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Original article

Synthesis, molecular docking and anti-mycobacterial evaluation of new imidazo[1,2-a]pyridine-2-carboxamide derivatives



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ABSTRACT

New anti-tubercular agents, imidazo[1,2-a]pyridine-2-carboxamide derivatives (**5a–q**) have been designed and synthesized. The structural considerations of the designed molecules were further supported by the docking study with a long-chain enoyl-acyl carrier protein reductase (InhA). The chemical structures of the new compounds were characterized by IR, ¹H NMR, ¹³C NMR, HRMS and elemental analysis. In addition, single crystal X-ray diffraction has also been recorded for compound **5f**. Compounds were evaluated *in vitro* against *Mycobacterium tuberculosis* H37Rv, and cytotoxicity against HEK-293T cell line. Amongst the tested compounds **5j**, **5l** and **5q** were emerged as good anti-tubercular agents with low cytotoxicity. The structure-anti TB activity relationship of these derivatives was explained by molecular docking.

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1. Introduction

TB is a chronic bacterial infection is often contracted through an airborne bacterium known as *Mycobacterium tuberculosis*. Although most *M. tuberculosis* infections, known as pulmonary TB, are in the lungs, 5 to 10 percent of TB patients can develop the disease in organs such as lymph nodes, bones and joints, eyes, intestines, larynx, or the urinary and reproductive systems, skin, and stomach, known as extrapulmonary TB [1,2]. In recent years, the emergence of MDR and XDR tuberculosis strains has amplified the incidences of TB. In addition, TB is a co-infection of HIV-AIDS and

accounts for 26% of AIDS related death worldwide [3–7]. In 2012, an estimated 8.6 million people affected by *M. tuberculosis* and 1.3 million died from the disease, including 320,000 deaths among HIV-positive people [8]. To address these issues, design, synthesize and develop potent anti-mycobacterial agents are necessary.

Imidazopyridine derivatives are very important, versatile motifs with significant applications in medicinal chemistry [9–14]. Different compounds containing the moiety imidazo[1,2-a]pyridine have significant biological applications such as anti-mycobacterial [15–21], anticancer [22,23], antiviral [24–27], antimicrobial [28–30], anti-HIV [31], antiulcer [32,33], antihelminthic [34] and anticoccidial activity [35,36]. As a result of our interest in the synthesis of imidazopyridine-containing compounds and their antimicrobial activity [37], we initiated a program directed towards the synthesis of the new imidazopyridine amide derivatives. Imidazopyridine amides (IPA) are a new class of therapeutic agents against MDR and XDR tuberculosis [18–21]. Recently, Quriat Therapeutics discovered Q203 (Fig. 1), a highly innovative drug for MDR and XDR tuberculosis and the first drug in its class with an original mechanism of action [21]. On the basis of above beneficial

Abbreviations: TB, tuberculosis; MDR, multiple drug-resistant; XDR, extensively drug-resistant; HIV-AIDS, human immunodeficiency virus-acquired immunodeficiency syndrome; DIPEA, diisopropylethylamine; HATU, 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxid hexafluorophosphate; MIC, minimum inhibitory concentration.

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information, we earmarked to design new imidazo[1,2-a]pyridine-2-carboxamide derivatives anticipating enhanced biological activity to combat this lethal disease. The structural considerations of the designed molecules were further supported by the docking study with target enzyme InhA, an enzyme essential for mycolic acid biosynthesis in *M. tuberculosis*. The new target compounds were designed based on the assumptions of Lipinski rule to fulfil the drug likeness properties of the molecules. We report herein, synthesis, crystal structure, molecular docking and anti-mycobacterial evaluation of new imidazo[1,2-a]pyridine-2-carboxamide derivatives.

2. Results and discussion

2.1. Chemistry

The synthetic strategy of new polyfunctional imidazo[1,2-a]pyridine-2-carboxamides were described in Scheme 1. The imidazo[1,2-a]pyridine ring system was accomplished by the condensation of 2-amino-5-iodopyridine (**1**) with ethyl bromopyruvate (α -halocarbonyl compound) in refluxing ethanol to gave ethyl-6-iodo-*H*-imidazo[1,2-a]pyridine-2-carboxylate (**2**) [38]. ^1H NMR spectrum of **2** showed a triplet at δ 1.30 (3H) and a quartet at δ 4.30 (2H) ppm corresponds to an ethyl ester group at position 2. ^{13}C NMR spectrum of **2** showed peaks at δ 167.3 (COO—CH₂—CH₃), 60.3 (O—CH₂), 14.8 (CH₃) ppm also revealed that the presence of ethyl ester group. IR spectrum of **2** revealed that appearance of the band at 1748 cm^{−1} characteristic for ester C=O stretch. The ester hydrolysis reaction of **2** with lithium hydroxide monohydrate gave 6-iodo-*H*-imidazo[1,2-a]pyridine-2-carboxylic acid (**3**). ^1H NMR and ^{13}C NMR spectra of **3** exhibited a broad singlet peak at δ 11.50 ppm and a peak at δ 167.1 ppm were assigned for carboxylic acid, while its IR spectrum showed a strong band at 1755 cm^{−1} also revealed that the presence of carboxylic acid. The peptide coupling reaction between **3** and 4-fluorobenzylamine was accomplished by famous peptide coupling reagent, HATU and Hunig's base (DIPEA) in DMF gave scaffold **4a**. IR spectrum of **4a** showed that the appearance of the band at 1650 cm^{−1} characteristic for amide C=O stretch. ^1H NMR spectrum of **4a** showed a triplet at δ 9.00 ppm revealed that the presence of the carboxamide group at position 2, while its ^{13}C NMR spectrum showed δ 162.4 ppm also revealed that the presence of carboxamide group. The remaining scaffolds (**4b–g**)

were synthesized by using the same experimental protocol with different aromatic or aliphatic amines ($\text{R}^1\text{—NH}_2$). The Suzuki reaction of **4a** with 1-methylpyrazole-4-boronic acid pinacol ester, catalysed by Pd(0) complex in the presence of Na₂CO₃ gave final product **5a**. IR spectrum of **4a** showed that the appearance of the band at 1650 cm^{−1} characteristic for amide C=O stretch. ^1H NMR and ^{13}C NMR spectra of **5a** were revealed that the presence of the carboxamide group at position 2, showed a triplet at δ 8.93 ppm and δ 162.3 ppm, respectively. The band at 1652 cm^{−1} in the IR spectrum of **5a** characteristic for the amide C=O stretch. The HRMS spectrum of **5a** showed 350.1405 [M+H]⁺ corresponding with proposed isotopic mass (349.1338). The obtained elemental analysis values are in consonance with theoretical data. The remaining final compounds (**5b–q**) were synthesized using the same experimental procedure with different aromatic or hetero aromatic boronic acids (R^2). The structures of the final products were assigned on the basis of their IR, ^1H NMR, ^{13}C NMR, HRMS and elemental analysis. The structure of the compound **5f** (Fig. 2) was unequivocally established by X-ray crystallographic analysis. The details of the crystal data and structure refinement was shown in Table 1.

2.2. Pharmacology

All the synthesized compounds were also screened for their *in vitro* anti-tubercular activity against *M. tuberculosis* H37Rv (ATCC 27294) using microplate alamar blue assay (MABA) with drug concentrations from 50 $\mu\text{g/mL}$ to 0.78 $\mu\text{g/mL}$ in duplicates. The MIC was determined for each compound which was measured as the minimum concentration of compound required to completely inhibit the bacterial growth. Isoniazid and rifampicin were used as reference compounds for comparison. The *in vitro* test results for title compounds were tabulated in Table 2 as the MIC and the activity ranged from 6.25 to >50 $\mu\text{g/mL}$. Various substitutions were attempted at R¹ and R² position of the imidazo[1,2-a]pyridine core as steps towards the derivation of structure–activity relationship and to understand the ideal site for introducing chemical diversity. Out of the various compounds tested, compounds **5h**, **5j**, **5k**, **5l**, **5o** and **5q** inhibited mycobacterial growth very effectively compared to others in the series with MIC values ranging from 6.25 to 12.5 $\mu\text{g/mL}$. The highest activity, 6.25 $\mu\text{g/mL}$ was registered for compounds **5j** (R¹ = pyridin-4-yl methyl, R² = 4-chlorophenyl), **5l** (R¹ = benzo

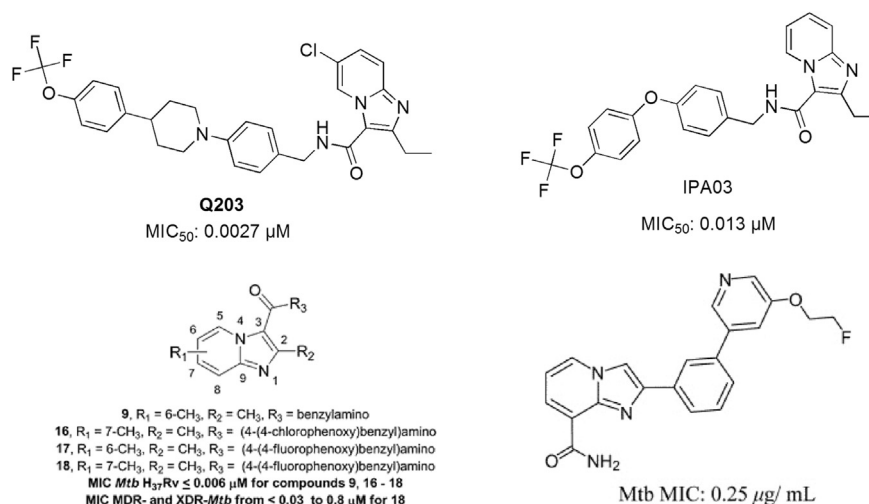
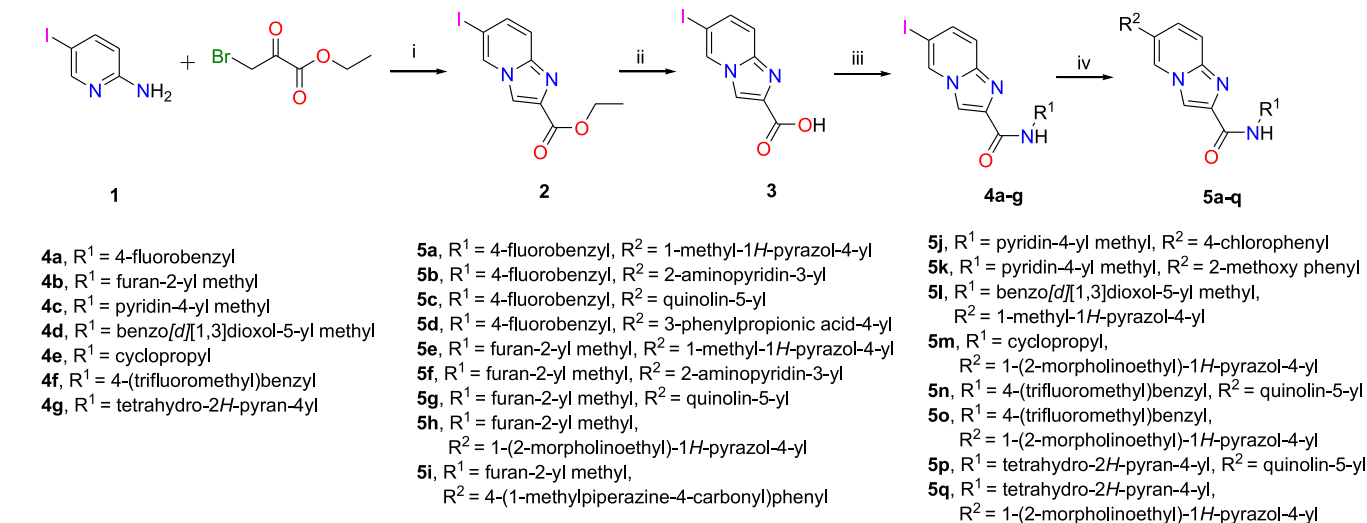


Fig. 1. Some of the imidazopyridine amide based anti-tubercular agents.



