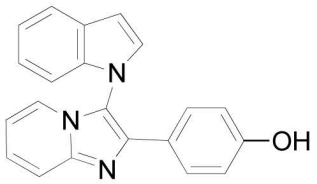
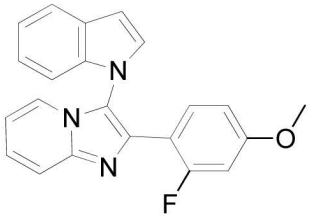
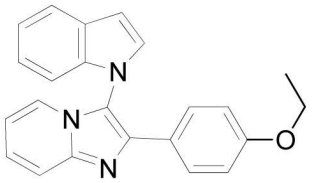
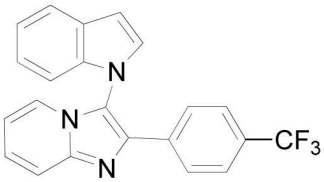
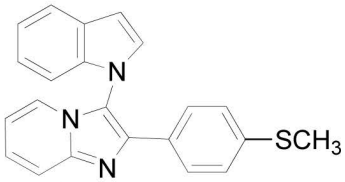
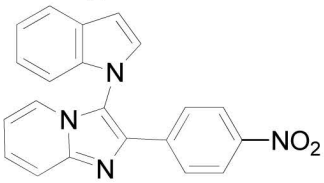
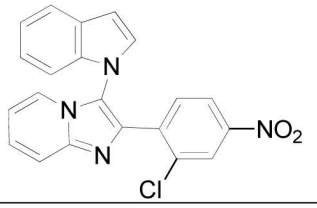
2-(2-Bromophenyl)-3-(1*H*-indol-1-yl)imidazo [1,2-a]pyridine, 4b [$C_{21}H_{14}BrN_3$], No. of H 14: Solid (Light brown). m.p.128ºC. Yield 65%. R_f = 0.42 (40% Ethyl Acetate/ Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (1H,d,J = 9.16hz), 7.67-7.65 (1H, m), 7.53 (1H, dd, J_1= 1.06 Hz, J_2=7.98 Hz), 7.48-7.46 (1H, m), 7.40-7.38 (1H, dd, J_1=1.72 Hz, J_2=7.64 Hz), 7.31 (1H, dd, J_1=1.72hz, J_2=7.64Hz), 7.31-7.27 (1H, m), 7.23-

Table I — List of compounds synthesized

Compd	Compd Structure	Time	Yield (%)	Lipinski rule of 5			
				Mol. wt.	Log P	HBD	HBA
4a		4 h	61	309.36	4.034	0	0
4b		4 h 30 min	65	388.26	4.823	0	0
4c		4 h 20 min	63	339.39	3.949	0	1
4d		4 h 30 min	62	327.35	4.195	0	1
4e		5 h 30 min	60	339.39	3.949	0	1
4f		5 h 10 min	65	343.80	4.656	0	0
4g		5 h 20 min	62	359.42	5.300	0	0

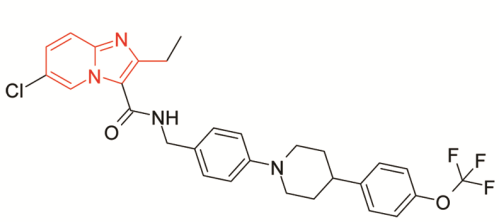
(*contd.*)

Table I — List of compounds synthesized (*contd.*)

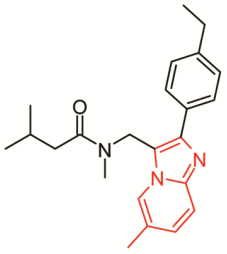
Compd	Compd Structure	Time	Yield (%)	Lipinski rule of 5	Compd	Compd Structure	Time
4h		4 h 15 min	63	327.38	3.894	1	3
4i		4 h 40 min	64	359.40	4.376	0	4
4j		4 h 35 min	64	353.42	4.646	0	1
4k		5 h 15 min	60	377.36	4.959	0	3
4l		4 h 30 min	65	355.46	4.776	0	0
4m		5 h 15 min	61	354.36	3.574	0	2
4n		4 h 15 min	65	388.80	4.196	0	2

