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Research paper

Design, synthesis and antimycobacterial activity of novel imidazo[1,2-*a*]pyridine-3-carboxamide derivatives

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ABSTRACT

We report herein the design and synthesis of "novel imidazo [1,2-*a*]pyridine-3-carboxamides (IPAs)" bearing a variety of different linkers, based on the structure of IMB-1402 discovered in our lab. Results reveal that 2,6-dimethyl-*N*-[2-(phenylamino)ethyl] IPAs with an electron-donating group on the benzene ring as a potent scaffold. Compounds **26g** and **26h** have considerable activity (MIC: 0.041–2.64 μM) against drug-sensitive/resistant MTB strains, and they have acceptable safety indices against MTB H37Rv with the SI values of 4395 and 1405, respectively. Moreover, *N*-[2-(piperazin-1-yl)ethyl] moiety was also identified as a potentially alternative linker (compound **31**), opening a new direction for further SAR studies.

1. Introduction

Tuberculosis (TB) is a chronic infectious disease caused mainly by Mycobacterium *tuberculosis* (MTB). The World Health Organization (WHO) 2015 TB report estimated that approximately one-third of the world population is infected with MTB, and 9.6 million people were infected and 1.5 million died from TB worldwide in 2014 [1]. The high prevalence of multidrug-resistant MTB (MDR-MTB) and the emergence of extensively drug-resistant MTB (XDR-MTB), together with coinfection with Human Immunodeficiency Virus (HIV), have intensified the need for new anti-TB drugs [2–4]. Bedaquiline (an ATP synthase inhibitor) was, for the first time since 1970s, approved by the US FDA for clinical management of MDR-TB in 2012 [5], but some adverse events have been noted [6]. Therefore, it is urgent to identify new molecules with alternative scaffolds as effective anti-TB drug candidates.

Recently, imidazo[1,2-*a*]pyridine-3-carboxamides (IPAs) as TB antibiotics have garnered great interest. Two candidates Q203 (Fig. 1) [7,8] and ND09759 (Fig. 1) [9,10] were reported to have strong inhibitory potency against drug-sensitive, MDR and XDR strains by targeting the QcrB subunit of the menaquinol cytochrome c oxidoreductase (bc1 complex) [8,11]. Structure–activity relationship (SAR) studies of IPAs demonstrated that the carboxamide linker with the *N*-benzylic group is critical for antimycobacterial activity [7]. However, many 2,6-dimethyl IPAs bearing a *N*-(2-phenoxy)ethyl moiety were also found to demonstrate highly potent activity (MIC: 0.025–0.054 μg/mL) against both drug-sensitive MTB and MDR-MTB strains in our lab. Among them, IMB-1402 (Fig. 1) displays acceptable safety and pharmacokinetic properties [12]. This suggests that other 3-carboxamide linkers between the imidazo[1,2-*a*]pyridine core and the benzene ring would be tolerated within the SAR of this IPA series. Accordingly, a series of novel 2,6-/2,7-dimethyl IPAs bearing a variety of different linkers were designed and synthesized as new anti-TB agents in this study (Scheme 2). Our primary objective was to identify alternative linkers with potent antimycobacterial activity. A preliminary SAR study was also explored to facilitate the further development of IPAs.

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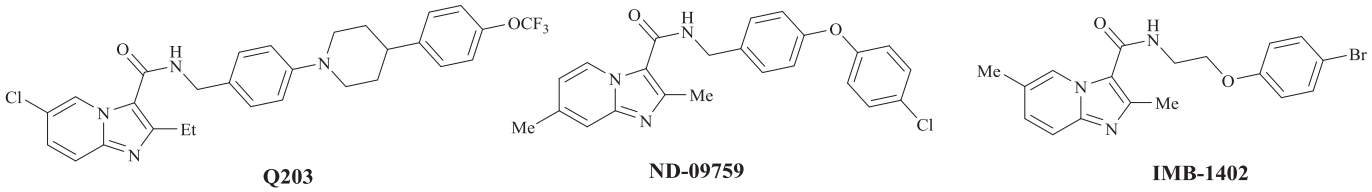


Fig. 1. Structures of Q203, ND-09759 and IMB-1402.

2. Results and discussion

2.1. Chemistry

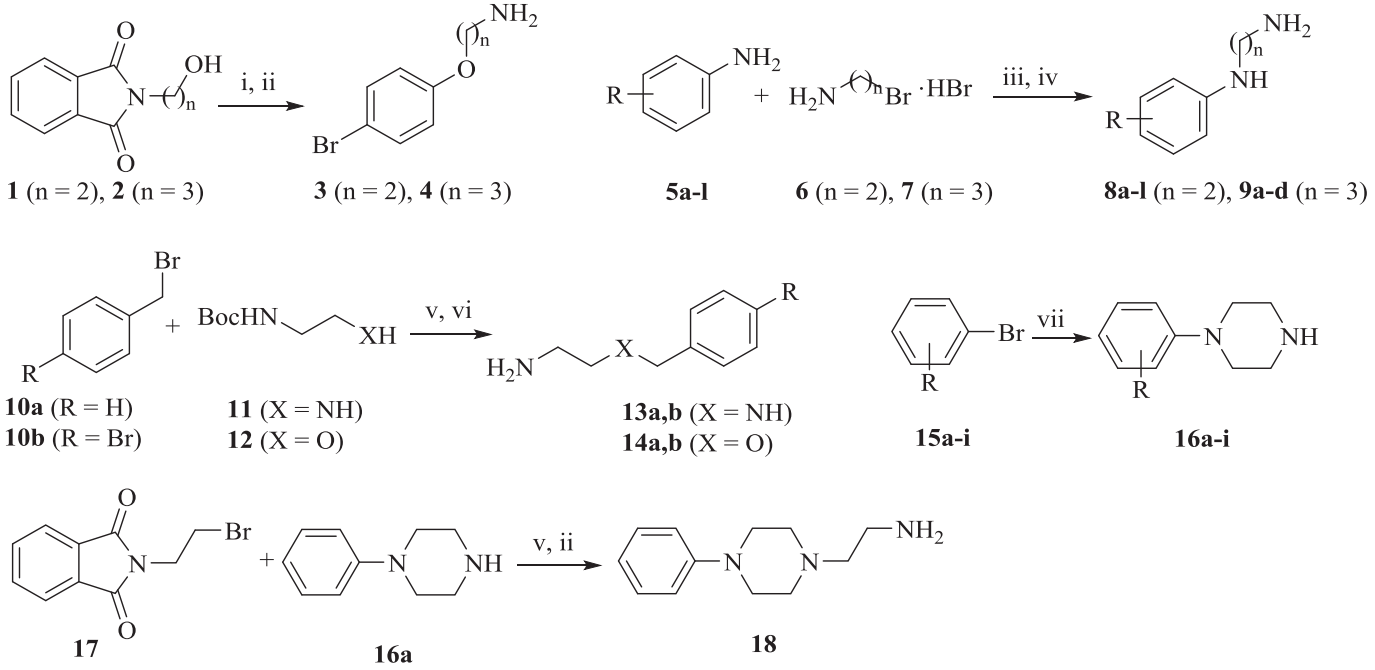
Detailed synthetic pathways to amine derivatives **3**, **4**, **8a-l**, **9a-d**, **13a-b**, **14a-b**, **16a-i**, and **18** which are commercially unavailable are depicted in Scheme 1. Coupling of 4-bromophenol with hydroxy phthalimide **1**, **2** in the presence of diethyl azodicarboxylate (DEAD) and PPh_3 followed by treatment with hydrazine hydrate in ethanol yielded amine **3**, **4**. Treatment of anilines **5a-l** with compounds **6**, **7** in toluene under reflux condition gave the desired 1, 2-diamines **8a-l** and 1,3-diamines **9a-d**. Nucleophilic substitution of benzyl bromides **10 a, b** with compounds **11, 12** followed by deprotection the Boc-group furnished *N*-benzylethane-1,2-diamines **13a, b** and 2-(benzyloxy)ethan-1-amines **14a,b**. Buchwald-Hartwig coupling of bromobenzenes **15a-i** with piperazine in toluene afforded compounds **16a-i**. Condensation of compound **16a** with *N*-(2-bormoethyl)phthalimide **17**, and then treatment of the resulting condensate with hydrazine hydrate in ethanol yielded 2-(4-phenylpiperazin-1-yl)ethan-1-amine **18.**

Core acids **21a, b** were obtained from 2-aminopyridines **19a, b** in two steps using our published procedures [13]. Direct amidation of the acids **21a, b** with the above amines **3**, **4**, **8a-l**, **9a-d**, **13a, b**, **14a, b**, **16a-i**, **18** and commercially available 1-(pyridine-2/4-yl) piperazines **22a, b** and 4-(4-fluorophenyl) piperidine **23** in the presence of Bis-(2-oxo-3-oxazolidinyl) phosphinic chloride (BOPCl) and triethylamine (Et_3N) gave target compounds **24-33** (Scheme 2).