Scheme 1. Synthesis of imidazo[1,2-a]pyridine-2-carboxamide derivatives; Reagents and conditions: (i) ethyl alcohol, reflux, 4 h; (ii) LiOH, methanol/THF/H₂O, 60 °C, 1 h; (iii) R¹-NH₂, DIPEA, HATU, DMF, rt, 12 h (iv) R²-B(OH)₂, Na₂CO₃, Pd(PPh₃)₄, 1,4-dioxane/H₂O, 90 °C, 8 h.

[d][1,3]dioxol-5-yl methyl, R² = 1-methyl-1H-pyrazol-4-yl) and **5q** (R¹ = tetrahydro-2H-pyran-4-yl, R² = 1-(2-morpholinoethyl)-1H-pyrazol-4-yl). It was observed that the presence of the hydrophobic substituents on both R¹ and R² position of the imidazo [1,2-a]pyridine core brought about an enhancement of the anti-mycobacterial potency as the overall hydrophobic nature might have enabled these molecules to penetrate the quite complex mycobacterial cell wall, a major hurdle faced in anti-tubercular drug discovery. Lipophilicities of the compounds **5a–q** and the standard drugs, which were expressed as logP values, were determined using the logP method through online <http://www.molinspiration.com/cgi-bin/properties> site, as shown in Table 2.

The safety profile of the active leads was also accessed by testing *in vitro* cytotoxicity against Human Embryonic Kidney Cell-line 293T (HEK-293T) cells at 50 µg/mL concentration by (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Percentage inhibitions of cells are reported in Table 2. The entire tested compound demonstrated a good safety profile with very low toxicity towards the HEK cells and showed a good selectivity index (CC₅₀/MIC) indicating the suitability of these compounds for further drug development.

2.3. Molecular docking studies

The molecular docking of imidazo[1,2-a]pyridine carboxamide motifs (**5a–q**) with a long-chain enoyl-acyl carrier protein reductase (InhA) yielded best possible conformations with parameters including the docking energy, binding energy, inhibition constant and intermolecular energy (Table 3). The docking results are drawn based on both binding energy and the number of hydrogen bonds formed. The intermolecular hydrogen bond interactions play an important role in adduct binding in InhA, especially the hydrogen bonds of the pyrophosphate part. The main residues involved in these interactions are His 265, Tyr 259, Trp 249, Gly 3, Ile 194, and Arg 173. Compounds (**5a–q**) showed very good docking energy ranging from −12.07 kJ/mol to −9.42 kJ/mol because target compounds have formed one or more hydrogen bonds with amino acid residues in the active pocket of InhA (Fig. 3). Compounds containing the halogen atoms (**5a–d**, **5j**, **5n**, **5o**) also have the ability to form intermolecular bonds with the active site of InhA in a fashion that resembles hydrogen bonds. All compounds, except **5c**, **5g** and **5n** have formed two or more hydrogen bonds with amino acid residues of InhA. The maximum number of hydrogen bonds was found in the analogue **5o** (3 hydrogen bonds) with a binding energy (−9.20 kJ mol^{−1}), docking energy (−11.62 kJ mol^{−1}) and inhibition constant (1.79 × 10^{−7} M). In *in vitro* anti-mycobacterial studies, compounds **5h**, **5j**, **5k**, **5l**, **5o** and **5q** have emerged as active against microbe, so it can be predicted as the activity may be due to inhibition of enzyme InhA.

3. Conclusions

In conclusion, new anti-tubercular agents imidazo [1,2-a] pyridine-2-carboxamide derivatives **5a–q** was efficiently synthesized. The activity of these compounds against *M. tuberculosis* strain H37Rv was assessed and compounds **5j**, **5l** and **5q** were displayed good anti-tubercular activity. Their activity depends on both the substituent's R¹ and R². The *in vitro* cytotoxicity study against HEK-293T cells at 50 µg/mL by MTT assay revealed that the identified hits are found to be less cytotoxic. The molecular docking of InhA domain with synthesized compounds revealed that compounds **5h**, **5j**, **5k**, **5l**, **5o** and **5q** having the good inhibitory capability and are exhibiting the interactions with one or the other amino acids in the active pocket. With new antiTB agents desperately needed, we

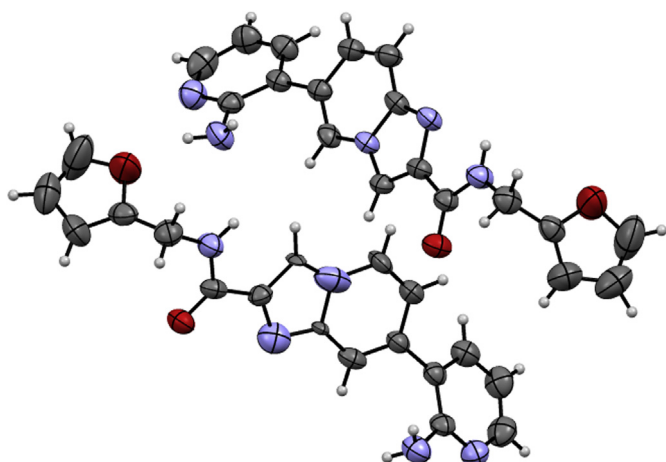


Fig. 2. X-ray crystal structure of **5f**.

Table 1
Crystal data and structure refinement for **5f**.

Identification code	5f
Empirical formula	C ₁₈ H ₁₅ N ₅ O ₂
Formula weight	333.344
Temperature/K	296.15
Crystal system	Monoclinic
Space group	P2 ₁ /c
a/Å	31.097(6)
b/Å	9.3652(19)
c/Å	10.816(2)
α/°	90.00
β/°	90.084(11)
γ/°	90.00
Volume/Å ³	3149.9(11)
Z	4
ρ _{calc} mg/mm ³	1.383
m/mm ^{−1}	0.090
F(000)	1368.0
Crystal size/mm ³	0.21 × 0.18 × 0.26
Radiation	MoKα (λ = 0.71073)
2θ range for data collection	2.62–50°
Index ranges	−36 ≤ h ≤ 36, −11 ≤ k ≤ 10, −12 ≤ l ≤ 12
Reflections collected	35,922
Independent reflections	5523 [R _{int} = 0.1491, R _{sigma} = 0.1080]
Data/restraints/parameters	5523/0/454
Goodness-of-fit on F ²	1.016
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0908, wR ₂ = 0.2394
Final R indexes [all data]	R ₁ = 0.1799, wR ₂ = 0.2817
Largest diff. peak/hole/e Å ^{−3}	0.44/−0.60

believe that the new imidazopyridines reported in this work provide an interesting potential for further optimization. Further structural modifications of the identified hits are in progress in order to enhance the efficacy of these compounds active against *M. tuberculosis*.

4. Experimental section

4.1. General methods

All chemicals and solvents were purchased from commercial suppliers. All reactions were performed under an inert atmosphere of dry nitrogen using dry solvents. The progress of the reactions was monitored by using Si gel 60 F₂₅₄ thin layer chromatography plates and spots were detected by UV/254 nm. Compounds were purified by column chromatography on silica gel 230–400 using petether/ethyl acetate or dichloromethane/methanol solvent mixtures as eluent. All the compounds were characterized by IR, ¹H NMR, ¹³C NMR, HRMS and elemental analysis. Melting points of the samples were determined in open capillary tubes using Buchi Melting point B-540 apparatus and are uncorrected. IR spectra were obtained on a PerkinElmer Frontier™ FT-IR spectrometer, were recorded in KBr. ¹H and ¹³C NMR spectra were recorded on a Bruker NMR spectrometer (400 and 100 MHz, respectively) using deuterated DMSO as solvent with TMS as internal standard. The mass recorded in Agilent LCMS 1100 series instrument using API-ES positive-ion mode and negative-ion mode. HRMS was recorded in positive-ion mode by Microflex LT MALDI-ToF mass spectrometer (Bruker Daltonics, Germany). The CHN analysis was recorded in an Elementar vario MICRO cube.

4.2. Experimental procedure for the synthesis of ethyl 6-iodoH-imidazo[1,2-a]pyridine-2-carboxylate (**2**)

A mixture of 2-amino-5-iodo pyridine **1** (20 g, 90.90 mmol) and ethyl bromopyruvate (53.17 g, 272.70 mmol) were refluxed in 200 mL of ethanol for 4 h. The solvent was concentrated under

reduced pressure. The residue was neutralized with 10% NaHCO₃ solution (250 mL). The solid formed was collected by filtration, washed with water and dried. Off white solid (26.7 g, 94%); mp 135.8–138.6 °C; IR (KBr, ν_{max}, cm^{−1}): 3163 (C–H_{arom.}), 2918 (C–H_{aliph.}), 1748 (C=O_{ester}), 1575 (C–C_{arom.}); ¹H NMR (400 MHz, DMSO-D₆): δ 8.94 (s, 1H, H-5), 8.43 (s, 1H, H-3), 7.53 (d, J = 9.6 Hz, 1H, H-7), 7.47 (d, J = 9.6 Hz, 1H, H-8), 4.30 (q, J = 7.2 Hz, 2H, O–CH₂–CH₃), 1.30 (t, J = 7.2 Hz, 3H, CH₂–CH₃); ¹³C NMR (100 MHz, DMSO-D₆): δ 167.3 (COO–CH₂–CH₃), 156.4 (C-5), 149.3 (C-9), 144.5 (C-7), 138.8 (C-2), 118.9 (C-3), 118.1 (C-8), 96.2 (C-6), 60.3 (O–CH₂), 14.8 (CH₃); LC/MS (API-ES) m/z calcd. for C₁₀H₉IN₂O₂: 315.971, found: 317.0 [M+H]⁺; Anal. calcd. for C₁₀H₉IN₂O₂: C, 38.00; H, 2.87; N, 8.86; found C, 37.98; H, 2.859; N, 8.81.

4.3. Experimental procedure for the synthesis of 6-iodoH-imidazo[1,2-a]pyridine-2-carboxylic acid (**3**)

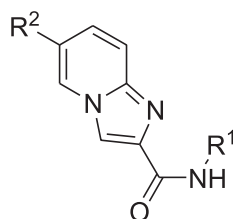
A mixture of compound **2** (26.7 g, 84.46 mmol) and lithium hydroxide monohydrate (10.63 g, 253.38 mmol) and 270 mL of methanol/THF/water (7:2:1) were heated at 60 °C for 1 h. The solvent was concentrated under reduced pressure. The residue was dissolved in 80 mL of water. The P^H of the reaction mixture was adjusted to 6 by using 10% citric acid solution. The solid formed was collected by filtration, washed with water and dried. White solid (22.6 g, 93%); mp 185.9–188.4 °C; IR (KBr, ν_{max}, cm^{−1}): 3166 (C–H_{arom.}), 2520 (O–H_{acid}), 2920 (C–H_{aliph.}), 1755 (C=O_{acid}), 1576 (C–C_{arom.}), 1221 (C–O_{acid}); ¹H NMR (400 MHz, DMSO-D₆): δ 11.50 (br s, 1H, COOH), 8.94 (s, 1H, H-5), 8.30 (s, 1H, H-3), 7.48 (d, J = 9.6 Hz, 1H, H-7), 7.43 (d, J = 9.6 Hz, 1H, H-8); ¹³C NMR (100 MHz, DMSO-D₆): δ 167.1 (COOH), 156.4 (C-5), 149.4 (C-9), 144.5 (C-7), 138.9 (C-2), 118.8 (C-3), 118.2 (C-8), 96.1 (C-6); LC/MS (API-ES) m/z calcd. for C₈H₅IN₂O: 287.940, found: 287.0 [M-H]⁺; Anal. calcd. for C₈H₅IN₂O: C, 33.36; H, 1.75; N, 9.73; found: C, 33.32; H, 1.758; N, 9.69.

