Fused Heterocycles: Synthesis and Antitubercular Activity of Novel 6-Substituted-2-(4-methyl-2-substituted phenylthiazol-5-yl)*H*-imidazo[1,2-*a*]pyridine

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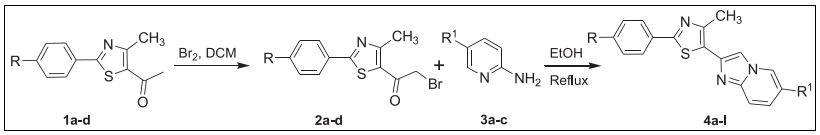

A series of 6-substituted-2-(4-methyl-2-substituted phenylthiazol-5-yl)*H*-imidazo[1,2-*a*]pyridine derivatives **4a–4l** is described. The antitubercular activity of the synthesized compounds was determined against *Mycobacterium smegmatis* MC^2 155 strain. From the activity result, it was found that the phenyl or 4-fluorophenyl group at 2 position of thiazole nucleus and bromo substituent at 6 position of imidazo [1,2-a]pyridine showed good antitubercular activity.

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INTRODUCTION

Mycobacterium tuberculosis infects about 32% of the world's population, and it is a contagious disease with comparatively high mortality worldwide [1–3]. The last major clinical advance in TB chemotherapy was the introduction of rifampin in 1968 [4,5]. The current situation clearly shows that TB is far from under control and requires the new effective drug to treating TB. With the worldwide emergence of multidrug-resistant TB and extensively drug-resistant TB, the World Health Organization has declared TB a global emergency [6–8].

Literature revealed that thiazole ring-containing and pyridine ring-containing compounds showed antitubercular and antimicrobial activities. Thiazole and their derivatives are an important pharmacophore, and its coupling with other rings could furnish new biologically active compounds [9–11]. Thiazole compounds have exhibited a broad range of biological activities such as antitumor [12], anticancer [13], antibiotic [14], anti-inflammatory [15–18], antibacterial and antifungal [19–23], antitubercular [24–26], and antiviral [27] activities.

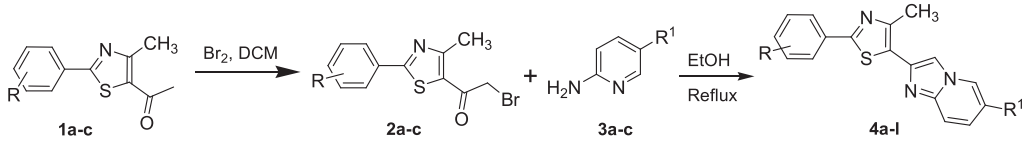
Isoniazid derivatives and pyridine-containing heterocyclic compounds are known for the antimycobacterial activity [28–31]. 2-Anilino-4-(thiazol-5-yl)pyrimidine derivatives show potent inhibitors of cyclin-dependent kinase-2 activity [32], oxadiazinylimidazopyridines, pyrimidines, and thiazoles [33]; 6-methylimidazo[2,1-*b*]thiazole-5-carbohydrazide derivatives show antimicrobial activities [34]; and oxazolines, oxazoles, thiazolines, and thiazoles to imidazo[1,2-a]pyridines show antitubercular activity [35]. For searching the new scaffold for antimycobacterial agents, it was thought to synthesize novel clubbed 6-substituted-2-(4-methyl-2-substituted phenylthiazol-5-yl)*H*-imidazo[1,2-*a*]pyridine derivatives and screen for their antitubercular activity.