7.10 (5H,m) 6.97-6.95 (1H, m), 6.68-6.67 (1H, dd, J_1=0.72 Hz, J_2=3.29 Hz); ^{13}C NMR (200 MHz, $CDCl_3$): δ 156.8, 142.8, 137.8, 137.1, 131.4, 129.7, 129.1, 128.9, 125.0, 122.7, 122.5, 121.6, 121.0, 120.7, 120.5, 117.9, 112.6, 110.7, 110.4, 104.5, 54.5; HRMS (ESI): MH+ found 388.0444 requires 388.0444.

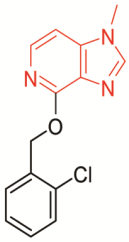
3-(1*H*-Indol-1-yl)-2-(2-methoxyphenyl) imidazo [1,2-a]pyridine, 4c [$C_{27}H_{17}ON_3$], No. of H 17: Solid (off white). m.p.145ºC. Yield 63%. R_f = 0.50 (40% Ethyl Acetate/ Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.756-7.64 (3H, m),7.48 (1H,s), 7.23-7.12 (4H,m), 6.95-6.92(3H,m),6.65-6.61 (3H,m),2.94 (3H,s);



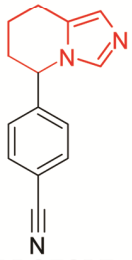
6-chloro-2-ethyl-N-(4-(4-(4-(trifluoromethoxy) phenyl) piperidin-1-yl) benzyl)imidazo [1,2-a]pyridine-3-carboxamide **(Q203)**



NECOPIDEM
N-([2-(4-ethylphenyl)-6-methylimidazo [1,2-a]pyridin-3-yl]methyl)-N,3-dimethylbutanamide

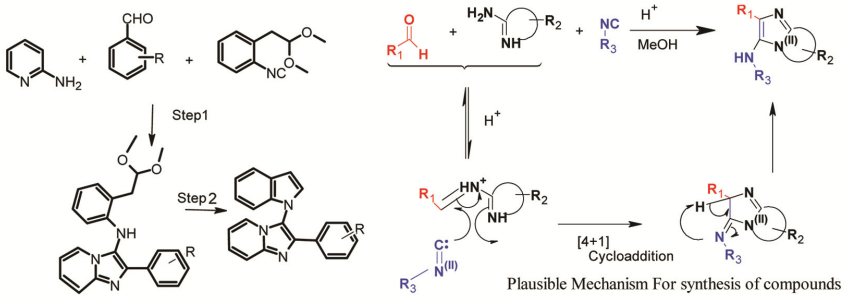


BAMALUZOLE
4-[(2-chlorophenyl)methoxy]-1-methyl-1H-imidazo[4,5-c]pyridine



FADROZOLE
4-(5,6,7,8-Tetrahydroimidazo [1,5-a]pyridin-5-yl)benzonitrile

Scheme — I



Reagents: Step 1: Dioxane, reflux 5-6 h, $ZnCl_2$; Step 2: DCM: TFA (1:1), RT, 4-5 h

