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Synthesis and antitubercular evaluation of novel dibenzo[*b,d*]thiophene tethered imidazo[1,2-*a*]pyridine-3-carboxamides

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ABSTRACT

A series of novel dibenzo[*b,d*]thiophene tethered imidazo[1,2-*a*]pyridine carboxamides **7a-s** were designed and synthesized. The required building block, 2-dibenzo[*b,d*]thiophenyl imidazo [1,2-*a*]pyridine carboxylic acid **(5)** was synthesized from commercial dibenzo[*b,d*]thiophene in good yields following five-step reaction sequence. The desired carboxamides **7a-s** was prepared through coupling of acid **5** with various benzyl amines. All the new analogues **7a-s** was characterized by their NMR and mass spectral analysis. Among nineteen new compounds **7a-s** screened for *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv, three compounds **7k** (MIC: 0.78 µg/mL); **7e** and **7n** (MIC: 1.56 µg/mL) were identified as potent analogues with low cytotoxicity. The results reported here will help global efforts for identification of potential lead antimycobacterial agents.

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Tuberculosis (TB), caused by intracellular bacterial pathogen *Mycobacterium tuberculosis* (*Mtb*) is one of the most prevalent and deadliest pandemic diseases worldwide.[1] World Health Organization (WHO) *Global tuberculosis report* 2015 estimated that TB killed 890,000 men, 480,000 women and 140,000 children in 2014 alone and ranked alongside HIV as a leading killer in infectious diseases.[2] Also, TB is more frequent and rampant in immune-compromised individuals suffering from human immune deficiency virus (HIV).[3] In fact, the significant proportion of TB cases and deaths occurred in HIV positive people.[4] This disease was further aggravated by the emergence of multi-drug resistant (MDR) and extensively drug resistant (XDR) TB.[5] These resistant strains, in turn, requires prolonged treatment up to 24 months with the use of a cocktail of 6-8 first and second-line drugs, which are more toxic, less effective and expensive.[5] More recently totally-drug-resistant (TDR) TB also reported.[6] With someone dying of TB nearly every 20s, and continuous increase in number of drug-resistant cases, there is an urgent need for development of fast and long acting antitubercular agents with high potency against TB and other latent infections.[7]

Recently Kim,[8] Miller[9] and other groups[10] used imidazo[1,2-*a*] pyridine-3-acetamide of anti-insomnia drugs Zolpidem (**I**) and Alpidem (**II**) as core skeleton for the development of newer anti-tubercular agents. Among the several imidazo[1,2-*a*]pyridine amides (IPAs) reported, two potent analogues Q-203[8b] & PA-824[11] (Figure 1) progressed to preclinical and Phase-II clinical evaluations respectively. Moreover, IPAs seems to be remarkably selective since while they are potently active against *M. tuberculosis*, they are not active against other mycobacteria, other gram-positive or gram-negative bacteria.[9d] Owing that IPAs are inexpensive and readily synthesized, they have ideally suited to structure-activity-relationship (SAR) studies with MIC values ranging in low micro molar levels.[8,9] Interestingly, some of the IPs **III-VII** showed *Mtb* inhibition activities comparable to the first-line anti-TB drugs.[8b]

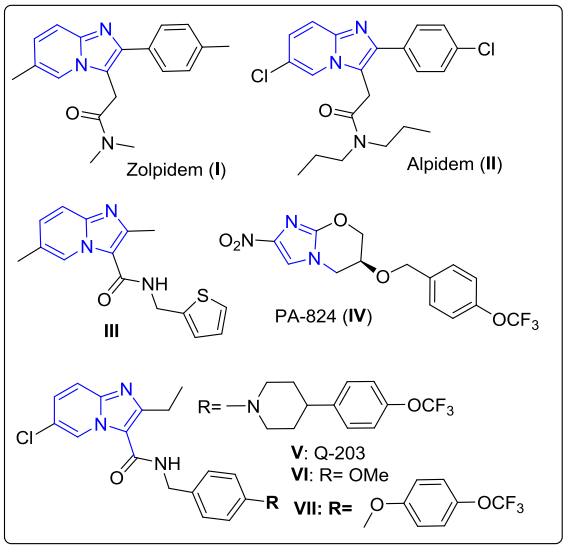

Figure 1: Clinical anti-insomnia drugs **I** & **II** and antitubercular agents **III-VII** possessing imidazo[1,2-*a*]pyridine (IP) core.

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We recently reported[12] antimycobacterial activity of various di benzo[*b*,*d*]furan, dibenzo[*b*,*d*]thiophene and N-methyl carbazole tethered substituted heterocycles. Structure-activity relationships (SAR) studies suggested that dibenzo[*b*,*d*]thiophene tethered heterocycles (**VIII** & **IX**, Figure 2) exhibited *M. tuberculosis* inhibition at lower concentrations compared to the corresponding dibenzo[*b*,*d*]furan and N-methylcarbazole derivatives.[13] Apart from antitubercular activity, dibenzo[*b*,*d*]thiophene derivatives **X-XIII** (Figure 2) exhibited DNA-dependent protein kinase (DNA-PK) inhibition.[14] These observations led us to focus on further development of dibenzo[*b*,*d*]thiophene derived newer scaffolds for improving antitubercular activity. We, therefore, envisaged that combining dibenzo[*b*,*d*]thiophene with IPA core could lead to the more modern framework to evaluate as inhibitors of *Mycobacterium tuberculosis*.

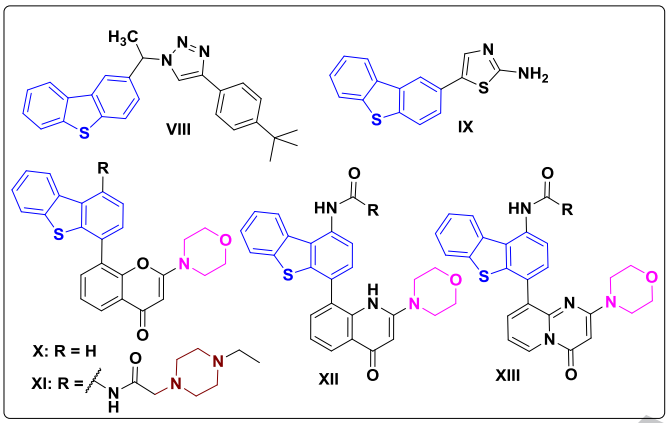


Figure 2: Dibenzo[*b*,*d*]thiophene derived anti-tubercular agents **VIII** & and **IX** DNA-PK inhibitors **X-XIII**.