The synthesis of 6-substituted-2-(4-methyl-2-substituted phenylthiazol-5-yl)*H*-imidazo[1,2-*a*]pyridine **4a–l** is illustrated in Scheme 1. The starting material 1-(4-methyl-2-phenylthiazol-5-yl)ethanone **1a–d** was synthesized by cyclocondensation of aryl thioamide with 3-bromopentane-2,4-dione. 1-(4-Methyl-2-phenylthiazol-5-yl)ethanone [36,37] **1a–d** on bromination with bromine in dichloromethane (DCM) gave 2-bromo-1-(4-methyl-2-substituted phenylthiazol-5-yl)ethanone **2a–d**, which on cyclocondensation with substituted 2-aminopyridine **3a–c** furnished target compounds **4a–l**. The physical properties of synthesized compounds are given in Table 1.

RESULTS AND DISCUSSION

The structure of the title compounds **4a–4l** was confirmed by IR, NMR, and HRMS. The IR (KBr) spectra of compound **4d** showed C=C/C=N absorption bands at 1608–1493 cm^{-1}. The ^1H NMR spectra of compound **4d** showed two singlets at δ 2.65 for methyl group and δ 8.19 because of imidazo[1,2-*a*]pyridine CH. The signals, a double of triplet at δ 6.86, multiplet at δ 7.21–7.26, doublet at δ 7.51, and doublet of doublet at δ 8.46 are accountable for the protons of pyridine ring, whereas doublets at δ 7.45 and δ 7.90 correspond to orthoprotons and metaprotons of 4-chlorobenzene ring. The ^{13}C NMR spectrum of

Scheme 1



Compound	R	R^1	Compound	R	R^1	Compound	R	R^1	Compound	R	R^1
4a	H	H	**4d**	4-Cl	H	**4g**	4-F	H	**4j**	4-Me	H
4b	H	Br	**4e**	4-Cl	Br	**4h**	4-F	Br	**4k**	4-Me	Br
4c	H	Cl	**4f**	4-Cl	Cl	**4i**	4-F	Cl	**4l**	4-Me	Cl

Table 1

Antitubercular activity of synthesized compounds **4a–4l**.

Compound	R	R^1	Yield (%)	Mp (°C)	*M. smegmatis*[a]	MIC (μg/mL)
4a	H	H	60	172–174	2.5	>50
4b	H	6-Br	62	100–112	55.6	25
4c	H	6-Cl	62	178–180	9.8	>50
4d	Cl	H	64	180–182	NA	—
4e	Cl	6-Br	65	190–192	4.4	>50
4f	Cl	6-Cl	60	187–188	1.8	>50
4g	F	H	60	172–174	29.5	27.9
4h	F	6-Br	64	206–208	50.5	20.8
4i	F	6Cl	60	178–179	NA	—
4j	CH_3	H	66	242	12.3	>50
4k	CH_3	6-Br	62	256	4.7	>50
4l	CH_3	6-Cl	60	188–190	4.4	>50
Isoniazid					96	5.07

[a]% inhibition.

compound **4d** showed signal at δ 16.9 for methyl group, whereas the aromatic and heterocyclic carbon showed signals at δ 109.7 to δ 162.2. Compound **4d** was further confirmed by HRMS and molecular ion peaks at *m/z* 326.0371 $(M+H)^+$. The mass spectra for the respective compounds with chlorine and/or bromine substitution showed M + 2 peaks.

Antitubercular activity. As an initial screening, the synthesized compounds (**4a–4l**) were screened for their antitubercular activity against *Mycobacterium smegmatis* as a surrogate organism, at 30-μM compound concentration [38]. The percentage inhibition was determined against DMSO, and those compounds that showed inhibition at 30% or more were further analyzed to determine their minimum inhibitory concentration (MIC) values. Isoniazid was used as reference drug. The result of antitubercular activity is reported in Table 1.

From *in vitro* antitubercular activity data, the structure–activity relationship of compounds was studied. Various substituents, viz. Br, Cl, F, and CH_3 on the phenyl ring of 2 position of thiazole, were introduced, and substituent at 6 position of imidazo[1,2-*a*]pyridine nucleus was exchanged with Br and Cl. It was found that these substituents affect the activity. From the activity data, compounds **4b** and **4h** recorded good activity at 30-μM concentration. A closer look into structure activity relationships (SARs) of these compounds reveals the following points.