4.4. General experimental procedure for the synthesis of **4a–g**

Synthesis of N-(4-fluorobenzyl)-6-iodo1H-imidazo[1,2-a]pyridine-2-carboxamide (4a) as an example: To a mixture of compound **3** (1 g, 3.47 mmol), 4-fluorobenzylamine (0.65 g, 5.21 mmol) and DIPEA (2.4 mL, 13.89 mmol) in DMF (10 mL), HATU (1.98 g, 5.21 mmol) was added portion wise at 0 °C. The resulting reaction mixture was stirred at rt for 12 h. The solvent was removed under reduced pressure. The reaction mixture was dissolved in DCM (50 mL) and the organic layer was washed with water (25 mL) and brine (25 mL). The organic layer was separated and dried over anhydrous MgSO₄. The organic layer was concentrated in vacuum. The crude product was purified via flash column chromatography on silica gel (230–400 mesh) to provide **4a** as pale yellow solid (1.27 g, 93%).

4.4.1. N-(4-Fluorobenzyl)-6-iodo1H-imidazo[1,2-a]pyridine-2-carboxamide (**4a**)

mp 195.1–197.0 °C; IR (KBr, ν_{max}, cm^{−1}): 3354 (N–H_{amide}), 3163, 3076 (C–H_{arom.}), 2918 (C–H_{aliph.}), 1650 (C=O_{amide}), 1574 (C–C_{arom.}); ¹H NMR (300 MHz, DMSO-D₆): δ 9.00 (t, J = 6.0 Hz, 1H, CO–NH–CH₂), 8.95 (s, 1H, H-5), 8.26 (s, 1H, H-3), 7.46 (d, J = 10.4 Hz, 2H, H-2', H-6'), 7.36–7.32 (m, 2H, Ar–H), 7.11 (d, J = 12.0 Hz, 2H, H-3', H-5'), 4.41 (d, J = 8.4 Hz, 2H, CO–NH–CH₂–Ar); ¹³C NMR (100 MHz, DMSO-D₆): δ 162.4 (CO–NH), 162.1 (C-4'), 159.7 (C-9), 156.3 (C-5), 144.5 (C-7), 136.0 (C-1'), 135.9 (C-2), 129.4 (C-2'), 129.3 (C-6'), 118.8 (C-3), 118.2 (C-8), 114.9 (C-3'), 114.7 (C-5'), 96.2 (C-6), 41.2 (CO–NH–CH₂–Ar); LC/MS (API-ES) m/z calcd. for C₁₅H₁₁FIN₃O: 394.993, found: 396.1 [M+H]⁺; Anal. calcd. for C₁₅H₁₁FIN₃O: C, 45.59; H, 2.81; N, 10.63, found: C, 45.56; H, 2.808; N, 10.60.

Table 2Anti-mycobacterial activity and cytotoxicity of compounds **5a–q**.

Compound	R ¹	R ²	MIC (μg/mL) ^a	Cytotoxicity at 50 μg/mL ^b	LogP
5a			25	36.12	2.420
5b			25	40.8	2.578
5c			25	28.12	4.302
5d			>50	NT	3.985
5e			>50	NT	1.513
5f			25	26.12	1.672
5g			25	24.8	3.396
5h			12.5	34.06	1.389
5i			25	30.12	1.994
5j			6.25	26.12	3.268
5k			12.5	31.62	2.598

Table 2 (continued)

Compound	R ¹	R ²	MIC (μg/mL) ^a	Cytotoxicity at 50 μg/mL ^b	LogP
5l			6.25	25.56	2.146
5m			25	29.12	1.099
5n			25	37.80	5.034
5o			12.5	22.16	3.027
5p			25	30.7	1.232
5q			6.25	30.06	3.114
Isoniazid	—	—	0.36	—	−0.70
Rifampicin	—	—	0.02	—	2.770

^a Anti-mycobacterial activity against *M. tuberculosis* strain H37Rv.^b Percentage of cell inhibition at 50 μg/mL against HEK-293T cells; NT denotes not tested.

4.4.2. *N*-(Furan-2-ylmethyl)-6-iodo-1*H*-imidazo[1,2-*a*]pyridine-2-carboxamide (**4b**)

Prepared from **3** (1 g, 3.47 mmol), furfurylamine (0.51 g, 5.21 mmol), DIPEA (2.4 mL, 13.89 mmol), HATU (1.98 g, 5.21 mmol) in DMF (10 mL). **4b** was formed as a pale brown crystal (1.11 g, 87%); mp 201.2–203.0 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.96 (s, 1H, H-5), 8.78 (t, *J* = 6.0 Hz, 1H, CO–NH–CH₂), 8.28 (s, 1H, H-3), 7.55–7.50 (m, 2H, Ar–H), 7.43 (d, *J* = 9.6 Hz, 1H, H-5'), 6.36 (t, *J* = 3.2 Hz, 1H, H-4'), 6.22 (d, *J* = 3.1 Hz, 1H, H-3'), 4.43 (d, *J* = 6.1 Hz, 2H, CO–NH–CH₂–Ar); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 161.8 (CO–NH), 156.3 (C-5), 152.5 (C-9), 144.5 (C-7), 141.8 (C-2'), 139.4 (C-5'), 135.9 (C-2), 119.0 (C-3), 118.2 (C-8), 110.4 (C-4'), 106.6 (C-3'), 96.2 (C-6), 35.3 (CO–NH–CH₂–Ar); LC/MS (API-ES) *m/z* calcd. for [C₁₃H₁₀IN₃O₂]: 366.982, found: 368.0 [M+H]⁺; Anal. calcd. for C₁₃H₁₀IN₃O₂: C, 42.53; H, 2.75; N, 11.45; found: C, 42.56; H, 2.759; N, 11.43.

4.4.3. 6-Iodo-*N*-(pyridin-4-ylmethyl)-1*H*-imidazo[1,2-*a*]pyridine-2-carboxamide (**4c**)

Prepared from **3** (1 g, 3.47 mmol), 4-(aminomethyl)pyridine (0.56 g, 5.21 mmol), DIPEA (2.4 mL, 13.89 mmol), HATU (1.98 g, 5.21 mmol) in DMF (10 mL). **4c** was formed as an off white solid (1.17 g, 89%); mp 165.8–168.3 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.13 (t, *J* = 6.4 Hz, 1H, CO–NH–CH₂), 8.97 (s, 1H, H-5), 8.48 (d, *J* = 6.0 Hz, 2H, H-2', H-6'), 8.29 (s, 1H, H-3), 7.53 (d, *J* = 11.1 Hz, 1H, H-7), 7.45 (d, *J* = 9.5 Hz, 1H, H-8), 7.29 (d, *J* = 5.8 Hz, 2H, H-3', H-5'), 4.47 (d, *J* = 6.3 Hz, 1H, CO–NH–CH₂–Ar); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 162.3 (CO–NH), 156.4 (C-5), 149.4 (C-9), 148.7 (C-2', C-

6'), 144.5 (C-7), 139.9 (C-4'), 135.1 (C-2), 122.2 (C-3', C-5'), 118.6 (C-3), 118.2 (C-8), 96.3 (C-6), 41.1 (CO–NH–CH₂–Ar); LC/MS (API-ES) *m/z* calcd. for C₁₄H₁₁IN₄O: 377.998, found: 379.1 [M+H]⁺; Anal. calcd. for C₁₄H₁₁IN₄O: C, 44.46; H, 2.93; N, 14.82; found: C, 44.44; H, 2.925; N, 14.83.

4.4.4. *N*-(Benzo[d][1,3]dioxol-5-ylmethyl)-6-iodo-1*H*-imidazo[1,2-*a*]pyridine-2-carboxamide (**4d**)

Prepared from **3** (1 g, 3.47 mmol), piperonylamine (0.79 g, 5.21 mmol), DIPEA (2.4 mL, 13.89 mmol), HATU (1.98 g, 5.21 mmol) in DMF (10 mL). **4d** was formed as an off white solid (1.34 g, 92%); mp 211.0–213.2 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.95 (s, 1H, H-5), 8.88 (t, *J* = 6.4 Hz, 1H, CO–NH–CH₂), 8.26 (s, 1H, H-3), 7.49 (d, *J* = 12.0 Hz, 1H, H-7), 7.41 (d, *J* = 12.0 Hz, 1H, H-8), 6.88 (s, 1H, H-4'), 6.83–6.76 (m, 2H, Ar–H), 5.94 (s, 2H, O–CH₂–O), 4.33 (d, *J* = 5.8 Hz, 2H, CO–NH–CH₂–Ar); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 161.9 (CO–NH), 156.5 (C-5), 147.1 (C-9), 145.9 (H-3a'), 144.5 (C-7), 135.9 (C-2), 133.7 (H-7a'), 120.6 (C-5'), 118.8 (C-3), 117.8 (C-6'), 118.2 (C-8), 108.1 (C-7'), 107.9 (C-4'), 100.7 (O–CH₂–O), 96.3 (C-6), 41.7 (CO–NH–CH₂–Ar); LC/MS (API-ES) *m/z* calcd. for C₁₆H₁₂IN₃O₃: 420.992, found: 422.0 [M+H]⁺; Anal. calcd. for C₁₆H₁₂IN₃O₃: C, 45.63; H, 2.87; N, 9.98; found: C, 45.60; H, 2.871; N, 10.00.

4.4.5. *N*-Cyclopropyl-6-iodo-1*H*-imidazo[1,2-*a*]pyridine-2-carboxamide (**4e**)

Prepared from **3** (1 g, 3.47 mmol), cyclopropylamine (0.3 g, 5.21 mmol), DIPEA (2.4 mL, 13.89 mmol), HATU (1.98 g, 5.21 mmol)

Table 3
Molecular docking of imidazo[1,2-a]pyridine-2-carboxamide motifs (**5a–q**) with InhA.

Compound	Binding energy (kJ/mol)	Docking energy (kJ/mol)	Inhibition constant (M)	Intermolecular energy (kJ/mol)	H-bonds	Bonding
5a	−8.31	−9.42	8.12×10^{-7}	−9.55	2	5a ::DRG1:HAZ:INHA:B:HIS265:O 5a ::DRG1:NAM:INHA:A:TYR259:HH 5b ::DRG1:HBA:INHA:A:GLN32:OE1 5b ::DRG1:OAM:INHA:A:TRP249:HE1 5c ::DRG1:OAM:INHA:B:ILE194:HN 5d ::DRG1:OBE:INHA:A:ILE21:HN 5d ::DRG1:OBD:INHA:A:ALA22:HN 5e ::DRG1:HAY:INHA:B:GLY3:O 5e ::DRG1:OAR:INHA:B:TRP249:HE1 5f ::DRG1:HAZ:INHA:B:ILE194:O 5f ::DRG1:NAQ:INHA:B:ILE194:HN 5g ::DRG1:OAM:INHA:B:ILE194:HN 5h ::DRG1:OAU:INHA:A:LYS8:H22 5h ::DRG1:OBC:INHA:B:ASN231:HN 5i ::DRG1:NAI:INHA:B:ARG153:HH1 5i ::DRG1:OAL:INHA:B:HIS265:HD1 5j ::DRG1:NAR:INHA:B:MET98:HN 5j ::DRG1:OAM:INHA:B:TYR158:HH 5k ::DRG1:NAR:INHA:A:TRP249:HE1 5k ::DRG1:NAI:INHA:B:TRP249:HE1 5l ::DRG1:HBC:INHA:B:HIS265:O 5l ::DRG1:NAM:INHA:B:ARG225:HH1 5m ::DRG1:HBE:INHA:A:ILE257:O 5m ::DRG1:OAR:INHA:B:ARG173:HH12 5n ::DRG1:OAM:INHA:A:TRP249:HE1 5o ::DRG1:HAQ:INHA:A:ASP256:OD1 5o ::DRG1:NAM:INHA:B:ARG173:HH21 5o ::DRG1:OAR:INHA:A:TYR259:HH 5p ::DRG1:NAM:INHA:A:THR2:HN1 5p ::DRG1:OAR:INHA:B:TRP249:HE1 5q ::DRG1:HAL:INHA:B:GLY3:O 5q ::DRG1:OAM:INHA:B:TRP249:HE1
5b	−9.64	−11.16	8.60×10^{-8}	−10.88	2	
5c	−10.56	−12.07	1.81×10^{-8}	−11.81	1	
5d	−9.85	−11.86	6.02×10^{-8}	−12.03	2	
5e	−8.75	−10.16	3.83×10^{-7}	−10.00	2	
5f	−9.46	−10.95	1.16×10^{-7}	−10.71	2	
5g	−9.66	−11.16	8.34×10^{-8}	−10.90	1	
5h	−8.72	−10.33	4.06×10^{-7}	−10.90	2	
5i	−8.66	−10.59	4.51×10^{-7}	−10.53	2	
5j	−9.00	−10.08	2.53×10^{-7}	−10.25	2	
5k	−8.55	−10.18	5.38×10^{-7}	−10.11	2	
5l	−8.85	−9.94	3.25×10^{-7}	−10.1	2	
5m	−9.04	−10.28	2.37×10^{-7}	−10.91	2	
5n	−9.53	−10.95	1.03×10^{-7}	−11.09	1	
5o	−9.20	−11.62	1.79×10^{-7}	−11.69	3	
5p	−9.43	−10.09	1.23×10^{-7}	−10.36	2	
5q	−10.03	−10.61	4.44×10^{-8}	−10.96	2	