2.2. Pharmacology

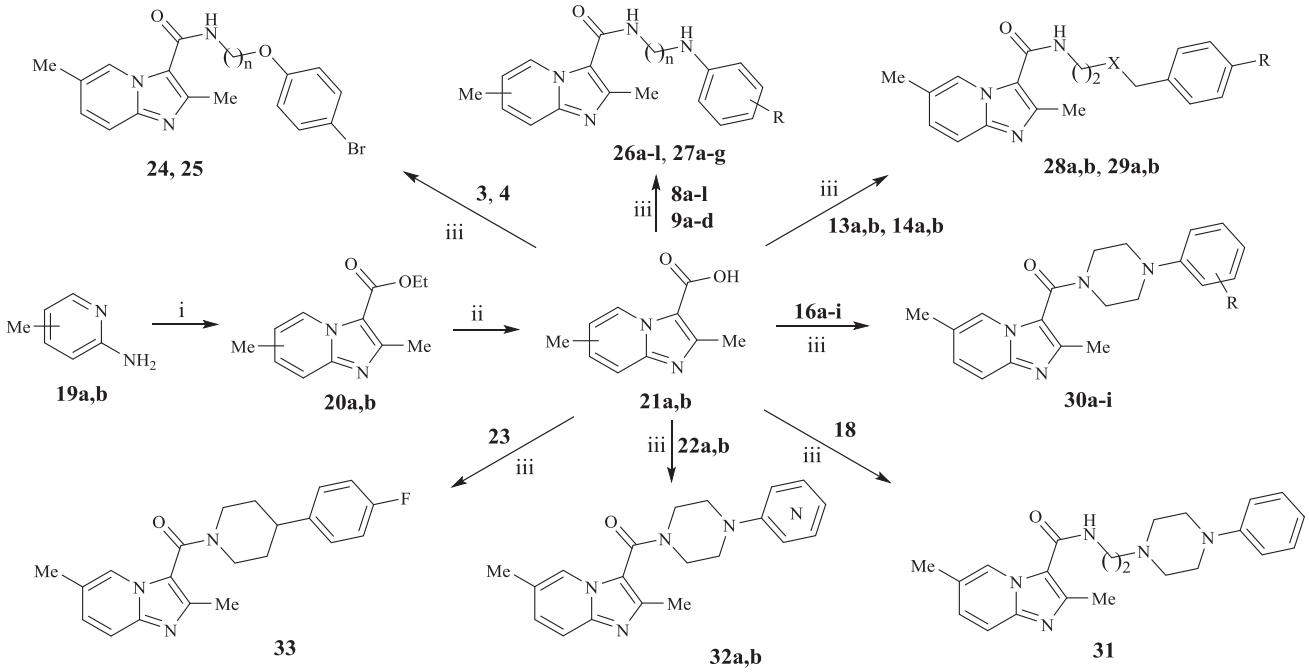
The target compounds **24-33** were initially screened for *in vitro* activity against MTB H37Rv ATCC 27294 strain using the Microplate Alamar Blue Assay (MABA) [14,15]. The minimum inhibitory concentration (MIC) is defined as the lowest concentration effecting a reduction in fluorescence of >90% relative to the mean of replicate bacterium-only controls. The MIC values of the compounds along with isoniazid (INH) and rifampicin (RFP) for comparison are presented in Table 1.

Synthesized compound **25** exhibits significantly reduced activity (MIC: 0.62 μM) compared to IMB-1402 (**24**, MIC: 0.038 μM), suggesting that ethyl seems to be more favorable for activity than propyl. Therefore, structural modifications were focused on the *N*-(2-phenoxy)ethyl linker in this study. First, the linker was replaced by the isostere *N*-(2-phenylamino)ethyl one giving compounds **26a-k**, and SAR of the substitution on the benzene ring was investigated. It is clear that the anti-MTB potency is visibly influenced by the nature and position of the substitution on the benzene ring. For example, introduction of one or two halogen atoms on the



i) 4-bromophenol, DEAD, PPh_3, THF, 0-5 °C; ii) hydrazine hydrate, EtOH, reflux; iii) toluene, reflux;
iv) NaOH, rt; v) K_2CO_3, MeCN, reflux; vi) TFA, DCM, rt; vii) piperazine, $Pd(OAc)_2$, *t*-BuONa, BINAP, toluene, reflux

Scheme 1. Synthesis of compounds **3**, **4**, **8a-l**, **9a-d**, **13a-b**, **14a-b**, **16a-i**, and **18**.



Reagents and conditions: (i) ethyl 2-chloroacetoacetate,Et_3N, MeCN, reflux; (ii) LiOH, H_2O, EtOH, rt, and then HCl; (iii) BOP-Cl, Et_3N, CH_2Cl_2, rt

Scheme 2. Synthesis of target compounds **24**–**31**.

benzene ring does not much affect the activity (**26b-e** *vs* **26a**). The presence of electron-donating groups leads to obviously enhanced potency. Compounds with a methoxyl group **26g** or a *tert*-butyl one **26h** at the *para*-position demonstrate the strongest activity with the MIC values of 0.044 μM and 0.041 μM, respectively, and compound **26f** with two methyl groups at the *para*- and *meta*-positions shows also potent activity (MIC: 0.18 μM). Conversely, introduction of an electron-withdrawing group is detrimental. For instance, when a trifluoromethyl group is merged to the *meta*-position, the resulting compound **26k** (MIC: 5.31 μM) is 6-fold less potent than **26a**, and introduction of a nitro group (**26i**) or a trifluoromethyl one (**26j**) at the *para*-position leads to complete loss of activity. These results indicate that electron-donating groups are preferred over electron-withdrawing ones or halogens.

Secondly, compounds with a *N*-(3-phenylamino)propyl moiety **27a-d** were designed and synthesized. As expected, compounds **27a** and **27c** are significantly less active than the corresponding *N*-2-(phenylamino)ethyl ones **26a** and **26h**, respectively, and compound **27d** is inactive. And, surprise, compound **27b** displays slightly better activity (MIC: 1.47 μM) than **26b** (MIC: 1.53 μM). Moreover, the impact of the position of the methyl group on the pyridine ring of the cores was also investigated and the 6-position was identified to be optimal for substitution (**26g** *vs* **26l**, **27a** *vs* **27e**, **27c** *vs* **27f**). In further modifications, it is shown that replacement of the phenyl moiety with the corresponding benzyl one significantly decreases the activity by 15–60-fold (**28a** *vs* **26a**, **28b** *vs* **26d**, **29b** *vs* **24**).

Finally, the *N*-2-(phenylamino)ethyl linker was replaced by phenyl/pyridyl heterocyclic amines (piperazine, piperidine) and none of the resulting compounds **30a-i**, **32a,b** and **33** demonstrate any inhibition (MIC: 43.47 - > 90 μM).

Interestingly, replacement of the anilino group of **26a** by 4-phenylpiperazinyl one (**31**) remains good activity (MIC: 0.66 μM). It is clear that compound **31** has the advantage of improving the aqueous solubility through protonation of the tertiary amino nitrogen of the piperazine ring. The activity of the molecule (**31**) could be enhanced through introduction of various groups on the benzene ring, extensive SAR studies are currently carried out in our lab and the study results will be reported in due course.

Compounds **24**, **26g** and **26h** were further evaluated against two clinical isolated 11168 and 9160 MDR strains resistant to both of INH and RFP. It is shown that the MIC values of compounds **26g** and **26h** are much higher than **24** (MIC: <0.041–0.20 μM) against these two MDR strains, but both of them display good activity (MIC: 0.57–2.64 μM). The cytotoxic potential of compounds **26g** and **26h** was also investigated in a mammalian Vero cell line. The results are shown in Table 2. Neither of the tested compounds is toxic in the cell line, and they have acceptable safety indices against MTB H37Rv with the SI values of 4395 and 1405, respectively.

3. Conclusion

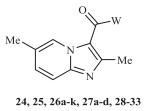
In conclusion, we have rediscovered 2,6-dimethyl-*N*-(2-phenylamino)ethyl IPA with an electron-donating group on the benzene ring as a potent scaffold. Compounds **26g** and **26h** display excellent to good activity (MIC: 0.041–2.64 μM) against both drug-sensitive MTB strain H37Rv and drug-resistant clinical isolates. Moreover, *N*-[2-(piperazin-1-yl)]ethyl moiety was also identified as a potentially alternative linker between the IPA core and the benzene ring, and extensive SAR studies of compound **31** (MIC: 0.66 μM against MTB H37Rv) having the advantage of improving the aqueous solubility are currently carried out in our lab.