The compound 2-(4-methyl-2-phenylthiazol-5-yl)*H*-imidazo [1,2-*a*]pyridine (**4a**) is inactive. When the phenyl ring was substituted by 4-fluorophenyl and 4-methylphenyl in compounds **4g** and **4j**, increase in activity is reported. The compound **4b** reported moderate activity with MIC 25 μg/mL. If the phenyl ring was substituted by 4-chlorophenyl (**4e**) or 4-methyl phenyl (**4k**), the activity decreases. Whereas when the phenyl ring was substituted by 4-fluorophenyl (**4h**), the activity retains. The substitution at imidazo[1,2-*a*]pyridine also affects the activity. The compound **4a** is inactive, whereas the substitution of hydrogen of 6 position of imidazo [1,2-*a*]pyridine by bromine (**4b**) and chlorine (**4c**) increases the activity by 22-fold and fivefold, respectively. The compound **4d** is found to be inactive. Further, the substitution of hydrogen of 6 position of imidazo[1,2-*a*]pyridine by bromine (**4e**) and chlorine (**4f**) did not affect the activity. The compound **4g** showed moderate activity. The substitution of hydrogen of 6 position of imidazo[1,2-*a*]pyridine by bromine in compound **4h** reported moderate activity, while the substitution of hydrogen by chlorine in compound **4i** was inactive. With the substitution of hydrogen of 6 position of compound

4j by bromine and chlorine in compounds **4k** and **4l**, the activity decreases.

CONCLUSION

To summarize, we have synthesized a series of novel 6-substituted-2-(4-methyl-2-substituted phenylthiazol-5-yl) *H*-imidazo[1,2-*a*]pyridine **4a–l**. The *in vitro* antitubercular activity results revealed that compounds **4b** and **4h** reported moderate activity. From SARs, it is noted that the phenyl or 4-fluorophenyl group at 2 position of thiazole nucleus and bromo substituent at 6 position of imidazo[1,2-*a*]pyridine contributed to the activity. The antitubercular activity results make them interesting lead molecules for further synthetic and biological evaluation.

EXPERIMENTAL

All the reactions were monitored, and purity of the products was checked by thin-layer chromatography (TLC). TLC was performed on Merck 60 F-254 silica gel plates with visualization by UV light. Melting points were determined in capillary tubes in silicon oil bath using a Veego melting point apparatus and are uncorrected. ^{1}H (300 MHz) NMR and ^{13}C (75 MHz) NMR spectra were recorded on Varian mercury XL-300 and BRUKER AVANCE II 400 NMR spectrometer (Bruker Instruments Inc., Billerica, MA, USA) at either 400-MHz (^{1}H NMR) and 100-MHz (^{13}C NMR) spectrometer instruments. Chemical shifts are reported from internal tetramethylsilane standard and are given in δ units. Infrared spectra were taken on Shimadzu FTIR (KBr) (Shimadzu Corporation, Kyoto, Japan) – 408 in KBr. Electron-impact HR mass spectra were obtained using MAT model 8400 mass spectrometer using an ionizing voltage of 70 eV. Column chromatography was performed on silica gel (100–200 mesh) supplied by Acme Chemical Co. (Mumbai, Maharashtra, India). The chemicals and solvents used were laboratory grade and were purified as per literature methods.

Synthesis of 1-(4-methyl-2-phenylthiazol-5-yl)ethanone (1a). A mixture of thiobenzamide (6.62 mmol) and of 3-bromopentane-2,4-dione (6.62 mmol) was refluxed in ethanol. After completion of reaction (TLC), the solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate. Organic layer was extracted with sodium bicarbonate and then water, dried over sodium sulfate, and distilled under vacuum. The product obtained was purified by column chromatography using hexane: ethyl acetate (9:1) as eluate.