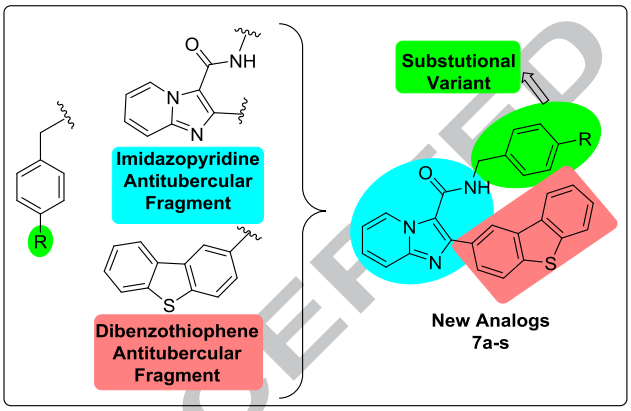
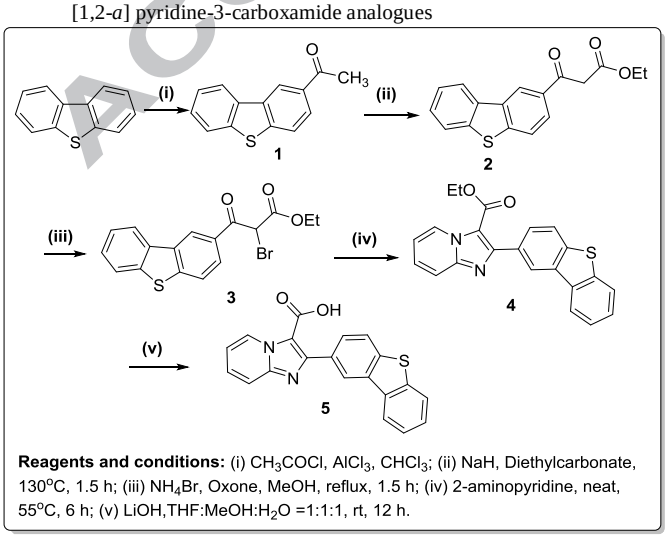
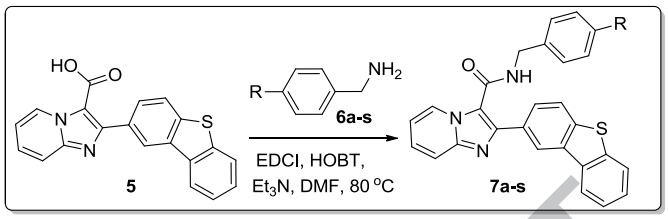


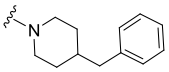
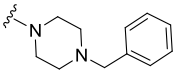
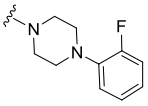
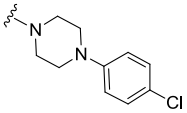
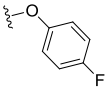
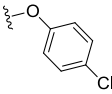
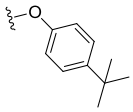
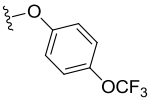
Figure 3: Design strategy for synthesis of dibenzothiophene tethered imidazo [1,2-*a*] pyridine-3-carboxamide analogues



Scheme 1: Synthesis of 2-(dibenzo[*b*,*d*]thiophen-2-yl)imidazo[1,2-*a*]pyridine-3-carboxylic acid (**5**)

Table 1: Synthesis of novel dibenzo[*b*,*d*]thiophene tethered imidazo[1,2-*a*] pyridine-3-carboxamide analogues **7a-s**.[a]



S.No	Amine (6a-s)	R	Product (7a-s)	Yield (%)[a]	CLogP[b]
1.	**6a**	-H	**7a**	86	7.21
2.	**6b**	-F	**7b**	71	7.36
3.	**6c**	-Cl	**7c**	72	7.93
4.	**6d**	-CH_3	**7d**	78	7.71
5.	**6e**	-^{t}Bu	**7e**	63	9.04
6.	**6f**	-OCH_3	**7f**	72	7.13
7.	**6g**	-CF_3	**7g**	74	8.10
8.	**6h**	-OCF_3	**7h**	73	8.24
9.	**6i**		**7i**	55	6.67
10.	**6j**		**7j**	60	7.50
11.	**6k**		**7k**	61	9.99
12.	**6l**		**7l**	53	8.95
13.	**6m**		**7m**	45	8.98
14.	**6n**		**7n**	37	9.55
15.	**6o**		**7o**	58	9.31
16.	**6p**		**7p**	55	9.46
17.	**6q**		**7q**	50	10.03
18.	**6r**		**7r**	68	11.14
19.	**6s**		**7s**	62	10.34

[a]Isolated yield.
[b]Calculated using Chembiodraw 12.0 programme.

Continuing our work on the development of novel antitubercular agents,[12,13,15] we herein report the synthesis and antitubercular evaluation of novel dibenzo[*b*,*d*]thiophene tethered imidazo[1,2-*a*]pyridine-3-carboxamide analogues **7a-s**. *In vitro* screening of all nineteen new analogs **7a-s** against *Mycobacterium tuberculosis* H37Rv (*Mtb*) resulted in **7k** (MIC:

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0.78 µg/mL), **7e** and **7n** (MIC: 1.56 µg/mL) as promising IPA analogs with lower cytotoxicity profile.

Broadly, the designer scaffold contains three segments (Figure 3). First segment is imidazo[1,2-*a*]pyridine, an active pharmacophore from clinical antitubercular TB drug Q-203 (Figure 1). Bioactive dibenzo[*b,d*]thiophene is the second segment tethered to imidazo[1,2-*a*]pyridine core for desired pharmacological behavior. Anti-TB activity profile of the proposed scaffold was tuned with the choice of appended substituted benzyl amines in the third segment.

To start synthesis, commercially available dibenzo[*b,d*] thiophene was acetylated using acetyl chloride and anhydrous $AlCl_3$ in chloroform by following literature procedure[13,16] to yield 2-acetyl dibenzo[*b,d*]thiophene (**1**), in 70% yield. Compound **1** was reacted with sodium hydride in diethyl carbonate heated at 130°C for 1.5 h to give Ethyl 3-(dibenzo[*b,d*]thiophen-2-yl)-3-oxopropanoate (**2**) in 69% yield.[17] Reaction of **2** with equimolar NH_4Br/ Oxone, refluxing in methanol for 1.5 h gave ethyl 2-bromo-3-(dibenzo[*b,d*]thiophen-2-yl)-3-oxopropanoate (**3**) in 74% yield.[18] Mono brominated β-keto ester **3** was further condensed with 2-aminopyridine at 55°C to give **4** in excellent yield *via* formation of imine-enamine.[19] Saponification with lithium hydroxide followed by acidic work up gave the desired imidazo[1,2-*a*] pyridine-3-carboxylic acid **5** in 82% yield.[20] Further to built the desired amide analogues, 2-(dibenzo[*b,d*] thiophen-2-yl)imidazo[1,2-*a*]pyridine-3-carboxylic acid **5** was coupled with various benzyl amines **6a-s** using classical EDCI-HOBT protocol[21] (Table 1). For example, compound **5** was reacted with 4-Fluoro benzyl amine **6b** using EDCI/ HOBT in presence of triethyl amine in DMF at 80 °C to give 2-(dibenzo [*b,d*]thiophen-2-yl)-N-(4-fluorobenzyl)imidazo[1,2-*a*] pyridine-3-carboxamide **(7b)** in 71% yield. Similarly, all the compounds **7a-s** were prepared in excellent yields and were fully characterized by their ^1H & ^{13}C NMR, IR and Mass spectral data.[22] ClogP required assessing the lipophilic character of new analogs was calculated using Chembiodraw 12.0 programme (Table 1).

All the newly synthesized dibenzo[*b,d*]thiophene tethered imidazo[1,2-*a*]pyridine-3-carboxamide analogues 7**a-s** were screened for *in vitro* antimycobacterial activity against *M. tuberculosis* H37Rv (ATCC27294) by agar dilution method.[23] The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required for complete inhibition of the bacterial growth. The MIC values (µg/mL) of **7a-s** determined in triplicate along with the standard drugs for comparison are listed in figure 4. All nineteen new compounds were screened showed *in vitro* activity against *Mtb* with MIC ranging from 0.78-25.0 µg/mL. When compared to first line anti-TB drugs all the compounds are less potent than isoniazid (0.1 µg/mL). Three compounds **7k** (MIC 0.78 µg/mL) and **7e, 7n** (MIC 1.56 µg/mL) exhibited greater *in vitro* potency than standard drugs ethambutol and pyrazinamide. Two compounds **7a** and **7b** (MIC 3.13 µg/mL) is equipotent to standard drug ethambutol and more potent than pyrazinamide. Among other derivatives, two compounds **7f** and **7o** exhibited MIC 6.25 µg/mL, and another three derivatives **7d, 7g** and **7s** showed MIC 12.5 µg/mL and were more potent than pyrazinamide.