4. Experimental protocols

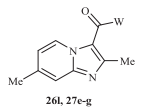
4.1. Chemistry

Melting points were determined in open capillaries and are uncorrected. 1H NMR spectra were determined on a Varian Mercury-400 spectrometer in DMSO-d_6 or $CDCl_3$ using

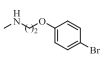
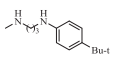
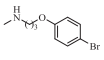
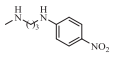
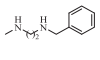
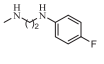
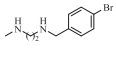
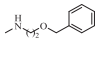
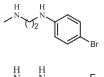
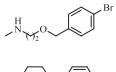
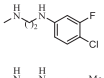
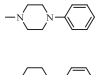
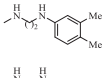
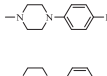
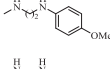
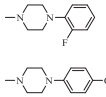
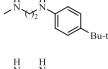
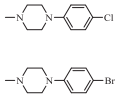
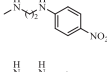
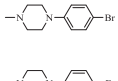
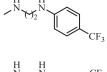
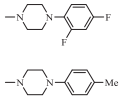
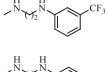
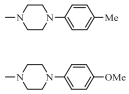
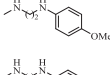
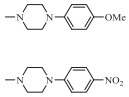
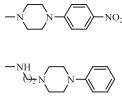
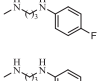
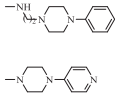
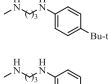
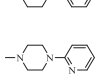
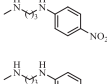
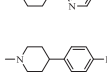
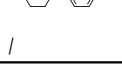
Table 1
Structures and *in vitro* activity of **24**–**33** *against MTB H37Rv ATCC 27294.*



24, 25, 26a-k, 27a-d, 28-33



26l, 27e-g

Compd.	W	MIC (μM)	Compd.	W	MIC (μM)
24 (IMB-1402)		0.038	**27f**		10.58
25		0.62	**27g**		>87
26a		0.81	**28a**		49.61
26b		1.53	**28b**		9.97
26c		0.76	**29a**		1.93
26d		0.64	**29b**		0.62
26e		1.39	**30a**		95.42
26f		0.18	**30b**		90.35
26g		0.044	**30c**		>90
26h		0.041	**30d**		43.47
26i		>90	**30e**		>77
26j		42.55	**30f**		>86
26k		5.31	**30g**		45.98
26l		47.31	**30h**		>87
27a		6.21	**30i**		84.43
27b		1.47	**31**		0.66
27c		1.32	**32a**		95.04
27d		>87	**32b**		>95
27e		12.43	**33**		90.33
RIP	/	0.071	**INH**	/	0.36

INH: isoniazid; RFP: rifampicin.

tetramethylsilane as an internal standard. Electrospray ionization (ESI) mass spectra and high resolution mass spectra (HRMS) were obtained on an MDSSCIEX Q-Tap mass spectrometer. Fast Atom Bombardment (FAB) mass spectra and high resolution mass spectra (HRMS) were obtained on a MICROMASS AutoSpec Ultima-TOF mass spectrometer. The reagents were all of analytical grade or chemically pure. TLC was performed on silica gel plates (Merck, ART5554 60F254).

Table 2
In vitro activity against MDR-MTB strains, and cytotoxicity of selected compounds.

Compd.	MIC (μM)		CC_{50}[b] (μM)	SI[c]
	MDR-MTB11168[a]	MDR-MTB9160[a]		
24	<0.041	0.20	NT	–
26g	1.47	2.64	193.38 ± 18.01	4395
26h	1.37	0.57	57.63 ± 1.54	1405
INH	>291	>291	NT	–
RFP	>57	>57	NT	–

INH: isoniazid; RFP: rifampicin; NT: not tested.
[a] MDR-MTB11168 and MDR-MTB9160 were isolated from patients in Beijing ChestHospital.
[b] CC_{50}: 50% cytotoxic concentration on Vero cell line.
[c] SI: selectivity index for MTB H37Rv ATCC 27294.

4.2. Synthesis

4.2.1. General synthesis procedure for the synthesis of compound *3, 4*

To a stirred solution of 4-bromophenol (3.46 g, 20 mmol), Ph_3P (7.86 g, 30 mmol) and compound **1**, **2** (20 mmol) in anhydrous THF (50 mL) was added dropwise DEAD (4.7 mL, 30 mmol) at 0 °C over 15 min. The mixture was stirred overnight and concentrated. The residue was purified by column chromatography (hexane:EtOAc = 3: 1) to give a white solid (22–34%).

To a stirred solution of above solide (5 mmol) in ethanol (20 mL) was added hydrazine hydrate (0.6 mL, 85%, 10 mmol) at room temperature. The mixture was refluxed for 3 h, cooled to room temperature and filtered. The filtrate was poured into DCM (100 mL) and washed by saturated brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to give the crude compounds **3, 4** (yield 70–80%) as brown oils which were used directly in the next step.

4.2.2. General synthesis procedure for the synthesis of compounds *8a-l* and *9a-d*

To a stirred solution of **5a-l** (21 mmol) in anhydrous toluene (40 mL) was added compounds **6**, **7** (7 mmol) at room temperature. The mixture was refluxed for 5 h, cooled to room temperature and filtered. The filtered solid was treated with NaOH solution (1 M, 50 mL) and extracted by DCM (50 mL × 3). The combined extraction was dried over anhydrous $MgSO_4$ and filtered. The filtration was concentrated to yield the crude compounds **8a-l**, **9a-d** which were not further purified and used directly for the next step.

4.2.3. General synthesis procedure for compounds *13a-b* and *14a-b*

To a stirred solution of compounds **11**, **12** in acetonitrile was added potassium carbonate and benzyl bromides **10a, b**. The mixture was refluxed for 3 h, cooled to room temperature and concentrated. The residue was treated with EtOAc, washed with water and saturated brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column (DCM: MeOH = 50: 1) to yield oils.

To a solution of above oils in DCM was added TFA at room temperature. The mixture was concentrated to afford the crude compounds **13a-b**, **14a-b** which were not further purified and used directly for the next step.

4.2.4. General synthesis procedure for compounds *16a-i*

To a stirred solution of piperazine and *t*-BuONa in anhydrous toluene was added $Pd(OAc)_2$ and BINAP in anhydrous toluene under argon at room temperature, and the resulting mixture was stirred for 15 min at the same temperature. To the reaction was added bromobenzenes **15a-i**, and the mixture was refluxed for 20 h.

The mixture was cooled to room temperature, filtered through celite. The filtrate was concentrated. The residue was treated with EtOAc, extracted by HCl solution (1 N, 20 mL × 2). The water phase was adjusted to pH 7 by NaOH solution (1 N) at 0 °C, extracted by EtOAc. The combined organic phase was washed by water and saturated brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated to yield compounds **16a-i** as yellow oils which were not further purified and used directly for the next step.

*4.2.5. Synthesis of compound **18***

To a stirred solution of compound **16a** (638 mg, 3.94 mmol) in acetonitrile (20 mL) was added potassium carbonate (545 mg, 3.94 mmol) and compound **17** (1.0 g, 3.94 mmol). The mixture was refluxed for 3 h, cooled to room temperature and concentrated. The residue was treated with EtOAc, washed with water and saturated brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was treated with EtOH (10 mL) to yield a yellow solid (1.06 g, 80%) which was not further purified and used directly for the next step.

To a stirred solution of above solid (1.06 g, 3.15 mmol) in ethanol (20 mL) was added hydrazine hydrate (0.6 mL, 85%, 10 mmol) at room temperature. The mixture was refluxed for 3 h, cooled to room temperature and filtered. The filtrate was poured into DCM (50 mL) and washed by saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give the title compound **18** (210 mg, 32%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.21–7.15 (m, 2H), 6.90–6.85 (m, 2H), 6.75–6.73 (m, 1H), 3.39 (s, 8H), 3.06–2.88 (m, 2H), 2.50–2.38 (m, 2H), 1.80 (m, 2H); MS-ESI (*m*/*z*):206.2 $(M + H)^+$.

*4.2.6. General procedure for the synthesis of target compounds (**24, 25, 26a-l, 27a-g, 28a,b, 29a,b, 30a-i, 31, 32a,b, 33**)*

To a stirred solution of compounds **21a, b** (0.5 mmol) in anhydrous DCM (20 mL) was added BOP-Cl (0.6 mmol), Et_3N (1.5 mmol) and the amino parts (**3, 4, 8a-l, 9a-d, 13a,b, 14a,b, 16a-i, 18, 22a,b** and **23**) at room temperature. The mixture was stirred overnight at the same temperature, and washed by H_3PO_4 solution (1%), saturated $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by Flash column chromatography (DCM/MeOH, 0–10%) to afford the crude target compounds as yellow solids. The solid was further purified by treating with EtOAc and hexane (11 mL, 1: 10) to yield the target compounds (**24, 25, 26a-l, 27a-g, 28a,b, 29a,b, 30a-i, 31, 32a,b, 33**).

*4.2.6.1. N-(2-(4-bromophenoxy)ethyl)-2,6-dimethylimidazo [1,2-a] pyridine-3- carboxamide **24**.* According to the general procedure, employing compound **21a** and **3** afforded compound **24** as a white solid (26.9%),mp: 170–172 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.48 (t, *J* = 4.8 Hz, 1H), 7.17 (dd, *J* = 14.4, 9.0 Hz, 2H), 6.79 (d, *J* = 9.0 Hz, 1H), 4.16 (t, *J* = 6.0 Hz, 2H), 3.92 (dd, *J* = 12.6, 6.6 Hz, 2H), 2.69 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.78, 157.66, 145.35, 145.13, 132.60, 130.26, 126.06, 123.26, 116.36, 115.81, 115.17, 113.68, 67.21, 38.80, 18.49, 16.68; MS-ESI (*m*/*z*): 388.22 $(M + H)^+$; HRMS-ESI (*m*/*z*): Calcd. for $C_{18}H_{19}BrN_3O_2$ $(M + H)^+$: 388.06552; Found: 388.06665.