Synthesis of 2-bromo-1-(4-methyl-2-(4-substituted phenyl)thiazol-5yl)ethanone (2a). A mixture of 1-(4-methyl-2-phenylthiazol-5-yl)ethanone (10 mmol) and *p*-toluenesulfonic acid (5 mmol) in DCM (50 mL) was stirred at 0 °C for 10 min; then, Br_2 (10 mmol) in DCM (20 mL) was added dropwise in the reaction mixture. The reaction mixture was stirred for 12 h at room temperature (TLC). After completion of the reaction, sodium bicarbonate solution was added in the reaction mixture and stirred for 10 min. The aqueous layer was extracted with DCM, and combined organic layer was washed with water, dried with sodium sulfate, and distilled under vacuum. The product was used without further purification.

Representative procedure for synthesis of compounds 4a–4l. A mixture of 2-bromo-1-(2-(4-substituted-phenyl)-4-methyl thiazol-5yl)ethanone (1 mmol) and 2-aminopyridine (1.1 mmol) was refluxed in dry ethanol (15 mL). The reaction was monitored on TLC. After the completion of reaction, solvent was evaporated under vacuum, and residue was dissolved in ethyl acetate. The organic layer was washed with sodium bicarbonate and water. The solvent was dried over sodium sulfate and distilled under vacuum. The product was purified by crystallization in ethanol. The structure of all the synthesized compounds was confirmed by spectral analysis.

2-(4-Methyl-2-phenylthiazol-5-yl)H-imidazo[1,2-a]pyridine (4a). IR (KBr): 3060, 3028, 1602, 1498, 1432, 1394, 1340, 1232, 1089, 1060, 1001, 930, 824 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.69 (s, 3H CH_3), 6.79 (dt, J = 6.84 and 1.00 Hz, 1H, Ar-H), 7.17–7.21 (m, 1H, Ar-H), 7.37–7.45 (m, 3H, Ar-H), 7.63 (d, J = 8.72 Hz, 1H, Ar-H), 7.72 (s, 1H, imidazol-H), 7.94–7.97 (m, 2H, Ar-H), 8.10 (dd, J = 6.84 and 1.00 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.9, 109.8, 112.2, 116.4, 125.3, 126.3, 127.4, 127.5, 128.5, 129.6, 132.4, 134.1, 144.2, 149.0, 163.2; HRMS calculated (*m/z*): 292.0908, found (*m/z*): 292. 0777 $(M + H)^+$.

6-Bromo-2-(4-methyl-2-phenylthiazol-5-yl)H-imidazo[1,2-a]pyridine (4b). IR (KBr): 3060, 3032, 1605, 1490, 1429, 1395, 1330, 1228, 1196, 1089, 1060, 1001, 932, 820, 756 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.70 (s, 3H, CH_3), 7.26 (dd, J = 9.56 and 1.84 Hz, 1H, Ar-H), 7.40–7.46 (m, 3H, Ar-H), 7.52 (d, J = 9.52 Hz, 1H, Ar-H), 7.71 (s, 1H, imidazol-H), 7.96 (dd, J = 8.08 and 1.88 Hz, 2H, Ar-H), 8.27–8.28 (m, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.3, 107.6, 109.2, 118.1, 125.4, 126.9, 128.2, 128.9, 129.5, 132.1, 135.7, 138.1, 143.5, 149.4, 164.9; HRMS calculated (*m/z*): 370.0014, found (*m/z*): 369.9898 $(M + H)^+$.

6-Chloro-2-(4-methyl-2-phenylthiazol-5-yl)H-imidazo[1,2-a]pyridine (4c). IR (KBr): 3058, 3022, 1599, 1488, 1413, 1387, 1329, 1218, 1148, 1078, 1058, 1001, 928, 820, 803 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3): δ 2.61 (s, 3H, CH_3), 7.34–7.55 (m, 5H, Ar-H), 7.67 (s, 1H, imidazol-H), 7.85–7.89 (m, 2H, Ar-H), 8.20 (d, J = 1.2 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 109.3, 116.1, 116.7, 117.8, 123.4, 126.5, 127.0, 128.8, 129.5, 131.8, 133.6, 143.5, 149.1, 164.7; HRMS calculated (*m/z*): 326.0519, found (*m/z*): 326.0379 $(M + H)^+$.