Scheme — II

Table II — Biological activity of synthesized compounds

Compd	Inhibition at 5μM conc (%)	ADME-T						
		CYP_ 2C19	CYP_2D6	CYP_3A4	HIA	PlasmaProteinBinding	Carcino Mouse	Carcino Rat
4b	51.07	NON	NON	NON	100	93.52	Positive	Positive
4c	13.09	NON	NON	NON	100	92.75	Positive	Negative
4d	8.07	NON	NON	NON	100	91.43	Positive	Positive
4e	10.03	NON	NON	NON	100	92.17	Negative	Negative
4f	28.04	NON	NON	NON	100	94.19	Positive	Negative
4g	44.04	NON	NON	NON	100	95.10	Positive	Negative
4h	28.06	NON	NON	NON	96.81	94.42	Negative	Negative
4i	33.06	NON	NON	NON	100	91.60	Negative	Positive
4j	41.01	NON	NON	NON	100	91.48	Negative	Negative
4k	64.0	NON	NON	NON	100	98.61	Positive	Negative
4l	9.09	NON	NON	NON	98.11	99.80	Positive	Negative
4m	26.08	NON	NON	NON	97.47	94.36	Positive	Positive
4n	24.03	NON	NON	NON	97.55	95.95	Positive	Negative

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 142.8, 137.8, 137.1, 131.4, 129.7, 129.1, 128.9, 125.0, 122.7, 122.5, 121.6, 121.0, 120.7, 120.5, 117.9, 112.6, 110.7, 110.4, 104.5, 54.5; HRMS (ESI): MH+ found 340.1435 requires 340.1444.

2-(3-Fluorophenyl)-3-(1*H*-indol-1-yl)imidazo [1,2-a]pyridine, 4d [$C_{21}H_{15}FN_3$], No. of H 15: Solid (Light brown). m.p.161ºC. Yield 62%. R_f = 0.42 (40% Ethyl Acetate/ Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (1H,d, *J* = 9.12 Hz), 7.70 (1H, d, *J* = 7.88Hz), 7.63 (1H,m), 7.41 (1H, d, *J* = 6.84), 7.30 (1H,m), 7.28-7.10 (6H,m), 6.97-6.90 (2H, m), 6.79- 6.74 (2H, m); ^{13}C NMR (200 MHz, $CDCl_3$): δ 161.3, 158.8, 143.1, 137.1, 135.7, 131.0, 130.9, 130.28, 130.20, 128.8, 125.9, 124.3, 124.2, 123.1, 122.7, 121.3, 121.1, 120.3, 120.2, 118.0, 117.9, 116.1, 115.9, 113.1, 110.2, 105.3; HRMS (ESI): MH+ found 328.1236 requires 328.1245.

3-(1*H*-Indol-1-yl)-2-(3-methoxyphenyl)imida zo[1,2-a]pyridine, 4e [$C_{22}H_{17}N_3O$], No. of H 17: Solid (Light brown). m.p.150ºC. Yield 60%. R_f = 0.5 (40% Ethyl Acetate/ Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (2H, t, *J* = 7.29 Hz), 7.41-7.40 (1H, m), 7.28-7.26 (1H, m), 7.22-7.20 (1H, m), 7.18-7.11 (4H, m), 6.99 (1H,s), 6.95-6.93 (1H,m), 6.85-6.84 (1H,m), 6.78- 6.71 (2H,m), 3.50 (3H,s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 143.0, 139.9, 136.8, 133.4, 129.6, 129.0 128.5, 125.7, 123.4, 122.4, 121.4, 121.3, 119.1, 117.9, 115.9, 115.2, 112.9, 110.7, 110.4, 106.0, 54.9;; HRMS (ESI): MH+ found 340.1430 requires 340.1444.

2-(3-Chlorophenyl)-3-(1*H*-indol-1-yl)imidazo [1,2-a]pyridine, 4f [$C_{21}H_{13}ClN_3$], No. of H 13: Solid (Light brown). m.p.181ºC. Yield 65%. R_f = 0.52 (40% Ethyl Acetate/ Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76- 7.70 (3H,m), 7.37-7.05 (7H,m), 6.91-6.86 (2H,m), 6.74 (1H, t, *J* = 6.46 Hz); ^{13}C NMR (200 MHz, $CDCl_3$): δ 143.1, 138.6, 136.6, 134.0, 129.8, 129.1, 128.3, 128.2, 126.9, 126.1, 124.4, 123.5, 122.5, 121.5, 117.9, 116.3, 113.2, 110.2, 106.3; HRMS (ESI): MH+ found 344.0952 requires 344.0949.