*4.2.6.2. N-(3-(4-bromophenoxy)propyl)-2,6-dimethylimidazo [1,2-a] pyridine-3- carboxamide **25**.* According to the general procedure, employing compound **21a** and **4** afforded compound **25** as a white solid (30%), mp: 195–197 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 7.87 (t, *J* = 5.6 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 9.2 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 6.90 (dd, *J* = 9.2, 1.6 Hz, 1H), 4.06 (s, 2H), 3.47 (t, *J* = 5.6 Hz, 2H), 2.51 (s, 3H), 2.29 (s, 3H), 2.03–198 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.78, 157.66, 144.61, 143.76, 132.09, 129.08, 124.62, 121.88, 116.71, 115.76, 115.45, 111.82, 65.77, 35.95, 28.90, 17.77, 15.60; MS-ESI (*m*/*z*): 402.1, 404.1 $(M + H)^+$.

*4.2.6.3. 2,6-dimethyl-N-(2-(phenylamino)ethyl)imidazo [1,2-a]pyridine-3- carboxamide **26a**.* According to the general procedure, employing compound **21a** and **8a** afforded compound **26a** as a white solid (45%), mp: 127–129 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.86 (s, 1H), 7.83–7.79 (m, 1H), 7.47 (d, *J* = 9.0 Hz, 1H), 7.23 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.10–7.06 (m, 2H), 6.65–6.61 (m, 2H), 6.53 (t, *J* = 7.2 Hz, 1H), 5.73 (s, 1H), 3.51–3.46 (m, 2H), 3.28–3.23 (m, 2H), 2.54 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.29, 147.97, 145.32, 145.11, 130.17, 129.51, 126.03, 123.17, 118.03, 115.76, 115.16, 113.01, 44.16, 39.22, 18.50, 16.72; MS-ESI (*m*/*z*): 309.20 $(M + H)^+$.

*4.2.6.4. N-(2-((4-fluorophenyl)amino)ethyl)-2,6-dimethylimidazo [1,2-a]pyridine-3- carboxamide **26b**.* According to the general procedure, employing compound **21a** and **8b** afforded compound **26b** as a white solid (20.2%), mp: 138–140 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 7.83 (t, *J* = 5.6 Hz, 1H), 7.48 (d, *J* = 9.2 Hz, 1H), 7.25 (dd, *J* = 9.2, 1.2 Hz, 1H), 6.93 (t, *J* = 8.8 Hz, 2H), 6.72–6.56 (m, 2H), 3.48 (dd, *J* = 12.8, 6.4 Hz, 2H), 3.23 (t, *J* = 6.4 Hz, 2H), 2.54 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.13, 154.10 (d, *J* = 229 Hz) 145.40, 144.73, 143.76, 129.29, 124.78, 122.04, 115.65, 115.30 (d, *J* = 87.2 Hz), 112.61, 112.54, 42.87, 38.26, 17.78, 15.61; MS-ESI (*m*/*z*): 327.14 $(M + H)^+$.

*4.2.6.5. N-(2-((2-fluorophenyl)amino)ethyl)-2,6-dimethylimidazo [1,2-a]pyridine-3- carboxamide **26c**.* According to the general procedure, employing compound **21a** and **8c** afforded compound **26c** as a white solid (26%),mp: 118–120 °C; ^{1}H NMR (500 MHz, CDCl3) δ 9.16 (s, 1H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.27–7.20 (m, 2H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.84 (s, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.19 (s, 1H), 4.49 (s, 1H), 3.68–3.63 (m, 2H), 3.33–3.29 (m, 2H), 2.68 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.17, 155.37, 153.08, 145.39, 144.87, 143.84, 129.18, 124.76, 121.96, 115.63, 115.47, 115.42, 115.20, 112.61, 112.54, 42.88, 38.26, 17.78, 15.67; MS-ESI (*m*/*z*): 327.13 $(M + H)^+$.

*4.2.6.6. N-(2-((4-bromophenyl)amino)ethyl)-2,6-dimethylimidazo [1,2-a]pyridine-3- carboxamide **26d**.* According to the general procedure, employing compound **21a** and **8d** afforded compound **26d** as a white solid (25%), mp: 164–167 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.48 (d, *J* = 9.0 Hz, 1H), 7.28–7.26 (m, 1H), 7.25–7.23 (m, 1H), 7.20 (dd, *J* = 9.1, 1.6 Hz, 1H), 6.57–6.53 (m, 2H), 6.15 (s, 1H), 4.24 (s, 1H), 3.77–3.73 (m, 2H), 3.42–3.38 (m, 2H), 2.64 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.17, 147.94, 144.88, 143.84, 131.42, 129.16, 124.76, 121.93, 115.60, 115.44, 113.80, 106.15, 42.26, 38.11, 17.79, 15.68; MS-ESI (*m*/*z*): 387.09 $(M + H)^+$; HRMS-ESI (*m*/*z*): Calcd. for $C_{18}H_{20}BrN_4O$ $(M + H)^+$: 387.0815; Found: 387.0814.

*4.2.6.7. N-(2-((4-chloro-3-fluorophenyl)amino)ethyl)-2,6-dimethylimidazo [1,2-a] pyridine-3-carboxamide **26e**.* According to the general procedure, employing compound **21a** and **8e** afforded compound **26e** as a white solid (40.0%),mp: 180–183 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (d, *J* = 7.0 Hz, 1H), 7.32 (s, 1H), 6.96–6.92 (m, 1H), 6.77 (d, *J* = 6.8 Hz, 1H), 6.66–6.62 (m, 1H), 6.50–6.45 (m, 1H), 6.12 (s, 1H), 4.26 (s, 1H), 3.77–3.72 (m, 2H), 3.38–3.33 (m, 2H), 2.64 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.21, 148.97 (d, *J* = 232 Hz), 146.28, 144.89, 143.86, 129.18, 124.77, 121.94, 119.56, 119.38, 117.05, 116.84, 115.61, 115.46, 111.92, 111.65, 111.59, 42.49, 38.11, 17.79, 15.67; MS-ESI (*m*/*z*): 361.04 $(M + H)^+$; HRMS-ESI (*m*/*z*): Calcd. for $C_{18}H_{19}FClN_4O$ $(M + H)^+$: 361.1225; Found: 361.1223.

*4.2.6.8. N-(2-((3,4-dimethylphenyl)amino)ethyl)-2,6-dimethylimidazo [1,2-a] pyridine-3-carboxamide **26f**.* According to the general procedure, employing compound **21a** and **8f** afforded compound **26f** as a white solid (23.8%),mp: 147–149 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.52 (d, J = 9.0 Hz, 1H), 7.21 (dd, J = 9.1, 1.5 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.52 (d, J = 2.3 Hz, 1H), 6.49–6.45 (m, 2H), 3.77–3.72 (m, 2H), 3.46–3.42 (m, 2H), 2.64 (s, 3H), 2.37 (s, 3H), 2.18 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.20, 146.07, 145.31, 145.09, 137.63, 130.51, 130.10, 126.24, 126.05, 123.10, 115.76, 115.20, 115.07, 110.59, 44.38, 39.31, 20.15, 18.81, 18.50, 16.72; MS-ESI (m/z): 337.10 $(M + H)^+$; HRMS-ESI (m/z): Calcd. for $C_{20}H_{25}N_4O$ $(M + H)^+$: 337.20229; Found: 337.20186.

*4.2.6.9. N-(2-((4-methoxyphenyl)amino)ethyl)-2,6-dimethylimidazo [1,2-a] pyridine-3-carboxamide **26g**.* According to the general procedure, employing compound **21a** and **8g** afforded compound **26g** as a white solid (33.9%), mp: 119–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.47 (d, J = 9.1 Hz, 1H), 7.18 (dd, J = 9.1, 1.5 Hz, 1H), 6.81–6.76 (m, 2H), 6.68–6.63 (m, 2H), 6.22 (s, 1H), 3.75–3.72 (m, 5H), 3.42–3.38 (m, 2H), 2.63 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.15, 150.71, 144.83, 143.83, 142.93, 129.16, 124.76, 121.95, 115.68, 115.46, 114.69, 112.99, 55.31, 43.29, 38.44, 17.78, 15.67; MS-ESI (m/z): 339.07 $(M + H)^+$; HRMS-ESI (m/z): Calcd. for $C_{19}H_{23}N_4O_2$ $(M + H)^+$: 339.18155; Found: 339.18121.

*4.2.6.10. N-(2-((4-(tert-butyl)phenyl)amino)ethyl)-2,6-dimethylimidazo [1,2-a] pyridine-3-carboxamide **26h**.* According to the general procedure, employing compound **21a** and **8h** afforded compound **26h** as a white solid (26.9%),mp: 147–149 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.47 (d, J = 9.0 Hz, 1H), 7.22 (d, J = 8.6 Hz, 2H), 7.18 (dd, J = 9.1, 1.3 Hz, 1H), 6.65 (d, J = 8.6 Hz, 2H), 6.18 (s, 1H), 3.76–3.73 (m, 2H), 3.46–3.42 (m, 2H), 2.1 (s, 3H), 2.36 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.17, 146.28, 144.86, 143.84, 137.86, 129.12, 125.51, 124.77, 121.91, 115.66, 115.45, 111.67, 42.66, 38.42, 33.40, 31.46, 17.78, 15.68; MS-ESI (m/z): 365.09 $(M + H)^+$; HRMS-ESI (m/z): Calcd. for $C_{22}H_{29}N_4O$ $(M + H)^+$: 365.23359; Found: 365.23341.