2-(2-(4-Chlorophenyl)-4-methylthiazol-5-yl)H-imidazo[1,2-a]pyridine (4d). IR (KBr): 3062, 3036, 1608, 1493, 1432, 1397, 1336, 1236, 1199, 1087, 1062, 1003, 933, 826, 804 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.65 (s, 3H, CH_3), 6.86 (dt, J = 6.72 and 1.04 Hz, 1H, Ar-H), 7.21–7.26 (m, 1H, Ar-H), 7.45 (d, J = 8.6 Hz, 2H, Ar-H), 7.51 (d, J = 8.8 Hz, 1H, Ar-H), 7.90 (d, J = 8.6 Hz, 2H, Ar-H), 8.19 (s, 1H, imidazol-H), 8.46 (dd, J = 8.8 and 1.04 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.9, 109.7, 112.3, 116.2, 125.3, 126.7, 127.2, 127.6, 128.9, 131.9, 134.6, 136.9, 144.4, 148.6, 162.2; HRMS calculated (*m/z*): 326.0519, found (*m/z*): 326.0371 $(M + H)^+$.

6-Bromo-2-(2-(4-chlorophenyl)-4-methylthiazol-5-yl)H-imidazo[1,2-a]pyridine (4e). IR (KBr): 3055, 3027, 1602, 1486, 1426, 1392, 1330, 1232, 1188, 1085, 1060, 1001, 930, 822, 802, 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.69 (s, 3H, CH_3), 7.27 (dd, J = 7.2 and 2.1 Hz, 1H, Ar-H), 7.41 (d, J = 8.1 Hz, 2H, Ar-H), 7.52 (d, J = 9.6 Hz, 1H, Ar-H), 7.71 (s, 1H, imidazol-H), 7.89 (d, J = 8.1 Hz, 2H, Ar-H), 8.28 (s, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.3, 107.4, 109.0, 117.9, 125.5, 126.6, 127.4, 128.8, 129.1, 132.1, 135.8, 139.2, 143.6,

149.8, 164.2; HRMS calculated (*m/z*): 403.9624, found (*m/z*): 403.9622 $(M+H)^+$.

***6-Chloro-2-(2-(4-chlorophenyl)-4-methylthiazol-5-yl)H-imidazo[1,2-a]pyridine* (4f)**. IR (KBr): 3060, 3032, 1601, 1489, 1430, 1394, 1335, 1232, 1193, 1084, 1058, 1003, 933, 820, 807 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.62 (s, 3H, CH_3), 7.13 (d, $J = 8.64$ Hz, 2H, Ar-H), 7.27 (dd, $J = 9.56$ and 1.92 Hz, 1H, Ar-H), 7.49 (d, $J = 9.56$ Hz, 1H, Ar-H), 7.65 (s, 1H, imidazol-H), 7.85–7.89 (d, $J = 8.64$ Hz, 2H, Ar-H), 8.11 (d, $J = 1.4$ Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 109.2, 115.9, 116.1, 117.6, 123.3, 126.4, 126.7, 128.2, 130.2, 139.4, 143.6, 149.6, 162.5, 164.5; HRMS calculated (*m/z*): 360.0129, found (*m/z*): 360.0122 $(M+H)^+$.