in DMF (10 mL). **4e** was formed as an off white solid (0.96 g, 85%); mp 125.5–128.3 °C; ^1H NMR (300 MHz, DMSO- D_6): δ 8.95 (s, 1H, H-5), 8.38 (d, J = 4.7 Hz, 1H, CO–NH–CH), 8.24 (s, 1H, H-3), 7.49 (d, J = 12.0 Hz, 1H, H-7), 7.39 (d, J = 9.4 Hz, 1H, H-8), 2.86–2.82 (m, 1H, C-1'), 0.65–0.50 (m, 4H, H-2', H-3'); ^{13}C NMR (100 MHz, DMSO- D_6): δ 163.2 (CO–NH), 156.5 (C-5), 144.6 (C-9), 144.4 (C-7), 138.3 (C-2), 125.8 (C-3), 118.2 (C-8), 96.3 (C-6), 24.9 (C-1'), 5.7 (C-2'), 5.5 (C-3'); LC/MS (API-ES) m/z calcd. for $\text{C}_{11}\text{H}_{10}\text{IN}_3\text{O}$: 326.987, found: 328.0 $[\text{M}+\text{H}]^+$; Anal. calcd. for $\text{C}_{11}\text{H}_{10}\text{IN}_3\text{O}$: C, 40.39; H, 3.08; N, 12.85; found: C, 40.41; H, 3.074; N, 12.85.

4.4.6. *N*-(4-(Trifluoromethyl)benzyl)-6-iodoH-imidazo[1,2-a]pyridine-2-carboxamide (**4f**)

Prepared from **3** (1 g, 3.47 mmol), 4-(trifluoromethyl)benzylamine (0.91 g, 5.21 mmol), DIPEA (2.4 mL, 13.89 mmol), HATU (1.98 g, 5.21 mmol) in DMF (10 mL). **4f** was formed as a pale yellow solid (1.44 g, 93%); mp 200.2–202.4 °C; ^1H NMR (300 MHz, DMSO- D_6): δ 9.13 (t, J = 6.0 Hz, 1H, CO–NH–CH₂), 8.96 (s, 1H, H-5), 8.28 (s, 1H, H-3), 7.66 (d, J = 8.1 Hz, 2H, H-3', H-5'), 7.51 (d, J = 8.4 Hz, 2H, H-2', H-6'), 7.49–7.39 (m, 2H, Ar–H), 4.52 (d, J = 6.2 Hz, 2H, CO–NH–CH₂–Ar); ^{13}C NMR (100 MHz, DMSO- D_6): δ 162.3 (CO–NH), 156.5 (C-5), 144.7 (C-9), 144.4 (C-7), 135.4 (C-2), 133.5 (C-1'), 127.8 (C-4'), 127.5 (C-2', C-6'), 125.1 (C-3', C-5'), 125.0 (Ar–CF₃), 118.8 (C-3), 118.2 (C-8), 96.4 (C-6), 41.7 (CO–NH–CH₂–Ar); LC/MS (API-ES) m/z calcd. for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{IN}_3\text{O}$: 444.99, found 446.0 $[\text{M}+\text{H}]^+$; Anal. calcd. for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{IN}_3\text{O}$: C, 43.17; H, 2.49; N, 9.44; found: C, 43.20; H, 2.504; N, 9.46.

4.4.7. 6-Iodo-*N*-(tetrahydro-2H-pyran-4-yl)H-imidazo[1,2-a]pyridine-2-carboxamide (**4g**)

Prepared from **3** (1 g, 3.47 mmol), 4-aminotetrahydropyran (0.53 g, 5.21 mmol), DIPEA (2.4 mL, 13.89 mmol), HATU (1.98 g, 5.21 mmol) in DMF (10 mL). **4g** was formed as an off white solid

(1.11 g, 86%); mp 111.3–113.6 °C; ^1H NMR (300 MHz, DMSO- D_6): δ 8.95 (s, 1H, H-5), 8.27 (d, J = 8.4 Hz, 1H, CO–NH–CH), 8.25 (s, 1H, H-3), 7.49 (d, J = 9.3 Hz, 1H, H-7), 7.41 (d, J = 9.3 Hz, 1H, H-8), 4.02–3.95 (m, 1H, H-4'), 3.84 (d, J = 11.2 Hz, 2H, H-2a', H-6a'), 3.41–3.35 (dt, J = 11.2, 4.0 Hz, 2H, H-2b', H-6b'), 1.74–1.66 (m, 4H, H-3', H-5'); ^{13}C NMR (100 MHz, DMSO- D_6): δ 161.2 (CO–NH), 156.4 (C-5), 147.9 (C-9), 144.5 (C-7), 135.9 (C-2), 118.8 (C-3), 118.2 (C-8), 96.5 (C-6), 66.1 (C-2', C-6'), 44.9 (C-4'), 32.3 (C-3', C-5'); LC/MS (API-ES) m/z calcd. for $\text{C}_{13}\text{H}_{14}\text{IN}_3\text{O}_2$: 371.013, found: 372.2 $[\text{M}+\text{H}]^+$; Anal. calcd. for $\text{C}_{13}\text{H}_{14}\text{IN}_3\text{O}_2$: C, 42.07; H, 3.80; N, 11.32; found C, 42.09; H, 3.809; N, 11.30.

4.5. General experimental procedure for the synthesis of **5a–q**

4.5.1. Synthesis of *N*-(4-fluorobenzyl)-6-(1-methyl-1H-pyrazol-4-yl)H-imidazo[1,2-a]pyridine-2-carboxamide (**5a**) as an example

An oven-dried Schlenk tube was charged with compound **4a** (300 mg, 0.76 mmol), 1-methylpyrazole-4-boronic acid pinacol ester (236.9 mg, 1.14 mmol), Na_2CO_3 (241.4 mg, 2.28 mmol) and 9.5:0.5 mixture of 1,4-dioxane/water (10 mL). The Schlenk tube was capped with a rubber septum, evacuated and backfilled with argon (this sequence was carried out four times). Tetrakis(triphenylphosphine)palladium(0) (43.9 mg, 0.04 mmol) was added and the Schlenk tube was sealed with a Teflon screw cap. The reaction mixture was heated to 90 °C for 8 h. The reaction mixture was filtered through a thin pad of celite (eluted with CH_2Cl_2) and the eluent was concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel (230–400 mesh) to provide **5a** as a white solid (225.4 mg, 85%).

4.5.1.1. *N*-(4-Fluorobenzyl)-6-(1-methyl-1H-pyrazol-4-yl)H-imidazo[1,2-a]pyridine-2-carboxamide (**5a**). mp 220.3–222.6 °C; IR (KBr, ν_{max} , cm^{-1}): 3355 (N–H_{amide}), 3163, 3076 (C–H_{arom.}), 2919

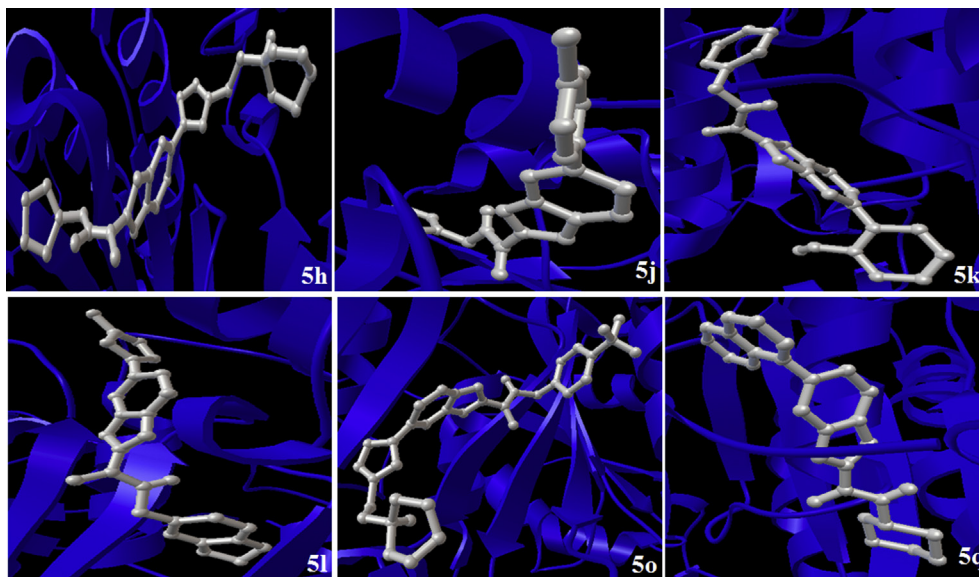


Fig. 3. Interaction of compounds **5h**, **5j**, **5k**, **5l**, **5o** and **5q** in the active pocket of InhA.

(C–H_{aliph.}), 1652 (C=O_{amide}), 1574 (C–C_{arom.}); ¹H NMR (400 MHz, DMSO–D₆): δ 8.93 (t, *J* = 6.0 Hz, 1H, CO–NH–CH₂), 8.81 (s, 1H, H–5), 8.27 (s, 1H, H–3), 8.15 (s, 1H, H–3''), 7.86 (s, 1H, H–5''), 7.57 (d, *J* = 10.4 Hz, 2H, H–2', H–6'), 7.38–7.35 (m, 2H, Ar–H), 7.12 (t, *J* = 8.8 Hz, 2H, H–3', H–5'), 4.44 (d, *J* = 6.4 Hz, 2H, CO–NH–CH₂–Ar), 3.87 (s, 3H, N–CH₃); ¹³C NMR (100 MHz, DMSO–D₆): δ 162.3 (CO–NH), 162.1 (C–4'), 159.8 (C–9), 142.8 (C–5), 139.7 (C–3''), 136.0 (C–1'), 135.9 (C–2), 129.4 (C–2'), 129.3 (C–6'), 128.1 (C–7), 125.8 (C–6), 121.9 (C–5''), 118.8 (C–3), 117.3 (C–8), 114.9 (C–3'), 114.7 (C–5'), 114.6 (C–4''), 41.3 (CO–NH–CH₂–Ar), 38.7 (N–CH₃); HRMS (MALDI–TOF) *m/z* calcd. for C₁₉H₁₆FN₅O: 349.1338, found: 350.1405 [M+H]⁺ (100%), 372.1235 [M+Na]⁺, 388.0978 [M+K]⁺; Anal. calcd. for C₁₉H₁₆FN₅O: C, 65.32; H, 4.62; N, 20.05; found: C, 65.30; H, 4.611; N, 20.09.