The safety profile of antitubercular active dibenzo[*b,d*] thiophene tethered imidazo[1,2-*a*]pyridine-3-carboxamides with MIC ≤ 6.25 µg/mL were assessed for *in vitro* cytotoxicity against Human Embryonic Kidney (HEK-293T) cells using 3-(4,5-di methylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.[24] The promising antitubercular compounds **7a-b, 7e-f, 7k, 7n** and **7o** exhibited 34.6%, 25.8%, 18.76%, 36.98%, 34.78%, 24.36% and 38.4% growth inhibition of HEK-293T cells at 50.0 µg/mL concentration (Figure 5). The results indicated that potent analogs **7e**, **7k** and **7n** are less toxic compared to other derivatives **7a-b, 7f** and **7o**.

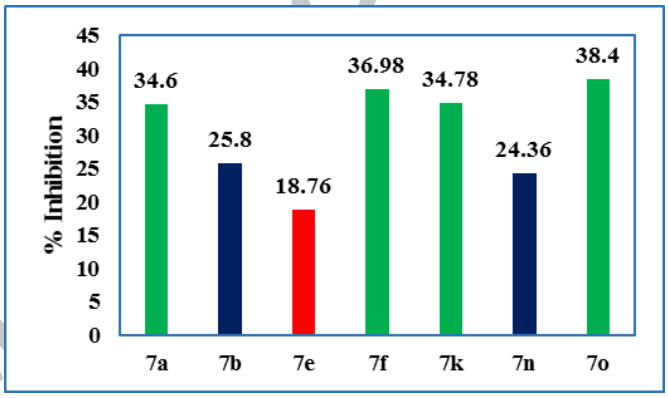

Figure 5: Percentage growth inhibition of HEK-293Tcells in the presence of dibenzothiophene tethered imidazo [1,2-*a*] pyridine-3-carboxamides at a concentration of 50 µg/mL.

On structure-activity relationship (SAR), we have not found the best correlation in SAR among the synthesized analogues **7a-s** but indicated some unusual patterns. To describe SAR in general; *Mtb* inhibition activity for all the dibenzo[*b,d*]thiophene tethered imidazo[1,2-a]pyridine-3-carboxamides is varied large extent with substituent appended in the benzyl amine unit. For example, 4-benzyl piperidine analogue **7k** exhibited best *M. tuberculosis* inhibition activity (MIC: 0.78 µg/mL) among all the synthesized compounds. Interestingly, *Mtb* inhibition activity was reduced to half (MIC 1.56 µg/mL) when replaced 4-benzyl piperidine unit of **7k** with 4-chlorophenyl piperazine **7n**, or with simple *tert*-butyl group in **7e**. Further changing substitutions on benzyl group with phenyl ethers reduced *Mtb* inhibition activity to the large extent with MIC up to 25.0 µg/mL (**7p-s**; Table 1).

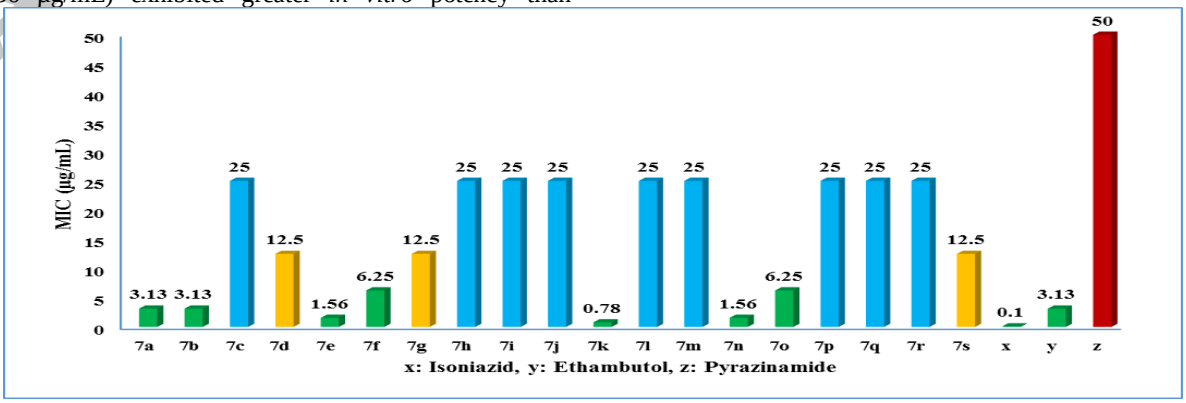

Figure 4. Antitubercular activity of dibenzo[*b,d*]thiophene tethered imidazo[1,2-*a*]pyridine-3-carboxamide analogues **7a-s**.

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Structure-activity correlation of potent analogs **7e**, **7k** and **7n** was made with recently reported preclinical IPA derivatives **VII**, **XIV** and **XV** (Figure 6).[8b] Compound **7k** exhibited *Mtb* inhibition activity (MIC_{100}:1.3 μM) comparable to the reported **XIV** (MIC_{50}:1.86 μM) and **XV** (MIC_{50}:2.63 μM).[8] These results indicate that dibenzo[*b*,*d*]thiophene tethered imidazo[1,2-*a*] pyridine-3-carboxamide analogues **7e**, **7k** and **7n** could be lead analogues for further development as antitubercular drugs. The results described here demonstrate the potential utility of dibenzo[*b*,*d*] thiophene as pharmacophore tethered to imidazo[1,2-*a*]pyridine-3-carboxamide unit for the development of lead antitubercular agents.

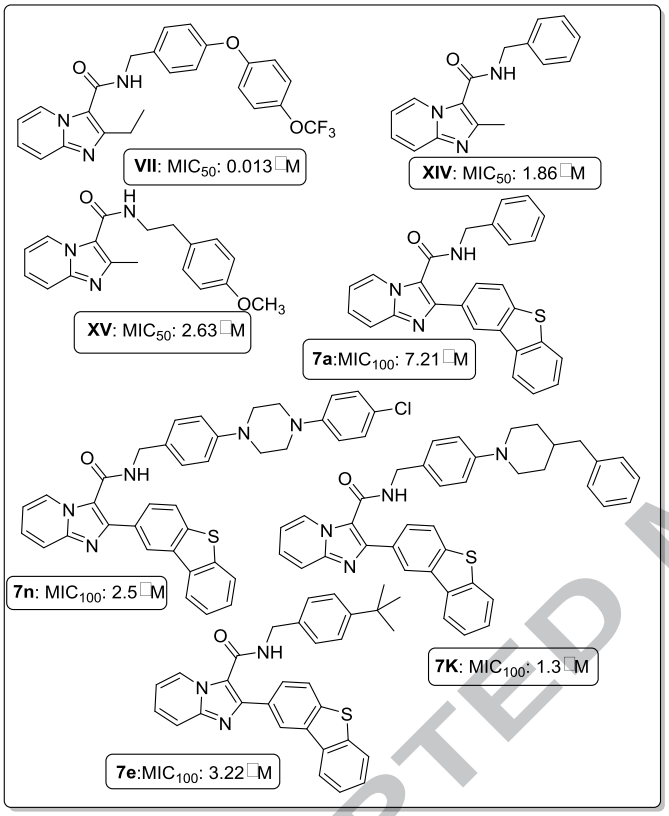

Figure 6: SAR of preclinical IPA derivatives **VII**, **XIV** and **XV,** with synthesized potent IPAs **7e**, **7k** and **7n**