2-(2-(4-Fluorophenyl)-4-methylthiazol-5-yl)H-imidazo[1,2-a]pyridine (4g). IR (KBr): 3085, 3025, 1608, 1497, 1430, 1399, 1340, 1237, 1196, 1088, 1059, 1006, 931, 835, 799 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.65 (s, 3H, CH_3), 6.86 (dt, $J = 6.72$ and 1.04 Hz, 1H, Ar-H), 7.02 (t, $J = 8.6$ Hz, 2H, Ar-H), 7.21–7.26 (m, 1H, Ar–H), 7.52 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.88–7.91 (m, 2H, Ar-H), 8.19 (s, 1H, imidazol-H), 8.46 (dd, $J = 8.8$ and 1.04 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.0, 109.6, 112.5, 116.0, 116.8, 125.2, 126.6, 128.9, 129.2, 130.5, 133.5, 144.3, 148.6, 162.2, 165.8; HRMS calculated (*m/z*): 310.0814, found (*m/z*): 310.0809 $(M+H)^+$.

6-Bromo-2-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)H-imidazo[1,2-a]pyridine (4h). IR (KBr): 3101, 3030, 1609, 1487, 1434, 1389, 1333, 1240, 1187, 1080, 1055, 1007, 930, 828, 810, 760, 738 cm^{-1}; ^1H NMR (300 MHz, CDCl3): δ 2.70 (s, 3H, CH_3), 7.01 (t, $J = 8.6$ Hz, 2H, Ar-H), 7.26 (dd, $J = 7.6$ and 1.0 Hz, 1H, Ar-H), 7.52 (d, $J = 7.6$ Hz, 1H, Ar-H), 7.71 (s, 1H, imidazol-H), 7.89–7.91 (m, 2H, Ar-H), 8.28 (d, $J = 1.0$ Hz, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.0, 109.0, 113.5, 115.1, 116.5, 117.9, 125.4, 128.9, 129.3, 132.1, 136.2, 143.8, 149.6, 162.5, 164.2; HRMS calculated (*m/z*): 387.9919, found (*m/z*): 387.9912 $(M+H)^+$.

6-Chloro-2-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)H-imidazo[1,2-a]pyridine (4i). IR (KBr): 3122, 3043, 1601, 1527, 1483, 1447, 1394, 1288, 1246, 1183, 1069, 1009, 974, 916, 826, 815, 761, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.71(s, 3H, CH_3), 7.02 (t, $J = 8.6$ Hz, 2H, Ar-H), 7.49 (dd, $J = 8.8$ and 1.4 Hz, 1H, Ar-H), 7.58 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.73 (s, 1H, imidazol-H), 7.88–7.91 (m, 2H, Ar-H), 8.18 (d, $J = 1.4$ Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 109.5, 113.8, 116.4, 117.7, 123.3, 125.0, 127.8, 129.2, 130.0, 132.2, 143.8, 149.5, 162.2, 164.7; HRMS calculated (*m/z*): 344.0424, found (*m/z*): 344.0419 $(M+H)^+$.

2-(4-Methyl-2-p-tolylthiazol-5-yl)H-imidazo[1,2-a]pyridine (4j). IR (KBr): 3084, 3037, 1600, 1557, 1530, 1443, 1404, 1377, 1305, 1212, 1185, 1003, 903, 820, 759 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.45, (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 6.86–6.88 (m, 1H, Ar-H), 7.05–7.08 (m, 2H, Ar-H), 7.20 (d, $J = 8.6$ Hz, 2H, Ar-H), 7.88 (d, $J = 8.6$ Hz, 2H, Ar-H), 8.19 (s, 1H, imidazol-H), 8.46 (dd, $J = 8.0$ and 1.04 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.9, 29.1, 109.5, 112.7, 116.1, 125.2, 126.4, 127.3, 129.2, 130.0, 130.8, 133.7, 136.8, 144.3, 148.8, 163.6; HRMS calculated (*m/z*): 306.1065, found (*m/z*): 306.0834 $(M+H)^+$.