4.5.1.2. N-(4-Fluorobenzyl)-6-(2-aminopyridin-3-yl)H-imidazo[1,2-a]pyridine-2-carboxamide (5b). Prepared from **4a** (300 mg, 0.76 mmol), 2-aminopyridine-3-boronic acid (157.1 mg, 1.14 mmol), Na₂CO₃ (241.4 mg, 2.28 mmol), Pd(PPh₃)₄ (43.9 mg, 0.04 mmol) in 1,4-dioxane/water (10 mL). **5b** was formed as an off white solid (0.23 g, 84%); mp 242.0–244.6 °C; IR (KBr, ν_{max}, cm^{−1}): 3448 (N–H_{amide}), 3284 (N–H_{amine}), 3175, 3138, 3065, 3038 (C–H_{arom.}), 2931 (C–H_{aliph.}), 1651 (C=O_{amide}), 1606 (N–H_{amine}), 1568 (C–C_{arom.}), 1261 (C–N_{amine}); ¹H NMR (400 MHz, DMSO–D₆): δ 8.96 (t, *J* = 6.4 Hz, 1H, CO–NH–CH₂), 8.64 (s, 1H, H–5), 8.35 (s, 1H, H–3), 7.99–7.97 (dd, *J* = 4.8, 1.6 Hz, 1H, H–6''), 7.63 (d, *J* = 9.2 Hz, 1H, H–4''), 7.42–7.33 (m, 4H, Ar–H), 7.12 (t, *J* = 8.8 Hz, 2H, H–3', H–5'), 6.65 (t, *J* = 4.8 Hz, 1H, H–5''), 5.83 (s, 2H, Ar–NH₂), 4.44 (d, *J* = 6.0 Hz, 2H, CO–NH–CH₂–Ar); ¹³C NMR (100 MHz, DMSO–D₆): δ 162.3 (CO–NH), 162.1 (C–4'), 159.8 (C–9), 157.1 (Ar–C–2''–NH₂), 147.7 (C–6''), 143.1 (C–5), 139.7 (C–4''), 137.8 (C–1'), 136.1 (C–2), 129.3 (C–2'), 129.2 (C–6'), 128.1 (C–7), 126.6 (C–6), 123.5 (C–3''), 117.2 (C–3), 116.2 (C–8), 115.0 (C–3'), 114.7 (C–5'), 112.7 (C–5''), 41.3 (CO–NH–CH₂–Ar); HRMS (MALDI–TOF) *m/z* calcd. for C₂₀H₁₆FN₅O: 361.1338, found: 362.1403 [M+H]⁺ (100%), 384.1236 [M+Na]⁺; Anal. calcd. for C₂₀H₁₆FN₅O: C, 66.47; H, 4.46; N, 19.38; found: C, 66.50; H, 4.452; N, 19.33.

4.5.1.3. N-(4-Fluorobenzyl)-6-(quinolin-5-yl)H-imidazo[1,2-a]pyridine-2-carboxamide (5c). Prepared from **4a** (300 mg, 0.76 mmol), quinoline-5-boronic acid (197 mg, 1.14 mmol), Na₂CO₃ (241.4 mg,

2.28 mmol), Pd(PPh₃)₄ (43.9 mg, 0.04 mmol) in 1,4-dioxane/water (10 mL). **5c** was formed as a white solid (0.259 g, 86%); mp 199.6–201.9 °C; IR (KBr, ν_{max}, cm^{−1}): 3406 (N–H_{amide}), 3144, 3124, 3091, 3061 (C–H_{arom.}), 2861 (C–H_{aliph.}), 1662 (C=O_{amide}), 1574 (C–C_{arom.}); ¹H NMR (400 MHz, DMSO–D₆): δ 9.03 (t, *J* = 6.4 Hz, 1H, CO–NH–CH₂), 8.97–8.95 (dd, *J* = 4.0, 1.6 Hz, 1H, H–2''), 8.78 (s, 1H, H–5), 8.42 (s, 1H, H–3), 8.30–8.27 (dd, *J* = 8.8, 0.8 Hz, 1H, H–8''), 8.12 (d, *J* = 8.4 Hz, 1H, H–4''), 7.86 (t, *J* = 8.4 Hz, 1H, H–7''), 7.70 (d, *J* = 8.8 Hz, 1H, H–6''), 7.55 (d, *J* = 10.4 Hz, 2H, H–2', H–6'), 7.50–7.47 (dd, *J* = 9.2, 1.6 Hz, 1H, H–3''), 7.40–7.36 (m, 2H, Ar–H), 7.13 (t, *J* = 8.8 Hz, 2H, H–3', H–5'), 4.46 (d, *J* = 6.4 Hz, 2H, CO–NH–CH₂–Ar); ¹³C NMR (100 MHz, DMSO–D₆): δ 162.3 (CO–NH), 162.0 (C–4'), 159.9 (C–9), 150.6 (C–2''), 147.9 (C–8a''), 143.1 (C–5), 140.1 (C–1'), 136.0 (C–2), 135.4 (C–5''), 133.5 (C–4''), 129.4 (C–2'), 129.3 (C–6'), 129.1 (C–7''), 128.9 (C–7), 127.8 (C–8''), 127.3 (C–6''), 126.2 (C–6), 124.3 (C–4a''), 121.9 (C–3''), 116.8 (C–3), 115.2 (C–8), 115.0 (C–3'), 114.7 (C–5'), 41.3 (CO–NH–CH₂–Ar); HRMS (MALDI–TOF) *m/z* calcd. for C₂₄H₁₇FN₄O: 396.1386, found: 397.1459 [M+H]⁺ (100%), 419.1282 [M+Na]⁺, 435.1019 [M+K]⁺; Anal. calcd. for C₂₄H₁₇FN₄O: C, 72.72; H, 4.32; N, 14.13; found: C, 72.74; H, 4.316; N, 14.15.

4.5.1.4. 3-(4-(2-((4-Fluorobenzyl)carbamoyl)H-imidazo[1,2-a]pyridin-6-yl)phenyl)propanoic acid (5d). Prepared from **4a** (300 mg, 0.76 mmol), 4-(2-carboxyethyl)benzeneboronic acid (220.9 mg, 1.14 mmol), Na₂CO₃ (241.4 mg, 2.28 mmol), Pd(PPh₃)₄ (43.9 mg, 0.04 mmol) in 1,4-dioxane/water (10 mL). **5d** was formed as a white solid (0.256 g, 81%); mp 230.1–232.7 °C; IR (KBr, ν_{max}, cm^{−1}): 3298 (N–H_{amide}), 3187, 3088, 3059, 3034 (C–H_{arom.}), 2949, 2921, 2857 (C–H_{aliph.}), 2516 (O–H_{acid}), 1703 (C=O_{acid}), 1646 (C=O_{amide}), 1580 (C–C_{arom.}), 1222 (C–O_{acid}); ¹H NMR (400 MHz, DMSO–D₆): δ 12.14 (br s, 1H, COOH), 8.96 (t, *J* = 6.4 Hz, 1H, CO–NH–CH₂), 8.91 (s, 1H, H–5), 8.35 (s, 1H, H–3), 7.67–7.61 (m, 4H, Ar–H), 7.38–7.35 (m, 4H, Ar–H), 7.13 (t, *J* = 8.8 Hz, 2H, H–3', H–5'), 4.44 (d, *J* = 6.4 Hz, 2H, CO–NH–CH₂–Ar), 2.87 (t, *J* = 7.2 Hz, 2H, CH₂–CH₂–Ar), 2.56 (t, *J* = 7.6 Hz, 2H, HOOC–CH₂–CH₂); ¹³C NMR (100 MHz, DMSO–D₆): δ 173.7 (COOH), 162.3 (CO–NH), 162.0 (C–4'), 159.9 (C–9), 143.1 (C–5), 140.8 (C–1''), 140.0 (C–1'), 136.0 (C–2), 133.9 (C–4''), 129.4 (C–2'), 129.3 (C–6'), 129.0 (C–7), 126.4 (C–2''), 126.3 (C–3''), 125.8 (C–6), 124.4 (C–3'), 117.1 (C–3), 115.0 (C–8), 114.7 (C–5'), 41.3 (CO–NH–CH₂–Ar), 35.1 (CH₂–CH₂–COOH), 29.9 (CH₂–CH₂–Ar); HRMS (MALDI–TOF) *m/z* calcd. for C₂₄H₂₀FN₃O₃: 417.1488, found:

418.1559 [M+H]⁺ (100%), 440.1385 [M+Na]⁺; Anal. calcd. for C₂₄H₂₀FN₃O₃: C, 69.05; H, 4.83; N, 10.07; found: C, 69.09; H, 4.839; N, 10.04.

4.5.1.5. N-(Furan-2-ylmethyl)-6-(1-methyl-1H-pyrazol-4-yl)H-imidazo[1,2-a]pyridine-2-carboxamide (5e). Prepared from **4b** (300 mg, 0.82 mmol), 1-methylpyrazole-4-boronic acid pinacol ester (255 mg, 1.23 mmol), Na₂CO₃ (259.8 mg, 2.45 mmol), Pd(PPh₃)₄ (47.2 mg, 0.04 mmol) in 1,4-dioxane/water (10 mL). **5e** was formed as a white solid (0.228 g, 87%); mp 188.2–190.6 °C; IR (KBr, ν_{max}, cm⁻¹): 3286 (N–H_{amide}), 3155, 3087 (C–H_{arom.}), 2929 (C–H_{aliph.}), 1655 (C=O_{amide}), 1577, 1565 (C–C_{arom.}); ¹H NMR (400 MHz, DMSO-D₆): δ 8.82 (s, 1H, H-5), 8.70 (t, J = 6.4 Hz, 1H, CO–NH–CH₂), 8.28 (s, 1H, H-3), 8.16 (s, 1H, H-3''), 7.86 (s, 1H, H-5''), 7.61–7.58 (m, 2H, Ar–H), 7.55 (d, J = 2.8 Hz, 1H, H-5'), 6.37 (t, J = 2.0 Hz, 1H, H-4'), 6.24 (d, J = 2.8 Hz, 1H, H-3'), 4.45 (d, J = 6.4 Hz, 2H, CO–NH–CH₂–Ar), 3.87 (s, 3H, N–CH₃); ¹³C NMR (100 MHz, DMSO-D₆): δ 161.8 (CO–NH), 152.5 (C-9), 142.7 (C-5), 141.8 (C-2'), 139.4 (C-5'), 135.9 (C-2), 128.1 (C-7), 126.0 (C-6), 122.0 (C-3''), 118.9 (C-3), 117.8 (C-5''), 117.3 (C-8), 114.6 (C-4''), 110.4 (C-4'), 106.6 (C-3'), 38.7 (N–CH₃), 35.3 (CO–NH–CH₂–Ar); HRMS (MALDI-TOF) m/z calcd. for C₁₇H₁₅N₅O₂: 321.1225, found: 322.1301 [M+H]⁺ (100%), 344.1124 [M+Na]⁺, 360.0861 [M+K]⁺; Anal. calcd. for C₁₇H₁₅N₅O₂: C, 63.54; H, 4.71; N, 21.79; found: C, 63.57; H, 4.703; N, 21.77.