*4.2.6.11. 2,6-dimethyl-N-(2-((4-nitrophenyl)amino)ethyl)imidazo [1,2-a]pyridine -3-carboxamide **26i**.* According to the general procedure, employing compound **21a** and **8i** afforded compound **26i** as a white solid (42.7%),mp: 238–240 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.08 (d, J = 9.1 Hz, 2H), 7.53 (d, J = 9.0 Hz, 1H), 6.60 (d, J = 9.2 Hz, 2H), 6.43 (s, 1H), 5.75 (s, 1H), 5.30 (s, 1H), 3.86–3.81 (m, 2H), 3.53–3.47 (m, 2H), 2.70 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 161.76, 155.06, 145.43, 144.35, 136.19, 129.71, 126.73, 125.22, 122.45, 115.97, 42.22, 38.52, 18.24, 16.14; MS-ESI (m/z): 354.06 $(M + H)^+$; HRMS-ESI (m/z): Calcd. for $C_{18}H_{20}N_5O_3$ $(M+H)^+$: 354.15607; Found: 354.15589.

*4.2.6.12. 2,6-dimethyl-N-(2-((4-(trifluoromethyl)phenyl)amino) ethyl)imidazo [1,2-a]pyridine-3-carboxamide **26j**.* According to the general procedure, employing compound **21a** and **8j** afforded compound **26j** as a white solid (19.8%),mp: 155–158 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 7.83 (t, J = 5.6 Hz, 1H), 7.47 (d, J = 9.2 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.24 (dd, J = 9.2, 1.7 Hz, 1H), 6.74 (d, J = 8.4 Hz, 2H), 6.54 (t, J = 6.4 Hz, 1H), 3.48 (dt, J = 14.4, 7.2 Hz, 2H), 3.39–3.29 (m, 3H), 2.53 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.22, 151.67, 144.92, 143.85, 130.69, 129.23, 126.31, 126.27, 124.77, 121.98, 115.59, 115.48, 111.22, 41.78, 38.04, 17.78, 15.65; MS-ESI (m/z): 377.08 $(M + H)^+$; HRMS-ESI (m/z): Calcd. for $C_{19}H_{20}F_3N_4O$ $(M + H)^+$: 377.15837; Found: 377.15813.

*4.2.6.13. 2,6-dimethyl-N-(2-((3-(trifluoromethyl)phenyl)amino) ethyl)imidazo [1,2-a]pyridine-3-carboxamide **26k**.* According to the general procedure, employing compound **21a** and **8k** afforded compound **26k** as a white solid (19.8%), mp: 169–170 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.51 (d, J = 9.1 Hz, 1H), 7.27–7.20 (m, 2H), 6.92 (d, J = 7.6 Hz, 1H), 6.84 (s, 1H), 6.79 (d, J = 8.2 Hz, 1H), 6.19 (s, 1H), 4.49 (s, 1H), 3.68–3.63 (m, 2H), 3.33–3.29 (m, 2H), 2.68 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.27, 147.94, 145.29, 145.14, 130.04, 129.39, 125.96, 124.77, 123.03, 117.98, 115.71, 115.14, 112.88, 44.15, 39.19, 18.48, 16.69; MS-ESI (m/z): 377.08 $(M + H)^+$; HRMS-ESI (m/z): Calcd. for $C_{19}H_{20}F_3N_4O$ $(M + H)^+$: 377.15837; Found: 377.15815.

*4.2.6.14. N-(2-((4-methoxyphenyl)amino)ethyl)-2,6-dimethylimidazo [1,2-a] pyridine-3-carboxamide **26l**.* According to the general procedure, employing compound **21b** and **8g** afforded compound **26l** as a white solid (26.9%),mp: 147–149 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.48 (d, J = 9.0 Hz, 1H), 7.19 (d, J = 8.6 Hz, 2H), 7.18 (dd, J = 9.1, 1.3 Hz, 1H), 6.79 (d, J = 8.6 Hz, 2H), 6.69 (d, J = 8.6 Hz, 2H), 6.25 (brs, 1H), 3.76 (s, 3H), 3.76–3.73 (m, 2H), 3.41–3.39 (m, 2H), 2.61 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.15, 150.72, 144.84, 143.83, 142.94, 129.16, 124.77, 121.95, 115.68, 115.45, 114.69, 112.99, 55.31, 43.30, 38.45, 17.78, 15.67; MS-ESI (m/z): 339.1 $(M + H)^+$.

*4.2.6.15. 2,6-dimethyl-N-(3-(phenylamino)propyl)imidazo [1,2-a] pyridine-3- carboxamide **27a**.* According to the general procedure, employing compound **21a** and **9a** afforded compound **27a** as a white solid (20.2%), mp: 156–158 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 7.85 (t, J = 5.6 Hz, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.22 (dd, J = 9.2, 1.6 Hz, 1H), 6.55–6.58 (d, J = 9.5 Hz, 2H), 6.51 (t, J = 9.0 Hz, 1H), 5.58 (t, J = 5.6 Hz, 1H), 3.43–3.88 (m, 2H), 3.12–3.07 (m, 2H), 2.53 (s, 3H), 2.29 (s, 3H), 1.87–1.80 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.01, 148.91, 144.57, 143.54, 129.07, 128.88, 124.59, 121.89, 115.85, 115.48, 111.97, 40.58, 36.94, 28.77, 17.78, 15.57; MS-ESI (m/z): 323.2 $(M + H)^+$.

*4.2.6.16. N-(3-((4-fluorophenyl)amino)propyl)-2,6-dimethylimidazo [1,2-a]pyridine -3-carboxamide **27b**.* According to the general procedure, employing compound **21a** and **9b** afforded compound **27b** as a white solid (20.2%), mp: 170–172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 7.84 (t, J = 5.6 Hz, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.23 (d, J = 1.6 Hz, 1H), 7.21 (dd, J = 9.2, 1.6 Hz, 1H), 6.58–6.53 (m, 2H), 5.53 (s, 1H), 3.43–3.38 (m, 2H), 3.07 (t, J = 5.2 Hz, 2H), 2.53 (s, 3H), 2.30 (s, 3H), 1.87–1.79 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.00, 155.30, 153.00, 145.66, 144.53, 143.74, 129.09, 124.59, 121.90, 115.84, 115.48, 115.33, 115.11, 112.69, 112.62, 41.26, 36.94, 28.72, 17.77, 15.57; MS-ESI (m/z): 341.2 $(M + H)^+$.

*4.2.6.17. N-(3-((4-(tert-butyl)phenyl)amino)propyl)-2,6-dimethylimidazo [1,2-a] pyridine-3-carboxamide **27c**.* According to the general procedure, employing compound **21a** and **9c** afforded compound **27c** as a white solid (26.9%), mp: 115–117 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 7.84 (t, J = 5.6 Hz, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.23 (dd, J = 9.2, 1.6 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 8.4 Hz, 2H), 5.41 (s, 1H), 3.43–3.38 (m, 2H), 3.10–3.06 (m, 2H), 2.54 (s, 3H), 2.29 (s, 3H), 1.86–1.79 (m, 2H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.99, 146.51, 144.54, 143.75, 137.71, 129.06, 125.45, 124.60, 121.89, 115.84, 115.48, 111.77, 40.79, 39.94, 33.40, 31.48, 28.84, 17.77, 15.58; MS-ESI (m/z): 379.1 $(M + H)^+$.

*4.2.6.18. 2,6-dimethyl-N-(3-((4-nitrophenyl)amino)propyl)imidazo [1,2-a]pyridine -3-carboxamide **27d**.* According to the general procedure, employing compound **21a** and **9d** afforded compound **27d** as a white solid (42.7%),mp: 225–228 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 7.98 (d, J = 9.3 Hz, 2H), 7.85 (t, J = 5.5 Hz,

1H), 7.47 (s, 1H), 7.34 (t, $J = 5.4$ Hz, 1H), 7.22 (dd, $J = 9.1$, 1.6 Hz, 1H), 6.65 (d, $J = 9.3$ Hz, 2H), 3.42 (q, $J = 6.6$ Hz, 2H), 3.26 (dd, $J = 12.7$, 6.7 Hz, 2H), 2.54 (s, 3H), 2.29 (s, 3H), 1.88 (p, $J = 6.8$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.07, 154.53, 144.63, 143.78, 135.54, 129.10, 126.26, 124.60, 121.91, 115.78, 115.48, 40.22, 36.74, 28.44, 17.76, 15.62; MS-ESI (m/z): 368.1 $(M + H)^+$.