In conclusion, we have synthesized a series of novel dibenzo [*b*,*d*]thiophene tethered imidazo[1,2-*a*]pyridine-3-carboxamides **7a-s** *via* acid-amine coupling in the penultimate step. The required building block, 2-(dibenzo[*b*,*d*]thiophen-2-yl)imidazo [1,2-*a*]pyridine-3-carboxylic acid **(5)** was synthesized from commercial dibenzo[*b*,*d*]thiophene in excellent yields following five step reaction sequence described in scheme-1. All the new analogues were fully characterized by their NMR and mass spectral data. Among nineteen new compounds **7a-s** screened for *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv, three compounds **7k** (MIC: 0.78 μg/mL); **7e** and **7n** (MIC: 1.56 μg/mL) were identified as potent analogues with low cytotoxicity. SAR study and *Mtb* inhibition activity profile indicated that dibenzo[*b*,*d*]thiophene tethered imidazo [1,2-*a*]pyridine-3-carboxamide analogues **7e, 7k** and **7n** could be lead analogues for further development as antitubercular drugs. With new anti-TB agents desperately needed, we believe that the analogues reported in this work will help global efforts for identification of potential lead antimycobacterial agents for further development.

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17. **Synthesis of Ethyl 3-(dibenzo[*b,d*]thiophen-2-yl)-3-oxopropanoate (2):** To a mixture of **1** (5.0 g, 22 mmol) and diethyl carbonate (50 mL) was added NaH (60% in mineral oil, 1.59 g, 66 mmol) at room temperature under N_2. The mixture was heated at 130°C for 1.5 h. After quenching the reaction with H_2O, the organic materials were extracted with $CHCl_3$, organic layer was washed with brine, dried over anhyd. Na_2SO_4, and concentrated in vacuum. The crude residue was purified over silica gel column eluting with hexane/ethyl acetate (1:9) to give Ethyl 3-(dibenzo[*b,d*]thiophen-2-yl)-3-oxopropanoate **(2)** as colorless crystals. Yield: 4.6 g, 69%; m.p: 107-109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J*= 1.5 Hz, 1H), 8.25-8.20 (m, 1H), 8.01 (dd, *J*= 8.3, 1.6 Hz, 1H), 7.94-7.83 (m, 1H), 7.54-7.48 (m, 2H), 4.24 (q, *J*= 7.1 Hz, 2H), 4.11 (s, 2H), 1.27 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 167.4, 144.9, 139.4, 135.3, 134.6, 132.2, 127.3, 125.9, 124.7, 122.6, 121.6, 61.3, 45.9, 13.9; IR (KBr) 3059, 2980, 1733, 1676, 1229, 1022, 761 cm^{-1}; MS (ESI) *m/z* 299 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{17}H_{14}O_3NaS$ $[M+Na]^+$: 321.05559, found: 321.05345.
18. **Ethyl 2-bromo-3-(dibenzo[*b,d*]thiophen-2-yl)-3-oxo propanoate (3):** Oxone (6.8 g, 11 mmol) was added to the well stirred solution of **2** (3.0 g, 10 mmol) and NH_4Br (1.0 g, 11 mmol) in methanol (10 ml) and the reaction mixture was allowed to stir at reflux for 1.5 h. After completion (monitored by TLC), the reaction mixture was quenched with saturated aqueous sodium thiosulphate, extracted with $CHCl_3$ (3x25 mL), combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. Crude residue thus obtained was purified over silica gel column chromatography to afford pure product **3** as colorless crystals. Yield: 2.8 g, 74%; m.p: 115-117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (d, *J*= 1.6 Hz, 1H), 8.25-8.21 (m, 1H), 8.05 (dd, *J*= 8.3, 1.6 Hz, 1H), 7.94 (d, *J*= 8.3 Hz, 1H), 7.55-7.51 (m, 2H), 5.79 (s, 1H), 4.31 (q, *J*= 7.1, 1.2 Hz, 2H), 1.27 (t, *J*= 7.1 H, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.6, 165.1, 145.8, 139.5, 135.7, 134.7, 129.6, 127.6, 126.5, 125.0, 122.9, 122.8, 122.6, 121.8, 63.3, 46.5, 13.8; IR (KBr) 3059, 2981, 1733, 1675, 1498, 1227, 1081, 761 cm^{-1}; MS (ESI) *m/z* 376 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{17}H_{14}BrO_3S$ $[M+H]^+$: 376.98415, found: 376.98376.
19. **Ethyl 2-(dibenzo[*b,d*]thiophen-2-yl)imidazo[*1,2-a*]pyridine-3-carboxylate (4):** Mixture of Ethyl 2-bromo-3-oxo proanoate **3** (3.0 g, 10 mmol) and 2-aminopyridine (1.13 g, 12 mmol) was heated at 55°C for 3 h. After completion, the mixture was made basic (pH 8–9) by addition of saturated Na_2SO_3 solution. The product was extracted with EtOAc (3×10 mL), combined organic layers washed with saturated Na_2SO_3 (2×10 mL), dried over anhydrous Na_2SO_4, filtered and the combined organic solvent was removed under reduced pressure. Crude residue thus obtained was subjected to column chromatography over silica gel to afford pure Ethyl 2-(dibenzo[*b,d*]thiophen-2-yl)imidazo[*1,2-a*]pyridine-3-carboxylate (**4)** as colorless crystals. Yield: 2.80 g, 74%; m.p: 147-149°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.49-9.46 (m, 1H), 8.62-8.59 (m, 1H), 8.24-8.18 (m, 1H), 7.94-7.86 (m, 3H), 7.82-7.76 (m, 1H), 7.51-7.44 (m, 1H), 7.08 (td, *J*= 6.8, 1.0 Hz, 1H), 4.32 (q, *J*= 7.1 Hz, 2H), 1.19 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 153.3, 147.1, 139.9, 139.6, 135.5, 135.0, 130.7, 128.9, 128.3, 128.0, 126.6, 124.4, 123.3, 122.7, 121.7, 121.6, 117.3, 114.0, 60.4, 14.0; IR (KBr) 2978, 1688, 1469, 1217, 1043, 756 cm^{-1}; MS (ESI) *m/z* 373 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{22}H_{17}N_2O_2S$ $[M+H]^+$: 373.10053, found: 373.09961.