3-(1*H*-Indol-1-yl)-2-(naphthalen-1-yl)imidazo[1,2-a]pyridine, 4g [$C_{25}H_{17}N_3$], No. of H 17: Solid (Pink). m.p.193ºC. Yield 62%. R_f = 0.55 (40% Ethyl Acetate/ Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (1H, d, *J* = 7.64 Hz), 7.77 (3H, 2d, J_1=8.41Hz, J_2= 20.25 Hz), 7.65 (1H, d, *J* = 7.24 Hz), 7.49-7.38 (3H, m), 7.33-7.13 (5H,m), 6.98 (2H, d, *J* = 3.32 Hz), 6.77 (1H,t,*J* = 6.73 Hz), 6.60 (1H,s) ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 137.0, 133.8, 131.9, 129.5, 129.0, 128.9, 128.1, 127.6, 126.4, 126.0, 125.8, 125.4, 125.1, 123.1, 122.8, 121.4, 121.1, 118.2, 112.9, 110.2, 105.3; HRMS (ESI): MH+ found 360.1490 requires 360.1495.

4-(3-(1*H*-Indol-1-yl)imidazo[1,2-a]pyridin-2-yl)phenol, 4h [$C_{21}H_{15}N_3O$], No. of H 15: Solid (Light brown). m.p.170ºC. Yield 63%. R_f = 0.3 (40% Ethyl Acetate/ Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1H NMR (400 MHz, $CDCl_3$) 7.79-7.68 (2H,m), 7.61 (1H, d, *J* = 8.24 Hz), 7.49 (1H, d, *J* = 8.32 Hz) 7.35 (2H,t, *J* = 8.64 Hz), 7.28-7.14 (5H,m), 6.94 (1H, t, *J* = 7.14Hz),6.84 (1H, d, J = 2.84 Hz), 6.75-6.70 (2H, m) ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 129.0, 128.6, 128.3 128.2, 126.7, 125.8, 125.6, 123.9, 123.6, 123.3, 122.6, 122.3, 121.6, 121.3, 118.0, 117.3, 115.8, 114.8, 113.4, 112.9, 110.4, 110.2, 106.4, 105.9; HRMS (ESI): MH+ found 326.1287 requires 326.1288.

2-(2-Fluoro-4-methoxyphenyl)-3-(1*H*-indol-1-yl)imidazo[1,2-a]pyridine, 4i [$C_{22}H_{16}FN_3O$], No. of H 16: Solid (brown). m.p.109ºC. Yield 64%. R_f = 0.3 (40% Ethyl Acetate/ Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (2H, dd, J_1=8.94 Hz, J_2=23.45 Hz), 7.52 (1H, t, *J* = 8.55Hz), 7.37 (1H, d, *J* = 6.96 Hz), 7.28-7.24 (1H, m), 7.19-7.10 (3H, m), 6.89 (1H, d, *J* = 7.76 Hz), 6.73-6.70 (2H,m), 6.64 (1H,dd, J_1=2.194 Hz, J_2=8.68 Hz), 6.48 (1H,dd, J_1=2.15 Hz, J_2=12.32 Hz), 3.70 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 161.2, 161.0, 159.5, 143.1, 137.1, 136.0, 131.4, 131.3, 128.9, 128.8, 125.6, 123.0, 122.5, 121.2, 121.1, 117.8, 117.2, 112.9, 112.7, 112.6, 110.3, 110.2, 105.2, 102.0,101.7, 55.4; HRMS (ESI): MH+ found 358.1343 requires 358.1350.