4.2.6.19. 2,7-dimethyl-N-(3-(phenylamino)propyl)imidazo [1,2-a] pyridine-3- carboxamide ***27e****.* According to the general procedure, employing compound **21b** and **9a** afforded compound **27e** as a white solid (20.2%), mp: 156–158 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 7.85 (t, $J = 5.6$ Hz, 1H), 7.46 (d, $J = 9.2$ Hz, 1H), 7.22 (dd, $J = 9.2$, 1.6 Hz, 1H), 6.55–6.58 (d, $J = 9.5$ Hz, 2H), 6.51 (t, $J = 9.0$ Hz, 1H), 5.58 (t, $J = 5.6$ Hz, 1H), 3.43–3.88 (m, 2H), 3.12–3.07 (m, 2H), 2.53 (s, 3H), 2.29 (s, 3H), 1.87–1.80 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.01, 148.91, 144.57, 143.54, 129.07, 128.88, 124.59, 121.89, 115.85, 115.48, 111.97, 40.58, 36.94, 28.77, 17.78, 15.57; MS-ESI (m/z): 323.2 $(M + H)^+$.

4.2.6.20. N-(3-((4-(tert-butyl)phenyl)amino)propyl)-2,7-dimethylimidazo [1,2-a] pyridine-3-carboxamide ***27f****.* According to the general procedure, employing compound **21b** and **9c** afforded compound **27f** as a white solid (26.9%),mp: 115–117 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 7.84 (t, $J = 5.6$ Hz, 1H), 7.46 (d, $J = 9.2$ Hz, 1H), 7.23 (dd, $J = 9.2$, 1.6 Hz, 1H), 7.08 (d, $J = 8.4$ Hz, 2H), 6.51 (d, $J = 8.4$ Hz, 2H), 5.41 (s, 1H), 3.43–3.38 (m, 2H), 3.10–3.06 (m, 2H), 2.54 (s, 3H), 2.29 (s, 3H), 1.86–1.79 (m, 2H), 1.20 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.99, 146.51, 144.54, 143.75, 137.71, 129.06, 125.45, 124.60, 121.89, 115.84, 115.48, 111.77, 40.79, 39.94, 33.40, 31.48, 28.84, 17.77, 15.58; MS-ESI (m/z): 379.1 $(M + H)^+$.

4.2.6.21. 2,7-dimethyl-N-(3-((4-nitrophenyl)amino)propyl)imidazo [1,2-a]pyridine-3- carboxamide ***27g****.* According to the general procedure, employing compound **21b** and **9d** afforded compound **27b** as a white solid (42.7%),mp: 225–228 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 7.98 (d, $J = 5.6$ Hz, 2H), 7.79 (t, $J = 5.6$ Hz, 1H), 7.35–7.32 (m, 2H), 6.84 (d, $J = 8.4$ Hz, 2H), 6.64 (d, $J = 8.4$ Hz, 2H), 3.43–3.38 (m, 2H), 3.29–3.23 (m, 2H), 2.54 (s, 3H), 2.29 (s, 3H), 1.86–1.79 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.08, 154.53, 145.22, 144.86, 137.04, 135.54, 126.28, 115.46, 115.11, 114.52, 110.70, 40.22, 36.73, 28.48, 20.69, 15.67; MS-ESI (m/z): 368.1 $(M + H)^+$.

4.2.6.22. N-(2-(benzylamino)ethyl)-2,6-dimethylimidazo [1,2-a]pyridine-3- carboxamide ***28a****.* According to the general procedure, employing compound **21a** and **13a** afforded compound **28a** as a white solid (13.6%),mp:149–151 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.46 (s, 1H), 7.04 (d, $J = 5.6$ Hz, 2H), 6.88 (m, 4H), 3.54 (s, 2H), 3.13 (d, $J = 5.6$ Hz, 3H), 2.14 (s, 3H), 2.08 (s, 1H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.71, 145.48, 144.33, 129.68, 129.37, 128.79, 128.08, 125.26, 122.40, 115.99, 51.87, 47.73, 37.72, 18.28, 16.25; MS-ESI (m/z): 323.2 $(M + H)^+$.

4.2.6.23. N-(2-((4-bromobenzyl)amino)ethyl)-2,6-dimethylimidazo [1,2-a]pyridine-3- carboxamide ***28b****.* According to the general procedure, employing compound **21a** and **13b** afforded compound **28b** as a white solid (26.9%),mp: 112–114 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.79 (s, 1H), 7.59 (t, $J = 5.4$ Hz, 1H), 7.47 (d, $J = 9.0$ Hz, 1H), 7.44 (d, $J = 8.4$ Hz, 4H), 7.31 (d, $J = 8.4$ Hz, 4H), 7.23 (dd, $J = 9.0$, 1.2 Hz, 1H), 3.57 (s, 4.8H), 3.45 (dd, $J = 12.6$, 6.6 Hz, 2H), 3.34 (s, 3H), 2.59 (t, $J = 6.6$ Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.85, 144.60, 143.82, 138.67, 131.00, 130.72, 129.15, 124.70, 121.93, 119.87, 115.55, 115.47, 56.83, 52.60, 36.65, 17.84, 15.74; MS-ESI (m/z): 401.1, 403.0 $(M + H)^+$.

4.2.6.24. N-(2-(benzyloxy)ethyl)-2,6-dimethylimidazo [1,2-a]pyridine-3- carboxamide ***29a****.* According to the general procedure, employing compound **21a** and **14a** afforded compound **29a** as a white solid (24.8%), mp: 86–87 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.46 (d, $J = 9.0$ Hz, 1H), 7.35–7.27 (m, 5H), 7.16 (d, $J = 9.0$ Hz, $J = 1.0$ Hz, 1H), 6.24 (s, 1H), 4.56 (s, 2H), 3.72–3.68 (m, 4H), 2.64 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 145.16, 144.98, 137.80, 130.06, 128.64, 127.97, 126.05, 123.05, 115.71, 115.29, 77.41, 77.16, 76.91, 73.45, 68.90, 40.54, 39.21, 18.47, 16.60; MS-ESI (m/z): 324.20 $(M + H)^+$.

4.2.6.25. N-(2-((4-bromobenzyl)oxy)ethyl)-2,6-dimethylimidazo [1,2-a]pyridine-3- carboxamide ***29b****.* According to the general procedure, employing compound **21a** and **14b** afforded compound **29b** as a white solid (26.9%), mp: 112–114 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 7.84 (t, $J = 5.6$ Hz, 1H), 7.52 (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 9.2$ Hz, 1H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.24 (dd, $J = 9.2$, 1.6 Hz, 1H), 4.51 (s, 2H), 3.61 (t, $J = 5.6$ Hz, 2H), 3.52 (q, $J = 5.6$ Hz, 2H), 3.32 (s, 1H), 2.51 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.94, 144.71, 143.76, 137.94, 131.12, 129.64, 129.21, 124.61, 121.99, 120.45, 115.71, 115.46, 70.99, 68.45, 38.57, 17.77, 15.48; MS-ESI (m/z): 402.1, 404.0 $(M + H)^+$.

4.2.6.26. (2,6-dimethylimidazo [1,2-a]pyridin-3-yl)(4-phenylpiperazin-1-yl) methanone ***30a****.* According to the general procedure, employing compound **21a** and **16a** afforded compound **30a** as a white solid (23.8%), mp: 120–123 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.46 (d, $J = 9.1$ Hz, 1H), 7.25–7.18 (m, 3H), 6.96–6.93 (m, 2H), 6.83–6.79 (m, 1H), 3.69 (s, 4H), 3.19 (s, 4H), 2.38 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.80, 150.93, 145.45, 144.19, 129.54, 129.37, 124.48, 122.66, 120.84, 116.87, 115.99, 114.97, 63.81, 50.12, 18.34, 15.43; MS-ESI (m/z): 335.20 $(M + H)^+$; HRMS-ESI (m/z): Calcd. for $C_{21}H_{25}N_4O$ $(M+H)^+$: 335.18664; Found: 335.18631.

4.2.6.27. (2,6-dimethylimidazo [1,2-a]pyridin-3-yl)(4-(4-fluorophenyl)piperazin-1-yl) methanone ***30b****.* According to the general procedure, employing compound **21a** and **16b** afforded compound **30b** as a white solid (26.5%), mp: 110–112 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.46 (d, $J = 9.1$ Hz, 1H), 7.19 (dd, $J = 9.1$, 1.2 Hz, 1H), 7.09–7.03 (m, 2H), 7.00–6.94 (m, 2H), 3.69 (s, 4H), 3.13 (s, 4H), 2.38 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.41, 157.52, 155.18, 147.67, 144.11, 143.11, 129.05, 124.21, 121.89, 117.91, 117.84, 115.48, 115.27, 114.94, 49.60, 45.55, 44.47, 17.60, 14.78, 8.53; MS-ESI (m/z): 353.2 $(M + H)^+$.

4.2.6.28. (2,6-dimethylimidazo [1,2-a]pyridin-3-yl)(4-(2-fluorophenyl)piperazin-1-yl) methanone ***30c****.* According to the general procedure, employing compound **21a** and **16c** afforded compound **30c** as a white solid (46.1%), mp: 135–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.50 (d, $J = 9.1$ Hz, 1H), 7.16 (dd, $J = 9.1$, 1.4 Hz, 1H), 7.10–7.03 (m, 2H), 7.01–6.93 (m, 2H), 3.87 (s, 4H), 3.15 (s, 4H), 2.51 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.79, 149.47, 145.54, 144.32, 129.68, 129.22, 125.74, 124.53, 122.62, 120.16, 118.04, 116.53, 115.93, 114.86, 51.20, 45.43, 18.35, 15.52; MS-ESI (m/z):353.2 $(M + H)^+$.