20. **2-(Dibenzo[*b,d*]thiophen-2-yl)imidazo[*1,2-a*]pyridine-3-carboxylic acid (5):** To a solution of **4** (5.0 g, 13.4 mmol) in MeOH and THF (1:1, 20 mL) was added lithium hydroxide (27 mmol in 10 mL of water), and stirred at room temperature overnight. The organic solvent was evaporated and 1 N HCl was added until the pH reached 4. The pale solid was collected by filtration, washed with water, and dried to give **5** as a light brown solid. Yield: 3.80 g, 82%; m.p: 169-171 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.14 (*br*s, 1H), 9.45 (d, *J*= 7.1 Hz, 1H), 8.76 (d, *J*= 1.1 Hz, 1H), 8.46-8.39 (m, 1H), 8.14-8.04 (m, 2H), 7.93 (dd, *J*= 8.2, 1.6 Hz, 1H), 7.85 (d, *J*= 9.0 Hz, 1H), 7.66-7.52 (m, 3H), 7.25 (td, *J*= 6.8, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7, 151.9, 146.2, 138.7, 138.6, 134.9, 134.3, 131.1, 129.0, 128.2, 128.1, 127.0, 124.7, 123.4, 123.3, 123.0, 121.8, 116.9, 114.3, 112.0; IR (KBr) 3378, 2980, 1678, 1520, 1446, 1132, 758 cm^{-1}; MS (ESI) *m/z* 345 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{20}H_{13}N_2O_2S$ $[M+H]^+$: 345.06904, found: 345.06859.
21. **General Procedure for synthesis of N-substituted 2-(dibenzo[*b,d*]thiophen-2-yl)imidazo[*1,2-a*]pyridine-3-carboxamides 7a-s.** To a solution of2-(dibenzo[*b,d*]thiophen-2-yl)imidazo[*1,2-a*]pyridine-3-carboxylic acid **5** (2.83 mmol) in anhydrous DMF (10 mL) were added 1-[3-(dimethyl amino)propyl]-3-ethylcarbodiimide (EDCI, 3.84 mmol), 1-hydroxybenzo triazole (HOBt, 1.54 mmol), triethyl amine (TEA, 5.12 mmol) and **6a-s** (2.56 mmol) at room temperature, and the resulting solution was heated at 70°C with stirring. After 12 h, the reaction mixture was cooled to room temperature and evaporated. Water (50 mL) was added into the crude residue, the resulting solid was collected by filtration, and the filtered cake was washed with water (50 mL) and dried to afford crude product. The resulting crude compound was purified by column chromatography over silica gel (n hexane / EtOAc = 1:1) to give **7a-s** as a white solid.
22. ***N*-Benzyl-2-(dibenzo[*b,d*]thiophen-2-yl)imidazo[*1,2-a*]pyridine-3-carboxamide (7a):** Yield: 0.32 g, 86%; m.p. 247-249 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.88 (d, *J*= 6.8 Hz, 1H), 8.71 (d, *J*= 1.1 Hz, 1H), 8.63 (t, *J*= 5.7 Hz, 1H), 8.32-8.24 (m, 1H), 7.85 (dd, *J*= 8.2, 1.6 Hz, 1H), 7.74 (d, *J*= 8.8 Hz, 1H), 7.60-7.42 (m, 3H), 7.36-7.18 (m, 5H), 7.10 (td, *J*= 6.8, 1.1 Hz, 1H), 4.48 (d, *J*= 6.0 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.8, 145.0, 144.6, 138.7, 138.6, 138.5, 135.0, 134.7, 130.3, 128.1, 127.6, 127.5, 127.1, 126.7, 126.6, 124.8, 122.9, 122.7, 121.9, 121.8, 116.7, 115.8, 113.3, 42.6; IR (KBr) 3136, 2923, 1632, 1548, 1498, 748, 727 cm^{-1}; MS (ESI) *m/z* 434 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{27}H_{20}N_3OS$ $[M+H]^+$: 434.13216, found: 434.13100. **2-(Dibenzo[*b,d*]thiophen-2-yl)-*N*-(4-fluorobenzyl)imidazo[*1,2-a*]pyridine-3-carboxamide (7b)** Yield: 0.28 g, 71%; m.p. 243-245 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (d, *J*= 6.9 Hz, 1H), 8.38 (d, *J*= 1.1 Hz, 1H), 8.07-7.99 (m, 1H), 7.94-7.86 (m, 1H), 7.82 (d, *J*= 8.3 Hz, 1H), 7.70-7.59 (m, 1H), 7.57-7.42 (m, 2H), 7.41-7.31 (m, 1H), 7.09-6.92 (m, 3H), 6.81-6.69 (m, 2H), 6.27 (t, *J*= 5.6 Hz, 1H), 4.41 (d, *J*= 5.6 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.7, 145.1, 144.7, 138.7, 138.5, 134.9, 134.8, 134.7, 130.3, 129.6, 129.5, 127.6, 127.1, 126.7, 126.6, 124.7, 122.9, 122.7, 121.9, 121.8, 116.7, 114.9, 114.6, 113.3, 41.9; IR (KBr) 3168, 2922, 1639, 1549, 1504, 1219, 729 cm^{-1}; MS (ESI) *m/z* 452 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{27}H_{19}FN_3OS$ $[M+H]^+$: 452.12274, found: 452.12144. ***N*-(4-Chlorobenzyl)-2-(dibenzo[*b,d*]thiophen-2-yl)imidazo[*1,2-a*]pyridine-3-carboxamide (7c):** Yield: 0.29 g, 72%; m.p. 238-240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.90 (d, *J*= 6.8 Hz, 1H), 8.68 (d, *J*= 1.1 Hz, 1H), 8.62 (t, *J*= 5.7 Hz, 1H), 8.28-8.21 (m, 1H), 8.10-8.03 (m, 2H), 7.85 (dd, *J*= 8.5, 1.6 Hz, 1H), 7.74 (d, *J*= 8.8 Hz, 1H), 7.60-7.43 (m, 3H), 7.29 (q, *J*= 8.5 Hz, 4H), 7.10 (td, *J*= 6.8, 1.1 Hz, 1H), 4.45 (d, *J*= 5.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8, 145.2, 144.7, 138.7, 138.5, 137.7, 135.0, 134.7, 131.3, 130.3, 129.4, 128.0, 127.7, 127.1, 126.8, 126.6, 124.7, 123.2, 122.8, 121.9, 116.7, 115.6, 113.4, 41.9; IR (KBr) 3138, 2922, 1632, 1542, 1494, 752, 728 cm^{-1}; MS (ESI) *m/z* 468 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{27}H_{19}ClN_3OS$ $[M+H]^+$: 468.09319, found: 468.09098. **2-(Dibenzo[*b,d*]thiophen-2-yl)-*N*-(4-methylbenzyl)imidazo[*1,2-a*]pyridine-3-carboxamide (7d):** Yield: 0.30 g, 78%; m.p. 214-216 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (d, *J*= 6.9 Hz, 1H), 8.40 (d, *J*= 1.1 Hz, 1H), 8.09-8.02 (m, 1H), 7.92-7.86 (m, 1H), 7.79 (d, *J*= 8.3 Hz, 1H), 7.69-7.62 (m, 2H), 7.55-7.43 (m, 2H), 7.41-7.33 (m, 1H), 7.01-6.82 (m, 5H), 6.21 (t, *J*= 4.9 Hz, 1H), 4.41 (d, *J*= 5.4 Hz, 2H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 147.9, 146.1, 140.3, 139.7, 137.0, 135.8, 134.9, 134.2, 129.8, 129.1, 128.1, 127.7, 127.5, 127.1, 124.5, 123.0, 122.7, 122.5, 121.9, 116.9, 114.7, 113.5, 43.1, 20.9; IR (KBr) 3132, 2925, 1632, 1544, 1496, 754 cm^{-1}; MS (ESI) *m/z* 448 $[M+H]^+$;