2-(4-Ethoxyphenyl)-3-(1*H*-indol-1-yl)imidazo [1,2-a]pyridine, 4j [$C_{23}H_{19}N_3O$], No. of H 19: Solid (Pale brown). m.p.171ºC. Yield 64%. R_f = 0.64 (40% Ethyl Acetate/ Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (2H, dd, J_1= 7.84 Hz, J_2= 12.20 Hz), 7.44 (2H, d, *J* = 8.88 Hz), 7.27 (1H, d, *J* = 5.24 Hz), 7.21-7.17

(2H,m), 7.13- 7.09 (2H,m), 6.89 (1H, d, J = 8.08 Hz), 6.81 (1H, d, *J* = 3.12 Hz), 6.72 (2H, d, *J* = 8.84 Hz), 6.64 (1H, t, *J* = 6.72 Hz), 4.12- 4.06 (2H, q, J_1= 7.12 Hz, J_2= 14.28 Hz) 1.31 (3H, t, J = 6.96 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 159.0, 142.9, 140.0, 136.7, 129.0, 128.6, 128.0, 125.5, 124.6, 123.3, 122.2, 121.3, 117.5, 114.8, 114.5, 112.7, 110.3, 105.8, 63.2,14.7; HRMS (ESI): MH+ found 354.1611 requires 354.1601.

3-(1*H*-Indol-1-yl)-2-(4-(trifluoromethyl)phenyl) imidazo[1,2-a]pyridine, 4k [$C_{22}H_{14}F_3N_3$], No. of H 14: Solid (Light brown). m.p.162ºC. Yield 60%. R_f = 0.65 (40% Ethyl Acetate/ Hexane), 1HNMR (400 MHz, $CDCl_3$): δ 7.75 (2H, dd, J_1=7.92Hz, J_2=16.36 Hz), 7.62 (2H, d, *J* = 8.28 Hz), 7.48 (2H, d, *J* = 8.4 Hz), 7.39 (1H, d, *J* = 6.80 Hz), 7.32-7.14 (4H, m), 6.93-6.87 (2H, m), 6.76 (1H, t, J-=6.76 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 138.5, 136.6, 135.7, 130.0, 129.7, 129.1, 128.2, 126.7, 126.2, 125.6, 125.5, 125.5, 125.4, 123.6, 122.7, 122.5, 121.6, 121.6, 118.0, 116.7, 113.3, 110.2, 106.4. HRMS (ESI): MH+ found 378.1210 requires 378.1213.

3-(1*H*-Indol-1-yl)-2-(4-(methylthio)phenyl) imidazo[1,2-a]pyridine, 4l [$C_{22}H_{17}N_3S$], No. of H 17: Solid (Light brown). m.p.119ºC. Yield 65%. R_f = 0.55 (40% Ethyl Acetate/ Hexane), ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.76 (1H, d, *J* = 7.85 Hz), 7.71 (1H, d, *J* = 9.01 Hz), 7.43 (2H, d, *J* = 8.55 Hz), 7.34 (1H, d, *J* = 6.80 Hz), 7.28-7.22 (2H, m), 7.18-7.13 (2H, m), 7.10 (2H,d, *J* = 8.55 Hz), 6.93 (1H,d, *J* = 8.15 Hz), 6.85 (1H, d, *J* = 3.20 Hz), 6.72 (1H, t, *J* = 6.7 Hz), 2.40 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.1, 139.6, 138.9, 136.7, 129.0, 128.8, 128.5, 126.9, 126.3, 125.8, 123.4, 122.4, 121.4, 121.4, 117.7, 115.5, 112.9, 110.4, 106.0, 15.3; HRMS (ESI): MH+ found 356.1228 requires 356.1216.