4.5.1.6. 6-(2-Aminopyridin-3-yl)-N-(furan-2-ylmethyl)H-imidazo[1,2-a]pyridine-2-carboxamide (5f). Prepared from **4b** (300 mg, 0.82 mmol), 2-aminopyridine-3-boronic acid (269.8 mg, 1.23 mmol), Na₂CO₃ (259.8 mg, 2.45 mmol), Pd(PPh₃)₄ (47.2 mg, 0.04 mmol) in 1,4-dioxane/water (10 mL). **5f** was formed as a white crystal (0.228 g, 84%); mp 250.3–252.9 °C; ¹H NMR (400 MHz, DMSO-D₆): δ 8.74 (t, J = 6.0 Hz, 1H, CO–NH–CH₂), 8.64 (s, 1H, H-5), 8.37 (s, 1H, H-3), 7.99–7.97 (dd, J = 4.8, 1.6 Hz, 1H, H-6''), 7.63 (d, J = 9.2 Hz, 1H, H-4''), 7.55 (d, J = 2.8 Hz, 1H, H-5'), 7.45–7.43 (dd, J = 7.2, 1.6 Hz, 1H, H-8), 7.36–7.33 (dd, J = 9.6, 2.0 Hz, 1H, H-7), 6.67 (t, J = 4.8 Hz, 1H, H-5''), 6.38 (t, J = 1.6 Hz, 1H, H-4'), 6.24 (d, J = 3.2 Hz, 1H, H-3'), 5.95 (s, 2H, Ar–NH₂), 4.46 (d, J = 6.0 Hz, 2H, CO–NH–CH₂–Ar); ¹³C NMR (100 MHz, DMSO-D₆): δ 161.9 (CO–NH), 156.8 (Ar–C-2''–NH₂), 152.5 (C-9), 147.1 (C-6''), 143.1 (C-5), 141.8 (C-2'), 139.6 (C-5'), 138.2 (C-2), 128.1 (C-7), 126.7 (C-6), 123.3 (C-4''), 117.2 (C-3), 116.5 (C-8), 115.1 (C-3''), 112.7 (C-5''), 110.4 (C-4'), 106.6 (C-3'), 35.4 (CO–NH–CH₂–Ar); HRMS (MALDI-TOF) m/z calcd. for C₁₈H₁₅N₅O₂: 333.1225, found: 334.1301 [M+H]⁺ (100%), 356.1121 [M+Na]⁺, 372.0860 [M+K]⁺; Anal. calcd. for C₁₈H₁₅N₅O₂: C, 64.86; H, 4.54; N, 21.01; found: C, 64.88; H, 4.549; N, 21.03.

4.5.1.7. N-(Furan-2-ylmethyl)-6-(quinolin-5-yl)H-imidazo[1,2-a]pyridine-2-carboxamide (5g). Prepared from **4b** (300 mg, 0.82 mmol), quinoline-5-boronic acid (212 mg, 1.23 mmol), Na₂CO₃ (259.8 mg, 2.45 mmol), Pd(PPh₃)₄ (47.2 mg, 0.04 mmol) in 1,4-dioxane/water (10 mL). **5g** was formed as an off white solid (0.258 g, 86%); mp 201.9–204.1 °C; IR (KBr, ν_{max}, cm⁻¹): 3401 (N–H_{amide}), 3124 (C–H_{arom.}), 2862 (C–H_{aliph.}), 1665 (C=O_{amide}), 1572 (C–C_{arom.}); ¹H NMR (400 MHz, DMSO-D₆): δ 8.97–8.95 (dd, J = 4.0, 1.6 Hz, 1H, H-2''), 8.85 (t, J = 6.0 Hz, 1H, CO–NH–CH₂), 8.80 (s, 1H, H-5), 8.44 (s, 1H, H-3), 8.29 (d, J = 8.4 Hz, 1H, H-8''), 8.12 (d, J = 8.8 Hz, 1H, H-4''), 7.86 (t, J = 7.2 Hz, 1H, H-7''), 7.74–7.67 (m, 2H, Ar–H), 7.57–7.47 (m, 3H, Ar–H), 6.39 (t, J = 2.0 Hz, 1H, H-4'), 6.26 (d, J = 2.4 Hz, 1H, H-3'), 4.49 (d, J = 6.0 Hz, 2H, CO–NH–CH₂–Ar); ¹³C NMR (100 MHz, DMSO-D₆): δ 161.8 (CO–NH), 152.5 (C-9), 150.6 (C-2''), 149.7 (C-8a''), 147.9 (C-5''), 143.1 (C-5), 141.8 (C-2'), 139.9 (C-5'), 136.7 (C-4''), 135.4 (C-2), 133.5 (C-7''), 130.4 (C-8''), 129.4 (C-6''), 129.1 (C-4a''), 127.8 (C-7), 126.2 (C-6), 124.3 (C-3''), 121.9 (C-3), 116.8 (C-8), 110.4 (C-3'), 106.6 (C-4'), 35.4 (CO–NH–CH₂–Ar); HRMS (MALDI-TOF) m/z calcd. for C₂₂H₁₆N₄O₂: 368.1273, found: 369.1349 [M+H]⁺ (100%),

391.1172 [M+Na]⁺; Anal. calcd. for C₂₂H₁₆N₄O₂: C, 71.73; H, 4.38; N, 15.21; found: C, 71.76; H, 4.373; N, 15.19.

4.5.1.8. N-(Furan-2-ylmethyl)-6-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)H-imidazo[1,2-a]pyridine-2-carboxamide (5h). Prepared from **4b** (300 mg, 0.82 mmol), 1-(2-morpholinoethyl)-1H-pyrazole-4-boronic acid pinacol ester (376.5 mg, 1.23 mmol), Na₂CO₃ (259.8 mg, 2.45 mmol), Pd(PPh₃)₄ (47.2 mg, 0.04 mmol) in 1,4-dioxane/water (10 mL). **5h** was formed as a pale brown solid (0.271 g, 79%); mp 222.4–224.7 °C; IR (KBr, ν_{max}, cm⁻¹): 3341 (N–H_{amide}), 3093, 3044, (C–H_{arom.}), 2954, 2856 (C–H_{aliph.}), 1658 (C=O_{amide}), 1576 (C–C_{arom.}), 1241 (C–O); ¹H NMR (400 MHz, DMSO-D₆): δ 8.82 (s, 1H, H-5), 8.69 (t, J = 6.0 Hz, 1H, CO–NH–CH₂), 8.28 (s, 1H, H-3), 8.22 (s, 1H, H-3''), 7.88 (s, 1H, H-5''), 7.61–7.58 (m, 2H, Ar–H), 7.56–7.54 (dd, J = 6.4, 1.2 Hz, 1H, H-5'), 6.37 (t, J = 2.0 Hz, 1H, H-4'), 6.24 (d, J = 2.8 Hz, 1H, H-3'), 4.46 (d, J = 6.4 Hz, 2H, CO–NH–CH₂–Ar), 4.25 (t, J = 6.4 Hz, 2H, morpholine-N–CH₂–CH₂), 3.55–3.53 (m, 4H, CH₂–O–CH₂), 2.73 (t, J = 6.4 Hz, 2H, morpholine-N–CH₂–CH₂), 2.42–2.39 (m, 4H, CH₂–N–CH₂); ¹³C NMR (100 MHz, DMSO-D₆): δ 161.9 (CO–NH), 152.5 (C-9), 142.8 (C-5), 141.8 (C-2'), 139.9 (C-5'), 139.5 (C-3''), 135.8 (C-2), 127.6 (C-7), 125.9 (C-6), 121.9 (C-5''), 118.9 (C-3), 117.4 (C-8), 114.6 (C-4''), 110.4 (C-4'), 106.6 (C-3'), 66.1 (CH₂–O–CH₂), 57.6 (CH₂–N–CH₂), 53.1 (pyrazole-N–CH₂), 48.8 (morpholine-N–CH₂), 35.3 (CO–NH–CH₂–Ar); HRMS (MALDI-TOF) m/z calcd. for C₂₂H₂₄N₆O₃: 420.1909, found: 421.1985 [M+H]⁺ (100%), 443.1807 [M+Na]⁺; Anal. calcd. for C₂₂H₂₄N₆O₃: C, 62.84; H, 5.75; N, 19.99; found: C, 62.81; H, 5.742; N, 20.02.

4.5.1.9. N-(Furan-2-ylmethyl)-6-(4-(1-methylpiperazine-4-carbonyl)phenyl)H-imidazo[1,2-a]pyridine-2-carboxamide (5i). Prepared from **4b** (300 mg, 0.82 mmol), 4-(4-methylpiperazine-1-carbonyl)phenyl boronic acid pinacol ester (404.8 mg, 1.23 mmol), Na₂CO₃ (259.8 mg, 2.45 mmol), Pd(PPh₃)₄ (47.2 mg, 0.04 mmol) in 1,4-dioxane/water (10 mL). **5i** was formed as a Pale yellow solid (0.283 g, 78%); mp 233.0–235.3 °C; ¹H NMR (400 MHz, DMSO-D₆): δ 9.02 (s, 1H, H-5), 8.76 (t, J = 5.6 Hz, 1H, CO–NH–CH₂), 8.39 (s, 1H, H-3), 7.81–7.67 (m, 4H, Ar–H), 7.57–7.55 (m, 3H, Ar–H), 6.37 (t, J = 2.0 Hz, 1H, H-4'), 6.25 (d, J = 2.8 Hz, 1H, H-3'), 4.47 (d, J = 5.6 Hz, 2H, CO–NH–CH₂–Ar), 3.63–3.60 (m, 4H, CH₂–N(CO)–CH₂), 3.01–2.70 (m, 4H, CH₂–N(CH₃)–CH₂), 2.56 (s, 3H, N–CH₃); ¹³C NMR (100 MHz, DMSO-D₆): δ 168.6 (piperazine-N–CO–Ar), 161.8 (CO–NH), 152.5 (C-9), 143.2 (C-5), 141.8 (C-2'), 139.9 (C-5'), 137.6 (C-1''), 134.6 (C-2), 127.9 (C-7), 126.6 (C-4''), 126.2 (C-6), 125.2 (C-3''), 125.1 (C-2''), 117.4 (C-3), 115.3 (C-8), 110.4 (C-4'), 106.7 (C-3'), 53.1 (CH₂–N(CH₃)–CH₂), 45.5 (CH₂–N(CO)–CH₂), 43.7 (N–CH₃), 35.3 (CO–NH–CH₂–Ar); HRMS (MALDI-TOF) m/z calcd. for C₂₅H₂₅N₅O₃: 443.1957, found: 444.2031 [M+H]⁺ (100%), 466.1853 [M+Na]⁺; Anal. calcd. for C₂₅H₂₅N₅O₃: C, 67.70; H, 5.68; N, 15.79; found: C, 67.68; H, 5.689; N, 15.80.

4.5.1.10. 6-(4-Chlorophenyl)-N-(pyridin-4-ylmethyl)H-imidazo[1,2-a]pyridine-2-carboxamide (5j). Prepared from **4c** (300 mg, 0.79 mmol), 4-chlorophenylboronic acid (186.1 mg, 1.19 mmol), Na₂CO₃ (252.2 mg, 2.38 mmol), Pd(PPh₃)₄ (45.8 mg, 0.04 mmol) in 1,4-dioxane/water (10 mL). **5j** was formed as a white solid (0.25 g, 87%); mp 166.8–169.0 °C; IR (KBr, ν_{max}, cm⁻¹): 3409 (N–H_{amide}), 3199, 3136, 3071, 3033 (C–H_{arom.}), 2919 (C–H_{aliph.}), 1645 (C=O_{amide}), 1602, 1566 (C–C_{arom.}); ¹H NMR (400 MHz, DMSO-D₆): δ 9.11 (t, J = 6.4 Hz, 1H, CO–NH–CH₂), 8.97 (s, 1H, H-5), 8.49 (d, J = 5.2 Hz, 2H, H-2', H-6'), 8.37 (s, 1H, H-3), 7.74 (d, J = 8.4 Hz, 2H, H-2'', H-6''), 7.68 (m, 2H, Ar–H), 7.56 (d, J = 8.4 Hz, 2H, H-3'', H-5''), 7.30 (d, J = 5.6 Hz, 2H, H-3', H-5'), 4.49 (d, J = 6.0 Hz, 2H, CO–NH–CH₂–Ar); ¹³C NMR (100 MHz, DMSO-D₆): δ 162.3 (CO–NH), 149.4 (C-9), 148.7 (C-2', C-6'), 143.2 (C-5), 139.9 (C-4'), 135.1 (C-2), 132.8 (C-1''), 129.1 (C-4''), 128.3 (C-3'', C-5''), 126.2 (C-2'', C-6''), 125.0 (C-7), 124.7 (C-6), 122.2

(C-3', C-5'), 117.3 (C-3), 115.3 (C-8), 41.1 (CO–NH–CH₂–Ar); HRMS (MALDI-TOF) *m/z* calcd. for C₂₀H₁₅ClN₄O: 362.0934, found: 363.1010 [M+H]⁺ (100%), 385.0833 [M+Na]⁺; Anal. calcd. for C₂₀H₁₅ClN₄O: C, 66.21; H, 4.17; N, 15.44; found: C, 66.19; H, 4.179; N, 15.47.