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HR-MS (ESI) Calcd for $C_{28}H_{22}N_3OS$ $[M+H]^+$: 448.14781, found: 448.14664. ***N*-(4-(*tert*-Butyl)benzyl)-2-(dibenzo[*b,d*]thiophen-2-yl) imidazo[*1,2-a*]pyridine-3-carboxamide (7e):** Yield: 0.31 g, 63%; m.p. 234-236 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (dt, *J*= 7.0, 1.0 Hz, 1H), 8.49 (d, *J*= 1.2 Hz, 1H), 8.19-8.15 (m, 1H), 7.93-7.88 (m, 1H), 7.80 (d, *J*= 8.0 Hz, 1H), 7.73-7.65 (m, 2H), 7.56-7.47 (m, 2H), 7.44-7.38 (m, 1H), 7.08-7.04 (m, 2H), 7.01 (dt, *J*= 7.0, 1.2 Hz, 1H), 6.99-6.95 (m, 2H), 6.10 (t, *J*= 5.4 Hz, 1H), 4.45 (d, *J*= 5.6 Hz, 2H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 150.2, 147.7, 145.9, 140.1, 139.6, 135.7, 134.9, 134.2, 129.7, 127.9, 127.7, 127.4, 127.0, 125.3, 124.6, 122.8, 122.7, 122.4, 121.9, 116.7, 114.7, 113.3, 43.0, 34.3, 31.1; IR (KBr) 3135, 2924, 1635, 1544, 1495, 753 cm^{-1}; MS (ESI) *m/z* 490 $[M+H]^+$ HR-MS (ESI) Calcd for $C_{31}H_{28}N_3OS$ $[M+H]^+$: 490.19476 found: 490.19031. **2-(Dibenzo[*b,d*]thiophen-2-yl)-*N*-(4-methoxybenzyl)imidazo[*1,2-a*] pyridine-3-carboxamide (7f):** Yield: 0.29 g, 72%; m.p. 228-230 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (d, *J*= 7.0 Hz, 1H), 8.41 (d, *J*= 1.3 Hz, 1H), 8.07-8.05 (m, 1H), 7.90-7.87 (m, 1H), 7.81 (d, *J*= 8.0 Hz, 1H), 7.68-7.65 (m, 2H), 7.53-7.45 (m, 2H), 7.40-7.36 (m, 1H), 7.00-6.94 (m, 3H), 6.58-6.55 (m, 2H), 6.14 (*br* t, 1H), 4.39 (d, *J*= 5.4 Hz, 2H), 3.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 158.8, 148.0, 146.2, 140.4, 139.7, 135.9, 135.0, 129.8, 129.4, 128.9, 128.2, 127.8, 127.3, 127.1, 124.6, 123.1, 122.7(x2), 121.9, 117.0, 114.8, 113.8, 113.6, 55.1, 42.8; IR (KBr) 3134, 2924, 1630, 1545, 1492, 753 cm^{-1}; MS (ESI) *m/z* 464 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{28}H_{22}N_3O_2S$ $[M+H]^+$: 464.14272, found: 464.14045. **2-(Dibenzo[*b,d*]thiophen-2-yl)-*N*-(4-(trifluoromethyl) benzyl)imidazo[*1,2-a*]pyridine-3-carboxamide (7g):** Yield: 0.32 g, 74%; m.p. 240-242 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (d, *J*= 7.0 Hz, 1H), 8.40 (d, *J*= 1.0 Hz, 1H), 8.04 (d, *J*= 7.6 Hz, 1H), 7.89 (d, *J*= 7.7 Hz, 1H), 7.83 (d, *J*= 8.2 Hz, 1H), 7.68-7.61 (m, 2H), 7.54-7.45 (m, 2H), 7.40-7.33 (m, 3H), 7.20 (d, *J*= 7.9 Hz, 1H), 6.97 (td, *J*= 7.0, 0.9 Hz, 1H), 6.34 (t, *J*= 5.6 Hz, 1H), 4.49 (d, *J*= 5.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 148.5, 146.4, 141.7, 140.6, 139.8, 136.0, 134.8, 129.9, 128.3, 127.8, 127.7, 127.5, 127.3, 125.4(x2), 124.7, 123.2, 122.9, 122.6, 121.7, 117.1, 114.4, 113.8, 42.8; IR (KBr) 3142, 2924, 1637, 1550, 1326, 1119, 753 cm^{-1}; MS (ESI) *m/z* 502 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{28}H_{19}F_3N_3OS$ $[M+H]^+$: 502.11954, found: 502.11819. **2-(Dibenzo[*b,d*] thiophen-2-yl)-*N*-(4-(trifluoromethoxy)benzyl)imidazo[*1,2-a*] pyridine-3-carboxamide (7h):** Yield: 0.33 g, 73%; m.p. 203-205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, *J*= 6.9 Hz, 1H), 8.41 (d, *J*= 1.2 Hz, 1H), 8.09-8.05 (m, 1H), 7.91-7.88 (m, 1H), 7.82 (d, *J*= 8.1 Hz, 1H), 7.67-7.62 (m, 2H), 7.54-7.45 (m, 2H), 7.40-7.35 (m, 1H), 7.13-7.09 (m, 2H), 7.00-6.92 (m, 3H), 6.28 (t, *J*= 5.6 Hz, 1H), 4.45 (d, *J*= 5.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 148.3, 148.1, 146.2, 140.4, 139.7, 136.4, 135.8, 134.8, 129.7, 129.0, 128.0, 127.6, 127.2, 124.6, 122.9, 122.8, 121.7, 120.9, 116.8, 114.5, 113.5, 42.5; IR (KBr) 3144, 2925, 1635, 1554, 1325, 1112, 759 cm^{-1}; MS (ESI) *m/z* 518 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{28}H_{18}F_3N_3O_2S$ $[M+H]^+$: 518.11446, found: 518.11347. **2-(Dibenzo [*b,d*]thiophen-2-yl)-*N*-(4-morpholinobenzyl)imidazo[*1,2-a*]pyridine-3-carboxamide (7i):** Yield: 0.25 g, 55%; m.p. 200-202 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (dt, *J*= 7.0, 1.0 Hz, 1H), 8.41 (d, *J*= 1.2 Hz, 1H), 8.11-8.07 (m, 1H), 7.90-7.86 (m, 1H), 7.78 (d, *J*= 8.0 Hz, 1H), 7.67-7.60 (m, 2H), 7.54-7.45 (m, 2H), 7.38-7.33 (m, 1H), 6.99-6.91 (m, 2H), 6.56-6.51 (m, 2H), 6.17 (t, *J*= 5.4 Hz, 1H), 4.38 (d, *J*= 5.4 Hz, 2H), 3.82 (t, *J*= 4.8 Hz, 4H), 2.99 (t, *J*= 4.8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 150.4, 147.7, 146.0, 140.1, 139.6, 135.7, 135.0, 129.8, 128.6, 128.4, 128.0, 127.7, 127.1, 127.0, 124.6, 122.9, 122.6, 122.5, 121.9, 116.8, 115.4, 114.8, 113.4, 66.7, 49.0, 42.8; IR (KBr) 3218, 2958, 1637, 1514, 1225, 759 cm^{-1}; MS (ESI) *m/z* 519 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{31}H_{27}N_4O_2S$ $[M+H]^+$: 519.18492, found: 519.18417. **2-(Dibenzo[*b,d*] thiophen-2-yl)-*N*-(4-thiomorpholinobenzyl)imidazo[*1,2-a*] pyridine-3-carboxamide (7j):** Yield: 0.28 g, 60%; m.p. 213-215 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (dt, *J*= 7.0, 1.0 Hz, 1H), 8.45 (d, *J*= 1.2 Hz, 1H), 8.15-8.11 (m, 1H), 7.92-7.88 (m, 1H), 7.82 (d, *J*= 8.2 Hz, 1H), 7.71-7.66 (m, 2H), 7.55-7.46 (m, 2H), 7.43-7.38 (m, 1H), 7.00 (td, *J*= 7.0, 1.2 Hz, 1H), 6.93-6.89 (m, 2H), 6.53-6.47 (m, 2H), 6.06 (t, *J*= 5.3 Hz, 1H), 4.38 (d, *J*= 5.4 Hz, 2H), 3.41-3.36 (m, 4H), 2.70-2.65 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 150.3, 147.7, 146.1, 140.3, 139.7, 135.9, 135.0, 129.7, 128.7, 128.2, 127.8, 127.4, 127.1, 124.7, 123.1, 122.7, 121.9, 116.9, 116.8, 114.8, 113.6, 51.8, 42.9, 26.5; IR (KBr) 3216, 29235, 1638, 1520, 1224, 761 cm^{-1}; MS (ESI) *m/z* 535 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{31}H_{27}N_4O_2S$ $[M+H]^+$: 535.16208, found: 535.16169. ***N*-(4-(4-Benzyl piperidin-1-yl)benzyl)-2-(dibenzo[*b,d*]thiophen-2-yl)imidazo[*1,2-a*] pyridine-3-carboxamide (7k):** Yield: 0.32 g, 61%; m.p. 212-214 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, *J*= 6.8 Hz, 1H), 8.70 (d, *J*= 1.1 Hz, 1H), 8.45 (d, *J*= 5.7 Hz, 1H), 8.32-8.26 (m, 1H), 8.09-7.96 (m, 2H), 7.84-7.79 (m, 1H), 7.72 (d, *J*= 9.0 Hz, 1H), 7.57-7.40 (m, 3H), 7.34-7.26 (m, 2H), 7.23-7.15 (m, 3H), 6.66 (d, *J*= 8.8 Hz, 2H), 4.35 (d, *J*= 5.5 Hz, 2H), 3.52 (d, *J*= 12.3 Hz, 2H), 2.55-2.48 (m, 5H), 1.61 (d, *J*= 12.1 Hz, 2H), 