4.2.6.29. (4-(4-chlorophenyl)piperazin-1-yl)(2,6-dimethylimidazo [1,2-a]pyridin-3-yl) methanone ***30d****.* According to the general procedure, employing compound **21a** and **16d** afforded compound **30d** as a white solid (36.5%), mp: 179–181 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.29–8.26 (m, 1H), 8.20–8.17 (m, 2H), 7.47 (d, $J = 9.1$ Hz, 1H), 7.22 (dd, $J = 9.2$, 1.6 Hz, 1H), 6.86–6.83 (m, 2H), 3.67 (s, 4H), 3.44 (s, 4H), 2.37 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.88, 149.58, 145.55, 144.33, 129.61, 129.25, 125.75,

124.52, 122.71, 118.10, 116.05, 114.90, 50.11, 45.23, 18.36, 15.50; MS-ESI (*m*/*z*): 369.2 $(M + H)^+$; HRMS-ESI (*m*/*z*): Calcd. for $C_{20}H_{22}ClN_4O$ $(M+H)^+$: 369.14767; Found: 369.14734.

4.2.6.30. (4-(4-bromophenyl)piperazin-1-yl)(2,6-dimethylimidazo [1,2-a]pyridin-3-yl) methanone ***30e***. According to the general procedure, employing compound **21a** and **16e** afforded compound **30e** as a white solid (36.9%), ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.46 (d, *J* = 9.1 Hz, 1H), 7.17 (dd, *J* = 9.1, 1.2 Hz, 1H), 7.13–7.09 (m, 2H), 6.90–6.86 (m, 2H), 3.80 (s, 4H), 3.23 (s, 4H), 2.42 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.83, 149.52, 145.45, 144.29, 129.72, 129.30, 125.76, 124.49, 122.64, 117.06, 115.88, 114.76, 50.41, 45.36, 18.40, 15.52; MS-ESI (*m*/*z*): 413.2415.1$(M + H)^+$; HRMS-ESI (*m*/*z*): Calcd. for $C_{20}H_{22}BrN_4O$ $(M+H)^+$: 413.09715; Found: 413.09687.

4.2.6.31. (4-(2,4-difluorophenyl)piperazin-1-yl)(2,6-dimethylimidazo [1,2-a] pyridin-3-yl)methanone ***30f***. According to the general procedure, employing compound **21a** and **16f** afforded compound **30f** as a white solid (46.5%), mp: 126–128 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.46 (d, *J* = 9.1 Hz, 1H), 7.13 (dd, *J* = 9.1, 1.6 Hz, 1H), 6.94–6.88 (m, 1H), 6.85–6.79 (m, 2H), 3.88 (s, 4H), 3.07 (s, 4H), 2.49 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 161.44, 158.50 (d, *J* = 47.6 Hz), 156.11 (d, *J* = 48.0 Hz), 155.89 (d, *J* = 37.2 Hz), 153.65 (d, *J* = 48.8 Hz), 144.20, 143.30, 136.37 (d, *J* = 12.8 Hz), 128.96, 124.18, 121.83, 120.54, 115.53, 114.86, 111.08, 104.95, 104.69, 104.44, 63.79, 50.82, 44.66, 17.61, 14.84; MS-ESI (*m*/*z*):371.2 $(M + H)^+$; HRMS-ESI (*m*/*z*): Calcd. for $C_{20}H_{21}F_2N_4O$ $(M+H)^+$: 371.16779; Found: 371.16746.

4.2.6.32. (2,6-dimethylimidazo [1,2-a]pyridin-3-yl)(4-(p-tolyl)piperazin-1-yl) methanone ***30g***. According to the general procedure, employing compound **21a** and **16g** afforded compound **30g** as a white solid (36.7%), mp: 160–163 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.48 (d, *J* = 9.1 Hz, 1H), 7.14 (dd, *J* = 9.1, 1.5 Hz, 1H), 7.12–7.08 (m, 2H), 6.88–6.85 (m, 2H), 3.84 (s, 4H), 3.19 (s, 4H), 2.50 (s, 3H), 2.33 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.83, 149.32, 145.50, 144.24, 129.49, 129.30, 124.66, 124.69, 120.78, 117.62, 116.12, 114.94, 58.27, 48.34, 20.20, 18.34, 15.49; MS-ESI (*m*/*z*): 349.2 $(M + H)^+$; HRMS-ESI (*m*/*z*): Calcd. for $C_{21}H_{25}N_4O$ $(M + H)^+$: 349.20229; Found: 349.20195.

4.2.6.33. (2,6-dimethylimidazo [1,2-a]pyridin-3-yl)(4-(4-methoxyphenyl) piperazin-1-yl)methanone ***30h***. According to the general procedure, employing compound **21a** and **16h** afforded compound **30h** as a white solid (41.0%),mp: 213–215 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.47 (d, *J* = 9.1 Hz, 1H), 7.14 (dd, *J* = 9.1, 1.6 Hz, 1H), 6.94–6.89 (m, 2H), 6.88–6.83 (m, 2H), 3.84 (s, 4H), 3.77 (s, 3H), 3.12 (s, 4H), 2.50 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.60, 154.26, 149.78, 144.20, 143.32, 128.99, 124.25, 121.79, 115.51, 114.86, 108.53, 45.62, 44.75, 43.97, 17.60, 14.82; HRMS-ESI (*m*/*z*): Calcd. for $C_{21}H_{25}N_4O_2$ $(M + H)^+$: 365.19720; Found: 365.19687.

4.2.6.34. (2,6-dimethylimidazo [1,2-a]pyridin-3-yl)(4-(4-nitrophenyl)piperazin-1-yl) methanone ***30i***. According to the general procedure, employing compound **21a** and **16i** afforded compound **30i** as a white solid (25.2%), mp: 218–220 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.17–8.13 (m, 2H), 7.47 (d, *J* = 9.1 Hz, 1H), 7.15 (dd, *J* = 9.1, 1.6 Hz, 1H), 6.89–6.85 (m, 2H), 3.87 (s, 4H), 3.51 (s, 4H), 2.50 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.95, 150.27, 145.68, 144.59, 129.64, 129.31, 125.77, 124.59, 122.89, 118.87, 116.76, 115.22, 50.24, 45.29, 18.41, 15.57; MS-ESI (*m*/*z*):380.2$(M + H)^+$; HRMS-ESI (*m*/*z*): Calcd. for $C_{20}H_{22}N_5O_3$ $(M + H)^+$: 380.17172; Found: 380.17136.

4.2.6.35. 2,6-dimethyl-N-(2-(4-phenylpiperazin-1-yl)ethyl)imidazo [1,2-a]pyridine-3- carboxamide ***31***. According to the general procedure, employing compound **21a** and **18** afforded compound **31** as a white solid (28.4%), mp: 138–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.46 (d, *J* = 9.1 Hz, 1H), 7.31–7.26 (m, 2H), 7.16 (dd, *J* = 9.1, 1.7 Hz, 1H), 6.97–6.92 (m, 2H), 6.88 (t, *J* = 7.3 Hz, 1H), 6.70 (s, 1H), 3.66–3.61 (m, 2H), 3.24–3.22 (m, 2H), 2.78–2.66 (m, 11H), 2.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.65, 151.15, 145.25, 145.03, 129.87, 129.27, 126.07, 122.95, 120.08, 116.18, 115.77, 115.33, 56.25, 52.87, 49.46, 35.66, 18.49, 16.96; MS-ESI (*m*/*z*): 378.37 $(M + H)^+$; HRMS-ESI (*m*/*z*): Calcd. for $C_{22}H_{28}N_5O$ $(M + H)^+$: 378.22884; Found: 378.22857.

4.2.6.36. (2,6-dimethylimidazo [1,2-a]pyridin-3-yl)(4-(pyridin-4-yl) piperazin-1-yl) methanone ***32a***. According to the general procedure, employing compound **21a** and **22a** (commercial available) afforded compound **32a** as a white solid (52.3%).mp: 99–101 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (s, 1H), 8.19 (d, *J* = 5.4 Hz, 2H), 7.47 (d, *J* = 9.1 Hz, 1H), 7.21 (d, *J* = 9.1 Hz, 1H), 6.84 (d, *J* = 5.2 Hz, 2H), 3.67 (s, 4H), 3.44 (s, 4H), 2.37 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.81, 151.02, 145.48, 144.26, 129.64, 129.33, 124.43, 122.69, 122.62, 117.75, 116.20, 54.08, 49.73, 18.39, 15.52; MS-ESI (*m*/*z*):336.2$(M + H)^+$; HRMS-ESI (*m*/*z*): Calcd. for $C_{19}H_{22}N_5O$ $(M + H)^+$: 336.18189; Found: 336.18157.