3-(1*H*-Indol-1-yl)-2-(4-nitrophenyl) imidazo [1,2-a]pyridine, 4m [$C_{21}H_{14}N_4O_2$], No. of H 14: Solid (Yellow). m.p.228ºC. Yield 61%. R_f = 0.4 (40% Ethyl Acetate/ Hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (2H,d, *J* = 9.00Hz), 7.78 (2H, dd, J_1=7.83 Hz, J_2= 19.35 Hz), 7.65 (2H, d *J* = 8.95 Hz), 7.44 (1H, d, *J* = 6.80 Hz), 7.37-7.34 (1H, m), 7.28 (1H, d, *J* = 7.65 Hz), 7.20 (1H, t, *J* = 7.75 Hz), 7.15 (1H, d, *J* = 3.25 Hz), 6.93-6.81 (3H,m) ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6, 137.6, 129.1, 127.9, 127.1, 126.6, 124.0, 123.7, 122.6, 121.8, 121.7, 113.6, 110.1, 106.8;; HRMS (ESI): MH+ found 355.1198 requires 355.1190.

2-(2-Chloro-4-nitrophenyl)-3-(1*H*-indol-1-yl)imidazo[1,2-a]pyridine, 4n [$C_{21}H_{13}ClN_4O_2$], No. of H 13: Solid (Orange). m.p.128ºC. Yield 65%. R_f = 0.60 (40% Ethyl Acetate/ Hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.46 (1H, d, *J* = 2.75 Hz), 8.07 (1H, dd, J_1=2.75 Hz, J_2=8.8Hz), 7.78 (1H, d, *J* = 9.15Hz), 7.69-7.67 (1H,m), 7.57 (1H, d, *J* = 6.85 Hz), 7.46 (1H, d, *J* = 8.80 Hz), 7.39-7.35 (1H,m) 7.19-7.16 (2H, m), 7.09 (1H, d, *J* = 3.30Hz), 6.92 (1H, d, *J* = 8.05Hz), 6.87-6.85 (1H, m), 6.74 (1H, d, *J* = 3.30Hz) ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.4, 143.1,140.5, 136.5, 136.2, 133.6, 130.8, 128.9, 128.2, 127.1, 126.2, 124.1, 123.4, 122.9, 121.4, 118.7, 118.4, 113.5, 110.2, 106.0.; HRMS (ESI): MH+ found 389.0803 requires 389.0800.

Biological Activity

Inverted membrane vesicles of *M. smegmatis* ATCC 607. The protein in the preparation was estimated using the Bradford method. For the assay, membrane vesicles were diluted to a concentration of 100 g protein/mL with 50 mM MOPS (*p*H 7.5) containing 10 mM $MgCl_2$. The membrane vesicles were pre-incubated with test compounds at two-fold serial dilutions ranging from 50 M to 0.39 M and N,N′-dicyclohexylcarbodiimide (DCCD) at 100 M under stirring condition at room temperature for 10 min. Subsequently, 2.5 mM NADH (final concentration) was added and was further incubated with vigorous shaking for 1 min. The reaction was started by addition of 1 mMADP (final concentration) and 10 mM potassium phosphate (final concentration). After 1 h of incubation at room temperature, 0.05 mL aliquots were added to 0.2 mL of stop solution [2 mM ethylene diamine tetra-acetic acid (EDTA), 1% trichloroacetic acid (TCA)]. Then, 0.005 mL of this mixture was added to 0.1 mL of Tris–acetate buffer (100 mM Tris, 2 mM EDTA, *p*H 7.75) in a 96-well plate. After addition of 0.1 mL of luciferase reagent (BacTiter-GloTM; Promega, Madison, WI), luminescence was measured with a luminometer (POLARstar Galaxy Microplate Reader).

Drug Likeliness

Lipinski rule of 5 was determined in Chem doodle software.

ADME-T

ADME-T of all molecules was determined from https://preadmet.bmdrc.kr/adme.

Conclusion

All imidazopyridine derivatives are marginally active on ATP synthase enzyme. All molecules obey Lipinski rule of five. The predicted Human intestinal absorption (HIA) for all compounds was greater than 95%. The compounds were found to be an inhibitor of CYP2C19, and CYP3A4 and non-substrate of CYP2D6. Plasma protein binding was less than 95% in all molecules. Further exploration can be done in Indole ring for potent derivatives.

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