4.5.1.11. 6-(2-Methoxyphenyl)-N-(pyridin-4-ylmethyl)H-imidazo[1,2-a]pyridine-2-carboxamide (5k). Prepared from **4c** (300 mg, 0.79 mmol), 2-methoxyphenylboronic acid (180.8 mg, 1.19 mmol), Na₂CO₃ (252.2 mg, 2.38 mmol), Pd(PPh₃)₄ (45.8 mg, 0.04 mmol) in 1,4-dioxane/water (10 mL). **5k** was formed as a white solid (0.244 g, 86%); mp 144.5–146.9 °C; IR (KBr, ν_{\max} , cm⁻¹): 3359 (N–H_{amide}), 3139, 3091, 3029, 3001 (C–H_{arom.}), 2936, 2837 (C–H_{aliph.}), 1664 (C=O_{amide}), 1600, 1570 (C–C_{arom.}); ¹H NMR (400 MHz, DMSO-D₆): δ 9.10 (t, *J* = 6.4 Hz, 1H, CO–NH–CH₂), 8.71 (s, 1H, H-5), 8.49 (d, *J* = 6.0 Hz, 2H, H-2', H-6'), 8.41 (s, 1H, H-3), 7.61 (d, *J* = 9.2 Hz, 1H, H-6''), 7.51–7.48 (dd, *J* = 9.6, 1.6 Hz, 1H, H-4''), 7.42–7.38 (m, 2H, Ar–H), 7.30 (d, *J* = 5.6 Hz, 2H, H-3', H-5'), 7.15 (t, *J* = 4.4 Hz, 1H, H-5''), 7.06 (d, *J* = 6.8 Hz, 1H, H-3''), 4.49 (d, *J* = 6.4 Hz, 2H, CO–NH–CH₂–Ar), 3.80 (s, 3H, Ar–O–CH₃); ¹³C NMR (100 MHz, DMSO-D₆): δ 162.5 (CO–NH), 156.4 (C-2''–O–CH₃), 149.4 (C-9), 148.7 (C-2', C-6'), 142.9 (C-5), 139.5 (C-4'), 135.2 (C-2), 129.6 (C-4''), 129.0 (C-6''), 126.4 (C-1''), 125.3 (C-7), 123.8 (C-6), 122.2 (C-3', C-5'), 120.8 (C-5''), 116.0 (C-3), 115.1 (C-8), 111.8 (C-3''), 55.6 (Ar–O–CH₃), 41.2 (CO–NH–CH₂–Ar); HRMS (MALDI-TOF) *m/z* calcd. for C₂₁H₁₈N₄O₂: 358.1429, found: 359.1505 [M+H]⁺ (100%), 381.1326 [M+Na]⁺; Anal. calcd. for C₂₁H₁₈N₄O₂: C, 70.38; H, 5.06; N, 15.63; found: C, 70.40; H, 5.055; N, 15.61.

4.5.1.12. N-(Benzo[d][1,3]dioxol-5-ylmethyl)-6-(1-methyl-1H-pyrazol-4-yl)H-imidazo[1,2-a]pyridine-2-carboxamide (5l). Prepared from **4d** (300 mg, 0.71 mmol), 1-methylpyrazole-4-boronic acid pinacol ester (222.3 mg, 1.07 mmol), Na₂CO₃ (226.5 mg, 2.14 mmol), Pd(PPh₃)₄ (41.2 mg, 0.04 mmol) in 1,4-dioxane/water (10 mL). **5l** was formed as a white solid (0.225 g, 84%); mp 251.0–253.4 °C; IR (KBr, ν_{\max} , cm⁻¹): 3343 (N–H_{amide}), 3148, 3087 (C–H_{arom.}), 2940, 2921 (C–H_{aliph.}), 1654 (C=O_{amide}), 1579 (C–C_{arom.}), 1243 (C–O_{ether}); ¹H NMR (400 MHz, DMSO-D₆): δ 8.83 (t, *J* = 6.4 Hz, 1H, CO–NH–CH₂), 8.81 (s, 1H, H-5), 8.26 (s, 1H, H-3), 8.15 (s, 1H, H-3''), 7.86 (s, 1H, H-5''), 7.59–7.54 (m, 2H, Ar–H), 6.91 (s, 1H, H-4'), 6.84–6.78 (m, 2H, Ar–H), 5.95 (s, 2H, O–CH₂–O), 4.36 (d, *J* = 6.4 Hz, 2H, CO–NH–CH₂–Ar), 3.87 (s, 3H, N–CH₃); ¹³C NMR (100 MHz, DMSO-D₆): δ 161.9 (CO–NH), 147.1 (C-9), 145.9 (H-3a'), 142.8 (C-5), 139.8 (C-3''), 135.9 (C-2), 133.7 (H-7a'), 128.1 (C-7), 125.8 (C-6), 121.9 (C-5''), 120.6 (C-5'), 118.8 (C-3), 117.8 (C-6'), 117.3 (C-8), 114.5 (C-4''), 108.1 (C-7'), 107.9 (C-4'), 100.7 (O–CH₂–O), 41.7 (CO–NH–CH₂–Ar), 38.7 (N–CH₃); HRMS (MALDI-TOF) *m/z* calcd. for C₂₀H₁₇N₅O₃: 375.1331, found: 376.1402 [M+H]⁺ (100%), 398.1228 [M+Na]⁺; Anal. calcd. for C₂₀H₁₇N₅O₃: C, 63.99; H, 4.56; N, 18.66; found: C, 64.01; H, 4.553; N, 18.67.

4.5.1.13. N-Cyclopropyl-6-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)H-imidazo[1,2-a]pyridine-2-carboxamide (5m). Prepared from **4e** (300 mg, 0.92 mmol), 1-(2-morpholinoethyl)-1H-pyrazole-4-boronic acid pinacol ester (422.6 mg, 1.38 mmol), Na₂CO₃ (291.6 mg, 2.75 mmol), Pd(PPh₃)₄ (53 mg, 0.05 mmol) in 1,4-dioxane/water (10 mL). **5m** was formed as a pale brown solid (0.269 g, 77%); mp 135.1–137.6 °C; ¹H NMR (400 MHz, DMSO-D₆): δ 8.81 (s, 1H, H-5), 8.30 (d, *J* = 4.8 Hz, 1H, CO–NH–CH), 8.25 (s, 1H, H-3), 8.21 (s, 1H, H-3''), 7.87 (s, 1H, H-5''), 7.59–7.54 (m, 2H, Ar–H), 4.25 (t, *J* = 6.4 Hz, 2H, pyrazole–N–CH₂–CH₂), 3.55–3.51 (m, 4H, CH₂–O–CH₂), 2.89–2.85 (m, 1H, H-1'), 2.73 (t, *J* = 6.4 Hz, 2H, morpholine–N–CH₂–CH₂), 2.42–2.37 (m, 4H, CH₂–N–CH₂), 0.67–0.64 (m, 4H, H-2', H-3'); ¹³C NMR (100 MHz, DMSO-D₆): δ 163.2 (CO–NH), 144.3 (C-9), 142.7 (C-5), 139.8 (C-3''), 138.3 (C-2), 135.8 (C-7), 127.6 (C-6), 125.8 (C-3), 121.9 (C-5''), 117.2 (C-8), 114.3 (C-4''), 66.1 (CH₂–O–CH₂), 57.6

(CH₂–N–CH₂), 53.0 (pyrazole–N–CH₂), 48.8 (morpholine–N–CH₂), 24.9 (C-1'), 5.7 (C-2'), 5.5 (C-3'); HRMS (MALDI-TOF) *m/z* calcd. for C₂₀H₂₄N₆O₂: 380.1961, found: 381.2035 [M+H]⁺ (100%), 403.1859 [M+Na]⁺; Anal. calcd. for C₂₀H₂₄N₆O₂: C, 63.14; H, 6.36; N, 22.09; found: C, 63.19; H, 6.370; N, 22.10.

4.5.1.14. N-(4-(Trifluoromethyl)benzyl)-6-(quinolin-5-yl)H-imidazo[1,2-a]pyridine-2-carboxamide (5n). Prepared from **4f** (300 mg, 0.67 mmol), quinoline-5-boronic acid (175 mg, 1.01 mmol), Na₂CO₃ (214.3 mg, 2.02 mmol), Pd(PPh₃)₄ (39 mg, 0.03 mmol) in 1,4-dioxane/water (10 mL). **5n** was formed as a white solid (0.26 g, 86%); mp 177.1–179.6 °C; IR (KBr, ν_{\max} , cm⁻¹): 3404 (N–H_{amide}), 3144 (C–H_{arom.}), 1666 (C=O_{amide}), 1570 (C–C_{arom.}), 1328 (C–F); ¹H NMR (400 MHz, DMSO-D₆): δ 9.16 (t, *J* = 6.4 Hz, 1H, CO–NH–CH₂), 8.97–8.95 (dd, *J* = 4.0, 1.6 Hz, 1H, H-2''), 8.79 (s, 1H, H-5), 8.43 (s, 1H, H-3), 8.29 (d, *J* = 8.4 Hz, 1H, H-8''), 8.12 (d, *J* = 8.4 Hz, 1H, H-4''), 7.86 (t, *J* = 8.4 Hz, 1H, H-7''), 7.67 (d, *J* = 8.0 Hz, 2H, H-3', H-5'), 7.53 (d, *J* = 8.0 Hz, 2H, H-2', H-6'), 7.40–7.36 (m, 2H, Ar–H), 7.16–7.11 (m, 2H, Ar–H), 4.56 (d, *J* = 6.0 Hz, 2H, CO–NH–CH₂–Ar); ¹³C NMR (100 MHz, DMSO-D₆): δ 162.3 (CO–NH), 150.7 (C-2''), 147.9 (C-8a''), 144.7 (C-9), 143.2 (C-5), 139.9 (C-1''), 135.4 (C-2), 133.5 (C-1'), 129.4 (C-4''), 129.1 (C-7''), 129.0 (C-8''), 127.9 (C-7), 127.8 (C-4'), 127.5 (C-2', C-6'), 127.3 (C-6''), 126.2 (C-6), 125.1 (C-3', C-5'), 125.0 (Ar–CF₃), 124.3 (C-4a''), 121.9 (C-3''), 116.8 (C-3), 115.2 (C-8), 41.7 (CO–NH–CH₂–Ar); HRMS (MALDI-TOF) *m/z* calcd. for C₂₅H₁₇F₃N₄O: 446.1354, found: 447.1433 [M+H]⁺ (100%), 469.1251 [M+Na]⁺, 485.0989 [M+K]⁺; Anal. calcd. for C₂₅H₁₇F₃N₄O: C, 67.26; H, 3.84; N, 12.55; found: C, 67.28; H, 3.833; N, 12.52.