1.31-1.14 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 150.0, 144.9, 144.6, 140.1, 138.7, 138.4, 134.9, 134.8, 130.3, 128.9, 128.3, 128.0, 127.6, 127.0, 126.6, 126.5, 125.6, 124.8, 122.9, 122.7, 122.0, 121.8, 116.7, 115.9, 115.3, 113.2, 48.7, 42.2, 42.1, 37.1, 31.0; IR (KBr) 3420, 2924, 1634, 1552, 1515, 754 cm^{-1}; MS (ESI) *m/z* 607 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{39}H_{35}N_4OS$ $[M+H]^+$: 607.25261, found: 607.25225. ***N*-(4-(4-Benzylpiperazin-1-yl)benzyl)-2-(dibenzo[*b,d*]thiophen-2-yl) imidazo[*1,2-a*]pyridine-3-carboxamide (7l):** Yield: 0.28 g, 53%; m.p. 221-223 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.49 (d, *J*= 7.0 Hz, 1H), 8.42 (s, 1H), 8.12-8.08 (m, 1H), 7.89-7.85 (m, 1H), 7.78 (d, *J*= 8.2 Hz, 1H), 7.66-7.60 (m, 2H), 7.51-7.45 (m, 2H), 7.38-7.32 (m, 5H), 6.98-6.89 (m, 3H), 6.54 (d, *J*= 8.6 Hz, 2H), 6.17 (t, *J*= 5.1 Hz, 1H), 4.37 (d, *J*= 5.4 Hz, 2H), 3.57 (s, 2H), 3.05 (t, *J*= 4.8 Hz, 4H), 2.57 (t, *J*= 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 150.4, 147.7, 146.0, 140.1, 139.6, 137.7, 135.7, 135.0, 129.8, 129.1, 128.5, 128.1, 127.9(x2), 127.7, 127.0, 124.6, 122.9, 122.6, 122.4, 121.9, 116.8, 115.6, 114.8, 113.3, 62.9, 52.8, 48.7, 42.8; IR (KBr) 3418, 2935, 1633, 1549, 1518, 747 cm^{-1}; MS (ESI) *m/z* 608 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{38}H_{34}N_5OS$ $[M+H]^+$: 608.24786, found: 608.24691. **2-(Dibenzo[*b,d*]thiophen-2-yl)-*N*-(4-(4-(2-fluorophenyl)piperazin-1-yl)benzyl)imidazo[*1,2-a*]pyridine-3-carboxamide (7m):** Yield: 0.24 g, 45%; m.p. 198-200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.49 (d, *J*= 7.0 Hz, 1H), 8.42 (s, 1H), 8.12-8.08 (m, 1H), 7.89-7.85 (m, 1H), 7.78 (d, *J*= 8.2 Hz, 1H), 7.66-7.60 (m, 2H), 7.51-7.45 (m, 2H), 7.38-7.32 (m, 5H), 6.98-6.89 (m, 3H), 6.54 (d, *J*= 8.6 Hz, 2H), 6.17 (t, *J*= 5.1 Hz, 1H), 4.37 (d, *J*= 5.4 Hz, 2H), 3.57 (s, 2H), 3.05 (t, *J*= 4.8 Hz, 4H), 2.57 (t, *J*= 4.8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 156.6, 154.7, 150.4, 147.8, 146.1, 140.2, 139.9, 139.7, 135.8, 135.0, 129.8, 128.6, 128.4, 128.1, 127.8, 127.2, 127.1, 124.6, 124.4, 123.0, 122.7, 122.6, 121.9, 118.9, 116.9, 116.2, 116.0, 114.8, 113.5, 50.4, 49.1, 42.9; IR (KBr) 3449, 2923, 1658, 1635, 1499, 1229, 1084, 737 cm^{-1}; MS (ESI) *m/z* 612 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{37}H_{31}FN_5OS$ $[M+H]^+$: 612.22279, found: 612.22186. ***N*-(4-(4-(4-Chlorophenyl)piperazin-1-yl) benzyl)-2-(dibenzo[*b,d*]thiophen-2-yl)imidazo[*1,2-a*]pyridine-3-carboxamide (7n):** Yield: 0.20 g, 37%; m.p. 228-230 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (d, *J*= 7.0 Hz, 1H), 8.44 (d, *J*= 1.2 Hz, 1H), 8.13-8.10 (m, 1H), 7.89-7.86 (m, 1H), 7.81 (d, *J*= 8.2 Hz, 1H), 7.70-7.66 (m, 2H), 7.53-7.46 (m, 2H), 7.41-7.37 (m, 6H), 6.60 (d, *J*= 8.6 Hz, 2H), 6.12 (*br* t, 1H), 4.39 (d, *J*= 5.4 Hz, 2H), 3.28-3.24 (m, 4H), 3.20-3.15 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 150.2, 149.7, 145.9, 140.5, 139.7, 135.9, 135.0, 129.0, 128.7, 128.2, 127.8, 127.6, 127.1, 124.9, 124.7, 123.2, 122.7, 122.0, 117.5, 116.8, 116.2, 114.9, 113.8, 49.2, 49.0, 42.9; IR (KBr) 3338, 2917, 1619, 1520, 1495, 1227, 759 cm^{-1}; MS (ESI) *m/z* 628 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{37}H_{31}ClN_5OS$ $[M+H]^+$: 628.19324, found: 628.19171. **2-(Dibenzo[*b,d*]thiophen-2-yl)-*N*-(4-(4-fluorophenoxy)benzyl)imidazo[*1,2-a*]pyridine-3-carboxamide (7p):** Yield: 0.26 g, 55%; m.p. 230-232 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, *J*= 6.9 Hz, 1H), 8.45 (d, *J*= 0.9 Hz, 1H), 8.12-8.07 (m, 1H), 7.88-7.81 (m, 2H), 7.71-7.64 (m, 2H), 7.52-7.34 (m, 3H), 7.06-6.95 (m, 5H), 6.92-6.85 (m, 2H), 6.66 (d, *J*= 8.5 Hz, 2H), 6.25 (*br* t, 1H), 4.43 (d, *J*= 5.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 159.7, 157.8, 156.9, 152.5, 148.0, 146.2, 140.5, 139.7, 135.9, 134.9, 132.0, 129.8, 129.1, 128.2, 127.8, 127.5, 127.2, 124.7, 123.2, 122.8, 122.7, 121.8, 120.5, 118.0, 117.0, 116.3, 114.6, 113.7, 42.8; IR (KBr) 3152, 2928, 1634, 1550, 1498, 1251, 748 cm^{-1}; MS (ESI) *m/z* 544 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{33}H_{23}FN_3O_2S$ $[M+H]^+$: 544.14895, found: 544.14747. ***N*-(4-(4-(*tert*-Butyl)phenoxy)benzyl)-2-(dibenzo[*b,d*]thiophen-2-yl)imidazo[*1,2-a*] pyridine-3-carboxamide (7r):** Yield: 0.34 g, 68%; m.p. 216-218 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (d, *J*= 6.8 Hz, 1H), 8.44 (d, *J*= 1.2 Hz, 1H), 8.11-8.06 (m, 1H), 7.87-7.81 (m, 2H), 7.70-7.62 (m, 2H), 7.51-7.42 (m, 2H), 7.40-7.31 (m, 2H), 7.06-7.01 (m, 2H), 6.96 (dt, *J*= 7.1, 1.2 Hz, 1H), 6.89-6.84 (m, 2H), 6.75-6.69 (m, 2H), 6.26 (t, *J*= 5.6 Hz, 1H), 4.43 (d, *J*= 5.6 Hz, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 156.8, 154.3, 147.7, 146.1, 146.0, 140.1, 139.5, 135.7, 134.8, 131.9, 129.7, 129.1, 127.9, 127.6, 127.0(x2), 126.4, 124.6, 122.8, 122.6, 122.3, 121.8, 118.4, 118.3, 116.7, 114.6, 113.3, 42.7, 34.2, 31.4; IR (KBr) 3154, 2957, 1638, 1551, 1500, 1241, 753 cm^{-1}; MS (ESI) *m/z* 582 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{37}H_{32}N_3O_2S$ $[M+H]^+$: 582.22097, found: 582.21978. **2-(Dibenzo[*b,d*]thiophen-2-yl)-*N*-(4-(4-(trifluoromethoxy)phenoxy) benzyl)imidazo[*1,2-a*]pyridine-3-carboxamide (7s):** Yield: 0.33 g, 62%; m.p.216-218 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (td, *J*= 7.0, 1.0 Hz, 1H), 8.43 (d, *J*= 1.2 Hz, 1H), 8.10-8.07 (m, 1H), 7.87-7.82 (m, 2H), 7.68 (dd, *J*= 8.2, 1.6 Hz, 1H), 7.64 (td, *J*= 9.0, 1.0 Hz, 1H), 7.50-7.43 (m, 2H), 7.37 (dq, *J*= 6.8, 1.2 Hz, 1H), 7.19-7.14 (m, 2H), 7.06 (d, *J*= 8.5 Hz, 1H), 6.97 (dt, *J*= 7.0, 1.2 Hz, 1H), 6.92-6.88 (m, 2H), 6.72-6.68 (m, 2H), 6.26 (t, *J*= 5.6 Hz, 1H), 4.44 (d, *J*= 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 155.9, 155.4, 147.8, 146.1, 144.3, 140.2, 139.5, 135.7, 134.8, 132.9, 129.8, 129.2, 127.9, 127.7, 127.1, 124.6, 122.9, 122.7, 122.4, 121.7, 119.4, 118.8, 116.7, 114.5, 113.4, 42.7; IR (KBr) 3143, 2923, 1636, 1549, 1497, 1246, 1163, 753 cm^{-1}; MS (ESI) *m/z* 610