6-Bromo-2-(4-methyl-2-p-tolylthiazol-5-yl)H-imidazo[1,2-a]pyridine (4k). IR (KBr): 3107, 3030, 1610, 1518, 1496, 1383, 1333, 1197, 1060, 890, 802, 761, 716 cm^{-1}; ^1H NMR (300 MHz, CDCl3): δ 2.46 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 7.26 (d, $J = 8.1$ Hz, 2H, Ar-H), 7.29 (dd, $J = 7.2$ and 1.6 Hz, 1H, Ar-H), 7.52 (d, $J = 7.2$ Hz, 1H, Ar-H), 7.71 (s, 1H, imidazol-H), 7.88 (d, $J = 8.1$ Hz, 2H, Ar-H), 8.28 (d, $J = 1.6$ Hz, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.1, 29.2, 107.8, 110.1, 114.7, 117.6, 125.3, 127.7, 129.5, 130.6, 132.0, 135.9, 139.0, 143.7, 149.6, 164.1; HRMS calculated (*m/z*): 384.0170, found (*m/z*): 384.0155 $(M+H)^+$.

6-Chloro-2-(4-methyl-2-p-tolylthiazol-5-yl)H-imidazo[1,2-a]pyridine (4l). IR (KBr): 3388, 3022, 1604, 1510, 1492, 1378, 1335, 1199, 1058, 891, 830, 756 cm^{-1}; ^1H NMR (400 MHz, CDCl3): δ 2.46 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 7.13 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.26 (dt, $J = 8.8$ and 1.4 Hz, 1H, Ar-H), 7.49 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.65 (s, 1H, imidazol-H), 7.89 (d, $J = 8.4$ Hz, 2H, Ar-H), 8.11 (d, $J = 1.4$ Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 29.2, 109.0, 115.1, 116.4, 123.3, 125.2, 127.1, 128.0, 129.7, 130.4, 132.5, 139.0, 143.5, 149.6; 164.0; HRMS calculated (*m/z*): 340.0675, found (*m/z*): 340.0658 $(M+H)^+$.

Antitubercular activity: The compounds were tested for their antimycobacterial ability on *M. smegmatis* MC^2 155 strain. The series of compounds was obtained in 10-mM stock concentrations. Further, each compound was diluted with the required 100% (v/v) DMSO to achieve a working concentration of 1.5 mM. The inoculum for the assay was prepared by reviving a glycerol stock in Middlebrook 7H9 Broth supplemented with 0.1% Tween 80 (Sigma Aldrich, USA) and 0.5% glycerol. At the time of inoculation, 10% Albumin-Dextrose-Saline (ADS) was added to the media, and the culture was incubated in a shaker incubator at 37 °C and 200 rpm. When the optical density (O.D.) of the inoculum reached 0.8–1 approximately, a secondary inoculum was inoculated and subsequently incubated. This was incubated overnight till the O.D. of the inoculum reached 0.4 approximately; following which, the inoculum was diluted 1:1000 times. In a 96-well microtiter plate, a 2-μL aliquot of the 1.5-mM dilution of compound was added to each well in triplicate, to which 98 μL of inoculum dilution was added, making the final concentration of compound 30 μM. To each plate, a set of controls was added to better ascertain the activity of the compounds. These included DMSO, which was taken as a growth control, and media control (blank) and rifampin and isoniazid, which were taken as positive controls of inhibition of *M. smegmatis*. After the completion of the period of 32 h, the absorbance of the inoculum in wells was measured at 600 nm using a multimode reader. Absorbance is considered directly proportional to the increase in growth of bacteria; thus, it gives a measure of the growth of bacteria in each well. The percentage inhibition was determined against DMSO, and those compounds that showed inhibition at 30% or more were further analyzed to determine their MIC values. In order to attain this objective, the inhibition was tested at increasing concentrations of compound from 6.25 to 100 μM. After the period of 30-h incubation, the absorbance of the inoculum was observed at 600 nm using a multimode reader, and the MIC values were calculated for the respective compounds.

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