4.5.1.15. N-(4-(Trifluoromethyl)benzyl)-6-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)H-imidazo[1,2-a]pyridine-2-carboxamide (5o). Prepared from **4f** (300 mg, 0.67 mmol), 1-(2-morpholinoethyl)-1H-pyrazole-4-boronic acid pinacol ester (310.5 mg, 1.01 mmol), Na₂CO₃ (214.3 mg, 2.02 mmol), Pd(PPh₃)₄ (39 mg, 0.03 mmol) in 1,4-dioxane/water (10 mL). **5o** was formed as a pale yellow solid (0.265 g, 79%); mp 199.9–202.6 °C; IR (KBr, ν_{\max} , cm⁻¹): 3344 (N–H_{amide}), 3140 (C–H_{arom.}), 2994, 2856 (C–H_{aliph.}), 1645 (C=O_{amide}), 1578 (C–C_{arom.}), 1330 (C–F); ¹H NMR (400 MHz, DMSO-D₆): δ 9.07 (t, *J* = 6.4 Hz, 1H, CO–NH–CH₂), 8.82 (s, 1H, H-5), 8.29 (s, 1H, H-3), 8.22 (s, 1H, H-3''), 7.88 (s, 1H, H-5''), 7.67 (d, *J* = 8.0 Hz, 2H, H-3', H-5'), 7.60–7.59 (m, 2H, Ar–H), 7.53 (d, *J* = 8.0 Hz, 2H, H-2', H-6'), 4.55 (d, *J* = 6.4 Hz, 2H, CO–NH–CH₂–Ar), 4.25 (t, *J* = 6.4 Hz, 2H, pyrazole–N–CH₂–CH₂), 3.54 (t, *J* = 4.8 Hz, 4H, CH₂–O–CH₂), 2.73 (t, *J* = 6.4 Hz, 2H, morpholine–N–CH₂–CH₂), 2.41 (t, *J* = 4.4 Hz, 4H, CH₂–N–CH₂); ¹³C NMR (100 MHz, DMSO-D₆): δ 162.3 (CO–NH), 144.7 (C-9), 142.8 (C-5), 139.6 (C-3''), 135.8 (C-2), 133.5 (C-1'), 127.9 (C-7), 127.6 (C-4'), 127.5 (C-2', C-6'), 125.9 (C-6), 125.1 (C-3', C-5'), 125.0 (Ar–CF₃), 121.9 (C-5''), 118.9 (C-3), 117.3 (C-8), 114.7 (C-4''), 66.1 (CH₂–O–CH₂), 57.6 (CH₂–N–CH₂), 53.1 (pyrazole–N–CH₂), 48.8 (morpholine–N–CH₂), 41.6 (CO–NH–CH₂–Ar); HRMS (MALDI-TOF) *m/z* calcd. for C₂₅H₂₅F₃N₆O₂: 498.1991, found: 499.2065 [M+H]⁺ (100%), 521.1889 [M+Na]⁺, 537.1622 [M+K]⁺; Anal. calcd. for C₂₅H₂₅F₃N₆O₂: C, 60.23; H, 5.05; N, 16.86; found: C, 60.20; H, 5.044; N, 16.89.

4.5.1.16. 6-(1-Methyl-1H-pyrazol-4-yl)-N-(tetrahydro-2H-pyran-4-yl)H-imidazo[1,2-a]pyridine-2-carboxamide (5p). Prepared from **4g** (300 mg, 0.81 mmol), 1-methyl-1H-pyrazole-4-boronic acid pinacol ester (252.3 mg, 1.21 mmol), Na₂CO₃ (257 mg, 2.42 mmol), Pd(PPh₃)₄ (46.7 mg, 0.04 mmol) in 1,4-dioxane/water (10 mL). **5p** was formed as an off white solid (0.216 g, 82%); mp 125.0–127.4 °C; IR (KBr, ν_{\max} , cm⁻¹): 3335 (N–H_{amide}), 3153, 3124, 3043 (C–H_{arom.}), 2952, 2929, 2839 (C–H_{aliph.}), 1640 (C=O_{amide}), 1558 (C–C_{arom.}); ¹H NMR (400 MHz, DMSO-D₆): δ 8.80 (s, 1H, H-5), 8.25 (s, 1H, H-3), 8.17 (d, *J* = 8.4 Hz, 1H, CO–NH–CH), 8.15 (s, 1H, H-3''), 7.86 (s, 1H, H-5''),

7.60–7.55 (m, 2H, Ar–H), 4.04–3.97 (m, 1H, H-4'), 3.87 (s, 3H, N–CH₃), 3.85 (d, $J = 8.8$ Hz, 2H, H-2a', H-6a'), 3.41–3.34 (dt, $J = 11.2$, 3.2 Hz, 2H, H-2b', H-6b'), 1.71–1.65 (m, 4H, H-3', H-5'); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 161.2 (CO–NH), 147.9 (C-9), 142.7 (C-5), 139.8 (C-3''), 135.9 (C-2), 128.1 (C-7), 125.9 (C-6), 121.9 (C-5''), 118.8 (C-3), 117.2 (C-8), 114.5 (C-4''), 66.1 (C-2', C-6'), 44.9 (C-4'), 38.7 (N–CH₃), 32.3 (C-3', C-5'); HRMS (MALDI-TOF) m/z calcd. for C₁₇H₁₉N₅O₂: 325.1538, found: 326.1611 [M+H]⁺ (100%), 348.4138 [M+Na]⁺; Anal. calcd. for C₁₇H₁₉N₅O₂: C, 62.75; H, 5.89; N, 21.52; found: C, 62.74; H, 5.882; N, 21.50.

4.5.1.17. 6-(Quinolin-5-yl)-N-(tetrahydro-2H-pyran-4-yl)H-imidazo [1,2-*a*]pyridine-2-carboxamide (5q). Prepared from **4g** (300 mg, 0.81 mmol), quinoline-5-boronic acid (209.7 mg, 1.21 mmol), Na₂CO₃ (257 mg, 2.42 mmol), Pd(PPh₃)₄ (46.7 mg, 0.04 mmol) in 1,4-dioxane/water (10 mL). **5q** was formed as an off white solid (0.253 g, 84%); mp 143.8–146.0 °C; IR (KBr, ν_{max} , cm⁻¹): 3337 (N–H_{amide}), 3099, 3066, 3034 (C–H_{arom.}), 2936, 2848 (C–H_{aliph.}), 1644 (C=O_{amide}), 1563 (C–C_{arom.}); ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.96–8.95 (dd, $J = 4.4$, 1.6 Hz, 1H, H-2''), 8.77 (s, 1H, H-5), 8.41 (s, 1H, H-3), 8.29 (d, $J = 8.8$ Hz, 1H, H-8''), 8.17 (d, $J = 8.4$ Hz, 1H, CO–NH–CH), 8.12 (d, $J = 8.4$ Hz, 1H, H-4''), 7.86 (t, $J = 8.4$ Hz, 1H, H-7''), 7.73–7.66 (m, 2H, Ar–H), 7.55 (d, $J = 8.8$ Hz, 1H, H-7), 7.49–7.47 (dd, $J = 9.2$, 1.6 Hz, 1H, H-3''), 4.08–3.98 (m, 1H, H-4'), 3.87 (d, $J = 11.2$ Hz, 2H, H-2a', H-6a'), 3.41–3.35 (dt, $J = 11.2$, 4.0 Hz, 2H, H-2b', H-6b'), 1.74–1.66 (m, 4H, H-3', H-5'); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 161.2 (CO–NH), 150.6 (C-2''), 147.9 (C-9), 143.0 (C-5), 140.3 (C-8a''), 135.4 (C-2), 133.4 (C-5''), 129.4 (C-4''), 129.0 (C-7''), 128.9 (C-8''), 127.8 (C-7), 127.2 (C-6''), 126.1 (C-6), 124.2 (C-4a''), 121.9 (C-3''), 116.7 (C-3), 115.1 (C-8), 66.2 (C-2', C-6'), 45.1 (C-4'), 32.4 (C-3', C-5'); HRMS (MALDI-TOF) m/z calcd. for C₂₂H₂₀N₄O₂: 372.1586, found: 373.1661 [M+H]⁺ (100%), 395.1482 [M+Na]⁺ 395.1484; Anal. calcd. for C₂₂H₂₀N₄O₂: C, 70.95; H, 5.41; N, 15.04; found: C, 70.93; H, 5.403; N, 15.03.

4.6. X-ray crystallographic analysis

The X-ray crystallographic analysis of **5f** was carried out on a white crystal, with dimensions 0.21 mm × 0.18 mm × 0.26 mm, grown from the slow evaporation of a dichloromethane and methanol solvent mixture at room temperature. A suitable crystal was selected and mounted on a Bruker APEX-II CCD diffractometer. The crystal was kept at 296.15 K during data collection. Using Olex2 [39], the structure was solved the Superflip [40] structure solution program using Charge Flipping and refined with the ShelXL [41] refinement package using Least Squares minimization. CCDC 1007948 contains the supplementary crystallographic data for **5f**. These data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html>, or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or email: deposit@ccdc.cam.ac.uk.

4.7. In vitro Mtb MABA assay procedure

The anti-mycobacterial activities of compounds **5a–q** have been assessed against *M. tuberculosis* ATCC 27294 using the microplate alamar blue assay (MABA) [42]. Briefly, the inoculum was prepared from fresh LJ medium re-suspended in 7H9-S medium (7H9 broth, 0.1% casitone, 0.5% glycerol, supplemented oleic acid, albumin, dextrose, and catalase [OADC]), adjusted to a McFarland tube No. 1, and diluted 1:20; 100 μ L was used as inoculum. Each drug stock solution was thawed and diluted in 7H9-S at four-fold the final highest concentration tested. Serial two-fold dilutions of each drug were prepared directly in a sterile 96-well microtiter plate using 100 μ L 7H9-S. A growth control containing no antibiotic and a sterile

control was also prepared on each plate. Sterile water was added to all perimeter wells to avoid evaporation during the incubation. The plate was covered, sealed in plastic bags and incubated at 37 °C in normal atmosphere. After 7 days incubation, 30 μ L of alamar blue solution was added to each well, and the plate was re-incubated overnight. A change in colour from blue (oxidised state) to pink (reduced) indicated the growth of bacteria, and the MIC was defined as the lowest concentration of drug that prevented this change in colour. Isoniazid and Rifampicin were used as standards.

4.8. Cytotoxicity

All the new compounds synthesized were further examined for cytotoxicity against Human Embryonic Kidney Cell-line 293T (HEK-293T) cells at the concentration of 50 mg/mL. After 72 h of exposure, viability was assessed on the basis of cellular conversion of (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) into a formazan product using the Promega Cell Titer 96 non-radioactive cell proliferation assay.

4.9. Molecular docking study procedure

The three dimensional structure of target protein InhA, the enoyl acyl carrier protein reductase (ENR) from *M. tuberculosis*, is one of the key enzymes involved in mycobacterial fatty acid elongation cycle, which has been validated as an effective antimicrobial target, having keyword 2X22 was downloaded from PDB (www.rcsb.org/pdb) structural database. This file was then opened in SPDB viewer edited by removing the heteroatoms, adding C terminal oxygen. The active pockets on target protein molecule were found out using CASTp server [43]. The ligands were drawn using ChemDraw Ultra 6.0 and assigned with proper 2D orientation (ChemOffice package). 3D coordinates were prepared using PRODRG server [44]. Autodock V3.0 was used to perform Automated Molecular Docking in AMD Athlon (TM)2x2 215 at 2.70 GHz, with 1.75 GB of RAM. AutoDock 3.0 was compiled and run under Microsoft Windows XP service pack 3. For docking, grid map requires in AutoDock, the size of the grid box was set at 114, 116 and 100 Å (R, G, and B), and grid center –12.755, –22.815, 32.099 for x, y, and z-coordinates. All torsions were allowed to rotate during docking. The Lamarckian genetic algorithm and the pseudo-Solis and Wets methods were applied for minimization, using default parameters [45]. The newly synthesized compounds were taken as ligands and docked against target molecule InhA.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at <http://dx.doi.org/10.1016/j.ejmech.2014.10.079>. These data include MOL files and InChIKeys of the most important compounds described in this article.

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