4.2.6.37. (2,6-dimethylimidazo [1,2-a]pyridin-3-yl)(4-(pyridin-2-yl) piperazin-1-yl) methanone ***32b***. According to the general procedure, employing compound **21a** and **22b** (commercial available) afforded compound **32b** as a white solid (52.3%), mp: 99–101 °C; Mp: 141–144 °C, ^{1}H NMR (500 MHz, DMSO-d_6) δ8.27 (s, 1H), 8.13 (d, *J* = 3.5 Hz, 1H), 7.59–7.52 (m, 1H), 7.46 (d, *J* = 9.1 Hz, 1H), 7.20 (d, *J* = 9.1 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 1H), 6.68–6.65 (m, 1H), 3.68–3.56 (m, 8H), 2.37 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.59, 158.69, 147.58, 144.17, 143.23, 137.65, 128.91, 124.21, 121.76, 115.50, 114.98, 113.36, 107.34, 44.88, 44.29, 17.58, 14.82; MS-ESI (*m*/*z*): 336.2 $(M + H)^+$; HRMS-ESI (*m*/*z*): Calcd. for $C_{19}H_{22}N_5O$ $(M + H)^+$: 336.18189; Found: 336.18154.

4.2.6.38. (2,6-dimethylimidazo [1,2-a]pyridin-3-yl)(4-(4-fluorophenyl)piperidin-1-yl) methanone ***33***. According to the general procedure, employing compound **21a** and **23** (commercial available) afforded compound **33** as a white solid (16.5%), mp: 117–119 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.46 (d, *J* = 9.0 Hz, 1H), 7.32–7.30 (m, 2H), 7.19 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.14–7.10 (m, 2H), 4.15–4.10 (m, 2H), 3.09–3.07 (m, 2H), 2.87–2.82 (m, 1H), 2.37 (s, 3H), 2.30 (s, 3H),1.83–1.81 (m, 2H),1.61–1.58 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.74, 159.82, 144.06, 142.99, 141.69, 128.81, 128.61, 128.55, 124.22, 121.72, 115.53, 115.28, 115.14, 114.98, 40.99, 17.66, 14.81; MS-ESI (*m*/*z*): 353.2 $(M + H)^+$.

4.3. MIC determination

MICs against replicating M. tuberculosis were determined by the microplate Alamar blue assay (MABA). RIF and INH were included as positive controls. M. tuberculosis H37Rv and clinical isolate strains was grown to late log phase (70–100 Klett units) in Difco Middlebrook 7H9 Broth (catalog no. 271310) supplemented with 0.2% (vol/vol) glycerol, 0.05% Tween 80, and 10% (vol/vol) albumin-dextrosecatalase (BBL Middlebrook ADC Enrichment, catalog no. 212352) (7H9-ADCTG). Cultures were centrifuged, washed twice,

and then suspended in phosphate phosphate-buffered saline. Suspensions were then passed through an 8 μm-pore-size filter to remove clumps, and aliquots were frozen at −80 °C. Two fold dilutions of target compounds were prepared in 7H9-ADC-TG in a volume of 100 μl in 96-well, black, clear-bottom microplates (BD Biosciences, Franklin Lakes, NJ). *M. tuberculosis* (100 μl containing 2×10^5 CFU) was added, yielding a final testing volume of 200 μl. The plates were incubated at 37 °C; on day 7 of incubation, 12.5 μl of 20% Tween 80 and 20 μl of Alamar blue were added to all wells. After incubation at 37 °C for 16–24 h, the fluorescence was read at an excitation of 530 nm and an emission of 590 nm. The MIC was defined as the lowest concentration effecting a reduction in fluorescence of ≥90% relative to the mean of replicate bacterium-only controls.

4.4. Cytotoxicity

Compounds **26g** and **26h** were further examined for toxicity (CC_{50}) in a mammalian Vero cell line at concentrations from 1000 to 4 μg/mL. The Vero cells were maintained in culture medium (Minimum Essential Medium with Earle's salt, supplemented with 10% fetal bovine serum) at 37 °C under 5% CO_2. Cells were seeded in 96-well plates at the plating density of 1×10^4 cells per well and allowed to recover for 24 h. Culture medium was replaced by assay medium containing the compound to be tested or drug-free. After 72 h of exposure, cells were harvested and cell viability was assessed by MTT assay. The CC_{50} values were calculated by Bliss analyses.

Notes

The authors declare no competing financial interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2017.05.044.

References

[1] L. Anderson, A. Dean, D. Falzon, et al., Global Tuberculosis Report. 2015, twentieth ed., World Health Organization, Geneva, 2015.
[2] R.S. Wallis, M. Maeurer, P. Mwaba, J. Chakaya, R. Rustomjee, G.B. Migliori, B. Marais, M. Schito, G. Churchyard, S. Swaminathan, M. Hoelscher, A. Zumla, Tuberculosis–advances in development of new drugs, treatment regimens, host-directed therapies, and biomarkers, Lancet Infect. Dis. 16 (2016) e34–46.
[3] A. Nusrath Unissa, L.E. Hanna, S. Swaminathan, A note on derivatives of isoniazid, rifampicin, and pyrazinamide showing activity against resistant Mycobacterium tuberculosis, Chem. Biol. drug Des. 87 (2016) 537–550.
[4] D. Schraufnagel, J. Abubaker, Global action against multidrug-resistant tuberculosis, JAMA 283 (2000) 54–55.
[5] D. Jones, Tuberculosis success, Nature reviews, Drug Discov. 12 (2013) 175–176.
[6] D.T. Hoagland, J. Liu, R.B. Lee, R.E. Lee, New agents for the treatment of drug-resistant Mycobacterium tuberculosis, Adv. Drug Deliv. Rev. 102 (2016) 55–72.
[7] S. Kang, R.Y. Kim, M.J. Seo, S. Lee, Y.M. Kim, M. Seo, J.J. Seo, Y. Ko, I. Choi, J. Jang, J. Nam, S. Park, H. Kang, H.J. Kim, J. Kim, S. Ahn, K. Pethe, K. Nam, Z. No, J. Kim, Lead optimization of a novel series of imidazo[1,2-a]pyridine amides leading to a clinical candidate (Q203) as a multi- and extensively-drug-resistant anti-tuberculosis agent, J. Med. Chem. 57 (2014) 5293–5305.
[8] K. Pethe, P. Bifani, J. Jang, S. Kang, S. Park, S. Ahn, J. Jiricek, J. Jung, H.K. Jeon, J. Cechetto, T. Christophe, H. Lee, M. Kempf, M. Jackson, A.J. Lenaerts, H. Pham, V. Jones, M.J. Seo, Y.M. Kim, M. Seo, J.J. Seo, D. Park, Y. Ko, I. Choi, R. Kim, S.Y. Kim, S. Lim, S.A. Yim, J. Nam, H. Kang, H. Kwon, C.T. Oh, Y. Cho, Y. Jang, J. Kim, A. Chua, B.H. Tan, M.B. Nanjundappa, S.P. Rao, W.S. Barnes, R. Wintjens, J.R. Walker, S. Alonso, S. Lee, J. Kim, S. Oh, T. Oh, U. Nehrbass, S.J. Han, Z. No, J. Lee, P. Brodin, S.N. Cho, K. Nam, J. Kim, Discovery of Q203, a potent clinical candidate for the treatment of tuberculosis, Nat. Med. 19 (2013) 1157–1160.
[9] Y. Cheng, G.C. Moraski, J. Cramer, M.J. Miller, J.S. Schorey, Bactericidal activity of an imidazo[1, 2-a]pyridine using a mouse M. tuberculosis infection model, PloS one 9 (2014) e87483.
[10] G.C. Moraski, L.D. Markley, P.A. Hipskind, H. Boshoff, S. Cho, S.G. Franzblau, M.J. Miller, Advent of imidazo[1,2-a]pyridine-3-carboxamides with potent multi- and extended drug resistant antituberculosis activity, ACS Med. Chem. Lett. 2 (2011) 466–470.
[11] K.A. Abrahams, J.A. Cox, V.L. Spivey, N.J. Loman, M.J. Pallen, C. Constantinidou, R. Fernandez, C. Alemparte, M.J. Remuinan, D. Barros, L. Ballell, G.S. Besra, Identification of novel imidazo[1,2-a]pyridine inhibitors targeting M. tuberculosis QcrB, PloS One 7 (2012) e52951.
[12] Z. Wu, Y. Lu, L. Li, R. Zhao, B. Wang, K. Lv, M. Liu, X. You, Identification of *N*-(2-Phenoxyethyl)imidazo[1,2-a]pyridine-3-carboxamides as new antituberculosis agents, ACS Med. Chem. Lett. 7 (2016) 1130–1133.
[13] L.H. Li, Z.Y. Wu, M.L. Liu, Z.R. Li, H.Y. Guo, Q.R. Zhang, Microwave assisted synthesis ofdisubstituentedimidazo[1,2-a]-pyridine-3-carboxylic esters in ethanol, Heterocycles 91 (2015) 2087–2095.
[14] L. Collins, S.G. Franzblau, Microplate alamar blue assay versus BACTEC 460 system for high-throughput screening of compounds against Mycobacterium tuberculosis and Mycobacterium avium, Antimicrob. agents Chemother. 41 (1997) 1004–1009.
[15] Y. Lu, M. Zheng, B. Wang, L. Fu, W. Zhao, P. Li, J. Xu, H. Zhu, H. Jin, D. Yin, H. Huang, A.M. Upton, Z. Ma, Clofazimine analogs with efficacy against experimental tuberculosis and reduced potential for accumulation, Antimicrob. agents Chemother. 55 (2011) 5185–5193.