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$[M+H]^+$; HR-MS (ESI) Calcd for $C_{34}H_{23}F_3N_3O_3S$ $[M+H]^+$: 610.14067, found: 610.13693.

23. **Antitubercular evaluation assay**: Two-fold serial dilutions (50.0, 25.0, 12.5, 6.25, 3.13, 1.56, 0.78 and 0.4 µg/mL) of each test compounds **7a-s**, and drugs were prepared and incorporated into Middlebrook 7H11 agar medium with OADC Growth Supplement. Inoculum of *M. tuberculosis* H37Rv (ATCC 27294) was prepared from fresh Middlebrook 7H11 agar slants with OADC (oleic acid, albumin, dextrose and catalase; Difco) Growth Supplement adjusted to 1 mg/mL (wet weight) in Tween 80 (0.05%) saline diluted to 10^{-2} to give a concentration of ~ 10^7 cfu/mL. A 5 µL amount of bacterial suspension was spotted into 7H11 agar tubes containing two-fold serial dilutions of drugs per mL. The tubes were incubated at 37 ºC, and final readings were recorded after 28 days. This method is similar to that recommended by the National Committee for Clinical Laboratory Standards for the determination of MIC in triplicate.
24. **Evaluation of cytotoxicity:** Antitubercular active compounds with MIC ≤ 12.5µg/mL were further examined for toxicity in a HEK-293T cell line at the concentration of 50 µg/mL. After 72 h of exposure, viability of HEK-293T cells were assessed based on cellular conversion of MTT into a formazan product using the Promega Cell Titer 96 non-radioactive cell proliferation assay.

Supplementary Material

Copies of ^1H, ^{13}C NMR and mass spectra of all the compounds **7a-s** can be obtained free of charge from the internet.

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Graphical Abstract

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Synthesis and antitubercular evaluation of novel dibenzo[*b,d*] thiophene tethered imidazo[1,2-*a*]pyridine-3-carboxamides.

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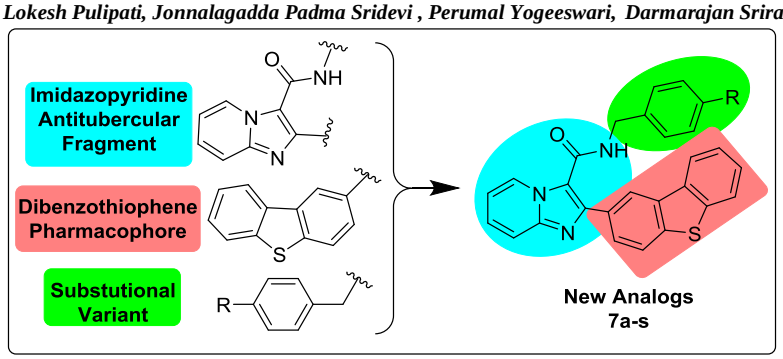
*Lokesh Pulipati, Jonnalagadda Padma Sridevi , Perumal Yogeeswari, Darmarajan Sriram and Srinivas Kantevari**



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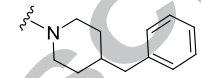
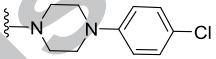
7k		0.78
7n		1.56

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